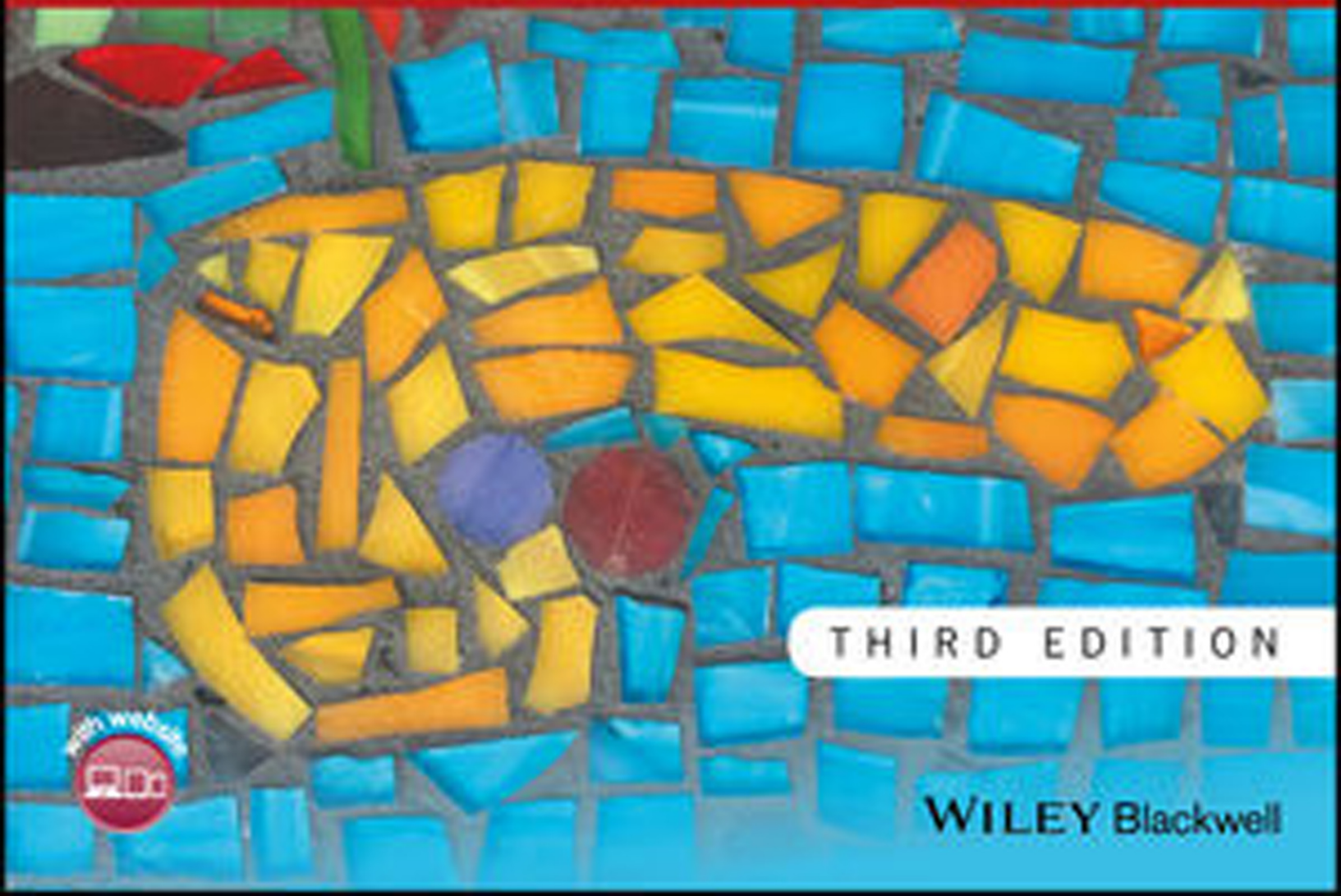
# The PANCREAS

## AN INTEGRATED TEXTBOOK OF BASIC SCIENCE, MEDICINE, AND SURGERY

EDITED BY HANS BEGER, ANDREW WARSHAW, RALPH HRUBAN, MARKUS BÜCHLER, MARKUS LERCH, JOHN NEOPTOLEMOS, TOORU SHIMOSEGAWA AND DAVID WHITCOMB



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# The Pancreas

## An Integrated Textbook of Basic Science, Medicine, and Surgery

**Third Edition**

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# Preface

The pancreas has long been an underappreciated organ. Although Aristotle first acknowledged the pancreas in *Historia animalium*, written between 347 and 335 BCE, Galen insisted that the only function of the pancreas was to pad the abdominal vessels, and so the organ was ignored. It took more than a thousand years for Wirsung to describe, in 1642, the ductal morphology of the gland, as well as the communications of the pancreatic duct with the lumen of the small intestine. Today, we recognize the critical importance of the gland, and understanding the pancreas, its normal and abnormal functions and its morphological pathology has become an international focus of established scientists. The understanding of functions and dysfunctions of the exocrine and endocrine pancreas is derived from molecular biological data on the actions of compounds in subcellular compartments and intracellular transcription pathways. In clinical medicine, new and improved technical devices enable the gastroenterologist and the gastrointestinal surgeon to identify lesions by high-resolution imaging techniques, imaging of metabolic processes, and intrapancreatic ductal investigations. In the last 20 years, the spectrum of diseases of the pancreas has been extended by recognition of new and increasingly identified common disorders of the pancreas such as cystic neoplasms and autoimmune pancreatitis. In pancreatology only ductal pancreatic cancer remains largely an uncontrollable mystery disease.

Medical science is not uniform around the world. However, the impact of information technology, international data exchange, and global communication networks have resulted in a broad, increased level in the understanding and practice of pancreatology. The synergistic interaction of basic scientists, pathologists, gastroenterologists, and gastrointestinal tract surgeons in the field of investigative and clinical pancreatology has led to better understanding of pancreatic diseases through combining the knowledge of each to achieve the best management. Decision making is increasingly based on the evidence of data from clinical trials on treatment. New technical devices—endoscopic visualization of cellular abnormalities, laparoscopic minimal invasive surgical approaches, and robotic surgery—have led to the establishment of a local, parenchyma-sparing surgical approach for neoplastic and inflammatory pancreatic diseases. Although care of patients cannot be made a global affair, this book brings the most recent knowledge on the pancreas from international experts to readers everywhere.

The goal of this third edition of *The Pancreas: An integrated textbook of basic science, medicine, and surgery* is to provide the clinician with the most current data-based synthesis of understanding of pancreatic diseases, functional assessment, diagnostic and technical devices, and treatment options. All chapters are written by leading international experts on the topic. A major part of this edition has been contributed by international basic scientists, who provide an understanding of the molecular basis of pancreatic functions and diseases. The editors acknowledge and are deeply indebted to all authors who have contributed to this edition. Their diligent efforts have provided state-of-the-art knowledge, particularly in regard to clinical decision making based on evidence.

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## Abbreviations

| | |
|---|---|
| 4EBP1 | initiation factor 4E binding protein 1 |
| 5-FU | 5-fluorouracil |
| 5-HIAA | 5-hydroxyindoleacetic acid |
| 5-HT | 5-hydroxytryptamine; serotonin |
| 25(OH)D | 25-hydroxyvitamin D |
| α-gal | alpha-galactosylated |
| α-GI | alpha-glucosidase inhibitor |
| αSMA | alpha smooth muscle actin |
| ABP | acute biliary pancreatitis |
| ACC | acinar cell carcinoma |
| ACE | angiotensin-converting enzyme |
| ACG | American College of Gastroenterology |
| ACh | acetylcholine |
| ACP | alcoholic chronic pancreatitis |
| ACS | abdominal compartment syndrome |
| ACS | American Cancer Society |
| ACTH | adrenocorticotropic hormone |
| ADH | alcohol dehydrogenase |
| ADM | acinar-to-ductal metaplasia |
| ADP | adenosine diphosphate |
| ADPKD | autosomal dominant polycystic kidney disease |
| AFIP | Armed Forces Institute of Pathology |
| AFP | alpha-fetoprotein |
| AGA | American Gastroentrological Association |
| AHPBA | American Hepato-Pancreato-Biliary Association |
| AID | autoinhibitory domain |
| AIDS | acquired immune deficiency syndrome |
| AIH | autoimmune hepatitis |
| AJCC | American Joint Committee on Cancer |
| AIP | autoimmune pancreatitis |
| ALDH | acetaldehyde dehydrogenase |
| ALI | acute lung injury |
| ALT | alanine transaminase |
| ALT | alternative lengthening of telomeres |
| ANC | acute necrotic collection |
| anti-SSA | anti-Sjögren syndrome A |
| anti-SSB | anti-Sjögren syndrome B |
| AP | acute pancreatitis |
| AP-1 | activator protein-1 |
| APA | American Pancreatic Association |
| APACHE | acute physiology and chronic health evaluation |
| APBDU | anomalous pancreaticobiliary ductal union |
| APC | activated protein C |

| | |
|---|---|
| APC | antigen-presenting cells |
| APFC | acute pancreatic fluid collection |
| ARDS | acute respiratory distress syndrome |
| ARF | acute renal failure |
| Arg | arginine |
| ARP | acute recurrent pancreatitis |
| ARTN | artemin |
| ARX | aristaless-related homeobox |
| ASA | acetylsalicylic acid |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate transaminase |
| ATIII | antithrombin 3 |
| ATMDS | alpha-thalassemia myelodysplastic syndrome |
| ATP | adenosine triphosphate |
| ATRX | alpha-thalassemia/mental retardation X-linked |
| AUROC | area under the receiver operating characteristic curve |
| BAPTA-AM | 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid |
| BCAA | branched-chain amino acid |
| BD-IPMN | branch-duct intraductal papillary mucinous neoplasm |
| BE | balloon enteroscopy |
| BHOB | β-hydroxybutyrate |
| BilIN | biliary intraepithelial neoplasia |
| BMI | body mass index |
| BMP | bone morphogenic protein |
| *BRCA1* | breast cancer 1 gene |
| *BRCA2* | breast cancer 2 gene |
| BRPC | borderline resectable pancreatic cancer |
| BR-PDAC | borderline resectable pancreatic ductal adenocarcinoma |
| BSA | body surface area |
| BSG | British Society of Gastroenterology |
| BUN | blood urea nitrogen |
| BWS | Beckwith–Wiedemann syndrome |
| CA 19-9 | carbohydrate antigen 19-9 |
| CA | carbonic anhydrase |
| CA | celiac axis |
| cADPR | cyclic ADP-ribose |
| CAP | College of American Pathologists |
| CAPS | Cancer of the Pancreas Screening programs |
| CARS | compensatory anti-inflammatory response syndrome |
| CAS | celiac artery stenosis |
| CASR | calcium-sensing receptor |
| CBCT | cone beam computed tomography |
| CBD | common bile duct |
| CBER | Center for Biologics Evaluation and Research |
| CBP | CREB-binding protein |
| CCK | cholecystokinin |
| CDX | caudal-related homeobox transcription factor |
| CEA | carcinoembryonic antigen |
| CE-CT | contrast-enhanced computed tomography |
| CEL | carboxyl ester lipase |
| CF | cystic fibrosis |
| CFRD | cystic fibrosis-related diabetes mellitus |
| CFTR | cystic fibrosis transmembrane conductor regulator |
| CG | celiac ganglion |
| CGRP | calcitonin gene-related peptide |
| ChA | chromogranin A |

| | |
|---|---|
| CHI | congenital hyperinsulinism |
| Chr | chromosome |
| CI | confidence interval |
| CIT | Clinical Islet Transplantation |
| CITR | Collaborative Islet Transplant Registry |
| *CLDN2* | claudin 2 gene |
| CNI | calcineurin inhibitor |
| CNS | central nervous system |
| CONKO | Charité Onkologie |
| COX-2 | cyclooxygenase 2 |
| CP | chronic pancreatitis |
| CPA1 | carboxypeptidase A1 |
| CPB | celiac plexus block |
| CPN | celiac plexus neurolysis |
| CPNT | cystic pancreatic neuroendocrine tumor |
| CRAC | $Ca^{2+}$ release activated $Ca^{2+}$ |
| CREB | cAMP response element binding |
| CRF | corticotropin-releasing factor |
| CRH | corticotropin-releasing hormone |
| CRP | C-reactive protein |
| CRT | chemoradiation therapy |
| CSF-1 | colony-stimulating factor 1 |
| CSF-1/R | colony stimulating factor-1/receptor |
| CT | computed tomography |
| CTC | circulating tumor cells |
| ctDNA | circulating tumor DNA |
| CTGF | connective tissue growth factor |
| CTL | cytotoxic T-lymphocytes |
| CTLA-4 | cytotoxic T-lymphocyte associated protein-4 |
| CTRC | chymotrypsin C or chymotrypsinogen C |
| CTSB | cathepsin B |
| CTSI | CT severity index |
| Cy | cyclophosphamide |
| CYP2E1 | cytochrome P450 2E1 |
| DAMP | damage-associated molecular pattern molecule |
| DAXX | death domain-associated protein |
| DBC | determinant-based classification |
| DBDC | distal common bile duct carcinoma |
| DBE | double-balloon enteroscopy |
| DBTC | dibutyltin chloride |
| DCD | deceased cardiac death donor |
| DEN | direct endoscopic necrosectomy |
| DGE | delayed gastric emptying |
| DKA | diabetic ketoacidosis |
| DM | diabetes mellitus |
| DMV | dorsal motor nucleus |
| DNA | deoxyribonucleic acid |
| DOPA | dihydroxyphenylalanine |
| DOTA | 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid |
| DOTA-NOC | DOTA-Nal-octreotide |
| DOTA-TATE | DOTA-Tyr-octreotate |
| DOTA-TOC | DOTA-Tyr-octreotide |
| DP | distal pancreatectomy |
| DPDS | disconnected pancreatic duct syndrome |
| DPP-4 | dipeptidyl-peptidase-4 |
| DPPHR | duodenum-preserving pancreatic head resection |

| | |
|---|---|
| DPPHR-P | duodenum-preserving partial head resection |
| DPPHR-S | duodenum-preserving total head resection plus segment resection of duodenum and CBD |
| DPPHR-T | duodenum-preserving total head resection but conserving duodenum and CBD |
| DRG | dorsal root ganglion |
| DSS | disease-specific survival |
| DTPA | diethylenetriaminepentaacetic acid |
| DWI | diffusion-weighted imaging MRI |
| DXA | dual X-ray absorptiometry |
| E8.5 | embryonic day 8.5 |
| EBL | estimated blood loss |
| EBRT | external beam radiation |
| ECG | electrocardiogram |
| ECM | extracellular matrix |
| ED | emergency department |
| EGF | epithermal growth factor |
| eIF2α | eukaryotic initiation factor 2 alpha |
| eIF4F | eukaryotic initiation factor 4F |
| eIF4G | eukaryotic initiation factor 4G |
| ELISA | enzyme-linked immunosorbent assay |
| EMT | epithelial mesenchymal transition |
| ENETS | European Neuroendocrine Tumor Society |
| EORTC | European Organization for Research and Treatment of Cancer |
| EPI | exocrine pancreatic insufficiency |
| EPO | erythropoietin |
| ER | endoplasmic reticulum |
| ERCP | endoscopic retrograde cholangiopancreatography imaging |
| ERK | extracellular regulated kinase |
| ERP | endoscopic retrograde pancreatography |
| ES | endoscopic sphincterotomy |
| ESDO | European Society of Digestive Oncology |
| ESGE | European Society of Gastrointestinal Endoscopy |
| ESMO | European Society for Medical Oncology |
| ESPAC | European Study Group for Pancreatic Cancer |
| ESR | erythrocyte sedimentation rate |
| ESRD | end-stage renal disease |
| ESWL | extracorporeal shock wave lithotripsy |
| EUROPAC | European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer |
| EUS | endoscopic ultrasound |
| EUS-AG | EUS-guided antegrade stenting |
| EUS-BD | endoscopic ultrasonography-guided biliary drainage |
| EUS-CDS | EUS-guided choledochoduodenostomy |
| EUS-CGN | EUS-guided celiac ganglia neurolysis |
| EUS-CPN | endoscopic ultrasound celiac plexus neurolysis |
| EUS-FNA | endoscopic ultrasound guided fine-needle aspiration |
| EUS-HGS | EUS-guided hepaticogastrostomy |
| EUS-RV | EUS-rendezvous technique |
| FAEE | fatty acid ethyl ester |
| FAP | familial adenomatous polyposis |
| FCεR | high-affinity IgE or Fc epsilon receptor |
| FCPD | fibrocalculous pancreatic diabetes |
| fcSEMS | fully covered self-expandable metal stents |
| FDA | Food and Drug Administration (USA) |
| FDG-PET | [$^{18}$F]fluoro-2-deoxy-D-glucose positron emission tomography |
| FDP | [$^{18}$F]fluorodipalmitin |
| FE-1 | fecal elastase-1 |
| FFA | free fatty acid |

| | |
|---|---|
| FGF | fibroblast growth factor |
| FIBS | fibroinflammatory biliary stricture |
| FNA | fine-needle aspiration |
| FNB | fine-needle biopsy |
| FOLFIRINOX | 5-fluorouracil [5-FU], oxaliplatin, irinotecan, and leucovorin |
| FPC | familial pancreatic cancer |
| Ga | gallium citrate |
| GAP-43 | growth-associated protein-43 |
| G-CSF | granulocyte colony-stimulating factor |
| GDA | gastroduodenal artery |
| GEL | granulocytic epithelial lesion |
| GEP-NET | gastroenteropancreatic neuroendocrine tumor |
| GFAP | glial fibrillary acidic protein |
| GFR | glomerular filtration rate |
| GH | growth hormone |
| GHRH | growth hormone-releasing hormone |
| GI | gastrointestinal |
| GIP | gastric inhibitory peptide |
| GIP | glucose-dependent insulinotropic polypeptide |
| GITSG | Gastrointestinal Tumor Study Group |
| GJ | gastrojejunostomy |
| GLP-1 | glucagon-like peptide 1 |
| Gly | glycine |
| GM-CSF | granulocyte macrophage-colony stimulating factor |
| GNAS | guanine nucleotide binding protein alpha stimulating |
| GNPNA | *N*-glutaryl-L-phenylalanine-*p*-nitroanilide |
| GRAGIL | Group de Recherche Rhin, Rhône-Alpes et Genève pour la Transplantation d'Ilots de Langerhans |
| GRF | growth hormone-releasing factor |
| GTX | gemcitabine, docetaxel, and capecitabine |
| GWAS | genome-wide association studies |
| H2R | histamine 2 receptor |
| H&E | hematoxylin and eosin (histologic stain) |
| $HbA_{1c}$ | hemoglobin $A_{1c}$ |
| HB-EGF | heparin-binding EGF-like growth factor |
| HBV | hepatitis B virus |
| hCG | human chorionic gonadotropin |
| hENT1 | human equilibrative nucleoside transporter 1 |
| HES1 | hairy and enhancer of split 1 |
| HGD | high-grade dysplasia |
| HGF | hepatocyte growth factor |
| HIF | hypoxia-induced factor |
| HIV | human immunodeficiency virus |
| HJ | hepaticojejunostomy |
| HLA | human leukocyte antigen |
| HMG-CoA | 3-hydroxy-3-methylglutaryl-coenzyme A |
| HNF | hepatocyte nuclear factor |
| HNPCC | hereditary nonpolyposis colorectal cancer syndrome |
| HPF | high power field |
| HR | hazard ratio |
| HTG | hypertriglyceridemia |
| HTK | histidine–tryptophan–ketoglutarate |
| HTP | hydroxytrytophan |
| HUS | hemolytic uremic syndrome |
| IAH | impaired awareness of hypoglycemia |
| IAK | islet after kidney |
| IAP | International Association of Pancreatology |

| | |
|---|---|
| IAPN | intra-ampullary papillary tubular neoplasm |
| IBD | inflammatory bowel disease |
| IC | immune complex |
| IC | invasive carcinoma |
| ICDC | International Consensus Diagnostic Criteria for AIP |
| ICGC | International Cancer Genome Consortium |
| ICU | intensive care unit |
| IDCP | idiopathic duct-centric pancreatitis |
| IDDM | insulin-dependent diabetes mellitus |
| IDDS | intrathecal drug delivery systems |
| IEQ | islet equivalent |
| IFN-γ | interferon γ |
| Ig | immunoglobulin |
| IgE | immunoglobulin E |
| IGF | insulin-like growth factor |
| IGF-1 | insulin-like growth factor 1 |
| IgG | immunoglobulin G |
| IgG4-MOLPS | IgG4-related multiorgan lymphoproliferative syndrome |
| IgG4-RD | IgG4-related disease |
| IL | interleukin |
| IL-10 | interleukin 10 |
| IL-1β | interleukin 1β |
| IL-6 | interleukin 6 |
| IL-8 | interleukin 8 |
| IMRT | intensity modulated radiation therapy |
| iNOS | inducible nitric oxide synthase |
| IOPN | intraductal oncocytic papillary neoplasm |
| IORT | intraoperative radiation therapy |
| IOU | intraoperative ultrasound |
| $IP_3$ | inositol 1,4,5-trisphosphate |
| IPHM | inflammatory pancreatic head mass |
| IPMN | intraductal papillary mucinous neoplasm |
| IPTR | International Pancreas Transplant Registry |
| IQR | interquartile range |
| IR | insulin receptor |
| IRE | irreversible electroporation |
| IRG | immunoreactive gastrin |
| IRI | immunoreactive insulin |
| ISGPF | International Study Group on Pancreatic Fistula |
| ISGPS | International Study Group of Pancreatic Surgery |
| IT | intrathecal |
| ITA | intraductal tubular adenoma |
| ITA | islet transplant alone |
| ITC | intraductal tubular carcinoma |
| ITPN | intraductal tubulopapillary neoplasm |
| ITU | intensive therapy unit |
| IVE | interventional endoscopy |
| IVR | interventional radiology |
| JASPAC | Japan Adjuvant Study Group of Pancreatic Cancer |
| JBS | Johanson–Blizzard syndrome |
| JPN CTSI | Japanese CTSI |
| KRAS | Kirsten rat sarcoma viral oncogene homolog |
| LA | locally advanced |
| LAMP | lysosomal-associated membrane protein-2 |
| LAMS | lumen-apposing metal stent |
| LAPC | locally advanced pancreatic cancer |

| | |
|---|---|
| LAR | long-acting release |
| LDP | laparoscopic distal pancreatectomy |
| LEF1 | lymphoid enhancer-binding factor 1 |
| LH | luteinizing hormone |
| LIF | leukemia inhibitory factor |
| LKM | liver-kidney-microsomal |
| lncRNA | long noncoding RNA |
| LNR | lymph node ratio |
| LOH | loss of heterozygosity |
| LOS | length of stay |
| LOT | ligament of Treitz |
| LP | left pancreatectomy |
| LPJ | lateral pancreaticojejunostomy |
| LPL | lipoprotein lipase |
| LPLD | lipoprotein lipase deficiency |
| LPS | lipopolysaccharide |
| LPSP | lymphoplasmacytic sclerosing pancreatitis |
| LR | lactated Ringer's |
| LR–LPJ | local resection with lateral pancreaticojejunostomy |
| M3 | muscarinic M3 receptors |
| MAEC | mixed acinar endocrine carcinoma |
| MAL | median arcuate ligament |
| MANEC | mixed adenoneuroendocrine carcinoma |
| MAPK | mitogen-activated protein kinase |
| MARPN | minimal access retroperitoneal pancreatic necrosectomy |
| MBPR | master production batch record |
| MCN | mucinous cystic neoplasm |
| MCP1 | monocyte chemotactic protein 1 |
| MCS | mean component score |
| MCT | medium-chain triglycerides |
| MD | main duct |
| MDCT | multidetector computed tomography |
| MD-CTSI | modified CT severity index |
| MD-IPMN | main-duct intraductal papillary mucinous neoplasm |
| MDSC | myeloid-derived suppressor cell |
| MEN1 | multiple endocrine neoplasia type 1 |
| MGOO | malignant gastric outlet obstruction |
| MHC | major histocompatibility complex |
| MIP | maximum intensity projection imaging |
| miRNA | microribonucleic acid |
| MIS | minimally invasive surgery |
| MIST1 (BHLHA15) | basic helix–loop–helix family member A15 |
| MLL | mixed-lineage leukemia |
| MMC | migrating motor complex |
| MMF | mycophenolate mofetil |
| MMP | matrix metalloproteinase |
| MOCA | multivariate organization of combinatorial alterations |
| MODS | multiple organ dysfunction syndrome |
| MODY | maturity-onset diabetes of the young |
| MPD | main pancreatic duct |
| MPN | mucin-producing neoplasms |
| MPTP | mitochondrial permeability transition pore |
| MRC | magnetic resonance cholangiography |
| MRCP | magnetic resonance cholangiopancreatography |
| MRI | magnetic resonance imaging |
| MSI | microsatellite instability |

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|---|---|
| MSKCC | Memorial Sloan Kettering Cancer Center |
| mtDNA | mitochondrial DNA |
| mTORC1/2 | mammalian target of rapamycin complex 1/complex 2 |
| MUC | mucin protein |
| MX | mixed type |
| NAADP | nicotinic acid adenine dinucleotide phosphate |
| NADC | nonampullary duodenum duodenal carcinoma |
| NADCP | nonalcoholic duct-destructive chronic pancreatitis |
| NADPH | nicotinamide adenine dinucleotide phosphate |
| NAFLD | nonalcoholic fatty liver disease |
| NAPS2 | North American Pancreatitis Study 2 |
| NC | noncontrast |
| NCCN | National Comprehensive Cancer Network |
| NCDB | National Cancer Database |
| NEC | neuroendocrine carcinoma |
| NEN | neuroendocrine neoplasm |
| NET | neuroendocrine tumor |
| NET | neutrophil extracellular trap |
| NEUROD | neuronal differentiation 1 |
| NF | neurotrophic factors |
| NF1 | neurofibromatosis type 1 |
| NFAT | nuclear factor of activated T cells |
| NFκB | nuclear factor kappa light-chain enhancer of activated B cells |
| NFκB | nuclear factor-κB |
| NG | nodose ganglion |
| NGF | nerve growth factor |
| NGN3 | neurogenin 3 |
| NGS | next generation sequencing |
| NIPHS | noninsulinoma pancreatogenous hypoglycemia syndrome |
| NK-1R | neurokinin 1 receptor |
| NKX2.2 | NK homeobox 2 |
| NO | nitric oxide |
| NOS | not otherwise specified |
| NPD | nasal potential difference |
| NR5A2 | nuclear receptor subfamily 5 group A member 2 |
| NSAID | nonsteroidal anti-inflammatory drug |
| NSE | neuron-specific enolase |
| NTR | neurotrophic factor receptors |
| NTS | nucleus tractus solitarius |
| OOI | other organ involvement |
| OP/SL | open packing/staged laparotomy |
| OR | odds ratio |
| OS | overall survival |
| OTS | ovarian type stroma |
| PA | pancreas transplantation alone |
| PACAP | pituitary adenylate cyclase-activating peptide |
| PACC | Polyanalgesic Consensus Conference |
| PAF | platelet activating factor |
| PAK | pancreas transplantation after a kidney transplant |
| PAMP | pathogen-associated molecular pattern |
| PanC4 | Pancreatic Cancer Case–Control Consortium |
| PanIN | pancreatic intraepithelial neoplasia |
| PanNEC | pancreatic neuroendocrine carcinoma |
| PanNET | pancreatic neuroendocrine tumor |
| PAR-2 | proteinase-activated receptor-2 |
| PAS | periodic acid–Schiff |

| | |
|---|---|
| PAS-D | periodic acid–Schiff with diastase |
| PAX4 | paired box 4 |
| PBC | primary biliary cholangitis |
| PBD | preoperative biliary drainage |
| PBF | pancreatic blood flow |
| PBS | pencil beam scanning |
| PBT | proton beam therapy, proton therapy |
| PCA | pancreatic cancer |
| PCD | percutaneous catheter drainage |
| PCL | pancreatic cystic lesion |
| PCN | pancreatic cystic neoplasm |
| PCS | physical component score |
| PCT | procalcitonin |
| PD | pancreatoduodenectomy |
| PD-1 | programmed death-1 |
| PDAC | pancreatic ductal adenocarcinoma |
| PDEC | poorly differentiated endocrine carcinoma |
| PDGF | platelet-derived growth factor |
| PDGFβ | platelet-derived growth factor β |
| PD-L1/2 | programmed death-ligand 1/2 |
| PD-NEC | poorly differentiated neuroendocrine carcinoma |
| PDP | paraduodenal (groove) pancreatitis |
| PDS | polydiaxone sutures |
| PDX1 | pancreatic and duodenal homeobox 1 |
| PEG | percutaneous endoscopic gastrostomy |
| PEI | pancreatic exocrine insufficiency |
| PERK | endoplasmic reticulum-resident protein kinase |
| PERT | pancreatic enzyme replacement therapy |
| PET | positron emission tomography |
| PFC | pancreatic fluid collections |
| PFS | progression-free survival |
| PG | pancreatogastrostomy |
| PG | plasma glucose |
| pHi | intramucosal pH |
| PHPI | purified human pancreatic islet product |
| PI3′K | phosphoinositide 3′-kinase |
| PI3K | phosphatidylinositol 3-kinase |
| PICU | pediatric intensive care unit |
| PIK3CA | phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha |
| PJ | pancreaticojejunostomy |
| PJS | Peutz–Jeghers syndrome |
| PKA | protein kinase A |
| PKB | protein kinase B |
| PLA-2 | phospholipase A2 |
| PLC | phospholipase C |
| PMCA | plasma membrane $Ca^{2+}$-activated ATPase |
| PMD | pancreatic main duct |
| PMN-elastase | polymorph-nuclear cell elastase |
| PMSR | pancreatic middle segment resection |
| PNET | pancreatic neuroendocrine tumor |
| PNI | perineural invasion |
| POF | persistent organ failure |
| POPF | postoperative pancreatic fistula |
| PP | pancreatic polypeptide |
| PP1 | protein phosphatase 1 |
| PPARγ | peroxisome proliferator-activated receptor gamma |

| | |
|---|---|
| PPC | pancreatic pseudocyst |
| PPI | proton-pump inhibitor |
| PPoma | pancreatic polypeptide-producing tumor |
| PPPD | pylorus-preserving pancreaticoduodenectomy |
| PROX1 | prospero homeobox 1 |
| PRRT | peptide receptor radionuclide therapy |
| *PRSS1* | protease, serine 1 gene (also known as cationic trypsinogen gene) |
| PS | performance status |
| PSC | pancreatic stellate cells |
| PSC | primary sclerosing cholangitis |
| PSP | pancreatic stone protein |
| PSTI | pancreatic secretory trypsin inhibitor |
| PTBD | percutaneous transhepatic biliary drainage |
| PTC | percutanous transhepatic cholangiography |
| PTEN | phosphatase and tensin homolog |
| PTF1A | pancreas-specific transcription factor 1A |
| PTH | parathyroid hormone |
| PTH-rP | parathyroid hormone-related polypeptide |
| PTLD | posttransplant lymphoproliferative disorder |
| PV | portal vein |
| PYY | peptide YY |
| QOL | quality of life |
| RAC | revised Atlanta classification |
| RADIANT | RAD001 in advanced neuroendocrine tumors |
| RAF | rapidly accelerated fibrosarcoma |
| RAMPS | radical antegrade modular pancreatosplenectomy |
| RANTES | regulated on activation, normal T-cell expressed, and secreted |
| RAP | recurrent acute pancreatitis |
| RBPJk | recombination signal binding protein for immunoglobulin kappa J region |
| RCT | randomized controlled trial |
| RECIST | response evaluation criteria in solid tumors criteria |
| RER | rough endoplasmic reticulum |
| RF | retroperitoneal fibrosis |
| RFA | radiofrequency ablation |
| ROS | reactive oxygen species |
| RR | relative risk |
| Rt | response to steroids |
| RT | radiation therapy |
| RTOG | Radiation Therapy Oncology Group |
| RTX | rituximab |
| RyR | ryanodine receptor |
| S6K | small ribosomal subunit 6-kinase |
| SAA | serum amyloid A |
| SACI | selective arterial calcium injection |
| SAPE | sentinel acute pancreatic event |
| SASI | selective arterial secretagogue injection |
| SBE | single-balloon enteroscopy |
| SBRT | stereotactic body radiation therapy |
| SC | sclerosing cholangitis |
| SCA | serous cystadenoma |
| SCN | serous cystic neoplasm |
| SDF-1α | stromal-derived factor 1α |
| SDS | Shwachman–Diamond syndrome |
| SEER | Surveillance, Epidemiology, and End Results |
| SEMS | self-expandable metal stents |
| SF | short form questionnaire |

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|---|---|
| SGLT-2 | sodium–glucose cotransporter-2 |
| SHE | severe hypoglycemic episodes |
| SHH | sonic hedgehog |
| SHIPS | systemic IgG4-related plasmacytic syndrome |
| SIK | simultaneous islet kidney |
| SIRS | systemic inflammatory response syndrome |
| SIRT | selective internal radiotherapy |
| SMA | smooth muscle actin |
| SMA | superior mesenteric artery |
| sMRCP | secretin-enhanced magnetic resonance cholangiopancreatography |
| SMV | superior mesenteric vein |
| SMV-PV | superior mesenteric vein–portal vein |
| SN | greater splanchnic nerve |
| SNP | single nucleotide polymorphism |
| SNRI | serotonin–norepinephrine reuptake inhibitors |
| SOC | store-operated $Ca^{2+}$ channels |
| SOD | sphincter of Oddi dysfunction |
| SOFA | sequential organ failure assessment |
| SOP | standard operating procedure |
| SP | substance P |
| SPECT | single-photon emission computed tomography |
| SPINK1 | serine protease inhibitor Kazal type 1 |
| SPK | simultaneous pancreas–kidney transplantation |
| SPN | solid-pseudopapillary neoplasm |
| SR | somatostatin receptor |
| SRS | somatostatin receptor scintigraphy |
| SSAT | Society for Surgery of the Alimentary Tract |
| SSO | Society for Surgical Oncology |
| SSRI | selective serotonin reuptake inhibitor |
| SST | somatostatin |
| SSTR | somatostatin receptor |
| STZ | streptozotocin |
| sub-CT | subtraction color map based on dual-energy CT |
| T cells | thymus cells |
| T1D | type 1 diabetes |
| T1W | T1 weighted |
| T2W | T2 weighted |
| TACE | transarterial chemoembolization |
| TAE | transarterial embolization |
| TAM | tumor-associated macrophage |
| TAP | trypsinogen activation peptide |
| TCGA | The Cancer Genome Atlas |
| TCP | tropical chronic pancreatitis |
| TERT | telomerase reverse transcriptase |
| TFF1 | trefoil factor 1 |
| TGF-β | transforming growth factor β |
| Th | T helper |
| TIGAR-O | toxic–metabolic inflammatory genetic autoimmune recurrent and severe pancreatitis obstructive |
| TIMP | tissue inhibitor of metalloproteinases |
| TKI | tyrosine kinase inhibitor |
| TLNC | total lymph node count |
| TLR | toll-like receptor |
| TME | tumor microenvironment |
| TNF | tumor necrosis factor |
| TNF-α | tumor necrosis factor α |
| TOF | transient organ failure |

| | |
|---|---|
| TP | total pancreatectomy |
| TPC | two-pore channel |
| TPIAT | total pancreatectomy with islet autotransplantation |
| TPN | total parenteral nutrition |
| Treg | regulatory T cell |
| TRP | transient receptor potential |
| TRPA1 | transient receptor potential cation channel, subfamily A, member 1 |
| TRPV1 | transient receptor potential cation channel subfamily V, member 1 |
| TSC2 | tuberous sclerosis complex 2 |
| TSD | thoracoscopic splanchnic denervation |
| TSE | turbo spin echo |
| TUS | transabdominal ultrasonography |
| UC | ulcerative colitis |
| UGT1A1 | UDP glucuronyltransferase 1A1 |
| UICC | Union for International Cancer Control (formerly International Union Against Cancer) |
| UICC/AJCC | Union for International Cancer Control/American Joint Cancer Committee |
| ULN | upper limit of normal |
| UNOS | United Network for Organ Sharing |
| UNSW | University of New South Wales |
| UPDAC | uncinate process pancreatic ductal adenocarcinoma |
| UPR | unfolded protein response |
| US | ultrasonography, ultrasound |
| UVB | ultraviolet B |
| VARD | video-assisted retroperitoneal debridement |
| VAS | visual analog scale |
| VEGF | vascular endothelial growth factor |
| VHL | von Hippel–Lindau syndrome |
| VIP | vasoactive intestinal polypeptide |
| VIPoma | vasoactive intestinal peptide-releasing tumor |
| VLDL | very low-density lipoprotein |
| VLS | vascular leak syndrome |
| VMAT | volumetric arc therapy |
| VN | vagus nerve |
| VPA | valproic acid |
| VR | volume-rendered imaging |
| VR1 | vanilloid receptor type 1 |
| WBC | white blood cells (leukocytes) |
| WDEC | well-differentiated endocrine carcinoma |
| WDHA | watery diarrhea, hypokalemia, and achlorhydria |
| WD-NET | well-differentiated neuroendocrine tumor |
| WES | whole-exome sequencing |
| WHO | World Health Organization |
| WNT | wingless-type MMTV integration site family |
| WOPN | walled-off pancreatic necrosis |
| WT | wild type |
| XBP1 | x-box binding protein 1 |
| XCR1 | C–X–C motif receptor |
| YY1 | Yin Yang 1 |
| ZES | Zollinger–Ellison syndrome |
| ZG | zymogen granules |

## About the Companion Website

This book is accompanied by a companion website:

**www.wiley.com/go/beger/thepancreas**

The website includes:

- PowerPoints of all figures from the book for downloading
- Videos

# Section 1

# Anatomy of the Pancreas

# 1

# Development of the Pancreas and Related Structures

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## Anatomy of the Pancreas

The pancreas is a unique exocrine and endocrine organ located in the retroperitoneal region of the upper abdominal cavity. In humans, when fully formed, the organ has a distinct head, body, and tail, with the head of the pancreas contacting the duodenal region of the intestines (the main pancreatic duct drains into the duodenum) and the tail of the pancreas abutting the spleen. The greatest mass of the organ is present in the head, which is composed of tissue derived from two independent anlagen (see later). In other mammals, such as dogs and mice, the organ has a far less distinct structure and is identified as an amorphous pink tissue adjacent to the mesentery that runs along the upper intestinal wall.

The cells of the pancreas are arranged into distinct lobules composed primarily of the digestive enzyme-producing cells of the exocrine pancreas, which are arranged into acini (so-called acinar cells), the ductal structures that conduct these digestive enzymes to the intestines, and distinct clusters of endocrine cells, the islets of Langerhans, that secrete hormones and function to regulate glucose uptake and release and serum glucose levels. There are five recognized cell types within the islets, the α, β, δ, ε, and PP cells, which produce the hormones glucagon, insulin, somatostatin, ghrelin, and pancreatic polypeptide, respectively. The majority of the pancreatic tissue mass (more than 90–95%) is present within the exocrine compartment of the organ, with the islets of Langerhans, scattered throughout the tissue. The pancreas also has connective tissue, derived from the embryonic mesenchyme, which forms the septa that separate the many lobules of the organ. Mesenchyme-derived stromal cells are also present in the interlobular regions surrounding the pancreatic ducts, blood vessels, and nerves. In the following sections, we explore how these disparate cell types come together to form the pancreas.

## Organogenesis in the Region of the Pancreas

Around day 14, the embryonic bilaminar germ disk is composed of a layer of epiblast and a layer of hypoblast. At this time, a faint groove appears along the longitudinal midline of the germ disk that develops into a structure called the primitive streak [1]. Around day 15, epiblast cells near the primitive streak undergo a morphologic change and migrate through the primitive streak into the space between the epiblast and hypoblast in a process known as gastrulation (Fig. 1.1). Some of the ingressing epiblast cells invade the hypoblast, which is eventually replaced by a new layer of epiblast-derived cells known as the definitive endoderm. Additional migrating epiblast cells occupy the space between the epiblast and the definitive endoderm to form a third layer of cells called the intraembryonic mesoderm (Fig. 1.1). As cells of the germinal disk migrate anteriorly to form a head process and lateral regions roll underneath to form an approximately cylindrical body shape, the endoderm is rolled into a tube that projects into the developing head region of the embryo surrounded by the mesoderm layer. This is the primitive digestive tube. The pancreas is specified by two separate outgrowths that arise on the dorsal and ventral surfaces of the primitive digestive tube. The epithelial cells of the pancreas originate from the interior lining of the primitive gut tube, which consists of a single layer of endoderm. A layer of

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

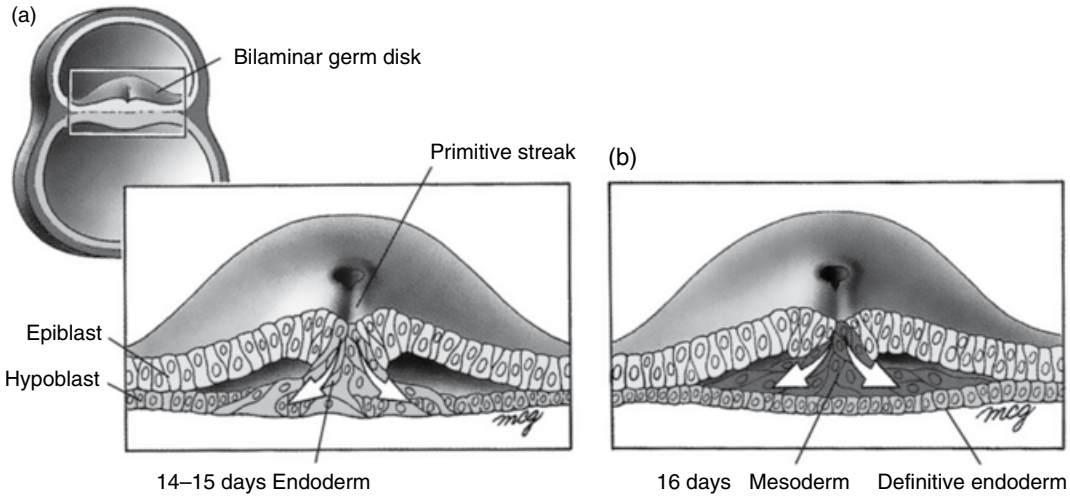


**Figure 1.1** Germ disks sectioned through the region of the primitive streak, showing gastrulation. (a) On days 14 and 15, the ingressing epiblast cells replace the hypoblast to form the definitive endoderm. (b) The epiblast that ingresses on day 16 migrates between the endoderm and epiblast layers to form the intraembryonic mesoderm. Source: Larsen 2001 [1]. Reproduced with permission of Elsevier.

mesenchyme, from which the muscle and connective tissue of the gastrointestinal organs are derived, surrounds the endoderm.

The anterior regions of the endoderm form the foregut; regions posterior to the foregut form the midgut and hindgut. The most anterior regions of the foregut give rise to the esophagus and stomach. Just posterior to the foregut, the endoderm is continuous with the yolk sac, which extends outside the embryo, in a region known as the anterior intestinal portal. Endodermally derived cells close to the anterior intestinal portal specify the pancreas. The duodenum and liver are also specified by foregut endoderm in this region.

Thus, many gastrointestinal tissues are specified at the same time from a fairly restricted region of the gut endoderm. How are each of these organs specified in the appropriate anatomic location, and how do they differentiate properly into mature functional organs? The epithelial organs of the developing embryo originate as buds from the endoderm as the appropriate temporal and spatial cues are received. Thus, proper initiation and location of endodermally derived organs are regulated by the activation status of important signal transduction pathways involved in animal development, including the hedgehog, notch, and fibroblast growth factor signaling pathways.

## Early Pancreatic Development

During the fourth week of gestation, two buds appear on the dorsal and ventral sides of the foregut near the anterior intestinal portal. These epithelial buds indicate the specification of the pancreas. These buds initially grow and differentiate independently, but later fuse to form a single organ. The anlage on the dorsal side, the dorsal pancreatic bud, appears first and gives rise to the dorsal pancreas. The cells of the dorsal pancreas will give rise to the head, body, and tail of the mature pancreas. The second pancreatic anlage appears shortly after the appearance of the dorsal pancreatic bud. This bud, which appears on the ventral side of the gut tube, is appropriately called the ventral pancreatic bud and develops into the ventral pancreas, which forms part of the head of the pancreas. Both pancreatic buds develop simultaneously, and the proliferating epithelial cells grow as projections into the surrounding mesenchymal tissue. During this time, the development of the intestines, and importantly the duodenum, continues. Rotation and asymmetric growth of the duodenum move the originally ventral part to a dorsal location, carrying with it the ventral pancreas and the primordial common bile duct. As the duodenum begins to rotate into its appropriate anatomic location, the ventral pancreas also rotates around the gut tube such that the ventral and dorsal pancreata lie adjacent to each other. These pancreatic rudiments then fuse to form a single organ. While both developing pancreatic buds independently form pancreatic ducts, the lumens of which are continuous with the lumen of the primitive gut, after they fuse their primary ducts anastomose to form the main pancreatic duct (Fig. 1.2). The region of the primary duct of the ventral pancreas proximal to the duodenum fuses with the primary duct of the dorsal pancreas and becomes the primary drainage into the duodenum, entering the duodenum immediately adjacent to the common bile duct. The proximal region of the primary duct of the dorsal pancreas sometimes remains as an accessory drainage but often regresses.

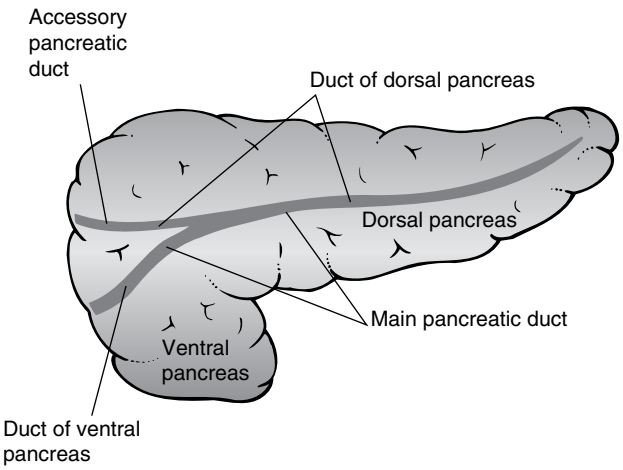


**Figure 1.2** Contributions of the dorsal and ventral pancreas to the definitive organ. The ventral pancreas becomes most of the head. The dorsal pancreas becomes the remainder of the head, plus the body and tail. The duct of the dorsal pancreas contributes a large part of the main pancreatic duct plus the accessory duct. The duct of the ventral pancreas becomes the part of the main duct nearest the duodenum.

The ducts sometimes fail to fuse, in which event two independent duct systems drain into the duodenum.

### Signaling Governing Early Pancreatic Development

Early pancreatic development and establishing pancreatic identity are governed by the interplay between several critical transcription factors and intercellular signaling pathways. PDX1 and PTF1A are among the earliest transcription factors expressed in the pancreatic progenitor populations, and their functions are critical for pancreatic development [2–5]. In mice, PDX1 expression is first detected in the primitive gut tube at embryonic day 8.5 (E8.5), demarcating the prospective pancreatic domain, which is then followed by PTF1A expression in pancreatic endoderm at E9.5 [5–7]. Mice lacking either transcription factor display pancreatic agenesis [2,3,5,8].

In addition to the transcription factors, several key intercellular signaling pathways between gut endoderm and mesenchyme, including the hedgehog and fibroblast growth factor (FGF) pathways, play important roles in establishing the pancreatic identity and controlling the expression of these transcription factors. Research studies have shown that sonic hedgehog (SHH) is excluded from the prospective pancreatic region, but is present in the region of foregut that becomes the duodenum, and ectopic expression of SHH in the pancreas induces an intestinal fate, suggesting that SHH signaling may specify a duodenal versus pancreatic fate in the posterior foregut [9,10]. Another well-understood pathway mediating the mesenchymal–epithelial interaction is the FGF signaling pathway, in particular the FGF10–FGFR2 ligand–receptor pair. During early pancreatic development, FGF10 is highly expressed in the primitive mesenchyme, whereas its receptor FGFR2 is present in the pancreatic epithelium [11]. Mouse genetic experiments demonstrated that FGF10 provides the pro-proliferative signal to promote the expansion of the progenitor pool in the pancreatic epithelium [11]. In addition, FGF10 signaling from the mesenchymal cells is critical for maintaining the epithelial expression of SOX9 [12]. SOX9 is another transcription factor critical for early pancreatic development, and it exerts its function in part by controlling the expression of the FGF10 receptor FGFR2 [12,13]. Together, the complex regulatory loop between these signaling pathways and transcription factors in the epithelium and mesenchyme coordinates early organ growth and the establishment and maintenance of pancreatic identity.

## Differentiation of Pancreas Cell Types

The acinar, ductal, and endocrine cells of the pancreas are all produced through the proliferation and differentiation of the epithelial cells of both pancreas primordia. The cells appear homogeneous during the early stages of development as they proliferate and grow into the surrounding mesenchyme as finger-like projections. The epithelial cells form undifferentiated tubules that branch and anastomose as they penetrate into the mesenchyme to generate a tubular network, which resembles an immature (and nonfunctional) duct system. The acinar cells appear as clusters of cells at the ends of branches of this tubular network. The endocrine cells appear as cells that delaminate from the tubular epithelium and reaggregate in isolated clusters embedded within the developing parenchyma. The existing cells within these small isolated endocrine clusters proliferate, and these clusters therefore expand to form the islets.

Apparent differentiation of pancreas epithelial cells into endocrine cells can be identified beginning at 12 weeks of gestation with the detection of endocrine granules. Most of the endocrine differentiated cells identified at this time express glucagon and are therefore believed to be α cells. Importantly, lineage-tracing experiments performed in mice demonstrated that these early α cells do not act as endocrine progenitors, as β cells, the predominant cell type in the mature islet, are derived from glucagon-negative cells [14]. Differentiation of acinar cells is detected at approximately 16 weeks, as identified by the appearance of zymogen granules. Interestingly, not all enzymes are elaborated at once—detection of

trypsinogen does not occur until approximately 22 weeks. The digestive enzyme-positive cells arise as clusters from the undifferentiated tubules, the expansion of which is rapid such that the acinar cells become the dominant population within the organ. Although they are not yet mature acinar cells, the cells in the acinar clusters display some of their hallmark features, including basolaterally located nuclei. As differentiation continues, the cells become arranged in recognized acini and defined lobules surrounded by connective tissue. The ductal system arises after maturation of the immature tubular network. The specific morphologic changes that accompany this change are unclear, although some work suggests that WNT signaling is involved in this transition [15].

## Transcriptional Mechanisms Underlying Pancreatic Cell Fate Decision

Much information about pancreatic cell fate determination and cell type differentiation has been obtained from studies in animal models. Elegant genetic and cell-based experiments in mice have identified a gene regulatory network controlled by many transcription factors to specify different cell lineages in the developing pancreas.

### Development of the Endocrine Lineage

Endocrine cell specification begins with the expression of NGN3, a bHLH (basic helix loop helix) transcription factor, in a subset of progenitor cells within the trunk region of the pancreatic bud [16–18]. The NGN3-expressing cells eventually give rise to all endocrine cell types: insulin-producing β cells, glucagon-producing α cells, somatostatin-producing δ cells, ghrelin-producing ε cells, and pancreatic polypeptide-producing PP cells [16–18]. NGN3 initiates endocrine lineage specification by inducing the expression of downstream transcription factors, including NeuroD, NKX2.2, PAX4, and ARX. Among them, NKX2.2, NeuroD, and PAX4 play key roles in the specification of β cells [19–21]. Mutant mice lacking any of these transcription factors display a phenotype of dramatic or total loss of β cells [19–21]. Further studies revealed that the opposing actions of PAX4 and ARX determine the fate choice between α and β cells. During endocrine differentiation, loss of ARX leads to a complete loss of α cells, but a concomitant increase in β and δ cells [22], whereas loss of PAX4 results in an opposite phenotype with loss of β and δ cells and expansion of α cells [20,22]. It is believed that this effect on cell fate choice is mediated by the reciprocal transcriptional repression between these factors.

### Differentiation of Acinar Cells

Pancreatic acinar cells are primarily derived from precursor cells in the tip region, and their differentiation is coordinated by the transcription factor PTF1A, a master regulator of pancreatic development. Prior to exocrine differentiation, PTF1A forms a complex with the bHLH transcription factor RBP-Jk, and is required for activation of RBP-Jl, an acinar-specific paralog of RBP-Jk [23,24]. The more active RBP-Jl then replaces RBP-Jk to form the complex with PTF1A, thereby directly inducing the expression of many acinar-specific genes, including secretory peptides and digestive enzymes [23,24]. Interestingly, PDX1, another factor important for early pancreatic morphogenesis, is also involved in acinar differentiation. Although not essential for initial acinar specification, it appears that PDX1 is required for terminal differentiation of acinar cells [25]. Other transcription factors, such as NR5A2 and MIST1, are also required for acinar differentiation and homeostasis, likely through the interaction with the PTF1A/RBP-Jk/l complex [26,27].

### Ductal Cell Differentiation and Lineage Plasticity

In comparison with the endocrine and exocrine lineages, how ductal cells undergo differentiation remains poorly understood. It appears that, during development, NGN3-positive cells in the trunk region of the pancreatic bud give rise to endocrine cells, whereas NGN3-negative trunk epithelial cells contribute to the ductal system [28,29]. A number of transcription factors, such as SOX9, PROX1, HES1, and HNF6, are expressed in the ductal lineage and play various roles in ductal differentiation, including primary cilia formation in the ductal epithelial cells [30–33]. Although the three lineages (endocrine, exocrine, and ductal) are specified during early development, the adult pancreatic cells from different lineages show remarkable plasticity and trans-differentiation capacity in pancreatic injury, pancreatitis, and tumorigenesis, which may shed light on the mechanisms underlying these pancreatic pathologies.

## Development and Disease

Molecules important in the development of the pancreas are also causally associated with pancreatic disorders. Several of the signaling pathways involved in normal pancreas development, such as the notch, hedgehog and WNT signaling pathways, are commonly activated in

pancreatic ductal adenocarcinomas [34–38]. Aberrant activation of WNT signaling drives the development of other pancreatic tumor types such as acinar carcinomas, pancreatoblastoma, and mucinous cystic neoplasms [39–42].

In diabetes, mutation of the transcription factor PDX1, which is important for pancreas specification and for proper β-cell maturation and function, is a cause of maturity-onset diabetes of the young (MODY) [43]. Other transcription factors that are critical for β-cell development (as determined by genetic studies in the mouse), such as hepatocyte nuclear factor 1α (HNF1α), HNF1β, HNF4α, and NeuroD, are all also mutated in additional MODY complementation groups [43]. More recently, scientists have utilized our growing understanding of normal pancreas development to promote the differentiation of induced pluripotent stem cells into insulin-producing cells in a new potential therapeutic approach for diabetes [44,45].

Collectively, these findings illustrate the importance of key regulators of pancreas development and differentiation in pathologic disease states and how knowledge of normal pancreas development may drive new therapeutic strategies for pancreatic diseases.

## Acknowledgment

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# 2

# Anatomy, Histology, and Fine Structure of the Pancreas

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## Introduction

This chapter reviews the anatomy, histology, and ultrastructure of the pancreas, including the exocrine and endocrine portions. The exocrine pancreas produces and secretes digestive enzymes into the duodenum and includes acinar cells and ducts with associated connective tissue, vessels, and nerves that comprise more than 95% of the pancreatic mass. The endocrine pancreas (islets) makes and secretes insulin, glucagon, somatostatin, and pancreatic polypeptide into the blood. The islets comprise 1–2% of pancreatic mass.

When the anatomic terms *anterior* and *posterior* are used in this chapter, they pertain to relationships in the human, standing erect. Similarly, *superior* and *inferior* mean toward the head and toward the feet, respectively. We will adopt the convention that *right* and *left* (unqualified) indicate the subject's right-hand and left-hand sides. However, when describing the location of structures within an image, *image right* and *image left* are used to denote relationships without reference to the subject's right or left side.

The organization and content of this chapter are based in part on a recent Pancreapedia chapter on pancreatic anatomy and histology [1].

## Gross Anatomy

The pancreas (meaning all flesh) lies in the posterior portion of the upper abdomen behind the stomach. It is largely retroperitoneal and is covered by peritoneum on the anterior surface of the head and body and is surrounded by fat in this region. It is customary to refer to various portions of the pancreas as head, body, and tail. The head abuts the C-shaped second portion of the duodenum in the right upper quadrant of the abdomen. The tail emerges into the peritoneal cavity (covered by peritoneal serosa) and extends to the hilum of the spleen in the left upper quadrant. The pancreas weighs about 100 g and is 14–25 cm long [2]. Figure 2.1 shows a human pancreas that has been dissected to isolate it from surrounding fat and adjacent organs and Fig. 2.2 depicts a pancreas that has been dissected to reveal the pancreatic and common bile ducts.

The pancreas is intimately associated with several adjacent organs. Relationships of the pancreas to surrounding organs and structures are depicted in Figs 2.3, 2.4, 2.5, and 2.6. As noted above, as the duodenum exits the stomach it loops around the head of the pancreas. The tail of the pancreas lies near the hilum of the spleen. The body of the pancreas lies posterior to the pyloric region of the stomach.

The portion of the pancreas that lies anterior to the aorta is somewhat thinner in the anterior–posterior axis than the adjacent portions of the head and body of the pancreas. This region is designated as the neck and marks the junction of the head and body (Fig. 2.1b). The proximity of the neck of the pancreas to major blood vessels posteriorly, including the superior mesenteric artery, superior mesenteric-portal vein, inferior vena cava, and aorta, limits the option for a wide surgical margin during pancreatectomy (Fig. 2.5).

There is no anatomic landmark for the junction between the body and tail of the pancreas [3]. Hellman defined the tail as one-fourth of the pancreas from the

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

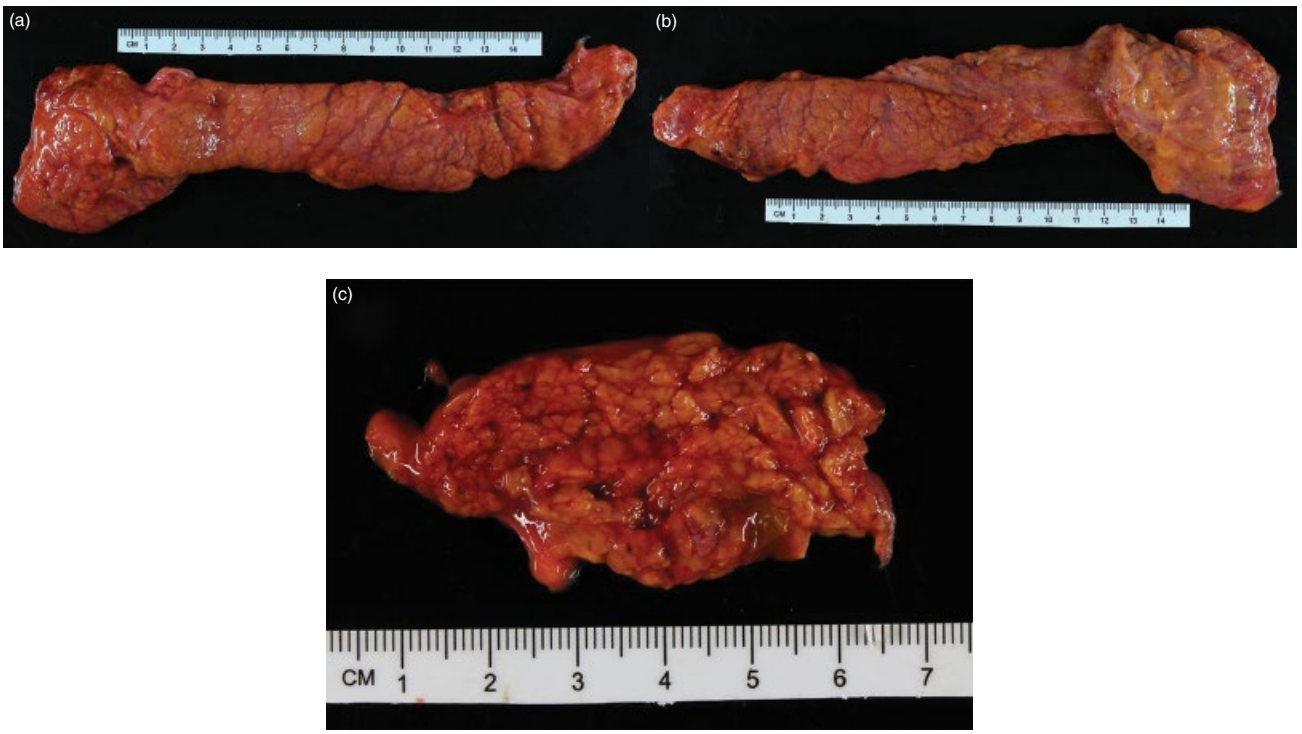


**Figure 2.1** This pancreas, from the autopsy of a 47-year-old woman, measures 22.5 cm in length and has been dissected free of most surrounding fat. (a) Anterior view with the head at image left. (b) Posterior view. A thin layer of fat (translucent yellow) covers a portion of the head at image right. Note the thin neck region just to the left of the head. (c) Cut surface of a transection through the head of the pancreas showing the lobular pancreatic parenchyma. *Source:* Dissection and photo by Catherine M. Nicka, MD.

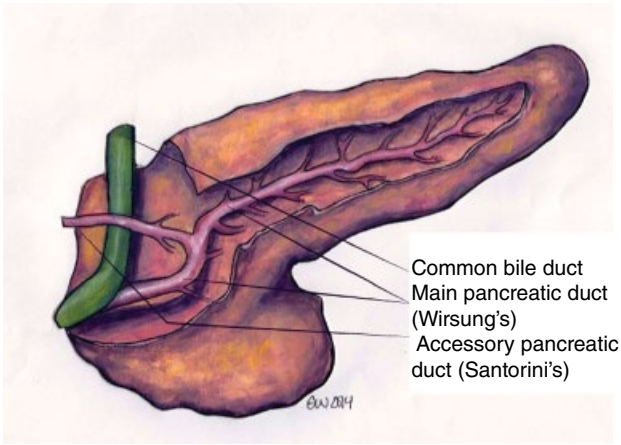


**Figure 2.2** A pancreas dissected to reveal the pancreatic ducts and common bile duct as it traverses the head of the pancreas, ending as it joins the main pancreatic duct near the ampulla of Vater. Interlobular branches of the main duct are depicted but smaller ducts (intralobular ducts and ductules) are not. Eponyms identify the anatomist, embryologist, or physician who is credited with first describing a structure. Wirsung and Santorini were such scientists. *Source:* Drawing by Emily Weber.

tip of the tail to the head [4] whereas Wittingen and Frey defined the junction between the body and tail as the point where the gland sharply narrows [5]. This point is difficult to define in some pancreases.

The common bile duct passes behind the upper portion of the head and then runs through the pancreas to join the main duct in the duodenal wall (Figs 2.2, 2.5, and 2.7b). The accessory pancreatic duct drains into the duodenum at the minor papilla in most humans, and the main pancreatic duct enters the duodenum at the major papilla (Fig. 2.3). See Chapter 3 for discussion of pancreas divisum and other anomalies with possible clinical significance.

Typically, the bile duct and main pancreatic duct join into a "common channel" referring to the fused portion of the bile and pancreatic ducts proximal to its entry into the duodenal lumen. The common channel varies in length from a few millimeters to about 1 cm. A long common channel due to junction of the bile and pancreatic ducts proximal to the duodenal wall is regarded as an anomaly [6]. Less often, there is no common channel because the

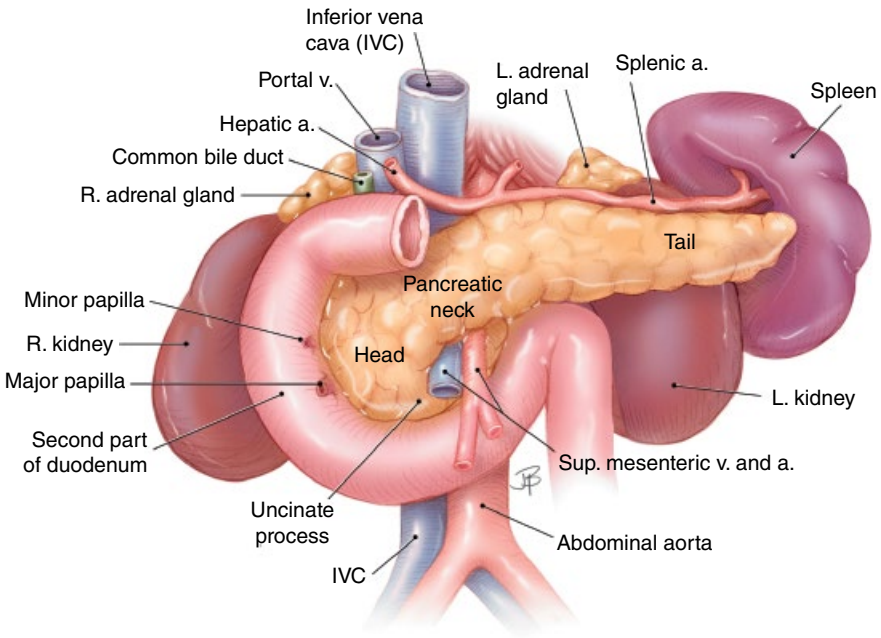


**Figure 2.3** Relationships of the pancreas to surrounding organs. This two-dimensional drawing depicts structures that lie in several different planes; for example, the kidneys lie lateral to the spine and posterior to the pancreas. The superior mesenteric artery and vein lie anterior to the aorta and inferior vena cava. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

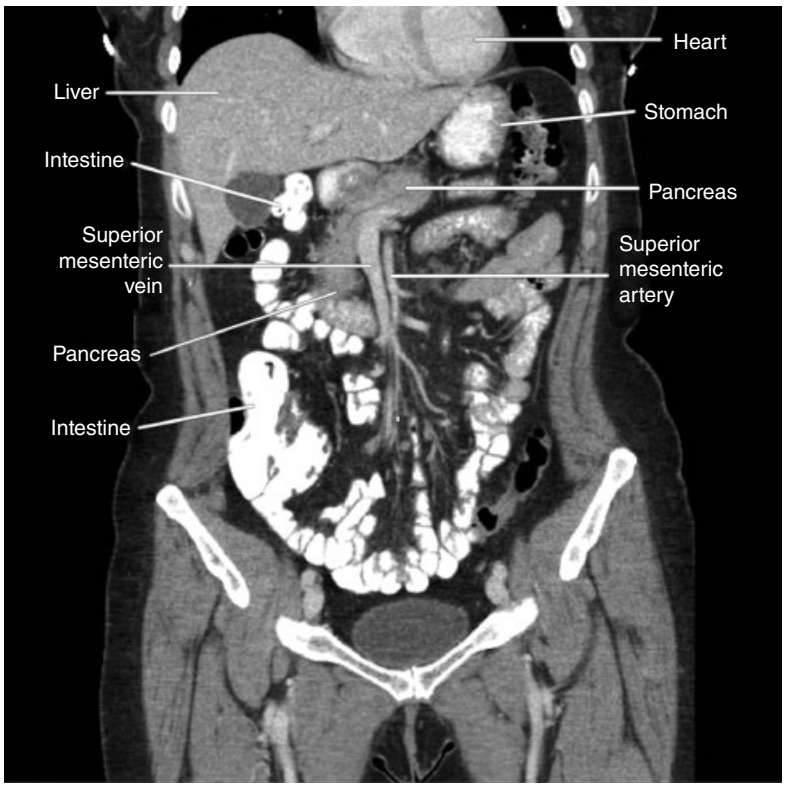


**Figure 2.4** Frontal CT scan in the plane of the head and body of the pancreas. The technology dictates that all structures shown lie in the same plane. The tail of the pancreas is not shown because it lies posterior to the depicted plane. *Source:* Image provided by Jason Ferreira.

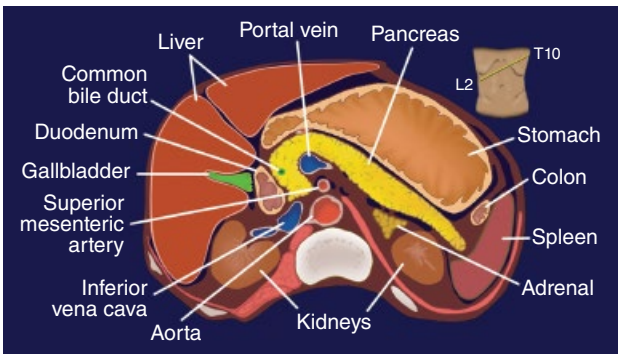


**Figure 2.5** Diagram of the upper abdomen at the level of the pancreas based on a CT scan. Note that the plane of the image is angled upward on the left as indicated, upper image right. The vertebral column is unlabeled bottom center. *Source:* Image contributed by Fred Gorelick.

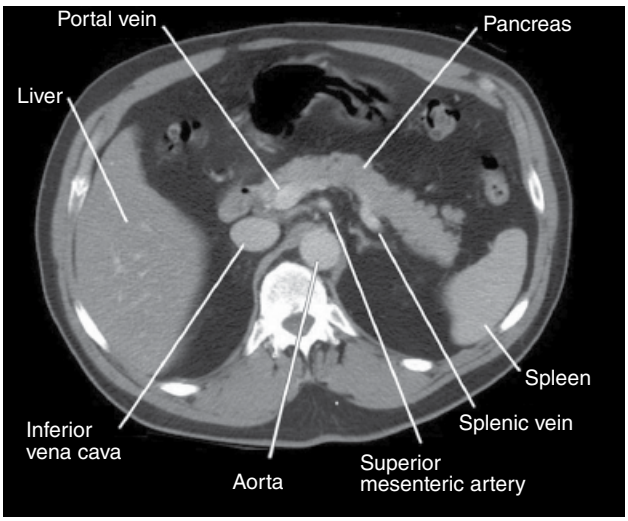


**Figure 2.6** Axial CT scan of the upper abdomen at the level of the pancreas. This scan is oriented with the abdominal wall at the top and the spine and muscles of the back at the bottom as viewed from below. Key structures are labeled. *Source:* Image provided by Jason Ferreira.

ducts open separately into the duodenum at the major ampulla. The common channel has received much attention because stones in the biliary tract (gallstones) may lodge in the common channel, causing obstruction of both pancreatic and biliary duct systems. Such an obstruction is frequently the cause of acute pancreatitis.

The arterial blood supply to the pancreas is through branches of the celiac trunk and the superior mesenteric artery (Fig. 2.7). Both arise from the abdominal aorta and have multiple branches that supply several organs. Anastomosis of their branches provides collateral circulation that generally assures a secure arterial blood supply to the pancreas. Most of the arteries are accompanied by veins that drain into the superior mesenteric, portal, and splenic veins as they pass behind the pancreas, as shown in Fig. 2.7b. The superior mesenteric vein becomes the portal vein when it joins the splenic vein (Fig. 2.7b).

The typical locations of lymph nodes surrounding the pancreas are shown in Fig. 2.8. There is significant individual variation in the location of lymph nodes, so the locations shown are a generalization. In general, two systems of lymph nodes drain the organ: one surrounding the edges of the pancreas (Fig. 2.8a), and the other associated with the anterior surface of the aorta and celiac trunk (Fig. 2.8b). Various node groups have been assigned "station numbers" that may be used to designate their location [1,2,7]. These are rarely used in Western literature and are not illustrated here. Lymphatics arise in the interstitium of the pancreas and course with blood vessels and nerves draining to the nodes and then to the thoracic duct.

A rich plexus of autonomic nerves lies behind the head, neck, and body of the pancreas connecting to the celiac ganglia that lie along the aorta (Fig. 2.9).

## Histology and Ultrastructure

### Overview

The exocrine pancreas is a network of tubules composed of acinar and duct cells that synthesize, secrete, and carry digestive enzymes into the intestine. The small tubules in the lobular tissue are largely composed of acinar cells. The acinar tubules connect to the smallest terminal portions of the duct system that are commonly called ductules, although intercalated duct has also been used to denote these components of the duct system. In this chapter, we will use *ductule* to denote these small terminal portions of the duct system that link the acinar tubules to larger ducts, including small intralobular ducts. At the level of gross anatomy, the acinar tubules, ductules, and small ducts appear as solid lobular tissue as seen in Fig. 2.1c. The following descriptions include both histology and ultrastructure for each major cell type.

### Acinar Tissue

An acinus is a cluster of acinar cells that contain zymogen granules, the storage compartment for pancreatic digestive enzymes. For many years, it was considered that acinar tissue was composed of clusters of acini arranged like grapes at the ends of a branching duct system. However, more recent studies have demonstrated that pancreatic acini and tubules are arranged as an anastomosing tubular network [8]. The duct cells at the interface of acinar tubules and ductules are referred to as centroacinar cells and these cells may also be

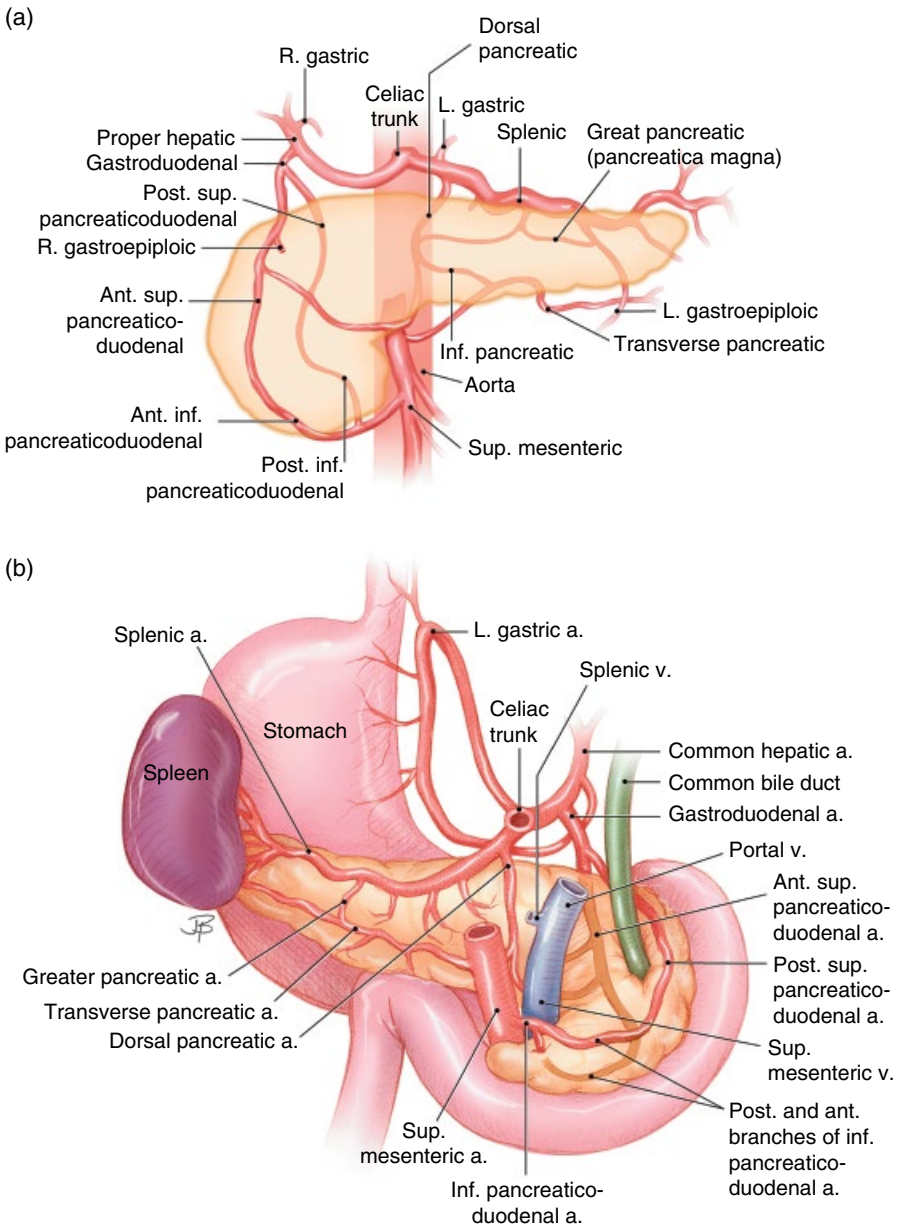


**Figure 2.7** The arterial blood supply of the pancreas. Image (a) is visualized from the front and (b) is seen from the back. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

interspersed within acini. An acinus may occur as a culde-sac at the end of a tubular network and also as an intermediate structure with ductules on either side. Recognizing this pattern provides a basis for understanding the changes that the pancreas undergoes with the development of cancer and pancreatitis [9,10]. The tubular complexes that are observed as a result of these diseases are contributed to by the transition of acinar cells into ductular-like cells, a process sometimes referred to as acinar to ductal metaplasia [11].

At the histologic level in sections stained with hematoxylin and eosin (H&E), individual acinar cells have bluish cytoplasm in the basal (perinuclear) region, reflecting the high content of RNA (Fig. 2.10). Central to the nucleus, the cytoplasm is eosinophilic (pink), reflecting the higher content of protein in the Golgi and zymogen granules. Many acinar cells are binucleate [12,13]. Although the detailed histologic analysis of binucleation is based on the rat pancreas, the observation also appears to pertain for the humans but is of unknown significance.

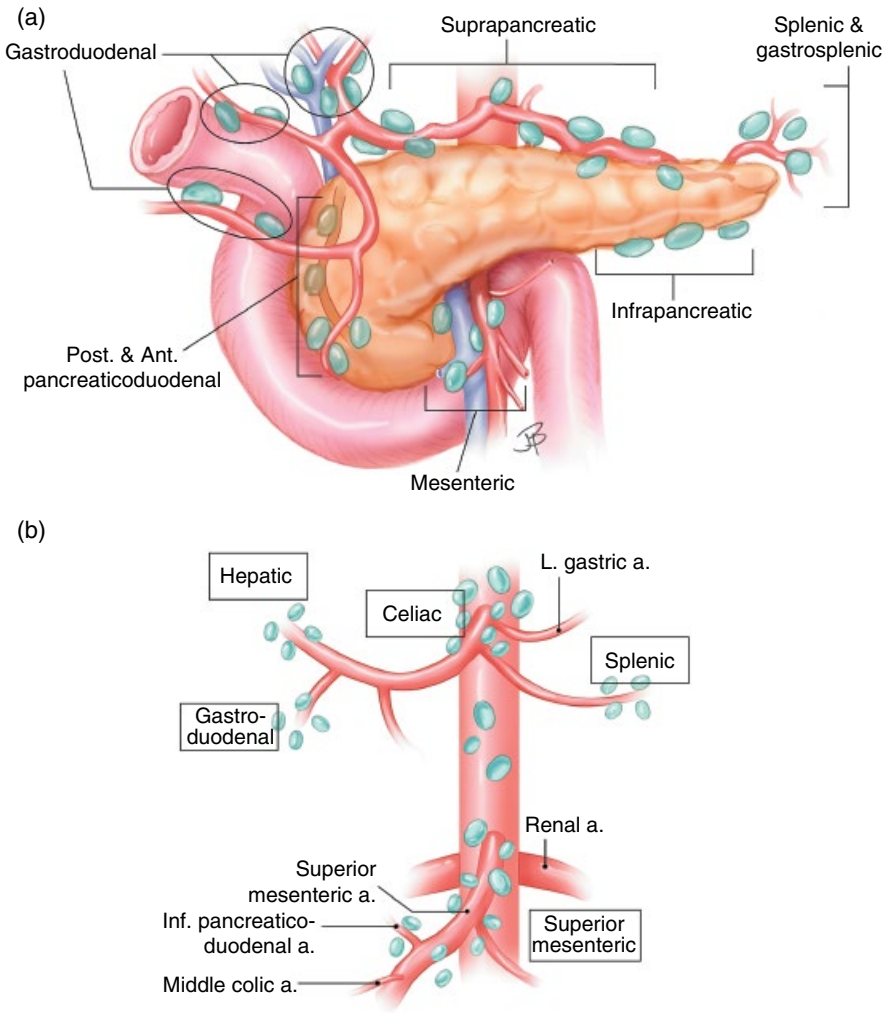


**Figure 2.8** Lymph nodes draining the pancreas. There is considerable individual variation in the location and size of lymph nodes, so this drawing is somewhat schematic. Both (a) and (b) are anterior views; (b) includes some nodes that lie posterior to the pancreas. *Source:* Drawing by Jennifer Parsons Brumbaugh, in Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007: Chapter 1. Reproduced with permission.

The acinar cell ultrastructure reflects cell function, that is, the synthesis and secretion of digestive enzymes, and it will be described in the context of this function. The basal cell membrane has an extracellular basement membrane that abuts the interstitial space where capillaries and nerve endings lie (Fig. 2.11). The lateral cell membranes are closely apposed to the cell membranes of adjacent acinar or centroacinar cells and these membranes are linked by linear tight junctions (Figs 2.12 and 2.13). The most distinctive feature of the luminal membrane is the formation of microvilli, which are narrow, finger-like extensions into the lumen (Fig. 2.13).

The basal and perinuclear cytoplasm of acinar cells contains abundant rough endoplasmic reticulum (RER) that forms flattened cisternae with a smooth luminal side, whereas the external surface is studded with ribosomes (giving rise to the "rough" designation). The RER is folded into stacks that generally lie in the plane of the adjacent cell membrane (Fig. 2.12).

Mitochondria are scattered throughout the cytoplasm of the acinar cells but their density is highest in the basal and central portion of the cell (Fig. 2.12). They are sparse in the cytoplasm adjacent to the luminal surface.

On the luminal side of the nucleus, small membrane-bound transport vesicles appear to bud from the RER and then to lie free in the cytoplasm. Central to this region are small stacks of flattened smooth-walled vesicles called the Golgi that appear to arise from the fusion of multiple transport vesicles. At the luminal side of the Golgi, the vesicles begin to round up and progressively to contain homogeneous densities. These are nascent

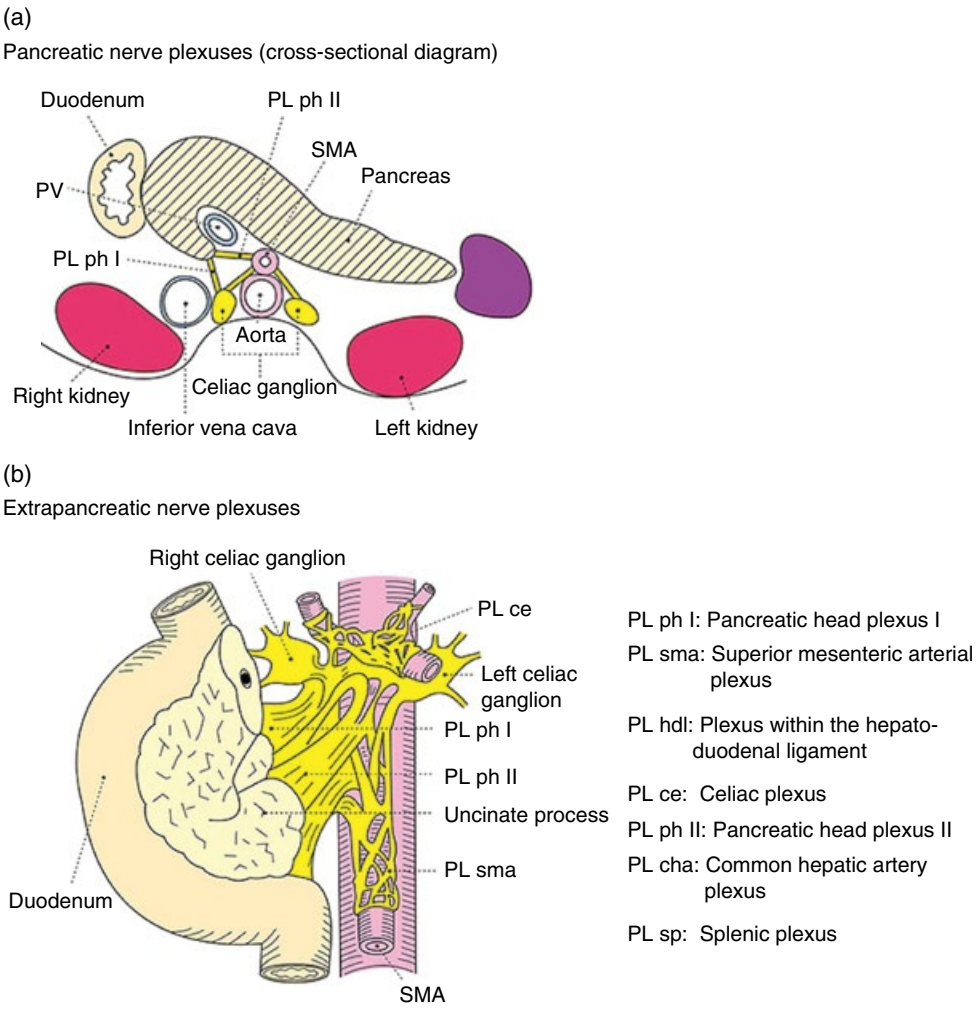


**Figure 2.9** Nerves (yellow) serving the pancreas. The cross-sectional image (a) emphasizes the location of the celiac ganglia of the autonomic system lateral to the aorta while (b) emphasizes the rich nerve plexus that connects these ganglia to the pancreas. SMA, superior mesenteric artery; PL, plexus. *Source:* Classification of Pancreatic Carcinoma, 2003 [7], Fig. 3a and 3b. Reproduced with permission of the Japan Pancreas Society.

zymogen granules (also termed immature zymogen granules or condensing vacuoles) and they progressively lose membrane as contents condense to become mature zymogen granules.

The apical cytoplasm near the acinar lumen is occupied by variable numbers of mature zymogen granules. These are usually spherical (appearing round in cross-section) with a single bilayer membrane surrounding homogeneous dense content (see Figs 2.12, 2.13, 2.18, and 2.22). Fusion of the membranes of zymogen granules and adjacent lumenal cell membrane is observed prior to secretion of the zymogen into the lumen. See Longnecker [1] for additional electron micrographs that illustrate acinar cell ultrastructure.

Acinar cell cytoplasm may contain fat or autophagic vacuoles (sometimes called residual bodies) that are walled-off areas of damaged cytoplasm (Fig. 2.12).

## Duct System

The components of the duct system are the main pancreatic duct (duct of Wirsung); its major branches, called interlobular ducts, that drain into the main duct throughout the pancreas as depicted in Fig. 2.2; smaller intralobular ducts; and ductules that link acinar tubules to the smallest intralobular ducts. The small intralobular ducts and ductules are ordinarily seen only at the level of light and electron microscopy. The accessory duct (duct of Santorini; Fig. 2.2) that connects the main duct to the duodenum at the minor papilla in some humans (Fig. 2.3) is of variable importance and is similar in structure to the main duct, although typically it is slightly smaller.

Enzymes from acinar cells are released into a bicarbonate-rich solution that is secreted by the centroacinar and ductal cells and flows from the acini and acinar

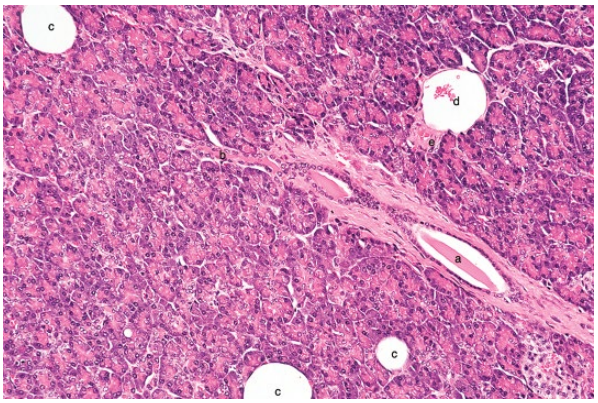


**Figure 2.10** Pancreatic lobular tissue with acinar cells, small duct, ductule, and small islet. This H&E-stained section is largely composed of acini and acinar tubules cut in cross-section or tangentially. A small intralobular duct (a) is shown image right and at its upper end it gives rise to a ductule (b) with virtually no connective tissue evident in its wall. Liquid content of the duct and ductule is homogeneous and pink (eosinophilic). Large, clear spaces are fat cells (c). A small vein (d) and artery (e) are at image right above center. A small islet is near the lower image right corner. *Source:* Hruban RH, Pitman MB, Klimstra DS. Tumors of the pancreas. AFIP Atlas of Tumor Pathology, 4th series, fascicle 6. Washington, DC: American Registry of Pathology, 2007. Reproduced with permission.

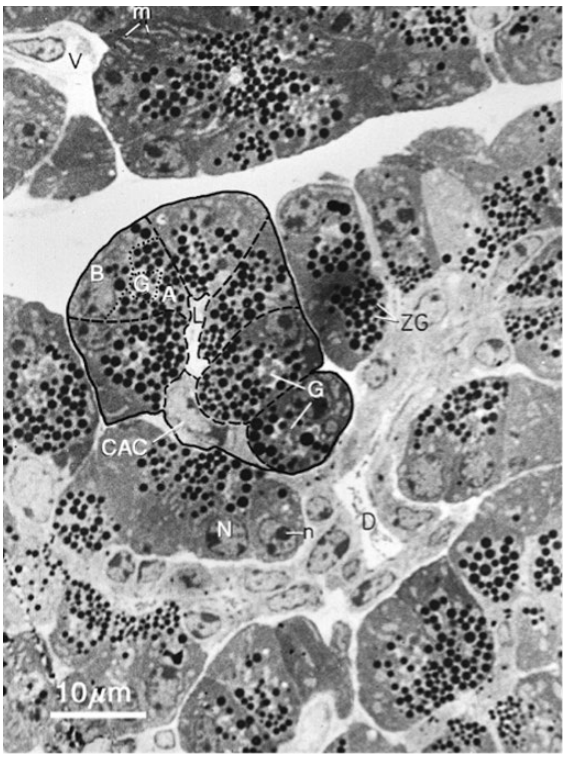


**Figure 2.11** Pancreatic tissue with acinar, centroacinar, and ductal cells. The acinar cells are easily identified because of the darkly stained zymogen granules (ZG) and are larger than centroacinar and ductal cells. The basal portion (B) of the acinar cells lies next to the interstitial space that contains vessels (V), nerves, and connective tissue. Nuclei (N) with nucleoli (n) are in the basal portion of the acinar cells. The golgi (G) lies at the junction of the basal and apical (A) portions of the cell. Centroacinar cells (CAC) have pale cytoplasm with no secretory granules. A small ductule (D) extends from image right to below center. Mitochondria (m) are identified at the top of the field. This is a 1 µm thick section of plastic embedded tissue prepared for electron microscopy that was stained with toluidine blue. *Source:* Micrograph contributed by James Jamieson.

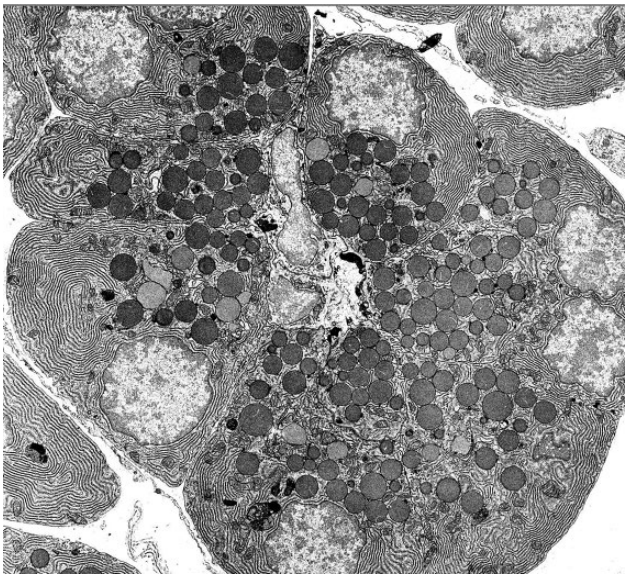

**Figure 2.12** Acinar cells with RER, mature, and immature zymogen granules. Two centroacinar cells are near the center. The acinar cell at 3 o'clock, image right, is binucleate. Numerous mitochondria are present in the acinar cells and lower centroacinar cell. There are several electron-dense residual bodies in the acinar cells. It appears that two have been extruded into the interstitial space at the top of the image and others are being extruded into the acinar lumen near the center of the image. *Source:* Micrograph contributed by James Jamieson.

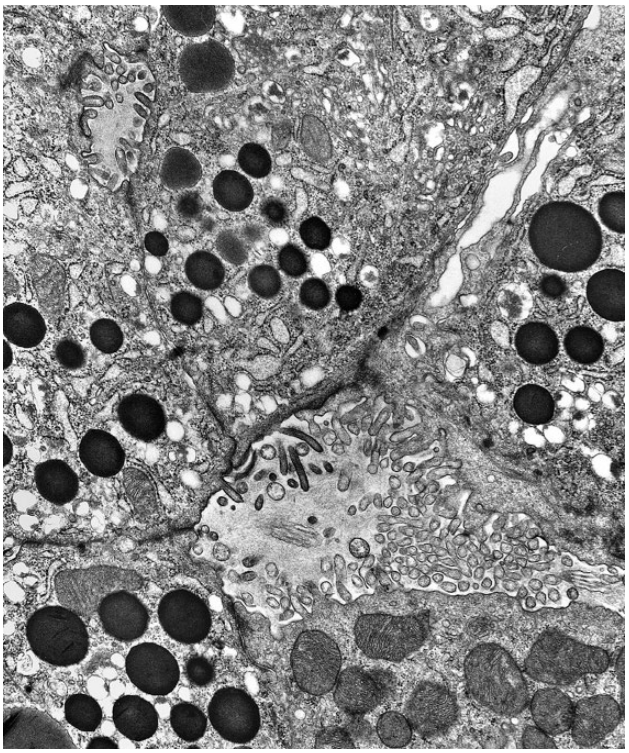

**Figure 2.13** Apical portions of several acinar cells border two luminal spaces, lower image right and upper image left. A centroacinar cell with numerous mitochondria borders the lumen, lower image right. Microvilli protrude into the lumens from the luminal aspect of the acinar and centroacinar cells. Zymogen granules are prominent in all acinar cells. *Source:* Micrograph contributed by James Jamieson.

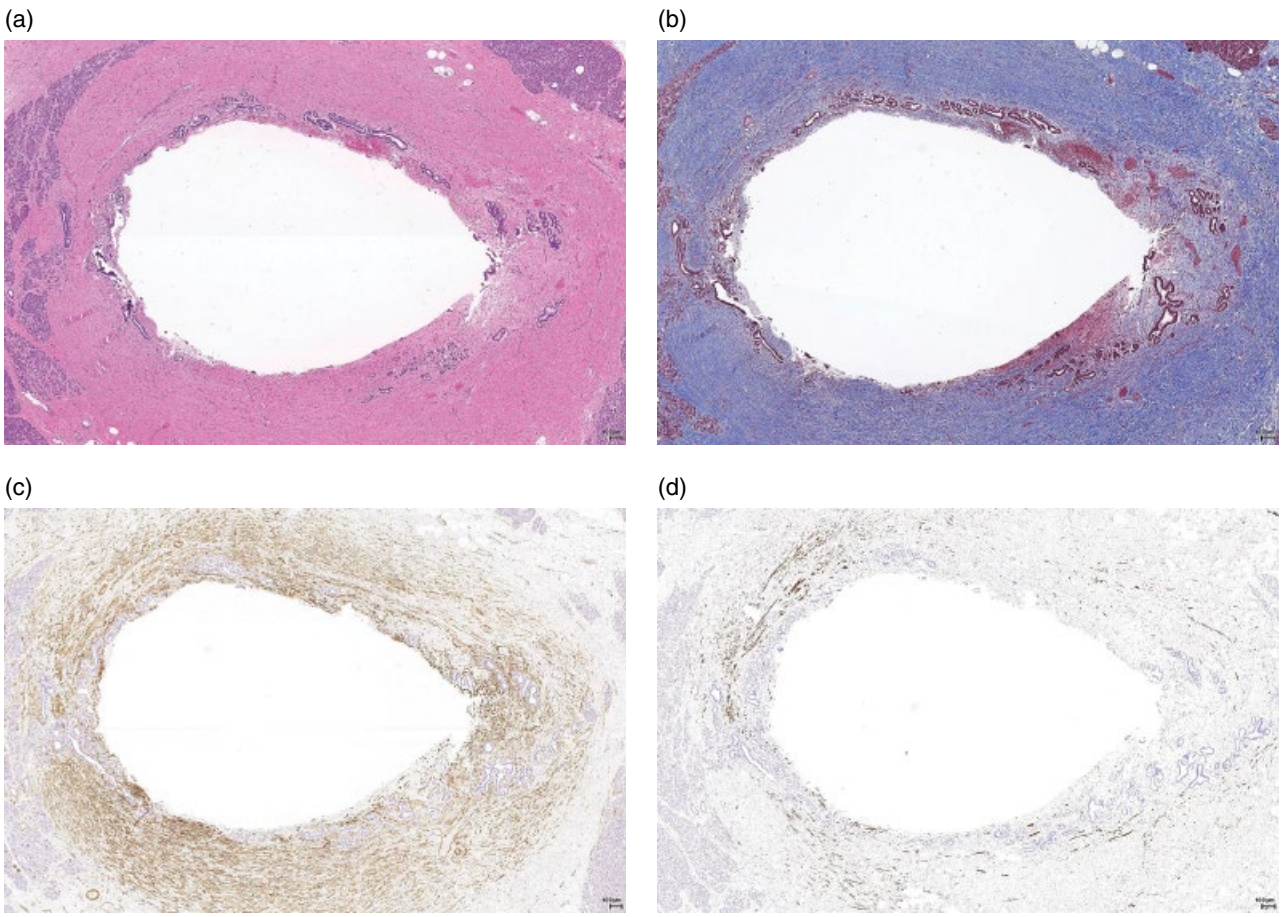


**Figure 2.14** Serial cross-sections of main pancreatic duct (a) (H&E stain) stained to demonstrate collagen (b) (trichrome stain), myofibroblasts (c) (immunoperoxidase stain to demonstrate smooth muscle actin, a marker for myofibroblasts), and smooth muscle (d) (immunoperoxidase stain to demonstrate desmin, a marker for smooth muscle). The lining epithelium has been lost, probably reflecting preoperative ERCP and stenting of the pancreatic duct. The patient underwent a Whipple procedure because of chronic pancreatitis. There are many myofibroblasts and fewer smooth muscle cells in the wall of the main duct. *Source:* Micrographs contributed by Arief A. Suriawinata.

tubules into the ductules that join to form the intralobular ducts, then into the interlobular ducts and main duct, and finally into the duodenum at the major or minor papillae. Ducts are illustrated in Figs 2.10, 2.11, 2.14, 2.15, and 2.16.

The integrity of the duct system is of key importance in preventing entry of the exocrine enzymes into the interstitial space, where they may be activated and cause tissue damage manifested as pancreatitis. As ductules anastomose to form intralobular ducts, the duct walls begin to develop a connective tissue wall (Fig. 2.10) that becomes progressively thicker as the smaller ducts join to form larger ducts and the main pancreatic duct. The main and interlobular ducts have thick, dense, collagenous walls that contain myofibroblasts and smooth muscle cells (Fig. 2.14). The connective tissue component of the duct wall becomes progressively thinner and contains fewer myofibroblasts and smooth muscle cells as the ducts branch and become narrower in the lobules (Fig. 2.15). The smallest intralobular ducts lack smooth muscle cells. Intercellular tight junctions, also called zonula occludens, between duct cells, centroacinar cells, and acinar cells play a major role in preventing leakage of the duct system. Kern provided excellent images and discussion of these tight junctions [14].

The lumen of the duct system is normally lined by a single layer of cuboidal epithelial cells that have a single nucleus and a smaller amount of cytoplasm than acinar cells (Figs 2.10, 2.15, and 2.16). The cytoplasm is pale pink and homogeneous in H&E-stained sections. The duct lumen may contain homogeneous material reflecting the protein content of the secretions (Figs 2.10 and 2.16). Sometimes epithelial cells may be shed into the lumen.

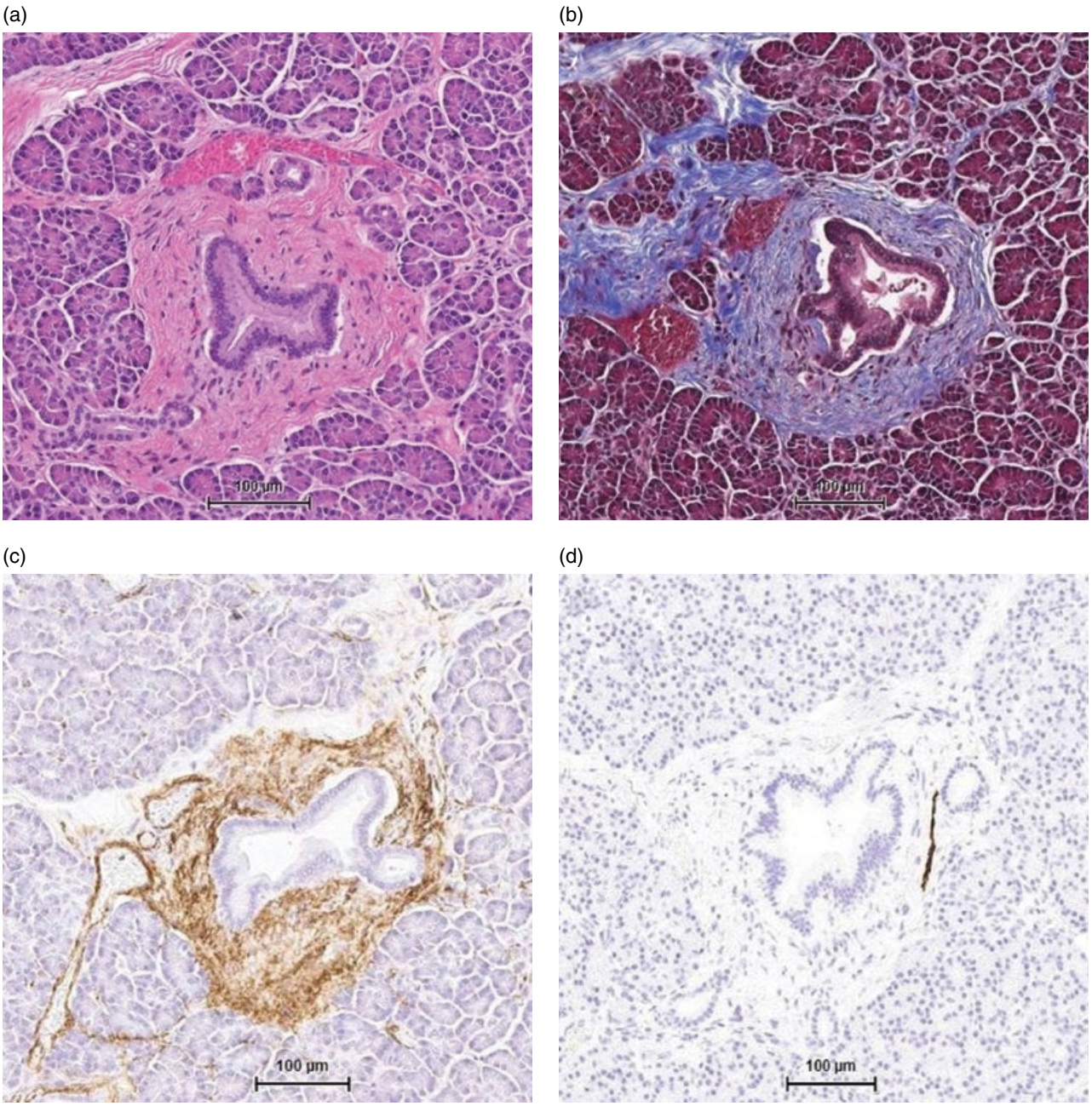


**Figure 2.15** Serial cross-sections of a small intralobubular duct surrounded by acinar tissue from the same patient as in Fig. 2.14. (a) H&E stain. Note the origin of a ductule branching into acinar tissue at 7 o'clock. (b) Trichrome stain with blue-staining collagen. There is fibrosis around acinar lobules (upper image left). (c) Immunoperoxidase stain with antibody to smooth muscle actin (SMA) to demonstrate the abundant myofibroblasts. (d) Immunoperoxidase stain with antibody to desmin to demonstrate smooth muscle cells. There is little staining. *Source:* Micrographs contributed by Arief A. Suriawinata.

Ductal epithelium may undergo squamous metaplasia or mucinous metaplasia. In the latter process, the ducts are lined by tall columnar cells with abundant pale apical cytoplasm that contains mucin. This type of change is characteristic of low-grade PanIN lesions.

At the ultrastructural level, duct cells have a simple structure compared with acinar cells. RER is sparse but mitochondria are numerous, and there are no secretory granules. The luminal surface gives rise to numerous microvilli, similar in appearance to those arising from

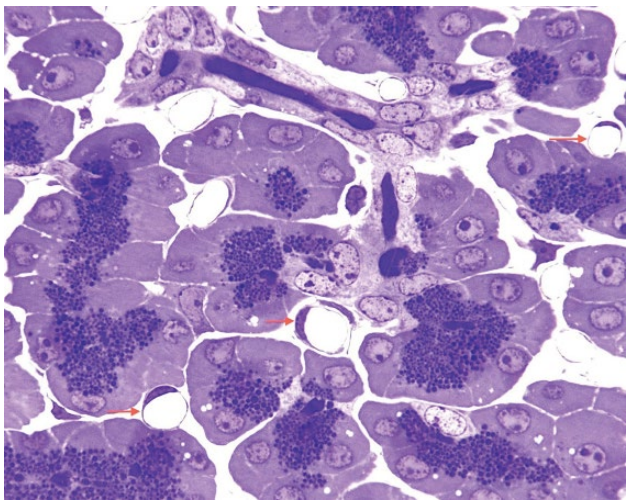

**Figure 2.16** Pancreas ductule (top center) branches (upper image right) to reach several acini or acinar tubules (upper image right and near the center). Blue zymogen granules are conspicuous in the acinar cells and the liquid content of the ductule is also dark blue. Ductal and centroacinar cells have pale cytoplasm. The presence of numerous round empty capillaries (arrows) in the interstitial spaces indicates that the pancreas was perfused with fixative. Toluidine blue stain, 1 μm thick plastic embedded tissue. *Source:* Micrograph contributed by James Jamieson.

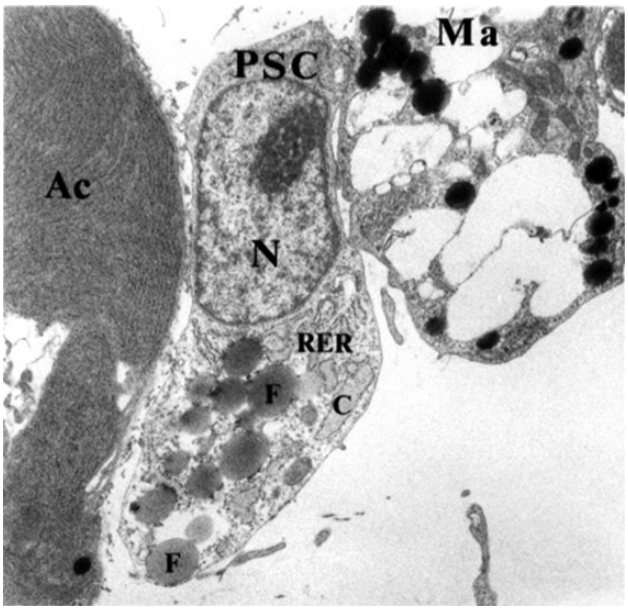


**Figure 2.17** Pancreatic stellate cell (PSC) from a patient with acute pancreatitis. The PSC is near a macrophage (Ma), image right, and an acinar cell (Ac), image left. Fat droplets (F) and RER are conspicuous in the PSC cytoplasm below the nucleus (N). Original magnification 6000×. *Source:* Bachem et al. 1998 [16].

acinar cells (Fig. 2.13). Ductal cells have single cilia, although they are difficult to detect without special tissue preparation and labeling [15].

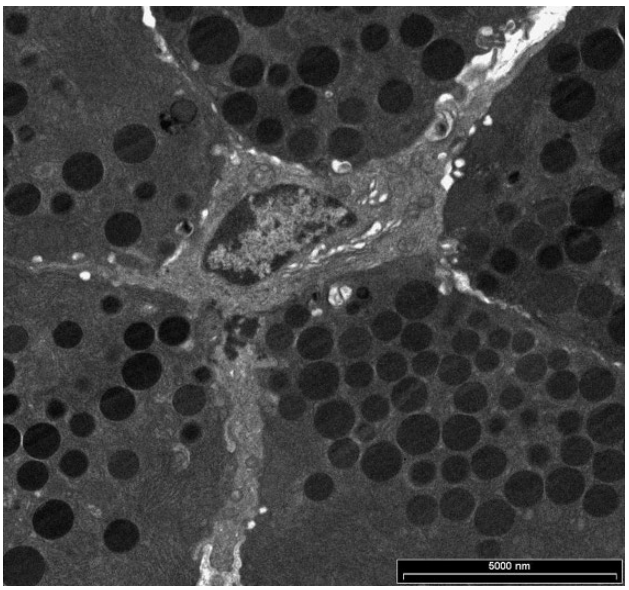


**Figure 2.18** A pancreatic stellate cell (PSC) *in situ* is surrounded by multiple acinar cells containing zymogen granules. Extensions of PSC cytoplasm between acinar cells are conspicuous, upper image right and lower image left. The dark, irregular cytoplasmic inclusions at the origin of the latter interstitial extension may represent lipid droplets—a characteristic of PSC. *Source:* Contributed by the Pancreatic Research Group, UNSW, Australia, with special thanks to Dr Murray Killingsworth.

### Interstitial Tissue

The interstitium contains capillaries, arteries, veins, lymphatics, nerve fibers, fat cells, and stellate cells. The stellate cells are undifferentiated connective tissue cells with characteristic structure (Figs 2.17 and 2.18) that are activated by inflammation to form fibroblasts and contribute to fibrosis associated with chronic pancreatitis and some neoplasms [16] (see Chapter 10).

## Endocrine Pancreas

The pancreatic islets (islets of Langerhans) collectively comprise the endocrine pancreas that synthesizes and secretes insulin, glucagon, pancreatic polypeptide, and somatostatin. Most islets are too small to be seen by gross examination, hence they were not depicted in Figs 2.1 to 2.7. Islets vary greatly in size and ~70% are in the size range 50–250 μm in diameter in humans, with an average in the range 100–150 μm [17]. Small islets are dispersed throughout the acinar lobules (Fig. 2.19) and most larger islets lie along the main and interlobular ducts of the pancreas. Most islets are spherical or ellipsoid, but they can be irregular in shape—sometimes reflecting the presence of an adjacent structure, often a

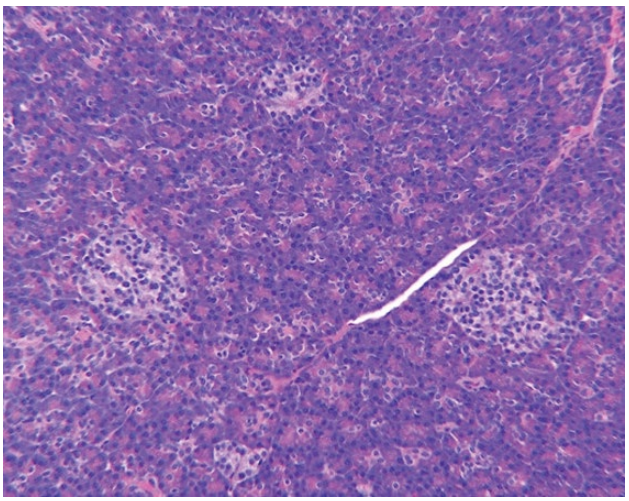

**Figure 2.19** Pancreatic lobules with acinar cells and four islets at 12, 3, 6–7, and 9 o'clock. The islets are paler than the surrounding acinar tissue. The upper and lower islets are small and the lateral islets are medium size. H&E stain.

duct, or limitation by a tissue plane. Several reports provide support for the presence of a higher population density of islets in the tail of the pancreas than in the head and body [5,18], although another study found no difference [19]. In adult humans, the number of islets is estimated to be $5 \times 10^5$–$10^6$ [20], whereas there are far fewer in smaller animals [21]. Islets comprise 1–2% of the pancreas in adults of most mammalian species. In addition to the islets, isolated islet cells may be found dispersed in the acinar lobules or in association with ducts.

Several of the images of islets are from sections that have been immunostained using antibodies to specific islet peptide hormones to demonstrate various islet cell types, including β cells (insulin), α cells (glucagon), δ cells (somatostatin) (Fig. 2.20), and pancreatic polypeptide (PP) (Fig. 2.21). In the portion of the pancreas derived from the dorsal pancreatic anlage, the majority of islet cells are β cells (75–80%), followed by α cells (about 15%), δ cells (about 5%), and very few PP cells. Most PP cells are in the portion of the pancreas derived from

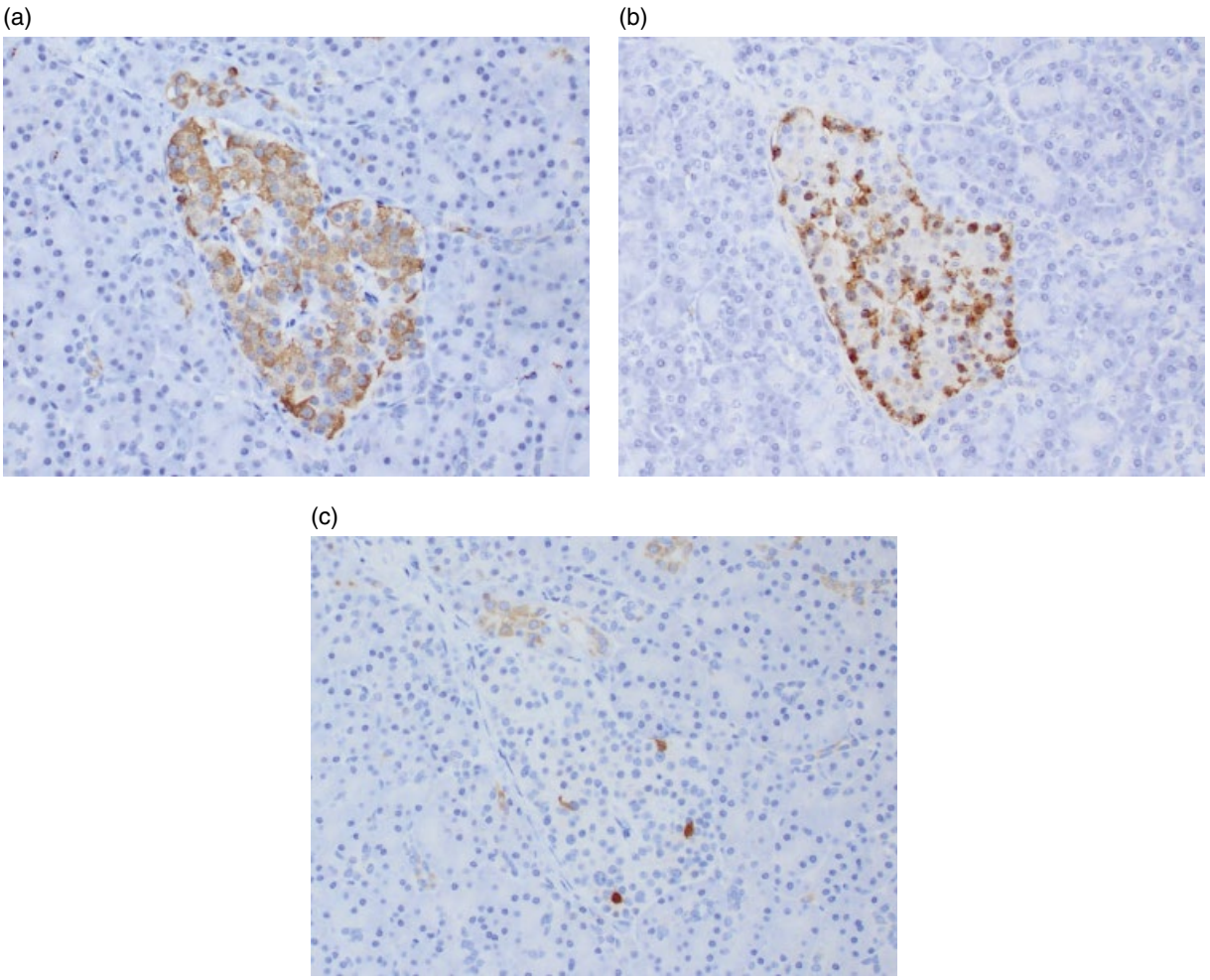


**Figure 2.20** Serial sections of a human islet immunostained using antibodies to insulin (a), glucagon (b), and somatostatin (c). The presence of the hormones is indicated by brown staining. The predominance of insulin secreting β cells is obvious. In (b) and (c), the location of α cells and δ cells is primarily at the border of groups of β cells. *Source:* Photos provided by Arief A. Suriawinata.

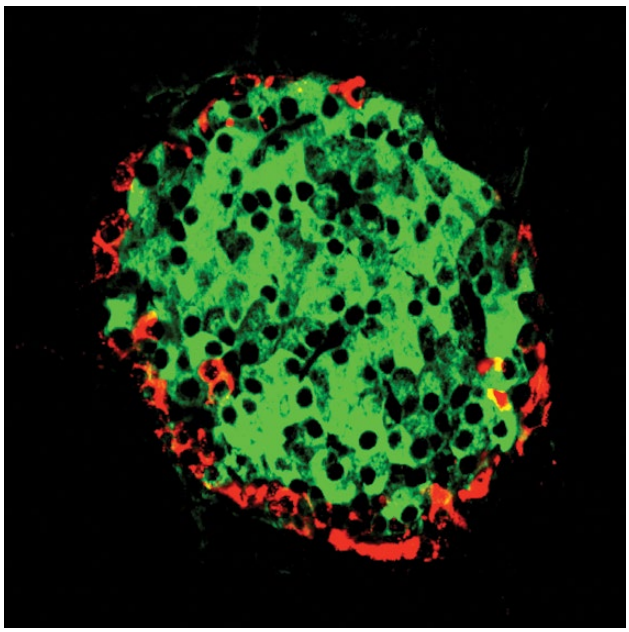

**Figure 2.21** Mouse islet stained to demonstrate pancreatic polypeptide (red) and insulin (green). Immunofluorescence using antibodies to insulin and neuropeptide Y (NPY) that cross-reacts with PP. *Source:* Micrograph contributed by Susan Bonner-Weir.

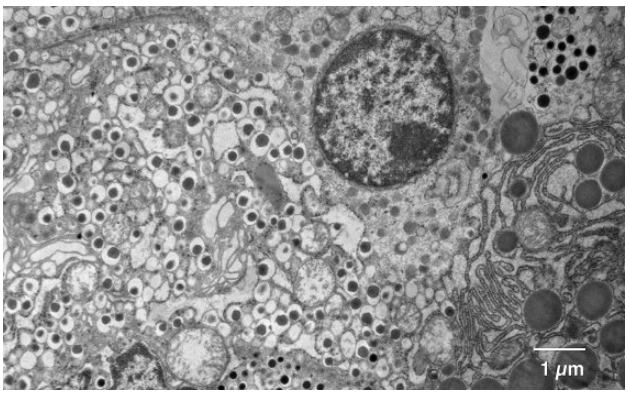


**Figure 2.22** Mouse islet with β-cell cytoplasm containing insulin granules (image left), a δ cell with nucleus and less dense secretory granules (right of center), and α-cell cytoplasm with glucagon granules (upper image right corner) and at the bottom margin near the center. In murine species, β-cell granules have a wide halo surrounding the dense core. Acinar cell cytoplasm with zymogen granules, RER, and mitochondria is present (lower image right). *Source:* Micrograph contributed by Fred Gorelick.

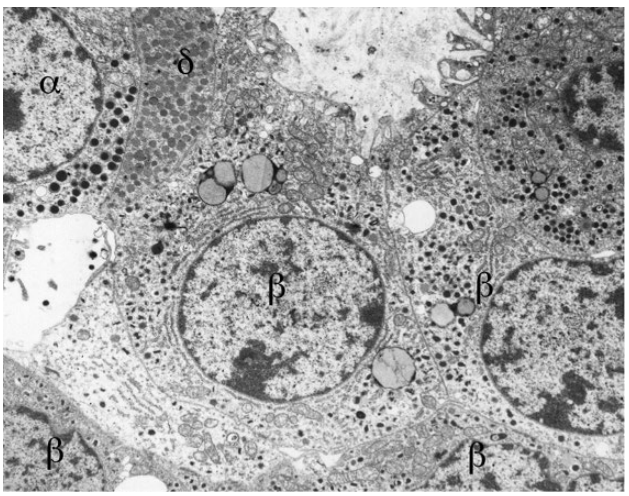


**Figure 2.23** Human islet from transplant isolation with α, β, and δ cells labeled. The α-cell granules are typically slightly larger than β-cell granules; δ-cell granules are typically less densely stained than the granules in α and β cells. The cytoplasm of several islet cells contains lipid—most notably in the central β cell where lipid bodies lie at 4 and 11–12 o'clock around the nucleus. *Source:* Micrograph contributed by Susan Bonner-Weir.

the ventral pancreatic anlage, namely the uncinate process, that is reported to comprise about 10% of the pancreas [22,23]. In the uncinate process, islets contain few α cells and many more PP cells. Stefan et al. presented data from a study of 13 nondiabetic human pancreases, showing that the PP cells comprise 54.3–93.7% of the volume of islets in the uncinate region, displacing most α cells and some β cells [23]. They provided data that indicated that PP cells were the second most prevalent endocrine cell type overall in the pancreases of their 13 subjects.

At the ultrastructural level, islet cells contain numerous mitochondria, a modest amount of RER, and small secretory granules (islet hormones). The granules vary in size and density with cell type and hormone and show some variation between species (Figs 2.22 and 2.23).

Capillaries in the islets connect with capillaries serving the adjacent acinar cells before draining into veins. These proximal acinar cells are exposed to higher concentrations of islet hormones than the majority acinar cells that are more distant from islets. The proximal acinar cells sometimes are larger and contain more zymogen than more distant acinar cells, and they form a halo around the islets. This unique feature of islet–acinar blood supply has been referred to as an insulo-acinar portal system [24].

## Acknowledgments

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3

# Congenital and Inherited Anomalies of the Pancreas

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## Introduction

The development of the pancreas from dorsal and ventral buds, which physiologically fuse to form one organ and a common ductal system, explains a number of developmental disorders that can lead to anatomic abnormalities of either the pancreas or its ducts. Most anomalies of the pancreas are discovered incidentally either at endoscopy, during diagnostic imaging, particularly magnetic resonance cholangiopancreatography (MRCP), or at autopsy. Some of them may cause clinically relevant problems. Clinical symptoms are related either to damage caused by proteolytic processes or inflammation (pancreatitis), displacement or compression of neighboring organs, or to an abnormal (mostly decreased) quantity of secretory and incretory products. However, owing to the high functional reserve of both the endocrine and the exocrine parts of the pancreas, deficiencies in hormone or zymogen production do usually not become clinically apparent until more than 90% of the respective cells have lost their function. Pancreatic anomalies and functional defects can also be part of complex disorders that affect multiple organ systems or of metabolic abnormalities that cause abnormal development of the pancreas as part of a multiorgan process, or that merely increase the lifetime risk for developing pancreatitis or pancreatic diabetes. This chapter reviews some of the congenital developmental and inherited disorders that can affect the endocrine and exocrine pancreas.

## Primary Malformations

### Pancreatic Agenesis and Hypoplasia

Primary agenesis of the pancreas represents a very rare disorder of pancreatic development. Its exact incidence is not known. Complete absence of the pancreas not only manifests postnatally with diabetes mellitus and malabsorption, it is also consistently associated with intrauterine growth retardation, which appears to relate to the fact that insulin is a major intrauterine growth factor. In most cases, the condition is rapidly fatal [1]. Pancreatic agenesis may occur as a monogenic condition (OMIM 260370). Mutations in the gene for insulin promoter factor-1 *IPF1* (also known as *PDX1*) and mutations in a distal enhancer of the *PTF1A* gene have been found in families with autosomal recessive inheritance of isolated pancreatic agenesis [2,3]. *PTF1A* encodes pancreas transcription factor 1α, which is known to play a pivotal role in mammalian pancreatic development [4]. Recessive mutations of *PTF1A* itself are responsible for a syndromic disorder comprising pancreatic and cerebellar agenesis (OMIM 609069) [5]. The association of congenital heart defects with variable pancreatic defects ranging from agenesis to hypoplasia has been found to be caused by dominant mutations of the *GATA6* gene (OMIM 600001) [6]. All of these human genetic disorders are extremely rare. In mice, a lack of *TCF2*/*vHNF1* also leads to pancreas agenesis [7,8].

In contrast to complete agenesis, pancreas hypoplasia or partial agenesis is unlikely to be symptomatic because

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of the high functional reserves of both the endocrine and the exocrine pancreas. Partial agenesis of the pancreas mostly affects the dorsal part (also known as congenitally short pancreas), probably reflecting the fact that dorsal pancreas formation relies on different genes and signaling events from those of the ventral pancreas [9]. With this entity, only a pancreatic head is seen on imaging techniques and the body and tail of the organ are missing. Agenesis of the dorsal pancreas has been found to be associated with diabetes and pancreatitis [10,11]. The short pancreas can occur as solitary finding or in association with polysplenia syndrome [12]. Since most of the islet cells are located in the missing distal pancreas, patients with this anomaly have an increased risk of diabetes mellitus [13]. Magnetic resonance imaging (MRI) can assist in establishing the diagnosis.

## Annular Pancreas

Annular pancreas means the complete encirclement of the second part of the duodenum by a ring-like band of pancreatic tissue that may lead to partial or complete duodenal obstruction. Annular pancreas has an estimated incidence of one in 20,000 and is found in 8–21% of patients with neonatal duodenal obstruction. The exact pathogenesis of annular pancreas is not known. Several hypotheses have been proposed to account for annular pancreas, including gut rotation defects, increased outgrowth of both the dorsal and ventral pancreas, persistence of the left ventral bud, or a combination of these events.

Annular pancreas is often associated with other congenital anomalies, including intestinal atresias, malrotation, tracheoesophageal fistula, heart defects, and others. A considerable number of affected individuals have chromosomal disorders, particularly Down syndrome (11–16%) [14,15]. This suggests that annular pancreas represents an early embryologic malformation. Agenesis of the dorsal pancreatic anlage [16] (congenital short pancreas) may also be associated with annular pancreas.

Although most cases of annular pancreas are sporadic, there have been some instances of familial recurrence with different patterns of transmission [17,18], suggesting that this anomaly may also be caused by a monogenic defect. One such disorder associated with annular and/or hypoplastic pancreas is Mitchell–Riley syndrome (OMIM 615710), which includes severe neonatal diabetes, intestinal malrotation, and gallbladder agenesis, among other characteristics. Recessive mutations in the *RFX6* gene, encoding a transcription factor that directs islet cell differentiation, have recently been reported to cause Mitchell–Riley syndrome [19].

Another syndrome involving annular pancreas formation is associated with mutations in the *FOXF1* gene, which are otherwise associated with severe vascular abnormalities of the lungs (OMIM 265380) [20,21].

In mice, homozygous inactivation of Indian hedgehog (*Ihh*) results in 42% annular pancreas, and inactivation of sonic hedgehog (*Shh*) may also lead to annular pancreas in certain genetic backgrounds [22,23]. In addition to the hedgehog pathway, tetraspanin (Tm4sf3) appears to have a fundamental regulatory role in pancreatic development. Experimental deletion of tetraspanin promotes a phenotype similar to pancreas divisum (see later), whereas its overexpression induced the formation of an annular pancreas [24].

Annular pancreas may present at any age, but roughly half of the patients are symptomatic during the first year of life with duodenal obstruction [14]. The earliest presentation may be prenatal with polyhydramnios and may be confirmed by fetal ultrasonography. In infants, the diagnosis is often made by abdominal ultrasound or a "double bubble" sign on plain abdominal radiography in an upright position; owing to post-duodenal obstruction, not only the stomach but also the upper duodenum is filled with gas—hence the double bubble on plain X-ray film. Patients in whom annular pancreas becomes symptomatic later in life may suffer from recurrent vomiting, chronic gastric distension, pain resulting from mild pancreatitis, or peptic ulcers [25–27]. Upper gastrointestinal studies or even contrast-enhanced computed tomography (CT) or MRI, which allows direct visualization of the ring, may help with the diagnosis. Patients are sometimes diagnosed by endoscopic retrograde cholangiopancreatography (ERCP) (Fig. 3.1), albeit this invasive technique is now rarely used for diagnostic purposes. The differential diagnosis of duodenal obstruction should include duodenal atresia and intestinal volvulus.

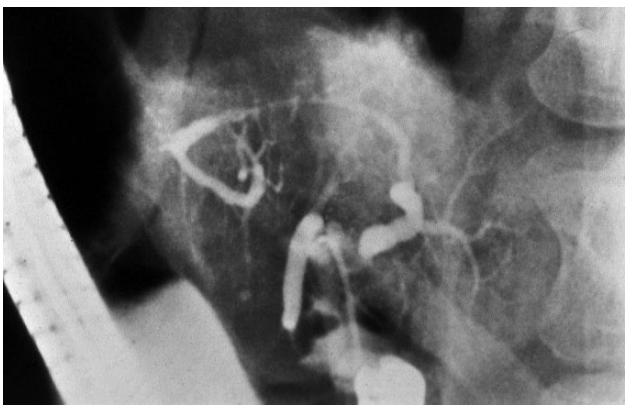

**Figure 3.1** ERCP of pancreas annulare in an adult. Note the ring-shaped pancreatic duct encircling the duodenum.

Surgical management of symptomatic annular pancreas is performed by duodenoduodenostomy as a bypass operation with an excellent long-term prognosis [14]. Resection of the ring is not recommended because of the risk of pancreatic peritonitis, postoperative pancreatitis, fistulae, and late fibrosis.

## Pancreas Divisum

In pancreas divisum, there is absent or incomplete fusion between the dorsal duct of Santorini and the ventral duct of Wirsung [13], resulting in the majority of the gland draining via the smaller duct of Santorini into the minor papilla. The pancreatic head and the processus uncinatus with less tissue mass and secretory load then drain via the duct of Wirsung through the larger papilla of Vater. Multiple variants of the divisum have been described anatomically or on the basis of ERCP findings [28]. Pancreas divisum is the most common anatomic variant of the pancreas [13]. Its estimated incidence varies from approximately 4–14% in autopsy series to 2–7% in ERCP studies and with a reported 9.6% in a population-based secretin-stimulated MRCP study [29]. Diagnosis of pancreas divisum relies on ERCP or MRCP to visualize the duct of Santorini draining the pancreas (Fig. 3.2).

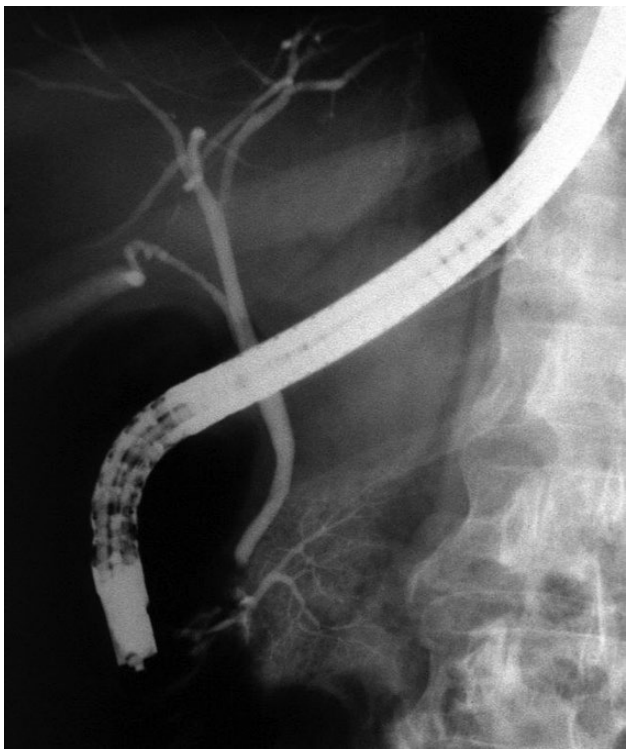

**Figure 3.2** Pancreas divisum on ERCP. Whereas the intra- and extrahepatic bile ducts are of regular size and proportions, the pancreatic duct is short and tender (already overfilled with contrast medium) and supplies only the head of the pancreas.

It has been suggested that the small accessory duct may lead to functional obstruction and a propensity to pancreatitis, but a causal relationship remains controversial. Since the prevalence of a pancreas divisum is identical in the healthy control population and patients with chronic pancreatitis, it is no longer regarded as a risk factor for pancreatitis [30]. Recent evidence even suggests that the prevalence of *SPINK1* and *CFTR* mutations, which are frequently associated with idiopathic pancreatitis, are just as common among chronic pancreatitis with pancreas divisum as without pancreas divisum [31]. This suggests that chronic pancreatitis with pancreas divisum is essentially idiopathic pancreatitis with the same genetic risk factors, of which mutations in the *CFTR* gene are the most conspicuous [31–33]. Although drainage is usually satisfactory, it can, in patients with chronic pancreatitis, add to the problem of impaired ductal flow. In these circumstances, the question arises of whether endoscopic sphincterotomy and stent insertion at the minor papilla are of benefit for the patient or can affect the natural history of chronic pancreatitis [34–36].

## Ectopic Pancreas

Ectopic pancreatic tissue is an aberrant focus of normally developed pancreatic tissue that lacks anatomic and vascular continuity with the main organ and can be found in various locations. Autopsy studies suggest that ectopic pancreatic tissue is fairly common (prevalence from 1% to over 13%), but its clinical manifestation is very rare [37]. Most ectopic pancreatic tissue is discovered endoscopically in the stomach (particularly antrum), duodenum (Fig. 3.3), jejunum, or a Meckel diverticulum. Ectopic pancreatic tissue is mostly located in the submucosa but in some instances it can be found in the muscularis or serosa. Other locations include the ileum, liver, spleen, biliary tract, mesentery, or umbilicus [13].

The exact mechanisms leading to ectopic formation of pancreatic tissue have remained elusive. A key regulator for the appropriate localization of pancreatic stem cells in the forgut appears to be Hes-1 [38]. Ectopic pancreatic tissue has been observed in knockout mice for the homeobox gene *cdx2*. Inhibition of *Shh* signaling also leads to ectopic pancreas in chickens [39].

Although ectopic pancreatic tissue can undergo similar changes to the orthotopic pancreas, particularly cystic degeneration, ectopic pancreatitis [40], and even pancreatic cancer formation [41], in most cases ectopic pancreas remains asymptomatic. In many cases it is an incidental finding during surgery or endoscopy for another indication. If patients with ectopic pancreatic tissue become symptomatic, this may be due to the mass effect, which can cause either obstruction of the intestinal passage (mainly in the prepyloric localization) [42] or

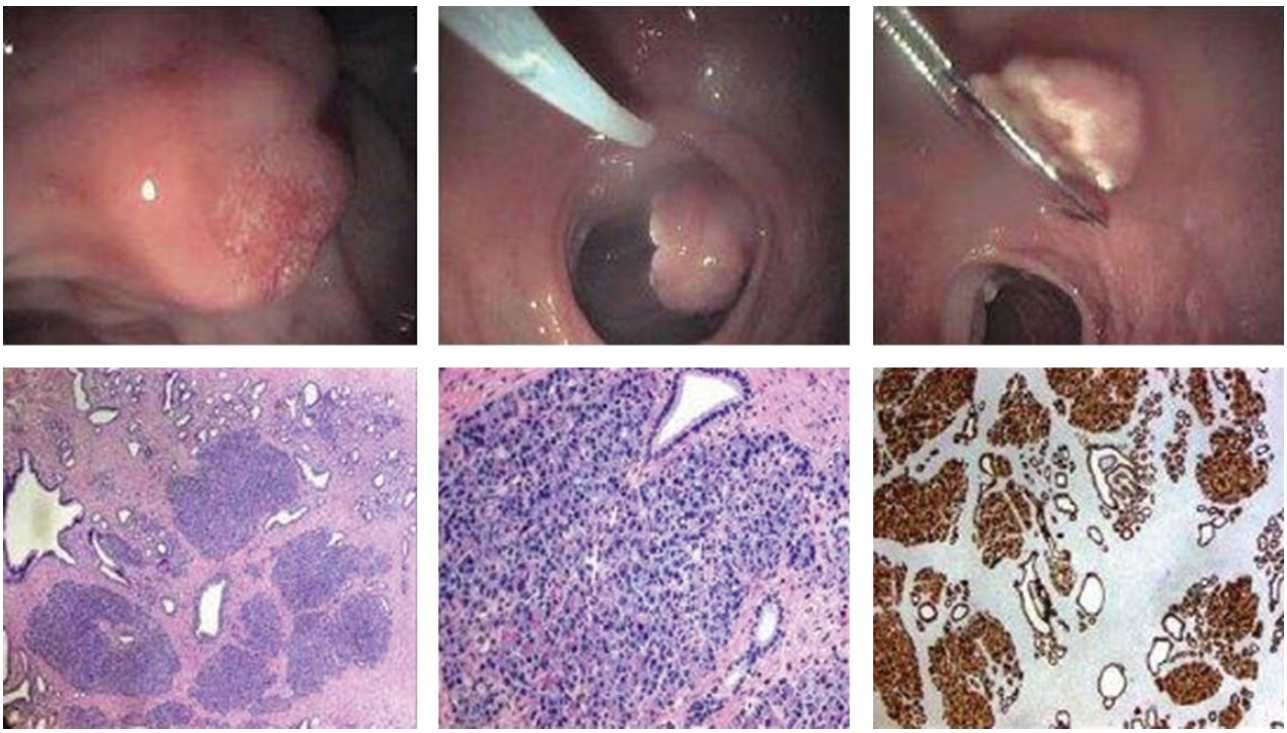

**Figure 3.3** Ectopic pancreas 4 cm distant from the duodenal papilla under endoscopic vision and during endoscopic snare dissection (top images) and histologically (bottom panels, at bottom right cytokeratin staining). Note the complete absence of endocrine cells on histology, which corresponds to a type II ectopic pancreas according to Heinrich (1909), that is, composed only of exocrine cells. *Source:* Histology courtesy of M. Androshchuk and G. Lorenz, Greifswald.

bowel intussusception, gastrointestinal hemorrhage secondary to mucosal ulcerations close to the pancreatic tissue [43], pain secondary to pancreatitis [40], and exceptional malignant transformation [41,44].

Diagnosis is made endoscopically or radiographically in antral localization. In other localizations, diagnosis is made at the time of surgery. The definite diagnosis relies on histology. Treatment of symptomatic ectopic pancreas is either surgical or endoscopic.

## Ductal Anomalies

Variability in the development of the dorsal and ventral ductal systems can give rise to a number of anatomic variations. Most of them are incidental findings at endoscopy/ERCP or by MRI/MRCP during systematic studies [29]. Ductal abnormalities that have been implicated in the pathogenesis of clinical disease include fusion failure of the dorsal and ventral ductal systems, which results in a ductal pattern known as pancreas divisum (see earlier), and the pattern of the junction with the common bile duct known as "common channel syndrome."

Common channel syndrome (pancreaticobiliary maljunction) results from an abnormally long common pancreatobiliary channel due to a junction of the ventral pancreatic duct with the common bile duct outside the duodenum wall [45]. This may permit the reflux of pancreatic enzymes into the common bile duct. Pancreaticobiliary reflux has been confirmed by dynamic MRCP after secretin stimulation [46] but does not appear to play a role in pancreatitis associated with gallstone disease [47]. Reflux of pancreatic juice into the bile duct may result in bile duct cyst formation. Reflux of bile into the pancreas, on the other hand, is much less likely to occur since pancreatic secretory pressure exceeds bile duct secretory pressure consistently. Ductal content flowing in either direction may result in pancreatitis or choledochal cyst formation. Common channel syndrome can be found in the majority of children with choledochal cyst [48]. The diagnosis of a choledochal cyst is mostly made by abdominal ultrasonography. Visualization of the common channel relies on invasive procedures, such as ERCP, percutaneous transhepatic cholangiography, or noninvasive MRCP. Treatment of a choledochal cyst is surgical. Endoscopic sphincteroplasty may be curative in common channel syndrome without choledochal cyst but with pancreatic ductal ectasia [45].

## Congenital Pancreatic Cysts

The great majority of cysts in the pancreas are (a) multiple cysts, (b) pseudocysts (no true epithelial lining), and

(c) a complication of chronic pancreatitis. True single congenital cysts of the pancreas are extremely rare. However, in population-based MRCP studies, small cysts (<1 cm) of unknown etiology (but most likely dysontogenetic) are fairly common and affect one-quarter of healthy volunteers [29]. Larger congenital cysts have a female predominance and may present as an asymptomatic palpable mass, or with epigastric pain, jaundice, and vomiting related to compression of surrounding visceral structures [49]. These cysts are most commonly located in the tail and body of the pancreas and are typically unilocular cysts with thin-walled cavities ranging in size from microscopic to up to 5 cm in diameter [50]. Ductal communication is rare. These cysts are usually anechoic on ultrasound and are low-attenuation cystic structures on CT or MRI examination with no wall enhancement. Associated congenital anomalies may include renal tubular ectasia, polydactyly, anorectal malformations, polycystic kidneys, and asphyxiating thoracic dystrophy [50]. Multilocular cysts may also be part of von Hippel–Lindau disease and autosomal dominant polycystic kidney disease (see below), but in both conditions pancreatic cysts are rarely congenital. Most congenital cysts with the symptoms mentioned and clinical manifestation are diagnosed in children. When they are found in adults, the differential diagnosis of chronic pancreatitis-associated cysts on the one hand, and cystic tumors of the pancreas (cystic adenomas and carcinomas, also more common in females) on the other, becomes an important and sometimes difficult differential diagnosis [51].

Gastrointestinal duplication cysts are abnormalities of the developing foregut that have, in contrast to the pseudocysts seen in chronic pancreatitis (Fig. 3.4), alimentary tract epithelial lining. A majority of these cysts contain gastric mucosa or pancreatic tissue, and digestive secretions can facilitate hemorrhage within the cyst. Juxtapancreatic duplication cysts typically originate from the stomach or duodenum and may compress the pancreas. Rarely, the cysts may be sequestered within the pancreas itself [49]. Communication between the cyst and the pancreatic duct is uncommon and, if present, rather pathognomonic for pancreatitis-associated pseudocysts.

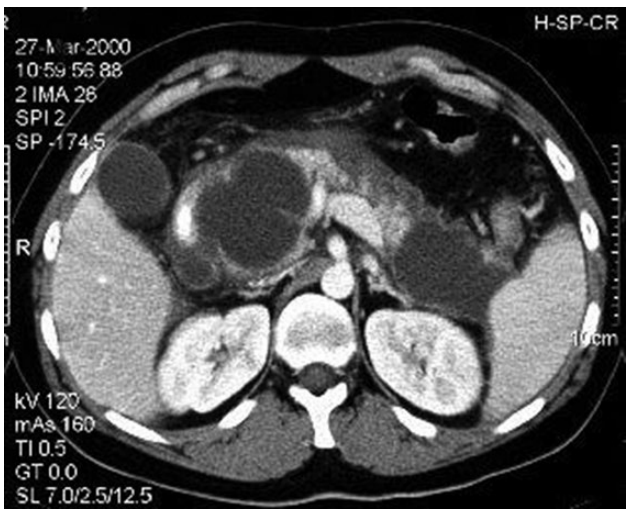


**Figure 3.4** Large cysts in the head and tail of the pancreas in a patient with chronic pancreatitis.

## Congenital Secretory Insufficiency (Excluding Cystic Fibrosis)

Congenital exocrine pancreatic insufficiency is rare. Cystic fibrosis, which leads to progressive destruction of the pancreas and may result in clinical symptoms of secretory insufficiency from birth, accounts for the majority of cases with congenital exocrine pancreatic insufficiency [52]. Mutations in the *CFTR* gene that do not cause cystic fibrosis (including lung disease) but raise the susceptibility for developing pancreatitis have been shown to partially impair pancreatic exocrine secretion [53]. Pancreatic disease in cystic fibrosis is discussed separately in Chapter 47.

Congenital pancreatic secretory insufficiency, if complete, manifests from birth with loose and voluminous stools, steatorrhea, failure to thrive, and hypoproteinemia. However, as the functional capacity of the exocrine pancreas is good, exocrine failure may not become manifest unless more than 90% of the exocrine cells have been destroyed [54].

Congenital exocrine pancreatic insufficiency without diabetes is not due to a primary malformation of acinar cells, because in the absence of acinar tissue endocrine cells do not develop properly. Instead, congenital secretory insufficiency of the pancreas reflects either isolated enzyme deficiencies or early-onset degeneration of acinar cells resulting in fibrosis or lipomatosis of the organ. Owing to the destructive nature of the disorder in the latter group, progression to combined insufficiency is common. Some of the disorders associated with congenital secretory insufficiency are discussed in the following.

### Isolated Enzyme Deficiencies

Isolated deficiencies of several pancreatic zymogens have been described, but all of them are extremely rare. The enzymes affected include lipase, colipase, trypsinogen, and amylase [55].

When lipid digestion is involved, the leading symptoms are chronic diarrhea and steatorrhea, which are readily detected with or without malnutrition. Congenital absence of pancreatic lipase was described as a familial trait with probable autosomal recessive inheritance (OMIM 614338) [56]. Colipase deficiency was reported

in two brothers [57] and the combined defect of both lipase and colipase in another family and one isolated case [58,59]. Mutations in *PNLIP*, the gene encoding pancreatic lipase, have been reported in two families with autosomal recessive inheritance of pancreatic triglyceride lipase deficiency [60,61]. Pancreatic amylase deficiency may lead to diarrhea induced by a diet that is rich in starch, but the functional capacity of the carbohydrate-digesting enzymes is rather high, and therefore amylase deficiency may remain compensated [62,63]. Children with trypsinogen deficiency were reported to present with growth failure, diarrhea, hypoproteinemia, and edema [64]. Enterokinase deficiency, although enterokinase is not an enzyme of the pancreas itself, presents as a pancreatic protease defect, because this enzyme is critical for the activation of pancreas-derived zymogens in the duodenum [65,66]. Mutations in the proenteropeptidase gene *PRSS7* have been reported as the molecular basis of this condition in one family (OMIM 226200) [67]. All these isolated enzyme deficiencies have in common the extreme paucity of reported cases and—apart from very few exceptions—the lack of molecularly proven defects (Table 3.1). This may indicate that alternative sources of lipolytic, proteolytic, and glycolytic activity exist that can compensate for isolated deficiencies. In all conditions of isolated pancreatic enzyme deficiency, enzyme replacement therapy is very effective.

## Shwachman–Diamond Syndrome

After cystic fibrosis, Shwachman–Diamond syndrome (SDS) (OMIM 260400) is the second most common inherited cause of exocrine pancreatic insufficiency. It has an approximate incidence of one in 50,000 in the North American population. Manifestations outside the pancreas sometimes concern skeletal features (e.g., metaphyseal dysplasia) but most often involve hematologic abnormalities, typically intermittent neutropenia, but other blood cell fractions may also be affected. Affected patients are short in stature and most commonly suffer from one or more symptoms, which include diarrhea due to malabsorption, failure to thrive, and recurrent infections [68]. In contrast to cystic fibrosis, sweat chloride concentration is normal. Imaging features with replacement of pancreatic tissue by fat (Fig. 3.5) or diffuse fatty infiltration are rather characteristic [69]. Although a majority of the pancreatic tissue is replaced by fat, resulting in a variable degree of steatorrhea, which can even somewhat improve when the children get older, the islet cells of Langerhans and the ductal architecture remain largely intact [70,71]. Hence neither diabetes nor pancreatitis is a consistent feature of SDS. Virtually all patients with SDS have consistent evidence of exocrine pancreatic insufficiency, although clinical signs and symptoms of maldigestion may be absent.

The pathogenesis of the exocrine pancreatic defect in SDS has been partly elucidated. In SDS cells, ribosome biogenesis and protein synthesis are altered and the most likely underlying mechanism is a Complex IV impairment with resulting defects in oxidative phosphorylation, ATP depletion, increased glycolysis, and endoplasmic reticulum stress, the last associated with high intracellular

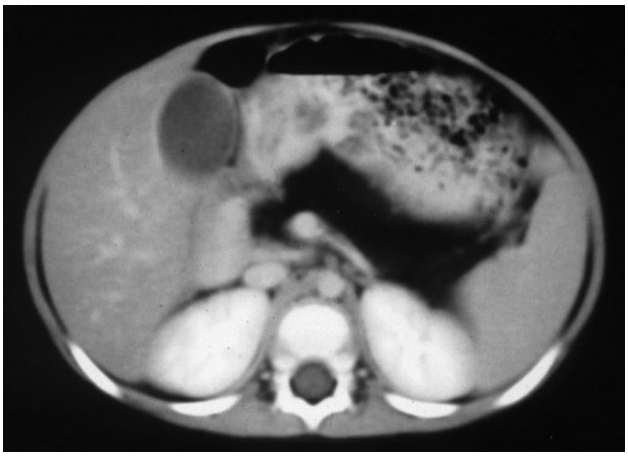

**Figure 3.5** Fatty replacement of the entire pancreas (black central box on the abdominal CT) in Shwachman–Diamond syndrome. *Source:* Wilschanski M et al. J Pediatr Gastroenterol Nutr 1994;19:111–113, Fig. 1. Reproduced with permission of Wolters Kluwer Health.

**Table 3.1** Isolated deficiency of pancreatic enzymes.

| Enzyme | Gene | Locus | Defect genetically confirmed in affected patients |
|---|---|---|---|
| Trypsinogen | *PRSS1* | 7q35 | No |
| Lipase | *PNLIP* | 10q26 | Yes (two families) |
| Colipase | *CLPS* | 6pter–p21.1 | No |
| Pancreatic amylase | *AMY2A* *AMY2B* | 1p21 | No |
| Enterokinase[a] | *PRSS7* | 21q21 | Yes (one family) |

[a] Duodenal brush border enzyme; deficiency presents like trypsinogen deficiency.

calcium concentrations [72]. Unlike in cystic fibrosis, where pancreatic disease is caused by ductal obstruction, in SDS the pancreatic acini fail to develop properly or undergo a very early degeneration. Histologically, the SDS pancreas shows normal ductal architecture and islets, absent or sparse acinar cells, and extensive fatty replacement [73].

Inheritance of SDS is autosomal recessive. The disease is caused by mutations in the *SBDS* gene (denoting the full name Shwachman–Bodian–Diamond syndrome) on chromosome 7q11 [74]. *SBDS* encodes a predicted protein of 250 amino acids. A pseudogene copy (*SBDSP*) with 97% nucleotide sequence identity resides in a locally duplicated genomic segment of 305 kb. Interestingly, recurrent mutations often (89%) result from gene conversion with at least one of two pseudogene-like sequence changes that result in protein truncations. The protein SDBS is a member of a highly conserved protein family involved in ribosome formation function with putative orthologs in diverse species, including archaea and eukaryotes. The protein is thus involved in RNA metabolism.

Diagnosis of SDS is based on the characteristic clinical findings, but it may be delayed in atypical or mild cases. Treatment is symptomatic. Most recently, biallelic mutations in DNAJC21 have apparently been found in association with SDS [75].

A distinct autosomal recessive syndrome with pancreatic, hematopoietic, and skeletal features has been termed "exocrine pancreatic insufficiency, dyserythropoietic anemia, and calvarial hyperostosis" (OMIM 612714) and related to mutations in the *COX4I2* gene [76].

### Pearson Marrow Pancreas Syndrome

Pearson syndrome (OMIM 557000) is characterized by refractory sideroblastic anemia with vacuolization of marrow precursors and exocrine pancreatic dysfunction. Severe, transfusion-dependent, macrocytic anemia usually starts in infancy. In contrast to SDS, the pancreas rather shows fibrosis in Pearson syndrome and the disorders also differ in bone marrow morphology. Pearson syndrome was found to be a mitochondrial disorder resulting from deletions of mitochondrial DNA (mtDNA) [77]. The disorder may be progressive and a phenotypic shift from a predominantly hematopoietic disorder (Pearson syndrome) to a disease with overt muscle dysfunction (mitochondrial myopathy) was repeatedly observed, with eventual evolution to a fully developed Kearns–Sayre syndrome, depending on the distribution of deleted mtDNA [78].

### Johanson–Blizzard Syndrome

Johanson–Blizzard syndrome (JBS) (OMIM 243800) is characterized by congenital pancreatic exocrine insufficiency and a peculiar malformation of the nose with hypoplasia or aplasia of the nasal wings (Fig. 3.6). Additional features that are present in a large proportion of patients include short stature, scalp defects, oligodontia, deafness, hypothyroidism, imperforate anus, and intellectual disability [79]. The condition is inherited as an autosomal recessive trait and has an estimated incidence of one in 250,000 [80].

It was shown that JBS is caused by mutations in the gene *UBR1*, leading to severe deficiency of the homonymous ubiquitin ligase of the N-end rule pathway [80]. As this pathway is responsible for the degradation of intracellular proteins, it is likely that the excess or increased half-life of hitherto unknown proteins is involved in the pathogenesis of the pancreatic and other defects of JBS.

Pancreatic disease is an obligate feature of JBS [81]. Histologically, the pancreas of infants who died from complications of the syndrome was shown to lack almost completely acinar cells, which are replaced by fat and connective tissue, whereas the ductal architecture and islets are fairly well preserved [82,83]. Corresponding to these findings, it was demonstrated that JBS patients had preserved ductular output of fluid and electrolytes with decreased secretion of zymogens [84]. It has been shown that the acinar cell loss is likely caused by an intrauterine destruction of these cells resembling a pancreatitis of prenatal onset [85]. Mice deficient in *UBR1* were shown to have milder abnormalities of pancreatic function,

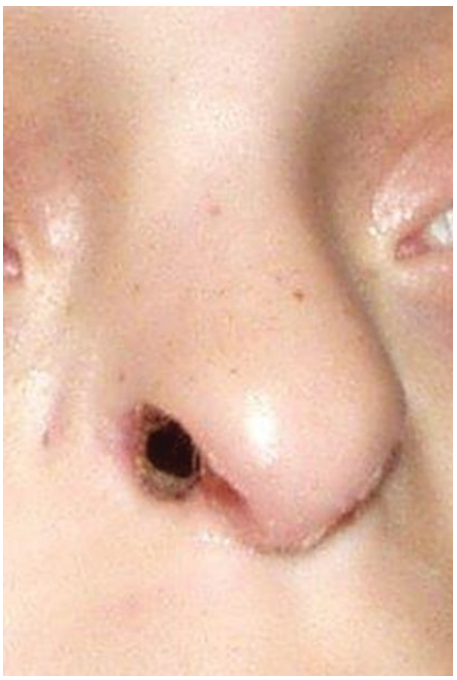

**Figure 3.6** Prominent aplasia of the nasal wings as a characteristic feature of Johanson–Blizzard syndrome.

including decreased zymogen secretion and increased susceptibility to experimental pancreatitis.

Diagnosis of JBS is established on the basis of the characteristic clinical picture and treatment is symptomatic.

## Isolated Congenital Disorders of Pancreatic Endocrine Function

### Congenital Hyperinsulinism

Hyperinsulinemic hypoglycemia of neonatal onset is a clinically and etiologically heterogeneous disease [86,87]. Congenital hyperinsulinism (CHI) was formerly called "nesidioblastosis," assuming abnormal proliferation of β cells from ductal epithelium as the underlying cause [88], but it was later demonstrated that this histologic pattern may normally be found in early infancy and that "nesidioblastosis" does not correspond to an abnormal β-cell proliferation [89,90]. In fact, two major histopathologic types of CHI can be differentiated: The diffuse form (60–70%) is characterized by the presence of islet cells with enlarged nuclei, abundant cytoplasm, and histologic evidence of increased metabolic activity throughout the pancreas. In the focal form (30–40%), hyperplasia of apparently normal islets involves a limited region of the pancreas, whereas β cells outside the focal lesion have small nuclei and sparse cytoplasm corresponding to suppression of insulin secretion [91]. A third, mosaic type has more recently been proposed [92]. In contrast, insulin-producing adenomas, the most common cause of hyperinsulinism in older children and adults, are merely seen in infants. Islet cell hyperplasia may be a consequence of chronic fetal exposure to hyperglycemia due to maternal diabetes. In this case, hyperinsulinism is transient and rarely lasts for more than a few days or weeks. Transient hyperinsulinism due to islet cell hyperplasia is also a feature of Beckwith–Wiedemann syndrome (see later). It may also occur in other syndromic conditions such as Costello syndrome (OMIM 218040), Kabuki syndrome (OMIM 147920), Sotos syndrome (OMIM 117550), congenital disorders of glycosylation (OMIM 212065), and other rare diseases [86,87]. Many cases, particularly of transient CHI, are sporadic without an obvious underlying cause.

Persistent hyperinsulinemic hypoglycemia of infancy is considered to have a strong genetic contribution and most cases have an identifiable monogenic cause (synonym: familial hyperinsulinism; OMIM 256450). Inheritance may be autosomal recessive or dominant and several genes in which mutations cause familial hyperinsulinism are known [86,87]. Some genetic entities have specific features associated with hyperinsulinemic hypoglycemia that make them recognizable clinically, such as hyperammonemia in hyperinsulinism–hyperammonemia syndrome caused by *GLUD1* mutations, abnormal levels of 3-hydroxyglutaric acid in urine in 3-hydroxyacyl-CoA dehydrogenase deficiency (*HADH* gene), and exercise-induced hypoglycemia caused by mutations of the *SLC16A1* gene [86,87].

The most common cause of familial hyperinsulinism is genetic defects affecting the subunits of the pancreatic β-cell ATP-dependent potassium channel ($K_{ATP}$), SUR1 and Kir6.2, encoded by *ABCC8* and *KCNJ11*, respectively [87]. Recessive and a few dominant $K_{ATP}$ mutations are associated with the *diffuse* type of CHI. The *focal* type instead requires a paternally inherited $K_{ATP}$ channel mutation and a second somatic event leading to a loss of the maternal allele within the focal lesion. The imbalance in the expression of various imprinted genes in the chromosomal region 11p15.5 where *ABCC8* and *KCNJ11* are located has been shown to promote β-cell hyperplasia [87]. Other monogenic forms of CHI are caused by mutations in the genes *GCK*, *HNF4A*, *HNF1A*, and *UCP2* [86,87]. Treatment of CHI includes glucose infusions, dietary measures, and medical options (diazoxide, octreotide). Surgery is the treatment of choice in cases with severe focal CHI, where it leads to complete remission, but may also be an option in refractory cases with diffuse CHI [93,94].

Congenital hyperplasia of other endocrine cells or deregulation of their hormone output is extremely rare.

### Isolated Congenital Endocrine Insufficiency

Blum et al. described a newborn with congenital absence of the insulin-producing β cells from otherwise normal-appearing pancreatic islets, causing insulin-dependent neonatal diabetes mellitus [95]. An isodisomy of chromosome 6 was found in this child, suggesting that the gene responsible for this disorder is located there [96]. The imbalance in the expression of imprinted genes of the region 6q24 is now established as the most common cause of *transient* neonatal diabetes mellitus (TNDM; OMIM 601410) [97]. Affected newborns are usually small for gestational age. Hyperglycemia usually requires insulin and resolves by the age of 18 months, but recurrence of diabetes mellitus in adolescence or adulthood is common. 6q24-related TNDM can be caused by paternal uniparental disomy (41%), duplications of the paternal allele (29%), and hypomethylation of the maternal differentially methylated region (30%). The last may represent an isolated epimutation or may be caused by homozygous or compound heterozygous *ZFP57* mutations. Accordingly, while the majority of patients with TNDM are sporadic cases, familial occurrence is also possible. In a study of

97 patients with TNDM, 72% had an abnormality at the 6q24 locus, whereas of the remaining 28 TNDM patients without 6q24 abnormalities, 26% were found to have a mutation in the *ABCC8* or *KCNJ11* genes, which usually cause *permanent* neonatal diabetes mellitus (PNDM; OMIM 606176) [98].

In contrast to the *ABCC8* and *KCNJ11* changes in congenital hyperinsulinism, the PNDM-related mutations in these genes cause a gain of function of $K_{ATP}$ and are inherited in a dominant manner. PNDM may also be caused by mutations in the genes encoding pancreatic glucokinase (*GCK*) and insulin (*INS*). Inheritance for GCK-related PNDM is autosomal recessive [99]. Abnormal morphologic findings of the pancreatic islets have not been described in patients with TNDM or PNDM. Aside from these functional islet cell defects, neonatal diabetes may also result from any type of agenesis or severe hypoplasia of the pancreas, as already mentioned.

Congenital absence of the islets of Langerhans may be part of the X-linked immunodysregulation, polyendocrinopathy, and enteropathy syndrome (IPEX; OMIM 304790) [100]. It has been shown to be caused by mutations in the *FOXP3* gene, and overwhelming systemic autoimmunity starting in early life is supposed to be the pathogenetic basis of the islet cell defect [101]. Infantile-onset (often within the neonatal period) diabetes mellitus is also a typical sign of Wolcott–Rallison syndrome (OMIM 226980), which is caused by recessive mutations in *EIF2AK3*. This gene is highly expressed in pancreatic islet cells and presumed to act as a regulator of protein synthesis [102]. A syndrome of neonatal diabetes mellitus with congenital hypothyroidism (OMIM 610199) has been associated with mutations of *GLIS3* encoding a pancreatic transcription factor involved in the transcriptional regulation of neurogenin-3 and insulin [103]. A number of other extremely rare syndromes may also present with neonatal diabetes.

Inherited disorders of insulin secretion leading to adult noninsulin-dependent diabetes mellitus or maturity-onset diabetes of the young (MODY) are not discussed here, with the sole exception of carboxyl ester lipase (CEL), a bile salt-dependent lipolytic enzyme produced by acinar cells, mutations in which had initially been identified in Norwegian patients with MODY diabetes. An extended search recently identified a hybrid allele *(CEL-HYB*) originating from a crossover between *CEL* and its neighboring pseudogene, *CELP*. In a cohort with familial chronic pancreatitis, the *CEL-HYB* was found with an odds ratio (OR) of 15.5 and in three replication cohorts of nonalcoholic chronic pancreatitis patients with an OR of 5.2, making this variant the most recent addition to the growing list of pancreatitis-causing genes [104].

## Other Hereditary Disorders with Variable Pancreatic Involvement and Metabolic Diseases Affecting the Pancreas

Pancreatic abnormalities have been described in a number of congenital or inherited multisystem disorders where they are rarely one of the leading symptoms or may even remain clinically inapparent. In addition, several metabolic disorders may be associated with pancreatic manifestations, mainly pancreatitis.

### Polycystic Kidney Disease

Multiple cysts of the pancreas can be present as part of polycystic systemic disorders, including autosomal recessive (ARPKD, OMIM 263200) and autosomal dominant polycystic (ADPKD; OMIM 173900) disease. ARPKD is caused by mutations in the *PKHD1* (polycystic kidney and hepatic disease 1) gene on chromosome 6p12 [105]. The disease presentation of ARPKD is highly variable. In newborns, the disease results in significantly enlarged polycystic kidneys, and may be associated with pulmonary hypoplasia resulting from oligohydramnios as a major cause of morbidity and mortality. Liver involvement is detectable in approximately half of infants and comprises cysts and periportal fibrosis. Pancreatic cysts and pancreatic fibrosis have been reported repeatedly as an imaging finding or at autopsy in children with ARPKD, but clinical symptoms of pancreatic involvement are exceptional. The same is true for ADPKD, where the development of sonographically visible pancreatic cysts is a much more common feature. ADPKD is a common condition affecting one in 800 live births from all ethnic groups. It results in progressive loss of renal function, with more than half of affected individuals requiring renal replacement therapy by the age of 60 years or older. Pancreatic cysts are present in about 10% of the patients, but rarely in infancy, and pancreatic involvement is typically less severe than renal and hepatic involvement. Occasionally, pancreatic cysts may lead to pancreatitis [106]. Genetic heterogeneity exists but mutations in one gene (*PKD1* on chromosome 16p) are responsible for most cases (approximately 85%) [107]. A second gene termed *PKD2* located on chromosome 4 has also been recognized as underlying the disease [108], and most recently *GANAB*, encoding the glucosidase II-α subunit, was reported to cause autosomal-dominant polycystic kidney and liver disease [109].

### Von Hippel–Lindau Syndrome

One of the inherited disorders that are associated with single or multiple cysts in different parenchymal organs including the pancreas is von Hippel–Lindau syndrome (VHL; OMIM 193300). VHL is an autosomal dominant familial cancer syndrome predisposing to a variety of benign and malignant neoplasms. It is caused by mutations in the VHL tumor suppressor gene on chromosome 3p25 [110], but genetic changes in the cyclin D1 gene on chromosome 11q13 may further modify the phenotype [111]. The incidence is estimated at one in 36,000 and affected patients are at risk for developing cerebellar, spinal, and retinal hemangioblastoma, renal cell carcinoma, pheochromocytoma, pancreatic neuroendocrine tumors, pancreatic and renal cysts, and epididymal cystadenoma [112]. VHL has previously been classified as type 1 (without pheochromocytoma) and type 2 (with pheochromocytoma). Other authors have subdivided VHL further into type 2 and type 2A (with pheochromocytoma) and type 2B (with pheochromocytoma and renal cell carcinoma). Pancreatic lesions in VHL include multiple cysts, serous cystadenoma, and neuroendocrine tumors. Pancreatic carcinoma and adenocarcinoma of the ampulla of Vater have also been reported. Pancreatic cysts are relatively common in VHL, and involvement can range from a single cyst to multiple cysts, virtually replacing the pancreas. Cysts are reported in up to 30% of patients in imaging studies [49], but can be found in up to 72% in patients with VHL at autopsy. Peripheral calcifications may also be present. These cysts may be the first indication of disease during routine screening and may precede any other manifestation of VHL by several years.

### Beckwith–Wiedemann Syndrome

The cardinal features of Beckwith–Wiedemann syndrome (BWS; OMIM 130650) are exomphalos, macroglossia, and gigantism in the neonate. Hypertrophy of the pancreas is an imaging feature and severe hypoglycemia of affected neonates caused by transient hyperinsulinism is the most threatening early clinical complication of BWS. No other clinical symptoms related to the pancreas are common features of BWS. During childhood, BWS patients are at increased risk for developing specific tumors, including adrenal carcinoma, nephroblastoma, hepatoblastoma, and rhabdomyosarcoma. Pancreatoblastoma has been described in a few instances and may also be congenital [113]. BWS is genetically heterogeneous. Epigenetic and genomic alterations of the imprinted region on chromosome 11p15.5 are the underlying cause, including paternal methylation patterns on the maternal chromosome, paternal uniparental disomy for chromosome 11p15, and mutations of the *CDKN1C* gene [114]. Most cases are sporadic.

### Jeune Syndrome and Other Ciliopathies

Jeune syndrome (OMIM 208500) is an autosomal recessive ciliopathy characterized by skeletal abnormalities of the thorax and extremities and nephronophthisis. It may be associated with pancreatic cysts and pancreatic fibrosis, leading to exocrine pancreatic insufficiency [115,116]. The leading symptom is, however, nephronophthisis, a childhood kidney disease with progressive symmetrical destruction of the kidneys involving both the tubules and glomeruli. It characteristically results in anemia, polyuria, polydipsia, isosthenuria (decreased ability to concentrate the urine), and progressive and terminal renal failure, which in itself is a risk factor for disturbed exocrine pancreatic function. Mutations in more than 15 genes have been identified to be responsible for the phenotype of Jeune syndrome. *DYNC2H1* mutations account for about half of the cases [117].

Fibrotic and cystic changes of the pancreas are a common feature in renal–hepatic–pancreatic dysplasia (OMIM 208540), another entity within the clinically overlapping and genetically extremely heterogeneous spectrum of ciliopathies. The two known genes for renal–hepatic–pancreatic dysplasia, *NPHP3* and *NEK8*, are also involved in Meckel syndrome and nephronophthisis, respectively [118]. Similar involvement of the pancreas may also be found in other ciliopathies. A recent study using a mouse model suggested that chronic pancreatitis with perturbed acinar homeostasis and differentiation plays a role in the pathogenesis of ciliopathy-related pancreatic defects [119].

## Inherited Metabolic Disorders Affecting the Pancreas

Acute and chronic recurrent pancreatitis has been reported in patients with a variety of rare inborn errors of metabolism (Table 3.2). In most of these, pancreatitis is not very common, with the exception of some disorders of lipid metabolism as briefly discussed in the following [120].

Hyperlipidemia is one of the most common metabolic causes of recurrent pancreatitis [121]. A number of familial disorders, including lipoprotein lipase deficiency, apolipoprotein C-II deficiency, and common hypertriglyceridemia, can result in massive plasma accumulations of chylomicrons or triglycerides. Triglyceride levels above 2000 mg/dL (22.6 mmol/L) are generally considered to put patients at a significant risk for developing pancreatitis.

Hereditary lipoprotein lipase (LPL) deficiency (OMIM 246650) is an autosomal recessive condition with an estimated incidence of one in $10^6$. The first symptoms often

**Table 3.2** Inherited metabolic diseases with increased risk of pancreatitis

| Disorder | OMIM | Gene | Locus | Nature of pancreatitis |
|---|---|---|---|---|
| Lipoprotein lipase deficiency | 238600 | *LPL* | 8p22 | Recurrent |
| Apolipopoprotein C-II deficiency | 207750 | *APOC2* | 19q13.2 | Recurrent |
| Familial hypertriglyceridemia and chylomicronemia | 145750 | *APOA5*<br>*LIPI* | 11q23<br>22q11.2 | Recurrent |
| Glycogen storage disorders (glycogenosis type 1) | 232200 | *G6PC* | 17q21 | Acute |
| Branched-chain ketoaciduria (maple syrup urine disease) | 248600 | *BCKDHA*<br>*BCKDHB*<br>*DBT*<br>*DLD* | 19q13<br>6p22–p21<br>1p31<br>7q31–q32 | Acute |
| Isovaleric acidemia | 243500 | *IVD* | 15q14–q15 | Acute |
| Methylmalonic acidemia | 251100<br>251110<br>277400<br>251000 | *MMAA*<br>*MMAB*<br>*MMACHC*<br>*MUT* | 4q31<br>12q24<br>1p34.1<br>6p12 | Chronic? |
| Propionic acidemia | 606054 | *PCCA*<br>*PCCB* | 13q32<br>3q21–q22 | Acute |
| Homocystinuria | 236200 | *CBS* | 21q22.3 | Acute–chronic |
| 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency | 246450 | *HMGCL* | 1p36–p33 | Acute |
| Acute intermittent porphyria | 176000 | *HMBS* | 11q23.3 | Acute |
| Pyruvate kinase deficiency | 266200 | *PKLR* | 1q21 | Acute[a] |
| Cytochrome *c* oxidase deficiency | 220110 | Heterogeneous | Multiple | Chronic |
| MELAS/MERFF | 540000<br>545000 | Heterogeneous | mtDNA | Acute–chronic |
| Cystinuria | 220100 | *SLC3A1*<br>*SLC7A9* | 2p16.3<br>19q13.1 | ? |
| Lysinuric protein intolerance (and other cationic aminoacidurias) | 222700 | *SLC7A7* | 14q11.2 | ? |
| Ornithine transcarbamylase deficiency | 311250 | *OTC* | Xp21.1 | Acute |

[a] Related to gallstones.

arise in early childhood and the most common clinical presentation includes abdominal pain caused by recurrent attacks of pancreatitis, eruptive cutaneous xanthomatosis, and hepatosplenomegaly. Almost 30% of patients with LPL deficiency develop pancreatitis [120,122]. The pancreatitis associated with LPL deficiency is most often recurrent, sometimes severe and necrotizing, and only rarely leads to diabetes, pancreatic calcifications, or exocrine pancreatic deficiency. The diagnosis of LPL deficiency should be suspected in hyperlipidemic patients when chylomicrons are detectable in refrigerated fasting plasma and no significant very low-density lipoprotein (VLDL) elevation is found. The diagnosis of LPL deficiency can be made by measuring the enzyme activity in post-heparin plasma (heparin releases the enzyme into the bloodstream) with a commercially available enzyme-linked immunosorbent assay (ELISA). The treatment of pancreatitis in these patients is not different from that with other causes of the disease, but an aggressive lipid-lowering therapy by dietary restriction of fat intake is paramount to prevent recurrence. Medium-chain triglycerides can serve as a substitute because they are not incorporated into chylomicrons after absorption. Hereditary LPL deficiency has, as of 2012, become the first and only disorder for which a gene therapy has been approved in the European Union. The agent alipogene tiparvovec (Glybera) addresses the enzyme deficiency by introducing an LPL gain-of-function allele delivered by an adeno-associated virus-type vector via intramuscular injection. The effect (and the reason for approval by the regulatory authorities) is a lowering of the rate of pancreatitis episodes in affected patients [123].

Apolipoprotein C-II deficiency is caused by mutations in the *APOC2* gene, and is inherited as an autosomal recessive disorder with a worldwide distribution. The

defect results in an impaired clearance of chylomicrons from the blood. Apolipoprotein C-II deficiency is less common than LPL deficiency. As apolipoprotein C-II functions as an activator for LPL, its deficiency clinically resembles LPL deficiency, but it generally has a milder course and later onset of symptoms (between 13 and 60 years). However, pancreatitis represents a more frequent and sometimes severe complication of apolipoprotein C-II deficiency, and up to 60% of patients are affected by episodes of pancreatitis [124]. The diagnosis is made by measuring LPL activity in post-heparin plasma as already described or on gel electrophoresis of VLDL apolipoproteins. A distinction from LPL deficiency can be readily made because the addition of apolipoprotein C-II to the assay completely restores lipolytic activity but does not affect the plasma of patients with LPL deficiency. Also, for apolipoprotein C-II deficiency, treatment modalities based on gene therapy concepts are under investigation.

Several other disorders of lipid metabolism have been reported that can lead to either chylomicronemia or hypertriglyceridemia and are not associated with defects in the LPL system. The incidence of patients with lipid disorders that result in such elevated triglyceride levels is estimated to be between 10 and 20 per 100,000 and is therefore much higher than that of disorders caused by inborn errors of the LPL system. Often, the high triglyceride levels are not caused by the disorder alone, but are precipitated by additional factors such as diabetes mellitus, alcohol, β-adrenergic blockers, glucocorticoids, estrogens, diuretics, and other drug therapies. All of these factors can greatly increase the extent of hypertriglyceridemia and raise it above the threshold level for developing pancreatitis. The most common familial disorders associated with chylomicronemia are the type I and type V hyperlipoproteinemias (according to Levy and Fredrickson [125]). They comprise a diverse group of primary and secondary disorders with moderate to severe hypertriglyceridemia. Individuals with monogenic familial hypertriglyceridemia are rare and often have only mild hypertriglyceridemia, and the above-mentioned additional factors are often required before the risk of developing pancreatitis becomes significant. Pancreatitis associated with metabolic diseases is further discussed elsewhere in this book.

In addition to the hyperlipidemias, various disorders of branched-chain amino acid degradation, homocystinuria, hemolytic disorders, acute intermittent porphyria mitochondrial disorders, and several amino acid transporter defects may also be associated with pancreatitis (Table 3.2). The clinical, biochemical, and genetic characteristics of those inborn errors of metabolism differ from those of other pancreatic disorders and they need to be distinguished from other hereditary causes of pancreatic diseases.

### Hereditary Pancreatitis

Pancreatic changes associated with cationic trypsinogen mutations (hereditary pancreatitis; OMIM 167800) and *CFTR* and *SPINK1* mutations (idiopathic pancreatitis) are discussed in dedicated chapters of this book.

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## Section 2

## Physiology and Pathophysiology of Pancreatic Functions

# 4

# Physiology of Acinar Cell Secretion

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## Introduction

The acinar cell is the dominant cell type in the pancreas. In terms of percentage volume, the pancreas consists of 82% acinar cells, 4% duct cells, 4% blood vessels, 2% endocrine cells, and 8% extracellular matrix [1]. However, the acinar cell itself is not the functional unit in the exocrine pancreatic tissue because acinar cells are organized into acini consisting of up to several hundred acinar cells linked by numerous gap-junctional channels that allow both direct chemical and electrical intercellular communication [2,3]. There is an additional cell type that has not previously featured much in descriptions of acinar cell function, namely the pancreatic stellate cells (PSC). These very thin periacinar cells come very close to the acinar cells, but are nevertheless functionally isolated from the acinar cells [4–6]. The PSC play an important role under pathophysiologic conditions where they exert effects on the acinar cells [4–7], but it is unknown whether they have any physiologic role in the control of acinar cell secretion. The principal function of the acinar cells is to secrete a potent mixture of digestive enzymes in response to food intake. This secretory response is mediated by vagal nerve stimulation, releasing acetylcholine (ACh) from nerve endings close to the acinar cells, and the circulating hormone cholecystokinin (CCK). The digestive (pro)enzymes are packaged into secretory vesicles called zymogen granules (ZG) and the secretion process itself occurs by exocytosis, that is, fusion of the granule membrane with the apical (luminal) cell membrane and subsequent opening of a pathway (pore) allowing direct movement of the zymogens from the granule interior to the acinar lumen. In order to move the zymogens into the duct system and thereafter into the gut, there is also a need for fluid secretion. The acinar cells secrete a neutral $Cl^-$-rich fluid, produced in response to stimulation with ACh and CCK. Additionally the small ducts secrete a $HCO_3^-$-rich fluid when stimulated by the hormone secretin. The aim of this chapter is to explain the cellular mechanisms underlying the very acute and finely controlled normal physiologic regulation of acinar fluid and enzyme secretion.

## Composition of Pancreatic Acinar Juice

ACh or CCK activates acinar cells to secrete an isotonic NaCl-rich fluid (Fig. 4.1a) containing a multitude of enzymes and precursor enzymes. The protease precursors are trypsinogen, chymotrypsinogen, and procarboxypeptidases. These precursors are activated in the small intestine, initiated by conversion of trypsinogen to trypsin by the intestinal enzyme enteropeptidase. Trypsin then activates trypsinogen autocatalytically and also activates the other precursors. The acinar fluid also contains active α-amylase, lipases, and colipase as well as various other enzymes (e.g., collagenase, elastase, phospholipase A, and ribonuclease) [11]. The neutral NaCl-rich fluid containing these enzymes and enzyme precursors is delivered to the small ducts, where it is mixed with the $HCO_3^-$-rich fluid produced by the duct cells in response to stimulation with secretin (Fig. 4.1b,c).

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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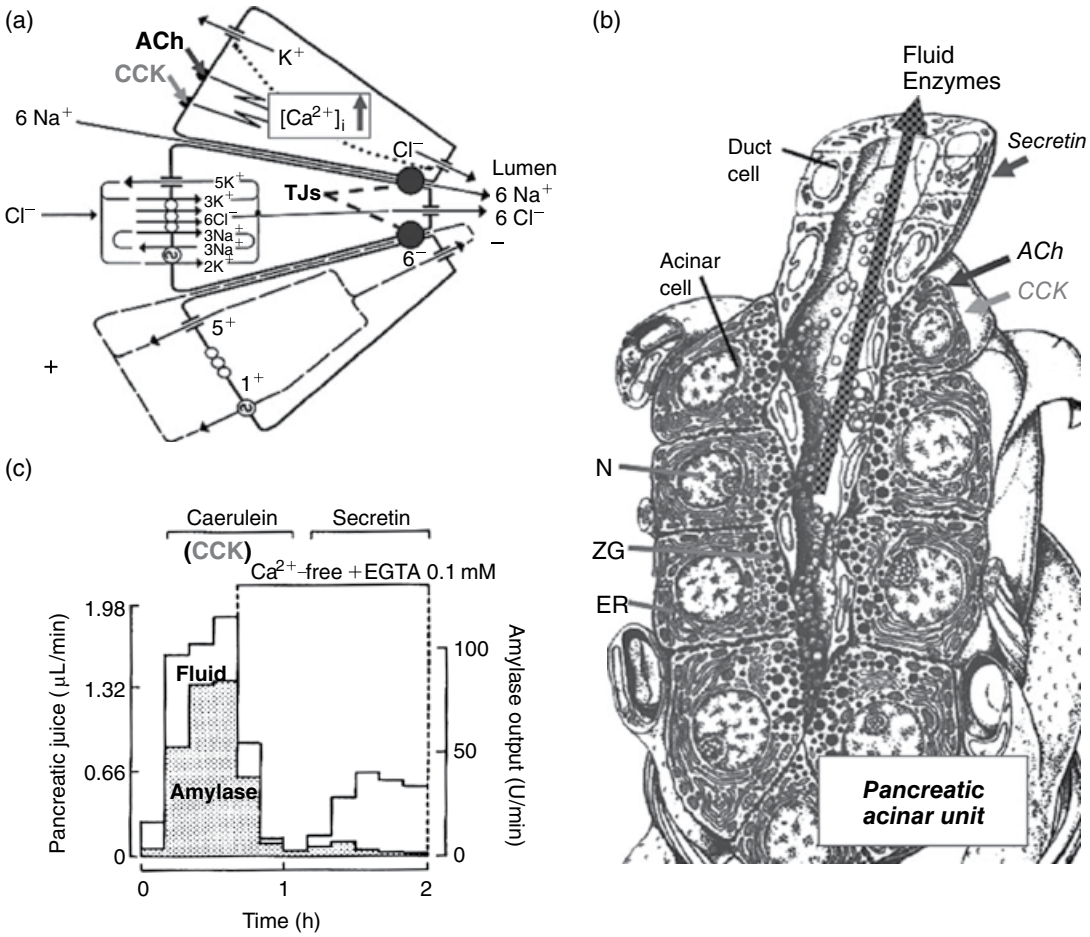


**Figure 4.1** Fluid and enzyme secretion from acinar cells. (a) Acinar transport model illustrating the individual ion transport events that work together to produce an isotonic NaCl-rich fluid. For graphical convenience, different aspects of the processes are shown in separate cells. In the top cell it is shown that ACh or CCK stimulation of their respective specific receptors on the basolateral membrane elicits a rise in the cytosolic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$), which in turn activates $Cl^+$ channels in the apical (luminal) membrane and $K^+$ channels in the basolateral membrane (for graphical convenience all events in the basolateral membrane are shown only in the basal membrane). The middle cell illustrates transcellular $Cl^-$ transport. The $Na^+/K^+/2Cl^-$ cotransporter, the $K^+$ channel, and the $Na^+/K^+$ pump are shown in the basal membrane and it is indicated that the net transport event is uptake of $Cl^-$, whereas at the apical membrane $Cl^-$ exit into the lumen simply occurs through a $Cl^-$ channel. The lower cell illustrates the overall electrical circuit and explains the transepithelial electrical potential difference. The $Na^+/K^+/2Cl^-$ cotransporter is electrically neutral, so the only electrogenic event at the basolateral membrane is the transport of cations ($K^+$ and $Na^+$) through the $K^+$ channel and $Na^+/K^+$ pump ($3Na^+$ pumped out for $2K^+$ taken in). This net outward (cation exit) current has to be matched by an inward (anion exit) current across the apical membrane and the completion of the circuit depends on the high conductance of the so-called tight junctions (TJs). *Source:* Adapted from [8] with permission. (b) Model drawing of acinar unit with small duct segment attached. The polarity of acinar cells is shown with the nucleus (N) surrounded by endoplasmic reticulum (ER) in the basal part and zymogen granules (ZG) in the apical part. *Source:* Adapted from [9] with permission. (c) Fluid and amylase secretion from isolated perfused rat pancreas stimulated by the frog skin peptide cerulein (analog of CCK) and secretin. *Source:* Adapted from [10] with permission.

## Acinar Fluid and Enzyme Secretion

There is separate control of acinar and duct secretion, as shown in experiments on the isolated perfused pancreas (Fig. 4.1c). Sustained fluid and enzyme secretion, due to stimulation with either ACh or CCK, is acutely dependent on the presence of $Ca^{2+}$ in the extracellular solution, whereas the $HCO_3^-$-rich fluid secretion evoked by secretin in the ducts occurs normally in the complete absence of external $Ca^{2+}$ (Fig. 4.1c).

It is well established that exocytosis in general is activated by a rise in cytosolic $Ca^{2+}$ concentration ($[Ca^{2+}]_i$) [11]. In nerve and endocrine cells, exocytosis is normally activated by $Ca^{2+}$ entering the cell interior via special voltage-activated $Ca^{2+}$ channels in the plasma membrane, which open on membrane depolarization caused by action

potentials [11]. However, the pancreatic acinar cell is electrically nonexcitable and cannot fire action potentials [12]. $Ca^{2+}$ needed for stimulus–secretion coupling is therefore delivered to the cytosol from intracellular stores [12]. It was established many years ago that the initial secretory response to stimulation with either ACh or CCK is independent of extracellular $Ca^{2+}$ [13], whereas sustained secretion is acutely dependent on external $Ca^{2+}$ (Fig. 4.1c). This is explained by the limited capacity of the intracellular $Ca^{2+}$ stores and the fact that release of $Ca^{2+}$ from stores into the cytosol inevitably activates $Ca^{2+}$ pumps in the plasma membrane extruding $Ca^{2+}$, so that after a shorter or longer period of stimulation (depending on the intensity of stimulation) the contents of the intracellular $Ca^{2+}$ stores have been exported to the extracellular solution [14]. A reduction of $[Ca^{2+}]$ in the intracellular stores activates a process known as store-operated $Ca^{2+}$ entry. A signal is transmitted from the stores to the plasma membrane activating special $Ca^{2+}$ channels (store-operated channels) that allow $Ca^{2+}$ entry [15]. It is this $Ca^{2+}$ entry process that sustains the secretory response during prolonged stimulation, after the stores have been emptied.

## $Ca^{2+}$ Signaling

It is well established that stimulation of acinar cells with either ACh or CCK elicits a rise in $[Ca^{2+}]_i$ (Fig. 4.2). At low, physiologically relevant, concentrations of neurotransmitter or hormone, the typical $Ca^{2+}$ signal pattern consists of repetitive $[Ca^{2+}]_i$ spikes confined to the apical (granular) pole. Increasing the stimulating agonist concentration causes $Ca^{2+}$ signal globalization, a process whereby a local $Ca^{2+}$ signal initiated in the apical pole spreads as a wave from the apex to the base of the cell (Fig. 4.2).

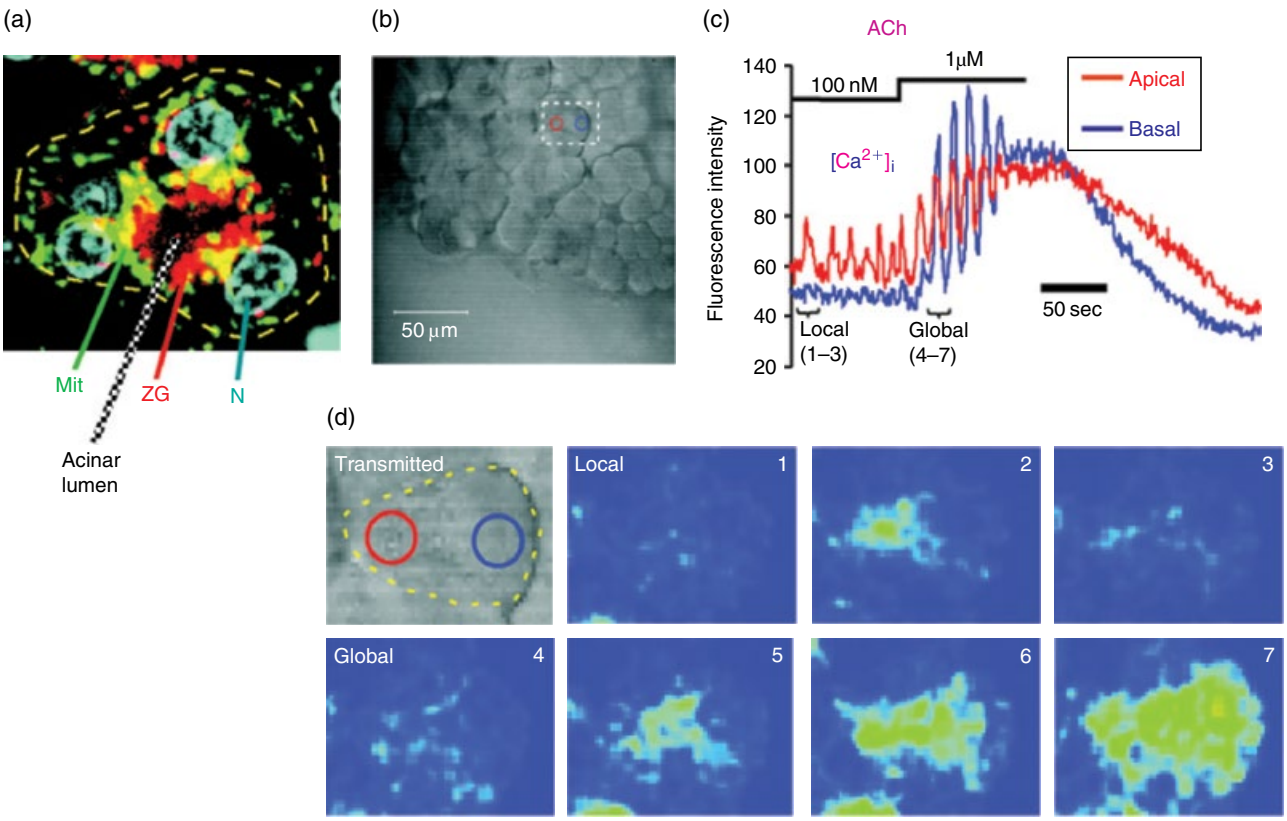


**Figure 4.2** $Ca^{2+}$ signaling and organelle distribution in the intact mouse pancreas. (a) Merged confocal images showing distribution of specific fluorescent markers for zymogen granules (ZG – red), nuclei (N – blue), and mitochondria (Mit – green). The optical slice goes through three cells (nuclei). The ZG are seen distributed around the lumen and are surrounded by mitochondria. Mitochondria are also located around the nuclei and close to the plasma membrane. (b) Confocal image of larger part of the pancreas showing many acinar units. One cell is highlighted by white dashed lines and in this cell apical (red) and basal (blue) regions of interest are signposted. The traces shown in (c) are from these two regions. (c) ACh-elicited cytosolic $Ca^{2+}$ signals. At the low ACh concentration of 100 nM, repetitive $Ca^{2+}$ spikes are seen exclusively in the apical pole. When the ACh concentration is increased to 1 µM, there is a rise in $[Ca^{2+}]_i$ in both the apical and basal regions. (d) Fluorescent images showing (upper row) a single local apical $Ca^{2+}$ spike (numbers refer to time points in (c)) and (lower row) the initial $Ca^{2+}$ wave generation following the increase in ACh concentration (numbers again refer to time points signposted in C). *Source:* Adapted from Ashby et al. 2003 [16].

## Organelles Important for $Ca^{2+}$ Homeostasis

The earliest work on $Ca^{2+}$ transport in exocrine glands indicated that ACh evokes $Ca^{2+}$ signals in acinar cells by causing release of $Ca^{2+}$ from the endoplasmic reticulum (ER) [17]. In 1972, the link between ACh occupation of muscarinic receptors on the cell surface and the outflow of $Ca^{2+}$ from the ER was obscure. About 10 years later, Irene Schulz and coworkers discovered that the intracellular water-soluble messenger inositol 1,4,5-trisphosphate ($IP_3$), generated inside the cell by receptor-activated phospholipase C action on a membrane phospholipid, phosphatidylinositol 4,5-bisphosphate ($PIP_2$), releases $Ca^{2+}$ from the ER in permeabilized pancreatic acinar cells [18]. All subsequent work on many different cell types confirmed the generality of the concept that hormone- or neurotransmitter-elicited intracellular $Ca^{2+}$ release is mediated principally via $IP_3$-evoked $Ca^{2+}$ release from the ER [19]. Although the original discovery of $IP_3$-evoked $Ca^{2+}$ release was made on pancreatic acinar cells [18], there are difficulties in applying this concept to these particular cells. The problem is that the physiologically relevant $Ca^{2+}$ signals occur specifically in the apical granular pole (see Fig. 4.2), which contains mostly ZG and little ER. This difficulty was finally overcome by the results of the so-called $Ca^{2+}$ tunnel experiments, in which it could be shown that $Ca^{2+}$ taken up at the base of the cell into the ER could diffuse easily in the ER lumen and reach the apex via thin ER extensions penetrating deeply into the granular area between the ZGs (see Fig. 4.3). Upon stimulation, $Ca^{2+}$ is released primarily from the ER elements in the apical pole due to the high concentration of ER $Ca^{2+}$ release channels specifically in this part of the cell (Fig. 4.3) [20,22].

It was initially a surprise that cytosolic $Ca^{2+}$ signals initiated in the apical pole could remain local in such a relatively small cell (~20 µm diameter). This could not be easily understood before it was discovered that the mitochondria in the acinar cell are distributed in a very specific manner [23]. The mitochondria are primarily localized in a belt surrounding the ZG, separating the

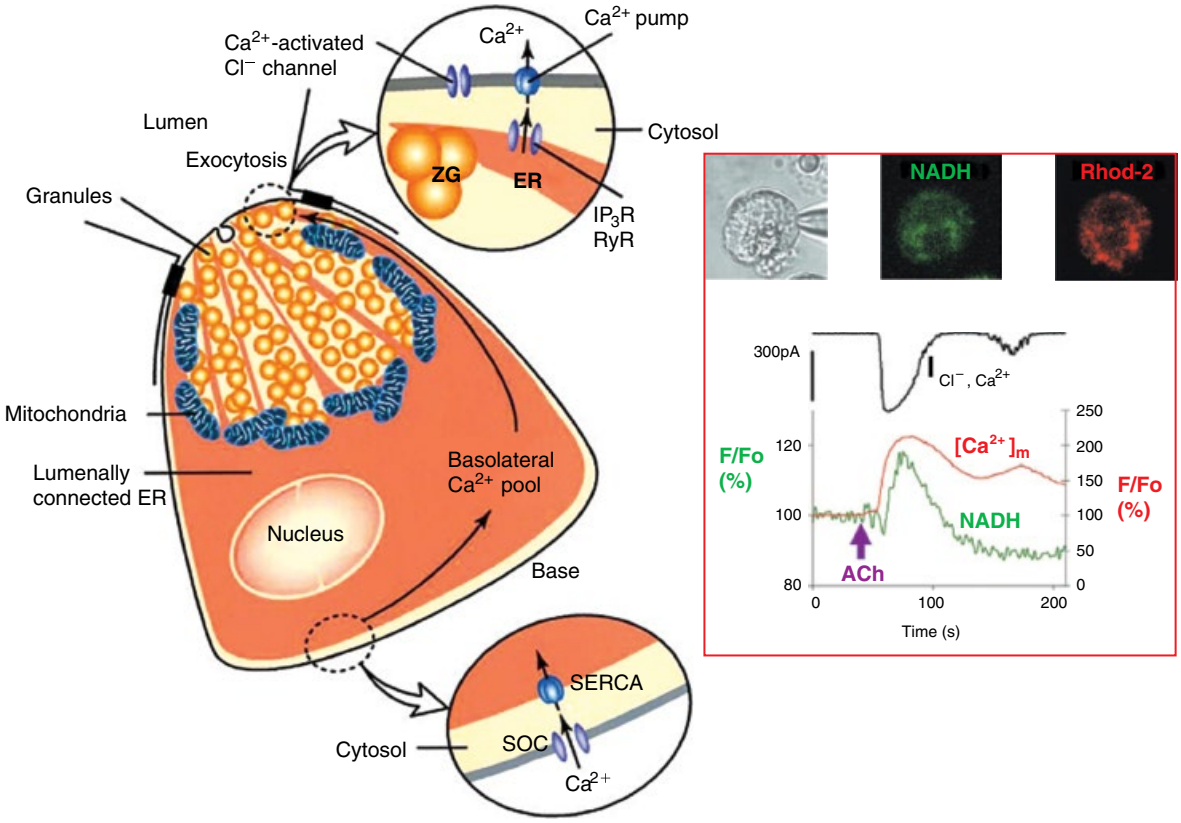


**Figure 4.3** Organelle distribution and $Ca^{2+}$ transport events in acinar cell. The main part of the figure shows a model cell with the distribution of organelles and $Ca^{2+}$ transport pathways signposted. Insert (in red frame) shows triple measurements of $Ca^{2+}$-activated $Cl^-$ current ($I_{Cl-,Ca^{2+}}$), mitochondrial $Ca^{2+}$ concentration ($[Ca^{2+}]_m$—measured by Rhod-2 fluorescence—and concentration of NADH (autofluorescence). It is seen that ACh evokes a rapid rise in $I_{Cl-,Ca^{2+}}$, which is followed immediately by a rise in $[Ca^{2+}]_m$ and after a small delay by an increase in the NADH concentration signifying activation of mitochondrial metabolism and therefore ATP production. *Source:* Adapted from Petersen et al. 2001 [20] and Voronina et al. 2002 [21].

apical granular pole from the rest of the cell (see Figs 4.2 and 4.3). Due to their ability to take up $Ca^{2+}$, the mitochondria function as a $Ca^{2+}$ diffusion barrier, effectively acting as a firewall preventing the spread of cytosolic $Ca^{2+}$ signals from the apical pole into the basal part of the cell containing the nucleus (Fig. 4.3). The nucleus is well protected against $Ca^{2+}$ signal invasion from the apical pole, since there is an additional mitochondrial belt surrounding the nucleus (Fig. 4.2). Finally, there is a concentration of mitochondria just beneath the plasma membrane (Fig. 4.2). The general concept that has emerged from studies of $Ca^{2+}$ transport in the cytosol, ER, and mitochondria is that $Ca^{2+}$ moves easily in the ER lumen, but with much more difficulty in the cytosol, due to the barriers created by the mitochondria [24].

The fact that the physiologically most important $Ca^{2+}$ signals occur in the apical granular area has also prompted interest in the possibility that $Ca^{2+}$ could be released from ZG and possibly other acid pools in the apical pole. In studies on isolated ZG, it was shown that both $IP_3$ and another $Ca^{2+}$-releasing messenger, cyclic ADP-ribose (cADPR, derived from NAD) can liberate $Ca^{2+}$ stored in this organelle (see Fig. 4.4). This has been

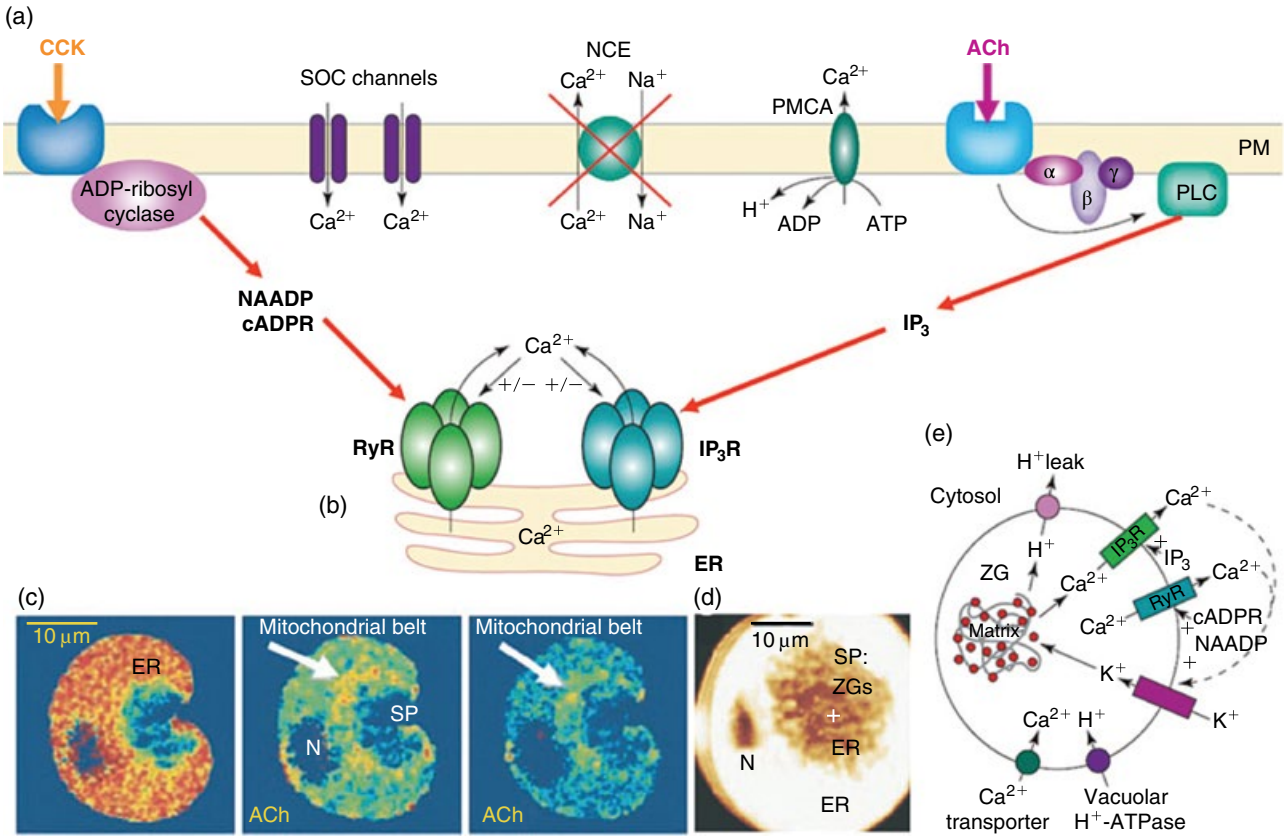


**Figure 4.4** $Ca^{2+}$ transport and signaling events in acinar cell. (a) Events at the plasma membrane. Two receptor pathways are shown. CCK interaction with CCK1 receptors results in activation—via an unknown mechanism—of the cytosolic enzyme ADP-ribosyl cyclase, which generates two separate messengers, namely cADPR and NAADP. ACh binding to muscarinic M3 receptors activates, via interaction with a classical trimeric G-protein, phospholipase C (PLC) generating the messenger $IP_3$ (as well as diacyl glycerol—not shown in diagram). The absence of the $Na^+/Ca^{2+}$ exchanger is highlighted. $Ca^{2+}$ extrusion by the plasma membrane $Ca^{2+}$-activated ATPase is shown. $Ca^{2+}$ entry occurs through store-operated $Ca^{2+}$ channels (SOC). (b) Schematic illustration of $Ca^{2+}$ release from the ER through the $IP_3R$ elicited by $IP_3$ and through the RyR by NAADP or cADPR. Positive and negative $Ca^{2+}$ interactions between the two $Ca^{2+}$ release channels are also shown. (c) Confocal fluorescent images illustrating changes in organellar $[Ca^{2+}]$ following ACh stimulation. The left image shows the high resting $[Ca^{2+}]$ in the ER (mostly in the basal (left) part of the cell). After maximal ACh stimulation, $[Ca^{2+}]$ in the ER has been reduced markedly (shift from warm (red) to cold (green) color) and the perigranular mitochondrial belt is now clearly seen (yellow). This indicates that $Ca^{2+}$ lost from the ER has been taken up in part by the mitochondria. The third image shows the almost complete loss of $Ca^{2+}$ from the ER and the still elevated $[Ca^{2+}]$ in the perigranular mitochondria. (d) Confocal image showing the distribution of fluorescent thapsigargin (white), a very specific marker for the ER $Ca^{2+}$ pump. The optical slice goes through two cells (but only through one nucleus – N). It is seen that by far the highest ER $Ca^{2+}$ pump density is in the basolateral parts of the cell, but it is important to note that there are some light elements in the darker granular (secretory pole – SP) areas signifying ER elements with $Ca^{2+}$ pumps also in this part of the cell. (e) Schematic drawing of $Ca^{2+}$, $H^+$, and $K^+$ transports across the ZG membrane. *Source:* Adapted from Petersen and Sutton 2006 [25].

confirmed in a study of permeabilized pancreatic acinar cells, in which it was shown that $IP_3$, cADPR, and yet another $Ca^{2+}$-releasing messenger, nicotinic acid adenine dinucleotide phosphate (NAADP, derived from NADP), can all release $Ca^{2+}$ from the ER as well as from acid pools in the apical granular area, which is dominated by the ZG [26]. The $Ca^{2+}$ release from the acid pools in the apical pole has been dissected further in a recent study on internally perfused acinar cells, in which it was shown that $Ca^{2+}$ release occurs not only from ZG but also from lysosomes and endosomes [27]. Although all messengers can release $Ca^{2+}$ from all the pools, the balance of the contributions from these various sources depends critically on the specific messenger employed. This allows generation of specific $Ca^{2+}$ signal patterns by differential coupling between various stores and messengers [27]. This may explain the somewhat different $Ca^{2+}$ signal patterns that can be generated by CCK and ACh [28].

## Mechanisms of $Ca^{2+}$ Signal Generation

Fig. 4.4 illustrates some of the most important steps. There are two major signal transduction pathways, one initiated by hormonal (CCK) stimulation and the other by nervous (ACh) stimulation. CCK acts on high-affinity CCK1 receptors in the basolateral plasma membrane [29,30], whereas ACh acts on muscarinic M3 receptors which are also localized predominantly in the basolateral membrane [16]. With state-of-the-art imaging technology, it is now possible to visualize some of the most important signal transduction steps.

Fig. 4.5 demonstrates the ACh-elicited breakdown of $PIP_2$ in the basolateral membrane and the appearance of the water-soluble $Ca^{2+}$-releasing messenger $IP_3$ in the cytosol. The enzyme responsible for $PIP_2$ breakdown, phospholipase C, can in some cases be $Ca^{2+}$ activated. However, the experimental result shown in Fig. 4.5

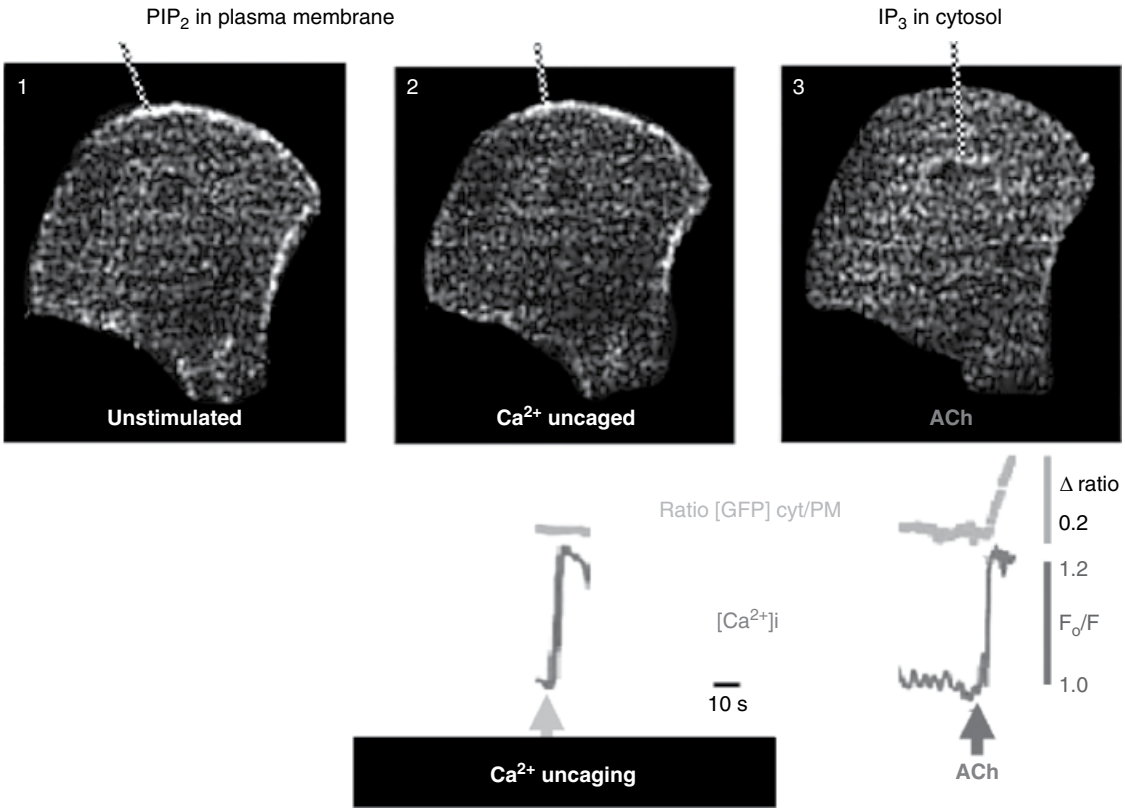


**Figure 4.5** Acetylcholine (ACh)-induced breakdown of phosphatidylinositol 4,5-bisphosphate ($PIP_2$) in the plasma membrane (PM) and generation of inositol 1,4,5-trisphosphate ($IP_3$) in the cytosol (cyt). The green fluorescent protein (GFP)-linked PH domain of $PLC_\delta 1$ binds with high affinity to both $PIP_2$ and $IP_3$. (1) Before stimulation, the main GFP fluorescence is seen in the basolateral membrane, indicating the presence of $PIP_2$ at this site. (2) Generation of a substantial rise in $[Ca^{2+}]_i$ by photolytic release of $Ca^{2+}$ into the cytosol from caged $Ca^{2+}$ does not cause any reduction in the $PIP_2$ concentration in the membrane. (3) ACh (1 μmol/L) causes a rise in $[Ca^{2+}]_i$ of similar magnitude to that seen after $Ca^{2+}$ uncaging, but in this case there is loss of GFP fluorescence from the basolateral membrane, signifying loss of $PIP_2$, and appearance of fluorescence in the cytosol indicating appearance of $IP_3$. *Source:* Adapted from [31] with permission.

demonstrates that, at least in the pancreatic acinar cell, the disappearance of $PIP_2$ from the plasma membrane and the appearance of $IP_3$ in the cytosol are not secondary to $Ca^{2+}$ signal generation, since a directly generated $Ca^{2+}$ signal (via uncaging of $Ca^{2+}$ in the cytosol) does not induce these effects, whereas ACh does.

Direct infusion of $IP_3$ into isolated cells elicits repetitive cytosolic $Ca^{2+}$ spikes confined to the apical granular pole (see Fig. 4.6), in this way mimicking the effect of externally applied ACh (see Fig. 4.2). The importance of functional $IP_3$ receptors ($IP_3R$) for ACh-elicited $Ca^{2+}$ signal generation and secretion in pancreatic acinar cells has been demonstrated very clearly by knockout experiments, in which it was shown that knockout of either type 2 or type 3 $IP_3R$ had very little effect, whereas double knockout of both these receptors abolished ACh-elicited $Ca^{2+}$ signal generation as well as secretion [34]. This directly confirms earlier data in which it was shown that intracellular infusion of the $IP_3R$ antagonist heparin abolished both $IP_3$- and ACh-elicited $Ca^{2+}$ spiking [35].

There is no doubt about the crucial importance of $IP_3R$ in controlling $Ca^{2+}$ signals and thereby secretion, but $IP_3$ is not the only important internal messenger. More than 10 years ago, it was already known that cADPR can evoke $Ca^{2+}$ signals that are very similar to those elicited by $IP_3$. Pharmacologic data indicate that cADPR primarily activates the ryanodine receptor (RyR), a different class of intracellular $Ca^{2+}$ channel from the $IP_3R$ (see Fig. 4.4) [36]. The physiologic importance of this finding only became clear several years later, when it was shown that $Ca^{2+}$ signals generated by physiologic CCK concentrations (low picomolar) could be blocked by a cADPR antagonist, whereas this was not the case for ACh-elicited $Ca^{2+}$ signaling [37].

More recently, it has become clear that the novel $Ca^{2+}$-releasing messenger NAADP has a very specific role in $Ca^{2+}$ signal generation. NAADP is a real intracellular messenger for CCK-induced activation of pancreatic acinar cells. Work from Galione's group in Oxford shows that physiologic CCK concentrations (1–10 pmol/L)

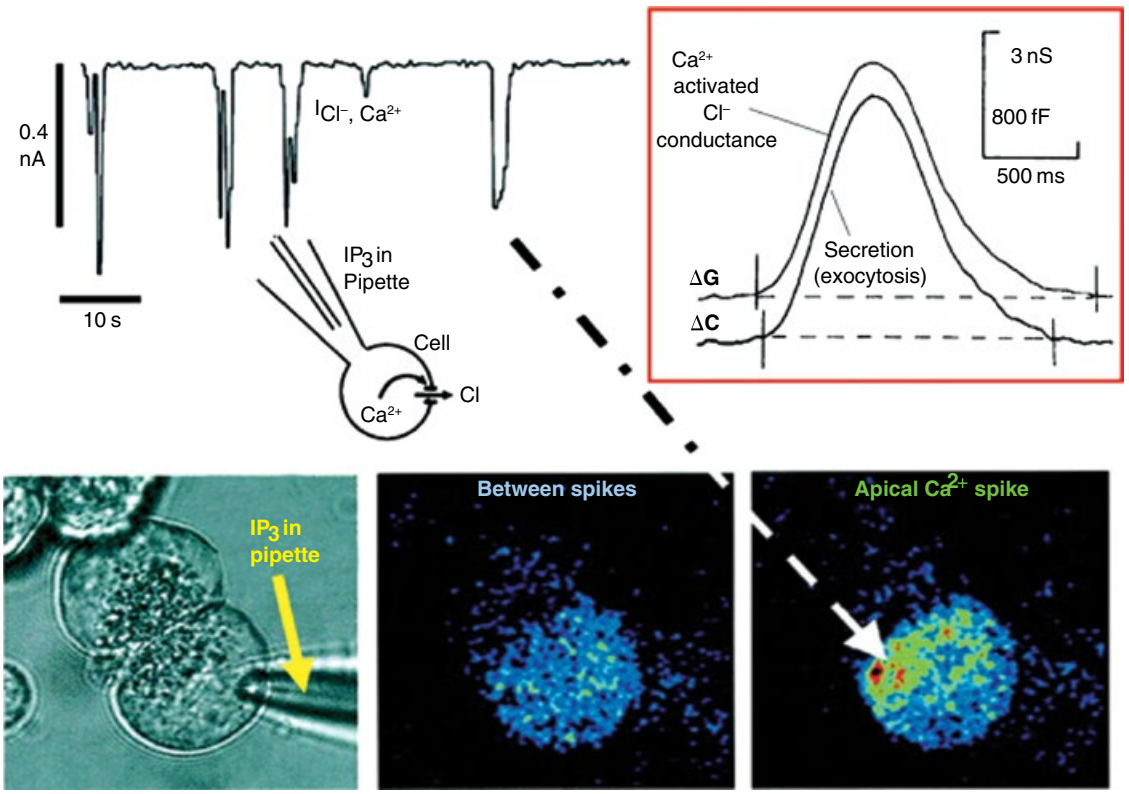


**Figure 4.6** $IP_3$-elicited local apical $Ca^{2+}$ spikes and exocytotic secretion. The main part of the figure shows the result from a patch clamp experiment with internal acinar cell perfusion. The trace shows the repetitive spikes of $Ca^{2+}$-dependent $Cl^-$ current elicited by intracellular $IP_3$ infusion (10 µM). The images below illustrate the configuration and the distribution of the elevated $[Ca^{2+}]_i$ during the height of a spike. It is clearly seen that the $Ca^{2+}$ signal occurs in the apical granular pole. *Source:* Adapted from Cancela et al. 2002 [32]. The insert (in red frame) shows correlation between a single apical $Ca^{2+}$ spike (during $IP_3$ infusion), recorded here as an increase in $Cl^-$ conductance (ΔG), and the exocytotic response recorded as an increase in membrane capacitance (ΔC). It is seen that the increase in $Cl^-$ conductance (a sensitive indicator of $[Ca^{2+}]_i$) slightly precedes the rise in capacitance and that the secretory response is completed just before $[Ca^{2+}]_i$ returns to the inter-spike level. *Source:* Adapted from Maruyama and Petersen 1994 [33].

evoke clear and dose-dependent increases in the cellular NAADP concentration. This effect is specific for CCK, since ACh has no effect on the NAADP level [38].

Intracellular infusion of NAADP, even at concentrations much lower (nanomolar) than those needed to obtain effects of $IP_3$ or cADPR, elicits repetitive cytosolic $Ca^{2+}$ spikes in the apical pole that look very similar to those generated by $IP_3$ and cADPR [32]. The NAADP receptor has the interesting property that it can be inactivated by relatively high (micromolar) intracellular NAADP concentrations. Using such selective inhibition of the NAADP receptor, it has been shown that $Ca^{2+}$ spiking evoked by physiologic CCK concentrations (<10 pmol/L) is blocked by a high intracellular NAADP concentration. This blocking effect is specific for the CCK response, since ACh-elicited $Ca^{2+}$ spiking is unaffected [39]. Studies on isolated nuclei (basically a pure ER preparation) have shown that the primary $Ca^{2+}$-releasing effect of both cADPR and NAADP is mediated by RyR, whereas $IP_3$ primarily activates $IP_3R$ [40].

$Ca^{2+}$ signaling events in intact acinar cells are complex, since it has been demonstrated that repetitive $Ca^{2+}$ spiking requires cooperation between functionally active $IP_3$ and RyR [24]. These conclusions are summarized in Fig. 4.4, highlighting $IP_3$-mediated $Ca^{2+}$ release from $IP_3R$ in the ER and cADPR- and NAADP-elicited $Ca^{2+}$ release from RyR. The important $Ca^{2+}$-mediated positive and negative interactions between $IP_3R$ and RyR are also shown (Fig. 4.4). These positive and negative interactions are functionally important. For example, a $Ca^{2+}$ signal initiated by an increase in the intracellular $IP_3$ concentration will subsequently activate RyR, inducing further $Ca^{2+}$ release. This positive feed-forward effect explains the rising phase of the cytosolic $Ca^{2+}$ spike. However, at a higher level of $[Ca^{2+}]_i$, a further $[Ca^{2+}]_i$ rise inhibits opening of both $IP_3R$ and RyR. This explains the falling phase of the spike [41]. Fig. 4.4 also shows that very similar processes occur in the ZG. They also contain both $IP_3R$ and RyR. Furthermore, there is now also evidence in pancreatic acinar cells (not illustrated in Fig. 4.4) demonstrating $Ca^{2+}$ release from other acid stores, such as lysosomes and endosomes [27]. It has recently become clear that there is another class of channel involved in intracellular $Ca^{2+}$ release, namely the so-called two-pore channel (TPC). In the pancreatic acinar cells, these channels are important specifically for the $Ca^{2+}$ release evoked by CCK, which is mediated by NAADP. The sequence of events with regard to CCK-elicited $Ca^{2+}$ signal generation is likely to be an initial release of a very small (trigger) amount of $Ca^{2+}$ from endosomes/lysosomes, which is then amplified by a much more substantial liberation of $Ca^{2+}$ from the ER and the zymogen granules occurring via RyR [42].

## $Ca^{2+}$ Entry and Exit

Although the primary event responsible for activation of secretion by ACh or CCK is intracellular $Ca^{2+}$ release, it is also very important for both physiology and pathology to consider the overall cellular $Ca^{2+}$ homeostasis, that is, $Ca^{2+}$ entry and exit. All cells have to be protected against cellular $Ca^{2+}$ overload, since it is well established that this causes cell death [43]. The plasma membrane must therefore be relatively impermeable to $Ca^{2+}$ and there must be mechanisms for cellular $Ca^{2+}$ extrusion. As shown in Fig. 4.4, $Ca^{2+}$ entry and exit across the plasma membrane of pancreatic acinar cells is controlled by specific transport mechanisms. Unlike many electrically excitable cells (e.g., cardiac cells), the acinar cells do not possess functional $Na^+/Ca^{2+}$ exchangers, so that the only mechanism for extruding $Ca^{2+}$ across the plasma membrane is via the plasma membrane $Ca^{2+}$-activated ATPase (PMCA) (Fig. 4.4). This pump is activated by increases in $[Ca^{2+}]_i$ above the basal level of 0.1 µmol/L, but has limited capacity. Interestingly, this pump is not uniformly distributed over the plasma membrane, but is specifically concentrated in the apical plasma membrane and therefore extrudes $Ca^{2+}$ principally into the acinar lumen (see Fig. 4.7). The concentration of the pump in the apical membrane is functionally important, since the principal intracellular $Ca^{2+}$ release sites are located in the apical pole (Figs 4.2 and 4.6), but carries the risk that $Ca^{2+}$ overload, due to inappropriate $Ca^{2+}$ entry across the basal membrane in pathologic conditions, cannot be dealt with adequately [25].

Physiologic stimulation of acinar cells does not primarily increase the permeability of the plasma membrane for $Ca^{2+}$, but after depletion of the ER $Ca^{2+}$ store there is specific opening of the so-called store-operated $Ca^{2+}$ channels in the basolateral membrane. This can most easily be visualized by measuring the uptake of $Ca^{2+}$ entering the base of the cell into the peripheral mitochondria situated immediately beneath the plasma membrane, as shown in Fig. 4.7. In these types of experiments, the ER $Ca^{2+}$ store is depleted by poisoning the $Ca^{2+}$ pump in the ER very specifically with thapsigargin in the absence of external $Ca^{2+}$. Thereafter, $Ca^{2+}$ is readmitted to the external solution and an increase in the $Ca^{2+}$ concentration of those mitochondria situated very close to the plasma membrane can be visualized directly (Fig. 4.7). The nature of the store-operated $Ca^{2+}$ channels in the pancreatic acinar cells has been clarified by patch clamp studies, in which it has been possible to record directly the tiny $Ca^{2+}$ currents flowing across the baso-lateral membrane upon depletion of the ER $Ca^{2+}$ store. The biophysical properties of this current shows that the

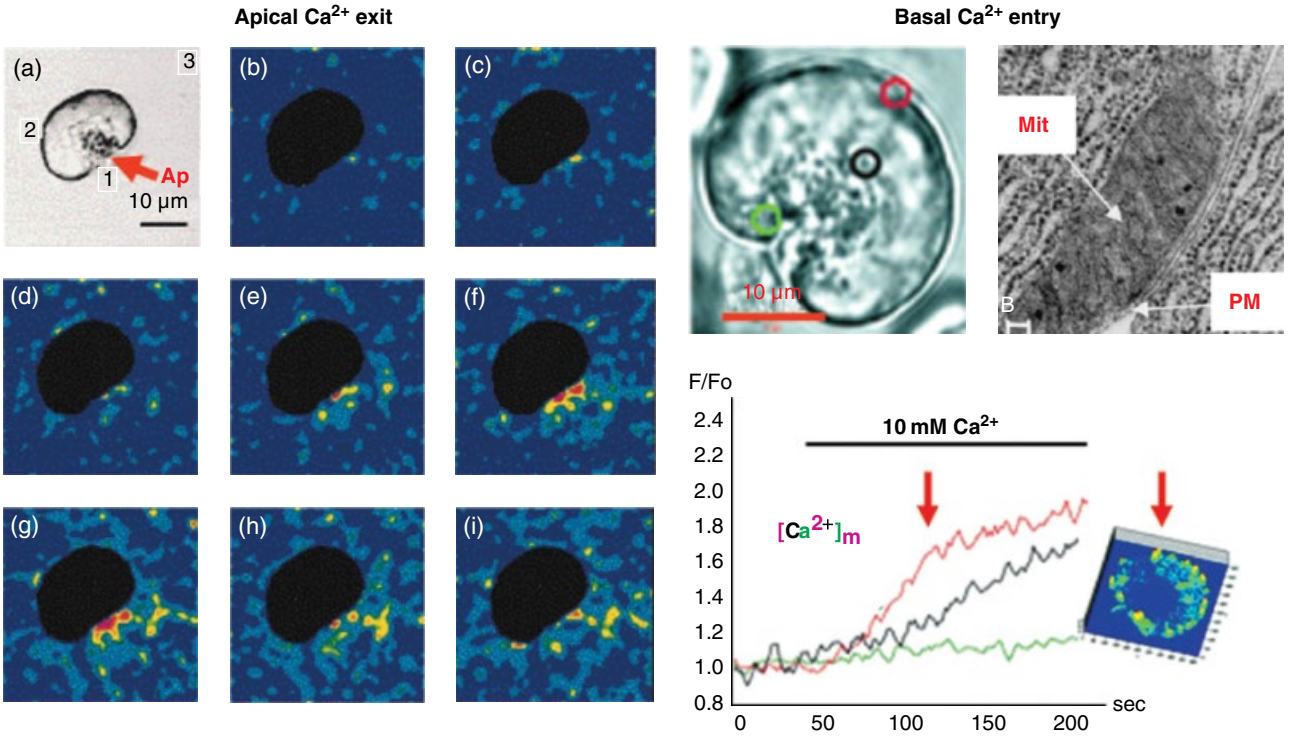


**Figure 4.7** Overall $Ca^{2+}$ homeostasis: $Ca^{2+}$ entry and exit. The left part illustrates an experiment in which $[Ca^{2+}]$ is measured outside an isolated acinar cell by using a $Ca^{2+}$-sensitive fluorescent indicator linked to high molecular weight dextran, thereby limiting the indicator mobility. The morphology of the cell, with clear identification of the granular apical (Ap) pole is shown in (a). (b) to (i) are fluorescent images (taken at 3-s intervals) showing the distribution of the extracellular $[Ca^{2+}]$ rise immediately following stimulation with ACh (10 µM). It is clear that the $Ca^{2+}$ extrusion from the cell occurs predominantly across the apical membrane. The right part of the figure illustrates the rise in $[Ca^{2+}]$ of mitochondria close to the basal plasma membrane during store-operated $Ca^{2+}$ entry. Mitochondrial $[Ca^{2+}]$ ($[Ca^{2+}]_m$) was measured with a fluorescent probe and traces from three regions of interest (red, black, and green) are shown. The cell was initially poisoned with thapsigargin in the absence of external $Ca^{2+}$ to deplete the ER of $Ca^{2+}$. During the time period indicated by the bar labelled 10 mM $Ca^{2+}$, $Ca^{2+}$ was readmitted to the external solution and it is seen that there was a marked rise in $[Ca^{2+}]_m$ particularly in the red region of interest, very close to the basal plasma membrane. The image marked with a red arrow shows the distribution of the elevated $[Ca^{2+}]$ at the time indicated by a similar red arrow above the fluorescence traces. Clearly the elevation of $[Ca^{2+}]_m$ has essentially occurred in a region very close to the plasma membrane. The EM picture shows a mitochondrion (Mit) situated very close to the plasma membrane (PM). *Source:* Adapted from Belan et al. 1996 [44] and Park et al. 2001 [45].

channels belong to the very $Ca^{2+}$-selective CRAC ($Ca^{2+}$ release activated $Ca^{2+}$) channel type, which is also present in various immune cells [46]. These channels, including those in the acinar cells, can be blocked by very specific CRAC channel inhibitors [46,47].

During sustained stimulation with either ACh or CCK, one can usually observe a plateau of elevated $[Ca^{2+}]_i$, which represents a delicate balance of $Ca^{2+}$ entry through store-operated $Ca^{2+}$ channels in the basal membrane and $Ca^{2+}$ exit mainly through $Ca^{2+}$ pumps located in the apical plasma membrane. $Ca^{2+}$ extrusion is energy-dependent. Therefore, if intracellular ATP levels fall during pathologic conditions, for example when cells are exposed to nonoxidative alcohol metabolites [48], $Ca^{2+}$ extrusion stops and dangerous $Ca^{2+}$ overload occurs, resulting in necrosis [48,49].

## $Ca^{2+}$-Mediated Control of Enzyme Secretion

It has been known for many years that intracellular $Ca^{2+}$ is the main acute regulator of exocytosis [50]. In experiments on the isolated perfused pancreas, it has been demonstrated that during sustained stimulation with high concentrations of ACh or CCK, both fluid and enzyme secretion are acutely dependent on the presence of external $Ca^{2+}$ (see Fig. 4.1). During this phase of the secretory response, the ER will have been partly depleted of $Ca^{2+}$ and $Ca^{2+}$ therefore has to be supplied by entry from the external solution through store-operated $Ca^{2+}$ channels as described earlier. However, during physiologic stimulation, with low concentrations of CCK or

ACh, there is not a sustained elevated $[Ca^{2+}]_i$ but rather a series of short-lasting $Ca^{2+}$ spikes localized specifically in the critical apical region (Figs 4.2 and 4.6). These spikes are essentially independent of external $Ca^{2+}$ and are due to repetitive release of small amounts of $Ca^{2+}$ from the ER [51] and acid stores in the apical pole [27].

Can the short-lasting local $Ca^{2+}$ spikes, evoked by low agonist concentrations or direct intracellular messenger infusion, control secretion? The most sensitive method for evaluating exocytotic secretion is measurement of membrane capacitance. When granules fuse with the plasma membrane, the surface area of the plasma membrane increases, but only transiently since the additional membrane inserted is subsequently removed by the process of endocytosis. As shown in Fig. 4.6 (inset), there is indeed a transient increase in the pancreatic acinar membrane capacitance during an individual short-lasting $Ca^{2+}$ spike, which can most easily be recorded by electrophysiologic methods. It appears that the $Ca^{2+}$ sensitivity of exocytosis is slightly lower than that of $Cl^-$ channel activation in the apical membrane, since the membrane conductance increase precedes the capacitance increase and the membrane capacitance returns to normal before the $Cl^-$ conductance has returned to the prespike resting level (Fig. 4.6). Results, such as those recorded in Fig. 4.6, demonstrate clearly the very fine control exerted by the local apical $[Ca^{2+}]_i$ on exocytotic secretion.

## $Ca^{2+}$-Mediated Control of Fluid Secretion

How is acinar fluid secretion regulated? The generally accepted model for isotonic fluid secretion by exocrine glands is illustrated in Fig. 4.1a. The principal step for activation of fluid secretion is $Ca^{2+}$-activated opening of $Cl^-$ channels, which are specifically located in the apical plasma membrane [52]. This will cause $Cl^-$ exit into the acinar lumen. The increased lumen negativity will attract cations and the principal extracellular cation, $Na^+$, will move through the very leaky junctions between the acinar cells, which are named (inappropriately!) tight junctions. These junctions sit very close to the apical membrane and separate the luminal fluid compartment from the basal and interstitial compartments, and also separate the very different properties of the apical and basolateral membranes (Fig. 4.1a). NaCl in the acinar lumen will osmotically attract water, which can pass through both the cell membranes (via aquaporins) and the tight junctions.

The principal activating step of acinar fluid secretion, namely the exit of $Cl^-$ from the cell interior to the lumen through $Ca^{2+}$-activated $Cl^-$ channels, only occurs if there is an electrochemical gradient favoring transport in this direction. The intracellular $Cl^-$ concentration must be held above thermodynamic equilibrium and a $Cl^-$-accumulating mechanism is therefore needed. As shown in Fig. 4.1a, an $Na^+/K^+/2Cl^-$ cotransporter is situated in the basolateral membrane (for graphical convenience shown in Fig. 4.1a only in the basal membrane). Energy for this process comes from the transmembrane $Na^+$ gradient established by the $Na^+/K^+$ pump, which is also situated in the basolateral membrane. Increased $Cl^-$ secretion requires stimulation of the $Na^+$ pump, which occurs via the increased intracellular $Na^+$ concentration mediated by enhanced turnover of the $Na^+/K^+/2Cl^-$ cotransporter. This in turn requires additional $K^+$ cycling across the plasma membrane, which is mediated by $Ca^{2+}$ activation of specific $K^+$ channels situated in the basolateral membrane (Fig. 4.1a).

As seen in Fig. 4.1a, it is the concerted $Ca^{2+}$ activation of $Cl^-$ and $K^+$ channels that controls the fluid secretion process. It is important to understand that the whole of the basolateral membrane is uniform with regard to distribution of surface membrane ion channels. Thus, the $Ca^{2+}$-activated $K^+$ channels are found not only in the basal membrane as illustrated in Fig. 4.1a, but also in the lateral membranes, up to the tight junctions. Therefore, local apical $Ca^{2+}$ signals will be able to activate both $Cl^-$ channels in the apical membrane and $K^+$ channels in the part of the lateral membrane close to the tight junctions. A limited amount of fluid secretion can proceed without special activation of $K^+$ channels, since rodent pancreatic acinar cells lack $Ca^{2+}$-activated $K^+$ channels [12]. If the resting $K^+$ permeability is sufficiently high, recirculation of $K^+$ can still occur. However, human pancreatic acinar cells, like all salivary and lacrimal glands in all species so far studied, do possess very sensitive $Ca^{2+}$-activated $K^+$ channels, which undoubtedly contribute to the fine regulation of human acinar fluid secretion [53]. In the human acinar cells, these $Cl^-$ and $K^+$ channels will be activated by the short-lasting repetitive local $Ca^{2+}$ signals in the secretory granule region, which have been directly demonstrated in response to stimulation with either ACh or physiologic concentrations (low pM) of CCK [54].

## Dangers of $Ca^{2+}$ Signaling

As described in this chapter, local $Ca^{2+}$ signaling elicited by physiologically relevant agonist concentrations is a remarkably precise mechanism for fine regulation of pancreatic acinar secretion (Fig. 4.6). These $Ca^{2+}$ signals also control the production of ATP (Fig. 4.3), which is required to fuel both fluid and enzyme secretion. However, $Ca^{2+}$ signaling carries a risk of cellular

$Ca^{2+}$ overload, which has the capacity to kill cells [43]. This occurs when acinar cells are hyperstimulated with, for example, CCK. In this situation $Ca^{2+}$ spiking is replaced by a sustained elevated $[Ca^{2+}]_i$ which, by a still poorly understood mechanism, activates the digestive proteases inside the cells [25]. The sustained elevated $[Ca^{2+}]_i$ is due to open CRAC channels and can be severely reduced by CRAC channel inhibitors [46,47]. A sustained elevated $[Ca^{2+}]_i$, unlike repetitive short-lasting $Ca^{2+}$ spikes, does not stimulate mitochondrial ATP production, but inhibits it [55]. The combination of a global and sustained high $[Ca^{2+}]_i$ with a low cytosolic ATP level is lethal [56]. Intracellular digestive enzyme activation is a hallmark of pancreatitis, which is mostly related to biliary disease or excessive alcohol intake. Both bile-related and alcohol-related acute pancreatitis are due to cytosolic $Ca^{2+}$ overload and the associated reduced cytosolic ATP level, which have been brought about by excessive opening of CRAC channels in the plasma membrane triggered by excessive release of $Ca^{2+}$ from intracellular stores. Both bile acids and the combination of ethanol and fatty acids (generating fatty acid ethyl esters) have the capacity to elicit excessive release of $Ca^{2+}$ from intracellular stores [48,57]. The cytosolic $Ca^{2+}$ overload leads to mitochondrial $Ca^{2+}$ overload which causes opening of the so-called mitochondrial permeability transition pore (MPTP) and this depolarizes the inner mitochondrial membrane resulting in loss of ATP production [58,59]. The dangerous effects of bile acids or fatty acid ethyl esters can be markedly inhibited by reducing the intracellular $Ca^{2+}$ release via caffeine inhibition of $IP_3$ receptors [35,58], by reducing $Ca^{2+}$ inflow via CRAC channels using specific CRAC channel inhibitors [46,60] or by inhibiting the MPTP [59]. The pancreatic acinar cell therefore lives dangerously. It very effectively employs $Ca^{2+}$ signaling as a finely coordinated mechanism for regulation of both fluid and enzyme secretion, but excessive intracellular $Ca^{2+}$ release or $Ca^{2+}$ entry has the capacity to cause necrosis.

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# 5

# Physiology of Duct Cell Secretion

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## Introduction

The cardinal function of the pancreatic duct is fluid and $HCO_3^-$ secretion. Pancreatic ductal secretion is a fundamental function of the pancreas that determines the volume and the electrolyte composition of the pancreatic juice and guards the acinar cells from damage by various stressors. Ductal fluid and electrolyte transport is compromised in diseases that stress the pancreas, such as cystic fibrosis and pancreatitis. Ductal secretion is coupled to acinar cell secretion that provides the initial isotonic, plasma-like fluid. The duct then secretes the bulk of the fluid in the pancreatic juice by making economical and recirculating use of the electrolytes provided by acinar cells. Therefore, to understand ductal secretion and physiology, we have to understand the mechanism of acinar secretion and its regulation. The generation and secretion of fluid of defined composition by acinar and duct cells are mediated by selective transporters at the basolateral and luminal membranes that mediate vectorial transport of osmotically active ions. Ductal and acinar cell secretion is highly regulated at both the resting and secreting states by multiple inputs that transmit their signals through the two main second messengers $Ca^{2+}$ and cAMP. The $Ca^{2+}$ and cAMP inputs are integrated into a synergized high-fidelity final response. Other important regulators of the entire secretory process are the transported ions. This is highlighted in the regulation of ductal transporters and secretion by intracellular $Cl^-$. This chapter discusses the principles of ductal fluid and $HCO_3^-$ secretion and its regulation and how it can be corrected in pancreatic disease states.

## Sequential Secretion by Acinar and Duct Cells

### Fluid and Electrolyte Secretion by Acinar Cells

Pancreatic fluid and electrolyte secretion is a two-step, sequential process. The acinar cells secrete a small amount of isotonic, NaCl-rich fluid and the duct secretes most of the fluid and determines the final ion composition of the pancreatic juice [1]. Understanding ductal secretion requires an understanding of acinar cell secretion. The key transporters and the mechanism of fluid secretion by acinar cells are modeled in Fig. 5.1. Vectorial ion transport depends on the $Na^+$ and $K^+$ gradients and the membrane potential that are set by the basolateral $Na^+$,$K^+$-ATPase pump [2]. The $Ca^{2+}$-activated $K^+$ channel at the basolateral membrane Kcnma1 sets the membrane potential near the $K^+$ diffusion potential of about −60 mV [3]. About 60–70% of acinar cells' salt uptake is mediated by the ubiquitous basolateral $Na^+/K^+/2Cl^-$ cotransporter NKCC1 [1]. The remaining salt uptake is mediated by the basolateral $Na^+/H^+$ exchanger NHE1 and by a $Cl^-/HCO_3^-$ exchange activity. It is generally assumed that the ubiquitous AE2 mediates the $Cl^-/HCO_3^-$ exchange that supports fluid flux. However, recent work on salivary glands revealed that another $Cl^-/HCO_3^-$ exchange called AE4 mediates the exchange that drives fluid secretion [4]. NHE1 and AE2 also control the cytoplasmic pH ($pH_{in}$) to prevent large fluctuations of $pH_{in}$ during the secretion [5,6]. Under resting conditions, NKCC1, AE2, and AE4 maintain intracellular $Cl^-$ ($Cl^-_{in}$) at 40–60 mM [7]. The importance of $Cl^-_{in}$ is

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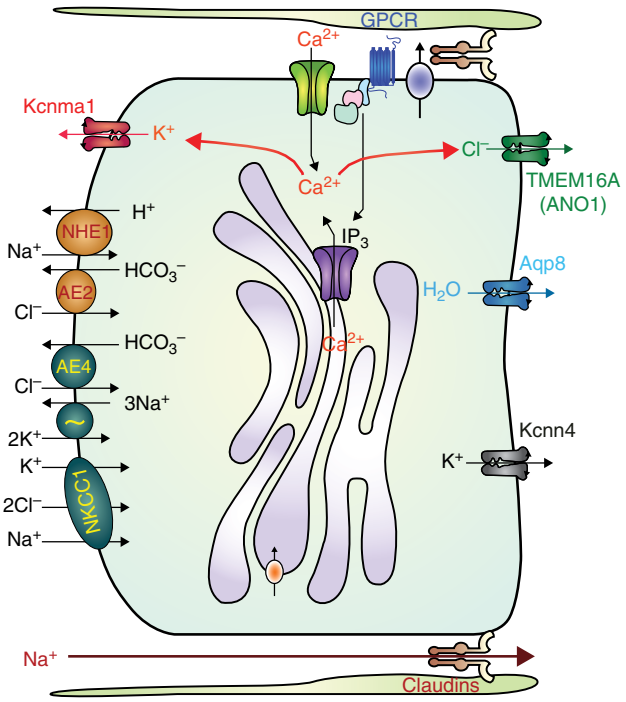


**Figure 5.1** Mechanism of fluid and electrolyte secretion by acinar cells. The model shows the key transporters and the relationships between them that mediate the bulk of fluid and electrolyte secretion by acinar cells.

discussed later in relation to regulation of the secretory process. $Cl^-$ exits across the luminal membrane through the $Ca^{2+}$-activated $Cl^-$ channel TMEM16A/Ano1 [8] and water flows through the water channel AQP8 [9]. The acinar cells' tight junction is the main route of transcellular $Na^+$ flux, which may be mediated by one of the acinar claudins [10].

Acinar cell fluid and electrolyte secretion is regulated by Gq-coupled receptors that increase free cytoplasmic $Ca^{2+}$ ($[Ca^{2+}]_i$) and is enhanced by the cAMP/PKA pathway. Physiological stimulation involves activation of only 1–5% of the G proteins that evoke $Ca^{2+}$ oscillations to prevent $Ca^{2+}$ toxicity by a much stronger stimulation. The $Ca^{2+}$ oscillations initiate at the apical pole and often propagate to the basal pole [11,12]. Acinar cell secretion starts by an increase in apical $[Ca^{2+}]_i$ to activate Ano1 [8], propagation of $[Ca^{2+}]_i$ to the basal pole to activate the $K^+$ channels [13], $Cl^-$ efflux into the luminal space, and $K^+$ efflux to the interstitial space. $Na^+$ transport through the tight junctions results in the net secretion of NaCl and generation of an osmotic gradient that drives water flow through Aqp8. The resulting cell shrinkage reduces $[Ca^{2+}]$ and activates the volume-sensitive NKCC1 [14], NHE1 [15], and AE2 [16] to recover cytoplasmic electrolytes and cell volume. The cycle is repeated with each $Ca^{2+}$ spike making acinar cells function as a $Ca^{2+}$-driven ion and water pump.

## Fluid and Electrolyte Secretion by Duct Cells

The main transporters mediating ductal fluid and $HCO_3^-$ secretion are shown in Fig. 5.2. Transport is fueled by the $Na^+$ gradient and the membrane potential set the $Na^+$,$K^+$-ATPase pump [17], the $K^+$ channels $K(Ca^{2+})1.1$ [18], and an unknown basolateral $K^+$ channel. $HCO_3^-$ enters the ducts by basolateral $1Na^+$–$2HCO_3^-$ cotransport [19,20] mediated by the electrogenic NBCe1-B isoform [21] that accumulates cytoplasmic $HCO_3^-$ and osmolytes. The basolateral $Na^+/H^+$ exchanger NHE1 [20] and $Cl^-/HCO_3^-$ exchange, likely AE2, control $pH_{in}$ and $Cl^-_{in}$, which is required for stimulated secretion [22].

The bulk of $HCO_3^-$ exit across the luminal membrane is mediated by the interrelated activity of the cAMP-activated $Cl^-$ channel cystic fibrosis transmembrane conductance regulator (CFTR) and the exchanger slc26a6 [1]. Slc26a6, is an electrogenic $1Cl^-/2HCO_3^-$ exchanger [23,24] that mediates net solute transport and therefore, in addition to $HCO_3^-$ secretion, slc26a6 is essential for ductal fluid secretion. CFTR has finite $HCO_3^-$ permeability [25] and CFTR-mediated $HCO_3^-$ flux becomes important at the distal portion of the ducts when luminal and cytoplasmic $Cl^-$ are low. Other luminal membrane ductal transporters of note are the $Na^+/H^+$ exchanger NHE3 [26] and $H^+$,$K^+$-ATPase pump ATP12A [27]. Recent work showed that expression of ATP12A in the luminal membrane and pharmacological inhibition of ATP12A reduced ductal secretion suggested to be due to inhibition of $H^+$ absorption [27]. However, molecular studies showed expression of ATP12A in the airway epithelium that secretes $H^+$ in exchange for $K^+$ and contributes to the pathology in cystic fibrosis [28], a disease that prominently affects the pancreas. It is clear that ATP12A plays an important role in the duct, but the underlying mechanism remains to be established. We have suggested that $H^+$-secreting transporters such as NHE3 and perhaps ATP12A function to salvage $HCO_3^-$ in the ductal resting state [26] (Fig 5.2a).

Ductal secretion is stimulated by the Gs-coupled secretin receptor that transmits its signal by increasing cAMP to activate protein kinase A (PKA) [1]. PKA phosphorylates the R domain of CFTR to activate the channel. CFTR then activates the slc26a6 by interaction of CFTR R domain with the slc26a6 STAS domain [29]. In turn, this interaction further activates CFTR. At the same time, CFTR inhibits NHE3 to prevent $H^+$ secretion into the lumen [30]. The $Cl^-$ absorbed by slc26a6 is recycled by CFTR to maintain $HCO_3^-$ secretion by slc26a6. Net osmolyte secretion by slc26a6 in the form of $HCO_3^-$ together with paracellular $Na^+$ flow drives osmotic water secretion to generate the final volume of the pancreatic juice.

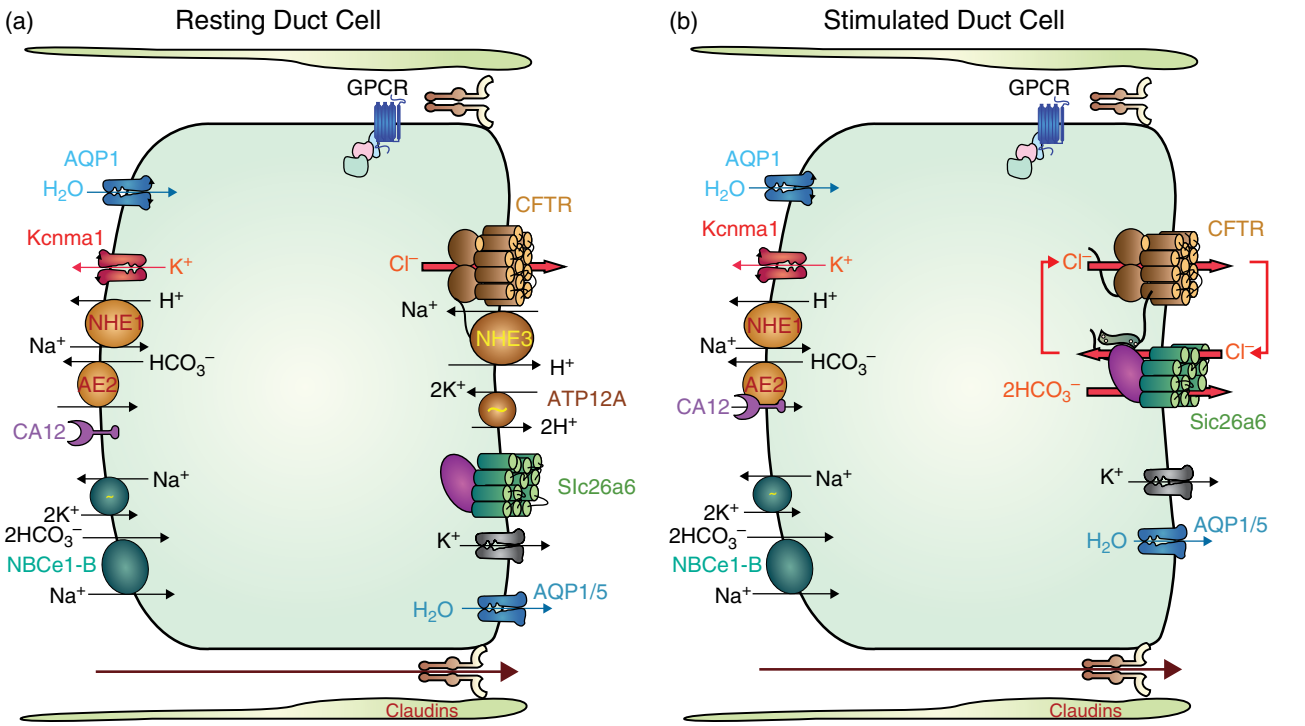


**Figure 5.2** Mechanism of fluid and electrolyte secretion by duct cells. The models show the key transporters and the relationships between them in the resting (a) and stimulated ducts (b). The resting duct can secrete $H^+$ by NHE3 and perhaps ATP12A to salvage $HCO_3^-$, while slc26a6 is away from CFTR and not active. In the stimulated state the $H^+$-secreting transporters are inhibited and slc26a6 and CFTR are mutually activated to cause fluid and electrolyte secretion.

## Regulation of Ductal Secretion

Ductal secretion is dynamically regulated in both the resting and stimulated states by kinase and phosphatase pathways and scaffolding proteins. In addition, $Cl^-_{in}$ regulates the transporters that mediate ductal secretion by affecting their activity and selectivity. The resting state is set by the WNKs and SPAK/OSR1 kinases. Mammals have four WNK [31], with WNK1, WNK3, and WNK4 expressed in the pancreas [1]. The WNKs regulate $Na^+$, $K^+$, $Cl^-$, $HCO_3^-$, and $Ca^{2+}$ transporters in epithelia by determining their surface expression and/or activity [31]. SPAK and OSR1 are homologous stress-activated kinases that act downstream of the WNKs, with the WNKs serving as scaffolds to the SPAK/OSR1. The SPAK/OSR1 can affect surface expression and inhibit or activate the ion transporters [32]. Another level of regulation of the WNK kinases is through interaction with kelch-like 3 (KLHL3) and cullin 3 (CUL3) that regulate WNK levels by ubiquitination and degradation [33].

In the pancreatic duct, the WNKs and the SPAK/OSR1 kinases function in the same pathway, with the WNKs acting as scaffolds for the SPAK/OSR1 kinases. The WNK/SPAK pathway regulates ductal NBCe1-B [34], Slc26a6 [25], and CFTR [34,35] by inhibiting surface expression and the activity of the transporters. Notably, knockdown of the WNKs and of SPAK enhanced stimulated ductal fluid secretion, indicating that the kinases exert tonic inhibition of the secretion [34] to set the basal nonsecretory state (see the model in Fig 5.3a).

The multifunctional protein IRBIT ($IP_3$-binding protein released with $IP_3$) regulates the pancreatic duct-stimulated secretory state. IRBIT was discovered as a protein that binds to the $IP_3$ receptors ($IP_3R$) [36] and as an activator of the NBCe1-B [37]. The IRBIT has an N-terminal protein phosphatase 1 (PP1) binding motif, a PEST domain, a coiled-coil domain, and a PDZ ligand at the end of the C-terminus [38]. The PEST domain has multiple phosphorylation sites that are required for all IRBIT function [38,39]. The coiled-coil domain participates in activation of target proteins by IRBIT [40] and the PDZ ligand locates IRBIT close to the $HCO_3^-$ transporters [34]. IRBIT activates transporters by two mechanisms, by increasing their surface expression and their transport activity. This is best understood with NBCe1-B. The first 85 residues of NBCe1-B form an autoinhibitory domain (AID) [41]. IRBIT interacts with the AID to prevent the NBCe1-B self-inhibition [37]. In addition, IRBIT reverses the inhibition of NBCe1-B by WNK/SPAK by recruiting PP1 to the transporter that dephosphorylates the SPAK phosphorylated Ser65 [42].

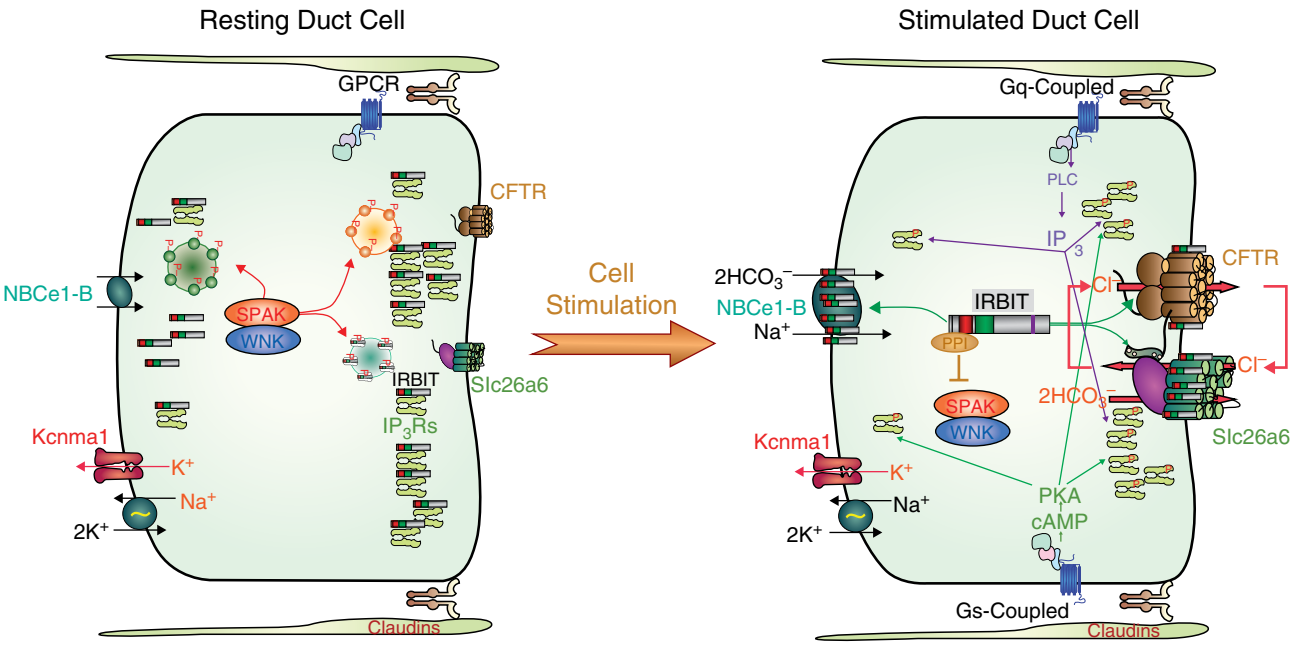


**Figure 5.3** IRBIT mediates synergistic activation of the cAMP and $Ca^{2+}$ signaling pathways. In the resting state, the WNK/SPAK kinases associate with the transporters and SPAK phosphorylates NBCe1-B AID, Slc26a6, and CFTR to sequester most of them in intracellular organelles and IRBIT is sequestered by the $IP_3Rs$. When the cells are stimulated with physiologic concentrations of $IP_3$ and cAMP generating agonists, PKA phosphorylates the $IP_3R$ to facilitate release of IRBIT from the $IP_3R$ by $IP_3$ binding. IRBIT recruits PP1 to the transporters to dephosphorylate them at the SPAK phosphorylation sites and target them to the plasma membrane. IRBIT remains bound to the transporters AIDs further activate the transporters and ductal secretion.

IRBIT also interacts with and potently activates CFTR [34,40] and slc26a6 [42] by interacting with a sequence similar to the NBCe1-B AID that is present in the CFTR R domain and slc26a6 STAS domain [42]. IRBIT similarly recruits the PP1 to NBCe1-B, CFTR, and slc26a6 [34,42]. The key role of IRBIT in ductal secretion was established by showing that knockout of IRBIT in mice markedly inhibits ductal fluid secretion. The reduced secretion due to IRBIT knockdown was partially recovered by knockdown of SPAK [34], showing the interplay between the IRBIT/PP1 and the WNK/SPAK pathways in modulating ductal secretion, as illustrated in Fig 5.3b.

$HCO_3^-$ secretion depends on strict regulation of both intracellular and surface membrane $HCO_3^-$ concentrations, which are determined by carbonic anhydrases (CA). CA are either cytoplasmic or membrane anchored with their active site at the extracellular cell surface [43]. The surface CA control the supply or removal of $HCO_3^-$ at the surface of the plasma membrane and the cytoplasmic CA buffer cytoplasmic $HCO_3^-$. The plasma membrane-localized CA interact with many $H^+$ and $HCO_3^-$ transporters [44]. We know very little about the role and molecular identity of the CA that are important in ductal secretion. Some information became available from human disease in which mutations in CA12 causes salt wasting [45,46]. CA12 is a critical activator of AE2 and ductal secretion. Deletion or mutation in CA12 inhibits ductal secretion by about 50% and overexpression of CA12 markedly increases ductal secretion [22]. Hence activation of CA12 is a potential treatment of ductal hypofunction.

Another prominent regulator of ductal function is $Cl^-_{in}$. $Cl^-_{in}$ has a key role in ductal function by driving $HCO_3^-$ secretion through slc26a6, controlling the luminal membrane potential through CFTR and of $pH_{in}$ through AE2 (Fig 5.2). Sensing $Cl^-_{in}$ is therefore essential for tuning the secretory process. $Cl^-_{in}$ regulates the function of at least two $HCO_3^-$ transporters, NBCe1-B and CFTR. $Cl^-_{in}$ regulates CFTR $HCO_3^-$ permeability [25]. At $Cl^-_{in}$ below 8 mM CFTR became the $HCO_3^-$ channel to increase pancreatic juice $HCO_3^-$ concentration from 120 to 140 mM [47]. A more dramatic regulation by $Cl^-_{in}$ is seen with NBCe1-B. IRBIT-activated NBCe1-B is regulated between 5 and 20 mM $Cl^-_{in}$ [48]. Ductal secretion starts when resting $Cl^-_{in}$ is about 35 mM and decreases to 4 mM toward the latter phase of $Cl^-$ absorption and $HCO_3^-$ secretion [1,49]. At $Cl^-_{in}$ above 20 mM, the activity of NBCe1-B is inhibited by 70%, which is sufficient to support $HCO_3^-$ secretion at the proximal duct. As the demand for cytoplasmic $HCO_3^-$ increases in the face of accumulation of luminal $HCO_3^-$, $Cl^-_{in}$ is reduced toward 4 mM to increase the activity of NBCe1-B threefold [48], which ensures continued $HCO_3^-$ supply.

## The $Ca^{2+}$ and cAMP Pathways Synergize to Activate Ductal Secretion

Synergism between signaling pathways is a fundamental concept in biology that serves to prevent cell toxicity by overstimulation. Signaling pathways function at 1–3% of capacity and synergize to generate the maximal physiological response. The $Ca^{2+}$ and cAMP signaling pathways synergize in a mechanism mediated by IRBIT [42]. At the resting state, IRBIT is bound to $IP_3$ receptors. Physiologic secretin stimulation increases ductal cAMP to phosphorylate the $IP_3$Rs to increase their affinity for $IP_3$ and reduce their affinity for IRBIT [42]. A small increase in $IP_3$ by physiologic stimulation with $Ca^{2+}$-mobilizing receptors releases IRBIT from the $IP_3$R that then binds to CFTR, slc26a6, and NBCe1-B and activates them and ductal secretion [42]. This important physiologic mode of synergism is illustrated in Fig. 5.3.

## Ductal Secretion-Associated Pancreatic Diseases

Ductal fluid and $HCO_3^-$ secretion not only washes digestive enzymes to the intestine, but also protects the parenchyma from damage due to stresses to the pancreas. In addition, as a chaotropic ion, $HCO_3^-$ is essential for solubilization of macromolecules such as digestive enzymes and mucins and divalent ions in biological fluids [1,50]. The duct is the first line of defense of the pancreas that must be breached before damage to acinar cells take place. Damage to ductal secretion occurs in several diseases of the pancreas, including cystic fibrosis (CF) and pancreatitis. CF leads to the destruction of the pancreas and pancreatic insufficiency [51], due to inhibition of ductal fluid and $HCO_3^-$ secretion [1]. Moreover, several studies have identified mutations in CFTR that are associated with chronic pancreatitis [52] and specifically inhibit CFTR-dependent $HCO_3^-$ transport [53] and CFTR $HCO_3^-$ permeability [54], independent of $Cl^-$ channel activity. The importance of the duct in protection of the pancreas and of CFTR in ductal function [55] led to the examination of the state of CFTR in chronic autoimmune [56] and alcoholic pancreatitis [56,57], which revealed mislocalization of CFTR in these forms of pancreatitis. Notably, treatment of autoimmune pancreatitis with corticosteroids ameliorated the disease primarily by increasing ductal $HCO_3^-$ secretion [56]. In animal models, induction of acute pancreatitis by cerulein stimulation, bile infusion, and alcohol treatment impaired ductal function [58].

The intimate involvement of the duct in the health of the pancreas and pancreatic diseases suggests that the duct should be a prime target for therapy. There are several potential targets. One can be activators of IRBIT together with inhibitors of the WNK/SPAK/OSR1 kinases. Because of their involvement in renal salt homeostasis and hypertension [33], such drugs may became available in the future. Another potential target is CA12, which affects ductal function [22] and is modified in several cancers [59]. Drugs affecting CA12 activity are being developed in the cancer field and may become useful for the treatment of pancreatitis. A very promising option is the use of CFTR potentiators and correctors that are approved for the treatment of CF [60]. These drugs should repair CFTR localization and increase ductal secretion to slow progress of the disease and may even improve the function of acinar cells.

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# 6

# Pathophysiology of Experimental Pancreatitis

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## Introduction

Acute pancreatitis is an inflammatory disorder of the pancreas that results in significant morbidity, mortality, and hospitalizations [1,2]. In the United States alone, over 300,000 patients are admitted each year with pancreatitis, with more than $2 billion spent on their care [3]. Currently, there is no specific therapy for acute pancreatitis and treatment of patients revolves around supportive measures. The development of specific therapy for acute pancreatitis will require precise modeling of this disease in animal models and detailed elucidation of its pathogenesis. Over the last few decades, studies in animal and *in vitro* models of acute pancreatitis have led to the emergence of valuable information on both early and late events in the pathogenesis of acute pancreatitis. In this chapter, the major events in the pathogenesis of acute pancreatitis, as observed in experimental models, are described. It appears that although inflammation during acute pancreatitis is initiated in acinar cells, over the course of the disease the inflammation spills into systemic circulation. Uncontrolled systemic inflammation can lead to multiorgan failure, which is the primary cause of morbidity and mortality in acute pancreatitis.

## Models of Acute Pancreatitis

The pathogenesis of pancreatitis has been studied *in vitro* using pancreatic acini isolated from animals and *in vivo* using various animal model systems. Stimulation of acinar cells isolated from the pancreas of mice or rats with secretagogues such as caerulein (cholecystokinin analogue) or carbachol (cholinomimetic agent) leads to secretion of digestive enzymes. Higher doses of these secretagogues leads to inhibition of secretion, a phenomenon that is believed to be critical for acinar cell injury. This *in vitro* acinar cell injury induced by supramaximal stimulation has been used as a tool to model acinar cell injury during acute pancreatitis. Experiments in this relatively simple *in vitro* caerulein hyperstimulation acinar cell model has helped researchers to understand many important early events of pancreatitis, including cytosolic calcium changes, colocalization, intra-acinar zymogen activation, nuclear factor kappa B (NFκB) activation, and inhibition of secretion.

With respect to the animal models, the caerulein hyperstimulation model, in which a supramaximal concentration of the cholecystokinin (CCK) analogue caerulein is used to induce acute pancreatitis in rodents, is most widely used because of its ease of induction, noninvasiveness, and reproducibility. The arginine-induced pancreatitis model, in which administration of L-arginine leads to induction of severe acute pancreatitis, is another commonly used model. The duct obstruction model of acute pancreatitis mimics gallstone obstruction-induced acute pancreatitis in the clinical setting and does not require a sophisticated surgical technique. However, duct ligation in rodents produces only mild pancreatitis without extensive necrosis or infectious complications, and therefore is unsuitable for evaluating these clinically important features. In the duct perfusion model, pancreatitis is induced by infusion of various noxious stimuli, such as bile salts, into the pancreatic duct. Importantly, the severity of pancreatitis in this model can be modulated by controlling the type, concentration, and volume of infusate and the duration and pressure of infusion. The pancreatitis in this model tends to be patchy and limited to the head of the pancreas. The choline-deficient ethionine-supplemented (CDE) diet-induced acute pancreatitis model is another less commonly used model.

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Although these unique but complementary models have been very useful for the elucidation of the early events in pancreatitis, their relevance to human disease has been questioned. For example, administration of supramaximal doses of cholecystokinin analogues to rodents leads to induction of acute pancreatitis but the presence of cholecystokinin receptors on human acinar cells has not been confirmed. Similarly, with the exception of case reports, excessive levels of L-arginine is not a common cause of pancreatitis in humans. The duct obstruction model and the duct perfusion models are the only animal models that come close to modeling gallstone pancreatitis, the most common cause of acute pancreatitis in humans. Furthermore, no good model for alcohol-induced acute pancreatitis, the second most common cause of human pancreatitis, is available. Ethanol feeding alone in animals causes a mild and variable pathologic response in the pancreas, making investigations into the cellular and molecular mechanisms of ethanol's effect exceedingly difficult. The lack of valid models of acute pancreatitis may partially explain why many investigational therapies (antiplatelet activating factor, antiprotease) that had shown promise in animal models have not lived up to expectations in clinical trials. Although these models are not perfect, they accurately mimic the histopathology and pathophysiology of acute pancreatitis, including some of the clinical aspects. Although better models are needed, a wealth of information on the pathophysiology of acute pancreatitis has been generated using these models and this information should eventually lead to the development of novel and effective therapies. The important early events in acute pancreatitis learned from the experimental models are described in the following.

## Phases of Acute Pancreatitis

Acute pancreatitis is initiated in acinar cells. Injurious stimuli lead to multiple intra-acinar events that culminate in local acinar cell injury and activation of inflammatory pathways and secretion of various cytokines and chemokines. These cytokines and chemokines interact with and activate resident immune cells and also attract inflammatory cells from circulation into the pancreas. The activated neutrophils and immune cells and inflammatory cytokines are responsible for the systemic injury that is the major cause of morbidity and mortality in acute pancreatitis. Furthermore, as discussed later, the systemic inflammation can actually aggravate the local injury by various mechanisms.

When patients with acute pancreatitis present for medical attention, most of the intra-acinar events have already transpired and the inflammation has progressed to the systemic level. Unfortunately, most of the older acute pancreatitis experimental studies evaluated various therapeutic strategies in prophylactic fashion, that is, with the agent of interest administered before induction of acute pancreatitis, which is clinically irrelevant except in cases of endoscopic retrograde cholangiopancreatography (ERCP)-induced acute pancreatitis. This may be another reason why various therapies that have been shown to be effective in animal models have failed to induce clinical improvement. Hence it is important to evaluate novel therapies in experimental models not only prophylactically but also therapeutically.

## Early Intra-Acinar Events in Acute Pancreatitis

### Intrapancreatic Enzyme Activation

The pancreas is an enzyme factory that synthesizes and secretes large amounts of digestive enzymes. These enzymes are stored intracellularly as inactive zymogens to prevent autodigestion of the pancreas. Furthermore, there are many intracellular mechanisms that protect the acinar cells against low levels of intracellular zymogen activation occurring under physiologic conditions. The presence of trypsin inhibitors, nonoptimal pH, and the presence of proteases that degrade the activated enzymes help to protect the acinar cells against damage caused by intra-acinar cell activation of proteases. In healthy organisms, pancreatic proteases remain inactive during their synthesis, secretion from acinar cells, and transport through the pancreatic duct. Once the enzymes have reached the intestinal lumen, enterokinase cleaves the pancreatic zymogen trypsinogen to form trypsin. Trypsin then activates all other pancreatic zymogens (e.g., proelastase, procarboxypeptidase) and thus helps in the digestion of food. In acute pancreatitis, the enzymes are believed to be activated inside the acinar cells. That pancreatitis is autodigestion of the pancreas was first proposed by Chiari in 1896 [4]. This "autodigestion" hypothesis triggered research looking into premature activation of digestive enzymes as a possible mechanism. Since then, a number of studies have demonstrated the findings of premature activation of digestive enzymes, both in experimental models (Fig. 6.1) and in clinical studies. During experimental acute pancreatitis, activation of trypsinogen and other pancreatic zymogens is observed [5–7] as early as 15 min after caerulein-induced acute pancreatitis. That trypsin activation is important for the pathogenesis of acute pancreatitis is supported by the fact that all of the other markers of pancreatitis, such as hyperamylasemia, pancreatic edema, and acinar cell vacuolization, are observed only after the intra-acinar

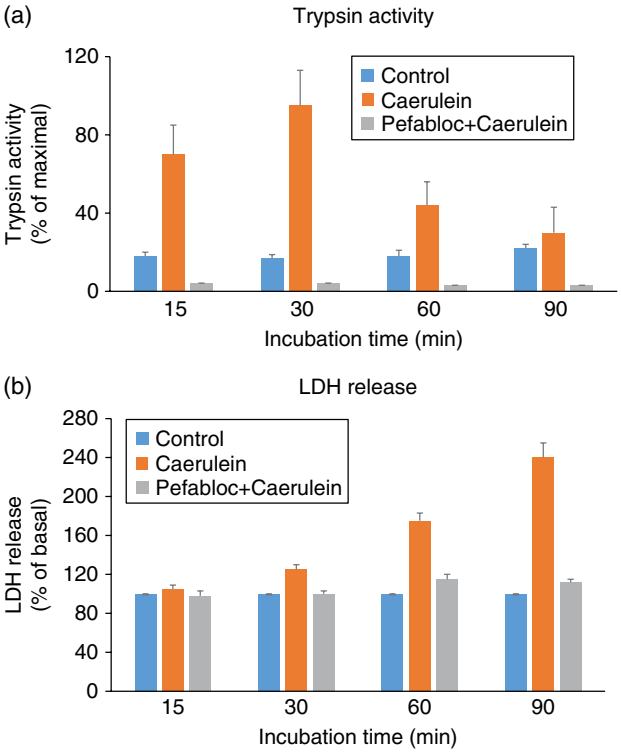


**Figure 6.1** Trypsin activation is observed early on in acute pancreatitis and it contributes to acinar cell injury. (a) Effect of stimulation with a high concentration of caerulein (0.1 μM) on trypsin activation in rat pancreatic acini. Acini were stimulated with either caerulein alone (0.1 μM) or in the presence of Pefabloc (2 mM, added 15 min before addition of caerulein) or incubated in buffer alone for specified times. (b) Increase in trypsin activity in response to a high dose caerulein stimulation resulted in increased release of lactate dehdrogenase (LDH) in the incubation medium, indicating acinar cell injury. This effect was blocked in the presence of the trypsin inhibitor Pefabloc. *Source:* Modified from Hofbauer et al. 1988 [44]. Reproduced with permission.

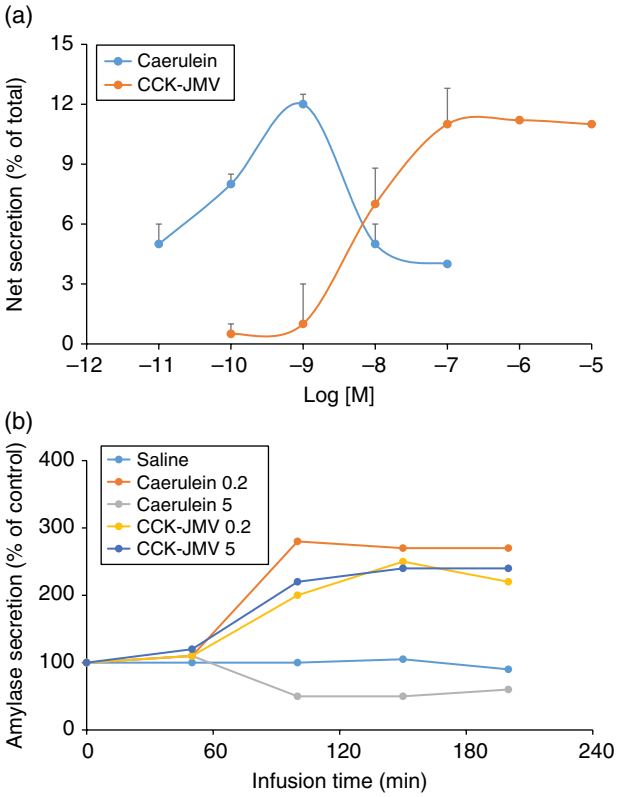


**Figure 6.2** Caerulein but not CCK-JMV-180 leads to inhibition of secretion at supramaximal doses. (a) Effect of caerulein or CCK-JMV-180 on secretion from rat pancreatic acini *in vitro*. (b) Effect of caerulein and CCK-JMV-180 on *in vivo* amylase secretion. Rats were infused with heparinized saline alone or saline containing caerulein (0.2 μg/kg/h, maximal dose), caerulein (5 μg/kg/h, supramaximal dose), CCK-JMV-180 (0.2 mg/kg/h, maximal dose), CCK-JMV-180 (5 mg/kg/h, supramaximal dose), or caerulein (5 μg/kg/h) plus CCK-JMV-180 (5 mg/kg/h). All animals were infused with saline alone for the first 30 min. *Source:* Modified from Saluja et al. 1989 [45]. Reproduced with permission.

zymogen activation has occurred. Furthermore, studies that demonstrated that pretreatment with protease inhibitors (presumptively inhibiting trypsin) reduces the severity of acute pancreatitis in animal models also supported the trypsin central hypothesis of acute pancreatitis. Pretreatment of acinar cells with cell-permeable protease inhibitors (such as Pefabloc) (Fig. 6.1b) prior to supramaximal stimulation by caerulein prevents both zymogen activation and acinar cell injury [8,9]. Hence intrapancreatic enzyme activation is believed to be key for acinar cell injury during acute pancreatitis.

### Inhibition of Secretion

Interestingly, the experimental models of acute pancreatitis suggest that during acute pancreatitis, not only are the zymogens prematurely activated but actually they are also retained inside the acinar cells. As discussed, supramaximal caerulein stimulation is commonly used as an *in vitro* and animal model of acute pancreatitis. It has been observed that at low doses caerulein, being an analogue of secretagogue CCK, stimulates secretion. However, with increasing doses the secretion is actually inhibited (Fig. 6.2a), and it is at the higher secretion-inhibiting doses that changes to acute pancreatitis are observed in both *in vitro* and animal models (Fig. 6.2b), suggesting a role of inhibition of secretion in the pathogenesis of acute pancreatitis. A similar pattern is observed on evaluating other secretagogues. Carbachol at higher doses inhibits acinar cell secretion and induce changes consistent with acute pancreatitis. On the other hand, CCK-JMV-180, an analogue of CCK, stimulates pancreatic secretion and does not inhibit secretion at high doses (Fig. 6.2a). Consistent with the role of inhibition of secretion in the pathogenesis of acute pancreatitis, this secretagogue does not induce acinar cell injury or other changes of acute pancreatitis.

Studies also suggest that reversal of the inhibition of secretion could actually decrease the severity of acute pancreatitis. Proteinase-activated receptor-2 (PAR-2) is expressed on pancreatic acinar cells and is actually activated during acute pancreatitis. The possible ligand for these receptors during acute pancreatitis is trypsin. Interestingly, genetic deletion of PAR-2 increases the severity of acute pancreatitis. Furthermore, stimulation of PAR-2 with the agonist SIGRIL [10] leads to reduced severity of acute pancreatitis and also reversal of the inhibition of secretion observed during acute pancreatitis [11] (Fig. 6.2b).

### Colocalization

Despite all the inbuilt protective systems, there is premature activation of zymogens during acute pancreatitis. Studies have evaluated the mechanism of this premature activation and it appears that early on in acute pancreatitis, the zymogens and lysosomes come together, a phenomenon called colocalization, which has been confirmed by both subcellular fractionation (Fig. 6.3a) and immunolocalization studies (Fig. 6.3b). Colocalization brings the zymogen enzymes and lysosomal enzymes in contact and, in these colocalized organelles, cathepsin B, a lysosomal enzyme, activates the trypsinogen to trypsin. Activated trypsin then has the capability to activate other enzymes. Colocalization has been observed as early as 15 min after initiation of the injury and all other features of acute pancreatitis such as pancreatic edema, hyperamylasemia, and acinar cell injury occur subsequently.

The role of colocalization and cathepsin B in trypsin activation has been confirmed by multiple methods. Pharmacologic inhibition of cathepsin B prevents activation of trypsinogen and results in a reduction of pancreatic injury in models of acute pancreatitis [12]. Similarly, the importance of the cathepsin B in activation of trypsin and induction of injury during acute pancreatitis has been evaluated using cathepsin B knockout mice in which the cathepsin B gene had been deleted by targeted disruption. After induction of experimental secretagogue-induced pancreatitis, the trypsin activity in the pancreas of cathepsin B knockout mice was more than 80% lower than in the wild-type animals [13]. Also, pancreatic damage, as indicated by various parameters, including the extent of acinar tissue necrosis, was substantially lower in the knockout animals [13]. Furthermore, studies suggest that phosphatidylinositol 3-kinase (PI3K) activation and increased cytosolic calcium are required for colocalization. Inhibition of colocalization by inhibiting PI3K [14] and also attenuation of cytosolic calcium by calcium chelator prevents trypsin activation and acinar cell injury during acute pancreatitis, again suggesting that colocalization is the cause rather than the effect of intra-acinar enzyme activation and acute pancreatitis.

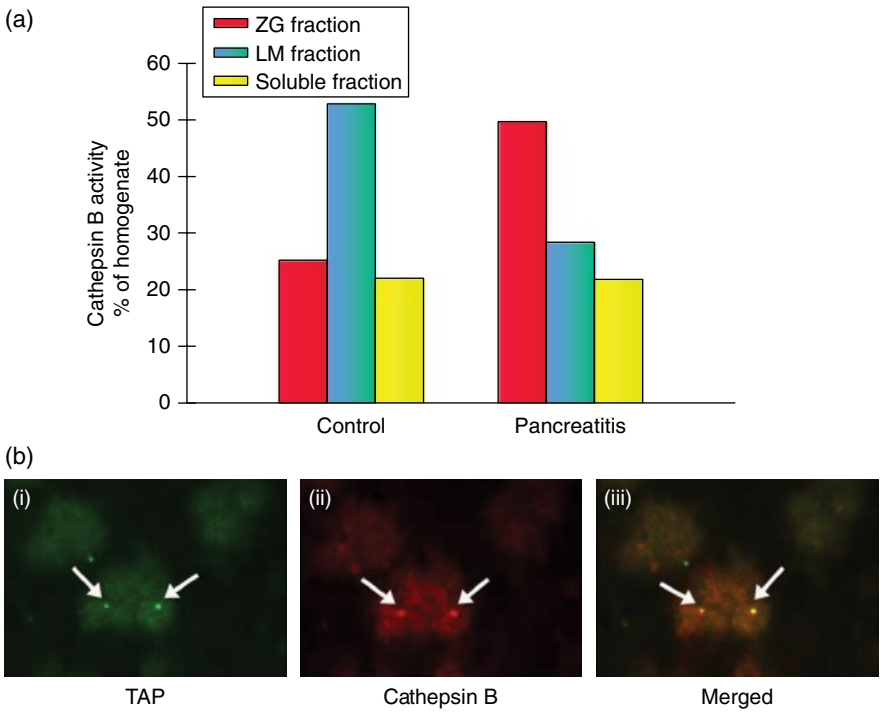


**Figure 6.3** During acute pancreatitis there is colocalization of zymogen enzymes and lysosomes. (a) Subcellular fractionation of acinar cells stimulated with supramaximal caerulein demonstrates increased cathepsin B activity in the zymogen fraction and a decrease in the lysosomal fraction. *Source:* Modified from Saluja et al. 1987 [46]. Reproduced with permission. (b) Supramaximal caerulein stimulation of the acinar cells leads to activation of trypsin as observed by generation of trypsinogen activation peptide (TAP). TAP activity colocalizes with cathepsin B, suggesting that trypsin is activated in the same compartment as cathepsin B.

### Calcium Signaling During Acute Pancreatitis

Intracellular and extracellular calcium homeostasis is important for the survival of a cell. Calcium signaling is closely linked to both the physiology and pathology of pancreatic acinar cells. However, the nature of the calcium signal observed during acute pancreatitis seems to be different with respect to the amplitude and the temporal pattern from that observed during physiologic stimulus–secretion coupling. Physiologically, a secretory signal such as CCK leads to smaller, transient, sometimes oscillatory increases in intracellular calcium, which leads to secretion of the zymogens, whereas a pathologic stimulus leads to a much larger spike followed by a sustained increase in intracellular calcium. Studies suggest that calcium signaling is required but not sufficient for acinar cell injury and other events during acute pancreatitis. The attenuation of the calcium changes during acute pancreatitis by the cytosolic calcium chelator 1,2-bis(*o*-aminophenoxy)ethane-*N*,*N*,*N*′,*N*′-tetraacetic acid (BAPTA) prevents zymogen activation, suggesting that calcium is essential for zymogen activation [9,15]. Prevention of sustained calcium increases by using $Mg^{2+}$, a natural calcium antagonist, also reduces trypsinogen activation and the severity of acute pancreatitis. Interestingly, artificial elevation of intracellular calcium by using different agents, such as thapsigargin or ionomycin, does not cause activation of trypsinogen and other changes of acute pancreatitis, suggesting that although sustained increases in calcium changes are required, they are not sufficient for the induction of acute pancreatitis.

The source of the pathologic calcium changes during acute pancreatitis has also been evaluated. The abnormal increase in cytosolic calcium is due either to excess release from intracellular stores or to influx with or without inadequate clearance of the calcium. Release from endoplasmic and mitochondrial stores, increased influx, and inadequate clearance have all been shown to contribute to the pathologic calcium increase observed during acute pancreatitis.

### Activation of Inflammatory Pathways During Acute Pancreatitis

As time progresses, the local intra-acinar events eventually lead to initiation and progression of systemic inflammation. It is the uncontrolled systemic inflammation that is the major cause of mortality and morbidity during human disease. Studies in experimental models suggest that early on during acute pancreatitis there is activation of intra-acinar inflammatory pathways that induces the synthesis and release of various cytokines and chemokines. NFκB, the master regulator of inflammatory pathways, is activated as early as 15–30 min after initiation of acute pancreatitis in both *in vitro* and animal models. It seems that intra-acinar cytosolic calcium changes in addition to activation of protein kinase C is required for activation of NFκB. Intriguingly, activation of trypsin and of NFκB are independent events. This is clear from experiments in which inhibition of trypsin, by pharmacologic inhibitors, did not influence NFκB activity. That NFκB activation and also local and systemic inflammation are independent of trypsin activation has been further confirmed using mice that lack trypsinogen-7 (T7-KO) gene. It appears that mice have numerous isoforms of trypsinogen but trypsinogen-7 is the isoform responsible for intra-acinar activation of trypsin during acute pancreatitis. Interestingly, T7-KO mice that lack intra-acinar trypsinogen activation have similar degrees of local and systemic inflammation (Fig. 6.4), again suggesting the independence of inflammation and intra-acinar zymogen activation [16]. As already discussed, cathepsin B is essential for activation of trypsin during acute pancreatitis. Halangk et al. [13] showed that cathepsin B knockout (CB-KO) mice have less necrosis than wild-type mice. However, the degree of leukocyte infiltration in the pancreas or lungs during pancreatitis was not affected by the absence of cathepsin B, indicating cathepsin B- and thus trypsin-independent evolution of systemic inflammation.

Once NFκB has been activated, it leads to the synthesis and secretion of cytokines and chemokines. Blockage of NFκB activation (by *N*-acetylcysteine, for example) prevents this induction of cytokine transcription by caerulein hyperstimulation, thus indicating the involvement of NFκB in cytokine activation by caerulein [17]. These chemokines and cytokines then not only attract neutrophils and macrophages into the pancreas but also lead to their activation. It has been postulated that activation of the innate immune system and also release of cytokine and chemokines then propagate the inflammatory injury to the systemic level. There is some controversy with respect to the role of NFκB in the pathogenesis of acute pancreatitis. The inhibition of NFκB activation in the caerulein hyperstimulation model of pancreatitis and also other models of pancreatitis significantly reduces the severity of pancreatitis. When NFκB activation was prevented by use of the antioxidant *N*-acetylcysteine or other means, all parameters of rat caerulein pancreatitis were diminished [17,18]. The only study that has actually shown the beneficial effect of NFκB in acute pancreatitis is that by Steinle et al. [19], in which inhibition of NFκB by pharmacologic inhibition led to greater pancreatic damage, thus suggesting a protective role of NFκB in acute pancreatitis. In a follow up study, the same group demonstrated similar results in genetic NFκB knockout mice [20]. However, the overall consensus in the field suggests that NFκB activation during acute pancreatitis leads to activation of an inflammatory cascade that leads

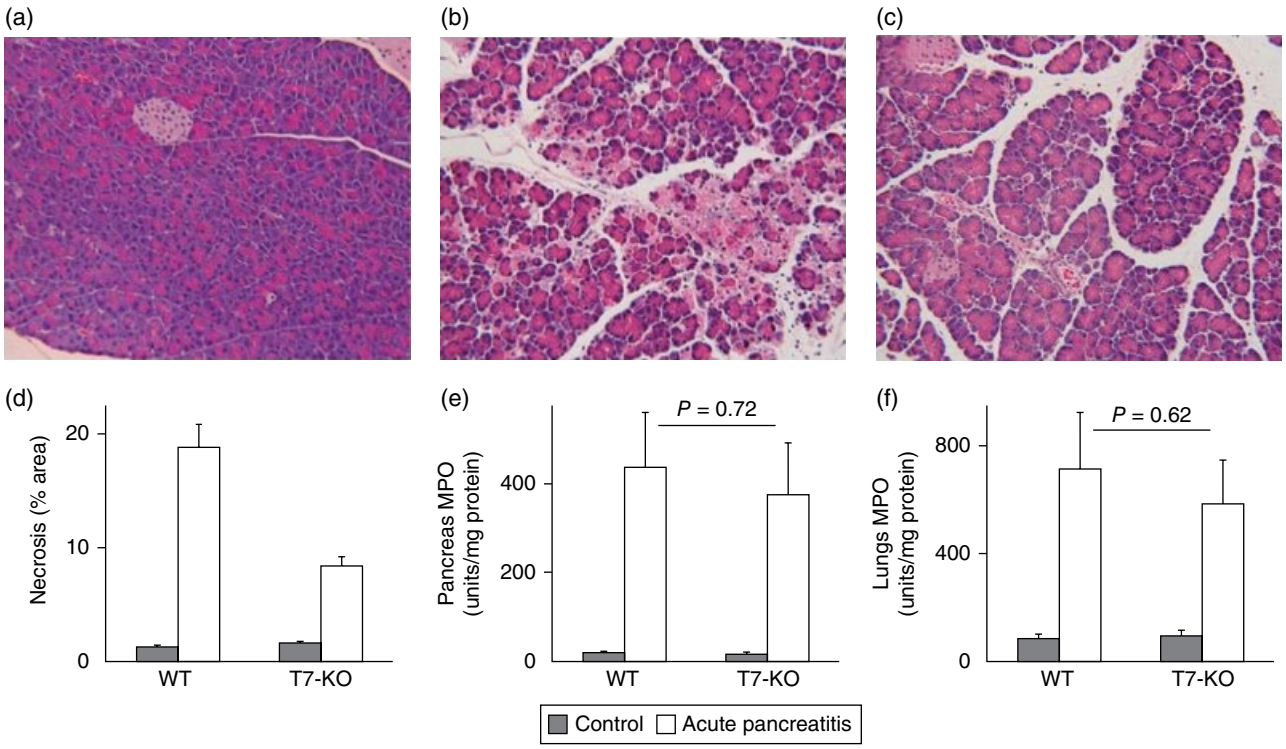


**Figure 6.4** Trypsin partially contributes to acinar cell injury during acute pancreatitis and local and systemic inflammation is independent of trypsin. Compared with (a) untreated mice, (b) supramaximal caerulein administration to wild-type mice leads to acinar cell necrosis, edema, and neutrophil infiltration. Although the acinar cell injury caused by supramaximal caerulein stimulation is reduced in (c) T7-KO mice, it is not completely prevented, suggesting that there are trypsin-independent mechanisms of acinar cell necrosis. (d) Quantification of acinar cell necrosis observed in caerulein model of acute pancreatitis in wild-type and T7-KO mice. Compared with untreated controls, wild-type and T7-KO mice had similar degrees of (e) pancreas and (f) lung inflammation as measured by myeloperoxidase levels. *Source:* Modified from Dawra et al. 2011 [16]. Reproduced with permission of Elsevier.

to cytokine and chemokine production, activation of inflammatory cells, and local and systemic injury. Future studies evaluating mechanisms to control this systemic inflammatory response syndrome should lead to the development of novel therapies for acute pancreatitis.

## Critical Analysis of the Role of Trypsin in Acute Pancreatitis

Studies suggest that inhibition of trypsin by pharmacologic inhibitors inhibits the severity of acute pancreatitis [12,21]. As already discussed, cathepsin B is important for the activation of trypsinogen to trypsin. Inhibition of trypsinogen activation by inhibiting the activity of cathepsin B or by deleting the cathepsin B gene also decreases pancreatic injury during acute pancreatitis [12,13]. Support for the trypsin-centric theory also comes from the identification of mutations in the cationic trypsinogen gene PRSS1 in patients with hereditary pancreatitis [22]. Biochemical studies of the pancreatitis-associated pR122H mutations of recombinant human cationic trypsinogen preparations show that this trypsinogen variant has an increased propensity for autoactivation and is resistant to degradation by chymotrypsin C. The role of trypsin in acute pancreatitis has been investigated in numerous experimental studies. Gaiser et al. [23] demonstrated that low constitutive expression of rat anionic trypsinogen PRSS2 in acini was sufficient to induce pancreatitis. Although the model utilized in this study lacked the transient, high-level trypsin activation observed in the experimental models of acute pancreatitis, this study again supports the role of trypsin activation in pathogenesis of pancreatitis [23]. However, this study needs to be interpreted with caution as this overexpression model is somewhat artificial and lacks the stimuli and other intra-acinar processes observed during acute pancreatitis.

Further insight into the role of trypsin in acute pancreatitis has been gained by the development and use of novel knockout mice lacking trypsinogen isoform-7 (mouse paralogue of human cationic trypsinogen [PRSS1]). In this mouse, the pathologic intra-acinar and intrapancreatic trypsin activation during acute pancreatitis is not observed. Intriguingly, in these novel T7KO mice, the acinar cell necrosis observed in experimental models of pancreatitis is reduced but not completely

obliterated (Fig. 6.4). Furthermore, NFκB activation and local and systemic inflammation are not altered by the absence of trypsin in these mice (Fig. 6.4). These studies suggest that trypsin is only partly responsible for the acinar cell necrosis observed during acute pancreatitis and local and systemic inflammation is independent of trypsin. It appears that trypsin is required only for initiation of the injury and trypsin-independent inflammatory pathways (importantly NFκB) determine disease progression and severity.

### Mechanism by which Trypsin Leads to Acinar Cell Injury

Although it is established that trypsin plays a role in acinar cell injury, the exact mechanism of this process has been elusive. This mechanism was recently investigated and it was demonstrated that trypsin leads to permeabilization of the colocalized vesicles that causes cathepsin B to escape from colocalized organelles into the cytosol, which in turn causes cell death during pancreatitis [24]. This conclusion was supported by the finding that supramaximal stimulation by caerulein causes leakage of cathepsin B in cytoplasm and this release is dependent on trypsin, as in its absence, either in T7KO mice as already described or by pharmacologic inhibition of trypsin, the release of cathepsin B into the cytosol during acute pancreatitis was prevented (Fig. 6.5). The role of trypsin in inducing apoptotic cell death in acinar cells was further proven by an experiment in which supramaximal caerulein stimulation induced apoptosis in acinar cells, and this was prevented by pretreatment with cathepsin B and trypsin inhibitors. Interestingly, when cathepsin B or trypsin was added to the permeabilized acini, to simulate the presence of cathepsin B or trypsin in the cytosol, dose-dependent activation of apoptosis was seen with the presence of cytosolic cathepsin B but not trypsin [24] (Fig. 6.5). This suggests the role of cytosolic cathepsin B but not trypsin in inducing acinar cell apoptosis. These observations have been conclusively supported by similar findings from experiments using

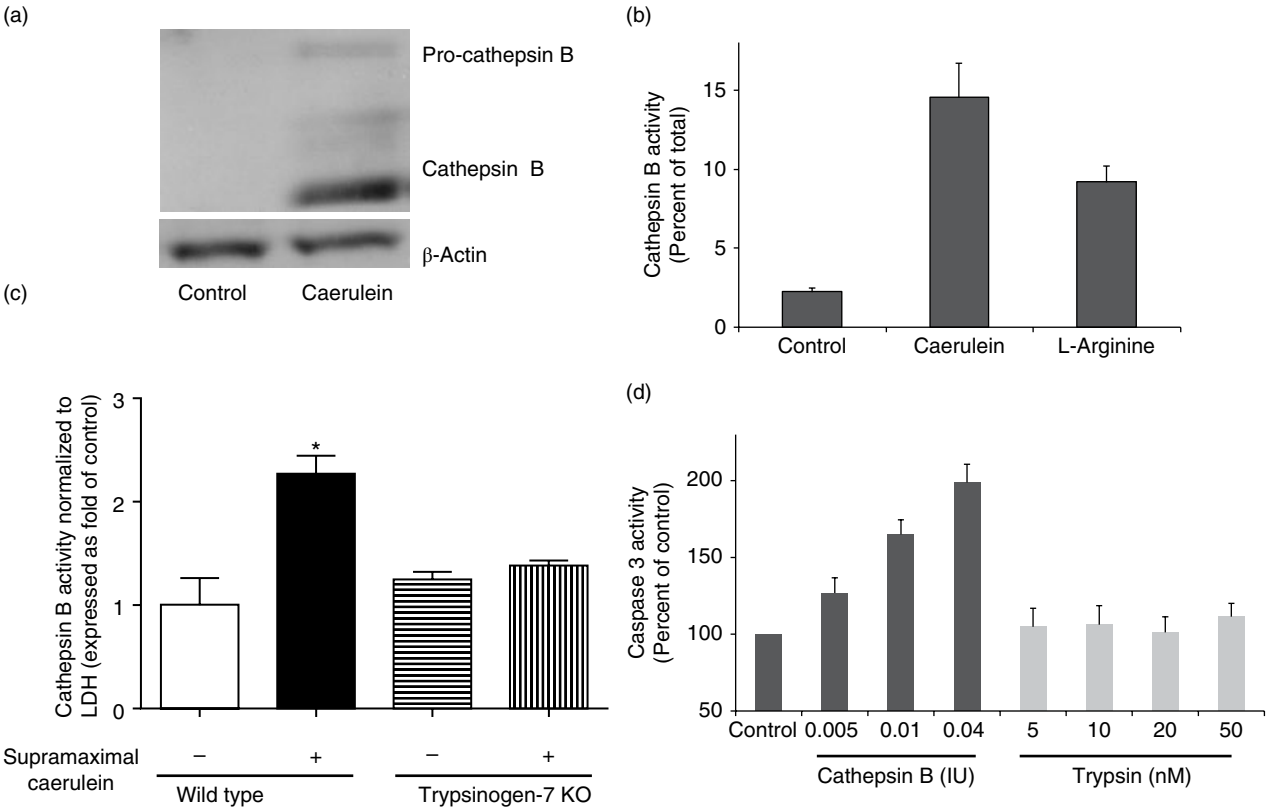


**Figure 6.5** Trypsin induces cell death in acinar cells indirectly through inducing release of cathepsin B into the cytosol. (a) Treatment of rat acinar cells *in vitro* with supramaximal caerulein leads to release of cathepsin B into the cytosol. (b) During caerulein and L-arginine pancreatitis in rats, there is release of cathepsin B into the cytosol. (c) Cathepsin B is released into the cytosol in a trypsin-dependent fashion as the T7-KO mice did not demonstrate release of cathepsin B into the cytosol in response to caerulein hyperstimulation. (d) Addition of cathepsin B, but not trypsin, to SLO-permeabilized acinar cells leads to activation of caspase-3, suggesting that during acute pancreatitis cytosolic cathepsin B, but not trypsin, activates apoptosis. *Source:* Modified from Talukdar et al. 2016 [24]. Reproduced with permission of Elsevier.

T7-KO and CBKO animals [24]. From these studies, the most logical inference is that active trypsin within the colocalized organelles is involved in making the organelles "leaky," causing leakage of cathepsin B into the cytosol, where the newly released cathepsin B activates apoptotic pathways. Inhibition of trypsin prevents the colocalized organelles from becoming fragile, thereby preventing the release of cathepsin B into the cytosol. Exogenous trypsin failed to activate caspase when incubated with streptolysin O (SLO)-permeabilized acinar cells, suggesting that trypsin does not directly cause acinar cell death.

There are two major pathways through which apoptosis occurs, namely extrinsic and intrinsic pathways. The extrinsic pathway involves death receptors and occurs in response to external signals, whereas the intrinsic pathway involves mitochondria and occurs in response to internal signals. Lysosomal disruption has been implicated in initiating the intrinsic apoptotic pathway involving cleavage of the proapoptotic Bcl-2 family member Bid. Upon apoptotic stimuli, the Bcl-2 apoptosis-promoting protein Bax undergoes a conformational change and translocates to mitochondria, where it oligomerizes and forms pores that allow the release of cytochrome *c* into cytoplasm. It has also been shown that in the early stages of experimental acute pancreatitis, there is a release of cytochrome *c* into the cytosol, which in turn activates caspase-9, subsequently leading to caspase-3 activation. Caspase-3 then executes the intracellular changes of apoptosis via different downstream mediators. A recent study suggests that during acinar cell death, cathepsin B is released into the cytosol and induces apoptosis predominantly via the intrinsic pathway by inducing Bid cleavage and Bax activation. Truncated Bid and activated Bax cause release of cytochrome *c* from mitochondria, which in turn leads to caspase-3 activation and acinar cell apoptosis.

#### Altered Autophagy Pathways During Acute Pancreatitis

Autophagy is a homeostatic process involving lysosomal degradation of long-lived protein and damaged organelles. During autophagy, there is the formation of double-membrane vacuoles called autophagosome containing the proteins and organelles that are to be recycled. The autophagosomes fuse with endosomes and then with lysosomes, thus generating autolysosomes. The sequestered material is degraded by lysosomal enzymes and the degradation products such as amino acids are recycled back into the cytoplasm. Given the high levels of protein synthesis and degradation in pancreatic acinar cells, these cells have a high autophagic flux. Studies have demonstrated that during pancreatitis, there is accumulation of autophagic vacuoles that are largely autophagolysosomes [25]. This is further supported by increased levels of LC3II, a marker of autophagic vacuoles. Interestingly, during acute pancreatitis, there is decreased autophagic efficiency, as suggested by increased levels of p62. Together this suggests that during acute pancreatitis, there is increased formation of autophagic vacuoles, but the steps beyond these initial steps including lysosomal enzyme-induced degradation of the contents of autolysosomes are blocked. It appears that well-functioning autophagy machinery is important for homeostasis of the pancreas and its impairment can lead to pancreatic injury in the form of atrophy, fibrosis, and chronic pancreatitis [26,27].

#### Mitochondrial Dysfunction

Mitochondria are the power plants of cells and provide most of the energy required for normal cellular processes. Mitochondrial dysfunction has been observed in acute pancreatitis. Excessive reactive oxygen species (ROS) and other stimuli during acute pancreatitis lead to direct damage to the mitochondria, leading to mitochondrial permeability, transition pore opening, and loss of mitochondrial potential. There are two major consequences of these events: (i) there is release of mitochondria content into the cytosol, and many of these contents, such as cytochrome *c*, activate the cell death pathway; and (ii) there is lack of production of ATP. Studies suggest that in the absence of ATP, the cell death pathways channel toward necrosis as apoptosis requires energy. However, how these pathways are different from mitochondria-dependent cell death pathways in other diseases is unclear.

#### ER Stress During Acute Pancreatitis

Unfolded protein response (UPR) is one of the early events in acute pancreatitis. It is now established that pathologic conditions such as hypoxia and oxidative stress lead to the accumulation of unfolded proteins in the endoplasmic reticulum (ER) lumen and ER stress. This leads to activation of the UPR, which augments protein folding and helps cell survival. However, if the UPR is overwhelmed, there is activation of cell death pathways. Given that the protein synthesis demands of pancreatic acinar cells are greater than those of any tissue in the body, acinar cells have a robust UPR system. Previous studies [28,29] showed the activation of the UPR during experimental pancreatitis. In mammalian cells, the UPR is controlled by three ER sensors, namely PERK (PKR-like ER kinase), IRE1 (inositol-requiring enzyme 1), and ATF6 (activating transcription factor 6). When ER homeostasis is perturbed, the accumulating misfolded proteins bind Grp78, thus activating the ER sensors. IRE1 initiates downstream signaling through an unconventional splicing of the transcription factor

Xbp-1, which binds to the ER stress response element leading to transcription of ER chaperones. PERK activation leads to the phosphorylation of the translational initiation factor eIF2α, which leads to inhibition of protein synthesis, thus decreasing the load of unfolded protein on ER. Activation of ATF6 also increases transcription of grp78 and CHOP. Limited studies in pancreatitis suggest that all of these pathways are activated upon induction of acute pancreatitis [29,30]. However, how ER stress integrates in the known paradigm of acute pancreatitis, that is, its relationship to zymogen activation, colocalization, and activation of inflammatory pathways, is unclear.

The role of ER stress in pancreatitis has also been evaluated in models of alcoholic pancreatitis. In an interesting study, Lugea et al. [31] demonstrated that feeding mice an ethanol diet led to activation of UPR and increased levels of XBP-1 and protein disulfide isomerase (PDI), a well-known XBP-1 target. Although ethanol feeding in animal models activates UPR, the damage to the acinar cells is minimal. However, if the UPR was perturbed, for example by XBP-1 deficiency, ethanol feeding reduced expression of ER regulators, upregulation of proapoptotic signals, and activation of authophagy, and increased acinar cell injury. How the balance shifts from ER stress being a beneficial to a harmful event during ethanol-induced acute pancreatitis is not clear.

## Systemic Injury

The intra-acinar events and activation of inflammatory pathways lead to the synthesis of chemokines and cytokines. These signaling molecules recruit inflammatory cells such as neutrophils and macrophages to the pancreas. Secretion of cytokines by resident macrophages and endothelial and epithelial cells also helps in the recruitment of these inflammatory cells. The infiltrating cells then induce further acinar cell injury and lead to the secretion of multiple proinflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-2, IL-6, and other chemokines and anti-inflammatory factors such as IL-10 and IL-1 receptor antagonist. This leads to magnification and propagation of inflammation to the systemic level. Systemic inflammation is primarily responsible for determining the severity of pancreatitis and is responsible for the mortality and the majority of the morbidity of acute pancreatitis. Given the role of various proinflammatory cytokines in the pathogenesis of systemic injury, the therapeutic potential of downregulating levels of a few individual cytokines has been evaluated in experimental models. For example, mice with genetic deletion of some of these cytokines, such as TNF-α, have a reduced severity of acute pancreatitis [32]. Downregulation of platelet activating factor (PAF) by accelerating its degradation by recombinant PAF acetylhydrolase [33] or PAF antagonists [34] ameliorates the severity of experimental pancreatitis. Similarly, the severity of experimental pancreatitis is reduced in mice lacking substance P receptors or pretreated with substance P receptor antagonist [35]. Unfortunately, these findings were evaluated in clinical studies and did not show benefit. The discordance of experimental and clinical findings can be explained potentially by the fact that many of these therapies were evaluated in experimental models in prophylactic fashion, whereas in clinical situations, when the patients present the cytokines are already elevated and the treatments may not be as effective in reversing the damage that has already been done. Moreover, the cytokine system is very redundant and the effects of multiple cytokines are overlapping. Hence abolishing one cytokine may not provide dramatic results.

### Neutrophil-Inducing Local Injury

There is abundant experimental evidence to indicate that the sequestration of neutrophils into the pancreas, in response to initial injury from intra-acinar events, further contributes to tissue damage. The sequestration of neutrophils into the pancreas requires upregulation of endothelial adhesion molecules and their interaction with leukocytes. Elevated levels of endothelial adhesion molecules such as P- and E-selectins have been observed in acute pancreatitis and correlates with the severity of pancreatic and systemic injury. Initial experimental evidence with respect to the role of neutrophils in the pathogenesis of acute pancreatitis was based upon experiments in which neutrophils were depleted by treatment with antineutrophil serum [36] or anti-Gr-1 antibody [37,38] before induction of experimental pancreatitis. In these experiments, the severity of pancreatitis was significantly reduced, indicating a role of neutrophils in tissue injury. In subsequent studies, experimental approaches to achieve a reduction in neutrophil infiltration in pancreatic tissue either targeted P-selectin [39] or used CXCR2 antagonist [40]. In these experiments also, along with a significant decrease in neutrophils, a decrease in pancreatic injury was observed. Platelet-derived CXCL4 regulates neutrophil infiltration [41]. Administration of antiplatelet antibody prior to initiation of acute pancreatitis reduced CXCL4 levels, neutrophil infiltration, and pancreatitis-related tissue damage. Mechanisms of neutrophil-mediated pancreatic injury have been investigated. There is evidence to indicate that the presence of activated neutrophils in the pancreas activates trypsinogen [37] and active trypsin can further enhance damage to the tissue. Neutrophil infiltration is considered to be responsible for the second phase of trypsin activation observed during pancreatitis; however, initial activation of trypsinogen is independent

of neutrophils. Neutrophil-dependent activation of trypsin is considered to be mediated through NADPH oxidase [36]. Matrix metaloproteinase-9 (MMP-9) is present in neutrophils [42] and released after activation; use of its specific inhibitor (BB-94) also resulted in decreased trypsinogen activation but the mechanism of MMP-9-mediated trypsin activation is not clear. In addition to trypsinogen activation, other mechanisms such as increased ROS and neutrophil elastase-mediated injury have been considered. Recent studies point to the role of neutrophil extracellular traps (NET) in tissue injury, which again is considered to be mediated through increased trypsin activation, but how NET induce activation of trypsinogens is not clear [43]. Given the important role of neutrophils in both local and systemic injury during acute pancreatitis, a better understanding of the mechanism by which neutrophils become activated and induce injury in acute pancreatitis will lead to the development of strategies to modulate their function selectively for therapeutic gain.

## Conclusion

In summary, experimental studies have provided much needed information on the pathophysiology of acute pancreatitis. Although the currently used *in vitro* and animal models have significant shortcomings, they precisely model the histopathology and pathophysiology of acute pancreatitis. These models have elucidated multiple key pathophysiologic events such as zymogen activation, colocalization, inhibition of secretion, intracellular calcium changes, autophagy dysfunction, ER stress, NFκB activation, and mitochondrial dysfunction. Recent studies have proved that trypsin contributes only partially to acinar cell injury and the local and systemic inflammation are independent of trypsin activation. The local and systemic inflammation are the major sources of mortality and morbidity during acute pancreatitis. A better understanding of the pathophysiology and progression of inflammation during acute pancreatitis will lead to the development of strategies to modulate it and thus change the outcomes of patients with acute pancreatitis.

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# 7

# Physiology and Pathophysiology of Function of Sphincter of Oddi

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## Introduction

The presence of the gallbladder and biliary tract was described in some of the earliest recorded observations of humans [1], but their role in digestion was not appreciated until much later. In the sixteenth century, a membrane near the distal end of the common bile duct thought to impede reflux of duodenal contents into the bile duct was described, but it was not until 1887 that this structure was described as a sphincter and named after Rugero Oddi, who published a detailed description of its anatomy as a result of dissections undertaken while studying medicine [2]. The physiologic role of the sphincter of Oddi was further appreciated after the hormone cholecystokinin (CCK) was shown to contract the gallbladder and reduce sphincter of Oddi resistance. These and subsequent studies firmly established that an intimate relationship existed between gallbladder contraction, sphincter of Oddi function, and the flow of bile into the duodenum.

## Anatomy and Morphology

The terminal parts of the common bile duct and pancreatic duct, the common channel, and major duodenal papilla of Vater are invested with varying thicknesses of smooth muscle that together form the sphincter of Oddi segment (Fig. 7.1). The major part of the human sphincter of Oddi lies within the duodenal wall, and is anatomically and functionally independent of the duodenal muscle.

Distinct sphincters are present at the terminal end of the common bile duct (sphincter choledochus), pancreatic duct (sphincter pancreaticus), and common channel (sphincter ampullae) [3]. However, studies using a combination of radiologic, duct cast techniques, and histologic sectioning methods did not distinguish separate sphincters [4], and human autopsy studies have concluded that the common bile duct and pancreatic duct become fused in a common connective tissue sheath outside the duodenal wall and pass together through a slit in the duodenal muscle known as the "choledochal window." However, the lumina do not join at this level but are separated by a thick, muscular septum. In most subjects, fusion of the two lumina occurs in the submucosal layer of the duodenum to form a common channel that varies in length between 2 and 17 mm. Before entering the duodenum, each duct becomes completely surrounded by circular muscle, some of which forms a figure-of-eight pattern around the two ducts. The point at which the smooth muscle starts on each duct is readily identified radiologically as a notch. Distal to the notch, each lumen becomes narrow as it traverses the duodenal wall, this narrowing being associated with thickening of the duct wall due to smooth muscle, connective tissue, and mucous glands. As the ducts pass through the duodenal wall longitudinal muscle, fibers interdigitate between the circular ductular muscle fibers and the duodenal muscle. The ducts emerge from the duodenal muscle layers and pass through the duodenal submucosa for a variable distance before opening onto the papilla of Vater; throughout this submucosal course, the ducts are ensheathed by circularly oriented smooth muscle. Manometric studies in humans support Hand's description of the sphincter of Oddi in that separate sphincteric zones have not been identified [5].

The mucosa of the human sphincter of Oddi segment is lined by columnar epithelium and contains numerous mucus-secreting glands. The mucosa is thrown into

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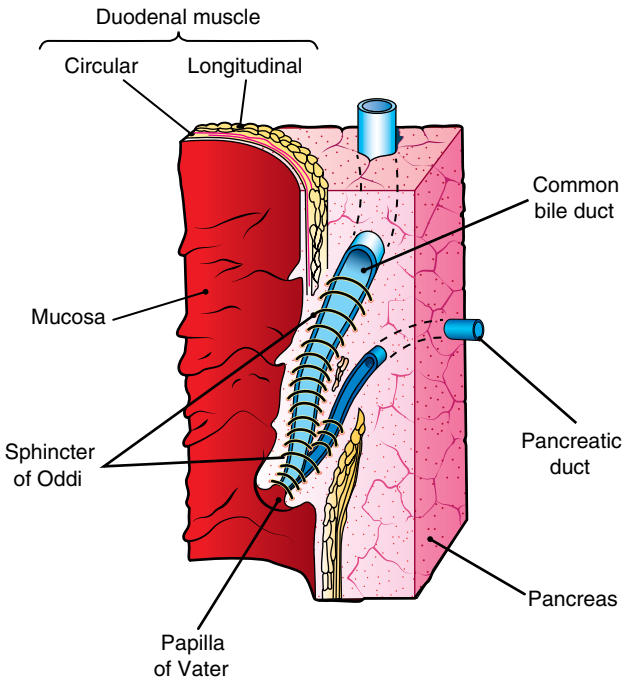


**Figure 7.1** Anatomy of the human sphincter of Oddi at the junction of the bile and pancreatic ducts with the duodenum.

longitudinal folds likened to mucosal valvules [6]. These folds are least marked proximally and increase distally, becoming maximal in the common channel. The mucosal folds may occasionally be seen projecting through the orifice of the duodenal papilla.

## Innervation

The extrahepatic biliary tract is innervated by dense networks of extrinsic and intrinsic nerves that regulate smooth muscle tone and epithelial cell function of the extrahepatic biliary tree. The celiac ganglia contribute both motor and sensory nerves made up of sympathetic fibers that originate in the T7–T10 spinal segments. The hepatic plexus is formed by nerve fibers from both vagi and supplies parasympathetic motor nerves to the extrahepatic biliary system [7].

The wall of the biliary tract is composed of three layers: serosal, muscularis, and mucosal. Ganglionated nerve plexuses are located in the subserosal and subepithelial layers. The sphincter of Oddi has a rich ganglionic plexus. It has a predominance of cholinergic ganglia and a smaller number of adrenergic ganglia. Immunohistochemical studies in our laboratory have demonstrated the presence of a wide range of peptidergic neurons in the sphincter region, including galanin-, substance P-, and somatostatin-containing nerves. In addition, the inhibitory transmitter nitric oxide has been demonstrated in nerves to the sphincter and is thought to have an important function in modulating sphincter relaxation. It has been shown that the nerves in the sphincter region communicate with the proximal biliary tract, the gallbladder, and the duodenum [8,9].

## Physiology

Bile reaches the sphincter of Oddi via the common hepatic and common bile ducts. The sphincter of Oddi not only regulates the flow of bile and pancreatic juice into the duodenum, but is also the regulatory valve to prevent reflux of duodenal contents into the pancreatobiliary passages. The role of the common bile duct in the control of bile flow has been confused owing to anatomic differences in the species studied. Histologic studies in humans have demonstrated only thin, longitudinally oriented layers of smooth muscle within the walls of the common bile duct [10]. The major tissue component appears to be elastic fibers. However, in other species, such as sheep, the common bile duct is invested with circularly oriented smooth muscle that exhibits peristaltic activity.

The weight of evidence suggests that the human common bile duct does not have a primary propulsile function. However, the elastic fibers and the longitudinally oriented smooth muscle provide a tonic pressure that may help overcome the tonic resistance of the sphincter of Oddi. The diameter of the human common bile duct before and after cholecystectomy has been the subject of controversy. Part of the disagreement is due to the methodology used in determining duct size. It has become obvious that duct size as determined by ultrasonography and magnetic resonance cholangiography (MRC) cannot be equated with duct size determined by endoscopic retrograde cholangiopancreatography (ERCP) or intraoperative extraluminal measurements. Ultrasound and MRC record the nondistended lumen, whereas the contrast used during ERCP produces distension. Intraoperative measurements include wall thickness. In general, the normal diameter of the common bile duct as determined by ultrasound is less than 6 mm, by ERCP less than 10 mm, and by intraoperative extraluminal measurements less than 12 mm. What has become clear is that the common bile duct does not increase in diameter significantly following cholecystectomy [11,12]. The major cause of a dilated common bile duct is increased intraluminal pressure, which generally is produced by either primary or secondary obstruction at the sphincter of Oddi.

## Motility of the Sphincter of Oddi

The primary function of the sphincter of Oddi is to control the delivery of bile and pancreatic juice into the duodenum. This is possible because of low pressure within the bile duct. Approximately 800–1500 mL of bile flows through the human sphincter of Oddi. Various studies in animals and humans have tried to evaluate the mechanism by which the sphincter of Oddi controls the flow of bile and pancreatic secretions. These studies have shown that there is anatomic variability between species and that sphincter of Oddi motility differs from one species to another. Hence, although many commonalities exist, one has to be circumspect in comparing animal data directly with the motility and function of the human sphincter of Oddi.

## Sphincter of Oddi Motility Studies in Animals

*In vivo* studies in dogs, cats, rabbits, and monkeys have demonstrated that the sphincter of Oddi exhibits muscle contractions that are independent of duodenal activity. The common bile duct and pancreatic duct proximal to the sphincter do not demonstrate spontaneous motor activity. Results from the dog studies have suggested that the sphincter of Oddi has a milking effect on bile, thus propelling small volumes of fluid from the common bile duct into the duodenum [13]. Manometric and electromyographic studies of the opossum sphincter of Oddi have demonstrated that the predominant mechanism of common bile duct emptying in the opossum is the antegrade sphincter of Oddi phasic contractions that propagate the entire length from the cephalic to the caudal end [14,15]. However, the frequency of the phasic contractions varies periodically during fasting. In cats, CCK inhibits the sphincter phasic contractions and produces a fall in sphincter tone by stimulation of nonadrenergic, noncholingeric inhibitory neurons – this effect overriding a lesser, direct smooth muscle stimulatory action of the hormone [16].

Studies have shown that the sphincter may act as a pump or a resistor and that bile duct pressure influences it [17]. This intrinsic activity is controlled by interstitial nerves of Cajal and is modulated by hormones [16], ATP and adenosine [18], and nitric oxide [19].

Neurohistochemical studies have demonstrated both adrenergic and cholinergic neurons within the sphincter of Oddi, and experiments in animals have determined the pharmacologic effects of histaminergic, cholinergic, and adrenergic stimulation on the sphincter muscle [14]. However, the physiologic significance of these drug actions on the sphincter of Oddi requires further investigation.

The function of the vagus nerve in sphincter of Oddi physiology remains obscure. Sphincter of Oddi neurons likely receive vagal input and their activity is modulated by release of neuropeptides from sensory fibers, a significant source of excitatory synaptic input to these cells arising from the duodenum. This duodenum–sphincter of Oddi circuit likely plays an important role in the coordination of sphincter of Oddi tone with gallbladder motility in the process of gallbladder emptying [20]. Studies in dogs have suggested that following vagal transection, the resistance to flow across the sphincter of Oddi is decreased [21]. However, in the prairie dog, increased resistance to flow through the sphincter of Oddi occurs after truncal vagotomy. Results from vagal stimulation studies have failed to define clearly the role of the vagus in biliary dynamics.

The Australian possum sphincter of Oddi demonstrates activity similar to that of the human sphincter. In this species, inhibition of sphincter phasic contractions promotes flow of bile. It has been shown that this inhibition is mediated by neural release of nitric oxide [16]. There is evidence that nitric oxide mediates the cerulein- and CCK octapeptide-mediated relaxation of the canine sphincter of Oddi [22]. The neuropeptide galanin selectively stimulates longitudinally oriented sphincter of Oddi smooth muscle via a direct mechanism, leading to a moderate reduction in trans-sphincteric flow [23]. Table 7.1 illustrates the effects of various bioactive agents on the sphincter of Oddi.

**Table 7.1** Effects of various bioactive agents on the sphincter of Oddi.

| Effect | Agent |
|---|---|
| Stimulators | Morphine met-enkephalin |
| | Galanin |
| | Substance P |
| | Cholecystokinin |
| | Neuropeptide Y |
| | Nitric oxide |
| Inhibitors | Tramadol |
| | Glucagon |
| | Calcitonin gene-related peptide |
| | Cholecystokinin |
| | Peptide YY |
| | Somatostatin |

## Sphincter of Oddi Motility in Humans

Cineradiographic studies showed that the human sphincter of Oddi exhibits rhythmic contractions that propel contrast into the duodenum [24]. Sphincter of Oddi pressure studies conducted at the time of biliary tract surgery have demonstrated variations in pressure thought to be the manometric equivalent of the cineradiographic contractions [25]. Resistance to outflow of fluid from the common bile duct into the duodenum has also been demonstrated by intraoperative studies. This resistance was reduced after administration of CCK octapeptide or smooth muscle relaxants such as amyl nitrite [26].

Manometric recordings from within the sphincter of Oddi segment have been made via a pressure-sensitive catheter introduced into the sphincter of Oddi via a duodenoscope (Fig. 7.2) [27]. They demonstrated that the human sphincter of Oddi is characterized by prominent phasic contractions superimposed on a basal sphincter of Oddi pressure 3 mmHg above the pressure in the common bile duct and pancreatic duct (Fig. 7.3). The amplitude of the phasic contractions is approximately 130 mmHg and the mean frequency is 4/min. Analysis of the direction of propagation of the phasic contractions during a continuous 3 min period demonstrated that the majority of contractions (60%) are oriented in an antegrade direction from the common bile duct toward the duodenum. A smaller number of contractions occurred either simultaneously (24%) or had a retrograde orientation (15%). Intravenous bolus injection of CCK octapeptide (20 ng/kg) normally produces inhibition of the phasic contractions and a fall in the basal sphincter of Oddi pressure.

Table 7.2 shows the pressures recorded from the sphincter of Oddi of normal subjects. Studies in patients with T-tubes inserted in the common bile duct following bile duct exploration [28] have shown that the frequency of sphincter of Oddi phasic contractions during fasting exhibits a periodicity in relation to duodenal migrating

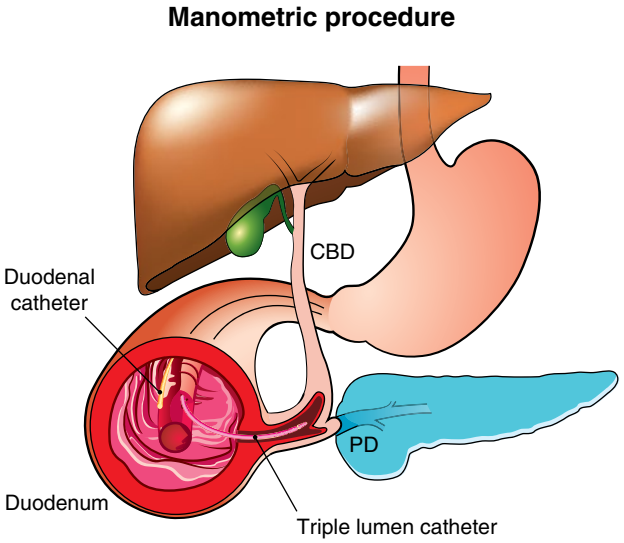


**Figure 7.2** Manometric recording from the human sphincter of Oddi. A triple-lumen pressure-sensitive catheter is positioned in the sphincter via the biopsy channel of the duodenoscope. A separate catheter records duodenal pressure. CBD, common bile duct; PD, pancreatic duct.

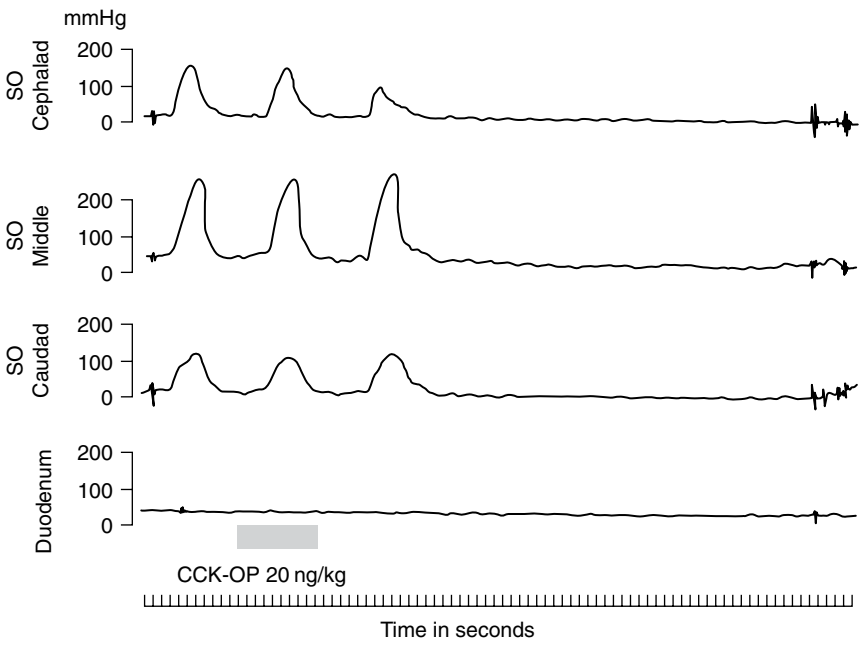


**Figure 7.3** Manometric recording from the human sphincter of Oddi (SO) showing prominent phasic contractions, which are inhibited after injection of cholecystokinin octapeptide (CCK-OP).

motor complexes, similar to that demonstrated in the opossum (Fig. 7.4).

Following the ingestion of a meal, bile flow across the sphincter of Oddi is promoted by inhibition or reduction in the amplitude of the phasic contractions and a fall in the sphincter of Oddi basal pressure. This effect on the human sphincter of Oddi is similar to that following intravenous injection of CCK octapeptide. In humans, bile flow occurs mainly between sphincter of Oddi phasic contractions during the period of diastole. The phasic contractions propel small volumes of bile into the duodenum, but this is not the major means by which bile flow occurs. The phasic contractions in humans may function to prevent reflux of duodenal contents into either the bile or the pancreatic ducts, and to maintain the ducts free of small debris. In order to promote flow across the human sphincter of Oddi, inhibition or reduction of the phasic contractions and a fall in basal pressure are necessary.

**Table 7.2** Pressures recorded from the sphincter of Oddi of normal subjects.

| | Normal | | |
|---|---|---|---|
| | **Median** | **Range** | **Abnormal** |
| Basal pressure (mmHg) | 15 | 3–35 | >40 |
| Amplitude (mmHg) | 135 | 95–195 | >300 |
| Frequency (/min) | 4 | 2–6 | >7 |
| Sequences | | | |
| Antegrade (%) | 80 | 12–100 | |
| Simultaneous (%) | 13 | 0–50 | |
| Retrograde (%) | 9 | 0–50 | |

## Pathophysiology of the Sphincter of Oddi Dysfunction (SOD)

According to the Rome III expert consensus [29], the term SOD implies motility abnormalities of the sphincter of Oddi associated with pain, elevations of liver or pancreatic enzymes, common bile duct dilatation, or episodes of pancreatitis. The most common presentations of this symptom complex include persistent or recurrent "biliary" symptoms postcholecystectomy (10–20%) [30] or features consistent with idiopathic recurrent acute pancreatitis (abnormal sphincter of Oddi manometry has been recorded in 30.5% [31]).

The diagnostic criteria for sphincter of Oddi disorders laid down by the Rome III expert consensus [29] include the presence of episodes of pain located in the epigastrium and/or right upper quadrant along with all of the criteria listed in Table 7.3. The consensus statement also listed supportive criteria, the presence of one or more of which in association with the pain may help in arriving at the diagnosis. These included nausea and vomiting, radiation to the back and/or right infrascapular region, or pain that awakens the patient from sleep in the middle of the night.

The most clinically relevant classification system for SOD is the modified Milwaukee Classification described for both biliary [32] and pancreatic [33] disorders

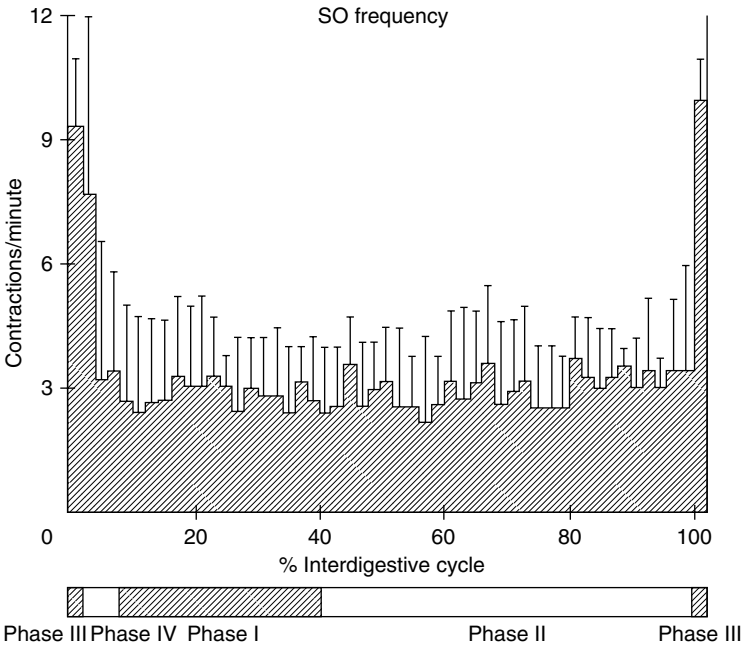


**Figure 7.4** Manometric recordings of the human sphincter of Oddi showing changes in frequency of contraction in relation to the duodenal interdigestive motility pattern.

(Table 7.4). These have been modified from the original Milwaukee Classification proposed by Hogan and Geenen [34].

Based on manometric recordings, we have previously subdivided SOD into two groups [35], namely those exhibiting a stenotic pattern (abnormally raised basal sphincter pressure >40 mmHg) and those displaying a dyskinetic pattern including paradoxical response to CCK injection, rapid contraction frequency, high percentage of retrograde contractions, or short periods of raised basal pressure [36]. These patients display an abnormal response to morphine or a fatty meal stimulus. It has been hypothesized that the latter may contribute to the development of adult choledochal cysts [37,38].

The stenotic subtype of SOD is characterized by pathomorphologic changes evident on histologic examination of sphincter complexes resected at the time of transduodenal sphincteroplasty for patients with severe postcholecystectomy pain. The changes contributing to the high basal pressure include inflammation of the papilla and its transampullary septum or fibrosis with or without inflammation, papillary cholesterolosis [39], muscle hypertrophy, or mucosal edema [40]. These findings have been reported in 58% of patients undergoing transduodenal sphincteroplasty and transampullary septectomy for postcholecystectomy pain [39] and have been hypothesized to be due to the chronic passage of small gallstones [39]. This subtype corresponds to the Modified Milwaukee type 1 and responds best to sphincterotomy (surgical or endoscopic). We have previously demonstrated that surgical sphincteroplasty and septectomy when performed for manometrically confirmed sphincter of Oddi stenosis in patients with recurrent pancreatitis resulted in a good clinical outcome in a majority of patients [41,42].

The dyskinetic subtype, on the other hand, is believed to be the result of a functional or neurohormonal disturbance in the absence of any pathologic reproducible abnormalities [35]. Infections such as *Cryptosporidium* and HIV have also been shown to lead to features of SOD [43]. This subtype corresponds to the type 2 and 3 of the Milwaukee Classification. Sphincter of Oddi manometry is essential to arrive at the diagnosis. The paradoxical response to CCK injection noted by us [40] may be the result of a defect in the enteric nervous system akin to that described for achalasia of the esophagus [44]. Whereas sphincterotomy relieves symptoms of type 1 SOD, it is less effective in alleviating symptoms of this subtype [45] and is associated with a risk of early recurrence of symptoms on follow-up [46]. However, results of sphincterotomy, in terms of pain relief, are more encouraging in those patients with type 2 and 3 SOD who had demonstrable preprocedure abnormalities in manometry [47]. The response to sphincterotomy in this subtype is not uniform. We have elucidated experimentally the various mechanisms by which galanin may be involved in the pathogenesis of acute pancreatitis [48]. Given the action of galanin on the sphincter of Oddi [23], its contribution to SOD-induced acute pancreatitis [49]

**Table 7.3** Rome III compulsory diagnostic criteria for sphincter of Oddi disorders.

1) Episodes lasting 30 minutes or longer
2) Recurrent symptoms occurring at different intervals (not daily)
3) The pain builds up to a steady level
4) The pain is moderate to severe enough to interrupt the patient's daily activities or lead to an emergency department visit
5) The pain is not relieved by bowel movements
6) The pain is not relieved by postural change
7) The pain is not relieved by antacids
8) Exclusion of other structural disease that would explain the symptoms

**Table 7.4** Modified Milwaukee Classification for biliary and pancreatic sphincter of Oddi dysfunction.

| | Diagnostic criteria | |
|---|---|---|
| **Classification** | **Biliary** | **Pancreatic** |
| Type 1 | A) Biliary-type pain<br>B) Elevated ALT, AST, ALP >1.1 times the upper limit of normal on one occasion<br>C) Bile duct diameter ≥9 mm | A) Pancreatic-type pain<br>B) Serum amylase or lipase level of 1.1 times the upper limit of normal on one occasion<br>C) Duct dilatation of >6 mm in the head and >5 mm in the body of the pancreas |
| Type 2 | A) Biliary-type pain with either B or C in the criteria mentioned in Type 1 | A) Pancreatic-type pain with either B or C in the criteria mentioned in Type 1 |
| Type 3 | A) Biliary-type pain only without other abnormalities | A) Pancreatic-type pain only without other abnormalities |

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

is worthy of consideration. Use of galanin antagonists [50–53] may thus offer a potential therapy in this subgroup of patients.

The underlying causes of pain in SOD remain conjectural and include relative obstruction of flow through the sphincter of Oddi resulting in bile duct or pancreatic duct distension, "ischemic" pain arising from spastic contractions, hypersensitivity of the papilla, and severance of nerves supplying the sphincter of Oddi during cholecystectomy. Other potential explanations include duodenal-specific visceral hyperalgesia (in type 3 SOD) [54], continuous visceral pain (biliary pain) caused by local inflammatory/sensitizing processes or persistent hyperexcitability of the nociceptive neurons in the central nervous system [55], or other functional gastrointestinal disorders including intestinal dysmotility [56], irritable bowel syndrome (IBS), and nonulcer dyspepsia.

## Conclusion

The sphincter of Oddi is a small but important complex muscle that modulates flow of bile and pancreatic juice across one of the busiest anatomic junctions of the body. Its activity is controlled by an interaction of neuronal and hormonal modulators. In such a complex structure, it is not surprising that at times disorders in motility arise and these disorders lead to significant clinical syndromes.

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# 8

# Neurohormonal and Hormonal Control of Pancreatic Secretion

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## Introduction

The pancreas, one of the most important organs in the digestive tract, has both exocrine and endocrine functions. The exocrine pancreas secretes digestive enzymes and $HCO_3^-$ to facilitate digestion and absorption of nutrients. The endocrine pancreas releases hormones that regulate metabolism and the disposition of the breakdown products of food.

The human pancreas secretes about 1 L of juice daily, containing mostly water, electrolytes, and digestive enzymes. Mediation of postprandial pancreatic secretion has been ascribed mainly to the hormones secretin and cholecystokinin (CCK) and to vagovagal reflexes that activate cholinergic postganglionic neurons in the pancreas. In addition to these classical pathways, other regulatory peptide hormones and neurotransmitters may be involved.

## Stimulation of Pancreatic Secretion

### Hormonal Mechanisms

#### Secretin

Secretin is the most potent and efficacious stimulant of pancreatic fluid and $HCO_3^-$ secretion in humans and all other species tested. It is synthesized by small intestine S-type enteroendocrine cells and is released postprandially. Duodenal pH is the major regulator of secretin release. A threshold pH of 4.5 triggers secretin release and stimulates pancreatic $HCO_3^-$ secretion [1,2]. Below this pH, pancreatic $HCO_3^-$ output is related to the total amount of titratable acid presented to the duodenum. Secretin levels in humans increase by only a few picomoles postprandially because food buffers much of the gastric acid and pancreaticobiliary secretion neutralizes the remaining acid entering the duodenum by [3]. The mechanism by which acid stimulates secretin release is unclear. In rodents it was shown that $H^+$ may release a secretin-releasing factor into the proximal intestinal lumen to stimulate secretin release [4]. Secretin-producing cells appear to have acid-sensing ion channels belonging to the transient receptor potential (TRP) channel family. Hence luminal acid likely stimulates secretin release by more than one mechanism.

Nonacid factors may influence postprandial secretin release. Nutrients such as oleic acid and other digestive products of fat can increase plasma secretin levels and pancreatic $HCO_3^-$ secretion [5,6]. Bile in the upper gut can also stimulate secretin release [7]. However, the physiologic importance of these nonacid factors in postprandial secretin release is questionable, as the postprandial plasma secretin level does not increase in achlorhydria or in health if meal-induced acid secretion is neutralized with $NaHCO_3^-$.

The pancreas appears highly sensitive to the small amounts of secretin released into the circulation postprandially [7,8]. *In vitro* animal models show that secretin stimulates $HCO_3^-$ secretion by isolated ducts or duct fragments [9,10]. $^{125}$I-labeled secretin and autoradiography revealed a secretin-binding site on pancreatic acini and duct cells [11], suggesting that secretin acts directly on the pancreas to stimulate pancreatic secretion. Conversely, *in vivo* studies have shown that the effect of secretin at physiologic doses is highly sensitive to atropine [12,13]. Receptor autoradiography, immunocytochemistry, and electrophysiology demonstrate the presence of secretin receptors in vagal afferent fibers [14–16]. Vagal nodose ganglia also contain high-affinity $CCK_1$ receptors [16]. Injection of a subthreshold dose of CCK-8 (5 pM) significantly enhances the neural response

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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to 5 pM secretin. This synergistic interaction helps to explain the robust postprandial pancreatic $HCO_3^-$ and enzyme secretion of the despite a modest postprandial increase in plasma CCK and secretin.

**Cholecystokinin**

CCK is the other gut hormone that plays an important role in pancreatic secretion. It is synthesized in specific enteroendocrine I cells in the proximal intestine and released by hydrolytic products of digestion such as amino acids and fatty acids [17]. Undigested fat is ineffective, but products of lipolysis such as fatty acids are the most potent stimulants of CCK release [18]. The CCK response to fatty acids is influenced by chain length, saturation, concentration, and total load [19].

Fasting plasma CCK levels are low, averaging about 1 pM in humans [20–22]. Postprandially, the plasma CCK concentration increases to 6–8 pM within 10–30 min, then gradually declines to basal levels during the ensuing 3 h [21,22]. Several molecular forms of CCK appear to be released into the circulation postprandially, including CCK-58, CCK-33, CCK-22, CCK-12, and CCK-8 [23], CCK-58 being predominant in dogs and humans and the only form detected in rats [24–26].

Nutrients may stimulate CCK secretion by a number of mechanisms. In species such as the rat, in which feedback inhibition of pancreatic enzyme secretion occurs, CCK release is mediated by a trypsin-sensitive CCK-releasing peptide [27]. Duodenal peptone stimulates serotonin (5-hydroxytryptamine; 5-HT) release from intestinal enterochromaffin cells, which in turn activates submucosal sensory substance P neurons. Signals are then transmitted to cholinergic interneurons and to epithelial CCK-releasing peptide-containing cells by way of cholinergic secretomotor neurons [27]. CCK release may be controlled by the level of active intraluminal proteases [28–30]. Protein, the major food stimulant of CCK secretion in rats, may bind or inhibit intraluminal endopeptidases, which would otherwise inactivate the CCK-releasing peptide [31] (Fig. 8.1).The mechanisms responsible for the actions of CCK-releasing peptide in humans are unclear, but may be similar to those in rats as feedback regulation of CCK release by proteases also occurs in humans. Study of CCK secretion from purified CCK-producing cells shows that amino acids stimulate CCK release by binding to the $Ca^{2+}$-sensing receptor [32], whereas fatty acids bind to specific G-protein-coupled fatty acid receptors [33]. Thus CCK secretion may be mediated by more than one mechanism.

CCK plays an important role in the stimulation of postprandial pancreatic enzyme secretion. The infusion of physiologic doses of CCK produces the same level of pancreatic enzyme secretion as during the postprandial state [34]. Furthermore, administration of the potent CCK antagonist lorglumide or MK-329 produces a 50–60% inhibition of meal-stimulated pancreatic secretion in dogs [35] and humans [36]. CCK can also stimulate fluid and $HCO_3^-$ secretion [37]. The effect on $HCO_3^-$ secretion is weak but physiologically relevant because CCK potentiates the action of secretin on the pancreas [38]. In intact dogs and humans, CCK-stimulated pancreatic enzyme secretion is not potentiated by secretin [34,39,40]. The mechanisms by which CCK stimulates pancreatic enzyme secretion remain controversial. *In vitro* studies using dispersed rat pancreatic acini show that CCK-stimulated amylase release is

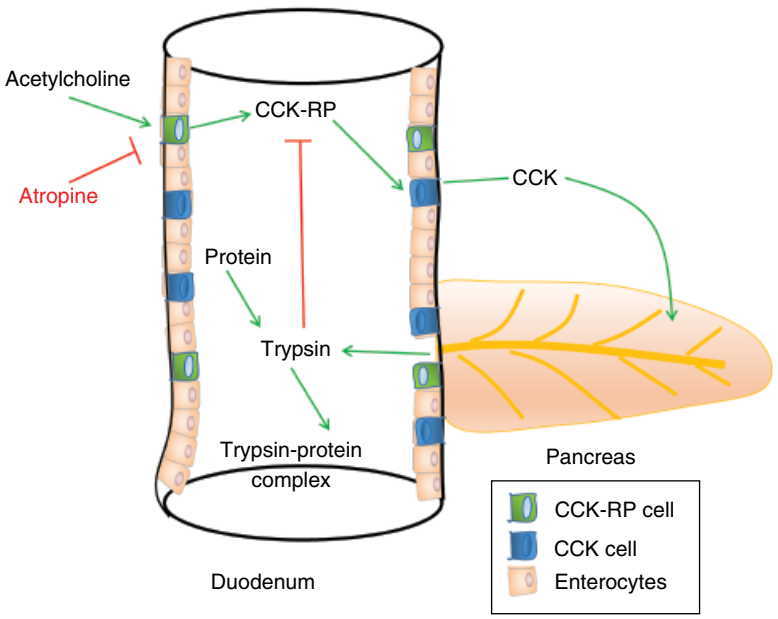


**Figure 8.1** The postulated mechanism by which cholecystokinin-releasing peptide (CCK-RP) stimulates the postprandial secretion of CCK. CCK-RP is secreted into the proximal small intestine under the influence of cholinergic pathway and inactivated by trypsin. When food enters the duodenum postprandially, protein binds to trypsin and prevents the inactivation of CCK-RP. CCK-RP stimulates CCK cells in the duodenum to release CCK into the bloodstream. CCK, in turn, stimulates pancreatic enzyme secretion.

insensitive to atropine or tetrodotoxin, indicating a direct action on pancreatic acini [41]. However, *in vivo* studies of humans and dogs have shown that atropine can block CCK-stimulated pancreatic secretion, implying involvement of cholinergic pathways [42–44]. Furthermore, enzyme output in response to low-dose CCK is reduced after vagotomy [45]. It appears that CCK can act through atropine-sensitive and atropine-insensitive pathways to stimulate pancreatic exocrine secretion. Human studies have shown that CCK-8 infusions at physiologic doses can stimulate pancreatic enzyme output predominately in an atropine-sensitive fashion [42]. Furthermore, studies in rats indicate that physiologic doses of CCK act through stimulation of vagal afferent pathways originating from the duodenal mucosa [46] (Fig. 8.2). CCK receptors have been detected in the rat vagus nerve using *in vitro* autoradiography [47]. Vagal $CCK_1$ receptors exist in high- and low-affinity states [48–50]. Under physiologic conditions, CCK appears to act through high-affinity vagal $CCK_1$ receptors to mediate pancreatic enzyme secretion [49]. In contrast, the effect of CCK on satiety is mediated by low-affinity vagal CCK receptors [51]. These findings suggest that different affinity states of the vagal CCK receptors mediate different digestive functions. Under physiologic conditions, CCK seems to stimulate postprandial pancreatic enzyme secretion through cholinergic pathways rather than through direct action on pancreatic acinar cells. M1 and M3 muscarinic receptors on pancreatic acini appear to mediate these responses [52,53] (Fig. 8.2). The molecular cloning of the CCK receptor gene and subsequent recognition that its expression is virtually absent in human pancreas [54,55] suggest that CCK acts at an extrapancreatic site. One study indicated that human acini do not respond to CCK agonists, although they respond to a muscarinic agonist [54]. In contrast, acini responded to CCK agonists after adenovirus-mediated CCK receptor gene transfer [54]. Quantitative reverse transcription polymerase chain reaction showed that $CCK_1$ receptor mRNA expression was ~30-fold lower than that for $CCK_2$ receptors, and ~10-fold lower than for $M_3$ muscarinic receptors. *In situ* hybridization did not detect $CCK_1$ receptor mRNAs in adult human pancreas, supporting the concept that CCK acts at an extrapancreatic site to stimulate enzyme secretion. By contrast, a study of isolated human pancreatic acini showed that physiologic levels of CCK induced $Ca^{2+}$ signaling, activated mitochondrial function, and stimulated enzyme secretion [56]. The physiologic relevance of these observations is unclear. $CCK_1$ receptors are expressed in human pancreatic stellate cells, which lie near acinar cells [57]. Low CCK concentrations (20 pM) stimulate acetylcholine release, which evokes enzyme secretion from pancreatic acini. Thus, it appears that CCK may regulate cholinergic stimulation of the pancreas through both neural and nonneural pathways.

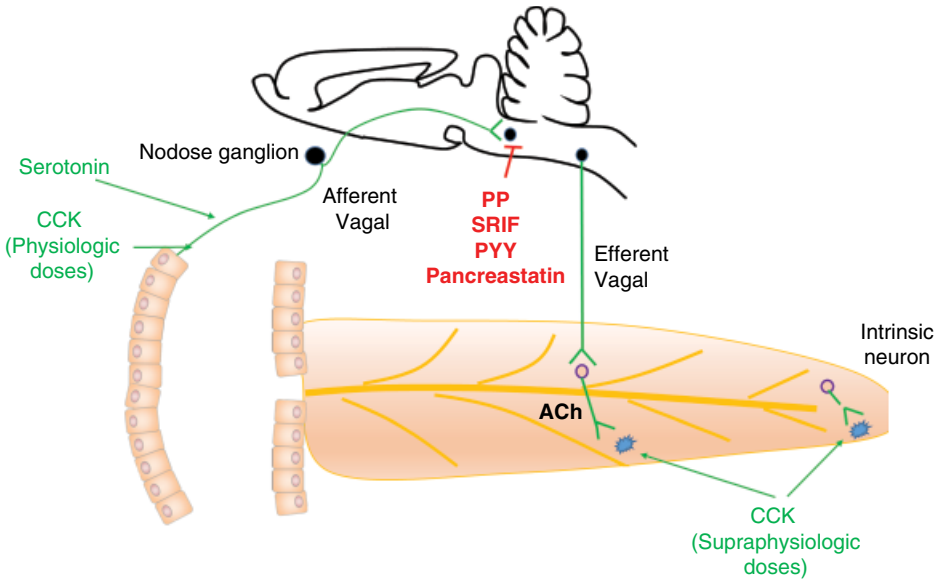


**Figure 8.2** Sites and mechanisms of action of stimulatory and inhibitory hormones to modulate pancreatic enzyme secretion. Dosages of cholecystokinin-8 (CCK-8) that produce physiologic plasma CCK levels act through stimulation of the vagal afferent pathway, which originates from the gastroduodenal mucosa. In contrast, dosages that produce supraphysiologic plasma CCK levels act on intrapancreatic neurons and, to a lesser extent, on pancreatic acini. Serotonin (5-HT), another stimulatory hormone, also acts via the vagal afferent pathway to evoke pancreatic enzyme secretion. In contrast, most of the inhibitory hormones such as PP, SRIF, PYY, and pancreastatin act at a central vagal site to inhibit pancreatic secretion. ACh, acetylcholine; PP, pancreatic polypeptide; SRIF, somatostatin; PYY, pancreatic polypeptide YY.

### Serotonin

Apart from CCK, intestinal serotonin (5-HT) appears to play an important role in mediating postprandial pancreatic enzyme secretion [58–61]. Although 5-HT is found in the myenteric plexus, the major source in the gastrointestinal tract appears to be mucosal enterochromaffin cells [62]. 5-HT is released in response to various stimuli [62], including duodenal acidification [62], instillation of hypertonic glucose, sucrose, or maltose solutions [58,63], vagal stimulation [64], and mechanical stimulation [65]. 5-HT may increase the discharge of vagal afferent fibers from the stomach and proximal intestine [66,67], which in turn can stimulate pancreatic secretion by way of a vagovagal reflex mediated by a cholinergic afferent pathway [58]. *In vivo* studies show that vagal responses to luminal osmolarity and the digestion products of carbohydrates depend on the release of endogenous 5-HT from mucosal enterochromaffin cells, which acts on $5\text{-HT}_3$ receptors on vagal afferent fibers [58] (Fig. 8.2).

5-HT and CCK are the principal mediators of postprandial enzyme secretion. A $CCK_1$ receptor antagonist inhibited 54% of postprandial protein secretion in rats. $CCK_1$ receptor and $5\text{-HT}_3$ antagonists combined almost completely abolished exocrine pancreatic secretion [58], suggesting that 5-HT-dependent pancreatic stimulants account for about 50% of postprandial pancreatic secretion. Vagal CCK and 5-HT receptors act synergistically to mediate pancreatic secretion [61], explaining how a small increase in the plasma CCK level is sufficient to produce a robust postprandial pancreatic secretion.

### Other Hormones and Stimulatory Factors

*Insulin* plays a significant role in modulating exocrine pancreatic secretion [68]. Animal studies have demonstrated that insulin potentiates the secretory response of secretin plus CCK [69], and that ouabain, an inhibitor of $Na^+,K^+$-ATPase activity, abolishes the stimulatory action of insulin. Physiologically, the actions of insulin are important because immunoneutralization experiments in conscious rats showed that pancreatic secretion of water, $HCO_3^-$, and protein stimulated by a meal or by a combined intravenous infusion of physiologic doses of secretin and CCK is markedly reduced when the circulating insulin is neutralized with a rabbit anti-insulin antibody [70]. It is well known that pancreatic enzyme secretion is often reduced in diabetes without overt pancreatic disease [71]. This may be mediated by enhanced activation of the TRESK $K^+$ channel in the nodose ganglia of diabetic rats, reducing the excitability of the nodose ganglia and contributing to decreased pancreatic secretion mediated by the vagovagal reflex [72].

*Bombesin* (a gastrin-releasing peptide in mammals), a polypeptide isolated from the skin of frogs and also found in the human digestive tract, stimulates pancreatic secretions that contain small amounts of $HCO_3^-$ and high concentrations of enzymes in humans [73,74]. Bombesin can act directly on the pancreas, or indirectly by promoting CCK release from the small intestinal mucosa [75]. In other systems, bombesin reportedly exerts its effect by way of a cholinergic pathway [76]. Hence bombesin may act through different pathways to stimulate pancreatic secretion. However, the physiologic importance of bombesin in pancreatic secretion is uncertain as bombesin receptor antagonists do not influence postprandial enzyme secretion in mammals [77].

*Neurotensin* appears to stimulate pancreatic enzyme secretion in humans and dogs [78,79]. In rats, the stimulation appears to be neurally mediated, involving cholinergic vagal afferent pathways [80]. Neurotensin is released by intestinal fatty acids, suggesting a role in mediating fat-stimulated pancreatic secretion [79]. However, exogenous infusion of neurotensin in doses that stimulate pancreatic secretion results in a plasma level much higher than after a normal meal [78,79].

*Ghrelin*, found in gastric endocrine cells and in neurons of the hypothalamic arcuate nucleus [81–83], has been shown to stimulate pancreatic enzyme secretion. It acts as an endogenous ligand for the growth hormone secretagogue receptor [81–83], which is found throughout the body, including the hypothalamus and the pancreatic islet and acinar cells. Depending on the animal species, ghrelin acts directly [84] on acinar cells or centrally through the vagal cholinergic pathways [85].

*Nitric oxide* (NO) is present in pancreatic neurons and vascular endothelium [86], and appears to play a significant role in regulating pancreatic secretion. In humans, L-NAME, an inhibitor of NO production, dose dependently reduces enzyme secretion stimulated by secretin and cerulein [87]. *In vitro*, NO synthase inhibition has no effect on amylase release or intracellular $Ca^{2+}$ concentration in rat pancreatic acinar cells stimulated by carbachol and CCK-8 [88]. L-NAME also reduces CCK-stimulated pancreatic microvascular blood flow and at the same time decreases pancreatic fluid and protein output in rats [89]. This observation may have clinical importance because inadequate blood flow has been associated with clinical pancreatitis. Interestingly, treatment with the NO donor L-arginine before and after cerulein injection increases pancreatic blood flow and reduces the severity of cerulein-induced hemorrhagic pancreatitis. These observations suggest that NO may protect the pancreas from injury, possibly because it increases pancreatic blood flow.

## Neural Mechanisms

### Parasympathetic Nervous System

The pancreas is innervated by parasympathetic and sympathetic nerve fibers. The parasympathetic fibers pass through the pancreas directly through the vagus nerve and indirectly by the celiac ganglion, the splanchnic nerves, and perhaps through the intramural plexus of the duodenum. In humans, the vagus nerve appears to play an important role in mediating pancreatic secretion. Insulin-induced hypoglycemia, which is presumed to stimulate the vagus nerve centrally, augments secretin-stimulated pancreatic protein output [90]. Vagotomy reduces the $HCO_3^-$ secretory response to exogenous hormones. Furthermore, vagotomy also reduces pancreatic enzyme responses to intestinal stimulants and food [45,91]. Cholinergic stimulation appears primarily to modulate the actions of gut peptides on pancreatic secretion but has no physiologically relevant effect on CCK or secretin release [92].

In humans, stimulation of duodenal volume receptors and osmoreceptors elicits a pancreatic enzyme response mediated by cholinergic neurons [93,94]. Increased firing in peripheral afferent vagal neurons and in central sites has been recorded after gastric distension and intestinal perfusion with amino acids and HCl [95–97].

Intrapancreatic postganglionic cholinergic neurons regulate enzyme and $HCO_3^-$ secretion. These neurons are activated by central input during the cephalic phase and by vagovagal reflexes initiated by gastric- and intestinal-phase stimulation. Acetylcholine released by pancreatic neurons may act directly on acinar cells or potentiate the action of secretin on $HCO_3^-$ secretion from duct cells *in vitro*. Acetylcholine and CCK interaction is additive. The enteropancreatic reflex may also play a role in mediating postprandial enzyme secretion [94]. This is especially important after chronic vagotomy [98].

### Sympathetic Nervous System

Adrenergic innervation of the pancreas occurs mainly through the splanchnic nerves, which are distributed to blood vessels, with a few passing to acini and ducts [38].

Activation of splanchnic nerves usually inhibits exocrine and endocrine pancreatic secretion; splanchnic nerve stimulation decreases and splanchnicectomy increases pancreatic secretion in response to pancreatic stimulants [38,99]. These responses are likely mediated by vasoconstriction caused by stimulation of α-adrenergic receptors on blood vessels. Physiologically, the major role for adrenergic activation appears to be the inhibition of fluid and $HCO_3^-$ secretion, which is mainly mediated by vasoconstriction.

### Enteropancreatic Neural Reflex

Functional and anatomic enteropancreatic neural connections have been demonstrated by anterograde and retrograde tracing. Neurons in the ganglia of the myenteric plexus of the stomach and duodenum project directly to the pancreas [100]. Stimulation of duodenal myenteric neurons can influence endocrine and exocrine pancreatic functions in the rat. These enteropancreatic neural pathways have cholinergic and serotonergic components [100,101]. The cholinergic nerves from the duodenum stimulate intrapancreatic neurons through nicotinic synapses. In contrast, stimulation of enteropancreatic serotonergic axons inhibits pancreatic secretion through presynaptic $5\text{-}HT_{1P}$ receptors on cholinergic nerves [100]. The physiologic role of the serotonergic enteropancreatic neural pathways is unclear.

## Inhibition of Pancreatic Secretion

The regulation of pancreatic secretion depends on the balance between inhibitory and stimulatory influences exerted through hormones and the autonomic nervous system. The inhibitory phase of pancreatic secretion is mediated by many hormones.

### Pancreatic Polypeptide (PP)

PP is localized in the islets of Langerhans and between the acinar cells of the exocrine pancreas [102]. PP secretion is regulated mainly by a cholinergic mechanism [103]. Postprandial PP release is mediated by a long vagovagal reflex and short local cholinergic pathways [103].

In humans and dogs, infusion of physiologic concentrations of PP inhibits basal and stimulated pancreatic secretion [103,104]. *In vivo*, PP appears to act preferentially by inhibiting vagal stimulation [105]. *In vitro*, PP inhibits pancreatic enzyme secretion by way of presynaptic modulation of acetylcholine release [106]. Because its secretion is under cholinergic control and it acts by interfering with cholinergic transmission, PP is an ideal candidate to modulate pancreatic secretion stimulated by the cholinergic enteropancreatic reflex. PP may also act centrally, as suggested by the presence of PP receptors in discrete locations in the hypothalamus, limbic system, brain stem, and other central locations [107,108]. Microinjection of PP into the dorsal motor nucleus (DMV) inhibits CCK-stimulated pancreatic secretion, suggesting that the DMV is an important site for neural feedback inhibition of pancreatic exocrine secretion [109]. Hence PP acts at multiple brain stem sites to modulate vagal cholinergic efferent output to the pancreas [110].

### Glucagon

Glucagon also inhibits pancreatic exocrine secretion stimulated by secretin and CCK or by ingestion of a test meal in dogs, cats, rats, and humans [111–113]. The inhibitory characteristics are reduced flow volume and decreased $HCO_3^-$ and enzyme secretion. Currently, the sites of action are unclear.

### Somatostatin

Somatostatin, present in the pancreas and also the upper gastrointestinal tract and central nervous system, may also play a role in the inhibition of pancreatic secretion. Research indicates that somatostatin does not act on peripheral vagal afferent or efferent pathways or directly on pancreatic acinar; it exerts its inhibitory action at a central vagal site [114]. Somatostatin injected into the DMV significantly inhibits pancreatic exocrine secretion evoked by intravenous administration of CCK-8 or 2-deoxy-D-glucose, suggesting that somatostatin acts through a central cholinergic mechanism [115,116].

### Enteroglucagon

Enteroglucagon is an intestinal hormone believed to mediate the inhibitory action of hypertonic glucose infusion into the jejunum. In animal studies, infusion of oxyntomodulin, a 37-amino acid glucagon-containing peptide isolated from porcine lower intestine, inhibits basal and cerulein-stimulated pancreatic secretion of $HCO_3^-$ and enzymes [117]. The inhibitory action of enteroglucagon is 10-fold more potent than that of pancreatic glucagon.

### Peptide YY (PYY)

PYY is a 36-amino acid peptide found in the distal intestine and colon of humans and experimental animals [118]. It is released by fat and, to a lesser extent, protein in the ileum or colon. PYY infusion in dogs significantly inhibits basal and meal-stimulated pancreatic $HCO_3^-$ and enzyme secretion [119]. Physiologic experiments demonstrate that intraileal, but not colonic, carbohydrate increases plasma PYY levels and decreases amylase secretion in dogs [120]. In humans, ileal carbohydrate perfusion inhibits exocrine pancreatic secretion. Therefore, PYY may represent a late postprandial event, serving as a physiologic signal to reduce exocrine pancreatic secretion after completion of digestion and nutrient absorption.

### Glucagon-Like Peptide 1 (GLP-1)

GLP-1 is another ileal hormone that is elevated in the circulation during ileal carbohydrate infusion. GLP-1 does not appear to act directly on the pancreas to inhibit exocrine secretion. In anesthetized pigs with cut splenic nerves, intravenous GLP-1 infusion inhibits hypoglycemia-induced pancreatic $HCO_3^-$ and protein secretion, effects absent in vagally stimulated, isolated, and perfused porcine pancreas [121], suggesting that GLP-1 acts through a central mechanism. Studies in rats indicate that GLP-1 inhibitory action depends on intact vagal nerves [122].

### Other Peptides

Although the list of peptides known to inhibit exocrine pancreatic secretion continues to expand, little is known about the mechanisms through which these and other hormones or neurotransmitters inhibit pancreatic enzyme secretion. Most of these peptides lack direct inhibition of pancreatic acinar cells and most suppress pancreatic enzyme secretion *in vivo* but do not act directly on acinar cells to reduce pancreatic enzyme release. Animal studies suggest that peptides such as PP, somatostatin, calcitonin gene-related peptide (CGRP), enkephalin, and pancreastatin inhibit pancreatic enzyme secretion by modulating cholinergic transmission, and most, if not all, act through a central vagal site [123–129].

## Feedback Regulation of Pancreatic Secretion

A series of observations in rats suggest that intraluminal actions of pancreatic proteases play an important role in regulating pancreatic enzyme secretion [28,130]. It was demonstrated that diversion of pancreatic juice in the duodenum stimulates CCK release and pancreatic enzyme secretion [29]. Conversely, intraduodenal administration of trypsin or chymotrypsin inhibits CCK release and pancreatic enzyme secretion [29]. This phenomenon is specific for activated proteases, and not with inactivated trypsin, amylase, lipase, or $HCO_3^-$.

Feedback regulation of pancreatic secretion by proteases appears to be mediated by a trypsin-sensitive substance secreted by the proximal small intestine, originally designated CCK-releasing factor (CCK-RF) [29,31]. When trypsin is present, this peptide is cleaved and inactivated. CCK-RF may mediate pancreatic enzyme secretion in response to dietary protein intake in rats. Dietary protein in the intestine competes for the trypsin that would otherwise inactivate CCK-RF [30]. The resulting increase in CCK-RF in the intestinal lumen stimulates CCK release and pancreatic enzyme secretion (Fig. 8.1).

Efforts to demonstrate a protease-sensitive feedback mechanism in humans remain controversial because of

technical limitations in removing or blocking intraluminal protease activity. Using a different approach, investigators reported that intraluminal administration of trypsin or chymotrypsin in humans suppresses CCK release and partially reduces the CCK response to intestinal administration of amino acids or oral ingestion of a test meal [22,131]. These observations support the existence of feedback regulation of pancreatic enzyme secretion in humans. Liener et al. demonstrated that Bowman–Birk soybean trypsin inhibitor, an inhibitor of chymotrypsin and elastase, strongly stimulates pancreatic enzyme secretion in humans [132].

The existence of a feedback regulation of pancreatic enzyme secretion in humans may have important clinical implications. In patients with chronic pancreatitis, decreased pancreatic enzyme secretion may result in elevated plasma CCK levels, reflecting a failure in the feedback modulation of CCK release. This may cause hyperstimulation of the pancreas and produce pain. Effective enzyme replacement therapy may reduce pancreatic stimulation, decrease intraductal pressure, and diminish pain. Large doses of pancreatic extract have reduced pain in some patients with chronic pancreatitis [133,134].

## Conclusion

Under physiologic conditions, in rodents and humans, cholinergic vagal afferent pathways rather than pancreatic acinar cells represent the primary targets on which CCK may act as a major mediator of postprandial pancreatic secretion. The vagal afferent pathways also transmit sensory information about the mechanical and physiologic state of the digestive tract, mediated in part by 5-HT, which in turn influences pancreatic secretion. A synergistic interaction between CCK and 5-HT at the level of the nodose ganglia may explain the robust postprandial pancreatic enzyme secretion despite a modest increase in plasma CCK after a meal. Interestingly, most hormones such as PP, somatostatin, CGRP, and pancreastatin act through a central vagal site to inhibit pancreatic enzyme secretion. This supports the Pavlovian concept that the neural system is the major regulator of pancreatic secretion.

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9

# Regulation of Pancreatic Protein Synthesis and Growth

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## Introduction

Regulation of pancreatic protein synthesis and growth allows the exocrine pancreas to provide an adequate supply of digestive enzymes for nutrient assimilation. In young animals, the pancreas grows along with general body growth and thereby provides an increasing amount of digestive enzymes. In the adult, digestive enzyme synthesis is regulated at both transcriptional and translational levels to match the need for both total and specific digestive enzymes. If the need for digestive enzymes is greater than can be met through these mechanisms, the pancreas can grow or regenerate. This can occur either as a result of increased food intake or because of decreased pancreatic mass due to disease. Some of the same systemic regulatory signals that regulate enzyme secretion, that is, the vagal nerve and gastrointestinal (GI) hormones, also participate in the regulation of pancreatic protein synthesis and growth, although the intracellular regulatory pathways involved are significantly different. An additional regulatory influence is provided by nutrients, especially amino acids and islet hormones, particularly insulin, which do not directly affect secretion. The purpose of this chapter is to provide a brief overview of the regulation of pancreatic protein synthesis and growth. Not all areas can be covered in depth owing to page limitations. Areas of recent progress are featured with review articles being cited to cover the older literature.

## Regulation of Protein Synthesis

Protein synthesis plays a central role in the maintenance of the pancreas and provision of digestive enzymes. Both the mRNA profile and autoradiographs of newly synthesized proteins are dominated by digestive enzymes. Whether the acinar cell can regulate digestive enzyme synthesis independent of the synthesis of cellular structural proteins is unclear. In general, the GI tract, including the exocrine pancreas, atrophies in the absence of food and protein synthesis that occurs in response to food intake helps to maintain normal function. Individual dietary components also regulate protein synthesis. In most cases, as reviewed in the following, this involves transcriptional regulation of digestive enzyme mRNA. By contrast, shorter term meal-stimulated protein synthesis is regulated primarily at the translational level. Finally, increased protein synthesis is necessary for pancreatic growth.

### Long-Term Regulation by Diet

Since the original work by Pavlov, the adaptation of the exocrine pancreas to dietary changes has been observed in a variety of species [1,2]. The content and secretion of the major digestive enzymes, proteases, amylase and lipases change in proportion to the dietary content of their respective substrates, protein, carbohydrate and fat, by stimulation of both, transcriptional and translational mechanisms [3–5]. Various hormones mediate many of these effects and in most cases their release is increased by the nutrients whose digestion they regulate. In some cases the genetic elements regulated in the promoter region have been identified although the full intracellular pathway leading to their regulation is not yet known [1].

#### Protein

Feeding a high-protein diet (typically 60–80% casein or other high-quality protein) increases the content of multiple proteases and the mRNA levels of trypsinogen, chymotrypsinogen, and proelastase [1,6], with activation

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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of the mTORC1 pathway and independently of cholecystokinin (CCK) [7]. There are, however, differential effects on different isoforms of enzymes such as trypsinogen and this increase is not mimicked by feeding a mixture of amino acids [8–10]. In another study, feeding mice a protein-free diet for 4 days resulted in a decrease in the relative pancreatic digestive enzyme content and secretion [11]. Other data showed that the stimulation of protease synthesis, by isolated pancreatic lobules following infusion of the CCK analogue caerulein, *in vivo*, was greatly increased compared with a small increase in translatable mRNA, suggesting a post-transcriptional locus for this regulation.

#### Carbohydrates

The level of carbohydrate in the diet has long been known to have significant effects on pancreatic amylase content and amylase mRNA [1,2]. This is seen when dietary carbohydrate replaces either dietary fat or protein, provided that dietary protein is adequate. Starch and sugars all similarly affect amylase, as does intravenous glucose. The effects of carbohydrate are believed to be primarily mediated by insulin. When animals are rendered diabetic, the amylase content and synthesis and mRNA levels fall dramatically, whereas lipase increases moderately [2,12]. Insulin restores the amylase synthesis and content and mRNA levels in diabetic rats. Similar decreases in amylase have been seen in obese rat and mouse models with insulin resistance. However, insulin administration to normal rats either decreases or does not change amylase, and other evidence suggests a more direct role for glucose in addition to effects on insulin. Amylase is also regulated by glucocorticoids [13], although this may not mediate dietary effects of carbohydrate. A dietary response sequence in the promoter of the amylase *Amy2.2* gene has been identified that mediates dietary adaptation and the effect of insulin [14].

#### Fat

In response to a high-fat diet (40–70% of calories as triglycerides), the content and synthesis of pancreatic triglyceride lipase increase [1]. This is accompanied by an increase in its mRNA [15,16]. Adaptation of other pancreatic lipases and colipase have been much less well studied. In neonate mice and rats, bile salt-stimulated lipase and pancreatic lipase-related protein 2 are the two predominant lipases [17]. Secretin has been proposed as a mediator of the effect of dietary lipid [18]. Fatty acids can stimulate secretin release and infusion of secretin in conscious rats led to an increase in the relative synthesis of lipase [1]. Gastric inhibitory peptide (GIP) has also been shown to increase pancreatic lipase and colipase content and mRNA levels [19]. Finally, ketones, metabolites of ingested fat, have also been proposed as a mediator of the increase in pancreatic lipase [1].

### Meal-to-Meal Regulation of Translation by Hormones and Nutrients

Whereas long-term dietary changes in digestive enzymes may be mediated by changes in mRNA expression, short-term meal-to-meal control needs to be immediate, reversible, and flexible. Such control of protein synthesis is mainly at the translational level. This section reviews the effects of food intake and hormones, especially CCK and insulin, on the exocrine pancreas translational machinery. Translation of mRNA into protein can be divided into three phases: initiation, elongation, and termination. For details on these three mechanisms, the reader is referred to recent reviews on translation [20–23]. Only a few studies have evaluated the immediate regulation of the pancreatic translational synthetic machinery after food intake. Early studies showed that fasting reduces total protein synthesis in the pancreas and refeeding stimulates it [24,25]. We have demonstrated that feeding a regular meal activates protein synthesis in the mouse pancreas at the translational level without an increase in the mRNA of the digestive enzymes [26]. In humans, feeding increases both the rate of secretion and synthesis of digestive enzymes, although the rate of turnover of zymogens remains fairly constant during feeding and fasting [27]. In rats and mice, feeding stimulates the protein kinase B (PKB/Akt)/mammalian target of rapamycin complex 1 (mTORC1) pathway and the phosphorylation of 4E-BP1 and ribosomal protein S6, downstream of mTORC1, in addition to the formation of the eIF4F complex [26] as illustrated in Fig. 9.1.

Dietary protein and amino acids have also been shown to be necessary to stimulate pancreatic protein synthesis at the translation initiation level in mice after 2 h of feeding [28]. This study demonstrates that when protein or leucine was removed from the diet, there was a strong inhibition of total protein synthesis and decreased polysomal fraction, with an increased eIF2α phosphorylation; the general controlled nonrepressed (GCN2) kinase was phosphorylated when leucine was not present. Dietary protein and amino acids have also been shown to stimulate pancreatic protein synthesis and pancreatic growth in rats [29] and mice [7] fed for several days. Branched-chain amino acids (BCAAs), particularly leucine, also stimulate the phosphorylation of 4EBP1 and S6K and the formation of the eIF4F complex in mice and rats, without the need for an increase in the hormones CCK and insulin [30]. A mechanism has been described for a direct stimulation of protein synthesis by amino acids through mTORC1 [26,30–32], and it seems that amino acids are necessary both as a signal and as a substrate for pancreatic digestive enzyme synthesis after a meal [28].

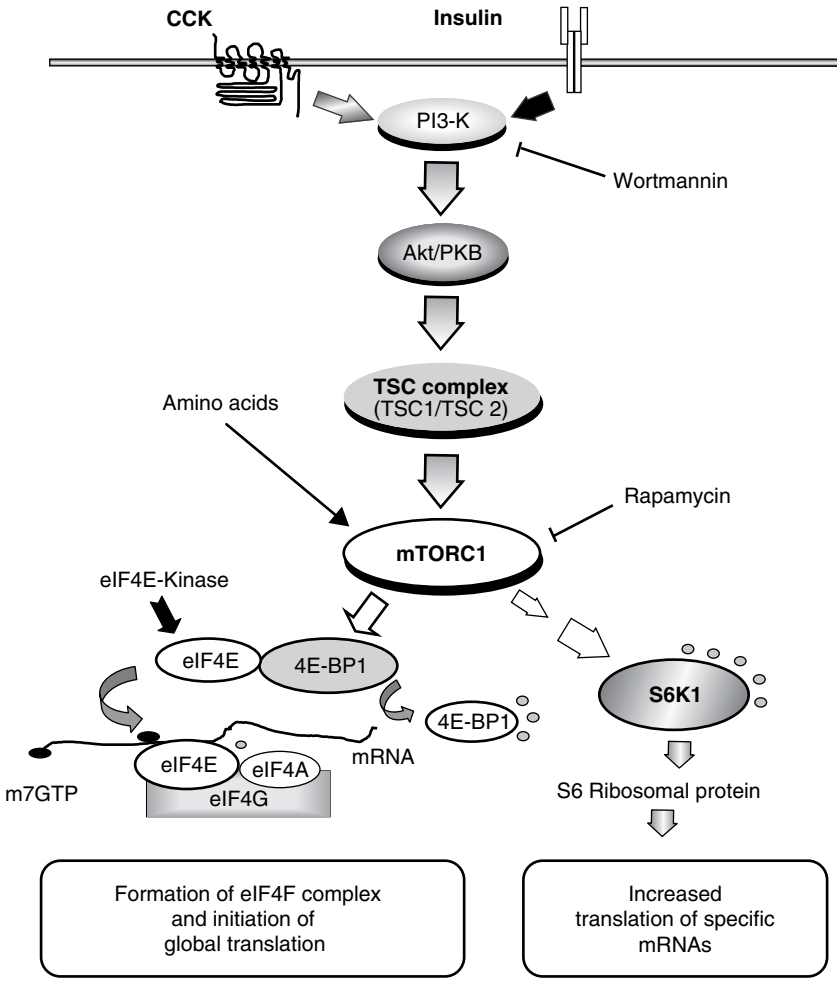


**Figure 9.1** CCK and insulin stimulate translational initiation through the P13K–PKB–mTORC1 pathway. mTORC1, which can be inhibited by rapamycin, phosphorylates the eIF4E-binding protein (4E-BP1) that allows the release of eIF4E and the formation of the eIF4F complex necessary for a global increase in translation. mTORC1 also phosphorylates S6K1 which is responsible for phosphorylating S6, thereby increasing the translation of a specific subset of mRNAs. CCK also increases the activity of an eIF4EK, leading to phosphorylation of eIF4E. Together, these effects lead to an increase in protein synthesis.

The effects of food can also be mediated by GI and systemic hormones and neurotransmitters. Their stimulatory mechanisms have been mainly studied in isolated pancreatic acini [33]. CCK, carbachol, insulin, and bombesin all stimulate the synthesis of total protein, trypsinogen, chymotrypsinogen, lipase, and amylase in isolated rat acini [34–36]. These *in vitro* studies demonstrate that CCK and insulin, at their stimulatory doses, have an additive effect on protein synthesis after 30 min, and that this effect is mainly at the translational level because it occurs without a change in mRNA levels and in the presence of actinomycin D [36,37]. Increased synthesis of both digestive enzymes and structural proteins was observed, although differences between individual proteins suggested nonparallel translational effects [37].

CCK stimulates protein synthesis in isolated rat acini and in the whole animal [38–40], by increasing the rate of translation initiation [38–41] and elongation [42], at concentrations that stimulate digestive enzyme secretion. Additionally, CCK or its analogue caerulein, activates the S6 kinase (S6K) [43,44] and the phosphorylation of eIF4E [40,41] and activates the formation of the eIF4F complex by stimulating the release of eIF4E from its binding protein 4E-BP1 and increasing the association of eIF4E with eIF4G [26,41]. These actions are summarized in Fig. 9.1. The activation of S6K, the formation of the eIF4F complex, and the activation of the elongation processes and eEF2 appear to be regulated through a rapamycin-sensitive pathway and to be downstream of phosphatidylinositol 3-kinase (PI3K) [39,42,43]. The calcium–calmodulin-activated phosphatase calcineurin is also involved in the activation of CCK-stimulated pancreatic protein synthesis and the regulation of the translational machinery [40]. As mentioned earlier,

insulin also stimulates protein synthesis in pancreatic acini *in vitro* [35] by activating the eIF4F complex formation, in a similar manner to CCK [39]. Insulin stimulates pancreatic digestive enzyme synthesis *in vivo*, after a meal. This has been demonstrated with the use of pancreatic acinar cell conditional insulin receptor (IR) knockout mice [44]. The activation of the Akt/mTORC1 pathway is reduced in the pancreas of these mice after 2 h of a meal feeding, and also the translational machinery and polysomal fraction. Additionally, the protein content of the stimulated pancreatic juice is reduced, but not the total pancreatic juice volume, compared with their littermate controls. This demonstrates that insulin is an important physiologic regulator of the pancreatic digestive enzyme synthesis and acinar cell homeostasis that could lead to pancreatic insufficiency during diabetes.

At concentrations of CCK and cholinergic analogues that inhibit secretion [33], protein synthesis is also inhibited [34,38,45]. In minced rabbit pancreas, however, only a decrease in protein synthesis was observed in response to CCK, and this was accompanied by a decrease in the number of polysomes [45].

### Inhibition of Pancreatic Protein Synthesis. Endoplasmic Reticulum (ER) Stress and Unfolded Protein Response (UPR)

*In vivo*, inhibition of pancreatic protein synthesis occurs during the development of acute pancreatitis [46]. This inhibition is accompanied by a reduction in the activity of the guanine nucleotide exchange factor eIF2B, an increase in eIF2α phosphorylation, and a decrease in the formation of the eIF4F complex [38,40,46] (Fig. 9.2). Additionally, this inhibitory effect appears to be calcium related, because the incubation of isolated acini in calcium-free media or with A23187 and thapsigargin to release intracellular $Ca^{2+}$ increases eIF2α phosphorylation and inhibits eIF2B activity. This suggests that pancreatic acinar cells adapt to short-term stress induced by reduction in calcium stores by inhibiting protein synthesis of pancreatic enzymes [38,45]. The ER-resident kinase (PERK) [47] mediates eIF2α phosphorylation in the exocrine pancreas [48,49] and activates the ER stress mechanisms. The inhibition of protein synthesis associated with high concentrations of CCK could therefore be an adaptive or protective mechanism in response to stress localized in the ER [38,46].

ER stress mechanisms are protective cellular responses to stress in the ER, due to an accumulation of unfolded or misfolded proteins in this cellular compartment that trigger the UPR [49]. ER stress and UPR mechanisms have been described in some experimental models of acute pancreatitis [46,50], in pancreatic acinar cell damage *in vitro* [51], and in induced pancreatic acinar cell damage due to alcohol abuse *in vivo* [52].

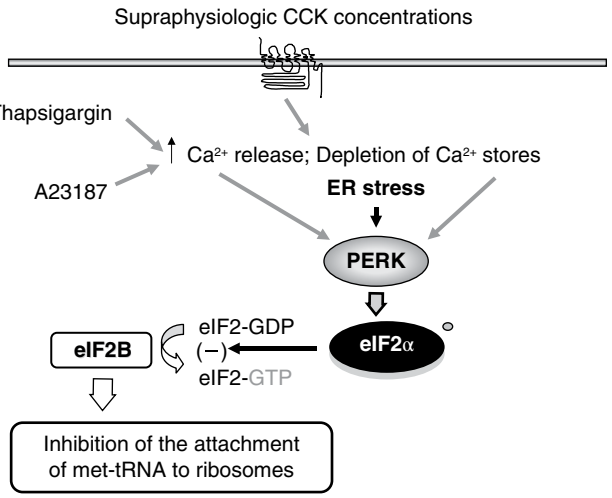


**Figure 9.2** Mechanism by which high concentrations of CCK and induction of ER stress inhibit initiation of translation. Depletion of intracellular $Ca^{2+}$ stores or other forms of ER stress activates a kinase (such as PERK), which phosphorylates eIF2α and thereby inhibits eIF2B. This inhibition results in a decrease in protein synthesis.

It is possible that all these highly regulated mechanisms of protein synthesis and associated ER stress are present in pancreatic cancer.

## Regulation of Pancreatic Growth

The pancreas arises embryologically as an outgrowth of the foregut that develops through a relatively undifferentiated duct-like state into acini, islets, and mature ducts under the influence of mesenchyme and a number of transcriptional regulators [53]. By birth, the pancreas has assumed its fully differentiated form and histology but continues thereafter to grow in parallel with body growth. In the adult animal, acinar and islet cells were originally assumed to be no longer dividing but in fact they both show a small but finite turnover that can be accelerated by hormones and diet. Hence the acinar and beta islet cells are considered to exist in the Go phase of the cell cycle rather than being terminally differentiated. Whether undifferentiated stem cells remain in the adult pancreas or if small duct cells can function as stem cells remains controversial.

In the exocrine pancreas, enhanced growth in response to hormones or diet can take the form of cellular hypertrophy in which protein increases in excess of DNA resulting in larger cells, or cellular hyperplasia marked by an increase in DNA resulting in more cells. Normally in hyperplasia, protein increases in parallel with DNA so the endpoint is normal-sized cells. In hypertrophy and hyperplasia, there is usually an increased total digestive

enzyme content in the pancreas, although the concentration relative to DNA or total protein may or may not change. Although not well studied, glandular atrophy can result from loss of cellular protein, as seen with protein-deficient diets [11], or from loss of cells, as seen with some forms of pancreatitis following apoptosis or necrosis. Two distinct types of *in vivo* growth to be discussed are adaptive growth in response to diet and hormones and regeneration following the loss of functional cells. The use of cell culture as a model for pancreatic growth will also be reviewed.

## Adaptive Growth in Response to Nutrients and Hormones

To insure adequate nutrient absorption, the amount and composition of digestive enzymes secreted by the pancreas must complement the size and macronutrient composition of a meal. Although the synthesis and secretion of digestive enzymes can increase with consumption of larger and/or more frequent meals, this capacity is finite. Another mechanism whereby the pancreas can adapt to increased feeding is through growth of the acinar cells. Both a high-protein diet and hyperphagia that occurs with cold exposure, pregnancy, and lactation are associated with pancreatic growth.

GI hormones released after a meal may contribute to the growth-promoting effects of feeding on the exocrine pancreas as CCK, secretin, and gastrin have all been shown to induce pancreatic growth [54,55]. The effects of CCK have been studied extensively in rodents and have been reviewed previously [56,57]. Direct administration of CCK or caerulein induces acinar cell growth *in vivo* [54,55,58] and *in vitro* [59]. Feeding a high-protein diet and especially synthetic or naturally occurring trypsin inhibitors, such as those found in raw soy flour, prevents feedback regulation of CCK secretion and culminates in maintained high concentrations of circulating CCK [60], which also stimulates pancreatic growth [61]. Oral trypsin inhibitor-induced pancreatic growth is blocked by coadministration of CCK antagonists [62] and is absent in CCK [63] and CCK-A receptor-deficient mice [64]. In the rat, CCK-stimulated growth is primarily through cellular hypertrophy, but with some hyperplasia, whereas in mice it is primarily through hyperplasia. In both cases, the hyperplasia involves DNA synthesis and replication of mature acinar cells [65]. Although CCK can mediate adaptive growth, it does not appear essential for growth during development and CCK or its receptors are not necessary in most studies for maintenance of normal pancreatic size. In contrast to CCK, the hormone secretin had little effect by itself but can potentiate the action of CCK [54].

More recently, information has emerged on intracellular pathways mediating pancreatic growth (Fig. 9.3). CCK is known to activate a number of intracellular pathways potentially related to growth, including an increase in intracellular $Ca^{2+}$, three MAPK pathways, and the PI3K–mTOR pathway [33]. Most of these pathways are activated in the pancreas in response to endogenous CCK release following feeding of camostat [66]. Pharmacologic and genetic evidence exists for three major intracellular pathways, calcineurin–NFAT, mTORC1, and ERK1/2, playing nonredundant roles in

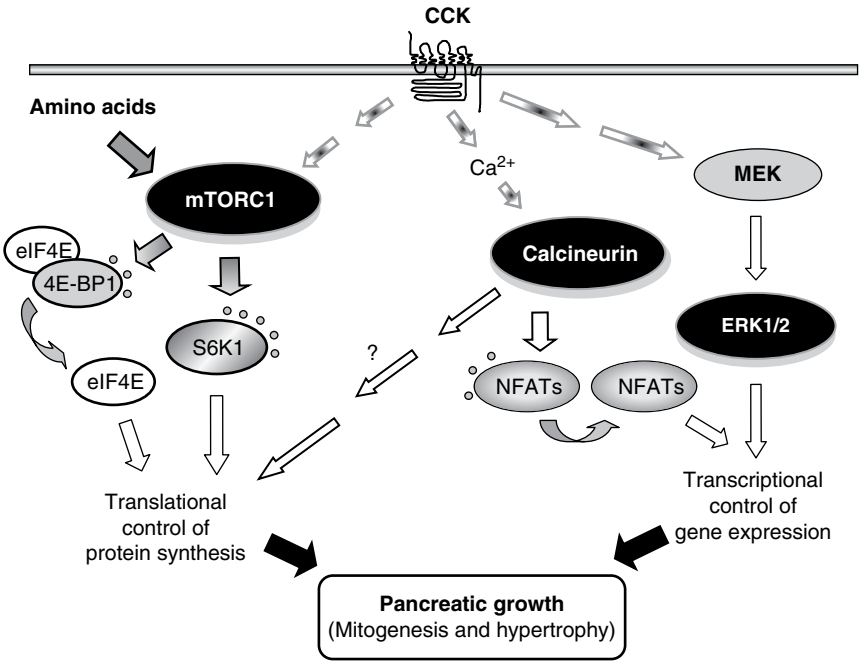


**Figure 9.3** Intracellular pathways through which CCK stimulates pancreatic growth. At least three pathways involving calcineurin–NFAT, mTORC1, and ERK1/2 have been shown to be necessary for growth of rodent pancreas either in vivo or in vitro. Inhibitors of all three pathways can block growth.

adaptive pancreatic growth. The calcineurin–NFAT pathway can be blocked pharmacologically with the calcineurin inhibitors FK506 and cyclosporin A and genetically by overexpression of *Rcan1* [63,67,68]. The mTORC1 pathway can be blocked with rapamycin [69] or by acinar cell-specific deletion of Raptor, an essential component of mTORC1 (S.J. Crozier, M.D. Sans, and J.A. Williams, unpublished data). The ERK pathway can be blocked with specific MEK inhibitors active *in vivo* such as PD-0325901 [70]. Blockage of each of these pathways blocks pancreatic adaptive growth induced by feeding camostat. These pathways are important regulators of mRNA transcription and translation and it is likely through modulation of these processes that CCK affects pancreatic growth by activating the cell cycle.

Polyamines have also been studied as mediators of pancreatic growth induced by CCK and other hormones [71]. The naturally occurring polyamines putrescine, spermidine, and spermine are normal cell components involved in protein and DNA synthesis. Biosynthesis of polyamines is initiated by ornithine decarboxylase and its inhibitor difluoromethylornithine inhibits pancreatic growth in response to CCK. However, there is no clear role for polyamines in pancreatic growth and it may be that they are simply a cellular component necessary for pancreatic growth similar to their role in intestinal adaptation and liver regeneration.

Growth of the pancreas in response to CCK administration is greatly diminished in rats fed a low-protein diet [72]. Conversely, consumption of large amounts of protein induces pancreatic hypertrophy in rodents [73], even in the presence of a CCK receptor antagonist [74] and in CCK-deficient mice [75]. Therefore, it appears that dietary protein both potentiates the effects of CCK on pancreatic growth and also stimulates pancreatic growth via CCK-independent mechanisms. These CCK-independent mechanisms are undoubtedly mediated, at least in part, by amino acids. Purified amino acids do not stimulate CCK secretion, yet ingestion of large quantities of amino acids stimulates pancreatic growth [74]. This action is mediated in large part by the mTORC1 pathway, which is activated by amino acids [7]. Interestingly, growth of the pancreas in mice fed a high-protein diet occurs predominately via cellular hypertrophy [75] whereas that associated with supraphysiologic levels of CCK, such as direct CCK administration and trypsin inhibitor feeding, in mice is primarily hyperplastic [63]. It may be that a threshold level of CCK exists, above which signal transduction pathways are activated that permit cell division following cellular hypertrophy.

Although less well studied, other hormones may also regulate pancreatic growth in response to meal feeding. Thyroid hormone, for instance, stimulates pancreatic growth *in vivo* when administered at high concentrations [76]; whether it does so at more physiologic concentrations has yet to be tested. Insulin stimulates protein synthesis in the pancreas and also growth of acinar-like AR42J cells *in vitro* [12]. Glucocorticoids can induce pancreatic hypertrophy in adult rats [77].

Activation of vagal nerve fibers to the pancreas during feeding stimulates the release of additional peptides associated with secretion of bicarbonate and digestive enzymes. Some of these neuropeptides may also play a role in the regulation of pancreatic growth and their effects have been reviewed previously [78]. In particular, vasoactive intestinal polypeptide (VIP) potentiates the effects of caerulein on pancreatic growth in a manner similar to secretin and gastrin-releasing peptide and bombesin stimulate pancreatic growth, although not as strongly as CCK.

## Regeneration

Despite the low rate of cellular turnover normally observed in the adult pancreas, studies in rodents have demonstrated its ability to regenerate in response to tissue injury. This has been studied both after pancreatitis and following surgical resection. Experimental pancreatitis induced by caerulein, arginine, bile salts, or ethionine leads to cell death by a combination of apoptosis and necrosis. The remaining acinar cells dedifferentiate and form tubular complexes that express both acinar and ductal characteristics and also some markers of embryonic pancreas. These cells divide and grow and eventually differentiate back into mature acinar cells [79–81]. At present, there is little definitive evidence for regeneration from stem cells.

Following surgical resection of 50–90% of the rat pancreas, the remnant pancreas increases in size and protein and DNA content, with the increase being greater after more complete resection [82]. However, the pancreas never regains its normal size and islets appear to regenerate to a greater extent than exocrine tissue. In some reports differentiated acinar cells are said to incorporate thymidine or show mitotic figures, whereas in other studies regeneration is reported to occur in the injured margin and show tubular complexes and express embryonic markers [83]. In mice, a 75% resection was followed by growth of the remnant by 40%, with evidence for proliferation of differentiated acinar cells [84].

Similarly to adaptive growth, dietary protein, CCK, and insulin play a significant role in the regeneration of exocrine cells following pancreatic injury. The pancreas is incapable of regeneration in rats fed a protein-free diet. Both exogenous and endogenous CCK enhance and CCK receptor antagonists slow the rate of pancreatic regeneration following pancreatitis [85]. There is also a significant decrease in the rate of pancreatic regeneration

in mice lacking the CCK-A receptor in the pancreas [86]. The importance of insulin is shown by the fact that in diabetic rats, CCK administration fails to induce pancreatic regeneration following pancreatitis unless exogenous insulin is also administered [87]. Pertinently, it has been demonstrated that the expression of IGF-1 mRNA is significantly increased following pancreatitis and resection, indicating that both insulin and IGF may be important in pancreatic regeneration.

The expression of cellular oncogenes that regulate the cell cycle and thereby control cellular proliferation rates is significantly increased in models of pancreatic regeneration [88,89]. Many genes associated with embryonic development, and whose expression is normally repressed in the adult, are re-expressed during pancreatic regeneration following pancreatitis [80]. Only a little is known of signal transduction pathways that mediate these changes in gene expression. The p42/p44 MAPK pathway, which modulates the expression of cell-cycle regulators, is activated in the regenerating pancreas [90]. Activation of the PI3K pathway has been shown to be necessary for pancreatic regeneration following resection, as inhibition of the pathway via pharmacologic inhibitors or siRNA severely diminished regeneration [84]. Moreover, the PI3K pathway activation in response to resection decreased with age and may contribute to the lessened regenerative capacity of the aged pancreas. Further identification of the signal transduction pathways, and also the factors modulating these pathways, will be important for improving our understanding of pancreatic regeneration.

### Growth of Pancreatic Cells in Culture

*In vitro* culture of differentiated or immortalized cells can be used as models for cell growth. Most pancreatic cancer cell lines, however, are undifferentiated and will not be considered here. Primary dissociated pancreatic cells, although not dividing, can be maintained in suspension culture under conditions such that they retain the differentiated phenotype or where they dedifferentiate and adopt a more plastic phenotype. When isolated acinar cells or acini are placed on an extracellular matrix such as collagen or matrigel, the cells will initiate division and remain viable for several weeks but almost invariably lose their differentiated appearance. CCK or its analogue caerulein can stimulate cell division and growth, as do insulin, epithermal growth factor (EGF), and other growth factors [59,91]. This model has been applied to evaluating which intracellular pathways mediate growth, with evidence for participation by Ras [92], PI3K/Akt [84], and MAPK pathways [93]. The dedifferentiated phenotype of cultured acinar cells was originally reported as duct like [94,95]. Subsequently, they were characterized as similar to precursor cells that can transdifferentiate into insulin-containing islet cells [96] and that the dedifferentiated cells can simultaneously express acinar, ductal, or beta-cell proteins. Another report showed retention of acinar cell phenotype with an altered medium containing a high amino acid level [97]. In a similar manner, pancreatic duct cells have been grown in monolayer culture. They retain their ion-transporting phenotype and have been used to study duct function. Their growth in culture is stimulated by EGF, TGFα, and insulin, inhibited by TGFβ, but not affected by secretion or other GI peptides [98].

Although no real differentiated pancreatic acinar cell line exists, considerable research has been carried out with AR42J cells, a rat cell line derived from a azoserine-induced tumor which under the influence of glucocorticoids assumes a more acinar phenotype [99]. However, these cells were subsequently shown also to have neuroendocrine properties and can even be driven toward an islet phenotype such that they appear more like an undifferentiated ductal epithelium. Their growth can be stimulated by CCK, gastrin, PACAP, and other peptides, but only to 25–30% and not after exposure to dexamethasone, which induces acinar differentiation but inhibits growth [99].

In summary, all the cultured pancreatic cells studied to date, although dividing and regulated by hormones, possess a relatively undifferentiated phenotype. Hence they are more a model for regenerating pancreas after pancreatitis than they are a model for diet- or hormone-driven acinar proliferation.

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# 10

# Fibrogenesis in the Pancreas: The Role of Stellate Cells

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## Introduction

Fibrogenesis is defined as the development or production of fibrous tissue. In the healthy pancreas, fibrogenesis is a well-controlled, regulated process that is essential for regular turnover of extracellular matrix (ECM) in the parenchyma, thereby maintaining normal pancreatic architecture. In diseased states, however, this process is hijacked such that the fine balance between production and degradation of fibrous tissue is disrupted, leading to the deposition of excessive amounts of ECM proteins in the organ, eventually resulting in pathologic fibrosis.

Cellular and molecular mechanisms involved in pancreatic fibrogenesis have only begun to be understood since 1998, when methods were developed to isolate and culture pancreatic stellate cells (PSC), now established as key cells in the fibrogenic process, from rodent and human pancreas [1–3]. Interestingly, the presence of these cells in the pancreas was first reported by Watari et al. [4] in Japan a decade and a half earlier (in 1982), and confirmed by Ikejiri [5] in 1990. However, little was known of their function at the time. It was the subsequent development of techniques to isolate viable PSC from the pancreas that provided the much-needed *in vitro* tool that enabled researchers to interrogate the functions of these cells both in health and in pancreatic disease.

## Pancreatic Stellate Sells (PSC)

### PSC in Health

PSC are resident cells of the pancreas located around the basolateral aspects of acinar cells (Fig. 10.1a), blood vessels, and small pancreatic ducts [1,2] and also around and within pancreatic islets [6]. In the healthy pancreas, PSC make up a relatively small proportion (4–7%) of the total parenchymal cell population [1]. In their quiescent (non-activated) state, PSC store abundant vitamin A (retinoids) in their cytoplasm. This characteristic feature identifies a cell type that is part of a larger "stellate cell system" in the body, comprising retinoid storing cells in several other organs, including the liver, lungs, intestine, kidney, spleen, and adrenal glands [7]. This vitamin A storing capacity was exploited by Apte et al. [1] to develop the density gradient centrifugation method for the isolation of quiescent PSC from the pancreas. PSC in early culture exhibit a polygonal shape with abundant lipid droplets surrounding a central nucleus (Fig. 10.1b). It is the presence of these cytoplasmic vitamin A droplets, and also the expression of selective markers such as the intermediate filaments desmin, glial fibrillary acidic protein (GFAP), and nestin, and the neuroectodermal proteins neural cell adhesion molecule and nerve growth factor, that serve to differentiate PSC from fibroblasts (Fig. 10.2).

In addition to synthesizing ECM proteins (collagen types I–IV, fibronectin, and laminin) that constitute fibrous tissue, PSC also produce matrix metalloproteinases (MMP), the enzymes that degrade ECM proteins and their inhibitors TIMPs (tissue inhibitors of matrix metalloproteinases) [8]. Thus, in the healthy pancreas, PSC are thought to regulate normal ECM turnover by maintaining a fine balance between the production and degradation of ECM proteins. Interestingly, the role of PSC in the normal pancreas is not limited to regulation of matrix turnover. Additional postulated functions for PSC in the healthy pancreas include (i) acting as intermediary cells in cholecystokinin (CCK)-dependent exocrine pancreatic secretion in humans [9]; (ii) contributing to innate immunity via expression of toll-like receptors

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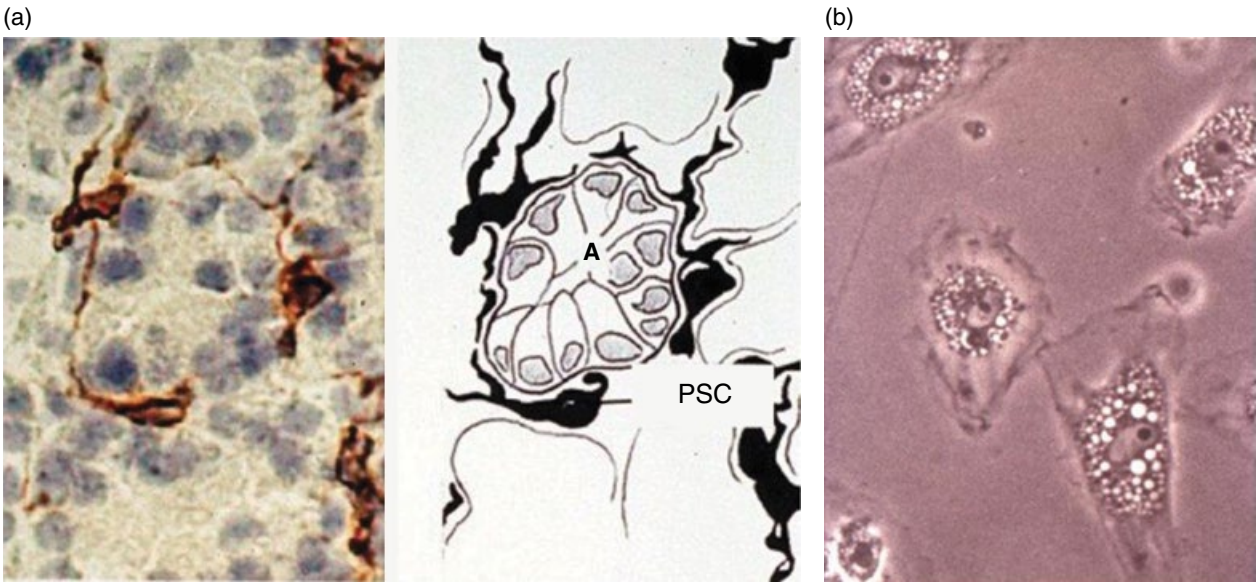


**Figure 10.1** (a) Expression of the cytoskeletal protein desmin in pancreatic stellate cells: a representative photomicrograph of a normal rat pancreatic section immunostained for the stellate cell selective marker desmin is shown on the left with a corresponding line diagram on the right. Desmin-positive (brown) PSC with long cytoplasmic projections can be seen along the basolateral aspects of acinar cells. (b) PSC in early culture exhibiting a typical flattened polygonal shape. The nucleus is surrounded by numerous vitamin A-containing lipid droplets in the cytoplasm. *Source:* Apte et al. 1998 [1]. Reproduced with permission of BMJ Publishing Group Ltd.

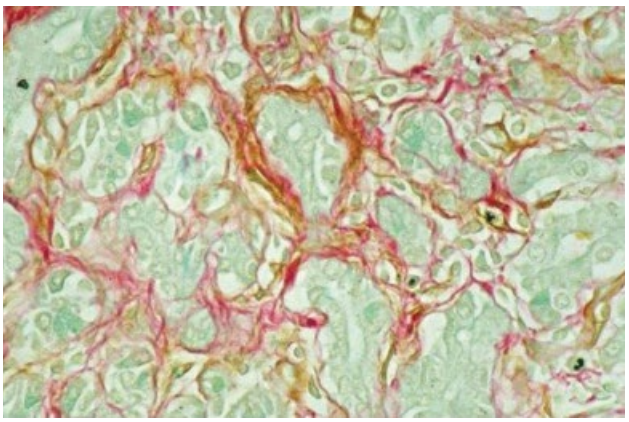

**Figure 10.2** Activated PSC in chronic pancreatitis: a dual-stained section of the pancreas from a patient with chronic pancreatitis showing colocalization of staining for the PSC activation marker alpha smooth muscle actin (aSMA, brown) and collagen using Sirius Red (red) in fibrotic areas. *Source:* Haber et al. 1999 [16]. Reproduced with permission of Elsevier.

(TLR 2, 3, 4, 5, 9), which recognize pathogen-associated molecular patterns (PAMP) [10,11]; PSC may thus actively protect the gland from initial injury [12]; and (iii) a role as progenitor cells (based on their transplantability, survival in circulation, ability to differentiate into other cell types, and expression of several stem-cell markers, including CD133, SOX9, nestin, and GDF3) [13,14].

## PSC in Disease

During pancreatic injury, PSC undergo a process of activation whereby they transform from their quiescent state to a myofibroblast-like phenotype characterized by loss of vitamin A lipid droplets, expression of the activation marker alpha smooth muscle actin (αSMA), and increased proliferation, migration, and ECM synthesis [15,16] (Table 10.1). The excessive production of ECM proteins by activated PSC outstrips the ability of the cells to degrade these proteins, ultimately leading to fibrosis of the gland. Activation of PSC can be caused by a wide range of factors, each of which is pertinent to pancreatic pathophysiology either as a factor that is upregulated/modulated during pancreatic disease or as a compound that is directly injurious to the gland. Thus, PSC are activated by alcohol and its metabolites, endotoxin, protease enzymes, oxidative stress, hypoxia, hyperglycemia, angiogenic factors and a variety of growth factors, cytokines, and chemokines, among others (Table 10.2). Notably, in addition to being activated by exogenous cytokines (released by surrounding acinar or inflammatory cells) via paracrine routes, PSC are capable of producing their own cytokines (transforming growth factor beta [TGFβ], connective tissue growth factor [CTGF], interleukins 8 and 15, CXCR1, monocyte chemotactic protein 1 [MCP1], and regulated on activation, normal T-cell expressed, and secreted [RANTES]), which can act on

**Table 10.1** Characteristics of quiescent and activated PSC phenotypes.

| Characteristic | Quiescent PSC | Activated PSC |
|---|---|---|
| Vitamin A lipid droplets | Present | Absent |
| α Smooth muscle actin | Absent | Present |
| Proliferation | Limited | Increased |
| Migration | Limited | Increased |
| Extracellular matrix production | Limited | Increased |
| Matrix metalloproteinases (MMP) and tissue inhibitors of matrix proteinases (TIMP) | Complement of MMP and TIMPs to maintain normal ECM turnover | Change in types of MMP and TIMPs to facilitate ECM deposition |
| Production of cytokines | Limited | Increased (PDGF, TGFβ, CTGF, IL-1, IL-6, IL-15) |
| Capacity for phagocytosis | Absent | Present |
| Proteomic analyses | Basal protein expression | Differential expression of proteins related to the cell cytoskeleton, cell metabolism, motility, growth, and invasion |

**Table 10.2** Pancreatic stellate cell activating factors.

| |
|---|
| Ethanol and its metabolites (acetaldehyde, fatty acid ethyl esters) |
| Inflammatory mediators (cytokines, growth factors, complement 5) |
| Proteases |
| Pigment epithelium-derived factor |
| Galectin 1 |
| Hyperglycemia |
| Parathyroid hormone-related protein (PTFrP) |
| Oxidant stress |
| Hypoxia |
| Endotoxin |
| Cyclooxygenase 2 (COX-2) |
| Endothelin-1 |
| Angiotensin |
| Fibrinogen |

**Table 10.3** Pancreatic stellate cells: signaling pathways.

| Signaling pathway | PSC functions |
|---|---|
| Mitogen-activated protein kinase (MAPK) [30,93,94] | αSMA expression, proliferation, migration, ECM protein synthesis |
| Phosphatidylinositol 3-kinase (PI3K) [32] | Migration, proliferation, ECM protein synthesis |
| Protein kinase C (PKC) [94] | ECM protein synthesis |
| Hedgehog [95] | Migration |
| JAK-STAT [96] | Proliferation |
| Smads [97] | ECM protein synthesis |
| Rho, Rho kinase [98] | Actin cytoskeleton, stress fiber formation |
| Transcription factors (AP-1, NF κB, Gli-1) [95,99] | Activation, migration, proliferation, ECM protein synthesis |
| Wnt and β-catenin [100] | Proliferation, αSMA expression, cytokine expression |
| Peroxisome proliferator-activated receptor gamma (PPARγ) [12] | αSMA expression, proliferation, phagocytosis |
| Intracellular calcium modulation [33–35] | PSC activation |

the cells in an autocrine manner [17–20]. As a consequence, a process of perpetuated activation of PSC is set up, ensuring progression of fibrosis, even in the absence of the initial activation triggers.

In contrast to activating factors, quiescence of PSC has been shown to be induced by exposure to retinol and its metabolites [21,22], curcumin (a polyphenol found in turmeric) [23], melatonin, the anthraquinone derivative rhein [24], bone morphogenic protein (BMP) [25], troglitazone (a ligand for the peroxisome proliferator activated receptor PPARγ) [26], and calcipotriol (a vitamin D receptor ligand) [27]. Most recently, kinase inhibitors such as sorafenib, sunitinib, trametinib, and dactolisib have been shown to inhibit PSC proliferation and ECM synthesis [28,29]. Interestingly, trametinib also decreases the expression of two autocrine mediators of PSC activation, IL-6 and TGFβ [29].

Several intracellular signaling pathways that mediate PSC activation or quiescence have now been identified (listed and referenced in Table 10.3). It is important to

note that although numerous discrete pathways regulating PSC functions have been identified, there is significant cross-talk between the major signaling pathways, such that modulation of one can affect the functions of the other [30–32]. This built-in redundancy has to be taken into account during any development of novel therapies targeting PSC signaling pathways. Furthermore, studies have now indicated that a number of the signaling pathways described converge into a common secondary messenger system within the PSC, namely intracellular calcium [33–35]. Attention has also been focused in recent times on microRNA, which are small, noncoding RNA implicated in cell functions such as proliferation, differentiation, apoptosis, and protein synthesis. Significant differences between the microRNA profiles of quiescent cells and activated PSC have been reported, relevant to development and growth, movement, and survival of cells [36]. Other investigators have identified miR-15b and -16 as regulators of PSC apoptosis via their effects on the antiapoptotic factor Bcl-2 [37] and miR21 as a possible cofactor in connective tissue growth factor (CCN2)-mediated PSC activation [38].

The role of PSC in pathologic pancreatic fibrogenesis has been studied mainly with respect to three disease conditions of the gland—acute pancreatitis, chronic pancreatitis, and pancreatic cancer. Whereas the last two are characterized by the presence of abundant fibrous deposits within the pancreas, the first, acute pancreatitis, is well acknowledged as a self-limiting disease in a majority of patients. As described in the following, PSC play a critical role, not only in the pathologic fibrosis of chronic pancreatitis and pancreatic cancer, but also in the regeneration/repair of the pancreas after acute pancreatitis.

## Acute Pancreatitis

PSC proliferation is evident early in acute pancreatitis in response to the cytokines and chemokines secreted by damaged acinar cells and inflammatory cells [39]. Studies using chimeric models indicate that while the increased numbers of PSC observed in the inflamed pancreas are due predominantly to local proliferation of resident PSC, a small proportion (7–18%) of the PSC population may be derived from circulating bone marrow cells [40]. The activated PSC population produces increased ECM proteins that provide a scaffold and physical support for the regenerating ductal and acinar cells during the repair phase of acute pancreatitis. It is now well demonstrated that the ECM is critical for appropriate, integrin-mediated interactions between cell membranes and the surrounding matrix, which in turn is essential for cell differentiation and growth [41]. Indeed, using conditional β1-integrin knockout animals, it has been shown that the absence of integrin receptor expression on PSC results in reduced ECM production, hampering acinar cell–ECM interactions, resulting in acinar apoptosis and reduced proliferation [42].

PSC may also play a central role during recovery from severe necrotizing pancreatitis [43]. Pancreatic sections from patients with severe necrotizing pancreatitis exhibit hypercellular regenerative spheres comprising vascular granulation tissue, ductular cells, residual lobular elements, and stellate cells. Sprouting outwards from the margins of these spheres into surrounding tissue are pilot ductules lined by flattened epithelial cells and surrounded by a mantle of stellate cells. It has been speculated that this mantle of PSC provides the essential stimulus for proliferation of the cells lining the pilot ductules and for their differentiation into mature acinar and duct cells, thereby facilitating pancreatic regeneration.

An essential step for complete recovery of the gland from an acute inflammatory state to a normal pancreas is the removal of excess ECM within the gland and restitution of cell populations to their normal relative proportions. PSC play a role in fibrolysis via their capacity to produce the matrix-degrading enzymes MMP. Loss of excess PSC may occur via (i) apoptosis, (ii) reversion to quiescence, as is demonstrable upon treatment with the retinol metabolite all-*trans*-retinoic acid [21,22] or vitamin D receptor ligand calcipotriol [27]; and/or (iii) senescence, as reported by Fitzner et al. [44] in a model of dibutyltin chloride (DBTC)-induced pancreatitis.

## Chronic Pancreatitis

Chronic necroinflammation of the pancreas (chronic pancreatitis) is characterized histologically by abundant fibrosis that surrounds islands of atrophied acini and distorted pancreatic ducts [45]. Over the past 15 years, *in vitro* and *in vivo* studies have helped characterize the central role of PSC in this process.

The earliest studies involved histologic and immunohistochemical staining of pancreatic sections from patients with chronic pancreatitis [2,16]. Dual staining for collagen and the PSC activation marker αSMA (using Sirius Red stain and immunohistochemistry, respectively) demonstrated colocalization of both stains in the same cells, indicating the presence of activated PSC in fibrotic areas of the pancreas [16] (Fig. 10.2). More importantly, dual staining for αSMA and procollagen mRNA clearly demonstrated that activated PSC were the predominant source of collagen I in the fibrotic pancreas [16].

During chronic pancreatitis, PSC are likely activated by numerous factors, including (i) the profibrogenic growth factor TGFβ, which is found to be highly expressed in spindle-shaped cells within fibrotic areas and also in acinar cells adjacent to the areas of fibrosis (but not in acinar cells away from fibrotic areas), supporting the notion that TGFβ exerts paracrine and autocrine effects on PSC to stimulate cell activation [16]; (ii) platelet-derived growth factor (PDGF) – the receptor for this mitogenic and chemotactic factor is upregulated in fibrotic areas, thereby providing a possible mechanism for the observed increase in proliferation and migration of PSC to injured areas during pancreatic necroinflammation [16]; (iii) nerve growth factor (NGF), which has been demonstrated in PSC in areas of fibrosis, and which has been implicated in the pain of chronic pancreatitis via its ability to induce neurite growth [46]; and (iv) oxidative stress, as evidenced by increased staining of oxidant stress marker 4-hydroxynonenal [47].

Although studies with human tissue offer a point-in-time snapshot of the presence of activated PSC and relevant activating factors *in situ*, it is only through animal studies that chronological events in the development of fibrosis and the role of PSC in fibrogenesis have been able to be chronicled. Numerous different mouse and rat models of experimental chronic pancreatitis/pancreatic fibrosis have been reported in the literature (for a review, see [48]). Approaches to induce fibrosis in these models include (i) causing repetitive acute pancreatic injury (based on knowledge of the necrosis–fibrosis sequence of injury) by repeated injections of caerulein [49] or superoxide dismutase inhibitor [50]; (ii) injecting toxins into the pancreatic duct [16,51]; (iii) exposure of animals to chronic ethanol administration followed by secondary challenge with caerulein [52,53], cyclosporin [54], or endotoxin [11] (the last is considered to be a more physiologically relevant approach given the well-demonstrated increase in serum endotoxin levels in heavy drinkers [55]); (iv) transgenic methods involving overexpression of cytokines or profibrogenic factors such as IL-1β, TGFβ, and heparin-binding EGF-like growth factor (HB-EGF) [56,57]. Rats developing spontaneous chronic pancreatitis (WBN–Kob rats [58]) and type 2 diabetes (Goto–Kakizaki rats) [6] have also been used.

Space limitations preclude a detailed discussion of the described models. However, the overall results of all of the studies indicate that known PSC-activating factors (TGFβ, PDGF, oxidant stress, etc.) are upregulated early during pancreatic injury, leading to PSC activation (as evidenced by proliferation and increased ECM synthesis). The increased numbers of PSC are mainly sourced from the resident PSC population, although a small fraction (5–18%) may be derived from pluripotent circulating bone marrow cells [59]. As mentioned earlier, the ability of activated PSC to secrete endogenous cytokines that act on the cells via an autocrine loop helps to perpetuate PSC activation, ultimately resulting in pathologic fibrosis.

Whereas the majority of the described models were focused on the role of PSC in fibrosis of the exocrine pancreas, recent reports suggest a role for PSC in the fibrosis of endocrine pancreas also. Studies with rodent models of diabetes (Goto–Kakizaki rats [6] and db/db mice [60]) have demonstrated activated PSC within fibrotic areas in and around the islets of Langerhans. PSC have been shown to inhibit insulin secretion by beta cells and also to stimulate beta-cell apoptosis; these detrimental effects of PSC on beta cells are aggravated by hyperglycemia [61]. Indeed, repeated caerulein injections have been reported to cause more severe chronic pancreatitis in hyperglycemic mice than in normoglycemic mice [62]. These findings suggest the presence of a positive feedback loop between PSC and islet cell function and support an active role for PSC in the diabetes of chronic pancreatitis.

## Reversal of Pancreatic Fibrosis

The advances made over the past decade in our understanding of PSC biology, particularly with regard to their key roles in the fibrosis of chronic pancreatitis, have underpinned recent research efforts to develop targeted approaches to inhibit the process of PSC activation, so as to prevent, retard, and/or reverse the fibrogenic process, thereby limiting disease progression. To date, most of these novel treatments have been utilized mostly in experimental models and involve (i) inhibition of profibrogenic growth factors TGFβ and tumor necrosis factor alpha (TNFα) [63–65]; (ii) antioxidants such as vitamin E [66], ellagic acid, a plant polyphenol [67], and salvianolic acid, a herbal medicine [68]; (iii) protease inhibitors [69]; (iv) modulation of signaling molecules (e.g., troglitazone binding to the peroxisome proliferator receptor gamma, PPARγ [26]; retinoic acid-induced PSC quiescence via suppression of the Wnt–catenin pathway [22]); (v) inhibition of collagen synthesis by targeted treatment of PSC with collagen siRNA [70]; (vi) an anthraquinone derivative Rhein [24] and a flavonoid, apigenin [71]; (vii) a prostacyclin analogue ONO-1301, which inhibits proinflammatory and profibrogenic cytokine production [72]; and (viii) in the case of alcoholic pancreatitis, withdrawal of alcohol administration [73]. This list of potential treatments is an exciting step forward in the field, one that is expected to drive the development of clinical trials that can assess the efficacy of such approaches in the treatment of human chronic pancreatitis.

## Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is characterized by an abundant stromal/desmoplastic reaction that surrounds tumor elements. This fibrotic stroma comprises extracellular matrix proteins including collagen type I, fibronectin, and laminin, noncollagenous factors such as glycoaminoglycans (e.g., hyaluronan), glycoproteins, and proteoglycans, and several cell types, including stellate cells, endothelial cells, neural elements and immune cells. Studies with human pancreatic cancer sections involving dual staining for PSC-selective markers and *in situ* hybridization for collagen mRNA, have now unequivocally established that PSC are the major source of the fibrosis of pancreatic cancer [74] (Fig. 10.3). Furthermore, activated PSC have been identified surrounding the earliest (premalignant) lesions of pancreatic cancer, namely pancreatic intraepithelial neoplasms (PanIN), indicating that PSC activation is an early feature in carcinogenesis [75]. Interestingly, an association has been reported between the extent of activated PSC in the stroma and poor clinical outcome (as assessed by overall survival) [76,77].

It is increasingly evident that the role of PSC in pancreatic cancer extends beyond merely producing the fibrotic stroma. Using *in vitro* (cocultured PSC and cancer cells) and *in vivo* (subcutaneous xenografts, orthotopic implants, genetically engineered models) approaches, a close bidirectional interaction between PSC and cancer cells has been identified, which facilitates local tumor growth and distant metastasis (for a review, see [78]). Pancreatic cancer cells induce PSC activation, as evidenced by increased proliferation, ECM production, and migration. These effects are mediated by factors such as TGFβ, fibroblast growth factor (FGF), PDGF [79], cyclooxygenase 2 (COX-2, the enzyme involved in conversion of arachidonic acid to prostaglandin) [80], and trefoil factor 1 (TFF1, a stable secretory protein that is upregulated in pancreatic cancer but not expressed in the normal pancreas) [81]. In turn, PSC significantly increase pancreatic cancer cell proliferation, while at the same time inhibiting their apoptosis, thereby increasing cancer cell survival. PSC also stimulate cancer cell migration, an effect that is associated with enhanced epithelial–mesenchymal transition (EMT) of cancer cells (as demonstrated by increased expression of mesenchymal markers such as Snail and vimentin associated with a corresponding decrease in the expression of epithelial markers such as E-cadherin) [82]. In addition, PSC have been shown to induce stemness in cancer cells—such a stem-cell niche is thought to be responsible for the well-known propensity of pancreatic cancer for recurrence [83]. Ikenaga et al. [84] identified a subset of cancer-associated PSC that have significantly more aggressive effects on cancer cell migration and proliferation than the parent population. This PSC subset exhibits increased expression of CD10 (a cell membrane-associated matrix metalloproteinase), which is capable of degrading basement membrane, thereby facilitating invasion into surrounding tissue and also into blood vessels. PSC-induced cancer cell proliferation is mediated, at least in part, by PDGF [85], while hepatocyte growth factor (HGF) plays a role in PSC-induced cancer cell migration [86]. Other candidate factors that require further study as possible

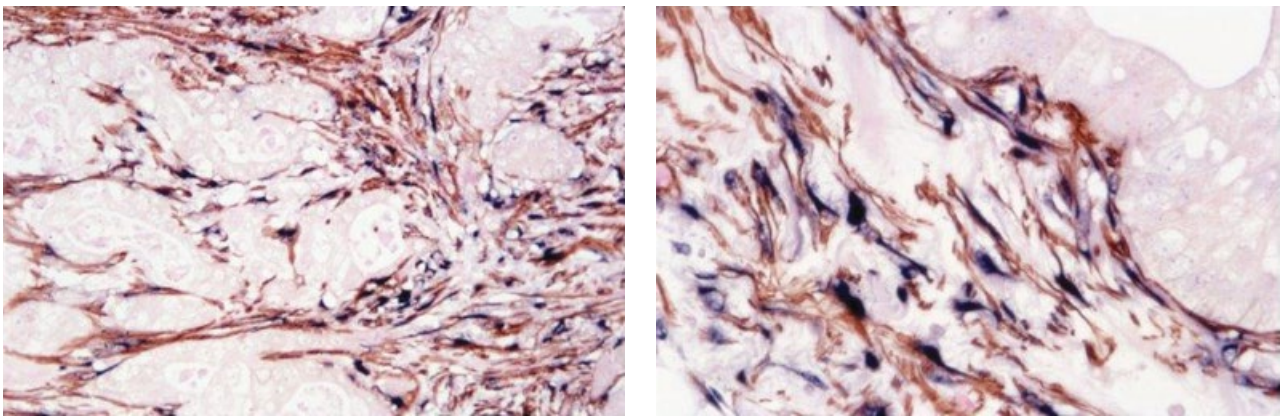

**Figure 10.3** Low- and high-power views of a human pancreatic cancer section dual stained for alpha smooth muscle actin (αSMA) and collagen mRNA: immunostaining for αSMA (brown) combined with *in situ* hybridization for collagen mRNA (blue) reveals colocalization of the two stains in stromal areas of the section with no staining in tumor cells. This pattern of staining indicates that pancreatic stellate cells are the main source of collagen in pancreatic cancer stroma. *Source:* Apte et al. 2004 [74]. Reproduced with permission of Wolters Kluwer Health.

mediators include insulin-like growth factor (IGF), epithermal growth factor (EGF), TGFβ, and other proinflammatory cytokines. Interactions of PSC with other cell types in the stroma, such as endothelial cells (influencing angiogenesis), immune cells (facilitating immune evasion), and neuronal cells, are being increasingly described, but are beyond the scope of this chapter (for a review, see [87]).

The fibrotic stroma is thought to contribute to chemoresistance by acting as a physical barrier to the penetration of drugs to the cancer cells. However, accumulating data indicate that PSC may also directly influence the response of cancer cells to chemotherapeutic agents via the production of stromal-derived factor 1α (SDF-1α), which acts on its receptor CXCR4 on cancer cells to phosphorylate downstream signaling pathways including mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) in cancer cells. This induces the production of IL-6 by cancer cells, which exerts an autocrine effect to protect the cells from gemcitabine-induced apoptosis [88]. PSC themselves have been shown to survive chemoradiation and to exhibit an even more activated phenotype post-treatment, a feature that may enable the cells to induce proliferation of residual cancer stem-cell niches, thereby aiding cancer recurrence [89].

Although the weight of evidence to date supports a facilitatory role for PSC in pancreatic cancer progression, this tumor-permissive function of PSC has been brought into question by two recent studies reporting that conditional depletion of αSMA myofibroblasts [90] or targeting a specific signaling pathway (hedgehog pathway) [91] in mouse models of pancreatic cancer paradoxically resulted in reduced survival of animals. These discrepant findings may be explained by the possibility that the impact of PSC on cancer behavior is a dynamic and stage-dependent process. The presence of activated PSC at the earliest stages of pancreatic cancer (PanIN) may represent a protective reaction within the gland as the fibrosis laid by the PSC attempts to sequester the malignant cells from the normal pancreas. As the disease progresses, cancer cells can overcome this "protective" barrier and recruit PSC to their own advantage, converting them into "helper" cells.

Therapeutic targeting of PSC and the microenvironment to improve pancreatic cancer outcome have attracted significant attention in recent years. These studies have mostly involved preclinical models of pancreatic cancer, although a few have progressed to early clinical trials, with encouraging, albeit modest, results. An exhaustive discussion of this work is not within the scope of this chapter (for reviews, see [87,92]). However, given that (i) targeting cancer cells alone has failed to improve patient outcome for several decades and (ii) the influence of the stroma on cancer biology is becoming increasingly clear, there is general agreement in the field that it would be reasonable to consider measures to modulate PSC behavior as novel treatment options for pancreatic cancer.

## Conclusion

In summary, it is now unequivocally established that the cells responsible for fibrogenesis in the pancreas are pancreatic stellate cells (PSC). In health, PSC maintain a fine balance between ECM production and degradation, thereby ensuring normal ECM turnover in the gland. Accumulating evidence suggests that PSC may also have additional roles in the healthy pancreas as progenitor cells, immune cells, and intermediary cells in CCK-regulated pancreatic exocrine secretion. In diseased states, PSC are transformed into an activated myofibroblast-like state, producing excessive amounts of ECM proteins. When the activation of PSC is limited, as in resolving acute pancreatitis, PSC can aid the regenerative/repair process. However, perpetuated activation of the cells, as seen in chronic pancreatitis and pancreatic cancer, ultimately leads to pathologic fibrosis. Notably, it is now becoming increasingly evident that PSC have functions beyond the fibrotic process in both chronic pancreatitis and pancreatic cancer. In chronic pancreatitis, PSC have been shown to promote islet (beta) cell dysfunction, whereas in pancreatic cancer, PSC interact closely with cancer cells and other stromal cells such as endothelial cells and immune cells to influence cancer progression. Understanding the biology of these multifunctional PSC will underpin the development of novel therapeutic approaches for difficult-to-treat fibrotic diseases of the pancreas such as chronic pancreatitis and pancreatic cancer.

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# 11

# Fibrogenesis of the Pancreas: The Role of Macrophages

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## Introduction

Macrophages are cells of the innate immune system and are highly efficient phagocytic cells that play a central role in tissue homeostasis, infection, inflammation, wound repair, and healing [1]. In addition to their phagocytic abilities, although not as efficient as their counterpart myeloid-derived dendritic cells, macrophages are also capable of antigen processing and can play an important role in promoting adaptive immune responses [2]. In disease states, however, macrophages can contribute to pathogenic roles that promote chronic inflammation and cancer [3]. Improved molecular and cellular techniques have led to the appreciation of phenotypic and functional macrophage diversity and a better understanding of their heterogeneity and highly dynamic nature with the capacity to respond readily to environmental changes.

Chronic pancreatitis is associated with pancreatic stellate cell activation and fibrosis. Both human and animal model studies show that macrophages are one of the major immune cell infiltrates in chronic pancreatitis [4–6]. Experimental model findings also support the recruitment of these myeloid cells early on during disease development, suggesting an important role for macrophages in fibrogenesis. Ongoing destruction of the exocrine pancreas associated with chronic inflammation and activated pancreatic stellate cells leads to the development of fibrosis. Management of chronic pancreatitis with its progressive fibrosis that gradually replaces the organ remains a clinical challenge. In addition, patients with chronic pancreatitis have an increased risk of developing pancreatic cancer [7].

Pancreatic ductal adenocarcinoma (PDAC), the most common and lethal form of pancreatic cancer, is also associated with a dense stromal reaction where fibrosis surrounds tumor areas [8]. Interestingly, macrophages are also the major immune cell infiltrate in PDAC and also in most solid tumors [9]. Tumor-associated macrophages (TAM) have distinct gene transcript profiles [10]; however, at least phenotypically, TAM resemble those infiltrating fibrotic areas in chronic pancreatitis and other fibrotic diseases. These observations suggest that similar mechanism(s), at least in part, are probably involved in both benign and malignant-associated fibrogenesis and analogous approaches potentially can target macrophages with goals of modulating fibrotic areas. This chapter focuses on the role of macrophages in fibrosis associated with chronic pancreatitis (independent of etiology) and pancreatic cancer based on the available evidence and body of literature.

## Macrophages

Macrophages are highly efficient phagocytic myeloid cells discovered over a century ago by the Nobel Laureate Ilya Metchnikoff [11]. Circulating monocytes derived from bone marrow myeloid progenitors enter tissues and undergo differentiation into either macrophages or dendritic cells depending on the presence of local growth factors, cytokines, and exogenous or microbial signals [12]. Macrophages represent a highly functionally diverse and heterogeneous population and as a result are involved in health and many diseases [13,14]. Unlike terminally differentiated cells, they have the ability to respond to changes in environmental signals and alter their phenotypic and functional characteristics [15]. As a result, macrophages are highly diverse, dynamic, and a population with a high degree of plasticity that enables them to adjust to physiologic and pathologic changes.

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Although macrophages exist along a functional and dynamic continuum, classically (M1 or type 1)- and alternatively (M2 or type 2)-activated macrophages are generally accepted as those on the extreme or opposite side of this continuum [13,14]. Other studies classify macrophages according to their functional role such as proinflammatory, profibrotic, proresolution or prowound healing, proresolving, and tissue regenerating [16–19]. For the purpose of this chapter, we will use the classically and alternatively activated (M1/M2) terms based on the general and common uses of these terminologies in the literature. Classically activated macrophages (M1) develop due to inflammatory signals such as IFNγ or lipopolysaccharide (LPS) and as a result are associated with T helper (Th) type 1 immune responses and are involved in effector or proinflammatory functions. In contrast, the alternatively activated macrophages (M2) develop in response to Th2-type responses (cytokines such as IL-4 and IL-13) and are associated with immunosuppression, tissue repair, and wound healing [20].

M2 macrophages have been further subdivided into M2a, M2b, M2c, and M2d (also known as tumor-associated macrophages or TAM) [14,21,22] This subdivision is also based on gene, surface receptor, and cytokine expression (Fig. 11.1). M2a are induced by factors such as IL-4, IL-13, or IL-10 and are associated with antiparasitic, allergic, and Th2 responses, and have been termed "tissue reparative and wound healing" [13,20,23]. M2a are also associated with fibrosis. M2b (induced by IL-1, LPS, immune complexes or ICs) and M2c (induced by IL-10 and TGFβ) are generally referred to as "regulatory" with pro- and anti-inflammatory properties, respectively [23–25]. M2c are also associated with tissue remodeling, fibrosis, and tumor promotion [23]. Relevant to the pancreas, chronic injury can lead to a dysregulated macrophage wound-healing response and development of pathologic fibrosis that impairs normal tissue function [26]. M2d or TAM, induced by tumor-enriched factors such as colony-stimulating factor 1 (CSF-1) and IL-6, promote tumor growth, invasion, and metastasis [27].

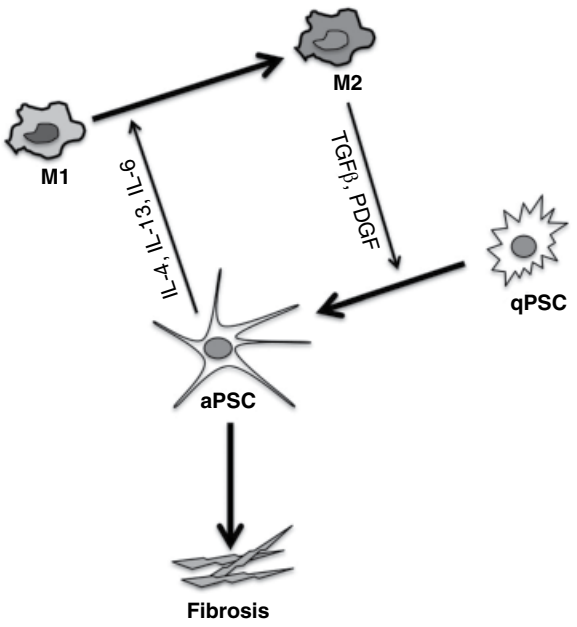


**Figure 11.1** Macrophage–pancreatic stellate cell (PSC) interaction in promoting fibrogenesis [35]. Activated (a) and quiescent (q) PSC; classically (M1) and alternatively (M2) activated macrophages. PDGF, platelet-derived growth factor; TGFβ, transforming growth factor beta.

## Origin and Characteristics of Pancreatic Macrophages

Experimental models using congenic mouse strains have allowed the separate tracing of donor and host cells in cell transfer studies. In addition, the use of bone marrow chimeras, parabiosis (conjoined animals in order to assess turnover of cells), and yolk sac or embryogenic cell transfers has allowed investigators to determine macrophage ontogeny in different tissues. Prior to the establishment of bone marrow, primitive hematopoiesis originating from yolk sac progenitor cells takes place (in the mouse embryo: E7.5) [28]. Interestingly, lineage-tracing analysis showed that adult brain-specific macrophages (microglia) are derived exclusively from the primitive yolk sac precursors [29]. In contrast, although yolk sac- and fetal liver-derived macrophages are present in the neonatal intestine, they do not persist into adulthood [30], suggesting that although the intestine is seeded by embryonic precursors, intestine macrophages are replenished by bone marrow-derived monocytes from the circulation throughout adulthood. The differences in brain and intestinal macrophage ontogeny highlight environment and context dependence, where recruitment of monocytes to the intestine, for example, is largely dependent on the presence of microbiota [30].

Although bone marrow and yolk sac-derived macrophages appear similar, Schulz et al. showed that although the transcription factor Myb was necessary for the development of monocytes and macrophages derived from hematopoietic stem cells or bone marrow, it was dispensable for the development of yolk sac-derived macrophages [31]. They also investigated macrophage origin in multiple tissue sites and found that a significant proportion of the pancreatic macrophages were derived from primitive hematopoiesis or yolk sac. More recently, Calderon et al. investigated the origin and characteristics of pancreas macrophages in the mouse in more detail [32]. In the steady state, the pancreas macrophages were long lived with minimal exchange with blood monocytes.

Notably, macrophages in the interacinar parenchyma were distinct in origin and phenotype compared with those in the islets of Langerhans. Macrophages in the interacinar parenchyma were of alternatively activated phenotype or M2 and composed of two subgroups, one derived from yolk sac and the other from bone marrow precursors. Macrophages in the islets of Langerhans were derived from bone marrow stem cells but had minimal exchange with circulating monocytes and had a profile of classically activated macrophages or M1. These findings highlight and underscore the heterogeneity of the macrophage lineage not only in different organs but also within the microenvironment of a single tissue such as the pancreas. Nevertheless, under myeloablative conditions, pancreas-resident macrophages, regardless of their site of origin or microenvironmental location, were replaced with donor bone marrow-derived monocytes [32], indicating that under inflammatory conditions, circulating monocytes are likely to play an important role in reconstituting the tissue macrophages.

## Role of Macrophages in Chronic Pancreatitis-Associated Fibrosis

Immune cell infiltrates are observed in fibrous areas of the pancreas in patients with chronic pancreatitis [33]. Macrophages are the most abundant myeloid cells in the inflamed pancreas in chronic pancreatitis [4,5,34]. Macrophages with alternatively activated profiles are found in high numbers in the fibrosis area and the vicinity of activated pancreatic stellate cells [5,35]. A marked increase in immune cell infiltrate has been reported in patients with alcohol-related chronic pancreatitis [36]. Using histologic staging of the pancreas of alcoholic patients, it was proposed that alcoholic chronic pancreatitis was initiated via a cytokine-mediated interaction between macrophages and myofibroblasts as a result of tissue injury [37]. In addition, the potential role of macrophages in fibrosis was demonstrated *in vitro* by LPS-activated macrophages that stimulated pancreatic stellate cell activation and collagen and also fibronectin synthesis [38]. Activation of pancreatic stellate cells was also observed when cocultured with macrophage cell lines [39].

Similar to findings in the human pancreas, macrophages are also present in the vicinity of areas of fibrosis in experimental models of chronic pancreatitis [6,35]. Unlike in acute pancreatitis, where classically activated macrohages (M1) are dominant, chronic pancreatitis is dominated by alternatively activated macrophages (M2) [35]. Coculture of pancreatic stellate cells with M2- as opposed to M1-polarized macrophages significantly upregulates stellate cell fibrosis genes. Moreover, pancreatic stellate cells were shown to secrete Th2 cytokines in culture and influence macrophage polarization toward M2. In addition, alternatively activated macrophages (M2) were also more efficient than classically activated macrophages (M1) at activating pancreatic stellate cells, indicating that a feed-forward process and interaction between pancreatic stellate cells and macrophages exist in chronic pancreatitis (Fig. 11.2).

The functional significance of alternative macrohpage polarization in fibrogenesis is also emphasized by the fact that blockade of macrophage IL-4 receptor signaling via genetic and pharmacologic means inhibits progression of experimental chronic pancreatitis-associated fibrosis *in*

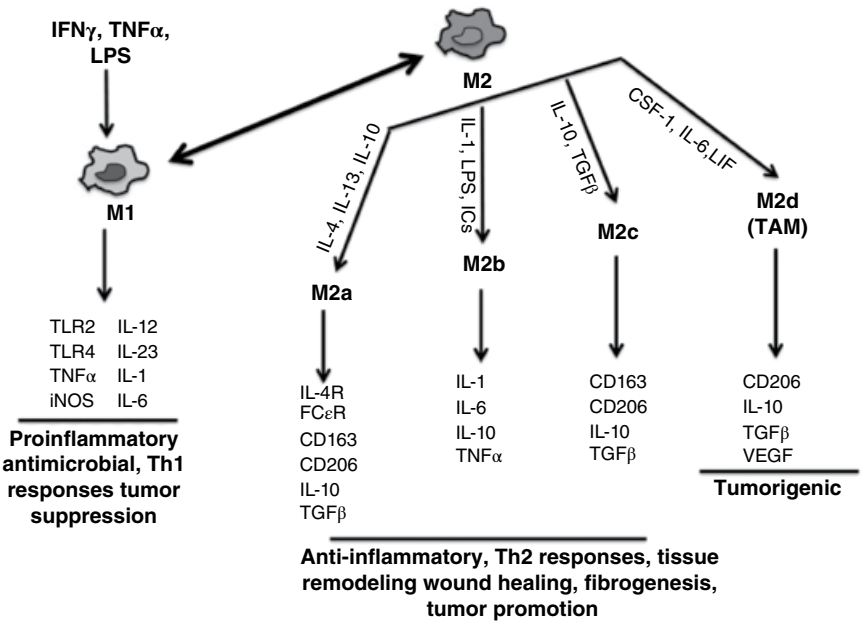


**Figure 11.2** Macrophage phenotypic and functional heterogeneity [3,10,13,20,23,25]. The diagram depicts stimulating conditions that induce M1 and M2 functional subtypes that upregulate unique receptor and cytokine expressions. CD206, mannose receptor; FCεR, high-affinity IgE or Fc epsilon receptor; IC, immune complexes; iNOS, inducible nitric oxide synthase; IL, interleukin; M1, classically and M2, alternatively activated macrophage subsets; CSF-1, colony-stimulating factor 1; LIF, leukemia inhibitory factor; LPS, lipopolysaccharide; Th, T helper; TAM, tissue-associated macrophage; TLR, toll-like receptor; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor.

*vivo* [1]. Moreover, inhibition of IL-4 receptor signaling using peptide-targeting IL-4/IL-13 also was effective in decreasing the progression of fibrosis in established disease. This mechanism offers a potential therapeutic target that alters macrophage–pancreatic stellate cell interaction and alter the natural progression of fibrosis, at least as observed in animal models of chronic pancreatitis. The IL-4 receptor pathway and blocking peptide findings were also consistent with *ex vivo* experiments that used primary human macrophages and pancreatic stellate cell cocultures, demonstrating potential future translation to clinical application [6]. However, future clinical studies are crucial to test the validity and efficacy in patients with chronic pancreatitis.

Addition of alcohol feeding to caerulein treatment in a model of chronic pancreatitis had a combined effect on the upregulation of macrophage arginase-1 expression [40]. Arginase-1 is a urea cycle enzyme, which converts L-arginine into L-ornithine and urea, and is generally accepted as a protypic M2 marker [13]. L-Ornithine is thought to enter polyamine and collagen synthesis, thus promoting fibrosis and wound healing [41]. Hence alcohol likely further promotes fibrosis, at least in part, via induction of arginase-1 expressing alternatively activated macrophages. Many studies have demonstrated the importance of nuclear factor kappa light-chain enhancer of activated B cells (NFκB) activation in pancreatitis. Sustained activation of NFκB results in chronic pancreatitis [42,43]. The contribution of macrophages is further emphasized by the requirement for myeloid and not acinar NFκB activation in promoting fibrosis in experimental chronic pancreatitis [44].

Macrophages contribute not only to fibrogenesis but also to the remodeling of fibrotic areas. Macrophages, in particular alternatively activated or M2-like macrophages, were shown to be critical in degrading and remodeling collagen scaffolds in models of skin fibrosis [45]. Other tissue model systems have also shown that macrophages produce metalloproteinases and other enzymes that degrade the fibrotic extracellular matrix and thus facilitate the resolution of fibrosis [17,46,47]. Further investigations are needed to identify conditions and define mechanisms that lead to the opposing roles of macrophages in fibrosis generation and degradation. These studies are likely to offer methods via which fibrosis can be modulated to alter chronic pancreatitis-associated fibrosis progression.

## Role of Macrophages in Pancreatic Cancer-Associated Fibrosis

A strong desmoplastic reaction surrounds PDAC areas and poses a major therapeutic challenge [8,48]. Juxtatumoral stroma is enriched by tumor-infiltrating macrophages and fibroblasts, highlighting the significance and pathogenic role of macrophages in PDAC [49]. Macrophages are major immune cells infiltrating many solid tumors and their presence is associated with cancer prognosis. In fact, an increase in PDAC-infiltrating macrophage burden is associated with a poor patient outcome [50]. Consistent with the profibrogenic role of M2, increased tumor infiltration with M2-polarized macrophages was associated with shorter survival, whereas the presence of M1-polarized macrophages was associated with longer survival in patients with PDAC [51].

Increases in extracellular matrix protein were observed with progression of pancreatic cancer and correlated with increases in myofibroblasts and macrophages in both human and mouse PDAC studies [39]. In that report, *in vitro* coculture findings suggested cross-regulation between macrophages and pancreatic stellate cells. In another study, immune-targeted therapy (antibody-based CD40 agonist) in experimental models of PDAC led to the re-education of macrophages, immune activation, and altered tumor stroma that were associated with improved response to chemotherapy [52,53]. These studies suggest that targeting tumor-infiltrating macrophages is likely to alter fibrogenesis in pancreatic cancer and improve chemotherapy response.

## Conclusion

Macrophages need to be evaluated in the context of the environment and settings owing to their heterogenity and dynamic nature. Alternatively activated macrophages play an important role in matrix synthesis and degradation, making these cells an attractive future target for modulating fibrosis in pancreatic diseases. Experimental models so far have elucidated the critical role played by macrophages in fibrogenesis and the interaction of macrophages especially with pancreatic stellate cells to promote fibrosis. Studies have shown that pancreatic stellate cells and alternatively activated macrophages influence fibrogenesis in a feed-forward process. Recent studies have highlighted the dynamic nature of macrophages, although more studies are needed to understand the natural course of fibrotic pancreatic diseases and macrophage heterogeneity during disease development and progression. Moreover, studies are needed to understand macrophage behavior and pancreas-specific regulators of macrophage function during mild versus severe inflammation and during early and late disease. The ability of macrophages to be reprogrammed, sense environmental signals, and interact with and impact pancreatic stellate cell behavior makes them a suitable candidate to target in order to alter fibrogenesis.

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# 12

# Insulo–Acinar Relationship

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## Introduction

The pancreas consists of two separate organ systems—the exocrine pancreas and the endocrine pancreas—both of which arise from a primordial outgrowth of the primitive gut. The pancreatic islets are interspersed throughout the acini of the pancreatic exocrine tissue. Pancreatic exocrine secretion is highly regulated by several regulatory peptides and neurotransmitters [1–4]. Islet hormones directly reach acinar cells through the insulo-acinar portal system [5–8], and they play important roles in the regulation of acinar cell function. Based on morphologic and hemodynamic studies of the islet–acinar portal system and physiological regulation of acinar cell function by islet peptides, Williams and Goldfine [9] proposed the novel concept of an "insulin–pancreatic acinar axis." However, since many other peptides released by the islets and neuropeptides released by the nerve terminals in the islets have recently been shown to influence exocrine function, the term "islet–acinar axis" appears to be more appropriate [10,11]. Moreover, because a functional relationship between islet cells and duct cells has been demonstrated, a newer concept, called an "acinar–duct–islet axis," is now being considered [12].

## Structural Relationships Between Pancreatic Islets and Exocrine Pancreas

The normal human adult pancreas contains about 1 million islets scattered throughout the organ, consisting of 2–3% of the gland. One islet contains an average of about 5000 endocrine cells, of which there are four major types: those that synthesize and secrete insulin and amylin (β cells), those that synthesize and secrete glucagon (α cells), those that synthesize and secrete somatostatin (δ cells), and those that synthesize and secrete pancreatic polypeptide (PP) and adrenomedullin (PP/F cells). These account for 68%, 20%, 1%, and 2%, respectively, of the cells in pancreatic islets. Another type of endocrine cells, ghrelin-producing cells, have recently been found in islets and named "ε cells" [13,14]. All islets contain β cells and δ cells, whereas α cells are almost exclusively present in islets located in the tail, body, and superior part of the head of the pancreas, and PP cells are mainly observed in islets in the head of the pancreas. Because no capsule or basement membrane surrounds the islets, they are in close contact with pancreatic acinar cells.

Acini located around the islets are called peri-insular acini, and are recognized by the presence of larger cells containing larger nuclei and more abundant zymogen granules than remote acini, which are called tele-insular acini. The constant high concentrations of islet hormones conveyed from the islets to the acinar parenchyma may be responsible for the morphological and functional characteristics of the peri-insular acini [10,11,15]. The islets are densely innervated by both central nervous system and autonomic nervous system. Many neuropeptides and neurotransmitters have been found to be involved in the regulation of islet hormone release.

All islet cell types differentiate from precursor cells present in the epithelial lining of the expanding ductal system [16]. Anatomical and functional associations between islets and ducts have been suggested to exist in the adult pancreas as well as in the fetal pancreas [17,18]. Recent immunohistochemical studies have demonstrated expression of insulin, glucagon, somatostatin, and PP in adult human pancreatic duct cells [19], and Yu et al. [20] demonstrated widespread occurrence of insulin-producing acinar β cells in the adult human pancreas

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and coexpression of both amylase and insulin in the acinar β cells. The acinar–duct–islet axis is thought to play an important role in the differentiation and development of endocrine cells [12].

## Insulo-Acinar Portal System

The arterial blood supply to the pancreas predominantly flows first to the islets and then via the islets to the exocrine portion of the gland. Lifson et al. [21] found that 11–23% of pancreatic blood flow in the rabbit pancreas flows directly to the islet, whereas the other 77–89% flows directly to the acini (Fig. 12.1). A capillary-like microvascular connection between the endocrine and exocrine portions of the pancreas has been identified in various mammals. Fujita and colleagues confirmed the existence of an "insulo-acinar portal system" by electron microscopic studies of the pancreas of humans and other mammals [5–7]. Pancreatic intralobular arteries give off branches to the islets in the form of an afferent vessel that divides into a capillary glomerulus within the islets, and numerous efferent vessels extend into the surrounding exocrine pancreas to form an insulo-acinar portal system [5–8]. The capillaries from the exocrine tissue coalesce into a venule, and all of the efferent islet blood flows into acinar capillaries before leaving the pancreas. Thus, the exocrine pancreas receives a large part of its blood supply via the islets, and islet hormones reach the acinar cells in high concentrations via this insulo-acinar portal system, with the peri-insular acini being exposed to particularly high concentrations of the islet hormones. Because pancreatic ducts are surrounded by a vascular plexus that is supplied by venous blood from the acini [22], ductal cells are also exposed to high local concentrations of islet hormones.

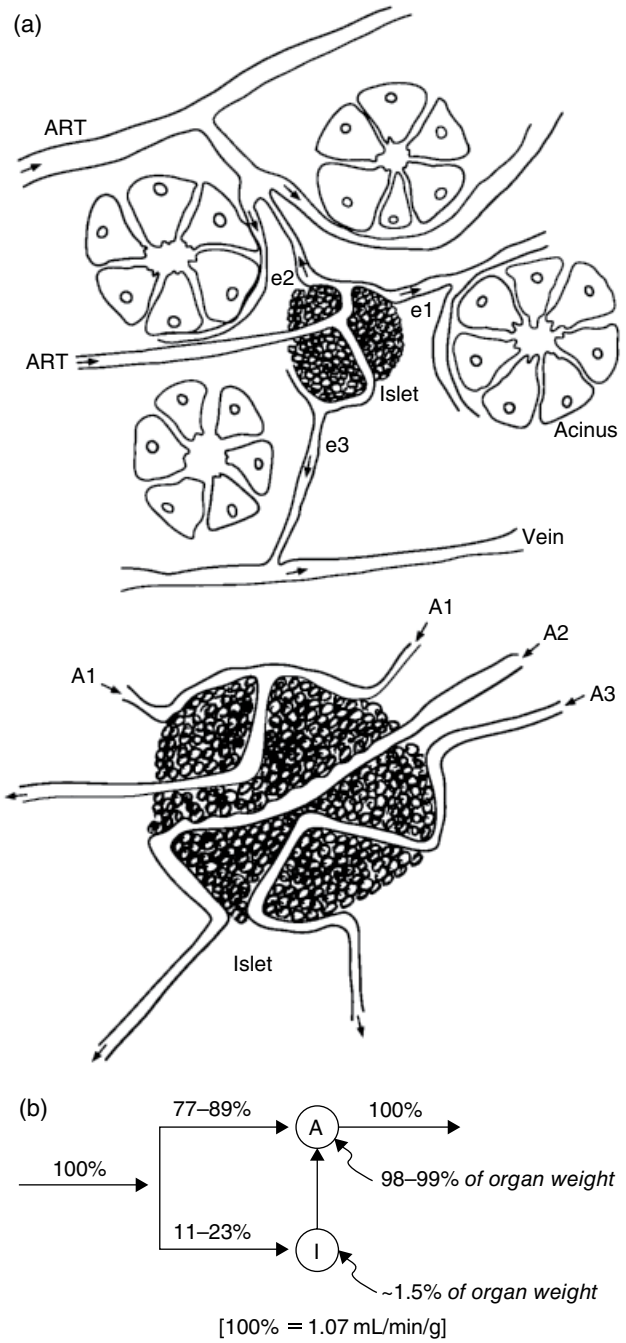


**Figure 12.1** (a) Schematic diagram illustrating the dual blood supply of the exocrine pancreas. *Source:* Barreto et al. 2010 [11]. Reproduced with permission of the American Physiological Society. (b) Schematic diagram of the distribution of blood in the rabbit pancreas based on the results of microsphere studies. *Source:* Lifson et al. 1980 [21]. Reproduced with permission of Elsevier.

## Regulation of Pancreatic Exocrine Secretion by Islet Hormones

### Insulin

Insulin secreted by the β cells in the islets plays a pivotal role in the regulation of pancreatic exocrine secretion. Insulin stimulates basal amylase secretion and potentiates secretagogue-stimulated amylase secretion. Many studies have shown that exogenous insulin potentiates cholecystokinin (CCK)-stimulated amylase secretion [23–26]. Although glucose clamping has been shown to inhibit secretin-stimulated pancreatic secretion, there have been several conflicting reports concerning the effect of hyperglycemia on pancreatic secretion [27–30]. Berry and Fink [27] used the euglycemic hyperinsulinemic clamp technique in a study on innervated and denervated dog pancreata and reported finding that insulin inhibited secretin-stimulated pancreatic bicarbonate secretion. The inhibitory action of exogenous insulin on

secretin-induced pancreatic bicarbonate secretion in dogs has been shown to be mediated by a cholinergic mechanism [27,29]. Lam et al. [31] demonstrated that basal pancreaticobiliary secretion in humans is also reduced by hyperglycemia and euglycemic hyperinsulinemia, and that CCK-stimulated secretion is reduced only in the presence of hyperglycemia. Pretreatment with atropine abolished the exogenous insulin-induced increase in pancreatic secretion despite persistent hypoglycemia [32], suggesting that the increase might be mediated by vagal cholinergic activation induced by hypoglycemia.

Saito et al. [23] clearly showed that the endogenous insulin released in response to glucose infusion of a perfused rat pancreas significantly potentiated pancreatic secretion in response to CCK. Iwabe et al. [33] demonstrated that intravenous glucose infusion increased intravenous CCK- and intraduodenal casein-stimulated pancreatic secretion in rats. An important role of endogenous insulin was clearly shown in the studies conducted by Lee et al. [34–36] in which they immunoneutralized insulin with a specific antiserum. They found that intravenous administration of anti-insulin serum to rats resulted in significant depression of pancreatic secretion in response to ingestion of a meal (Fig. 12.2) and to intravenous administration of secretin and CCK [34]. Pancreatic exocrine secretion stimulated with secretin, CCK, or a combination of both in isolated perfused rat and dog pancreata was also inhibited by anti-insulin serum [35,36]. Anti-insulin serum infusion also increased the somatostatin and PP levels in the portal venous efferent vessels, and co-infusion of both anti-somatostatin and anti-PP serum abolished the inhibition of pancreatic secretion induced by anti-insulin serum. These results indicated that the suppression of pancreatic secretion by anti-insulin serum may in part be mediated by local release of somatostatin and PP [36]. Insulin binds its own receptor on the acinar cell, which leads to stimulation and potentiation of amylase secretion by various mechanisms [37–40].

## Glucagon

The effect of glucagon on pancreatic secretion in early studies using extracted glucagon was controversial, because the extracted glucagon was contaminated by a variety of unidentified biologically active peptides. Although biologically active synthetic glucagon showed no stimulatory effect of glucagon on pancreatic secretion [41], the inhibitory action of glucagon on pancreatic secretion *in vivo* has been shown [42,43] and may be indirect and related to stimulation of somatostatin release by glucagon [42]. von Schonfeld and Muller [44] demonstrated that CCK-stimulated amylase secretion in the isolated perfused rat pancreas is unaffected by exogenous glucagon but that it is inhibited by arginine-released endogenous glucagon, and that immunoneutralization with glucagon antibodies blocks the inhibitory effect of endogenous glucagon released in response to arginine.

## Somatostatin

Somatostatin is present in islet δ cells, the intestine, and nerve terminals. It has an inhibitory action on exocrine pancreatic secretion in the islet–acinar axis [45], but the mechanism of the inhibitory effect has been debated. One of the proposed mechanisms is that as a paracrine messenger somatostatin directly inhibits acinar cell function by binding to the somatostatin receptors on the acinar cells, and another is an indirect mechanism in which somatostatin inhibits the release of secretin, CCK, and insulin. In an experiment performed on the isolated perfused rat pancreas, Muller et al. [46] showed that the role of somatostatin in the regulation of exocrine pancreatic secretion is mediated by its effect on pancreatic α and β cells. Somatostatin receptors (SSTR2) have been shown to be located on α and β cells in humans [3]. A neuron-mediated mechanism for somatostatin's regulation of pancreatic exocrine secretion has been suggested,

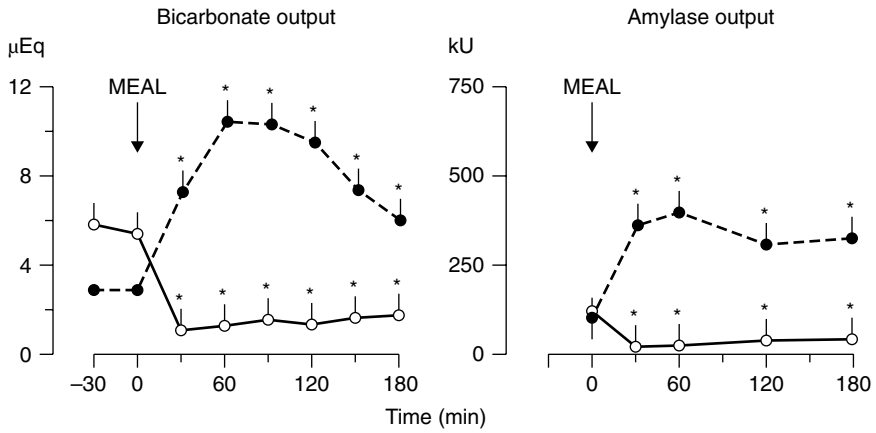


**Figure 12.2** Effects of normal rabbit serum (closed circles) and anti-insulin serum (open circles) on pancreatic secretion of bicarbonate and amylase in response to a test meal in rats [34]. Immunoneutralization with anti-insulin serum resulted in complete suppression in bicarbonate and amylase output in response to ingestion of a meal.

because somatostatin does not inhibit enzyme secretion in either isolated arterially perfused preparations or acinar cells *in vitro*.

## Pancreatic Polypeptide

PP is secreted by the PP cells of the pancreatic islets and released into the circulation after a meal. In the fasting state, endogenous PP is released cyclically and its release is closely linked to the cyclic migrating motor complex (MMC) of the duodenum [47–49]. Immunoneutralization of circulating PP in dogs has been found to result in a significant increase in pancreatic exocrine secretion in the interdigestive state as well as in the postprandial state [49]. Intravenous administration of PP inhibits both basal and stimulated pancreatic secretion of amylase and bicarbonate. However, PP has failed to suppress CCK-stimulated amylase secretion by either isolated rat pancreatic acini or pancreatic lobules preparations [50]. Thus, the inhibitory action of PP on amylase secretion may be achieved indirectly through its inhibitory effect on insulin secretion. Recent studies have shown that PP inhibits somatostatin and glucagon release [51,52], and that PP receptors are present on the α cells of both mouse and human pancreatic islets [52].

## Ghrelin

Ghrelin is a 28-amino-acid peptide that was initially discovered in the stomach and later found to be produced in the pancreas. Ghrelin-producing cells have been named ε cells [14], and their presence has been confirmed in both fetal and adult human pancreas [53]. Lai et al. [54] detected ghrelin and its receptor at both the protein level and mRNA level in acinar cells of the rat pancreas, suggesting that ghrelin regulates exocrine functions by a paracrine and/or autocrine mechanism. Ghrelin has been found to be a potent inhibitor of pancreatic amylase secretion in rats *in vivo* and in pancreatic lobules *in vitro* [55], and ghrelin has been shown to stimulate pancreatic secretion via a vagal cholinergic pathway [56]. Several studies have shown that ghrelin inhibits insulin release in humans, rats, and mice and by clonal β cells [53]. These findings indicate that the ghrelin released in the islets may act as a paracrine inhibitor of insulin secretion.

## Amylin

Amylin is a 37-amino-acid peptide hormone that is co-secreted with insulin by pancreatic β cells in response to nutrient stimuli [57]. Amylin is an effective and potent inhibitor of stimulated pancreatic enzyme secretion. Young et al. [58] reported *in vivo* dose–response relationships in the inhibitory effects of amylin on CCK-stimulated amylase and lipase secretion in rats. Neither inhibitory effect was observed in AR42J cells nor isolated pancreatic acini. Thus, the inhibitory effect of amylin on pancreatic secretion appears to be the result of an indirect mechanism or is possibly mediated by an extrapancreatic mechanism.

## Pancreastatin

Pancreastatin is a 49-amino-acid peptide that was first isolated and purified from porcine pancreas [59]. Chromogranin A is the prohormonal precursor of pancreastatin. Pancreastatin appears to be localized in the α, β, and δ cells of the islets and it inhibits insulin release induced by various physiological and hormonal stimuli [59,60]. Efendic et al. [61] found that pancreastatin inhibits arginin-induced somatostatin secretion *in vivo* in rats and potentiates arginine-induced glucagon release in the isolated perfused pancreas. Pancreastatin has been shown to have an inhibitory effect on exocrine pancreatic secretion stimulated by ingestion of a meal, CCK-8, and central vagal nerve stimulation *in vivo* in rats [60,62]. However, CCK-stimulated amylase secretion by isolated rat pancreatic acinar cells is unaffected by pancreastatin [62]. The inhibitory effect of pancreastatin seems to be mediated by presynaptic modulation of acetylcholine release by the vagal system [62]. A recent clinical study has reported elevated pancreastatin levels and overexpression in patients with type 2 diabetes [63].

## Peptide YY

Peptide YY (PYY) is a 36-amino-acid peptide that was originally isolated from the porcine intestine [64], and immunoreactive PYY has been detected in α and PP cells in rats [65]. PYY has been shown to have an inhibitory effect on secretin- and CCK-stimulated pancreatic secretion in cats [64], and PYY secretion stimulated by ingestion of a meal and duodenal oleate administration has been demonstrated in dogs and rats [66]. Two receptors, PYY1 and PYY2, are known to mediate physiological actions of PYY. PYY2 receptors have been demonstrated on guinea pig pancreatic acini [67]. The inhibitory effect of PYY on pancreatic secretion in dogs has been reported to be mediated by PYY2 receptors [68], and in isolated perfused rat pancreas by PYY1 receptors [69].

## Galanin

Galanin is a 29-amino-acid peptide that was originally isolated from porcine upper intestine [70]. The presence of galanin has been immunohistochemically demonstrated in the neural elements of the pancreas of several

species including humans [71,72]. Baltazar et al. [73] also detected galanin-like immunoreactivity in islet endocrine cells, and demonstrated colocalization of galanin and insulin. Galanin has been shown to influence pancreatic islet secretion, most notably by inhibiting insulin secretion. The colocalization of galanin and insulin suggests an autocrine interaction between these two hormones. Although the first study showed an inhibitory effect of galanin on amylase secretion in isolated rat pancreatic acinar cells, numerous subsequent studies have found neither an inhibitory effect nor a stimulatory effect. Barreto et al. [74] reported that galanin inhibits caerulein-stimulated amylase secretion by acting on cholinergic neurons and/or islet cells via galanin receptor 2 and thereby regulates insulin release.

### Adrenomedullin

Adrenomedullin is a multiregulatory peptide that was discovered by Kitamura et al. [75]; it is expressed in a wide variety of tissues. Adrenomedullin has been demonstrated in the pancreatic islets in mammals, including humans, and has been found to colocalize with PP in islet PP/F cells [76]. Adrenomedullin receptors have been detected in β cells. Adrenomedullin has been shown to inhibit insulin secretion in a dose-dependent manner both in isolated rat islets and in rats *in vivo* [77]. Tsuchida et al. [78] demonstrated specific adrenomedullin binding sites on rat pancreatic acini and a dose-dependent inhibitory effect of adrenomedullin on CCK-stimulated amylase release from acini. A recent study showing overexpression of adrenomedullin in pancreatic cancer has indicated that adrenomedullin may be a biomarker for early diagnosis of pancreatic cancer [79].

### Pancreatic Stone Protein and Regenerating Pancreas

A sequence comparison has been shown that the pancreatic stone protein (PSP) identified in pancreatic stones and the regenerating protein (Reg) identified in regenerating islets are identical [80]. PSP/Reg has been shown to be predominantly synthesized by acinar cells, and neither pancreatic duct dells nor islet cells seem to contribute significantly to its production. Kimura et al. [81] showed that PSP/Reg mRNA is expressed in the acinar cells of normal human pancreas and pancreatic cancer cells. PSP/Reg expression is associated with β-cell growth and proliferation during islet regeneration. Increased serum PSP levels have been reported in patients with acute and chronic pancreatitis, pancreatic cancer, and type 2 diabetes [82,83]. PSP may be useful as a predictor of pancreatic exocrine and endocrine diseases.

### Cholecystokinin

CCK binds to the CCK-A receptors and regulates gallbladder contraction and pancreatic exocrine secretion [1]. It is also a neuropeptide that binds to the CCK-B receptors and regulates anxiety, satiety, and other behaviors. CCK-producing cells were identified in rat pancreatic islets [84], and further study showed that CCK is expressed in the pancreatic β cells of rats [85]. CCK-A receptors have also been detected immunohistochemically in the β and α cells of rats, pigs, and humans [86]. A stimulatory effect of CCK on insulin secretion has been demonstrated in mice, in diabetic rats, and in humans with type 2 diabetes. CCK has been shown to protect β-cell mass in rats and mice with streptozotocin (STZ)-induced diabetes [85,87]. Islet-derived CCK may have an important paracrine/autocrine effect in protecting β cells from apoptosis and mitogenesis [86]. The effects of CCK on the exocrine pancreas were thought to be almost exclusively mediated by enteropancreatic reflexes [1,88,89] because human pancreatic acini are now known to lack functional CCK-A receptors [90].

## Pancreatic Exocrine Function and Diabetes Mellitus

### Pancreatic Exocrine Function in Patients with Diabetes

Pancreatic exocrine dysfunction is well known in patients with type 1 and type 2 diabetes [91,92]. Chey et al. [93] observed reduced amylase secretion in response to injection of CCK–secretin in 36% of 50 patients with diabetes and 77% of juvenile patients with diabetes. Vacca et al. [94] reported an abnormal secretin test in 73% of 55 patients with diabetes on insulin therapy, and Lankisch et al. [95] demonstrated pancreatic exocrine insufficiency in 43% of 53 patients with insulin-dependent diabetes. A multicenter study conduced in 1021 German patients with diabetes by Hardt et al. [96] showed normal concentrations of fecal elastase-1 in 59.3% of the patients and much lower concentrations in 22.9%, and there was a significant difference in the prevalence of reduced fecal elastase-1 concentrations between the type 1 group (51%) and the type 2 group (35%). Ewald et al. [97] reported that fecal elastase-1 concentrations were inversely correlated with diabetic duration and $HbA_{1c}$ levels, and that both C-peptide levels and body mass index (BMI) were positively correlated with fecal elastase-1 concentrations.

### Pancreatic Exocrine Function in Experimental Animal Models of Diabetes

Shimizu et al. [98] observed impaired basal and CCK-stimulated pancreatic exocrine secretion in rats with STZ-induced diabetes and restoration of pancreatic

secretion in response to administration of the thiazolidine derivative troglitazone, a peroxisome proliferator-activated receptor γ (PPARγ) agonist, even though the insulin content of the pancreas was unaffected. Troglitazone has been shown to reduce insulin resistance and increase pancreatic weight and pancreatic enzyme content in WBN/Kob rats and OLETF rats, which spontaneously develop diabetes and chronic pancreatitis [99,100]. Thus, the insulin resistance of peripheral tissues as well as the amount of circulating insulin affects pancreatic exocrine function. Patel et al. [101] observed decreased CCK-8-evoked amylase secretion in rats with STZ-induced diabetes and in acinar cells isolated from such rats, and suggested that the reduced amylase secretion might be due to reduced cytosolic free calcium concentrations and amylase gene expression, and not to gene expression of the CCK-A receptor in pancreatic acinar cells. Korc et al. [102] clearly demonstrated decreased pancreatic amylase mRNA in rats with STZ-induced diabetes, and that insulin reversed this effect and induced a selective increase in amylase mRNA in the pancreas. It has recently been suggested that reduced adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide phosphate (NADPH) production in mice with STZ-induced diabetes may contribute to the development of exocrine insufficiency [103].

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# Section 3

# Acute Pancreatitis

13

# Epidemiology and Etiology of Alcohol-Induced Pancreatitis

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## Introduction

The association of the overuse of alcohol with pancreatitis was first reported in the medical literature in 1815 [1,2] with subsequent more systematic analyses being made by Freidreich in 1878 [3] and Fitz in 1889 [4]. Over the past 100 years or so, considerable effort has been expended in exploring the clinical and epidemiological features of alcoholic pancreatitis and possible cofactors in the disease as well as mechanisms whereby alcohol (ethanol) may be directly injurious to the pancreas. (Note: In this text, the words "alcohol" and "ethanol" are used interchangeably.)

Alcoholic pancreatitis represents a clinical paradox. On the one hand, the risk of developing the disease increases with the amount of alcohol consumed, suggesting direct toxic effects of alcohol on the pancreas. On the other hand, only a minority (5% or less) of heavy drinkers develop the disease, suggesting a role for individual susceptibility factors.

## Epidemiology

In Western countries, alcohol ranks with gallstone disease as a major cause of acute pancreatitis, and is the major cause of chronic pancreatitis. There has been variation in attribution rates among different studies [5–8]. This variation most likely relates to the background alcohol consumption of the population under study, the types of institutions surveyed (e.g., private facility vs. county or Veterans Affairs facilities in the United States), the difficulties associated with eliciting an accurate alcohol consumption history and the growing awareness of possible cofactors in the disease (e.g., smoking).

For a long time, acute alcoholic pancreatitis and chronic alcoholic pancreatitis were considered separate diseases [9]. It is now generally recognized that they a part of the same continuum. There is good clinical [10,11] and experimental evidence [12,13] that repeated attacks of pancreatic necroinflammation lead to chronic pancreatitis (the necrosis–fibrosis sequence).

With respect to the amount of alcohol consumption required to produce pancreatitis, there has been confusion. Episodic binge drinking or the isolated alcoholic debauch rarely, if ever, causes pancreatitis [14]. However, with regard to the common situation of chronic alcohol intake, an early study suggested that the risk of developing pancreatitis was linear, even at relatively low (social) levels of consumption [15]. Later studies have suggested that there is a threshold above which pancreatitis is more likely to occur [6,16,17]. Most clinicians, basing their views on clinical experience, would agree that the diagnosis is not made in the absence of chronic heavy alcohol consumption (80–100 g of alcohol per day for at least 5 years). However, alcoholic pancreatitis is now emerging as a polyfactorial/polygenic disease (see later), so that lesser amounts of alcohol consumed may be responsible for the phenotype. It is clear that more work needs to be done on this concept.

## Pathogenesis

### Large Duct Theories

Historically, studies of pathogenesis of alcoholic pancreatitis centered first on the sphincter of Oddi and the large pancreatic ducts. This work was inspired by the observations of Opie with respect to gallstone pancreatitis. The biliary–pancreatic reflux, duodeno-pancreatic

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Companion website: www.wiley.com/go/beger/thepancreas

reflux, and obstruction–hypersecretion theories gradually lost support because of a failure of consensus on the effects of alcohol on sphincter of Oddi motility, the effect of alcohol on pancreatic secretion, and other factors. These so-called "large duct" theories have been discussed in greater detail elsewhere [18].

## Small Duct Theory

In the 1970s, attention moved to the small pancreatic ducts, due predominantly to the landmark research of Henri Sarles and his colleagues in Marseilles. This group proposed that the initial event in alcoholic pancreatitis was the deposition of protein plugs in small pancreatic ducts, leading to local injury and possible upstream effects as a result of obstruction of pancreatic secretion [9]. These plugs are the forebears of pancreatic intraductal calculi, a major feature of chronic alcoholic pancreatitis. The major problem with Sarles' theory was the uncertainty as to whether these protein plugs were primary or secondary lesions. The plugs contain the readily precipitable protein lithostathine S1, formed from lithostathine by autocatalysis or hydrolysis by trypsin [19]. Since alcohol predisposes to premature activation of trypsinogen to trypsin in acinar cells [20], prior upstream events may precede plug formation. Nonetheless, the work of Sarles and colleagues was important in suggesting that ductular dysfunction may play a role in the pathogenesis of alcoholic pancreatitis, especially as they provided the initial suggestion (via sweat electrolyte studies) that cystic fibrosis transmembrane conductance regulator (CFTR) dysfunction may play a role [9].

## Direct Cellular Effects of Alcohol on the Pancreas

From the 1980s, attention focused on the direct effects of alcohol on pancreatic acinar cells, then from around 2000, on pancreatic stellate cells, and, most recently, on pancreatic duct cells. The results of these studies, conducted largely in rodents, are depicted in Fig. 13.1.

It should be remembered that there is no satisfactory model of alcoholic pancreatitis. In experimental animals, alcohol by itself induces a number of changes that

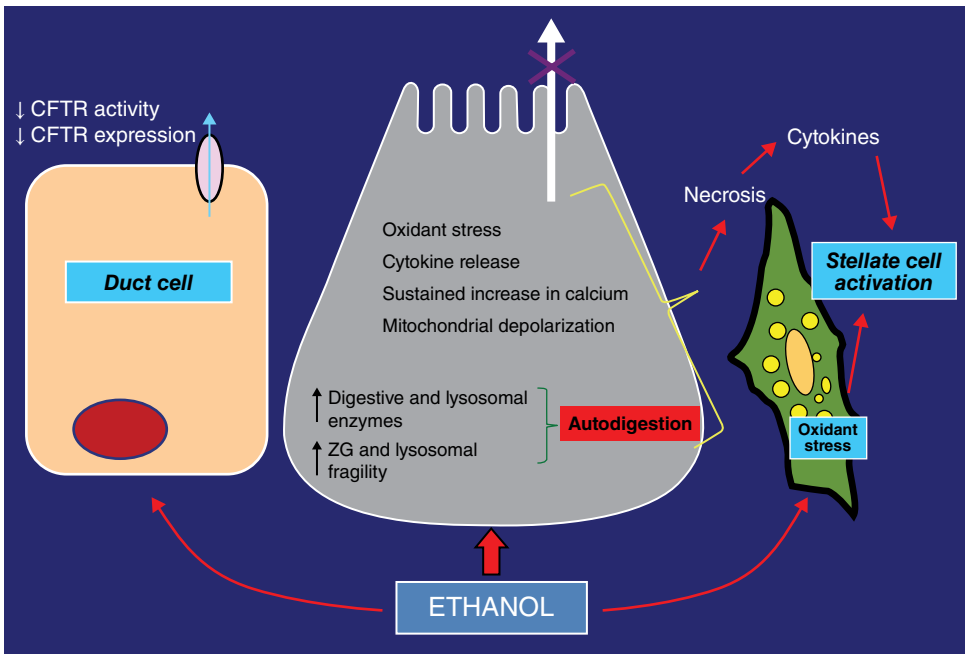


**Figure 13.1** Effects of alcohol and its metabolites on the acinar cell, duct cell, and stellate cell of exocrine pancreas. Ethanol induces an increase in digestive and lysosomal enzyme synthesis in the acinar cell, while at the same time decreasing exocytosis and impairing organelle stability. These effects predispose the cell to premature intracellular enzyme activation and autodigestion. Ethanol metabolism within the cell leads to oxidant stress, which damages subcellular membranes, proteins, and nucleic acids. In addition, ethanol causes a sustained increase in intracellular calcium, leading to mitochondrial depolarization and cell death. The ethanol-induced injury to the acinar cell also results in the release of cytokines by the cell, which can subsequently damage neighboring cells. Ethanol impairs duct cell function by decreasing CFTR expression and activity. With regard to the pancreatic stellate cell (PSC), ethanol and its metabolites and oxidant stress activate "PSCs" leading to production of excessive amounts of extracellular matrix proteins. Cytokines released from acinar cells can also activate "PSCs" via paracrine pathways, while cytokines synthesized by "PSCs" themselves can further activate the cells in an autocrine manner, leading to progressive fibrosis, even in the absence of the initial trigger. ZG, zymogen granule.

predispose the pancreas to autodigestion, necroinflammation, and fibrosis, but that are insufficient to cause overt pancreatitis. However, coadministration of an additional "hit," such as bacterial endotoxin, produces pancreatitis. This will be discussed in greater detail later.

#### Metabolism of Alcohol by the Pancreas

Many of the direct effects of alcohol on the pancreas are a consequence of the metabolism of alcohol (ethanol) by the gland via oxidative and nonoxidative pathways.

The oxidative pathway of alcohol metabolism involves sequential oxidation by alcohol dehydrogenase (ADH) to acetaldehyde and then to acetate via acetaldehyde dehydrogenase (ALDH). Catalase in peroxisomes can also metabolize ethanol to acetaldehyde but its activity is thought to be low as it is determined by the availability of its substrate hydrogen peroxide ($H_2O_2$). Additionally, cytochrome P450 2E1 (CYP2E1) can metabolize ethanol at high concentrations to acetaldehyde and this is enhanced by enzyme induction following chronic ethanol exposure [21]. Both ADH and CYP2EI have been identified in pancreatic tissue (catalase is ubiquitous) [22–24]. The oxidative pathway results in depletion of antioxidant defenses (mainly glutathione) and the production of reactive oxygen species capable of disruption of membranes, proteins, and DNA.

The nonoxidative pathway involves esterification of ethanol with free fatty acids (FFA) to form fatty acid ethyl esters (FAEE). The enzymes catalyzing this reaction are FAEE synthases. There appears to be no one enzyme responsible for this reaction, and carboxyl ester lipase (CEL) and triglyceride lipase have been implicated. It has been reported that the pancreas has the highest FAEE synthesizing capacity of any parenchymal organ [25].

FAEE are believed to exert toxicity via:

- direct perturbation of biological membranes following intercalation and
- a transport shuttle mechanism with local release of FFA resulting in disturbance of intracellular membrane function with decreased lysosomal stability (see later) and altered intracellular calcium homeostasis with resultant calcium overload, mitochondrial dysfunction, and cell death.

The pancreatic acinar cell possesses the enzymatic machinery for both oxidative and nonoxidative ethanol metabolism, with the former representing the major pathway for alcohol metabolism [22–24] in rats. Kinetic studies using rat pancreatic acini suggest that ethanol is metabolized in acinar cells predominantly by class III (high $K_m$) ADH [22,23]. However, a recent study has reported that the predominant class of ADH in human pancreatic acini is ADH I, with ADH III contributing little to pancreatic alcohol oxidation [26]. These disparate findings may reflect species differences and the relative magnitudes of the oxidative and nonoxidative pathways in human pancreatic tissue remain to be determined. However, even in rat pancreatic acinar cells, where oxidative metabolism of ethanol seems to dominate, the contribution of the nonoxidative pathway cannot be discounted because FAEE are produced in sufficient amounts to produce local injury [27]. Interestingly, pharmacologic inhibition of the FAEE synthase CEL ameliorates alcohol-induced pancreatic damage in mice [28].

Rat pancreatic stellate cells (PSC) can also oxidize alcohol to acetaldehyde via a pyrazole-sensitive (class I) ADH [29]. These observations are well supported by a recent study reporting activity of an ADH class I isozyme, namely ADH1C, in quiescent human PSC which was inhibited by pyrazole [26]. Interestingly, this study also showed that the expression of ADH1C was increased in activated human PSC in chronic pancreatitis [26]. The capacity of PSC for nonoxidative ethanol metabolism is yet to be determined.

#### Effects of Ethanol on Pancreatic Acinar Cells

Chronic alcohol administration to rodents results in a number of changes in acinar cells which may predispose the cells to injury. *In vitro* and *in vivo* approaches have now established that ethanol and its metabolites exert multiple effects on acinar cells, including:

- an increase in intracellular levels of digestive enzymes (trypsin, chymotrypsin, and lipase) mediated, at least in part, by increases in their respective mRNA levels [30] and possibly also by decreased secretion secondary to acetaldehyde-induced apical microtubule disruption [31] and inhibition of binding of secretagogues to their receptors [32];
- an increase in lysosomal enzyme content [20,30];
- decreased stability of lysosomes mediated by accumulation of FAEE and cholesteryl esters (transesterification products of FAEE) in the cells [27,33];
- decreased zymogen granule stability [34], possibly mediated by an ethanol-induced reduction of GP2 [35], the predominant protein in zymogen granule membranes that is responsible for zymogen granule shape and membrane stability.

Taken together, the effects of alcohol on lysosomes and zymogen granules create a situation whereby there is an increased potential for contact between trypsinogen and lysosomal hydrolases, with subsequent generation of active trypsin, leading to activation of an intracellular digestive enzyme cascade and autodigestion.

Other effects of alcohol on pancreatic acinar cells include the following:

- FAEE cause a sustained rise in intracellular calcium levels via stimulation of calcium release from endoplasmic reticulum following stimulation of inositol trisphosphate ($IP_3$) receptors and defective clearance of cytosolic calcium via inhibition of $Ca^{2+}$-ATPase pumps in plasma membrane and endoplasmic reticulum. The sustained rise in calcium levels subsequently causes mitochondrial overload and cell death [36].
- The transcription factors NFκB and AP-1 (which are important regulators of cytokine expression) are induced by alcohol and acetaldehyde as well as by FAEE [22].
- The unfolded protein response/endoplasmic reticulum (ER) stress and autophagy are two homeostatic mechanisms for maintaining cellular integrity in all cells. Recent studies have demonstrated that chronic alcohol consumption induces ER stress [37] and impaired autophagy [38] in pancreatic acinar cells.

#### Effects of Ethanol on Pancreatic Stellate Cells

PSC are the principal source of collagen and other extracellular matrix proteins in the fibrosis of chronic alcoholic pancreatitis. PSC are directly activated upon exposure to ethanol [29,39]. This activation is thought to be mediated via the metabolism of alcohol to acetaldehyde and the subsequent generation of reactive oxygen species within the cells [29].

PSC are also activated by inflammatory cytokines (released during pancreatic necroinflammation) and, in turn, produce their own inflammatory cytokines resulting in an autocrine loop allowing perpetuation of activation even after the initial insult has been removed [40–44].

#### Effects of Ethanol on Pancreatic Duct Cells

Inspired by the original observations of Sarles et al. [9] on pancreatic intraductal abnormalities and sweat electrolytes in patients with chronic alcoholic pancreatitis (see earlier), Maleth et al. [45] have recently examined the effect of ethanol on CFTR function. In recently abstinent alcoholics and in acutely drinking alcoholics with very high blood alcohol concentrations, CFTR function (as determined by sweat chloride concentration) was impaired, but this was not the case in normal individuals with acute consumption of alcohol. In addition, it was found that in duct cells isolated from alcoholic pancreatitis tissue, CFTR expression was decreased at both mRNA and membrane protein levels, with evidence of impaired posttranslational processing. In *in vitro* experiments using duct cell lines and tissue from mice and guinea pigs, ethanol decreased CFTR mRNA as well as membrane CFTR levels and stability; these effects were reported to be mediated by nonoxidative metabolites of ethanol.

## Individual Susceptibility to Alcoholic Pancreatitis

Despite the substantial experimental evidence supporting direct toxic effects of alcohol and its metabolites on the pancreas, it is well established that only a minority of people with alcoholism develop clinically evident pancreatitis [46,47], suggesting that an additional factor is required to induce the disease in heavy drinkers. The search for this cofactor/susceptibility factor/trigger factor/second "hit" has prompted many studies, as summarized in Table 13.1.

Ideally, studies into individual susceptibility to alcoholic pancreatitis should compare alcoholics *with* the disease and alcoholics *without* the disease so that the index and the control groups differ in only one variable (i.e., the presence or absence of pancreatitis). This has not always been the case, with several studies using only the healthy population as a control group.

Many susceptibility factors have been examined to date. These can best be classified as being environmental or hereditary. Environmental factors include diet, amount and type of alcohol consumed, the pattern of drinking, smoking, obesity, lipid intolerance, and endotoxemia. Hereditary factors include genes relevant to alcohol metabolism, digestive enzymes and their inhibitors, proinflammatory cytokines, oxidant stress, and cystic fibrosis [8,48,49].

#### Environmental Factors

##### *Dietary Factors*

There is no clear evidence that dietary factors play a role in individual susceptibility to alcoholic pancreatitis [50]. This is certainly true with respect to macronutrients [50]. Properly controlled studies of dietary micronutrients, antioxidants, and other micronutrients are yet to be performed.

##### *Beverage Type and Periodicity of Drinking*

Similarly, there is no evidence that the type of alcoholic beverage consumed plays any part in susceptibility to alcoholic pancreatitis [50], although it must be acknowledged that the congeners of alcoholic beverages have not been studied exhaustively.

Additionally, it has not been established that the periodicity of drinking is a susceptibility factor in this disease [50]. Although there have been occasional reports implicating binge drinking, most patients imbibe alcohol at high levels constantly from one day to the next, prior to the initial presentation.

**Table 13.1** Individual susceptibility to alcoholic pancreatitis.

| Factor | Association | |
|---|---|---|
| Drinking pattern | No | Wilson et al., 1985 [50] |
| Beverage type | No | Wilson et al., 1985 [50] |
| | Yes | Nakamura et al., 2003 [95] |
| Diet | No | Wilson et al., 1985 [50] |
| Smoking | Yes | Lowenfels et al., 1987 [96] |
| | No | Haber et al., 1993 [97] |
| | Yes | Maisonneuve et al., 2005 [54] |
| Obesity | Yes | [a]Ammann et al., 2010 [55] |
| **Inherited factors** | | |
| HLA | No | Wilson et al., 1984 [88] |
| α1-antitrypsin deficiency | No | Haber et al., 1991 [89] |
| Cystic fibrosis genotype | No | Norton et al., 1998 [98] |
| Cytochrome P4502E1 polymorphism | No | Frenzer et al., 2002 [93] |
| ADH genotype | No | Frenzer et al., 2002 [93] |
| | Yes | Shimosegawa et al., 2008 [64] |
| | Yes | Maruyama et al., 1999 [65] |
| | Yes | Matsumoto et al., 1996 [66] |
| | Yes | Maruyama et al., 2008 [67] |
| | Yes | Zhong et al., 2015 [68] |
| Anionic trypsinogen gene mutation | Yes | [a]Witt et al., 2006 [74] |
| | Yes | [a]Whitcomb et al., 2012 [75] |
| | Yes | Derikx et al., 2015 [76] |
| *PSTI/SPINK1* mutations | Yes | Witt et al., 2001 [78] |
| Claudin 2 | Yes | [a]Whitcomb et al., 2012 [75] |
| | Yes | Derikx et al., 2015 [76] |
| TNF-α, TGF-β, IL-10, IFNγ polymorphisms | No | [a]Schneider et al., 2004 [90] |
| Detoxifying enzymes | | |
| Glutathione *S*-transferase | No | Frenzer et al., 2002 [93] |
| UDP-glucuronosyl transferase | Yes | [a]Ockenga et al., 2003 [91] |
| Carboxyl ester lipase (CEL) polymorphism | Yes | Miyasaka et al., 2005 [70] |
| | No | [a]Ragvin et al., 2013 [71] |
| Hybrid allele of CEL (*CEL-HYB*) | Yes | [a]Fjeld et al., 2015 [72] |

[a] Studies that did not include alcoholics without pancreatitis as controls.

### *Smoking*

The role of smoking as a trigger factor for alcoholic pancreatitis has been a particularly contentious subject [51,52]. This is largely because the vast majority of heavy drinkers are also smokers, making it difficult to demonstrate unequivocally an independent role for smoking in the initiation of pancreatitis. Law et al. [53] concluded that smoking is independently associated with chronic pancreatitis, after adjusting for alcohol and other risk factors. However, the authors acknowledged that the retrospective nature of the study made it difficult to stratify accurately the extent of smoking and alcohol use. Furthermore, the study population included patients with chronic pancreatitis with a variety of etiologies; only a small proportion of the study subjects could be classified as heavy drinkers.

Although the role of smoking as an initiating factor in alcoholic pancreatitis remains uncertain, there is evidence to suggest that it may facilitate the progression of the disease as evidenced by the accelerated development

of pancreatic calcifications and endocrine dysfunction in patients with alcoholic pancreatitis who smoke [54].

#### *Obesity*

Another recently explored risk factor for alcoholic pancreatitis is obesity. Using a prospectively recruited cohort of patients with alcoholic chronic pancreatitis and age- and sex-matched healthy subjects as controls, Ammann et al. [55] reported that obesity prior to onset of chronic pancreatitis, defined as body mass index (BMI) greater than 30, was fivefold more frequent in patients with alcoholic chronic pancreatitis compared to healthy controls, but had no effect on disease progression. However, as obesity is highly prevalent in asymptomatic alcoholics compared to the general population [56], the lack of an appropriate control group (alcoholics without pancreatitis) in the Ammann study [55] precludes any definitive conclusions regarding obesity as a susceptibility factor for the development of alcoholic pancreatitis.

#### *Lipid Intolerance*

Alcohol abuse can cause hypertriglyceridemia and hypertriglyceridemia is a known cause of acute pancreatitis, at least at very high levels of serum triglycerides. These facts have led to speculation that those alcoholics who develop pancreatitis do so via the development of hypertriglyceridemia. However, when postprandial lipid tolerance was studied in patients with alcoholic pancreatitis (index group) no difference was found compared with a control group comprising alcoholics without pancreatitis [57]. This study emphasized the importance of appropriate controls in studying susceptibility to alcoholic pancreatitis.

#### *Endotoxin*

Serum endotoxin levels are increased in alcoholics, even after a single binge, most likely due to an alcohol-induced increase in gut permeability permitting translocation of gram-negative bacteria (such as *E. coli*) across the mucosal barrier and decreased clearance of endotoxin by Kupffer cells in the liver [58,59]. Recently, Forsyth et al. [60] have shown that alcohol increases the permeability of Caco-2 intestinal epithelial cell monolayers via CYP2E1-induced oxidant stress, which in turn induces the circadian clock proteins CLOCK and PER2.

Experimental studies support the concept of bacterial endotoxin (lipopolysaccharide [LPS]) as a promising susceptibility factor for alcoholic pancreatitis. A study by Vonlaufen et al. [61] has provided convincing evidence that endotoxin (LPS) challenge in alcohol-fed rats initiates overt pancreatic injury and also stimulates progression to chronic disease manifesting as acinar atrophy and fibrosis. Importantly, this effect was abrogated in TLR4 (Toll-like receptor 4, LPS receptor) knockout rodents [62], demonstrating the specificity of the effects of LPS on pancreatic cells.

Further work is needed to determine whether genetic polymorphisms pertinent to the alcohol-induced hyperpermeability/endotoxin paradigm may explain individual susceptibility to alcoholic pancreatitis (see later).

In summary, in terms of environmental factors, a clear and single susceptibility factor for alcoholic pancreatitis remains to be identified.

### Hereditary Factors

#### *Polymorphisms of Alcohol-Metabolizing Enzymes*

Alcohol toxicity is most likely to depend on its metabolism generating toxic metabolites such as acetaldehyde, FAEE, and reactive oxygen species. Increased or decreased activities of alcohol-metabolizing enzymes (ADH, ALDH, CYP2E1, FAEE synthases) may result in the accumulation of toxic metabolites and tissue damage (see earlier).

ADH and ALDH are the major enzymes of oxidative alcohol metabolism in the body. There are multiple ADH and ALDH enzymes encoded by different genes which can exist as several allelic variants. These variants can influence rate of metabolism and their distribution varies between ethnic groups as well as different tissues in the body [21].

Based on amino acid sequence and structural similarities, human ADH enzymes are now classified into five classes. The three class I enzymes (ADH1A, ADH1B, and ADH1C) are the major contributors to ethanol clearance in the liver [21].

There are two main groups of ALDH enzymes: cytosolic ALDH1 and mitochondrial ALDH2. ALDH2 is the major enzyme responsible for the oxidation of acetaldehyde to acetate [21].

Most attention to ADH-mediated metabolism/damage in alcoholic pancreatitis has been centered on the *ADH1B* gene. In Asian populations, the *ADH1B*2* allele predominates and encodes for the more active β2-ADH subunit that produces acetaldehyde at a much faster rate than the more common *ADH1B*1* allele (wild-type) [63,64]. Several Japanese studies have demonstrated that the frequency of the *ADH1B*2* allele is increased in patients with alcoholic pancreatitis compared to alcoholics without pancreatitis [64–66]. In the Japanese population, a decreased frequency of the *ADH1B*1* allele has also been reported, suggesting that this allele "reduces vulnerability" [66,67].

A recent meta-analysis of eight case–control studies evaluating the association of ADH1B, ADH1C, and ALDH2 variants in alcoholic pancreatitis found a higher risk for carriers of the *ADH1B*2* allele and a lower risk for the *ALDH2*2* allele (coding for a metabolically nearly inactive protein) in Asian patients [68]. In non-Asian

subjects, the *ADH1C*2* allele was associated with decreased risk [68].

Genetic polymorphisms have been described in the promoter region as well as in intron 6 of the *CYP2E1* gene, some of which are associated with altered function [69]. However, no polymorphism has been associated with alcoholic pancreatitis in studies of alcoholics without pancreatitis as controls.

#### *Mutations of FAEE Synthase Enzymes*

One study reported a positive association between the risk of developing alcoholic pancreatitis and a polymorphism of the gene for one of the candidate FAEE synthase enzymes, CEL, in Japanese subjects [70]. The investigators employed alcoholics without pancreatitis as controls. The functional significance of this polymorphism has not yet been elucidated, and the study findings have not been corroborated in a study involving European subjects [32,71]. A more recent study has reported an association between a hybrid allele of the CEL gene (*CEL-HYB*) and alcoholic chronic pancreatitis [72]; however the controls used were healthy subjects and not alcoholics without pancreatitis. Based on *in vitro* studies using HEK293 cells, the authors report that the resulting CEL-HYB protein may play a role in cell injury by impairing autophagy [72].

#### *Trypsinogen Gene Mutations*

The landmark report of Whitcomb et al. [73] in 1996 implicating a mutation in the cationic trypsinogen gene (R122H) in hereditary pancreatitis greatly strengthened the notion that trypsin may be central to the pathogenesis of pancreatitis. Certainly this discovery inspired a great amount of work into the pathogenesis of hereditary pancreatitis, and a number of other mutations were subsequently described.

Using a similar candidate gene approach, studies in alcoholic pancreatitis have largely been negative. A protective variant (G191R) of the anionic trypsinogen gene *PRSS2*, which results in a form of trypsin that is easily degraded, was reported to be significantly less common in patients with alcoholic chronic pancreatitis compared to healthy controls, but the prevalence of this variant in alcoholics without pancreatitis was not tested [74].

Most recently, the results of two large genome-wide association studies (GWASs), one from North America [75] and the other from Europe [76], have been published. A significant association in the *PRSSI/PRSS2* locus at 7q34 was detected (rs10273639). This single nucleotide polymorphism (SNP) is located in the 5′ promoter region of *PRSS1* and may affect expression of the trypsinogen gene. Both investigating teams found a decrease in alcoholic pancreatitis risk with rs10273639. This association was not observed in nonalcoholic chronic pancreatitis, nor in patients with alcoholic liver disease, although, the investigators did not study a control group of "healthy" alcoholics (i.e., those without pancreatic or liver disease). The functional significance of rs10273639 awaits clarification.

#### *Claudin 2 Mutations*

A second association of alcoholic pancreatitis was revealed by the aforementioned GWASs [75,76], involving the *CLDN2–RIPPLY1–MORC4* locus (Xp23.3, SNPs rs7057398 and rs12688220). *CLDN2* encodes claudin 2, a tight junction protein. The authors again found a decreased risk of alcoholic pancreatitis associated with the *CLDN2* locus SNP rs12688220. The functional significance of this *CLDN2* SNP remains unclear.

In chronic pancreatitis tissue sections, claudin 2 is expressed in duct cells and acinar cells and there is aberrant expression along the basolateral membrane of acinar cells in the presence of the high-risk SNP [75]. There is an intriguing possibility that the SNP reported influences the function of claudin 2 in the intestine, influencing intestinal permeability and the possibility of endotoxemia in those alcoholics susceptible to pancreatitis (see earlier). Upregulation of pore-forming claudin 2 has been implicated in increased intestinal permeability in Crohn's disease [77].

#### SPINK 1 *Mutations*

An association between mutated *SPINK1* and alcoholic pancreatitis has also been described. The N34S mutation, a c.101A > G transition leading to substitution of asparagine by serine at codon 34, was found in 5.8% patients with alcoholic pancreatitis, compared to 1.0% alcoholic controls without pancreatitis [78]. A more recent study on Romanian patients has reported that 5% of patients with ACP had the N34S mutation compared to 1% of healthy controls [79]. A recent meta-analysis found a significant association of the N34S mutation with alcoholic pancreatitis with an odds ratio of 4.98 (95% confidence interval: 3.16–7.85) but the association was the weakest among categories analyzed, including tropical pancreatitis, idiopathic chronic pancreatitis, and hereditary pancreatitis [80]. Since the N34S mutated human *SPINK1* does not show any altered trypsin inhibitor capacity, the functional consequences of this mutation are unclear.

#### *Chymotrypsin Gene Mutations*

Chymotrypsin C (CTRC) is a minor isoform of chymotrypsin. In a German study, in individuals with idiopathic or hereditary chronic pancreatitis, various CTRC variants have been found and the two most frequent variants were detected in 3.3% of pancreatitis patients but only in

0.7% of controls [81]. In individuals with alcoholic pancreatitis both variants have been detected more often (2.9%) than in patients with alcoholic liver disease (0.7%) [81]. In a Chinese population more CTRC variants were detected in chronic pancreatitis patients but the overall frequency of mutations was 2.3% and thus lower than in the European study [82].

#### CFTR *Mutations*

*CFTR* mutations have been implicated in a subset of patients with idiopathic pancreatitis [83,84]. In addition, it has been demonstrated, in both animal and human studies, that CFTR expression and function are impaired by alcohol [45]. However, there is an overall lack of evidence implicating *CFTR* mutations in the pathogenesis of alcoholic pancreatitis. A small study from Brazil showed that patients with alcoholic pancreatitis showed a higher frequency of the T5/T7 genotype in the noncoding region of thymidines in intron 8, suggesting reduced transcription of the *CFTR* gene [85]. Clearly additional and larger studies are needed.

#### *Other Hereditary Factors*

A number of other hereditary factors have also been examined as possible triggers for alcoholic pancreatitis. These include blood group antigens [86,87], HLA serotypes [88], $\alpha_1$-antitrypsin phenotypes [89], genotypes of the cytokines transforming growth factor β (TGF-β) [90], tumor necrosis factor α (TNF-α) [90], interleukin 10 [90], and interferon γ [90], and genotypes of detoxifying enzymes such as UDP-glucuronosyl transferase (*UGT1A7*) [91,92] and glutathione *S*-transferase [93]. Most studies have failed to show any association with alcoholic pancreatitis, although one recent study has reported a positive association between the risk of developing alcoholic pancreatitis and fucosyl transferase (FUT2) nonsecretor status as well as with ABO blood group B status [94]; further work is awaited.

## Summary

Since the first association of alcohol excess with pancreatitis more than 200 years ago, understanding of the disease "alcoholic pancreatitis" has undergone considerable conceptual refinement. Although alcohol excess remains a central and definitional component of the disease phenotype, it is clear that the disease is multifactorial/polygenic and that further work is needed to tease out the various pathogenetic components and their interrelationships.

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14

# Epidemiology and Etiology of Acute Biliary Pancreatitis

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## Introduction

Many authorities have contributed to our understanding of the link between the biliary tree and acute pancreatitis over the years (Table 14.1), but none more so than Eugene Opie, a pathologist at the Johns Hopkins Hospital in Baltimore, who wrote:

> During whatever stage of the disease operation is performed the condition of the bile passages is important and may offer an imperative indication for interference. The common bile duct should be examined so far as it is possible, and bearing in mind the mechanism by which a small calculus may produce the lesion, the operator should, if feasible, exclude the possibility that a stone is still lodged in the diverticulum of Vater. If such impaction should be found, removal of the calculus is essential in order to prevent further destruction of the pancreas. The temporary lodgement of a calculus within the diverticulum may produce an extensive pancreatic lesion, yet, finally expelled into the duodenum the stone may no longer be demonstrable either at operation or autopsy. Hence in a considerable number of cases the gallbladder will be found to be filled with gallstones, even though the bile ducts are free. The stones may be of such size that any one of them lodged at the orifice of the common duct might divert bile into the pancreatic duct [30].

This demonstrates both his understanding of the pathophysiologic mechanism of acute pancreatitis (i.e., the passage of gallstones and their lodgement at the ampulla of Vater) but also the importance of removal of such stones for the prevention of further attacks. Claude Bernard had previously shown that injection of bile and sweet oil into the pancreatic duct of dogs caused peritonitis, but he failed to connect this with the development of pancreatitis [12]. Lancereaux, in 1899, suggested that a stone in the lower main bile duct might obstruct the main pancreatic duct and allow penetration of microorganisms into the pancreas [16], but again did not link this to the development of acute pancreatitis. Instead it was Opie who finally linked gallstones with the pathogenesis of acute pancreatitis [17].

## Etiology of Gallstone Pancreatitis

It is now widely accepted that gallstone-associated pancreatitis results from the passage of stones through the sphincter of Oddi, into the duodenum (Fig. 14.1a,b). In a landmark study, Acosta and Ledesma analyzed the feces of patients with gallstones and pancreatitis [24]. They identified stones in the feces of 94% of patients with gallstone-associated pancreatitis but in only 8% of patients with uncomplicated biliary colic without pancreatitis. There are essentially three hypotheses to account for how gallstones induce acute pancreatitis: (i) common channel, (ii) duodenal reflux, and (iii) ductal hypertension.

### Common Channel Hypothesis

Opie described the discovery of a stone impacted at the ampulla of Vater in a common biliary/pancreatic channel of a patient who had died of acute pancreatitis [17]. He suggested that reflux of bile into the pancreatic duct may have been the precipitating cause of acute pancreatitis.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 14.1** Landmarks in the understanding of the relationship between the biliary tree and acute pancreatitis.

| Landmark | Authors | Date |
|---|---|---|
| Description of the pancreas | Herophilus of Chalkidon [1] | ~300 BC |
| Naming of the pancreas | Rufus of Ephesus [2] | ~100 |
| Case report of pancreatic inflammation | S. Alberti [3] | 1578 |
| Main pancreatic duct | Johann G. Wirsung [4] | 1642 |
| Secretory function | Regnier de Graaf [5] | 1664 |
| Sphincter mechanism | Francis Glisson [6] | 1681 |
| Duodenal papilla | J.C. Brunner [7] | 1683 |
| Papilla and ampulla | G. Bidloo [8] | 1685 |
| Lower bile duct diverticulum | Abraham Vater [9] | 1720 |
| Accessory pancreatic duct | G.D. Santorini [10] | 1724 |
| Acute pancreatitis | F. Claessen [11] | 1842 |
| Experimental "biliary pancreatitis" | Claude Bernard [12] | 1856 |
| Sphincter mechanism | Ruggero Oddi [13] | 1887 |
| Clinical overview | Reginald Fitz [14] | 1889 |
| Theory of autodigestion | Hans Chiari [15] | 1896 |
| Main pancreatic duct obstructed by a gallstone | E. Lancereaux [16] | 1899 |
| Common channel hypothesis | Eugene L. Opie [17] | 1901 |
| Role of biliary surgery | W.J. Mayo [18] | 1908 |
| Sphincter dysfunction | E. Archibald [19] | 1919 |
| Classic surgical paper | B. Moynihan [20] | 1925 |
| Role of nonoperative management | O. Mikkelsen [21] | 1934 |
| Sphincter complex | E.A. Boyden [22] | 1937 |
| Prevention of further attacks by cholecystectomy | Raker and Bartlett [23] | 1953 |
| Frequent spontaneous passage of gallstones | Acosta and Ledesma [24] | 1974 |
| Prognostication | J.H. Ranson et al. [25] | 1974 |
| First randomized trial controlled by prognostic stratification | C.W. Imrie et al. [26] | 1978 |
| Endoscopic stone extraction in acute pancreatitis | M. Classen et al. [27] | 1978 |
| First randomized trial of ERCP/sphincterotomy | J.P. Neoptolemos et al. [28] | 1988 |
| Ductal hypertension hypothesis | M.M. Lerch et al. [29] | 1993 |

Experimentally, Opie was able to demonstrate that forcible injection of bile into the pancreatic ducts of dogs did indeed induce inflammation of the pancreas, a finding that has been confirmed by other investigators [31]. It has become apparent, however, that no more than two-thirds of the population have such a common ductal channel [32,33] and in many cases this is so short that a stone obstructing the common bile duct would also obstruct the pancreatic duct. Nevertheless, common channels are found more commonly among patients with biliary acute pancreatitis than in the general population [34]. Even in the absence of a significant anatomic common channel, however, it is possible that passage of a stone may cause a functional common channel in some patients by causing a stenosis of the ampulla of Vater [35]. This assumes that bile reflux is the trigger for pancreatitis, even though at normal pressures bile is not injurious to the pancreas [36]. The pressure in the pancreatic duct is, in fact, normally two to three times higher than that in the bile duct and would therefore tend to favor reflux of pancreatic secretions into the biliary tract rather than vice versa [37,38].

## Duodenal Reflux Hypothesis

A second potential mechanism of pancreatitis induced by the passage of gallstones invokes the reflux of duodenal content into the pancreatic duct. This is a

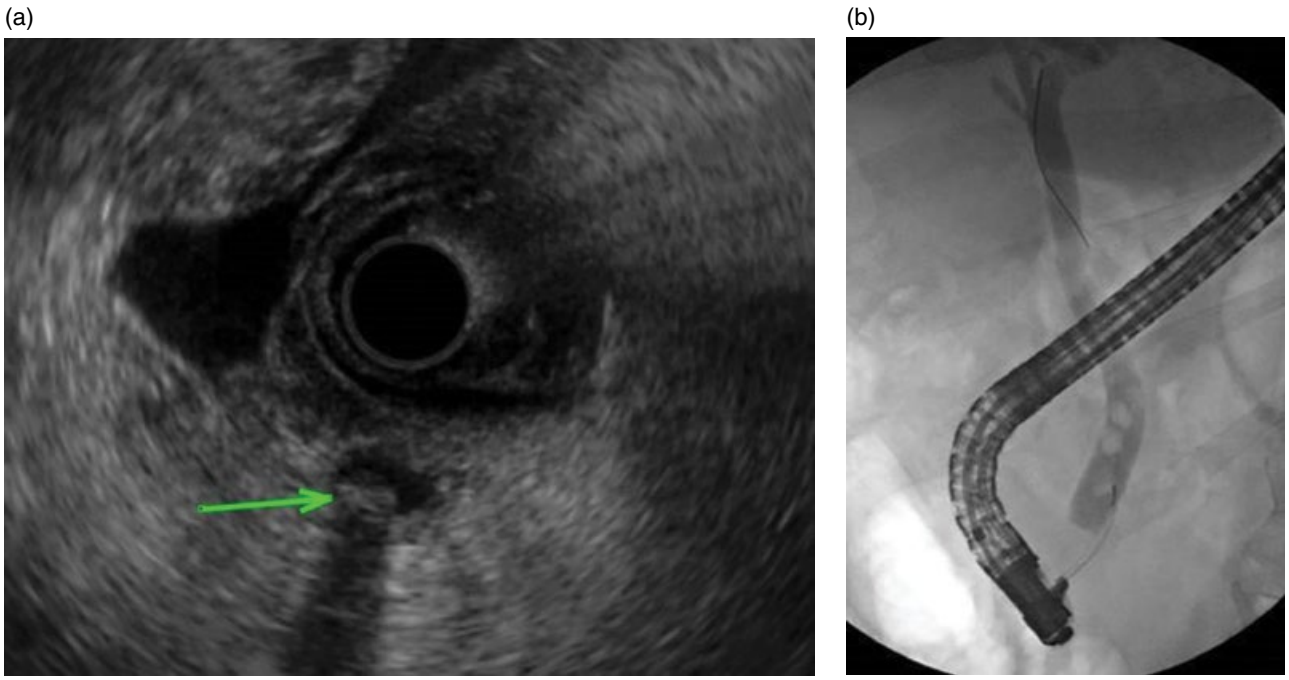



**Figure 14.1** A 78-year-old man presented with mild acute pancreatitis with a normal bilirubin but elevated liver enzymes alkaline phosphatase and gamma-glutamyltransferase. Transabdominal ultrasound was unhelpful, but endoscopic ultrasound demonstrated at least one stone in the common bile duct (a). Several stones were removed at subsequent endoscopic retrograde cholangiopancreatography (b).

mechanism that has been utilized in experimental studies on dogs [39] in which a closed duodenal loop is created. The subsequent development of pancreatitis appears to be due to reflux of contents since it may be prevented by ligation of the pancreatic duct [40–42]. This does have an infrequent parallel in humans in that obstruction of the afferent loop after Polya gastrectomy or gastroenterostomy may occasionally cause acute pancreatitis [43,44], however, the normal pancreatic duct is protected by several mechanisms to prevent this occurrence (i.e., the oblique course of the duct, the sphincter of Oddi, and the mucosal folds around the opening) [45]. Passage of a gallstone may allow reflux of duodenal contents either directly at the time of passing or later by damaging the sphincter mechanism, but surgical sphincterotomy at endoscopic retrograde cholangiopancreatography (ERCP) is usually protective against further episodes of biliary pancreatitis and does not appear to predispose to pancreatitis due to duodenal reflux [46–48]. In cases of pancreatitis due to duodenal obstruction, not only is there duodeno-pancreatic reflux but this also occurs at a high pressure, and it is likely that ductal hypertension is at least as significant as the duodenal content. It is possible to induce pancreatitis experimentally in rats by infusion of isotonic saline solution alone (M Brady, unpublished data).

## Ductal Hypertension Hypothesis

Lerch et al. evaluated the effect of obstruction at different sites in the pancreaticobiliary ductal tree on the development of pancreatitis in opossums [29]. They showed that obstruction of the main pancreatic duct alone is sufficient to induce pancreatitis in this animal model and that separate ligation of the common bile duct or ligation of the common biliopancreatic channel did not affect the severity of disease caused. Other studies have shown that continued stimulation of secretion in the presence of an obstructed pancreatic duct exacerbates the damage [49], but that relief of the obstruction ameliorates the severity of pancreatitis [50]. Obstruction of the pancreatic duct in the presence of continued stimulation of secretion induces pancreatic ductal hypertension. Ductal hypertension would also be generated by several of the other, less common, causes of acute pancreatitis, such as ampullary tumors, helminthic infestations, and ERCP. Indeed, injection of many compounds into the pancreatic duct at supraphysiologic pressure is sufficient to induce acute pancreatitis [31], but it is likely that the pressure of injection is of more significance than the precise chemical compound used.

The mechanism by which increased ductal pressure leads to pancreatitis has been the subject of much debate over the years. It has been generally assumed that it acts either by causing rupture of small pancreatic ductules

and extravasation of secretions into the interstitium of the gland with subsequent activation of enzymes, or by prevention of discharge of secretions from the acinar cells into the ductal space with consequent intracellular changes. Since the first observable changes after duct ligation occur within the acinar cells rather than in the interstitium or periductally, the latter would seem more likely. High pressure within the acinar lumen may impair both exocytosis of zymogens and $Ca^{2+}$ extrusion from the apical plasma membrane [51]. Disruption of the plasma membrane and its transport channels also impairs the restoration of normal $Ca^{2+}$ levels after physiologic cholecystokinin (CCK) stimulation, and CCK stimulation is known to compound the effects of ductal obstruction [50,52]. It is known that disruption of acinar $Ca^{2+}$ signaling is a key early event in the initiation of intra-acinar enzyme activation [53] and $Ca^{2+}$ signaling is indeed disrupted by experimental duct obstruction [54,55]. $Ca^{2+}$ signals may also be disrupted by the uptake into acinar cells of bile acids, which thereby induce cell death [56,57]; this may compound the effect of obstruction if a common biliopancreatic channel does exist.

## Two-phase Hypothesis of Gallstone Acute Pancreatitis

These three proposed pathogenetic mechanisms are not mutually exclusive, and may compound each other, as is the case with biliopancreatic reflux in the presence of ductal obstruction and hypertension. Indeed, obstruction alone often leads to biliary complications rather than pancreatitis, and therefore a two-phase hypothesis has been proposed to explain the development of acute pancreatitis [58]. Initially, the passage of a gallstone in a patient with a common pancreatobiliary channel induces acute pancreatitis, but migration of the stone allows free drainage of activated pancreatic enzymes and the pancreas can recover, resulting clinically in a mild attack of acute pancreatitis. Such is the case for the majority of attacks of acute pancreatitis. In a minority, however, further obstruction to the flow of activated enzyme-rich pancreatic juice results in exacerbation of the pancreatic damage and a severe attack of pancreatitis. Secondary obstruction may be due to:

- edema of the head of the pancreas or ampulla after passage of a gallstone;
- repeated transient obstruction due to passage of multiple small stones;
- a large stone impacted in the distal main bile duct causing compression of the main pancreatic duct which lies alongside;
- impaction of a larger stone at the ampulla of Vater itself.

The first and second phases of this mechanism may be separated by minutes, hours or days, but the hypothesis implies that there may be a window of opportunity in some patients in which to prevent further obstruction and avert a severe attack of pancreatitis.

## Other Causes of "Biliary" Acute Pancreatitis

Although biliary acute pancreatitis is often equated with pancreatitis secondary to gallstones, and in reality most often is, a number of other less common etiologies cause pancreatitis via a similar mechanism and should be considered in the same category (Box 14.1). Biliary sludge is almost certainly not a cause of pancreatitis but is a common finding in patients with acute pancreatitis due to reduction in gallbladder motility (see later). As with gallstones, the essential pathophysiologic mechanism is obstruction to the pancreatic duct at the level of the ampulla of Vater.

Cholesterolosis has been described as affecting 11% of gallbladders removed at surgery [59]. In most cases, cholesterol polyps were found in association with gallstones, but in one study of 55 cases with cholesterolosis alone, 27 (55%) presented with recurrent acute pancreatitis, suggesting that cholesterol polyps themselves may cause transient pancreaticobiliary obstruction (Fig. 14.2). A larger, more recent series, however, of 6868 patients who had undergone cholecystectomy, found no association between cholesterolosis and acute pancreatitis [60].

Biliary sludge is a mixture of particulate matter that precipitates from bile, generally consisting of cholesterol monohydrate crystals, calcium bilirubinate, and other calcium salts embedded in mucin [61] (Fig. 14.3). Biliary sludge often coexists with gallstones [62] and it is

**Box 14.1 Causes of "biliary" acute pancreatitis**

Gallstones
Cholesterolosis
Extracorporeal shock-wave lithotripsy for gallstones
Complications of endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy
Surgery of the biliary tract
Ampullary tumors
Cholangiocarcinoma
Periampullary diverticulum
Intraluminal diverticulum
Choledochocele
Choledochal cyst
Anomalous union of pancreatobiliary ducts
Parasitic infestation
Sclerosing cholangitis
Sphincter dysfunction
Biliary stenting

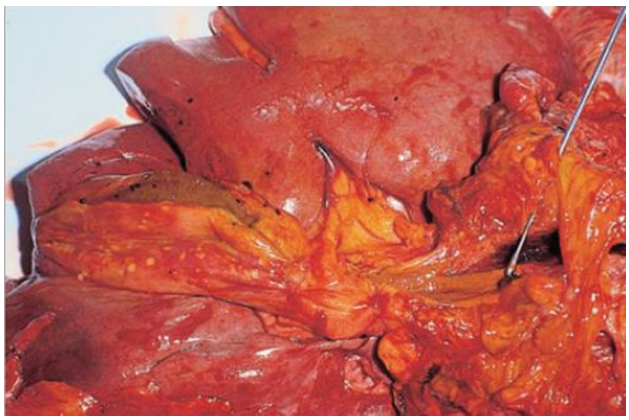
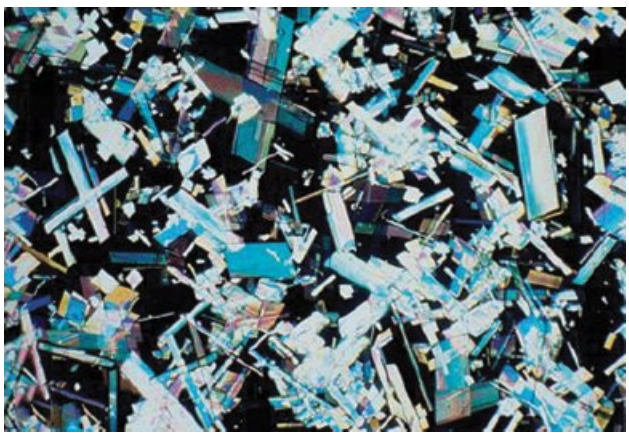


**Figure 14.2** A gallbladder specimen demonstrating cholesterolosis and multiple cholesterol polyps.

(a)



(b)

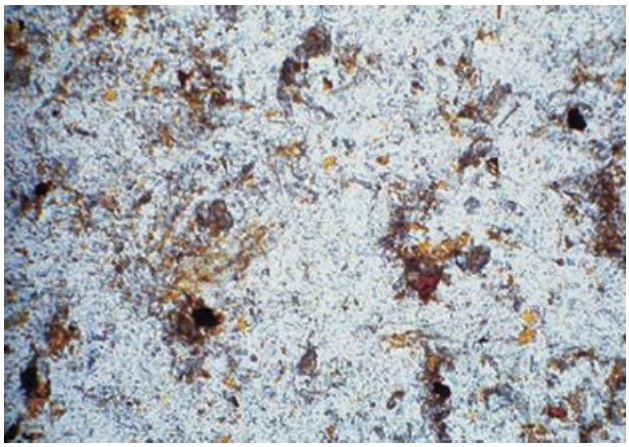


**Figure 14.3** Microscopy of biliary "sludge" containing calcium bilirubinate granules.

questionable whether the formation of sludge represents an early stage of gallstone formation. Biliary sludge has been reported as causing acute pancreatitis in 3.1% of cases [63], although whether this is due to sludge per se or to associated microlithiasis is difficult to judge. A study performed by Lee et al. assessed 86 patients who had been diagnosed with "idiopathic pancreatitis" and found evidence of biliary sludge in the majority (67%). Although the presence of biliary sludge was not shown to have a causal relationship, its presence was predictive for recurrent episodes of acute pancreatitis [64].

ERCP, with or without sphincterotomy, is associated with the development of acute pancreatitis in up to 7% of cases [65]. Factors associated with an increased risk were a history of previous ERCP-induced pancreatitis (odds ratio [OR] 5.4), suspected sphincter of Oddi dysfunction (OR 2.6), female gender (OR 2.5), biliary sphincter balloon dilatation (OR 4.5), difficult cannulation (OR 3.4), pancreatic sphincterotomy (OR 3.1), and one or more injections of contrast into the pancreatic duct (OR 2.7).

Biliary surgery has been infrequently linked with acute pancreatitis, usually after exploration of the main bile duct. In a study of 1041 patients undergoing surgery for gallstones, Vernava et al. [66] found three cases of pancreatitis following cholecystectomy in 842 patients (0.35%) but nine cases of pancreatitis after 199 bile duct explorations (4.5%), of whom three patients died. Operations involving transduodenal bile duct exploration are especially likely to trigger acute pancreatitis. In one study, 23 of 208 patients died following transduodenal exploration of the main bile duct [67].

Parasites may cause acute pancreatitis by obstruction of the ampulla of Vater, either by inducing the formation of gallstones or by direct infestation of the main pancreatic duct. Such causes are unusual in Western countries but common in parts of Africa and Asia where the commonest pathogens are *Ascaris*, *Clonorchis sinensis*, echinococcal hydatid disease, *Giardia*, and malaria [68–72].

Tumors at or around the level of the ampulla of Vater may present as acute pancreatitis in around 6% of cases [73–76]. More proximal lesions have also been reported as presenting with acute pancreatitis, possibly due to ampullary obstruction by tumor fragments or mucoid secretions [77]. There are a few anecdotal reports of sclerosing cholangitis as a cause of acute pancreatitis [78,79].

Sphincter of Oddi dysfunction, either dyskinesia or organic stenosis, may present as recurrent acute pancreatitis [80], although many patients with sphincter dyskinesia also have gallstones, and there is some evidence that dyskinesia is more common in patients with gallstones [81].

## Epidemiology of Biliary Acute Pancreatitis

Between 3% and 8% of patients with symptomatic gallstones develop acute pancreatitis [82,83], representing an increase in relative risk of developing pancreatitis for

patients with gallstones of up to 35 times that of the general population. Around 80% of patients will have a mild attack, 20% will have a severe attack, and 5% will die as a result of acute biliary pancreatitis (ABP) [84]. Like gallstones in general, gallstone pancreatitis is more common in women than in men and tends to occur in an older age group than pancreatitis due to alcohol ingestion [85]. The precise incidence varies with the population prevalence of gallstones [86] but ranges from 150 to 420 per million population in Western countries [87–89].

The development of gallstone acute pancreatitis is related to the size and number of the gallstones present. Patients with gallstones who present with acute pancreatitis tend to have smaller stones, in larger numbers, and with preserved gallbladder motility when compared with patients with otherwise symptomatic gallstones without pancreatitis [90]. Such criteria would obviously favor migration of small stones from the gallbladder into the biliary tree. This study also suggested that patients with pancreatitis had a higher concentration of mucin in their bile than patients with gallstones causing other symptoms. Higher mucin levels appear to correlate with the number of gallstones, suggesting that mucin encourages stone formation. A further study also showed a correlation with the diameter of the cystic duct, again in keeping with the passage of stones from the gallbladder into the biliary tree [91]. In a study of 528 patients with gallstones, those presenting with pancreatitis had smaller stones ($3 \pm 1$ mm) than those with obstructive jaundice ($4 \pm 1$ mm), acute cholecystitis ($8 \pm 1$ mm), or asymptomatic stones ($9 \pm 1$ mm; $P = 0.01$) [92].

In most series, gallstones account for approximately 60% of cases of acute pancreatitis [87,88,93,94]. Detailed studies of patients with "idiopathic" acute pancreatitis, however, suggest that a high proportion of these cases are due to microlithiasis, which may be detected by endoluminal ultrasound if performed early enough after the onset of disease. Such studies suggest that up to 80% of "idiopathic" cases are actually due to gallstones [64,95–99] (Fig. 14.4).

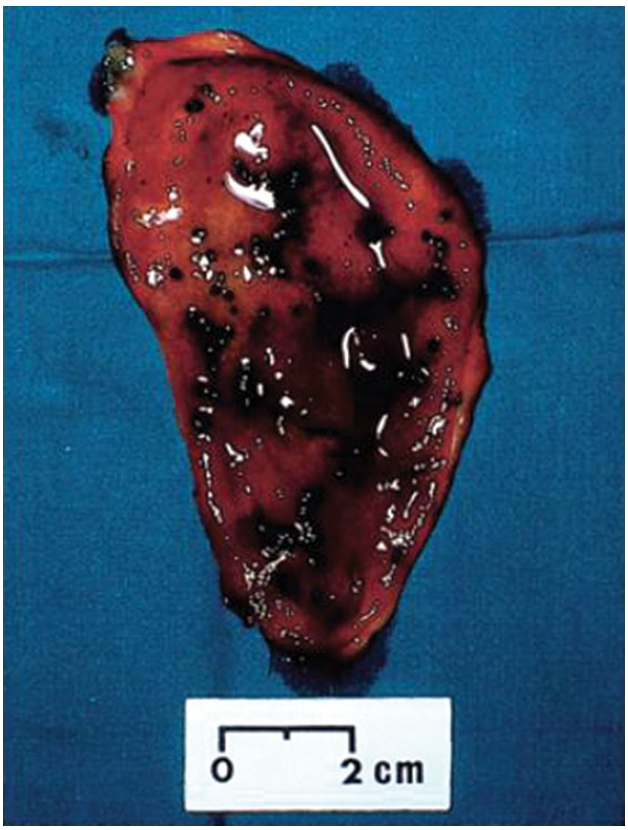



**Figure 14.4** A gallbladder specimen containing microlithiasis that had been missed by all investigations, including bile crystal analysis and endoscopic retrograde cholangiopancreatography.

## Confirmation of Gallstones as the Cause of Pancreatitis

It is important to confirm the presence of gallstones in acute pancreatitis in three distinct clinical settings:

1) during the acute phase in a patient with prognostically severe pancreatitis in whom early ERCP and sphincterotomy may be of therapeutic benefit;
2) in the convalescent phase, to identify patients in whom laparoscopic cholecystectomy and/or endoscopic sphincterotomy (ES) will prevent further attacks;
3) in the identification of patients with microlithiasis or cholesterolosis who may have previously been deemed "idiopathic" but who may also benefit from cholecystectomy.

Although transabdominal ultrasound is the investigation of choice for gallbladder stones, with an overall accuracy in excess of 95%, in the setting of acute pancreatitis it is much less accurate, detecting stones in only 70–80% of cases [100,101]. It is even less satisfactory in the detection of main bile duct stones, even in the absence of acute pancreatitis, with a sensitivity of 19–55% [102]. Endoluminal ultrasound is much more sensitive for ductal stones, even in acute pancreatitis, with sensitivity and overall accuracy of 93% and 85%, respectively [103]. Endoluminal ultrasound is also useful for the detection of other causes of acute pancreatitis, such as small periampullary tumors or anatomic anomalies. Historically, ERCP has been the gold standard for the detection of main bile duct stones but has now been largely superseded by endoluminal ultrasound, which is becoming much more widely available. When required, subsequent ERCP may be employed for therapeutic purposes, but diagnostic ERCP with its

**Table 14.2** Accuracy of three separate systems in predicting gallstones as the cause of acute pancreatitis.

| Predictive analysis | System 1 (%) | System 2 (%) | System 3 (%) |
|---|---|---|---|
| Correct prediction | 74 | 76 | 71 |
| Sensitivity | 75 | 74 | 62 |
| Specificity | 74 | 78 | 80 |
| Positive predictive value | 79 | 82 | 80 |
| Negative predictive value | 69 | 70 | 62 |

Based on serum values within 48 hours of onset in 391 consecutive patients, of which 220 (56%) were due to gallstones.
System 1: alanine transaminase (ALT)/aspartate transaminase (AST) >60 IU/L.
System 2: one of the following; alkaline phosphatase >225 IU/L, ALT/AST >60 IU/L, bilirubin >40 μmol/L.
System 3: three or more of the following: female, amylase >4000 IU/L, ALT/AST >100 IU/L, alkaline phosphatase >225 IU/L.

associated morbidity and mortality is no longer necessary in many cases [104,105].

It has been proposed that the serum lipase/amylase ratio may be used to differentiate alcoholic and biliary causes of acute pancreatitis, but this has not proved useful in practice [106]. Instead, elevated levels of serum transaminases (alanine transaminase [ALT] or aspartate transaminase [AST]) have proven to be better predictors of gallstones if measured within 48 hours of the onset of the attack. In a comparison of two multifactorial systems with serum AST/ALT alone, the latter proved to be equally accurate in the prediction of gallstones, correctly predicting the etiology in 74% of cases [107] (Table 14.2).

## Clinical Features

Gallstone pancreatitis tends to follow an acute intermittent disease pattern, with individual attacks being clinically very similar to those of other etiologies [86]. Bacteremia and ascending cholangitis are more common in association with gallstones than with other nonobstructive causes, however [108,109].

As well as increased susceptibility to infection, some studies have shown a higher mortality rate among patients with gallstones compared with other causes of pancreatitis [110]. This study showed a mortality rate of 13% among patients with gallstones compared with 3% for alcohol-induced cases. This may partly be explained by the higher average age of the patients in the gallstone group, as 75% of the fatalities were in patients aged over 60, but this study also revealed a generally more severe disease course among patients with gallstones. A separate study [111] showed mortality rates of 5.3% for alcohol-induced pancreatitis, 10% for biliary pancreatitis, and 5.5% for other etiologies. However, these differences were not statistically significant.

## Treatment of Acute Biliary Pancreatitis

ERCP ± ES has been employed in order to relieve biliary obstruction in ABP since 1973. The landmark randomized controlled trial (RCT) performed by Neoptolemos et al. demonstrated early ERCP ± ES in ABP significantly improved patient outcome, and the continuing utility of ERCP in decompressing biliary obstruction is without question, however there is still much controversy regarding the patients who are most likely to benefit from this intervention.

Several RCTs have been conducted to compare conservative management of ABP versus early ERCP ± ES (within 72 hours) and have yielded conflicting results [28,77,112–115]; subsequent meta-analyses have not clarified the situation. The most contemporary Cochrane database systematic review conducted by Tse and Yuan concluded that there was no significant difference between mortality, or local and systemic complications between different intervention groups [116]. The most recent meta-analysis performed by Burstow et al. included 1314 patients (662 conservative management vs. 652 ERCP ± ES) and showed no significant difference in mortality between the two groups, even when subgroup analysis was performed for mild/severe ABP, but did demonstrate a significant reduction in ABP-related complications in the ERCP ± ES group (OR 0.43, 95% confidence interval 0.27–0.68, $P = 0.0001$) [117].

There appears to be clear international consensus on the role of immediate ERCP ± ES in ABP and cholangitis (grade 1A/B evidence, strong agreement) from the American Gastroenterology Association (AGA), American College of Gastroenterologists, British Society of Gastroenterologists (BSG), International Association of Pancreatologists, American Pancreatic Association, and Japanese guideline 2015 [94,118–121]. The BSG also recommend ERCP in ABP of suspected gallstone etiology with predicted or actual severe pancreatitis.

There is mounting evidence to support the theory that it is not necessarily the severity of ABP that should determine the urgency of ERCP intervention, but the duration of the biliary obstruction [28,115] and the most recent Japanese 2015 guidelines reflect this by recommending early ERCP ± ES in ABP in the presence of complications such as cholangitis or when a prolonged passage disorder is suspected (grade 1A evidence, strong agreement) [121].

Further clarity on patient selection for ERCP following ABP requires further data from high-quality RCTs with key focused questions around the main areas of

controversy. The Dutch Pancreatitis Study Group intend to perform such a study, assessing early ERCP ± ES versus conservative management in an assessor-blinded multicenter trial of patients with ABP who are randomized within 24 hours of presentation.

### Timing of Cholecystectomy Following Acute Biliary Pancreatitis

Without treatment of gallstones the risk of recurrent attacks following a single episode of ABP is in the region of 30% [122,123] and the average delay before the second attack in one series was 108 days [124]. Another study has reported an incidence of 8% within 4 weeks of the first attack [125]. Additional complications include cholecystitis, cholangitis, and recurrent biliary colic.

Unfortunately, despite these figures, and both International Association of Pancreatology and national guidelines [94,126,127] supporting cholecystectomy within the same index hospital admission, or the AGA and the BSG suggesting early "interval" surgery (within 2–4 weeks of discharge), long delays before cholecystectomy are still reported. The lack of international consensus has been reflected in the outcomes of several national level audits performed across Europe and the United States. Reports vary, but patients wait on average at least 6 weeks for a cholecystectomy following a mild ABP attack, and in the United Kingdom a recent study highlighted that nearly one-third of patients had not undergone definitive treatment for gallstones at 1 year following pancreatitis attack [128,129].

Delay in definitive surgical treatment in patients who are surgical candidates appears to originate from the perceived risk of complications of cholecystectomy such as conversion to an open procedure or a bile duct injury due to challenging dissection and distorted anatomy from peripancreatic inflammation and edema [129].

The same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO) trial was published in the *Lancet* in 2015 [130]. This multicenter, parallel-group, assessor-masked, randomized controlled superiority trial is the first RCT to assess same-admission cholecystectomy (recommended by international guidelines) and the more commonly practiced interval cholecystectomy as demonstrated by audit. This study showed that same-admission cholecystectomy significantly reduces the number of gallstone disease-related readmissions compared to interval cholecystectomy. There were minimal complications seen in either group. It is now recommended that all patients admitted with a mild attack of ABP should receive a cholecystectomy during their index admission.

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# 15

# Genetic Factors in Acute Pancreatitis

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## Introduction

Acute pancreatitis is a clinical syndrome characterized by injury to the pancreas that invokes an acute inflammatory response, which leads to a range of potential local and systemic complications, typically resolving over time [1]. The premature activation of trypsinogen, or similarly the failure to eliminate active trypsin, is the most important mechanism of pancreatic injury. Not only does trypsin regulate the activity of other digestive enzymes, but it can also cross-activate the immune system directly [2]. This trypsin-mediated process can be influenced by genetic variations; indeed, the 1996 discovery of the gain-of-function mutations in the cationic trypsinogen gene (*PRSS1*) serves as the prototypical example [3]. Following pancreatic injury, an inflammatory response cascade is initiated. Dysregulation or variation of the inflammatory response is likely important in determining severe clinical course and systemic complications.

Several clear examples of the importance of genetic variability in susceptibility and severity of acute pancreatitis have been reported. The prototype susceptibility genes include not only *PRSS1*, but also the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene [4]. Loss-of-function mutations in the pancreatic secretory trypsin inhibitor gene (*SPINK1*) [5] have also been identified as susceptibility factors. The prototype disease-modifier gene is the monocyte chemotactic protein-1 (MCP-1) [6], which demonstrates a promoter variant that significantly increases severity of disease. Multiple genes have been associated with progression to chronic pancreatitis, including variants in chymotrypsin C (*CTRC*), calcium-sensing receptor (*CASR*), and claudin 2 (*CLDN2*). These are addressed more completely in Chapter 47.

More research is needed to understand the complex interactions between additional genetic factors and the immune response, which, in clinical practice, may turn out to be the most important factors. This chapter highlights specific genetic variants, with prototype mutations being emphasized.

## Genetic Susceptibility Factors

Factors that increase the likelihood of pancreatic injury determine susceptibility to acute pancreatitis, especially when genetic and environmental risk factors overlap in the same patient [7]. The pancreas is divided into different anatomic and functional compartments that are predisposed to different types of injury [2]. Certain genetic factors are directly linked to the proper function of either the acinar cell or duct cell compartments, and it is useful to understand them in context of these compartments (Table 15.1).

### Acinar Cell-Associated Susceptibility Factors

Calcium dysregulation appears to be the pathway for triggering acute pancreatitis in acinar cells [8]. Intracellular hypercalcemia can lead to damage in any cell, but it is especially dangerous within acinar cells because of the high concentrations of trypsinogen [9,10]. When calcium occupies the calcium-binding domains of the trypsinogen molecule it results in both trypsinogen activation and prevents its degradation. Therefore, any factors that increase the entry of calcium into the acinar cell, increase calcium release from intracellular stores, disrupt calcium reuptake, or diminish calcium removal from the acinar cell enhance susceptibility to acute pancreatitis.

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**Table 15.1** Genetic factors involved in the pathogenesis of acute pancreatitis.

| | |
|---|---|
| **Susceptibility factors** | |
| Acinar cell-associated | *PRSS1* mutations (R122H, N29I, A16V, R122C) |
| | *SPINK1* polymorphisms (N34S, P55S) |
| | *CLDN2* |
| Duct-associated | *CFTR* mutations ($CFTR^{sev}$/$CFTR^{m-v}$) |
| | Bicarbonate conductance: R74Q, R75Q, R117H, R170H, L967S, L997F, D1152H, S1235R, and D1270N |
| | Calcium homeostasis mutations |
| | *CASR* |
| | *CTRC* (G60G, R254W) |
| **Modifying factors** | |
| Proinflammatory cytokines | MCP-1 polymorphisms (−2518G allele) |
| | TNF-α polymorphisms (−1031C and −863A alleles) |
| | IL-8 polymorphisms (−251A allele) |
| Other | GST polymorphisms (*GSTT-1*A*) |
| | HSP70 |

Any genetic alteration that affects the calcium-dependent regulatory domains of the trypsinogen molecule can potentially increase the risk of unregulated pancreatic injury.

Although both environmental and metabolic risk factors can increase susceptibility to acute pancreatitis through an acinar cell-associated mechanism, the presence of any of these risk factors alone does not necessarily trigger acute disease [8]. Indeed, most people who are exposed to pancreatitis-associated extrinsic risk factors, such as excessive alcohol consumption, will never develop acute pancreatitis [11]. This observation applies to individuals with significant genetic risk as well [12,13]. Thus, the convergence of several risk factors is required to develop an episode of acute pancreatitis [7]. The risk of acute pancreatitis is dependent on the balance between environmental/metabolic stressors and the strength of protective counter-mechanisms, which are linked to genetic variations of their translated products [2,7]. Thus, the magnitude of an extrinsic stressor that is required to trigger acute pancreatitis appears to be reduced in proportion to the effect of genetic polymorphisms related to the mechanisms protecting the pancreas from injury. The prototype acinar cell susceptibility gene is the one that codes for cationic trypsinogen, *PRSS1*.

### Cationic Trypsinogen: *PRSS1*

Hereditary pancreatitis is characterized by acute recurrent or chronic pancreatic injury, typically inherited in an autosomal dominant pattern and most commonly attributed to mutations in the gene (serine protease 1, *PRSS1*) coding for cationic trypsinogen. PRSS1 is a prototypic serine protease with two globular domains connected by a single side-chain. Pancreatic acinar cells synthesize trypsinogen, which is activated to trypsin on cleavage of a short exposed peptide chain called trypsinogen activation peptide (TAP). Enterokinase or a second trypsin molecule can cleave TAP, allowing for the transformation of trypsinogen to active trypsin. Trypsin then activates most of the inactive pancreatic digestive enzymes in the duodenum. Trypsin can also inactivate trypsin by attacking the arginine residue coded by codon 122 (R122) in the side-chain. Trypsin has two calcium-binding domains, one at the activation site and one at the autolysis site, and nearly all the mutations associated with hereditary pancreatitis affect one of these two calcium-regulated sites.

The cationic trypsinogen gene, *PRSS1*, was the first pancreatitis susceptibility gene to be discovered, and mutations within *PRSS1* are associated with hereditary pancreatitis. This rare autosomal dominant disorder has a high but variable disease penetrance (~80% by age 20 years). It usually presents in childhood at a median age of 10 years with recurrent episodes of acute pancreatitis [12–14]. After these repeated episodes of acute pancreatitis, about half of these patients progress to some degree of chronic pancreatitis [13,15]. Furthermore, approximately 40% of patients with chronic pancreatitis develop pancreatic cancer [13,16]. The R122H and N291 mutations are the most common pancreatitis-associated mutations in *PRSS1* [2,3,17].

The first *PRSS1* mutation to be identified was the arginine-(R)-(CGC) → histidine-(H)-(CAG) substitution in codon 122 (R122H) [18]. Arginine 122 is the initial site of hydrolysis of trypsin by trypsin itself. In the case of the *PRSS1* mutation, the arginine to histidine substitution renders trypsin resistant to fail-safe autolysis. As a consequence, trypsin activation can lead to prolonged trypsin survival inside the acinar cells, which in turn can result in acute pancreatitis. Interestingly, a 2009 Korean study found that 40% of patients with hereditary pancreatitis (and zero controls) carried the R122H mutation, but there were no other variants reported in this population with hereditary pancreatitis [19].

More than 20 *PRSS1* mutations have been discovered, such as A16V and N291 in Caucasians and the D162D variant in Chinese populations [20]. Most are gain-of-function mutations that cause either premature/excessive trypsin activation or failure of autolysis. Despite

sharing a common genetic mutation, family members may exhibit clinical symptoms and complications that range across a broad spectrum. This wide variation in phenotype and incomplete penetrance suggests that additional modifying environmental and/or genetic factors are involved in the pathogenesis of hereditary pancreatitis [21,22].

#### Serine Protease Inhibitor Kazal Type 1: *SPINK1*

The pancreatic secretory trypsin inhibitor (PSTI) directly inhibits the premature activation of trypsinogen. It is encoded by the serine protease inhibitor Kazal type 1 (*SPINK1*) and expressed in acinar cells during acute inflammation. SPINK1 is a 56-amino-acid acute-phase protein that directly blocks the active catalytic site of trypsin. The proportion of SPINK protein to its RNA has been shown to range from less than 1:1000 in the normal pancreas to at least 6:1 in the inflamed pancreas [22]. This indicates that *SPINK1* expression is rapidly increased *after* pancreatic injury, and therefore likely plays a role in limiting the extent and duration of an attack by inhibiting trypsin. These findings also fit with the observation that the pattern of SPINK1 in the blood after surgery or severe inflammation is that of an acute-phase reactant [23,24].

Although several mutations have been identified in the *SPINK1* gene, the N34S haplotype is the most prevalent throughout the world and is found in 1–3% of the general population [25]. *SPINK1* gene mutations are found in 25–50% of cases of idiopathic chronic pancreatitis in children [26,27] and tropical chronic pancreatitis [28–31]. However, these mutations are only found in a few percent above controls in sporadic acute pancreatitis [32]. It follows that *SPINKI* mutations alone are not sufficient to cause acute pancreatitis. This matches the observation that those with a high-risk *SPINK1* haplotype actually have a low risk of developing pancreatitis (<1%) [25,27].

Among those who develop pancreatic disease associated with *SPINK1* mutations, the phenotype is widely variable [33]. The risk and severity of pancreatitis appears to be similar between subjects with heterozygous, homozygous, or compound heterozygous genotypes, suggesting that the genetics underlying the disease state is complex [27] and likely related to other susceptibility factors. This observation matches the notion that *SPINK1* is only necessary when there is excessive trypsin activation upstream. Although the *SPINK1* N34S haplotype has been proposed to enhance susceptibility to acute pancreatitis, the frequency of the high-risk haplotype is relatively low (7.8% of patients and 2.6% of controls) [32]. Furthermore, *SPINKI* mutations increase susceptibility to recurrent acute [34] and chronic pancreatitis both as an autosomal recessive disorder and as part of non-Mendelian complex traits [7], but do not appear to be a major risk factor for sentinel acute pancreatitis.

### Duct-Associated Susceptibility Factors

Acute pancreatitis can originate from delayed or blocked drainage of the pancreatic duct. This is illustrated most clearly by gallstone pancreatitis, which is the most common cause of acute pancreatitis in adults [35,36]. However, there are additional important duct-associated factors that can contribute to the development of acute pancreatitis.

The acinar cells are connected to the duodenum by the pancreatic duct system. The pancreas duct lumen has an elevated calcium concentration, but in a state of physiologic homeostasis, premature activation of trypsinogen within the pancreatic duct is prevented by a high pH, the presence of trypsin inhibitors, and the rapid evacuation of activated enzymes from the duct [2].

The pancreatic duct cell differs from many other types of epithelial cells in its expression of a combination of ion channels and transporters. The primary apical (luminal) ion channel of the duct cell is CFTR [37], which is permeable to chloride and, to a lesser degree, bicarbonate [38,39]. The continuous entry of bicarbonate into the duct cell is facilitated by a sodium–bicarbonate cotransporter on its basolateral surface [40]. Simultaneously, minimal chloride permeability on the basolateral surface results in bicarbonate being the dominant diffusible anion within the duct cell. In this setting, a concentration gradient across the apical membrane favors bicarbonate secretion [41]. This ion secretion is dependent on CFTR, so any alterations in CFTR function can potentially limit fluid secretion from the duct. Failure to flush the pancreatic duct is a susceptibility factor for acute pancreatitis, and *CFTR* mutations represent the prototype genetic defect.

#### Cystic Fibrosis Transmembrane Conductance Regulator: CFTR

CFTR is an anion channel present in the plasma membranes of epithelial cells in multiple organs (i.e., lungs, small bowel, and pancreas) [42], and mutations in the gene encoding CFTR can cause pancreatitis, even in the absence of phenotypic cystic fibrosis. Pancreatic acinar cells secrete a protein-rich fluid, which is diluted and alkalinized by the duct epithelium as it flows through the pancreatic duct. This is accomplished by CFTR-mediated bicarbonate excretion [43]. Brisk bicarbonate secretion is critical for maintaining a high pH so that trypsin remains inactive [44]. This secretion must also rapidly and efficiently flush digestive enzymes out of the pancreatic duct against any distal resistance. Failure of the duct cells to secrete bicarbonate anions increases susceptibility to

acute pancreatitis [45]. Furthermore, it is suggested that *CFTR* mutations also augment the inflammatory response, predisposing to severe disease [46].

*CFTR* mutations were first identified in 1989, and since then, more than 2000 variants in *CFTR* have been identified. Although the functional role of many of these variants remains unknown, several patterns have emerged to define *CFTR*-associated pancreatitis. For example, severe mutations in both copies of the *CFTR* gene ($CFTR^{sev}/CFTR^{sev}$) result in the complete loss of CFTR function and the classic cystic fibrosis phenotype [42]. As the pancreas is one of the first organs to fail in cystic fibrosis, children affected by cystic fibrosis typically develop pancreatic insufficiency from infancy [43]. Pancreatic histology in cystic fibrosis shows all the features of chronic pancreatitis (i.e., parenchymal fibrosis and atrophy, ectatic pancreatic ducts), as well as scattered ducts that are dilated and obstructed by protein-rich material [7].

Another pattern is that of "atypical" cystic fibrosis in those with incomplete involvement of the classically affected organs, including the pancreas [47]. These patients are often compound heterozygotes, having one $CFTR^{sev}$ allele plus one mild variable CFTR mutation ($CFTR^{m\text{-}v}$), or homozygotes with two mild alleles. $CFTR^{m\text{-}v}$ mutations reduce CFTR function to 10–30% of normal levels [42] and the risk of chronic pancreatitis is increased 40–80 times over that in the general population [43]. An important example, the *CFTR* p.R75Q variant, results in defective bicarbonate secretion with preservation of chloride secretion, increasing the risk for chronic pancreatitis without the classic cystic fibrosis phenotype [48,49]. In addition, the heterozygous *CFTR* mutation confers a moderate risk (3–4 times) of chronic pancreatitis over that of the general population, which is typically heightened by concomitant mutations (*SPINK1*, etc.) [48,50,51].

Finally, there is a group of *CFTR* variants that result in the selective deficiency of bicarbonate conductance through CFTR (CFTRBD). A recent study identified nine variants (CFTR R74Q, R75Q, R117H, R170H, L967S, L997F, D1152H, S1235R, and D1270N) that were associated with an increased risk of recurrent acute pancreatitis and chronic pancreatitis without an increase in lung disease [52].

## Multiple Genetic Defects and Susceptibility

Because of the multiple complementary protective mechanisms that exist at each site of potential pancreatic injury, the risk of developing acute or recurrent acute pancreatitis is quite low. As illustrated above, genetic mutations can disrupt these protective mechanisms or alter key regulatory sites, increasing the risk of pancreatitis when environmental or metabolic insults are present. Indeed, patients with multiple genetic predispositions are at increased risk for pancreatic injury [7], and in a multistep pathologic process, the probability of a late effect is dependent on the presence and severity of more proximal effects [53].

It has been hypothesized that *SPINK1* could, in fact, act as a disease-modifier gene [28,54]. This is supported by the observation that the *SPINK1* N34S haplotype is relatively common, although there is no associated specific phenotype. Furthermore, the severity of disease is similar between patients with homozygous and heterozygous genotypes. A small study of subjects with $CFTR^{sev}/CFTR^{m\text{-}v}$ genotypes, a subgroup of whom also had *SPINK1* mutations [55], led to the hypothesis that defects in these gene products may act synergistically to increase the risk of pancreatitis. A subsequent study confirmed that a subset of patients with idiopathic pancreatitis and abnormal *CFTR* genotypes had an excess of *SPINK1* mutations [56]. Pancreatitis risk is increased 10-fold in individuals with a *SPINK1* mutation, 40-fold in individuals with *CFTR* compound heterozygosity, and 500-fold in individuals who have both [43].

Patients with an isolated mutation in the calcium-sensing receptor gene (*CASR*), manifested as hypocalciuric hypercalcemia, tend to have elevated serum calcium levels, which represent a risk factor for acute pancreatitis. It has been observed that those patients with both *CASR* and *SPINK1* mutations develop chronic pancreatitis [57], likely a consequence of recurrent acute pancreatitis [2]. Thus, the combination of genetic defects affecting serum calcium levels (*CASR*) and trypsin inhibition (*SPINK1*) leads to subclinical recurrent acute and chronic pancreatitis.

The above findings support the concept that pancreatitis can be a complex genetic disorder. In addition, mutations in immune-modulating genes appear to modify the severity and complications of acute pancreatitis.

### Genetic Modifying Factors

The intensity of the inflammatory response rather than the degree of pancreatic injury seems to determine the severity of acute pancreatitis, as those with seemingly mild pancreatic injury sometimes develop severe acute pancreatitis, whereas other subjects with profound pancreatic injury might have a relatively mild course [58]. Thus, there appear to be other factors determining the extent of the immune response after initial pancreatic injury.

### Cytokine Polymorphisms

Alteration in the expression of regulatory cytokines/chemokines through genetic variations can affect the inflammatory response to pancreatic injury. A clear example of this is seen with MCP-1, a key chemokine in the regulation of inflammation, which is released by mononuclear cells to attract additional monocytes, lymphocytes, mast cells, and eosinophils. A single-nucleotide polymorphism in the distal regulatory region of the MCP-1 gene (G → A) at position −2518 results in a significantly greater MCP-1 response to inflammatory stimuli than the wild-type sequence [59].

In preliminary studies, the *MCP-1* – 2518A/G polymorphism predicted that the physiologic response to pancreatitis would be severe and associated with death [6]. Among 77 prospectively studied subjects with pancreatitis and 116 controls, the G allele was present in 87% of patients with severe pancreatitis, 45% of those with mild pancreatitis, and 43 % of controls. The presence of the G allele significantly increased the risk of severe acute pancreatitis from any cause about sevenfold (~40%), whereas subjects with an AA genotype had a low risk of severe acute pancreatitis (~5%). Supporting these findings, a group from Italy recently found that among patients with acute pancreatitis, recurrent acute pancreatitis, chronic pancreatitis, and controls, those with evidence of pancreatic inflammatory disease had significantly higher serum MCP-1 levels [60].

The acute inflammatory response is a highly regulated process, with proinflammatory and anti-inflammatory factors interacting in sequential and coordinated ways. Indeed, a number of cytokines that regulate the local inflammatory response in acute pancreatitis have been studied, including tumor necrosis factor α (TNF-α), interleukin 1 (IL-1), IL-8, and IL-10 [61]. TNF-α, the earliest cytokine to be released, is a principal mediator of immune responses to endotoxin. Multiple groups have evaluated the association between pancreatitis and the −308G > A and −238G > A polymorphisms in the TNF-α gene, finding variable associations between these mutations and disease severity [62–67]. A recent meta-analysis [68] found that neither susceptibility nor severity of pancreatitis was altered by the presence of these TNF-α polymorphisms, but more research in individual populations is needed. A subsequent study reported that TNF-α promoter variants do not alter susceptibility to acute pancreatitis, but rather the TNF-α expression-enhancing −1031C and −863A alleles significantly increase the risk of progression to multisystem organ failure [69].

IL-8 is a proinflammatory chemokine produced by macrophages and other cells, which attracts neutrophils to the site of inflammation. Polymorphisms in the gene encoding IL-8 appear to be associated with a more severe course of acute pancreatitis [70]. A recent meta-analysis [71] with a total of 1220 patients with acute pancreatitis and 1351 controls examined the relationship between interleukin gene polymorphisms and acute pancreatitis. It showed that there was a significant association between the IL-8 – 251 T/A (rs4073) polymorphism and an increased risk for developing acute pancreatitis.

## Progression to Chronic Pancreatitis

Chymotrypsinogen C is a calcium-dependent serine protease that autodigests trypsinogen in a protective manner. It follows that loss-of-function mutations in the *CTRC* gene can disrupt this mechanism and lead to pancreatic injury [72–75]. Groups from Asia and Europe have identified rare *CTRC* variants, such as R254W and K246_R25del, that are associated with chronic pancreatitis, but the specific associations have been difficult to replicate [72,76–78]. These rare variants exist in the North American population, but at a lower frequency than elsewhere. Although they are strongly associated with chronic pancreatitis, the variant G60G (c.180 T) is not associated with recurrent acute pancreatitis, suggesting that *CTRC* modifies the risk of progression to chronic pancreatitis but is not a susceptibility gene for acute pancreatitis [79].

Claudin 2 is a highly regulated tight junction protein forming cation-selective ion and water channels between endothelial cells, normally expressed between pancreatic acinar and islet cells. The high-risk claudin 2 locus, located on the X-chromosome with variant rs12688220, acts as a disease modifier and is associated more with chronic than with recurrent acute pancreatitis. It is also strongly associated specifically with alcoholic chronic pancreatitis [80–82].

## Future Directions

With our expanding knowledge of the genetics of acute pancreatitis, a system is required to integrate all this information and to determine strategies for rapid identification of patients at risk of severe acute pancreatitis. New, patient-specific strategies must be developed so that this knowledge can be applied in a way that minimizes morbidity and mortality from severe acute pancreatitis.

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# The Role of the Intestine and Mesenteric Lymph in the Development of Systemic Inflammation and MODS in Severe Acute Pancreatitis

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## Introduction

Acute pancreatitis is a protean disease of unpredictable course [1]. Its severity and outcome are primarily determined by local and systemic factors, such as the presence of infected (peri)pancreatic necrosis (e.g., "acute necrotic collections" and/or "walled off necrosis") and persistent end-organ dysfunction (e.g., cardiovascular, pulmonary and/or renal failure) [2]. The pattern of this organ dysfunction is broadly similar across many different severe diseases, suggesting common drivers for the multiple organ dysfunction syndrome (MODS) [3]. This pattern appears valid for acute pancreatitis [4,5].

The aim of this chapter is to review the evolving understanding of the intestine's role in the development of MODS, to look at the evidence for the gut–lymph concept in promoting MODS in acute pancreatitis, and to discuss the potential to translate this to clinical treatment.

## Role of the Intestine and Mesenteric Lymph in Multiple Organ Dysfunction Syndrome

The concept that the intestine drives critical illness was developed in the 1960s when bacterial endotoxin was demonstrated in the systemic circulation of patients with infective and noninfective severe diseases [6]. This gave rise to the bacterial translocation hypothesis, where gut organisms were thought to cross the intestinal barrier to create a "septic-like state" [7]. In the 1980s the "gut motor" hypothesis expanded this concept to acknowledge the contribution of changes in the intestinal flora and the increased permeability of the gut barrier, postulating that bacterial pathogens and endotoxins enter the systemic circulation from the portal venous system [8]. This was largely discredited when it was not possible to prospectively demonstrate bacteria in the portal vein or systemic circulation in patients with major trauma [9]. A further concept was advanced where neutrophil priming occurred in the mesenteric circulation and that this contributed to both local gut injury and distant organ injury [10–12]. This was the basis of the second-hit hypothesis, which implicates the intestine but does not rely on a direct bacterial role.

Using experimental models of hemorrhagic shock and trauma Deitch and colleagues introduced the concept that mesenteric lymph could cause distant organ failure. They suggested that primed neutrophils and other intestine-derived toxic factors were the mediators of MODS, and that this occurred in association with increased gut permeability but independent of bacterial translocation [13]. Deitch went on to demonstrate that these intestine-derived factors were transported by thoracic duct lymph to reach the systemic circulation to promote systemic inflammation and organ dysfunction [13,14]. He termed this the "gut–lymph hypothesis" [15]. Lung injury mediated by hemorrhagic shock-conditioned mesenteric lymph was key to validating this concept in the experimental setting. Ligation of the mesenteric lymph duct before hemorrhagic shock prevented lung injury in a rodent model, whereas division after shock but prior to resuscitation partially prevented lung injury [16]. It was found that mesenteric lymph from these rats was cytotoxic to endothelial cells and increased permeability to both a monolayer of endothelial cells and lung tissue, whereas portal vein plasma did not [16,17]. The early failure of lung function [3–5] has also been demonstrated in experimental models of burns [18], shock [19], and sepsis

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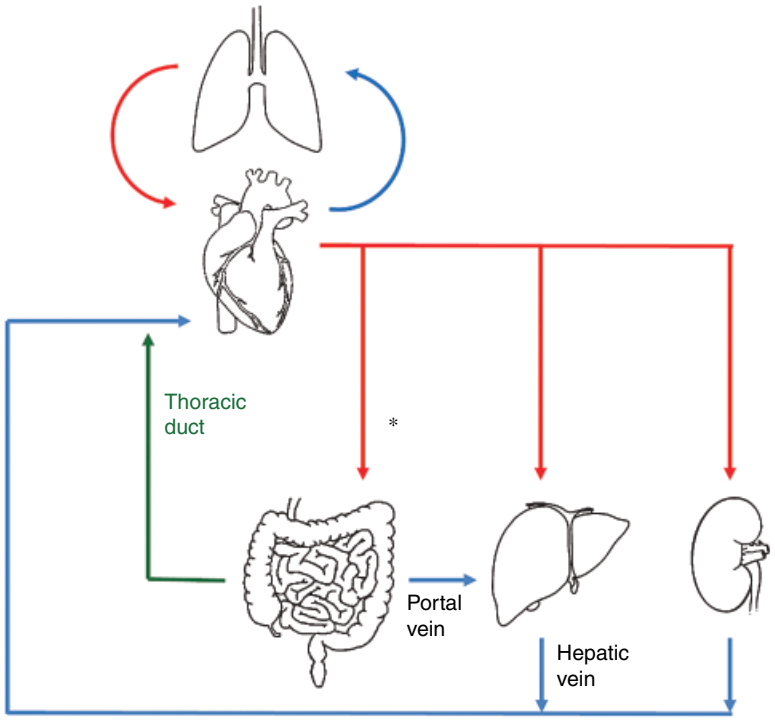


**Figure 16.1** Schematic of the gut–lymph concept emphasizing the preferential vasoconstriction (*) of the intestinal arterial supply that promotes intestinal ischemia and the drainage of lymph from the intestine via the thoracic duct, which bypasses the liver.

[20] and acute pancreatitis [21]. Furthermore, ligation of the mesenteric or thoracic duct ligation in these different models has been shown to prevent neutrophil priming [22], reduce red blood cell deformity [23,24], reduce cardiac dysfunction [25–27], protect against renal injury [28], and increase adenosine triphosphate (ATP) and ATPase renal activity [29].

The gut–lymph concept is best understood in relation to the anatomy of the mesenteric/thoracic lymphatics [30]. Mesenteric lymph drains from the intestine and mesentery to the cisterna chyli and then ascends through the mediastinum in the thoracic duct. Almost 75% of thoracic duct lymph arises from the abdomen and pelvis [31]. The thoracic duct lymph drains into the internal jugular or subclavian veins on the left side of the neck, immediately upstream of the heart, lungs, and kidneys, the organs most often involved in MODS. It is noteworthy that this lymph does not enter the portal venous system and it bypasses the liver and its detoxification processes (Fig. 16.1).

## Role of the Intestine in Severe Acute Pancreatitis

Although there has been interest in how intestinal injury contributes to the severity of acute pancreatitis for more than two decades, the gut–lymph concept has only recently been considered of potential relevance [32]. The mechanism of injury to the intestine in acute pancreatitis is multifactorial. Splanchnic vasoconstriction is a key mechanism (Fig. 16.1), and is the reflex response to hypovolemia; this can be profound in severe acute pancreatitis with substantial retroperitoneal third space fluid loss. The microanatomy of the intestinal mucosa makes it particularly prone to ischemic injury. The villous tip readily becomes ischemic due to the countercurrent flow of oxygen via the rich capillary network between the parallel artery and vein [33]. This is further compounded with fluid resuscitation because the intestine is the last organ to be reperfused and is subject to ischemia–reperfusion injury. This ischemic injury can be compounded by the use of nonselective inotropes in persistently hypotensive patients. Intestinal ischemia is related to the severity of acute pancreatitis [34], and a lower gastric intramucosal pH ($pH_i$) has been noted in patients admitted to intensive care than those who remain on the ward. $pH_i$ is also correlated with the risk of mortality [35,36]. Ischemic injury to the intestine is also known to contribute to the breakdown of protective mucus [37], which is compounded by the action of pancreatic proteases [38,39]. The ischemic environment also induces mucosal atrophy, mitochondrial dysfunction [40], oxidative stress, and cell death. Interestingly the mitochondrial dysfunction witnessed early in acute pancreatitis appears to be selective to the pancreas, lung, and jejunum, with relative sparing of the liver, heart, and kidneys [40].

As with other acute and critical diseases, there is strong evidence for intestinal dysfunction in acute

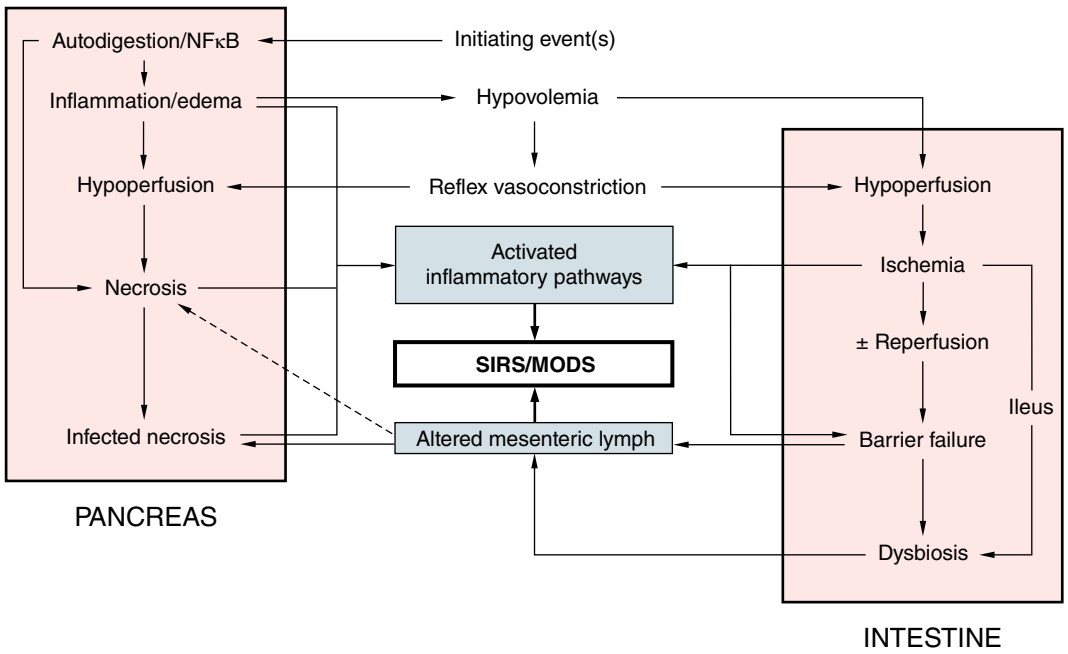


**Figure 16.2** A summary of the complex interactions between the pancreas and the intestine in the development of systemic inflammation (SIRS) and multiple organ dysfunction (MODS) in the pathogenesis of severe acute pancreatitis. *Source:* Adams et al. 2017 [51].

pancreatitis (Fig. 16.2), and it is estimated to occur in 60% of patients [41]. Clinically this dysfunction can be evident as an ileus (dysmotility) [42], feeding intolerance [43], and, at the severe end of the spectrum, nonocclusive intestinal ischemia [44,45]. There is clear clinical evidence that increased intestinal permeability to enterally administered polyethylene glycol is associated with the risk of MODS in acute pancreatitis [46]. Increased urinary intestinal fatty acid-binding protein, a marker of intestinal mucosal injury, has been correlated with the severity of acute pancreatitis [34,47]. The depletion of immunoglobulin G (IgG) anti-endotoxin antibodies, indicative of exposure to endotoxin and "gut barrier failure," is strongly associated with the development of organ failure and death in severe acute pancreatitis [48]. The administration of enteral nutrition, rather than starvation or parenteral nutrition, has been clearly associated with a reduction in infections, complications, and mortality in patients with acute pancreatitis [49], giving rise to the concept of "gut rousing" in seeking to maintain and improve intestine function [50].

## Altered Gut–Lymph Composition in Acute Pancreatitis

There is a significant body of experimental evidence that in critical diseases such as hemorrhagic shock, sepsis, trauma, and burns, mesenteric lymph undergoes significant compositional change [13]. Comparable evidence in acute pancreatitis is only now emerging. A canine model of acute pancreatitis with thoracic duct cannulation demonstrated that a significant proportion of pancreatic amylase and lipase is transported via thoracic duct lymph but not absorbed from the peritoneum from pancreatic ascites [52]. A rodent model of acute pancreatitis revealed a profound change in the proteome of mesenteric lymph [53]. Of the eight proteins exhibiting a significant increase in mesenteric lymph, seven were pancreatic proteases, and the increase was up to 40-fold. Despite this there was no commensurate increase in antiproteases. Lipase generates free and unsaturated fatty acids in mesenteric lymph, which are directly toxic to umbilical vein cells [54]. These exhibit systemic toxicity and are associated with MODS [55]. The lymph profile of noncoding microribonucleic acid (miRNA) is altered in acute pancreatitis, in both experimental and clinical settings [56]. The clinical significance of these changes have yet to be determined, but these molecules can regulate gene expression and influence cell function in remote organs. Interestingly there were seven miRNAs that were increased in intestinal lymph during experimental acute pancreatitis and their log abundance correlated with acute pancreatitis severity [56]. Other groups have demonstrated changes in mesenteric lymph composition in acute pancreatitis. For example, it has been found that the tryptophan metabolites kynurenine and 3-hydroxykynurenine are elevated in rodent mesenteric lymph and plasma during acute pancreatitis and this elevation correlates with disease severity [57].

## Gut–Lymph Toxicity in Acute Pancreatitis

The pathophysiologic significance of the profound compositional changes in mesenteric lymph in acute pancreatitis is still to be elucidated. Some progress has been made by testing the toxicity of the altered mesenteric lymph. In our own studies we have tested toxicity on three levels: organelle (e.g., mitochondrial function [58]), cell (e.g., endothelial and cardiac cell cultures), and whole organ (e.g., isolated perfused heart and lung). Mesenteric lymph from experimental acute pancreatitis incubated with either endothelial cells or cardiac fibres was toxic. In the case of cardiac fibers there was lymph-induced toxicity that induced mitochondrial complex dysfunction [58]. Mesenteric lymph from a rodent model of ischemia–reperfusion injury was intravenously infused into other rats with acute pancreatitis [59], causing an increase in acute pancreatitis severity, augmented microcirculatory collapse, and evidence of lung injury [59]. Experimental acute pancreatitis is associated with a reduction in cardiac output, reduced contractility, and impaired relaxation, which can be replicated by infusion of mesenteric lymph collected from an experimental model of acute pancreatitis and then infused into an isolated and paced heart model. Significantly, this cardiac dysfunction can be prevented by thoracic duct ligation [27] (Fig. 16.3). Experimentally, thoracic duct ligation [21] and lymph diversion [60] have also been shown to ameliorate lung injury in acute pancreatitis. However, thoracic duct ligation might aggravate pancreatic and intestinal injury, possibly because the toxic factors were less able to drain from these tissues. This suggests that the preferred approach to intervention might be external drainage, rather than thoracic duct ligation, because there is no backpressure effect.

## Translating the Gut–Lymph Concept to Clinical Treatments for Acute Pancreatitis

There is a history of open surgical drainage of thoracic duct lymph in a number of clinical diseases, attested to by over 70 publications [61] in the literature, although none since 2004. The reasons for this abeyance is probably a combination of the invasive nature of the thoracic duct cannulation and the predominance of underpowered, nonrandomized, and uncontrolled study designs. Within this seemingly forgotten literature there were four studies [62–65] in which external lymph drainage was used for the treatment of acute pancreatitis. One uncontrolled study of 10 patients reported an improvement in abdominal pain, peritonism, and shock in a "dose-dependent" manner related to the volume of lymph drained [62]. Three of these studies investigated the effect of thoracic duct lymph drainage on pulmonary function in the setting of acute pancreatitis-associated acute respiratory distress syndrome. One study noted that arterial oxygenation improved immediately once drainage was instituted [63]. Another case series demonstrated elevated levels of pancreatic enzymes and cytokines in lymph and plasma but no clinical improvement [65].

The evidence that proteases contribute to lung injury in acute pancreatitis [66] and the evidence that thoracic

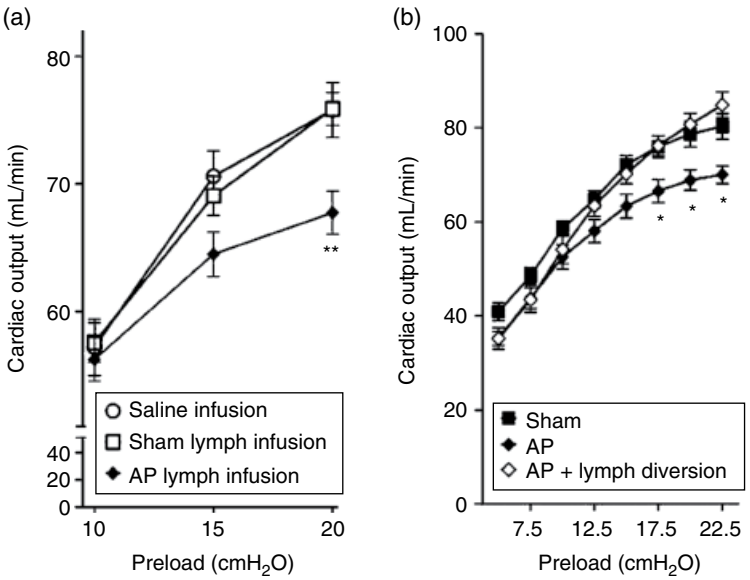


**Figure 16.3** (a) Cardiac output is reduced in *ex vivo* working hearts by acute pancreatitis (AP)-conditioned gut–lymph when compared to saline or sham lymph. (b) Cardiac output is maintained in rats with acute pancreatitis when compared to sham rats or rats with acute pancreatitis in which the thoracic duct is ligated. $^{*}P < 0.05$, $^{**}P < 0.02$.

duct lymph is flooded by pancreatic proteases in acute pancreatitis [53] suggests that external drainage is a treatment strategy that warrants more careful evaluation. A canine model of thoracic duct external drainage has shown that this is effective in reducing plasma amylase and lipase in acute pancreatitis [52].

Another potential treatment strategy, in addition to external drainage of lymph, might be to deliver treatments that target toxic factors in mesenteric lymph. In an experimental rodent model it was demonstrated that inhibition of tryptophan metabolites kynurenine and 3-hydroxykynurenine, which are elevated in mesenteric lymph of rats with acute pancreatitis, is protective against MODS [67]. In another experiment it was found that antiprotease treatment with naramostat significantly reduced endothelial cell death when combined with mesenteric lymph from experimental hemorrhagic shock and acute pancreatitis (Fig. 16.4). This raises the possibility of delivering antiprotease treatment to mesenteric lymph by supplementing enteral nutrition with lipophilic transporters.

The gut lymph concept has been largely derived from experimental studies. Translating this to new approaches to the treatment of severe acute pancreatitis will require a more complete understanding of the role of mesenteric lymph in the pathogenesis of the systemic inflammatory response and organ dysfunction. The major barrier has been the lack of a reliable, safe, and minimally invasive techniques for sampling, monitoring, and draining thoracic duct lymph in patients with severe acute pancreatitis.

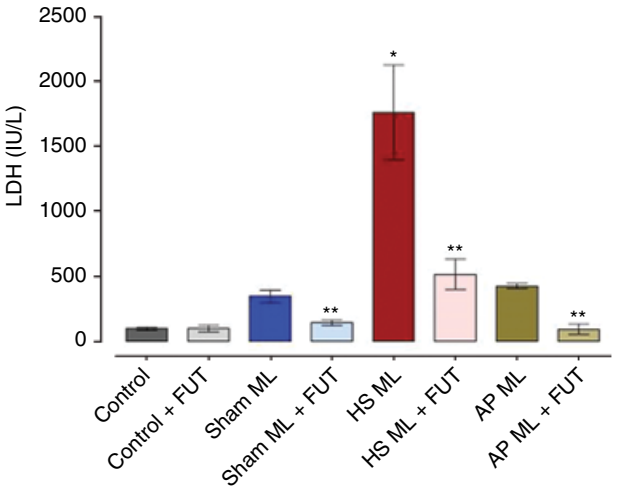


**Figure 16.4** Cell death (LDH level) of endothelial cells (HMEC) was increased on treatment with hemorrhagic shock (HS) or acute pancreatitis-conditioned gut–lymph (ML) when compared to control media or mesenteric lymph (ML) from sham-treated rats (*$P < 0.05$). Cotreatment with the antiprotease nafamostat (FUT) reduced cell death (**$P < 0.05$).

## Conclusion

There is emerging experimental evidence that altered mesenteric lymph contributes to the systemic inflammation and MODS that characterizes severe acute pancreatitis. The "gut–lymph" concept provides a new disease paradigm, a new field of research, and a long-awaited opportunity to develop new and specific treatments for severe acute pancreatitis.

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# 17

# The Role of Neurogenic Inflammation in Pancreatitis

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Pancreatitis is a complex inflammatory disease with multiple etiologies that include both genetic and environmental (internal and external) components. Whereas the inciting factors that lead to pancreatic inflammation can be varied, the resulting pathology has a common histologic presentation, including edema, vasodilation, invasion of immune cells, and varying degrees of breakdown in the barriers between different tissue compartments within the pancreas. Recently, a major role has been recognized for the peripheral nervous system as a driver of inflammatory pancreatic responses, such that it is being investigated as a potential therapeutic target. Animal model studies indicate that manipulation of the peripheral nervous system can alter the course of the disease. Specifically, these manipulations have targeted sensory innervation of the pancreas based on studies that go back to the early twentieth century which found that activation of the primary sensory neurons produced vasodilation [1]. The studies by Bayliss [1] were the beginning of the recognition that sensory neurons have an "efferent" function through the peripheral release of small molecules such as substance P (SP), calcitonin gene-related peptide (CGRP), glutamate, cholecystokinin (CCK) and ATP. These molecules can act on blood vessels and immune cells to establish "neurogenic inflammation" [2–7]. Here we review the current state of our understanding of the role of neurogenic inflammation in pancreatitis and how this information might be translated into new treatments for human disease.

The pancreas is innervated by two types of sensory afferents: fibers that run in the vagus nerve and ones arising in spinal sensory ganglia that travel in splanchnic nerves (the greater splanchnic in human, both greater and lesser splanchnic in rodents), traverse the celiac ganglia and then enter the pancreas [8] (Fig. 17.1). The vagus nerve comprises both sensory (about 88% of the fibers in the hepatic branch innervating the rat pancreas) and parasympathetic preganglionic fibers [8]. The parasympathetic preganglionic fibers that travel to the pancreas synapse on parasympathetic postganglionic neurons located in small ganglia throughout the organ. Cell bodies of sensory axons that travel in the vagus nerve are located in the nodose ganglia. These cells transmit information to the nucleus tractus solitarii (NTS). The splanchnic nerves also contain sympathetic preganglionic neurons that form synapses on postganglionic sympathetic neurons within the celiac ganglia that in turn project to the pancreas where their targets include acinar and islet cells and vascular smooth muscle [9].

Sensory afferents that have been most closely identified with neurogenic inflammation are unmyelinated, peptidergic C-fibers that release one or more peptides, primarily SP and CGRP, although a review of the literature indicates that over 20 peptides and small molecules may be released from sensory endings [6]. Unmyelinated, peptidergic afferents that arise from cell bodies located in both nodose and spinal ganglia are the predominant type of fiber that innervates the pancreas [10–14]. Electrophysiological recordings from both nodose and spinal sensory neurons show similar responses to visceral stimulation (e.g., thresholds for firing, pattern of action potential discharge) [15–17]. However, activity in nodose afferents is correlated with affective sensations associated with visceral organ function, whereas the activity in visceral spinal afferents is associated with sensations more typically recognized as pain. A subset of both spinal and vagal afferents can release CGRP and/or

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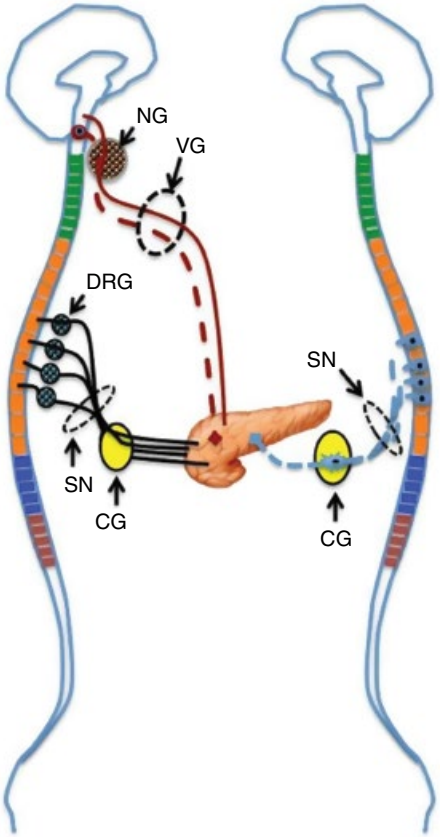


**Figure 17.1** Thoracic and abdominal organs (including the pancreas) receive sensory input from primary afferents whose cells bodies are located in the nodose ganglion (NG; solid red lines) and run in the vagus nerve (VN). Sensory innervation from dorsal root ganglia (DRG; also known as spinal ganglia) to the pancreas travel with sympathetic preganglionic axons (shown on right side of diagram) in the greater splanchnic nerve (SN) and pass through the celiac ganglion (CG). The VN also contains axons from parasympathetic preganglionic neurons (dashed red lines) whose cell bodies are located in the brainstem (in the dorsal motor nucleus of the vagus, not shown). These axons synapse on parasympathetic postganglionic neurons (not shown) that are in the organ wall. Sympathetic innervation arises from sympathetic preganglionic neurons (blue dashed lines on right side of diagram) whose cell bodies are located in the spinal cord intermediolateral cell column (not shown) at T5–9 vertebral levels. Axons from these neurons innervate sympathetic postganglionic neurons in paravertebral ganglia located along side the vertebral column (not shown) or prevertebral ganglia found near the organ. The prevertebral ganglia include the CG, whose neurons innervate pancreas. Anatomy shown for human, but rodents are organized in a similar fashion, varying only in the details.

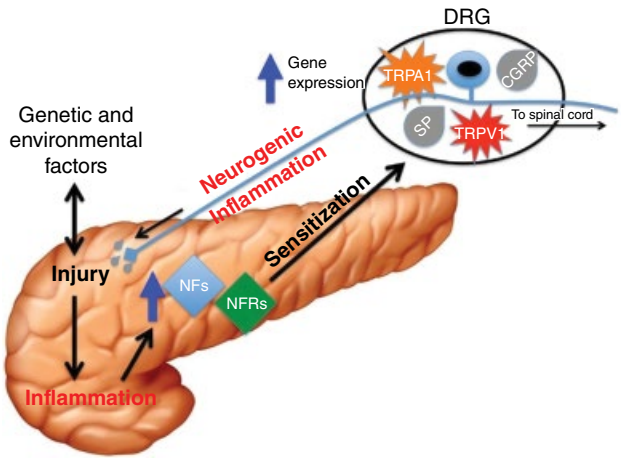


**Figure 17.2** Pancreatic injury, exacerbated or induced by environmental and genetic factors, leads to pancreatic injury and inflammation. This inflammation is accompanied by an increase in neurotrophic factors (NFs, e.g., nerve growth factor and artemin) as well as neurotrophic factor receptors (NFRs, e.g., TrkA). The NFs produce sensitization of sensory fibers innervating the pancreas and this leads to an increase in sensory neuron gene expression for receptors/channels that detect noxious stimuli (e.g., TRPA1 and TRPV1) as well increased production and release of small molecules that produce neurogenic inflammation in the pancreas (e.g., substance P [SP], calcitonin gene-related peptide [CGRP]). This feed-forward loop, if not blocked, can lead to fibrosis and permanent damage associated with chronic pancreatitis, as well as setting the stage for cancer development.

SP (as well as other small molecules) in the pancreas upon stimulation by chemical factors released by the pancreas as well as in response to mechanical stimulation produced by distension of ducts and blood vessels.

The idea that the sensory nervous system, via neurogenic inflammation (Fig. 17.2), plays a role in pancreatitis has led a number of investigators to test this hypothesis by inducing pancreatic inflammation and manipulating pancreatic sensory input, either surgically or chemically. Nathan et al. [3] hypothesized that sensory neurons were a "final common pathway" for neurogenic inflammation associated with pancreatitis. Using two experimental models of pancreatitis (repeated caerulein injections and common pancreaticobiliary duct ligation), they were able to show that sensory denervation (via neonatal capsaicin treatment) dramatically reduced multiple measures of pancreatic inflammation. Subsequent studies expanded on this concept by using pharmacologic approaches to block pancreatic afferent activity. Michalski and coworkers [18,19] demonstrated that cannabinoid receptors were expressed in the pancreas (on both nerves and other cell types) and then used cannabinoid agonists to decrease experimental pancreatitis pain and tissue damage. Schwartz et al. used a similar strategy in animal models of both acute [20] and chronic [21] pancreatitis. In these studies, antagonists for TRPV1 and TRPA1 (two excitatory ionotropic receptors expressed on pancreatic afferents; see later) were shown to be effective in blocking both pain and inflammatory markers, including upregulation of myeloperoxidase and neutrophil infiltration (acute pancreatitis), as well as fibrosis and nerve sprouting (chronic pancreatitis). The question then becomes what are the signals released by

the damaged pancreas that produce abnormal activation of pancreatic afferents?

The majority of pancreatic afferents express receptors on their pancreatic terminals that can induce activation and calcium influx into the presynaptic terminal, which can contribute to the release of inflammatory molecules (Fig. 17.2). The receptor in sensory endings that has received the most attention in recent years is the transient receptor potential cation channel subfamily vanilloid type 1 (TRPV1). This receptor is expressed in 80–90% of neurons that express CGRP and/or SP and is upregulated in pancreatic afferents during pancreatitis [10,22–24]. A significant percentage of these neurons also express a related family member, TRPA1 [20,21]. Both of these channels have been shown to be required for the development of inflammatory pain [25–27]. Moreover, both transient receptor potential channels are themselves upregulated by growth factors that are highly expressed in inflamed pancreata (e.g., nerve growth factor [NGF] and artemin [ARTN]) [28–31]. Whereas these receptors are best known for their response to plant-derived molecules (capsaicin; TRPV1, and mustard oil; TRPA1), endogenous molecules that can activate these receptors are present or increased following pancreatic injury including anandamide (an endogenous cannabinoid), protons, leukotriene B4, hydrogen peroxide, and products of lipid peroxidation such as 4-hydroxynonenal [32–35]. In addition, trypsin released from the injured acinar cells directly activates protease-activated receptor 2 (PAR2) expressed on sensory neurons and this has been shown to sensitize TRPV1 [32,36,37]. Assuming that pancreatic sensory terminals are similar to other visceral nerve endings, they will express a wide range of receptors that allow them to respond in an autocrine/paracrine fashion. These include multiple excitatory ionotropic and metabotropic receptors for nucleotides (e.g. ATP, ADP, adenosine), glutamate, 5-hydroxytryptamine, SP, acetylcholine, and prostaglandins [8,15,16,38,39]. These receptors could respond to molecules released by adjacent sensory fibers as well as to ATP and norepinephrine released from pancreatic sympathetic postganglionic neurons [40,41]. Many of these molecules may act locally on sensory endings to induce release in the absence of action potential generation. However, once an action potential is generated in a sensory fiber, this will trigger release of inflammatory molecules. Once this activity reaches the spinal cord it can rebound via a process known as a dorsal root reflex. This reflex produces a retrograde action potential that travels back out to the periphery and initiates release of inflammatory molecules [6,42–44]. The efficacy of this reflex is exaggerated by spinal cord inflammation, which has been shown to accompany pancreatitis [45,46].

Although nerve-targeted interventions effectively reduce pancreatitis symptoms in preclinical models, in most experimental paradigms these interventions are applied either simultaneously with the disease-inciting stimulus (e.g., caerulein) or early in the disease process. Thus, their relevance for treatment of patients is unclear, especially for acute pancreatitis where the primary symptom of pain is treated medically with nonsteroidal anti-inflammatory drugs and opioids. Clinicians are reluctant to use more aggressive procedures that include injections into splanchnic nerves or celiac ganglia due to occasional adverse affects that can be severe and difficult to justify for a disease that in many cases resolves relatively quickly. However, for chronic pancreatitis, nerve injections are an important option. There are three primary techniques that are utilized to manage intractable pancreatic pain: celiac plexus block (CPB), celiac plexus neurolysis (CPN), and thoracoscopic splanchnic denervation (TSD). Importantly, there is little or no evidence that these treatments affect nonpain disease features (which would be difficult to assess in the absence of large controlled trials). TSD can effectively reduce adrenomedullary function, pain scores, and opioid use in patients with chronic pancreatitis [47,48]. A meta-analysis of 16 studies reveals that TSD significantly reduces pain and improves quality of life. However, the pain returns in half of those initially achieving relief after just 1.5 years [49,50].

The efficacy of silencing sensory neurons for patients with pancreatitis will be worth revisiting in the future with the development of new drugs that have been developed for pain and that act by blocking either sensory nerve function or the inflammatory molecules released by sensory fibers. For examples, clinical trials are now under way for both anti-NGF and anti-CGRP antibodies and drugs [51–55]. These drugs may make it possible to conduct sufficiently powered clinical trails to determine if these types of therapies are both safe and effective for this difficult disease.

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# 18

# Molecular, Biochemical, and Metabolic Abnormalities in Acute Pancreatitis

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## Introduction

Acute pancreatitis is the most frequent cause for hospital admission among all nonmalignant gastrointestinal diseases [1]. It represents an inflammatory disorder of the exocrine pancreas caused, in most cases, by immoderate alcohol consumption or the passage of gallstones. Recent studies involving animal and isolated cell models have elucidated many of the pathophysiologic, cellular, and molecular processes involved in the disease onset. More than 100 years ago it was proposed that pancreatitis is essentially a disease in which the pancreas falls prey to its own, prematurely activated digestive enzymes. Why and how digestive zymogens undergo activation within the pancreas early in the disease process has been the topic of extensive research efforts and debate. Premature activation of pancreatic zymogens results in biochemical and later metabolic alterations, the mechanisms of which will be reviewed in this chapter.

Regardless of the underlying etiology, the natural course of pancreatitis, a primarily sterile inflammatory disorder, proceeds in three steps: (i) a local inflammatory reaction in conjunction with acinar tissue necrosis, (ii) a systemic inflammatory response, and (iii) eventually microbial superinfection of the pancreatic necrosis which frequently results in multiorgan failure and is closely associated with a rise in mortality. Mortality in severe acute pancreatitis peaks at two different time points: patients either pass away during the first 7 days after the onset of pain from an overwhelming inflammatory response syndrome resulting in multiorgan failure (approximately 30%) or they die late in the disease course facilitated by a compensatory anti-inflammatory response syndrome which permits translocation of gut bacteria into pancreatic necrosis, resulting in uncontrollable sepsis. Frequently, however, a mixed picture of a systemic inflammatory response and a compensatory anti-inflammatory reaction, called MARS (mixed anti-inflammatory response syndrome), is observed.

The pathogenesis of the inflammatory response in acute pancreatitis is indistinguishable from that of other traumatic or infectious immune reactions. Thirty per cent of all patients admitted to hospital suffering from acute pancreatitis have organ failure of two systems. Outside the pancreas the most frequently affected organs are the lungs, kidneys, and the gut [2].

## Molecular and Biochemical Abnormalities

### Pathophysiologic Significance of Digestive Protease Activation

Trypsinogen and other pancreatic proteases are synthesized by acinar cells as inactive proenzyme precursors and stored in membrane-confined zymogen granules. After activation in the small intestine, trypsin converts other pancreatic zymogens, such as chymotrypsinogen, pro-elastase, pro-carboxypeptidase, or pro-phospholipase A2, to their active forms [3]. Although small amounts of trypsinogen are probably activated within the pancreatic acinar cell under physiologic conditions, two protective mechanisms normally prevent cell damage from proteolytic activity: (i) Pancreatic secretory trypsin inhibitor (PSTI), the product of the *SPINK1* gene, is co-secreted with pancreatic zymogens. PSTI can inhibit up to 20% of potential trypsin activity in humans

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[3], but this number may vary considerably among species. The fact that mutations in the *SPINK1* gene are associated with certain forms of human pancreatitis [4–7] indicates that this protective mechanism may play a role in pancreatic pathophysiology. The implications of *SPINK1* overexpression in a disease model of pancreatitis have recently been reported [8]. (ii) Cell biological experiments using living rodent acini provided evidence that trypsin limits its own activity by autodegradation under conditions that mimic pancreatitis [9] (see later). Furthermore, certain mutations associated with human hereditary pancreatitis stabilize cationic trypsin either against autolysis [10–12] or against degradation via chymotrypsin C [13], suggesting that proteolysis of trypsin might play a role in safeguarding the human pancreas against excess intrapancreatic trypsin activity. Although not demonstrated experimentally yet, it is probable that other pancreatic proteases in addition to chymotrypsin might participate in a similar protective mechanism. In humans, mesotrypsin has been labeled a candidate for this function [14,15]. This minor trypsin isoform constitutes less than 5% of total secreted trypsinogens. Interestingly, due to a Gly198 → Arg substitution (Gly193 → Arg in chymotrypsin numbering), this isoform is poorly inhibited by PSTI, which led to the suggestion that mesotrypsin might participate in degradation of other zymogens and proteases [16,17]. However, mesotrypsin is grossly defective not only in inhibitor binding, but also in cleaving protein substrates [18]. A pathophysiologic role of mesotrypsin in intracellular protease degradation and a protective function in pancreatitis is therefore somewhat unlikely.

The presence of another unknown enzyme activity effective in degrading protease zymogens was also observed in human pancreatic juice. This uncharacterized activity was named enzyme Y, and was proposed as one of the protective factors against pancreatitis [19]. It has recently been identified to be identical with chymotrypsin C and was found to play a major role in degrading activated trypsin [13].

Theoretically, premature activation of large amounts of trypsinogen could overwhelm these protective mechanisms, lead to damage of the zymogen-confining membranes and the release of activated proteases into the cytosol. Moreover, the release of large amounts of calcium from zymogen granules into the cytosol might activate calcium-dependent proteases such as calpains, which, in turn, could contribute to cell injury.

The suggestion that prematurely activated digestive enzymes play a central role in the pathogenesis of pancreatitis is based on the following observations: (i) The activities of both pancreatic trypsin and elastase increase early in the course of experimental pancreatitis [20,21]. (ii) The activation peptides of trypsinogen and carboxypeptidase A1 (CPA1), which are cleaved from the respective proenzyme during the process of activation, are released into either the pancreatic tissue or the serum early in the course of acute pancreatitis [2,17,22–25]. (iii) Pretreatment with gabexate mesilate, a serine protease inhibitor, reduces the incidence of endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis [26]. (iv) Serine protease inhibitors reduce injury in experimental pancreatitis [26]. (v) Hereditary pancreatitis is often associated with various mutations in the cationic trypsinogen gene that could either render trypsinogen more prone to premature activation or render active trypsin more resistant to degradation by other proteases [11,13]. (vi) Triplication of the trypsinogen locus in humans (i.e., an assumed gain in the trypsin activity) that is expressed in affected subjects leads to hereditary pancreatitis [27]. (vii) Mutations in the *SPINK1* gene, which might render PSTI less effective, are associated with certain forms of chronic pancreatitis [4–7].

On the cellular level, the initiating role of trypsin has come under debate by the observation that the deletion of trypsin 7, an isoform, largely prevents premature protease activation in a mouse model of pancreatitis but has little effect on the disease course and its severity [28]. Moreover, when cathepsin B-mediated trypsinogen activation is prevented, this appears to affect apoptosis, rather necrosis in the pancreas [29].

In clinical and experimental studies that investigated the time course of pancreatitis it was found that zymogen activation occurs very early in the disease course. One study that employed the caerulein model of acute pancreatitis reported a biphasic pattern of trypsin activity that reached an early peak after 1 hour and a later second peak after several hours [25]. This observation is interesting because it suggests that more than one mechanism may be involved in the activation of pancreatic zymogens and the second peak may require the infiltration of inflammatory cells into the pancreas [25,30,31]. Taken together, these observations represent compelling evidence that premature, intracellular zymogen activation plays a critical role in initiating acute pancreatitis.

## Clinical Evidence for Digestive Protease Activation

A number of recent studies involving patients have greatly contributed to our understanding of the role of zymogen activation in pancreatitis. In patients who underwent ERCP, an interventional medical procedure that requires cannulation of the pancreatic duct and is associated with a significant complication rate for pancreatitis, the prophylactic administration of a small molecular weight protease inhibitor reduced the

incidence of pancreatitis [32]. Although protease inhibitors have not been found to be effective when used therapeutically in patients with clinically established pancreatitis [33], the result of the prophylactic study supports the conclusion that activation of pancreatic proteases is an inherent feature of the disease onset. Moreover, since reasonably specific antibodies have become available that detect the trypsinogen activation peptide (TAP) but do not crossreact with either active trypsin or inactive trypsinogen [34], the presence of TAP in serum and urine of patients with acute pancreatitis provides direct evidence for an activation of trypsinogen during pancreatitis. The amount of TAP released also appears to correlate with the disease severity [35].

## Cathepsin B in Premature Digestive Protease Activation

Several lines of evidence have suggested a possible role for the lysosomal cysteine protease cathepsin B in the premature and intrapancreatic activation of digestive enzymes [35]. The largely circumstantial evidence for this "cathepsin B hypothesis" is based on the following observations: (i) Cathepsin B has been shown to activate trypsinogen *in vitro* [36]. (ii) During the initial phase of acute pancreatitis in several animal models a redistribution of cathepsin B into a zymogen granule-containing subcellular compartment was detected by density gradient centrifugation [37]. (iii) In the same pancreatitis models lysosomal enzymes were detected by immunogold electron microscopy in secretory organelles that also contained digestive enzymes (e.g., trypsinogen) [38]. Experimental approaches to show an essential role of cathepsin B in premature zymogen activation by inhibition of this lysosomal enzyme with synthetic inhibitors rendered contradictory results, either increasing [39] or decreasing premature zymogen activation [40], or failing to improve the course of experimental pancreatitis.

To test the cathepsin B hypothesis more directly and to overcome the shortcomings of lysosomal enzyme inhibitors, which have only limited specificity for cathepsin B, a cathepsin B-deficient mouse strain that was generated by targeted disruption of the *ctsb* gene was studied in experimental pancreatitis [41]. The results of these studies were unequivocal: 90% of intrapancreatic trypsinogen activation during pancreatitis depends on the presence of cathepsin B [41]. What remained puzzling was the observation that acinar cell injury did not decline to the same degree to which trypsinogen was reduced. The explanation for this discrepancy came from recent studies that investigated the cell death mechanisms involved in cathepsin B-mediated trypsinogen activation and found that neither induces necrosis, whereas both appear to be involved in apoptosis, a much less injurious kind of all death in terms of its systemic consequences [29,42]. The relevance for human disease, however, remained another matter.

First attempts to establish the relevance of the cathepsin B–pancreatitis hypothesis in humans focused on the capacity of the lysosomal enzyme to activate human trypsinogen, and specifically varieties of human trypsinogen, into which disease-relevant mutations had been introduced that were identified in the context of hereditary pancreatitis studies. Hereditary pancreatitis, as mentioned above, is a disease that follows an autosomal dominant inheritance pattern, is associated with an early onset of chronic pancreatitis (usually in children and young adults), and is associated with various germline mutations in the cationic trypsinogen gene (*PRSS1*) [43]. When recombinant trypsinogen with hereditary pancreatitis mutations was subjected to activation by cathepsin B *in vitro* it was indeed found that some trypsins behaved differently from their wild-type counterparts [13,44], an observation that clearly supported the cathepsin B hypothesis of pancreatitis. On the other hand, the most common *PRSS1* mutations, such as R122H and N29I, did not convincingly vary from wild-type trypsin in their activation kinetics by cathepsin B [45]. The same study demonstrated further that cathepsin B is abundantly secreted from the human exocrine pancreas, plentiful in pancreatic secretory zymogen granules (rather than in lysosomes), and active within the secretory pathway [45]. Thus, all cellular conditions for the cathepsin B–pancreatitis hypothesis to be operative in humans were met. Moreover, the proposed requirement for a subcellular redistribution of cathepsin B into the secretory compartment [37] could finally be put to rest because most cathepsin B in the pancreas was found to already reside in the secretory compartment under physiologic conditions [45,46], rather than having to be redistributed there from lysosomes. Nevertheless, no direct evidence for an active involvement of cathepsin B in the onset of human pancreatitis—at least not in hereditary pancreatitis caused by the most common trypsin mutations—could be produced from these studies.

This has finally been achieved in a recent study in which a group from India has sequenced the entire coding region of the *ctsb* gene in 140 Indian patients with pancreatitis and 155 controls and reported that *ctsb* germline changes may explain the disease onset [47]. Unfortunately these data could not be confirmed in a Western population with idiopathic pancreatitis [48].

So far it must be remain open whether cathepsin B-induced activation of trypsinogen plays a role in human as much as in experimental pancreatitis. Moreover, whether this mechanism determines disease onset and

severity is also unclear [29,42]. Finally, whether or not other lysosomal cathepsins that can clearly counteract the effects of cathepsin B, such as cathepsin L [49] predominate the events in early human and animal pancreatitis remains the object of ongoing studies.

### Conclusions

Recent advances in cell biological and molecular techniques have permitted investigators to address the intracellular pathophysiology in a much more direct manner than was previously considered possible. Initial studies that have employed these techniques have delivered a number of surprising results that appear to be incompatible with long-standing dogmas and paradigms of pancreatic research. Some of these insights will lead to new and testable hypotheses that will bring us closer to understanding the pathogenesis of pancreatitis. Only progress in elucidating the intracellular and molecular mechanisms involved in the disease onset will permit the development of effective strategies for the prevention and cure of this debilitating and still somewhat enigmatic disease.

## Metabolic and Systemic Abnormalities

In the past, patients with acute pancreatitis have been categorized according to the presence or absence of complications and the definitions of severe disease, and the recently revised Atlanta classification [50] has codified this concept. Complications include systemic organ failures as well as local disease manifestations. Recently, it has been shown that organ failure during the first week of admission is invariably associated with a high mortality rate of >50% [51]. An investigation of 290 patients with predicted severe acute pancreatitis showed that early organ failure was present in 60% of patients. When organ failure was only transient, clinical outcome was good (mortality below 1%), whereas persistent organ failure resulted in a mortality rate of 35% [2]. A better understanding of the pathogenesis of early multiorgan failure might therefore be essential for the development of new strategies for the prevention or treatment of acute pancreatitis.

### Pathogenesis of Pulmonary Failure

Acute respiratory distress syndrome (ARDS), later termed acute lung injury (ALI) is a frequent manifestation of organ dysfunction in an intensive care setting and can be the cause of death in critically ill patients. The exact incidence remains unknown but may be as high as 75 per 100 000 population in the United States [52]. Overall, acute pancreatitis is a condition in which patients rarely develop ARDS (8% of total), but severe attacks are frequently associated with ALI and ARDS [53]. The definition set in 1994 for ALI is a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension [54,55]. The distinction between ALI and ARDS is the degree of hypoxemia. The incidence of pulmonary complications in acute pancreatitis varies between 15% and 55% and their severity ranges from mild hypoxemia without clinical or radiologic signs to severe ARDS. The major cause of hypoxemia is ventilation/perfusion mismatch which results in right to left pulmonary shunting. In ARDS the injured lung is believed to go through three phases: exudative, proliferative, and fibrotic, but the course of each phase and the overall disease progression are variable. The pathophysiologic features of the lung in ARDS arise from severe injury to the alveolocapillary unit. The histologic features are dense eosinophilic hyaline membranes and alveolar collapse. The endothelial cells swell, the intercellular junctions widen, and pinocytic vesicles increase, causing capillary leak and edema formation. Approximately 10% of patients with acute pancreatitis show alveolar edema on chest radiographs and a third of patients develop progressive hypoxemia during the first week of hospitalization [56]. The cause for the development of alveolar edema is an increase in microvascular permeability in the context of systemic inflammatory response syndrome (SIRS) [57,58]. This was shown by applying labeled transferrin as an indicator for lung vascular permeability within 48 hours after hospital admission. This was found to be significantly increased in the lung tissue of patients who had later died in the disease process [59]. A similar observation was reported more recently in which an increase in the gallium–transferrin pulmonary leak index strongly correlated with the mortality rate [60].

Lankisch and coworkers determined the incidence of pulmonary infiltrates in 140 consecutive patients with acute pancreatitis with 26% within 24 hours after admission to hospital [61] (Fig. 18.1). The mortality rate of acute pancreatitis significantly correlated with the presence of pulmonary infiltrates and effusions. Logistic regression analysis showed that radiologic abnormalities were associated with a 15-fold increase in mortality rate [62]. A reduced $PaO_2$ on hospital admission has long been regarded as a prognostic factor for the severity of pancreatitis and is part of the Ranson Score, the Imrie Score, and the International Guidelines which recommend to hold peripheral oxygen saturation above 95% to prevent organ failure as a treatment goal [63].

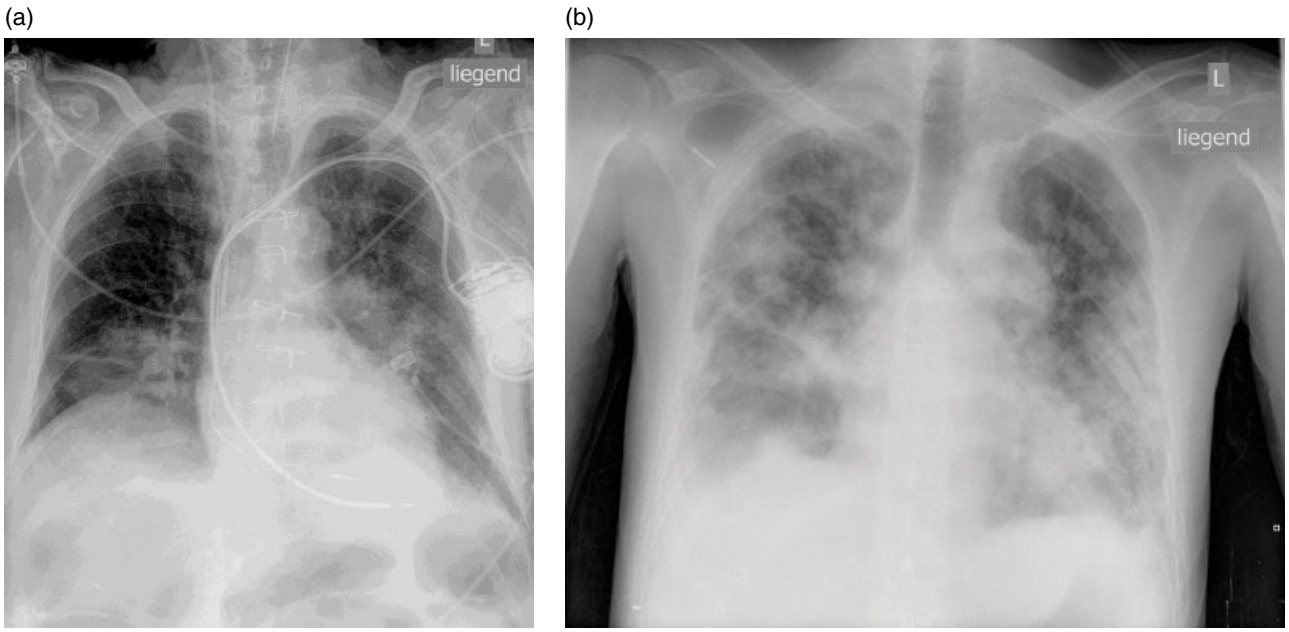



**Figure 18.1** Pulmonary infiltrates in severe acute pancreatitis.

With respect to the pathophysiology of ARDS in acute pancreatitis, two case series showed that massive cytokine release may have a contributing role in SIRS. Interleukin 8 (IL-8) was reported to be significantly higher at admission in patients who later developed acute severe lung injury [64]. In pleural effusions tumor necrosis factor α (TNF-α), IL-1, IL-6, and polymorphnuclear cell elastase (PMN-elastase) were significantly higher in serum in patients with ARDS, which may point to a direct impact of these cytokines on the development of ARDS but could also occur because of a diminished excretion of cytokines into pleural effusions [65]. Futhermore, in patients who later developed ARDS, elevated serum levels of thromboxane and prostacyclin were reported [66].

Phospholipase A2 (PLA-2) has long been regarded as a major cause of ALI in acute pancreatitis. Studying PLA-2 one needs to consider that there are numerous subtypes, of which two—PLA-2 type I and PLA-2 type II—could have a role in the pathogenesis of pancreatitis. Older studies suggested that PLA-2 type II (leukocyte-derived PLA-2) is responsible for the cell necrosis in acute pancreatitis by converting its endogenous substrate lecithin (part of the lipid bilayer of cell membranes) into the more toxic compound lysolecithin [67,68]. Thus PLA-2 could break down pulmonary surfactant, which consists of phospholipids, and could therefore impair oxygenation and increase vascular permeability. This notion was confirmed as elevated circulating plasma levels of PLA-2 correlated with more severe pulmonary changes in patients with gram-negative septic shock [69]. Furthermore, intratracheal application of nonpancreatic PLA-2 induced lung injury with interstitial edema and accumulation of inflammatory cells, but the concept that release of pancreatic PLA-2 from necrotic acinar cells mediates lung injury had to be abandoned [69–71]. In addition to the hypthesis of a direct impact of PLA-2, other pancreatic zymogens and nitric oxide released from pulmonary macrophages have been implicated in contributing to pulmonary complications in acute pancreatitis [72]. An experimental study testing this concept showed that intravenous application of elastase or trypsin resulted not only in pulmonary damage through NFκB activation and TNF-α release with subsequent transmigration of neutrophils, but also in an increase in lung vascular permeability [73–78].

Neutrophils have been implicated in mediating lung injury in acute pancreatitis and inhibition of neutrophil-derived serine proteases such as PMN-elastase seem to be promising treatment targets [30,31]. In an attempt to remove activated pancreatic zymogens to prevent systemic injury, two rather small studies (recruiting 12 and 6 patients) performed thoracic duct drainage. One of the two studies found an improved pulmonary gas exchange and a reduction in time on mechanical ventilation [65], whereas the second study failed to confirm these data [79] and the benefit of this approach is still doubtful.

In conclusion, severe attacks of acute pancreatitis are frequently associated with ALI. Arterial hypoxemia, pulmonary infiltrates, pleural effusions, and ARDS may

develop as complications of the disease. Within the first few days following the onset of severe acute pancreatitis, lung injury develops as a consequence of acute pancreatitis. Sepsis is the predominant cause of lung injury in the later phase of the disease. Besides best supportive care, protective mechanical ventilation, hemodynamic monitoring, as well as enteral nutrition and renal replacement therapy have been considered to be of potential benefit to treat pulmonary complications and have therefore been extensively studied [80–86]. Unfortunately, even if the results from animal experiments were very promising, the results obtained from clinical trials were rather disappointing [87–91]. The pathogenesis of pulmonary injury still remains incompletely understood.

## Pathogenesis of Renal Failure

Acute renal failure (ARF) occurs in 19% of patients with moderate sepsis, 23% with severe sepsis, and 51% with septic shock when blood cultures are positive [92,93]. The cytokine-mediated induction of nitric oxide synthesis that occurs in SIRS and sepsis decreases systemic vascular resistance. This arterial vasodilatation predisposes patients with SIRS to ARF [94]. Patients who develop ARF in the setting of critical illness are more likely to die than dialysis-dependent patients admitted to intensive care, suggesting that the bad outcome associated with the recent development of renal failure is due to SIRS, rather than merely due to renal dysfunction [95]. The clinical syndrome of ARF in the setting of critical illness, manifested by rising serum creatinine and decreasing urine output, results from injury to the tubular epithelial cells or acute tubular necrosis. In necrotizing pancreatitis, renal insufficiency occurs in 21% of patients after a median time period of 8.3 days after the onset of pancreatitis. The extent of pancreatic necrosis correlates with the development of ARF but infection of the pancreatic necrosis is not associated with a higher rate of ARF [96]. ARF has never been studied systematically either in the clinical setting of pancreatitis or in pancreatitic animal studies.

In analogy to the pathogenesis of ARF in critically ill patients with SIRS, a combined pathomechanism of prerenal failure due to extensive fluid loss into the third space, together with a prolonged cytokine-mediated organ failure even after fluid resuscitation can be assumed to be operative. Simmons and coworkers showed that increased plasma proinflammatory cytokine levels (TNF-α, IL-1b, IL-6) predict the mortality in patients with ARF [97] and an anti-TNF-α-directed therapy was found to improve several early events during experimental pancreatitis, including protease activation [98]. This finding is supported by the fact that in animal models infusion of high concentrations of proinflammatory cytokines can lead directly to the development of multiorgan system failure [99,100]. Furthermore, patients with SIRS and associated ARF show signs of intense endothelial damage and hypercoagulability as indicated by increased von Willebrand factor, thrombomodulin, tissue plasminogen activator, plasminogen activator inhibitor-1, and D-dimer activity [101]. Vasoactive mediators appear to be a contributing factor of some importance [102].

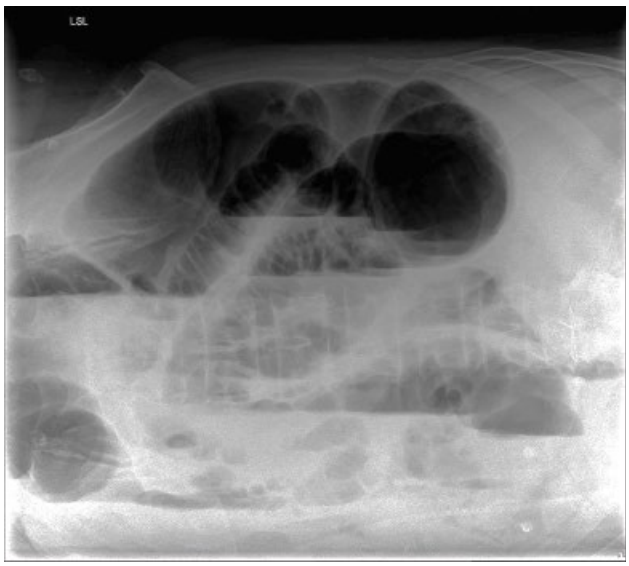
In conclusion, ARF is a frequent extrapancreatic complication of acute pancreatitis, but further studies on the pathogenesis of ARF are urgently needed to treat this potentially fatal complication.

## Pathogenesis of Paralytic Ileus and Gut Permeability

Patients with acute pancreatitis often suffer from severe intestinal motility disturbances which render them prone to bacterial translocation into the pancreatic necrosis due to bacterial overgrowth and increased gut permeability, which is then burdened with an increase in mortality (Fig. 18.2). The mechanisms of impaired intestinal motility are largely unknown [103]. Studies on mice fed a CDE (choline-deficient, ethionine-supplemented) diet revealed that acute necrotizing pancreatitis inhibits gastric emptying and intestinal transit *in vivo*. The global reduction in jejunal contractility is explained by the disruption of the intestinal motor function at the postreceptor level, which plays an important role in the development of an intestinal ileus during acute pancreatitis [104–107]. This notion suggests why conventional pharmacologic gut stimulation (e.g., by parasympathomimetics) in daily clinical routine has a rather disappointing effect. However, clinical trials systematically investigating the impact of parasympathomimetics in acute pancreatitis are currently not available.

Clinical as well as experimental studies have shown that the intestinal tract becomes more permeable for macromolecules during the course of acute pancreatitis and this permeability increase correlates with greater bacterial translocation, greater severity, and an increased rate of infected necrosis [106,107]. The early changes in intestinal permeability have been associated with corresponding levels of systemic endotoxin exposure [107]. The pathogenesis of gut barrier failure can be attributed to local (instestinal) factors, namely mucosal ischemia, disruption of mucosal epithelial integrity, reperfusion injury, disruption of intestinal bacterial ecology, and impaired mucosal immunity. On the cellular level, human and animal studies have attributed these changes to alterations in epithelial tight and adherent junctions,

(a)



(b)

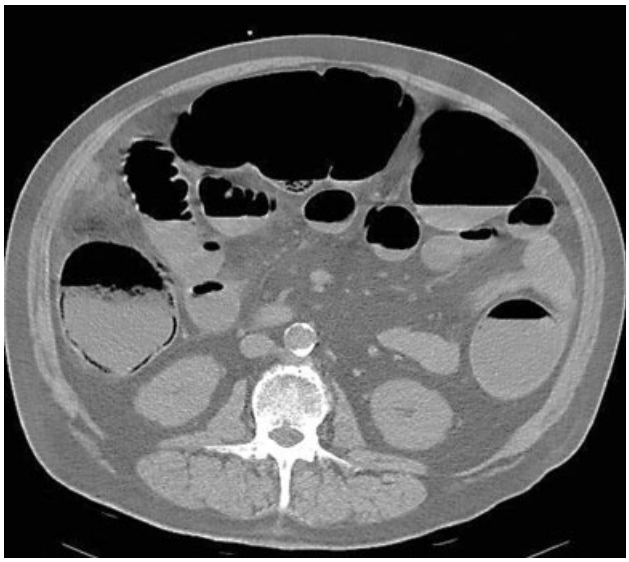


**Figure 18.2** Paralytic ileus in severe acute pancreatitis.

including protein classes such as claudins [108,109], occludins [110], and myosins [111,112], all of which can represent susceptibility factors for pancreatitis per se, as well as for bacterial translocation during pancreatitis. Furthermore, systemic factors, such as impaired systemic immunity, endotoxemia, cytokines and chemokines, malnutrition, and/or parenteral nutrition, have been implicated in impaired gut permeability. Some of the factors affecting gut barrier failure mentioned earlier can be effectively treated with early enteral nutrition or by immune-enhancing nutritional regimens [113,114]. Thoracic epidural analgesia for pain also augments ileal mucosal capillary perfusion and improves survival in severe acute pancreatitis [115].

## Pathogenesis of Coagulopathies

The systemic inflammatory reaction and the development of organ failure in acute pancreatitis share similarities with a complicated course of sepsis, major trauma, or burns [116,117]. As early as 1977 Ranson and coworkers noted abnormalities in coagulation factors during severe acute pancreatitis. They concluded from a prospective analysis of 35 patients in which they correlated amylase levels with respiratory, renal, and hepatic dysfunction that enzyme-related intravascular coagulation is involved in the pathogenesis of these coagulation complications during acute pancreatitis [118]. In systemic inflammation a rapid activation of coagulation may turn into a global or selective exhaustion of physiologic anticoagulant systems.

The interactions between coagulation and inflammatory pathways are essential for the pathogenesis of disseminated intravascular coagulation. For example, the proinflammatory cytokines TNF-α, IL-1, and IL-6 upregulate thrombin formation and downregulate physiologic antithrombotic defense mechanisms, especially the protein C pathway [119]. The protein C pathway is both a major physiologic anticoagulant system and a central link between inflammation and coagulation. The zymogen protein C is converted to activated protein C (APC) by thrombin bound to thrombomodulin on the endothelial surface [120]. This effect is enhanced by the endothelial PC receptor [121]. APC conveys its anticoagulant function mainly by proteolytic inactivation of coagulation-activated factor V and activated factor VIII. APC also exhibits distinct anti-inflammatory and antiapoptotic properties [122]. Although the underlying mechanism is incompletely understood, recombinant APC decreased the levels of IL-6 and D-dimer and reduced mortality in severe sepsis patients. Investigating levels of APC, protein C, and D-dimer in 31 patients with severe acute pancreatitis showed that protein C deficiency and decreased APC generation contributed to a compromised anticoagulant and anti-inflammatory defense, which subsequently aggravated multiorgan failure [123]. Clinical trials evaluating treatment with protein C are warranted in severe acute pancreatitis.

In addition to the therapeutic impact of restoring coagulation in severe acute pancreatitis a recent clinical study has shown that signs of disseminated intravascular coagulation are also of high prognostic value. The aggravated

coagulation parameters predict a fatal outcome in patients with acute pancreatitis. An antithrombin III level <69% was the most accurate marker for poor outcome of acute pancreatitis at admission [124,125]. Experimentally, the substitution of antithrombin III has long been shown to have a beneficial effect on pancreatitis severity [126].

## Electrocardiographic Abnormalities in Acute Pancreatitis

Acute pancreatitis has been reported to be associated with electrocardiographic abnormalities including arrhythmias, bradycardia, T-wave changes, intraventicular conduction disturbances, and ST-segment elevation termed "pseudoinfarction" (Fig. 18.3). The clinical relevance and causes of such electric abnormalities are poorly understood. However, experimental studies performed on a murine model of acute pancreatitis have reported ultrastructural disturbances including interstitial edema and cardiomyocyte hypoxia, myofiber overcontractility, intracellular edema between cardiomyocytes, and cardiomyocyte hypertrophy with collagenization of myocardial stroma [127]. Albrecht and Laws [128] proposed a direct cardiotoxic effect of proteolytic pancreatic enzymes as a cause of ST-segment elevation and myocardium-specific enzyme increase (particularly phosphokinase MB fraction).

Other mechanisms that have been proposed to explain electrocardiographic abnormalities appearing during acute pancreatitis are those associated with metabolic disturbances, hemodynamic instability, vasopressor drug use, pericarditis, myocarditis, exacerbation of underlying cardiac disease, coagulopathy, and coronary artery spasm [128–130].

Patients with acute pancreatitis have a high risk of developing metabolic abnormalities. The consequences of low or high serum electrolyte levels on cardiac electric activity include changes in the T-wave morphology, bundle branch blocks, arrhythmias, QT-internal shortening or prolongation, asystoly, prominent U-wave, ST-segment depression or elevation, and ventricular fibrillation [131–134]. Recently two prospective studies have reported abnormalities on electrocardiogram (ECG) and correlated these changes to the severity of acute pancreatitis. The study by Rubio-Tapia concluded that 55% (28 patients) of patients displayed abnormalities on ECG but most changes are transient and are related to electrolyte

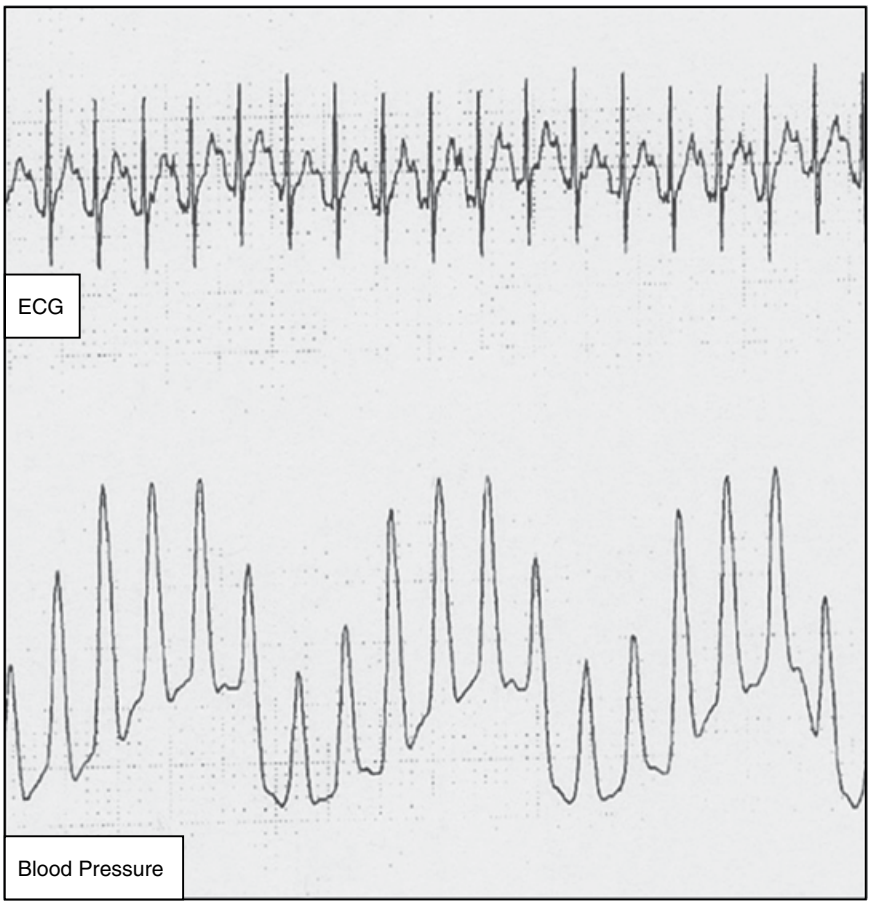



**Figure 18.3** ECG changes in severe hypovolemia and hypokalemia.

alterations [135]. In contrast, the study by Stimac and coworkers investigating 303 patients observed significantly different results for heart rate, PQ interval, and ST elevation when mild pancreatitis was compared to severe pancreatitis. They explained an increase in heart rate and shortened PQ interval as a result of increased sympathetic activity [136].

## The Role of Hypocalcemia and Hypomagnesemia

Hypocalcemia is a frequent finding in patients with severe acute pancreatitis and has been implicated to be of prognostic value by Ranson and Imrie, who included it in their respective severity scores of acute pancreatitis [137–139]. Calcium levels below 2 mmol/L are considered to be a poor prognostic sign. Several pathogenetic mechanisms contribute to the development of hypocalcemia and need to be considered in evaluating hypocalcemia: (i) Serum calcium levels reflect only part of the physiologically active ionized calcium. More than half of the circulating calcium is bound to albumin and serum calcium levels need to be corrected for serum albumin levels. During acute pancreatitis, albumin is lost in the third space and therefore serum calcium levels decrease. When calcium levels are corrected for albumin, the majority of patients display normocalcemia, which explains the absent symptoms of hypocalcemia, such as arrhythmias and tetany [140–142].

(ii) In response to decreased serum calcium levels circulating parathyroid hormone levels (PTH) are increased. This subsequently leads to calcium mobilization from bone, and calcium reabsorption in the kidneys is increased. In a prospective study by McKay PTH levels were determined to be invariably elevated in response to hypocalcemia in acute pancreatitis but significantly increased concentrations were found in patients with a complicated course of the disease [143]. Inadequate mobilization of calcium from bone indicating end-organ failure could offer an alternative explanation for hypocalcemia. This hypothesis was refuted, however, by Robertson et al. [144]. Patients suffering from acute pancreatitis were shown to react with an adequate rise in serum calcium levels and urinary cyclic adenosine monophosphate upon infusion of exogenous PTH. These findings had been previously substantiated by data from animal experiments [144].

Hypomagnesemia, together with hypocalcemia, can inhibit PTH secretion as well as peripheral actions of PTH. Ryzen and Rude determined intracellular magnesium levels in patients with acute pancreatitis. They concluded that patients with acute pancreatitis and hypocalcemia commonly also show intracellular magnesium deficiency despite normal serum magnesium concentrations. Magnesium deficiency could therefore play a significant role in the pathogenesis of hypocalcemia in acute pancreatitis [145]. Magnesium is known to be a cofactor for multiple enzymatic reactions, including zymogen activation *in vitro*. The bivalent cation $Mg^{2+}$ counteracts intracellular calcium signaling and thereby antagonizes the deleterious effects of high and sustained intracellular $Ca^{2+}$ levels on premature zymogen activation [146,147]. In experimental pancreatitis models oral $Mg^{2+}$ given as a food supplement had significant beneficial effects on the course of the disease [148]. Currently two multicenter, multinational, randomized, placebo controlled phase II trials investigating the efficacy of magnesium for either recurrent idiopathic pancreatitis or the prevention of ERCP-induced pancreatitis are being conducted [149].

(iii) The role of increased free fatty acids (FFAs) in the pathogenesis of hypocalcemia in acute pancreatitis has not been clearly elucidated and different pathophysiologic mechanisms have been proposed. Circulating lipase and phospholipase released from necrotic pancreatic acinar cells may cleave triglycerides and thereby lead to elevated serum FFAs. Warshaw et al. determined the effect of FFAs on serum calcium levels in an animal model. Their findings suggested that (i) changes in the concentration of FFA occur spontaneously but may have an impact on calcium levels, (ii) the observed depression of calcium may be due to intravascular sequestration of calcium by FFA-albumin, but increased flux of circulating calcium–FFA complexes into extravascular and intravascular sites may also be important, (iii) the markedly increased FFA concentration in some patients with acute pancreatitis may contribute significantly to hypocalcemia and calcium flux in these patients [150].

Recent experimental work has demonstrated that fatty acid ethyl esters (FAEEs), although less damaging than their parent fatty acids [151], are directly involved in intracellular calcium toxicity via the inositol trisphosphate ($IP_3$) receptors and ATP depletion [152]. As shown for a direct interference with pathologic calcium signaling via magnesium substitution [148,149] this $IP_3$-dependent mechanism offers itself to therapeutic intervention—or at least prevention—by caffeine [153]. This may be the reason why coffee consumption has recently been identified as a protective epidemiologic factor for pancreatitis [154].

To what extent fat necrosis outside the pancreas and the lipolytic generation of unsaturated fatty acids contribute to the onset and severity of pancreatitis is still incompletely understood and a very active research field [155].

In conclusion, hypocalcemia is a frequent finding in severe acute pancreatitis. Hypocalcemias in acute pancreatitis frequently turn out to be normocalcemias if corrected for serum albumin. Experimental studies have proven an important effect of high intracellular calcium concentrations and, more importantly, a beneficial effect of antagonizing calcium with magnesium on premature zymogen activation and the severity of pancreatitis. The clinical benefit of a magnesium substitution still needs to be shown in clinical trials.

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# 19

# Histopathology of Acute Pancreatitis

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## Introduction

In this chapter, the histopathology of acute pancreatitis is reviewed and the various patterns of tissue damage that have been described so far are related to the known etiologic factors and the discussed pathogenetic mechanisms. Finally, an attempt is made to correlate the histopathologic findings with the clinical and radiologic criteria of the 2012 Atlanta Classification of Acute Pancreatitis [1] that revised the 1992 Atlanta classification [2].

## Definition

Acute pancreatitis is histologically a necroinflammatory tissue reaction to functional and/or structural acinar cell damage and rarely duct cell necrosis, usually caused by noninfectious factors and only rarely by infectious agents [3]. It can be separated into a mild form called acute interstitial edematous pancreatitis affecting 90–95% of patients, and a severe form called acute necrotizing pancreatitis affecting only 5–10% of patients. The mild form of acute pancreatitis is often associated with gallstone disease, whereas the severe form is usually linked to alcoholism.

## Histopathologic Patterns of Tissue Necrosis

Central to the development of acute pancreatitis is the initial damage to exocrine cells of the pancreas. Histologically this damage is recognized as tissue necrosis, which is followed by an inflammatory reaction. The observed patterns of necrosis can be classified into three types (Fig. 19.1). Type 1 shows a necrotic process that initially affects the fatty tissue in the interstitial spaces within the pancreas and in the peripancreatic area; in the second type, necrosis affects the duct epithelium; and in the third type it is the acinar cell that shows necrosis. Whereas the first type is frequent, the second and third types are rare [4].

## Acute Pancreatitis with Type 1 Necrosis Pattern

This necrosis pattern characterizes the type of acute pancreatitis that is most common. The severity of its changes can be correlated to either interstitial acute pancreatitis or necrotizing acute pancreatitis [1] (Table 19.1).

### Initial Phase

In interstitial acute pancreatitis the pancreas shows an edematous swelling, but may also look normal. In addition it displays tiny white disseminated spots of fatty tissue necrosis on its surface and also in the interlobular fatty tissue [5] (Fig. 19.2).

In necrotizing acute pancreatitis there are numerous large and confluent white areas of fat necrosis in the peripancreatic tissue (Fig. 19.3). In addition, the pancreas shows parenchymal necrosis, although it is usually less extensive than the peripancreatic necrosis and seems to depend in its extent on the amount of interlobular fatty tissue present in the individual pancreas. This means that in the pancreas of obese subjects necrosis may be more severe than that seen in normal weight individuals. Where fat necrosis involves blood vessels, especially

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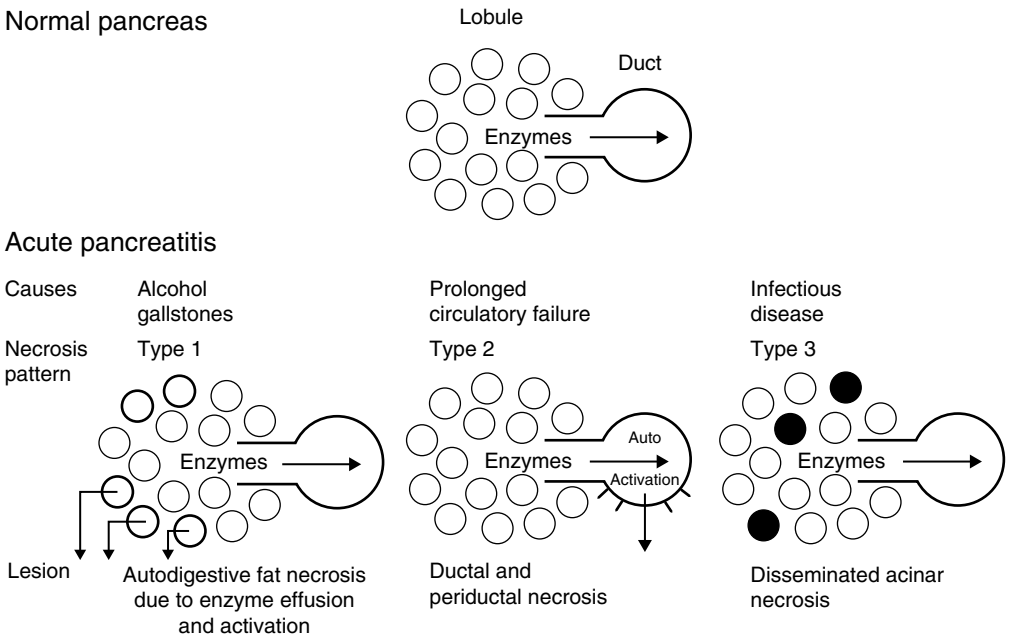


**Figure 19.1** Schematic presentation of three types of necrosis in the human pancreas related to their causative factors.

**Table 19.1** Correlation of the most important criteria of the Atlanta classification 2012 with the main histopathologic features of conventional acute pancreatitis.

| Type and severity | Complications | Histopathologic features |
|---|---|---|
| **Interstitial edematous pancreatitis** | | |
| Mild | No | Parenchymal edema with tiny fat necroses |
| Moderately severe | Transient organ failure and/or acute peripancreatic fluid collection (APFC) | Peripancreatic fat necrosis |
| | Pseudocyst (derived from unresolved APFC) | Pseudocyst (without debris) |
| **Necrotizing pancreatitis** | | |
| Severe | Persistent organ failure, systemic complications, acute necrotic collection (ANC) | Pancreatic and peripancreatic parenchymal and/or fat necrosis with or without hemorrhage |
| | Walled-off necrosis (derived from ANC) | Pancreatic and peripancreatic necrosis, well demarcated by granulation tissue and fibrosis, corresponding to pseudocyst with associated necrosis |

veins, the necrosis becomes hemorrhagic, because of vessel wall damage with subsequent thrombosis or rupture. Arteries, because of their thick walls, are more resistant to necrosis, but if damaged they may develop thromboses, which can result in panlobular ischemic necrosis. Another important result of expanding fat necrosis is the destruction and rupture of a duct, leading to duct leakage and effusion of secretions into the adjacent necrotic area. Non-necrotic acinar cells at the margin of fat necrosis appear well preserved despite their proximity to necrosis. As the only change they may show widened lumina, so-called tubular complexes, which may be filled with PAS-positive secretions. Islets are affected only in lobules that are largely or entirely necrotic. In the course of the disease, the necrotic areas are demarcated by a collar of foamy macrophages intermingled with granulocytes. These granulocytes later disappear, leaving macrophages and myofibroblasts to build up a wall of granulation tissue separating the necrosis from intact tissue.

## Outcome

In interstitial acute pancreatitis, the edema, which is probably rich in pancreatic enzymes, is usually resolved by macrophages within a few days and does not result in

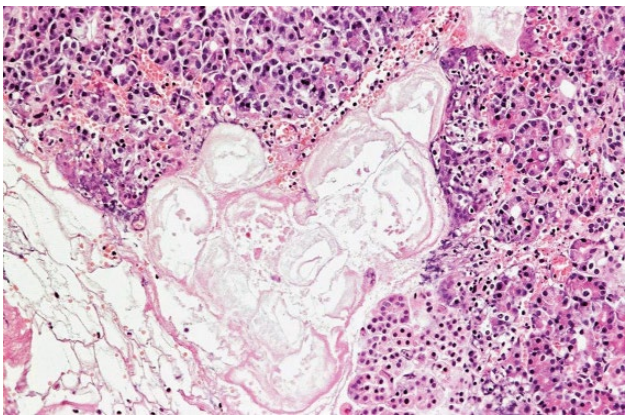

**Figure 19.2** Interstitial type of acute pancreatitis. Tiny necrosis of peripancreatic fatty tissue. Note the preservation of the adjacent acinar cells.

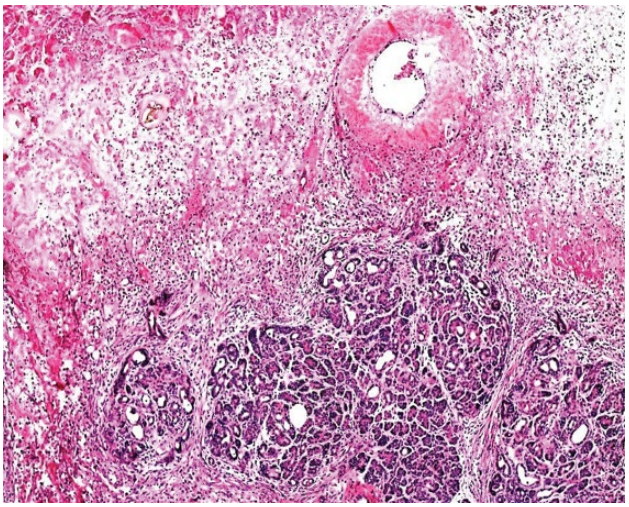

**Figure 19.3** Necrotizing type of acute pancreatitis. Advanced confluent peripancreatic fat necrosis (top) extending into the pancreas and involving a duct (top).

secondary changes. The same happens to the tiny foci of fat necrosis. The diameters of these usually do not exceed 10 mm, so they are barely detectable by imaging. Larger liquefied foci of peripancreatic fat necrosis, which probably correspond to the radiologic lesion called "acute peripancreatic fluid collection," are rare. If such a rare lesion does not resolve and gets encapsulated by granulation tissue (see later), it may become a pseudocyst.

In necrotizing hemorrhagic pancreatitis, the large fat necroses liquefy and, if not exceeding 2–5 cm in diameter, are slowly reabsorbed by macrophages. Larger necrotic areas (usually >5 cm), particularly when encompassing pancreatic parenchyma, may not resolve spontaneously and their liquefied and solid content is then lined by macrophages, which, together with some granulocytes and lymphocytes, form a thin layer of

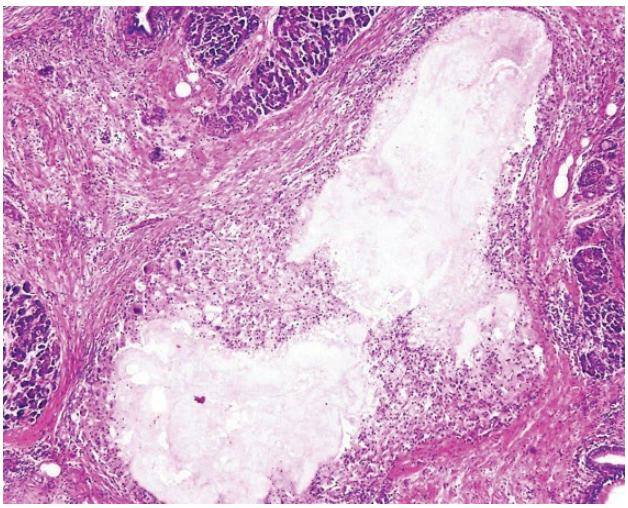

**Figure 19.4** Necrotizing type of acute pancreatitis 6 weeks after onset. Development of cell-rich interlobular fibrosis induced by the resorption of a fat necrosis (center). H&E, ×125.

granulation tissue within 10–20 days of the onset of the disease. This change may correspond with an "acute necrotic collection" as described by the radiologist [6]. Often the macrophages in the granulation tissue contain hemosiderin, since the content of these necrotic areas may be hemorrhagic. After 20–30 days, the granulation tissue starts to be replaced by fibrosis containing collagen types 1 and 3 and a well-defined wall is built up. If the demarcation is fully developed the change is radiologically called "walled-off necrosis," which corresponds to the older term "pseudocyst associated with necrosis" (Table 19.1). Most of these advanced lesions are found outside the pancreas, particularly around the head of the pancreas [7,8]. The fact that walled-off necrosis/pseudocysts contain amylase suggests communications with the pancreatic duct system. This may be particularly the case in those pseudocysts which, in time, increase in size and by growing compress or erode such structures as the bile duct, duodenum, stomach, vessels, or peritoneum. The involvement of vessels may lead to sudden hemorrhage.

Fat and/or parenchymal necrosis may become infected with (mostly gut-derived) bacteria or fungi. This usually takes place during the period (days 4–20) when the demarcation of the liquefied necrotic area still consists of only a small rim of granulation tissue.

The resolution of necrotic tissue within the pancreas is usually followed by the development of interlobular fibrosis replacing the necrotic tissue (Fig. 19.4) [9,10]. If this necrosis–fibrosis sequence [11] takes place repeatedly because of recurrent attacks of necrotizing acute pancreatitis and also involves the large interlobular ducts and the main duct, relapsing acute pancreatitis may evolve into chronic pancreatitis [12,13].

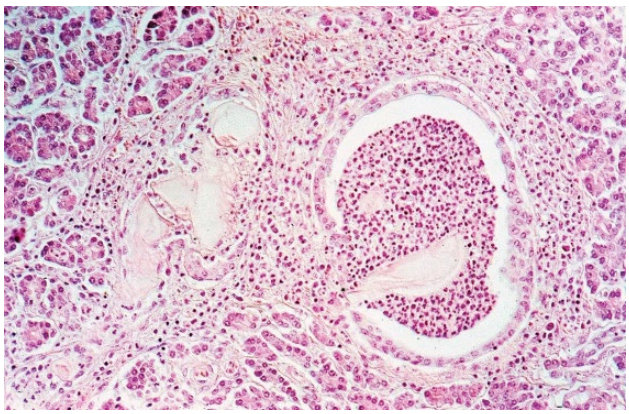

Figure 19.5 Acute pancreatitis with type 2 necrosis pattern. Interlobular duct containg secretions and granulocytes. Rupture of the duct epithelium with granulocytes infiltrating the interstitial space. H&E, ×120.

## Acute Pancreatitis with Type 2 Necrosis Pattern

### Initial Phase

Disseminated ductal necrosis of small to medium-sized interlobular ducts, which contain granulocytes mixed with precipitations of eosinophilic secretions, is the key lesion of type 2 necrosis. It results in duct rupture and extension of the necrosis into the periductal area (Fig. 19.5). This may be a sollitary change, but is also observed in association with foci of fat necrosis [14–16]. The ensuing acute pancreatitis seems to be usually mild.

### Outcome

In acute pancreatitis with type 2 necrosis the outcome is largely unknown because the patients in whom this necrosis pattern has been observed and described all died from prolonged circulatory failure that was usually not caused by acute pancreatitis, but by various extrapancreatic diseases such as hepatic failure. Our only observation of type 2 necrosis so far, made in a pancreatic resection specimen from a patient with hereditary pancreatitis [16], could suggest that in this setting the initial necrosis of the duct-lining cells, followed by an inflammatory involvement of the surrounding interstitial tissue, may result in structural changes such as irregular dilatations and periductal scarring of the affected pancreatic ducts.

## Acute Pancreatitis with Type 3 Necrosis Pattern

### Initial Phase

Scattered intralobular foci of acinar cell necrosis are the key lesions of type 3 necrosis (Fig. 19.6). It is accompanied by an inflammatory infiltrate consisting of neutrophil granulocytes and single macrophages. Fat or ductal necrosis is notably absent. It appears that these changes are indicative of a pancreatitis caused by an infection.

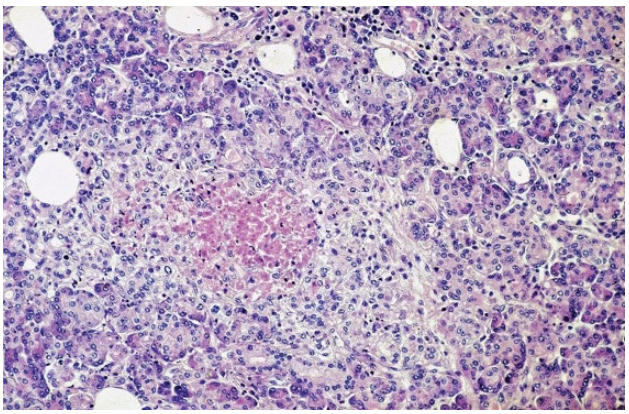

Figure 19.6 Acute pancreatitis with type 3 necrosis pattern. Focus of acinar cell necrosis within a lobule.

### Outcome

In acute pancreatitis with type 3 necrosis the outcome seems to be favorable in most cases. It is noteworthy that in the cases reported so far there was usually only mild pancreatitis [17].

## Histopathology Related to Etiologic Factors and Pathophysiologic Mechanisms

Acute pancreatitis with type 1 necrosis pattern is most frequently associated with alcohol abuse and gallstone disease. The only difference between the two etiologic factors regarding the resulting morphologic changes seems to be the disease severity, since biliary pancreatitis usually follows a mild course as compatible with interstitial pancreatitis, whereas alcoholic pancreatitis is a severe necrotizing disease. Rare causative factors are metabolic or drug-associated processes, and familial hereditary or acute hypoxia-related conditions.

Via as yet unidentified or hypothetical mechanisms these factors cause a limited or extensive sudden release of digestive enzymes from the acinar cells into the interstitial tissue, a release that is combined with their intrapancreatic activation [2]. The pathophysiology of this mechanism concentrates on assumed functional acinar cell damage, meaning a complex disturbance of acinar cell function, culminating in deranged intracellular compartmentalization and uncontrolled liberation of enzymes. These alterations could lead to intracellular enzyme activation by lysosomal hydrolases [18] and/or an abrupt effusion of enzymes into the interstitial space [19], resulting in fat necrosis as the first visible histologic

tissue damage. This necrosis is probably caused by lipase (one of the few pancreatic enzymes that do not require activation) [20,21]. Whether fat necrosis depends on the action of lipase alone or the combined action of lipase plus other enzymes, such as phospholipase A2 and trypsin, is not known, but it seems that proenzymes become activated during this process and may help to destroy interstitial tissues and finally also acini and ducts. Since these changes appear to occur predominantly in the lobule periphery where the cells are most remote from the arteries supplying the lobules, it is possible that the effects of the different etiologic factors might be mediated by microcirculatory changes.

Another pathophysiologic theory related to type 1 necrosis, which rests on the frequent association of gallstone disease with pancreatitis, is the duct obstruction–bile reflux theory (based on Opie's common channel theory) [22]. It postulates that temporary obstruction of the common bile duct and the main pancreatic duct by a gallstone (or tumor tissue or inspissated secretions as in cystic fibrosis) [23] causes increased intraductal pressure and/or ampullary incontinence, with duodenopancreatic and bile reflux. This in turn activates pancreatic proenzymes, which leak from small ducts into the interstitial space. However, despite the obvious clinical association between gallstone migration and pancreatitis, definite functional and histologic proof of the duct-obstruction pathogenesis is, thus far, lacking in human acute pancreatitis.

Acute pancreatitis showing type 2 necrosis, which focuses initially on the pancreatic duct epithelium, is associated with prolonged circulatory failure. In this case the tissue hypoxia in the pancreas seems to injure especially the medium-sized interlobular ducts and cause its necrosis. In addition, there could be an autoactivation of trypsinogen within the duct lumen, as the ducts in type 2 necrosis are filled with dense pancreatic secretions and neutrophil granulocytes [14]. This could be due to a stasis of pancreatic juice, which became viscous and sluggish because of a general slowdown of secretory processes in the exocrine pancreas as a result of a severe circulatory failure. Since we saw a comparable picture in a case of familial pancreatitis, it may be that similar duct damage as in prolonged circulatory failure occurs due to mutational changes to the trypsinogen molecule, allowing its uncontrolled activation.

In acute pancreatitis with type 3 necrosis, which focuses on acinar cell destruction without any significant autodigestive interstitial necrosis, there seems to be a direct cytotoxic damage to the acinar cells by microorganism such as mumps virus or bacterial agents.

## Unsolved Questions

There are a number of unsolved questions in acute pancreatitis. The most important one concerns its pathogenesis and pathophysiology. The concepts currently discussed usually refer entirely or to some extent to experimental pancreatitis models [24]. Although these models have markedly improved our knowledge of pathogenetic mechanisms in acute pancreatitis, it has to be emphasized that none of them are fully comparable to what is seen in humans.

Another question that remains to be solved relates to the severity of acute pancreatitis. It is not yet known which factors govern the mechanisms that determine a mild or severe course of the disease.

A third question is how the criteria that define the Atlanta 2012 classification [1] and are solely based on radiologic [6] and clinical features relate to the macroscopic and especially microscopic findings in acute pancreatitis. Table 19.1 attempts to summarize and correlate the most important criteria of the Atlanta 2012 classification with the histopathologic changes that can be observed in conventional acute pancreatitis.

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# 20

# Clinical Classification Systems of Acute Pancreatitis

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## Introduction

The accurate classification of acute pancreatitis severity is important for clinical and research reasons because it will "improve communication and advance our understanding of the disease and its management" [1]. When specific treatments become available for clinical trial in acute pancreatitis "an inclusive clinical classification system will assume increasing importance" [2]. Systems for classifying severity will continue to evolve with new scientific knowledge and for this reason they are best considered "working" classifications. The aim of this chapter is to outline the reasons for classifying severity, review the two new systems and studies that compare them, and identify areas for further improvements.

## Reasons for Classifying the Severity of Acute Pancreatitis

Classification systems are required in both clinical and research settings, and there are different reasons within each setting (Table 20.1). Many of these reasons are best met by prediction, rather than by classification, and it is common for these to be confused [3–5]. When the ultimate disease severity needs to be anticipated, prediction of severity is required. When the severity is needed at a particular time point, classification of severity is required. In this way prediction is about the future and classification is about the present and the past. Prediction is usually required early in the disease course, whereas classification is required at any time during the disease course.

## New Classification Systems

The first classification system for acute pancreatitis was published in 1983 [6], and with the later clinically based classification system from the Atlanta symposium [7], embedded the binary concept of mild and severe disease. There has never been difficulty in identifying patients with uncomplicated course of disease but the severe category encompasses subgroups with distinct outcomes, and this category is not sufficiently granular for clinical and research purposes.

Two new systems for classifying the severity of acute pancreatitis have recently been published (Table 20.2): the "determinant-based classification" (DBC) in 2012 with four categories of severity [8] and the "revised Atlanta classification" (RAC) in 2013 with three grades of severity [9].

There are a number of differences between the two classifications (Table 20.3). Having different classification systems has raised questions about which is more valid, which has higher utility, and which should be used. These differences should not raise concern as they are to be expected when the systems were derived by quite different methodologies [10]. And although the two classifications have been considered to have "few differences" [11] there are some worth noting.

The RAC definition of the "moderately severe" grade was added at the end of the 7-year process, in the second half of 2012. Prior to that, at least five "provisional" versions were published in peer-reviewed literature and all them contained only two grades of severity. The definition of the moderately severe grade includes "exacerbations of comorbid disease" and this is not considered to be a determinant of severity and is not included in the DBC. Patients with infected local complications (and

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 20.1** The reasons for classification systems in acute pancreatitis.

| | |
|---|---|
| Reasons related to clinical decision making | Triage of patients regarding initial treatment intensity[a] |
| | Transfer of patients to specialist unit or intensive care[a] |
| | Trajectory of patients clinical course |
| | Treatment early in disease course (e.g., enteral nutrition)[a] |
| Reasons related to research decision making | Audit of outcome |
| | Allocation of patients to trial arm[a] |
| | Analysis of interventions |

[a] Denotes reason that are more appropriate for prediction than classification systems.

**Table 20.2** New classifications for the severity of acute pancreatitis.

| | |
|---|---|
| **Determinant-based classification [8]** | |
| Mild | No (peri)pancreatic necrosis |
| | No organ failure |
| Moderate | Sterile (peri)pancreatic necrosis and/or transient organ failure |
| Severe | Infected (peri)pancreatic necrosis or persistent organ failure |
| Critical | Infected (peri)pancreatic necrosis and persistent organ failure |
| **Revised Atlanta classification [9]** | |
| Mild | No organ failure and no local or systemic complications |
| Moderately | Severe transient organ failure and/or local or systemic complications or exacerbations of preexisting comorbidities |
| Severe | Persistent organ failure (single or multiple) |

without persistent organ failure) are also defined as having "moderately severe" grade in the RAC. The explanation given for this was that "infected necrosis without persistent organ failure […] has a lesser mortality rate than infected necrosis with persistent organ failure." These patients have been shown to have a similar outcome to those with "severe" grade acute pancreatitis [12] which is consistent with the meta-analysis of 14 studies which demonstrated that infected (peri)pancreatic necrosis and persistent organ failure are independent and virtually equivalent determinants of mortality [13]. On this basis the DBC includes infected (peri)pancreatic complications in the "severe" category and the "critical" category is defined when it is present with persistent organ. The utility of the critical category has been questioned because of its relatively infrequency in some series [4], but in other series it has a significantly higher mortality and is endorsed [14–16].

**Table 20.3** Key differences between the two classification systems.

| | Severity classification systems | |
|---|---|---|
| **Criteria** | **DBC category** | **RAC grade** |
| Exacerbation of comorbid disease | Not included | Moderately severe |
| Infected (peri)pancreatic necrosis without persistent organ failure | Severe | Moderately severe |
| Infected (peri)pancreatic necrosis with persistent organ failure | Critical | Severe |

DBC, determinant-based classification; RAC, revised Atlanta classification.

## Validation and Comparison of Classification Systems

A number of studies have compared the validity of the two new classification systems (Table 20.4). Most of the studies have been from single tertiary centers and subject to selection bias. Only two of the 10 comparative studies were prospective. A review of the key findings indicate that there is little difference between the two classification systems, being considered "equivalent" or "comparable and complementary" [3,4]. All the 10 studies used an unsophisticated approach to the comparison of the two classifications and none employed the "gold standard" approach to determining the comparative usefulness of two or more classification systems, which is a calculation of the net reclassification improvement [17]. At present, the decision about which classification system to use has to be based on a combination of factors including the evidential base, method of development, the setting, validity, and ease of use. If a unified classification system is to be developed then it needs to be recognized that both classification systems have limitations and there is room for improvement.

## Future of Classification Systems

The differences in classification systems represent an opportunity for further improvement, and some research priorities have been recently published [18,19]. There is the need to determine whether classification systems should be matched to the setting. In a district or secondary center, the incidence of severe and critical acute pancreatitis is low and the fundamental clinical decision is whether the patient needs to be transferred to a tertiary center or not. In this setting a binary classification system might well suffice; that is, severe patients are transferred.

**Table 20.4** Studies that have compared the determinant-based classification (DBC) and revised Atlanta classification (RAC) systems from the same dataset.

| First author (year) | Ref | Setting | Study design | Key findings |
|---|---|---|---|---|
| Nawaz (2013) | 3 | Tertiary (SC) Pittsburgh | Retrospective (prospective database) | DBC and RAC comparable for predicting ICU admission, ICU length of stay, and mortality. The RAC was better at predicting hospital stay and DBC better for predicting the need for intervention |
| Acevedo-Piedra (2014) | 12 | Tertiary (SC) Spain | Retrospective (prospective database) | No significant differences in the distribution and outcomes between the two classifications, but very low incidence of severe and critical categories |
| Chen (2015) | 20 | Tertiary (SC) Nanjing | Retrospective (prospective database) | RAC and DBC comparable in relation to long-term clinical prognosis, major complications, and clinical interventions. Critical category very high risk and distinct from severe category in DBC |
| Mircea (2015) | 21 | Tertiary (SC) Bucharest | Retrospective | Similar for clinical outcomes, although RAC has slight advantage for hospital length of stay and DBC for ICU admission and length of stay. DBC easier to use |
| Xu (2015) | 22 | Tertiary (SC) Lanzhou | Retrospective | Similar distribution and outcomes. Recommended combining RAC and DBC |
| Guo (2105) | 23 | Tertiary (SC) Chengdu | Prospective | No significant difference between RAC and DBC. Mortality similar and distribution of severity marginally different |
| Kadiyala (2016) | 4 | Tertiary (SC) Boston | Retrospective (prospective database) | The RAC and DBC were essentially equivalent in predicting mortality, need for admission to the ICU, ICU length of stay, and hospital length of stay. Paucity of critical category, limited utility. Neither classification accounts for multisystem persistent organ failure, the strongest predictor of mortality |
| Bansal (2016) | 24 | Tertiary (SC) Birmingham | Retrospective (prospective database) | The RAC and DBC perform equally well. DBC critical category associated with doubled mortality risk, ICU stay and need for drainage or surgery greater than RAC, with definite implications for prognosis |
| Fernandes (2016) | 25 | Tertiary (SC) Portugal | Retrospective | RAC and DBC were similar for outcomes |
| Zubia-Olaskaoaga (2016) | 16 | Tertiary (MC) Spain etc. | Prospective observational | Proposed a modified DBC for only ICU patients. Superior to DBC and RAC for mortality. Similar to DBC for morbidity and superior to RAC. Severe DBC category separated into two groups: transient organ failure with infected local complications and persistent organ failure and no infected local complications |

ICU, intensive care unit.

In a tertiary center the requirements are different and there is a need for more than two categories of severity. With several options for intervention and intensive care, the need to accurately allocate patients to research arms and the intention to tailor treatments to individual patients, it is desirable to have distinct and homogeneous patient subgroups to study and treat. For instance, if there were a new treatment for organ failure to be tested it would confound interpretation of outcomes if all patients were included with organ failure, even if this contained those who would respond promptly (e.g., transient organ failure), those who might not respond (e.g., persistent organ failure), and those who cannot respond (e.g., no organ failure). Further, if the purpose of a treatment were to reverse established organ failure it would be necessary to exclude patients with transient organ failure. If the purpose were to prevent the development of persistent organ failure it would be necessary to include patients with transient organ failure. These examples indicate that the binary classification is probably sufficient for those in primary and secondary care settings, whereas more categories are required in the tertiary setting. Tailoring the severity classification needs to be tested, particularly in the secondary setting.

**Table 20.5** Modified determinant-based classification (DBC) system for patients admitted to intensive care with organ failure [16].

| | Parameters | | | | |
|---|---|---|---|---|---|
| Group | Organ failure | Infected necrosis | Mortality | Intensive care LOS | Intervention |
| 1 | TOF | No | 2% | Short | – |
| 2 | TOF | Yes | 6.6% | Long | + |
| 3 | POF | No | 41% | Short | – |
| 4 | POF | Yes | 59% | Long | + |

TOF, transient organ failure; POF, persistent organ failure; LOS, length of stay.

The exclusion of any local complications from the RAC "severe" grade requires rethinking (Table 20.2). Clinicians know that the development of infection is associated with increasing severity and the likely need for intervention. It has been shown that patients with infected necrosis, in the absence of persistent organ failure, can behave like severe disease [12,14,26]. Although considered to limit the utility of the DBC system, infection of local complications can be diagnosed in the vast majority of patients on the basis of a deteriorating patient clinical trajectory, a rise in C-reactive protein, and further cross-sectional imaging [27].

A modified DBC has been proposed for patients with organ failure admitted to intensive care [16]. In the only multicenter prospective study we find endorsement for the DBC and the critical category and the finding that the "severe" category contains two further subgroups with distinct outcomes. With mild patients excluded, four groups were defined (Table 20.5). The DBC severe category does not distinguish groups 2 and 3 and yet the mortality, need for intervention and length of intensive care stay is very different in this study. They also suggested including other local complications that impacted outcome, including abdominal hemorrhage and intestinal perforation. Other groups have also recognized subgroups within the DBC "severity" category [23].

Neither classification system formally accounts for patients with multiple organ failure in the first week of presentation [4,12,26,27] though it is noted that these patients almost certainly have persistent organ failure as well. This is one of the most challenging subgroups of patients with a high mortality risk [28–30] and this suggests that the timing of organ failure onset might need to be included in a new classification system [31]. Understanding the importance of different aspects of organ dysfunction is also required [32], including the duration, number, combination, and sequence of the organs affected. Data on these dimensions may allow more accurate classification of patients with severe and critical acute pancreatitis.

## Conclusions

The classification of severity of acute pancreatitis is important for the clinical care of patients and for research purposes. Classification is not prediction and has a more limited role. Advances in the care of patients with acute pancreatitis will require improvements on current methods for classifying severity, although the two new classifications are an important step forward. There are several reasons for classifying severity and these differ between secondary or tertiary settings. Ultimately, improvements in classifying severity will come from the discovery of early biomarkers of severity that accurately reflect the key changes in the pancreas, peripancreatic tissues, and distant organs. For now we are reliant on clinical indicators related to the presence of organ failure and infected local complications. The two new classifications of severity both rely on these factors, but there are important differences, as discussed, which highlight areas where further research is needed in the search for improvements in severity classification.

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# 21

# Clinical Assessment and Biochemical Markers to Objectify Severity and Prognosis

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## Introduction

Among the inflammatory digestive disorders, acute pancreatitis continues to challenge physicians as it is one of the most difficult to predict in terms of clinical course and outcome. Ever since the first classification system of acute pancreatitis was established in Marseille in 1965 [1] the definition of "severe" disease has been linked to the occurrence of disease-specific complications with an increased risk of mortality [2,3]. Stratification of severity is required to target individual patients (i) for interventions against evolving complications or for referral to specialist centers and (ii) for comparing patients for scientific purposes or recruitment into clinical trials. The type and clinical relevance of a complication that render the course of acute pancreatitis as "severe" has been subject of continuous development and changes. New insights into the pathomechanism and natural course of acute pancreatitis, the development of laboratory variables, diagnostic imaging procedures, and new therapeutic approaches have strongly influenced definitions and classification systems over the past decades.

## Historical Perspectives: Approaches to Severity Assessment

Attempts to stratify severity and prognosis date back to the second half of the last century and have been substantially driven by major advances in new imaging procedures and laboratory tests. The development of serum amylase measurement in 1929 [4] was instrumental in providing a noninvasive diagnosis of acute pancreatitis and it soon became evident that in the majority of patients a mild course with uneventful recovery was the rule rather than the exception. Supported by the availability of intensive care treatment and more restrictive indications for surgical interventions in patients with clinically severe disease, interest in prognostic assessment gained considerable headway in the 1960s. Attempts to define objective criteria for assessing disease severity and prognosis were pioneered by John Ranson in New York [5] and Clement Imrie in Glasgow [6] in the 1970s and these found widespread application in the pancreatic community.

During the early 1980s intraoperative findings revealed local morphological features, such as presence and extent of necrosis [7,8] and infection of necrosis [9], that showed an excellent correlation with systemic severity and outcome. With the introduction of contrast-enhanced computed tomography (CE-CT) and percutaneous guided fine-needle-aspiration (FNA), nonoperative assessment of these complications became possible, which further substantiated the predominance of morphology-based severity stratification. Hence, imaging has become indispensable for assessment of severity in acute pancreatitis and an integral part of new classification systems [2,3] and treatment algorithms [10–12] alike.

After almost two decades of mainly morphology-based severity stratification, the role of systemic aspects in terms of onset, severity, and persistence of pancreatitis-related organ failure was recognized as central determinant of severity [13–21]. Currently, early and persisting multiorgan dysfunction syndrome (MODS) has been found to outweigh morphological factors such as necrosis and even infection of necrosis as far as nonsurvival is concerned [16].

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## Dynamics of Organ Failure

The prognostic role of early pancreatitis-associated organ failure was first recognized during the early 1970s. Objective measurement of pulmonary failure by arterial oxygen pressure or renal failure by serum creatinine had become available and had been integrated into prognostic multiparameter scoring systems according to Ranson [5] and Imrie [6]. However, it took another three decades before pancreatologists realized that the occurrence of a temporary single organ failure does not necessarily indicate a life-threatening disease. Specific aspects such as onset, severity, and persistence of organ failure have gained special attention only recently.

### Early Organ Failure

The role of "early" organ failure, defined as failure of one or more organ systems within the first 3 days after onset of acute pancreatitis/hospital admission, was first described by Isenmann et al. in 2001 [13]. The presence of "early" single or multiple organ failure leads to a significant increase of mortality up to 56%, irrespective whether necrosis is sterile or infected [13–15,17,18]. Early multiple organ failure represents the most important risk factor of death and even seems to outweigh local morphological complications such as extent or infection of necrosis [16].

### Persistent Organ Failure

The dynamics of organ failure in terms of response/resolution or nonresponse/persistence despite intensive care treatment has been identified as another major determinant of complications and death. In several prospective and retrospective studies in patients with severe acute pancreatitis, resolution of organ failure within the first week of the disease resulted in mortality rates close to zero, whereas mortality rates rose to 55% if organ failure persisted beyond the first week [18–21]. Moreover, organ failure nonresponsive to intensive care treatment closely correlates with the development of pancreatic infections and death [22,23].

Currently, there is little doubt that organ failure is one of the most important determinants of prognosis and mortality in acute pancreatitis. The revised Atlanta classification of 2012 [3] defined organ failure as a central criterion in differentiating three severity groups of acute pancreatitis (Table 21.1).

**Table 21.1** Definition of three grades of severity in acute pancreatitis according to the revised Atlanta classification 2012 [3].

| | |
|---|---|
| Mild acute pancreatitis | No organ failure |
| | No local or systemic complications |
| Moderately severe acute pancreatitis | Organ failure that resolves within 48 h (transient organ failure) and/or |
| | Local or systemic complications without persistent organ failure |
| Severe acute pancreatitis | Persistent organ failure >48 h |
| | Single organ failure |
| | Multiple organ failure |

### Abdominal Compartment Syndrome

Abdominal compartment syndrome (ACS), defined as intra-abdominal pressure >20 mmHg and newly developed organ failure [24], has been recognized as a determinant of prognosis within recent years. Abdominal hypertension (intra-abdominal pressure >15 mmHg) is observed in up to 75% of patients with severe acute pancreatitis [25,26] and ACS in about 25% [27]. Several studies revealed a strong association between intra-abdominal hypertension and the development of multiple organ dysfunction which occurred in more than 90% of patients [14,25]. Multiple organ dysfunction in turn carries excessively high mortality rates. Clinical evidence suggests that "early" multiple organ failure may be the result of undiagnosed ACS arising from the extensive inflammatory process in the retroperitoneum and an aggressive fluid resuscitation.

Beyond its prognostic role, the diagnosis of ACS has therapeutic implications that have been impressively shown in some studies [28,29].

## Multiparameter Scoring Systems

Analysis of the numerous objective clinical and biochemical variables thought to contribute to complications and death led to the development of the very first multiple parameter scores by John Ranson [5] and Clement Imrie [6]. Both systems still offer a track record and a good level of accuracy, but have the disadvantage that valid calculation is restricted to primary admissions within the first 48 hours of treatment, and recalculation beyond 48 hours is impossible. Since their original description, the requirements of researchers and clinicians have changed and are driven more than ever by the need for speed and simplicity. Supported by the recognition of organ failure as a major determinant of outcome, new scoring systems such as the Marshall score [30] and sequential organ failure assessment (SOFA) [31] score, which have all been developed and validated in the intensive care setting, have led to more flexible and practicable assessments of severity and prognosis in acute pancreatitis.

## The APACHE II Score

Dissatisfaction with the temporal applicability of the Ranson and Imrie systems led pancreatologists to search for more flexible scoring systems. One of the first multiple parameter scores applied in acute pancreatitis was the acute physiology and chronic health evaluation (APACHE) score in the early 1980s. A modification of the initial system by the Intensive Care Research Group from Washington, DC, USA [32] reduced the number of physiological variables from 35 to 11 and was termed APACHE II score [33]. Despite further modifications, this remains the most commonly used version. Larvin et al. from Leeds, UK published the first evaluation in 290 attacks of acute pancreatitis [34]. Initial APACHE II scores of 10 or more revealed a sensitivity of 63% and a specificity of 81% (positive predictive value [PPV] 46%, negative predictive value [NPV] 90%) in predicting "severe" disease. By 24 hours APACHE II scores >10 provided a sensitivity of 71% and a specificity of 91% (PPV 67%, NPV 93%), which further rose to a sensitivity of 75% and a specificity of 92% (PPV 71%, NPV 93%) at values >9 after 48 hours.

The APACHE II scores at 24 hours outperformed both the Ranson scores and Imrie scores at 48 hours. The results of the Leeds study have been confirmed exhaustively in the years since it was published [35–38]. The original Atlanta classification incorporates an APACHE II score of 8 or more as denoting a severe attack [2].

The advantage of the APACHE II system is clearly its flexibility and greater speed, and the possibility of recalculation at any time throughout the course of the disease for monitoring purposes. On the other hand, calculation of this score is complex and time consuming and carries the risk of miscalculations.

## Organ Failure-Related Scoring Systems

Organ failure-related intensive care scores, such as the Marshall score [30] and the SOFA score [31], have been applied in acute pancreatitis by a number of studies to assess organ failure or outcome [19,22,23,38–44]. These two scores belong to the newer generation of organ failure-related systems, which can describe the evolution of individual and multiple organ dysfunction over time. Both scoring systems rely on six major organ systems: pulmonary, cardiocirculatory, renal, hepatic, and neurologic function, as well as coagulation. Failure of each organ system is scored as absent or up to 4 points with escalating severity. The SOFA score is basically a further development of the Marshall score, with the inclusion of treatments such as ventilation and vasopressors, thus reflecting clinically relevant severity of organ failure [31].

### Marshall Score

The first detailed validation study of the Marshall score was published by Halonen et al. in a large series of Finnish patients with severe acute pancreatitis. This scoring system provided a sensitivity of 59% and a specificity of 91% in predicting mortality within 72 hours of hospital admission. Comparable results were obtained using the APACHE II system (sensitivity 65%, specificity 91%) [42]. In another retrospective study of the same group in 113 patients with severe acute pancreatitis admitted to the intensive care unit, both admission and peak Marshall scores were as accurate as SOFA scores in assessing the risk of hospital mortality. Unfortunately, no information about optimum cut-off levels, sensitivity, and specificity was provided [41]. A modification of the Marshall score, excluding hepatic and neurologic function, has been applied in two prospective studies [19,20] and the original score in a retrospective study [21] from the United Kingdom to quantify organ failure. The components for pulmonary, cardiocirculatory, and renal function match well with the definitions of the original Atlanta classification, but hepatic (bilirubin), neurologic (Glasgow Coma Scale), and coagulation parameters (platelet function) may further increase total scores, even if true organ failure is absent. The revised Atlanta classification of 2012 has adopted the Marshall components for pulmonary, cardiocirculatory, and renal function to define and quantify early pancreatitis-associated organ failure [3].

### SOFA Score

Two detailed evaluation studies in acute pancreatitis are available for the SOFA score. In a prospective international multicenter study, SOFA scores >4 were predictive of death with a sensitivity of 86% and a specificity of 79% (PPV 27%, NPV 98%) 48 hours after onset of symptoms [43]. Corresponding results have been reported by a Finnish study for admission scores in an intensive care unit (ICU) population-based cohort at a cut-off level >8 [41]. Interestingly, a separate analysis of the six different components revealed, that not all "organ failures" affect mortality to the same degree: only cardiocirculatory, renal, and hepatic failure were independently associated with hospital mortality [40,44]. Among the critical care systems discussed, the SOFA system offers obvious advantages since it is easy to calculate and includes therapeutic requirements such as mechanical ventilation and inotropic substances.

The advantage of organ failure scores clearly lies in their widespread implementation in intensive care medicine, which allows good comparison with other critically ill patients (e.g., patients with sepsis). The introduction of the modified Marshall score in the revised Atlanta classification has overcome the problem of erronenously high scoring points by omitting the hepatic and

neurologic components. The latter are truly problematic in acute pancreatitis, because high bilirubin values or delirium tremens are frequent features of biliary or alcoholic pancreatitis, albeit not representing organ failure.

## Laboratory Variables

In the mid 1960s, the first evidence arose that the severity of acute pancreatitis is reflected by abnormalities of many serum/plasma variables [45]. Hence, a number of laboratory markers have been identified which allow early stratification of patients at risk of developing complications, such as necrosis, infection of necrosis, septic complications, organ failure, and death. As well as having the potential to predict disease severity, many of these parameters were found to be determinants of disease progression and subsequent complications in the pathomechanism of acute pancreatitis, such as proteases, cytokines, chemokines, adhesion molecules, and acute-phase proteins [46].

An ideal laboratory test to assess severity of acute pancreatitis should be simple to perform, readily available under routine and emergency conditions, accurate, and cost effective. However, despite a large array of potentially useful parameters being developed, their large-scale clinical use is limited by time-consuming and expensive assay procedures. As a consequence, only few tests have passed the threshold into routine clinical application.

### Routine Laboratory Variables

Since the introduction of the Ranson and Imrie scoring systems, the abilities of single routine laboratory components, such as hematocrit, creatinine or blood urea nitrogen (BUN), and blood glucose, to predict complications and thus "severe" disease have been extensively investigated, either alone or in combination.

#### Hematocrit

Admission hematocrit and its subsequent changes during fluid resuscitation still represents a simple and good prognostic estimate. An admission hematocrit >44% has been found to be closely associated with complications in terms of necrosis and organ failure [47] or pancreatic infection [48]. An overall high negative predictive value of around 90% excluding "severe" acute pancreatitis at admission hematocrit <44% [47] and <40% [49] was reported by some sauthors. However, admission hematocrit of >41% to >44% failed to predict severity, organ failure, or death in other large studies [35,49]. In a recent international multicenter analysis in 1612 patients with acute pancreatitis, admission hematocrit ≥44% and increasing BUN levels at 24 hours were able to predict persistent organ failure and pancreatic necrosis in 54% and 60% of patients, respectively [50]. Taken together, hematocrit serves as a widely available and simple rough estimate to exclude severe attacks, but is no reliable means to predict severity or any other specific complication accurately.

#### Serum Creatinine and Blood Urea Nitrogen

Creatinine and BUN are surrogate laboratory tests that indicate and define renal failure. Renal failure, defined as creatinine >2 mg/dL (177 μmol/L) by the Atlanta classification, is one of the most serious organ complications in acute pancreatitis and has been shown to be an independent risk factor for fatal outcome [41,42,51]. However, the widely used cut-off level >2.0 mg/dL is frequently not reached at the day of hospital admission, which limits the use of this variable for "early" risk estimation. As far as disease severity in terms of local or systemic complications is concerned, admission BUN achieved no satisfactory test performance [52,53], reaching a maximum sensitivity of 79% and a specificity of 67% (PPV 43%, NPV 91%) only [52]. In the largest patient cohort ever published, rising BUN within 24 hours after admission achieved a sensitivity of <60% in predicting persistent organ failure or pancreatic necrosis [50], but revealed increasing diagnostic accuracy rates beyond 48 hours after admission [54].

### Acute-phase Proteins

Acute-phase proteins constitute a family of inflammatory proteins that are mainly synthesized in the liver in response to infectious and noninfectious stimuli. The best-known member is C-reactive protein (CRP). Serum amyloid A protein (SAA) was also thought to be useful in the spectrum of acute-phase reactants for biochemical severity stratification of acute pancreatitis. Both parameters share an essential feature for a large-scale routine application—they are available as fully automated immunoassays.

#### C-Reactive Protein

Severity stratification of acute pancreatitis by CRP has a long tradition and still represents the "gold standard" for both early severity stratification and monitoring the course of the disease [53,55–59]. CRP is the laboratory variable of choice to differentiate necrotizing from interstitial edematous acute pancreatitis. However, the majority of studies have focused on the discrimination between mild and severe acute pancreatitis, according to the original Atlanta classification of 1993. Herein, CRP achieves

diagnostic accuracy rates between 70% and 80% at a cut-off level >150 mg/L within 48 hours after disease onset [56,60]. As is well documented for all acute-phase proteins, CRP is not useful for prediction of infected necrosis, organ failure, or death within the first week after disease onset [53,61]. Another shortcoming of CRP is the relatively long delay in its induction, with systemic peak values at 72–96 hours after disease onset, thus making very early severity assessment impossible.

#### Serum Amyloid A

Despite its earlier release and wider dynamic range, SAA failed to show any relevant benefit over CRP in estimating severity or prognosis of acute pancreatitis [55,57]. Therefore, this alternative acute-phase reactant has never achieved meaningful clinical application.

## Cytokines and Chemokines

A wealth of experimental and clinical studies during the 1990s convincingly demonstrated that cytokines and chemokines play a key role in the pathophysiology of acute pancreatitis by promoting local tissue destruction and mediating distant organ complications [62,63]. As a consequence, cyto- and chemokine measurement was thought to offer an excellent approach to biochemical severity assessment. Despite the development of fast and fully automated assay techniques, however, the vast majority of cytokine and chemokine family members play no role as biochemical markers for acute pancreatitis in the clinical setting. So far, only the cytokine interleukin 6 (IL-6) and the chemokine interleukin 8 (IL-8) have passed from pathophysiologic importance to clinical application.

#### Interleukin 6

Systemic concentrations of IL-6 have been found to be early and excellent predictors of severity. A large number of clinical studies have uniformly shown that IL-6 is dramatically increased in complicated attacks [53,59,64–66]. IL-6 concentrations generally rise 24–36 hours earlier than CRP levels and remain significantly elevated as long as complications persist. One of the first series in 24 patients from Glasgow found a sensitivity of 100% and a specificity of 71% (PPV 71%, NPV 100%) at a cut-off level >130 IU/mL for IL-6 in predicting a severe attack within 36 hours of symptom onset [64]. Beyond discriminating mild from severe attacks, IL-6 closely correlates with evolving organ failure [53,59,65]. IL-6 has been introduced as a routine parameter in some laboratories and represents an easy and rapid means to select patients at risk of developing severe disease. However, a large-scale application of IL-6 measurements in acute pancreatitis has never been carried out.

#### Interleukin 8

IL-8 was initially described as an early marker of disease severity within the first day after onset of symptoms, with a rapid decrease after 3–5 days [66,67]. However, beyond simple discrimination of mild from severe attacks an even more interesting aspect of IL-8 assessment was described by our group in 1997. In patients with necrotizing pancreatitis who developed septic multiple organ failure or died during the later stages of the disease, IL-8 has proven to be an excellent marker for monitoring these life-threatening complications [61]. As for IL-6, a fully automated assay is available for IL-8 and the use of this chemokine for disease monitoring has become possible on a routine basis in large hospitals, but is still not widely used as a marker in acute pancreatitis.

## Procalcitonin

Ever since its first description in 1993 [68], procalcitonin (PCT) has been an established marker for predicting bacterial/fungal infections, sepsis, and septic shock in the intensive care setting [69,70]. A close correlation between elevated PCT concentrations and the development of infected necrosis was first described in a cohort study comprising 51 patients with acute pancreatitis by our group in 1997. At a cut-off level of >1.8 ng/mL, PCT was able to predict this complication with a sensitivity and specificity of more than 90% within the first days after onset of symptoms [61]. An international multicenter trial in 104 patients with severe acute pancreatitis has shown that PCT is able to predict serious complications such as pancreatic infections or death with a sensitivity of 79% and a specificity of 93% (PPV 65%, NPV 97%) at a cut-off level >3.8 ng/mL within 48–96 hours after onset of symptoms [71]. This observation was confirmed by a number of subsequent studies which have been subjected to a meta-analysis and a systematic review. Herein, PCT reached a cumulative sensitivity of 80% and a specificity of 90% for predicting infected necrosis in acute pancreatitis [54,72]. Notably, PCT is of little or no value for simple stratification of patients as "mild" or "severe" according to the original Atlanta classification of 1993. PCT measurements are available as fully automated assay for routine use; a semiquantitative strip test is an alternative for fast and easy quantification. On the basis of the data available, PCT is a valuable tool for early stratification and consecutive monitoring of patients at risk of developing the most serious complications in acute pancreatitis.

**Table 21.2** Relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

| Variable | Severity | Pancreatic infection | Overall prognosis |
|---|---|---|---|
| Ranson/Imrie score | ++ (48 h) | – | ++ (48 h) |
| APACHE II score | ++ | – | +++ (>7 d) |
| SOFA/Marshall score | ++ | – | +++ (>7 d) |
| Hematocrit | ++ (48 h) | – | – |
| Creatinine/blood urea nitrogen | + | – | ++ (>7 d) |
| IL-6 | +++ (<48 h) | – | – |
| IL-8 | ++ (<48 h) | Sept. MODS (monitoring) | +++ (>7 d) |
| CRP | +++ (72–96 h) | – | – |
| PCT | – | +++ (72–96 h) | +++ (72–96 h, >7 d) |

Optimum accuracy after symptom onset of acute pancreatitis:
<48 h: within 48 h after symptom onset
72–96 h: within 72–96 h after symptom onset
>7 d: beyond the first week after disease onset
APACHE II, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; IL-6, interleukin 6; IL-8, interleukin 8; CRP, C-reactive protein; MODS, multiple organ dysfunction syndrome; PCT, procalcitonin.

## Overview

Table 21.2 provides an overview of relevant multiparameter scoring systems and laboratory markers for severity stratification and prediction of specific complications in acute pancreatitis.

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# 22

# Acute Pancreatitis Associated With Congenital Anomalies

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## Introduction

Acute pancreatitis secondary to congenital anomalies remains an uncommon cause of childhood abdominal pain, with a more varied etiology than adult-onset pancreatic inflammation. Although several hereditary syndromes have been associated with acute pancreatitis, the most commonly encountered congenital causes are developmental abnormalities of the pancreaticobiliary system, such as pancreas divisum, annular pancreas, ectopic pancreatic tissue sources, enteric duplication cysts, and choledochal cyst [1]. Congenital structural variants of the pancreas occur in up to 10% of the Western population [2], but the majority are silent as the incidence of pancreatitis is two orders of magnitude less [3]. Biliopancreatic ductal system variants encountered during diagnostic evaluation of idiopathic acute pancreatitis plague the clinician with a significant question of relevance regarding consequence and management.

## Pancreas Divisum

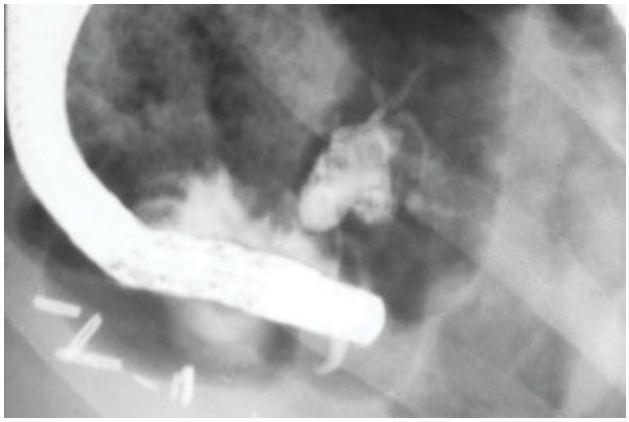
The cause, incidence, clinical relevance, and treatment of pancreatitis in patients with pancreas divisum has been hotly debated. In complete pancreas divisum, the ventral and dorsal pancreatic ducts do not communicate, and usually the dorsal pancreatic duct is larger than the ventral (Fig. 22.1a) [4]. Acute pancreatitis may result from obstruction at the minor papilla, a junction in the ductal system, or from localized ductal ectasia in the uncinate process [5]. Pancreatitis is experienced by 0.1% of the population, whereas pancreas divisum is present in 4–5%; this makes pancreas divisum questionable as the inciting source [6–8]. The disparity is likely due to selection bias because some patients are referred after endoscopic retrograde cholangiopancreatogram (ERCP) failure for suspected idiopathic pancreatitis, leading to a possible false association between idiopathic pancreatitis and pancreas divisum.

Whether by sphincteroplasty for acute pancreatitis or longitudinal pancreaticojejunostomy for more distal chronic obstruction, treatment is directed at relief of the obstruction. Accessory papilla sphincteroplasty for stenosis improved symptoms and was best predicted by presentation with pancreatitis and a positive ultrasound-secretin test [9]. Surgical dual sphincteroplasties for dysfunction of the pancreaticobiliary sphincters in pancreas divisum results in good to excellent outcomes [10]. Smaller studies have reported various success rates with endoscopic sphincterotomy and longitudinal pancreaticoduodenectomy, with morbidity rates ranging from 15% to 40% [5,10]. Duodenum-preserving pancreatic head resection in patients with chronic pancreatitis and pancreas divisum demonstrated significant improvement in symptoms (31%) [11]. Three-quarters of adults have a good response to surgery [9,12]. Treatment of pancreas divisum in acute pancreatitis yields better results than in chronic pancreatitis or chronic pain syndrome. Poor postsurgical results in chronic pancreatitis are reported in both adults and children [5,9].

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

(a)



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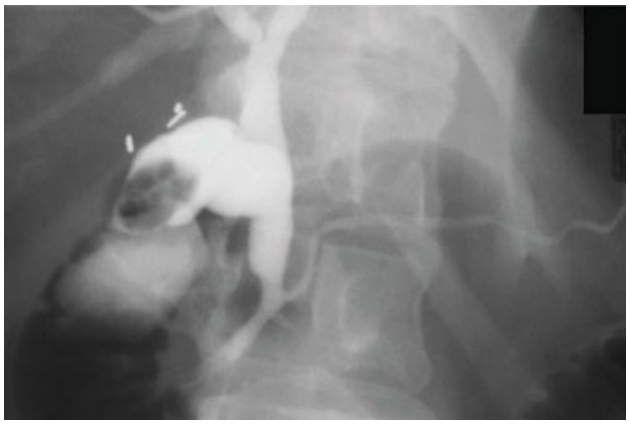


**Figure 22.1** (a) A 15-year-old girl presented with recurrent attacks of pancreatitis. Endoscopic retrograde pancreatography showed pancreas divisum with cystic dilation of the ventral pancreatic duct containing stones. She was treated by pancreaticoduodenectomy. (b) Cholangiopancreatogram in a 12-year-old boy with a choledochal cyst and anomalous pancreaticobiliary junction. The pancreatic duct inserts into the common bile duct more than 2 cm proximal to the ampullary orifice. Such patients are prone to acute and chronic pancreatitis.

## Anomalous Pancreaticobiliary Ductal Union

Anomalous pancreaticobiliary ductal union (APBDU) results from the pancreatic and common bile ducts joining proximally to the ampulla of Vater with a hypothesized resulting admixture of refluxed pancreatic and biliary secretions into the biliary tree or pancreas [13,14] and has been associated with a higher incidence of congenital choledochal dilation (Fig. 22.1b) [14–17]. APBDU has been further defined as a common channel greater than 15 mm in length or a contractile segment totally distal to the biliary and pancreatic ductal union [18,19]. APBDU is further delineated into B-P or P-B subtypes according to the order of insertion of the pancreatic and biliary ducts [19,20]. In B-P, the bile duct enters the main pancreatic duct and in P-B (or in some series, P-C for choledochal) the pancreatic duct enters the common bile duct [19].

APBDU has been considered a factor in the development of pancreatitis, choledochal cyst, and hepatobiliary cancers [19]. APBDU was identified by ERCP in 8.7% of patients with an incidence of 13.2% for biliary pancreatitis and 2.2% for nonbiliary pancreatitis. Patients with B-P subtype associated with choledochal cyst formation whereas the P-B subtype was associated with biliary pancreatitis, gallbladder cancer, and adenomyomatosis. A proposed mechanism for this relatively high rate of pancreatitis and the observation of recurrent pancreatitis in patients with APBDU is sphincter of Oddi dysfunction [21].

Surgical treatment of APBDU relies on disruption of the contiguous anatomical relationships. Roux-en-Y hepaticojejunostomy is offered [22], but cholecystectomy and alternate biliary tract reconstruction [23] or endoscopic sphincterotomy alone can be beneficial [21]. APBDU with choledochal cysts are often managed by cyst excision, although duodenopancreatectomy may be required [24].

## Choledochal Cyst/Choledochocele

Choledochal cysts are noted in 0.1% of adult ERCPs and in 1 in 150 000 North Americans [25,26]. Rates are higher in East Asia and in females, with a male to female ratio of 1:3–4, and associated pancreatitis is more common in younger patients aged 2–16 years (36%) [27]. The classic triad of abdominal pain, jaundice, and a palpable right upper quadrant abdominal mass occurred 6.7 times more frequently in children [28], with 50% of adult patients presenting with abdominal pain diagnosed as pancreatitis or biliary tract pathology prior to cyst identification [29]. Cyst rupture most commonly presents with pancreatitis, cholangitis, and biliary peritonitis [30]. Cysts greater than 5 cm were associated with pancreatitis in 90% of patients and resection led to lower rates of pancreatitis than surgical bypass (50% vs. 80%). Pancreatitis and cancer were more common in patients with both choledochal cyst and APBDU [31]. The possible role of APBDU in causing choledochal cysts is discussed in the previous section.

Choledochal cysts were first classified according to the 1977 Todani system [32,33]. Except in the case of type III disease, in which endoscopic approaches or marsupialization may be indicated, complete excision of the extrahepatic choledochal cyst with hepaticojejunostomy is

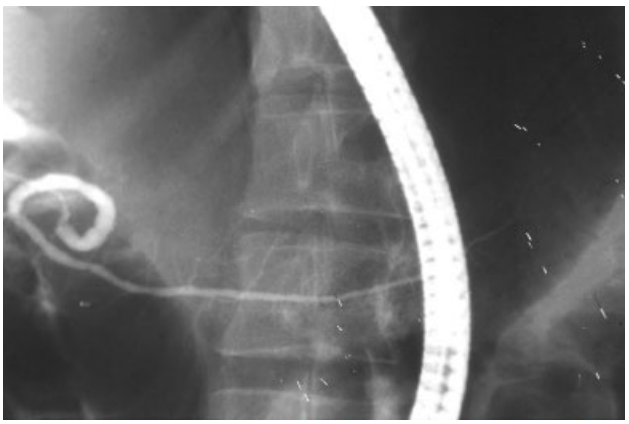
the goal [34,35]. Malignancy is identified increasingly with choledochal cyst retention; therefore internal drainage or bypass procedures should be accompanied by a near-complete resection [27]. Interposition of the jejunum or appendix are unsuitable due to high rates of graft dysfunction and cholangitis [36,37].

## Annular Pancreas

Annular pancreas, potentially arising from dorsal and ventral anlage hypertrophy or abnormal adherence of the ventral duct to the duodenum during rotation, envelops the duodenum (Fig. 22.2a,b) [38]. Obstruction or pancreatic inflammation secondary to annular pancreas occurs in the third decade of life or later with a prevalence of roughly 25% [39,40]. Pancreatitis secondary to annular pancreas is rare in the newborn and presents with duodenal blockage, with bilious emesis and "double bubble" on abdominal films [39,41]. Differentiation between upper obstruction etiologies, such as duodenal atresia, malrotation without volvulus, and annular pancreas, must not delay emergent operative care in the case of volvulus. Annular pancreas is associated with a high rate of congenital anomalies: 70% of infants with annular pancreas will have another anomaly, such as duodenal stenosis or atresia (40%), Down syndrome (16%), tracheoesophageal fistula (9%), or congenital heart defects (7%) [39].

Surgical correction of annular pancreas in childhood is usually undertaken by performing diamond duodenoduodenostomy and leads to faster feeding and discharge when compared to side-to-side anastomosis or duodenojejunostomy [42]. Gastrojejunostomy should be avoided in children as the most anatomic reconstructions are linked to the best growth outcomes [43]. Surgical correction in adults follows suit, with less concern about growth retardation with gastrojejunostomy. Pancreaticoduodenectomy with and without pyloric preservation for resection of annular pancreas and associated ampullary carcinoma has been described [44]. In any case of duodenal obstruction, volvulus must be first excluded as a life-threatening surgical emergency.

(a)



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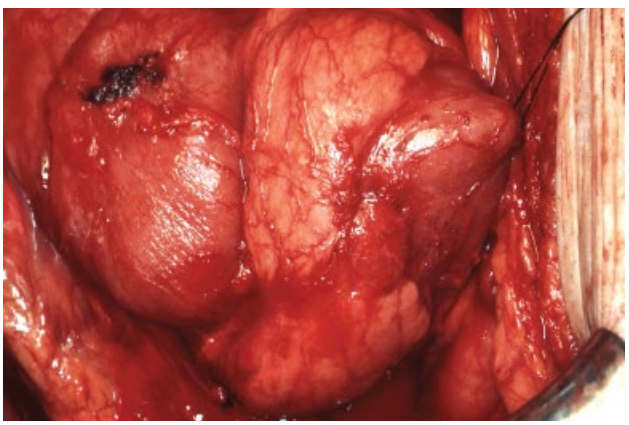


**Figure 22.2** (a) Pancreatogram in a young boy with annular pancreas. The proximal pancreatic duct encircles the duodenum within the annular segment. (b) Annular process.

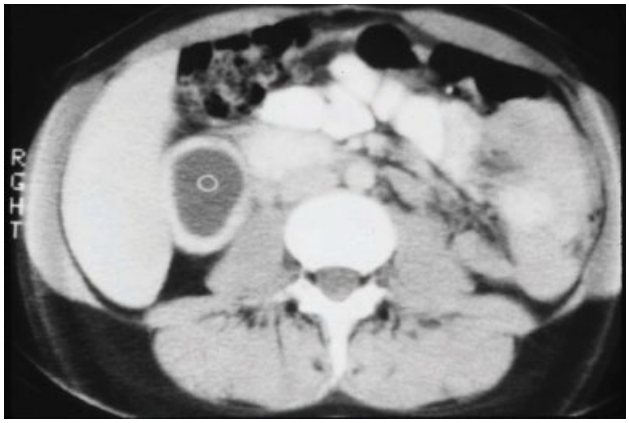
## Ectopic Pancreatic Tissue

Ectopic pancreatic tissue is a relatively common anomaly with an incidence of up to 13% [43,45]. A normally organized aberrant rest of pancreatic tissue is discontinuous with the entopic pancreas. A majority are identified in the submucosa of the stomach, duodenum, and jejunum [38] and although uncommon, come to clinical attention due to intussusception, obstruction, inflammation, or degeneration [46,47]. Inflammation of an ectopic pancreas without pseudocyst with both elevated serum amylase and lipase and ectopic tissue inflammation has been reported [45,48]. In a total of 32 histologically documented cases of ectopic pancreas, half were identified incidentally [49]. The remaining cases were clinically significant for hemorrhage, obstruction, or ulceration. A tentative link between ectopic pancreatitis in the duodenal wall and duodenal stenosis has been established in six pancreaticoduodenectomy specimens [50].

## Enteric Duplication Cysts

Gastrointestinal duplication cysts are congenital foregut anomalies with gastrointestinal mucosa of any type or pancreatic tissue and are named for their anatomic proximity rather than mucosal content [39]. Duplication

(a)

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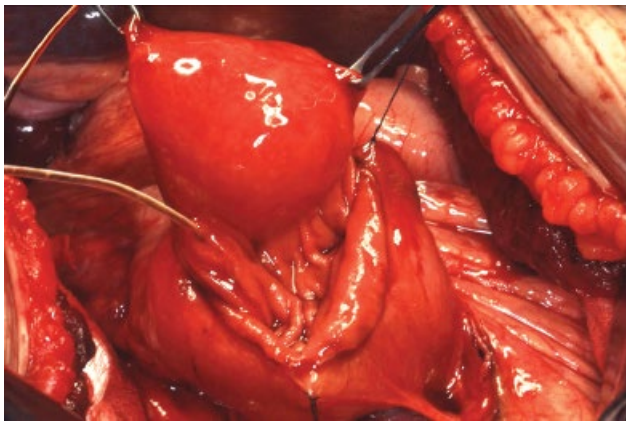

**Figure 22.3** (a) CT scan in a 21-year-old woman with a history of several years of recurrent acute pancreatitis. The white circle marks an abnormal thick-walled cystic structure adjacent to the head of the pancreas. (b) Operative photograph of the pancreatic duplication cyst bulging into the duodenal lumen as previously identified on abdominal CT. The catheter has been introduced through the ampulla into the pancreatic duct. Excision of the cyst with suture ligation of its narrow neck cured her recurrent pancreatitis.

cysts within the pancreas have been reported and are generally termed as duodenal or gastric duplications since they lack a contiguous structure (Fig. 22.3a,b) [46]. Although most enteric duplications do not present with pancreatitis, multiple cases have been identified [51]. Duodenal duplication occurs in 10% or fewer cases and may cause "obstructive pancreatitis" from compression between the duodenal wall and the biliopancreatic duct [52,53]. Juxta-pancreatic duplications with pancreatic ductal communication may shed blood or mucus into the main pancreatic duct, resulting in obstruction [54–56]. Pancreatitis may occur within the duplication itself, as is found in esophageal duplications containing gastric mucosa and pancreatic tissue (43%) [57]. Local resection is preferred; however, marsupialization of cysts with removal of mucosa may be employed if local resection is not possible [58].

## Conclusions

Infrequently, congenital anomalies may be the cause of idiopathic acute pancreatitis. Nonanatomic congenital causes must be assessed by diligent investigation. Regarding anatomic congenital anomalies, strict definition of the anatomic relationships and associated anomalies is necessary to direct appropriate therapy. Because congenital anomalies are often unique, unusual anatomic relationships may be discovered in each case. Previous case series in the literature provide useful longitudinal data to help in predicting outcomes and avoiding known pitfalls.

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# 23

# Acute Pancreatitis in Children

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## Introduction

The Second International Symposium in Marseilles in 1984 defined acute pancreatitis as acute abdominal pain accompanied by the finding of increased pancreatic enzymes in blood or urine [1]. However, the pathophysiology of acute pancreatic inflammation has remained difficult to describe, partly due to the relative inaccessibility of the pancreas on physical examination, and to the frequently nonspecific nature of symptoms resulting from diseases of the pancreas. Despite these difficulties, understanding of adult pancreatitis has increased in an exponential manner in recent decades. Unfortunately, the understanding of the pediatric counterpart has lagged behind, although progress has been made in recent years.

Pediatric acute pancreatitis poses a great challenge to clinicians. Depending on the age and developmental level of a child, it can be extremely difficult to assess the nonspecific symptoms of abdominal pain and nausea or vomiting. Defining the location and nature of the pain and identifying factors that aggravate or alleviate the pain can be particularly challenging in a pediatric patient. Compounding this challenge is that many healthcare professionals do not consider pancreatitis in the differential diagnosis of pediatric abdominal pathology. Hence, children may experience symptoms from pancreatic inflammation and be labeled as suffering from "viral gastroenteritis." For all these reasons, unraveling the complexities of pediatric acute pancreatitis remains an ongoing process.

The challenges in pediatric acute pancreatitis lie in three major areas:

- potential etiologies, many of which are more particular to children;
- diagnosis, including serum biochemistry and imaging techniques;
- assessing and following for disease severity and complications.

This chapter will strive to cover these areas as they pertain to pediatric acute pancreatitis.

## Incidence

The prevailing impression among pediatric specialists is that the incidence of pediatric acute acute pancreatitis is increasing. A number of population-based series have attempted to quantify the incidence of acute pancreatitis [2–8]. These studies suggest that the incidence of acute pancreatitis in children has truly increased over the past several decades. Since the initial study by Lopez showing a steady increase in the absolute number of cases of acute pancreatitis per year in a single institution, a number of other centers throughout the world have reported similar observations [2] (Table 23.1). An estimate of incidence ranged from 1 to 3 cases per 10 000 children. Proposed explanations for the increasing diagnosis of acute pancreatitis in children include increased awareness that the disease occurs in children, a true rise in new cases, increased referral of children to tertiary care centers, and an increase of acute pancreatitis in children with other systemic diseases [2,9,10]. Likely, a combination of these events explains the increased incidence.

## Etiology

An adult presenting with a first episode of acute pancreatitis is questioned and investigated to identify the presence of one of two major etiologies for adult acute

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**Table 23.1** Series looking at the incidence of acute pancreatitis. Studies reporting increase in number of cases of acute pancreatitis diagnosed in children over time.

| Location | Years | Author | Incidence in last year | Further study details |
|---|---|---|---|---|
| United States: Children's Medical Center of Dallas | 1993–1998 | Lopez [2] | Not reported | Total cases/yr: 5, 19, 20, 38, 79, 113 (1993–1998) |
| United States: Children's Hospital of Pittsburgh | 1993–2004 | Morinville [9] | 1.3 per 10 000 children | Number of cases increased from 28 to 141 per year |
| Australia: Royal Children's Hospital, Melbourne | 1993–2002 | Nydegger [3] | 0.35 per 10 000 children | Consistent, progressive increase in cases of AP per year over the study period |
| United States: Children's Hospital of Wisconsin | 1996–2011 | Werlin [5] | Not reported | Noted a consistent increase in number of AP cases over study period with the exception of 2001 |
| Mexico: Hospital of Pediatrics, Guadalajara | 1990–2005 | Sanchez-Ramirez [4] | 53 per 10 000 hospitalizations | Reported a nonlinear increase in new cases over the study years |
| United States: Yale-New Haven Hospital | 1994–2007 | Park [10] | 8.9 per 10 000 ED visits | Increase in number of patients admitted for AP over time. Normalization to number of ED visits showed same rate per 10 000 visits |
| United States: Healthcare Cost and Utilization Project Kids' Inpatient Database | 2000–2009 | Pant [6] | 35 per 10 000 hospitalizations | Relied on ICD9 codes to identify 55 012 patients |
| United States: Nationwide Emergency Department Sample | 2006–2011 | Pant [7] | 1.6 per 10 000 ED visits | Relied on ICD9 codes to identify 78 787 patients with ED visits for AP |
| United Kingdom: Liverpool | 1999–2009 | Wilkinson [8] | 0.3 per 10 000 children | Identified patients by ICD10 codes from Hospital Episode Statistics database |

AP, acute pancreatitis; ED, emergency department.

pancreatitis—biliary disease and alcohol ingestion. These, in fact, appear to account for the majority of cases in adults. In children, by contrast, the etiologies of acute pancreatitis are more broadly divided (Table 23.2). Table 23.3 and Fig. 23.1 summarize a number of recently published series of pediatric acute pancreatitis and the breakdown of presumed etiologies [2,5,11–17]. Of note, the large series by Benifla and Weizman included a summation of many previously published series [13]. In general, the largest categories are divided up among idiopathic (22%), trauma (17.3%), systemic (15%), structural (13.5%), and medications (10%). A large series by Tomomasa et al. [11] was not included in the Benifla and Weizman review, partially due to the large preponderance of biliary–anatomic causes reported in Japanese children [11,13]. As a child presenting to a major urban hospital may originate from any location around the globe, the Japanese experience was included in Fig. 23.1. Previously labeled "idiopathic" cases may in fact be related to unidentified infections, drugs, toxins, or trauma, and recent work on genetic influences suggests that many cases of "idiopathic" pediatric acute pancreatitis may in fact represent genetic predispositions [19]. Factors may act alone or jointly to lead to a clinical episode of acute pancreatitis.

## Pathophysiology

The pathophysiology of pediatric acute pancreatitis is believed to be identical to that of adult acute pancreatitis (Chapter 18).

## Investigations

The great diversity of potential etiologies of acute pancreatitis is demonstrated in Table 23.2. Clinical finesse is involved in determining which causes should be considered for each child presenting with a first episode of acute pancreatitis. Unlike many pediatric diseases, the etiology of acute pancreatitis does not vary significantly among individual age groups [20,21]. A stepwise consideration of probable, possible, and rare etiologies in conjunction with elicited history of present illness, past medical history, family history, and findings on physical examination will direct investigations and

**Table 23.2** Potential etiologies of acute pancreatitis. The differential list is extensive. A clinician must consider the particular patient's history of present illness, past medical history, and family history in considering the potential trigger of an attack of acute pancreatitis [2,5,10,11,14–16,20–27].

| Category | Examples |
|---|---|
| Anatomic abnormalities | Annular pancreas |
| | Anomalous choledochopancreaticoductal junction |
| | Choledochal cyst, choledochocele |
| | Intestinal duplication or cyst |
| | Pancreas divisum |
| Biochemical abnormalities | Diabetic ketoacidosis |
| | Hypercalcemia (hyperparathyroidism, familial hypocalciuric hypercalcemia) |
| | Hypertriglyceridemia |
| | Uremia |
| Gallstone disease | Biliary sludge |
| | Choledocholithiasis |
| | Microlithiasis |
| Genetic | Hereditary pancreatitis: *PRSS1* |
| | *SPINK1* |
| | *CFTR* |
| | *CTRC* |
| Iatrogenic | Following ERCP |
| | Following liver transplant (postsurgery anatomy + medications) |
| | Following nongastrointestinal surgery (Fontan heart operation, spinal fusion surgery) |
| Idiopathic | Unidentified infections, toxins, drugs, or trauma |
| Inborn errors of metabolism | Acute intermittent porphyria |
| | Branched-chain ketoaciduria (maple syrup urine disease) |
| | Cationic aminoacidurias |
| | Cystinuria |
| | Glycogen storage disorders |
| | Homocystinuria |
| | 3-Hydroxy-3-methylglutaryl-CoA lyase deficiency |
| | Pyruvate kinase deficiency |
| Infectious agents | Bacteria (*Campylobacter fetus*, *Escherichia coli*, *Legionella*, *Mycoplasma pneumoniae*, *Salmonella typhii*, *Yersinia*) |
| | Viruses (coxsackievirus, cytomegalovirus, enterovirus, echovirus, Epstein–Barr, hepatitis A, influenza A, influenza B, measles, mumps, rubella, rubeola, varicella) |
| | Other (*Ascaris lumbricoides* (obstruction), *Clonorchis ninensis* (obstruction), leptospirosis, malaria) |
| | Immunocompromised host (*Mycobacterium avium intracellulare*, *Pneumocystis carinii*, *Cryptosporidium parvum*) |
| Medications | Analgesics (acetaminophen overdose, aminosalicylic acid, sulindac, indomethacin, propoxyphene) |
| | Antacid (cimetidine, ranitidine) |
| | Anticonvulsants (fosphenytoin, phenytoin, valproic acid) |
| | Antimicrobials (erythromycin, sulfonamides, trimethoprim-sulfamethoxazole, tetracycline, isoniazid, metronidazole, nitrofurantoin, pentamidine) |
| | Chemotherapeutics (L-asparaginase, cytarabine) |
| | Diuretics (furosemide, ethacrynic acid, angiotensin-converting enzyme inhibitors, thiazides, chlorthalidone) |
| | illicit drugs (amphetamines, cocaine, heroin) |
| | Immunomodulators and anti-inflammatories (sulfasalazine, 5-aminosalicylic acid products, 6-mercaptopurine, azathioprine, gold) |
| | Sex hormone-related (estrogen, tamoxifen, danazol, corticosteroids) |
| | Others: cholestyramine, cyproheptadine, diazoxide, diphenoxylate, histamine, interleukin, methyldopa, phenformin, procainamide |

*(Continued)*

**Table 23.2** (Continued)

| Category | Examples |
|---|---|
| Obstruction, acquired | Neoplasm-associated |
| | Periampullary obstruction (celiac disease, Crohn disease, mucosal inflammation) |
| | Sphincter of Oddi problem (stenosis; dysfunction?) |
| Systemic illness | Crohn disease |
| | Hemolytic uremic syndrome |
| | Henoch–Schönlein purpura |
| | Kawasaki syndrome |
| | Polyarteritis nodosum |
| | Sarcoidosis |
| | Systemic lupus erythematosus |
| | Sickle cell disease |
| Toxins | Boric acid |
| | Ethanol and methanol |
| | Methylene chloride |
| | Organophosphates/insecticides |
| | Scorpion bite |
| Trauma | Accidental (bicycle handlebar injury, motor vehicle accident) |
| | Child abuse |

limit invasive and sometimes painful procedures for the pediatric patient, as well as minimize unnecessary costs.

Children in families already identified as having inherited predispositions to pancreatitis tend to be more quickly investigated for such a possibility. However, physicians should remember that a child may be the proband in a family that has never had a formal diagnosis of pancreatitis despite family members experiencing symptoms compatible with the diagnosis, or having had adult family members diagnosed with alcohol-induced pancreatitis, despite a rather small ingestion of ethanol. A large series of European families with clinical hereditary pancreatitis reported the cumulative risk of having had symptoms by age 10 years as 40.3% and by age 20 years as 72.6% [22]. Although the overall number of persons with inherited causes of acute pancreatitis is small, within these families a large majority will present within the pediatric age range. For this reason, a thorough family history for documented pancreatitis, pancreatic cancer, pancreatic insufficiency including insulin-dependent diabetes, and/or family members exhibiting symptoms that could be consistent with acute recurrent pancreatitis should be sought.

## Diagnosis

In 2012, a multicenter group of pediatric gastroenterologists published a consensus statement defining acute pancreatitis in childhood [18]. The clinical diagnosis of acute pancreatitis requires the presence of at least two out of three criteria:

- a combination of abdominal pain that is consistent with pancreatic origin;
- the presence of elevated amylase or lipase or both to at least three times the upper limit of normal;
- radiological imaging with findings consistent with acute pancreatitis.

Even with these criteria the diagnosis of acute pancreatitis can present challenges for the clinician. History and physical examination findings are variable: there may be epigastric to right upper quadrant pain, left upper quadrant pain, back pain, nausea, vomiting, jaundice, tachycardia, guarding, or even signs of shock. In children under the age of 3, pain may present as increased irritability, and abdominal distension and fever were more common than in older children [15]. Furthermore, there is no absolute cut-off value for amylase and lipase above which a person definitely has acute pancreatitis and below which the diagnosis is excluded. Imaging studies are often normal. Clinicians must maintain a high degree of suspicion, especially in younger children in whom verbal communicative skills may be limited.

A particular pediatric consideration is that newborn levels of pancreatic type isoamylase are very low to nondemonstrable, and total amylase levels reach normal adult values by only approximately 8–16 months of age [29,30]. Pancreatic isoamylase activity might not even

**Table 23.3** Summary of pediatric acute pancreatitis series detailing etiology in 1757 children.

| | 2002 Debanto [15] | 2003 Choi [14] | 2002 Lopez [2] | 2002 Pezzelli [16] | 2002 Tiao [17] | 2003 Alvarez Calatayud [12] | 2003 Werlin [5] | 2003 Benifla (review) [13] | 2009 Park [10] |
|---|---|---|---|---|---|---|---|---|---|
| Location | USA | Korea | USA | Italy | Taiwan | Spain | USA | Review | USA |
| Number | 301 | 56 | 274 | 50 | 61 | 31 | 180 | 589 | 215[c] |
| Age, mean (median) years | 9.1 | 7.4[a] | <1 up | (10.5) | 8.8 | 7.9 | (12.5) | 9.2 | 13.1 |
| Age, range years | 0.1–16 | 2–13[b] | | 2–17 | 2–18 | 2–15 | | 0.1–21 | |
| Male:female ratio | 0.7 | 0.8* | | 1.0 | NA | 1.2 | 0.9 | 1.2 | 0.7 |
| **Etiology** | | | | | | | | | |
| Systemic | 3.5 | 9 | 48 | | 15.0 | 7 | 14 | 14 | 9 |
| Gallstone/biliary | 10.5 | 14 | | 20 | | 16 | 12 | | 22 |
| Structural/divisum | 1.5 | 14 | <10 | 8 | 12 | | 7.5 | 15 | 6 |
| Infectious | 3.0 | 9 | <5 | 12 | 2 | 19 | 8 | 10 | 7 |
| Medications/toxins | 11 | 31 | <5 | | 7 | 10 | 12 | 12 | 22 |
| Trauma | 13.5 | 11 | 19 | 10 | 46 | 6.5 | 14 | 22 | 8 |
| Iatrogenic/post-ERCP | 3.5 | | | | | | 5.5 | | 4 |
| Familial/hereditary | 5.5 | | | 6 | | | 3 | 2 | |
| Cystic fibrosis | 3.0 | | 0.4 | | | | 0.5 | | 1.5 |
| Hypercalcemia | 2.0 | | 0 | | | | 0 | 1 | 0.3 |
| Hypertriglyceridemia | 1.5 | | 0 | | | | 1 | 1 | 1 |
| DKA | 0.5 | | 0.7 | | | | 4.5 | | 2 |
| Other | 6.5 | | 0.4 | 10 | | 7 | 10 | | |
| Idiopathic | 34 | 13 | 12.5 | 34 | 20 | 35 | 8 | 23 | 17 |

*Source:* Adapted from Whitcomb and Lowe 2008 [28].
Benifla and Weizman [13] reviewed prior series published between 1965 and 1999 in Canada, Israel, Hong Kong, Switzerland, Taiwan, UK, and USA.
[a] Based on 39 children.
[b] Based on 16 children.
[c] Some of the patients in this study had more than one etiology. The percentages of each etiology are calculated using the number of etiologies reported (253).
For each study, the percentage of cases based on etiologic category is listed. Due to rounding, percentages may not add exactly to 100.

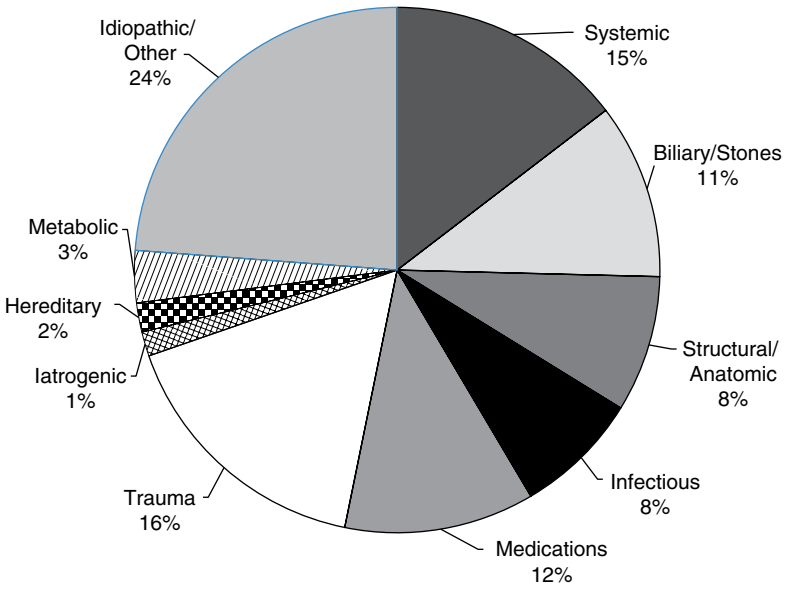


**Figure 23.1** Etiology of acute pancreatitis in 1961 children [2,5,10–17]. In contrast to adults, where biliary tree pathology and alcohol account for more than two-thirds of cases, children have a greater spread among the etiologic categories of acute pancreatitis. Please refer to Table 23.3 for breakdown of categories in each of the included series. The series of 204 children reported by Tomomasa in 1994 was not included in the Benifla review due to the large preponderance of biliary–anatomic causes reported in Japanese children [11,13]. The Japanese experience was included in this figure.

reach adult values until the age of 10–15 years [31]. In a similar fashion, lipase values at birth are significantly lower than those observed for adults and appear to have the greatest increase within the first year of life [32,33]. Hence, in a young patient, amylase and lipase levels may not always reflect potential pancreatic inflammation, particularly if adult ranges of normal enzyme levels are used as references. In addition, as has been demonstrated in adults, absolute elevation of amylase and/or lipase does not directly correlate with clinical severity or with imaging changes [34,35]. Even so, a recent publication demonstrated that serum lipase levels less than or equal to 7 times the upper reference limit were associated with a milder course [36].

Clinical scales are used to classify adults as having mild or severe disease [37–40]. Similar scales have not been widely applied or validated in children. In an attempt to classify the potential severity of acute pancreatitis in children, the Midwest Multicenter Pancreatic Study Group developed and validated a pediatric scoring system [15], in which age (<7 years), weight (<23 kg), admission white blood count (>$18.5 \times 10^9$/L), admission lactate dehydrogenase (>2000 IU/L), 48-hour fluid sequestration (>75 mL/kg per 48 hours), and a 48-hour rise in urea (>5 mg/dL) were each assigned a value of 1 point. Scale scores were found to correlate with disease outcome: a severe course (with associated higher morbidity and mortality) was predicted by a score of greater than 3 [15]. Subsequent authors have cautioned limitations of this severity scale [41]. More recently, a Japanese group published their experience using a pediatric version of a national acute pancreatitis severity scoring system that involves parameters collected 72 hours after onset of pancreatitis [42]. Within this system, base excess ≥ −3 or shock, $PaO_2 \leq 60$ mmHg, blood urea nitrogen (BUN) ≥40 mg/dL, lactate dehydrogenase (LDH) ≥2× upper limit of normal (ULN), platelet count ≤$1 \times 10^5$/mm$^3$, Ca ≤7.5 mg/dL, C-reative protein (CRP) ≥15 mg/dL, pediatric systemic inflammatory response score (SIRS) ≥3, and age <7 years and/or weight <23 kg were the factors of interest, with cut-off for predicting a severe outcome set at three criteria. They compared findings within this new scale to the Ranson, modified Glascow, and DeBanto scores and concluded that their scoring system, despite not being perfect, was sufficient to predict outcomes and identify children with severe acute pancreatitis. These few articles highlight that no single pediatric severity clinical scale has yet gained widespread acceptance and utilization, and thus pediatric severity indices represent an area of necessary research.

## Imaging

Imaging methods may be helpful in (i) diagnosis, (ii) determining severity and complications, and (iii) visualizing any anatomic factors leading to acute pancreatitis.

Transabdominal ultrasonography (TUS) is widely available, relatively inexpensive, and does not expose a child to radiation or contrast agent. In a well-looking child, TUS should strongly be considered as the initial diagnostic modality in suspected acute pancreatitis. It can be performed repeatedly in almost any setting to follow the course of illness and does not require procedural sedation [43]. Ultrasonography may demonstrate enlargement of the pancreas, altered echogenicity, duct diameter abnormalities, and fluid collections (intra- or extrapancreatic) [44], as well as abnormalities of the pancreaticobiliary drainage system, including the presence of a choledochal cyst or common bile duct stones. Limitations include air within the stomach interfering

with image acquisition from the body and tail of the pancreas, and differentiation of normal from abnormal pancreas in cases of pancreatitis where echogenic changes may or may not be present.

Computed tomography (CT) with contrast may be useful in more severe cases of acute pancreatitis and in order to assess for local complications [45–48]. Adult guidelines suggest using CT early in cases of diagnostic uncertainty or for assessment of acute pancreatitis severity 72–96 hours after onset of symptoms [49]. In this school of thought, CT would be best used not at initial presentation but only in necessary instances for assessment of severity in complex cases and for longer term follow-up of complications [5].

The capability of magnetic resonance cholangiopancreatography (MRCP) (with or without secretin) to diagnose most cases of pancreas divisum, choledochal cyst, cholelithiasis, pancreaticobiliary junction anomalies, and obstructive abnormalities has decreased the use of endoscopic retrograde cholangiopancreatography (ERCP) for diagnostic purposes [50–57]. Some have reported limitations in the (nonsecretin-enhanced) MRCP diagnosis of anomalous pancreaticobiliary junctions and so suggest ERCP may have a role in diagnosis of these. The use of certain fruit juices as enteral negative contrast agents may offer improved quality of MRCP images [58]. Although MRCP offers imaging without radiation, there are still pediatric factors to take into consideration. Due to the relatively long duration of the procedure (15–45 minutes), younger children will require sedation, ranging from oral chloral hydrate to intravenous general anesthesia and intubation. In addition, the quality of MRCP images depends on the protocol utilized for image acquisition as well as the radiologist's interpretation of these.

When indicated, pediatric ERCP in experienced hands is reported to be as safe and effective as it is in adults [59,60]. ERCP is particularly useful in assessing pancreatic duct anatomy, abnormalities, and duct disruption [61]. Published pediatric uses include the drainage of nonresolving pancreatic pseudocysts [62], sphincterotomy [63,64], stent placement [65,66], the assessment of trauma-related pancreatic ductal injuries [67], and the management of pediatric acute recurrent pancreatitis [63,68] and chronic pancreatitis [66,69]. An important but seldom encountered indication is urgent ERCP-guided removal of an impacted common bile duct stone leading to cholangitis [23,70]. Recent technological developments are making pediatric ERCP increasingly accessible [24]. Principles for determining when to perform ERCP in a child have paralleled those used in adults [60]. The obvious difficulties with ERCP include the need for sedation (typically general anesthesia), the use of ionizing radiation/fluoroscopy, and the relatively high rate of complications reported in adults.

Experience with pediatric endoscopic ultrasound (EUS) has increasingly been reported in recent years. EUS provides detailed imaging of pancreatic parenchyma and ducts without the use of radiation, but with the need for sedation. Its benefits include not only its role in imaging, but also in interventions, with the capacity to sample tissue and fluid collections through fine-needle aspiration and biopsy, as well as accomplish drainage of fluid collections such as pseudocysts [71,72]. As endoscopists increasingly become comfortable with pediatric use of EUS, its role in diagnosis and management of acute pancreatitis will become better defined.

All radiological and endoscopic tests may offer complementary information regarding the cause or complications associated with pediatric acute pancreatitis. Clinicians must weigh the potential benefits offered by an imaging technology against the drawbacks particular to each technique and decide on an algorithm for a particular patient. Typically, pediatric patients are best first assessed by TUS. Subsequently, with a prolonged acute pancreatitis course, there may be a need for either MRCP or CT to better delineate anatomy and to visualize potential complications. With the need for a therapeutic maneuver, both ERCP and EUS are becoming increasingly child-friendly and experience to date is showing them to be safe and effective.

## Management

The general measures undertaken in children with acute pancreatitis are similar to those in adults. In the majority of pediatric acute pancreatitis cases, clinical improvement occurs within a few days and discharge is possible in less than a week. Several changes in management of patients with acute pancreatitis have occurred in recent years. The International Association of Pancreatology and the American Pancreatic Association have recently published guidelines regarding optimal management of acute pancreatitis in adults [49]. Studies in adults and children suggest that aggressive fluid resuscitation early in the course improves outcomes [70,73–75]. Though, details of intravenous therapy, such as volume, rate, timing and composition of the fluid are not firmly established. In one pediatric study, fluid rates 1.5–2 times maintenance in the first 24 hours shortened length of stay and severity of disease [73]. The other major change in management is the recognition that early enteral feeding, whether by mouth or feeding tube, is safe and improves outcomes [73]. Until recently, all data on early enteral feeding was in adults. Abu-El-Haija et al. reported the results of early enteral feeding in children with acute pancreatitis [76]. All patients had mild acute pancreatitis and those allowed to eat within 24 hours of admission took food orally. Early feeds did not increase pain or

length of stay. Patients with higher fat intake had significantly lower pain scores [76].

## Outcomes

Overall, children generally have a mild clinical course and only a small fraction have severe complications. Pseudocysts represent the most frequent complication occurring in 10–30% of cases [4,5,13]. They typically present as a persistent abdominal discomfort, abdominal mass on physical examination, continued elevation of pancreatic enzymes, or on follow-up imaging. These pseudocysts usually resolve spontaneously and rarely require intervention: percutaneous catheter drainage (radiological placement or surgical), pancreatic duct stenting via ERCP, open surgical cyst–enteric anastomosis drainage and, perhaps, antibiotic therapy [77,78]. In expert hands, pseudocysts may be amenable to EUS intervention [72].

Despite a generally positive outcome for pediatric acute pancreatitis, 6% or fewer children develop multiorgan failure or pancreatic necrosis [23]. Some studies have found an association between particular triggers of acute pancreatitis and serious complications. As might be predicted, it appears that children who have complex medical histories, including those experiencing acute pancreatitis post liver transplantation, or in the context of a systemic disease, are more susceptible to severe and potentially fatal courses [23]. Mortality data have rarely been reported in children. Available data are listed in Table 23.4. The overall death rate for the 3899 reported patients was 6.2%. A database study from 2000 to 2009 of 55 012 children hospitalized with acute pancreatitis reported a mortality rate of about 1.0% [6].

## Acute Recurrent Pancreatitis

Acute recurrent pancreatitis (ARP) may be defined as at least two distinct episodes of acute pancreatitis separated by a return to normal baseline status [18]. It has been estimated that 10–35% of children have recurrent episodes of acute pancreatitis [23]. Upon the first presentation, etiologies that are amenable to therapy should be sought and, if identified, managed appropriately (including hypercalcemia, hypertriglyceridemia, biliary factors, and structural abnormalities). Any reversible cause should be eliminated whenever possible (including culprit medications). With additional attacks other investigations should be considered. Secretin-stimulated MRCP may unveil anatomic abnormalities predisposing

**Table 23.4** Mortality data in pediatric acute pancreatitis series [3–5,10,12–17,79].

| Author | Total subjects | Total deaths (percentage) | Notes about the study |
|---|---|---|---|
| Alvarez Calatayud [12] | 31 | 9.7 | 3 children died as a result of shock.<br>7 required surgical treatment |
| Benifla [13] | 589 | 9.7 | Review of 18 pediatric studies since 1965 |
| Choi [14] | 56 | 0 | Cases between 1994 and 1999 |
| DeBanto [15] | 301 | 2.0 | Deaths occurred in criterion hospitals only |
| Pezzilli [16] | 50 | 2.0 | 9 cases labeled as “severe” |
| Tiao [17] | 61 | 1.6 | 15 cases required surgery |
| Werlin [5] | 180 | 6.1 | All who died had underlying systemic illness |
| Goday [79] | 331 | 0.3 | Patients admitted to PICU with a primary diagnosis of AP |
| Goday [79] | 1695 | 6.8 | Patients admitted to PICU with a secondary diagnosis of AP |
| Park [10] | 271 | 1.9 | Only 1 of 4 deaths related to AP |
| Sanchez-Ramirez [4] | 55 | 0.0 | No deaths |
| Nydegger [3] | 279 | 11.1 | Deaths in patients with underlying disease |

The table lists, whenever available, the reported mortality rates for the pediatric acute pancreatitis series listed in Table 23.3, as well as other reported series without detailed etiologies. Overall, there is a 6.2% death rate reported (240 children out of 3899 total in the 11 studies listed below). Death occurs predominantly in children with co-occurring systemic illnesses (for example, hemolytic uremic syndrome or leukemia). In the series by Tiao, the single death was in a patient with acute necrotizing pancreatitis following L-asparaginase treatment for leukemia [17]. In the series by Pezzelli, the patient who died had developed multiorgan failure [16]. In the series by Goday, the percentage mortality is significantly higher in children admitted to the ICU with a primary diagnosis other than acute pancreatitis versus those admitted with a diagnosis of acute pancreatitis [79].
PICU, pediatric intensive care unit; AP, acute pancreatitis.

to ARP. A recurrence of an "idiopathic" attack of acute pancreatitis should direct the physician to seek for genetic predispositions via one-time comprehensive genetic testing [19,24]. A recent single-study retrospective review found that almost half of children with ARP having genetic testing had at least one mutation identified in *PRSS1*, *SPINK1*, or *CFTR* [25]. In another large multicenter study, almost half of patients with ARP had mutations in *PRSS1, SPINK1, CFTR*, or *CTRC* [76]. Since not all patients had genetic testing or were screened for fewer than four genes in this latter study, the percentage of patients harboring gene mutations is likely higher. In the same study, 75% of patients with chronic pancreatitis had genetic mutations. Mutational analysis is now commercially available for these genetic loci. It is anticipated that a high proportion of children with ARP and chronic pancreatitis will have genetic predispositions eventually identified. Along with mutational analysis, a comprehensive search for rare causes of acute pancreatitis is typically indicated. As it is believed that recurrent attacks of acute pancreatitis may eventually lead to morphological changes of chronic pancreatitis, prevention of further pancreatic injury is a key interventional goal, and identification of etiologic factors represents the first step.

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# 24

# Acute Pancreatitis Associated With Metabolic Disorders, Infectious Diseases, or Drugs

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## Introduction

Excessive alcohol consumption and gallstones are by far the most frequent etiologic factors for acute pancreatitis, accounting for up to 70% of all cases. The remaining 30% are patients where no triggering event can be identified (idiopathic pancreatitis, approximately 15%). In 15%, rare causes are identified in association with acute pancreatitis. These include anatomical variants, metabolic disorders, drugs, tumors, genetic abnormalities, and infectious diseases. In this chapter we review some of the rarer causes of acute pancreatitis.

## Metabolic Diseases

Hyperlipidemia and hypercalcemia are the best-known metabolic causes for acute pancreatitis. To a lesser extent, diabetic ketoacidosis (DKA), a severe complication of diabetes mellitus, can cause pancreatitis [1,2].

### Hypercalcemia

Hypercalcemia often results from primary hyperparathyroidism, a disorder of the parathyroid glands that is defined by an inappropriate secretion of parathyroid hormone (PTH) [2]. Elevated calcium levels affect other organs, including the gastrointestinal tract. However, determination of the incidence of hyperparathyroidism-related pancreatitis is difficult because patients often harbor comorbidities such as concomitant alcohol abuse, cholecystolithiasis, or hypertriglyceridemia. In many cases a definite assignment of the etiology of acute pancreatitis is not possible because patients have additional risk factors for acute pancreatitis. A coincidence of pancreatitis has been observed in 1.5–6.8% of patients with primary hyperparathyroidism, for example. The highest incidences were reported from India where a higher predisposition for (tropical) calcific pancreatitis was also observed [3,4]. Mean serum calcium levels are higher in patients with primary hyperparathyroidism and coexisting acute pancreatitis (12.8–13.3 mg/dL) compared to individuals with hyperparathyroidism who do not develop pancreatitis (11.6–12.1 g/dL) [3,5,6].

Hypercalcemia resulting in acute pancreatitis may also be attributed to unrelated disorders of the parathyroid glands, although these cases are extremely rare. Reports of malignant tumors [7,8] and iatrogenic causes of hypercalcemia such as calcium-containing infusions during cardiac surgery [9] or for parenteral nutrition [10] show that high circulating calcium levels predispose to pancreatitis.

The molecular mechanisms of hypercalcemia-induced pancreatitis are gradually being resolved. $Ca^{2+}$ is important for intracellular signaling and homeostasis. Disturbances in intracellular calcium levels impair its signaling function and high cytosolic levels within the exocrine acinar cells trigger premature protease activation [11,12]. Blocking the uptake of calcium into the cells or chelation of intracellular ionized $Ca^{2+}$ largely prevents digestive zymogen activation and pancreatic damage [13,14]. Several clinical trials have been set up to investigate the possibility of reducing the incidence and severity of pancreatitis by interfering with the intracellular effects of calcium.

### Hypertriglyceridemia

It is known that elevated lipid levels are associated with cardiovascular diseases. However, hyperlipidemia is also a rare but well-established cause of acute pancreatitis as

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well. This is mostly related to hypertriglyceridemia, because hypercholesterolemia by itself does not cause acute pancreatitis. Hypertriglyceridemia and hyperlipidemia in general are becoming more common in industrialized countries and it has been reported that over 1.5% of the US population has severe hypertriglyceridemia (defined as a serum concentration of 500–2000 mg/dL) [15]. Normal triglyceride levels for adults should be less than 150 mg/dL [16].

Acute pancreatitis secondary to hypertriglyceridemia is seen in between 1.3% and 3.8% of patients [17–19]. Typically, triglyceride levels above 1000 mg/dL (or 11.4 mmol/L) precipitate acute pancreatitis with a risk of around 5%. Triglyceride levels exceeding 2000 mg/dL more than double that risk to 10–20%.

Plasma triglycerides can be of exogenous or endogenous origin. Normally, dietary triglycerides are the main source and form the main lipid component in very low-density lipoproteins (VLDL). Once hydrolyzed in the small intestine they are resorbed and incorporated into chylomicrons and transported via lymphatic vessels to peripheral tissues for further utilization [19,20]. Cells of all parenchymal tissues secrete lipoprotein lipase that hydrolyze triglycerides and surface components of chylomicrons and VLDL to release free fatty acids for energy supply. Fatty acids are converted to fatty acid ethyl esters (FAEE) by carboxylester lipase (CEL), an enzyme also expressed in pancreatic acinar cells. FAEE themselves exert toxic direct effects on cells and also raise intracellular $Ca^{2+}$ concentrations that further promote cellular damage [21].

Patients with hypertriglyceridemia often have a concomitant history of diabetes mellitus (72%), hyperlipidemia (I, IV, and V according to Fredrickson's classification, 77%), alcohol abuse (23%), or gallstones (7%). Triglyceride levels are also elevated in the setting of DKA [18,22]. Typically, a lipid abnormality presents as a secondary factor (obesity, diabetes mellitus) whereas isolated hyperlipidemia (usually type I or V) is much less common [20]. Moreover, mild to moderate hypertriglyceridemia is not infrequently seen in alcoholic pancreatitis patients as a secondary effect of excessive alcohol consumption and this is much more common than hyperlipidemia-induced pancreatitis in association with primary or inherited forms of hypertriglyceridemia. Clinically, alcohol abuse still needs to be ruled out as the cause of acute pancreatitis whenever hypertriglyceridemia is diagnosed [20,23].

Diagnosis of hypertriglyceridemia-induced pancreatitis needs to be established early after disease onset because serum triglycerides levels usually fall rapidly after fasting periods and hypocaloric intravenous volume therapy [20].

It still remains controversial whether hypertriglyceridemia-induced pancreatitis tends to have a more severe course. Some data indicate that severe acute pancreatitis and organ complications may be more frequent in the presence of hypertriglyceridemia [23].

Initial treatment of hypertriglyceridemia-induced pancreatitis is the same as for other etiologies and includes fluid resuscitation, analgesia, and controlled oral food intake. In cases of severe acute pancreatitis and sustained excessive elevation of triglyceride levels lipid apheresis might be considered as a therapeutic option, but a clear benefit has not been consistently shown [24]. Emphasis should be laid on lifestyle modifications and lipid-lowering agents, fibrates in the first line, to prevent further attacks of pancreatitis [16].

### Diabetic Ketoacidosis

Acute pancreatitis can arise as a severe complication of DKA with a risk of a high mortality. Unfortunately it is often overlooked because abdominal pain or peritoneal irritation can result from ketoacidosis. Secondly hyperlipasemia/-amylasemia might be unspecifically elevated. Acute pancreatitis occurs in at least 10–15% of patients with DKA [22]. It has also been reported during nonketoacidotic hyperosmolar coma but this is very rare. The pathogenesis of acute pancreatitis in DKA is often attributed to hypertriglyceridemia that frequently occurs in parallel. Normally, hypertriglyceridemia is transient and resolves once DKA is corrected [22].

## Infectious Diseases

Data regarding the influence of microorganisms on acute pancreatitis and their incidence are rare and almost exclusively based on case reports. Sometimes it is not entirely clear whether other causes have been ruled out. Patients with acute pancreatitis based on an infectious agent often have a coexistent immunocompromising disorder or diabetes. The microbes involved include bacteria, viruses, fungi, and parasites (Table 24.1) [25].

### Bacteria

Numerous bacterial pathogens have been mentioned as causing acute pancreatitis but mostly they are described in single case presentations. Reports exist on *Mycoplasma*, *Legionella*, *Leptospira*, *Salmonella*, *Campylobacter*, and *Brucella* species as well as *Mycobacteria tuberculosis*. The pathogenesis of acute pancreatitis is most likely related to released bacterial toxins. Antimicrobial treatment was initiated upon diagnosis of bacteria-related acute pancreatitis in the majority of cases. However, some reports mention a resolution of pancreatitis with only symptomatic treatment.

**Table 24.1** Infectious agents associated with acute pancreatitis.

| Bacteria | Viruses | Fungi | Parasites |
|---|---|---|---|
| *Mycoplasma pneumoniae* | Paramyxovirus | *Aspergillus* | *Ascaris lumbricoides* |
| *Legionella pneumophila* | Hepatitis virus A–C, E | *Candida albicans* | *Toxoplasma gondii* |
| *Salmonella enteritidis* | Human immunodeficiency virus (HIV) | | *Cryptosporidium parvum* |
| *Campylobacter jejuni* | Varicella zoster virus<br>Coxsackievirus (most severe) | | *Plasmodium falciparum* |
| *Leptospira interrogans* | Herpes simplex virus | | *Strongyloides stercoralis* |
| *Brucella melitensis* | Cytomegalovirus | | *Fasciola hepatica* |
| *Mycobacterium tuberculosis* | Influenza virus (H1N1) | | *Clonorchis sinensis* |

### Viruses

Of all the infectious agents, most reports exist on mumps virus and its relation to acute pancreatitis. Paramyxovirus causes mumps and although this disease usually has a mild course, pancreatitis was reported in around 4% of mumps patients [26,27].

The association between hepatitis A, B, and C viruses and acute pancreatitis has also been described. Hepatitis E infections are increasingly diagnosed in Western countries and reports on associated acute pancreatitis have been published [28]. Acute pancreatitis usually has a favorable outcome when related to viral hepatitis.

Human immunodeficiency virus (HIV)-positive patients with the diagnosis of acquired immune deficiency syndrome (AIDS) are also at risk for acute pancreatitis. So far, data are not conclusive whether these patients suffer from a more severe course of the disease. Severe acute pancreatitis was reported in 10–50% of patients with AIDS [29]. Modern therapeutic regimens for HIV/AIDS are associated with a much lower incidence of acute pancreatitis and a lesser degree of severity than earlier regimes that included the use of high pentamidine and didanosine concentrations [30].

By far the greatest severity of pancreatitis via a non-HIV virus is that associated with coxsackievirus B infections, for which experimental animal models have also been established. Other suspected viruses include varicella zoster virus, causing chickenpox [30], influenza [31], herpes simplex, Epstein–Barr, and cytomegalovirus [25].

### Fungi

Data on fungal infections causing acute pancreatitis are extremely rare; more often fungi manifest as a late infectious complication of severe acute pancreatitis with infected necrosis. *Candida* sp. is the most common fungal microorganism that is seen secondary to pancreatitis [32]. There is one review that mentions *Aspergillus* species as a potential causative agent for pancreatitis [25]. Most fungal infections involving the pancreas are superinfections of pancreatic or extrapancreatic necrosis and thus secondary events. Once they occur they have a negative effect on outcome and mortality. Prior antibiotic treatment of (bacterially) infected necrosis does not appear to increase the rate of fungal infection of necrosis.

### Parasites

Some case reports exist on acute pancreatitis caused by *Toxoplasma*, *Cryptosporidium*, *Ascaris*, *Plasmodium falciparum* infections or helminths (*Strongyloides*) [25,33,34]. An immunomediated mechanism is discussed as being the underlying mechanism but even immunocompetent individuals can develop pancreatitis. For parasites such as *Ascaris lumbricoides*, *Fasciola hepatica*, and *Clonorchis sinensis* the disease mechanism is identical to that of gallstone-induced pancreatitis: impaction in the duodenal papilla and obstruction of the pancreatic duct. They account for up to 5% of cases of "biliary" pancreatitis in some parts of Asia and China and endoscopic removal of the parasite from the papilla remains the therapy of choice.

## Drug-Related Diseases

According to the World Health Organization (WHO) more than 525 drugs have been reported to cause acute pancreatitis as a potential side-effect. It is expected that the number of medications will increase in parallel with the approval of new drugs and accumulating case reports [35]. However, the level of evidence differs as knowledge is essentially extrapolated from case reports with varying strength in quality [36,37]. By definition, case reports only produce the lowest level of evidence in epidemiological studies. Moreover, drug-related acute pancreatitis is usually not accompanied by other clinical

or laboratory signs of adverse drug reactions, such as a rash, lymphadenopathy, or eosinophilia. Therefore diagnosis is often difficult to establish [38]. A rechallenge with the suspected drug and induction of an additional attack of pancreatitis (after initial withdrawal) allows researchers to conclude potential causality but is not definitive proof. Apart from this challenge, ethical considerations limit the use of re-exposure to a drug in order to trigger a second attack of pancreatitis with its potential complications.

The incidence of drug-induced pancreatitis is low and is estimated to account for 0.1–2% of all cases [39,40]. Very young and older people, women, and patients with immunosuppressive disorders (such as HIV) or inflammatory bowel disorders are at higher risk. Risk increases in these groups by up to fourfold and is most probably related to immune-mediated reactions and the types of drugs prescribed for these disorders [35,37,41].

There are different ways to classify drugs according to their risk of causing adverse events. With regard to acute pancreatitis the classification model of Badalov and coworkers from 2007 is currently the most frequently used. It subdivides drugs into four groups (class I–IV), based on the quality of published evidence for each agent reported as having caused acute pancreatitis [42]:

- *Class I*: Group with the highest level of evidence and the presence of a positive rechallenge test for the drug. Class I drugs can be further subdivided into those in which other potential causes for acute pancreatitis (i.e., alcohol, gallstones, hypertriglyceridemia) have been ruled out (Ia) and those where other causes were not excluded in the relevant reports (Ib).
- *Class II*: At least four case reports for the particular drug are required. In addition, ≥75% of the cases must show a consistent drug latency, meaning that time of onset of pancreatitis is within a reasonable time frame after drug consumption. The mean interval between initial drug intake and start of symptoms is around 5 weeks, with a wide range of 2–36 weeks [43].
- *Class III*: At least two case reports exist but there is neither a consistent latency among the cases nor a published rechallenge test.
- *Class IV*: Weakest level of evidence based on a single case report, no rechallenge test was done.

Alternatively, drug-related adverse effects are classified by application of the Bradford Hill criteria. Nine different criteria evaluate the evidence of causation and one of them is the claim for biological plausibility, meaning that the proposed causality must have been shown in an experimental laboratory setting [44].

A third classification system groups drugs according to a definite, probable, or possible causality for an adverse reaction. The main characteristics include (i) a reasonable temporal relationship from drug intake to onset of symptoms, (ii) a known underlying pharmacological mechanism, (iii) presence or absence of other causes for the particular side-effect, and (iv) recurrent disease after rechallenge [45]. Depending on the quality of the case report, it can happen that a suspected medication might be classified once as a definite and once as a probable risk factor [37].

The underlying mechanism of drug injury on the pancreas is likely based on idiosyncratic reactions. This type of reaction is characterized as being unpredictable, dose independent, and with varying latency. From a pathophysiological point of view idiosyncratic reactions are often mediated by an immunologic or cytotoxic mechanism of the specific compound or its metabolites. Unfortunately, they are difficult to reproduce in experimental animal models, whereas effects of intrinsic toxicity are mimicked more easily. Intrinsic toxicity implies organ damage in a dose-dependent way and is usually seen as toxicity after drug overdoses. With regard to the pancreas there are only a few reports based on an intrinsic mechanism covering acetaminophen, erythromycin, and carbamazepine [42].

A list of drugs often named in association with acute pancreatitis is given in Box 24.1. In addition, some of the most frequently cited drugs and their corresponding potential pathophysiological mechanisms are discussed here.

Nonsteroidal anti-inflammatory drugs (NSAID) have been proposed to induce acute pancreatitis, probably due to inhibition of prostaglandins. Prostaglandins seem to have a protective and membrane-stabilizing effect on pancreatic cells, as shown in experimental models [35,46]. The highest risks were reported for diclofenac (odds ratio [OR] 5.0) and the lowest for naproxen (OR 1.1). Use of selective COX-2 inhibitors can lower the risk for acute pancreatitis [37,47] and unselective NSAID given prophylactically as suppositories have been shown to lower the rate of endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis, at least in very high-risk patients.

Estrogens, which are also used in oral contraceptives, may induce acute pancreatitis by reducing lipoprotein lipase activity, which then increases serum triglycerides and fatty acids. These components are known to be precipitating factors for acute pancreatitis [48].

Angiotensin-converting enzyme (ACE) inhibitors such as captopril, enalapril, lisinopril, and others decrease degradation of bradykinins that are released during acute pancreatitis. Bradykinins cause a local angioedema that could favor tissue edema or pancreatic duct obstruction and subsequent organ damage. There is also evidence for a direct toxic effect of ACE inhibitors on the pancreas [49,50].

**Box 24.1 Drugs definitely and probably associated with acute pancreatitis**

**Definite association**

- Asparaginase
- Azathioprine
- Carbamazepine
- Cytarabine
- Didanosine
- Enalapril
- Erythromycin
- Estrogens
- Furosemide
- Lamivudine
- Mercaptopurine
- Mesalamine
- Opiates
- Pentamidine
- Pravastatin
- Steroids
- Sulfasalazine
- Trimethoprim/sulfamethoxazole
- Tetracycline
- Valproic acid

**Probable association**

- Cyclopenthiazide
- Oxaliplatin
- Mesalazine
- Rifampin
- Octreotide
- Metformin
- Hydrochlorothiazide
- Propofol
- Tamoxifen

*Source:* Adapted from Nitsche et al. 2012 [37] and Hung and Abreu Lanfranco 2014 [35].

Several studies report on the side-effects of azathioprine and 6-mercaptopurine, and these include acute pancreatitis. Interestingly azathioprine-induced pancreatitis is almost never reported outside the field of inflammatory bowel disease (IBD), especially Crohn disease [37]. Presumably the drug's toxicity is associated with the underlying disease. Affected individuals carry an up to 8- to 13-fold increased risk of acute pancreatitis [51,52]. With regard to 6-mercaptopurine, 3.25–6% of patients with IBD being treated with that drug develop acute pancreatitis [53,54]. It is noteworthy that 5-aminosalicylic acid (OR 0.7) and sulfasalazine (OR 1.5), which are also frequently used for IBD treatment, were not associated with significantly increased pancreatitis risk in a recent report [55].

3-Hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (commonly known as statins), such as simvastatin, pravastatin, and atorvastatin, are thought to have direct toxic effects and in a number of cases drug interactions involving cytochrome P450 3A4 (CYP3A4) seem to contribute to pancreatitis [50,56]. However the overall risk for acute pancreatitis is rather low with an OR ranging from 1.01 to 2.02, so statins seem to be of low importance for drug-induced pancreatitis [56].

Nucleoside reverse transcriptase inhibitors, such as didanosine, lamivudine, and stavudine, have a toxic effect on the pancreas. In addition they cause metabolic disturbances [50]. HIV patients with a low CD4 count are at a higher risk [37].

Consumption of valproic acid or other antiepileptic drugs is associated with an increased risk for acute pancreatitis, presumably mediated by direct toxic effects and an increase in reactive oxygen species [37,50]. According to recent studies and in contrast to older reports, selective serotonin reuptake inhibitors (SSRI) do not increase the risk of acute pancreatitis [57].

Soon after introduction of incretin mimetics (glucagon-like peptide-1 [GLP-1] agonists) safety concerns arose about the potential of acute pancreatitis as a side-effect, especially for exenatide and sitagliptin. Reports were also published on dipeptidyl-peptidase-4 (DPP-4) inhibitors [58,59]. Recent analyses failed to find an unequivocal effect on the incidence of pancreatitis and were explained by the fact that people with diabetes already at increased risk of developing acute pancreatitis [35,60,61]. A higher prevalence of gallstone disease or hypertriglyceridemia is also seen in this patient group [62]. Summing up, the role of incretin mimetics is not conclusively answered: preexisting risk factors such as diabetes mellitus and cardiovascular disorders explain most pancreatitis cases in this group and the large safety trials on DPP-4 inhibitors have largely calmed the initial concerns about an association with pancreatitis [63].

For all drug-associated forms of pancreatitis management consists of drug discontinuation and supportive care, as for other types of acute pancreatitis. If necessary, a drug of a different class will be selected for further therapy. However, drug-induced pancreatitis remains a rare entity and physicians should at first rule out other causes of acute pancreatitis including occult gallstone disease [64], immoderate alcohol consumption [65], and underlying genetic changes [66]. A critical review of the patient's medication profile is mandatory before assuming a drug to be causative for pancreatitis.

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# 25

# Radiologic Diagnosis and Staging of Severe Acute Pancreatitis

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## Introduction

The role of imaging is important in diagnosis and evaluation of severity in patients with known or suspected acute pancreatitis. Common imaging techniques for the evaluation of the pancreas include transabdominal ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI). Angiography and positron emission tomography (PET)-CT are sometimes used to diagnose special complications in acute pancreatitis patients. This chapter deals with these imaging techniques in the diagnosis of local and systemic inflammation associated with acute pancreatitis.

## Classification of Acute Pancreatitis

Acute pancreatitis represents a spectrum of inflammatory disease ranging from clinically mild to severe acute pancreatitis [1]. In recent years a radiological approach has been commonly used to diagnose acute pancreatitis and evaluate severity. For these purposes, CT is one of the most popular methods. Abdominal CT has been commercially available since the 1970s.

In 1983, Kivisaari et al. reported that pancreatic necrosis in acute pancreatitis could be diagnosed using CT [2]. Bradley et al. [3] and Johnson et al.[4] also reported the usefulness of CT in diagnosis of pancreatic necrosis in acute pancreatitis patients, in 1989 and 1991, respectively. These studies regarded pancreatic necrosis as one of the most important factors in predicting a poor prognosis (Table 25.1).

In contrast, based on broadening of inflammation, Balthazar et al. [5] established a CT grading system to define the severity of acute pancreatitis in 1985. This is called Balthazar's CT grade, and it became one of the most popular image-based grading systems of severity of acute pancreatitis. It was partially modified in 2002 [6]. In 1985 the Balthazar system classified acute pancreatitis into five grades: A—normal, B—focal or diffuse enlargement of the pancreas, C—peripancreatic inflammation with intrinsic pancreatic abnormalities, D—intra- or extrapancreatic fluid collections, and E—two or more large collections of gas in the pancreas or retroperitoneum. In the 2002 version, grades D and E were modified: D—single fluid collection and E—two or more fluid collections and/or retroperitoneal air, respectively.

The two concepts that assist in diagnosis—local pancreatic damage and evaluation of broadening of inflammation—were combined into the CT severity index to predict prognosis (see section on CT severity index later in this chapter).

According to these moves to diagnose and evaluate acute pancreatitis using CT, a newer classification of acute pancreatitis was discussed at the Atlanta conference in 1992 [7]. In Atlanta, following previous symposia [8–10], severity of acute pancreatitis was classified into two grades: mild and severe. In this classification, severe acute pancreatitis was associated with organ failure and/or local complications, such as pancreatic necrosis, pancreatic fluid collection, acute pseudocyst, or pancreatic abscess. Since it was considered that CT could diagnose these local complications accurately, descriptions of the Atlanta classification were largely devoted to diagnostic criteria of local complications on CT. Following this symposium, radiological findings associated with acute pancreatitis were described in medical reports based on these terminological definitions.

The Atlanta classification was universally applied for two decades from 1992. During these two decades, two important insights were reported. First, Casas et al.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 25.1** Diagnostic criteria of pancreatic necrosis and their accuracy.

| Study | *n* | Timing of performing CT | Scanning protocol | Diagnostic criteria | Accuracy for diagnosis of pancreatic necrosis | |
|---|---|---|---|---|---|---|
| | | | | | Sensitivity | Specificity |
| Kivisaari 1983 [2] | 28 | <1 day from administration | NC + CE-CT | <15 HU[a] | 100 | – |
| Block 1986 [29] | 77 | – | CE-CT | – | 85 | 50 |
| Nuutinen 1988 [30] | 28 | – | NC + CE-CT | <30 HU[b] | – | – |
| Bradley 1989 [3] | 37 | <2 days from administration | CE-CT | <40 HU[b] | – | – |
| Larvin 1990 [31] | 60 | <7 days from administration | CE-CT | <30 HU[b] | – | – |
| Johnson 1991 [4] | 13 | <3 days from administration | CE-CT | Lack of enhancement | 100 | 100 |
| Bradley 1993 [7][c] | – | – | CE-CT | <50 HU[b] or comparison to splenic enhancement | – | – |
| Casas 2004 [11] | 184 | <3 days from the onset | CE-CT | – | 53 | 90 |
| Takeda 2005 [27] | 102 | <7 days from the onset | CE-CT | Lack of enhancement | – | – |
| Tsuji 2007 [32] | 30 | <3 days from the onset | Perfusion CT | Comparison of hepatic perfusion | 100 | 95.3 |
| Spanier 2010 [33] | 166 | – | – | – | 0 | – |
| Tsuji 2014 [34] | 48 | <3 days from the onset | CE-CT | Lack of enhancement | 74.5 (64–82)[d] | 87.5 (78–97)[d] |
| | | | NC + CE-CT | | 77.5 (64–91)[d] | 88 (81–97)[d] |
| | | | CE + sub-CT | <15 HU[a] | 91 (82–100)[d] | 94.7 (89–100)[d] |
| Yadav 2015 [35] | 32 | <3 days from the onset | Perfusion CT | PBF <23 mL/100 mL/min | 87.5 | 100 |
| Pienkowska 2016 [36] | 79 | <1 day from the onset | Perfusion CT | Permeability <40 mL/100 mL/min | 100 | 84.2 |

NC, noncontrast; CE, contrast-enhanced; sub-CT, subtraction color map based on duel energy CT; PBF, pancreatic blood flow, –, not described.
[a] Difference of CT values between pre- and post-injection of contrast agent.
[b] CT values of post-injection of contrast agent.
[c] Atlanta criteria.
[d] Average values among three reviewer (minimum–maximum).

reported that the early CT, which was performed within 3 days from the onset, could not diagnose pancreatic necrosis accurately [11]. Second, a new concept, "walled-off necrosis (WON)," was proposed [12,13]. Early pancreatic complications (e.g., pancreatic and peripancreatic necrosis) could develop WON 4 weeks later than the onset. The concept of WON has clarified our understanding of pseudocysts (Table 25.2). Our improved knowledge of the pathophysiology of organ failure and necrotizing pancreatitis and their outcomes, as well as improved diagnostic imaging, made it necessary to revise the Atlanta classification.

The Atlanta classification was also revised in 2012 [14]. According to this classification of acute pancreatitis, known as the "revised Atlanta classification," the severity of acute pancreatitis is categorized into three groups: mild, moderate severe, and severe. In patients without local and systemic complication, the severity is judged to be mild. Patients with local complication without organ failure or transient organ failure which can be controlled within 48 hours from induction of treatment are classified in the moderate severe group. Patients with organ failure that resists treatment resulting in persistence for 48 hours or more are classified as severe (Table 25.2).

At the same time as the revised Atlanta classification, the determinant-based classification [15] was also published by another group. As with the revised Atlanta classification, the aim of this classification was to revise the original Atlanta classification. However, the determinant-based classification regards (peri)pancreatic necrosis as the more important factor to predict prognosis, compared to the revised Atlanta classification. According to determinant-based classification, the severity of acute

**Table 25.2** Diagnosis of local complications on imaging.

| Image on CT | | | | | | Terminology | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Location** | **Density** | **Wall** | **Perfusion** | **Timing from onset** | **Pathology** | **Atlanta** | **Revised Atlanta** | **Determinant-based** | **Late complication** |
| Pancreatic | Heterogeneous and nonfluid density | None | None or less | <3 days | Ischemic tissue | Pancreatic necrosis | ANC | (Peri) Pancreatic necrosis | Healing without necrosis or WON |
| | | | None | <4 weeks | Pancreatic necrosis | | | | WON |
| | | | | | Fat necrosis | | | | |
| | | | | | Inflammatory tissue | Pancreatic fluid collection | | | Resolving |
| Peripancreatic | Homogeneous fluid density | | | | Sterile fluid | | APFC | | PPC |
| | | | | | | Acute pseudocyst | PPC | Not described | |
| | | Well-defined | | ≥4 weeks | Infected fluid | Pancreatic abscess | | | |
| | Heterogeneous with fluid and nonfluid density | | | | Sterile | | WON | | WON |
| | | | | | Infected | | | | |

ANC, acute necrotic collection; APFC, acute pancreatic fluid collection; PPC, pseudocyst; WON, walled-off necrosis.

pancreatitis is categorized into four groups: mild, moderate, severe, and critical. If the patient has neither (peri) pancreatic necrosis nor organ failure, severity is judged to be mild. The patient with sterile (peri)pancreatic necrosis and/or transient organ failure is classified as moderate. The patient with infected necrosis or persistent organ failure (more than 48 hours from start of treatment) is classified into the severe group. The patient with both infected necrosis and persistent organ failure is classified into the critical group (Table 25.2).

Between the revised Atlanta and determinant-based classifications, there is a difference with regard to the radiological definition of pancreatic necrosis. According to determinant-based classifications, (peri)pancreatic necrosis is nonviable tissue without a radiologically defined wall. In contrast, the revised Atlanta classification makes categorizes pancreatic necrosis into two types according to a diagnosis of well-defined wall: acute necrotic collection (ANC) and WON (Table 25.2). In the determinant-based classification, there is no description with regard to necrotic tissue with radiologically well-defined wall, which was categorized into "acute pseudocyst or pancreatic abscess" and "pancreatic pseudocyst or walled-off necrosis" in the Atlanta and revised Atlanta classifications, respectively. Thus, it appears that the concept of pancreatic necrosis in the determinant-based classification is not the same as that in the revised Atlanta classification.

In both the revised Atlanta and determinant-based classifications, the development of persistent organ failure (48 hours or more from start of treatment) is needed to diagnose severe or critical acute pancreatitis. Thus, in the emergency room we can use only two grades of severity: mild or moderate. From this point of view, a patient with moderate acute pancreatitis is potentially at high risk of developing severe or critical acute pancreatitis. Accurate diagnosis of pancreatic necrosis is one of the most important factors to perform in the emergency room for appropriate triage based on the severity of recent classifications.

## Radiographic Diagnosis of Severe Acute Pancreatitis

Two major types of acute pancreatitis are known: acute edematous and necrotizing pancreatitis [14]. Since the prognoses and strategies of treatment of these two are totally different, it is necessary to diagnose them accurately.

### Acute Edematous Pancreatitis

According to Klöppel [16], the pancreas is enlarged without necrosis on gross pathology in acute edematous pancreatitis, although microscopic areas of parenchymal fat necrosis may also be found. Lack [17] stated that hemorrhage and intraparenchymal necrosis is absent in the pancreas. Importantly, in acute edematous pancreatitis, where fat necrosis does not come into contact with a blood vessel, it does not damage the vessel wall, leading to macroscopic pancreatic necrosis [16]. Thus contrast enhancement of pancreatic parenchyma is usually normal on contrast-enhanced CT (CE-CT). In addition, the revised Atlanta classification [14] described that CE-CT shows pancreatic swelling with relatively homogeneous enhancement in acute edematous pancreatitis (Fig. 25.1).

In the Atlanta classification [7], the macroscopic feature of mild acute pancreatitis was interstitial edema. Therefore, in those days, mild acute pancreatitis was

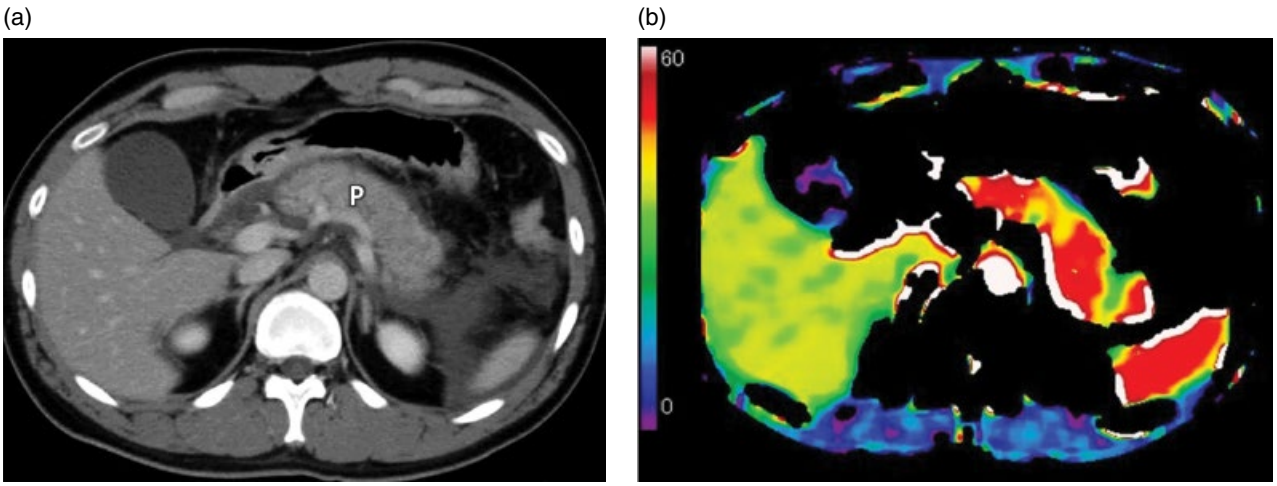


**Figure 25.1** Acute edematous pancreatitis. (a) Contrast-enhanced CT shows enlargement of pancreas (P). At the same time as (a), perfusion CT was obtained. (b) Tissue blood flow was demonstrated based on the left-sided scale bar. Pancreatic blood flow was red-yellow (about 40 mL/100 g/min), which indicates that pancreatic blood flow was high.

nearly equal to acute edematous pancreatitis. One of the important things to note is that the revised Atlanta classification [14] changes the definition of mild acute pancreatitis to "pancreatitis with no organ failure and no local or systemic complications." In the revised Atlanta classification, local complications are redefined as acute peripancreatic fluid collection (APFC), pancreatic pseudocyst (PPC), acute necrotic collection (ANC), and walled-off necrosis (WOF). Thus, using the revised Atlanta, acute edematous pancreatitis with APFC, one of the local complications, is classified into moderate severe acute pancreatitis, not mild. The prognosis of patients with acute edematous pancreatitis is much better than that of those with local complication.

### Acute Necrotizing Pancreatitis

Approximately 2–10% of acute pancreatitis patients develop necrosis of pancreatic parenchyma and/or peripancreatic tissue [14,18]. Both in the Atlanta and the revised, acute necrotizing pancreatitis is defined as "acute pancreatitis with pancreatic necrosis which involves pancreatic parenchymal necrosis and/or peripancreatic fat necrosis." Reports put the mortality rate for acute pancreatitis patients with pancreatic necrosis at roughly 30% [19].

Development of pancreatic parenchymal necrosis consists of three steps: acinar injury, vascular injury, and tissue injury. The initial pathway in the development of pancreatitis is ectopic activation of trypsinogen in acinar cells and/or activation of macrophages [20–23] or neutrophils [24]. The activation of trypsinogen in acinar cells leads to the acinar cells being destroyed, followed by releases of trypsin and damage-associated molecular pattern molecules (DAMP) [25] into the pancreatic vessels. Vascular epithelial cells are injured by the released trypsin and/or DAMP, resulting in damage to the coagulant–fibrinolytic system of the endothelial cells. In combination with this endothelial damage, periarterial fat necrosis, interstitial edema, and/or bleeding due to inflammation reduces tissue perfusion by compressing vessels. If this reduction of perfusion continues and/or ischemic–reperfusion damage occurs, serious tissue damage often develops, leading to acute necrotic collection (ANC) [26,27]. At 4 weeks or more later, ANC may develop WON. Since ANC and WON are irreversible, attempts to prevent the development of ANC or WON should be started based on a diagnosis of pancreatic ischemia [28] (see sections on acute necrotic collection and walled-off necrosis later).

To diagnose pancreatic necrosis (pancreatic ischemia, ANC, and WON), CE-CT, MRI, or CE-US are used. According to CE-CT criteria in the revised Atlanta classification, acute necrotizing pancreatitis is diagnosed based on lack of pancreatic parenchymal enhancement by intravenous contrast agent and/or presence of peripancreatic necrosis (Table 25.1) [2–4,7,11,27,29–36].

## Diagnosis of Local Complications of Acute Pancreatitis

As was described earlier, local complications are divided in to four types: APFC, ANC, WON, and PPC in the revised Atlanta classification.

### Acute Peripancreatic Fluid Collection

In the Atlanta classification [7], pancreatic fluid collections occurred early in the course of acute pancreatitis, were located in or near the pancreas and always lacked a wall of granulation or fibrous tissue. The precise composition of such collections was not known pathologically. Instead of the term "pancreatic fluid collections" [7], the use of the term APFC was suggested in the revised Atlanta classification [14]. APFC is peripancreatic fluid association with interstitial edematous pancreatitis and without necrosis. In CE-CT, APFC is a homogeneous collection with fluid density, without abnormal peripancreatic fascial planes, without defined wall encapsulating the collection, and without intrapancreatic extension (Table 25.2, Fig. 25.1).

### Acute Necrotic Collection

ANC includes parenchymal necrosis of pancreas and peripancreatic fat necrosis. Thus, acute pancreatitis with ANC is the same as acute necrotizing pancreatitis. A collection contains variable amounts of both fluid and necrotic tissues. As was previously described, ANC is a pre-stage of developing WON. The border between ANC and normal tissue is gray (Fig. 25.2).

Parenchymal necrosis of pancreas appears as a low attenuation or non-enhancing area on CE-CT [4,5,37]. Early studies reported that CE-CT was highly accurate for the detection of pancreatic necrosis [3,4,29]. These studies mostly included surgical cases, so very few patients in the early stage of acute pancreatitis were included. Four previous studies reported the accuracy of CE-CT in predicting pancreatic necrosis in the early stages of acute pancreatitis [11,33,34,38]. One study showed that pancreatic necrosis was not detected in any of 49 patients with acute pancreatitis on CE-CT performed within 72 hours of onset (sensitivity: 0%) [33], while the three other studies [11,34,38] showed that CE-CT had a sensitivity of 63%, 72%, and 75%, respectively, for the early phase of acute pancreatitis (within 1 day of admission or 72 hours of onset).

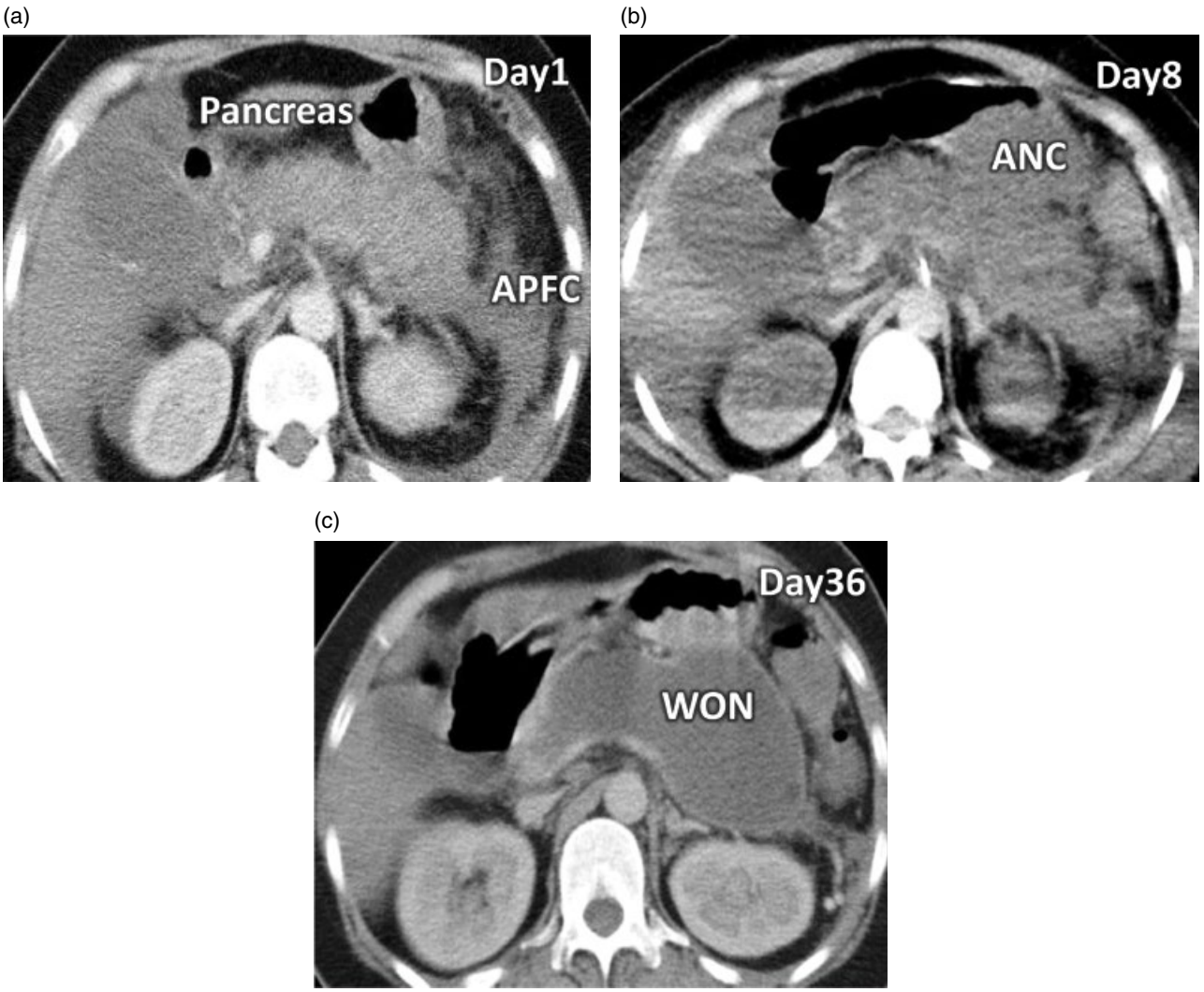


**Figure 25.2** Acute necrotizing pancreatitis and its natural history. Due to serious complications of acute pancreatitis, this patient had three CT scans during the course of the disease. Contrast-enhanced CT shows homogeneous enhancement of pancreas at day 1 (a). On day 8 (b), enhancement of pancreas was markedly reduced, so this case was diagnosed as acute necrotizing pancreatitis. (c) On day 36, the scan shows acute necrotic collection (ANC) and altered walled-off necrosis (WON), which was surrounded by a well-defined wall.

As Klöppel described previously [16], pancreatic inflammation can reduce pancreatic blood flow, resulting in development of pancreatic necrosis. Using angiography, Takeda also showed that pancreatic parenchyma with vasospasm of the intrapancreatic artery develops parenchymal necrosis with high ratio [27]. Perfusion CT [39,40], which can measure parenchymal blood flow accurately, has shown promise as a method that can accurately detect pancreatic necrosis at an early stage of acute pancreatitis with an estimated sensitivity of 88–100% and specificity of 84–100% [32,35,36] (Fig. 25.3). Perfusion CT can differentiate reversible from irreversible ischemic tissue, and thus has been used widely for diagnosing acute brain stroke (Fig. 25.1). According to Yadav et al. [35], pancreatic parenchyma with poor blood flow (cut-off value about 20 mL/100 g/min or less and normal pancreas 100 mL/100 g/min or more) could develop pancreatic necrosis with high ratio. At 24 hours from onset, Pienkowska et al. [36] showed that perfusion CT can predict development of pancreatic necrosis accurately. This suggests that the parenchymal blood flow is decreased even at an early stage of acute pancreatitis in areas of impending necrosis (Fig. 25.4 and 25.5).

Dynamic contrast-enhanced magnetic resonance imaging (CE-MRI) [41] may be an alternative to CE-CT for detecting pancreatic necrosis. Indeed, MRI has certain advantages over conventional CE-CT, including greater sensitivity in detecting ischemia. Moreover, when MR angiography is performed in conjunction with MRI, assessment of vessel patency is also possible.

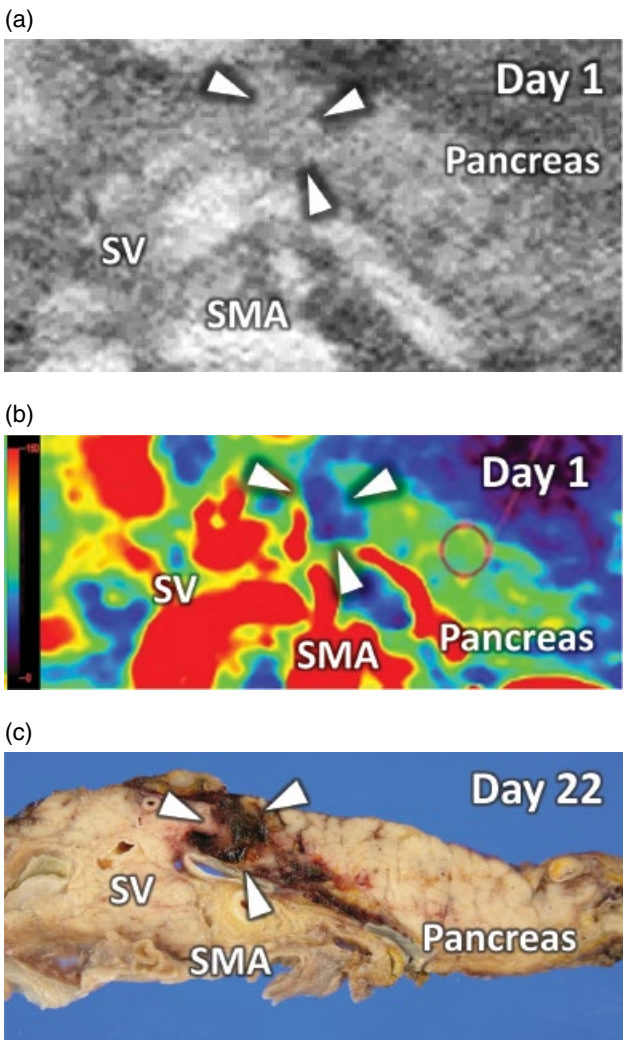


**Figure 25.3** Difficulty in identifying pancreatic parenchymal necrosis using conventional CT. (a) Using contrast-enhanced CT (day 1), regional necrosis on the pancreatic head was not identified (arrowheads). (b) However, perfusion CT showed markedly reduction of pancreatic perfusion. (c) The poor perfusion area on perfusion CT (b) was concordant with an area of pancreatic necrosis at autopsy.

### Walled-Off Necrosis

WON is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has a well-defined wall [12–14]. It arises secondary to ANC and usually occurs at >4 weeks after onset of acute pancreatitis. On CE-CT, WON often appears heterogeneous, with liquid and nonliquid density with varying degrees of loculations [14]. Ultrasound (both percutaneous and endoscopic) or MRI is better for diagnosing the heterogeneity of WON compared to CE-CT, because the identification of the liquid area in necrosis by MRI or ultrasound is more accurate than that by CE-CT.

Compared to ANC, WON has well-defined walls at marginal zone of necrosis, and therefore the border is clear. WON develops liquefaction of necrotic area heterogeneously and gradually [17]. Some areas of WON have inner walls, and WON can thus be separated into various sizes. In addition, WON develop in many areas, side by side or separately. Therefore, in acute pancreatitis patients with local complications, there is a possibility that many areas of WON will develop in the abdominal cavity.

In cases of suspected ANC/WON infection, rapid enlargement of the necrotic area, inflammatory changes in the neighboring fat, gas in the necrotic area, and surrounding paralytic ileus may help to diagnose the location of the infection (Fig. 25.6). One study suggests that PET-CT may be useful in identifying infected WON [42], although it is expensive.

### Pancreatic Pseudocyst

It should be noted that the definition of the term PPC has recently changed. Previously, PPC included both WON and encapsulating fluid [7]. In the latest international classification, the revised Atlanta [14], PPC is redefined as an encapsulating collection of fluid with a well-defined inflammatory wall. PPC usually occurs more than 4 weeks after onset, as well as WON. Any solid region is not identified as PPC, thus (endoscopic) US or MRI is useful to diagnose it (Fig. 25.7).

## Radiologic Staging of Severe Acute Pancreatitis

The concept of radiologic staging of severity of acute pancreatitis is based on two important findings: extent of inflammation and necrosis (ANC/WON).

### CT Severity Index

Combining the findings of broadening of inflammation and local pancreatic damage on CT, the CT severity index (CTSI) was published in 2002. In the CTSI, Balthazar CT grade A (normal pancreas) scores 0, grade B (enlargement of pancreas) scores 1, grade C (inflammatory changes in pancreas and peripancreatic fat) scores 2, grade D (single fluid collection) scores 3, and grade E (two or more poorly defined fluid collections) scores 4. The pancreatic condition is independently evaluated: no pancreatic necrosis on CT scores 0, pancreatic necrosis less than/equal to 30% of pancreas scores 2, >30–50% scores 4, and >50% scores 6. Grading severity is based on a CTSI score of 0–10: mild

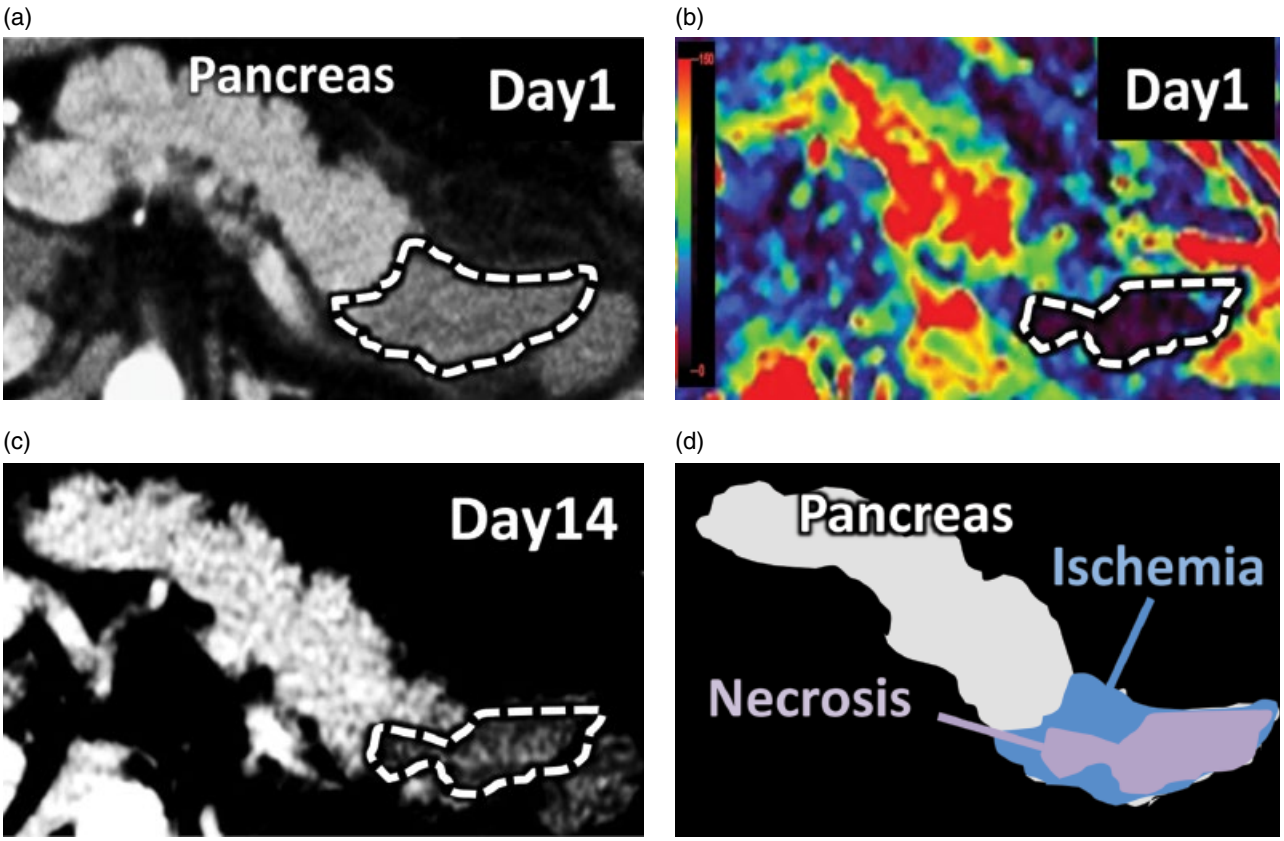


**Figure 25.4** Reversible ischemia and necrosis in early stage of severe acute pancreatitis. (a) Contrast-enhanced CT (day 1) showed a lack of enhancement of the pancreatic tail (area surrounded by dotted line). (b) Perfusion CT showed a poorly perfused area in the pancreatic tail, which was smaller than the area with lack of enhancement on contrast-enhanced CT. (c) The area with poor perfusion in the perfusion CT developed pancreatic necrosis. (d) Based on these findings, the schema shows that the marginal zone of pancreatic necrosis could have been reversible ischemia.

(score 0–3), moderate (score 4–6), and severe (score 7–10) [5,6]. The CTSI was modified in 2004 by Mortele et al. (MD-CTSI) [43]. The MD-CTSI resulted in higher interobserver agreement ratio, correlation with length of hospital stay, need for invasive therapy, incident organ failure, and the occurrence of infection (Table 25.3).

### Japanese CT Severity Index

In the latest Japanese definition of severe acute pancreatitis [44], Hiroto et al. established the JPN-CT severity score. In the definition, severe acute pancreatitis can be diagnosed either by the laboratory/clinical severity criteria or JPN-CT. The case mortality rate of patients with severe acute pancreatitis diagnosed by JPN-CT score was 14.8%. The case fatality of severe acute pancreatitis that fulfilled JPN-CT severity criteria (severity score ≥2 points) was as high as 30.8%.

## Limitations and Pitfalls of Radiological Diagnosis of Acute Pancreatitis

### Diagnosis of Early Necrosis of Pancreatic Parenchyma

The accuracy of CE-CT to diagnose pancreatic parenchymal necrosis within 3 days of onset is not adequate [11,37]. One potential explanation for this disappointing performance of CE-CT is that the attenuation of pancreatic parenchymal necrosis is similar to that of viable enhancing parenchyma on CE-CT in the early stages of acute pancreatitis, and the CT attenuation of pancreatic necrosis decreases over time as nonviable parenchyma liquefies [12,31]. Moreover, because the CT attenuation of pancreas may be altered by hemorrhage in necrosis or fatty infiltration, evaluation of regional variability in pancreatic enhancement becomes difficult with CE-CT.

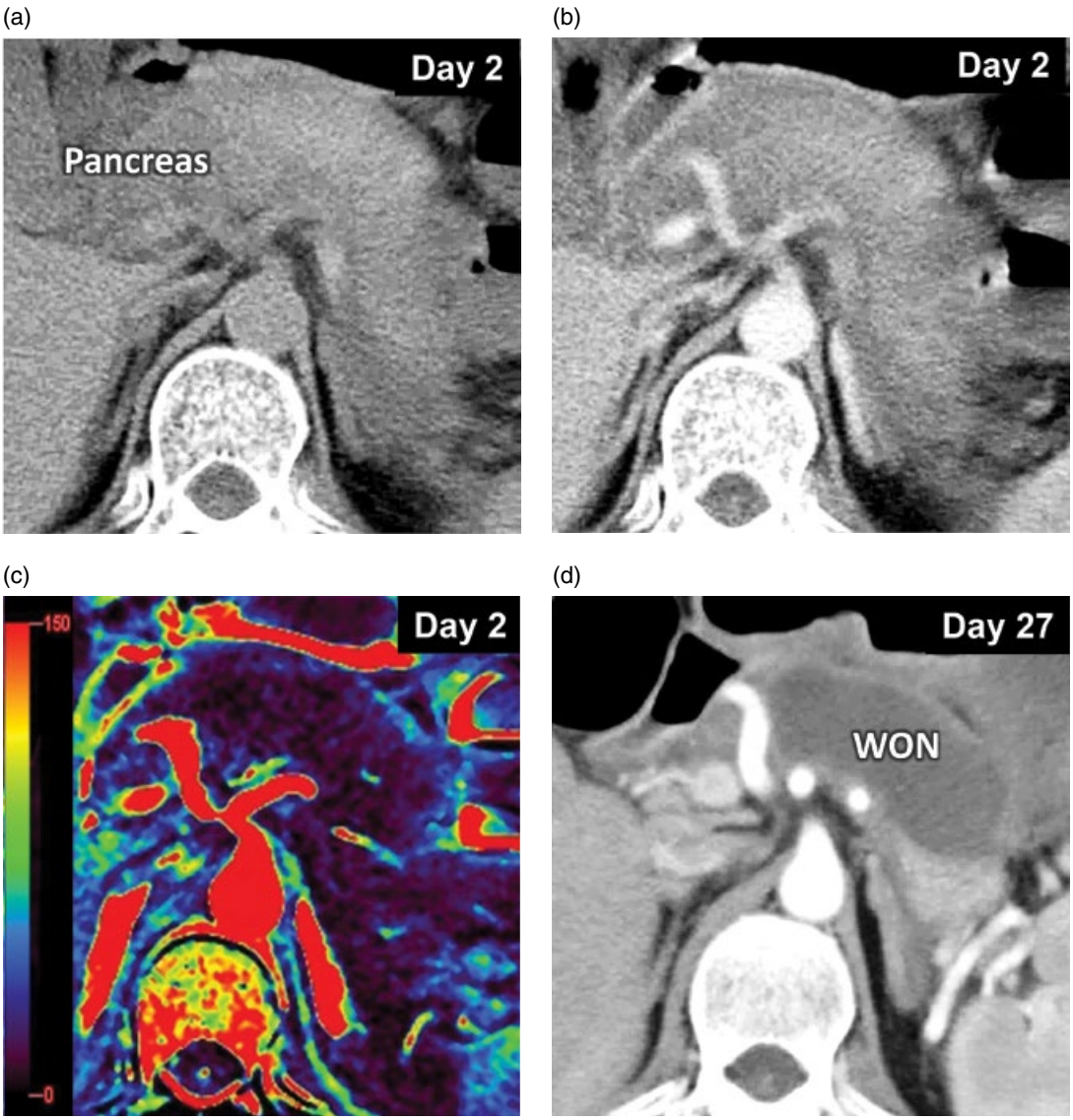


**Figure 25.5** Tissue hemorrhage makes it difficult to diagnose necrosis using contrast-enhanced CT alone. (a) Noncontrast CT showed elevation of CT values in pancreatic body. (b) On CE-CT alone, it is difficult to judge whether the elevation of CT value of pancreatic parenchyma was due to hemorrhage or enhancement by contrast agent. (c) Perfusion CT showed that pancreatic blood flow of the whole pancreatic body was extremely low. These findings show that the pancreatic body had already developed necrosis on day 2. (d) The poorly perfused area with slight elevation of CT values on noncontrast CT was concordant with the area with later necrosis.

Another reason why CE-CT may not be accurate in predicting parenchymal necrosis in the early stages may involve the difficulty of evaluating the effectiveness of contrast-enhanced material. Since the border of early parenchymal necrosis that is included in the ANC is not clear, selecting specific of areas with suspicious parenchymal necrosis in the case of early acute pancreatitis poses difficulties, in contrast to analyses of enhancements in well-defined lesions, such as a WON.

Although the detection of pancreatic parenchymal necrosis with CT imaging has led to the improved prognostic stratification of patients using the CT severity index [45], the inaccurate prediction of parenchymal necrosis using CE-CT and its large interobserver variability [43,46] may also lead to recent recommendations questioning the routine use of CT at an early stage of acute pancreatitis [47,48].

Despite the advantages discussed earlier, MRI is underused in the evaluation of patients with severe acute pancreatitis. This underutilization can be attributed to practical considerations—patients with severe acute pancreatitis have difficulty withstanding the lengthy MRI procedure. In addition, removal of all the magnetic instruments (e.g., sphygmomanometer,

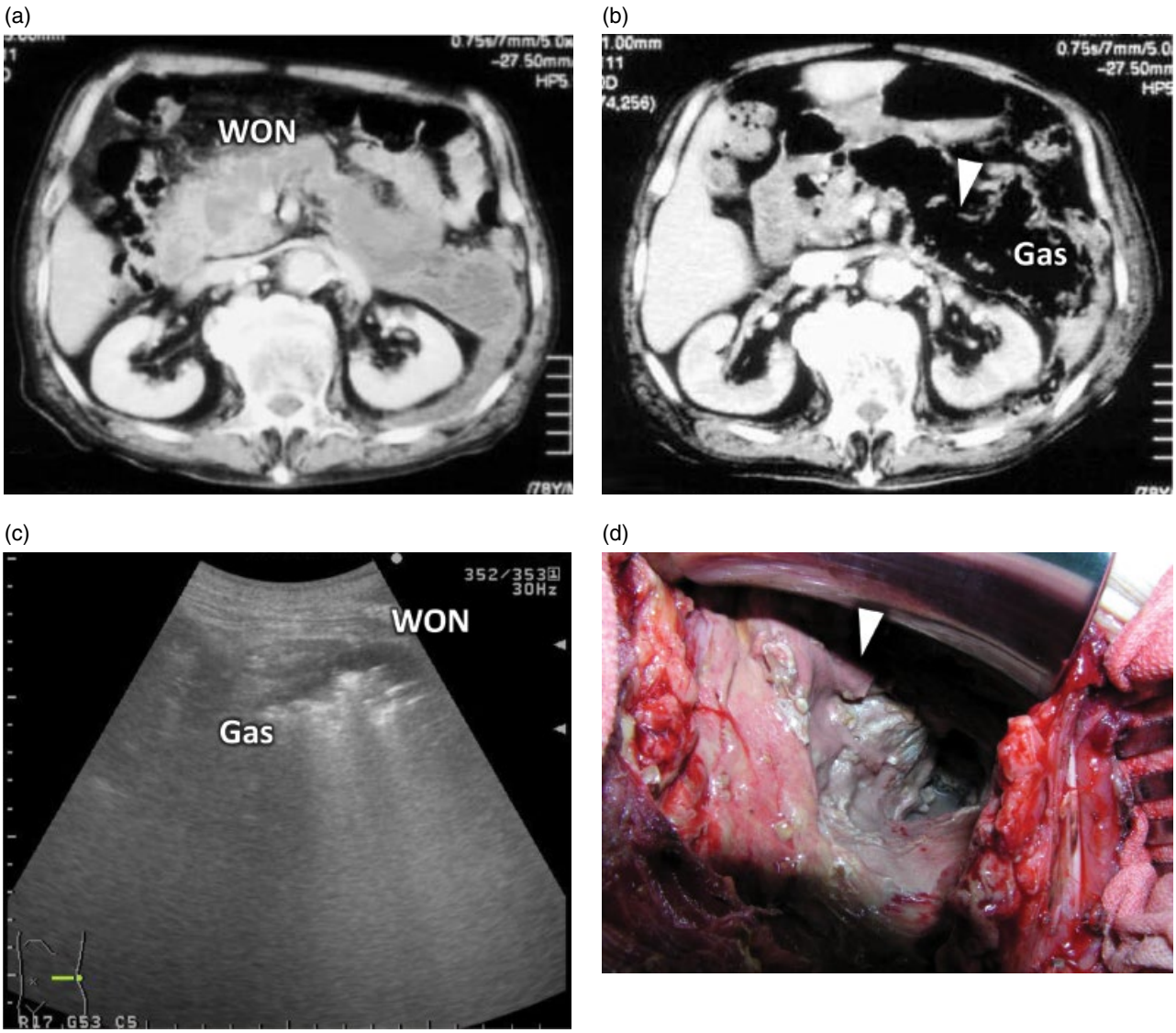


**Figure 25.6** Infected walled-off necrosis (WON). (a) Presented case has WON on contrast-enhanced CT. (b) Most of the WON on the pancreas body and tail was replaced with gas, due to infection. In the gas cavity of WON, the inner wall (arrowhead) was detected. (c) Percutaneous ultrasound showed high spotty areas due to gas in WON. (d) Surgical treatment was performed and a part of the inner wall (arrowhead) was shown in the cavity. The patient recovered 6 months later.

saturation monitor, multiple infusion pumps, etc.), which cannot be taken away from patients with severe acute pancreatitis even for a short period, must be done before the procedure is performed.

## Nephrotoxity of Contrast Material of CE-CT and CE-MRI

One of important systemic complications of acute pancreatitis is acute renal failure. Because CE-CT and dynamic CE-MRI has some nephrotoxicity, use of dynamic CE-MRI and CE-CT should be decided with care [41]. Perfusion CT is obtained from analysis of blood flow after a bolus injection of much less contrast materials (approximately 30–40%) than those used for conventional CE-CT [49]. Therefore, the nephrotoxity of perfusion CT is lower than that of CE-CT and dynamic CE-MRI.

Rickes et al. have recently shown that CE-US [50], which does not have a bad effect on the kidney, can also be used to diagnose pancreatic parenchymal necrosis reliably. However, a whole pancreatic scan with ultrasound is often difficult, because a common complication of acute pancreatitis patients is paralytic ileus. Pancreatic parenchyma with inflammation is often surrounded by digestive canal with gas [14], and so the accuracy of ultrasound for evaluating severity of pancreatitis is limited.

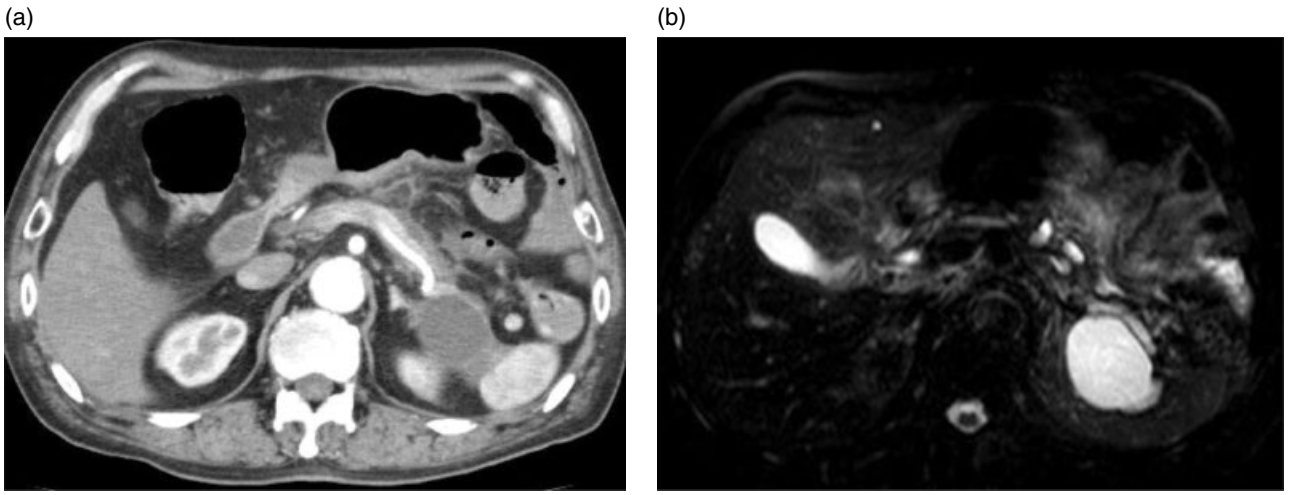


**Figure 25.7** Pancreatic pseudocyst. (a) After 4 weeks from onset of acute pancreatitis, a low-density area with well-defined wall was identified by contrast-enhanced CT. (b) Using MRI (T2 weighted), a low-density area including liquid contents was identified, so the patient was diagnosed with pancreatic pseudocyst.

**Table 25.3** Modified CT severity index.

| Radiological findings | Points |
|---|---|
| Normal pancreas | 0 |
| Intrinsic pancreatic abnormalities with or without peripancreatic inflammatory change | 2 |
| Pancreatic/peripancreatic fluid collection or peripancreatic fat necrosis | 4 |
| Pancreatic necrosis | |
| None | 0 |
| ≦30% gland necrosis | 2 |
| >30% gland necrosis | 4 |
| Extrapancreatic complications, i.e., pleural effusion, ascites, vascular or gastric involvement, parenchymal complications | 2 |
| CTSI score and disease severity of acute pancreatitis | |
| Score 0–3: mild | |
| Score 4–6: moderate | |
| Score 7–10: severe | |

### Radiation Dose of CE-CT and Perfusion CT

The radiation doses of CE-CT and perfusion CT should not be ignored. However, recent techniques regarding noise reduction and registration make it possible to perform CE-CT and perfusion CT using much lower radiation dose protocols. Radiation doses used for recent pancreatic perfusion CT were lower than those used for triple phase CT [49,51].

### Needs for Diagnosis of Pancreatic Necrosis in the Early Stage

As reported in a previous publication, neither APACHE II nor CE-CT give accurate predictions for patients in the early stages of acute pancreatitis [52]. Because of the absence of an ideal and established method for evaluating severity at an early stage, therapies often begin only after the patient has sustained serious damage. Since serious tissue damage (e.g., necrosis) may be irreversible, such treatments may be of limited benefit at later stages. Early and accurate predictions appear critical in establishing effective early care strategies. Accurate predictions of the severity may improve the accuracy of triage assignments and allow intensive treatment to begin earlier. Early inductions of aggressive fluid therapy [53] and enteral nutrition [54] may improve outcomes for patients with severe acute pancreatitis. Importantly, there is no strong evidence that early and accurate evaluations of severity can actually alter prognosis in acute pancreatitis. Prospective intervention trials based on early accurate predictive methods would be required to confirm this.

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# Clinical Course and Medical Treatment of Acute Pancreatitis

## 26

## Conservative Therapy of Acute Pancreatitis: Volume Substitution and Enteral and Parenteral Nutrition

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## Introduction

Acute pancreatitis is an often devastating inflammatory condition of the pancreas which leads to extensive worldwide morbidity and mortality [1–4]. In fact, in the United States, acute pancreatitis is the most common reason for patients to be hospitalized for a digestive illness [5]. The substantial human costs of this disease, with billions in annual healthcare dollars spent worldwide, has led to extensive efforts to establish a pharmacologic treatment for this disease. Unfortunately, as of 2016, there is no specific medical therapy that specially targets acute pancreatitis and has been useful to improve important clinical outcomes.

Over the past 50 years, extensive efforts have been made to develop targeted pharmaceutical products, but none have demonstrated benefit in randomized controlled trials. Agents directed at reducing pancreatic secretions, including histamine-2 blockers, such as cimetidine, glucagon, atropine, somatostatin and its analog octreotide, do not reliably affect morbidity or mortality [6–9]. Antiprotease therapy with aprotinin and gabexate mesilate are equally ineffective, as is therapy with lexipafant, a platelet-activating factor antagonist [10,11].

Recently, as discussed elsewhere in this textbook, rectal nonsteroidal anti-inflammatory drugs (NSAID) have been demonstrated to be helpful in reducing the risk of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis due to regulation of proinflammatory mediators in acute pancreatitis. Rectal NSAID work by inhibiting phospholipase A2 activity, including arachidonic acid products and platelet-activating factors [12–14]. One NSAID in particular, rectal indomethacin, has been used extensively since 2012 following the publication of a randomized, placebo-controlled trial in patients undergoing ERCP considered to be at high risk for pancreatitis [13]. The trial found that a single 100 mg dose of rectal indomethacin significantly reduced the risk of pancreatitis from 16.9% in those receiving placebo to 9.2% in those receiving indomethacin.

However, with the exception of rectal indomethacin, there are currently no specific pharmacologic therapies advocated for the treatment of acute pancreatitis [15,16]. Supportive measures, including the use of fluid resuscitation, nutrition, and aggressive intensive care unit care, have become the cornerstone of conservative therapies in treating this disease.

This chapter focuses specifically on the conservative therapies of fluid resuscitation and enteral and parenteral nutrition. It will review the importance of the pancreatic microcirculation and how this affects the pathogenesis and prognosis of acute pancreatitis. It will discuss animal and human clinical trials which have evaluated the role of different types, volumes, and rates of fluid resuscitation. Finally, current recommendations in regard to administering fluids in acute pancreatitis will be provided. The second part of the chapter will focus specifically on the role of enteral and parenteral nutrition in the treatment of acute pancreatitis, with a review of clinical trials and important recommendations for nutritional care on patients with this disease.

## Fluid Resuscitation

### The Pancreatic Microcirculation and Acute Pancreatitis

It is critically important to understand the intricacies of the pancreatic microcirculation when discussing the role of fluid resuscitation in acute pancreatitis. The arterial

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

supply to the pancreas is derived from the two main proximal trunks of the aorta: the celiac trunk and superior mesenteric artery. The splenic and common hepatic arteries (as well as the left gastric artery which does not supply the pancreas) arise from the celiac trunk. The splenic artery gives rise to the penetrating branches of the body and tail of the pancreas, while the common hepatic artery, via its branch the gastroduodenal artery, supplies the pancreatic head through the anterior and posterior superior pancreaticoduodenal arteries. The anterior and posterior inferior pancreaticoduodenal arteries, arising from the superior mesenteric artery, supply the head and neck of the pancreas, and form vascular anastomoses with the superior pancreaticoduodenal arteries. This vascular network features extensive collateralization, thus ensuring adequate pancreatic tissue perfusion.

From these large arteries arise the intralobular arteries, which run within the pancreas often parallel to the pancreatic ducts. The intralobular arteries give rise to the pancreatic microcirculation, a vast network of capillaries and venules which supply the pancreatic acinus with a rich blood supply [17]. An exocrine lobular plexus with multiple fine capillaries represents the basic vascular unit within the pancreas and flow from the vascular plexus is almost 20 times more likely to prefer the pancreatic islet cells than the acinus. Because of this, the pancreatic acinus is extremely prone to low vascular flow states when there is lack of circulating blood flow to the pancreas [18]. This is why the pancreatic acinus can be so prone to damage with even a slight perturbation in systemic blood flow.

Disturbance to the blood flow within the pancreatic microcirculation due to acute pancreatitis can occur for several reasons: hypovolemia, increasing capillary permeability, and hypercoagulability causing microthrombi, among others [19–22]. The generation of oxidative free radicals with subsequent capillary endothelial damage has also been implicated. This alteration in microcirculation significantly increases the degree of pancreatic ischemia, irrespective of etiology, thus exacerbating the systemic inflammatory response syndrome (SIRS) and leading to multisystem organ failure.

Once significant acinar blood flow has been disturbed, acinar cell injury occurs. Acinar cell injury than causes the release of multiple proinflammatory cytokines and vasoactive mediators, including tumor necrosis factor α, histamine, bradykinin, interleukin 1 (IL-1), IL-2, IL-6, platelet-activating factor, and endothelin-1, are recruited to the pancreatic microcirculation and delivered to the acinar cells [23–25]. Once this proinflammatory cascade is set into motion, the systematic sequalae of acute pancreatitis, including the collapse of the systemic circulation leading to multisystem organ failure, can occur. Once initiated, this process is exceedingly difficult to reverse.

The role of aggressive fluid resuscitation is essentially to try to adequately perfuse the acinar tissue in the face of such overwhelmingly antagonism of the normal physiologic maintenance of adequate tissue perfusion pressure. Although fluid resuscitation by itself does not have an effect on the proinflammatory mediators leading to circulatory collapse, the sequalae of maintaining adequate tissue perfusion may seek to slow or ameliorate at least part of the inflammatory cascade. The hope for intravenous fluid resuscitation in acute pancreatitis is that adequate tissue perfusion will perfuse the pancreatic microcirculation so that pancreatic necrosis and its subsequent complications can be minimized or even prevented.

## Animal Studies

There have been extensive animal studies in the pathophysiology and treatment of acute pancreatitis, specifically in regard to establishing a definitive pharmacologic therapies for blunting the proinflammatory content of this disease. However, despite the important role of fluid resuscitation in acute pancreatitis, relatively few animal studies have been exclusively devoted to this subject. The critical question asked by animal studies in acute pancreatitis are the same as in human studies—How much fluid should be given? What type of fluid should be given? Is colloid or crystalloid fluid a better choice? What are the complications of using overly aggressive fluid resuscitation?

Two animal studies have demonstrated the importance of aggressive fluid resuscitation, irrespective of the type of fluid utilized. Juvonen and colleagues, using a pig model of Na-taurocholate-induced pancreatitis, showed that the signs of splanchnic hypoperfusion can be prevented with fluid resuscitation [26]. The investigators found that the $PCO_2$ gap increased and portal venous blood flow decreased in pigs with acute pancreatitis, but did improve significantly with resuscitation. Niederau et al. have also demonstrated in a choline-deficient, ethionine-supplemented diet mice model that hydration by subcutaneous fluid markedly improved survival and normalized the hematocrit without having significant biochemical or morphologic effects [27].

Crystalloid resuscitation has been studied only sparingly in animal studies of acute pancreatitis. Knol et al. evaluated the effect of low and high infusion rates of lactated Ringer's solution in 14 dogs with bile trypsin pancreatitis [28]. They found that pancreatic blood flow decreased to a greater extent in the low infusion group compared to the high infusion group. Crystalloid resuscitation with a balanced salt solution adequately restored

plasma volume, supported tissue perfusion and prevented excessive hemodilution without detrimental effects on pulmonary pressures or oxygenation in a canine model of acute hemorrhagic pancreatitis [29].

The majority of animal studies dealing with fluid resuscitation have used colloid solutions, most notably dextran, and generally found improved outcomes compared with crystalloid resuscitation. One suspected reason for improved outcomes with colloids has been that they are not as permeable to leakage in the pancreatic microcirculation compared with crystalloids. By remaining in the luminal environment, circulatory blood flow is better maintained, and inflammatory mediators are less able to access the acinus [30–34].

Thus, in summary, animal studies have been relatively sparse, and the majority of these have been completed with colloid rather than crystalloid solutions. However, these studies have not been able to effectively answer the questions of which solution is most appropriate, what is the optimal rate of fluid resuscitation, and what are the consequences of overly aggressive resuscitation. Surprisingly, as detailed below, the clinical studies in humans have not appreciably answered these questions satisfactorily either.

## Human Studies

Despite the universally accepted paradigm that aggressive fluid resuscitation is an important element of supportive care in acute pancreatitis which leads to improvements in important clinical outcomes, few studies have been performed on this and even a rarer number of randomized controlled trials. Questions about the rate of resuscitation, type of fluids, and consequences of over-aggressive resuscitation remain unanswered. However, in the last decade more attention had been focused on this important clinical area, and several randomized trials are planned to try to answer these critically important questions.

The original investigation in humans about the importance of aggressive fluid resuscitation was carried out by Baillargeon, Banks, and colleagues in the 1990s. They emphasized the importance of resuscitation in improving clinical outcomes. In a retrospective cohort study, they found that hemoconcentration with an admission hematocrit >47% or failure of admission hematocrit to decrease at approximately 24 hours were strong risk factors for the development of pancreatic necrosis [35]. Multiple subsequent studies have validated these findings, including the Banks group which performed a retrospective study to determine whether fluid resuscitation could prevent pancreatic necrosis among patients with hemoconcentration at the time of admission [36–41].

As these data suggest, inadequate fluid resuscitation leading to poor pancreatic microcirculatory perfusion has been associated with acute necrotizing pancreatitis [39]. Specifically, we now know that early fluid resuscitation has more of a therapeutic effect than delayed fluid resuscitation. Although early fluid resuscitation is generally agreed upon as an intervention of paramount importance, there are currently no standard guidelines on the optimal fluid type, volume, rate, or duration of treatment. Although human studies on the rate of hydration consistently show decreased morbidity and mortality with aggressive hydration in the first 24 hours, the total volume of hydration at the 48-hour mark seems to have a limited effect on patient outcomes.

The current American College of Gastroenterology (ACG) guidelines recommend 250–500 mL/h of isotonic crystalloid solution in the first 12–24 hours, with frequent re-evaluation every 6 hours and an ultimate goal of decreasing the blood urea nitrogen (BUN) levels [42]. Some experts recommend that in addition to the 1–2 L fluid bolus given in the emergency department, the starting infusion should be at a rate of 250–300 mL/h or enough to produce a urine output of at least 0.5 mL/kg per hour [43]. The goal within the first 24 hours is a total infusion volume of 2.5–4 L, with adjustments to be made based on the patient's age, weight, physical exam, and comorbid conditions [44].

The type of resuscitation fluid has not been satisfactorily studied. However, in a widely cited manuscript Wu and colleagues found that the use of lactated Ringer's solution, in place of normal saline, resulted in less SIRS and a decreased C-reactive protein at 48 hours [45]. However, this study was limited by the fact that is was conducted in only 40 patients. In patients undergoing ERCP, aggressive fluid resuscitation using lactated Ringer's solution has been shown to be an effective deterrent for the development of post-ERCP pancreatitis [46,47]. Thus, although they are not in the same exact clinical scenario as patients not undergoing ERCP, these results do suggest that the use of lactated Ringer's solution has a beneficial effect.

The issue of over-aggressive hydration and risk of poor outcomes, particularly the development of abdominal compartment syndrome, has been highlighted by two studies. The first, a retrospective evaluation of 99 patients with severe acute pancreatitis in Sweden, determined that patients receiving 4000 mL or more of fluids during the first 24 hours ($n = 32$) developed more respiratory complications (66% vs. 53%; $P$ 0.001) than patients who received less than 4000 mL of fluid [48]. Mao and colleagues have also reported improved survival rates by controlling the amount of fluid resuscitation within the first 72 hours in 83 patients with severe pancreatitis [49]. In addition, in a randomized controlled trial of patients with predicted severe pancreatitis whose hematocrit was

**Table 26.1** Important human studies of fluid resuscitation in acute pancreatitis.

| Study type | Number of patients | Comparison group | Outcome |
|---|---|---|---|
| Retrospective [35] | 65 | Aggressive (Hct <47) vs. nonaggressive | Hct >47 developed necrosis |
| Retrospective [48] | 99 | Aggressive (4 L) vs. nonaggressive | Aggressive with more respiratory complications and increased ICU care |
| Retrospective [40] | 45 | Early vs. late resuscitation | Increased mortality in late |
| Retrospective [41] | 434 | Early vs. Late resuscitation | Less SIRS, organ failure, ICU admissions, LOS in early |
| RCT [45] | 40 | LR vs. normal saline | LR had decreased SIRS and CRP at 24 h |
| RCT [46] | 62 | Aggressive (3 mL/kg per h) vs. nonaggressive using LR in ERCP | Less hyperamylasemia and abdominal pain in aggressive group |
| RCT [50] | 115 | Aggressive (<35 Hct in 1st 24 h) vs. nonaggressive | A higher incidence of sepsis and decreased survival in aggressive group |

Hct, hematocrit; ICU, intensive care unit; SIRS, systemic inflammatory response syndrome; LOS, length of stay; LR, lactated Ringer's solution; CRP, C-reactive protein.

aggressively lowered upon admission, those with aggressive lowering of their hematocrit had greater morbidity and mortality [50].

Thus, although important inroads have been made into the role of aggressive fluid resuscitation in the critical issue of supporting the pancreatic microcirculation in acute pancreatitis, several questions remain, particularly how best to monitor the rate of resuscitation and at what point the critical juncture of over-resuscitation occurs. Lactated Ringer's solution appears to represent an important breakthrough in the type of crystalloid solution to be used in this regard but further randomized controlled trials stratifying by the type of crystalloid solution are necessary. Continued animal studies into the effects of crystalloid and colloid solutions on the pancreatic microcirculations are in order as well as carefully designed human clinical trials using varying fluid solutions and rates, with an emphasis on patient monitoring and safety (Table 26.1).

## Enteral and Parenteral Nutrition

Nutritional supplementation has long been an important component of conservative treatment in acute pancreatitis. Since most patients with acute pancreatitis must be "nothing by mouth" for at least part of their hospitalization, the mechanism of nutritional supplementation and type has been an active area of clinical research for many decades. Although the standard of care for many years included nothing per mouth and "resting" the pancreas by limiting enteral intake, recent studies have proved that early enteral feeding appears to be of significant benefit to clinical outcomes.

The problem with maintaining patients nothing by mouth is that bowel rest is associated with intestinal mucosal atrophy and increased infectious complications due to bacterial translocation [51]. In order to maintain gut barrier function, therefore, enteral feeding is preferred over parenteral feeding in the management of acute pancreatitis.This has been proven in multiple randomized controlled trials dating back to the early 1990s, and meta-analyses have consistently demonstrated the importance of enteral versus parenteral nutrition in both interstitial and predicted severe acute pancreatitis [52–54]. Currently there is no rationale to use parenteral over enteral nutrition in the setting of acute pancreatitis. Even in patients who cannot tolerate a full enteral diet, at least some degree of enteral nutrition should be provided to maintain gut barrier function.

In mild acute pancreatitis, early initiation of oral intake with a low-fat soft solid diet is often tolerated and has been demonstrated to be just as efficacious as tube feeding [55]. Further study has also demonstrated that even in patients with predicted severe acute pancreatitis, early oral versus on-demand tube feeding has demonstrated equivalent efficacy in a randomized controlled trial [56]. Enteral feeding is recommended within 3 days of hospitalization, typically after cessation of nausea, vomiting, discontinuation of parenteral analgesics, reduction in abdominal pain, and return of bowel sounds. Feeding can also be started with a low-fat solid diet and does not need to be initiated using the archaic clear liquid, mechanical soft, and low-fat method [57].

The choice between nasojejunal or nasogastric feeding has been debated for quite some time with nasjojejunal feeding being favored, again because of the issue of

achieving pancreatic rest. However, recent studies have suggested that nasogastric feeding may be just as efficacious and well tolerated as nasojejunal feeding when evaluated in a randomized controlled setting [58]

The issue of type of feeding has been inadequately studied, but there has been a meta-analysis evaluating 20 randomized controlled trials comparing different formulations [59]. The authors concluded that the use of polymeric, rather than (semi)elemental, formulation does not lead to a significantly higher risk of feeding intolerance, infectious complications, or death in patients with acute pancreatitis. Neither the supplementation of enteral nutrition with probiotics nor the use of immunonutrition significantly improved the clinical outcomes. A Cochrane Database review also found similar low-quality evidence differentiating the types of formulations and their benefit in acute pancreatitis [60]. In addition, a recent study of the use of probiotics in acute pancreatitis demonstrated worsening mortality due to bowel ischemia in the group receiving probiotics and thus it is advised that probiotics should not be used in patients with acute pancreatitis [61].

Thus, in summary, enteral feeding is favored over parenteral feeding in acute pancreatitis based on improvement in important clinical outcomes. Oral feeding should be initiated with 72 hours of admission in all patients using a low-fat diet. If patients cannot tolerate oral feeding, nasoenteric feeding, usually with a nasogastric feeding tube, can be employed. In those patient in whom appropriate enteral feeding is not tolerated, low-level "trickle" feeding should be used to help prevent gut translocation of bacteria which can lead to infected necrosis. Patients should not be given probiotics, as these formulations have demonstrated an increased risk of mortality due to mesenteric ischemia.

## Conclusions

Supportive care in acute pancreatitis is critical to achieving optimal patient outcomes in the context of no targeted pharmacologic options in this disease. Aggressive fluid resuscitation and the initiation of early enteral feedings have revolutionized the care of the patient with acute pancreatitis. Further study, specifically targeting the type of fluids and enteral nutrition formulations in a randomized controlled trial format are needed, however, to further optimize conservative care for these patients.

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# 27

# ICU Treatment of Severe Acute Pancreatitis

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## Introduction

Acute pancreatitis remains a complex, progressive, and variable acute inflammatory syndrome. In some cases the inflammatory response is so severe that a sequence of systemic inflammation defined by the systemic inflammatory response syndrome (SIRS), vascular leak syndrome (VLS), multiorgan dysfunction, shock, and death may occur. Patients with life-threatening complications should be managed in the intensive care unit (ICU), where early intervention and support may result in better outcomes. This chapter will focus on management following a general clinical pathway to emphasize the sequence of common events and evidence behind clinical decisions.

## Pre-ICU Management

Optimal treatment begins in the clinic or emergency department (Fig. 27.1). The primary goals in early evaluation include confirming the diagnosis, detecting early signs of organ dysfunction, and initiating fluid resuscitation. Fluid resuscitation (see Chapter 26) may be the most important early intervention for stabilizing and treating patients with evolving severe acute pancreatitis.

The initial physical examination is central to assessment and proper triage. The clinical histories are variable, but sudden onset of severe, sharp, unrelenting pain with nausea and vomiting is common. In addition to a routine physical examination the clinician should focus on early signs of severe acute pancreatitis, including severe pain, anxiety, confusion, scleral icterus, diaphoresis, dry mouth, tachycardia, thready pulses, acrocyanosis, tachypnea, lung rales, and abdominal tenderness with or without rebound pain. Postural changes (e.g., supine to standing) resulting in dizziness or tachycardia suggest significant intravascular hypovolemia [1].

The initial laboratory assessment should include standard diagnostic tests in addition to standard laboratory tests (Box 27.1). These tests serve both as baseline values for future comparisons and early biomarkers of organ dysfunction that may require ICU management. A chest X-ray may provide early evidence of pulmonary edema [2,3].

Early morbidity and mortality are complications of SIRS, especially when it leads to VLS [4] and organ dysfunction involving the lungs, cardiovascular system, intestines, and kidneys [5–8]. Early management focuses on fluid resuscitation and oxygenation. Patient comfort centers on treatment of pain and nausea.

Life-threatening hypovolemia in acute pancreatitis develops as a consequence of VLS, which occurs in an unpredictable subset of patients. The mechanism of hypovolemia in acute pancreatitis appears to overlap with trauma and VLS [4,9]. Blood pressure may not become significantly decreased until the patient has lost 30–40% of circulating blood volume [10]. Therefore, blood pressure correlates poorly with both blood volume and cardiac output. Furthermore, significant hypovolemia may be masked by splanchnic vasoconstriction and shunting of blood from the viscera to maintain circulation to the brain and heart.

Hypoperfusion and/or ischemia of visceral organs create two additional challenges to the problem of generalized tissue ischemia. First, hypoperfusion may continue long after systemic volume resuscitation has

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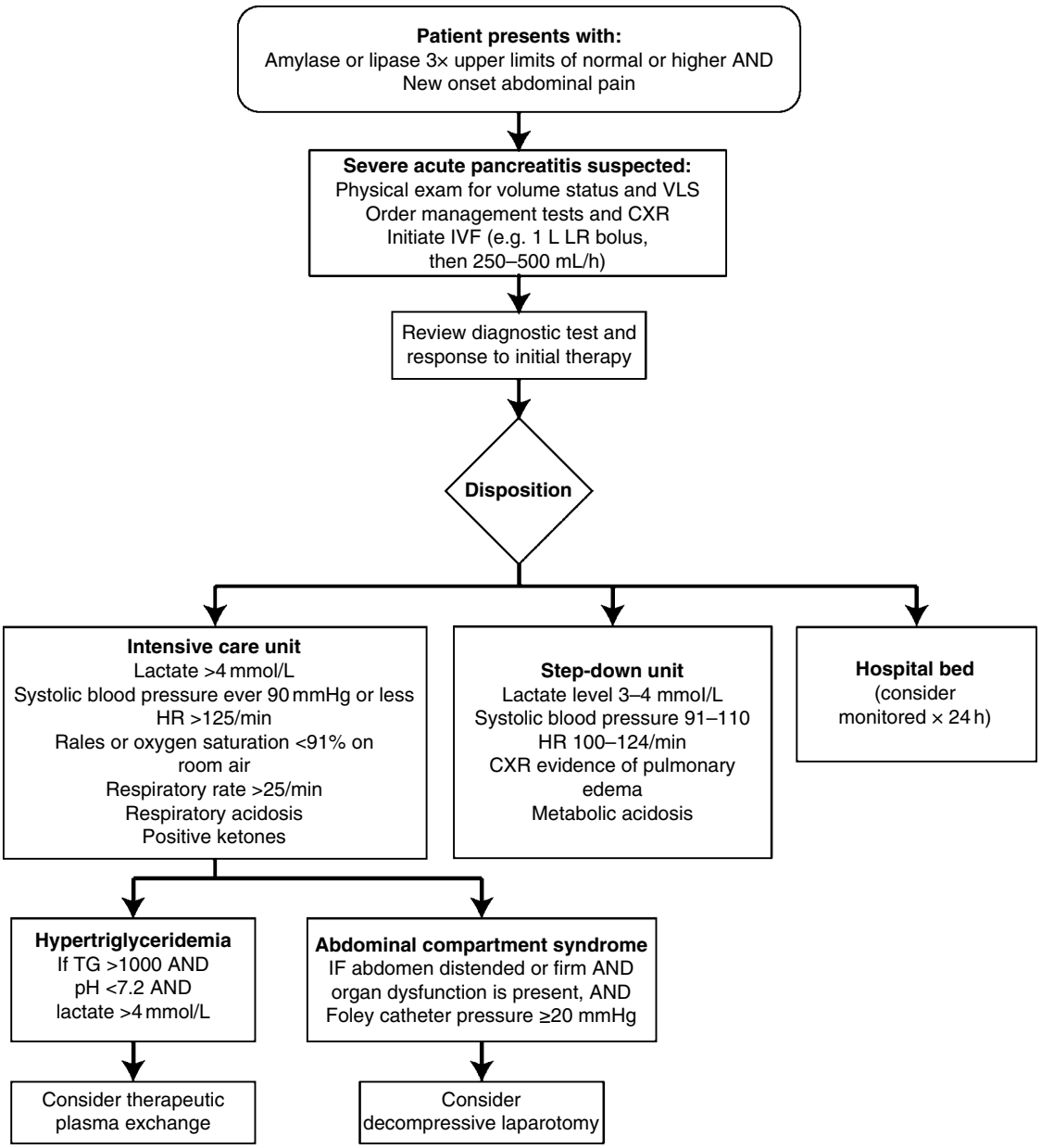


**Figure 27.1** An illustrative clinical pathway for managing patients during the initial evaluation and possible admission into the intensive care unit. CXR, chest X-ray; HR, heart rate; LR, lactated Ringer's solution; TG, triglyceride level; VLS, vascular leak syndrome.

occurred, resulting in continued ischemic stress on intestinal mucosal epithelial cells, the most vulnerable cells of the gut [11,12]. Second, mucosal epithelial cell injury results in breakdown of the mucosal barrier and translocation of bacteria and toxic factors that enter the circulation via the mesenteric lymphatics and drive SIRS [13–15]. Thus, in some patients, a vicious cycle develops with systemic inflammation leading to VLS, which causes intravascular hypovolemia and splanchnic vascular bed ischemia, leading to translocation of proinflammatory toxins from the gut lumen into the lymphatics that further drives systemic inflammation. Interruption of this cycle should begin with minimizing or preventing intravascular hypovolemia.

The usual systolic blood pressure of adults varies widely, so the relative change in both blood pressure and heart rate may be more important than an absolute value. A systolic blood pressure <90 mmHg, however, is likely to be a *late* sign of severe intravascular hypovolemia [16]. An elevated hematocrit indicates hemoconcentration and implies significant extravasation of serum from the bloodstream and is a harbinger of impending organ

**Box 27.1 Baseline blood-based laboratory tests**

**Diagnostic tests**

- Amylase
- Lipase level
- Triglyceride level
- Calcium
- Albumin

**Management tests**

- Electrolytes (sodium, potassium, chloride, bicarbonate)
- Blood urea nitrogen
- Creatinine
- Blood glucose
- Complete blood count (for white blood cell count and hematocrit)
- Liver injury tests
- Serum lactate
- Arterial blood gas (optional)

failure [17]. Elevated lactate levels also suggest that tissues may already be in shock [18]. We believe that optimal treatment includes the prevention of hypotension and shock, and resuscitation should not be delayed until signs of hemoconcentration and shock develop.

Treatment and prevention of progressive intravascular hypovolemia must begin before the patient is transferred to the ICU. We recommend that a liter of balanced salt solution should be given rapidly, as soon as the diagnosis of acute pancreatitis is made, with modifications for patients with existing comorbidities. In patients with a fluid deficit, repeated boluses and/or fluid support at rates of 250–500 mL per hour should be consider until the patient's cardiovascular system is stabilized [5,19]. Urinary output may be useful in determining fluid status.

Early use of supplemental oxygen is warranted with continuous monitoring of oxygen saturation via pulse oximetry or intermittent arterial blood gas analysis. The pulmonary edema seen in patients with severe acute pancreatitis and VLS is usually due to capillary injury and extravasation of plasma, not fluid overload. Therefore, the treatment should be positive pressure ventilation and not diuresis, unless the patient is absolutely volume overloaded.

For pain we recommend hydromorphone 0.5–2.0 mg intravenously every 15 minutes while the respiratory rate is >10 and systolic blood pressure is >90 mmHg. However, no differences between opiates were demonstrated in systematic reviews of variable quality clinical studies [20,21]. For nausea we give ondansetron 4–8 mg intravenously every 6 hours as needed.

## Special Considerations

As in trauma, management decisions made in the early minutes and hours of care have significant downstream consequences. The emergency in severe acute pancreatitis is fluid management and tissue oxygenation within the context of systemic inflammation. But unlike trauma where the insult is rapid and finite, the systemic inflammation of acute pancreatitis evolves, so continued attention to the evolution of the process over the first 24 hours is critical.

We strongly discourage the use of contrast computed tomography (CT) scan in early severe acute pancreatitis. The diagnosis can almost always be made by the combination of typical pain and elevated serum levels of pancreatic digestive enzymes [6,8]. Although contrast-enhanced CT scan remains useful for detecting and quantifying pancreatic necrosis and/or fluid collections, there are no urgent interventions, and the evaluation can be delayed for days. Early contrast CT poses at least two risks. First, the contrast may worsen the severity of pancreatic necrosis, as well as kidney injury in patients, especially if there is poor perfusion from hypovolemia and/or shunting of blood from visceral organs. Second, the process of obtaining a CT may interrupt evaluation and treatment, or delay transfer to the ICU. However, CT or other abdominal imaging modalities may be required if the diagnosis is in question.

Gallstone pancreatitis occurs when small gallstones become lodged at the sphincter of Oddi and trigger intrapancreatic digestive enzyme activation and acute pancreatitis. In some cases the gallstone remains lodged, whereas in others the stone passes on its own. Although there used to be great enthusiasm for urgent endoscopic retrograde cholangiopancreatography, biliary sphincterotomy, and stone removal, randomized studies failed to demonstrate a benefit for early intervention [22,23]. The exceptions are cases where an impacted gallstone results in ascending bacterial cholangitis [22]. This condition represents an urgent complication that requires a therapeutic intervention. In this setting, antibiotics should be started immediately. However, the priority of an ERCP is secondary to fluid resuscitation, airway management, and patient stabilization.

## Indications for ICU Admission

Early and appropriate treatment of patients with acute pancreatitis may result in rapid resolution of signs and symptoms of more severe disease. In these cases it is reasonable for patients to be treated and monitored on a step-down unit until the clinical course of the patient dictates a change in care level.

We recommend ICU admission for patients with persistent organ dysfunction who require a high level of care with frequent adjustments to the care plan. Examples include patients with lactate >4 mmol/L, systolic blood pressure at any time <90 mmHg, need for vasopressors, an ongoing heart rate of >125 per minute, rales on lung exam or oxygen saturation <91% on room air, a respiratory rate >25 per minute, any respiratory acidosis or positive serum ketones. In addition, patients with SIRS and VLS may require ICU admission for invasive monitoring of intravascular volume, and impending cardiac and/or pulmonary dysfunction.

## ICU Treatment of Severe Acute Pancreatitis

The evolution of severe acute pancreatitis dictates the concerns and management strategies over the first days of disease. The initial phase (0–48 hours after onset of pain) reflects the magnitude of the acute inflammatory response with SIRS, vascular leak, and early organ dysfunction of the cardiovascular system, lungs, and kidneys. The second phase (48–120 hours after onset of pain) focuses on managing recovery of organ systems from injury and preventing secondary problems such as infection in immunocompromised patients from the compensatory anti-inflammatory response syndrome (CARS) [24].

## Early ICU Management (0–48 Hours from Onset of Pain)

Managing patients with acute pancreatitis who require ICU admission is best done by a multidisciplinary team including intensivists and specialists in the medical and surgical management of pancreatitis.

### Management of Cardiovascular Dysfunction

Hypotension may be the result of inadequate cardiac output from intravascular volume depletion, reduced systemic vascular resistance, or both. Early therapy should center on restoration of adequate circulating blood volume to ensure adequate oxygen delivery. Ongoing hypotension despite volume resuscitation will require vasopressor support. We guide our volume resuscitation and the initiation of pressors based on repeated physical exam, biochemical markers of perfusion (lactate and mixed venous oxygen saturations), and dynamic measures of preload responsiveness, such as pulse pressure variation on the arterial line of intubated patients [25–27].

If the patient remains hypotensive after preload is optimized, we initiate pressors for maintenance of perfusion pressure. We target a mean arterial pressure of ≥65 mmHg. Once again, there are few study results to guide us in our choice of pressor. The literature suggests that neither norepinephrine nor epinephrine have a mortality benefit for patients with septic shock [18,28]. However, epinephrine may increase lactate levels despite achieving adequate perfusion pressure, so we start with norepinephrine. We do not routinely add vasopressin unless the patient exhibits significant complications from high-dose catecholamine therapy such as tachyarrhythmias [29].

### Management of Pulmonary Dysfunction

Acute respiratory distress syndrome (ARDS) is a well-recognized complication of acute pancreatitis. Initial management with supplemental oxygen may prove inadequate and many patients with ARDS will require more aggressive care. High-flow oxygen through a nasal cannula provides heated and humidified oxygen at flow rates high enough to develop some continuous positive airway pressure. In addition, high-flow oxygen may be more comfortable than noninvasive ventilation [30].

All patients who require intubation and mechanical ventilation for ARDS should be initially managed with a tidal volume of 6 mL/kg predicted body weight. Respiratory rates are adjusted to achieve a pH between 7.30 and 7.45 if possible. Positive end-expiratory pressure (PEEP) and fraction of inspired oxygen ($FiO_2$) should be titrated to maintain an arterial $PaO_2$ of between 55 and 80 mmHg [31]. Titrating PEEP or $FiO_2$ to achieve a $PaO_2 > 80$ mmHg may improve arterial blood gas values, but has not been shown to improve survival [32]. If hypoxia persists (i.e., a $PaO_2/FiO_2$ ratio of <150 mmHg) and PEEP and $FiO_2$ levels exceed 10 and 0.6, respectively, we start both neuromuscular blockade [33] and prone position ventilation [34] early.

### Management of Abdominal Compartment Syndrome

Abdominal compartment syndrome is a pathophysiologic process arising from increased tissue fluid within the peritoneal and/or retroperitoneal space. Like other compartment syndromes, when the abdominal cavity can no longer expand, further fluid collection results in increases in abdominal pressure with subsequent decreases in perfusion and ischemia to intra-abdominal organs. In patients with acute pancreatitis, swelling from pancreatic necrosis, ileus with gas distension, fluid collections, and volume overload from resuscitation may lead to abdominal compartment syndrome. Abdominal

compartment syndrome is suspected on physical examination when the abdomen is firm and/or distended.

Intra-abdominal pressure is the steady-state pressure within the abdominal cavity and is measured by instilling 25 mL of sterile saline through the Foley catheter and measuring the resultant pressure at end expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the midaxillary line [35]. A normal intra-abdominal pressure in critically ill adults is 5–7 mmHg. Intra-abdominal hypertension is a sustained pressure ≥12 mmHg.

Abdominal compartment syndrome is a sustained intra-abdominal pressure of ≥20 mmHg with new organ dysfunction or failure. Although some patients may respond to a trial of sedation and neuromuscular blockade (relaxing the abdominal wall and thereby decreasing intra-abdominal pressure) and nasogastric tube decompression, many patients with acute pancreatitis and abdominal compartment syndrome will need a decompressive laparotomy.

## Management of Metabolic Derangements

### Hypertriglyceridemia

Hypertriglyceridemic acute pancreatitis represents a spectrum of underlying genetic disorders and metabolic risks such as diabetes mellitus and obesity. Triglycerides alone are rather inert. However, it is believed that in the presence of lipase(s), the triglycerides are hydrolyzed to free fatty acids (FFA), and it is the FFA that are toxic, especially unsaturated FFA [36]. Hypertriglyceridemia is associated with more severe acute pancreatitis and persistent organ failure [37], and may require special attention. Thus, while the focus of physicians treating hypertriglyceridemic acute pancreatitis in the past has often been on reducing the triglyceride levels, the focus should be on clearing FFA [36]. Serum concentrations of FFA are a function of production and clearance. The lipolysis of triglycerides normally occurs within tissues such as muscle, fat, and visceral organs by lipoprotein lipase (LPL), a regulated enzyme. FFA are cleared by these tissues, with excess FFA binding to albumin and transported to the liver where FFA are transferred from albumin to the hepatocytes. In acute pancreatitis, the controlled hydrolysis of triglycerides by LPL is disrupted with the addition of pancreatic lipase(s) that also catalyzes triglycerides to FFA in an unregulated way, overwhelming the capacity of the body to manage the FFA pool generated by LPL, and leading to lipotoxicity. In this case, management of the FFA-associated toxicity should focus on prevention of hydrolysis of triglycerides by LPL (e.g., fluid resuscitation and maintaining good hydration, avoiding heparin) by (theoretically) inhibiting pancreatic lipases [36], and by facilitating clearance of FFA from the serum with insulin infusion or apheresis/plasma exchange [38]. In addition to driving SIRS, FFA can block mitochondrial function, leading to lactic acidosis (pH <7.2, lactate >4 mmol/L), often seen with low calcium (e.g., calcium <8.3 mg/dL). This requires emergency intervention in the ICU, especially in the presence of liver and/or kidney dysfunction. Note that a similar syndrome of lactic acidosis occurs with complications of metformin use [39].

### Diabetic Ketoacidosis with Acute Pancreatitis

Acute pancreatitis often develops in patients with diabetic ketoacidosis (DKA). The mechanism triggering acute pancreatitis appears to be linked to low pH. In a study of 100 subjects with DKA the subjects with coexisting acute pancreatitis had more severe metabolic acidosis (mean pH 7.15 vs. 7.31; $P = 0.0001$) and higher anion gap (38.17 mEq/L vs. 25.16 mEq/L; $P = 0.0001$) [40,41]. These patients may also have hypertriglyceridemia [42]. In these cases, addressing insulin deficiency, acidosis, and hydration generally results in rapid improvement.

Nutrition support is covered in Chapter 26.

## Late ICU Management (>48 Hours After the Onset of Pain)

Visceral organs share a compartment and, to some extent, regulation of blood flow. Thus, damage to one organ should raise awareness of damage to others. The easiest organ to monitor is the kidney by following serum creatinine levels and blood urea nitrogen (BUN). The increase of serum creatinine and BUN levels over the first 24 hours remain among the best predictors of pancreatic necrosis and persistent organ failure [43,44]. We hypothesize that acute kidney injury in acute pancreatitis represents one component of a common mechanism of injury for multiple visceral organs (i.e., kidneys, pancreas, and intestine) that are damaged by hypoperfusion and ischemia. Intestinal ileus may be a parallel sign of visceral organ ischemia. Early recognition of high risk for pancreatic necrosis determines future management strategies, and thus further evaluation is warranted.

After resuscitation and stabilization, abdominal imaging remains central to the eventual evaluation of pancreatic morphology, intra-abdominal fluid collections, and other complications. The radiologic evaluation and

staging of severe acute pancreatitis is covered in Chapter 25.

### Alcohol Withdrawal Syndrome

Alcohol abuse is a common cause of severe acute pancreatitis and alcohol withdrawal may be a complication encountered in the late ICU phase. We start treatment with escalating doses of benzodiazepines [45]. Maximal doses of benzodiazepines are defined by their diluent, propylene glycol, which can have potentially toxic effects. For benzodiazepine-resistant alcohol withdrawal syndrome, we add either phenobarbital or ketamine.

## Management of Infectious Risks

The use of antibiotics is discussed in Chapter 28. The management of infected pancreatic necrosis is discussed in Chapters 29–31.

## Transition Planning

As the clinical course of the patient becomes clear and the intensity of organ support is reduced, transition out of the ICU must be considered. We consider transfer out of the ICU when the organ system dysfunction that necessitated ICU admission has resolved.

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28

# Use of Antibiotics in Severe Acute Pancreatitis: Indications and Limitations

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## Introduction

Although 85% of patients with acute pancreatitis experience an uneventful recovery, this disease bears a high risk for severe and even lethal complications. Cardiocirculatory, pulmonary, or renal failure, alone or in combination, are common problems in patients with severe acute pancreatitis. The treatment is conservative, including mechanical ventilation, hemofiltration, or hemodialysis as well as cardiocirculatory support, if required. The majority of patients respond to such an approach. Nevertheless, mortality of severe acute pancreatitis remains at about 10%.

The poorest prognosis is observed in patients with necrotizing pancreatitis who develop local bacterial infection. Surgical or interventional management is generally required in these cases and mortality rates exceeding 30% been reported [1,2]. Despite progress in our understanding of the pathology of pancreatic sepsis and in intensive care treatment, the mortality rates of infected pancreatic necrosis have not changed in recent decades. Recent attempts with nonsurgical or interventional treatment have been promising [1,3] but there is no doubt that bacterial infection will remain a life-threatening complication in patients with necrotizing pancreatitis.

The recently revised Atlanta classification of acute pancreatitis discriminates between mild acute pancreatitis, moderately severe acute pancreatitis, and severe disease, depending on the occurrence of organ failure and/or local and systemic complications [4]. In contrast to former classification systems, where the term "infected pancreatic necrosis" has been used for all locally infected pancreatic entities, the revised classification distinguishes between morphologically different local infectious complications.

## Infectious Complications

During the course of acute pancreatitis, either systemic or local pancreatic infections may occur. The incidence of these complications varies widely, depending on definition and patient selection.

### Local Pancreatic Infection

In approximately 30–40% of the patients with necrotizing pancreatitis local infections of the necrotic areas develop [5]. Bacterial infection of pancreatic necrosis is the most important determinant of outcome [6]. The revised Atlanta classification discriminates between different morphological entities and comprises acute peripancreatic fluid collections (APFC), pancreatic pseudocysts, acute necrotic collections (ANC), and walled-off necrosis (WON). These morphologic entities have a variable potential for bacterial infection (Table 28.1) with pancreatic necrosis and WON bearing the highest risk.For our understanding of relevance of infectious complications and the role of antibiotics in the treatment algorithm, discrimination between these morphologies therefore is important. Irrespective of the morphologic differences, bacterial infection is a phenomenon of the later phase of acute pancreatitis, commonly observed after the third or fourth week after onset of the disease. This might be one of the reasons why all efforts to reduce the infection rate by prophylactic antibiotics have failed. There is a wide time frame for infection and it is difficult to impossible to define the exact period when prophylactic antibiotics might be effective.

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Companion website: www.wiley.com/go/beger/thepancreas

**Table 28.1** Complications of severe acute pancreatitis with the potential risk of bacterial infection, according to the current revised Atlanta Classification [4].

| | Characterization | Estimated potential for infection |
|---|---|---|
| Necrotizing pancreatitis | Inflammation associated with pancreatic parenchymal necrosis and/or peripancreatic necrosis | High |
| Walled-off necrosis (WON) | Necrotic tissue surrounded by a wall of tissue, usually >4 weeks after onset of pancreatitis | High |
| Acute necrotic collection (ANC) | Collection of necrosis and fluid during the first 4 weeks of AP | Moderate |
| Pancreatic pseudocyst | Walled of fluid collection weeks after AP. May require surgical drainage if persistent | Low–moderate |
| Acute peripancreatic fluid collection (APFC) | During the early phase of AP, resolve spontaneously | Low |

AP, acute pancreatitis.

### Systemic Bacterial Infection

Extra-abdominal bacterial infection is a common finding during severe acute pancreatitis. Its incidence varies widely in different studies. In a multinational European study, more than 40% of the patients had extra-abdominal infections, with respiratory tract infections being the most frequent ones (28%), followed by bloodstream infections (14%), and catheter-related infections as well as genitourinary tract infections (4%) [7]. In the author's own investigation, 25% of the patients of the control group (not treated with antibiotics) had extrapancreatic infection, with pneumonia being the most frequent one [8].

The clinical relevance of extrapancreatic infection has been clearly demonstrated: it increases mortality and adversely affects the outcome of acute pancreatitis [9]. Whether its relevance is equal to that of pancreatic sepsis is subject to discussion.

## Spectrum of Bacteria

In the first description of infected pancreatic necrosis in the 1980s, the bacterial spectrum of infection was dominated by gram-negative enteric germs [5]. During the past three decades, there has been some change, but gram-negative bacteria still play a dominant role in the bacterial spectrum. Nevertheless, gram-positive microorganisms, especially staphylococci and enterococci are increasingly coming into focus. The bacterial spectrum is polymicrobial and comprises anaerobic bacteria as well (Table 28.2).

The role of multidrug resistance among these germs has recently been addressed. Many gram-positive species are resistant to methicillin, as are many extended spectrum beta-lactamase (ESBL)-producing gram-negative germs. In one recent study, 63% of the patients with infected pancreatic necrosis were infected with multiresistant germs [12]. As in other infectious pathologies, these multiresistant germs are of therapeutic and prognostic importance. Their isolation should prompt treatment with an adequate antibiotic drug according to the tested bacterial susceptibilities.

In addition, a considerable percentage of patients with necrotizing pancreatitis develop fungal infections. The prognostic impact of this has been discussed extensively during the past decade. Most often, fungal infection is caused by *Candida* species and is regarded to be predictive of worse outcome. It is generally accepted that antibiotic treatment promotes overgrowth of unaffected or resistant pathogens and is thus regarded to be a risk factor of both fungal and multiresistant infection [13,14].

## Rationales for Antibiotics in Acute Pancreatitis

The use of antibacterial agents in acute pancreatitis has been debated since the 1970s. At first, antibiotics were regarded as a part of the treatment regime without clear definition of their indication. Our increasing knowledge about the impact and relevance of infection during the 1980s and 1990s has led to the definition of two potential settings for the use of antibiotics: for prevention of infection and for treatment of infection.

### Prevention of Infection

The clinical relevance of bacteral infection with its poor prognosis supports treatment algorithms for its prevention. This led to the idea of prophylactic administration of antibiotics with the intention of preventing bacterial

**Table 28.2** Development of the bacterial spectrum of infected pancreatic necrosis during the past 30 years. Selected strains from different studies. Note the increase in the incidence of enterococci and fungi.

| | Beger 1986 [5] | Isenmann 2004 [6] | Dellinger 2007 [10] | Schmidt 2014 [11] |
|---|---|---|---|---|
| No. of isolates | 75 | 19 | 30 | 88 |
| **Percentage of strains** | | | | |
| Enterococci | 8% | 11% | 23% | 28% |
| *E. coli* | 32% | 32% | 7% | 26% (Enterobacteriaceae) |
| *Pseudomonas* | 7% | – | 10% | 7% |
| Anaerobic bacteria | 7% | – | 3% | n.d. |
| Fungi | 4% | 10% | 10% | 14% |

n.d., no data.

superinfection. In recent years, there has been considerable scientific effort to prove such a concept as discussed later in this chapter.

### Treatment of Infection

In combination with surgical debridement, antibiotic treatment is the mainstay in the treatment of any intra-abdominal infection, including infected pancreatic necrosis. It is well known that inappropriate antibiotic treatment in severe sepsis results in a fivefold increase in mortality [15]. For acute pancreatitis a selective uptake of antibiotics into the pancreas has been described [16], which should be taken into account. As a consequence the antibiotics for treatment of pancreatic infection should not only be chosen according to the bacterial spectrum and their antibacterial activity, but also according to their ability to penetrate into the infectious focus [16,17].

## Clinical Studies with Antibiotics

During the past 20 years, there have been numerous controlled and uncontrolled, blinded and unblinded studies addressing the issue whether early administration of antibiotics in severe acute pancreatitis could reduce the incidence of local bacterial infection and consequently could improve the prognosis of the disease (Table 28.3). Among these, four had adequate scientific power for meaningful conclusions [8,10,18,19]. None of them has been able to give a definite answer to this question and according to the latest meta-analyses, there is no evidence to support the routine use of prophylactic antibiotics in patients with severe acute pancreatitis [20,21].

Consequently, neither the current guidelines of the International Association of Pancreatology/American Pancreatic Association [33] nor of the American College of Gastroenterology recommend prophylactic antibiotics in severe acute pancreatitis [34].

What are the reasons for our inability to demonstrate a beneficial effect of prophylactic antibiotics on the infection rate in acute pancreatitis? First, acute pancreatitis is a heterogeneous disease with highly variable course ranging from mild and self-limiting to devastating with severe septic complications. The majority of patients with acute pancreatitis will never develop infectious complications. To date, there are no reliable parameters which allow the identification of patients at risk for developing pancreatic sepsis. Second, pancreatic infection is a phenomenon of the later course of the disease. Thus the ideal timing and optimal duration of antibiotic administration as prophylaxis is not clear. Antibiotics given too early and too long may be uneffective and promote bacterial resistance. Third, new concepts in the therapy of acute pancreatitis such as early enteral nutrition and treatment of organ dysfunctions may directly or indirectly affect the incidence of septic complications.

These facts, together with others, make it unlikely that we will ever be able to elaborate pathways for the prophylactic use of antibiotics in severe acute pancreatitis [35].

## Indications for Antibiotic Treatment

The main indications for initiation of antibiotic treatment in acute pancreatitis are evidence or strong suspicion of local and/or systemic bacterial infection. Therefore, all current guidelines aim at the timely identification of infected necrosis. The recommended standard comprises close monitoring of infectious parameters, imaging by contrast-enhanced computed tomography and, in cases with strongly suspected bacterial infection, the fine-needle aspiration for Gram stain and culture (FNA) [34]. Pancreatic infection

**Table 28.3** Studies on antibiotic prophylaxis in severe acute pancreatitis. Note that only a few had adequate scientific power for meaningful conclusions.

| Author | | | Double-blind | Patients | Effect on infected necrosis | Effect on mortality |
|---|---|---|---|---|---|---|
| Pederzoli [22] | 1993 | Imipenem vs. None | No | 41/33 | Reduction in imipenem group | No |
| Delcenserie [23] | 1996 | Ceftazidime + amikacin + metronidazole vs. none | No | 11/12 | Reduction in antibiotic group | No |
| Schwarz [24] | 1997 | Ofloxacin + metronidazole vs. none | No | 13/13 | no | No |
| Nordback [25] | 2001 | Early imipenem vs. imipenem delayed | No | 25/33 | Reduction in early treatment group | No |
| Spicak [26] | 2002 | Ciprofloxacin + metronidazole vs. ciprofloxacin + metronidazole on demand | No | 33/30 | No | No |
| Spicak [27] | 2003 | Meropenem vs. meropenem on demand | No | 20/21 | No | No |
| Rokke [28] | 2007 | Imipenem vs. none | No | 36/37 | No | No |
| Barreda [29] | 2009 | Imipenem vs. none | No | 24/34 | No | No |
| Xue [30] | 2009 | Imipenem vs. none | No | 29/27 | No | No |
| Yang [31] | 2009 | Imipenem vs. none | No | 28/26 | No | No |
| **Randomized/placebo-controlled with the best scientific power** | | | | | | |
| Sainio [18] | 1995 | Cefuroxime vs. none | No | 30/30 | No | Reduction in the cefuroxime group |
| Bassi [19] | 1998 | Pefloxacin vs. imipenem | No | 30/30 | Reduction in the imipenem group | No |
| Isenmann [13] | 2004 | Ciprofoxacin + metronidazole vs. placebo | Yes | 58/56 | No | No |
| Dellinger [10] | 2007 | Meropenem vs. placebo | Yes | 50/50 | No | No |
| Garcia-Barrasa [32] | 2009 | Ciprofoxacin vs. placebo | Yes | 22/19 | No | No |

should be suspected in patients with pancreatic or extrapancreatic necrosis and clinical deterioration or failure to improve over 7–10 days.

## Antibiotic Treatment on Demand

The experience from the Severe Acute Pancreatitis Study group (ASAP) study [8] showed that antibiotic treatment was initiated in a considerable percentage of patients with clinical deterioration. The criteria for initiating this so-called "antibiotic treatment on demand" in this study were:

- newly developed sepsis/SIRS;
- newly developed organ failure (pulmonary, renal, cardiocirculatory);
- increase in serum C-reactive protein and strongly suspected/proven extrapancreatic infection;
- increase in serum C-reactive protein and strongly suspected/proven pancreatic infection.

In 37% of the patients of this study, the double-blind study medication was terminated and switched to open antibiotic treatment. The low rate of infected pancreatic necrosis (10.5%) as well as the favorable outcome (mortality 6% in the overall study) can be taken as rationale to initiate antibiotic treatment at these given indications.

## Choice of Antibiotics

The choice of antibiotics in necrotizing pancreatitis has to be taken into consideration:

- the bacterial spectrum,
- the antibiotic concentrations at the site of infection, and
- the results of clinical studies.

Based on these criteria, carbapenems, chinolones, and broad-spectrum cephalosporins are first choice drugs for the initial treatment of pancreatic infection. The latter two should be combined with metronidazole as they lack sufficient antibacterial activity in the anaerobic spectrum. Based on their pharmacokinetic properties, acylaminopenicillins/beta-lactamase inhibitor combinations can be regarded to be effective as well, although there are no clinical studies with these drugs.

Following initiation of an empirical antibiotic therapy, a step down should be followed as soon as the results of bacterial susceptibility testing are available.

Up to now, there is no rationale to initiate a "blind" antifungal therapy. Antifungal agents should only be given when bacterial smears yield fungal infection.

## Limitations of Antibiotic Treatment

Antibiotic treatment is an essential part of the therapeutic regime in patients with infected pancreatic necrosis, but is not enough on its own for successful treatment of these critically ill patients. The mainstay for success is source control of the infectious focus and debridement of the infectious material is an essential part of the treatment regime.

Today, open or laparoscopic surgical debridement and interventional drainage are subject to debate. Scientific evidence suggests that a "step-up approach" might provide favorable results as the best surgical approach in pancreatic infection [1]. Following such an approach, the patient is managed by conservative treatment as long as possible. In the case of strongly suspected or proven pancreatic infection, percutaneous drainage is used as an initial approach for source control. If this fails, surgical necrosectomy (minimally invasive or open) follows [36].

Whether or not pancreatic infection can be treated with antibiotics alone and without debridement is under current investigation. The first studies following such an approach have been criticized [37], but a recent meta-analysis shows that in selected patients this can be safely done with low mortality [3]. Nevertheless, it is necessary to define criteria that characterize the group of patients who are eligible for such a conservative approach.

Most recently, a global overview on the use of antibiotics among physicians indicated that their use, both as prophylaxsis and as treatment in acute pancreatitis, is widespread [38]. Irrespective of the national treatment guidelines for the disease, antibiotics are frequently given without clear indication, even in mild pancreatitis or when pyrexia is present. This overuse poses not only healthcare problems in terms of unnecessary expense but also risks for the patients, including antibiotic-associated side-effects and selection of multiresistant bacteria.

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# Interventional and Surgical Management of Acute Pancreatitis

## 29

## Indications for Interventional and Surgical Treatment of Necrotizing Pancreatitis

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### Introduction

Whereas interstitial acute pancreatitis is typically a self-limited disease process that usually responds to supportive care, the more severe necrotizing pancreatitis can be seen in approximately 20% of patients. This is characterized by necrosis of the pancreatic parenchema or peripancreatic tissue, manifestations of the systemic inflammatory response syndrome (SIRS), with risks for infection and multiorgan failure [1]. High rates of morbidity are associated with mortality of up to 15% in the setting of necrotizing pancreatitis and as high as 30% in the subset of patients who develop infected pancreatic necrosis [2,3]. A variety of surgical and interventional approaches have been used in an attempt to limit the substantial morbidity and mortality of necrotizing pancreatitis.

Over the last few decades, there has been a significant change in the indications for intervention in necrotizing pancreatitis, timing of intervention, and methods of surgical, minimally invasive, radiologic, and endoscopic intervention. Recent revision of the 1992 Atlanta classification of acute pancreatitis [4] to more precisely describe the clinical behavior and imaging characteristics of acute pancreatitis [5] has occurred in parallel with a progressively less interventional and less invasive approach to necrotizing pancreatitis. Although no universally accepted management algorithm exists to guide management, evidence-based consensus continues to develop [6].

### Interventions for Pancreatic Necrosis: Historical Perspective

Just a few decades ago, the association of pancreatic necrosis with systemic inflammation and secondary infection led to the goal of surgically removing all necrotic pancreas regardless of the presence of infection [7–9]. In 1991, Bradley and Allen published a small series of 11 patients successfully managed nonoperatively with sterile pancreatic necrosis [10]. The general acceptance of nonoperative management for sterile pancreatic necrosis was facilitated by the publication of large series demonstrating favorable overall mortality and complications [11,12]. In this new paradigm, intervention was primarily limited to surgical debridement for cases of infected pancreatic necrosis as demonstrated by computed tomography (CT)-guided fine-needle aspiration (FNA) of the pancreas. Banks et al. showed a sensitivity and specificity of 96.2% and 99.4%, respectively, for detection of infected necrosis, with a positive predictive value of 99.5% and a negative predictive value of 95.3% [13]. The presence of infection or positive Gram stain on CT-guided pancreatic aspiration, however, was considered an absolute indication for debridement, as superinfection of the necrotic parenchyma had been associated with a mortality of virtually 100% without debridement [14].

The absolute necessity of surgical debridement for infected necrosis was subsequently questioned with the

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

demonstration of successful nonoperative management in some patients. Runzi et al. [15] showed in a series of over 80 patients with documented infected pancreatic necrosis that initial conservative therapy can be instituted, including antibiotic therapy and maximal supportive care. Mortality in patients managed with surgery was identical to that in those managed nonoperatively. Surgical therapy, when required, was often delayed to a later stage of disease, when the systemic inflammatory response has been stabilized and necrotic pancreas had become demarcated. In other patients, surgical therapy was avoided altogether. Subsequent studies have confirmed this strategy: Garg et al. describe a 10-year series of 80 patients with infected pancreatic necrosis in whom 47 were treated with antibiotics alone [16]. The paradigm of urgent surgical debridement for all patients with infected pancreatic necrosis is therefore no longer considered valid.

## Indications and Timing of Intervention

Unlike the prior delineation of pancreatic necrosis to infected and sterile versions, the revised Atlanta classification [5] divides collections associated with necrotizing pancreatitis according to time of disease onset. A collection that develops early and lacks a discrete wall is referred to as an acute necrotic collection (ANC), whereas a collection that persists after 4 weeks is referred to as walled-off necrosis (WON). Both forms may be sterile or infected. Although the presence or absence of infection is crucial for prognosis and affects management decisions, the presence of clinical symptoms rather than suspicion of infection is considered paramount for intervention.

## Pancreatic Necrosis with Infection

Despite demonstrated success with nonsurgical management for infected necrosis, many if not most patients with infected pancreatic necrosis require some form of intervention. Some series suggest that clinically stable and relatively asymptomatic patients with infected necrosis can be managed with antibiotics alone [15–17]. Nonetheless, patients with infection are prone to clinical decline and require surgical, endoscopic, or radiographic intervention with the onset of clinical signs not responding to medical management. In the era of surgical management, delayed intervention was far preferable to early surgery. A randomized trial has shown that early surgical intervention is associated with higher morbidity and mortality than when intervention is delayed at least 12 days [18]. Other reviews have confirmed lower mortality with delayed surgical intervension [19,20] and other data suggest that early surgery is in fact an independent predictor of poor outcome in necrotizing pancreatitis [21].

Expedited intervention may be required in patients demonstrating progressive systemic sepsis or hemodynamic instability. In the absence of such systemic signs, clinically stable patients may generally be managed at least temporarily with antibiotics to allow further organization of the inflammatory process. Delayed surgical, endoscopic, or radiologic management may then proceed if clinical symptoms do not improve [6].

Delayed surgical intervention of infected pancreatic necrosis has been facilitated by the use of percutaneous catheter drains. A 1998 series by Freeney et al. [22] demonstrated that some patients with infected pancreatic necrosis might have surgical management delayed or potentially avoided altogether with the use of large-bore percutaneous catheters placed under CT guidance. This strategy was validated in a multicenter trial in which patients were randomized to standard pancreatic debridement versus a "step-up" approach in which debridement was used only if necessary [23]. Using a "step-up" approach, complications were significantly lower, and about one-third of patients were treated with catheter drainage alone.

Infected necrosis is suspected with clinical deterioration of a previously stable patient with acute pancreatitis or pancreatic necrosis. Some patients may demonstrate gas within necrotic debris on abdominal imaging via the presence of gas-forming organisms or via a fistula to the colon, small bowel, or stomach. Alternatively, infection may be proven by culture or Gram stain obtained by image-guided FNA [24]. Although a Gram stain positive for organisms was previously thought to mandate surgical early intervention [11], patients with suspected infection are increasingly managed with antibiotics and supportive care to allow less invasive and delayed management of a walled-off collection [3]. Diagnostic FNA is therefore used less routinely in the management of suspected infection.

## Symptomatic Pancreatic Necrosis/ Walled-Off Necrosis

The precise role of radiographic drainage, endoscopic or surgical debridement in sterile pancreatic necrosis is less clear. Although most patients with sterile pancreatic necrosis respond to supportive care without the need for intervention, others will experience clinical decline,

including organ failure despite the presence of demonstrable infection. Historically, some authors had therefore suggested the need for surgical debridement in patients with progression of disease or failure to improve, regardless of the status of infection [25,26]. Unfortunately, no uniform criteria defined which patients with sterile pancreatic necrosis might benefit from debridement. In the era of surgical debridement as the primary intervention for necrotizing pancreatitis, some authors suggested criteria for intervention including the extent of necrosis of more than 50% of the pancreatic parenchyma [25], rapid clinical deterioration with multiple organ failure [27], or the presence or persistence of organ failure [28,29]. However, evidence is lacking to support the use of these criteria as an absolute indication for debridement or drainage. Close analysis of one study of 89 patients with severe sterile necrosis identified only two patients who died that might have theoretically benefitted from earlier surgical debridement, though no clinical parameters were able to easily differentiate these patients from others with severe sterile necrosis [12].

As noted above, in the absence of clinical confirmation of infection by image-guided FNA or suggestive imaging, intervention is typically based on the clinical course and trajectory. Patients are therefore often brought to intervention for not just documented infection, with positive pancreatic FNA, but also for suspected infection based on persistent sepsis or progressive clinical deterioration [30]. Given the additional morbidity and mortality associated with open surgery, radiologic or endoscopic drainage is used prior to surgical intervention [31].

The process of walled-off pancreatic necrosis recognized in the revised Atlanta classification was previously described by Baron as "organized pancreatic necrosis" [32]. In this condition, an intrapancreatic or extrapancreatic heterogeneous semisolid collection develops in the context of acute necrotizing pancreatitis and has an encapsulated wall [5]. A subset of patients with WON may experience a prolonged clinical course marked by persistent pain, malaise, and inability to eat. This symptom complex was described by Warshaw as "persistent unwellness" [33]. The precise indications and timing of intervention are not precisely defined for these patients.

Asymptomatic WON does not require intervention regardless of the size of the collection, and may resolve with conservative management (Fig. 29.1). Symptomatic WON, however, can be marked by pain, intestinal, or biliary obstruction, or later infection. In one series, approximately 10% of patients with sterile pancreatic necrosis underwent surgery for persistent pain and organized necrosis at a mean of 29 days after initial presentation [12].

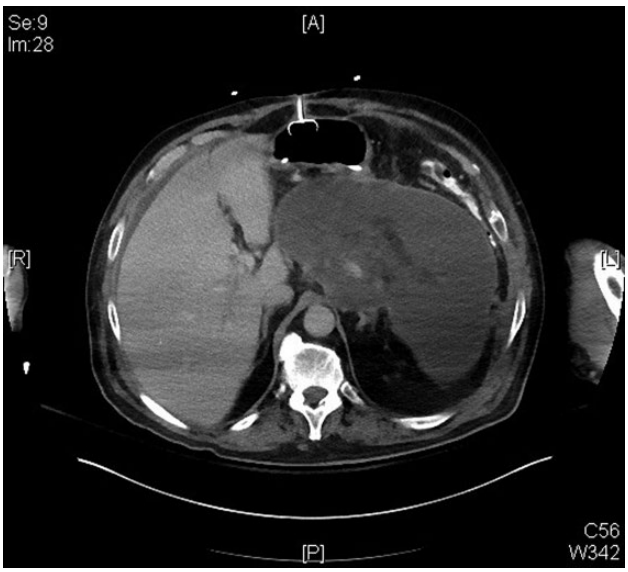


**Figure 29.1** Walled-off necrosis. A 55-year-old man presented with severe acute pancreatitis and an acute necrotic collection. He was managed conservatively, and imaging 6 weeks after presentation revealed a large area of walled-off necrosis involving the entire body and tail of the pancreas. The patient remained asymptomatic and no intervention was pursued.

## Surgical and Interventional Procedures

The use of various radiologic, surgical, and endoscopic interventions for necrotizing pancreatitis will vary among institutions [6]. Although open surgical necrosectomy was previously considered the definitive management, a number of minimally invasive techniques have been developed. As noted above, delayed intervention is preferable in all patients if possible, particularly when open surgical management is used [34]. However, interventional radiologic techniques may be performed earlier with suspected infection [19]. Even in the setting of suspected or known infection, there is a growing trend to treat with supportive care and antibiotics unless there are signs of sepsis, until the pancreatic collection becomes walled off [3].

## Surgical Debridement

Open surgical debridement for years was considered the gold standard of surgical intervention for pancreatic necrosis, by removing necrotic pancreatic and peripancreatic tissue and establishing a means of postoperative drainage while preserving viable pancreatic parenchyma. Methods have included debridement with closure over drains, debridement with open packing of the pancreatic

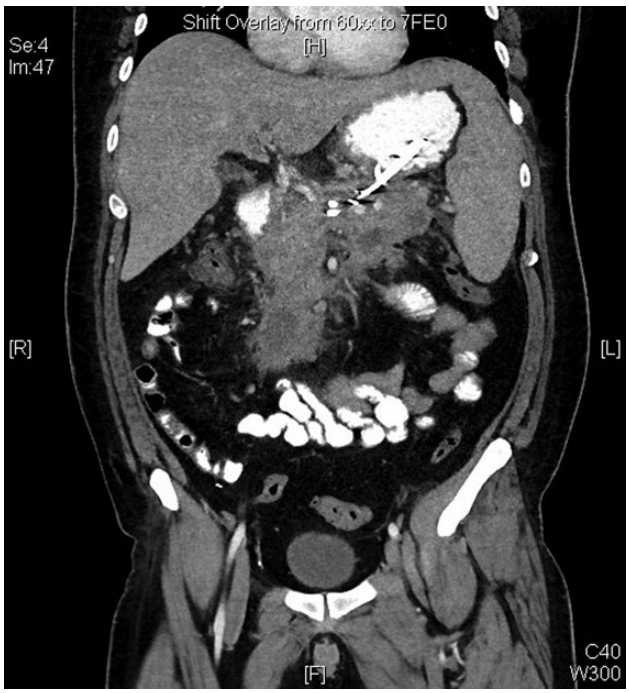


**Figure 29.2** Undrained mesenteric abscess after endoscopic debridement. A 50-year-old man underwent uncomplicated endoscopic debridement for symptomatic walled-off pancreatic necrosis. He represented with fevers, pain, leukocytosis, and a phlegmonous abscess tracking down into the small bowel mesentery. Endoscopic debridement and CT-guided drainage were not felt to be possible. Surgical debridement was required.

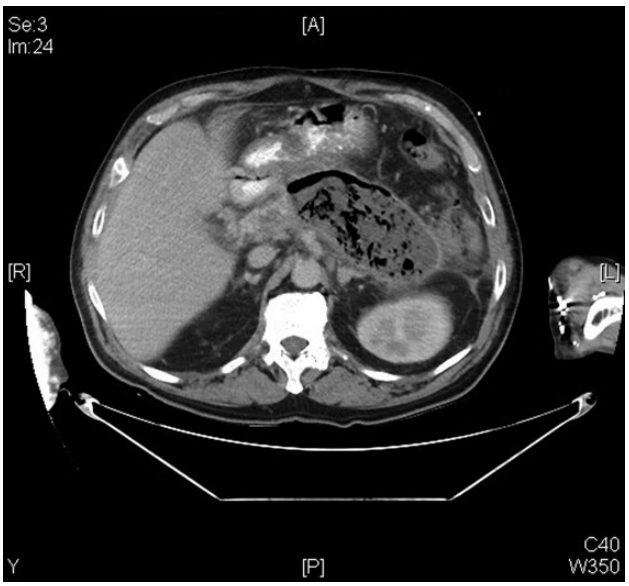


**Figure 29.3** Infection of walled-off necrosis with fistula to colon. The patient in Fig. 29.1 presented 12 months after his original episode of pancreatitis with fever and bacteremia. Imaging demonstrated gas in the area of walled-off necrosis, consistent with infection. Endoscopic debridement was attempted, though contrast injection to the cavity demonstrated a fistula to the transverse colon. Open surgical debridement was pursued.

bed, or debridement with closure over irrigation drains [9,35–37]. Mortality and complication rates for published series utilizing these techniques vary widely, although comparisons between studies are confounded by the lack of standardization of disease severity or operative indications.

One advantage of open surgical necrosectomy is that it may offer the best chance to completely remove all necrotic tissue and address other associated complications in a single procedure. Due to its invasiveness and associated perioperative complications, open surgery is typically reserved for patients in whom less invasive methods have failed.

In the setting of minimally invasive options such as image-guided catheter drainage and direct endoscopic necrosectomy as described below, several important potential indications for surgery remain. In some cases, collections may not be accessible via image-guided techniques, may be multifocal, or persistent after minimally invasive necrosectomy (Fig. 29.2). In other instances, a patient may not be deemed clinically stable for minimally invasive measures. Surgical therapy in these instances should be delayed as long as possible given the increased risk of early surgical intervention. Other indications for surgical debridement include the presence of bowel perforation, obstruction, fistula to a hollow viscus such as the colon, and abdominal compartment syndrome [38] (Fig. 29.3).

Of note, minimally invasive forms of surgical debridement have been used in addition to traditional "open" necrosectomy. Laparoscopic approaches are well described, and may be more successful in completely removing all necrotic material compared to other minimally invasive methods [39]. Video-assisted retroperitoneal debridement is a procedure by which the retroperitoneal collection is accessed via the tract of a percutaneous catheter [40]. This avoids the pneumoperitoneum and peritoneal seeding possible with a laparoscopic procedure, but multiple interventions may be required for complete drainage [6]. While open necrosectomy can be avoided in many patients, limited data are available comparing outcomes of these procedures [41].

## Percutaneous Catheter Drainage

Percutaneous catheter drainage (PCD) can be performed either as a "step-up" toward endoscopic or surgical necrosectomy once WON has developed, or in some cases as definitive therapy [23]. One significant advantage

of PCD is the opportunity to address symptomatic or infected necrotic collections before WON has developed. PCD may be particularly useful in patients deemed unfit for surgical intervention, or to address residual collections after debridement [6]. Catheters are placed using CT or ultrasound guidance, using either a transperitoneal or retroperitoneal approach. Often multiple catheters are required, and follow-up procedures are often indicated to place additional or larger catheters [40].

As noted, catheter drainage alone is often effective without necrosectomy. In the PANTER trial, use of catheter drainage resulted in significantly decreased morbidity with equal mortality compared to surgical necrosectomy [23]. Other studies have shown an approximately 50% success rate in treating necrotizing pancreatitis, whether sterile or infected [42]. PCD is less likely to be successful as a definitive intervention in patients with duct disruption, who may require eventual surgical or endoscopic therapy [43].

## Direct Endoscopic Necrosectomy

Endoscopic necrosectomy is a recognized alternative to surgical debridement, though its availability is limited to specialized centers. A series of 104 patients at six centers showed resolution of WON in 91% with endoscopic necrosectomy, with only 4% requiring surgical debridement [44]. Furthermore, data suggest that endoscopic necrosectomy is associated with fewer complications, less organ failure, and decreased periprocedural inflammation [30].

Similar to PCD, multiple procedures may be required, and not all patients may be candidates for endoscopic therapy. Ideally, collections for endoscopic access are not only walled off but also are adjacent to the gastric or duodenal lumen. Some acute necrotic collections cannot be approached endoscopically due to lack of abutment of the stomach or duodenum. Early collections are not ideally suited for endoscopic therapy due to the risk of intra-abdominal spread of an infected collection, and multifocal collections are less easily approached in this manner.

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# 30

# Management of Infected Pancreatic Necroses: An Endoscopic Approach

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## Pancreatic Necrosis

Pancreatic fluid collections (PFC) can occur as a complication of acute pancreatic injury (acute pancreatitis, trauma, surgical resection, or injury to the pancreas during abdominal surgery) or chronic injury (chronic pancreatitis, autoimmune pancreatitis). At the basis of this pancreatic injury is disruption of the main pancreatic duct and/or side branches. Acute necrotizing pancreatitis is at the severe end of a spectrum of inflammation associated with pancreatitis, resulting in cell death. Pancreatic necrosis is defined as nonviable pancreatic parenchyma usually with associated peripancreatic fat necrosis. It is reported by some to occur in approximately 15–20% of all episodes of pancreatitis [1]. The resultant devitalized tissue becomes a potential bed for infection. Approximately 30% of patients with pancreatic necrosis develop infection [2,3]. The amount of necrotic tissue is the strongest predictor of mortality in necrotic pancreatitis. Fortunately, with early recognition and improvements in critical care most patients survive the early phase of systemic inflammatory response syndrome and many survive multisystem organ failure.

In the acute period, pancreatic necrosis can be an acute necrotic collection in which there is a variable amount of fluid and necrosis [4]. It is detected radiographically on contrast-enhanced computed tomography (CT) by the presence of nonenhancing pancreatic parenchyma. By around 4 weeks after onset the collection continues to evolve and may expand the initial area of necrosis. Such collections contain both liquid and solid debris and are referred to as walled-off necrosis (WON) or walled-off pancreatic necrosis (WOPN), in which the collection is defined by a fibrotic and inflammatory wall. The term infected necrosis refers to bacterial invasion of necrotic pancreatic tissue and can lead to clinical infection, and sepsis and death. Infected necrosis is rare during the first week [5,6]. Most of the evidence suggests no absolute correlation between the extent of necrosis and the risk of infection and duration of symptoms [2,5]. The mortality rate approaches 100% if intervention and drainage are not undertaken for infected necrosis. Even with aggressive intravenous fluid replacement, nutritional support, and early intervention of pancreatic necrosis, the presence of pancreatic necrosis is associated with an overall increase in mortality. The mortality rate from sterile pancreatic necrosis is 10% and rises to 30% when infected [7]

## Mechanical Intervention

Mechanical intervention for pancreatic necrosis can take the form of surgical, percutaneous, and endoscopic debridement. Open surgical therapy is no longer considered the gold standard [8] and has been replaced by minimally invasive approaches [9,10] using flexible endoscopic, and rigid endoscopic [11], percutaneous and laparoscopic approaches, alone or in combination [6]. It has been almost 20 years since the first report of endoscopic drainage of pancreatic necrosis [12]. Optimal management of necrotizing pancreatitis requires a multidisciplinary team including dedicated surgeons, interventional radiologists, and gastrointestinal endoscopists. Such a multidisciplinary team needs to be involved from the onset of the disease to decide if, when, and how an intervention needs to be performed.

Recent guidelines state that there is no need for intervention in asymptomatic patients with sterile necrosis,

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Companion website: www.wiley.com/go/beger/thepancreas

regardless of its size, location, and extension [13,14]. In the vast majority of patients, the necrosis will resolve spontaneously. An intervention for sterile pancreatic collections is only indicated in patients with persistent gastric outlet, intestinal, or biliary obstruction due to mass effect of WOPN at least 4–8 weeks after onset of symptoms. In case of persistent symptoms such as pain and "failure to thrive" intervention is more debated and current guidelines suggest that in such cases, intervention can be considered 8 weeks after onset [14]. In case of infected, but minimally symptomatic necrosis, it is advisable to delay any surgical, radiologic, or endoscopic approach for more than 4 weeks in order to facilitate the formation of WOPN with liquefaction of the contents. Infected necrosis with clinical instability requires immediate drainage in order to avoid fatal complications. In these cases, minimally invasive methods of necrosectomy should be preferred to open surgery. The distinction of sterile from infected necrosis is difficult but very important as it greatly affects prognosis and management. Routine percutaneous fine-needle aspiration (FNA) of pancreatic and peripancreatic collections for the detection of infection should not be routinely performed. It may postpone interventions, give false negative results, or induce secondary infection [6]. Suspicion of infection is usually based on clinical deterioration despite medical support, high fever with rising inflammatory markers, and/or positive blood cultures. The presence of gas on imaging studies is highly suggestive of infection, likely due to fistula, but it is only present in a minority of cases [15,16]. Infection can be confirmed by FNA or through cultures obtained at the time of drainage, and can be used to guide antibiotic therapy [13,14].

The goals of endoscopic therapy for infected WOPN are (i) drainage of fluid and removal of solid components using a transmural approach (transgastric or transduodenal) and (ii) treatment of pancreatic ductal leaks and/or disruptions using a transpapillary approach, in selected patients. Theoretically, addressing pancreatic disruptions may lead to better long-term outcomes [17]. Transpapillary endoscopic drainage as primary therapy of WOPN is not an adequate method to remove solid debris. Removal of solid debris is vital to any type of intervention during transmural drainage, which can be "mechanical," by irrigation, or a combination.

Endoscopic access is best performed when the wall is mature, usually 4 weeks or more after the episode of pancreatitis. This period of time between onset of the disease and intervention is suggested to be associated with lower mortality and intervention is delayed if the clinical condition allows [2]. As necrotic collections become organized into WOPN, they are more amenable to intervention. In case of proven or suspected infected necrotizing pancreatitis, intervention should be delayed where possible until at least 4 weeks after initial presentation [2,14]. An endoscopic transgastric access can be created even as early as 2–3 weeks after the onset of acute pancreatitis in the setting of sepsis and acute necrotic collection as long as they are organized as determined by CT or magnetic resonance imaging.

## Transmural Drainage

The evolution of endoscopic therapy of WOPN began with pseudocysts drainage using small-diameter transmural tracts (8 mm), placement of 10Fr stents and a nasocystic irrigation tube [12]. Early in the endoscopic experience many patients required adjunctive percutaneous drains, especially to treat large paracolic gutter extensions [18]. In patients who were intolerant to nasocystic irrigation tubes and/or in whom it was anticipated that irrigation may be required for many weeks, an alternative to nasocystic lavage was the placement of a percutaneous endoscopic gastrostomy tube (PEG) with placement of a "jejunal" extension tube into the collection [19]. Larger diameter transmural dilations were then added to the irrigation approach. Nasocystic irrigation tubes can be used for continuous flushing with sterile fluid per 24 hours or lavaged every 3–4 hours for several days to weeks depending on the amount of debris present and patient tolerance and may avoid the need for subsequent necrosectomy [20]. However, they are uncomfortable, and with the advent of large-diameter transluminal metal stents, their use is not mandatory. Such nasocystic irrigation tubes are no longer routinely placed [21].

Direct endoscopic necrosectomy (DEN) was introduced by Siefert et al. [22], and subsequently Seewald et al. [23], as a method to remove necrotic tissue by passing forward- or side-viewing endoscopes transmurally into the collection; baskets, grasping forceps, and snares are used to remove solid debris [20,24]. Transmural placement of large-diameter covered (esophageal) self-expandable metal stents (SEMS) [25,26] or 15 mm lumen self-expandable lumen-apposing metal stents can facilitate necrosectomy and avoid the need for repeated balloon dilation of the gastric or duodenal wall (Figs 30.1, 30.2, and 30.3) [24]. Hydrogen peroxide may facilitate the removal of necrotic debris during DEN and reduce the likelihood of further necrosectomies [27].

In conjunction with interventional radiology, several hybrid approaches have also been described [28]. In some patients with peripheral collections that are not accessible from a transluminal approach, a percutaneous

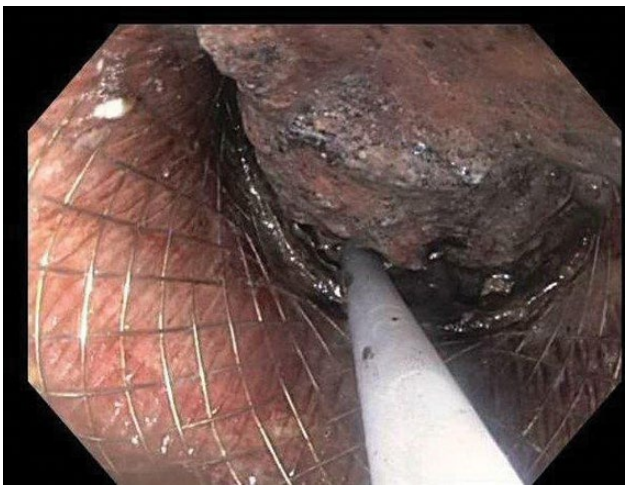

**Figure 30.1** Endoscopic view of pancreatic necrosis. The endoscope is positioned just in front of a recently deployed fully covered self-expandable 15 mm luminal apposition stent. A snare is being used to evacuate solid debris.

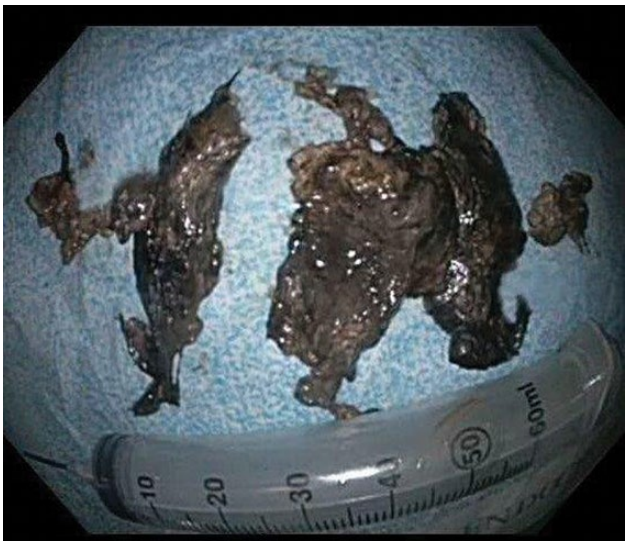

**Figure 30.2** Necrotic debris evacuated from the patient presented in Fig. 30.1.

drain is placed. Subsequently, a large-bore SEMS is placed through the percutaneous tract to allow for DEN with a flexible endoscope.

Gluck and colleagues at the Virginia Mason Medical Center in Seattle, Washington, USA described a dual-modality drainage technique. CT-guided percutaneous irrigation/drainage catheter placement is followed by endoscopic transmural drainage. The percutaneous catheter is used for irrigation, with egress internally. This allows avoidance of DEN. In their institution this approach resulted in decreased length of hospitalization and number of radiologic and endoscopic procedures compared with either modality alone [29]. This method

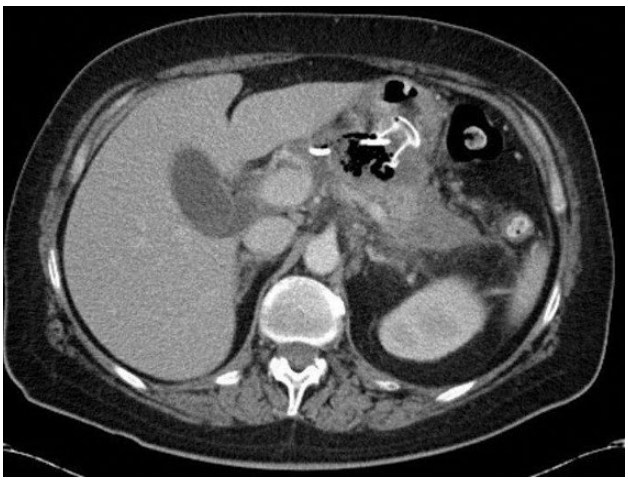

**Figure 30.3** CT scan from the patient shown in Figs 30.1 and 30.2 shows the expandable stent in place and near resolution of necrotic cavity.

of treatment was reported to be superior to a strictly percutaneous approach, not only in speeding resolution, but also in precluding the development of external fistulas [26] and bleeding.

For complex organized necrosis, Varadarajulu and colleagues described an endoscopic ultrasound (EUS)-guided multi-gateway approach [30], which utilizes two or more transmural entry approaches to permit irrigation, aiming to improve drainage of the often multiseptated necrotic collections. Nasocystic irrigation enters one site and egresses from another. Following the procedure, 200 mL of saline is irrigated every 4 hours through the nasocystic tube, shifting patient position between flushes.

## Transmural Entry Devices

Devices used to perform transmural puncture of WOPN can be divided into cautery and noncautery devices. Cautery devices include standard diathermy wires (needle knifes), specialized fistulotomy devices (cystotome, CST-10, Cook Endoscopy, Winston-Salem, NC, USA) and specialized stent delivery systems with cautery incorporated (AXIOS EC, Boston Scientific, Marlborough, MA, USA). Noncautery devices include 19-gauge EUS-FNA needles and other miscellaneous aspiration needles (Marco-Haber variceal injector needle MHI-21, Cook Medical).

Most often the collection is punctured transmurally using EUS guidance. Fluid is aspirated to confirm entry and is sent for fluid analysis including Gram stain and culture. Correct positioning during entry can also be confirmed by contrast injection into the collection under fluoroscopy.

### Stent Placement

Plastic stents are not ideally suited to drain WOPN. Recently, the use of fully covered SEMS [31] are used instead. Specially designed biflanged short stents (Axios, Boston Scientific), either with or without electrocautery-incorporated delivery systems, seem to have a high technical and clinical success rates. Due to its ease of use, such devices have simplified and streamlined EUS-guided management of PFC, particularly for endoscopic debridement of WOPN. These devices have also promoted more widespread adoption of transmural drainage as an alternative to surgery [32,33].

If a noncautery device is used to enter into the collection, the transmural tract must then be traversed (over a 0.025–0.035″ guidewire) either with a biliary dilating balloon (4 mm diameter to allow passage of the delivery system) or with a 10 F cystotome; the metal stent is then deployed. When the recently commercially available electrocautery-tipped SEMS delivery system is used, the procedure is done in a single step (puncture and stent deployment). Particular care should be taken with regard to proper device deployment, particularly the final, crucial step involving proximal flange release. According to the manufacturer's instructions, the endoscope should be pulled back slightly in order to directly visualize 2–3 mm of the black catheter shaft marker in the gastrointestinal tract before deploying the proximal flange. An alternative option that does not sacrifice a stable scope position or risk placing excessive traction on the SEMS involves releasing the proximal flange while it is still inside the endoscope, and the endoscope tip remains close to the puncture site. At that point, advancing the delivery system while gently withdrawing the endoscope allows the proximal flare to spring open as the stent exits the endoscope. However, even with electrocautery-tipped SEMS delivery systems, it is important to secure an ample length of guidewire into the collection with at least one complete loop of wire. A double pigtail stent placed through or alongside the metal stent lumen may help to prevent migration and occlusion due to impaction of necrotic material [34,35].

Anticoagulant or antiplatelets drugs should preferably be discontinued prior to transmural drainage, and certainly prior to necrosectomy. In case of severe bleeding during the procedure which cannot be treated endoscopically, immediate assistance of an interventional radiologist should be requested. Endoscopic drainage and necrosectomy are preferably performed with patients under deep sedation or general anesthesia. DEN should be routinely performed using a forward-viewing endoscope at the time of the first endoscopic procedure; schedule debridements should be performed with the interval ranging from days to weeks depending upon the inpatient or outpatient status, anticipated volume of residual necrosis, and follow-up CT. Internal drains are endoscopically removed several weeks after complete resolution of the collection and removal of external drains (if placed). Patients with infected necrosis continue antibiotic therapy, either empirically or based upon culture data obtained during drainage and/or debridement. All procedures should be performed with carbon dioxide ($CO_2$) insufflation since fatal gas embolism has been described.

## Results of Endoscopic Therapy of Pancreatic Necrosis

There are increasing series showing that endoscopic treatment of WOPN is successful in achieving nonsurgical resolution in the majority of patients [34]. Retrospective studies have shown a treatment success rate of 45–63% for endoscopic drainage [17,20]. In a review of 10 series on endoscopic necrosectomy, the overall treatment success was 76%, mortality 5%, and procedure-related morbidity 27% [36]. Minimally invasive techniques were evaluated by a randomized trial [2,6], which showed lower morbidity rates, faster recoveries and shorter hospital stays. Evidence in favor of endotherapy is supported by others [34]. A recent systematic review considered DEN a safe (mortality rate of 6% and complication rate of 36%) and effective minimally invasive treatment (80% treatment success) in infected necrosis [37]. However, most of the studies included did not report on the most relevant parameters of disease severity or outcome measures. Guidelines now advocate that if an intervention is indicated in patients with infected necrosis, initial treatment should consist of either image-guided percutaneous catheter drainage or endoscopic transluminal drainage [14].

## Adverse Events of Endoscopic Therapy of Pancreatic Necrosis

Life-threatening adverse events may arise following attempted endoscopic drainage of pancreatic necrosis. It is recommended that endoscopic drainage is performed with the availability of surgical and interventional radiology support. The most feared adverse events of transmural drainage are bleeding and perforation. Bleeding after transmural drainage may be managed supportively, endoscopically, surgically, or with angiographic embolization. If perforation occurs during attempted transgastric drainage and is limited to the gastric wall (does not involve the collection), it may be

successfully managed nonsurgically if a stent is not mistakenly placed through the perforation and outside the gastric wall. If egress of gastric contents is prevented, the gastric wall rapidly closes with conservative treatment consisting of nasogastric suction and antibiotics. Large-diameter (esophageal) SEMS can be used to close perforations [38] and in some cases tamponade bleeding. Infectious adverse events usually occur from inadequate drainage of fluid and/or solid debris. Stent migration into the collection through the gastric or duodenal wall may occur during or after endoscopic stent placement. Endoscopic retrieval is possible if the collection has not completely collapsed and the transmural tract is still patent. Fatal air embolism has been reported following DEN [39]. This has prompted the use of $CO_2$ rather than air insufflation during drainage.

Endoscopic therapy may be associated with adverse events and/or failures that require surgical management. It is possible that the outcome of surgical therapy may be adversely altered when compared to those patients undergoing primary surgical therapy.

What is clear is that if endoscopic therapy is undertaken, commitment is required by the endoscopist, clinical care team, and, most importantly, the patient. Endoscopic debridement is a time-consuming, labor-intensive process not for the uncommitted [40] or faint of heart since adverse events occur more commonly than in any other pancreaticobiliary intervention and have the potential to be fatal. Therefore, even more importantly, perhaps, is the need for support from intensivists, endoscopists, surgeons, and interventional radiologists to manage these complicated patients.

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# Minimally Invasive Debridement and Lavage of Necrotizing Pancreatitis

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## Introduction

Pancreatic necrosis occurs in approximately 20% of patients with acute pancreatitis [1] with infection developing in approximately 30% [2,3]. Infected pancreatic necrosis is associated with considerable morbidity and a mortality rate of up to 32% [3]. Current International Association of Pancreatology (IAP)/American Pancreatic Association (APA) guidelines recommend intervention for necrotizing pancreatitis when there is conformation or suspicion of infected pancreatic necrosis with clinical deterioration [2]. In addition, intervention may be required for persistent sterile necrosis with organ failure and a lack of progress. Intervention should ideally be delayed until the necrosis has become walled off, typically after 4–6 weeks [4].

In recent years there have been multiple series and trials recommending a minimally invasive approach to pancreatic necrosectomy [5–9] and this has now become the standard approach for most centers. Studies have shown a significantly reduced incidence of postoperative organ failure and lower complication rates for patients undergoing minimally invasive treatment compared to an open necrosectomy. A nonsignificant reduction in mortality is demonstrated in many reports but these studies do not have the numbers required for this to be statistically significant [5,8,10].

## Technique

Multiple different techniques for minimal access necrosectomy have been described. This chapter will review retroperitoneal and laparoscopic approaches; endoscopic necrosectomy is discussed elsewhere.

Laparoscopic transperitoneal necrosectomy was first reported in 1996 [11] and several small-volume case series have been reported [12–14] but the technique is declining in popularity and no large series currently exist. The collection is visualized laparoscopically and debridement is performed, either with a hand-assisted or laparoscopic port. The necrotic cavity may be approached either directly, through the transverse mesocolon or gastrocolic omentum, or via a transgastric route. Approximately 20% of patients require reoperation either by open or laparoscopic routes [11,14]. The potential advantages of this technique include the ability to perform a simultaneous cholecystectomy [4,15] and a reduced length of stay compared to other minimal access techniques [13,14]. Laparoscopic cystogastrostomy has been reported in several series to be a safe and effective alternative operative technique but is only feasible once the necrosis has become walled off [16]. The major disadvantage of the laparoscopic route, however, is that infected necrotic tissue is allowed direct access into the previously sterile peritoneal cavity, thus infecting a second body compartment.

Most centers now prefer a percutaneous retroperitoneal approach, thereby restricting the spread of infection to a single body compartment. The exact technique varies between institutions, with procedures using a laparoscope, rigid nephroscope and flexible endoscope all having been reported [8,17,18] but the overall principles are similar.

For the minimal access retroperitoneal pancreatic necrosectomy (MARPN) technique, as used in Liverpool, initial access to the necrotic cavity is achieved by placement of a percutaneous drain into the necrotic collection under computed tomography (CT) guidance. This drain is normally placed through the left flank using the

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window between the spleen, left kidney, and colon (Figs 31.1 and 31.2) [8] but alternative access routes are possible and the exact site for access is chosen individually according to the distribution of necrosis. A randomized controlled trial reported that 35% of patients could be managed with percutaneous drainage alone and did not require further procedures [5]. If there is no clinical improvement following simple radiological drainage then further debridement is indicated.

In the operating theater, under sedation or general anesthesia, the patient is positioned supine but tilted so that the drainage tract is approximately horizontal. Using a sandbag directly under the point of entry and positioning the patient close to the left hand side of the operating table facilitates access to the tract with the operating nephroscope [7,15].

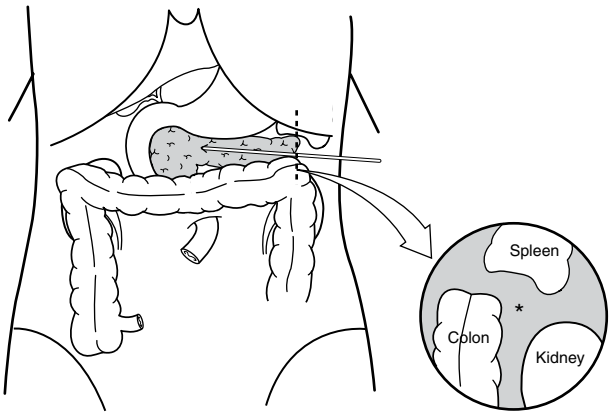


**Figure 31.1** Preferred retroperitoneal approach to infected pancreatic necrosis, avoiding the spleen, left kidney and colon. *Source:* Raraty et al. 2006 [19].

Under fluoroscopic guidance, the drainage catheter is exchanged for a guidewire and the tract dilated to 30 F using a renal dilator set or a balloon dilator [8,20]. A 2 cm skin incision allows the passage of the dilators and once they have passed the fascial and muscular layers of the retroperitoneum there should be very little resistance. Using fluoroscopy and previous CT images, care should be taken not to advance the dilators further than the extent of the necrotic cavity. Once the tract is dilated an Amplatz sheath is placed over the dilator to maintain the patency and position of the tract throughout the procedure [20]. Correct positioning is often apparent by the passage of pus and liquid debris through the Amplatz sheath.

An operating nephroscope with a wide-bore operating channel is introduced which allows visualization of the cavity as well as simultaneous irrigation and biopsy. Necrotic tissue is removed piecemeal using standard laparoscopic grasping forceps with constant irrigation of warm saline (Fig. 31.3). Samples of the removed necrotic tissue are sent to microbiology for culture and to guide antibiotic usage. Initial necrosectomy is often limited by immature necrosis which is adherent to the cavity walls; attempted removal of such adherent material can lead significant bleeding and only material which separates easily should be removed [15,21]. Repeated procedures are often required, therefore, before the cavity can be seen to be completely clean.

At the end of the procedure an irrigating drain, consisting of a 10 F or 12 F nasogastric tube sutured to a 28 F chest drain is inserted into the cavity (Fig. 31.4). The

(a) (b)

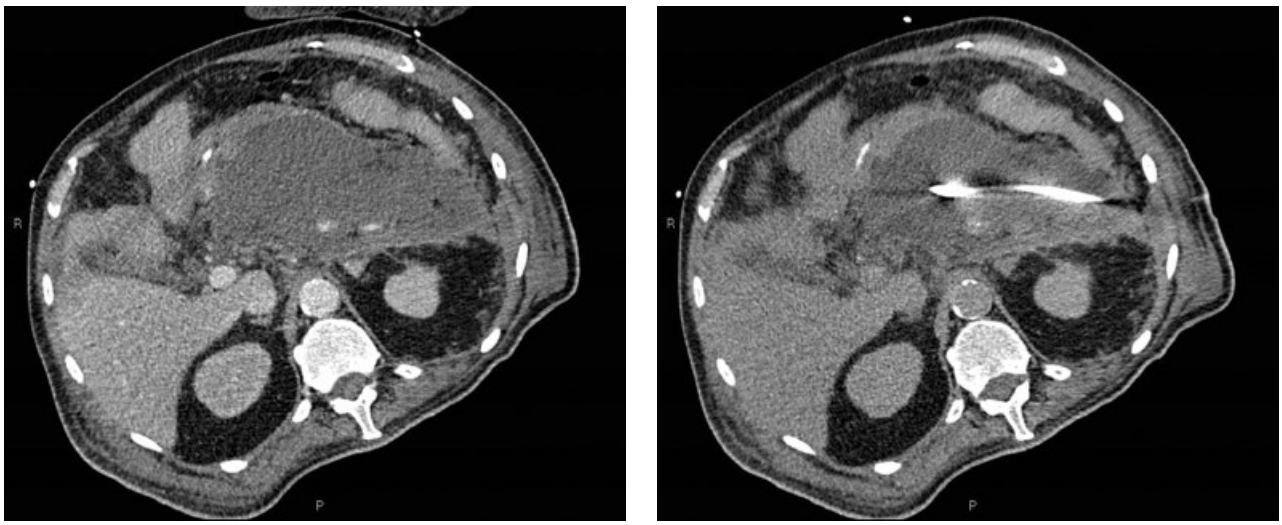

**Figure 31.2** (a,b) Radiological access to the necrotic cavity via the left flank. Tilting the patient with left side up facilitates access to the necrotic cavity.

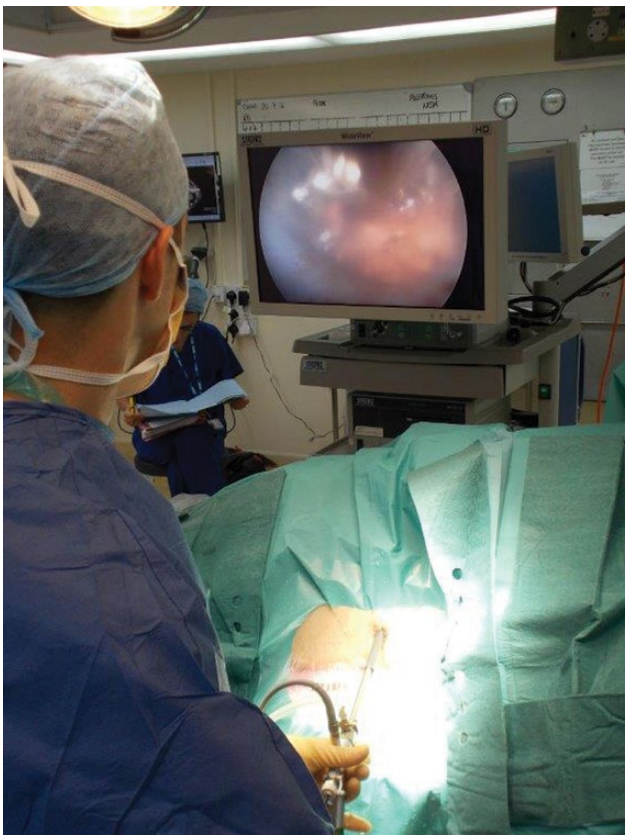

**Figure 31.3** Debridement of necrotic pancreatic tissue under direct vision using an operating nephroscope.

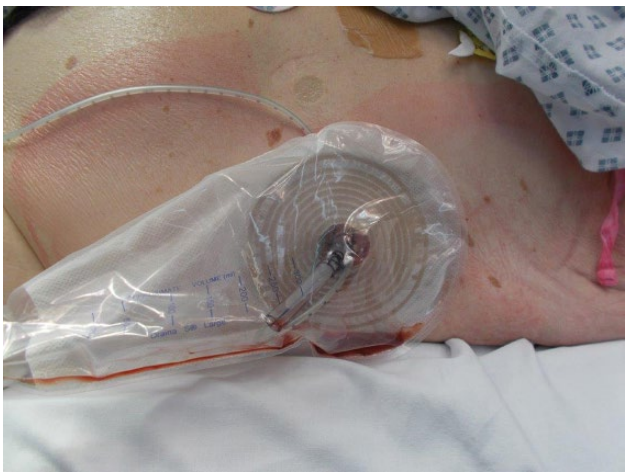

**Figure 31.4** A 12 F Ryles nasogastric tube and 28 F chest drain are placed into the cavity at the end of the procedure and used as an irrigating drainage system to continuously flush the necrotic cavity with 0.9% saline solution at a rate of 125 mL/h.

cavity is continuously irrigated with 0.9% saline solution at 125 mL/h [8,15]. The procedure is repeated at 7- to 10-day intervals until necrosectomy is complete [7,8]. Taking into account the patient's condition, inflammatory markers and radiology, as well as visual inspection of residual necrosis at operation, the rate of irrigation is eventually halved to 60 mL/h, then 30 mL/h and then stopped. A CT tubogram confirms that the cavity has collapsed and that no complex tracts are present. The irrigating drainage system is then downsized to a smaller bore, single-channel drain and the patient can often be discharged at this point [8], with the drain later removed in the outpatient setting.

An alternative method of retroperitoneal necrosectomy, used frequently in the United States and the Netherlands, is the video-assisted retroperitoneal debridement (VARD) technique first described by Horvath in 2001 [5,17]. VARD was initially performed using two laparoscopic ports but the technique has been modified over the subsequent years [9]. As for MARPN, initial access to the necrotic cavity is achieved by radiological placement of a percutaneous drain.

With the patient positioned as described above for the MARPN technique, a 4–5 cm incision is made 1–2 fingers below the left costal margin over the midaxillary line close to the percutaneous drain. The abdominal wall muscles are divided and the drain is located using the surgeon's finger. The drain can then be followed to the collection and the collection opened with finger dissection. Necrosis is primarily removed with suction, blunt finger dissection and forceps. A zero degree laparoscope is then inserted through the incision along with forceps introduced parallel to the scope to perform further necrosectomy under direct vision. Laparoscopic clips can be applied in the event of bleeding. Two large-bore drains are placed into the collection, one deep and the other more superficial and continuous lavage is attached. The fascia is closed over the drains to allow postoperative lavage. The skin may be closed or left open to heal by secondary intention [9,17,20].

The aim in both procedures is to remove free and easily accessible necrosis, not to perform a complete necrosectomy in one sitting [8,9].

## Techniques for Complex Collections

As centers have become more comfortable and experienced with the procedure, developments have occurred to enable drainage and necrosectomy on more complex necrotic collections. With a retroperitoneal route, right-sided or more central collections can be difficult to access due to surrounding abdominal viscera, but access is often still possible with skilled interventional radiology. An anterior approach through the gastrocolic omentum can sometimes be used for pancreatic head collections. Collections tracking in to the right or left retroperitoneal gutters may be drained and used as accessory tracks for MARPN or VARD-type necrosectomy [8].

A combination of percutaneous as well as endoscopic techniques can be employed in complex cases or where there is suboptimal drainage or progress with the initial intervention [20].

## Early Complications

Necrotizing pancreatitis is a condition associated with a high morbidity and patients undergoing necrosectomy for infected pancreatic necrosis frequently experience a significant physiological insult. Some will develop complications related to the disease process itself and others directly from the procedure [20,22].

Our recent series of 274 patients reported an overall conversion rate from minimal access to open necrosectomy of 13.1% (36/274) [8]. The conversion rate had reduced from 17.3% in the earlier part of the study (1997–2008) to 12.1% in later years (2009–2013), suggesting a learning curve with both percutaneous drainage and operative technique [7,8]. The most common reasons for conversion are the inability to place the initial drain, difficulties dilating the tract, inaccessible collections or bleeding [7,8]. In approximately 30% of patients minimal access necrosectomy is not possible due to such difficulties [8]. Approximately one-quarter of patients will require additional percutaneous drainage following minimal access necrosectomy [5,8].

Postoperative bleeding has been shown to be an independent poor prognostic factor and is associated with a high mortality rate [22,23]. The reported incidence of significant bleeding after necrosectomy is 11–18% [5,8,22,23]. Primary hemorrhage occurs either due to avulsion of a vessel when dilating the tract or from debriding adherent or granulating tissue during the procedure [15,20]. If bleeding occurs then the cavity should be packed. If this is unsuccessful and arterial bleeding is suspected then angiography with or without embolization is required. Venous bleeding is common, and should be considered if there is no obvious bleeding point on angiogram. It will usually settle after local pressure, occluding the drain and correcting any coagulopathy [20]. If embolization is not possible or fails to stop the bleeding then a laparotomy should be performed, although this is very rarely necessary. Secondary hemorrhage may also occur, most commonly from erosion of the necrosis into a vessel or from rupture of a pseudoaneurysm. This is often preceded by a small "herald" bleed and mesenteric angiography should be arranged urgently at this point [15].

Colonic necrosis has a reported incidence of up to 17% [22] in patients undergoing open necrosectomy but data from minimal access techniques demonstrate a far lower rate of around 1.5% [8,15]. The reasons behind this discrepancy are not entirely clear, but there are likely to be some differences between the two populations. The randomized controlled trials from the Dutch Pancreatitis groups do not report ischemic bowel as a specific complication given its low incidence [5,6]. Although the incidence of colonic necrosis is low, its mortality rate is high, and has been reported at 53% [24]. Bowel ischemia may not always be apparent with a minimal access technique and there is often a delayed diagnosis which may adversely affect prognosis. A high degree of suspicion should therefore be maintained for the development of this complication [22]. A focal area of colonic necrosis can lead to enteric fistula formation which may require control in the form of a defunctioning stoma or resection as deemed clinically appropriate. Enteric fistulas are caused by the spontaneous discharge of a necrotic collection into the adjacent gastrointestinal tract [20]. Gastric and duodenal fistulas can generally be managed conservatively, giving total parenteral nutrition (TPN) if nutritional needs are not being met [15]. A physiological duodenal fistula through the ampulla is not uncommon after MARPN of extensive necrosis which involves the pancreatic head.

Pancreatic fistulas are relatively common late complications following surgery for pancreatic necrosis. They occur in 5–28% [5,8] of patients and arise from a communication with the remnant pancreatic duct. The fistula should resolve with conservative management providing there is no downstream pancreatic duct obstruction [25]. Endoscopic retrograde cholangiopancreatography (ERCP) and transpapillary pancreatic duct stent insertion may help resolution of a persistent fistula [20].

## Postoperative Course

Postoperative multiorgan failure is frequent, although less so than after an open necrosectomy, occurring in 20–50% of patients and may prove fatal following intervention for necrotizing pancreatitis [5,6,8]. Between 16% and 50% of patients will require intensive therapy unit (ITU) care postoperatively, with a median ITU stay of 9–12.5 days [5,6,8].

Multiple procedures are often required; a median of 3 (interquartile range [IQR] 2–4) procedures for techniques using sinus tract dilation are needed, therefore patients frequently have an extended length of stay [8,15]. The median total hospital stay reported is 98 days (IQR 75–128), taking into account a median stay of 29 days prior to the first procedure [8]. For centers performing VARD, patients require fewer operations with a median of 1 (range 1–2). This is reflected in a lower overall reported hospital stay of 78 days [9].

Long-term follow-up is essential given the risk of delayed complications, reported to be as high as 62% [22].

Fistulas, pseudocyst formation, new-onset diabetes, and pancreatic insufficiency are all frequently seen and may require intervention if present [5,6,22].

## Outcome

Postoperative mortality following minimal access necrosectomy is now reported to be less than 15%, however over 60% of patients experience some form of complication [5,6,8]. Reported mortality from open necrosectomy ranges from 11% to 39% [7,26], but more recent series show that the mortality rate for both open and minimal access necrosectomy techniques has fallen to 12.5% and 11.2%, respectively [8]. This can be ascribed to a general improvement across all areas of care and the management of these patients using a multidisciplinary approach in specialist centers. Patient selection may also play a role.

The incidence of both operation specific (35.4% vs. 51.7%) and nonoperation-specific (16.8% vs. 26.7%) complications is lower with a minimal access approach compared to with open necrosectomy [8]. Postoperative multiorgan failure is also significantly reduced, occurring in 12–20% of patients following a minimal access or step-up approach and 35–40% of patients following open necrosectomy. The Liverpool data show a higher rate of postoperative ITU admission after open necrosectomy, although this is not demonstrated in the Dutch PANTER trial [5,8].

Long-term complications including pancreatic fistulas, new-onset diabetes, and use of pancreatic enzymes are significantly more common following open necrosectomy compared to minimal access surgery. However, the rate of postoperative deep-vein thrombosis (6.6% vs. 1.7%) was higher in the minimal access cohort, likely influenced by the longer length of stay in this group (median 98 vs. 71 days).

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# 32

# Open Surgical Debridement in Necrotizing Pancreatitis

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## Introduction

The management of necrotizing pancreatitis has changed over the last decades to a more conservative multidisciplinary therapeutic approach [1]. surgical debridement is needed For less than 20% of all patients with necrotizing pancreatitis [2]. Minimal invasive techniques seem to reduce the morbidity and mortality compared to open surgical debridement [3]. Open approaches are needed if minimal invasive procedures fail to achieve sufficient necrosectomy or are not available, or if complications of the pancreatic necrosis such as bleeding prohibit a minimal invasive approach.

The goals of open surgical debridement are to:

- remove all (infected) necrotic pancreatic and surrounding tissue in order to achieve local focus control and minimize inflammatory triggers leading to septic systemic inflammatory response, and
- preserve all vital pancreatic tissue to avoid long-term pancreatic exocrine and/or endocrine dysfunction.

Surgical debridement of necrotic pancreatic tissue should not be performed during the first 2 weeks after onset of the disease, but should ideally be postponed for least 4 weeks to achieve a better demarcation of devitalized pancreatic tissue and save vital pancreatic tissue [4–7]. The only prospective controlled study with focus on the ideal timing for necrosectomy was discontinued before completion because of a clear advantage in the group with a delayed surgical intervention (at least 12 days) compared to the early intervention group [5]. Surgical debridement later than 4 weeks after onset of symptoms gives no further advantage with regard to outcome and overall costs [8].

Contrast-enhanced computed tomography is the gold standard before the surgical approach and provides a roadmap for the operative strategy. Nevertheless, it has to be taken into account that the amount of necrotic pancreatic tissue can only be interpreted correctly during surgery. Pancreatic necrosis can be overestimated by preoperative imaging and an organ-sparing necrosectomy can often be performed even if the preoperative imaging suggests complete pancreatic necrosis. This is essential for morbidity, mortality, and the long-term quality of life with regard to endocrine and exocrine pancreatic function [9–13].

## General Technique of Open Surgical Debridement

The concept of necrosectomy includes surgical removal of devitalized peripancreatic and intrapancreatic tissue and evacuation of fluid collections.

The access to the lesser sac containing the pancreatic necrotic tissue can be achieved in different ways. The most commonly used routes are via diversion of the gastrocolic ligament or through the mesenterium of the transverse colon. If the access is obtained via the mesenterium of the transverse colon we recommend the left-sided route of the median colic vessels (Fig. 32.1). Other approaches to access the pancreatic necrotic tissue are left side of the ligament of Treitz (pancreatic tail) or right side of the middle colic vessels (body and part of the pancreatic head), depending on the location of the suspected necrotic tissue. If necrotic tissue is mainly present in the area of the pancreatic head, mobilization of the pancreatic head

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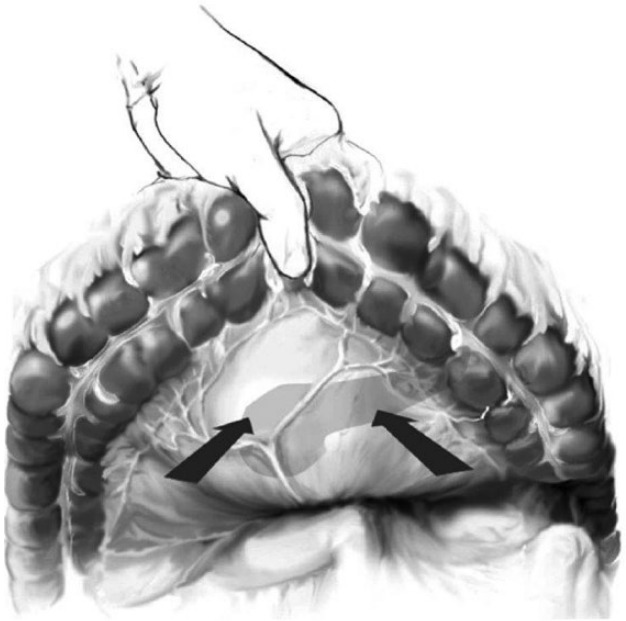

**Figure 32.1** Access to the lesser sac can be directly through the transverse mesocolon on either side of the middle colic vessel.

(Kocher maneuver) can provide adequate access for necrosectomy.

The necrotic tissue should be removed carefully by blunt digital dissection. Covering the surgeon's finger with a sponge can facilitate complete removal of the necrotic tissue. The left or right colonic flexure should be mobilized if fluid collections or necrotic tissue are present in the retroperitoneal, pararenal, or paracolic space. All necrotic tissue should be removed, remembering not to disturb friable tissue in order to minimize bleeding. An intraoperative fluid sample for bacterial culture should be taken for microbiological analysis to identify the organism(s) producing infection and guide antimicrobiological therapy.

Excessive lavage using 6–12 L of isotonic saline solution should be performed to remove infectious ascites and debris as well as to reduce the load of inflammatory mediators contained in these materials.

If possible, the lesser sac should be closed after debridement and placing of adequate drains to separate the infectious area from the rest of the abdominal cavity.

Cholecystectomy can be performed simultaneously if required.

To achieve the above-mentioned principal aims, different strategies have been developed as a one-stage procedure with initial necrosectomy and simple drainage of the pancreatic bed is often not effective and persisting or recurrent intra-abdominal sepsis can be a major problem [1,14]. This implies the need for an ongoing postoperative focus control.

## Continuous Closed Lavage

The concept of postoperative continuous closed lavage of the lesser sac was established in the early 1980s [15,16]. From several larger cohort studies, this strategy seems to have improved postoperative short- and long-term morbidity compared to other open techniques [13,17,18], although there are no prospective controlled data available.

For postoperative continuous closed lavage, large double-lumen flushing drainages (20–24F) are placed in the pancreatic bed at the end of open necrosectomy and lavage and brought out through either side of the abdominal wall. As mentioned above, the access to the lesser sac should possibly be adapted to create a closed compartment for a regionally restricted lavage. Afterwards, the abdominal wall is definitely closed as no re-exploration is planned in this surgical concept.

Postoperative initial lavage should be performed with at least 6 L/24 hours using isotonic saline solution. The amount of flushing volume can be adapted to the macroscopic aspects of the effluate, enzyme count (amylase/lipase), and the clinical condition of the patient. Lavage can be reduced and stopped when there are normal or clearly decreasing pancreatic enzymes in clear fluid produced by the drains. If none of the mentioned parameters are impaired after stopping the continuous lavage, the drains can be removed sequentially (Fig. 32.2). If the patient is in a good clinical condition a closed continuous lavage does not necessarily need to be performed on an intensive care unit. Although there are no planned re-operations required for this procedure, in some patients this may be necessary. Reasons for re-laparotomies include the development of undrained fluid collections that cannot be approached by a percutaneous drainage, intestinal fistulas, or bleeding. Table 32.1 gives an overview of data from published series on this concept with regard to mortality and morbidity, including preoperative disease severity, incidence of postoperative pancreatic fistulas, and postoperative bleeding.

## Debridement and Open Packing/ Staged Laparotomy

When a complete necrosectomy cannot be achieved by the primary operation for extended necrotic tissue in the retrocolic and/or mesenteric spaces there is a high probability of further sepsis. In this situation open packing/staged laparotomy (OP/SL) is an option for damage control. This approach was conceived 1981 to reduce the incidence of postoperative ongoing infection [19]. In patients where OP/SL is indicated, often

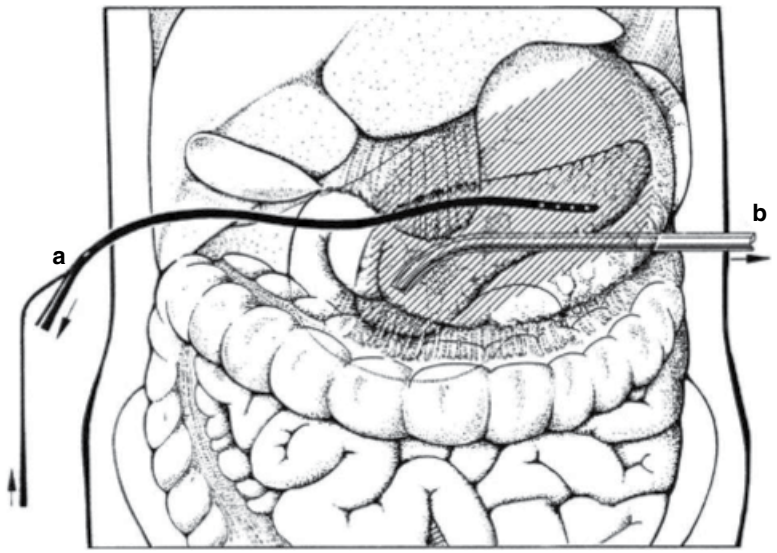


**Figure 32.2** Schematic diagram of (a) double-lumen and (b) single-lumen lavage catheters placed in the lesser sac for continuous closed lavage after necrosectomy.

**Table 32.1** Continuous closed lavage.

| Reference | Patients | Preoperative severity[a] | Deaths | Fistulas | Bleeding |
|---|---|---|---|---|---|
| Lavin et al. [26] | 14 | 5 (3–8) Ranson | 3 (21%) | 0 | 1 (7%) |
| Pederzoli et al. [27] | 263 | n.r. | 47 (18%) | 22 (8%) | 21 (8%) |
| Büchler et al. [28] | 28 | 4 (0–7) Ranson<br>13 (6–22) APACHE II | 6 (21%) | 8 (29%) | 2 (7%) |
| De Waele et al. [29] | 17 | 7 (±1.4) Ranson<br>26 (±9.3) APACHE II | 9 (53%) | 3 (18%) | 0 |
| Wig et al. [30] | 58 | 8 (3–17) APACHE II | 17 (29%) | 9 (16%) | 8 (14%) |
| Besselink et al. [18] | 53 | n.r. | 13 (25%) | n.r. | 17 (32%) |
| Farkas et al. [31] | 220 | 16 (11–32) APACHE II | 17 (8%) | 24 (11%) | 6 (3%) |
| Rau et al. [32] | 285 | 5 (0–10) Ranson<br>11 (0–28) APACHE II | 72 (25%) | 77 (27%) | 44 (15%) |
| Gomatos et al. [33] | 120 | 8 (4–11) APACHE II | 28 (23.3%) | 14 (11.7%) | 18 (15%) |
| van Santvoort et al. [34] | 45 | 15 (±5.3) APACHE II | 7 (16%) | 17 (38%) | 10 (22%) |
| Total | 1103 | | 219 (20%) | 174 (17%) | 127 (12%) |

[a] Scores are presented as mean or median with ranges or standard deviation in parentheses.
n.r., not reported.

more than 50% of the pancreas is found to be necrotic and the disease is ramified, making an adequate retroperitoneal minimal invasive necrosectomy impossible. Another reason for OP/SL is the development of an abdominal compartment syndrome in patients with necrotizing pancreatitis. Abdominal compartment syndrome is characterized by an increase of the abdominal pressure to more than 25 mmHg. Diagnosis can be made by the clinical evaluation of the abdomen and an additional measurement of the urinary bladder. Therefore, this pressure measurement should be performed in patients with necrotizing pancreatitis since an undetected abdominal compartment syndrome is fatal; laparotomy leads to an immediate release of the pressure and avoids subsequent complications such as bowel perfusion failure or respiratory failure, which may be caused by the need for an extremely high pressure during mechanical ventilation.

In OP/SL, relaparotomy is performed every 48–72 hours to remove further demarcated necrotic tissue until granulation tissue starts to develop. After careful debridement (see earlier), soft drains should be placed a distant from the large vessels and the cavities packed with gauze. A nonadhesive organ foil is placed on the

intestinum and the abdomen is closed temporarily, either with a nonadhesive mesh or with an adhesive foil dressing after placing gauze between the foil placed on the intestinum and the outside foil layer. Evaluation of the further need for relaparotomy should be made after every operative revision. If complete necrosectomy is achieved, the concept of open treatment should be switched to continuous closed lavage and definitive closure of the abdominal wall should be applied (see earlier).

Because of the indication, the morbidity rates of this procedure in the literature are high. The reported mortality rates are 24%. The most common morbidities are fistula formation (36%) and a bleeding rate of 18%. The mean number of explorations needed to complete the therapy is approximately 6–7 per patient (Table 32.2).

These results cannot be compared to those for other necrosectomy procedures because of the underlying severity of disease, which leads to the decision to perform OP/SL. Whenever possible, necrosectomy with continuous closed lavage should be preferred. Nevertheless, OP/SP is a suitable procedure for damage control if necrosectomy cannot be achieved in a single operative intervention or an abdominal compartment syndrome requires this procedure.

## Debridement and Closed Packing

The concept of debridement and closed packing implies an open necrosectomy as described earlier. After completion of necrosectomy and lavage, stuffed Penrose drains are placed in the debrided cavity and are exteriorized via the abdominal wall. Furthermore, suction drains are placed into the debrided cavity. The stuffed Penrose drains are removed stepwise until they can be finally taken out completely, which usually requires several days. The suction drains are left in place to drain potential pancreatic fistulas. This reduces the need for re-operations in comparison to the open packing staged laparotomy procedure (Fig. 32.3).

In the primary paper describing this procedure by the Boston group, morbidity with regard to pancreatic and enteric fistulas was 42% and 15%, respectively. Furthermore, re-operations had to be performed in 12.6% and an interventional percutaneous drain placement was required in 30% of the patients. The overall mortality rate was 11.4%, which correlated with the number of organ failures during the disease course [20]. In a later series of 68 patients undergoing open necrosectomy and closed packing the Boston group achieved an in-hospital mortality rate of 8.6% [21]. In this series, 74%

**Table 32.2** Open packing staged laparotomy.

| Reference | Patients | Preoperative severity[a] | Deaths | Fistulas | Bleeding | No. of explorations |
|---|---|---|---|---|---|---|
| Orlando et al. [35] | 15 | 4.5 (0–11) | 3 (15%) | 5 (33%) | 4 (27%) | 19.8 |
| Vauthery et al. [36] | 6 | 16–30 APACHE II | 0 | 3 (50%) | n.r. | 6.5 |
| Bradley et al. [37] | 71 | n.r. | 10 (15%) | 42 (59%) | 5 (71%) | 7.9 |
| Harris et al. [38] | 11 | n.r. | 2 (18%) | 6 (55%) | 0 | 10 |
| Fugger et al. [39] | 125 | 15 (4–30) APACHE II | 40 (32%) | 31 (25%) | 24 (19%) | n.a. |
| Hwang et al. [40] | 40 | n.r. | 6 (15%) | 4 (10%) | 2 (5%) | n.r. |
| Nordback et al. [41] | 22 | n.r. | 5 (23%) | 14 (64%) | 2 (14%) | 3 |
| van Goor et al. [42] | 10 | n.r. | 3 (30%) | 4 (40%) | 5 (50%) | 14.3 |
| Dominioni et al. [43] | 16 | n.r. | 3 (19%) | 4 (25%) | 3 (19%) | 8 |
| Gentile et al. [44] | 40 | n.r. | 12 (30%) | 10 (25%) | n.r. | 2.5 |
| Tsiotos et al. [13] | 72 | 10 (0–23) APACHE II | 18 (25%) | 25 (35%) | 13 (18%) | 2.2 |
| Branum et al. [45] | 50 | n.r. | 6 (12%) | 50 (100%) | n.r. | n.r. |
| Kriwanek et al. [46] | 77 | n.r. | 19 (25%) | 10 (13%) | 12 (16%) | n.r. |
| Nieuwenhuijs et al. [17] | 38 | 5 Ranson | 10 (26%) | 7 (18%) | 18 (47%) | n.r. |
| Tzovaras et al. [47] | 28 | n.r. | 5 (18%) | 5 (18%) | n.r. | 3.5 |
| Radenkovic et al. [48] | 35 | 10 (3–23) APACHE II | 12 (34%) | 16 (46%) | 5 (14%) | n.r. |
| Lee et al. [49] | 6 | 15 (6–20) APACHE II | 4 (67%) | 2 (33%) | 3 (50%) | 3.5 |
| Total | 662 | | 158 (24%) | 238 (36%) | 96/538 (18%) | 6.5 (2.2–19.8) |

[a] Scores are presented as mean or median with ranges or standard deviation in parentheses.
n.r., not reported.

of patients developed postoperative pancreatic fistula and 9% enterocutaneous fistula. All available data for this procedure are summarized in Table 32.3.

## Open Cystogastrostomy for Walled-Off Pancreatic Necrosis

If the main burden of pancreatic necrosis is located close to the posterior gastric wall, transgastric open cystogastrostomy is a further option for open necrosectomy. The prerequisite for this approach is the existence of walled-off pancreatic necrosis (WOPN). This usually occurs in the late course of necrotizing pancreatitis. Boland et al. described this procedure 2010 in a series of six patients who were successfully treated by this approach with a single laparotomy and no surgical re-explorations [22]. From the technical point of view, after laparotomy an anterior gastrostomy is performed and WOPN is identified by intraoperative ultrasound via the posterior wall of the stomach. The part of the posterior gastric wall that is attached to the WOPN is opened and an open debridement can be performed via this access. An anastomosis between the WOPN and the posterior stomach can be performed using single stich sutures or a stapler device. The rationale for this procedure is a direct drainage of the necrosis cavity into the intestinum to avoid fistulation into the abdominal cavity or the peripancreatic tissue. Based on the experience of the present publications, the time point for this procedure should be chosen between 2 and 3 months after the onset of symptoms [21–23]. The reported morbidity rates vary from 0 to 30% and mortality rates from 0–7% in series including between 6 and 46 patients [22,24,25]. As all reported patients could be sufficiently treated with only one operative debridement, this procedure seems to be effective in suitable patients. But it has to be considered that only a distinct subgroup of all patients with necrotizing pancreatitis may qualify for transgastric debridement due to the localization and extent of necrosis. Furthermore, the fact that the operative intervention needs to be postponed for 2 or 3 months may be a limitation in cases where an earlier time point of necrosectomy must be chosen due to the clinical condition. Nevertheless, reports on larger patient cohorts are awaited to re-evaluate this promising surgical approach.

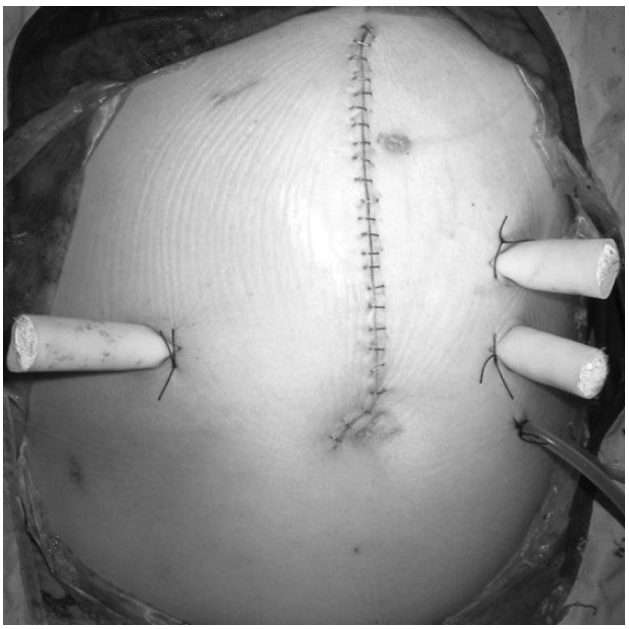

**Figure 32.3** Stuffed Penrose drains and closed suction drains are brought out through separate stab wounds and secured to the skin.

## Conclusion

Although minimally invasive approaches for necresectomy have become the primary standard of care in recent years, there is still an important role for open necrosectomy in severe necrotizing pancreatitis. The indication for open necrosectomy must be considered when minimally invasive approaches are not adequate or applicable to achieve a local focus control as well for complications including bleeding, bowel perforation, or intestinal fistulas. The standard techniques for open

**Table 32.3** Debridement and closed packing.

| Reference | Patients | Preoperative severity[a] | Deaths | Fistulas | Bleeding |
|---|---|---|---|---|---|
| Fernandez-del Castillo et al. [8] | 64 | 9 (0–23) APACHE II | 4 (6%) | 44 (68%) | 3 (5%) |
| Rodriguez et al. [20] | 167 | 9.5 (0–31) APACHE II | 19 (11.%) | 93 (56%) | 6 (4%) |
| Madenci et al. [21] | 68 | 10.9 (±0.8) APACHE II | 6 (8.8%) | 49 (74.2%) | 12 (17.7%) |
| Total | 299 | | 29 (10%) | 186 (62%) | 21 (7%) |

[a] Scores are presented as mean and standard deviation in parentheses.

necrosectomy include approaches with planned re-laparotomies (open packing, staged re-laparotomies) as well as those with a single surgical intervention (closed lavage, closed packing). In addition to these well-known techniques, transgastric debridement has been recently developed and may provide an additional possibility for a subset of patients who present with the prerequisites for this approach.

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# 33

# Endoscopic Treatment of Biliary Acute Pancreatitis

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## Pathogenesis of Acute Biliary Pancreatitis

Acute biliary pancreatitis (ABP) is caused by pancreatic duct obstruction mainly due to bile duct stones. Once a bile duct stone is impacted at the distal end of the bile duct or at the common channel, pancreatic duct outflow is obstructed directly or by the compression of the pancreatobiliary septum. Previous reports showed that bile duct stone impaction was found in 26–72% of patients who had ABP when surgery was performed soon after the attack [1]. Spontaneous passage of bile duct stones into the duodenum has been described in up to 50% of ABP cases [2,3]. Sphincter of Oddi spasm might be another cause of ABP. Therefore, the diagnosis of ABP is not always easy at the time of diagnosis of pancreatitis.

Biliary pancreatitis, as well as alcoholic pancreatitis, is a major etiology of acute pancreatitis. ABP accounts for 20–71.4% of cases of acute pancreatitis, but the rate varies depending on the country. Biliary pancreatitis is more common than alcoholic pancreatitis in Greece, Italy, the United Kingdom, Sweden, and the United States, whereas alcoholic pancreatitis is the most major cause in Hungary, France, Taiwan, Korea, and Japan [4–9].

## Diagnosis

In addition to the increased levels of serum pancreatic enzymes, such as amylase and lipase, increased levels of hepatobiliary enzymes and bilirubin suggest the possibility of ABP. In such cases, imaging tests are strongly recommended for diagnosis. Although transabdominal ultrasound is the most convenient imaging modality, the extrahepatic bile duct is often difficult to visualize clearly due to the retention of gastrointestinal gas, especially in patients with acute pancreatitis. Abdominal computed tomography (CT) is also relatively convenient and has high sensitivity in detecting calcified stones (Fig. 33.1), but its sensitivity to detect small stones without calcification is limited. Endoscopic retrograde cholangiopancreatography (ERCP) may be indicated in highly suspected cases such as those with bile duct dilation and/or cholangitis. Magnetic resonance imaging (MRI) or endoscopic ultrasonography (EUS) can be performed before ERCP because they are safer and more convenient. In addition, magnetic resonance cholangiopancreatography (MRCP) can provide an image similar to ERCP. It has high sensitivity and specificity in detecting common bile duct stones (more than 90%) [10], but its sensitivity decreases in cases with dilated bile duct and small stones [11]. EUS is recognized as the most reliable imaging modality in detecting bile duct stones [12], has fewer complications, and shows higher sensitivity in detecting small bile duct stones than ERCP [13].

## Indication of Endoscopic Treatment

Endoscopic treatments are indicated for patients in whom a bile duct stone was confirmed on imaging tests or highly suspected from clinical or laboratory findings. In addition, patients with persistent or repeated increasing levels of biliary and pancreatic enzymes are also indicated even if the presence of biliary stone was unclear. In such cases, a dysfunction in the sphincter of Oddi might be a cause of biliary pancreatitis.

The timing of endoscopic treatments is discussed later, but urgent ERCP should be considered when there is

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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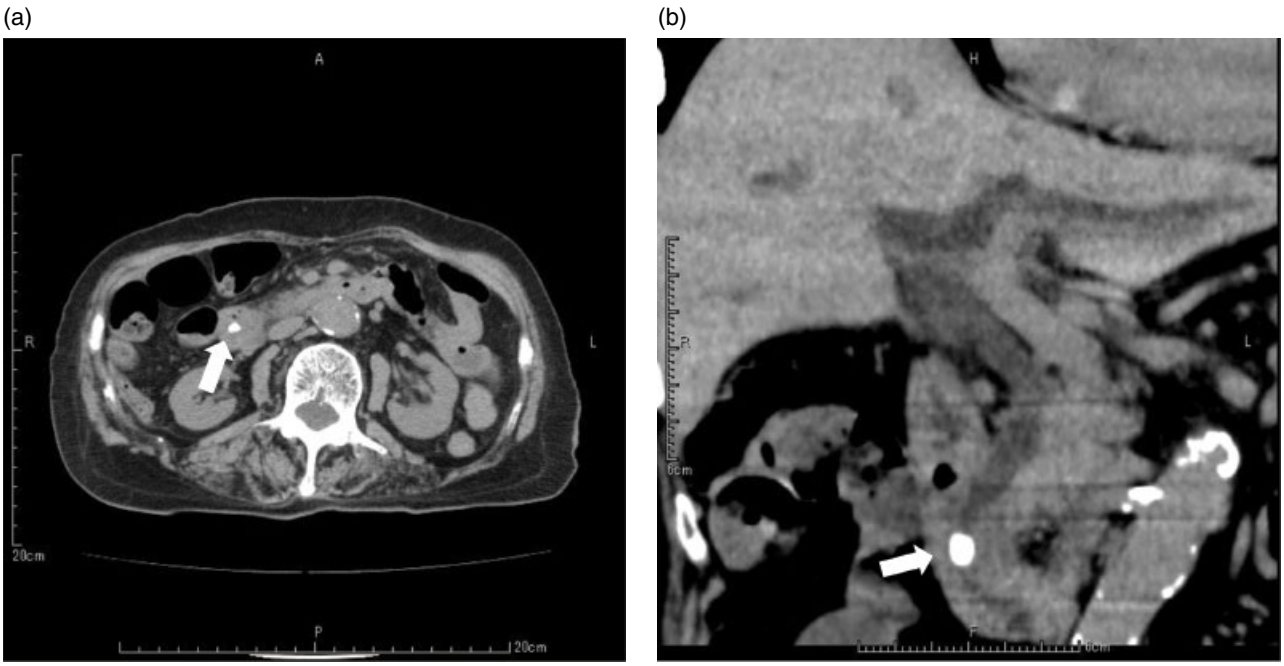


**Figure 33.1** Computed tomography image of an impacted stone at the duodenal papilla. White arrow indicates an impacted stone. Axial image (a) and multiplaner reconstruction image (b).

evidence of severe cholangitis and/or ongoing biliary obstruction. However, conservative treatments such as fasting, rehydration, and administration of antibiotics may be attempted first in patients with mild clinical symptoms and with mild abnormal laboratory data.

Several previous studies suggested that EUS is helpful in narrowing down subjects. They showed that a preceding EUS avoided unnecessary ERCP in 71.2–75.4% of patients without increasing the risk of adverse events [13–16].

## Techniques

The best way to treat biliary pancreatitis is the removal of the bile duct stone. Endoscopic sphincterotomy is generally performed for this. ERCP is initially attempted to confirm the stone in the bile duct, and endoscopic sphincterotomy is then performed using a sphincterotome if a stone is detected on cholangiogram. Subsequently, endoscopic stone extraction is performed using a retrieval basket or balloon. If the stone is impacted at the papilla, precut papillotomy using a needle knife would be preferred to conventional endoscopic sphincterotomy because cannulation into the bile duct is often difficult in such cases (Fig. 33.2).

Endoscopic sphincterotomy with subsequent stone extraction is currently a well-established technique with high success rate (approximately 90%) [17]. However, procedure-related adverse events, including pancreatitis, hemorrhage, perforation, and cholangitis, can occur in approximately 10% [18]. Aggravation of pancreatitis is a particularly big concern in patients with pancreatitis. Therefore, cannulation and contrast medium injection into the pancreatic duct should be avoided as much as possible; however, there is no evidence that accidental cannulation into the pancreatic duct harmfully affects the clinical course or outcome. Recently, the efficacy of pancreatic duct stenting was suggested in ABP following endoscopic sphincterotomy. In a nonrandomized study, complications were less frequent in the pancreatic duct stent group than in the control group without pancreatic duct stent (9.86% vs. 31.43%, $P < 0.002$) [19]. However, so far, there is no significant evidence to recommend pancreatic duct stenting after endoscopic treatment for ABP.

## Outcomes and Timing of Endoscopic Interventions

Endoscopic treatments for ABP were initially described in 1981 [20,21]. Since then, a number of prospective randomized controlled trials (RCTs) have compared early endoscopic treatments with conservative therapy for ABP. However, the role and timing of endoscopic intervention in ABP remain controversial. A number of clinical trials and meta-analyses have provided conflicting evidence.

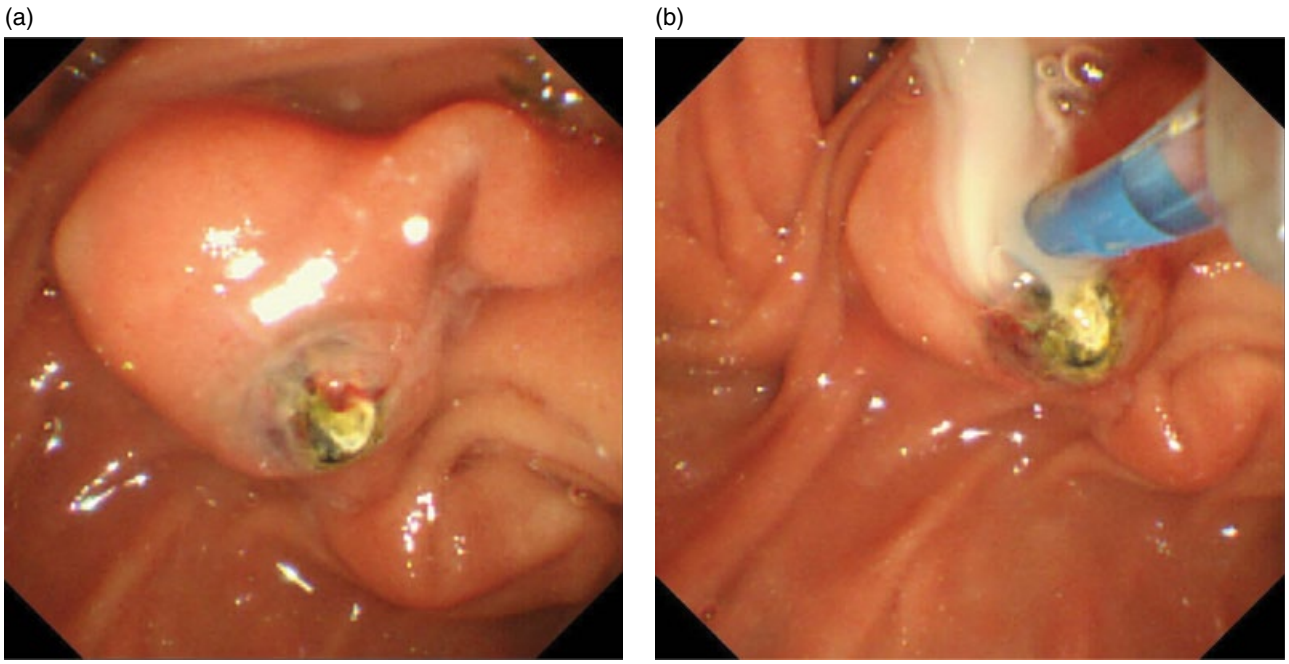


**Figure 33.2** Endoscopic view of an impacted stone at the duodenal papilla. A stone is impacting at the biliary orifice (a). Needle knife papillotomy is preferably performed in such a case. Whitish pus is discharged after cutting up the papilla from the orifice using a needle knife (b).

Two early RCTs showed lower complication rate, shorter hospital stay, and lower mortality rate in the urgent ERCP group than in the conservative group [22,23]. However, another RCT showed that the overall rate of complications was similar in the two groups, and patients in the early ERCP group had more severe complications [24]. The first meta-analysis published in 1999 showed high success rate of ERCP (92%) and concluded that early ERCP significantly reduced morbidity (25.0% vs. 38.2%, $P<0.001$) and mortality (5.2% vs. 9.1%, $P<0.05$) in ABP [25]. However, later studies suggested that early endoscopic intervention was beneficial in further limited patients.

Several studies concluded that urgent endoscopic intervention should be considered only in patients with severe biliary pancreatitis [26–28]. In a meta-analysis by Ayub et al. [27], early endoscopic intervention was associated with significant reduction in complications only in predicted severe biliary pancreatitis (odds ratio [OR] 0.27, 95% confidence interval [CI] 0.14 to 0.53), whereas reduction of mortality was not significant in both predicted mild and severe biliary pancreatitis. Later, a meta-analysis by Moretti et al. [28] also reported that a significant difference in the pooled rate for complications was found only in predicted severe pancreatitis (38.5%, 95% CI −53% to −23.9%, $P<0.0001$).

Meanwhile, several other studies suggested that the benefit of urgent endoscopic intervention was expected only in cases with cholangitis or cholestasis [29–34]. Petrov et al. [29] reviewed RCTs on early endoscopic intervention versus conservative management in patients with ABP without acute cholangitis. As a result, early endoscopic intervention in patients with predicted mild and predicted severe biliary pancreatitis did not lead to a significant reduction in the risk of overall complications and mortality. Later, van Santvoort et al. [35] conducted a prospective, observational multicenter study including patients with predicted severe ABP without cholangitis. They analyzed the outcomes in patients without and with cholestasis separately. As a result, endoscopic intervention was associated with fewer complications as compared with conservative treatment in patients with cholestasis (25% vs. 54%, $P=0.020$), whereas it was not associated with reduced complications (45% vs. 41%, $P=0.814$) in patients without cholestasis. A recent Cochrane review by Tse and Yuan [32] showed no evidence that early routine ERCP significantly affected mortality or local/systemic complications of pancreatitis, regardless of predicted severity. However, among trials that included patients with cholangitis, the early routine ERCP strategy significantly reduced mortality, local, and systemic complications. In addition, among trials that included patients with biliary obstruction, early routine ERCP strategy was associated with a significant reduction

in local and systemic complications. Finally, they concluded that early ERCP should be considered only in patients with coexisting cholangitis or biliary obstruction. From the latest systematic review [36] including 8 meta-analyses and 12 guidelines, there is consensus in guidelines and meta-analyses that early endoscopic intervention is indicated in ABP patients with coexisting cholangitis and/or persistent cholestasis. With the exception of the first meta-analysis [25], none of the included studies approved early ERCP in predicted mild ABP. Consensus is lacking on the role of routine early endoscopic intervention in patients with predicted severe ABP.

## Cholecystectomy After Endoscopic Treatment

Recurrence rates of ABP of up to 61% have been reported when definitive treatment was not provided [37,38]. Therefore, subsequent cholecystectomy after endoscopic treatment of bile duct stones has been recommended to prevent recurrent attacks of ABP [39,40], although 25–50% of patients do not undergo cholecystectomy for various reasons [41–43]. In cases of severe ABP, the current consensus is to postpone cholecystectomy until after resolution of local or systemic complications [38–40,44].

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# Strategies for the Treatment of Pancreatic Pseudocysts and Walled-Off Necrosis After Acute Pancreatitis: Interventional Endoscopic Approaches

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## Introduction

A series of trials following improvements in intensive care medicine and endoscopic techniques has led to a paradigm shift in the management of fluid collections developing after an attack of acute pancreatitis: if undertaken at all, interventions should be delayed as much as possible and the least-invasive methods should be considered first, before escalating treatment (step-up approach) [1–4]. Intervening a post-acute pancreatic fluid collection (PFC) endoscopically is considered safe once a well-defined wall has developed, roughly 4 weeks into the disease course [5]. Whether drainage of (infected) fluid collections is beneficial before a fibrous wall has formed is being investigated by a Dutch multicenter trial (POINTER). Post-acute pancreatic pseudocysts are considered a rare complication arising from a disruption of the main pancreatic duct or major duct branches without considerable necrosis and by definition contain only fluid rich in pancreatic enzymes. In contrast, collections with a fibrous wall originating from pancreatic and/or peripancreatic necrosis are called walled-off necrosis (WON), which will contain variable amounts of solid debris and may reach into areas distant from the gland [6].

## Indications for Endoscopic Treatment

In general, only collections that cause symptoms or are at a high risk for severe complications require intervention. Indications for endoscopic intervention are features of infection on imaging or a high suspicion for infection with persistent signs of sepsis that do not improve under adequate intravenous antibiotics. Less common indications are pain, persistent unwellness, jaundice caused by the collection compressing the bile duct, bleeding, disconnected duct syndrome, gastric outlet obstruction, or pancreatic fistulas.

## Endoscopic Drainage vs. Necrosectomy: Choosing the Right Patient

It is currently unclear which collections will improve with drainage alone, which ones need irrigation, and for which ones a patient should undergo advanced endoscopic necrosectomy, as reflected by discordant results of a recent international expert survey [5]. In many cases, patients will initially improve after a drainage procedure and optional nasocystic lavage with few plastic pigtail stents in place to ensure the patency of the tract. A systematic review and meta-analysis comparing 324 patients who underwent conservative management of infected pancreatic necrosis to 157 who underwent necrosectomy concluded that the conservative management was successful in 64% and that mortality was lower than in patients who underwent percutaneous treatment [7] although this result is fraught by significant selection bias. Multiple early case series which included pancreatic necrosis and pancreatic abscesses even reported full resolution of these collections without

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further necrosectomy in over 80% of cases [8–11]. Unfortunately a nonuniform nomenclature impairs the comparability of these observations. A Swedish trial comparing drainage of pseudocysts to pancreatic abscesses with variable amounts of debris showed that the rate of successful drainage was lower in abscesses (94% vs. 80%; $P = 0.04$) and the risk for complications five times higher ($P = 0.02$). Of note, all abscesses underwent necrosectomy and lavage later [12]. This suggests that in patients with a higher burden of necrotic material and/or infected collections a more invasive approach may be warranted. Transmural endoscopic necrosectomy has been shown to be a safe and efficient way to deal with necrotic collections accessible to endoscopy. It remains burdened, however, with serious complications even in the hands of experienced investigators [13–17]. In a retrospective comparison of conventional transmural drainage versus necrosectomy in patients with evidence of WON on contrast-enhanced computed tomography (CT), Gardner et al. showed superiority of direct necrosectomy in terms of treatment success, need for surgery or additional percutaneous drainage, and recurrence [18]. Another registry-based, matched cohort study comparing direct necrosectomy to initial percutaneous access as suggested by the original "step-up approach" in 12 patients showed favorable outcomes for the direct endoscopic approach [19]. Taken together, the current data suggest that mere endoscopic drainage is reasonable and often sufficient in defined collections with minimal amounts of solid material, whereas patients with WON and more extensive necrotic material will most likely profit from a more aggressive approach with sometimes repeated sessions of endoscopic removal of necrotic tissue [20]. In unstable patients who developed sepsis due to infected WON requiring ventilator support and vasopressors an initial endoscopic or even percutaneous drainage to achieve sepsis control and delayed more advanced endoscopic necrosectomy may be more appropriate. Endoscopic drainage is generally preferred over percutaneous drainage for infected fluid collections, not because it is more effective but because the latter very often leads to persistent fistulas [21]. If, however, drainage is required before a fibrous wall has formed (generally 4 weeks) percutaneous drainage is still a valid and frequently used alternative.

## Preventing Recurrence by Treating Disconnected Duct Syndrome

A disconnected pancreatic duct with pancreatic juice leaking into the connected PFC is a major complication of acute pancreatitis and a well-known risk factor for persistence or recurrence of PFC. This includes pseudocysts and WON, even after initially successful endoscopic treatment [22–24]. The integrity of the pancreatic duct should therefore be confirmed whenever pancreatic necrosis requiring an intervention is present and preferably by noninvasive methods such as magnetic resonance cholangiopancreatography (MRCP). Although found in up to 50% of patients with acute necrotizing pancreatitis, studies on the optimal management of PFC associated with disconnected pancreatic duct syndrome are scarce. A small randomized controlled trial ($n = 28$) recruiting patients with and without disconnected pancreatic duct showed a significant reduction of recurrence (0 vs. 5, $P = 0.013$) when stents were not removed [25]. The approach of long-term indwelling plastic stents has been adopted for the treatment of WON with disconnected pancreatic duct syndrome as reported in two retrospective series including 26 and 33 patients respectively, in which it appears to have led to a satisfactory outcome with regard to resolution of the collection [26,27]. Another approach involves stenting the pancreatic duct after transmural access and cavity stenting is established. This allows transpapillary drainage of both the content of the connected collection and, more importantly, pancreatic juice away from vital pancreatic tissue distal to the duct disruption [28]. ERCP should be performed with caution in these patients as it is associated with considerable rates of adverse events [29]. Recently a group from Mumbai, India described a promising strategy in 42 patients with symptomatic post-acute pancreatic pseudocysts. Three weeks after initially successful drainage using an expandable covered nitinol stent, the patients underwent MRCP. A pancreatic duct leak was detected in three patients and treated successfully by stenting the pancreatic duct with consecutive retrieval of the transmural stent [30]. Although only preliminary, these data suggests that a consecutively deferred combination of transmural and transpapillary stenting could be an alternative to long-term transmural stents.

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# Strategies for the Treatment of Pancreatic Pseudocysts and Walled-Off Necrosis After Acute Pancreatitis: Surgical Treatment

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## Introduction

The strategy for surgical intervention in patients with pancreatic pseudocysts (PPC) and walled-off necrosis (WON) has dramatically changed in recent decades and the optimal approach is still controversial. In the early 1980s, open drainage and closed lavage were the most common surgical procedures performed for "pancreatic abscess." A more aggressive approach resulting in earlier surgical intervention, with more extensive drainage and debridement of associated necrotic tissue has been recommended [1]. However, early intervention including open necrosectomy is associated with poor outcomes and the latest guidelines suggest that surgical intervention should be delayed as long as possible, until at least 4 weeks after the onset of the illness [2,3].

Peripancreatic fluid collections are frequently seen in the management of patients with acute pancreatitis. Acute pancreatitis is divided into interstitial edematous pancreatitis and necrotizing pancreatitis [4]. In interstitial edematous pancreatitis, fluid collections are usually resorbed spontaneously and clinical symptoms are improved after a week. However, remnant localized fluid collections sometimes require intervention in patients with necrotizing pancreatitis. The terminology for these remnant localized fluid collections was completely changed in 2012 by the revised Atlanta classification [4]. This chapter will focus on surgical strategies for the treatment of patients with PPC and WON after episodes of acute pancreatitis.

## Definition of Pancreatic Pseudocyst and Walled-Off Necrosis

In the Atlanta classification, advocated at the International Symposium on Acute Pancreatitis in Atlanta in 1992, acute fluid collections and pancreatic necrosis/infected necrosis were defined as local complications in the early stage of acute pancreatitis [5]. In addition, PPC and pancreatic abscess are also defined as local complications in the late stage. The term "pancreatic pseudocyst" had been used to describe a wide spectrum of fluid collections derived from necrotizing pancreatitis, interstitial edematous pancreatitis, and acute exacerbations of chronic pancreatitis. Capsulized liquefied necrotic pancreatic and/or peripancreatic tissue after necrotizing pancreatitis should be considered different from a capsulized collection of pure pancreatic exocrine secretions. If the same treatment had been performed, the outcome would be different [6,7]. In fact, pancreatic abscess was seldom encountered in either Western countries or East Asia. Based on this background, the concept of "walled-off pancreatic necrosis" was proposed for an encapsulated fluid collection derived from necrotic pancreatic and/or peripancreatic tissue in patients with necrotizing pancreatitis [8]. The term was changed to "walled-off necrosis (WON)" and the concept of this condition was then established by the revised Atlanta classification in 2012 [4] (Fig. 35.1). WON is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall and usually occurs more than 4 weeks after the onset of necrotizing pancreatitis [4].

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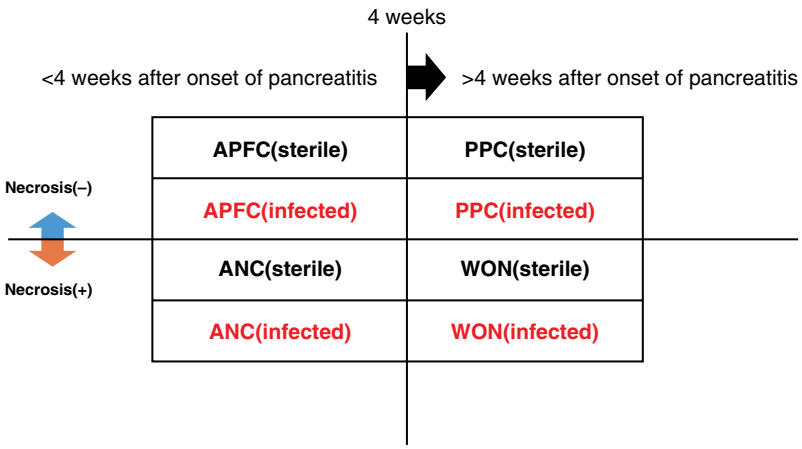


**Figure 35.1** Eight categories of local complications of acute pancreatitis defined by the revised Atlanta classification of 2012. APFC, acute peripancreatic fluid collection; ANC, acute necrotic collection; PPC, pancreatic pseudocyst; WON, walled-off necrosis.

A fluid collection originating from necrosis less than 4 weeks after the onset of necrotizing pancreatitis is referred to as an acute necrotic collection (ANC). The concept of a PPC was proposed to be limited to an encapsulated collection of fluid with a well-defined inflammatory wall, usually outside the pancreas, with minimal or no necrosis that occurs more than 4 weeks after the onset of interstitial edematous pancreatitis [4,9]. As the concept of PPC changed and the new concept of WON was developed in 2012, care must be taken to avoid confusion regarding the terms PPC and WON, especially when reviewing clinical studies reported before 2012.

The International Association of Pancreatology and the American Pancreatic Association (IAP/APA) guidelines were revised according to the revised Atlanta classification of 2012, and the IAP/APA evidence-based guidelines for the management of acute pancreatitis were published in 2013 [2]. At the same time, Japanese guidelines for the management of acute pancreatitis were revised and the fourth edition was published in 2015 [3]. The diagnosis and treatment of acute pancreatitis should be based on these guidelines.

## Indications for Surgical Intervention

Previously, surgical intervention with drainage and necrosectomy was the gold standard for treatment of the infectious complications of acute pancreatitis. In the early 2000s, minimally invasive interventions were developed and have been replacing highly invasive surgical procedures such as open drainage. Minimally invasive interventions include procedures such as endoscopic and laparoscopic drainage and necrosectomy. Both the IAP/APA guideline 2013 and the Japanese guideline 2015 recommend that interventions should be performed in patients with infections or other persistent symptoms, such as ongoing gastric outlet, intestinal, or biliary obstruction, pain, or complications due to a mass effect secondary to WON or PPC. Most patients with infected localized fluid collections that cannot be managed by the administration of wide-spectrum antibiotics will require some therapeutic intervention.

The terminology for drainage and necrosectomy should be appropriately used. Drainage is a procedure to drain fluid by percutaneous, transgastric, enteral, or transpapillary routes, or by open surgery. Necrosectomy is a procedure to remove necrotic tissue aggressively, using percutaneous, transgastric, or enteral approaches, or by open surgery. Confusion regarding the terminology for drainage and necrosectomy procedures must be considered when evaluating clinical studies reported before 2012.

## Timing of Interventions and Optimal Interventional Strategy for Walled-Off Necrosis

In the past, outcomes following early invasive surgical interventions were very poor [10–12]. In a prospective study of 629 patients, late intervention significantly decreased mortality and morbidity [13]. Both the IAP/APA guideline 2013 and the Japanese guideline 2015 refute the beneficial therapeutic effect of early intervention, and recommend that intervention should be delayed as much as possible, until at least 4 weeks after the onset of pancreatitis [2,3]. Interventions should be performed when fluid collections are encapsulated and the capsule wall is thickened.

The optimal interventional strategy is still controversial. Open surgery was the only choice for intervention before 2000. Minimally invasive interventions, including endoscopic drainage and necrosectomy, and laparoscopic necrosectomy, were introduced in the late 1990s and early 2000s. Though the use of these novel interventions has been increasing, they require advanced technical skills and should be done only in high-volume

centers. Some centers reported good results, although there is a large variance in the expertise in performing these novel interventions among centers. Further assessment is necessary for these interventions to become standard approaches.

The Dutch Pancreatitis Study Group proposed a step-up approach for the treatment of patients with suspected or confirmed infected necrotizing pancreatitis [14]. The step-up approach is composed of two parts, including initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage followed by endoscopic or surgical necrosectomy. Percutaneous catheter drainage alone is reported to reduce the necessity for necrosectomy in 23–50% of patients with infected necrotizing pancreatitis [2,14–19]. Additionally, the step-up approach is reported to decrease major short-term and long-term complications and reduce overall costs compared to conventional surgical necrosectomy [14]. At present, the step-up approach is thought to be the most effective approach and both the IAP/APA guideline 2013 and the Japanese guideline 2015 clearly recommend it as the optimal interventional strategy [2,3]. The IAP/APA guideline 2013 also states that no subgroup of patients requiring a different strategy can be defined, and the optimal method of necrosectomy (i.e., surgical or endoscopic necrosectomy) is unclear if catheter drainage fails [2].

Catheter drainage is always the first step for intervention in patients with local infectious complications of necrotizing pancreatitis. Less-invasive procedures, such as percutaneous drainage by ultrasonography or computed tomography, and endoscopic transluminal drainage are the primary recommendations [13–16] (Fig. 35.2).

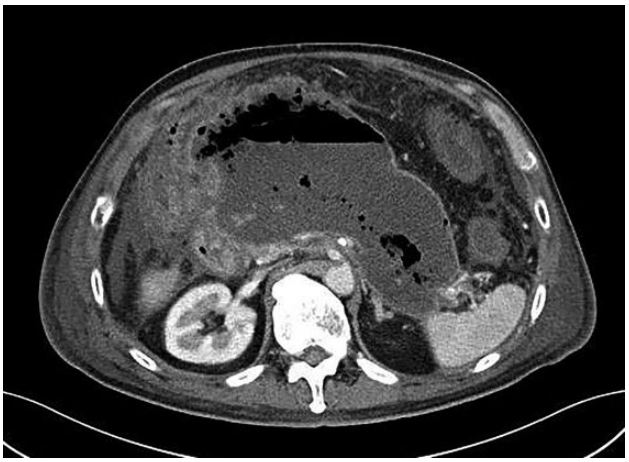

**Figure 35.2** Computed tomography scan findings of infected walled-off necrosis on the 170th day after the onset of necrotizing pancreatitis. Air bubbles were observed in the area of walled-off necrosis located in the lesser omentum, which strongly suggests the presence of infection.

Surgical drainage with a small incision is indicated in patients for whom percutaneous or endoscopic approaches are contraindicated or fail. Multiloculated cysts, multiple cysts, presence of significant necrotic debris, cysts in the pancreatic tail, and uncontrolled hemorrhage are also indications for surgical drainage. If catheter drainage fails to control infection, minimally invasive or open surgery or endoscopic transluminal necrosectomy are the next steps.

Laparoscopic and video-assisted retroperitoneal debridement (VARD) have become new choices for a second step intervention [14]. The results from 13 recent series of percutaneous drainage for necrotizing pancreatitis indicate a 26.4% conversion rate from percutaneous drainage to surgical drainage, with a 15.2% mortality rate [14,20–31]. The results from 17 recent series of surgical necrosectomy indicate the need for additional necrosectomy in 16.5%, additional drainage in 13.8%, and an overall 25.8% mortality rate [32–48]. However, the step-up approach has better outcomes. The results from nine recent series report a 17.4% conversion rate to the surgical approach with a 14.9% mortality rate [14,33,49–54]. Bleeding, pancreatic fistula, and gastrointestinal fistula are frequent complications of these interventions.

## Surgical Intervention for PPC

Since acute exacerbations of chronic pancreatitis are a leading cause of PPC, the strategy for the treatment of PPC should be different from that used for WON. Most small PPC spontaneously regress without specific interventions. Evidence of infection or persistent symptoms are a common indication for intervention in patients with PPC (Fig. 35.3). External or internal drainage is the first

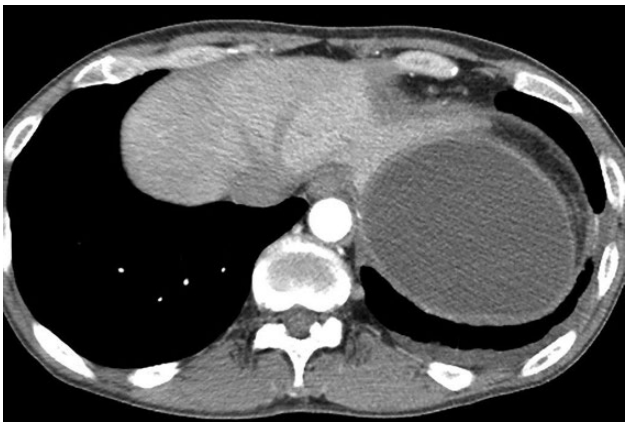

**Figure 35.3** Computed tomography scan findings of a pancreatic pseudocyst. The pancreatic pseudocyst resulted from an acute exacerbation of chronic pancreatitis, and is located in the left subphrenic space.

choice for infected PPC, and other novel interventions have been developed and evaluated clinically. Open cyst-enterostomy (i.e., cyst-gastrostomy or cyst-jejunostomy) is often used with a reported 25.4% morbidity and 0.2% mortality in five recent retrospective series [55–59]. Laparoscopic cyst-enterostomy, a minimally invasive approach, is becoming more common and performed by various methods, including a Roux-en-Y anastomosis and intragastric procedures [60–65]. The laparoscopic procedure has good outcomes, with 9.5% morbidity, 3.6% PPC recurrence, and 0% mortality in seven recent series [60–66]. Percutaneous cyst-gastrostomy, draining the PPC via both percutaneous and transgastric routes with a gastroscopic procedure, is feasible with 11.3% morbidity and 9.4% requiring an additional surgical cyst-gastrostomy [14,67–69]. Bleeding, abdominal abscess including cyst infection, pancreatic fistulas, and surgical site infections are common complications of surgical procedures for PPC [55–66]. Pancreatectomy, distal pancreatectomy, pancreaticoduodenectomy, or duodenum-preserving pancreas head resection are indicated in some patients with a PPC and persistent chronic pain [59].

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# 36

# Management of Fluid Collection in Acute Pancreatitis

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## Introduction

Acute pancreatitis is the most common cause for hospitalization in gastroenterology and has an incidence of 13–45/100 000 with regional variations [1]. Alcohol and gallstones are the main risk factors (30–50%) with alcohol as an etiology being more common in men [2,3].

Considering the variety of different courses of pancreatitis, ranging from mild abdominal pain to death, it is important to predict the likely severity of the disease early in the clinical course.

The current definition of acute pancreatitis, the grades of severity (mild, moderately severe, and severe) [4], and the detailed description of the systemic and local complications based on the revised Atlanta classification from 2013 [5] are discussed in Chapter 20.

## Definitions

The way acute fluid collections are classified depends on the timeframe of their development as well as some morphological imaging features. The acute peripancreatic fluid collection (APFC) is a typical complication of the interstitial and edematous subtype and often develops during the first 7 days of pancreatitis. It has no wall and a homogenous internal structure. The spread of an APFC is orientated along the fascial anatomy. Occasionally, APFC are found in multiple locations and they tend to regress spontaneously. If an APFC persists for longer than 4 weeks there is a high probability that a pseudocyst will develop.

A pseudocyst is defined as a fluid-filled space, similar to a real cyst, with a fibrotic wall. In contrast to real cysts, pseudocysts have no internal epithelial cell lining. Pseudocysts are considered complications of chronic pancreatitis and occasionally of acute pancreatitis. Following the latter they evolve from APFC usually later than 4 weeks after the onset of symptoms. The treatment strategies of pancreatic pseudocysts are described in Chapter 34.

Regions of nonvital tissue damaged by extravasated pancreatic juice or immune cells are defined as necrosis. It represents a form of tissue injury resulting in premature nonapoptotic cell death. The morphological characteristics of necrosis caused by acute pancreatitis are highly variable. The necrotic tissue may appear as solid in a fluid structure on imaging, although the sensitivity for detecting the solid component varies greatly between computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS).

An acute necrotic collection (ANC) arises within the first 4 weeks of the disease in the pancreatic parenchyma as well as the extrapancreatic tissue. It contains varying amounts of fluid or solid material. The solid parts are the crucial feature to distinguish an ANC from an APFC or a pseudocyst.

If a necrotic area is enclosed by a radiologically distinguishable capsule it is called walled-off necrosis (WON). The difference between WON and a pseudocyst is the presence of variable amounts of solid content in the cystic cavity. Usually it arises from an ANC later than 4 weeks from the onset of pancreatitis.

An originally sterile necrosis can maintain its status or become infected over the course of the disease. The diagnosis of infected necrosis is based on the patient's clinical presentation and the presence of gas in the necrotic cavity on radiological imaging. It is of note that an asymptomatic fistula from the necrotic cavern to the gastrointestinal tract also leads to the presence of gas within the necrosis but can be without any signs of infection. Fine-needle aspiration followed by microbiological

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analysis of the content can confirm the presence of infected necrosis but is not needed in most cases and has a high false negative rate. Moreover, microorganisms isolated from the blood of patients with the clinical presentation of an infection or signs of an infected necrosis on imaging are of greater relevance for choosing appropriate antibiosis than those isolated from cultured content of the necrotic cavity. Other than the extent, there are currently no features by which to predict whether necrosis will persist or regress over weeks and months.

## Imaging of Acute Fluid Collections

### Transabdominal Ultrasound

Transabdominal ultrasound is an inexpensive, immediately available technique to allow a first imaging impression of a patient with an acute abdomen. The imaging of the pancreatic gland is often impaired by abdominal pain and an atonic gut. Edematous pancreas is characterized by an inhomogeneous, hypoechoic structure with poorly defined boundaries [6]. The pancreatic main duct is often not visualized inside the edema. Necrotic and hemorrhagic tissue appears more hypoechoic than the inflamed parenchyma. The echo contrast gain or use of ultrasound contrast agent permits a somewhat better distinction between vital or nonperfused tissue. For the detection of small amounts of free fluids in the abdominal or pleural cavity ultrasound remains the undisputed gold standard. The presence of ascites or the mostly left-sided pleural effusions are predictors for a more severe course of acute pancreatitis. Another domain of sonography is the fast and reliable imaging of the gallbladder and, if present, gallstones, which can confirm or rule out a biliary pathogenesis.

### Computed Tomography, Endoscopic Ultrasound, and Magnetic Resonance Imaging

Contrast-enhanced CT scan is the fastest and most accurate method for the differential diagnosis of an acute abdomen. At hospital admission CT scan is not recommended for patients with clinical confirmed acute pancreatitis unless other differential diagnosis cannot be ruled out. Imaging via CT should not be performed to assess the severity of pancreatitis on admission [7], because the extent of necrosis can still evolve until up to 72 hours after the disease onset. Therefore, a CT scan should be delayed, if required at all, for 4 days after symptom onset [8].

Contrast-enhanced CT can confirm the size, shape, and volume of fluid collections or necrosis and is a valuable tool to identify extrapancreatic complications including hemorrhage or pseudoaneurisms.

Two alternative methods are EUS and MRI. Despite having cost and procedural disadvantages, both methods are more sensitive in detecting solid content within a fluid collection and thus in distinguishing between plain fluid collections and pseudocysts on the one hand and areas of necrosis and WON on the other. For more details Chapters 25 and 34 are recommended.

## Conservative Treatment of Pancreatitis and Pancreatic Fluid Collections

### Basic Support

All patients with acute pancreatitis should be monitored regularly within the first 48 hours after admission [4]. Important parameters include:

- heart frequency, 3 (or 6)-lead ECG, blood pressure, oxygenation (to detect circulatory respiratory failure and shock);
- blood gas analysis (in case of oxygenation <90%) (to detect respiratory failure);
- hourly urinary excretion measurements for the management of fluid resuscitation (for fluid management and to detect renal failure);
- abdominal pressure measurement via bladder pressure measurement (to detect compartment syndrome);
- blood electrolytes;
- blood glucose levels (to detect endocrine failure).

### Fluid and Electrolyte Management

Due to retroperitoneal edema and increased vessel permeability a massive fluid shift is typical for acute pancreatitis leading to APFC. Fluid resuscitation is currently the most important intervention for reducing patient mortality. Mortality can increase to 61% if less than 3.5 L of fluid are transfused in the first day [9,10]. An increase of blood urea nitrogen (BUN) of 5 mg/dL within 48 hours is a sign of prerenal kidney failure and increases mortality by a factor of 2.2 [11]. The recommended amount of fluid is 5–10 mL/kg bodyweight/h. Greater therapeutic fluid volumes lead to a mortality increase partially due to abdominal compartment syndrome (intra-abdominal pressure >20 mmHg), sepsis, or a prolonged stay in the intensive care unit (ICU) [12]. The monitoring of fluid resuscitation should use either invasive thermodilution techniques or, if unavailable, the following parameters:

- heart frequency <120 bpm;
- mean arterial pressure between 65 and 85 mmHg;

- urinary excretion >0.5–1 mL/kg per hour;
- hematocrit between 35 and 45%.

Another important point is the composition of administered fluid. Crystalline solutions are superior to colloids. Colloidal infusions are suspected of being associated with a higher incidence of renal insufficiency and should be avoided. The advantage of Ringer's solution is its similar composition to blood as well as the nonimpairment of electroneutrality by compensating the anion gap with lactate or acetate [13]. Moreover, the incidence of systemic inflammatory response syndrome (SIRS) is reduced within the first 24 hours if Ringer's solution is used rather than saline [4]. Ringer's solution is inappropriate for patients with hypercalcemia.

## Nutrition

Complete fasting has no positive influence on the outcome and course of pancreatitis [4]. In fact, fasting leads to atrophy of gut villi resulting in a more rapid translocation of intraluminal bacteria, facilitating the infection of necrotic areas. Starting enteral nutrition early is recommended [14]. If enteral nutrition is not advised because of paralytic ileus, parenteral nutrition is required until enteral nutrition can be administered [15]. If the patients are not able to take oral food, feeding by tube is the most effective method. Nasogastric and nasojejunal tubes have been shown to be equally effective and safe, although nasojejunal feeding tubes tend to dislocate more often. The best and most natural form of nutrition remains eating by mouth. Once patients are pain-free (with pain medication if required) and can tolerate food they should take oral food. If not, enteral nutrition is less expensive and more physiologic than parenteral nutrition. Starting enteral nutrition immediately after admission was not found to lead to better outcomes than withholding food for 72 hours [16]. The current approach to nutrition has become much more pragmatic than in the past when all patients were put on nil-by-mouth for long periods.

## Antibiotics

Prophylactic application of antibiotics is not necessary for patients with acute pancreatitis, regardless of its predicted severity, and could contribute to the rise of multiresistant bacteria. Neither the mortality nor the rate of infected necrosis is positively influenced by prophylactic antibiotics [17]. If, on the other hand, infected necrosis is suspected, antibiotic therapy must be initialized immediately. Antibiotics with appropriate pancreatic tissue levels are carbapenems, gyrase inhibitors, or metronidazole. If the response to the administered antibiotics is insufficient, fine-needle aspiration followed by microbiological testing allows switching to antibiotics based on resistograms. In patients with sepsis other infectious foci must be considered, such as peritonitis, cholangitis, or pneumonia. In general, microbes sampled from blood cultures of pancreatitis are often more informative than those from necrotic fluid collection because of the high rate of false negatives among the latter.

## Management of Edematous Fluid Collections

An APFC tends to regress spontaneously. If it persists longer than 4 weeks under conservative treatment it may develop into a pseudocyst or WON (see Chapter 34). Simple intra- or extrapancreatic fluid collections, the focus of this chapter, generally do not require interventional treatment unless they give rise to compartment syndrome as characterized by fluid overload and elevated urinary bladder pressure. An abdominal compartment syndrome is defined as an increased abdominal pressure (>20 mmHg) for longer than 12 hours and simultaneous organ failure.

## Minimally Invasive Treatment of Acute Fluid Collections in Acute Pancreatitis

When conservative management is unsuccessful, minimally invasive treatment is recommended. The following sections give an overview about the different modalities.

### Imaging-Guided Percutaneous Drainage

This is a technically easy and well-established method to treat pseudocysts or fluid collections. Ultrasound, CT, or MRI can be used for imaging. Although single-step needle aspiration is associated with a high relapse rate, continuous catheter-drainage systems are recommended based on their high success rate (70–100%) and a low recurrence rate [18,19]. The risk of fistula formation must be considered.

### Endoscopic Drainage

This method provides a minimal invasive access for draining a pseudocyst. Transpapillary and transmural approaches from the stomach or duodenum are available. The aim is to create an artificial connection between the cyst cavity and the gastrointestinal tract. For pseudocysts communicating with the pancreatic main or branch duct transpapillary techniques are preferable [20]. Transpapillary drainage has a success rate of 85% and a low morbidity of 6% in some studies. The authors' personal experience is much less optimistic. Endoscopic transmural drainage is recommended

for cysts that do not communicate with the pancreatic ductal system. Based on a better visualization of vessels, EUS-guided drainage is associated with a lower complication rate than the endoscopic technique without EUS visualization [21–23] and the latter should be abandoned.

For the treatment of pseudocysts with a location distant to gastric lumen and with a thick fibrotic capsule a laparoscopic approach should be favored. In Chapter 34 the strategies for surgical and endoscopic interventions for pancreatic pseudocysts, infected necrosis, and WON are outlined and discussed in detail.

## Conclusion

Fluid collections that arise in the context of acute pancreatitis generally regress under conservative treatment and do not require interventional treatment in most cases. They may require endoscopic or surgical treatment when they fulfil the morphological criteria of infected (walled-off) necrosis, when they represent complication-causing or complication-prone pseudocysts, or when they precipitate abdominal compartment syndrome. How early in the course of the disease a drainage procedure may be beneficial is currently being investigated in the multicenter POINTER trial.

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# 37

# Management of Pancreatic Fistula in Acute Pancreatitis

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## Introduction

A pancreatic fistula is defined as a leakage of pancreatic juice as a result of disruption of pancreatic ducts or parenchyma. During severe acute necrotizing pancreatitis, local complications—besides the systemic inflammatory response syndrome (SIRS) or sepsis-associated consequences—play a major role in the management of patients. Local complications include infected necrosis and pancreatic abscesses which cause destruction of the pancreatic parenchyma and eventually small or larger ducts leading to a leakage of pancreatic enzyme-rich fluid. This can either lead to the formation of pseudocysts or, in the case of erosion of surrounding structures, to fistulas. In most cases, parenchyma or duct leakages are self-limiting and can be covered by the surrounding organs, reabsorbed by the serosa, or encapsulated by a fibrous pseudowall followed by pseudocyst formation [1,2].

In the case of acute fistula-associated complications, including erosional bleeding or bowel perforation, immediate intervention and surgical treatment are required, which includes angiographic bleeding localization and management (i.e., stent placement in the eroded vessel) as well as emergency surgery [3]. However, if the pancreatic fistula does not cause acute complications, a continous leakage may occur and require therapy which needs to be adapted to the site and clinical symptomatology of the fistula. In this context, internal fistulas to the gastrointestinal tract, bronchi, pleural, mediastinal space, pericardium, and other organs [4,5] have to be differentiated from external—cutaneous—fistulas [6,7]. As internal fistulas are often clinically asymptomatic, they are more difficult to diagnose and may not immediately be detected [6]. In contrast, external fistulas are observed more often and can be easily diagnosed by analyzing the pancreatic enzyme content of the respective fluid [6,7].

## Pathogenesis and Classification

### Pathogenesis

The pathogenesis of pancreatic fistulas is multifactorial and seems to differ according to the site of origin of the fistula and the time at which the fistula occurs. On the basis of the necrotizing process in the pancreas, the peripancreatic fat and soft tissue, and the retroperitoneal space during severe acute pancreatitis, a widespread induction of autodigestion with a complex interaction between liberated pancreatic exocrine enzymes and local and systemic inflammatory mediators occurs [8]. Pancreatic parenchyma necrosis is understood to be a consequence of oxidative stress and potential calcium overload, leading to a combination of necrosis, apoptosis, pyroptosis, and autophagy, in which damage-associated molecular pattern molecules (DAMP) play a central role [9]. In addition, microcirculatory perfusion failure due to local thrombotic and inflammatory alterations of the microvascular architecture contributes to necrosis formation. Following parenchyma necrosis, proteases and the entire spectrum of all other activated pancreatic enzymes are released into the retroperitoneum and an autodigestive process is initiated. Local leukocyte recruitment and further activation of the inflammatory cascade helps to extend the necrotizing process throughout the peripancreatic region and the retroperitoneum, toward the mesocolon, small bowel mesentery, and paracolic retroperitonal gutters. The autodigestive process may extend to the skin, bowel, or any other organ to form fistulas.

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In addition, the development of colonic fistulas during acute pancreatitis may also be a consequence of colonic wall necrosis secondary to mesenteric thrombosis, which is quite frequently observed in the transverse mesocolon because of its close proximity to the pancreas. All ischemic complications can furthermore be a consequence of systemic hemodynamic instability due to a septic shock during the systemic inflammatory response in severe acute pancreatitis.

Besides spontaneous fistula formation, endoscopic, interventional, or surgical therapeutic measures play an important role in fistula formation. Intraoperative manipulation during exploration of the abdomen or during necrosectomy in particular may lead to unintended injury by surgeons. Consequently, open surgery in acute pancreatitis is no longer regarded as a standard but should be evaluated critically and reserved for patients in whom other treatment options have failed [10].

The incidence of fistula formation and other local postoperative injuries after necrosectomy differs significantly depending on the operative techniques used [3]. Four principal methods have been established, namely necrosectomy combined with open packing [11], planned staged relaparotomies with repeated lavage [12], closed continuous lavage of the lesser sac and retroperitoneum [13,14], and closed packing [15]. In the hands of experienced surgeons, mortality rates below 15% have been described for all four techniques [11,16–18]. To achieve sufficient debridement, blunt necrosectomy is performed in a more or less identical fashion in all approaches, but management after the initial necrosectomy differs significantly [12–21]. The first two methods—open packing [11,16,17] and planned staged relaparotomies [12,19]—require several relaparotomies before final closure of the abdomen. Since there is a positive correlation between repeated surgical interventions and morbidity, including gastrointestinal fistula, stomach outlet stenosis, incisional hernia, and local bleeding, these two procedures should only be considered when very early debridement is indicated and a single operation does not seem to sufficiently guarantee further postoperative exit of remaining debris and infected fluid.

The other two techniques—necrosectomy and subsequent closed continuous lavage of the lesser sac [20,21] and closed packing [15]—imply a postoperative method to continuously remove residual pancreatic necrosis. Consequently, relaparotomies are usually not necessary. The most commonly adopted approach is that of closed lavage, first described by Beger in 1982 [14]. This leads to a reduction of postoperative morbidity, especially pancreatic and gastrointestinal fistulas as well as hemorrhage and incisional hernias. The results of the latter two surgical strategies with regard to morbidity, relaparotomies, and mortality are comparable and thus dependent on the preference of the surgeon.

## Classification

In contrast to postoperative pancreatic fistulas, which are the most common major complications after pancreatic resections and have been classified (postoperative day 3 with an amylase level greater than three times the upper limit of the normal serum value) and graded (severity grade B–C) by the International Study Group of Pancreatic Fistula (ISGPS) in 2016, there is no comparable grading system for fistulas in acute pancreatitis [22]. Pancreatitis-associated fistulas can be basically divided into internal and external fistulas. If their orifice is located intracorporally—regardless of the organ or structure affected—they are classified as internal fistulas; if there is a connection to the skin, the fistula is defined as external. In addition, low- or high-flow fistulas are differentiated, but this is only applicable for external fistulas. A daily output cut-off of 200 mL/day discrimiates low- from high-flow fistulas [23].

Further characterization of fistulas includes description as simple (straight channel from the pancreas toward the skin or another organ) or complex (multiple channels and tracts to different organs or structures). Moreover, the fluid can be characterized as clear pure pancreatic juice (due to external drainage of a pseudocyst communicating with the pancreatic duct) or mixed (consisting of pancreatic juice in combination with gastrointestinal secretions or bile). In the latter case, the pancreatic juice might be activated by enterokinase, leading to proteolytic effects of the fluid and a more severe injury. The amount and duration of the drainage are closely related to the size of the involved duct (main duct or branches of first, second, or third order), localization of duct rupture (head, body, or tail of the pancreas), and functionality of the sphincter of Oddi. In the acute phase of the disease, edema or spasm of the sphincter of the papilla may impair outflow, leading to increased pressure within the ductal system and subsequent rupture of the duct or maintenance of the outlet via the fistula. Once outflow via the papilla is restored, secondary to resolution of either the edema or spasm, spontaneous healing of the fistula can be observed in most cases. This is also consistent with the observation that spontaneous healing is less frequent in chronic pancreatitis, since both fibrosis and calcification as the cause of outflow reduction in chronic pancreatitis do not resolve. Main pancreatic duct disruption with leakage of pancreatic juice is a complication resulting from necrotizing pancreatitis with or without surgical intervention. If the main pancreatic duct shows a complete

loss of continuity a disconnected pancreatic duct syndrome (DPDS) occurs, which is either characterized by a high-volume fistula or development of a pseudocyst, which may become evident even months after the initial episode of pancreatitis [24].

## Diagnosis

### External Fistulas

The vast majority of external fistulas form along the tract of interventional or surgical drainages that are inserted to treat pancreatic abscesses, pseudocysts, and infected necrosis. They can easily be recognized by their typical secretions, with a large amount of amylase and lipase. As mentioned above, in terms of pancreatitis-associated fistula, there is no clearly defined cut-off for the increase in amylase, amount of fluid, or duration of secretion. To differentiate between simple and complex fistulas, radiological imaging should be performed. Conventional fistulography, computed tomography (CT), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP) can be used for this purpose [25–27]. Comparing these methods, CT scan is the gold standard in the diagnosis of acute pancreatitis and may also show the extent of necrosis as well as any complications including pancreatic abscesses, pseudocysts, and infected necrosis, but has a lower accuracy in fistula detection than MRI/MRCP imaging [28]. Conventional fistulography is useful to determine additional connection of an external fistula to other organs (i.e., colon) and ERCP has additional therapeutic value in that a stent is placed to bridge the leak site, which may contribute to the definitive resolution of partial pancreatic duct disruption [24,29].

### Internal Fistulas

The presence of fluid within in the peritoneal cavity is a common event in severe pancreatitis and can be caused by either inflammatory exudation alone or by additional leakage of pancreatic ducts. Internal pancreatic fistulas, which are mostly clinically asymptomatic, are often difficult to recognize and diagnose, especially as peripancreatic fluid in severe acute pancreatitis may contain high enzyme levels even if no clinically relevant fistula is present. In the case of persistent pancreatic ascites and/or a pleural effusions, an internal fistula should be considered; in rare cases acute mediastinitis arising from pancreato-mediastinal fistula can also be observed [30]. Apart from this rather rare complication, unrecognized internal fistulas can lead to other life-threatening medical conditions in terms of erosional bleeding or abdominal sepsis on the basis of bowel erosion. Therefore, suspicion of an internal fistula should be raised if abdominal fluid collections are associated with sepsis or bleeding [31].

If an internal fistula is suspected, further work-up needs to be done quickly, including ultrasonography and CT scan with the option for an interventional drain placement. Drained pleural or ascitic fluid shows highly elevated amylase and lipase levels and contrast vizualization after drain placement may confirm the suspected fistula [32,33]. Additional modalities suitable for visualizing the complete extent of the defect include oral contrast radiography for fistulas involving the upper gastrointestinal tract, and MRCP or ERCP for those involving the bile duct [34] (Figs 37.1 and 37.2).

## Management of External Fistulas

The management of pancreatic fistulas depends on the presence of symptoms, the characteristics and location of the fluid collection on imaging and the presence of associated complications. External pancreatic fistulas are usually managed conservatively in the beginning using supportive and specific treatment regimens [7,35–37]. In general, these fistulas tend to close spontaneously within 2–3 months. Failure to heal is mainly due to larger defects of the pancreatic duct, resulting in high-volume output and fistulas with complications of necrotizing pancreatitis, especially infection. Although almost all peripheral leaks will seal in time, central defects will not resolve easily, especially if there is no internal drainage via the pancreatic duct system into the duodenum. If leaks do not resolve, the anatomy should be diagnosed by ERCP, CT, and fistulography.

Endoscopic stenting or percutaneous drainage is recommended in the majority of cases [38–40]. However, if all consevative and interventional treatment options fail, persistent fistulas require surgery as an alternative treatment option. Supportive management includes adequate fluid drainage, antibiotic treatment if infectious complications occur, as well as balancing the nutritional and electrolyte state. The first and most important treatment is to ensure adequate drainage of the fistula to avoid enzyme-rich fluid collections and infected cavities [7,41]. Furthermore, a fistula tract should be established to facilitate long-term drainage.

Pancreatic fluid should be sent for microbiological examination to rule out an infection or allow a specific anti-infectious treatment when indicated. Prophylactic antibiotics should not be given to patients with noninfected external pancreatic fistula when there is complete remission of the pancreatitis and especially if the fistula

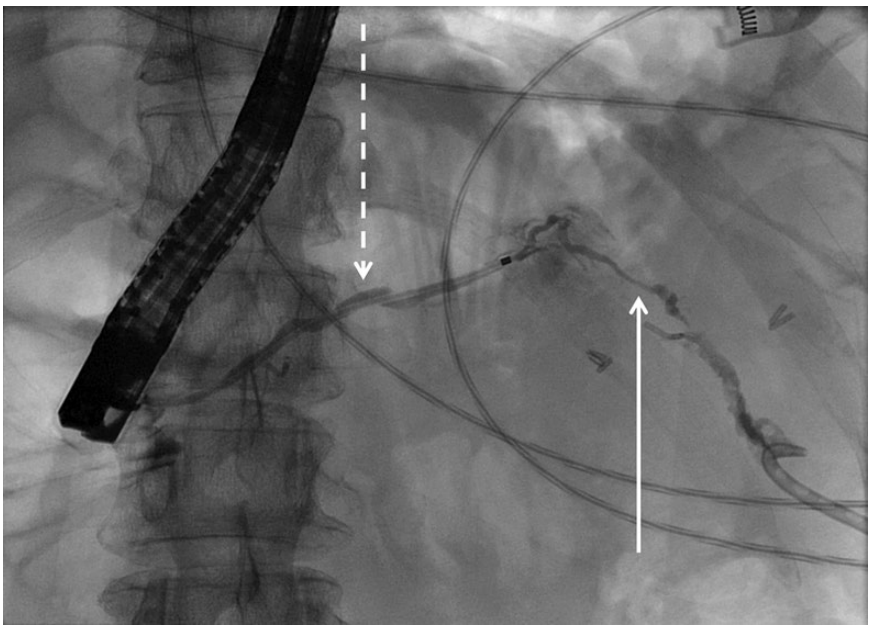

**Figure 37.1** Internal pancreatic fistula to the retroperitoneal space after severe necrotizing pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) showing the pancreatic duct (broken white arrow) and the leakage with contrast medium extravasation (white arrow).

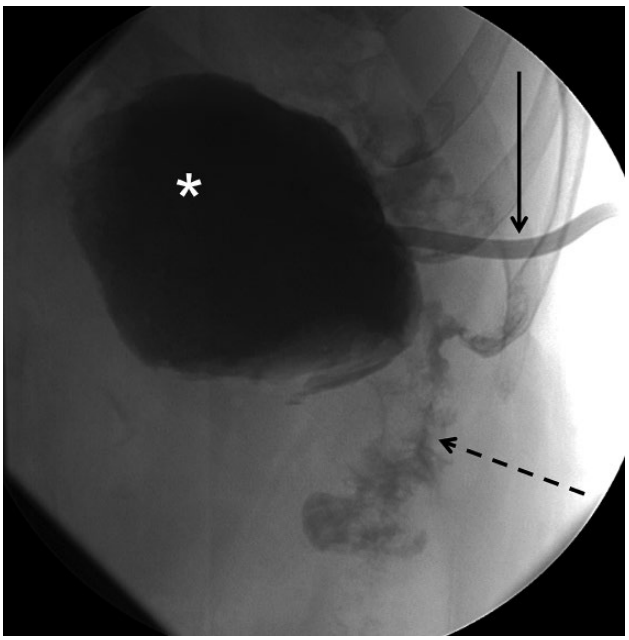

**Figure 37.2** Internal pancreatic fistula during severe necrotizing pancreatitis. X-ray after percutaneous catheter drainage (black arrow) of a large fluid collection (white star). Transition of contrast medium to the descending colon (broken black arrow).

is stabilized and well drained. However, in most cases, the focus of infection is still present by the time of fistula diagnosis and consequently antibiotic treatment is needed.

Supportive early enteral feeding and electrolyte balancing should follow the standards of acute pancreatitis care [42]. However, parenteral nutrition should be considered if enteral feeding is not sufficient to counteract the loss of electrolytes, proteins, and calories associated with acute pancreatitis itself.

In conjunction with parenteral and enteral nutrition, several drugs have been used to inhibit the secretory function of the pancreas. The use of somatostatin and its analogs has been studied extensively. Somatostatin preparations may be effective in the reduction of fistula output but do not affect the likelihood of fistula closure or the time to fistula closure [43]. Based on these results, the use of somatostatin should be limited to patients with high-output fistulas [44]. Endoscopic sphincterotomy with or without stenting facilitates drainage of pancreatic juice into the duodenum and can consequently release pressure from the disruption site. This accelerates healing and may even allow closure of partially disrupted pancreatic ducts within a median interval of 10 days [45–47]. This therapy is highly effective, especially if a bridging of the leakage site can be achieved.

In the case of complete disruption, such as a disconnected duct, pancreatic duct stenting may be technically difficult and even impossible as the distal part of the duct may not be reached after insertion of the guidewire [44,48]. After successful interventional and endoscopic management, gradual withdrawal and downsizing of drainage catheters allows the closure of persistent fistulas as long as they are low-flow fistulas [7].

Surgery is reserved for patients in whom the fistula persists for a prolonged period despite all nonsurgical interventions, which especially occurs in the case of

larger defects of the main pancreatic duct with anatomic discontinuity, persistence of the fistula due to an endoscopically untreatable obstruction of the pancreatic duct, and pancreatic infection. The aim of surgical therapy of external pancreatic fistulas is to redirect the drainage into the intestinal tract [37]. Surgical options available include fistulojejunostomy, distal pancreatectomy, or lateral pancreaticojejunostomy [40]. The surgical procedure chosen is based on the site of the fistula (proximal or distal), the thickness and nature of the fistula tract as well as the texture of the pancreatic tissue. If the fistula tract is located on the right side of the body of the pancreas or even in the head, resection should be avoided and internal drainage into a Roux-en-Y jejunal loop is preferred [7,49]. For persisting fistulas located in the tail of the pancreas distal pancreatetomies are suitable procedures to remove the fistula-bearing part of the pancreas [24]. If communication with the ductal system is present, internal drainage is more effective; if communication is not present, percutaneous drainage is indicated [49–52].

Crucial for surgical treatment of pancreatic fistula is the timing of the procedure as formal pancreatic resections are not possible in the early phase of fistula occurrence. The risk of developing complications during the further course of the disease and the chance of spontaneous closure need to be estimated. Fistulas in severe necrotizing pancreatitis may close even 6 months after the initial episode, since the underlying disease and especially the infection need to heal first. In addition to the patient's condition, it is important to consider the type of fistula before surgery is considered. Simple fistulas do not lead to complications and thus conservative management can be performed for much longer than is recommended for complex fistulas, which tend to develop potentially dangerous complications. These are due to the activated and contaminated intestinal secretions, which can further digest the surrounding tissue and thus induce penetration, hemorrhage, and sepsis.

## Management of Internal Fistulas

Internal fistulas are usually managed by conservative treatment in the beginning using supportive treatment regimens. With supportive care, case series have reported spontanous fistula closure in approximately 50–65% of internal fistulas over 4–6 weeks [53]. Internal pancreatic fistulas, either with pancreatic ascites or with pleural or mediastinal collections, respond well to interventional and endoscopic therapy. The pleural space or peritoneal cavity can be drained, although there is no secure way to place the drain close to the fistula itself in order to produce a controlled tract. The fistula tract will close spontaneously as soon as the sphincter pressure and the obstruction are relieved by papillotomy and/or stenting [54]. However, if all conservative and interventional therapies fail, complex internal fistulas require surgical treatment. This is required not only because of the existence of the fistula itself, but also because of the concomitant presence of complications of necrotizing pancreatitis, especially infected necrosis and abscesses. Thus, the surgical approach to internal fistulas focuses mainly on treatment of the underlying disease. Once infected necrosis is treated adequately, internal fistulas will close rapidly [55,56]. Bowel resections may be necessary in the case of ischemia-associated bowel necrosis and if fistula-associated perforations lead to septic complications, which are mainly observed in colonic involvement. In these situations, colon resections may require a diverting colostomy as there is a high risk of anastomotic leakage due to the intraperitoneal environment of activated pancreatic enzymes and infected fluid.

## Conclusions

External pancreatic fistulas are common sequelae of infected necrosis and interventions required to manage infected severe necrotizing pancreatitis. The majority of fistulas are low output and close spontaneously, which justifies an initial conservative management approach. If this is not successful, there are a wide range of therapeutic options available, including additional percutaneous drainage, endoscopic management, and surgical procedures. Endoscopic or surgical interventions should be considered if a fistula persists beyond 12 weeks or if local complications develop. Endoscopic treatment can aim at an improvement of pancreatic duct drainage via the sphincter of Oddi or a direct closure of the fistula if a bridging stent placement is possible. Surgery usually requires a resection of the fistula-bearing pancreatic region (i.e., distal pancreatectomy) and should be postponed as long as possible. Internal fistulas, which are rarely diagnosed, are usually managed by conservative treatment in the beginning.

If all conservative and interventional therapies fail, surgical treatment of the underlying disease is required. Once the underlying disease, such as infected pancreatic necrosis, is treated adequately, internal fistulas will generally close rapidly. Gastrointestinal fistulas often develop after surgical necrosectomy and can be managed conservatively in most cases. Bowel resection is needed in cases of ischemia-induced bowel necrosis or septic complications and often implies diverting procedures if colonic fistulas are present.

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# Long-Term Outcome After Treatment of Acute Pancreatitis

## 38

## Long-Term Outcome After Acute Pancreatitis

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### Introduction

Most patients with acute pancreatitis recover completely without any further symptoms or morphological alterations within days or weeks after discharge. This observation was described in the original definition of acute pancreatitis by the Consensus Symposium 1963 in Marseille [1]. However, recent reports on long-term outcome after acute pancreatitis show growing evidence that there is a certain risk for late pancreatitis-associated complications even after mild clinical courses [2–5].

Functional impairments can occur immediately or even years after sustaining acute pancreatitis [2,4–6], specifically loss of endocrine function resulting in diabetes mellitus type 3 or exocrine insufficiency with the need for pancreatic enzymes substitution, have been described in numerous studies [2,7–9]. Etiology or severity of the index episode are not clearly associated with the overall risk for an impairment of pancreatic function. In addition, episodes of pain with a considerable impact on quality of life can occur at any point of time after the initial event of acute pancreatitis. These possibly recurrent pain sensations bear a high risk for chronification and may be associated with recurrent pancreatitis; there is also a certain overlap with clinical courses of chronic pancreatitis [2,4,10,11]. This latter correlation has been examined in several recent publications [2–4,12–17]. It is sometimes difficult to distinguish between the primary episode of acute pancreatitis as a symptom of a chronic disease and chronic pancreatitis developing as a long-term consequence of pancreatitis. Morphological characteristics (i.e., those found in cross-sectional imaging at the initial episode of pancreatitis) can be useful for this differentiation as preexisting signs of subclinical chronic pancreatitis may be found in terms of fibrosis or calcifications and can be clearly distinguished from typical signs of new-onset acute pancreatitis.

In contrast to chronic pancreatitis, little is known about histomorphologic pathways and alterations of recurrent acute pancreatitis. One hypothesis is the so-called necrosis–fibrosis sequence [18], which suggests that acute inflammatory changes after an initial and acute damage of the pancreas result in mesenchymal cell activation with various patterns of subsequent fibrosis development and obstruction of pancreatic ducts. Another model is based on a "sentinel acute pancreatitis event (SAPE)," postulating a long-lasting intrapancreatic activation of immunomodulatory and stellate cells during the index episode. These alterations lead to hypersensitivity of the pancreas when responding to potential stimuli, resulting in recurrent attacks of acute and eventually chronic pancreatitis [19]. Despite these hypotheses, the possible pathophysiologic link between acute and chronic pancreatitis remains controversial and is not well understood [20].

Because there are no follow-up guidelines for clinical examinations and imaging after acute pancreatitis and histopathologic findings for such patients are rare due to the infrequent need for operations with respective tissue harvesting, the frequency of such alterations is unknown. In available cross-sectional imaging, alterations of the pancreatic duct, parenchyma, or surrounding areas (i.e., formation of pseudocysts or fluid collections) can be observed during both short- and long-term courses. These morphological findings may be correlated with the severity of the first attack and the type of treatment, in particular interventional or surgical necrosectomy. Their extent and the underlying initial etiology of the primary acute pancreatitis

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episode determine clinical outcome patterns. In alcohol-related acute pancreatitis a recurrent and eventually chronic course is observed more often than it is in a biliary genesis of the disease [11,13,16,17]. This fact underlines the importance of avoiding further exposure to risk factors such as alcohol and nicotine as a basic precaution following a first pancreatitis episode [12,21]. Furthermore, patient education can be regarded as a simple method to reduce the lifelong risk of recurrence and associated healthcare costs [17,21]. Follow-up examinations should therefore address the above-mentioned topics and should include clinical and laboratory as well as imaging examinations, when necessary. This chapter gives an overview of the long-term sequelae of acute pancreatitis with regard to risk factors, diagnosis, and management.

## Risk Factors

Risk factors for long-term complications of acute pancreatitis have been examined in several cohort studies in recent years [3,4,6,12]. With regard to recurrent episodes of acute pancreatitis, a recent meta-analysis including nearly 8500 patients showed an overall risk of 22% with a nearly twofold increase in alcoholic etiology (38%) and a lower risk for biliary etiology (17%) [3]. With regard to biliary etiology, early removal of the gallbladder after the index episode of pancreatitis reduces the risk of recurrence [4,12]. In nonbiliary etiology, persistence of smoking and alcohol consumption are well-documented risk factors for both recurrent acute episodes as well as progression of primary acute to chronic pancreatitis in the long term [4,6,12]. Nevertheless, some authors report experience with patients who show a progression to chronic pancreatitis despite stopping consumption of alcohol and nicotine [12,13]. In addition, male patients seem to have a higher risk of progression to chronic pancreatitis, even when lifestyle-associated risk factors are excluded [3]. Risk factors for functional failure after acute pancreatitis include preceding necrosectomy, which leads to both exocrine and endocrine insufficiency due to the procedure-associated loss of tissue itself and the disease-specific damage to the remaining tissue [4,22]. Again, the risk for developing progressive pancreatic dysfunction and diabetes mellitus or exocrine dysfunction is increased in men [3,5]. Moreover, a subset of patients may also have unrecognized genetic risk alterations leading to increased risk of progressive pancreatic failure and chronic pancreatitis through an effect on trypsinogen activation [23]. Tables 38.1 and 38.2 summarize studies on patterns and risk factors for long-term sequelae after acute pancreatitis.

## Endocrine Pancreatic Dysfunction

Hyperglycemia, impaired glucose tolerance, and diabetes mellitus occur frequently as a consequence of acute pancreatitis and have therefore been investigated as primary or secondary endpoints of several large studies on the loss of pancreatic function on long-term follow-up. A recent meta-analysis of 24 prospective studies published between 1968 and 2009 revealed that nearly 40% of patients showed a prediabetic metabolic situation or a full clinical manifestation of diabetes mellitus [2]. Within 12 months after the index episode of acute pancreatitis the prevalences of hyperglycemia and diabetes mellitus were 19% and 15%, respectively. After a 5-year observation period, the risk for diabetes mellitus showed a twofold increase compared with the prevalence after 12 months. A Dutch cohort study on 669 patients described a new onset of diabetes mellitus in 20% of the patients during a median follow-up time of 57 months [6]. These data are consistent with findings of a Taiwanese study, which showed a comparable twofold increase of diabetes risk after 10 years in nearly 3000 acute pancreatitis patients, regardless of the severity of the initial course of the disease [5].

In severe courses characterized by extensive parenchyma necrosis and the need for necrosectomy, the correlation between loss of tissue and function seems to provide an explanation for these observations, especially when the body and tail of the pancreas are affected. Decay of a considerable amount of islets predisposes for functional deterioration and 15–30% of patients undergoing extensive necrosectomy show insulin-dependency soon after recovery [4]. This is comparable to outcomes following distal pancreatectomy for other indications, with a rate of postoperative diabetes mellitus of approximately 10% [25–27], and underlines the relevance of the pancreatic body and tail for the endocrine function of the gland due to the pronounced location of islet cells in these segments of the pancreas. In contrast, the pathophysiologic explanation for mild episodes of acute pancreatitis resulting in endocrine insufficiency and an increased risk of diabetes mellitus remains unclear.

## Exocrine Dysfunction

In the early phase after acute pancreatitis, exocrine function is often compromised and is easily diagnosed by clinical symptoms of diarrhea, steatorrhea, and maldigestion. In the long term, the reported prevalence rates of exocrine dysfunction differ considerably in the available studies [4,6,22,28]. A study by Sand and Nordback

**Table 38.1** Patterns of long-term sequelae after acute pancreatitis.

| Author, year, country, observation period | Patients (*n*) etiology | Diabetes mellitus *n* (%) | Exocrine dysfunction *n* (%) | Recurrent pancreatitis *n* (%) | Chronic pancreatitis *n* (%) | Median follow-up |
|---|---|---|---|---|---|---|
| Pelli [13], 2000, Finland, 1972–1991 | 562 alcoholic | nm | nm | 260 (46%) | nm | 38 months |
| Lund [16], 2006, Sweden, 1995–1998 | 138 alcoholic: 61 biliary: 48 | nm | nm | 41% nonbiliary vs. 10% biliary | nm | 6 years |
| Yasuda [24], 2008, Japan, 1990–2006 | 45 alcoholic: 23 biliary: 10 | 16 (36%) | 18 (40%) | 8 (18%) | 8 (18%) | 56 months |
| Nøjgaard [15], 2011, Denmark, 1977–1982 | 352 alcoholic: 129 biliary: 44 | nm | nm | nm | 85 (24%) alcoholic: 41 (48%) | nm |
| Castoldi [14], 2013, Italy, 2001–2003 | 631 alcoholic: 36 biliary: 439 | 22 | 16 | 13% | nm | 52 months |
| Yadav [17], 2014, USA, 1996–2005 | 6010 alcoholic: 1223 biliary: 1647 | nm | nm | 1950 (32%) with at least 1 readmission due to pancreatitis | | 39 months |
| Ahmed Ali [6], 2016, Netherlands, 12/2003–03/2007 | 669 alcoholic: 153 biliary: 384 | 136 (20%) | 34 (5%) | 117 (17%) | 51 (8%) | 57 months |

nm, not mentioned.

reports 25% of patients having exocrine failure after necrosectomy in a follow-up period of 2–5 years [4], whereas other studies with comparable observation times reported much higher rates of 55% after mild and up to 83% after severe courses, independent of the etiology of acute pancreatitis [28–30].

Symptoms of exocrine failure can be controlled very well in most patients by oral enzyme replacement to prevent maldigestion, malabsorption, and consecutive malnutrition. Supplementation of the diet with fat-soluble vitamins in the follow-up period should also be considered [31]. A discontinuation of enzyme supplementation may be possible as several studies have reported a potential for long-term recovery of exocrine function within 12–24 months after acute pancreatitis [4,29], which is comparable to the functional recovery often observed after pancreatic resections for other indications.

## Recurrent Pancreatitis and Chronic Pancreatitis

Regarding the frequency and timeline of progressive pancreatic disease after acute pancreatitis, about 20% of all patients and 50% of patients with an alcoholic etiology show recurrent episodes within 10–20 years, but most recurrences occur during the first years after the initial attack [3,4,6]. Overall, one out of ten patients will suffer from a progression to chronic pancreatitis [3], which may be associated with few symptoms for a long period but may finally result in end-stage findings of chronic pancreatitis despite a subclinical course (Fig. 38.1). In the case of recurrent acute episodes, the risk of progression to chronic pancreatitis shows a 3- to 4-fold increase which is, again, pronounced in patients with an underlying alcoholic etiology [6].

**Table 38.2** Risk factors for long-term complications of acute pancreatitis.

| Author, publication year, country, number of patients | Lankisch [12], 2009, Germany, 532 | Ahmed Ali [6], 2016, Netherlands, 669 | Yasuda [24], 2008, Japan, 45 | Lund [16], 2006, Denmark, 155 | Nøjgaard [15], 2011, Denmark, 352 | Sankaran [3], 2015, meta-analysis, 8492 | Shen [5], 2015, Taiwan, 2966 |
|---|---|---|---|---|---|---|---|
| Recurrent acute pancreatitis | Age >40 years, male, biliary etiology without subsequent cholecystectomy | Younger age, nonbiliary etiology, smoking, pancreatic necrosis | Severity of initial attack | Alcohol abuse (OR 3.293) | Smoking | nm | nm |
| Progression to chronic pancreatitis | Alcohol consumption, heavy smoking, recurrent acute pancreatitis | Nonbiliary etiology, smoking, pancreatic necrosis | Severity of initial attack | nm | nm | Alcohol, smoking, men > women | nm |
| Death related to acute pancreatitis | nm | nm | nm | Age >70 years (OR 3.778) | nm | nm | nm |
| Diabetes mellitus | nm | nm | nm | nm | nm | nm | Men > women (HR 3.21 vs. 1.58) |

OR, odds ratio; HR, hazard ratio; nm, not mentioned.

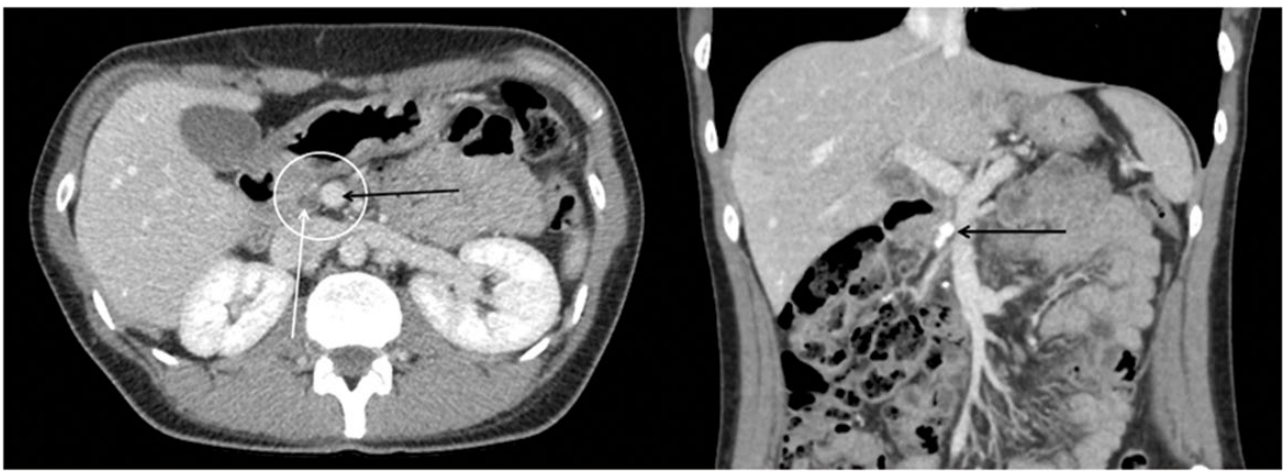

**Figure 38.1** A 39-year-old female patient 9 years after a solitary episode of severe acute pancreatitis following hemorrhagic shock and acute respiratory distress syndrome (ARDS) due to atonic bleeding after cesarean section. This was followed by complete recovery and primary discharge from hospital after 5 weeks and complete remission of residual pseudocysts over a 6-month period. Afterwards, the patient had no clinical symptoms for 8 years before recurrent abdominal pain attacks irradiating to the back occurred. CT scan revealed nearly complete atrophy of the pancreatic parenchyma (left side, white circle; black arrow: portal vein, white arrow: bile duct) and a calcification in the pancreatic head (right side, black arrow). As no signs of inflammation, tumor suspicion, or endocrine insufficiency were present, symptomatic treatment was successful (oral enzyme replacement and analgesia).

## Quality of Life and Pain

Several outcome studies report on the occurrence of pain and the quality of life after acute pancreatitis [4,6,10,11]. An observational study on 145 patients from Finland showed no impairment of quality of life, regardless of pancreatitis etiology, compared to the general population [10]. Similar results are shown in several smaller observational studies, even after necrosectomy [4]. In contrast, in a Polish study patients suffering from severe alcohol-induced acute pancreatitis showed a reduced quality of life in comparison to those with

a biliary origin of the disease with regard to social and family life as well as emotional well-being [11]. How far persisting alcohol consumption after the index episode of pancreatitis contributes to these findings, however, remains unclear from the study data. With regard to chronic pain, a large Dutch cohort study including 669 patients found that 13% had recurrent episodes of pain related to acute pancreatitis [6].

## Incisional Hernia

With the implementation of minimally invasive management of infected pancreatic necrosis during the initial episode of acute pancreatitis, open surgical interventions have considerably decreased and are regarded as the last resort in modern treatment concepts [32,33]. Less than 5% of patients with acute pancreatitis need to be treated by open surgery (e.g., in case of unsuccessful minimally invasive necrosectomy, for bleeding control, or due to organ perforation). These patients show a high rate of surgical site infections (80%) [34] and a correlating high risk of developing an incisional hernia (40%) [35]; surgical re-intervention is often required for symptomatic, functional, and cosmetic aspects of these, often large, hernias.

## Pancreatic Cancer and Pancreas-Related Death

In general, death related to acute pancreatitis, besides short-term mortality during a severe necrotizing course, seems to be rare and not related to progression to chronic pancreatitis and finally pancreatic cancer. A German study reported on four deaths of pancreatic cancer in 532 patients (0.8%) observed after acute pancreatitis during an average follow-up of 7.8 years, which occurred 9–56 months after acute pancreatitis, none of them with a diagnosis of chronic pancreatitis [12]. In an Italian study, three of 631 patients (0.5%) died of pancreatic cancer 5, 6, and 19.9 months after acute pancreatitis with unknown etiology in the first case and biliary etiology in the others [14]. These data support the conclusion that the initial pancreatitis event may be a symptom of an already existing tumor rather than pancreatic cancer and the related mortality is a long-term consequence of acute pancreatitis.

## Imaging Findings

Most episodes of mild acute pancreatitis do not result in any morphologic changes and, after restitution, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) scans show a normal pancreas without any damage to the gland or the duct system. Even when functional impairment occurs, this is not necessarily associated with any pathological imaging findings. This is also observed in most cases of diabetes mellitus of other genesis and in many patients with endocrine dysfunction without underlying chronic pancreatitis. In contrast, severe episodes of acute pancreatitis with or without the need for interventional or surgical treatment often result in morphologic pancreatic alterations of varying extent.

Common reversible or irreversible findings on CT or MRI imaging include:

- inhomogeneity of the parenchyma;
- atrophy of the parenchyma;
- duct alteration (strictures/dilation);
- residual peripancreatic fluid collections;
- pseudocysts.

Diagnosis of the above-mentioned alterations alone does not require any measures, unless accompanying symptoms are present. Further follow-up examinations should be performed to evaluate a potential dynamic of these changes and recognize potential need for any interventional or surgical therapy early to prevent ongoing destruction of the pancreatic parenchyma in the case of recurrent pancreatitis episodes or development of chronic pancreatitis or chronic pain. The management of pseudocysts and persisting postpancreatitis fistulas is described in Chapters 34 and 35.

Another important aspect is the recognition of cystic lesions as the cause of acute pancreatitis and their differentiation from residual pseudocysts. It has been reported that 13–67% of all patients with intraductal papillary mucinous neoplasia (IPMN) show an episode of acute pancreatitis as their initial symptom [36–38]. However, this is frequently misdiagnosed and studies in the past report on a delay in diagnosis of a cystic neoplasm as the trigger of acute pancreatitis of several years or even more than two decades [36–38]. With growing awareness of cystic neoplasms in recent years this may be avoided in the future as distinguishing postinflammatory duct dilatation and pseudocysts from IPMN is of high importance because of the malignant potential of IPMN.

## Postpancreatitis Care and Follow-Up Visits

Six to eight weeks after hospital discharge due to an episode of acute pancreatitis, a clinical control examination can be recommended to document the status, including symptoms and nutritional status with regard to pancreatic function, blood tests, and imaging in cases of severe acute pancreatitis. In case of biliary

acute pancreatitis, cholecystectomy (preferably by a laparoscopic approach) must be scheduled if it has not been performed during the initial hospital stay. There is good evidence concerning the indication and timing of cholecystectomy which shows that a delay of this operation results in an increased risk of recurrent biliary pancreatitis [3,4,39]. For mild biliary pancreatitis cholecystectomy should be performed during index admission. In contrast, in patients with severe pancreatitis, cholecystectomy can safely be performed after resolution of symptoms (4–6 weeks). A similar timeframe should be chosen for patients who undergo sphincterotomy during biliary pancreatitis [39]. Besides biliary pancreatitis, a Finnish study suggested that recurrence of idiopathic acute pancreatitis can also be prevented effectively by laparoscopic cholecystectomy, which should be evaluated for the respective patients [40].

No general guideline or consensus recommendations for long-term follow-up visits after acute pancreatitis exist to date. From the clinical point of view, follow-up at 6-monthly intervals during the first 2 years seems to be reasonable, followed by yearly examinations thereafter [41]. A possible scheme for follow-up could include:

- documentation of abdominal and unspecific symptoms;
- clinical examination;
- blood samples for the determination of routine parameters (including $HbA_{1c}$, electrolytes, creatinine, urea, liver enzymes, amylase, lipase, white and red blood cell counts, and C-reactive protein) as well as the serum tumor markers CEA and CA19–9;
- analyses of genetic factors (*PRSS1*, *SPINK1*, *CFTR*) in the case of unclear etiology of the underlying acute pancreatitis [3,23];
- cross-sectional imaging with abdominal CT or MRI scan.

## Conclusions

Overall, the majority of patients show a good long-term outcome after acute pancreatitis. However, one out of four patients will develop some kind of problem in the long run, including endocrine or exocrine dysfunction, recurrent acute pancreatitis, or transition to chronic pancreatitis even many years after the initial event. Risk factors for clinical deterioration are incompletely examined and understood at present. Lifestyle habits, such as ongoing consumption of alcohol and nicotine, have been shown to increase this risk, especially for patients with alcohol-induced first attack of acute pancreatitis. Following biliary pancreatitis, removal of the gallbladder is an essential measure for prevention of future relapses and should preferably be performed during the initial hospital stay in mild pancreatitis and 6–8 weeks after recovery from a severe episode. To detect long-term loss of function before progression to an irreversible stage, regular follow-up is recommended, including clinical examination and blood tests at 6- to 12-month intervals to check for new onset of diabetes mellitus as well as maldigestion due to pancreatic exocrine dysfunction even when patients are asymptomatic. In the case of abdominal complaints, cross-sectional imaging should be considered. Pathologic findings alone (i.e., atrophy of the pancreatic parenchyma) do not require immediate intervention but should be further monitored during regular follow-up. In the case of transition to chronic pancreatitis with fibrosis and calcifications of the pancreas or dilatation of the pancreatic duct in combination with episodes of pain, a tailored approach including timely surgery should be considered to prevent ongoing deterioration of function and symptoms.

Recommendations for follow-up schemes after acute pancreatitis have not yet been standardized by international guidelines. The number of recent studies shows that heterogeneous protocols are being used in clinical practice and underlines the need for better and evidence-based recommendations to examine the long-term outcome of patients after acute pancreatitis as it is one of the most frequent gastrointestinal indications for inpatient treatment. The rising interest in this area and the results themselves underline the need for implementation of regular follow-up. This would allow a systematic evaluation of the risk of diabetes mellitus, pancreatitis relapse, and development of chronic pancreatitis, all of which exert an immense impact on healthcare costs. The possibility of earlier recognition and prevention of these complications on a risk-stratified basis could offer significant benefits.

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# Section 4

# Chronic Pancreatitis

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# Molecular Understanding of Chronic Pancreatitis

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## Introduction

Chronic pancreatitis is a pathologic pancreatic process containing both fibrotic and immunologic responses to injury that result in destruction and replacement of the exocrine and endocrine features of glandular function. It is primarily a clinically described syndrome characterized by consistent cellular stress or repeated bouts of pancreatic injury, resulting in pancreatic atrophy, fibrosis, and duct distortion, a chronic pain syndrome (suggesting neural injury and responses), and, eventually, loss of both exocrine and endocrine function. Depending on the proposed etiology of the disease, there can be other secondary characteristics, including calcifications, duct centric inflammation with either lymphocytes or neutrophils, or primarily an obstructive phenotype. Focusing on the etiology of the injury and the subsequent pathologic response is important to direct our understanding of the molecular mechanisms of chronic pancreatitis. Importantly, chronic pancreatitis is currently described by specific features seen at the end stage of the disease; however, the molecular path taken to achieve these features can be drastically different. Therefore, although there are likely multiple distinct molecular mechanisms that initiate the pathologic process, the responses of the organ to recovery converge on overlapping immunologic and fibrogenic responses, resulting in a histologically similar result. This convergence of responses by the pancreas suggests that understanding both recovery and regenerative mechanisms resident within the pancreas are of equal importance.

## Risk Factors in Chronic Pancreatitis

The challenge to understanding the molecular mechanisms of chronic pancreatitis is determining the etiologic risk factors. There are several recognized etiologic factors thought to confer risk and allow progression to chronic pancreatitis (Fig. 39.1). These risk factors have been described by the TIGAR-O (toxic–metabolic inflammatory genetic autoimmune recurrent and severe replace with: obstructive pancreatitis) classification [1], which include genetic and environmental factors, obstructive etiologies such as anatomical or traumatic features, and immune-mediated etiologies. The typical organ response to injury and cellular stress promotes recovery and regeneration of the pancreas following injury. However, with repeated injury or prolonged cellular stress, the organ response may become pathologic and drive cellular loss and fibrotic replacement of exocrine and endocrine cells. A proper understanding of the molecular mechanisms leading to chronic pancreatitis requires that we address both the specific etiology, with its associated genetic and epigenetic modifiers, as well as the organ's pathologic response mediated through immune and stellate cells. Therefore, chronic pancreatitis describes a complex disorder. Each patient has a different panel of risk factors, a distinct progression of their clinical course, and will endure different complications, even though the final pathologic appearance of the gland may be indistinct [2].

The current attempts to define chronic pancreatitis focus on a clinical description of the end histologic appearance of the pancreas, which is a result of an immune-mediated response to stress or injury coupled

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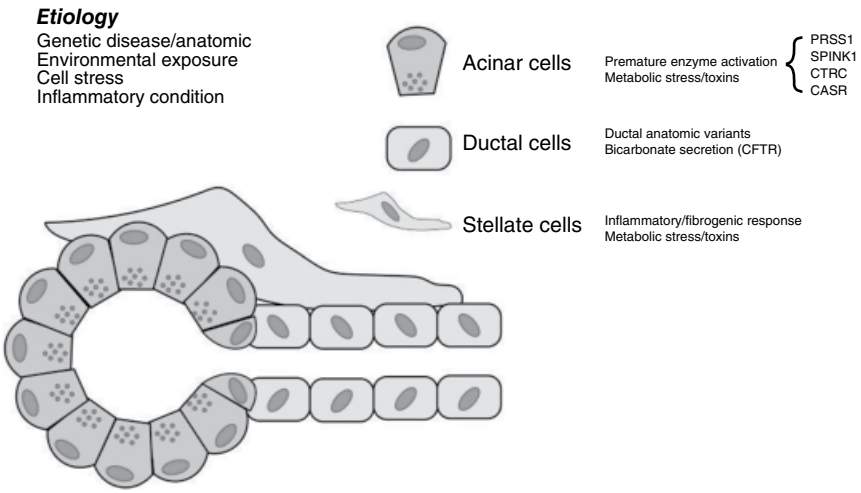


**Figure 39.1** Several etiologies exist for chronic pancreatitis. Specific etiologies affect unique cell types within the pancreatic parenchyma, leading to repetitive injury.

to a fibrogenic wound response. There are inherent challenges to the attempt to define this process. The definition of chronic pancreatitis starts by describing a syndrome that has already progressed to the end stages of the pathologic response. Syndromes describe characteristics rather than defining molecular mechanisms driven by etiologic factors. This attempt to define chronic pancreatitis is not without merit, as it has allowed the identification of the two main pathologic responses that drive the end stage of the disease, namely the immune and fibrotic responses.

Pancreatitis is an inflammatory disorder involving a complex immunologic cascade of events that drives the pathologic result. Environmental cues shape the initiation and progression of the immune system to accelerate or limit the immune response. This immunologic response can be modulated by epigenetic and genetic factors that alter the progression of the disease. The inflammatory response is modulated by the cytokines and chemokines produced by injured acinar cells that act as recruiting and signaling molecules. The etiology of initial and subsequent pancreatic injury or stress will drive or alter the immune response based on the molecular drivers associated with a particular etiology. There are likely multiple modifying factors and intervening steps that impact an individual patient's clinical course but at some point progression becomes similar because the end result of this process is a similar histological pattern.

In this chapter, we will focus on the current understanding of these two distinct stages of disease development, specific etiologies, and the immune-activated fibrogenic response. The first stage relates to specific etiologies and is especially challenging because the risk factor may only be realized after permanent damage has occurred. The second stage of chronic pancreatitis development—the fibrogenic response—is the organ response to injury, and it appears to be similar whatever the specific etiology of the repeated injury.

## Sentinel Acute Pancreatic Event Model

Recently, a disease model hypothesis was promoted to help provide a framework for understanding how different risk factors, including environmental, genetic, and toxin-mediated injury, could impact and allow progression towards chronic pancreatitis. The model, the sentinel acute pancreatitis event hypothesis (SAPE hypothesis) uses the TIGAR-O risk classification system to allow the organization of multiple possible risk factors in promoting the progression of chronic pancreatitis. In this model, a stressor (environmental exposure or toxin) or risk factor (genetic susceptibility factor) is present and impacts the pancreas through alterations in stress responses by parenchymal cells (acinar and duct cells). Once the stress reaches a particular threshold and overcomes the adaptive mechanisms within the pancreas, injury overwhelms the protective regenerative mechanisms, and clinical pancreatitis ensues. This leads to wound-healing responses within the pancreas, including the activation of the inflammatory (neutrophils and lymphocytes) and matrix remodeling systems (macrophages and stellate cells) to stop the injury and allow regeneration to occur. If the inciting factor is removed, healing can occur. However, if the inciting factor is only reduced or removed but then recurs, repeated injury can occur, leading to an injury–wound response cycle that over time leads to parenchymal loss and fibrotic matrix replacement of acinar cells.

Following an isolated episode of pancreatitis, the organ can appear normal histologically. If no other exposures occur then chronic pancreatitis does not develop. However, if the injury–wound cycle continues, the organ suffers loss of normal pancreatic cells and replacement of these cells with fibrosis promoted by macrophages and stellate cells, indicative of the progression towards chronic pancreatitis (Fig. 39.2). In addition to the ideas

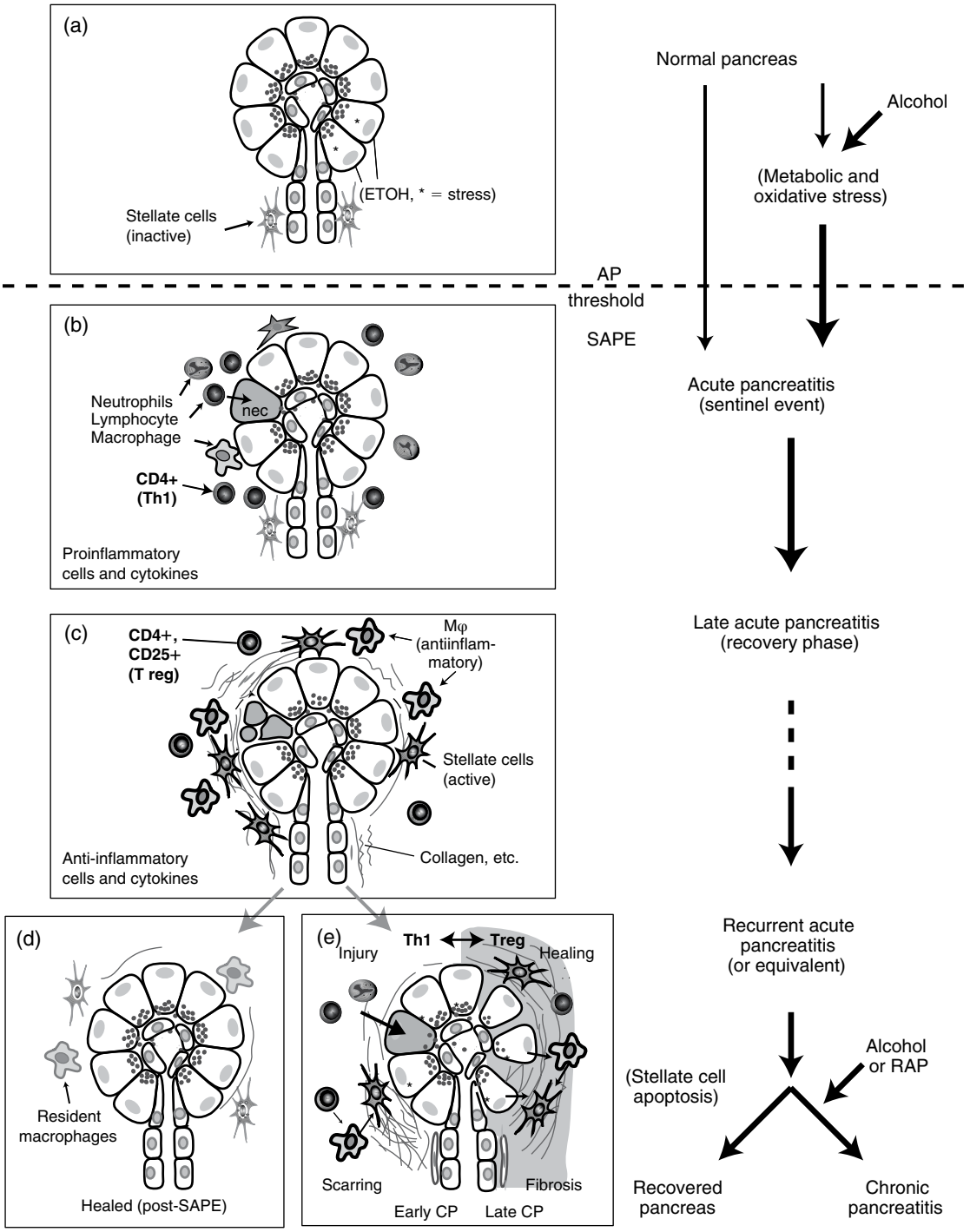


**Figure 39.2** Sentinel acute pancreatitis event (SAPE) hypothesis model. (a) Normal pancreas. If the subject is a heavy alcohol user, the acinar cells are under metabolic and oxidative stress (indicated by asterisks) but histology remains relatively normal. Alcohol increases the risk of crossing the acute pancreatitis (AP) threshold (bold line crossing the dashed line). (b) Acute pancreatitis with pancreatic injury and infiltration of proinflammatory cells. (c) Late acute pancreatitis is dominated by anti-inflammatory cells that limit further injury by proinflammatory cells and products, and promote healing. This includes activation of stellate cells, which produce collagen etc. (d) Recurrent acute pancreatitis (RAP): acinar cell injury or other factors that activate an acute inflammatory response (Th1) are immediately countered by an anti-inflammatory counterresponse (Treg) which, among other things, drives fibrosis. This vicious cycle results in both continued injury (top) and further fibrosis (bottom) leading to (e) extensive acinar cell loss and sclerosis (right) characteristic of chronic pancreatitis (CP). Both genetic factors and environmental factors play a role in this process by increasing susceptibility to acute pancreatitis, altering the severity and duration of acute pancreatitis and altering the healing processes that drive fibrosis. *Source:* Adapted from Whitcomb 2004 [3].

presented within this SAPE model, epigenetic mechanisms also likely occur following an environmental exposure or injury event that changes the organ response to subsequent stimuli.

## Epigenetics as a Modifying Factor in Chronic Pancreatitis

Epigenetics is the control of gene expression that does not involve a change in the primary DNA sequence. In other words, epigenetics refers to modifications of DNA by methylation or of chromatin structure through the posttranslational modification of histone proteins. The posttranslational modification of histones can alter chromatin structure or may alter the affinity of transcription factors to promoter regions. The epigenome can have significant effects on human health as well as disease susceptibility, and epigenetic alterations can be induced through environmental and prenatal exposures to toxins or stressors. Epigenetic changes can be stable and allow "memory" of past stresses to impact future exposures. Epigenetic alterations may be the result of "subclinical" stresses on the pancreas that over time allow molecular remodeling of stress responses to other stimuli. These "subclinical" stresses may alter the epigenetic pattern of genes with little or no immediate effect on gene expression; however, the gene may have an altered response in gene expression when exposed to a new specific environmental cues, which may activate the fibrogenic response and lead to chronic pancreatitis.

In experimental models of pancreatitis, chronically stressed animals (e.g., by ethanol exposure [4], fatty diet [5], or genetic mutation [6]) have an altered response to acute injury compared to animals that have no chronic stress. Ethanol has been shown to affect the action of several epigenetic proteins, including the histone acetylases CREB and CBP [7], as well as the histone deacetylases [8,9]. Recently an epigenetic acetylation mechanism was implicated in the control of acute pancreatitis [10]. Delayed recovery was demonstrated in mice treated with the antiepileptic drug and histone deacetylase inhibitor valproic acid (VPA). VPA is thought to be a definite cause of pancreatitis, especially in pediatric patients [11–13], but the mechanism by which VPA induces pancreatitis was unknown. In fact, chronically treating experimental animals with VPA does not induce pancreatitis but will cause pancreatic atrophy over time [14]. However, animals treated with VPA that are then subjected to a new injury-provoking stimulus develop pancreatitis that is severe and is delayed in its recovery. VPA does not induce pancreatitis but predisposes individuals to severe pancreatitis by altering the epigenetic landscape and thereby inhibiting the recovery mechanisms that allow regeneration to occur.

## Environmental Exposures as Modifying Factors in Chronic Pancreatitis

Chronic pancreatitis is thought to be initiated by several different but interacting mechanisms. A mechanism thought to initiate pancreatic injury is environmental exposure to substances that either sensitize or stress the parenchymal cells of the pancreas. These substances can include alcohol, byproducts of smoking, and other drugs or toxins [15]. They do not by themselves induce pancreatitis but alter the acinar cell's response to other stressors, leading to adaptations that compensate for the exposure. This adaptation by parenchymal cells allows homeostasis to be maintained; however if a second insult or exposure is presented, the cells are more susceptible to injury and have a clinically pathologic response. The response may be actualized by increased injury or conversely may be realized as a delay in regeneration by the pancreas.

Alcohol as disease modifier is a good example of this concept. Ethanol has long been accepted as a major contributor to disease progression in chronic pancreatitis [16,17]. However the number of heavy alcohol drinkers that develop acute or chronic pancreatitis are a minority. This has led many to suggest that there are usually concomitant risk factors necessary to tip the balance towards the development of pancreatitis. Ethanol has been shown to directly affect pancreatic cell types either through direct effects on specific cells or through the metabolism of the drug to toxic metabolites. Ethanol has many effects on the pancreatic acinar cell. These include the emergence of aberrant acinar cell calcium signaling [18], mitochondrial dysfunction [19,20], impairment of autophagic or lysosomal responses [21], and the induction of the unfolded protein response (UPR) with increased expression of x-box binding protein 1 (XBP1), a key regulator of endoplasmic reticulum (ER) function [22,23]. Ethanol appears to increase ER stress, as visualized by ER swelling and UPR induction, but also impacts protein trafficking and alters structural components of zymogen granules [24]. It has also been shown to alter the pathologic intra-acinar activation of digestive enzymes [25,26]. This effect may be due to increased expression of digestive enzymes such as trypsinogen, chymotrypsinogen, or lysosomal cathepsin B [27]. It is postulated that increased protein expression may allow early activation of these digestive enzymes or may cause organelle fragility, allowing early activation of digestive enzymes through inappropriate interaction between lysosomal and digestive enzymes.

## Genetic Influences in Chronic Pancreatitis

A second mechanism shown to mediate the pathologic response in the pancreas occurs through repeated injury by specific insults in a person who is susceptible due to genetic risk factors. Genetic or epigenetic alterations may allow subclinical or clinical repeated injury to occur, which over time results in the destruction of the pancreatic parenchyma and replacement by fibrosis through repeated activation of immune and fibrotic responses. This replacement results in loss of exocrine and endocrine pancreatic function. Hereditary pancreatitis is an example of this mechanism. This condition is caused by a mutation within the cationic trypsinogen gene (*PRSS1*), the primary proteolytic enzyme responsible for activating pancreatic digestive enzymes or zymogens. These gain-of-function mutations lead to premature trypsinogen activation. Several mutations have been identified, but the most common are R122H and N29I. Interestingly, although these mutations place an individual at higher risk of developing chronic pancreatitis, the disease course and ultimate outcome is dependent on other factors, including environmental and metabolic stressors. These additional modifiers are thought to mediate the differences among patients with identical mutations.

In the case of hereditary pancreatitis, the penetrance of the disease is only 80%. Environmental exposures or other genetic modifiers are thought to alter the disease course as individuals with the same genetic mutation can have significantly different disease courses despite having similar histopathology [28]. An extreme example of this was a case where identical twins had the same genetic defect but had different disease progressions, including one twin having no pancreatic disease [29]. This suggests that a single mutation or defect does not lead to chronic pancreatitis but rather a set of factors are required to allow progression from an isolated event to a chronic condition.

In addition to *PRSS1* mutations, there are other genetic mutations associated with increased risk for chronic pancreatitis; these include mutations within the *CFTR* (cystic fibrosis transmembrane conductance regulator) and *SPINK1* (serine protease inhibitor Kazal type 1) genes. As with *PRSS1* mutations, identical mutations within these genes do not predict a similar disease course for affected individuals. Overall, these observations suggest a complex disease process that requires careful analysis of multiple factors that impact and allow the disease to progress.

## Inflammatory Response in Chronic Pancreatitis

The secondary phase of progression to chronic pancreatitis involves the inflammatory and fibrotic responses to chronic stress or repeated injury (Fig. 39.3). Recently, progress has been made in

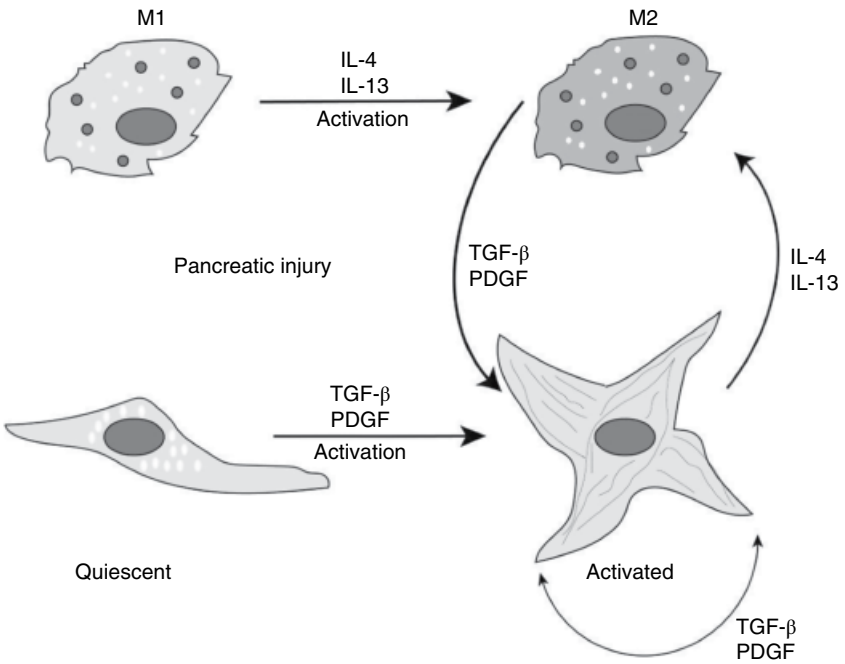


**Figure 39.3** Pancreatic injury activates resident immune cells as well as pancreatic stellate cells to promote pancreatic recovery. However, persistent injury or pathologic signaling between macrophages and stellate cells leads to persistent activation and fibrogenic replacement of the pancreatic parenchyma.

understanding this aspect of chronic pancreatitis. Injury within the pancreas results in damaged acinar cells that will either repair or undergo cell death through necrosis or apoptosis. The damaged cells promote a sterile inflammatory response to mediate the recovery and regeneration process [30]. The inflammatory response is signaled by cytokines released from injured acinar cells and mediated by neutrophils, monocytes, lymphocytes, and macrophages which mediate the resolution of the damaged cells and promote the regeneration of the pancreas [31]. During progression of chronic pancreatitis, inflammation appears to be mediated by different immune cells depending on the experimental model used [32–34]. These cells produce additional inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), IL-6, IL-10, and monocyte chemoattractant protein-1 (MCP-1). Initially, these signals are produced by damaged acinar cells but with repeated injury and activation of other resident pancreatic cells, such as macrophages and stellate cells, there appears to be a shift towards cytokine production from activated immune and stellate cells that promotes and allows progression towards chronic pancreatitis. Neutrophils are thought to activate trypsinogen and allow progression towards severe injury in acute pancreatitis, but in chronic pancreatitis T cells and macrophages are the predominant immune cell infiltrates [35–37].

Neutrophils and macrophages can play a dual role during inflammation, either releasing cytokines such as interferon γ (IFN-γ), leading to a proinflammatory phenotype repressing regeneration, or repairing signals necessary for regeneration to occur [38]. T cells are thought to help control the immune-mediated destruction initiated in chronic pancreatitis by secreting IL-10 [34]. Macrophages can promote healing and regeneration, depending upon macrophage polarity [39]. Activated M2 macrophages have been shown to play a pathogenic role in chronic pancreatitis in both rodents and humans [40]. These studies underscore the importance of the immune response as well as the specific microenvironment that exists in chronic pancreatitis. It is important to understand the course of injury that produces the chronic pathologic response in order to promote healing rather than perpetuating injury.

## Fibrogenesis in Chronic Pancreatitis

The immune system regulates and is regulated by cells within the pancreas, including the mesenchymal cells known as pancreatic stellate cells (PSC). PSC have emerged as critical players in mediating pancreatic recovery after injury [41–43]. They are localized in the periacinar region and are characterized at baseline (i.e., in the quiescent state) by vitamin A droplets [44]. In response to injury, PSC undergo transient activation and take on a fibroblast-like role, secreting extracellular matrix (ECM), particularly collagen [45,46], which is a necessary substrate scaffold for proper regeneration and recovery. The hallmarks of pancreatic injury and recovery are regenerative structures called acinar-to-ductal metaplasia (ADM) [47,48]. The stroma surrounding ADM is composed of activated PSC (aPSC) that function to remodel ECM and are thought to coax ADM to redifferentiate into new acinar cells.

Aberrant regulation of PSC has been implicated in the pathogenesis of chronic pancreatitis and pancreatic cancer [45,49–52]. PSC are not only activated by acinar cell injury but can be activated by cellular stress and ethanol byproducts. Transforming growth factor β (TGF-β) appears to be a major contributor to the fibrotic properties of PSC by increasing collagen and fibronectin expression but also by inhibiting metalloproteinases (MMPs). Once activated, PSC initially help to remodel the parenchyma through the removal of matrix proteins by MMP. Interestingly, PSC not only produce MMP but also the inhibitors of MMP, called tissue inhibitor of metalloproteinases (TIMP). A balance of these two factors likely affects the progression towards fibrosis. The destruction of matrix releases growth factors and cytokines that signal adjacent cells and stimulate parenchymal healing through interactions between the immune and exocrine and endocrine pancreatic cells. PSC not only orchestrate the destruction of matrix but also help orchestrate the regeneration of the framework to allow regenerating acinar and duct cells to proliferate and repopulate the parenchyma. However, if PSC remain activated through repeated injury to the pancreas or aberrant cell signaling from adjacent cells such as macrophages, a pathogenic response can exist that perpetuates the remodeling of the ECM and replaces acinar tissue with fibrosis, leading to the loss of pancreatic exocrine function.

Recently, PSC in chronic pancreatitis models have been shown to respond to adjacent macrophages that produce higher levels of TGF-β and platelet-derived growth factor β, suggesting that the macrophage–PSC interaction may be important in regulating pancreatic regeneration [40] and that when a pathologic state is present, PSC may be a target for therapy.

## Conclusions

Two general mechanisms are thought to result in chronic pancreatitis. These include a sentinel pancreatic event in a susceptible host that perpetuates a progressive

low-grade injury, resulting in fibrosis and loss of physiologic function. Alternatively, several repeated injury events of acute pancreatitis may lead to chronic injury and fibrotic replacement of parenchymal tissue. In light of these two proposed mechanisms for chronic pancreatitis, several animal models have been developed to help target specific aspects of injury and disease progression for the study of chronic pancreatitis. One must be careful when using animal models to mimic disease states in humans. However, with careful attention to the limitations of the experimental model, it is possible to begin to understand aspects of this complex, multifaceted disease. There are likely multiple risk factors and progressive steps that lead to the histopathologic disease known as chronic pancreatitis. The animal model systems used most frequently are rodent models due to cost and the ease of genetic manipulation. However, for certain etiologies, such as CFTR disease, the rodent models do not mimic the human condition, and other models (such as the porcine or ferret model for CFTR) must be used.

Models focused on mechanical injury have been used to study chronic pancreatitis. These models use a partial or complete ligation of the pancreatic duct to induce and allow progression of the disease. This model is species-specific as duct obstruction in rats only induces a mild pancreatitis injury pattern. With the use of a secondary injury stimulus or sensitizing factor, progressive and severe injury can be induced which leads to a histopathologic tissue similar to that seen in the pancreas from humans with chronic pancreatitis. These models have been used to study the fibrogenic response. Chronic inflammation and fibrosis, with increases in collagen and fibronectin, have been observed in rats following chronic duct obstruction [53].

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# Epidemiology and Pathophysiology of Alcoholic Chronic Pancreatitis

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## Introduction

The association between alcohol misuse and chronic pancreatitis has been recognized for a long time. As early as 1878, Friedrich [1] described "drunkard's pancreas" as chronic interstitial inflammation in the pancreas, which might result from alcohol misuse. In 1946, Comfort et al. [2] described the clinical presentation of chronic relapsing pancreatitis in subjects with alcohol misuse. Many studies thereafter established that alcohol misuse is a risk factor for the development of chronic pancreatitis [3–7]. However, unlike alcohol-induced liver injury, chronic pancreatitis develops in only a small portion of heavy drinkers and ethanol feeding alone does not cause pronounced pancreatic injury in animals [8]. It is therefore clear that additional genetic and/or environmental predisposing factors are required for the development of clinical chronic pancreatitis [9,10]. In this chapter we review the epidemiology and pathophysiology of alcoholic chronic pancreatitis.

## Epidemiology of Alcoholic Chronic Pancreatitis

Historically, alcohol misuse was considered the leading cause of chronic pancreatitis and it still accounts for approximately 60–90% of cases in industrialized nations worldwide [11]. An epidemiologic study in France in 2006 showed that 84% of chronic pancreatitis cases could be attributed to alcohol misuse [12]. However, in recent years, it is reported that the proportion of cases attributable to alcohol misuse may be smaller than expected. The North American Pancreatitis Study 2 (NAPS2) showed that the frequency of alcoholic chronic pancreatitis at tertiary referral centers in the United States was 44.5% [11]. A report from Italy showed a shift in the etiologic profile of chronic pancreatitis [13]. Alcoholic chronic pancreatitis was the leading cause of chronic pancreatitis (74%) between 1971 and 1995, but the proportion decreased to 43% in patients evaluated between 2000 and 2006 [13]. These findings suggest that the contribution of alcohol misuse to the pathogenesis of chronic pancreatitis might have been overestimated [11]. Referral bias might exist in tertiary referral centers and accurate assessment of alcohol exposure to determine the association with chronic pancreatitis is challenging because self-reports about alcohol consumption are usually unreliable [14]. On the other hand, in Asia, alcohol misuse accounted for 69.7% of chronic pancreatitis cases in Japan in 2011 [15]. Idiopathic pancreatitis was the most common type in India (tropical pancreatitis) and accounted for approximately 70% of the chronic pancreatitis cases [16]. In China, 35% of the chronic pancreatitis cases were alcoholic [17]. Importantly, alcohol consumption has been stable or decreasing in many North American and European countries as well as in Japan, whereas it has been increasing in India and China [16,17]. It would be of interest to see whether the trends in alcohol consumption affect the burden of alcoholic chronic pancreatitis in India and China in the future.

Many studies have attempted to clarify the dose–response relationship between alcohol consumption and pancreatitis [4–6,18]. The first study on this topic was published by Durbec and Sarles in 1978 [4]. They reported that the logarithm of the relative risk of chronic pancreatitis increased linearly as a function of the quantity of alcohol and protein consumed. In the NAPS2, the association between alcohol consumption and pancreatitis was evaluated in 540 cases and 695 controls [6]. Logistic regression analyses revealed a significant

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association between alcohol and chronic pancreatitis only in the very heavy drinkers who consumed ≥5 alcoholic drinks per day (odds ratio 3.1). In another case–control study [19], among patients with onset of chronic pancreatitis after the age of 35, alcohol intake, even less than 50 g/day, induced earlier disease characterized by more frequent severe pain, calcification, and complications such as pseudocysts. In a Japanese case–control study [18], compared with nondrinkers, the odds ratios (95% confidence interval [CI]) for alcohol consumption of ≤20 ~ <40 g/day, ≤40 ~ <60 g/day, ≤60 ~ <80 g/day, ≤80 ~ <100 g/day, and ≥100 g/day were 2.6 (95% CI: 1.2–5.5), 3.2 (95% CI: 1.5–7.1), 9.2 (95% CI: 4.1–20.3), 13.0 (95% CI: 5.3–31.6), and 19.6 (95% CI: 8.2–46.8), respectively.

In 2015, Samokhvalov et al. [20] reported a systematic review and meta-analysis of four studies (three case–control and one cohort studies) including the NAPS2 [6] and the Japanese case–control study [18] to assess the risk of pancreatitis and alcohol consumption. They showed that the risk of chronic pancreatitis increased monotonically according to the average alcohol consumption with no identifiable threshold in men (relative risks (95% CI) at 25 g/day = 1.58 (95% CI: 1.32–1.90); 50 g/day = 2.51 (95% CI: 1.74–3.61); 75 g/day = 3.97 (95% CI: 2.30–6.85); 100 g/day = 6.29 (95% CI: 3.04–13.02)) (Fig. 40.1). The risks calculated in the meta-analysis might be somewhat lower than those in the Japanese study [18]. One explanation may be related to genetic differences: a high proportion of Japanese individuals have a relative deficiency of alcohol dehydrogenase (ADH) and/or aldehyde dehydrogenase, resulting in higher blood levels of alcohol and/or acetaldehyde [21]. Another explanation may be the difference in body size between Japanese individuals and those from Western countries.

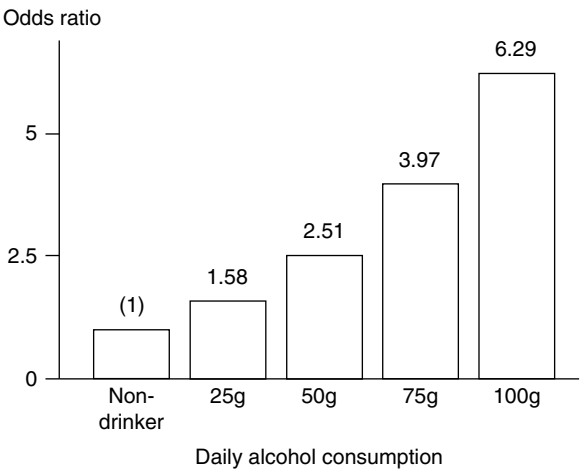


**Figure 40.1** Amounts of daily alcohol consumption and risk of chronic pancreatitis. *Source:* Based on data from [20].

It is well known that alcoholic chronic pancreatitis is predominantly a disease of men; 90–95% of the patients diagnosed with alcoholic chronic pancreatitis are male [22]. However, alcohol misuse is also an important health problem in women. Because of the increase in alcohol consumption by women in recent years the incidence of alcoholic chronic pancreatitis in women has been increasing in some countries, as reported for the Netherlands [23]. Importantly, it has been shown that susceptible women might develop alcoholic chronic pancreatitis with shorter duration of alcohol consumption and lower cumulative amounts of alcohol consumption than men [24].

## Pathophysiology

To date, several pathophysiologic mechanisms linking alcohol consumption and pancreatic injury have been suggested. These are described in the following sections [25–28].

### Ethanol Metabolism in the Pancreas

Pancreatic acinar cells are the main source of ethanol metabolism. Two pathways of ethanol metabolism have been described in pancreatic acinar cells: oxidative and nonoxidative pathways [29,30]. Ethanol oxidation involves the conversion of ethanol to acetaldehyde and acetate, a reaction catalyzed by ADH and cytochrome P450 2E1. The nonoxidative pathway of ethanol metabolism involves the esterification of ethanol with fatty acids to form fatty acid ethyl esters (FAEE) such as palmitic acid ethyl ester. This reaction is catalyzed by FAEE synthases. FAEE synthase activity in the pancreas is much greater than that in the liver, whereas pancreatic ADH and cytochrome P450 2E1 activities are low [29]. Therefore, the dominant nonoxidative metabolism is a characteristic feature of ethanol metabolism in the pancreas. It has been shown that ethanol intake results in the accumulation of FAEE in the blood and in several organs, with the highest concentrations in the pancreas [31]. FAEE synthases in the pancreas have not yet been fully characterized, but possible candidates include pancreatic triglyceride lipase and carboxyl ester lipase [32]. Patients with pancreatic diseases released FAEE synthase into their plasma in amounts proportional to those of amylase and lipase [33].

### Effects of Ethanol and its Metabolites on the Pancreas

Major targets of ethanol's actions in the pancreas include the sphincter of Oddi, pancreatic ductal cells, pancreatic acinar cells and pancreatic stellate cells (PSC) [25–28].

Animal studies showed an ethanol-induced spasmogenic effect on the sphincter of Oddi leading to occlusion of the main pancreatic duct (large duct), but both ethanol-induced decreased and increased Oddi activities have been reported in humans [25]. In the 1970s, the protein plug theory was proposed: alcoholic pancreatitis was thought to be caused by the blockade of small pancreatic ducts by protein plugs which were formed by the precipitation of secreted pancreatic proteins [34]. Thereafter, the focus of research has shifted to pancreatic acinar cells *in vitro* and *ex vivo*.

### *In Vitro* and *ex vivo* Studies

Ethanol might affect several aspects of homeostasis in pancreatic acinar cells. It induces a sustained elevation of the intracellular calcium levels [35] and increases the synthesis of digestive enzymes [36] (Box 40.1). It also increases the fragility of zymogen granules [37] and lysosomes [38], which sequester lysosomal enzymes such as cathepsin B within the cells. Mitochondrial dysfunction might play a role in ethanol-induced necrosis of the pancreatic acinar cells [39]. Some of these effects are mediated by metabolites of ethanol such as acetaldehyde and FAEE rather than ethanol itself. Gukovskaya et al. [29] showed that ethanol might regulate nuclear factor-κB (NFκB) and activator protein-1 (AP-1), the key transcription factors regulating the gene expression of inflammatory responses and cell survival. FAEE activate NFκB and AP-1, whereas ethanol and acetaldehyde inhibit NFκB activation. Thus, ethanol may regulate the activation of NFκB and AP-1 positively or negatively, depending on which metabolic pathway predominates. These effects may play a role in the ethanol-induced toxicity in the pancreas. Interestingly, ethanol and its metabolites altered the cholecystokinin 8-induced activation of these transcription factors [40]. As we will describe later, this may be a mechanism by which ethanol sensitizes pancreatic acinar cells to pancreatitis.

Recently, the pathophysiologic roles of autophagy have attracted the attention of researchers. Autophagy comprises several intracellular pathways of lysosome-mediated degradation and recycling of organelles, long-lived proteins, and lipids [41]. Evidence from animal models showed that autophagy is impaired in pancreatitis and lysosome dysfunction might be involved [42]. Fortunato et al. [43] reported that the combination of ethanol exposure and endotoxemia resulted in the depletion of several lysosomal proteins, including lysosomal-associated membrane protein-2 (LAMP-2), a protein required for the proper fusion of autophagosomes with lysosomes. LAMP-2 depletion was correlated with a switch from apoptotic to necrotic cell death. Importantly, human patients with ethanolic pancreatitis also exhibited local LAMP-2 depletion, indicating the crucial roles of LAMP-2 and autophagy in acinar cell death in humans.

A major breakthrough in this research field was the identification and characterization of PSC, a major effector cell type in pancreatic fibrosis, in 1998 [44]. *In vitro* culture of PSC provides a useful and unique platform to investigate the molecular mechanisms of alcohol-induced pancreatic fibrosis. Ethanol and its metabolites induced the activation, extracellular matrix production, and chemokine expression in PSC, leading to the perpetuated activation of PSC and pancreatic fibrosis [45,46].

**Box 40.1 Effects of ethanol and its metabolites on pancreatic cells**

**Pancreatic acinar cells**

- Sustained elevation of intracellular calcium level [35]
- Increased synthesis of digestive enzymes [36]
- Increased fragility of zymogen granules and lysosomes [37,38]
- Mitochondrial dysfunction [39]
- Activation of transcription factors NFκB and AP-1 [29]
- Impaired autophagy through depletion of LAMP-2 [43]
- Impaired regeneration [55]

**Pancreatic ductal cells**

- Protein plug formation [34]
- CFTR dysfunction [56]

**Pancreatic stellate cells**

- Activation (as assessed by increased α-smooth muscle actin expression) [46]
- Extracellular matrix synthesis (type I collagen) [45]
- Interleukin-8 production [46]

### *In vivo* Studies

Although a number of *in vitro* and *ex vivo* studies have shown the effects of ethanol and its metabolites on pancreatic cells, *in vivo* studies have shown that feeding ethanol to rats and mice even for a long time, with either liquid diet or continuous intragastric infusion, did not cause prominent injury to the pancreas [8,47,48]. Chronic ethanol feeding by the Lieber–DeCarli pair-feeding model [47] induces a number of metabolic changes in acinar cells, including an increase in the content of digestive enzymes and lysosomal enzymes and in the fragility of zymogen granules and lysosomes. However, chronic pathologic changes resembling chronic pancreatitis did not develop. On the other hand,

chronic ethanol exposure sensitizes the pancreas to other insults. Pancreatitis developed in rats that had received an ethanol-containing diet in response to low doses of cholecystokinin octapeptide or its analog caerulein, which do not cause pancreatitis by themselves [40]. The sensitization was accompanied by increased NFκB activation and the upregulation of proinflammatory cytokines and chemokines in the pancreas [40]. A combination of short-term administration of caerulein and long-term intraperitoneal administration of ethanol led to the activation of PSC and fibroinflammatory responses in the pancreas [49]. Chronic ethanol consumption accelerated pancreatic fibrosis in response to caerulein-induced pancreatitis in rats [50].

The findings in animal studies support the concept that, in humans, ethanol misuse alone does not cause chronic pancreatitis and additional cofactors such as smoking and genetic factors are required for the development of chronic pancreatitis in susceptible humans [9,10]. Animal studies have suggested that endotoxin in the microbiota might be such a cofactor. Gut permeability is increased in alcoholics, allowing translocation of Gram-negative bacteria across the mucosal barrier and allowing bacterial endotoxins to enter the circulation. A combination of Lieber–DeCarli ethanol-enriched diet and repeated injection of lipopolysaccharide (LPS) developed acute acinar cell injury, activation of PSC, and fibrosis [51]. Repeated LPS injection caused pancreatic fibrosis in ethanol-fed rats, but not in rats fed the control diet. When ethanol administration was continued, the activation of PSC and fibrosis persisted, but resolved soon after ethanol was discontinued [52]. Conversely, continued alcohol intake perpetuates pancreatic injury by inhibiting apoptosis and promoting the activation of PSC. These findings indicate the importance of abstinence to prevent the progression of acute pancreatitis to chronic pancreatitis [53].

Gukovsky et al. [8] reported that ethanol dramatically aggravated the pathologic effects of the combination of cyclosporine A and caerulein. In ethanol-fed, but not control diet-fed, animals, the combined treatment of cyclosporine A and caerulein resulted in severe pancreatic injury that displayed three key responses of human alcoholic chronic pancreatitis: loss of parenchyma, sustained inflammation, and fibrosis. On the other hand, for the repair of the exocrine pancreas, acinar cells could act as progenitor cells; mature acinar cells undergo dedifferentiation and redifferentiation back to the differentiated phenotype [54]. Clemens and Jerrells [55] reported that chronic ethanol administration delayed the structural and functional regeneration of the pancreas in mice. The delayed regeneration was associated with the decreased expression of pancreatic developmental factors including PDX-1. These findings suggest that ethanol might impair the recovery from acute pancreatic injury, thus facilitating the progression from acute pancreatic injury to chronic pancreatitis.

Recent studies have highlighted again the role of the pancreatic duct in the pathogenesis of alcohol-induced pancreatitis. Maléth et al. [56] showed that alcohol disrupted the expression, folding at the endoplasmic reticulum, and function of the cystic fibrosis transmembrane conductance regulator (CFTR) in pancreatic ductal cells. CFTR knockout mice given ethanol or fatty acids developed more severe pancreatitis than mice not given ethanol or fatty acids.

## Co-Predisposing Factors for the Development of Alcoholic Chronic Pancreatitis

The fact that only 1–5% of heavy drinkers develop pancreatitis [57] indicates that alcoholic pancreatitis is not caused by chronic alcohol misuse alone [9,10]. Some individuals may develop alcoholic pancreatitis with alcohol intake as low as 20 g/day, whereas most individuals do not develop pancreatitis no matter how much they drink or how long. Therefore, additional genetic and/or environmental factors such as cigarette smoking, high lipid diet, and gut microbiota [9,10,51] are required for the development of clinical chronic pancreatitis.

Most of the patients with alcoholic chronic pancreatitis are smokers and smoking has been established as an independent risk factor for the development of chronic pancreatitis [9,10,58]. Attention has been paid to identifying individuals at high risk of pancreatitis, and genetic studies might be useful to identify such individuals. The association between alcoholic chronic pancreatitis and pancreatitis susceptibility genes such as *PRSS1*, *SPINK1*, and *CTRC* has been shown in some studies, but the association exists primarily with nonalcoholic chronic pancreatitis [59]. Polymorphisms in the alcohol-metabolizing enzymes have been studied in patients with alcoholic chronic pancreatitis [60,61]. The frequency of the *ADH1B*2* allele was significantly higher in patients with alcoholic chronic pancreatitis compared with alcoholic subjects. The frequency of the *ALDH2*2* allele was significantly lower in patients with alcoholic chronic pancreatitis and in alcoholic subjects compared with healthy controls [60,61]. However, most of the studies have come from East Asia, and the data in Caucasians is very limited.

Genome-wide or exome-wide approaches overcome the limitations of a candidate gene approach, enabling the discovery of new and unsuspected pancreatitis susceptibility genes. A genome-wide study from North America has shown that the polymorphisms in the trypsin locus

(*PRSS1* rs10273639) and the claudin 2 locus (*CLDN2-RIPPLY1-MORC4* locus rs7057398 and rs12688220) conferred an increased risk of alcoholic chronic pancreatitis, but not with alcohol-associated cirrhosis or alcohol dependence [62]. The association of alcoholic chronic pancreatitis with polymorphisms in these loci has been replicated in Europe, Japan, and India [63–65], indicating that these polymorphisms are susceptible to alcoholic chronic pancreatitis worldwide. In such individuals at risk, lower levels of alcohol consumption might not be safe. Very recently, another genome-wide association study showed a novel association between alcoholic chronic pancreatitis and polymorphisms in the genes encoding fucosyltransferase 2 nonsecretor status (*FUT2* locus rs632111 and rs601338) and blood group B (*ABO* locus rs8176693) [66]. Obviously, further studies are required to clarify the underlying cellular events in the presence of these susceptibility polymorphisms.

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# Pain Mechanisms in Chronic Pancreatitis

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## Introduction

Chronic pancreatitis used to be defined as a continuing inflammatory disease of the pancreas, characterized by irreversible morphological change, and typically causing pain and/or permanent loss of function. Recently, however, a new mechanistic definition has been proposed: "Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [1]. This definition recognizes the complex nature of chronic pancreatitis, separates risk factors from disease activity markers and disease endpoints, and allows for a rational approach to early diagnosis, classification, and prognosis. About 65–70% of chronic pancreatitis cases are attributed to alcohol abuse. The remaining cases are classified as idiopathic chronic pancreatitis (ICP; 20–25%) and include tropical pancreatitis, which is a major cause of childhood chronic pancreatitis in tropical regions, or unusual causes such as hereditary pancreatitis, cystic fibrosis, and chronic pancreatitis-associated metabolic and congenital factors or autoimmune disorders [2,3]. Chronic pancreatitis is characterized by progressive remodeling processes leading to the replacement of the exocrine parenchyma by extensive fibrosis. However, the most clinically relevant feature is recurrent upper abdominal pain. Pain can be so intense and long-lasting that the follow-up care of patients is difficult and frustrating [3] and many patients become addicted to narcotics.

Three different typical pain profiles during the evolution of chronic pancreatitis have been described: (i) acute intense pain associated with repeated episodes of acute pancreatitis (acinar necrosis) in early stages, (ii) spontaneous lasting pain relief in association with severe pancreatic dysfunction in late stage of uncomplicated chronic pancreatitis, and (iii) persistent severe pain (or frequent recurrent episodes of pain) usually in association with local complications such as pseudocysts, ductal hypertension, or extrapancreatic complications such as partial obstruction of the common bile duct, peptic ulcer, and opiate addiction [4]. Several hypotheses have been advanced to explain pain genesis in chronic pancreatitis, including pancreatic and extrapancreatic causes. Today we have evidence for peripheral and central nervous system (CNS) involvement during chronic pancreatitis. It is believed that following injury, rapid and long-term changes occur in parts of the CNS that are involved in the transmission and modulation of pain (nociceptive information). A central mechanism in the spinal cord called "wind-up," also referred to as hypersensitivity or hyperexcitability, may occur. Wind-up occurs when repeated, prolonged, noxious stimulation causes the dorsal horn nerves to transmit progressively increasing numbers of pain impulses. This abnormal processing of pain within the peripheral nervous system and CNS may become independent of the original painful event in chronic pancreatitis [5].

## Extrapancreatic Pain

Bile duct stenosis and duodenal stenosis due to extensive pancreatic fibrosis and inflammation have been considered extrapancreatic causes of pain [6]. Becker and Mischke described a pathologic condition named "groove pancreatitis" in 19.5% of 600 patients with chronic pancreatitis [7]. This is characterized by the formation of a scar plate between the head of the pancreas and the duodenum. A scar in the groove is said to lead to complications that are determined by the topography: disturbance in the motility of the duodenum, stenosis of

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the duodenum, and tubular stenosis of the common bile duct, occasionally leading to obstructive jaundice. These alterations are suggested to be responsible for several symptoms present in chronic pancreatitis and for postprandial pain due to the compression of nerves and ganglia located between the pancreatic head and the duodenum [8].

## Pancreatic Pain

Many investigators have related the origin of pain to increased pressure in pancreatic ducts and tissue [9–12]. The "ductal hypertension hypothesis" as an explanation for pain in chronic pancreatitis is supported by observations that decompression of a dilated pancreatic duct or pseudocyst frequently relieves pain [13]. According to this hypothesis, administration of pancreatic enzymes reduces pancreas juice production in patients with chronic pancreatitis, producing lower intraductal pressure and thereby reducing pain. Interestingly, pancreatic insufficiency appearing in the late stage of the disease may be accompanied by reduction or complete relief of pain, thus suggesting that the disease can burn itself out [8]. However, the "burn-out theory" in chronic pancreatitis has been questioned by epidemiologic data which show that pain in many patients with chronic pancreatitis continues despite pancreatic insufficiency, the appearance of calcifications, alcohol withdrawal, or pancreatic surgery. In fact, it has been estimated that around 30% of the patients treated with decompressive surgery exhibit recurrent attacks of pain [14].

In addition, octreotide, a somatostatin analog which strongly inhibits pancreatic secretion and therefore should interrupt the postulated pain cycle described, failed to significantly reduce the pain syndrome in many patients with chronic pancreatitis [15]. In addition, Manes et al. found no relationship between pain score and pancreatic pressure, although the intrapancreatic pressure was positively correlated with ductal changes, and they concluded that pancreatic parenchymal pressure is not closely related to pain in chronic pancreatitis [12]. Another hypothesis suggests that pain is induced when increased pancreatic ductal and parenchymal pressure produce a compartment syndrome that causes ischemia [16]. This hypothesis is supported by experimental studies [17] that show increased interstitial pressure correlates with decreased blood flow in a feline model of chronic pancreatitis. These abnormalities were reversed by surgical incision of the gland and draining the pancreatic duct, but were affected minimally by stenting the pancreatic duct. This would suggest that incision of the gland may be more important in relieving pain than ductal drainage. In addition, different studies [18,19] revealed that the degree of pancreatic fibrosis has no significant influence on pain generation since no correlation between the degree of fibrosis and intensity of pain could be demonstrated. Pseudocysts of the pancreas can cause intense pain in patients with chronic pancreatitis. In the majority of cases (60%) treatment with octreotide results in a reduction in size and in the eventual disappearance of the pseudocysts together with reduction of pain [20]. Enlargement of pseudocysts, causing compression of adjacent structures, might be a mechanism for pain generation.

Several authors have described patients with chronic pancreatitis associated with autoimmune diseases. Sarles et al. [21] described a type of chronic pancreatitis that might be caused by an autoimmune mechanism and termed it "primary inflammatory sclerosis of the pancreas." Yoshida and colleagues [22] reported a similar case and proposed that pancreatitis with these characteristics has to be considered as autoimmune pancreatitis. Current accepted terminology for this condition is lymphoplasmacytic sclerosing pancreatitis or autoimmune pancreatitis [22,23]. Pain is often associated with this type of inflammation although the genesis of this clinical symptom has not yet been investigated.

## Neural Remodeling

Neurogenic inflammation as a result of pancreatic inflammation and neural remodeling has recently been linked to both acute and chronic pathological conditions of the pancreas. Neurogenic inflammation encompasses a series of vascular and nonvascular inflammatory responses, triggered by the activation of primary sensory neurons (C- or Aδ-type nerve fibers) and the subsequent release of inflammatory neuropeptides, including substance P (SP) and calcitonin gene-related peptide (CGRP), and has been validated in human as well as in animal models of acute and chronic pancreatic damage [24,25]. Pancreatic and central changes can be distinguished.

### Pancreatic Changes

Keith et al. suggested initially that neural and perineural alterations might be important in pain pathogenesis in chronic pancreatitis [26]. They concluded that pain severity correlated with the duration of alcohol consumption, pancreatic calcification, and the percentage of eosinophils in perineural inflammatory cell infiltrates, but not with duct dilatation.

A subsequent study demonstrated an increase in both number and diameter of pancreatic nerve fibers in the course of chronic pancreatitis [27]. In tissue specimens

from patients with chronic pancreatitis, foci of chronic inflammatory cells were often found surrounding pancreatic nerves (called pancreatic neuritis), which by electron microscopic analysis exhibit a damaged perineurium and invasion by lymphocytes. The changed pattern of intrinsic and possibly extrinsic innervation of the pancreas in chronic pancreatitis suggested that there could be an upregulation of neuropeptides that usually populate those enlarged nerves. In fact, a further study [28] showed that there were striking changes in peptidergic nerves in chronic pancreatitis. The changes consisted of an intensification of immunostaining for CGRP and SP in numerous nerve fibers. Because both of these peptides are generally regarded as pain neurotransmitters, these findings provided evidence for direct involvement of pancreatic nerves in the long-lasting pain syndrome in chronic pancreatitis.

Later reports [23,29] revealed that the presence of growth-associated protein-43 (GAP-43), an established marker of neuronal plasticity, directly correlated with the pain scores in patients with chronic pancreatitis. GAP-43 is a neuronal protein known to be involved in the development of axonal growth cones and presynaptic terminals, and mRNA and protein levels of GAP-43 are increased after neuronal lesions. In the chronically inflamed human pancreas, enzymatic and double fluorescence immunohistochemistry reveals a significant expression of GAP-43 in the majority of pancreatic nerve fibers. These immunohistochemical findings correlated with clinical and pathological findings in patients with chronic pancreatitis, including the parenchyma–fibrosis ratio and the degree of perineural immune cell infiltration. Furthermore, a strong relationship with individual pain scores was present. The infiltration of pancreatic nerves by immune cells is significantly related to pain intensity, whereas pain scores do not correlate with the degree of pancreatic fibrosis or with the duration of the disease.

The demonstration of a direct relationship between the degree of perineural inflammation and the clinical pain syndrome strongly supports the hypothesis of "neuroimmune interaction" as an important, if not predominant, factor in pain generation in patients with chronic pancreatitis.

An interesting question concerns the mechanisms that contribute to the enlargement of pancreatic nerves. A recent study analyzed the expression of nerve growth factor (NGF) and one of its receptors (TrkA) in patients with chronic pancreatitis [25]. NGF belongs to the neurotrophin family and plays a role in neuroblast proliferation and neuronal maturation, affecting neuronal phenotype and maintaining neuronal survival. NGF signaling is mediated via binding high- and low-affinity receptors. TrkA is present in dorsal root and peripheral ganglia cells of primary sensory nerves, and is involved in signal transduction of noxious stimuli and tissue injury. Inflammation results in an elevation of NGF levels in different diseases. Interestingly, NGF may itself have cytokine-like functions; it can modify mast cell, macrophage, and B-cell functions, but may also activate TrkA located on sensory and sympathetic nerve fibers innervating the site of inflammation, thus modulating neuroimmune interactions. In chronic pancreatitis tissue samples NGF and TrkA mRNA expressions are markedly increased and enhanced in pancreatic nerves and ganglia. Comparison of the molecular findings with clinical parameters revealed a significant relationship between NGF mRNA levels and pancreatic fibrosis and acinar cell damage and between TrkA mRNA levels and pain intensity. These findings indicate that the NGF/TrkA pathway is activated in chronic pancreatitis and that this activation might influence nerve growth and the pain syndrome, most probably by modulating the sensitivity of NGF-independent primary sensory neurons through increasing channel and receptor expression [25].

Similar results showing positive correlation with pain intensity and frequency in patients with chronic pancreatitis were reported for brain-derived neurotrophic factor gene expression, a member of the neurotrophin family [30]. In addition, upregulated NGF might influence the pain syndrome in chronic pancreatitis patients by regulating transcription and synthesis of SP and CGRP, as well as through the release of histamine. The neuropeptide SP is the main tachykinin involved in neural transmission of sensory information, smooth muscle contraction, nociception, sexual behavior, and possibly wound healing and tissue regeneration [31,32]. SP has wide-ranging functional effects, including the crosstalk between nervous and immune systems by acting through its specific receptor neurokinin 1 (NK-1R). A recent report by Shrikande et al. [33] demonstrated a significant correlation between NK-1R and clinical–pathologic findings in patients with chronic pancreatitis. In chronic pancreatitis samples, NK-1R mRNA expression and protein were localized mainly in nerves, ganglia, blood vessels, inflammatory cells, and occasionally in fibroblasts. A significant relationship between NK-1R mRNA levels and intensity, frequency, and duration of pain in chronic pancreatitis patients was reported. The expression of NK-1R in inflammatory cells and blood vessels also points to crosstalk between immunoreactive SP nerves and inflammatory cells and blood vessels, and further supports the existence of a neuroimmune interaction that probably influences the pain syndrome and chronic inflammatory changes in chronic pancreatitis.

In addition, a recent study demonstrated that SP mRNA expression levels were higher in chronic pancreatitis tissues compared to controls, whereas neprilysin (NEP) mRNA levels showed no significant

differences between chronic pancreatitis patients and healthy subjects. In chronic pancreatitis patients, SP serum levels correlated with those in tissue, and after surgical resection SP serum levels were reduced compared to preoperative values. Failure of NEP to overexpress in chronic pancreatitis tissues was associated with significant miR-128a overexpression, suggesting that in an SP/NEP-mediated pathway NEP fails to provide adequate surveillance of SP levels and this failure of NEP might be microRNA associated [34].

The exact mechanisms involved in the interaction between inflammatory cells and nerves and ganglia—neuroimmune crosstalk—are not yet fully clarified. Different cytokines have been shown to interact with SP in various paradigms for pain and inflammation. SP directly stimulates the release of interleukin 8 (IL-8) from macrophages. IL-8 release generates hyperalgesia by stimulation of postganglionic sympathetic neurons. A significant increase of IL-8 mRNA was reported in chronic pancreatitis tissue samples [35]. IL-8 was present mainly in macrophages surrounding the enlarged pancreatic nerves, in remaining acinar cells, and often in ductal cells. IL-8 mRNA expression was positively correlated with the inflammatory score and the presence of ductal metaplasia in chronic pancreatitis tissue samples.

The reported findings in the literature on the interaction of SP and IL-8, in combination with what was reported in chronic pancreatitis, suggests that the increased mRNA expression of IL-8 in chronic pancreatitis could in part be mediated by SP released from sensory pancreatic nerves. In addition, the release of IL-8 from the remaining exocrine pancreatic parenchyma suggests the fascinating hypothesis of an intrinsic maintenance of the inflammatory response after the initial damage to the pancreatic gland, thus sustaining progression and evolution of the disease. In addition, in a rat model it was found that repeated caerulein stimulation causes experimental pancreatitis that is mediated in part by stimulation of vanilloid receptor type 1 (VR1) on primary sensory neurons, resulting in endogenous SP release [36]. These results were confirmed in human pancreas [37]. In fact, an activation of the VR1 in pancreatic tissues from patients with pancreatic cancer and chronic pancreatitis is known. This increase was correlated with pain score in those patients. The release of SP and NKA from primary afferent (sensory) nerve endings to various stimuli is now considered to be induced by activation of the capsaicin (vanilloid) receptor (VR1).

### Central Involvement

Considering the noxious input described above from these pancreatic changes, it is not surprising that evidence for central sensitization is found in patients with chronic pancreatitis. In fact, patients with chronic pancreatitis have lower thresholds to pain in response to deep abdominal palpation than healthy individuals (reflecting secondary referred hyperalgesia in the musculature) [38]. Furthermore, the area of referred pain is expanded in patients with chronic pancreatitis who are subject to experimental electrical stimulation of viscera with changes in evoked potentials in the brain [39–41]; these data have also been confirmed by magnetic resonance imaging. In constrast, hyposensitivity to cutaneous stimulation has also been reported in these patients, probably as a result of altered descending inhibitory influences on spinal nociceptive neurons [42]. Patients with chronic pancreatitis have also been shown to have hyperalgesia to rectosigmoid stimulation, accompanied by impairment in diffuse noxious inhibitory control, a phenomenon that reflects descending central inhibition of pain, thought to be a countermeasure to noxious stimulation [43].

However, it is difficult to determine the importance of central sensitization in the pathogenesis of pain in humans with chronic pancreatitis with constant abnormal input into the CNS [44]. Central sensitization could simply reflect the expected response to an ongoing barrage of impulses from the periphery [45,46]. If so, then suppression or interruption of afferent signaling from the pancreas should also attenuate central sensitization, as has been suggested by the results of small studies on the effects of thoracic splanchnectomy/denervation on hyperalgesia in patients with chronic pancreatitis [47,48], as well as by the response to a peripherally acting κ-opioid antagonist.

## Conclusions

Clarifying the pathophysiologic mechanism for pain generation in chronic pancreatitis remains a major clinical problem. The recent concept of neuropeptides released from enteric and afferent neurons and their functional interactions with inflammatory cells might play a key role. An interesting recent finding is the presence of a spatial relationship between peptidergic neurons and inflammatory cells in chronic pancreatitis. Furthermore, there is the intriguing possibility of a functional interaction among neuropeptides, immune cells, cytokines, and NGF. A correlation between those molecules and pain has been demonstrated and the present information provides evidence for neuroimmune crosstalk in the pathogenesis of pain and inflammation in chronic pancreatitis.

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# 42

# Natural History of Recurrent Acute and Chronic Pancreatitis

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## Introduction

Pancreatitis, especially chronic, is a disease of low prevalence. Consequently, the epidemiologic focus has primarily been to define the disease at the level of individual patients. In the past two decades, the importance of understanding the distribution of risk factors and disease at the population level has been recognized. This has enabled determination of disease estimates and increased our understanding of the relationship between acute pancreatitis and chronic pancreatitis at the population level. The recognition that subsets of patients with acute pancreatitis develop recurrent acute pancreatitis (RAP) and/or progress to chronic pancreatitis provides empiric evidence that these conditions represent stages of a disease continuum. Knowledge of the risks and factors associated with disease progression will help in risk stratification, prediction, and developing strategies for altering the natural history of disease.

This chapter focuses on the burden of disease, natural course, and survival of acute, recurrent acute, and chronic pancreatitis. For acute pancreatitis, the emphasis will not be on the severity and outcome of the initial attack, but rather the risk of readmissions, recurrences, and progression to chronic pancreatitis. In chronic pancreatitis, the prevalence and natural history of clinical features (i.e., pain, endocrine and exocrine insufficiency) and the risk of pancreatic cancer will be discussed. Finally, we will summarize available data on quality of life.

## Natural History After First Attack of Acute Pancreatitis

### Disease Burden, Etiology, and Severity

Acute pancreatitis is one of the leading gastrointestinal causes of hospitalization in the United States [1]. The estimated incidence of acute pancreatitis in recent studies is between 30 and 50 per 100,000 population. Acute pancreatitis affects all age groups, but is most frequent in middle-aged and older individuals [2]. Gallstones and excessive alcohol consumption account for about 60–70% of all cases, the latter being more common in men than in women. Other etiologies include metabolic factors (hypertriglyceridemia, hypercalcemia), endoscopic retrograde cholangiopancreatography (ERCP), medications, genetic mutations (*PRSS1*, *SPINK1*, *CFTR*, *CTRC*), obstructive causes (such as pancreatic duct stricture etc.), and trauma. In 10–25% patients no identifiable etiology is found on evaluation [2]. The two main determinants of mortality in acute pancreatitis are the presence of organ failure and infected necrosis [3]. The risk of death increases with age and comorbidities [4]. Increased morbidity is seen in patients with local complications who do not have organ failure [5].

### Readmissions

After the first attack of acute pancreatitis, about 20–30% patients are readmitted to the hospital (Table 42.1). The reasons for readmission differ based on time since

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 42.1** Summary of recent studies examining rates and risk factors for readmission after a first attack of acute pancreatitis.

| Author, year design | Cohort size | Follow-up time (months) | Readmission rate (%) | | | | Time to readmission (months) | Risk factors for readmission |
|---|---|---|---|---|---|---|---|---|
| | | | Overall | Alcoholic | Biliary | Idiopathic | | |
| Whitlock et al., 2010 [7] Retrospective | 248 | 30.0 | 19 | 29 | 13 | 3 | 0.3 | Alcohol use<br>Severe disease at index attack<br>Positive symptoms at discharge<br>Nonsolid diet at discharge |
| Yadav et al., 2014 [10] Retrospective | 5239 | 39.0 | 22 | 40 | 15 | 32 | Unclear | Younger age alcoholic etiology<br>Subsequent diagnosis of CP |
| Vipperla et al., 2014 [6] Retrospective | 127 | 36.0 | 34 | 60 | 29 | 59 | 1.3 | Younger age<br>Male gender<br>Alcoholic or idiopathic etiology<br>Severe disease at index attack |
| Suchsland et al., 2015 [9] Retrospective | 373 | Unclear | 29 | Not stated | | | 7.8 | Increasing age<br>Substance abuse (alcohol, tobacco)<br>Concurrent liver disease<br>Alcoholic etiology |

CP, chronic pancreatitis.

discharge from the hospital. Vipperla et al. [6] differentiated between early (<30 days after index acute pancreatitis) and late (>30 days after index acute pancreatitis) readmissions and found that early readmissions were more likely due to smoldering symptoms from acute pancreatitis and/or local complications, whereas late admissions were more likely to be due from recurrent episodes of acute pancreatitis. Whitlock et al. [7] identified five factors at the time of discharge that independently predicted the risk of early readmission (<30 days after discharge): tolerance of less than a solid diet, gastrointestinal symptoms (nausea, vomiting, diarrhea), pain, pancreatic necrosis, and use of antibiotics and/or opiates. Using these parameters (one point each), they developed a scoring system to predict the risk of early readmissions (low risk 0–1 points; moderate risk 2–3 points; high risk 4–5 points) and tested this in a validation cohort. The risk of readmissions was approximately 5%, 15%, and over 65% in the low-, moderate-, and high-risk groups, respectively [8]. Younger age and concurrent alcohol use and/or alcohol-related etiology have also been identified to predict readmissions [6,7,9,10].

These data suggest that focused discharge planning may reduce the risk of early admissions (i.e., ensuring that the patients' symptoms are well controlled and they have received counseling for behavior modification). In patients with severe acute pancreatitis, close follow-up with relevant specialists (e.g., nutrition, gastroenterologist, surgeon) is helpful to determine the need and timing of cross-sectional imaging, duration of enteral feeds, and "step-up" therapy. Many patients with severe acute pancreatitis need short-term stay at a transitional care facility or rehabilitation unit prior to safe discharge home.

## First Recurrence

The risk of RAP after the first attack has been evaluated in several, mostly retrospective, population- and non-population-based studies (Table 42.2). The overall risk of a subsequent attack of acute pancreatitis is ~20% during a median follow-up period ranging from 4 to 8 years. Similar to the first attack, among patients with a second attack of acute pancreatitis, alcohol, gallstones, and idiopathic causes are the most common etiologies [11–14]. When compared with the first attack of acute pancreatitis, subsequent recurrence is generally milder, with an overall lower mortality [15].

The risk of recurrent attack is highest among patients with alcohol etiology (35–40%) followed by idiopathic and biliary acute pancreatitis (both 10–20%) [11–14]. Takeyama et al. noted that the risk of subsequent recurrence was directly related to continued alcohol consumption: the risk was highest in patients who continued drinking at the same level and lowest among patients who stopped drinking completely [17]. Contrary to what many physicians may believe, counseling against alcohol consumption has a significant impact on patient behavior. This was tested empirically in a randomized controlled trial, where repeated counseling of patients led to a significant decrease in the risk of abdominal pain attacks, acute pancreatitis episodes, and hospitalizations [18].

After an attack of biliary pancreatitis, the risk of recurrence can be dramatically reduced by early cholecystectomy. This has been demonstrated in randomized clinical trials, as well as in a meta-analysis of published data [19,20]. In patients with mild biliary pancreatitis, cholecystectomy should be considered as soon as possible following the attack of acute pancreatitis, preferably during the same admission. In patients with severe acute pancreatitis, cholecystectomy should be delayed until resolution of inflammatory changes in the pancreas/peripancreatic area. In patients with pancreatic/peripancreatic collections that need drainage, a surgical approach (preferably laparoscopic or minimally invasive) to address this along with a cholecystectomy should be considered [21]. In patients with another known etiology (i.e., medications, hypertriglyceridemia, hypercalcemia, etc.), addressing the inciting cause will decrease the risk of recurrence [22,23].

Because tobacco abuse is consistently associated with an increased risk of recurrent acute pancreatitis (odds ratio 1.5–2) [11,12,14,16], after an attack of acute pancreatitis, patients should be informed about this risk and counseled for tobacco cessation. This will be especially relevant in patients in whom the cause was related to alcohol, hypertriglyceridemia, genetic factors, or idiopathic, or if the acute pancreatitis attack was moderate to severe. Individual studies have also shown that age and severity of initial attack may also play a role in recurrence [11,13,14,16].

The burden of RAP at a population level is not well defined. Using information on the total number of admissions for acute pancreatitis in the United States and applying the incident acute pancreatitis rates from California, the approximate number of recurrent attacks can be estimated [1,24]. Among the 275,000 annual admissions for acute pancreatitis, approximately 150,000–160,000 would be incident attacks, while the remaining 115,000–125,000 would represent RAP (first or subsequent recurrences), readmissions for ongoing symptoms or complications of acute pancreatitis, or acute on chronic pancreatitis.

## Quality of Life After Acute Pancreatitis

Severe acute pancreatitis, with or without necrosis, results in worsened quality of life when compared with control populations [25–27]. A recent meta-analysis

**Table 42.2** Summary of recent studies examining the rate and risk factors for development of recurrent acute pancreatitis (RAP) after a first attack of acute pancreatitis.

| Author, year | Cohort size | Follow-up time (years) | RAP rate (%) | | | | Time to recurrence (months) | Risk factors for RAP |
|---|---|---|---|---|---|---|---|---|
| | | | Overall | Alcoholic | Biliary | Idiopathic | | |
| Lankisch et al., 2009 [13] Prospective | 532 | 8.0 | 17 | 33 | 12 | 14 | Unclear | Younger age<br>Alcoholic etiology<br>Male gender |
| Yadav et al., 2012 [14] Retrospective | 7456 | 3.3 | 29 | 52 | 18 | 26 | 7.2 | Younger age<br>Alcoholic etiology<br>Tobacco use |
| Bertilsson et al., 2015 [11] Retrospective | 1457 | 4.2 | 23 | 37 | 17 | 24 | 5.1 | Alcoholic etiology<br>Severe disease at index attack<br>Tobacco use |
| Cavestro et al., 2015 [12] Prospective | 196 | 4.4 | 20 | 31 | 9 | 38 | Unclear | Pancreas divisum<br>Idiopathic etiology<br>Alcohol or tobacco abuse |
| Ahmed Ali et al., 2016 [16] Prospective | 669 | 4.8 | 17 | Not stated | | | 5.0 | Younger age<br>Idiopathic etiology<br>Tobacco abuse<br>Severe disease at index attack |

analyzed 267 acute pancreatitis patients, accumulated from four prospective cohort studies. Overall, when compared with controls, the general health domain (which measures patients' abilities to conduct daily activities) and vitality domain (which measures patients' energy levels) were significantly impaired [28]. Subgroup analysis based on severity or types of intervention were not statistically feasible, and further studies are required to clarify the determinants of poor quality of life after acute pancreatitis more precisely.

### Subsequent Recurrences

As for the initial recurrence, alcohol is the most common etiology for subsequent recurrences, followed by idiopathic pancreatitis, genetic causes, hypertriglyceridemia, and underlying chronic pancreatitis as other important causes. The role of pancreas divisum and sphincter of Oddi dysfunction in causing initial or recurrent acute pancreatitis attacks is controversial [29,30].

Approximately one-third of patients who have a recurrence after the first attack of acute pancreatitis will have one or more subsequent recurrences. Burden of RAP was further quantified in two studies. Among 562 patients with first attack of alcoholic acute pancreatitis who survived the index admission, Pelli et al. reported at least one recurrence in 260 (46%) patients. Among these patients, 133 (51%) had only one recurrence, 49 (19%) had two recurrences, 39 (15%) had three recurrences, and 39 (15%) had four or more recurrences [31]. Among patients who underwent a cholecystectomy for presumed biliary pancreatitis, Trna et al noted the risk of subsequent attacks to be related to the presence of abnormal liver function tests and documentation of gallbladder stones or sludge. Among patients who did not have either, 26% had a second attack, and 9% had a third attack of acute pancreatitis [32]. Although few empiric data are available, the risk of multiple attacks of acute pancreatitis seems high in patients with certain genetic mutations (e.g. *PRSS1*, *CFTR*) [33]. The risk of recurrences would also appear to be higher in patients with uncommon causes of acute pancreatitis, such as hypertriglyceridemia, hypercalcemia, etc., especially if the underlying cause is not corrected, but definitive data on the burden of attacks in these patients are also lacking [23].

### Progression to Chronic Pancreatitis

Many recent studies evaluating the natural history after first attack of acute pancreatitis have determined the risk of progression to chronic pancreatitis (Table 42.3) [11–14,16,34]. Overall, the risk of progression to chronic pancreatitis varied from 5% to 25% during a follow-up period ranging from 4 to 8 years. The three factors consistently shown to have an independent effect on disease progression are alcohol etiology, tobacco abuse, and RAP. The association with severity of acute pancreatitis is less consistent and has been noted in some but not all studies.

Lankisch et al. noted that progression to chronic pancreatitis occurred almost exclusively in patients with alcohol etiology [13]. However, in other studies progression was also noted in patients with nonalcoholic or idiopathic chronic pancreatitis, albeit at a lower rate. The role of tobacco, especially in combination with alcohol in disease progression is important. Ahmed Ali et al. reported that while the cumulative risk of progression to chronic pancreatitis overall was 7.6%, it was 18% among current smokers, and increased to 30% in current smokers who also had alcohol etiology [16]. Therefore, including the counseling of tobacco cessation along with alcohol abstinence should be emphasized. Genetic factors also seem to play a role in the development of chronic pancreatitis, but outside of hereditary pancreatitis, few empiric data are available [33].

Perhaps the strongest risk factor for disease progression is RAP, and the risk of progression in these patients is ~30–40%. Bertilsson et al. noted that among patients who transitioned to chronic pancreatitis, 74% had at least two attacks of acute pancreatitis, and 54% had more than two attacks. When compared with alcohol or tobacco (hazard ratio 2–3), the risk of progression to chronic pancreatitis is much higher (hazard ratio ~6) [11].

Because the evolution to chronic pancreatitis may occur over several years, the duration of follow-up is also an important determinant of a study's ability to accurately characterize the risk of progression to chronic pancreatitis. Indeed, the study with the longest follow-up period observed the highest incidence of progression to chronic pancreatitis [34].

In a recent meta-analysis of 14 studies consisting of 8492 patients, Sankaran et al. summarized the natural history of progression from acute pancreatitis to chronic pancreatitis [35]. The pooled prevalence of RAP was 22% (38% for alcohol etiology, 17% for biliary etiology), and of chronic pancreatitis was 10%. As stated previously, the major risk factors were RAP, alcohol use, and tobacco smoking.

## Natural History of Chronic Pancreatitis

### Disease Burden, Demographics, and Etiology

The population distribution for chronic pancreatitis is becoming clearer. Annual incidence data have been reported from many populations and range from 4 to 14 per 100,000 population, with an estimated prevalence of ~50 per 100,000 population [2]. Alcohol continues to be the predominant cause of chronic pancreatitis worldwide,

**Table 42.3** Summary of recent studies examining the incidence and risk factors for development of chronic pancreatitis after an attack of acute pancreatitis.

| | | | CP rate (%) | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Author, year** | **Cohort size** | **Follow-up time (years)** | **Overall** | **Alcoholic** | **Idiopathic** | **RAP** | **Time to CP (months)** | **Risk factors for RAP** |
| Lankisch et al., 2009 [13] Prospective | 532 | 8.0 | 4 | 13 | 0 | 22 | Unclear | Alcoholic etiology<br>Recurrent acute pancreatitis<br>Tobacco use |
| Nojgaard et al., 2011 [34] Prospective | 352 | 30.0 | 24 | Not stated | | | 42.0 | Male gender<br>Tobacco abuse |
| Yadav et al., 2012 [14] Retrospective | 7456 | 3.3 | 13 | 28 | 10 | 32 | 10.4 | Alcoholic etiology<br>Recurrent acute pancreatitis<br>Tobacco use |
| Bertilsson et al., 2015 [11] Retrospective | 1457 | 4.2 | 5 | 17 | 6 | Not stated | 5.1 | Alcoholic etiology<br>Recurrent acute pancreatitis<br>Severe disease at index attack<br>Tobacco use |
| Cavestro et al., 2015 [12] Prospective | 196 | 4.4 | 8 | 21 | 9 | Not stated | 12.0 | Male gender<br>Severe disease at index attack<br>Tobacco abuse |
| Ahmed Ali et al., 2016 [16] Prospective | 669 | 4.8 | 8 | Not stated | | | 21.0 | Younger age<br>Idiopathic etiology<br>Tobacco abuse<br>Severe disease at index attack |

CP, chronic pancreatitis; RAP, recurrent acute pancreatitis.

followed by idiopathic chronic pancreatitis. The role of genetic factors is increasingly recognized and mutations in four susceptibility genes (*PRSS1*, *SPINK1*, *CFTR*, and *CTRC*) are now routinely tested in clinical practice in patients with unexplained chronic pancreatitis [33]. Alcoholic chronic pancreatitis is seen more commonly in men, whereas the other etiologies are more evenly distributed in both sexes. The median time to diagnosis of chronic pancreatitis is typically 5–10 years after that of acute pancreatitis [36].

## Natural Course of Clinical Symptoms

### Abdominal Pain

Abdominal pain is the most common symptom which prompts patients with chronic pancreatitis to seek medical attention. Approximately 85–90% patients with alcoholic chronic pancreatitis have pain at some point of time during their clinical course [37–40]. Differences have been described in the pain experience based on disease etiology: patients with alcoholic chronic pancreatitis and early-onset idiopathic chronic pancreatitis are more likely to have any or severe pain when compared with patients who have the onset of disease later in life [39–42]. Pain can be related to a multitude of factors, including mechanical (pancreatic or biliary duct obstruction), inflammatory (episodes of acute pancreatitis, peripancreatic collections), neuropathic, and visceral hyperalgesia.

In a study of 206 patients with alcoholic chronic pancreatitis, 56% of whom needed at least one surgical intervention, Ammann et al. described two main patterns of pain. Type A pain was defined by intermittent episodes of pain, sometimes severe needing hospitalization, lasting up to a few days at a time and could be managed medically. Type B pain was characterized by constant pain with exacerbations, often related to local complications, needing frequent hospitalization and surgical intervention for pain relief (most frequently for pseudocysts, less often for symptomatic large duct disease or cholestasis) [42]. Using a questionnaire modeled to mimic Ammann's pain categories, a recent multicenter cross-sectional study of 518 chronic pancreatitis patients of all etiologies from the United States assessed the pain pattern in the year preceding the enrollment. Overall, 84% patients reported having pain—described as intermittent by 32% and constant by 53%; mild-moderate by 18%, and severe by 67% [43]. Due to the cross-sectional design, the study could not examine the relationship between interventions (medical, endoscopic, surgical) and pain relief.

In most large series of patients with chronic pancreatitis, approximately 40–50% undergo some form of intervention (endoscopic, surgical) for pain relief [38–40,42]. There is controversy as to whether all chronic pancreatitis patients will achieve pain relief or "burnout" during the course; Ammann et al. proposed this based on their observation that >80% patients become pain free approximately 5–10 years after onset of symptoms, usually in parallel with the development of exocrine and endocrine insufficiency [37]. However, others argue that pain relief may not be universal, and that a significant proportion of patients continue to have pain even after developing pancreatic insufficiency [44].

Due to persistent and severe pain, there is a risk of narcotic dependence. As a consequence, management of pain related to chronic pancreatitis requires a multidisciplinary approach [45]. In recent years, increasing numbers of patients are undergoing total pancreatectomy with islet autotransplantation (TPIAT). Guidelines have been proposed on the selection of patients, timing of procedure, and pre- and postoperative follow-up of patients who are being considered for TPIAT [46].

### Endocrine and Exocrine Insufficiency

Chronic pancreatitis leads to progressive loss of functioning pancreatic tissue, and consequently can lead to "pancreatogenic or type 3c" diabetes and fat malabsorption. Diabetes in the setting of chronic pancreatitis has distinct characteristics from type 1 and 2 diabetes, which may have clinical and prognostic implications [47]. Both of these complications require lifelong therapy.

The incidence of diabetes and exocrine insufficiency in chronic pancreatitis ranges between 40% and 80% [37–40]. In the largest prospective study addressing this question (431 patients, 51% with surgical intervention), Malka et al. reported a cumulative risk of 50% at 10 years and 83% at 25 years after diagnosis of chronic pancreatitis, with a median time to diagnosis of 4.5 years [48]. Independent variables were pancreatic calcification, distal pancreatectomy, and alcohol etiology.

Subclinical exocrine insufficiency is more frequent in chronic pancreatitis, since clinical symptoms of steatorrhea develop only after significant destruction of the exocrine pancreas [49]. Patients with exocrine insufficiency develop fat-soluble vitamin deficiencies and osteopenia/osteoporosis with associated complications such as bone fractures [50]. Fortunately, exocrine insufficiency is easily addressed with the initiation of pancreas enzyme supplementation, which has been shown to improve symptoms, nutritional status, and quality of life [51,52].

### Pancreatic Cancer

Chronic pancreatitis is an established risk factor for pancreatic cancer. The risk increases with the duration of disease, and is similar for alcohol and nonalcoholic etiologies. In a meta-analysis of 22 published studies, the relative risk of pancreatic cancer was increased 5.1-fold for unspecified pancreatitis, 13.3-fold for chronic pancreatitis, and 69-fold for hereditary pancreatitis [53]. The

absolute risk of developing pancreatic cancer in a patient with chronic pancreatitis is low (5%), except for tropical pancreatitis and hereditary pancreatitis, where the risk can be as high as 25% and 40–50%, respectively [53].

### Quality of Life and Survival

Chronic pancreatitis negatively impacts quality of life independent of demographic factors, risk factors, and coexistent medical problems [54]. Among chronic pancreatitis patients, pain is one of the primary determinants of poor quality of life [55]. Patients frequently use healthcare services with significant associated cost [56,57]. The overall survival and the standardized mortality ratio in chronic pancreatitis patients are 2- to 4-fold higher than in the general population [34,58]. Most patients die from nonpancreatic causes.

## Conclusion

Studies in the past two decades have provided an insight into the population distributions and natural histories of different stages of pancreatitis. Readmission to hospital is frequent after acute pancreatitis. After the first episode of acute pancreatitis, about one in five patients develop a recurrence and one in ten progress to chronic pancreatitis. Alcohol and tobacco abuse are the main predictors of recurrence, and these, along with RAP, are the main predictors of progression to chronic pancreatitis. Abdominal pain is the main symptom of chronic pancreatitis, and a significant fraction of these patients develop exocrine and/or endocrine insufficiency during the disease course. Chronic pancreatitis is an established risk factor for pancreatic cancer, although the absolute risk of this is low.

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# 43

# Chronic Pancreatitis with Inflammatory Mass of the Pancreatic Head

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## Introduction

Chronic pancreatitis can present with enlargement and mass formation of the pancreatic head, mimicking virtually all symptoms of a malignant pancreatic head tumor and confronting the clinician with significant diagnostic and therapeutic challenges. This phenomenon has been termed the "inflammatory (pseudo) tumor" [1], "tumor-forming chronic pancreatitis" [2], and other terms. Here we will use the term inflammatory pancreatic head mass (IPHM).

From a pathophysiological point of view, IPHM is thought to result from recurrent acute and chronic inflammation of the pancreatic parenchyma. At the same time it acts as a "pacemaker," perpetuating the disease progression by causing obstruction of the main pancreatic duct (MPD) leading to chronic ductal hypertension [3]. There is no generally accepted definition of IPHM, but the following criteria may be applied: the presence of an abnormally enlarged pancreatic head, often accompanied by pancreatic calcifications, MPD dilatation and irregularities, and atrophy of the pancreatic parenchyma to the left of the mesentericoportal axis [4–6] (Figs 43.1 and 43.2).

## Incidence

The concept of the IPHM as a pacemaker of chronic pancreatitis was proposed by Beger et al. [3] and is followed mainly by European surgeons. The incidence of IPHM in surgical patients is in the range of 85%, although exact figures have rarely been reported in detail [5,7]. In this respect, the average size of the pancreatic head has been shown to be significantly larger in a study comparing German patients (median 4.5 cm) and North American patients (median 2.6 cm) undergoing surgery for chronic pancreatitis [5]. The significance of this finding lies in the fact that it explains regional differences in operative procedures used to treat chronic pancreatitis, although the underlying cause is not clear.

## Symptoms, Pathophysiology, and Clinical Problems

An IPHM can cause many clinical symptoms and complications, which in principle constitute the classic complications of chronic pancreatitis. Differential diagnosis and decision making may be complicated as almost all of these symptoms can also be caused by pancreatic head cancer.

One of the most frequently reported symptoms is pain [4,8,9]. Typically, the pain maximum is located to the epigastric area and may radiate to the flanks and back. In some cases, however, back pain may be the primary complaint. The pain can be episodic or continuous, with sudden exacerbations of variable frequency from daily to once in several months, often triggered by alcohol or food intake. Signs of acute pancreatitis-like elevation of serum amylase or lipase and edematous swelling of the pancreatic head are often found associated with severe acute pain attacks, but may also be missing, especially with longer duration of disease. In line with this, there is good evidence from histopathologic and experimental studies that pancreatic pain is not only caused by acute inflammation but also by chronic neuropathy of visceral nerves in the pancreas [8,9]. Importantly, about 50–90% of patients do not become pain-free even 10 years after disease onset [10].

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

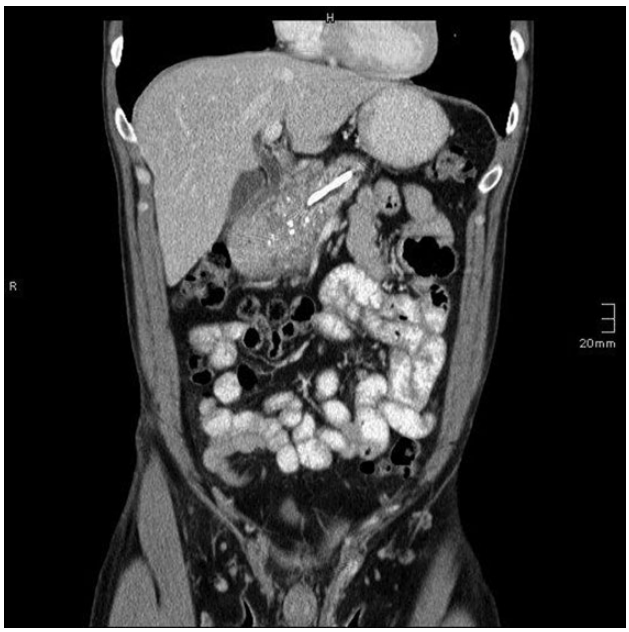


**Figure 43.1** Inflammatory pancreatic head mass. Computed tomography showing a large inflammatory pancreatic head mass in a patient with chronic pancreatitis, with typical diffuse pancreatic calcifications. The impacted dislocated main pancreatic duct stent was removed during surgery.

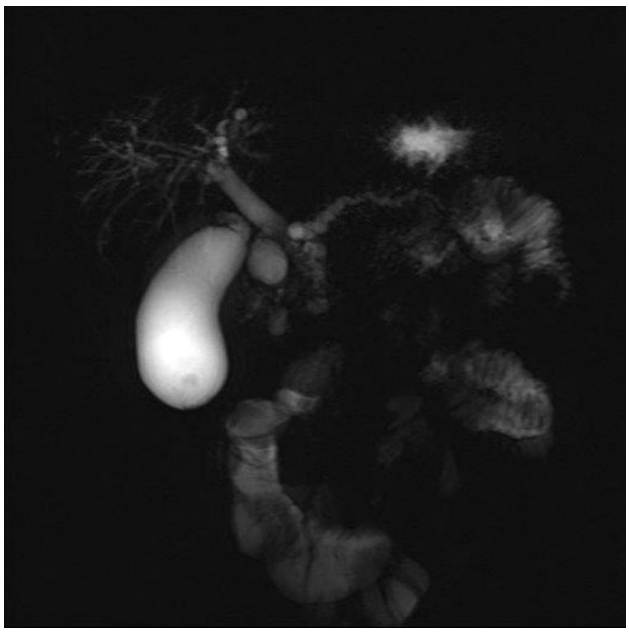

**Figure 43.2** Irregularities of the main pancreatic duct. Magnetic resonance cholangiopancreatography disclosing marked pancreatic duct irregularities and narrowing of the common bile duct in a patient with inflammatory pancreatic head mass.

Episodes of acute pancreatitis can lead to the development of pancreatic pseudocysts or walled-off necrosis (WON) (Fig. 43.3) [11], with secondary complications such as superinfection, hemorrhage, compression of the duodenum or bile duct, internal pancreatic fistula, and

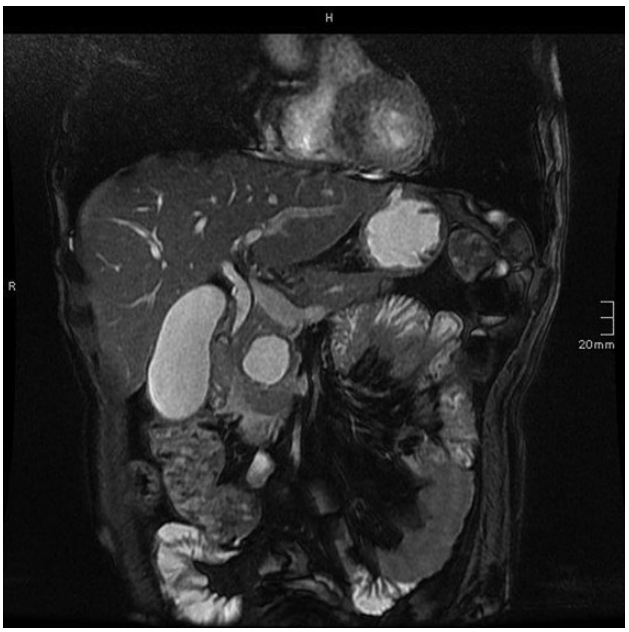


**Figure 43.3** Walled-off necrosis. Magnetic resonance imaging depicting an inflammatory pancreatic head mass with walled-off necrosis which developed after an episode of acute pancreatitis in a patient with chronic pancreatitis.

pancreatic ascites. Biliary stricture is reported in up to 35% of patients [6], leading to jaundice and recurrent cholangitis. Note that subclinical common bile duct (CBD) narrowing can be aggravated to frank obstruction by acute edematous swelling of the pancreatic head during episodes of acute pancreatitis. Maldigestion and malabsorption with steatorrhea, coagulopathy, and malnutrition occurs as a result of persistent cholestasis. Duodenal stenosis is found in about 10% of patients [6], resulting in gastric dilatation, postprandial bloating and vomiting, anorexia, and malnutrition. Malnutrition may be exaggerated by pancreatic exocrine insufficiency. Loss of endocrine function typically occurs later and will affect around 80% of patients [10]. Stenosis and finally thrombotic occlusion of the mesentericoportal vessels is usually a late complication. Occlusion of the splenic vein results in left-sided portal hypertension with development of gastric fundal varices and splenomegaly. As complete occlusion of the portal vein usually develops gradually, extensive collaterals develop around the pancreatic head, a phenomenon called cavernous transformation [6]. Patients with chronic pancreatitis have a tenfold elevated risk (about 3%) of developing pancreatic cancer [10].

## Clinical Workup and Differential Diagnosis

The most important differential diagnoses are pancreatic head cancer and autoimmune pancreatitis. Careful clinical history taking can yield important hints.

Long-standing complaints or recurrent attacks over a period of years rather than months, accompanied by signs of chronic malnutrition, point toward benign IPHM, whereas clinical deterioration over weeks to months with weight loss or new-onset diabetes mellitus are suggestive of malignancy. Jaundice can occur with IPHM but should always prompt efforts to rule out malignancy. Associated autoimmune disease points to autoimmune pancreatitis [12]. Laboratory workup should include serum amylase and lipase activity and carbohydrate antigen 19–9 (CA19–9), as elevated serum enzyme activity indicates an episode of acute pancreatitis, whereas marked elevation of the tumor marker in the absence of acute pancreatitis is suggestive of malignancy. Sensitivity and specificity of CA19–9 for discrimination of chronic pancreatitis from pancreatic ductal adenocarcinoma (PDAC) were reported as 84% and 75% [13]. Serum immunoglobulin G4 (IgG4) can be increased in autoimmune pancreatitis [14]. Because of the risk of tumor spillage and lack of therapeutic consequences, tissue biopsy is not recommended when resectable malignancy is suspected [15].

Cross-sectional imaging by contrast-enhanced computed tomography (CE-CT) or magnetic resonance imaging (MRI) is mandatory. In IPHM, the pancreatic head is enlarged with loss of the lobular parenchymal architecture, calcifications and narrowing of the pancreatic duct (Fig. 43.1). There can be mass-forming lesions in the pancreatic head virtually indistinguishable from pancreatic cancer. Upstream MPD dilatation is often absent in autoimmune pancreatitis [12]. Accuracy of modern cross-sectional imaging for differentiation of IPHM and pancreatic cancer has been reported in the range of 90% [16]. Magnetic resonance cholangiopancreatography can be a valid substitute for invasive endoscopic retrograde cholangiopancreatography (ERCP) to assess configuration of the biliary tree and MPD (Fig. 43.2) and has better ability to distinguish liver metastasis from other lesions [17]. In view of eventual surgical intervention, it is important to assess mesentericoportal vein status and signs of portal hypertension.

## Treatment

Asymptomatic IPHM almost does not exist, although symptom-free periods of weeks to months are common. Indications for invasive treatment are persistent pain or dependence on analgesics, recurrent acute pancreatitis, obstructive cholestasis, gastric outlet obstruction, development of persistent large or symptomatic pancreatic pseudocysts or WON, and suspicion of malignancy. Conservative management is chosen in case of inoperability or as a strategy to avoid operative treatment during a period of recovery, either after an episode of acute pancreatitis or as a bridge to operation.

Medical therapy consists of pain control and eventual substitution of pancreatic enzymes and insulin. It must be stressed that clinical remission of symptoms can be achieved by cessation of alcohol consumption in alcohol-induced chronic pancreatitis. Furthermore, the major role of tobacco smoke as a causal agent has recently been recognized [18,19]. At least initially, surveillance of a pancreatic head mass by cross-sectional imaging should be performed every 3–6 months to rule out malignancy.

Endoscopic stenting of the MPD can be effective to induce remission of pancreatic cysts, pancreatic fistula, and pain by decompression of the MPD. However, two randomized trials and a current Cochrane review show that surgical treatment provides more effective and durable pain control than endoscopic or conservative treatment [20–23]. Another disadvantage of endoscopic therapy is the necessity of regular stent exchange every 3–6 months to prevent cholangitis and tissue overgrowth. When a stent cannot be removed due to incrustation or migration, surgical intervention is needed (Fig. 43.1). Stenting of the CBD for obstructive jaundice is only a short-term option as remission of CBD obstruction can only be expected in cases of acute edematous swelling of the IPHM in acute pancreatitis.

Operative therapy can be divided into drainage and resectional procedures. Although drainage procedures aim at decompression of the MPD by pancreatojejunostomy, removal of the IPHM is the goal of resectional procedures, which can be combined with longitudinal MPD drainage. On surgical exploration, the IPHM is usually found to be heavily indurated and the inflammatory fibrotic process may extend into the peripancreatic tissues, causing heavy adhesions to nearby organs, such as the retropancreatic blood vessels, duodenum, and hepatoduodenal ligament. These conditions render operative procedures involving the pancreatic head very challenging and in rare cases even technically impossible, especially when associated mesentericoportal hypertension leads to diffuse bleeding.

Radical pancreatoduodenectomy with (Longmire–Traverso [24]) or without (Kausch–Whipple [25,26]) preservation of the pylorus is the procedure of choice when malignancy is suspected and offers very good long-term pain control in chronic pancreatitis. For the IPHM, duodenum-preserving pancreatic head resection (DPPHR) was developed by Beger and colleagues [3]. In the subsequently reported Frey procedure [27], pancreatic parenchyma is spared by excoriation of the IPHM without transection at the pancreatic neck, and laterolateral pancreatojejunostomy ensures adequate MPD decompression. The Berne/Farkas modification of the Beger procedure [28] omits pancreatic transection and laterolateral pancreatojejunostomy, while in the Hamburg modification [6], drainage of the MPD is extended by a V-shaped excision along the MPD.

With regard to the evidence for the choice between these surgical options, five randomized controlled trials (RCT) have shown reduced perioperative and short-term morbidity in DPPHR compared to pancreatoduodenectomy, whereas rates of pain relief and long-term outcomes seem to be equal [29]. However, a current Cochrane review of the reported RCT did not confirm significant differences [30]. A drawback of the reported RCT is a relatively low methodological quality [30] and the fact that they were not adequately powered for analysis of long-term results [29]. Equal results were reported from four RCT comparing Beger versus Frey procedures [29], and one RCT involved the Berne modification [31], reporting improved perioperative outcome compared to the Beger procedure.

Pure MPD drainage procedures such as the Puestow–Gillesby [32] (pancreatic left resection with splenectomy and laterolateral pancreatojejunostomy), Partington–Rochelle [33] (laterolateal pancreatojejonostomy) or Izbicki [34] (longitudinal V-shaped excision and laterolateral pancreatojejunostomy) operations do not remove the IPHM. MPD drainage in unselected patients only achieved 50–65% permanent pain control [6], which is inferior to that of pancreatic head resection with 75–95% [35–47]. Although no randomized trial has compared drainage versus resection procedures, drainage procedures are reserved for patients without IPHM. However, in case of mesentericoportal vein occlusion with portal hypertension and cavernous transformation, pancreatic head resection becomes impossible and therapy is limited to operative or endoscopic MPD drainage. Preoperative recanalization of the portal vein can be performed in selected patients with short-segment portal vein occlusion [48]. Gastroenterostomy and hepaticojejunostomy are measures of last choice for biliary or duodenal obstruction.

Correct timing is an important aspect in the management of patients with IPHM. A current systematic review confirms that the best results are achieved by early surgical therapy [49]. Maximum duration of a trial of nonoperative management of IPHM should be 6 months, as optimal operative treatment usually becomes impossible in an advanced stage. In the presence of mesentericoportal vein narrowing or partial thrombosis, elective surgery should be performed as soon as possible, and prophylactic anticoagulation is advocated prior to surgery.

Certain contraindications impede early surgery. Cachexia should be treated by high-caloric nutrition with adequate simultaneous supplementation of pancreatic enzymes and vitamins, and in case of gastric outlet obstruction by jejunal tube feeding, to achieve adequate nutritional status for operation. Elective surgery is also not indicated until at least 3 months have passed since the last episode of acute pancreatitis. Serum pancreatic enzyme activity can be used to monitor acute pancreatitis activity.

On histopathologic workup, IPHM is characterized by fibrotic atrophy of exocrine acinar epithelium, the remaining ductal and islet epithelia becoming "skeletonized" in fibrous connective tissue. Strong inflammatory granulocytic or lymphocytic infiltration is uncommon. In contrast, autoimmune pancreatitis typically shows duct-centric inflammation, with IgG4-positive plasma cells or granulocytic epithelial lesions [12]. As overall tissue organization is heavily disturbed and chronic pancreatitis can be associated with pancreatic intraepithelial neoplasia, distinction from PDAC can be difficult even for experienced pathologists. Intraoperative frozen section examination, at least of the surgical resection margins, is mandatory and in case of any doubt, radical oncologic resection is warranted.

## Conclusions

Chronic pancreatitis with IPHM is a domain of surgical therapy. The main differential diagnoses are pancreatic head cancer and autoimmune pancreatitis. Best results are achieved by resection of the pancreatic head mass with adequate drainage of the pancreatic duct early in the course of the disease, but pancreatic head resection may become impossible in advanced disease. Adequate workup and timing of conservative and surgical therapy ensure successful management.

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# Early Chronic Pancreatitis

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## Introduction

The concept of chronic pancreatitis as a disease was established by Comfort et al. at the Mayo Clinic in 1946. They proposed that chronic pancreatitis occurs when pancreatic fibrosis has been gradually enhanced by repetitive acute inflammation and is characterized by the progressive destruction of the pancreas [1]. Later, the disease concept was described by the Marseille classification [2], the revised Marseille classification in 1984 [3], the Cambridge classification in 1984 [4], and the Marseille–Rome classification in 1988 [5]. In these classification systems, irreversible pancreatic changes associated with chronic pancreatitis were considered to cause progressive or permanent loss of pancreatic endocrine and exocrine functions. Because it has been shown that the mean life expectancy of patients with chronic pancreatitis is short and their rate of contracting pancreatic cancer is high [6,7], preventing the progression of the disease through early diagnosis and early intervention is desirable. In addition, the identification of genes responsible for hereditary pancreatitis, the clarification of the genetic background of idiopathic pancreatitis [8–11], and the discovery of pancreatic stellate cells [12–14] have been reported. Furthermore, it has been shown in an animal model of chronic pancreatitis that the disease conditions can recover completely by early treatment intervention [15,16], suggesting the importance of early intervention as well as early diagnosis. These findings led to the revision of the Clinical Diagnostic Criteria for Chronic Pancreatitis in Japan in 2009 to include a category of early chronic pancreatitis.

## Diagnosis of Early Chronic Pancreatitis

In Japan, the clinical diagnostic criteria were revised in 2009 and published as the "Japanese Clinical Diagnostic Criteria for Chronic Pancreatitis 2009" [17]. Early chronic pancreatitis was defined and incorporated as a disease concept in the new criteria (Fig. 44.1).

Early chronic pancreatitis is a disease that does not satisfy the conditions for the definitive diagnosis or probable diagnosis in the Clinical Diagnostic Criteria for Chronic Pancreatitis 2009 but satisfies two or more of the following conditions: (i) repetitive episodes of upper abdominal pain, (ii) abnormal pancreatic enzyme values in the blood/urine, (iii) pancreatic exocrine dysfunction, and (iv) a history of persistently consuming 80 g of alcohol or more per day. In addition, a patient should also have imaging findings of early chronic pancreatitis, as shown in Box 44.1. With regard to diagnostic imaging for early chronic pancreatitis, findings on either endoscopic retrograde pancreatography (ERP) or endoscopic ultrasound (EUS) are used, with the Cambridge classification [4] as a reference for ERP and the Rosemont classification [18] as a reference for EUS. However, findings from EUS, which can be more easily obtained for outpatients, are valued more than findings from invasive ERP. In addition, the guidelines indicate that diagnostic imaging, including EUS, within 3 months of diagnosis is desirable for suspected cases of chronic pancreatitis and that EUS is essential for diagnosing early chronic pancreatitis [19]. International consensus guidelines for chronic pancreatitis are currently being created. In the near future international criteria for diagnosis of early chronic pancreatitis will be needed.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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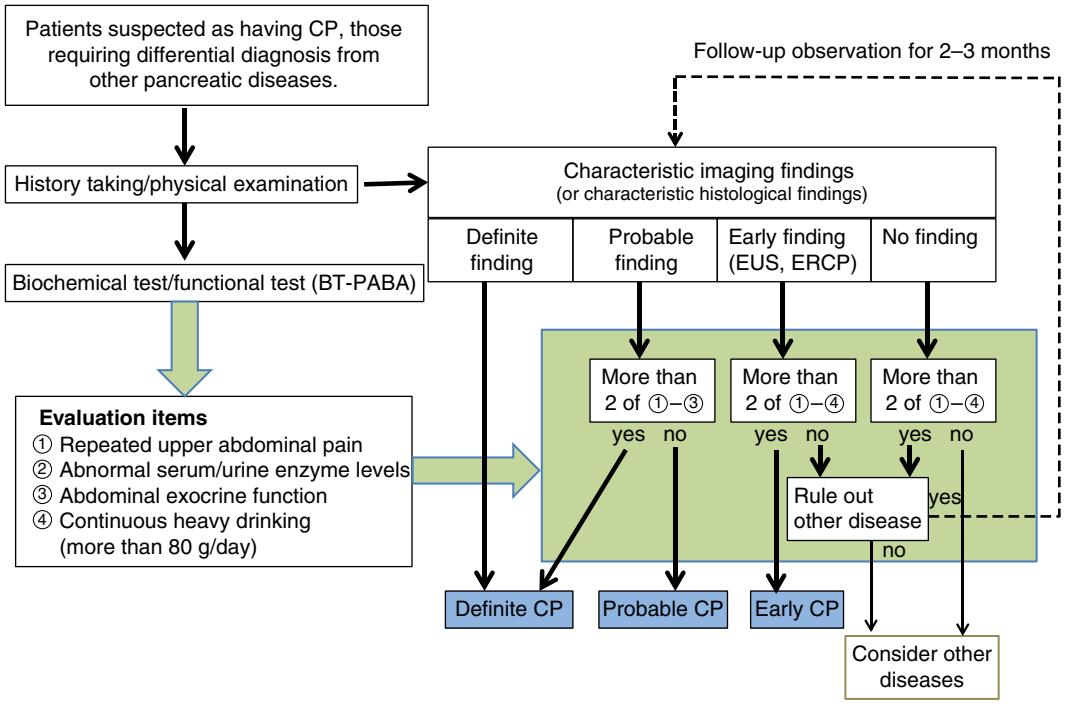


**Figure 44.1** Diagnostic path for chronic pancreatitis. The figure shows a schematic flow diagram for the diagnosis of chronic pancreatitis (CP). EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography. Source: Adapted from Ito et al. 2015 [19].

**Box 44.1 Imaging findings required for a diagnosis of early chronic pancreatitis**

**a. More than two features present from among the following seven features of EUS findings, including at least one of (1) through (4)**

1) Lobularity with honeycombing
2) Lobularity without honeycombing
3) Hyperechoic foci without shadowing
4) Stranding
5) Cysts
6) Dilated side-branches
7) Hyperechoic MPD margin

**b. Irregular dilatation of more than three duct branches on ERCP findings**

Either a or b is required for diagnosis

ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; MPD, main pancreatic duct.

*Source:* Adapted from Shimosegawa et al. 2010 [17].

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# Hereditary Chronic Pancreatitis: Molecular Pattern, Clinical Consequences, and Management Principles

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## Clinical and Genetic Definitions

Hereditary pancreatitis is a syndrome that encompasses acute pancreatitis, recurrent acute pancreatitis (RAP), and chronic pancreatitis. A new mechanistic definition of chronic pancreatitis is useful for framing hereditary pancreatitis as a process extending from asymptomatic risk to end-stage disease. Chronic pancreatitis is now defined both by its essence and its character as "a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress" [1]. In addition, "Common features of established and advanced chronic pancreatitis include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia" [1]. The definition was designed to assist in the early diagnosis of chronic pancreatitis, the prognosis, and in the type and timing of potential therapies.

Hereditary pancreatitis is defined by clinical presentation in a family or by genetic test results in an affected individual. In families, hereditary pancreatitis is defined as two or more first-degree relatives or three or more second-degree relatives with RAP or chronic pancreatitis in two or more generations, consistent with an autosomal dominant inheritance pattern [2, 3]. Less commonly, families may appear to follow alternative inheritance patterns (e.g., autosomal recessive and complex). Alternatively, hereditary pancreatitis can be diagnosed in an individual with pancreatitis and a known pathogenic germline mutation, regardless of family history. Of importance, the penetrance of *PRSS1* hereditary pancreatitis is incomplete and, therefore, identification of a pathogenic *PRSS1* mutation in an asymptomatic individual is not sufficient for a diagnosis but does indicate high risk. Some families presenting with hereditary pancreatitis have pathogenic variants in the serine protease inhibitor Kazal type 1 gene (*SPINK1*), the cystic fibrosis transmembrane conductance regulator gene (*CFTR*), *SPINK1* plus *CFTR*, the chymotrypsin C gene (*CTRC*), or a more complex genotype [4]. Therefore, the absence of a pathogenic *PRSS1* variant does not preclude the diagnosis of hereditary pancreatitis in a family. A diagnosis of hereditary pancreatitis should always be considered for patients with idiopathic pancreatitis or early-onset pancreatitis, or in a family with multiple affected individuals.

Familial pancreatitis refers to the occurrence of pancreatitis of any cause in a family with an incidence greater than would be expected by chance alone. Familial pancreatitis does not follow an observable monogenic pattern of inheritance. Kindreds with familial pancreatitis may have shared genetic and/or environmental (e.g., alcohol, smoking, stress) risk factors that predispose them to pancreatitis above the general population risk.

## Epidemiology

Hereditary pancreatitis is a rare genetic disorder. In 1952, Comfort and Steinburg described a large family with hereditary pancreatitis [5]. Since this initial report, hundreds of hereditary pancreatitis kindreds have been identified in several regions in the United States [5–7] and Europe [8–10]. A few families have also been identified in Japan [11, 12], Korea [13], China [14, 15],

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Malaysia [16], South America [17, 18], and Thailand [19]. The vast majority of hereditary pancreatitis kindreds identified in the United States are of European ancestry linked to large pedigrees (>500 people), suggesting founder effects (DC Whitcomb, unpublished data). However, haplotype analysis on local clusters of individuals with *PRSS1* R122H mutations in northern Germany suggested the presence of a mutation hotspot and excluded a single founder effect [20]. The reason that hereditary pancreatitis is rare in African and Asian populations is unknown.

The prevalence of hereditary pancreatitis differs by geographic region; hereditary pancreatitis has been observed most frequently in the United States and Europe. A national series of hereditary pancreatitis in France estimated a population prevalence of at least 0.3 per 100,000 [21]. In Denmark, 1% of persons with pancreatitis of unknown etiology were found to be positive for a *PRSS1* mutation [22]. The fraction of chronic pancreatitis patients with hereditary pancreatitis varies greatly from region to region and country to country as a result of founders originating from multiple generations in the past.

## Clinical Presentation

Hereditary pancreatitis typically presents with acute pancreatitis in early adolescence, with a high risk of progression to chronic pancreatitis by early adulthood (Fig. 45.1). In hereditary pancreatitis, the phenotypic features are confined to the pancreas, whereas *CFTR*-related disorders affect multiple organs as seen in cystic fibrosis. In patients who develop chronic pancreatitis, major comorbidities include pancreatic exocrine insufficiency, diabetes mellitus, and chronic pain syndromes. In comparison to chronic pancreatitis of other etiologies, hereditary pancreatitis has earlier age of onset and appears to have higher cumulative risks for exocrine and endocrine failure in patients that develop chronic pancreatitis, as well as increased risk for pancreatic cancer.

The disease penetrance for a *PRSS1* mutation has been consistently estimated as ~80% [9, 10, 23, 24]. However, a national series of *PRSS1*-tested patients in France identified a penetrance of 93% [21]. Of note, estimates of penetrance may be inflated by biased study ascertainments. This is evidenced by the discovery of an R122H *PRSS1* kindred with low penetrance of pancreatitis [18]. Penetrance may also differ by type of mutation and presence of modifying risk factors. Assessment of six families in northern Spain identified a penetrance of 40.9% for the R122C *PRSS1* mutation [25]. Lifespan is not reduced as compared to the general population, except in patients who develop pancreatic adenocarcinoma [26].

### Acute Pancreatitis

The median age of onset of acute pancreatitis is 10–12 years [10, 21]. Some studies have shown that the age of symptom onset is earlier in R122H *PRSS1* carriers compared to N29I carriers and mutation negative patients [10, 23, 27]. A multicenter European (EUROPAC) study of 418 subjects from 112 families identified an age of onset of 10 years for the *PRSS1* R122H mutation, 14 years for the N29I mutation, and 14.5 years in patients without an identified mutation [10]. Severity, length, and frequency of attacks are variable and can vary dramatically by family. In one large kindred, 58% of *PRSS1* R122H subjects were <5 years at the age of symptom onset [23]. Shared modifier genes and environmental factors in families contribute to age of onset and severity. For example, disease onset in four twin pairs differed by median of 1 year (range 0–2.4 years) as compared to 7 years (range 2–15 years) in a nonsibling comparison group matched for mutation, gender, and age [24].

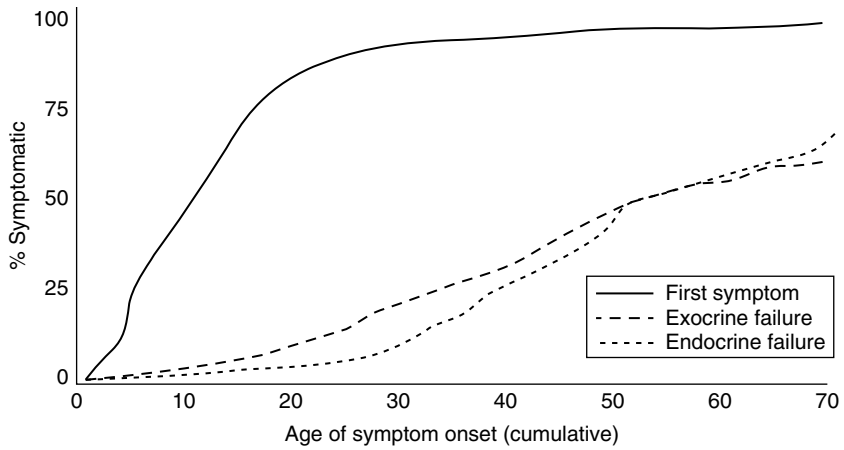


**Figure 45.1** Age at onset of first symptoms, pancreatic exocrine insufficiency and pancreatic exocrine insufficiency. *Source:* Data from [10].

At least 83% of patients experience epigastric abdominal pain [21]. The number of reported hospitalizations for acute pancreatitis varies by family and mutations status, with nearly 90% of affected individuals reporting more than five hospitalizations [10, 23, 27, 28]. The EUROPAC study found a significant reduction in hospital admission rates for patients with a *PRSS1* N29I mutation (0.19 per year) as compared to patients with a *PRSS1* R122H mutation (0.33 per year) [10]. However, the difference in number of attacks between patients with an N29I mutation (1.4 per year) and an R122H mutation (2 per year) was not significantly different, suggesting that the N29I mutation results in less severe attacks [10]. The same study found that the majority of attacks are ≤7 days in length [10], but smoldering pancreatitis and/or persistence of pain that lasts weeks or months has been reported in patients with hereditary pancreatitis [2].

### Chronic Pancreatitis

RAP progresses to chronic pancreatitis by the second or third decade of life in the majority of patients with hereditary pancreatitis. Rate and severity of pancreatic fibrosis and parenchymal destruction is highly variable, with a cumulative incidence of ~50% in a lifetime (Fig. 45.1). A trend exists between the number of attacks and degree of fibrosis, and this process is highly influenced by modifying factors. A study on pancreas histopathology in 10 patients with *PRSS1* hereditary pancreatitis demonstrated progressive lipomatous atrophy and adipose replacement of peripheral parenchyma [29].

### Pancreatic Exocrine Insufficiency

Progression of inflammation and fibrosis eventually leads to pancreatic exocrine insufficiency in a significant subset of patients. Pancreatic exocrine insufficiency occurs when the pancreas cannot supply a sufficient quantity of digestive enzymes to the intestines, leading to maldigestion. This is believed to occur with the loss of about 90% of pancreatic exocrine function [30]. The EUROPAC study identified cumulative risks for exocrine failure of 8.4% at 20 years, 37.2% at 50 years, and 60.2% at 70 years, with a median time to malabsorption of 53 years [10]. No significant difference in time to malabsorption was found between men and women [10].

### Diabetes Mellitus

As with other forms of chronic pancreatitis, chronic inflammation and progressive fibrosis also lead to islet cell injury. Glucose intolerance progresses to pancreatic endocrine insufficiency from loss of insulin-secreting beta cells. However, these patients also lose alpha cells so that they are at high risk for hypoglycemia. Diabetes mellitus from pancreatic exocrine disease and loss of the entire islets is classified as type 3c [31]. The danger of hypoglycemia is enhanced by untreated pancreatic exocrine insufficiency, since the ingestion of nutrients is not well coordinated with digestion and absorption. The cumulative risks for endocrine failure are 4.4% at 20 years, 47.6% at 50 years, and 79.1% at 80 years [10]. Median time to development of diabetes mellitus has been estimated to be 53 years and is not significantly influenced by gender and mutation status [10].

### Pancreatic Cancer

Hereditary pancreatitis is associated with a >50-fold increased risk for pancreatic adenocarcinoma [10, 26, 32–36]. Cumulative risk for pancreatic cancer at 70 years has been estimated to be as high as 40% to <54% [10, 21, 34]. The risk for pancreatic cancer is highest in smokers and individuals with diabetes mellitus. Smokers with hereditary pancreatitis have about a twofold increased risk for pancreatic cancer, with development of cancer 20 years earlier than nonsmokers [35]. The increased risk for pancreatic cancer appears to result from chronic inflammation rather than a *PRSS1* mutation itself, since all forms of chronic pancreatitis are associated with pancreatic cancer [37–40]. Early-onset pancreatitis in hereditary pancreatitis is one of the strongest known risk factors for pancreatic cancer.

Incidence of pancreatic cancer varies extensively between hereditary pancreatitis families, and some families have high incidences of pancreatic cancer in the absence of clear environmental factors, suggesting the presence of risk and/or protective variants. Screening for pancreatic cancer is recommended for patients with a known mutation associated with hereditary pancreatitis [41], but the approach remains unclear since hereditary pancreatitis is associated with significant morphologic changes in the pancreatic gland, making imaging approaches challenging.

## Management

As with pancreatitis of nongenetic etiology, management is aimed at prevention, reduction of symptoms such as fibrosis, pancreatic exocrine insufficiency and pancreatic endocrine insufficiency, and alleviation of pain. The approach should be based on targeting the underlying genetic factors, minimizing environmental stressors, and considering new therapeutic interventions as indicated. Alcohol, emotional stress, and dietary fat can exacerbate pancreatitis and should be avoided [9, 21]. Patients should also be counseled to refrain from smoking, which

doubles the already increased risk for pancreatic cancer [35]. Antioxidants may reduce pain in a subset of patients [42, 43]. Common recommendations include a low-fat diet with multiple small meals a day and proper hydration to reduce the risk of an attack, but these recommendations are not based on strong evidence.

Pancreatic exocrine insufficiency should be anticipated and managed with early initiation of pancreatic enzyme replacement therapy. The diagnosis of pancreatic exocrine insufficiency currently relies on clinical suspicion from abdominal bloating, diarrhea, steatorrhea, deficiency of fat-soluble vitamins or vitamin B12, or unexplained weight loss. The most common diagnostic tests include measuring low levels of human fecal elastase, low serum trypsinogen levels, or clinical response to a trial of pancreatic enzyme replacement therapy.

Diabetes mellitus is common both in patients with pancreatitis and in the general population. In hereditary pancreatitis, type 3c diabetes mellitus typically develops years after the onset of chronic pancreatitis [44]. The diagnosis is challenging, and standardized protocols are not widely accepted. However, the clinical context of advanced chronic pancreatitis, especially with pancreatic exocrine insufficiency, should indicate caution and a multidisciplinary approach involving endocrinologists and pancreatologists [44]. The destruction of the islets may limit the use of some antidiabetic medications, and the use of insulin must be balanced with the ingestion and digestion of the meal, which may require the addition of pancreatic enzyme replacement therapy.

In the absence of pancreatic cancer, the primary indication for surgery is pain [45, 46]. Total pancreatectomy with islet cell autotransplantation (TPIAT) can be considered in younger patients with intractable, narcotic-dependent pancreatic pain [47, 48]. Total pancreatectomy without islet autotransplantation can be considered in older patients with chronic pancreatitis for 20 years or more to reduce pain and as a last resort to reduce the risk of developing pancreatic cancer [45, 49]. The need and timing of this radical procedure requires both experience with the procedure and clear prognostic understanding of what will happen with and without TPIAT.

## Molecular Genetics

In 1996, a missense mutation in the cationic trypsinogen gene (*PRSS1*) was identified in a large hereditary pancreatitis family [50]. Mutations in *PRSS1* have since been identified in 65–100% of hereditary pancreatitis kindreds with an estimated penetrance of 80%. Since this discovery, additional genes associated with recurrent acute and chronic pancreatitis have been identified, particularly *SPINK1*, *CFTR*, and *CTRC* [51–54] (Tables 45.1 and 45.2). Other important genes that have been associated with chronic pancreatitis include *CLDN2* [55–57], *CASR* [3, 58], *CTSB* [59], *CPA1* [51, 55–57, 60], and *GGT1* [61]. Disease mechanisms for many of the genes associated with pancreatitis are complex, and gene–gene and gene–environment interactions are not fully defined [4, 51].

### *PRSS1*

Cationic trypsinogen is the most abundant isoform of trypsinogen (~65%), followed by anionic trypsinogen (*PRSS2,* ~30%) and mesotrypsinogen (*PRSS3*, ~5%) [62].

**Table 45.1** Genes associated with pancreatitis.

| Gene | Chromosome | Type of mutation | Mechanism |
|---|---|---|---|
| *CTRC* | 1 | Loss of function | Diminished trypsin degradation in pancreas |
| *CASR* | 3 | Loss of function; inappropriate localization | Elevated pancreatic calcium levels<br>Hypothesized premature activation of trypsin |
| *SPINK1* | 5 | Loss of function | Diminished trypsin degradation in pancreas |
| *PRSS1* | 7 | Gain of function<br>Loss of function | Premature activation of trypsinogen in pancreas<br>Hypothesized misfolding-induced endoplasmic reticulum stress; associated with nonalcoholic, early-onset CP |
| *CFTR* | 7 | Loss of function | Loss of or diminished bicarbonate conductance leads to detainment of trypsinogen in the pancreas |
| *CPA1* | 7 | Loss of function | Hypothesized misfolding-induced endoplasmic reticulum stress; associated with nonalcoholic, early-onset CP |
| *CTSB* | 8 | Unknown—hypothesized gain of function | Hypothesized to induce premature activation of trypsinogen |
| *CLDN2* | X | Altered regulatory element | Unknown; associated with alcoholic CP |

CP, chronic pancreatitis.

**Table 45.2** Genotype–phenotype correlations and multiorgan syndromes.

| Genotype (variants) | Phenotype (syndromes) | Comment |
|---|---|---|
| *PRSS1* | Hereditary pancreatitis | Genetic counseling recommended |
| *CFTR*$^{sev}$/*CFTR*$^{sev}$ | CF | Manage with a CF center |
| *CFTR*$^{sev}$/*CFTR*$^{m\text{-}v}$ | Atypical CF | Manage with a CF center |
| *SPINK1*/*SPINK1* | Familial pancreatitis | Usually progresses to severe CP |
| *CFTR*$^{bicarb}$/*CFTR*$^{any}$ | Pancreas/sinus/CBAVD | Newly defined syndrome |
| *CFTR*$^{any}$/*SPINK1* | RAP/CP | Pancreas only |
| *CTRC*/*SPINK1* | RAP/CP | Pancreas only—not well studied |
| *CASR*/*SPINK1* | RAP/CP | Pancreas only—not well studied |

*CFTR*: sev, severe mutations (typically functional class I–III); m-v, mild-variable mutations (typically *CFTR* functional class IV); bicarb, bicarbonate conductance-disrupting variant (e.g., R75Q); any, either severe, mild-variable, or bicarbonate-disrupting variants; CF, cystic fibrosis; CP, chronic pancreatitis; RAP, recurrent acute pancreatitis; CBAVD, congenital bilateral absence of the vas deferens.

Trypsinogen is the inactive zymogen of trypsin, a digestive enzyme and regulator of all pancreatic zymogens, except amylase and lipase. The trypsinogen activation peptide maintains the inactive enzyme until it is cleaved by enterokinase or another trypsin, generally in the duodenum. Self-destruction (autolysis) occurs at R122, which is located on the single chain that links the two globular domains of trypsin [63, 64]. Two calcium-binding pockets serve as "on–off" switches in response to calcium concentrations, inducing distinct conformational changes. Increased calcium concentrations facilitate trypsin activation, whereas reduced calcium levels permit autolysis [65].

*PRSS1* gain-of-function mutations fall into two categories: (i) premature activation of trypsin in the pancreas or (ii) resistance to degradation [27, 66, 67]. Archer et al. confirmed the pathogenicity of *PRSS1* R122H mutations in transgenic mice that presented with early-onset acinar cell injury and dedifferentiation, inflammatory cell infiltration, and progressive pancreatic fibrosis [68]. In humans, elevated levels of pancreatic trypsin lead to progressive lipomatous atrophy of the pancreatic parenchyma and adipose replacement [29]. Fibrosis is thin and loosely packed, in contrast to alcoholic and obstructive chronic pancreatitis [29]. Many of the less common *PRSS1* variants found in patients with pancreatitis do not appear to be gain-of-function mutations. Instead, they may represent coding region variants causing protein misfolding, and triggering an unfolded protein stress response that drives fibrosis in a poorly defined way [69].

The most common *PRSS1* mutations are R122H and N29I (90%), previously designated as R117H and N21I by the chymotrypsin numbering system [10, 21, 70]. Less common mutations include A16V, R122C, N29T, D22G, and K23R. Mutations have primarily been identified in exons 2 and 3, but rare variants have also been identified in the 5′ UTR, introns 1–4, and exons 4 and 5 (see www.pancreasgenetics.org). Copy number variations of the *PRSS1-PRSS2* locus have also been associated with chronic pancreatitis [71].

### *SPINK1*

The serine protease inhibitor Kazal type 1 (*SPINK1*; *PST1*) is a trypsin inhibitor secreted from pancreatic acinar cells. Loss-of-function mutations in *SPINK1* reduce its protective function and predispose to pancreatitis [72]. Mutations are found in ~2% of the population and confer a 12-fold increased risk for pancreatitis [72, 73]. Nevertheless, fewer than 1% of *SPINK1* carriers develop pancreatitis. Biallelic loss of function mutations in *SPINK1* may lead to autosomal recessive pancreatitis. However, the majority of affected patients with *SPINK1* mutations are heterozygous, indicating the presence of complex gene–gene and gene–environment interactions [74]. For example, *SPINK1* can act as a disease modifier, and compound heterozygosity for pathogenic variants in *SPINK1/PRSS1* and, more commonly, *SPINK1/CFTR* has been reported [53, 75].

*SPINK1* mutations have been detected in 16–23% of patients with idiopathic chronic pancreatitis [72, 76, 77]. The most common high-risk haplotype identified in the United States and Europe is *SPINK1* N34S [72]. The *SPINK1* IVS3 + 2 T > C splicing variant is common in Japan, China, and Korea [78–80].

### *CFTR*

Mutations in the cystic fibrosis transmembrane conductance regulator (*CFTR*) are more common among patients with idiopathic chronic pancreatitis [81–83]. *CFTR* mutations may impair both chloride and bicarbonate conductance (e.g., severe mutations) or only

bicarbonate conductance [84]. Homozygosity or compound heterozygosity for two "severe" *CFTR* mutations generally causes cystic fibrosis [85], whereas "mild-variable" or other mutations are associated with RAP, chronic pancreatitis, and/or other CFTR-related disorders [86]. *CFTR* carriers that develop pancreatitis are also likely to have an additional genetic (e.g., *SPINK1, CTRC*) or other (e.g., pancreas divisum) risk factor [53, 75, 87, 88]. CFTR-associated pancreatitis is considered in Chapter 47.

### *CTRC*

Chymotrypsin C (CTRC) is a digestive enzyme and the primary regulator of trypsin. The action of chymotrypsin C is twofold and dependent on calcium concentrations. In the calcium-rich duodenum, chymotrypsin C promotes trypsinogen activation, but in solutions with lower calcium concentrations, it mediates trypsin degradation [89]. As with *SPINK1*, chymotrypsin C is believed to protect the pancreas from premature trypsin activation, with genetic defects increasing the risk of trypsin-mediated pancreatitis [90, 91]. Two mutations, R254W and K247_R254del, were found to be overrepresented in patients with idiopathic or hereditary chronic pancreatitis [90, 92]. The c.180 T > G variant has been identified in about 10.8% of persons of European ancestry in North America and moderately increases the risk of progression from recurrent acute to chronic pancreatitis, particularly in the presence of alcohol, tobacco, or *PRSS1*/*SPINK1* mutations [93]. The independent effects of pathogenic *CTRC* variants appear to be low, but they clearly increase the risk of chronic pancreatitis in the context of other risk factors such as pathogenic *CFTR* variants [53], and can contribute to familial clustering of chronic pancreatitis cases.

## Genetic Testing and Counseling

When a patient or family is suspicious for hereditary pancreatitis, a (minimum) three-generation pedigree should be collected, including family history of pancreatitis, age of onset, age at diagnosis for multiple pancreatic episodes, and pancreatic cancer [94]. Other information valuable for assessment of a family includes smoking and alcohol exposure, diabetes mellitus, pancreatic insufficiency, male infertility, cystic fibrosis chronic sinusitis, and nasal polyps [94]. Calculation of risk in a family depends on genotype, pattern of inheritance in the family, and environmental exposures (e.g., tobacco, alcohol).

Indications to offer genetic testing in a symptomatic patient include unexplained RAP and/or chronic pancreatitis, a first- or second-degree relative with pancreatitis, and/or unexplained pancreatitis in a child requiring hospitalization [95]. Genetic testing is commercially available for *PRSS1, SPINK1, CFTR,* and *CTRC,* including full gene sequencing. Deletion/duplication analysis may be considered in a proband if a mutation is not identified from sequencing or targeted mutation analysis.

Genetic testing should always be preceded and followed by appropriate genetic counseling [96, 97]. Results may have implications for patient risk, risk to other family members, and family planning [96, 98]. Another concern for genetic testing in this patient population, especially in the United States, is insurance discrimination [98]. The Genetic Information Nondiscrimination Act of 2008 (GINA, Pub. L, 110–233) protects against genetic discrimination in health insurance and employment in the United States, but does not cover life, disability, or long-term care insurance. Patients and families should understand the benefits, limitations, and costs of genetic testing before the test is ordered [97]. Therefore, clinicians must understand the consequences of genetic testing and should provide counseling directly or refer patients to a genetic counselor to obtain appropriate informed consent.

Genetic testing in a symptomatic patient can clarify etiology and provide information on risk for related complications, such as pancreatic cancer. Identification of a responsible mutation may clarify risk for family members and provide information relevant to family planning. *PRSS1*-related hereditary pancreatitis follows an autosomal inheritance pattern, and each child of a parent with a *PRSS1* mutation has a 50% or 1 in 2 chance of inheriting the deleterious allele. About 80% of individuals who inherit a *PRSS1* mutation develop pancreatitis. Therefore, each child of a parent with a *PRSS1* mutation has a ~40% chance of developing hereditary pancreatitis. However, variation in penetrance and severity exists between hereditary pancreatitis kindreds, and family history should always guide interpretation of results and risk calculation. Identifying a responsible genetic mutation in a family may also expedite diagnosis of family members and prevent unnecessary evaluation for other etiologies.

Predictive genetic testing in an asymptomatic individual is available when a mutation has been identified in a close family member. Testing for this mutation can clarify risk to develop pancreatitis and risk to descendants. Genetic testing may also identify family members that would benefit from lifestyle interventions to reduce risk and severity, such as avoidance of alcohol, smoking, and fatty foods.

A negative test result in a patient from a family with a known mutation reduces but does not remove the risk for hereditary pancreatitis. Families may share additional, unidentified risk factors that predispose to pancreatic disease. Furthermore, not all families in which

hereditary pancreatitis appears have an identifiable mutation in *PRSS1*, *SPINK1*, *CFTR*, or *CTRC*. In a family without an identifiable mutation, genetic testing of asymptomatic family members will be uninformative and discussions of risk must be tailored according to the presentation of disease within the family.

### Genetic Testing in Children

The decision to pursue genetic testing in a child is the responsibility of the parents or legal guardian. When a child is 7 years or older, the child should provide assent for genetic testing. Testing of a symptomatic child can explain or confirm the diagnosis of pancreatitis and prevent unnecessary further evaluations.

Predictive genetic testing for hereditary pancreatitis is generally not recommended for patients less than 16 years of age [95]. There are no clear medical benefits to identifying asymptomatic carriers at a young age, and waiting to pursue testing gives the patient the opportunity to make an informed adult decision [96, 99]. Predictive testing to identify children who would benefit from diet, lifestyle, medication, or surveillance interventions has been advocated [99]. However, avoidance of pancreatitis risk factors, particularly fatty foods, alcohol, tobacco, and stress, are advised for all children regardless of mutation status [96].

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# 46

# Epidemiology and Pathophysiology of Tropical Chronic Pancreatitis

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## Introduction

In 1937, Kini [1] published a report on chronic calcific pancreatitis from India and in 1954 similar findings in autopsy studies were reported from the south of India [2]. Although the features presented in these reports were strikingly similar to the report on 45 malnourished patients from Indonesia published a couple of decades later, the credit for describing tropical (chronic) pancreatitis (TCP) as a distinct entity rests with Zuidema [3,4]. These patients were from poor families and were suffering from protein calorie malnutrition.

GeeVarghese [5,6] provided detailed descriptions of the features that constituted TCP based on his analysis of patients in Kerala, southern India. This body of work now forms the framework on which our understanding of TCP resides.

TCP is considered a distinct subtype of chronic pancreatitis, comprising calcifying, nonalcoholic chronic pancreatitis that affects younger, generally malnourished individuals from the tropical regions of Asia [7–11], Africa [12–15], and South America [16,17]. A male predominance was also noted [18–20]. There have been occasional reports of the disease from developed nations, usually due to diagnosis in migrants arriving from the developing world [21]. In the past, the entity has been given various names, including tropical calcific pancreatitis, tropical pancreatic diabetes, nutritional pancreatitis, juvenile pancreatitis syndrome, Afro-Asian pancreatitis, tropical calculous pancreatopathy, and fibrocalculous pancreatopathy, or fibrocalculous pancreatic diabetes (FCPD). However, the name most commonly employed today is tropical chronic pancreatitis [22,23].

GeeVarghese described the natural history of TCP as "recurrent abdominal pain in childhood, diabetes around puberty and death at the prime of life" [5]. Barman and colleagues presented the triad of symptoms that comprised TCP, namely, abdominal pain, maldigestion and steatorrhea, and diabetes mellitus [24].

To date, there have been few large-scale epidemiologic studies on the prevalence of TCP. A field study from Kerala in southern India, involving 28 567 inhabitants, determined the prevalence of TCP to be 1:793 in that region [8] based on well laid out criteria for diagnosis of the disease. The study revealed that contrary to previous hospital reports, TCP in Kerala appeared to have a female preponderance (male:female ratio of 1:1.8), older age at disease onset (mean 23.9 years), and evidence of milder disease. Early attempts to understand the nature of the disease had included hospital studies and a couple of monographs published by GeeVarghese [5,22] based on his experience of more than 1500 patients with the disease. Balaji et al. [8] pointed out that the findings in these prior studies were potentially influenced by need for healthcare (patients presenting only when symptomatic) as well as access to healthcare being preferentially available to males.

A large nationwide study from India that included 1086 chronic pancreatitis patients has determined that that idiopathic chronic pancreatitis is now the most common subtype of the disease in the country (accounting for 60% of cases) [25]. These findings are not too dissimilar from those of a survey in the Asia-Pacific region which found that the 70% of patients from India and China could be labeled as having idiopathic chronic pancreatitis [9]. Interestingly, in the study by Balakrishnan

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Companion website: www.wiley.com/go/beger/thepancreas

et al. [25], when well-defined criteria for TCP were applied, TCP was found in only 3.8% of patients. The authors conjectured that these findings may reflect overrepresentation of the disease owing to the interchangeable use of the terms "idiopathic chronic pancreatitis" and "tropical chronic pancreatitis," with the possibility that the true incidence of the TCP lies somewhere in between this wide variation.

A declining incidence of TCP has also been noted in other studies from India [26,27]. Whether this is a reflection of improving socioeconomic conditions accompanied by improved nutrition [25,28], an increase in smoking and alcohol consumption among young people [26], or simply a better definition of the entity "idiopathic chronic pancreatitis," leading to more individuals fitting these criteria rather than TCP [29], remains to be determined.

## Pathophysiology

The initial documentation of cases of TCP in malnourished patients from the tropics and from poorer populations [1,4] instinctively led researchers to focus on dietary components as a cause for the disease [30]. Over the years, detection of TCP in apparently healthy individuals with a normal nutritional status (as per their body mass index [BMI]) [31,32] led to micronutrient deficiency being more intensively investigated. Eloquent studies teasing out pathologic changes [33] and genetic mutations and comparing these with other subtypes of chronic pancreatitis have heralded a possibly more objective approach to the understanding of the entity [34,35].

### Pathology

Gross appearance of the gland depends on the duration of disease, degree of fibrosis, the presence of cysts, and location and size of calculi [36]. With the passage of time, the gland undergoes uneven fibrosis and atrophy, often leading to an eccentric ductal location [23] with the gland often appearing finger-like with a nodular and irregular surface [37].

One of the hallmarks of TCP is the presence of large calculi composed of 95.5% calcium carbonate (mainly in the form of calcite [38]), a small amount of calcium phosphate and traces of magnesium, urate, and oxalate distributed throughout the ductal system varying in color, shape, and size [23]. The calculi possess an amorphous nidus and a cryptocrystalline periphery [39]. The biochemical and structural nature of calculi in TCP is similar to those in other subtypes of chronic pancreatitis [23]. The larger stones tend to form towards the head, with their size decreasing towards the tail region.

On microscopic examination, the hallmark of TCP is the degree of intralobular fibrosis [33], which is uniform throughout the pancreatic parenchyma [40]. Nair [36] found that TCP was characterized by a lack of inflammation, and suggested that the name "tropical calcific pancreatopathy" would be more appropriate. However, these findings have not been corroborated by others. Shrikhande and colleagues [33] compared the histologic appearance of TCP with that of alcoholic chronic pancreatitis (ACP) and idiopathic chronic pancreatitis and revealed similar histologic features and a comparable inflammatory cell reaction in all three subtypes, although the extent of the pathologic change was variable in the individual types. The degree of endophlebitis and plasma cell density was significantly higher in TCP [33]. This finding of plasma cell infiltration of the pancreas is in keeping with the report of Nagalotimath, who also found a lymphocyte infiltration mainly around the ducts [37]. Cyriac and colleagues [41] have recently demonstrated that stellate cell activation occurs in a similar manner to other subtypes of chronic pancreatitis. Total fatty replacement of parenchyma has been noted to be a striking feature in TCP, and is seen exclusively in patients with diabetes with gross atrophy of the islets of Langerhans [40]. Moreover, in patients with established diabetes secondary to TCP (FCPD), histopathologic examination and immunohistochemistry have revealed varying extents of acinar atrophy and parenchymal destruction [23], along with a lack of alpha and beta cells and a reduction in glucagon positivity, and areas of nesidoblastosis [37,42].

An interesting observation in the pathologic assessment of tissues of patients with TCP when compared with alcoholic and idiopathic chronic pancreatitis is the increase in neural tissue and neural alterations associated with progression of the disease towards a stage amenable to surgery [43], a hallmark of pain accompanying chronic pancreatitis [44]. It is not only the neural alterations that are identical but other histologic aspects including the degree of endophlebitis, overall density of plasma cells, and inflammatory cell reaction, suggesting that independent of the underlying etiology, the pathologic changes accompanying chronic pancreatitis eventually reach a common immunologic stage beyond which chronic pancreatitis appears to progress as a single distinctive entity [33].

### Nutrition (Including Cassava)

The initial reports of TCP originating from regions in the developing world coupled with the clinical picture of young emaciated patients, intuitively led clinicians to focus on the nutritional aspect, or more specifically, protein calorie malnutrition [4,12,45]. However, over the years, a more objective approach to investigating the role

of malnutrition as a causative agent has led pancreatologists to infer that malnutrition in itself is not the main cause for TCP [46] and the nutritionally deprived state may rather be an effect of the malabsorption associated with disease [47,48]. Patients with kwashiorkor do not develop features of TCP [23,49]. Moreover, although malnutrition exists in many countries in the world, there are no reported cases of TCP/FCPD from some of them [50]; on the other hand TCP cases have been reported even among patients from well-nourished families [23]. Nonetheless, whether it is cause or effect, malnutrition remains a major issue in TCP and addressing it in its entirety forms an essential part of the work-up and management of patients with TCP [51].

Although malnutrition may not be the only etiologic factor in the causation of TCP, it is very likely that micronutrient deficiency, along with varying degrees of macronutrient deficiency and oxidant stress are cofactors in the causation of TCP.

#### Cassava Toxicity

Cassava (tapioca, *Manihot esculenta* Crantz) was implicated as a cofactor in the causation of TCP based on three factors: (i) the observation that the geographic area of Kerala where cassava is the staple diet of people of low socioeconomic class has a high incidence of TCP [52]; (ii) the cyanogenic glycoside composition of cassava (93% linamarin and 7% lotaustralin), which requires sulfur derived from the sulfur-containing amino acids (such as cysteine and methionine, which are believed to be inherently deficient in malnourished individuals) for its detoxification [53]; and experimental induction of hyperglycemia on feeding cyanide to rats [30] or hypoinsulinemia and histopathologic changes of necrosis, hemorrhage, and fibrosis of the exocrine and endocrine portions of the pancreas in dogs fed on cassava [54].

Although the activity of the cyanogen-detoxifying enzyme rhodanase has been shown to be reduced, accompanied by a decrease in sulfur-containing amino acids and antioxidants such as glutathione in TCP patients [55], neither this study [55], nor any of the other case–control or cohort clinical studies [49,56,57] were able to conclusively prove the role of cassava consumption in the causation of TCP. Besides, TCP has been reported even from regions where cassava is not consumed [9,25]. Even in the experimental setting, long-term ingestion of tapioca by rats failed to result in the development of diabetes or pancreatitis [58].

### Antioxidants (Including Micronutrients)

It has been hypothesized that escalating oxidative stress within the acinar cells as a result of cytochrome p450 superfamily induction, deficiency of micronutrients required to maintain stores of reduced glutathione, and exposure to bioactivated chemicals [59,60] plays a role in the development of chronic pancreatitis.

In patients with TCP the surrogate marker for p450I activity, namely theophylline clearance, was found to be faster in cases than in controls [61]. In addition, the bioavailability of ascorbic acid and beta-carotene that predispose to pancreatic oxidative stress was found to be signficantly reduced in South Indians (from Chennai) with TCP as compared to patients with chronic pancreatitis from Manchester [35]. Girish and colleagues [62] observed enhanced lipid peroxidation with concomitant decrease in antioxidant status in patients with TCP as compared to healthy subjects. Moreover, in the same study, they noted that zinc deficiency appeared to affect the oxidative status in patients with TCP. The same group also noted a correlation between zinc deficiency and exocrine and endocrine insufficiency in chronic pancreatitis patients [63]. They observed a marked effect of diabetes in zinc levels in patients with TCP as compared to those with ACP [63]. Other postulated mechanisms by which zinc deficiency could contribute to the progression of chronic pancreatitis include reduction of free radical scavengers, increased collagen deposition, and possibly an alteration in immune function [64].

### Genetics of Tropical Chronic Pancreatitis and Familial Clustering

The finding that aggregations of patients with TCP occur in certain families [65], reported as occurring in up to 8% of TCP patients [66], raised the possibility of heredity as another potential contributory factor to the development of TCP. Although there has been no further evidence to support this initial finding, the role played by genetic mutations as important regulators of pancreatic secretion, as well as the innate protective mechanisms against premature zymogen activation have been extensively studied in patients with TCP. Table 46.1 provides a comprehensive list of the most significantly proven mutations involved in the pathogenesis of TCP [34,67–74]. Mahurkar and colleagues [75] presented an interesting model called the "two-hit model" to hypothesize the pathogenesis of TCP. In this model they proposed that the first hit was the presence of persistent "super trypsin" within the acinar cell—the result of a loss of balance between activation events and degradation of active trypsin as a result of mutations in one or more of the aforementioned genes. This would lead to inflammation in the gland. A second hit in the form of another sequence of genetic mutations with or without environmental factors would then lead to the clinical disease entity of TCP.

**Table 46.1** Gene mutations involved in the pathogenesis of tropical chronic pancreatitis.

| Gene mutation | References |
|---|---|
| *SPINK1* | |
| pN34S variant | [67,69,70] |
| Loss-of-function variant c. – 142 T > C | [68] |
| *CTSB* | |
| Polymorphism p.L26V | [71] |
| *CTRC* | |
| c.217G > A (p.A73T) variant | [34] |
| c.703G > A (p.V235I) variant | [34] |
| Carboxypeptidase A1 | |
| p.D32H, p.R169H, and p.Y308H variants | [72] |
| Glycoprotein 2 | |
| c.1275A > G variant | [73] |
| Calcium-sensing receptor | |
| p.P163R, p.I427S, p.D433H, p.V477A variants | [74] |

*SPINK1*, serine protease inhibitor Kazal type 1 gene; *CTSB*, cathepsin B gene; *CTRC*, chymotrypsin C gene.

## Natural History of the Disease

In the original reports of TCP, the disease was noted to affect young individuals between the ages of 10 and 30 years who also demonstrated features of protein and calorie malnutrition, along with bilateral parotid enlargement and occasionally a cyanotic hue to the lips [5,76]. They also had recurrent severe upper abdominal pain radiating to the back that was relieved by bending forward. In the ensuing years it was noted that although some patients developed features of pancreatic exocrine insufficiency, such as maldigestion and steatorrhoea, others did not do so because of their low-fat diet. They developed diabetes mellitus within 10–20 years from the onset of the initial symptoms of pain [31]. Mohan and colleagues [77] determined that the median time to development of diabetes mellitus in patients with TCP was 9.6 years from diagnosis and this was associated with older age, higher body mass index, and lower fecal chymotrypsin level. The development of diabetes mellitus in TCP has been hypothesized to be a result of two mechanisms: the pathogenetic process of tissue fibrosis eliciting chronic pancreatitis and selective pancreatic beta-cell impairment [78]. TCP is associated with an increased risk of pancreatic cancer development [79]. In a study from Chennai (India), the relative risk of pancreatic cancer in patients with TCP was estimated to be significantly high at 100 (95% CI: 37–218) [80].

In comparison to the initial reports of the poor clinical course of TCP which resulted in death by early adulthood [22], a survival analysis of 370 patients in the mid-1990s determined that patients with TCP were living much longer than before [81], with 80% of patients being alive 35 years from the onset of the first episode of abdominal pain and a mean of 25 years from the diagnosis of diabetes mellitus. The causes of death in TCP include diabetes-related complications, pancreatic cancer [82], and severe infections [24].

## Conclusion

In conclusion, the incidence of TCP is reducing, even in developing countries. The disease is witnessing a paradigm shift in relation to a number of aspects, including the reduced emphasis on macronutrient, protein calorie malnutrition, and cassava ingestion as etiologic factors, in favor of micronutrient deficiency (including zinc) and oxidant stress, an increased appreciation of the role of gene mutations in the pathogenesis of the disease, and, finally, significantly improved survival, possibly as a result of better management of the disease and its attendant complications.

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# 47

# Cystic Fibrosis (CFTR)-Associated Pancreatic Disease

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## Introduction

There is a spectrum of pancreatic diseases associated with cystic fibrosis transmembrane conductance regulator (*CFTR*) [1, 2] mutations that includes classic cystic fibrosis (CF) (pancreatic insufficient or sufficient) and CFTR-associated pancreatitis. The pancreas pathology and damage are dependent on the amount of functional CFTR: the lower the function the more prominent and earlier the sequelae. In addition, *CFTR* mutations may contribute to the development of acute recurrent and chronic pancreatitis.

## Pathophysiology—Genotype and Phenotype Correlations

Although around 2000 *CFTR* mutations have been identified, the functional importance is known only for a small number of them. *CFTR* mutations can be classified into six types of defects (class I–VI mutations) [3]: absence of protein synthesis (class I); protein misfolding and premature degradation (class II); disordered regulation (class III); defective chloride ($Cl^-$) conductance or channel gating (class IV); a reduced number of *CFTR* transcripts due to a promoter or splicing abnormality (class V); and accelerated turnover from the cell surface (class VI) (Fig. 47.1) [4–6]. *CFTR* function is virtually absent with class I–III and VI mutations, whereas class IV and V mutations allow some residual *CFTR* function [7]. Pancreatic function correlates well with gene mutations at the *CFTR* locus. Exocrine pancreatic insufficiency is seen almost exclusively in association with class I–III and VI mutations [5]. The absence of phenylalanine at position 508 (F508del, a class II mutation) constitutes two-thirds of *CFTR* mutations in northern European and North American populations. No other single mutation accounts for more than 5% of *CFTR* mutations worldwide [4]. Patients with at least one mutation belonging to classes IV or V generally present with milder disease, symptoms in late childhood or adulthood and are pancreatic sufficient.

CFTR is expressed in epithelial cells of various organs, including pancreatic ducts, and it functions as an apical membrane anion channel, involved primarily in anion secretion [4, 8–10]. It is generally agreed that the lack of CFTR leads to acidic, dehydrated, and protein-rich secretions [11–15], which then plug the acinar and ductal lumen [16–24] and cause the destruction of the pancreas in CF. Although pancreatic disease is universal in CF, the timing of disease onset and the steps between the lumen-occluding secretions and the pancreatic damage are not well understood. The findings in the CF pig model suggest that the pathogenesis of progressive pancreatic damage in CF may be, in part, a consequence of the activation and progression of proinflammatory, proapoptotic, profibrotic, and complement cascade pathways [25].

Among the various gastrointestinal organs affected by CF, the exocrine pancreas shows the strongest association between genotype and phenotype. In patients with lowest CFTR function, considerable destruction of the pancreas starts *in utero* and functional loss of the exocrine pancreas develops at birth or in early infancy [26]. A group of patients with CF who have residual pancreatic exocrine function (pancreatic sufficient) are prone to recurrent attacks of pancreatitis and may become pancreatic insufficient over time [27, 28].

Early studies suggested that *CFTR* mutations contributed to the development of chronic pancreatitis alone or if additional risk factors were present [29–33]. Many of

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these studies were limited by relatively small numbers of patients, lack of control groups, and incomplete *CFTR* gene sequencing [18]. Recent studies with larger German, French, and North American cohorts confirmed these earlier findings that *CFTR* variants play a role in idiopathic chronic pancreatitis [34–36]. The recent studies show no increased risk for chronic pancreatitis with common polymorphic alleles T5 and TG12; the role of T5–TG12 complex allele remains to be determined [35]. The potential effect of *CFTR* mutations on risk for chronic pancreatitis is summarized in Table 47.1 [37]. It is not known whether other risk factors modulate CFTR levels and function to cause pancreatic inflammation, but a recent animal study suggests that this may be the case with alcohol-induced pancreatitis [38].

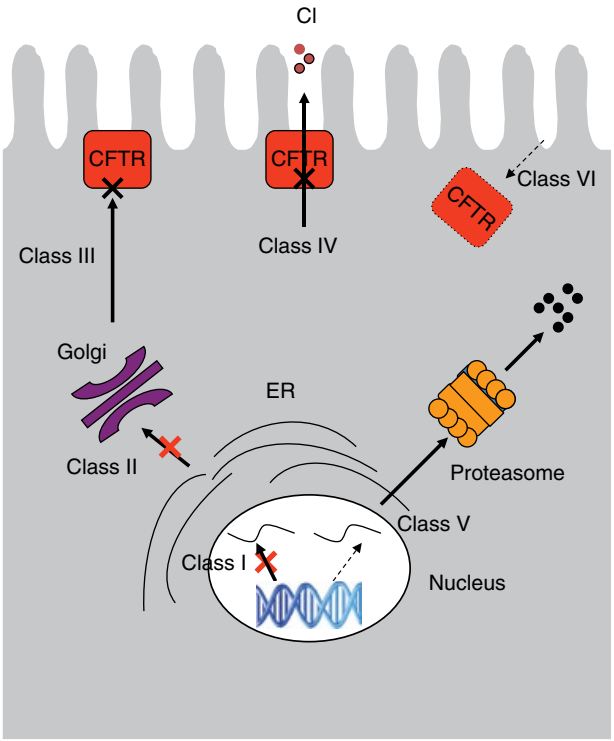


**Figure 47.1** Classes of *CFTR* mutations.

## Clinical Manifestations

The clinical manifestations of CFTR-associated pancreatic diseases correlate with the degree of pancreatic injury. Exocrine pancreatic damage in its severe form manifests as exocrine pancreatic insufficiency (EPI), which is present in 60–75% of infants at time of CF diagnosis [39, 40]. Pancreatic lesions begin *in utero* and continue into early childhood, when complete loss of pancreatic acinar tissue occurs [18, 39]. Fat maldigestion with resultant steatorrhea happens only when pancreatic colipase/lipase secretion falls below 1–2% of normal levels [41], with risk of malnutrition and fat-soluble vitamin deficiencies. A causal relationship between early pancreatic disease in CF and the development of CF-related diabetes has also been reported [42]. Patients with sufficient pancreatic function who either have CF or CFTR-related disorder are at risk of developing symptomatic acute and acute recurrent pancreatitis. Recurrent pancreatic inflammation is a risk factor for further loss of residual function and progression to EPI [43].

With increasing survival of patients with CF, an increased risk of malignancy in the gastrointestinal and

**Table 47.1** Effects of *CFTR* mutations on chronic pancreatitis risk.

| *CFTR* alleles | Pancreatitis risk | Examples |
|---|---|---|
| Severe/severe (compound heterozygotes) | No risk, patients have CF and EPI | F508del/F508del, F508del/G551D |
| Severe/mild-variable (compound heterozygotes) | Pancreatic sufficient CF; 15–20% may have pancreatitis | F508del/R117H; F508del/R334W |
| Mild-variable/mild-variable (compound heterozygotes) | Pancreatic sufficient CF; 15–20% may have pancreatitis | R117H/R117H; R117H/G85E |
| Severe/– (CF carrier) | Low, ~2-fold increase from general population | F508del/– |
| Mild-variable/– | Low, ~4-fold increase from general population | R117H/– |
| Non-CF causing | Possibly low; ~ < 1.5-fold increase from general population | p.R75Q, p.L997F |
| T5 | None | |
| TG12 | None | |
| T5-TG12 | Unknown | |

CF, cystic fibrosis; EPI, exocrine pancreatic insufficiency; CFTR, cystic fibrosis transmembrane conductance regulator.

biliary tracts has been observed [44]. The risk of malignancy in the pancreas was reported in a subanalysis to be greater than the overall risk of cancer in the digestive tract (odds ratio (95% CI) 31.5 (4.8–205) vs. 6.4 (2.9–14), respectively).

Despite treatment with pancreatic enzymes that prevent severe malnutrition, exocrine pancreatic involvement impairs growth and accelerates the progression of lung disease [45–48], the major cause of mortality in CF [49]. CF patients develop diabetes mellitus as they age: ~10% of patients have cystic fibrosis-related diabetes mellitus (CFRD) by 10 years of age, and ~50% of CF patients over 30 years of age have CFRD [50, 51]. CFRD is associated with a rapid decline in pulmonary function, higher morbidity, and greater mortality [26, 52]. The diagnosis of CFRD is preceded by a decline in body weight and lung function, along with insulin deficiency [51, 53].

Recurrent acute and chronic pancreatitis are known complications of CF, and they may occur in ~15–20% of patients with sufficient pancreatic function [4, 54]. It is not known why a subgroup of patients with CF develops pancreatitis, but preservation of acinar cells seems to be a prerequisite for this complication.

## Diagnosis

The rationale for testing for CF is the risk of multiorgan involvement in CF-affected organs and available effective therapies. Several studies have shown that a large proportion of pediatric and adult patients with idiopathic acute recurrent and chronic pancreatitis carry mutations in the *CFTR* gene. In a study of children affected by pancreatitis, *CFTR* mutations were identified in 30 of 89 (34%) and 24 out of 104 (23%) of children with acute recurrent and chronic pancreatitis, respectively [55]. In a separate study of 42 children and adults with idiopathic acute recurrent and chronic pancreatitis, extensive *CFTR* genotyping identified 50% of patients with either 1 or 2 *CFTR* variants [56].

Currently, the diagnostic criteria for CF require the presence of characteristic symptom(s) of CF disease or a positive family history, *plus* an abnormal sweat chloride value (≥60 mmol/L) and/or two CF disease-causing mutations [57]. Consensus guidelines [57, 58] recommend the diagnostic terminologies of: (i) "CF disease," to describe patients who fulfill the currently accepted diagnostic criteria; or (ii) "CFTR-related disorder," to describe individuals with the CF phenotype (e.g., pancreatitis), who have evidence of CFTR dysfunction but insufficient to fulfill the diagnostic criteria for CF disease (e.g., borderline sweat test and/or 1–2 non-CF causing mutation(s).

As the majority of nearly 2000 CFTR mutations have unclear clinical significance, genotyping is the least-sensitive diagnostic test for CF, compared to sweat testing and nasal potential difference (NPD) [32, 56]. If performed, genotyping results should be interpreted with experts in CF genetics since nondiagnostic mutations for CF may be identified [59]. In a study comparing the yield of various diagnostic tests for CF, genotyping identified 1 or 2 *CFTR* mutations in 21 of 42 (50%) patients with idiopathic acute recurrent or chronic pancreatitis but was unable to establish or exclude the diagnosis of CF in any of them [56]. In contrast, sweat chloride and transepithelial NPD were able to diagnose CF in 5% and 29% of patients, respectively [56]. Although NPD is a sensitive and reproducible determinant of CFTR function [60], it has limitations. It is complex to perform, time- and labor-intensive, and operator-dependent. Furthermore, NPD has neither been standardized nor validated for clinical use, and lacks consensus reference values [61]. Access to NPD is also limited to specialized centers with NPD expertise. False-positive results can occur with minor perturbations of the nasal epithelium, allergies, respiratory infections, and smoking.

The sweat test remains the primary diagnostic test for CF [57, 59]. Borderline (40–59 mmol/L) or abnormal (≥60 mmol/L) sweat chloride concentrations should lead to a referral to a CF clinic for further diagnostic evaluation, including for *CFTR* genotyping and alternative ion channel measurements (e.g., NPD or intestinal ion channel measurement), and various end-organ testing (e.g., lung function). Disease-specific counseling (e.g., fertility and smoking cessation) and genetic counseling are also important management considerations.

## Therapy

The only treatment currently available for patients with advanced pancreatic damage and EPI, is pancreatic enzyme replacement therapy [10]. Children <4 years of age require 1000 lipase units/kg per meal; 500 lipase units/kg per meal are used for those >4 years of age and 25,000–40,000 units/meal are used for adults [62, 63]. For snacks, half the dose is recommended. Infants may be given 2000 –4000 units per 120 mL of infant formula or per breastfeeding. The daily dose for most patients is less than 10,000 units of lipase/kg per day or 6000 units of lipase/kg per meal to prevent fibrosing colonopathy [62]. Aggressive nutritional management and fat-soluble vitamin supplementation is mandatory for all patients with EPI. Insulin is the treatment of choice for CFRD [64].

Currently there are no effective therapies to preserve pancreatic function in pancreatic sufficient CF patients or prevent recurrent attacks of pancreatitis. Ideally, the therapeutic strategy should be repairing the basic defect, which is the *CFTR* mutation. There are therapeutic agents designed to target class I (Ataluren) [65], class II (Lumacaftor), and class III (Ivacaftor) *CFTR* mutations [66, 67], some with promising success in improving lung function in patients with CF. Although these novel therapeutic approaches have revolutionized CF therapy, especially in the airways, there are no studies showing that these agents are effective in the pancreas. Gene therapy trials for CF are currently being conducted in the United Kingdom only using a cationic lipid-based vector, again targeting the lungs [68]. By utilizing a minimally invasive method and gene therapy vectors, Griffin et al. successfully targeted CFTR in porcine pancreatic ducts [69], but there are no human studies as yet.

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# Clinical and Laboratory Diagnosis of Chronic Pancreatitis

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## Introduction

For centuries, the pancreas was a "terra incognita" hidden behind the stomach, and its pathophysiologic role remained obscure. In 1761 Jean-Baptista Morgagni described the first case of chronic pancreatitis in his book *De sedibus et causis morborum* and it took 60 more years until Kuntzmann was able to connect fatty stool to diseases of the pancreas. Even in the twenty-first century the time interval between the onset of symptoms and the diagnosis of chronic pancreatitis is unacceptably long. This is mainly because routine blood tests are not usually helpful in diagnosing chronic pancreatitis and because clinical symptoms are often nonspecific. The modern clinical concept of clinical chemistry for pancreatic diseases began in 1929 with the introduction of serum amylase (diastase) measurements [1]. Thereafter Comfort and coworkers [2] combined clinical observations, surgical findings, and autopsy studies to characterize chronic pancreatitis and first reported a chronic relapsing course of the disease. They also commented on its frequent association with longstanding alcohol intake, its common onset in the third and fourth decade of life, and the typical complications of the disease such as exocrine and endocrine pancreatic insufficiency.

## Clinical Presentation

With an incidence of 8.2, a prevalence of 27.4 per 100,000 population and a frequency of 0.04–5% among all autopsies, chronic pancreatitis represents a rather common disorder of the gastrointestinal tract [3,4]. Chronic pancreatitis also accounts for substantial morbidity and healthcare costs. The worldwide incidence of chronic pancreatitis is reported to be between 1.6 and 23 per 100,000, and it has an increasing prevalence. Although most patients with chronic pancreatitis are treated as outpatients, in 2015 there were 18 612 (ICD-10: K86) hospital admissions for chronic pancreatitis in Germany alone (Federal Statistics Office). This does not include those patients who were coded as having acute pancreatitis, including those reporting an acute episode of chronic pancreatitis (55 221 cases). Records from the United States, United Kingdom, the Netherlands, and Finland confirmed an increasing number of annual hospital admission amounting to an 30% increase within 6 years [5]. This indicates the high socioeconomic significance of the disease. Mortality from chronic pancreatitis is reported to be 12.8–19.8% over a mean observation period of 6.3–9.8 years [6–8]. Total mortality in the same studies was reported to be 28.8–35%. Continued alcohol consumption results in a significantly reduced survival rate [9]. The number of patients who leave the workforce and abandon gainful employment due to prolonged illness or continued alcohol consumption, or become disabled and are forced to retire prematurely during the course of the disease amounts to 40%. The 10-year survival rate is 7% and the 20-year survival rate is 4%, in comparison with 93% and 65%, respectively, for an age-adjusted cohort.

With regard to the time interval between the onset of symptoms and the diagnosis of chronic pancreatitis a median interval of 30–55 months was reported in alcoholics [3,10]. In nonalcoholics the diagnosis was even more delayed (median 81 months) and frequently only established if complications of the disease such as pseudocysts or gastric outlet obstruction occurred. The

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major reason for this delay lies in the natural course of the disease. The clinical presentation of patients with chronic pancreatitis is highly dependent on the stage of the disease. It varies between severely ill patients with symptoms of an acute abdomen to slowly progressing cachexia. Often the first signs of the disease that prompt the patient to seek medical attention are belt-like abdominal pain that frequently radiates to the back, loss of body weight (in 80%), and steatorrhea (in less than 50%) [11].

Several attempts have been undertaken to establish histologic and morphologic criteria that clearly define chronic pancreatitis. Unfortunately an exact correlation between clinical symptoms, morphologic signs, and histologic criteria is still not available [12,13].

## Etiology

In Western countries alcohol consumption is assumed to be the leading cause (70–90%) of chronic pancreatitis [14]. The prevalence of chronic pancreatitis clearly correlates with the alcohol consumption in a given population [15].

It is reported that 24.1% of all patients suffering from acute pancreatitis will progress to chronic pancreatitis [16]. Of those, 48.2% have alcoholic pancreatitis and smoking was identified as the only independent but dose-dependent risk factor for disease progression [17]. With regard to the etiology of chronic pancreatitis more recent studies suggest that in addition to alcohol consumption smoking increases the risk and can independently cause chronic pancreatitis [18].

The second most common form of chronic pancreatitis (25%) is so-called idiopathic pancreatitis [19,20]. Patients without identifiable risk factor for chronic pancreatitis are classified as having idiopathic pancreatitis. This group has decreased in incidence since Comfort and Steinberg reported in 1952 an inherited form of chronic pancreatitis that follows an autosomal dominant inheritance pattern [2]. Knowledge about these genetic susceptibility factors is accumulating. Hereditary pancreatitis represents a genetic disorder closely associated with mutations in the cationic trypsinogen gene and presents with a disease penetrance of ≈ 80% [21]. Shortly after the identification of mutations in the trypsinogen gene associated with chronic pancreatitis another important observation was made by Witt et al. [22]. They found that mutations in the serine protease inhibitor Kazal type 1 (*SPINK1*) gene, which encodes the pancreatic secretory trypsin inhibitor (PSTI), were associated with idiopathic chronic pancreatitis in children. *SPINK1* mutations are frequently detected in patients who do not present with a family history of pancreatitis and are devoid of classical risk factors for chronic pancreatitis [23,24].

Cystic fibrosis is an autosomal-recessive disorder with an estimated incidence of 1:2500 characterized by pancreatic exocrine insufficiency and chronic pulmonary disease. The extent to which the pancreas is affected varies between a complete loss of exocrine and endocrine function to clinically normal pancreatic function. Recurrent episodes of pancreatitis occur in 1–2% of all patients with cystic fibrosis who have normal exocrine pancreatic function and much more rarely in patients with exocrine pancreatic insufficiency. This means that cystic fibrosis transmembrane conductance regulator (*CFTR*) gene mutations that would not cause cystic fibrosis still confer a twofold increased risk of developing pancreatitis.

Metabolic disorders associated with hypertriglyceridemia above 1000 mg/dL may be responsible for the development of recurrent episodes of pancreatitis [25]. In addition to lipidapheresis and glucose/insulin treatment to lower triglyceride levels, a gene therapy approach has recently been developed. Alipogene tiparvovec (Glybera®) is a gene therapy product approved in Europe under the "exceptional circumstances" pathway as a treatment for lipoprotein lipase deficiency (LPLD), a rare genetic disease resulting in chylomicronemia and a concomitantly increased risk of acute and recurrent pancreatitis, with potentially lethal outcome. In a retrospective study the frequency and severity of pancreatitis in 19 patients with LPLD up to 6 years after a single treatment with alipogene tiparvovec were analyzed. Therapy was associated with an approximately 50% reduction in pancreatitis events [26]. In a few cases chronic calcifying pancreatitis has been reported due to hypercalcemia in patients with untreated hyperparathyroidism. The underlying mechanism of hyperparathyroidism-associated pancreatitis is most likely related to the established role of calcium in the premature intracellular activation of digestive proteases [27–29].

## Pain

Pain is the most commonly encountered symptom in chronic pancreatitis (80–95% of patients) [24]. Up to 50% of patients with chronic alcoholic pancreatitis suffer from chronic pain, while the remaining portion either present with intermittent attacks followed by pain-free intervals or have never experienced severe pain due to pancreatitis [20,30,31]. Most patients report continual, numb pain lasting for more than 24 hours and 68% report epigastric pain. Pain that radiates to the back is reported in 39%, to the left upper quadrant in 50%, and to the right upper quadrant in 32%. About 6% of patients feel their pain radiating between the shoulders. In general, patients with abdominal pain take a "jackknife" posture to relax

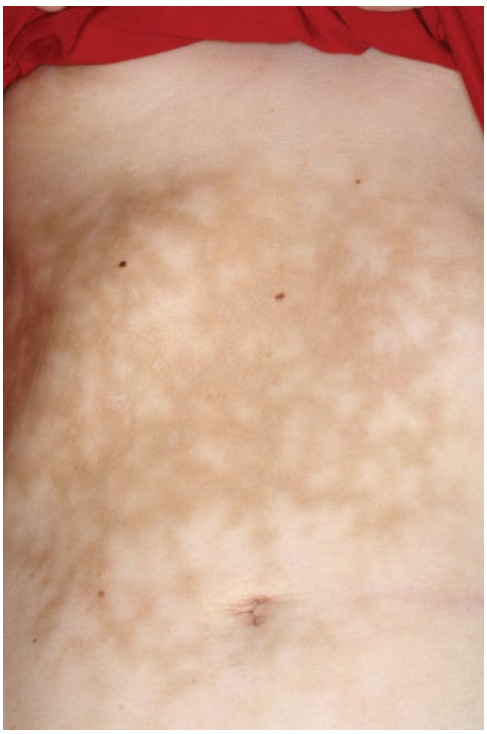

**Figure 48.1** Erythema ab igne in a female patient aged 45 with chronic alcoholic pancreatitis.

abdominal musculature affected by peritonitis. An erythema ab igne is associated with intense acute pain (Fig. 48.1). In chronic alcoholic pancreatitis a relationship between alcohol ingestion and recurrent pain has been described. Pain often begins between 12 and 48 hours after ceasing alcohol intake.

## Malabsorption and Weight Loss

Fat excretion of patients with pancreatic steatorrhea frequently exceeds that of patients with other causes of steatorrhea. Leaking oily stool from the anus is virtually pathognomonic of exocrine pancreatic insufficiency. In general, weight loss is a cardinal symptom of pancreatic exocrine insufficiency with steatorrhea, whereas hypoproteinemia or malabsorption of the fat-soluble vitamins is less common. Two publications have reported decreased bone mineral density, but no comparison to an age-matched control cohort was included [32,33]. Overt steatorrhea occurs in approximately 30% of patients with chronic calcific pancreatitis.

With rare exceptions, steatorrhea and azotorrhea (excessive discharge of nitrogenous substances in the feces or urine) only occur when the reduction in lipase and protease secretion, respectively, exceeds 90% [34,35] (Fig. 48.2).

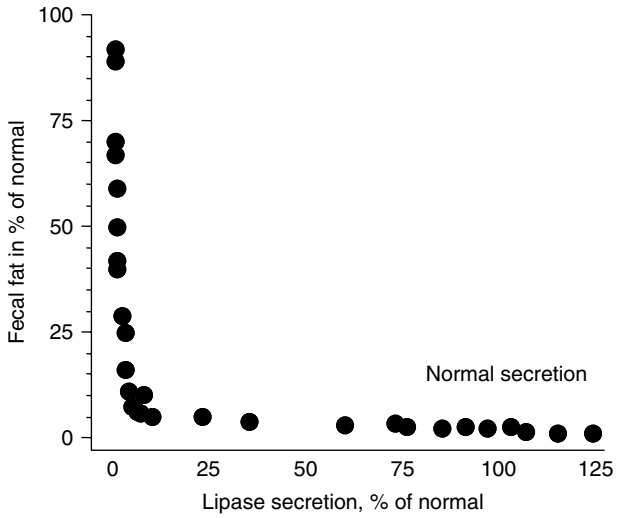


**Figure 48.2** Reduction in lipase secretion is paralleled by an increase in fecal fat. With rare exceptions, steatorrhea and azotorrhea only occur if there is greater than 90% reduction in pancreatic lipase and trypsin secretion. *Source:* Redrawn from [34].

In alcoholic chronic pancreatitis it is usually 10–20 years before severe exocrine insufficiency develops, but according to DiMagno and coworkers [34] lipase secretion decreases more rapidly than protease secretion. In decompensated chronic pancreatitis with less than 5% of the normal enzyme output, about 40% of nutrients from a readily digestible low-caloric meal are malabsorbed and enter the colon.

## Endocrine Insufficiency

More rarely, patients seek medical attention because they develop diabetes mellitus with a loss of endocrine function or cachexia as the initial symptoms of chronic pancreatitis. A history of diarrhea with recent onset of diabetes mellitus should always raise the suspicion of chronic pancreatitis as the underlying cause. The symptoms of diabetes "of other specific types" according to the World Health Organization (WHO) classification system released in 2003 (e.g., loss of insulin production due to diseases of the exocrine pancreas) are similar to those of diabetes mellitus of other causes. Overall, 45% of the patients with chronic pancreatitis suffer from overt diabetes. The cause of chronic pancreatitis bears no relationship to the subsequent likelihood of developing diabetes, but it does seem to influence the time lag between onset of pancreatitis and onset of diabetes. Alcoholics show symptoms of endocrine insufficiency earlier than nonalcoholics [7,36]. Diabetes mellitus is also an independent predictor of mortality in patients with chronic pancreatitis. The underlying pathophysiology

of diabetes in chronic pancreatitis is the loss of insulin-secreting cells, often combined with a peripheral and hepatic insulin resistance. Oral antidiabetics, especially metformin, might therefore have a role in the treatment of these patients, but control of blood sugar levels should be achieved with exogenous insulin supplementation [37,38].

## Jaundice

In 10–40% of cases of chronic pancreatitis a benign dominant stenosis of the common bile duct develops due to inflammation of the pancreatic head or due to pancreatic pseudocysts or phlegmons, all of which require either endoscopic or surgical intervention. An asymptomatic increase in alkaline phosphatase is the most common laboratory manifestation of a stenosis of the common bile duct secondary to chronic pancreatitis. Jaundice may develop later. However, a raised alkaline phosphatase or increased bilirubin alone does not always point to extrahepatic cholestasis but might be a symptom of parenchymal liver damage caused by hepatitis, steatosis, or even liver cirrhosis. Endoscopic intervention is clinically indicated if the patient presents with jaundice or recurrent episodes of cholangitis and in order to prevent secondary biliary cirrhosis.

## Laboratory Diagnosis

Even after two centuries of pancreatic research, a diagnostic serum marker for chronic pancreatitis is not available. Diagnosis is usually made by a combination of imaging procedures such as ultrasound, endoscopic ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) in combination with exocrine and endocrine function tests.

### Serum Tests for the Diagnosis and Etiologic Characterization of Chronic Pancreatitis

The simplest noninvasive tests would be to measure exocrine pancreatic enzymes or hormones in fasting blood samples. Total serum amylase, in contrast to pancreatic isoamylase or salivary isoamylase, has been measured routinely since 1929, but it is of little use for the diagnosis of chronic pancreatitis. Because amylase secretion into the gut decreases in chronic pancreatitis it has been hypothesized that low serum pancreatic amylase could be used to diagnose chronic pancreatitis. Unfortunately, pancreatic isoamylase is completely normal in many patients with mild to moderate chronic pancreatitis and the sensitivity was reported to be only 60% with a variation between 12% and 100% depending on the severity of the disease. The same problems apply to the measurement of lipase and trypsin. Therefore pancreatic serum enzyme testing lacks diagnostic accuracy as well as specificity.

Provocation tests, in which serum levels of pancreatic enzymes are measured after stimulation of pancreatic secretion by secretagogues or parasympathomimetics, have been found to be rather insensitive, nonspecific, burdened with great interindividual ranges and therefore just as unreliable as markers for chronic pancreatitis. At most they are abnormal in 25% of patients suffering from chronic pancreatitis and at least the same proportion of healthy volunteers show abnormal test results [39–42].

The only hormone measured in serum with some promise as a diagnostic tool for pancreatitis is human pancreatic polypeptide (PP). Pancreatic polypeptide is a 36-amino-acid peptide and is found in the islets of Langerhans as well as in the exocrine parts of the pancreas. Its exact function is unknown but it is known to inhibit exocrine pancreatic secretion. Plasma concentrations of PP rise and fall in synchrony with interdigestive pancreatic secretion and increase in the immediate postprandial period or when the pancreas is stimulated by exogenous factors. Fasting plasma levels below 125 pg/mL have been assigned a sensitivity for chronic pancreatitis of 70% by DiMagno and coworkers, and pancreatic cancer can be differentiated with a specificity of 65%. If normal, this assay will exclude chronic pancreatitis with an accuracy of 90%, although 35% of healthy volunteers will still show levels below 125 pg/mL [43,44].

### Pancreatic Exocrine Function Tests

Tests for exocrine and endocrine pancreatic function serve as a second line of diagnostic tools for chronic pancreatitis. Reduced exocrine function can precede overt morphologic changes and therefore the sensitivity to detect early changes is higher for exocrine pancreatic function tests than for imaging studies. These patients have exocrine pancreatic insufficiency because enzymes and chyme do not mix fully and their fat digestion is accordingly impaired. However, excreted enzymes (e.g., elastase or chymotrypsin) in stool will appear normal.

Several tests for exocrine pancreatic function are now well established in the diagnostic workup of patients with suspected chronic pancreatitis. Assays can be divided into direct and indirect methods, depending on the technique used for determining enzyme output (via duodenal tube or indirectly). When pancreatic function is measured directly, the stimulated output of enzymes and bicarbonate into the small intestinal lumen is

**Box 48.1 Direct and indirect pancreatic function tests**

**Direct tests**

- Secretin–cholecystokinin test
- Endoscopic secretin test

**Indirect tests**

**Serum tests**

- Pancreolauryl test
- NBT-PABA test (commercially discontinued)

**Fecal tests**

- Fecal elastase
- Chymotrypsin
- Stool weight
- Fecal fat quantification

collected via a nasoduodenal tube and then analyzed. Indirect methods detect a decreased amount of pancreatic enzymes in stool or serum or, alternatively, evaluate the digestion of synthetic substrates by pancreatic enzymes, which also indicate impaired exocrine function when reduced (Box 48.1). The disadvantage of indirect tests for pancreatic function is that they cannot distinguish between structural or functional abnormalities. The situation after gastrectomy is a good example of when an impaired synchrony between pancreatic secretion and the gastrointestinal passage of food signals exocrine insufficiency on pancreatic function tests without any structural damage to the pancreas (pancreaticocibale asynchrony) [45].

## Direct Pancreatic Function Tests

### Secretin–Cholecystokinin Test

Pancreatic enzyme activity and bicarbonate concentration are measured in the duodenal juice after stimulation with the enterohormones secretin (1 U/kg intravenously) and cholecystokinin (CCK; 25–100 ng/kg). The secretin–cholecystokinin test used to be the gold standard for pancreatic function testing and its overall sensitivity and specificity is 90%. However, the combined secretin–cholecystokinin test is no longer used since pharmaceutical CCK preparations for human use are no longer marketed (in most countries). Some authors used a standardized test meal (Lund test) rather than hormone stimulation of the exocrine pancreas but this more "physiologic" approach is ultimately less sensitive in detecting early functional changes and bicarbonate cannot be measured in the collected chyme.

As early as 1982 Gregg suggested a new method to determine exocrine pancreatic function by collecting pancreatic juice after intravenous secretin stimulation during endoscopic retrograde pancreatography (ERP) [46]. Until 2003 no large series of this promising approach had been conducted until DiMagno and coworkers presented a modified version of the endoscopic pancreatic function test in a study of 412 subjects. The overall accuracy of the endoscopic secretin test was 79%, with positive and negative predictive values of 73% and 85%, respectively [47].

One way of overcoming the limitations of invasive function testing might be to use secretin-stimulated MRI. Intravenous application of secretin causes the rapid washout of bicarbonate-rich fluid from the exocrine pancreas which can be quantified semiquantitatively but is significantly reduced in patients with impaired exocrine function [48–51]. The sensitivity of secretin-stimulated MRI was calculated to be 69%, while the specificity was 90% [52,53]. As MRI is becoming an alternative to CT scan examination for the diagnosis of chronic pancreatitis, secretin–MRCP could become a valuable diagnostic tool [54].

## Noninvasive Pancreatic Function Tests

### Fecal Elastase 1

Pancreatic elastase accounts for 6% of the protein in pancreatic juice. Compared to other serine proteases this enzyme is highly stable during its passage through the gut and can be detected with a 5- to 6-fold concentration in stool (median concentration of 1200 µg/g). Fecal elastase is measured using an enzyme-linked immunoassay (ELISA) and there are human-specific polyclonal and monoclonal test kits without crossreactivity commercially available so it is not necessary for the patient to discontinue enzyme supplementation treatment that would potentially contain traces of pork elastase. The overall sensitivity of fecal elastase testing is 63% for mild exocrine insufficiency and rises to 100% for severe exocrine insufficiency if compared to the gold standard of the secretin–cholecystokinin test [55,56]. Biochemically the elastase 1 assay is a misnomer since the human pancreas expresses elastase 2 and 3 isoforms but not the elastase 1 isoform, which is known only from pigs.

It is known that 5% of chymotrypsin secreted into the duodenum can be recovered enzymatically active in the feces and measured by a colorimetric enzyme reaction employing the substrate *N*-glutaryl-L-phenylalanine-*p*-nitroanilide (GNPNA). Sensitivity and specificity is thought to be equal or lower compared to fecal elastase but false-negative results occur in 4% of patients with severe exocrine insufficiency, 15–18% of patients with moderate exocrine insufficiency, and 25–40% of patients with mild pancreatic insuffiency [56,57].

Another noninvasive approach used to evaluate pancreatic exocrine insufficiency is the assessment of $CO_2$ exhalation after digestion of $^{13}C$-labeled synthetic substrates such as mixed triglyceride, triolein, and hiolein, which are enzymatically cleaved by pancreatic enzymes in the duodenum. The $^{13}CO_2$ component, which is rapidly resorbed, can therefore be detected in exhaled breath over time [53,58–61]. In patients with severe exocrine insufficiency, sensitivity of the detection of mixed triglycerides is 92–100%, but in patients suffering from mild impairment of exocrine function sensitivity is reduced to 46% [62]. However, in addition to the detection of pancreatic insufficiency these tests can be used for clinical workup of chronic diarrhea or to monitor the efficacy of enzyme supplementation [63,64].

Fecal fat quantification by the classical van de Kamer (alcohol extraction) technique is the standard test to determine steatorrhea as a characteristic symptom of reduced exocrine function. After a 90% loss of exocrine function, fat excretion in stool significantly increases as a sign of fat maldigestion. A mild or intermediate impairment of exocrine function is usually clinically compensated for. The van de Kamer test has fallen out of favor with patients, nurses, and technicians because it requires extensive handling of large amounts of smelly stool.

### Evaluation of Endocrine Function

Overt diabetes occurs in about 20% of patients with alcoholic chronic pancreatitis 6 years after disease onset. Ten years after disease onset about 50% of alcoholic pancreatitis patients display signs of impaired glucose metabolism with diminished insulin production [65]. Pancreatic endocrine function should be evaluated by measuring $HbA_{1c}$ according to the guidelines of the WHO for the diagnosis of diabetes mellitus.

### Genetic Testing

In addition to an evaluation of exocrine and endocrine function considerable attention is now paid to the etiology of the disease (Box 48.2). Recent results from molecular and genetic studies suggest that a significant number of patients with chronic pancreatitis have a genetically determined or inherited disease. This is mainly true for patients who were formerly classified as having idiopathic pancreatitis, for patients with an onset of the disease before the age of 25, or those with a positive family history for chronic pancreatitis or pancreatic cancer. Patients who have chronic pancreatitis due to mutations in the cationic trypsinogen gene are burdened with a 70- to 140-fold increased risk of developing pancreatic cancer, particularly if they smoke [66]. Whether, this is also true for patients who carry *SPINK1* or *CFTR* mutations needs to be determined. Genetic testing for the most common and clinically relevant trypsinogen gene mutations (N29I and R122H or R122C) can be recommended for chronic pancreatitis patients who have first-degree relatives with pancreatitis or pancreatic cancer, and for patients with chronic pancreatitis or recurrent bouts of acute pancreatitis before the age of 25 years and no identifiable risk factor [67]. Genetic testing for clinically unaffected relatives is not indicated and should only be performed within Ethics Committee approved research protocols.

**Box 48.2 Indications for genetic testing in idiopathic or hereditary pancreatitis**

- Recurrent (2 or more) episodes of acute pancreatitis without identifiable cause or etiology; or
- Idiopathic chronic pancreatitis—especially in children and young adults under the age of 25 years; or
- Pancreatitis in patients with a positive family history of pancreatitis (one or more first- or second-degree relatives)

A much more detailed analysis of the genetic risk factors of pancreatitis is found in other chapters of this book.

## Conclusion

Even in the twenty-first century the diagnosis of chronic pancreatitis is made by a combination of clinical symptoms, imaging procedures, such as ultrasound, endoscopic ultrasound, CT, and MRCP, and exocrine and endocrine function tests. Therapy is restricted to symptom control because of a lack of a causal treatment strategy and the time point from first symptoms to diagnosis has not been significantly shortened during the last 15 years. Single markers or tests are urgently needed but presently not available.

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# 49

# Evidence of Contrast-Enhanced CT and MRI/MRCP

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## Introduction

Chronic pancreatitis is a chronic inflammatory disease of the pancreas leading to progressive fibrosis and loss of exocrine and endocrine pancreatic parenchyma. Because sensitive and specific biomarkers are not available, diagnosis of chronic pancreatitis is based on morphologic and functional changes that develop in the gland over the natural history of the disease. Complications such as chronic pancreatic pseudocyst, biliary obstruction, and portal and splenic vein thrombosis are frequently seen in cases of severe chronic pancreatitis. Diagnosis of chronic pancreatitis is easy at late stages, when pancreatic atrophy, irregularities and dilatation of the main pancreatic duct and side-branches, and calcifications are present. However, diagnosis is challenging in the early phases, when infiltration of inflammatory cells and activated stellate cells with mild fibrosis are the only histologic signs of the disease.

With the exception of the endoscopic secretin test, pancreatic function tests play a minor role in the early diagnosis of chronic pancreatitis in clinical practice. Imaging methods are therefore the cornerstone of the diagnosis of the disease. Findings at imaging methods are the consequence of the pathology of chronic pancreatitis. Histologically, the two most common features of chronic pancreatitis are atrophy, due to loss of acinar tissue, and fibrosis.

Chronic pancreatitis is frequently a diffuse process, but it can be patchy early in the evolution of the disease, or a localized process with regional involvement as a consequence of ductal obstruction. However, with the exception of the autoimmune form of the disease and the so-called groove pancreatitis, histologic changes are basically not related to the etiology of chronic pancreatitis, and thus morphologic pancreatic changes seen on imaging cannot provide information about the cause of the disease.

Endoscopic ultrasound (EUS) is nowadays considered to be the most sensitive method for the diagnosis of chronic pancreatitis. The relatively poor interobserver agreement for EUS features of chronic pancreatitis limits the wide use of this technique, but EUS-elastography and dynamic EUS examination after contrast enhancement may be of help in providing objective information about the degree of pancreatic fibrosis [1].

Diagnosis of chronic pancreatitis by abdominal ultrasound relies on severe morphologic changes that develop in the setting of advanced disease, but it is not accurate enough to detect mild and moderate changes.

Computed tomography (CT) is widely available and allows for comprehensive detailed evaluation of the abdomen. CT scan is thus usually considered to be the best initial imaging test for chronic pancreatitis. Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) are more sensitive than CT scan for the diagnosis of chronic pancreatitis, mainly for early mild and moderate disease, and they are the most accurate noninvasive imaging methods in this setting. Wider availability and good image quality make CT the mostly used imaging technique, but due to its nonionizing nature, unmatched soft tissue contrast, higher safety profile of intravascular contrast media, and the accurate secretin-enhanced duct examination make MRI/MRCP highly valuable in most cases of chronic pancreatitis. Accepted CT and MRI-MRCP findings of chronic pancreatitis are shown in Table 49.1. Together with that, CT and MRI play a major role in the differential diagnosis between inflammatory pancreatic mass in the context of chronic pancreatitis

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 49.1** CT and MRI/MRCP findings of chronic pancreatitis.

| | CT findings | MRI/MRCP findings |
|---|---|---|
| Mild chronic pancreatitis | | Diminished signal intensity on T1-weighted fat-suppressed images<br>Slightly diminished and/or delayed enhancement after IV gadolinium<br>Reduced diffusion coefficient after diffusion-weighted MRI<br>Abnormal pancreatic duct compliance after secretin stimulation |
| Moderate chronic pancreatitis | Dilated MPD (2–4 mm)<br>Irregular MPD<br>Increased enhancement of the MPD wall<br>Slight gland enlargement<br>Heterogeneous parenchyma<br>Irregular gland contour<br>Small pseudocysts (<1 cm) | Dilated MPD (2–4 mm)<br>Irregular MPD<br>Dilated side- branches (>3)<br>Reduced duodenal filling after IV secretin<br>Moderately diminished and/or delayed enhancement after IV gadolinium<br>Slight gland enlargement<br>Heterogeneous parenchyma<br>Irregular gland contour<br>Small pseudocysts (<1 cm) |
| Severe chronic pancreatitis | Dilated MPD (>4 mm)<br>Calcifications<br>Ductal strictures<br>Gross gland enlargement<br>Parenchymal atrophy<br>Pseudocysts >1 cm<br>Contiguous organ invasion | Dilated MPD (>4 mm)<br>Calcifications<br>Ductal strictures<br>Markedly reduced duodenal filling after IV secretin<br>Markedly diminished and/or delayed enhancement after IV gadolinium<br>Gross gland enlargement<br>Parenchymal atrophy<br>Pseudocysts >1 cm<br>Contiguous organ invasion |

MPD, main pancreatic duct.

and pancreatic cancer, as well as in the diagnosis of local complications of the disease. Finally, some specific findings at CT and MRI may be of help to support the diagnosis of specific forms of chronic pancreatitis, such as autoimmune and groove pancreatitis.

## Diagnosis of Chronic Pancreatitis

### CT Scan for the Diagnosis of Chronic Pancreatitis

CT scan is a very accurate technique for detecting pancreatic calcifications, parenchymal atrophy, and inflammatory masses in the context of chronic pancreatitis [2] (Fig. 49.1). Pancreatic calcifications are the most specific though late finding of chronic pancreatitis, but parenchymal atrophy is neither sensitive, as it is only seen in advanced disease, nor specific, as it usually develops with aging. Most common ductal changes on CT include dilatation of the pancreatic duct and its side-branches, which correlate well with endoscopic retrograde pancreatography findings. The ductal contour on CT may be smooth, beaded, or irregular. Different CT findings of chronic pancreatitis can be seen in 30–70% of cases, mainly depending on the severity of the disease. Accuracy of CT scan to detect minimal parenchymal or ductal changes of chronic pancreatitis is even lower, and this technique often shows no abnormalities in early chronic pancreatitis [3]. Nevertheless, recent diagnostic studies are lacking and the accuracy of the most recently developed multiple detector CT (MDCT) for chronic pancreatitis is unfortunately unknown.

### MRI and MRCP for the Diagnosis of Chronic Pancreatitis

Compared to CT scan, association of MRI and MRCP appears to be more sensitive for early changes of chronic pancreatitis [4]. The normal high-intensity signal in T1-weighted sequences of the pancreas is lost in chronic pancreatitis. In addition, the maximal signal intensity of the pancreas after intravenous gadolinium administration is reduced and delayed to the venous phase, and the appearance of the gland becomes heterogeneous [4] (Fig. 49.2). Diffusion coefficient values during diffusion-weighted MRI are also lower in patients with chronic pancreatitis than in normal pancreas due to parenchymal fibrosis, which can be enhanced after intravenous secretin stimulation [5]. These dynamic parenchymal abnormalities, which frequently precede the ductal abnormalities, may be accurately quantified by MRI,

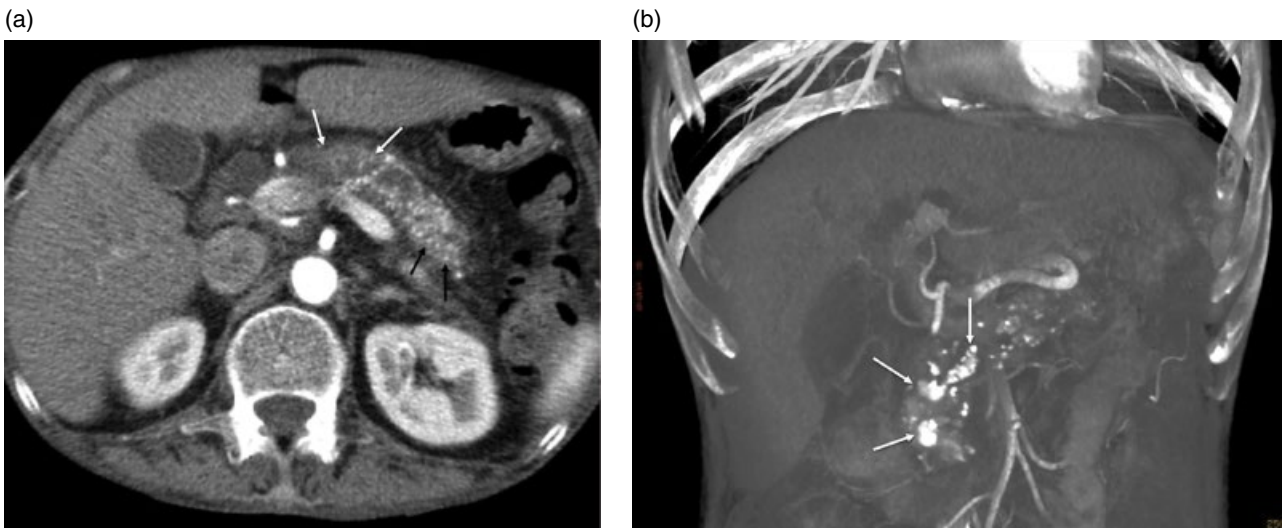


**Figure 49.1** Calcifying chronic pancreatitis on CT scan. (a) Axial contrast-enhanced arterial-phase CT image shows an area of inhomogeneous enhancement in the pancreatic parenchyma (white arrows) and multiple pancreatic calcifications (black arrows). (b) CT volumetric rendering maximum intensity projection in the same patient demonstrates multiple foci of calcification (white arrows).

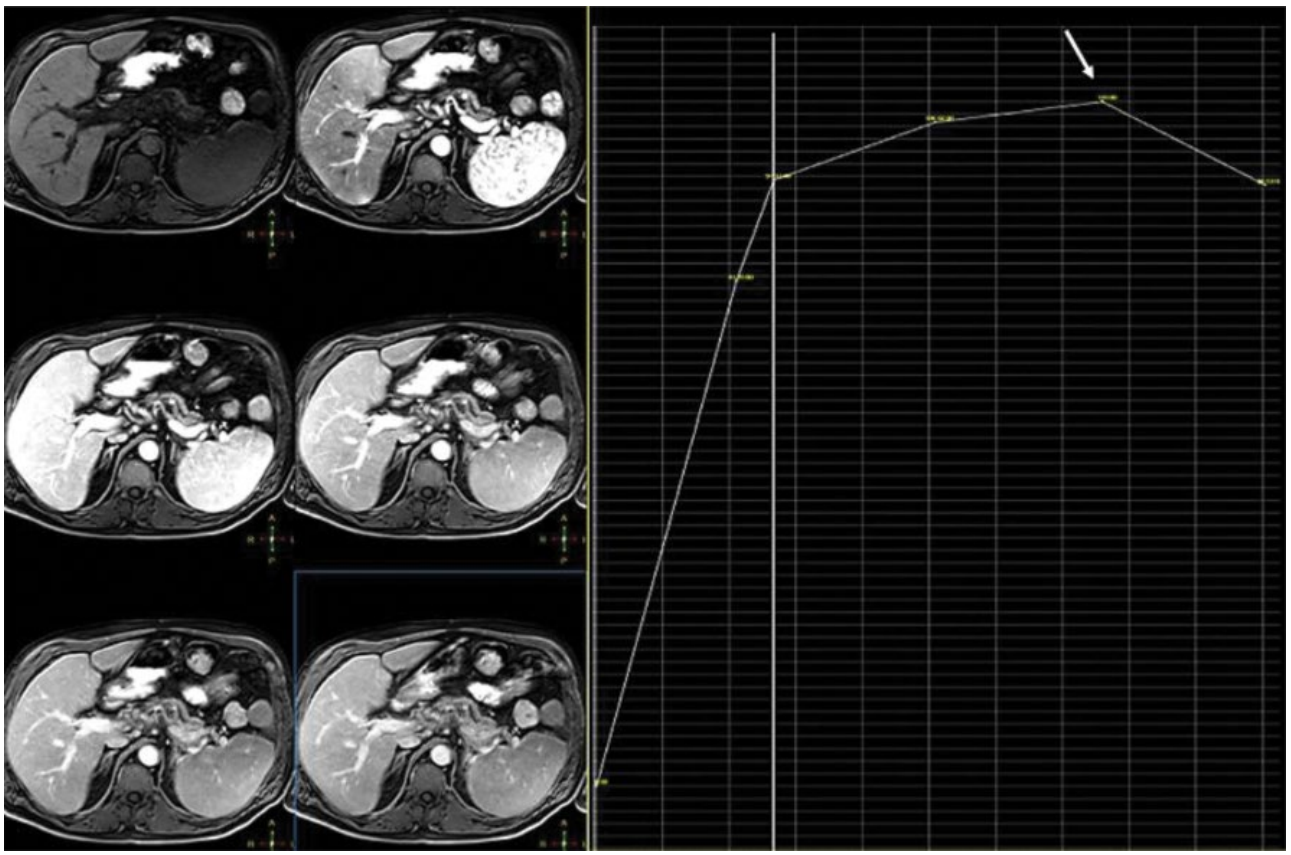

**Figure 49.2** Chronic pancreatitis on dynamic contrast-enhanced MRI. Dynamic contrast-enhanced axial fat-sat T1-weighted MR images (left) and time-intensity curve (right) show delayed enhancement of the pancreatic parenchyma (arrow).

although the accuracy of quantitative dynamic MRI in detecting early changes of chronic pancreatitis should be further investigated (Fig. 49.3).

MRCP is able to detect the typical ductal changes of chronic pancreatitis previously described for endoscopic retrograde pancreatography [6]. Pancreatic duct abnormalities include irregular dilatation and a beaded appearance of the main duct, which may contain intraductal calculi, and dilation of side-branches (Fig. 49.4). Intravenous injection of secretin significantly improves visualization of the main pancreatic duct and side-branches during MRCP (sMRCP) (Fig. 49.5); in addition, it allows the dynamic assessment of the duct compliance. The normal dynamic behavior of the duct after secretin is defined by a rapid distension of at least 1 mm or about 50% of the basal diameter, and recovery of the duct diameter to baseline 10 minutes after secretin stimulation (Fig. 49.6). This dynamic ductal compliance is early altered in chronic pancreatitis due to fibrosis [7]. The exocrine pancreatic secretion can also be evaluated by sMRCP; pancreatic secretion is frequently evaluated semiquantitatively based on a simple grading of the duodenal and jejunal filling after secretin stimulation (Fig. 49.6), but it can be measured quantitatively using a multislice fast T2-weighted sequence and a simple mathematical model. Taken together, the static and dynamic features of the pancreas at gadolinium-enhanced MRI, diffusion-weighted MRI, and sMRCP allow accurate information for the diagnosis of chronic pancreatitis to be obtained even at early phases (Table 49.1).

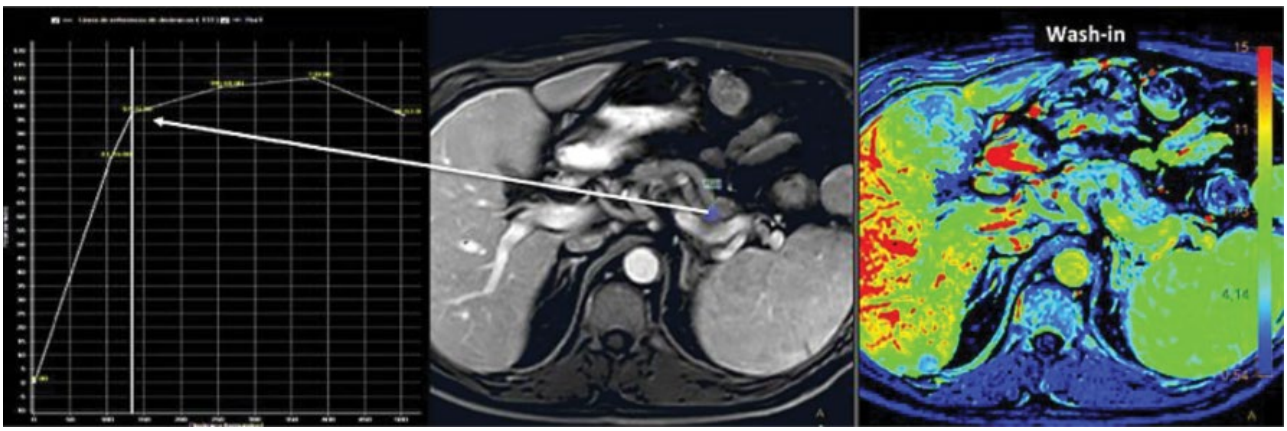


**Figure 49.3** MR perfusion study of the pancreas in chronic pancreatitis. Time-intensity curve (left), axial contrast-enhanced arterial-phase fat-sat T1-weighted MR images (middle), and wash-in parametric map (right).

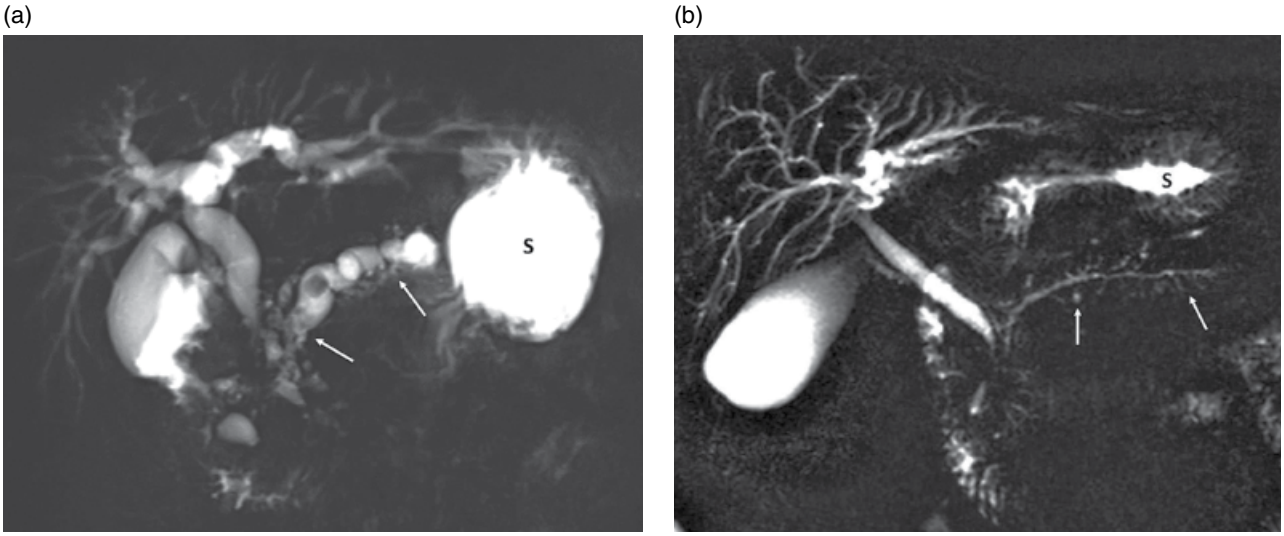


**Figure 49.4** Severe (a) and mild (b) ductal changes of chronic pancreatitis at MR cholangiopancreatography. (a) Diffuse pancreatic duct dilatation (arrows) with filling defects representing pancreatic calculi. The bile duct is dilated due to stricture at the level of the pancreatic head. (b) Diffuse dilatation of the lateral side-branches of the pancreatic duct (arrows) in a different patient. S, stomach.

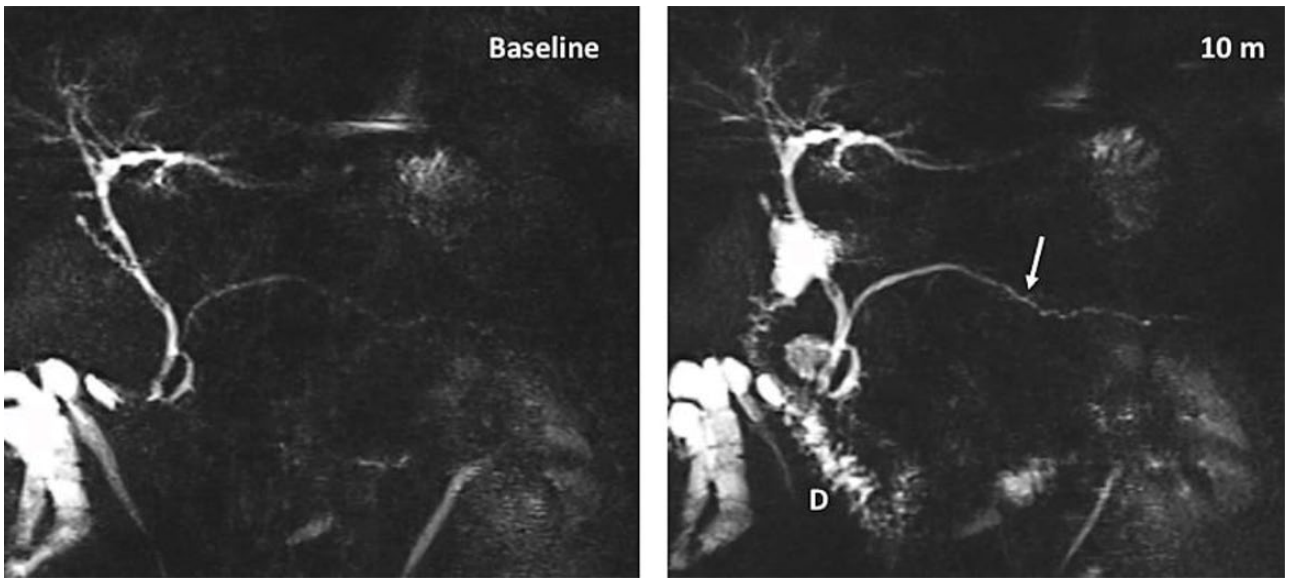


**Figure 49.5** Early ductal changes of chronic pancreatitis at secretin-enhanced MRCP. MR pancreatography obtained at baseline (left) and 10 minutes after intravenous administration of secretin (right). The use of secretin is able to demonstrate the dilatation of side-branches of the pancreatic duct (arrows) as a sign of early chronic pancreatitis.

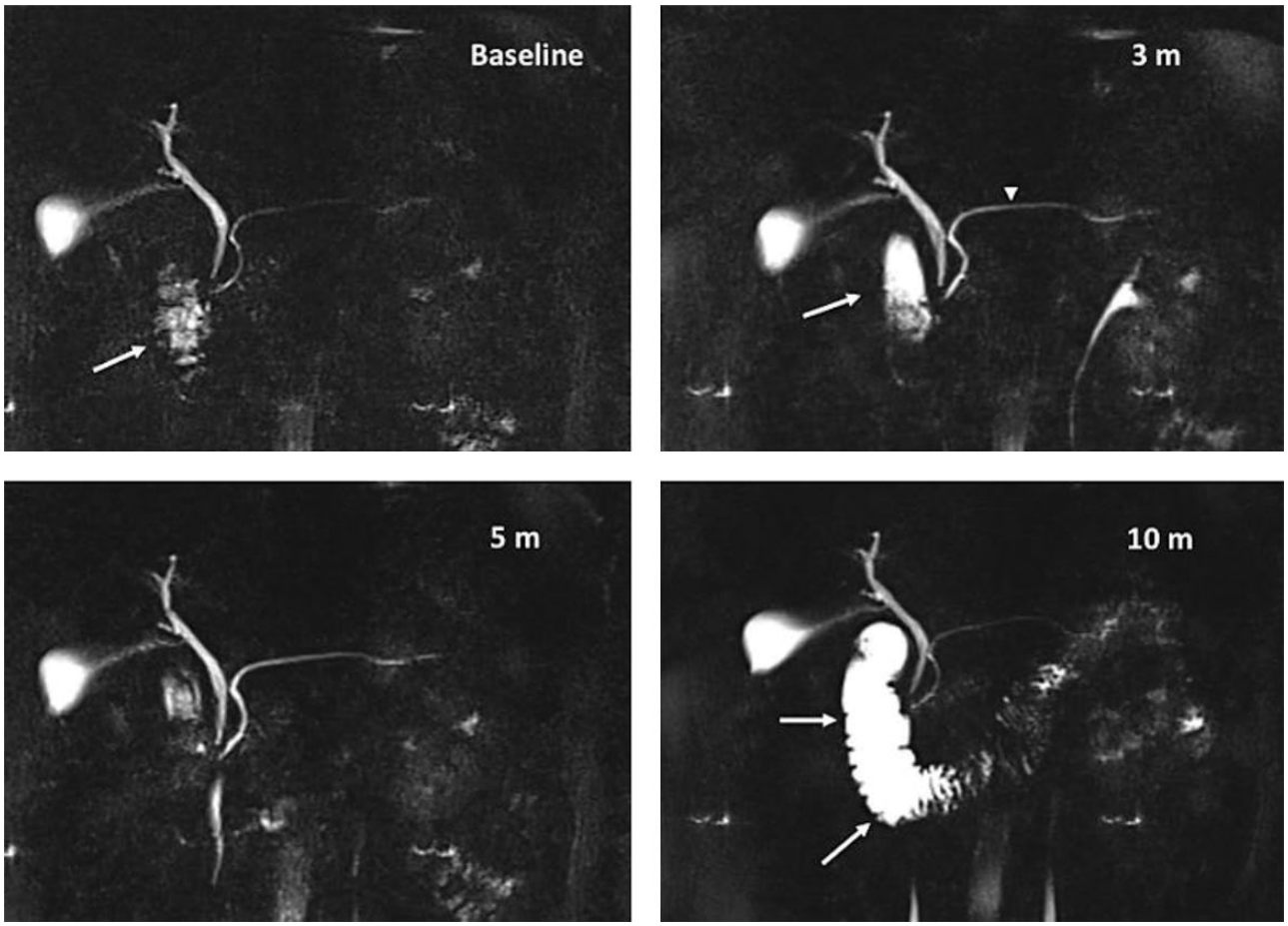


**Figure 49.6** Normal MR pancreatography obtained at baseline and at 3, 5, and 10 minutes after intravenous secretin administration. Normal dynamic changes of the pancreatic duct after secretin are characterized by early dilatation (arrowhead) and late recovery to normal size at 10 minutes. Increased duodenal filling after secretin stimulation correlates to pancreatic exocrine secretion (arrows at 10 minutes).

## Differential Diagnosis of Mass-Forming Chronic Pancreatitis and Pancreatic Cancer

Differential diagnosis of mass-forming chronic pancreatitis and pancreatic cancer remains a clinical challenge. In addition, chronic pancreatitis increases the risk for cancer and therefore both diseases may coexist. As for the diagnosis of chronic pancreatitis, CT scan and MRI are essential diagnostic tools in this setting.

### CT Scan

CT scan is the most widely used imaging modality for the evaluation of solid pancreatic masses and the most comprehensive tool for the diagnosis and staging of pancreatic malignancies. Nevertheless, differential diagnosis between mass-forming chronic pancreatitis and ductal adenocarcinoma based on CT scan can be challenging. Local pancreatic cancer is usually hypovascular and will therefore show a low attenuation on contrast-enhanced CT. In triple-phase CT scan, contrast enhancement peak in normal pancreatic tissue occurs during the first phase (early-washout pattern), it is delayed to the second phase in chronic pancreatitis (delayed-washout pattern), and it gradually increases in pancreatic cancer [8]. Secondary signs such as abrupt cut-off of the pancreatic duct with significant proximal dilatation and presence of double duct sign suggest pancreatic adenocarcinoma, whereas irregular dilatation of the main pancreatic duct with gradual narrowing and presence of intraductal calcifications are specific findings of mass-forming chronic pancreatitis. MDCT scan allows a better recognition of some typical signs of advanced malignancy such as vascular encasement, lymphadenopathy, or distant metastasis. Diagnostic sensitivity, specificity, and overall accuracy of this technique for pancreatic adenocarcinoma are 94.1%, 83.0%, and 90.4%, respectively [8]. The use of dual-energy CT can be used to improve the sensitivity and specificity of MDCT for differentiating mass-forming chronic pancreatitis from pancreatic cancer [9]. By the use of this technique, normalized iodine concentrations during two double phases are significantly lower in chronic pancreatitis than in pancreatic cancer.

### MRI/s-MRCP

MRI with the use of conventional sequences is considered to be less sensitive than other imaging modalities for the differential diagnosis of solid pancreatic masses. In fact, sensitivity of MRI for the diagnosis of pancreatic cancer was shown to be 84% in a meta-analysis, compared to the sensitivity of 91% obtained with CT scan [10]. However, MRI appears to be superior to other imaging modalities in visualizing tumors within areas of pancreatic inflammation. T1-weighted images have similar features but T2-weighted images show different signal intensity patterns in chronic pancreatitis and pancreatic cancer [11] (Figs 49.7 and 49.8). MRCP may provide additional information related to the involvement of the main pancreatic and bile ducts, which may be of help in this clinical setting. MRCP may demonstrate obliteration and dislocation of the dilated side-branches caused by a tumor, and duct distortion within the mass in chronic pancreatitis (Figs 49.7 and 49.8). After secretin injection, the main pancreatic duct remains irreversibly stenotic and obstructed due to the neoplastic process. However, it appears patent, although narrowed, in mass-forming chronic pancreatitis. The delineation of the duct penetrating through the stenotic area means that a smoothly stenotic or normal pancreatic duct penetrates through the mass, which is frequently seen in inflammatory pancreatic masses (Fig. 49.7). These findings have a sensitivity of 86% and specificity of 95% in distinguishing between benign and malignant pancreatic masses [12]. Finally, new techniques such as diffusion-weighted MRI, gadolinium-enhanced 3D gradient echo, time signal intensity curve during contrast enhanced MRI, and magnetic resonance spectroscopy may allow increased accuracy of MRI in this setting.

## CT and MRI for Autoimmune Pancreatitis

Autoimmune pancreatitis is important to distinguish from other forms of chronic pancreatitis and pancreatic cancer. Imaging plays an important role in the diagnosis of autoimmune pancreatitis, but it is not diagnostic by itself. Three different patterns of autoimmune pancreatitis can be recognized on imaging: diffuse or sausage-like pancreas enlargement, focal or well-defined mass, and multifocal. Thus, diffuse or localized enlargement of the pancreas with diffuse or segmental narrowing of the pancreatic duct with irregular wall are typical findings of autoimmune pancreatitis on CT and MRI [2].

On contrast-enhanced CT there is decreased enhancement of the involved parenchyma in the arterial phase and delayed enhancement in the late phase.

On MR imaging, the pancreas shows decreased T1 fat-suppressed signal intensity, increased T2 signal intensity, and delayed enhancement. A rim-like capsule of decreased

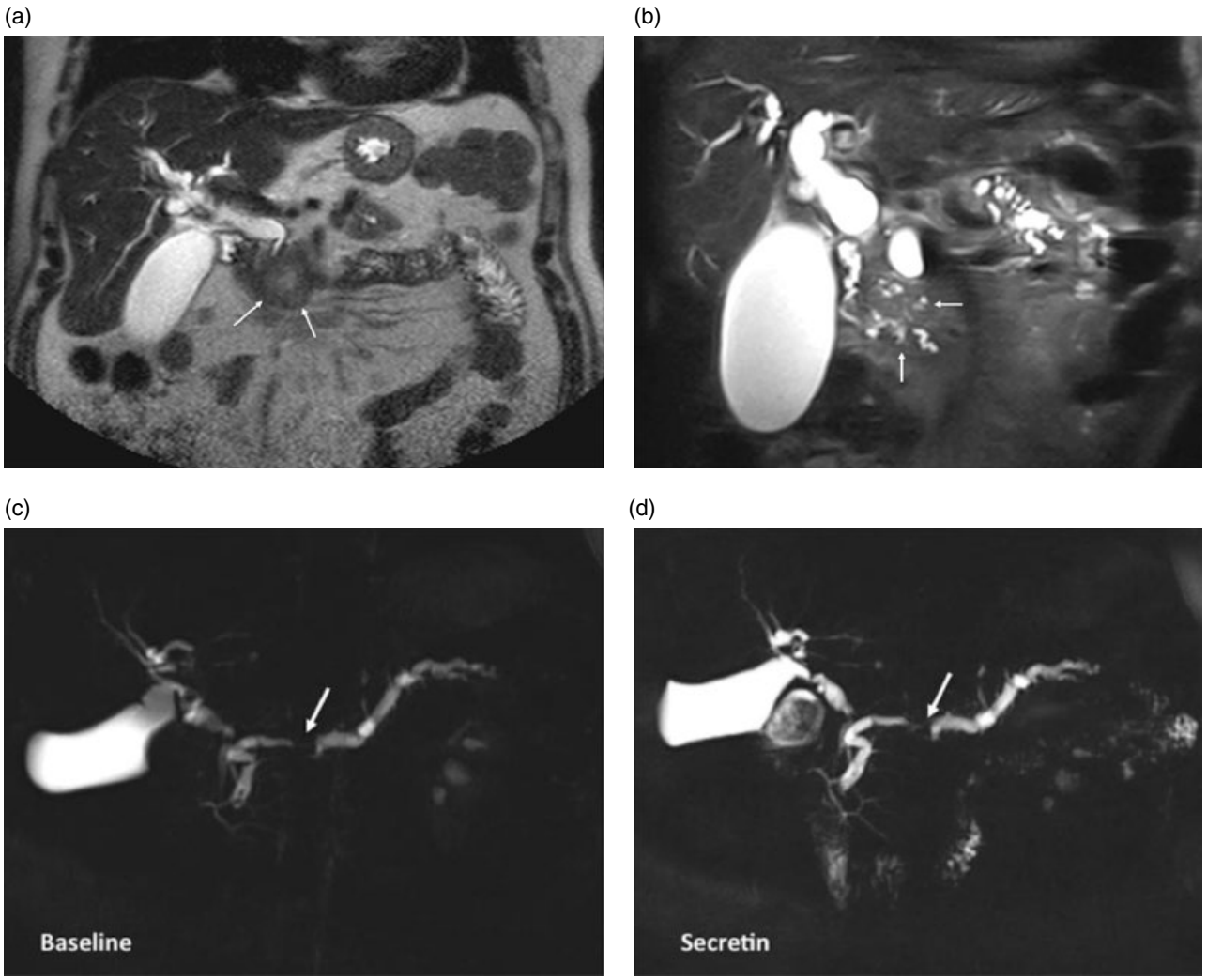


**Figure 49.7** MR imaging of inflammatory pancreatic mass in the context of chronic pancreatitis. (a) Coronal T2-weighted turbo spin echo (TSE) MR image reveals a heterogeneous mass in the head of the pancreas (arrows) associated with bile duct and gallbladder dilatation. (b) MR cholangiography demonstrates a bile duct dilatation and stricture at the level of the intrapancreatic segment in the same patient. The duct-penetrating sign is also evident. (c,d) Dynamic MR pancreatography does not show changes in ductal size after intravenous secretin administration but it allows the delineation of the duct penetrating through the stenotic area (arrows).

T1 fat-suppressed signal intensity and increased T2 signal intensity with associated delayed enhancement is suggestive of fibrosis [13]. MRCP can show diffuse or segmental irregular narrowing of the main pancreatic duct that usually resolves after steroid therapy.

In cases of focal mass, multiplicity, geographic shape, delayed enhancement, capsule-like rim enhancement, low apparent diffusion coefficient value, and segmental strictures of the common bile duct or main pancreatic duct favor focal autoimmune pancreatitis over pancreatic cancer [13].

## CT and MRI for Groove Pancreatitis

Groove pancreatitis is an uncommon type of focal chronic pancreatitis affecting the pancreaticoduodenal groove. The classic MDCT features are ill-defined soft tissue within the pancreaticoduodenal groove with or without delayed enhancement due to fibrosis. Small cysts may be seen along the medial wall of the duodenum or in the pancreatic groove. Fibrotic changes affecting the pancreatic head may also be observed as a hypointense mass-like appearance of the parenchyma.

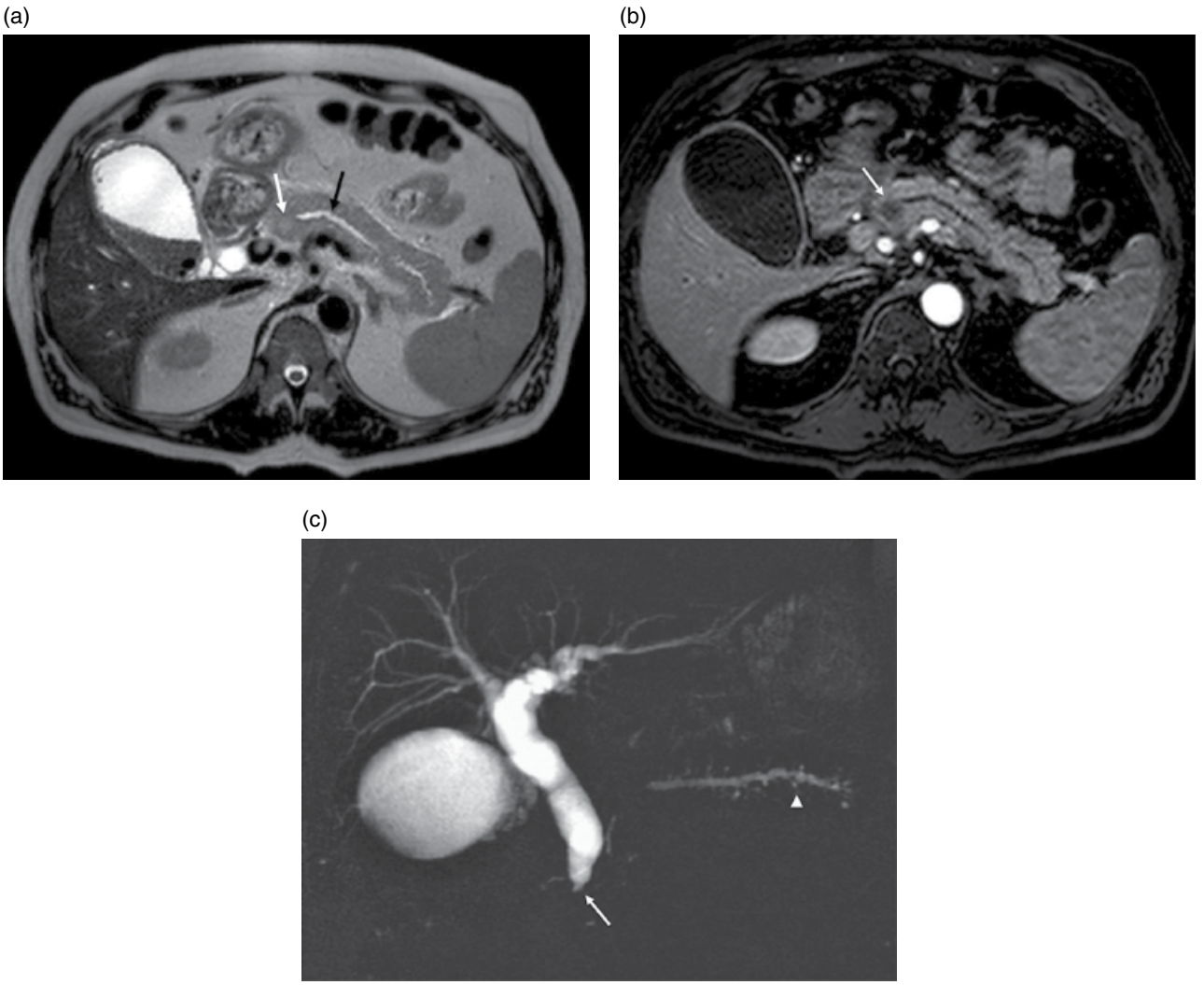


**Figure 49.8** MR imaging in a patient with a small pancreatic cancer. (a) Axial T2-weighted turbo spin echo (TSE) MR image at the level of the head of the pancreas evidences a discrete nodular mass (white arrow) associated with irregular ductal dilatation (black arrow). (b) Dynamic contrast-enhanced portal-phase axial fat-sat T1-weighted MR image evidences a hypovascular pattern of the lesion. (c) MRCP shows a bile duct dilatation and stricture (arrow) at the level of the intrapancreatic segment. Note the presence of changes suggestive of chronic pancreatitis in the tail of the gland with dilatation of the main duct and lateral branches (arrowhead).

On MR imaging, groove pancreatitis is characterized by sheet-like mass that is hypointense on T1-weighted images and isointense or slightly hyperintense on T2-weighted images relative to the pancreas (Fig. 49.9). As in CT scan, this mass may show a delayed and heterogeneous gadolinium enhancement on MRI. If the pancreatic head is affected, pancreatic parenchyma is hypointense on T1-weighted images, frequently associated with atrophy, smooth ductal narrowing, and pre-stenotic ductal dilatation. Duodenal thickening and cysts may be found and better displayed on T2-weighted images [2] (Fig. 49.9).

Focal thickening and abnormal increased enhancement of the second part of the duodenum, and cystic changes in the region of the pancreatic accessory duct support the diagnosis of groove pancreatitis over pancreatic cancer with an accuracy of 87.2% and negative predictive value for cancer of 92.2% [14].

## Complications of Chronic Pancreatitis

The most common complications of chronic pancreatitis include pseudocysts, portal and splenic vein thrombosis, biliary obstruction, duodenal obstruction, pseudoaneurysms, and pancreatic cancer. Diagnosis of pancreatic cancer in the context of chronic pancreatitis is discussed above. Non-neoplastic complications of chronic

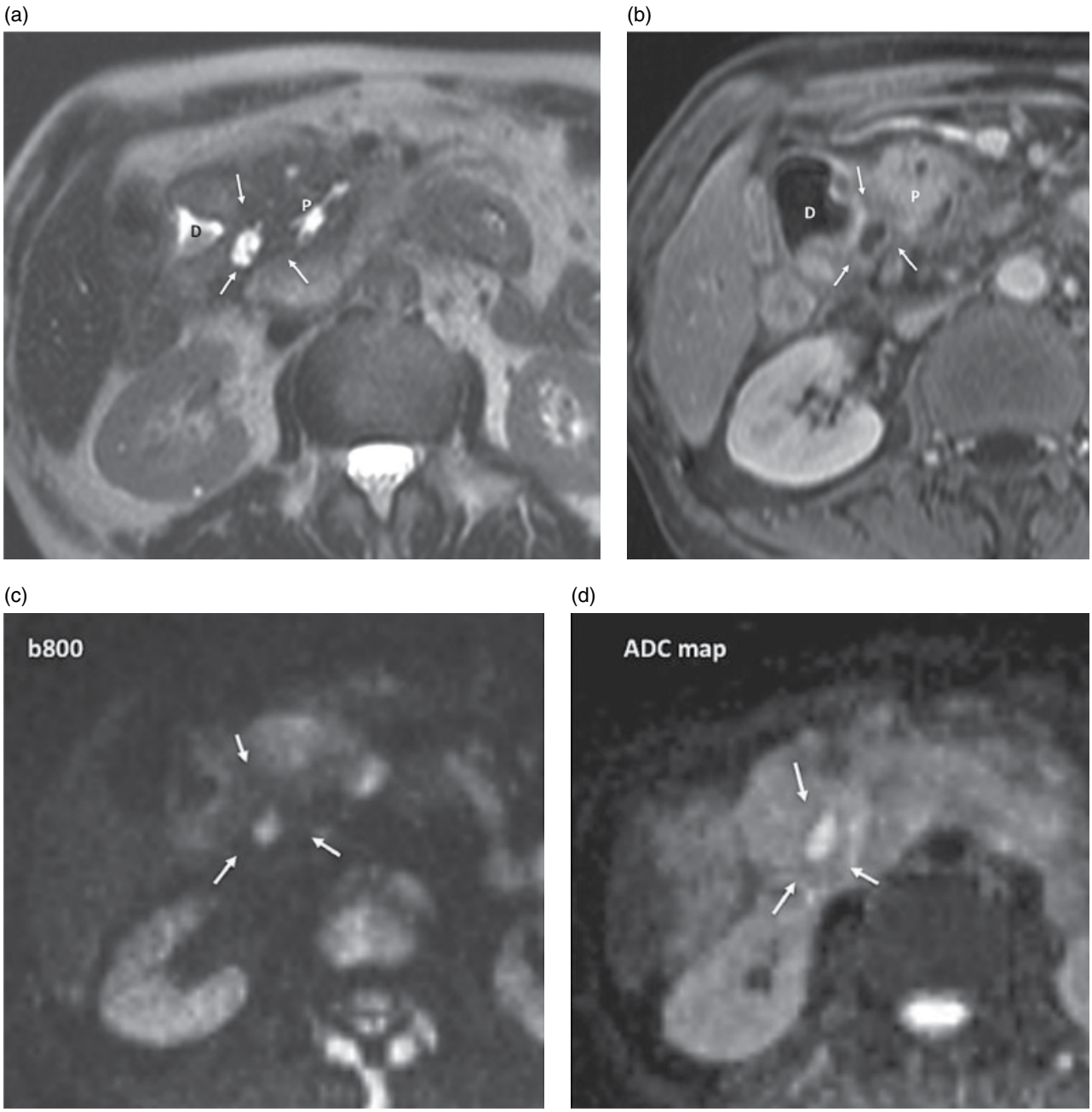


**Figure 49.9** Groove pancreatitis on MR imaging. (a) Axial T2-weighted turbo spin echo (TSE) MR image at the level of the head of the pancreas evidences a subtle hypointense mass (white arrows) involving the "groove" between the pancreatic head (P) and the duodenum (D). (b) Contrast-enhanced portal-phase axial fat-sat T1-weighted MR image shows a hypovascular mass (white arrows) with cystic areas in the duodenal wall. (c,d) Diffusion-weighted image (c) (*b* value = 800) and ADC map (d) do not evidence restriction at the level of the mass (arrows). Discrete low signal on ADC map and hypointensity on high *b*-values images (*b* = 800) suggest fibrosis.

pancreatitis are well detected and evaluated with CT and MRI (Figs 49.7 and 49.10). MRI and MRCP may be superior to CT in detecting specific complications such as pseudocysts, fistula formation, distal common biliary dilatation, and vascular complications [3]. However, CT is especially helpful because it can better exclude other causes of abdominal pain or weight loss besides chronic pancreatitis.

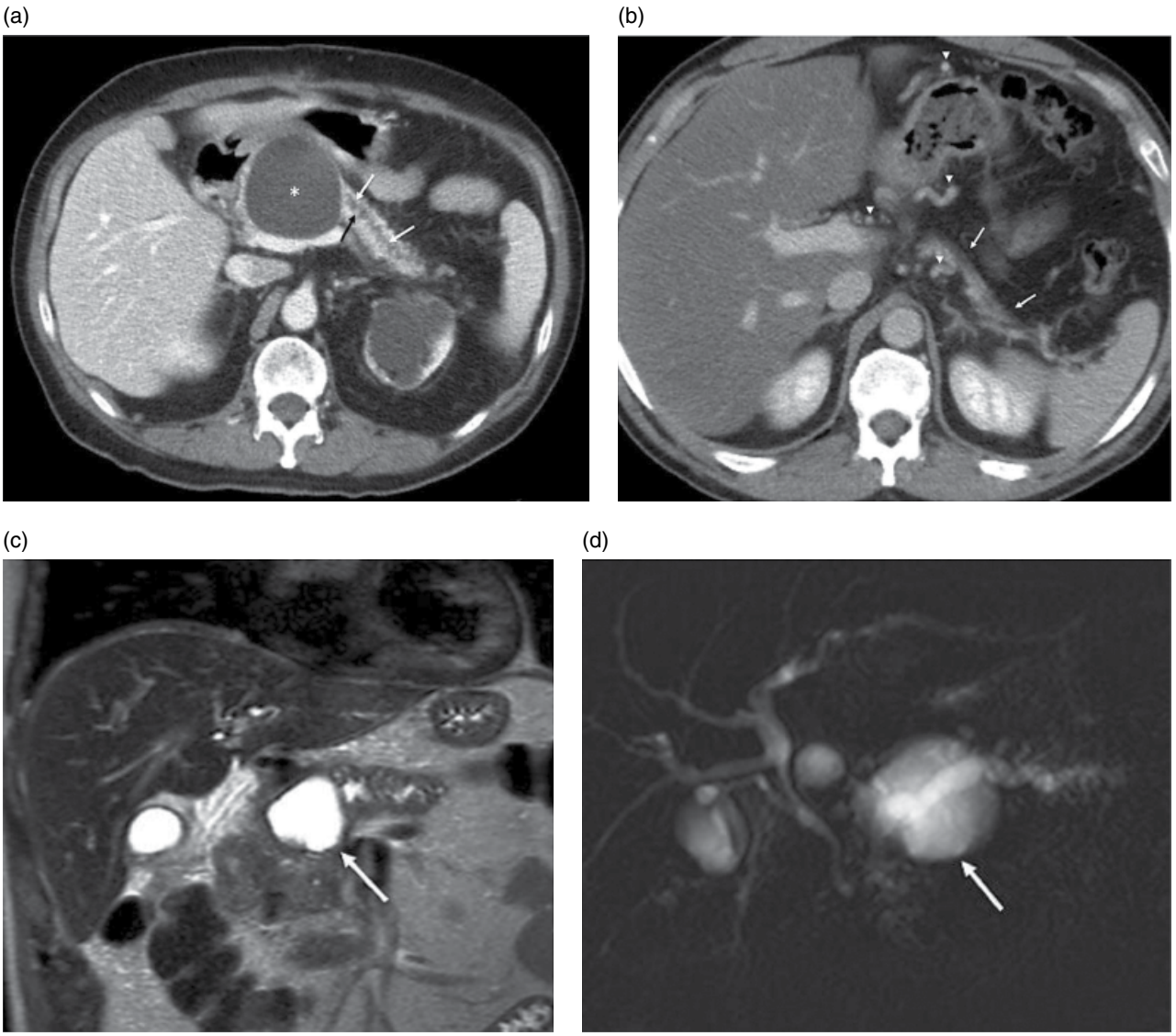


**Figure 49.10** Complications of chronic pancreatitis. (a) Axial contrast-enhanced portal-phase CT image demonstrates a pseudocyst (asterisk), dilatation of the main pancreatic duct and its side-branches (white arrows) and intraductal calculi (black arrow). (b) Axial contrast-enhanced portal-phase CT image demonstrates marked parenchymal atrophy (arrows) and collateral circulation secondary to splenic vein thrombosis (arrowheads). (c) Coronal T2-weighted turbo spin echo (TSE) MR and (d) MRCP show a cystic mass (white arrows) corresponding to a pseudocyst and imaging findings of chronic pancreatitis (dilatation of main duct and side-branches).

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# Chronic Pancreatitis: Risk Factors in Cancer

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## Introduction

In the late nineteenth century, the German pathologist Rudolf Virchow proposed that there was a close link between inflammation and cancer, based on cellular studies made possible by microscopy. Since then it has been observed that inflammatory diseases such as esophagitis, gastritis, and colitis sometimes precede the development of cancer in these organs. Throughout the twentieth century anecdotal reports of pancreatitis preceding pancreatic cancer have emerged. These isolated reports suggested a possible link between chronic pancreatitis and pancreatic cancer and eventually led to a large retrospective cohort analysis conducted near the end of the twentieth century. In this chapter we review and summarize the evidence linking chronic pancreatitis and pancreatic cancer.

## Descriptive Findings

Acute pancreatitis, chronic pancreatitis, and pancreatic cancer are the three most common pancreatic diseases. How does their incidence compare? Acute pancreatitis is one of the commonest gastrointestinal disorders and has an estimated incidence of about 13–45/100,000 per year [1]. The incidences of chronic pancreatitis and pancreatic cancer are similar to each other, with age-standardized incidence rates of around 10/100,000/year.

Figure 50.1 illustrates the relationship between these three diseases and the potential pathways for progression from acute to chronic pancreatitis and, in some patients, to pancreatic cancer. In patients with gallstone-related pancreatitis, cholecystectomy performed on a timely basis eliminates the major source for gallstones and precludes additional attacks. But acute pancreatitis also develops from many other causes, and if the cause is heavy drinking, smoking, or a genetic disorder, recurrent attacks of acute pancreatitis (recurrent pancreatitis) may occur and disease progression may then lead to chronic pancreatitis. Of patients who develop chronic pancreatitis, a small proportion will develop pancreatic cancer. The average age at diagnosis of chronic pancreatitis in patients with alcohol-related disease is about 45–55 years, approximately a decade earlier than the average age of onset of pancreatic cancer. This time sequence indicates that the direction of causality is compatible with a progression from benign to malignant disease.

Other than age, what are some of the other similarities and differences between chronic pancreatitis and pancreatic cancer? For both diseases smoking and obesity are recognized risk factors, whereas heavy drinking is strongly linked to chronic pancreatitis, but is associated only with a modest increased risk for pancreatic cancer [2]. Both diseases are also more frequent in black than in white populations, and diabetes frequently accompanies both diseases.

## Measuring the Strength of the Pancreatitis–Pancreatic Cancer Association

In the initial multicenter cohort study of 2015 patients with well-documented chronic pancreatitis followed up for a minimum of 5 years after the diagnosis of chronic pancreatitis, the risk of pancreatic cancer was 14.4 (95% CI: 8.5–22.8) times higher than that in the background population. The risk was similar in all six study countries and was also similar in patients with either alcoholic or

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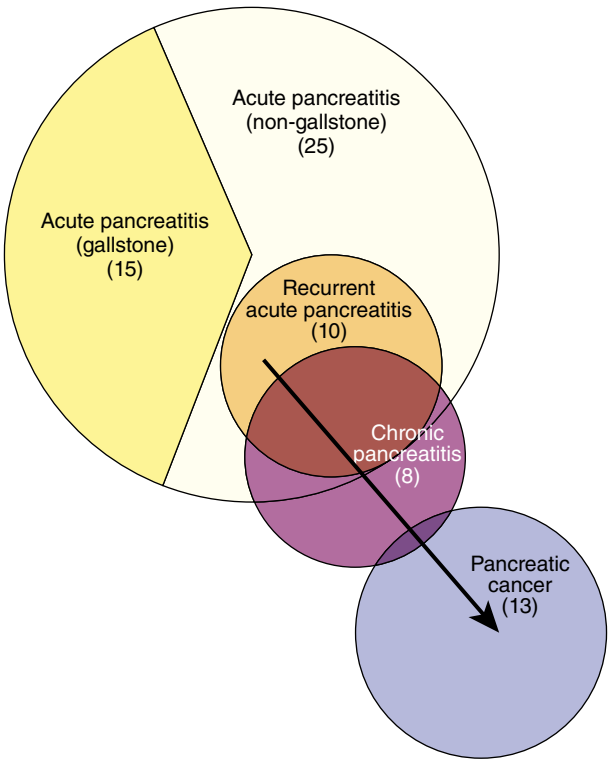


**Figure 50.1** Incidence rates for pancreatic diseases in the United States. Numbers inside circles indicate incidence rates per 100,000 population. The arrow indicates the progression from benign to malignant disease. Note the small overlap between the circles representing chronic pancreatitis and pancreatic cancer. *Source:* Yadav and Lowenfels 2013 [1]. Reproduced with permission of Elsevier.

nonalcohol pancreatitis [3]. Over a follow-up period of up to 20 years, the cumulative incidence of pancreatic cancer was 4%. This implies that chronic pancreatitis, although a strong risk factor, explains only a small proportion of the total burden of pancreatic cancer. Also, in contrast to the 29 patients who died from pancreatic cancer, 137 patients in the group died from other types of cancers. Because of lifestyle factors such as smoking and heavy alcohol drinking, most cancer deaths in patients with chronic pancreatitis will be from nonpancreatic cancer.

Since publication of this report, several additional studies have looked at the relationship between chronic pancreatitis and pancreatic cancer [4–6]. Raimondi and coworkers published a meta-analysis in 2010 which included 18 additional studies [4]. There were 11 studies of pancreatitis, type unspecified, four new studies of chronic pancreatitis, and three studies of hereditary pancreatitis. The pooled risk estimates were as follows: pancreatitis (type unspecified) relative risk (RR) = 5.1 (95% CI: 3.5–7.3), chronic pancreatitis RR = 13.3 (95% CI: 6.1–29), and hereditary pancreatitis RR = 69 (95% CI: 56–84). This meta-analysis also included one report of the risk of pancreatitis in tropical pancreatitis where the RR was 100 (95% CI: 37–218) (Fig. 50.2).

In 2014 Tong and coworkers published a systematic review of epidemiologic studies linking pancreatitis and pancreatic cancer [5]. This report contained 14 case–control studies and three cohort studies and found a pooled odds ratio of 7.1 (95% CI: 6.4–7.8). As in the previous meta-analysis, the results were stronger in cohort studies than in case–control studies. In another pooled analysis of 10 case–control studies, Duell and coworkers reported a nearly threefold increased risk of pancreatic cancer in patients where there was a minimum of 2 years separating the diagnosis of pancreatitis from pancreatic cancer [6].

A nationwide report from Denmark provides further evidence for a strong link between pancreatitis and pancreatic cancer [7]. In this follow-up study of nearly 12,000 patients with chronic pancreatis and nearly 120,000 matched controls the authors found a 6.9-fold increased risk of death from pancreatic cancer in pancreatitis patients as compared to the control population. Again, the risk of pancreatic cancer was similar in patients with either alcoholic or nonalcoholic pancreatitis.

## Discussion

Reviewing the evidence accumulated over several decades reveals a strong link between chronic pancreatitis and pancreatic cancer. Clinicians must still be aware of reverse causality because one symptom of pancreatic cancer can be sudden onset of pancreatitis in the absence of known risk factors. However, the evidence from several long-term follow-up studies with exclusion of early-onset pancreatic cancer confirms the pancreatitis–pancreatic cancer link. The findings of this relationship in the pancreas agrees with information from other organs, and confirms Virchow's nineteenth-century hypothesis. As yet we do not have a full understanding of the mechanisms underlying the transformation from a nonmalignant disease to cancer.

All the reports indicate that the cumulative risk of pancreatic cancer in patients with longstanding confirmed chronic pancreatitis is low—probably less than 5%. This implies that until we develop noninvasive screening procedures with greater sensitivity and specificity than are currently available, screening patients with chronic pancreatitis is not likely to be rewarding.

Hereditary pancreatitis is a rare inherited autosomal dominant genetic disorder that causes early-onset pancreatitis characterized by recurrent attacks eventually leading the chronic pancreatitis. As with other risk factors, such as smoking, long duration of exposure

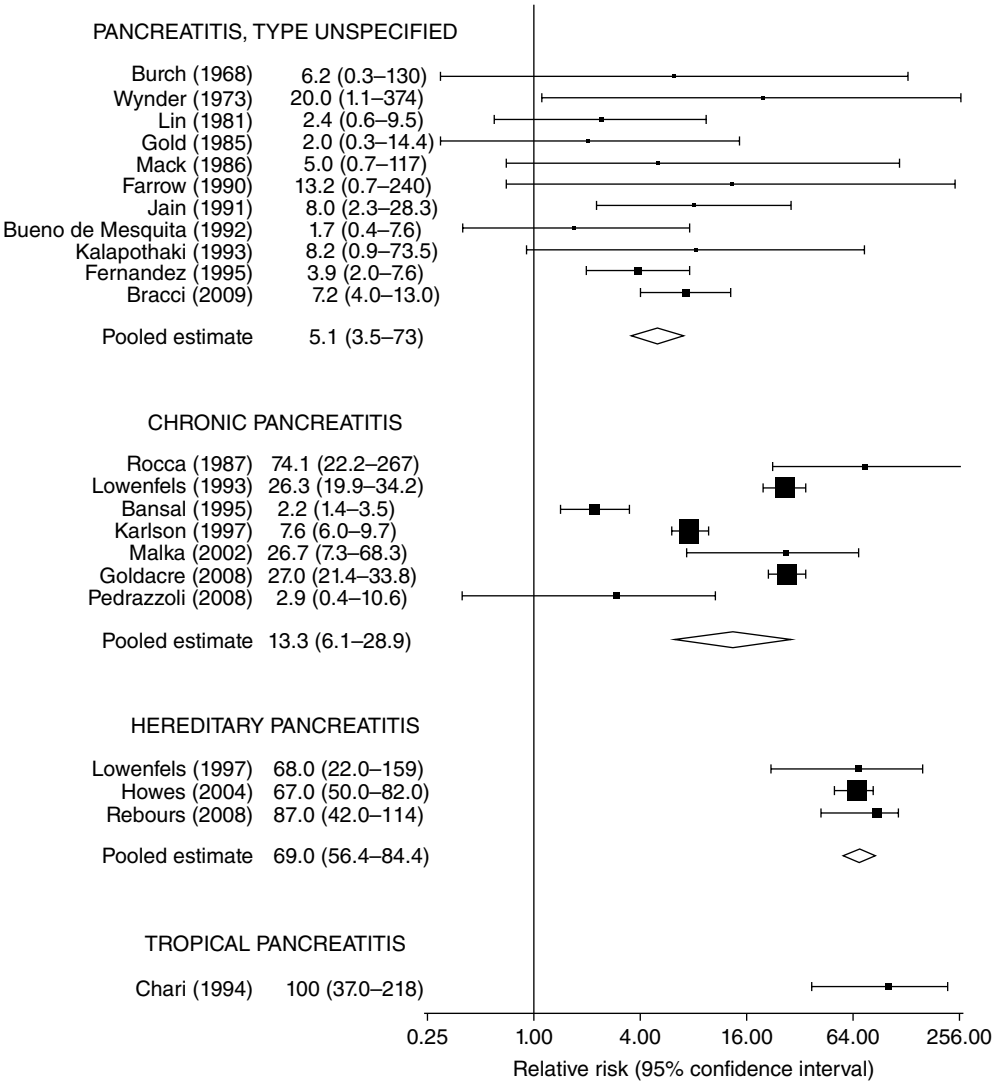


**Figure 50.2** Meta-analysis showing study-specific and summary risk estimates with 95% confidence intervals for the association between different types of pancreatitis and pancreatic cancer. *Source:* Raimondi et al. 2010 [4]. Reproduced with permission of Elsevier.

increases the risk of cancer. Because patients with this type of pancreatitis have about a 70% lifetime risk of developing pancreatic cancer, minimally invasive imaging screening with endoscopic ultrasound (EUS), multiphasic helical computed tomography (CT) or magnetic resonance imaging/magnetic resonance cholangiopancreatography (MRI/MRCP) have been proposed for patients with the hereditary pancreatitis phenotype, beginning at the age of 40 years [8].

What are fruitful areas for additional research that might benefit patients with underlying pancreatitis? Pancreatic cysts are now being detected with increasing frequency and we need to be able to identify subgroups of these patients who have an increased risk of pancreatic cancer. Pancreatic cancer can mimic nonmalignant disease such as autoimmune pancreatitis, leading in some patients to unnecessary pancreatic surgery [9,10]. We need to develop biological tests and/or biomarkers that can reliably distinguish between chronic pancreatitis and pancreatic cancer. Finally, collecting and storing biologic samples from patients with well-documented chronic pancreatitis will help us improve our understanding of the gradual transition of pancreatitis to pancreatic cancer.

The irreversible pathologic changes characteristic of chronic pancreatitis make this disease difficult to treat and the progressive cellular disruption of glandular and ductal tissues leads eventually, in some patients, to pancreatic cancer. Efforts to reduce lifestyle factors such as smoking and alcohol drinking in patients with recurrent bouts of acute pancreatitis offer an opportunity to reduce the burden of this disabling disease and prevent the occurrence of pancreatic cancer [2].

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# Conservative Treatment of Chronic Pancreatitis

## 51

## Pain Management in Chronic Pancreatitis

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### Introduction

Pain is the leading symptom in patients with chronic pancreatitis. The aim of treatment is symptom control, improvement in quality of life, and prevention of ongoing damage to the gland. Chronic pancreatitis cannot be cured.

The main reason for hospitalization in patients with chronic pancreatitis is a constant severe and dull pain located in the mid-epigastrium, which radiates to the back and worsens after fatty meals. Because the pain has a multifactorial etiology, treatment needs to be variable. There are various theories as to the origin of the pain but, to date, its development is not fully understood and various different theories exist. More detailed information is presented in Chapter 41.

### Neuropathologic Theory

The pancreas is highly innervated through the vagal and splanchnic nerves. Unlike other visceral organs, it has primary afferent nociceptors that only respond to pain stimuli. These fibers have a subgroup called "silent nociceptors," which are only active during inflammation. Pancreatic nociceptors are activated by a variety of noxious stimuli. Those located on the supplying blood vessels are activated mechanically through stretching, ischemia, and necrosis. Others are affected chemically by inflammatory mediators [1].

The inflammation is mostly caused by noxious stimuli (the most common being alcohol and nicotine). These damage the parenchyma and the damaged tissue supports the inflammation by releasing proinflammatory mediators. The nerve endings then become sensitized to further stimulation. The silent nociceptors can be activated by peripheral inflammation, which increases the afferent activity in the spinal cord. The stimulation is transferred to the central nervous system and by repeated stimulation a peripheral sensitization develops. Released neurotransmitters are also transported to nerve endings located on the pancreas where they act as proinflammatory transmitters, resulting in neurogenic inflammation which causes edema and the infiltration of inflammatory mediators.

In summary, three factors lead to neurogenic pain: chronic stimulation through nociceptive pathways, peripheral sensitization due to inflammatory processes in the pancreas itself, and neural damage [2]. Currently these neurophysiologic aspects are the main focus of studies on pain in patients with chronic pancreatitis.

### The Plumbing Theory

According to the "plumbing theory," pain in patients with chronic pancreatitis originates in the plumbing of the pancreatic duct and is caused by intraductal calculi or duct strictures, leading to increased pressure in the gland. This is the theory on which interventional therapy is based. Compared to recently discovered neuropathologic factors, the theory that pancreatic duct hypertension causes pain is rather old. It was first described in the 1970s and interventions to drain the pancreatic duct based upon it became an option for treating pain.

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Presently, few studies exist on the measurement of intraductal and intraparenchymal pressure. In addition, there is no evidence for the impact of developing chronic pancreatitis and evolving chronic pain in existing studies.

According to the plumbing theory, intrapancreatic pressure is described as a "compartment-like-syndrome," with chronic inflammation leading to fibrosis of the parenchyma and capsule, resulting in tension [3]. Different studies, however, have failed to substantiate these theories. The neurophysiologic theory seems to be closest to reality.

If pain in chronic pancreatitis develops due to a combination of the neuropathic pathway and the plumbing theory, it explains why treatments aiming at the nociceptive pain, such as opioid analgesia, and endoscopic or surgical interventions sometimes fail to ease the pain. To visualize possible central sensitization, electroencephalography and (functional) magnetic resonance imaging have been used [4].

## Pain Measurement

When evaluating therapy for a patient with chronic pancreatitis, objective parameters are needed to find out how much the patient is limited in his or her daily life by the symptoms of chronic pancreatitis. To measure quality of life, the European Organisation for Research and Treatment of Cancer (EORTC) questionnaire is a reliable base. The Izbicki pain score questionnaire correspondingly measures pain that lowers the quality of life with regard to pain frequency, its intensity (using a visual analog scale), the effectiveness of analgesia, and disease-related inability to work or take part in social activities [5] (Table 51.1). It is designed specifically for patients with chronic pancreatitis and is a reliable and comparable instrument, which focuses on the particular burdens of these patients. The score ranges from 0 to 100 in total [5]. A pain score of ≥50 is considered to be strong pain.

Examples of analgesic medication are given in Table 51.2.

**Table 51.1** Izbicki pain score.

| | | | | | | | | | | Points |
|---|---|---|---|---|---|---|---|---|---|---|
| **Frequency of pain attacks** | | | | | | | | | | |
| Daily | | | | | | | | | | 100 |
| Several times a week | | | | | | | | | | 75 |
| Several times a week | | | | | | | | | | 50 |
| Several times a week | | | | | | | | | | 25 |
| None | | | | | | | | | | 0 |
| **Visual analog scale (VAS)** | | | | | | | | | | |
| 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
| No pain | | mild | | moderate | | severe | | very severe | | worst imaginable pain |
| 0 points | | | | | | | | | | 100 points |
| **Analgesic medication** | | | | | | | | | | |
| Morphine | | | | | | | | | | 100 |
| Buprenorphine | | | | | | | | | | 80 |
| Pethidine | | | | | | | | | | 20 |
| Tramadol (μ-agonist, max. 600 mg/day) | | | | | | | | | | 15 |
| Metamizole | | | | | | | | | | 3 |
| Acetylic acid | | | | | | | | | | 1 |
| **Duration of inability to work due to disease** | | | | | | | | | | |
| Permanent | | | | | | | | | | 100 |
| 1 year | | | | | | | | | | 75 |
| 1 month | | | | | | | | | | 50 |
| 1 week | | | | | | | | | | 25 |
| No inability to work during the last year | | | | | | | | | | 0 |

**Table 51.2** Examples of analgesic medication for chronic pancreatitis.

| Medication | Dose |
|---|---|
| Morphine | |
| Buprenorphine | Partial opioid agonist with full effect at the μ-receptor |
| | Not first choice for acute pain |
| | Daily dose depends on chosen application form |
| Pethidine | Opioid agonist with high affinity to the μ-receptor |
| | max. 500 mg/day |
| | Metabolism through the liver with active metabolite norpethidine and elimination through the kidneys |
| | May induce a serotonin syndrome |
| Tramadol | Serotonin and noradrenaline reuptake inhibitor and μ-agonist (strong relation to nausea and vomitus, may induce a serotonin syndrome) |
| | Max. 400 mg/day |
| | Metabolism through the liver |
| Metamizole | As prodrug activation through hydrolysis, bioavailability is a bit higher when taken orally rather than parenterally |
| | Unselective COX inhibitor |
| | Analgesic, antipyretic, and spasmolytic |
| | Max. 4 g/day |
| | Elimination mostly through the kidneys |
| Acetylic acid (as representative for NSAID) | Unselective and irreversable COX inhibitor, analgesic, antipyretic, and anti-inflammatory, high first-pass effect |
| | Max. 3 g/day |
| | Inactivation through the liver and elimination through the kidneys |

This is not a complete list. Prior to any medical treatment the daily medication, individual risk factors, and side-effects should be evaluated.

## Treatment Options for Patients with Chronic Pancreatitis

As the cause of pain in chronic pancreatitis is not completely clear, the most useful hypothesis for optimal therapy might be a multifactorial understanding of the development of pain.

Change of lifestyle, diet, and medical treatment form the basis of initial treatment and in a small number of patients symptoms will be treated satisfactorily. In most cases, however, nutritional and medical treatments are the first step in the management of chronic pancreatitis before considering endoscopic or surgical approaches.

Even when patients remain abstinent from alcohol and nicotine, pain often persists. Abstinence is recommended to reduce the noxious stimuli to decelerate the progression of the chronic inflammation. Pain relief is attempted by analgesia, beginning with nonsteroidal anti-inflammatory drugs and ending with a combination of strong opioids (as recommended by the World Health Organization). Opioids may have substantial adverse gastrointestinal effects, including constipation, reflux, nausea, and abdominal pain—a phenomenon known as opioid-induced bowel dysfunction.

Recent studies have shown a positive effect of pregabalin in pain management, including in patients with persistent pain after surgery. The side-effects of pregabalin were only moderate. Patients complained of a slightly drunk feeling, which is negligible compared to strong opioids and their gastrointestinal side-effects [6,7].

Because of the pain, patients often abuse analgesics. Medical and dietary therapy can ameliorate the symptoms for a small number of patients. Nonetheless, alcohol abstinence does not disrupt the destructive progress nor alleviate the pain [8,9]. In patients where conservative treatment fails to provide improvement, interventional procedures are indicated.

The major challenge in managing chronic pancreatitis seems to be the evaluation of the optimal interventional treatment for each patient individually. Not only is it a question of what kind of therapy the patient will profit from, but also a question of finding the right time when each therapy is best.

The vast majority of patients present with dilatation of the duct or enlarged pancreatic head. Therefore, endoscopic procedures such as extracorporeal shock wave lithotripsy (ESWL) or stenting and surgical drainage or resection procedures are offered. Thoracoscopic splanchniectomy is also described as an alternative treatment with adequate pain relief [10].

Various interventional treatment options are available to restore pancreatic drainage. Endoscopic drainage of the pancreatic duct is an alternative to surgical intervention [11]. Another alternative is ESWL combined with endoscopic clearance [12,13]. Endoscopic interventions must often be repeated and are seen as more symptom control than definite therapy. Stents must be removed and replaced after a short period of time and are still accompanied by complications which may be severe.

Current studies have shown that a surgical approach is superior to endoscopic therapy with regard to pain reduction and drainage [14,15]. Studies also show that patients who undergo surgical treatment as initial therapy have fewer consecutive interventions, shorter hospital stay, and a better quality of life [16]. Nevertheless,

the surgical approach must be evaluated carefully with regard to personal risk of mortality and morbidity. There are different approaches depending on a patient's leading symptoms/complications. Therapeutic options are either drainage of a pancreatic or intestinal stricture, resection of the inflammatory center, or denervation of the supplying nerves [17].

In addition to the Whipple procedure, duodenum-preserving pancreatic head resection (DPPHR) has become the standard operation procedure for treatment of chronic pancreatitis [18]. Overall it can be concluded that because of the significantly better short-term outcome results and reproducible long-term results the DPPHR is the favorable surgical procedure.

## Timing

The greatest challenge seems to lie in evaluating the right time and the right treatment for each patient individually. Traditionally, surgery was evaluated as adequate treatment at an advanced stage of the disease because of its higher morbidity and mortality compared to conservative treatments.

Current studies have shown that an early surgical approach may be beneficial for pain relief and should be performed before the gland is irreversible damaged in its functional and morphology [19,20]. Patients who underwent surgical treatment earlier than 3 years after symptom onset had a higher chance of pain relief and lower odds of developing endocrine insufficiency, regardless of the surgical technique [21]. Therefore surgical treatment should be evaluated 1–3 years after onset of the disease.

## Conclusions

Pain treatment in patients with chronic pancreatitis is interdisciplinary. The baseline therapy for patients dealing with chronic pancreatitis lies in the reduction of noxious stimuli supporting the chronic inflammation and in the medical pain treatment. Endoscopic treatment is beneficial at the beginning of the disease, while dealing with complications, and prior to surgery to reduce the individual surgical risk. Considering the individual's reduction in quality of life and personal morbidity, surgical intervention should be evaluated at an early stage of the disease.

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# 52

# Medical Treatment of Chronic Pancreatitis: Pancreatic Digestive Enzymes: Lipases, Proteases

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## Introduction

The major macronutrients of the human diet are protein, fats, and carbohydrates. In the Western diet, proteins contribute about 15% of the total calories, carbohydrates as simple sugars or starches provide around 50%, and fats account for the remainder [1]. Dietary macronutrients require digestion into smaller molecules before uptake into the bloodstream. Proteases cleave proteins into short peptides and amino acids before transport into enterocytes (Table 52.1). A series of glycosidases release glucose from starch. Transporters in the intestinal epithelium absorb glucose and other simple sugars. Absorption of fats requires the release of the acyl chains by lipases and uptake of the fatty acids by enterocytes (Table 52.2). If digestion of macronutrients is incomplete, malabsorption results and macronutrients are excreted in the stool. The loss of energy and of building blocks for proteins, cell membranes, and signaling molecules compromises health in patients with chronic pancreatitis and pancreatic insufficiency.

Efficient digestion of macronutrients requires digestive enzymes produced by the exocrine pancreas. Pancreatic acinar cells are prodigious protein factories, secreting 6–20 g of protein every 24 hours. About 20 digestive enzymes account for most of the secreted protein [2]. The large number of digestive enzymes and their various specificities allow humans to adapt to varied diets and consume a wide range of foods. Failure of the exocrine pancreas to produce adequate digestive enzymes—exocrine pancreatic insufficiency (EPI)—occurs in 30–50% of patients with chronic pancreatitis, 85–90% of patients with cystic fibrosis, and 50–100% of patients after partial or complete pancreatic resection [3–5].

Patients with EPI have a number of symptoms and nutritional deficiencies related to maldigestion of dietary macronutrients. Maldigestion of starch can cause diarrhea; maldigestion of protein can lead to essential amino acid deficiency; maldigestion of fat can cause large-volume malodorous stools, abdominal pain, bloating, weight loss, and, in children, poor linear growth. Pancreatic insufficiency also leads to deficiencies of micronutrients including fat-soluble vitamins, magnesium, calcium, essential fatty acids, zinc choline, and folate [6]. Because incomplete digestion of dietary fats causes most of the clinical signs and symptoms of pancreatic insufficiency, treatment is guided by how well fat digestion and absorption is restored.

## Management of Exocrine Pancreatic Insufficiency

Pancreatic enzyme replacement therapy (PERT) with extracts of porcine pancreas has been the cornerstone of EPI management for over a century. Nevertheless, challenges still exist in the treatment of EPI [7]. First, the diagnosis of EPI can be problematic [8,9]. Second, PERT fails to resolve symptoms in some patients. The lack of a simple, accurate test for EPI hampers diagnosis and treatment [10]. At present, none of the tests for EPI perform adequately. For a long time the standard has been the quantitative 72-hour fecal fat test, but this presents difficulties with collection and analysis. The fecal elastase-1 test is only suitable as a screening test [11]. The endoscopic function test and mixed triglyceride breath test have their advocates, but both have shortcomings limiting their usefulness for identifying and treating patients with EPI.

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**Table 52.1** Predominant human pancreatic proteases.

| Enzyme | Abundance | Specificity | Products |
|---|---|---|---|
| Trypsins | 20% | Endopeptidase; cleaves after lysine or arginine | Oligopeptides |
| Cationic trypsinogen (*PRSS1*) | | | |
| Anionic trypsinogen (*PRSS2*) | | | |
| Mesotrypsin (*PRSS3*) | | | |
| Chymotrypsinogens | 10% | Endopeptidase; cleaves after aliphatic amino acids | Oligopeptides |
| Chymotrypsinogen B, B2 | | | |
| Chymotrypsin C | | | |
| Chymotrypsin-like elastases | 10% | Endopeptidase; cleaves after alanine, glycine, serine | Oligopeptides |
| Elastase 2A, 2B | | | |
| Elastase 3A, 3B | | | |
| Carboxypeptidase A1, A2 | 10% | Exopeptidase; cleaves aromatic amino acids from C-terminus | Aromatic amino acids and peptides |
| Carboxypeptidase B1 | 10% | Exopeptidase; cleaves arginine or lysine from C-terminus | Arginine, lysine and peptides |

**Table 52.2** Predominant human pancreatic lipases.

| Enzyme | Abundance | Specificity | Products |
|---|---|---|---|
| Pancreatic lipase (*PNLIP*)—requires colipase (*CLPS*) | 10% | sn-1 and sn-3 positions of glycerides | Fatty acids monoacylglycerols |
| Pancreatic lipase-related protein 2 (*PNLIPRP2*) | 4% | sn-1 and sn-3 positions of glycerides | Fatty acids lysophospholipids |
| | | sn-1 and sn-2 positions of galactolipids | |
| | | sn-1 position of phospholipid | |
| Carboxyl ester lipase (*CEL*) | 4% | All positions of glycerides | Fatty acids lysophospholipids |
| | | sn-1 and sn-2 positions of galactolipids, | |
| | | sn-1 and sn-2 positions of phospholipids | |
| Phospholipase A2 (*PLA2*) | 2% | sn-2 acyl chain of phospholipids | Fatty acids lysophospholipids |

As shown in Table 52.3, the dosage of PERT varies with age [12]. The timing of the dose has been much discussed. One study suggests that PERT is most effective when given during and after a meal [13]. PERT in infants taking formula and in patients with feeding tubes presents unique problems. Infants can be given PERT by mouth after mixing the microgranules with an acidic food such as applesauce. Microgranules mixed with soft food or thick liquid can be given in feeding tubes without causing clogging [14,15].

If the patient has persistent symptoms, weight loss, or nutrient deficiencies on PERT, you should consider other causes before escalating the dose. In the absence of signs and symptoms of other disease, you should assess diet, timing of dose, and compliance. If the reason is not uncovered, the dose of PERT can be increased up to the maximum for age. Next, a proton pump inhibitor can be trialed. If symptoms persist, evaluate for other diseases such as liver disease, celiac disease, enteric infection, bacterial overgrowth, delayed gastric emptying, Crohn disease, lactose intolerance, functional abdominal disorders,

**Table 52.3** Recommended pancreatic enzyme dose.

| Age | Dose |
|---|---|
| Infants | 2000–5000 lipase units per 120 mL of formula or with each breastfeed |
| 4 years and younger | 1000–2500 lipase units per kg per meal |
| | 500 lipase units per kg per snack |
| 4 years and older | 500–2500 lipase units per kg per meal |
| | 250 lipase units per kg per snack |
| Adolescents and adults | 25,000–75,000 lipase units per meal |
| | 10,000–25,000 lipase units with snacks |

and eating disorders. Aggressive restriction of dietary fat is not recommended, particularly in growing children.

## Emerging Therapies

Although PERT is the mainstay of therapy for EPI, several issues have driven the search for alternative therapies. PERT frequently does not eliminate steatorrhea, requires multiple capsules with each meal, can trigger allergic reactions, has a theoretical risk of transmitting new infections to humans, and may not be accepted by patients who do not eat pork. Consequently, the development of recombinant digestive enzymes to replace porcine extracts has drawn considerable interest. Both bacterial and fungal lipases are in development as single agents or in combination with a protease and amylase [16,17].

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# Nutritional Support of Chronic Pancreatitis

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## Introduction

Nutrition in chronic pancreatitis has been described as a problem area [1]. There is a high risk of undernutrition, and the etiology is multifactorial. Pancreatic exocrine insufficiency (PEI) results in the malabsorption of macro- and micronutrients. Moreover, pancreatic enzyme replacement therapy (PERT) is often underused and underprescribed [2], and may not fully restore normal digestive function [3]. Poor dietary intake is common due to abdominal symptoms, pain, heavy smoking, and alcohol abuse. However, not all patients with chronic pancreatitis are classically underweight, and many are overweight and even obese.

## Undernutrition

The mean body mass index (BMI) of patients with chronic pancreatitis varies considerably between different countries, reflecting the general nutritional status of the country. Examples of BMI values reported for patients with chronic pancreatitis include: 19.3 kg/m$^2$ in India, 21.9 kg/m$^2$ in Italy, 22.1 kg/m$^2$ in Poland, 23 kg/m$^2$ in Denmark, 24 kg/m$^2$ in the Netherlands, and 25.9 kg/m$^2$/25.5 kg/m$^2$ in males/females in Ireland. Patients with chronic pancreatitis have consistently lower BMIs, lower muscle mass, and handgrip strength than matched controls. The clinical impact of overweight and obesity among patients with chronic pancreatitis is uncertain, but obesity may mask micronutrient deficiencies and sarcopenia. Those who abuse alcohol have an increased risk of undernutrition. High alcohol users tend to have poor nutrient intakes, either due to effects on appetite or due to displacement of food [4]. High alcohol intake also independently increases the risk of osteoporosis, and may be associated with diarrhea and malabsorption [5].

## Nutrient Deficiency

Specific nutrient deficiencies may arise in chronic pancreatitis as a result of steatorrhea (loss of fat-soluble vitamins), alcoholism (increased requirement or loss of water-soluble vitamins), or poor/imbalanced dietary intake. The prevalence of specific nutrient deficiencies varies between studies and countries. For vitamin D, the prevalence varies according to the definitions of deficiency or insufficiency used in various studies. Using serum 25-hydroxyvitamin D (25(OH)D) of less than 50 nmol/L to define deficiency, the prevalence varied from 41% (Czech Republic [6]) to 86% (India [7]). Vitamin E (which should be measured as a ratio of serum lipids) ranged from 24% (Ireland [8]) to 75% (South Africa [9]). Vitamin A deficiency ranged from 3% (the Netherlands [10]) to 40% (Japan [11]). One study reported that 63% of chronic pancreatitis patients had low serum levels of vitamin K [10], but vitamin K deficiency is more correctly measured by undercarboxylated osteocalcin or by measurement of proteins of vitamin K absence, and not by measurement of serum vitamin K or prothrombin time, both of which are inaccurate [12]. There have been few studies on other micronutrients, but isolated studies identified low magnesium [13] and zinc levels [14] among chronic pancreatitis patients, whereas vitamin B12 deficiency [15] was reportedly rare.

Despite the ostensibly common occurrence of biochemical vitamin deficiency, there are few published reports on the clinical manifestation of such deficiencies in chronic pancreatitis. The exception is vitamin

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D, which contributes (among other factors) to the well-documented high prevalence of osteoporosis. Overt vitamin D deficiency resulting in osteomalacia (adult rickets) has also been reported in several case reports [16,17]. Neurologic abnormalities associated with vitamin E deficiency have also been rarely reported. One patient out of 13 with biochemical vitamin E deficiency had typical neurologic manifestations along with poorly controlled diabetes [18]. A condition known as brown bowel syndrome (associated with vitamin E deficiency) has also been reported in a deficient patient with vitamin chronic pancreatitis, celiac disease, and adenocarcinoma of the colon [19].

Clinical manifestations of vitamin A deficiency tend to manifest as visual defects. One case report [20] described a 45-year-old male with chronic pancreatitis, chronic alcoholism, diabetes, and a history of cholecystectomy. The patient presented with steatorrhea, cachexia, low BMI, and severe weight loss, along with ocular pain, photophobia, and decreased visual acuity. A second report [21] described a patient with chronic pancreatitis, malnutrition, and vitamin A deficiency who developed ulcerative keratitis in one eye and necrotizing stromal ulceration with hyphema in the other eye. In general, clinical deficiencies appear to take years to develop, and occur when there is an additional comorbidity, such as celiac disease or diabetes, or post surgery.

## Micronutrient Supplementation

There is a notable research gap regarding the management of nutrient deficiency in chronic pancreatitis, excepting vitamin D. In a study comparing oral vitamin D supplementation to ultraviolet B (UVB) radiation in chronic pancreatitis, oral supplementation (1520 IU/day) was significantly more effective in increasing serum 25(OH)D, achieving an increase of 32.3 nmol/L (95% 15–50 nmol/L) over 10 weeks [22]. High-dose, single-dose supplementation also appears to be safe and effective in increasing serum 25(OH)D. One study compared 600,000 IU or 300,000 IU single intramuscular injections or intramuscular saline, and found that the higher dose was more effective at increasing serum 25(OH)D, with no reports of hypervitaminosis or hypercalcemia [23].

There are few studies, if any, examining the effectiveness or safety of supplementing vitamins A, E, or K in patients with chronic pancreatitis and biochemical deficiencies. One study documented unexplained excess levels of vitamin A in patients with chronic pancreatitis who were not being supplemented [8]. Therefore mass supplementation of patients is not recommended, nor is it possible to recommended dosage, administration methods, or specific patient types that warrant supplementation. A precision medicine approach is warranted, with measurement of serum vitamins and attention given to optimizing dietary intake and PERT.

## Osteoporosis and Bone Health

Patients with chronic pancreatitis have a higher than normal risk of developing low bone mineral density. In a systematic review [24] of 513 patients who had undergone dual X-ray absorptiometry (DXA), 65% had osteoporosis or osteopenia [10,25–27]. Crucially, this high osteoporosis risk translates into a higher prevalence of low-trauma fractures compared to healthy controls [28,29]. The reasons for premature bone demineralization in chronic pancreatitis is multifactorial, and low serum 25(OH)D, poor dietary intake, heavy smoking, low physical activity, chronic inflammation [30], and malabsorption all contribute [24]. Basic preventative measures should be advised for all chronic pancreatitis patients, including adequate calcium and vitamin D intakes, regular weight-bearing exercise, and smoking and alcohol avoidance [31]. Where there is a diagnosis of osteopenia, a DXA should be repeated every 2 years, and for those with confirmed osteoporosis (or who have vertebral fractures), appropriate medication (such as bisphosphonates) should be prescribed. A referral to a bone specialist may also be required, as well as implemention of basic preventative measures (adequate calcium and vitamin D intakes, regular weight-bearing exercise, and smoking and alcohol avoidance) [31]. Sunshine exposure to optimize serum 25(OH)D should also be encouraged.

## Dietary Intervention

Nutritional status can be improved in chronic pancreatitis with the use of PERT when pancreatic insufficiency exists, and by individualized dietary intervention and dietary counseling by a pancreatic dietitian [32]. Nutritional requirements are up to 35 kcal/kg per day [5,33], and 1.2–1.5 g protein/kg per day [5,33,34]. Low-fat diets (or fat-free diets) are not recommended as they decrease energy intake and make food less palatable [5,35]. Rather, PERT should be optimized to allow for a moderate fat intake. Fat restriction may be trialled as a last resort for those with intractable malabsorption, once PERT has been optimized along with acid-suppression medications and other causes of malabsorption (such as small intestinal bacterial overgrowth) have been excluded. There is no evidence that vegetable fat is better tolerated than animal fat [5].

Where malabsorption continues with apparently adequate PERT, a restriction in dietary fiber might improve absorption, as dietary fiber may reduce enzyme availability [5,33]. However, long-term fiber restriction should be avoided as a diet rich in fruit and vegetables should always be recommended. A frequent, low-volume meal pattern should be advised. Some patients will require oral nutritional supplements, and whole-protein types could be tried first before progressing to peptide-based or medium-chain triglyceride (MCT)-enriched supplements. Antioxidant supplementation for the treatment of chronic pancreatic pain was considered a promising treatment option [36], but more recent studies have cast doubt on its effectiveness [37].

## Enteral and Parenteral Nutrition

The vast majority of patients with chronic pancreatitis will be maintained on an oral diet, with or without supplementation. Enteral nutrition is indicated for malnourished patients who are unable to meet their requirements orally [34,38,39]. Enteral feeding via the jejunal route should be performed in the case of delayed gastric emptying, chronic subacute obstruction of the upper gastrointestinal tract by pancreatic cysts [40], and persistent nausea or vomiting, or pain [34]. Nasojejunal feeding is associated with a reduction in pain, pseudocysts, and inflammation, as well as improvements in nutritional status [41,42]. Where jejunal feeding is required for a prolonged period, a surgical jejunostomy could be considered [34,43]. With regard to the composition of enteral feeds, peptide-based, MCT-based formulas may be trialled where standard feeds are not tolerated [40,42].

Some patients may require the administration of PERT along with enteral feeds. Parenteral nutrition should be avoided if possible as complication rates are higher in chronic pancreatitis due to pancreatic endocrine insufficiency (hyperglycemia) and immuno-incompetence (catheter sepsis). The use of transnasal endoscopic placement of distal jejunal feeding tubes in chronic pancreatitis usually avoids the need for commonly cited indications of parenteral nutrition, including gastric outlet obstruction secondary to duodenal stenosis, complex fistulating disease, and severe malnutrition prior to pancreatic surgery [38,40,44].

## Combined Pancreatic Exocrine and Endocrine Deficiency

With end-stage calcific chronic pancreatitis, pancreatic endocrine deficiency exacerbates malnutrition and makes nutritional management even more challenging. Type 3c diabetes is termed "brittle diabetes" and carries a high risk of hypoglycemia and neuroglycopenia, due to insulin therapy, glycogen deficiency, enhanced peripheral insulin sensitivity, malabsorption, poor dietary intake, and, for some, persistent excess alcohol intake. Rapid swings in blood glucose between hypoglycemia and hyperglycemia are common, the former due to impaired pancreatic glucagon and polypeptide responses, the latter exacerbated by unsuppressed hepatic glucose production [45]. Attempts to increase dietary intake and the addition of PERT to manage PEI may aggravate hyperglycemia further and have to be carefully covered by increased insulin therapy. Patients must be jointly managed with an endocrinologist, and careful dietary monitoring is essential [35,45].

## Structured Nutritional Assessment

Once diagnosed with chronic pancreatitis, patients should undergo thorough and regular nutritional assessment by a dietitian, along with the multidisciplinary team. Figure 53.1 summarizes the nutritional assessment of patients with chronic pancreatitis and includes six key elements:

1) There should be an anthropometric assessment (including BMI, mid-upper arm circumference, triceps skinfold), and a detailed assessment of current and habitual dietary intake [5].
2) Clinical evaluation should include the presence of nausea/vomiting, diarrhea, malabsorption, anorexia, early satiety, and pain.
3) Exocrine assessment should be performed, including the clinical symptoms and signs of malabsorption, and an objective measure of PEI.
4) A biochemical assessment of nutritional status should include measurement of fat-soluble vitamin levels, as well as measurement of fasting glucose and glycated hemoglobin, with a 75 g oral glucose tolerance test where equivocal.
5) Bone health should be evaluated by measurement of serum 25(OH)D and a baseline bone density scan.
6) The patient should be interviewed regarding smoking and alcohol status, physical activity, relevant social issues, and an assessment of quality of life should be performed.

Routine assessment will inform nutritional management, which should include optimization of dietary intake, appropriate and adequate PERT, and, for some, oral nutritional supplements and micronutrient supplementation. Routine nutritional assessment to maximize nutritional status is vital.

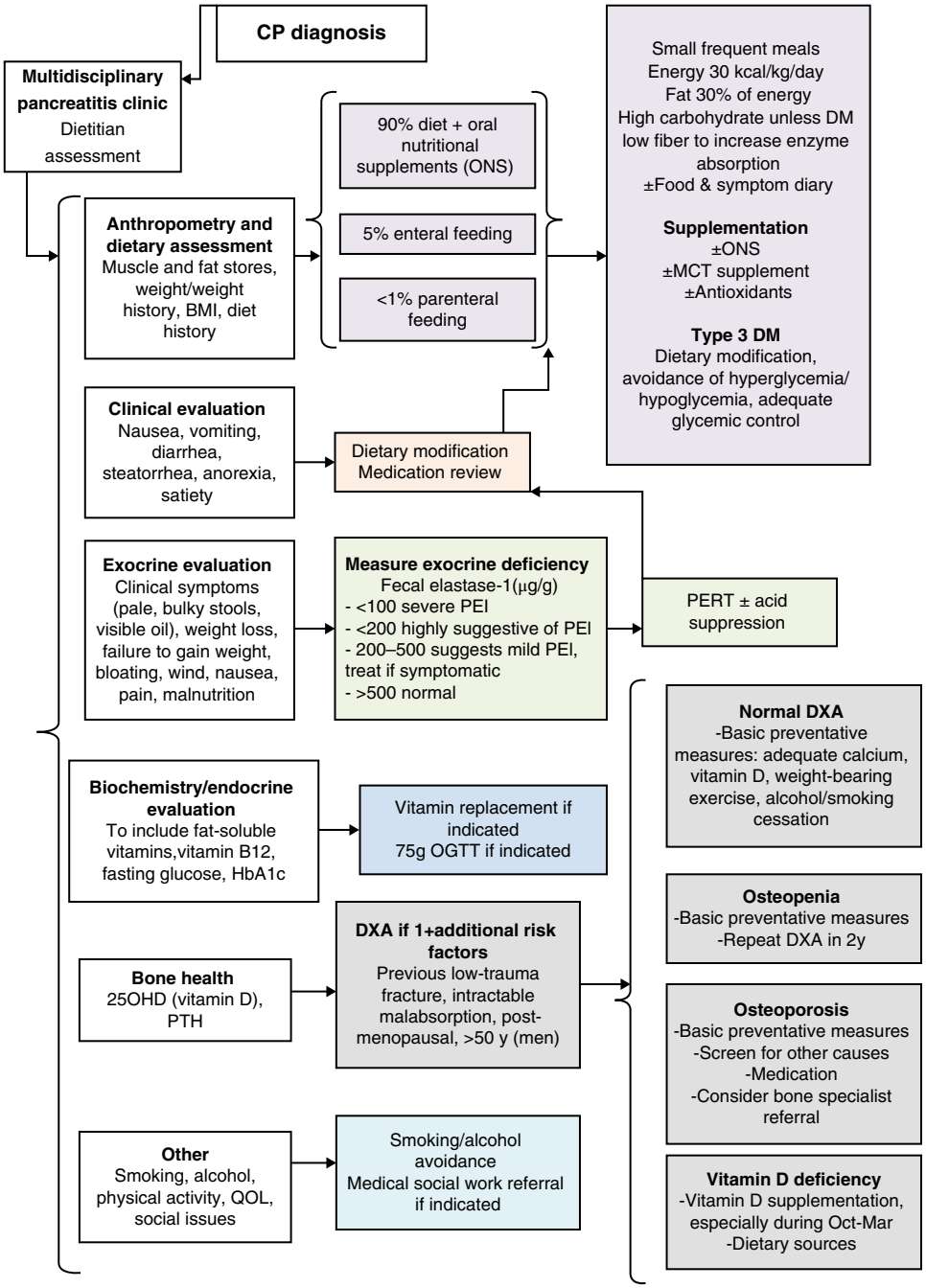


**Figure 53.1** Structured nutritional assessment and intervention for patients with chronic pancreatitis (CP). DM, diabetes mellitus; ONS, oral nutritional supplement; MCT, medium-chain triglyceride; PEI, pancreatic exocrine insufficiency; OGTT, oral glucose tolerance test; DXA, dual X-ray absorptiometry; PTH, parathyroid hormone; QOL, quality of life; PERT, pancreatic enzyme replacement therapy. *Source:* Duggan et al. 2010 [5].

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# Medical Therapy for Chronic Pancreatitis: Antioxidants

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## Introduction

The medical treatment of chronic pancreatitis includes nutritional assessment and targeted supplementation, avoidance of potential environmental toxins (alcohol and tobacco), replacement of pancreatic enzymes, management of associated diabetes, monitoring for complications, and control of abdominal pain. In many patients, pain is the dominant clinical feature and the most difficult to treat. The effectiveness of medical therapies to relieve or reduce pain is limited. These potential therapies for pain include abstinence from alcohol and tobacco (if applicable), oral analgesics, adjunctive agents (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors [SSRI], serotonin–norepinephrine reuptake inhibitors [SNRI], gabapentoids), and antioxidants. Antioxidants are attractive as a potential therapy, given the contribution of oxidant stress and reactive oxygen species to acinar cell injury, pancreatic fibrosis and possibly pain; and by the finding that some patients with chronic pancreatitis have deficiencies in antioxidants such as vitamins C and E, methionine, or selenium.

## Pain and Oxidative Stress

The mechanisms of pain in chronic pancreatitis are varied, and include ischemia, direct toxicity (alcohol and its metabolites, tobacco), increased pressure within the gland or duct, associated complications (pseudocyst, secondary malignancy), and neurotoxic mechanisms involving inflammatory cells, nociceptive neurotransmitters, nerve cell injury, and neural remodeling. Chronic pain of any type also produces changes in central neural signaling and processing, which produces a neuropathic pain with features of hyperalgesia (exaggerated pain in response to normal stimuli) and allodynia (pain in response to normal physiologic processes). This centrally sensitized neuropathic pain may persist despite treatment of the underlying cause (e.g., continued pain after total pancreatectomy), and severely limits the effectiveness of therapies for chronic pain syndromes.

Oxidative stress is implicated as a potential mechanism of pain in chronic pancreatitis, and has been documented in some patients with chronic pancreatitis. Deficiencies in baseline antioxidant levels [1,2], increases in antioxidant catalytic enzymes [2,3], and elevations in markers of oxidant-driven lipid peroxidation have been noted [2–5]. Most of these studies include patients with advanced chronic pancreatitis (due to alcohol or tobacco), as well as patients with tropical pancreatitis. These patients, particularly if they are malnourished, may be prone to preexisting deficiencies in antioxidant capacity. In addition, the proportions of patients who smoke vary from study to study, and smoking is a potent inducer of oxidative stress. Thus the presence of smoking or of malnutrition could be important confounders in assessing the pathologic contribution of antioxidants to chronic pancreatitis in general and pain in particular. These studies did not directly correlate the level of antioxidants with the severity (or even presence) of abdominal pain. Replacement or supplementation with antioxidants might change the micronutrient and antioxidant milieu in patients who are deficient, and remediate oxidative stress. This could potentially reduce pain, or could have other beneficial effects in protecting the remaining pancreas from additional damage. The precise mechanism by which a change in oxidative stress could reduce pain is not known. In addition to the treatment of pain in chronic pancreatitis, there has been interest in using antioxidants to treat acute pancreatitis,

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prevent relapses of acute pancreatitis, and prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [6], but these topics are not reviewed in this chapter.

## Clinical Studies of Antioxidants for Pain

A number of randomized trials have assessed the efficacy of various antioxidants in reducing the pain of chronic pancreatitis but have reached different conclusions on the overall effect, and on the magnitude of pain relief. They include the use of single antioxidant agents (e.g., allopurinol or curcumin) as well as mixtures of antioxidants (usually vitamins E and C, methionine, selenium, and β-carotene). These randomized studies have been the subject of several meta-analyses [6–10] and a Cochrane systematic review [11]. Interpreting the results is made more difficult by the various types of antioxidant agents and mixtures utilized, and by the various methods of measuring pain. In addition, the studies comprise patients with a wide variety of etiologies, are often small, may only exist in abstract form, and include a mixture of both chronic pancreatitis and relapsing acute pancreatitis. This chapter will focus on studies using mixtures of antioxidants.

An early and widely quoted study by Uden et al. recruited 23 patients with both acute relapsing and chronic pancreatitis in a blinded crossover study [12]. The patients were provided a mixture of selenium, β-carotene, vitamin C, vitamin E, and methionine (or matching placebo) for 10 weeks. Only 20 patients followed the protocol, including 15 patients with chronic pancreatitis. Patients on active therapy reported less background pain, and fewer exacerbations of pain. A trial by Kirk et al. [13] recruited 36 patients with painful chronic pancreatitis into a placebo-controlled crossover trial of a similar mixture of antioxidants. This trial reported on the 19 patients who completed both periods of treatment, and noted improved quality of life. Data from the pain diaries used to assess pain were not analyzed because they were not consistently completed, although there was improvement in pain based on a single question from the quality of life (QOL) instrument. Both of these studies had large numbers of dropouts, and did not employ a washout period between treatments. A washout may be particularly important, as those receiving antioxidants may exhibit improved levels of antioxidants in the subsequent placebo period.

A number of other crossover trials [14,15] and unblinded randomized trials [16,17] suggested benefit, although each was relatively small and had significant numbers of dropouts. Recently, larger and better designed trials have provided estimates of the potential effectiveness of antioxidants.

A large, placebo-controlled, randomized, and blinded study by Bhardwaj et al. [4] recruited 147 patients with painful chronic pancreatitis for a 6-month trial of antioxidants (600 μg selenium, 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, and 2 g methionine daily). The main outcome, reduction in number of painful days per month, was higher in the active treatment arm (10.5 ± 11.8 fewer days per month, vs. 4.4 ± 5.8 in placebo), which also corresponded to less use of analgesics. One-third of the antioxidant group became pain free during treatment, compared with 12.5% of the placebo group. The study also assessed baseline nutritional status and markers of oxidative stress and antioxidant status, and demonstrated significant improvement in these in the active treatment arm. The patients in this trial were relatively young (mean age 30) and two-thirds had idiopathic pancreatitis; with 36% being undernourished at initiation of the trial. There were a significant number of patients lost to follow-up during the trial (40/147 patients lost to follow-up at some time during the 6-month trial). The large number of dropouts is seen with most trials in chronic pancreatitis, but did create imbalances in the two groups which could have introduced bias.

The other large, randomized, blinded, placebo-controlled trial by Siriwardena et al. [18] recruited 92 patients with painful chronic pancreatitis for a 6-month trial of antioxidants (300 μg selenium, 740.4 mg [496 IU] α-tocopherol, 758 mg ascorbic acid, 2.88 g l-methionine, and 25.2 mg β-carotene daily). These dosages are higher than those in the study by Bhardwaj et al. [4]. The primary outcome was the change in pain, using a visual pain score. A variety of other pain scores were also calculated from pain diaries, as well as pain questions on QOL measures. Although the study initially planned to recruit 57 patients, a planned interim analysis by the steering committee led to an increase in sample size. Compared to the study by Bhardwaj et al., these patients were older (mean age 50), more likely to have alcohol and smoking as the etiology, not undernourished, more likely to be on chronic opioid therapy, and more likely to have undergone previous endoscopic or surgical therapy. After 6 months there was a general decrease in overall pain in both groups of around 2 points on the visual scale, but no difference between groups in these measures or in other measures using daily pain diaries, pain questionnaires, need for hospitalization, opiate use, or QOL. The level of antioxidants was significantly increased in the active treatment arm. During follow-up 22/92 patients withdrew or were lost to follow-up.

These two large randomized trials and several smaller trials have been the subject of several systematic reviews

and meta-analyses. A Cochrane review [11] analyzed 12 randomized controlled trials, of which 6 were double-blinded and placebo-controlled. They note that most trials were small and had high rates of dropout. Combining the studies, those randomized to antioxidants had less pain after 1–6 months of therapy (an average difference of 0.33 [95% CI: –0.64 to –0.02] points less on a visual analog scale of 0–10). The number of pain-free patients was not different between groups, and side-effects were more common in the antioxidant group (leading to 16% of participants stopping therapy). The data were not felt to be sufficient to be able to draw conclusions on the effect of antioxidants on analgesic use, exacerbations of pancreatitis, or QOL. It should be noted that although many of the analyzed studies used mixtures of antioxidants, the dose varied, and some studies used allopurinol or curcumin. This Cochrane review concludes that antioxidants can reduce pain slightly in patients with chronic pancreatitis, but that the clinical relevance of this slight decrease is uncertain.

Given this analysis of the existing data, it is logical to try to identify the subgroup of patients most likely to experience benefit from antioxidants. A number of expert opinion and additional meta-analyses have suggested that the response might vary with etiology of chronic pancreatitis [19,20], baseline levels of antioxidant reserve [21], adequacy of baseline nutrition, type of antioxidant [9], duration of opioid analgesia use [21], stage of disease [19], and others. Although many of these seem plausible, they remain unproven.

Antioxidants are not without risk. The randomized trials of antioxidants note a relative risk of side-effects (largely headache and gastrointestinal side-effects) approximately 5 times greater in the antioxidant group (occurring in 1 in 6 patients) [11]. In addition, mortality appears to be slightly increased in patients receiving antioxidants (vitamin E and β-carotene in particular) as part of large primary and secondary prevention trials [22], with a hazard ratio of 1.03–1.05.

## Conclusions

Oxidative stress and reactive oxygen species clearly play an important role in the pathogenesis of chronic pancreatitis. Although the two best studies reach opposite conclusions, the combined analyses of all randomized controlled trials demonstrate a measurable beneficial effect of antioxidants on pain. Even though the overall magnitude of this effect is quite small and not likely to be clinically meaningful, there is the potential that a subgroup of patients might be able to be identified who are much more likely to benefit. The varied and heterogeneous mechanisms of pain and the complexity of nociceptive signaling [19,23,24] imply that no single therapy will be effective in all patients, but the specific subgroup that might respond to antioxidants is not known. Additional studies will be required to identify this cohort.

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# Strategies for Endoscopic and Surgical Treatment of Chronic Pancreatitis

## 55

## Evidence of Endoscopic and Interventional Treatment of Chronic Pancreatitis and Pseudocysts

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### Indications for Interventional Endoscopic or Surgical Therapy

Belt-like upper abdominal pain is regarded as a cardinal symptom of chronic pancreatitis, together with weight loss, steatorrhea, and diabetes mellitus. In the absence of causal therapeutic options, treatment is restricted to symptom control by means of enzyme replacement, pain therapy, and optimal control of endocrine insufficiency. Between 30% and 60% of patients develop complications of their disease, such as strictures of the common bile duct, inflammatory masses, pancreatic pseudocysts, or pancreatic duct strictures or ductal stones, which require interventional or surgical treatment.

Chronic pancreatitis with severe pain requiring constant analgesics should be treated by interventional or surgical procedures dependent on the symptom causing pathogenic features [1]. The presence of an inflammatory mass clearly favors a surgical resection. In the case of a dilated pancreatic duct due to strictures and/or ductal stone, both endoscopic as well as surgical drainage procedures are effective. The indication of an endoscopic drainage has not been fully clarified in randomized controlled trials. Endoscopic treatment of a dominant stricture of the main pancreatic duct (MPD) is often followed by pain relief in the short term [2,3]. Retrospective studies reported long-term pain relief in 32–68% of patients [3]. Two randomized controlled studies directly compared endoscopic procedures with resection or a surgical drainage procedure [4–6]. Those studies proved surgery to be superior to endoscopy with respect to long-term outcome. However, endoscopic drainage can achieve a long-lasting complete or partial pain relief in at least one-third of patients, and it is associated with lower mortality and does not impede surgery as a second-line therapy [6].

In the presence of a resectable pancreatic mass suspected to be caused by pancreatic carcinoma surgical resection should be performed. Without surgery, life expectancy for patients with pancreatic carcinoma is less than 1 year; after successful resection 20–25% of patients may survive more than 5 years [7–9].

Gastric outlet obstruction secondary to chronic pancreatitis requires surgical or endoscopic treatment for persistent clinical symptoms. A noninterventional management supplemented by endoscopic dilatation may be sufficient for an adequate quality of life in at least 30% of cases. According to the natural course of chronic pancreatitis further intervention will be necessary in about 30–60% of patients. As there are no studies directly comparing the efficacy of pancreatic head resection, bypass surgery, and endoscopic insertion of self-expanding metal stents (fcSEMS) [10], the decision may be taken in consideration of the patient's comorbidities.

Symptomatic stenosis of the common bile duct (CBD) will develop in 10–40% of cases, requiring endoscopy with dilation and stent insertion. The outcome of endoscopic therapy in patients without acute inflammation of the pancreas improved with new techniques but is still not entirely satisfactory. Stent therapy rarely resolves a stricture beyond 1 year of therapy [11], in particular in the presence of calcifications within the pancreatic head [12]. Lasting patency rates have significantly improved with the use of fcSEMS. Surgical resection should be performed if symptoms or cholestasis persist after temporary endoscopic therapy for not longer than a year.

Fragmentation and removal of stones within the pancreatic duct by extracorporeal shock wave lithotripsy (ESWL) have somewhat replaced surgery since its introduction in 1989. Several retrospective studies have shown ESWL to be an effective and safe management

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option for pain relief in chronic calcifying pancreatitis, with pancreatic main duct stones greater than 5 mm [13], for which ESWL followed by endoscopic retrograde cholangiopancreatography (ERCP) may be the standard of care. Intraductal lithotripsy under direct endoscopic vision is a promising technique in evolution.

Interventional endoscopic options in chronic pancreatitis will be discussed in more detail below.

## Treatment of Pancreatic Cysts

According to the revised Atlanta classification a pancreatic pseudocyst is an encapsulated collection of fluid with a well-defined inflammatory wall usually outside the pancreas with minimal or no necrotic tissue content. This entity usually arises in connection with chronic pancreatitis [14]. A walled-off necrosis (WON) is defined as a mature, encapsulated collection of pancreatic and/or peripancreatic necrosis that has developed a well-defined inflammatory wall. WON usually occurs >4 weeks after the onset of necrotizing pancreatitis [14]. The prevalence of pancreatic pseudocysts in chronic pancreatitis ranges between 20% and 40% [15]. They occur with the highest frequency in patients with alcoholic chronic pancreatitis (70–78%), followed by idiopathic chronic pancreatitis patients (6–16%) and biliary pancreatitis patients (6–8%) [15,16]. Approximately 40% of the fluid collections resolve spontaneously within the first 6 weeks after an acute attack of pancreatitis. In contrast, spontaneous remission of pseudocysts after 12 weeks is a rare event. Complications are observed in up to two-thirds of cases, encompassing pain, infection, hemorrhage, cystic rupture, or obstruction of adjacent organs such as cholestasis, gastric outlet obstruction, or vascular stenosis. A multivariate analysis showed a pseudocyst/WON size <4 cm as the only favorable factor for spontaneous resolution [17]. The increase in size of a pseudocysts/WON to over 5 cm in diameter is associated with an increased risk of complications [18]. Asymptomatic pseudocysts >5 cm in diameter which do not resolve within 6 weeks can be an indication for treatment. However, symptomatic pseudocysts should undergo treatment regardless of their size.

Only limited information is available with regard to interventional therapy of pancreatic pseudocysts for pain management. Most of the data at hand are based on retrospective case series [19–22], but three systematic reviews are available [23–25]. Pain relief will be achieved in a large number of patients (about 80%). Although medical management of chronic pancreatitis can result in pain relief, in a certain percentage of patients, interventional or surgical drainage is still the more effective form of pain management regardless of the drainage procedure.

A diagnostic needle aspiration of the cyst may be performed for suspected infection or for suspected cancer. If needle aspiration of the cyst confirms an infection, then drainage is indicated. Surgical treatment should be carried out if malignancy is suspected. In 28% of all MRI scans of the abdomen, a cystic lesion of the pancreas is discovered as an incidental finding [26] when population-based cohorts are investigated, although most of these cysts are smaller than 1 cm in diameter. More than two-thirds of these lesions are dysontogenetic cysts or pancreatic pseudocysts. Of the cystic lesions that are not pancreatic pseudocysts but genuine cystic neoplasms, 30% are benign serous cystadenomas. It is found that 45% of the resected lesions are mucinous cystic neoplasms and 25% intraductal papillary mucinous neoplasms (IPMN). Solid pseudopapillary tumors or cystic acinar cell carcinoma are rather rare entities. For the differential diagnosis of cystic tumors in asymptomatic patients, the question of a connection to the pancreatic duct (IPMN and pancreatic pseudocysts) and of the size of the cystic lesion (indication for resection in the case of IPMN or therapeutic indication for pseudocyst) is essential. Diagnostic needle aspiration of a cyst with the aid of endoscopic ultrasound (EUS) helps in differentiating between premalignant cystic neoplasms, cystic malignancies, and pseudocysts. In case the fluid analysis reveals a carcinoembryonic antigen (CEA) >400 ng/mL, a variably increased or low amylase (lipase), high viscosity, mucin, or epithelial cells in the cyst content, then a mucinous neoplasm must be assumed [26–28]. If a connection to the pancreatic duct is excluded, the final diagnosis of a mucinous cystic neoplasm (MCN) can be made. A serous cystadenoma is diagnosed in 30% of cystic lesions and virtually never turns into a malignant lesion. In this case aspiration of the cyst is negative for mucin, CEA, and amylase. Cytology reveals a glycogen-rich epithelium.

Surgical percutaneous or endoscopic drainage of pancreatic pseudocysts demonstrate comparable results regarding technical success, efficacy, and recurrence rates [24,29]. Percutaneous drainage is associated with the risk of external fistula and may affect the patient's quality of life. Endoscopic drainage is less prone to complications if compared to surgical procedures. A systematic review of retrospective series of endoscopic and surgical drainage showed similar morbidity (13.3% vs. 16%) and long-term pseudocyst recurrence (10.7% vs. 9.8%) but lower mortality (0.2% vs. 2.5%) achieved by an endoscopic drainage [30]. Therefore, the endoscopic approach should have first preference as it is less invasive and more convenient for the patient. In a recent randomized controlled trial that compared endoscopic versus surgical cystogastrostomy for pancreatic pseudocyst drainage endoscopic treatment was associated with shorter hospital stays, improved physical and mental

health status of the patients, and lower costs [29]. However, the decision between endoscopic and surgical drainage should take into account the cyst location and additional pathophysiologic features. Surgical drainage may be the preferable therapy in hemorrhagic pseudocysts as endoscopic drainage is associated with a higher risk of bleeding. Approximately 10% of pseudocysts recur in the long term after endoscopic drainage (Table 55.1). Although initial therapy for nonhemorrhagic pseudocysts should be endoscopic drainage, surgery may follow in case of recurrence.

Drainage of pseudocysts can be carried out by transgastric, transduodenal, or transpapillary routes. Transmural drainage should be done under EUS guidance to assess the pseudocyst location, size, wall, content, and adjacent blood vessels. Two randomized controlled trials compared transmural drainage with and without EUS guidance [38,39]. No difference was observed in terms of morbidity and clinical outcome but technical success was higher with EUS. The success rate in 1018 published patients with transmural drainage of a pseudocyst was 87% (Table 55.1), with more recent studies reporting success rates of more than 90%. The mortality rate in larger case series involving more than 30 patients was 0.2%, the recurrence and complications rates are reported to be around 9% and 13%, respectively. Without antibiotic prophylaxis the procedure-related incidence of an infection of a pseudocyst and the risk of development of a pancreatic abscess increases [54,55]. Antibiotic prophylaxis for transmural or transpapillary drainage of

**Table 55.1** Summary of transmural endoscopic pseudocyst/walled-off pancreatic necrosis drainage, including studies of: traumatic pancreatic pseudocysts [31], pancreatic abscess [32,33], "acute pseudocysts" [34], "infected pseudocysts" [35], "symptomatic peripancreatic fluid collections" [36,37]. Two studies compared ultrasound-guided versus conventional transmural drainage of pseudocysts in a prospective randomized trial [38,39].

| | Number of patients | Success rate | Recurrence rate | Complications |
|---|---|---|---|---|
| Kozarek et al., 1985 [40] | 4 | 50% | 0% | 25% (1 dead) |
| Cremer et al., 1989 [41] | 33 | 85% | 12% | 9% |
| Sahel, 1991 [42] | 37 | 86% | 5% | 14% |
| Bejanin et al., 1993 [43] | 26 | 73% | 15% | 15% |
| Funnell et al., 1994 [31] | 5 | 100% | 0% | 0% |
| Binmoeller et al., 1995 [44] | 20 | 80% | 23% | 30% |
| Smits et al., 1995 [45] | 25 | 88% | 13% | 20% |
| Vitale et al., 1999 [46] | 27 | 82% | 18% | 4% |
| Libera et al., 2000 [47] | 17 | 88% | 6% | 24% |
| White et al., 2000 [48] | 20 | 100% | 0% | 10% |
| Giovannini et al., 2001 [32] | 15 | 100% | 0% | 7% |
| Norton et al., 2001 [49] | 17 | 82% | 7% | 18% |
| Baron et al., 2002 [34] | 64 | 81% | 12% | 17% |
| Sharma et al., 2002 [50] | 33 | 97% | 15% | 15% |
| Cahen et al., 2005 [51] | 64 | 70% | 5% | 39% |
| Antillon et al., 2006 [35] | 33 | 94% | 3% | 6% |
| Hookey et al., 2006 [36] | 101 | 95% | 16% | 11%<br>1% (1 dead) |
| Kahaleh et al., 2006 [52] | 99 | 94% | NA | 19% |
| Kruger et al., 2006 [33] | 35 | 94% | 12% | 0% |
| Weckman et al., 2006 [53] | 68 | 90% | 5% | 10% |
| Varadarajulu et al., 2008 [38] | 29 | 100% | NA | 3%<br>3% (1 dead) |
| Park et al., 2009 [39] | 60 | 83% | 15% | 8% |
| Varadarajulu et al., 2011 [37] | 154 | 100% | 1.5% | 5% |
| Will et al., 2012 [88] | 32 | 97% | 15% | 10% |
| Total | 1018 | 87% | 9% | 13% |

pancreatic pseudocysts is recommended in recent guidelines based on expert opinion [3,56].

Double-pigtail stents should be used for transmural drainage of pancreatic pseudocysts because straight stents are associated with more frequent and severe complications in a retrospective study [51]. Early stent retrieval within 2 weeks after cyst resolution was associated with a higher rate of recurrence in a prospective randomized trial, suggesting that long-term stent placement for more than 2 months may prevent recurrence without an increase of severe adverse events [57]. In its clinical guideline the European Society of Gastrointestinal Endoscopy (ESGE) recommends transmural drainage of pancreatic pseudocysts by inserting at least two double-pigtail plastic stents which should not be retrieved before at least 2 months following stenting [3]. Recently, short, lumen-apposing, fully covered, self-expandable metal stents (LAMS) have been developed for EUS-guided drainage of peripancreatic fluid collections. Due to its ease of use and the large diameter, the LAMS may make drainage of peripancreatic fluid collections more effective, particularly the endoscopic debridement of WON [58,59]. With regard to costs and possible serious adverse events, however, further and prospective studies are needed to investigate the safety, efficacy, and exact role of LAMS in the management of both pseudocysts and WON [60,61].

Whether an attempt should be made to drain the pseudocyst using an ERCP via the papilla instead of primarily transgastric or transduodenal drainage is still a matter of controversy. According to retrospective studies, transpapillary drainage seems to be associated with lower morbidity (mainly pancreatitis) and similar long-term success but was used for smaller pancreatic cysts than transmural drainage [3,36,44,62]. Between 22% and 57% of pancreatic pseudocysts may have a connection with the pancreatic ductal system [63]. Thus, an endoscopic retrograde pancreatography (ERP) can precede endoscopic transmural drainage in order to detect a connection with the duct or to exclude a rupture of pancreatic ducts (8% after acute necrotizing pancreatitis). Transmural drainage in the presence of an undetected rupture of the pancreatic duct or an association of the pancreatic pseudocyst with an obstructed pancreatic duct is less promising with regard to long-term outcome of therapy [64,65]. Treatment of pancreatic duct obstruction and—if possible—bridging of a pancreatic duct rupture is recommended in these cases.

## Therapy of Pancreatic Duct Stenoses and Ductal Stones

Ductal and interstitial hypertension and possible pancreatic ischemia accompanying outflow obstruction due to pancreatic duct stenoses or ductal stones may play an important role in the pathogenesis of pain. The aim of endoscopic and surgical decompression therapy in patients with chronic pancreatitis and pain and/or clinical episodes of acute pancreatitis is to remove the obstruction and to allow outflow of exocrine pancreatic juices into the duodenum. Biliary techniques such as sphincterotomy, dilatation, ESWL, and stent insertion have been modified for the pancreatic duct. Endoscopic decompression represents an alternative to surgery and is associated with low morbidity and low mortality. Endoscopic interventions do not interfere with surgery that might still be necessary later in the course of the disease. Clinical success after endoscopic reduction of the intraductal pressure does provide some indication of the later result of surgical drainage or a resection procedure.

Pancreatic ductal stones are a consequence rather than the cause of chronic pancreatitis. They can, however, lead to consecutive outflow obstruction and thus cause pseudocysts or fistula development, recurrent exacerbations or contribution to the pathogenesis of pain. Under these conditions, treatment of pancreatic ductal stones seems appropriate. Endoscopic treatment appears particularly suitable for treating solitary stones and obstructions close to the papilla or in the body of the pancreas. After pancreatic sphincterotomy, pancreatic duct stones <5 mm may be extracted without prior fragmentation. Radiopaque obstructing stones ≥5 mm should be fragmented by ESWL followed by extraction of the fragments by ERCP [3]. There is evidence from a prospective randomized trial that the subsequent endoscopic removal of the fragments is not a prerequisite for the effectiveness of the procedure [66]. One large-scale single-center retrospective study with follow-up of 272 patients after ESWL and ERCP for >60 months reported no pain in 60% of patients, mild to moderate pain in 36%, and episodic severe pain in 4% of patients [67]. Recurrence of intraductal calculi was seen in 23% of patients. A recent meta-analysis of 27 studies (total of 3189 patients) showed that ESWL is useful for clearing pancreatic duct stones greater than 5 mm and for decreasing pain [13]. The pooled proportion of patients with absence of pain at follow-up (median 2 years) was 53% (95% CI: 50.8–54.6) and mild to moderate pain was 33% (95% CI: 31.4–35.5). Quality of life improved in 88% and complete ductal clearance was achieved in 71%. However, no studies ever compared the treatment of ductal stones with the natural course or a sham intervention. In two studies in which endoscopic treatment was compared with surgery (i.e., drainage operation), the results after surgery were significantly better with respect to long-term pain reduction [4,5]. The treatment of pain in patients with diffuse calcifications by means of ESWL has not been substantiated in any studies.

Dominant pancreatic duct strictures with a prestenotic dilatation ≥6 mm in diameter, which may be responsible for pain, recurrent exacerbations, maintenance of a pseudocyst, fistula, or other complications, can be treated by endoscopic dilatation and plastic stent placement [3] (Fig. 55.1). Removal of the obstruction of the pancreatic duct is effective for the treatment of pain on short to intermediate terms. Success rates between 65% and 95% have been reported [3]. In the largest hitherto examined cohort of 1021 patients, a long-term reduction (mean 4.5 years) of pancreas-related pain was achieved in 85% of cases [68]. However, 24% underwent surgery during further follow-up, which—on an intention-to-treat basis—reduced the rate of successful treatment to 65%. In 79% of the patients stent therapy for control of pain had to be repeated within 1 year and in 97% within 2 years. The only randomized study recruited 41 consecutive patients with chronic pancreatitis with a dominant pancreatic duct stricture to either receive pancreatic duct stenting or to serve as control. During a mean follow-up of 62.5 ± 20.9 months pain recurred in 15% of patients with pancreatic duct stenting (3/20) and in 50.0% of control patients (11/22) ($P < 0.05$). Progression of exocrine insufficiency in the stent group was significantly slower than in the control group ($P < 0.05$), while endocrine function showed no difference between groups [69]. Preliminary studies suggest temporary placement of fully covered fcSEMS into the pancreatic duct for pain relief may be safe and effective short-term treatment [70–72]. Their potential advantage versus plastic stents is the longer period of stent patency. However, long-term results are so far not available. Uncoated self-expandable metallic stents are not recommended due to the rapid proliferation of duct epithelium as a reaction to the metal mesh graft.

Plastic stents inserted into the pancreatic duct can induce secondary changes with subsequent fibrosis and strictures [73,74]. There are currently no reliable data available regarding the necessary duration of stent therapy. Some authors recommend treatment over 1 year with an exchange of the stent at least every 3 months [3]. Other centers suggest exchanging the stent in the case of

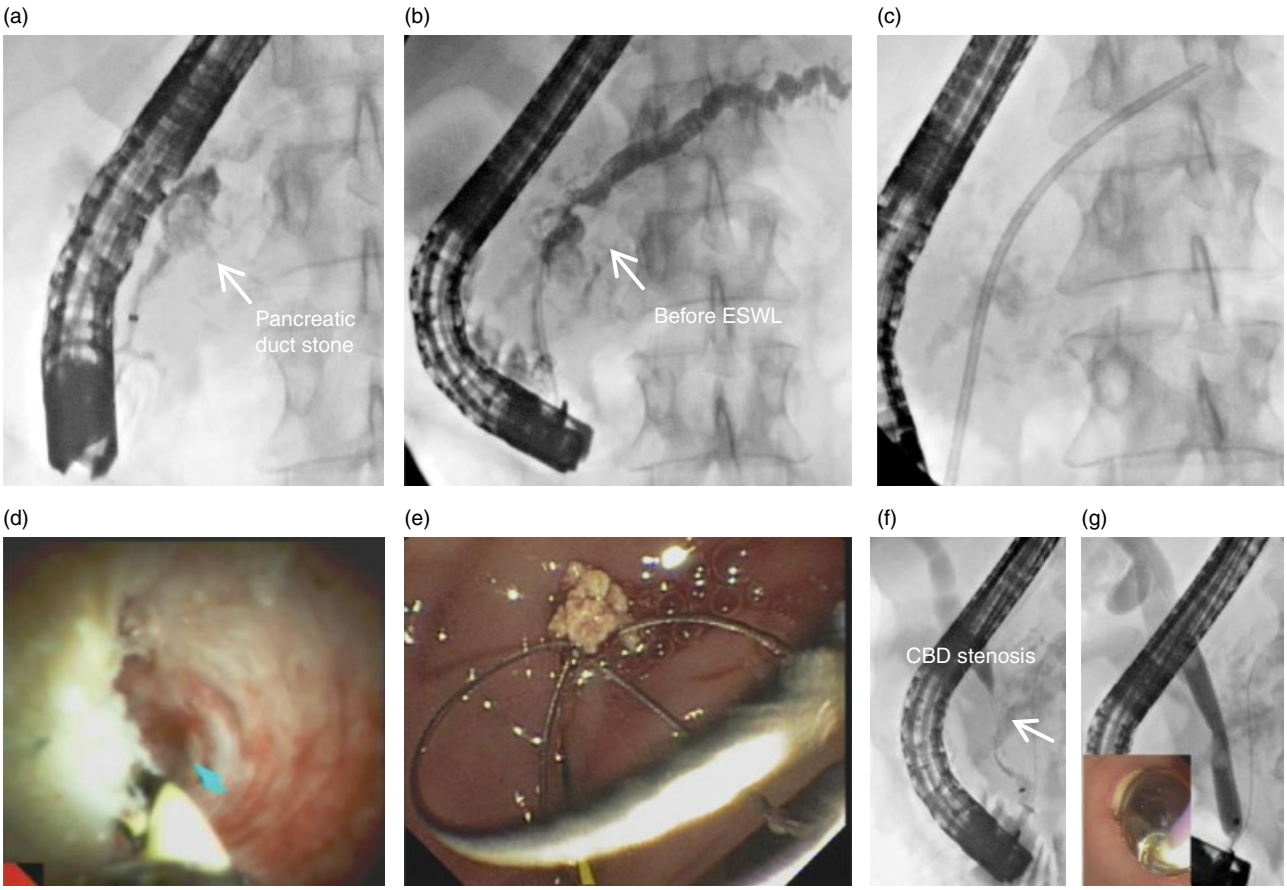


**Figure 55.1** A 48-year-old patient with symptomatic calcifying chronic pancreatitis. (a) Pancreatic duct with prepapillary stricture and a stone with a size of 8 × 10 mm behind the stricture. (b) Dilatation of the stricture and stent insertion (7F 12 cm). (c) Stent for extracorporeal shock wave lithotripsy. (d) Direct visualization of the pancreatic duct showing the impacted stone next to the guidewire. (e) Stone extraction using a dormia basket. (f) Common bile duct (CBD) stricture and balloon dilatation of the stricture before stent insertion (g).

recurring symptoms. This is a question that should be solved in a randomized trial. Improved pain management, however, was achieved by a pancreatojejunostomy in two randomized controlled studies [4–6]. Endoscopic therapy led to pain reduction or complete pain relief in 32% [5] and 61% [4], respectively, whereas this was achieved in 75% [5] and 86% [4], respectively, by pancreatojejunostomy. However, endoscopic drainage can achieve a long-lasting complete or partial pain relief in a substantial proportion of patients, and does not impede surgery as a second-line therapy.

## Endoscopic Treatment of Bile Duct Obstruction

Obstruction of the CBD will develop in 3–46% of patients with chronic pancreatitis [75]. Indications for endoscopic intervention include significant cholestasis, cholangitis, prevention of secondary biliary cirrhosis, and differentiation of the cause of pain (obstruction of the CBD vs. chronic pancreatitis). Long-term success rates can be achieved in one- to two-thirds of the patients, dependent on the endoscopic drainage modality [3]. Thus endoscopic therapy is indicated as an interim procedure until definitive surgery (e.g., as an acute intervention in septic patients, or in patients unfit for surgery or in those unwilling to undergo surgery). Complications include stent occlusion and cholangitis. Prophylactic antibiotic therapy together with ursodeoxycholic acid has not been proven to be effective [76–78]. Endoscopic drainage should be, therefore, of limited duration.

Immediate endoscopic drainage should be performed in the case of obstructive cholangitis. Although no published studies have compared endoscopic therapy to observation without drainage, treatment of mechanical cholestasis as part of the therapy for cholangitis is important and well substantiated by clinical experience. If chronic pancreatitis causes distal obstruction of the bile duct with cholestasis or obstructive jaundice, then either surgical treatment or endoscopic stent therapy can be performed. A retrospective analysis of all patients treated with an average observation period of 45 months demonstrated that stent therapy for the obstruction of the CBD in patients with chronic pancreatitis has no additional effect beyond 1 year [11]. Surgical treatment should therefore be pursued for recurrence of CBD obstruction after 1 year of stent therapy. A prospective study showed an even worse long-term effect of stent management of distal bile duct obstruction in patients with calcifying pancreatitis (long-term effect 9%) [12]. In these cases surgical treatment is clearly preferred.

The placement of multiple plastic stents into the biliary stricture of patients with chronic pancreatitis is superior to insertion of single plastic stents. In prospective, nonrandomized, and retrospective studies the success rate after insertion of up to five plastic stents into the CBD was higher than after a single stent, with long-term success rates of up to 92% of patients during a period of 12–48 months after stent removal [79–81]. The insertion of coated metal stents has demonstrated impressive results in case series [82,83]. A prospective nonrandomized study at 13 centers in 11 countries treated 187 patients with benign biliary strictures by fcSEMS [84]. Removal was scheduled at 10–12 months. On an intention-to-treat basis the stricture resolution rate was 76%, and the rate of stricture recurrence was 14.8% (95% CI: 8.2–20.9) during follow-up for 20 months. Thus, effective long-term success was achieved in 62.7% of patients.

A recent randomized controlled study compared insertion of multiple plastic stents with a single fcSEMS in 112 patients for treatment of benign biliary strictures over 1 year [85]. The resolution rate of biliary strictures was 85.4% with plastic stents and 92.6% with fcSEMS ($P < 0.001$). The mean number of ERCP to achieve resolution was significantly lower for fcSEMS as for plastic stents. The recurrence rate within 1 year of follow-up did not differ significantly between groups (14% with fcSEMS vs. 5% with plastic stents). Thus, fcSEMS placement appears to be an advantageous alternative to plastic stents in the management of benign biliary strictures. Exchange of single plastic stents should be undertaken at least every 3 months because otherwise occlusion of the stent may cause cholangitis. The exchange interval is less critical with the insertion of multiple stents and is unnecessary if fully coated metal stents are used. Those are patent for up to 9 months [86]. Currently, a high spontaneous migration rate of fcSEMS in approximately 30% of cases [84,85] will often require an earlier exchange.

The management of chronic bile duct obstruction after unsuccessful attempts at endoscopic treatment should be surgical. If there is an indication to treat cholestasis by surgery, a preoperative endoscopic insertion of a stent into the bile duct should only be undertaken if (i) surgery cannot be done promptly or (ii) cholangitis is present. A multicenter prospective randomized study examined the effect of preoperative endoscopic stent insertion into the CBD for mechanical cholestasis secondary to carcinoma of the head of the pancreas before pancreas resection. Preoperative drainage significantly increased the rate of complications [87]. A patient with a short individual life expectancy, high comorbidity, and the difficult, foreseeable technical feasibility of an operation (e.g., marked collateral circulation secondary to portal hypertension) are all factors in favor of endoscopic treatment for bile duct obstruction.

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# 56

# Indications and Goals of Surgical Treatment

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## Introduction

Chronic pancreatitis requires a multidisciplinary management strategy. Gastroenterologists, advanced endoscopists, radiologists, and pancreatic surgeons should collaborate to establish a plan of care. Accurate delineation of each patient's pancreatic anatomy is the first step in workup, and employs the sequential use of computed tomography (CT), magnetic resonance imaging (MRI) and cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP). Randomized studies performed more than a decade ago [1,2] demonstrated an advantage of surgery over endoscopic therapy for long-term control of pain associated with chronic pancreatitis. As endoscopic techniques have matured, however, more present-day patients are achieving an acceptable outcome without the need for surgical intervention [3]. Aside from cases of suspected cancer, most surgery for chronic pancreatitis is limited to cases where endoscopic treatment either is anatomically not feasible or has failed.

Indications for surgery typically include the following, either alone or in combination: intractable pain refractory to endoscopic stenting, suspected malignancy, or symptomatic local complications (such as bile duct or bowel obstruction, portal vein compression, splenic vein thrombosis, fistula, or pseudocyst).

When surgery of the pancreas itself is planned, the following factors are considered:

- When cancer is suspected or confirmed, oncologic resection is performed.
- When an inflammatory mass is present in the head of the gland, the head should be resected.
- Any dilated pancreatic duct (≥7 mm) which would not otherwise be resected should be drained.
- When splenic vein thrombosis exists, splenectomy should be performed.

Table 56.1 summarizes the commonly considered operative options based on the most common morphologic considerations. There are a host of less common clinical scenarios that would dictate other surgical options, and these are highlighted both in the text of this chapter, and expanded upon in subsequent chapters.

## Surgical Drainage of the Pancreatic Duct

Indications for a pure drainage operation include patients with the phenotype of a significantly dilated pancreatic duct (≥7 mm) *without* an associated inflammatory mass in the head of the pancreas. Main pancreatic ductal stones should be removed at the time of laterolateral pancreaticojejunostomy. If pancreaticolithiasis is extensive in side-branches within the head of the gland, consideration should be given to either "coring out" or resecting the pancreatic head.

Although the eponym "Puestow" is still commonly used to describe laterolateral pancreatojejunostomy, most modern pancreatic surgeons perform the operation as modified by Partington and Rochelle (Fig. 56.1) [4]. In this modification, the pancreatic tail resection advocated by Puestow is abandoned, which leaves more pancreatic parenchyma and lowers morbidity and mortality. Although operative safety was improved, these patients frequently experienced either immediate failure of pain control or delayed recurrence years later, often

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**Table 56.1** Authors' choice of operation for chronic pancreatitis based on pancreatic morphology typically present.

| Pancreatic morphology and clinical indications | Incidence | Operation |
|---|---|---|
| Main duct dilation without inflammatory head mass | Uncommon | Frey procedure |
| Main duct dilation with inflammatory head mass | Common | |
| + any concern for malignancy | | Pancreatoduodenectomy |
| – no concern for malignancy | | Frey procedure |
| Main duct dilation and very high stone burden in head of pancreas | Uncommon | Pancreatoduodenectomy with lateral pancreaticojejunostomy |
| Left-sided pancreatitis with main duct disruption ("disconnected duct syndrome") | Common | Distal pancreatectomy |
| Duodenal obstruction | Uncommon | Pancreatoduodenectomy |
| Common bile duct obstruction | Common | Pancreatoduodenectomy |
| Hemosuccus pancreaticus | Rare | Pancreatoduodenectomy or distal pancreatectomy[a] |

[a] In the acute bleeding phase, angiographic embolization is preferred; if embolization is definitive, surgery may not be required.

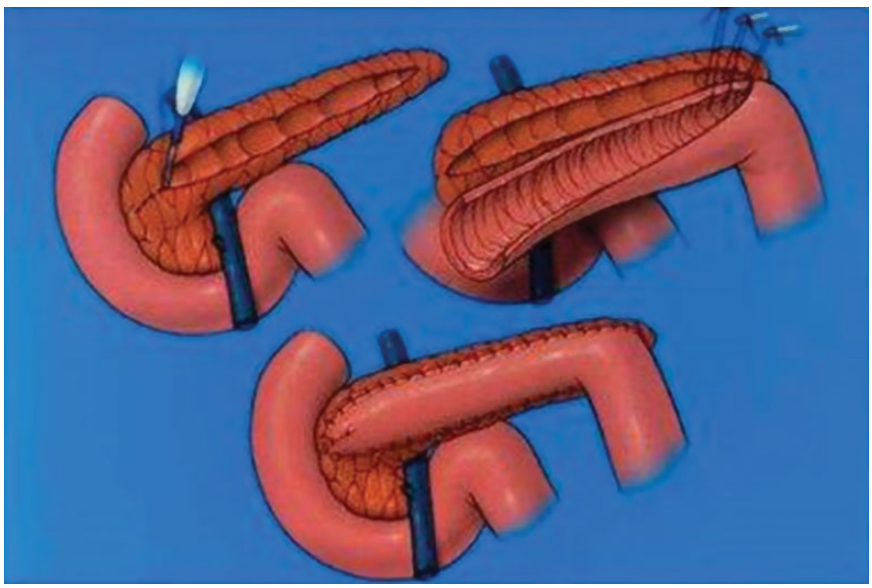

**Figure 56.1** Laterolateral pancreaticojejunostomy, as described by Partington and Rochelle. The pancreatic parenchyma is incised anteriorly to expose the duct. Pancreaticoliths should be thoroughly removed. A roux limb of small bowel is sutured to the open pancreatic parenchyma in a running fashion. *Source*: By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

due to an inflammatory mass in the head of the pancreas [5]. This realization has led to the current belief that the pancreatic head is the "pacemaker" of pain in patients with chronic pancreatitis, and pure ductal drainage procedures are now infrequently performed. The senior author now performs local resection of the pancreatic head and lateral pancreaticojejunostomy (LR–LPJ) in those patients with intractable pain and "large duct" (≥7 mm) chronic pancreatitis (Fig. 56.2).

## Surgical Resection of the Pancreas

When a mass exists in the pancreatic head and surgery is entertained, the pancreatic head should be resected. This can either involve a coring of the pancreatic head alone (Beger or Bern procedures), a combination of coring the pancreatic head and incising the lateral pancreatic duct (Frey procedure or LR–LPJ), or a pancreaticoduodenectomy. The Beger, Bern, and Frey procedures are detailed in Chapter 58. Although perioperative safety may be slightly better with duodenum-preserving procedures with coring of the pancreatic head, in randomized trials compared to pancreaticoduodenectomy, long-term follow-up reveals that both are highly effective in controlling pain [6–11]. Patients treated with pancreaticoduodenectomy at the Mayo Clinic for pain related to chronic pancreatitis ($n = 166$, median follow-up of 15 years) showed lower mean pain scores (scale 1 to 10) after surgery (1.6) as compared to before surgery (7.9, $P < 0.001$) [12]. There appears to be regional variation worldwide with respect to the morphologic phenotype of chronic

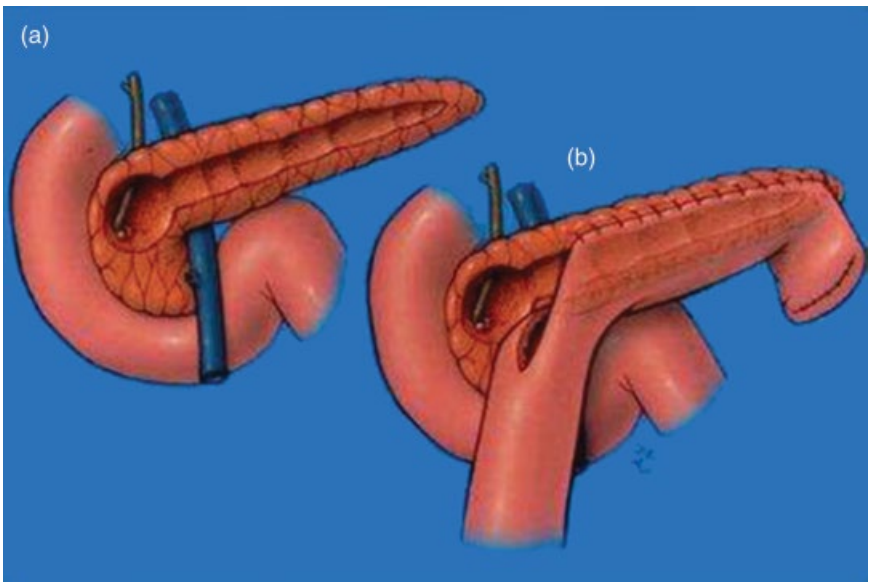


**Figure 56.2** Frey procedure, which combines local coring of the pancreatic head with an anterior pancreatotomy (a). Pancreatoliths should be thoroughly removed, and this is drained by a roux limb sutured to the open pancreatic edges (b). *Source*: By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

pancreatitis, which may clarify apparent differences in the preferred surgical approach in various countries. In Germany, inflammatory pancreatic head masses associated with chronic pancreatitis are nearly twice the size on average of those from a cohort from the United States (4.5 vs. 2.6 cm) [13].

Patients with chronic pancreatitis have an increased risk for pancreatic ductal adenocarcinoma, and differentiating cancer from a benign inflammatory mass can be difficult with imaging alone. Duct dilation distal to a mass and distal gland atrophy may signify cancer. Subtle extension of increased soft tissue density along arteries can sometimes be a clue to the presence of cancer on CT or MRI. In uncertain cases, CA 19-9 elevation raises the suspicion of malignancy. EUS can be used to identify and biopsy masses, although there is known poor interobserver agreement with this method in the setting of chronic pancreatitis [14]. When clinical suspicion is raised for cancer, oncologic resection is required, and a head-coring operation or a pure drainage procedure should be avoided.

Isolated left-sided pancreatectomy is reserved for focal disease in the distal gland. Indications for concurrent splenectomy in this setting include a perisplenic pseudocyst, splenic vein thrombosis, fibrotic encasement of the splenic vessels, and suspected malignancy. Hemosuccus pancreaticus from peripancreatic pseudoaneurysm formation is a very rare complication of pancreatitis [15]. In such patients, angiographic embolization is preferred in the setting of acute bleeding; when resective surgery is necessary, we recommend pancreaticoduodenectomy. Pancreatic ascites is a rare complication which can generally be managed using endoscopic techniques.

Total pancreatectomy (ideally with islet cell autotransplantation) is also rarely indicated, and usually used in the setting of severe whole-gland disease. This strategy results in 73% of patients free of narcotics at 5 years; when islet cells are autotransplanted, 40% of patients achieve independence from insulin [16]. Patients with hereditary pancreatitis syndromes (*PRSS1*, *SPINK1*, *CTFR*, etc.) should not undergo *prophylactic* resection. However, the young age at which many develop intractable pain coupled with severe whole-gland disease makes them among the best candidates for consideration of total pancreatectomy with islet cell autotransplantation.

## Surgical Management of Biliary Obstruction

Bile duct stricture with or without obstruction is unusual in the setting of chronic pancreatitis unless significant involvement of the pancreatic head is present. For this reason, most patients being considered for surgery will already be in consideration for a head-coring procedure or pancreaticoduodenectomy. Before surgical intervention, many patients will have undergone endoscopic efforts to relieve biliary obstruction, and indwelling stents may be present. A careful review of cholangiograms that pre-date endoscopic interventions is mandatory.

The level(s) of radiographic stricture in the biliary tree are important considerations in the operative plan. Patients with strictures at the level of the ampulla with a dilated bile duct into the pancreatic parenchyma will be adequately treated with either pancreaticoduodenectomy or a head-coring procedure; however, a head-coring procedure must include intrapancreatic bile ductotomy to ensure bile drainage into the roux limb. Patients with extrapancreatic biliary strictures will not

be helped by a head-coring procedure, and pancreaticoduodenectomy is recommended. An ongoing French multicenter randomized clinical trial (PASTEC) is comparing surgery and endoscopic stenting in the treatment of biliary obstruction related to chronic pancreatitis. This trial is expected to run through 2019.

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# 57

# Pancreatic Duct Drainage Procedure

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## Introduction

Compared to the general population, patients with chronic pancreatitis have a fourfold increase in mortality [1] and a tenfold increased risk of pancreatic malignancy [2]. Progressive inflammatory destruction of the pancreatic parenchyma in chronic pancreatitis is usually accompanied by intractable pain and a loss of exocrine and endocrine pancreatic function, clinically evident as malabsorption and pancreatogenic diabetes.

The pathogenesis of pain in chronic pancreatitis is likely multifactorial. One potential mechanism may be increased intraductal pressure and obstruction of the pancreatic ductal system. The inflammation itself, together with alterations in pancreatic nerve fibers, including an increase in nerve fibers and neurogenic inflammation, may also contribute to the typical pain commonly associated with chronic pancreatitis. Changes in the central nervous system and alterations in central pain processing may also lead to pain. The characteristic abdominal pain often leads to impaired social and work life due to frequent hospitalization [3].

Currently, endoscopic or interventional treatment is considered the first step in the treatment of patients with chronic pancreatitis. Endoscopic treatment that relieves the pancreatic ductal system (endoprothesis, stone extraction, extracorporeal shock wave lithotripsy, or ductal dilatation) improves pain for up to 1 year [4]. Multiple interventions improve pain in about 65% of cases and reduce the number of patients requiring surgical intervention [5].

However, stent replacement often has to be performed 3-monthly and may require multiple hospital admissions [6,7]. After unsuccessful endoscopic treatment, about 49% of the patients still require surgery within 1 year [8] (Fig. 57.1). Although endoscopic duct drainage may provide long-term success in the presence of isolated proximal duct stenosis and in the absence of an inflammatory mass of the pancreatic head and calcifications, surgery is superior to endoscopic therapy in the latter case [9] and may also be more cost-effective [10]. Moreover, early surgical intervention may also prevent disease progression, preserve pancreatic function, and improve long-term pain control [9,11–13].

## Indication for Surgery

The most common indication for surgery for chronic pancreatitis is intractable pain despite endoscopic intervention. Other indications for surgery are local complications, such as duodenal or biliary stenosis, symptomatic pseudocysts, pancreaticopleural fistula, a disconnected pancreatic duct, pancreatogenic ascites or suspicion of neoplasm. All procedures attempt to reduce pain and resolve organ complications while preserving exocrine and endocrine function. Their long-term efficacy is commonly evaluated by the restoration of quality of life and successful rehabilitation. Three distinct groups of procedures can be employed to treat chronic pancreatitis: drainage procedures, procedures combining drainage and resection, and resecting procedures. The choice of procedure depends on the morphological features of the pancreatitis. Drainage combined with resection of the pancreatic head (Beger procedure [14], Frey procedure [15]) is commonly chosen if an inflammatory mass of the pancreatic head is present, resecting procedures (pylorus-preserving pancreaticoduodenectomy, Whipple procedure) are used if malignancy is suspected. The majority of patients with chronic pancreatitis (85%) have an inflammatory mass of the pancreatic head and thus require drainage combined with resection or

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

resection of the pancreatic head [16] (Fig. 57.2a). However, drainage procedures are the procedure of choice in patients with a dilated pancreatic duct (≥5 mm) without an inflammatory mass [17] (Fig. 57.2b). Another indication for surgical drainage may be malignant transformation of the portal vein with collaterals in the case of long segment portal vein stenosis. However, short segmental portal vein or mesenterico-portal vein stenosis with portal hypertension may also be alleviated during pancreatic head resection by decompressing the stenosis [18]. Resection of the pancreatic head is even possible after interventional recanalization of the portal vein for nonfixated portal vein thrombosis. Drainage procedures are thus not mandatory in this situation [19].

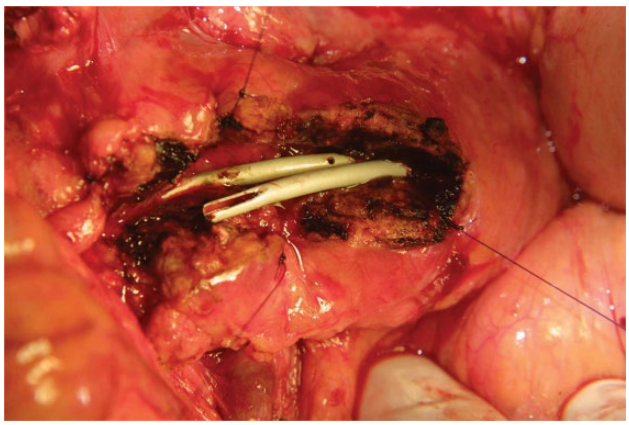


**Figure 57.1** "Lost stents" after endoscopic therapy of an inflammatory stenosis due to chronic pancreatitis. Intraoperative view during a Frey procedure.

## Drainage Procedures

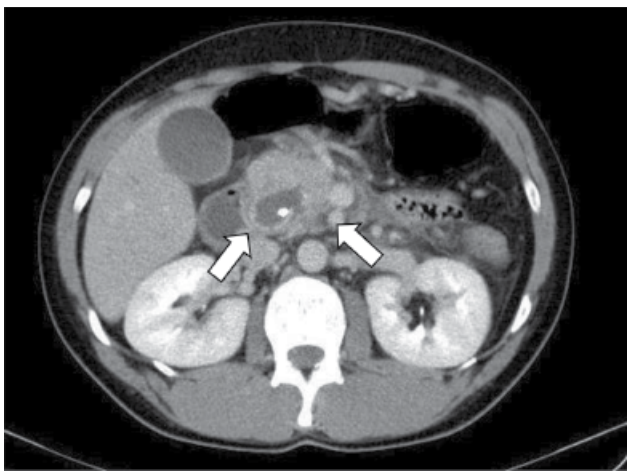
The first drainage procedure of the pancreas in humans was performed in 1911 through transcutaneous catheter placed in the pancreatic duct [20]. The procedure provided pain relief and the patient survived for 30 years. More than 50 years later, the procedure was modified and a distal pancreatectomy, splenectomy, and pancreaticojejunostomy were performed [21]. The procedure was further refined as a distal pancreatectomy and side-to-side pancreaticojejunostomy [22]. The latero-lateral panceaticojejunostomy still in use today was first described in 1960 [23].

A Partington–Rochelle procedure comprises an incision of the pancreatic duct at the anterior surface of the pancreas from the tail to the head of the pancreas. Calculi in the pancreatic ducts can then be removed and segmental stenosis can be relieved. The procedure is completed by a Roux-en-Y jejunal limb sutured side-to-side to the pancreatic duct [23].

Drainage procedures are associated with low morbidity and mortality rates (about 1%). However, drainage is inferior to resection with regard to pain management and complication management [24–36] (Fig. 57.3).

As a hybrid procedure with partial resection of the pancreatic head, the Frey procedure is often also considered a drainage procedure. It comprises excoriation of the pancreatic head combined with an incision of the pancreatic duct at the anterior surface of the pancreas to the tail of the pancreas. The procedure is completed by a Roux-en-Y jejunal limb sutured side-to-side to the excoriated pancreatic head and pancreatic duct [15]. Compared to the Partington–Rochelle procedure, the

(a)



(b)

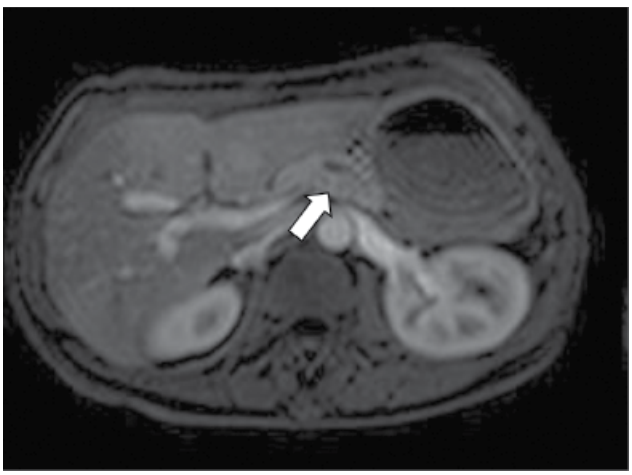


**Figure 57.2** CT scan of chronic pancreatitis. (a) The majority of patients with chronic pancreatitis have an inflammatory mass of the pancreatic head (arrow) and thus require drainage combined with resection or resection of the pancreatic head. (b) Drainage is the procedure of choice in patients with a dilated pancreatic duct (≥5 mm) without an inflammatory mass (arrow).

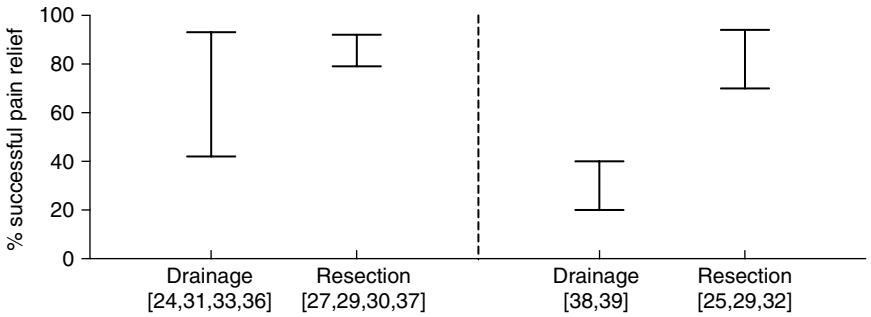



**Figure 57.3** Drainage procedures are inferior to resection with regard to pain management. The figure shows short-term (left) and long-term (right) pain relief after drainage or resection procedures [24,25,27,29,30–33,36–39].

Frey procedure improves the long-term outcome. Compared to other resection procedures, the outcome achieved by the Frey procedure is equivalent with regard to pain control, quality of life, and exocrine and endocrine organ function [32,40–43].

A rare form of chronic pancreatitis termed "small duct disease" affects the whole organ. It is not associated with a dilated pancreatic ductal system and may easily be misdiagnosed as autoimmune pancreatitis. Treatment of choice for this small duct disease is longitudinal V-shaped excision of the ventral pancreas. The procedure combines extensive drainage with a limited resection [44]. This drainage procedure may provide long-term pain relief and an improved quality of life in the majority of patients [45]. Compared to V-shaped excision, resection may not be as effective in the treatment of small duct disease [46].

## Conclusion

In summary, drainage procedures such as the Partington–Rochelle are often not sufficient to provide acceptable pain and complication control because of the frequently observed inflammatory mass of the pancreatic head. In the absence of this, they provide good results with low morbidity and mortality. In the presence of an inflammatory mass, hybrid procedures such as the Frey procedure or V-shaped excision are as effective as resection.

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# 58

# Duodenum-Preserving Pancreatic Head Resection

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## Introduction

Chronic pancreatitis is a pathologic fibroinflammatory syndrome of the pancreas in individuals with genetic, environmental, and/or other risk factors, which results in persistent pathologic responses to parenchymal injury and stress [1]. Common features of chronic pancreatitis include pancreatic atrophy, tissue fibrosis, upper abdominal pain, duct distortion, and strictures, and in the late course of the disease, inflammatory head mass, calcifications and pancreatic duct stones, duodenal dystrophy, functional exocrine insufficiency, diabetes mellitus, and cellular dysplasia.

The mechanistic definition of chronic pancreatitis, recently published as the result of an international proposal, reflects the complex nature of this disease. Alcohol abuse and cigarette smoking are the most frequent causes of chronic pancreatitis. After a preclinical period of up to 12 years, the majority of patients develop abdominal complaints and upper abdominal pain as first signs of the disease. In the late stages, local complications are caused by the progressive inflammatory process, and are enhanced by alcohol consumption and cigarette smoking. Patients referred for surgical treatment suffer severe abdominal pain; 30–50% show alcoholic chronic pancreatitis exhibiting an inflammatory mass in the head of the pancreas, frequently causing common bile duct (CBD) obstruction [2,3]. Infrequently, severe obstruction of the duodenum, portal vein compression or thrombosis, and splenic vein occlusion are clinically relevant. Pathomorphologically, main-duct stenosis with prestenotic duct dilation and side-branch duct stenoses are observed (Table 58.1). For discussion of the natural history of chronic pancreatitis, see Chapter 42; for early stage chronic pancreatitis, see Chapter 44; for epidemiology and pathophysiology of alcoholic chronic pancreatitis, see Chapter 40; for strategies for surgical treatment, see Chapter 56.

## Are Duct Stenting and Endoscopic Interventions an Alternative to Surgery?

Duct stenting, endoscopic dilatation of pancreatic main-duct stenosis, and endoscopic stone extraction for obstructive chronic pancreatitis have been reported by a number of recent studies with good results. However, sphincterotomy and stenting of the pancreatic main duct is considered a temporary treatment. The risk of stent occlusion and migration and the need for long-term control of upper abdominal pain are the limitations of the interventional endoscopic treatment modalities. Data from prospective, randomized, single-institute trials comparing endoscopic therapy with surgical treatment have been published [9,10]. Short-term pain relief was similar in both groups. The long-term outcome after a 1- to 3-year follow-up revealed major advantages for surgical treatment with regard to pain control and frequency of rehospitalization compared to interventional stenting.

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Companion website: www.wiley.com/go/beger/thepancreas

**Table 58.1** Chronic pancreatitis—frequency of local complications.

| | Frequency of local complications | | |
|---|---|---|---|
| | From the literature | | From Ulm[a] |
| CBD stenosis | 23% | Gregg 1982 [4] | 43% |
| Inflammatory head tumor | | Beger 1980 [2,47] | 74% |
| Pseudocysts | 30% | Ahmad 2006 [5] | 32% |
| Necroses | 49% | Amman 1996 [6] | 9% |
| Obstruction of duodenum | 0.8% | Aranka 1984 [7] | 23% |
| PV + SMV, SV obstruction thrombosis | 10–20% | Warshaw 1997 [8] | 16% |

[a] 1972–12/1998 Department of General Surgery, University of Ulm, Germany.
CBD, common bile duct; PV, portal vein; SMV, superior mesenteric vein; SV, splenic vein.

## Who Benefits from Surgical Treatment?

Surgery for chronic pancreatitis is essentially a palliative treatment. The primary goals of surgery are (i) long-term pain control and (ii) control of chronic pancreatitis-associated complications of adherent tissues. Upper abdominal pain refractory to medical treatment in combination with local complications is the most frequent setting for surgical treatment (Box 58.1). Preservation of exocrine and endocrine pancreatic functions are secondary but equally important goals of surgical treatment. Most patients with chronic pancreatitis are under 55 years and professionally active. Social and occupational rehabilitation and improvement of quality of life are additional primary goals for the long-term outcome.

## Kausch–Whipple Resection or Hemipancreatectomy—Still Standard Treatment for Chronic Pancreatitis?

Currently, pancreatoduodenectomy, left or distal hemipancreatectomy, and total pancreatectomy are still applied for chronic pancreatitis. The disadvantages of these major pancreatic resections are (i) the unnecessary sacrifice of pancreatic and peripancreatic biliary and gastroduodenal tissues and (ii) the surgery-inherent loss of duodenal and pancreatic tissue, which leads to impairment of endocrine and exocrine functions in the long-term outcome. New onset of diabetes mellitus and exocrine insufficiency after pancreatoduodenectomy and hemipancreatectomy have been extensively documented [11–24]. Long-term observations showed that patient survival was shorter after duodenopancreatectomy for chronic pancreatitis compared to after an organ-preserving surgical procedure [25].

**Box 58.1 Indications for duodenum-preserving pancreatic head resection for chronic pancreatitis**

- Upper abdominal pain refractory to medication
- Inflammatory mass of pancreatic head
- Biliary stenosis
- Single/multiple narrowing of pancreatic main duct
- Compression of portal vein/superior mesenteric vein
- Severe stenosis of peripapillary duodenum
- Clinical symptomatic pseudocyst / persisting
- Pseudocyst after failure of endoscopic treatment
- Pancreas divisum after failure of endoscopic treatment

## Indications and Rationale for Duodenum-Preserving Pancreatic Head Resection

Surgical treatment of chronic pancreatitis is presently dominated by organ-preserving surgical procedures. Introduced by Partington and Rochelle [26], intestinal drainage of the pancreatic main duct and duodenum-preserving subtotal pancreatic head resection and their modifications have the advantages of tissue sparing and maintenance of pancreatic function [27]. Based on contrast-enhanced computed tomography, magnetic resonance imaging, and magnetic resonance cholangiopancreatography, the majority of pathomorphologic changes of chronic pancreatitis are observed predominantly in the pancreatic head, frequently associated with an inflammatory mass and obstruction of the CBD. Infrequently, the inflammatory tumor in the pancreatic head causes portal vein and superior mesenteric vein compression and obstruction of the duodenum. To resolve these complications, resection of the pancreatic head is recommended. Duct drainage procedures in chronic pancreatitis are only indicated in the subgroup of patients with pancreatic main-duct stenosis and dilatation extending into the duct of the body and tail.

With regard to long-term pain control, duct drainage procedures without resection of the pancreatic head are associated with a re-appearance of abdominal pain in about one-third of patients observed after a >5-year follow-up (HG Beger, unpublished data). A duct drainage procedure in chronic pancreatitis is considered unnecessary in patients with a dilated body–tail duct without

duct obstructions when the pancreatic head is resected. Long-term follow-up observations after pancreatoduodenectomy and duodenum-preserving pancreatic head resection (DPPHR) have shown long-lasting pain control after head resection without an additional duct drainage procedure [28,29]. The effectiveness of DPPHR has been proved through randomized controlled trials (RCT) and long-term observations over 5–10 years which showed completely pain-free patients in 80–90% of cases. For patients with an inflammatory head mass who were treated with a duct drainage procedure without subtotal pancreatic head resection, a risk persists for the development of biliary stenosis in the long term, with the need for biliary stenting and/or re-surgery.

## Surgical Technique of DPPHR for Chronic Pancreatitis

DPPHR comprises three different surgical steps:

1) exposition of the pancreatic head with identification of the portal vein, respective inferior mesenteric vein and the supraduodenal CBD; tunneling of the pancreatic neck in front of the portal vein;
2) subtotal resection of the pancreatic head to conserve the intrapancreatic CBD;
3) reconstruction with an excluded jejunal loop, executing two pancreatic anastomoses.

Steps 1 and 3 are almost identical to the surgical steps performed in the Kausch–Whipple procedure.

An extensive Kocher maneuver should be avoided to preserve the vessels on the dorsal side of the pancreatic head. The anterior gastroduodenal artery is identified and ligated near the common hepatic arteries. The posterior superior branch of the pancreaticoduodenal artery and the inferior anterior pancreaticoduodenal artery should be carefully preserved. Subtotal resection of the pancreatic head is performed from the ligamentum hepatoduodenale along the intrapancreatic segment of the CBD, including the uncinate process (Figs 58.1, 58.2, and 58.3). Bleeding vessels arising in the transected tissue are immediately sutured (Fig. 58.4). Preservation of the dorsal capsule of the pancreatic head and the dorsal branch of the gastroduodenal and pancreaticoduodenal vessels is recommended to maintain sufficient perfusion of the wall of the duodenum and papilla. Reconstruction of the gastrointestinal tract is performed with an excluded jejunal loop (Fig. 58.5).

Two modifications of the DPPHR procedure are presently in use. In patients displaying a prepapillary CBD stenosis, which persists due to an inflammatory process in the wall of the CBD, after subtotal head resection, an additional biliary anastomosis by an incision of the CBD is executed [30] (Fig. 58.6). In patients who show multiple stenosis and dilations of the main duct in the body and tail, the pancreatic main duct is opened longitudinally on its ventral surface, extending towards the tail of the pancreas. A side-to-side anastomosis is executed in addition to the head resection [31].

## Early Postoperative Course

Early severe postoperative complications are infrequent (Table 58.2). Severe, surgery-related complications are <10% according to Clavien–Dindo III. Local bleeding,

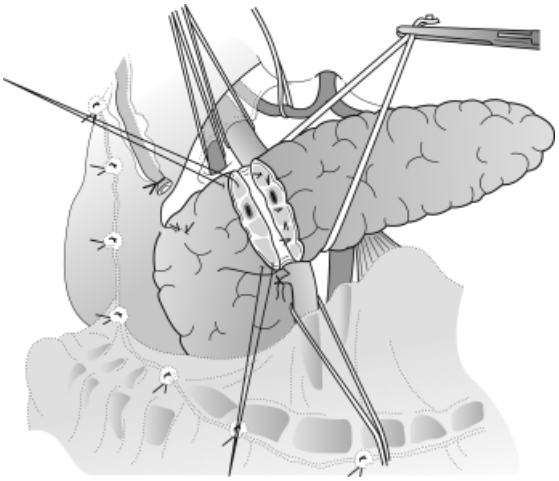

**Figure 58.1** Duodenum-preserving pancreatic head resection after tunneling of the portal vein behind the pancreas. The resection line is the duodenal side of the portal vein.

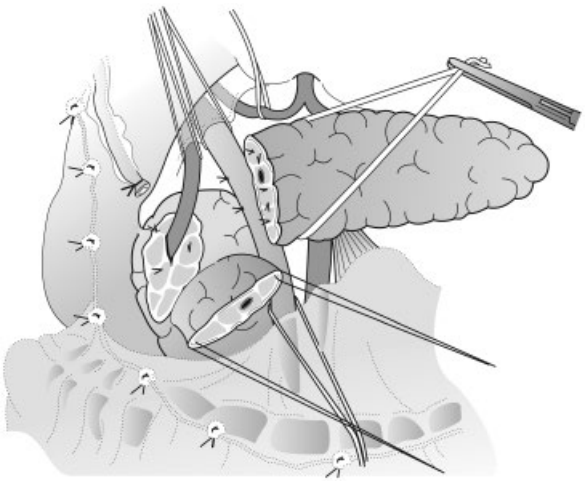

**Figure 58.2** Subtotal resection of the pancreatic head after ventral rotation. The common bile duct is identified at the level of the hepatoduodenal ligament and decompressed by resection of periductal pancreatic tissue, except for a small rim between common bile duct and duodenal wall.

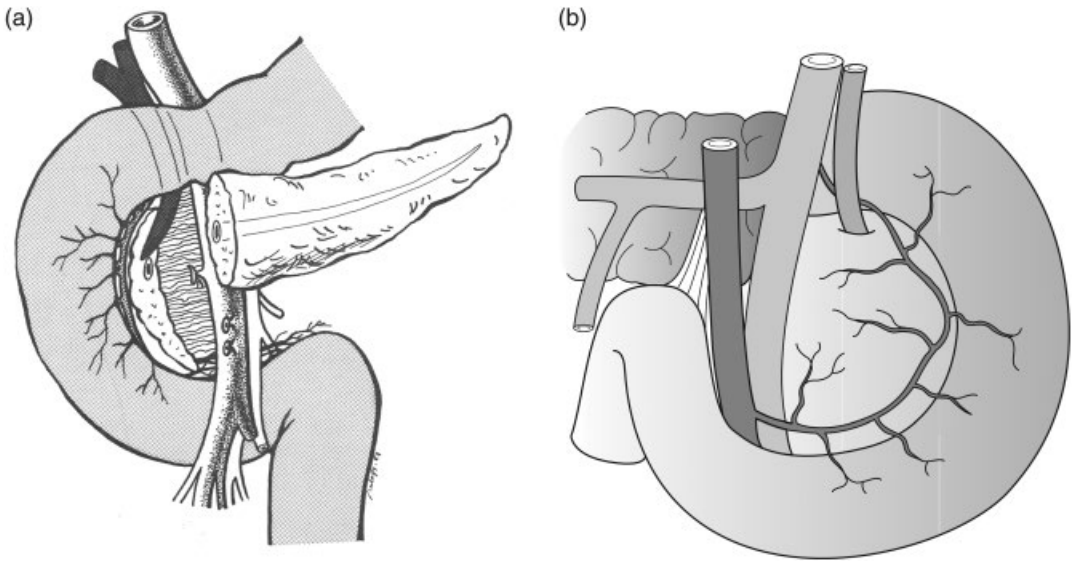


**Figure 58.3** (a) After finishing the subtotal pancreatic head resection, a shell-like remnant of the pancreatic head remains along the duodenal wall. Bleeding vessels are frequently closed by single stitches using 5-0 sutures. (b) The dorsal capsule of the pancreatic head is preserved to maintain blood flow to and from the duodenal wall. The dorsal pancreaticoduodenal arcades and inferior pancreaticoduodenal artery are preserved.

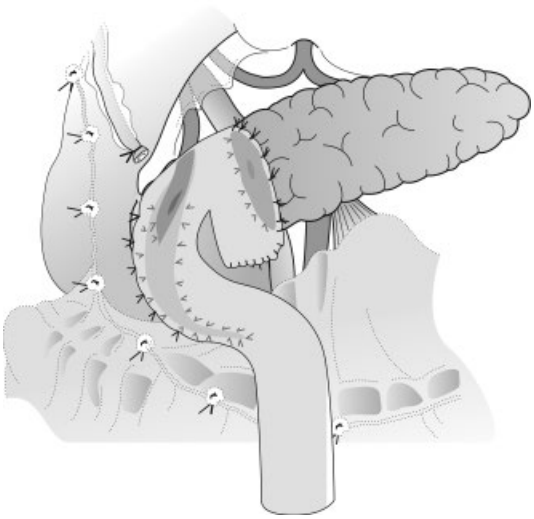

**Figure 58.4** Reconstruction of the upper jejunal loop after subtotal resection of the pancreatic head requires exclusion of the first jejunal loop and creation of an end-to-side duct-to-mucosa anastomosis between the pancreatic neck and the jejunum (two-layer anastomosis). Anastomosis between the shell-like remnant of the pancreatic head and the excluded jejunal loop (end-to-side anastomosis) is also performed. A Y-en-Roux anastomosis between the excluded jejunal loop and the first jejunal as side-to-end anastomosis is included.

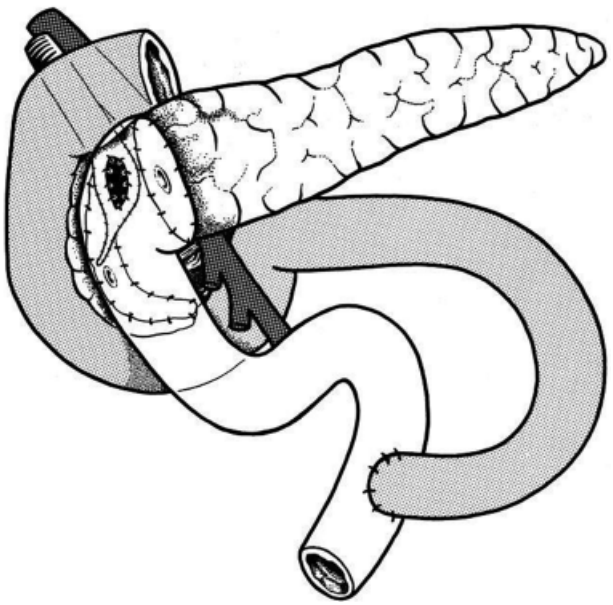

**Figure 58.5** In the case of extended narrowing of the intrapancreatic segment of the common bile duct caused by an inflammatory process in the wall of the common bile duct an internal biliary anastomosis is additionally executed by incision of the prepapillary common bile duct of 10–12 mm.

which appears as intestinal blood loss, caused by arterial leakage from the shell-like remnant of the pancreatic head and anastomotic leakage, which appears as evacuation of intestinal content into the drainage bag, is observed in <2% of cases. Severe intestinal bleeding, leakage of the pancreaticojejunostomy and surgical-side infection around the pancreatic head are reasons for reintervention [25]. Between the 2nd and 5th postoperative days, patients are on regular oral nutrition (Table 58.3). Glucose metabolism is maintained at preoperative levels up to the 5th postoperative year (Table 58.3). When C-peptide and insulin responses are measured 3–36 months postoperatively after intravenous and oral glucose load, they were

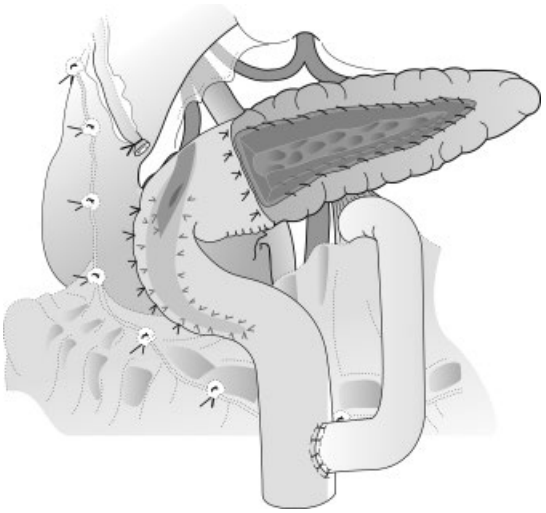

**Figure 58.6** Where the pancreatic main duct shows multiple duct stenosis and dilatations, duct drainage of the pancreatic main duct from the head to the tail is additionally applied by a side-to-side anastomosis with the excluded jejunal loop.

**Table 58.2** Early postoperative results after duodenum-preserving subtotal pancreatic head resection in 603 patients.

| | Patients *N* | Frequency |
|---|---|---|
| Pancreatic fistula | 20 | 3.3% |
| Pancreatic anastomosis leakage | 9 | 1.5% |
| Biliary leakage | 3 | 0.5% |
| Intra-abdominal abscess | 17 | 2.8% |
| Intra-abdominal hemorrhage | 17 | 2.8% |
| GI anastomosis-insufficiency | 2 | 0.3% |
| Delay of gastric emptying | 9 | 1.5% |
| Frequency of reoperation | 34 | 5.6% |
| Hospital mortality | 5 | 0.81% |

Data from [2].

found to be at preoperative levels. However, the concentrations of glucagon and pancreatic polypeptide (PP) displayed a highly significant decrease after stimulation [32–34]. The loss of glucagon and PP delivery into the blood explains the observation that up to 10–12 % of patients experienced postoperative improvement of the disrupted glucose metabolism, because both hormones are produced predominantly in the endocrine tissue of the pancreatic head.

## Long-Term Outcome After DPPHR

After a median observation period of 5.7 years and a follow-up rate of 94%, control of pancreatic pain is complete and long-lasting in approximately 90% of cases (Table 58.4). In terms of pain and attacks of pancreatitis, DPPHR changes the natural course to a silent disease. In our experience, preoperatively, each patient had 2.7 hospitalization periods, whereas after a median follow-up of 5.7 years, only 9% of the patients experienced a rehospitalization. Due to the persistent destruction of the functional parenchyma of the pancreas inherent in chronic pancreatitis, the frequency of diabetes mellitus increases as well as the level of exocrine insufficiency [35–37]. The major advantages of duodenum-preserving subtotal pancreatic head resection for chronic pancreatitis are conservation of the duodenum and the CBD and temporary maintenance of endocrine pancreatic functions. Several RCT have been published comparing DPPHR with Kausch–Whipple duodenopancreatectomy, with DPPHR found to be superior in terms of postoperative morbidity, maintenance of glucose metabolism, an absence of delayed gastric emptying, and a low frequency of rehospitalization [38–42] (Table 58.5). With regard to the Frey procedure, as performed in the majority of patients, the level of maintenance of glucose metabolism, frequency of postoperative morbidity, and quality of life in the long term are almost the same as the results after DPPHR [44].

**Table 58.3** Long-term endocrine and exocrine pancreatic functions after DPPHR for chronic pancreatitis.

| | | Bittner 1992 [32] (15 patients, 3 months) | Ikenaga 1995 [33] (42 patients, 36 months) | Eddes 1997 [34] (19 patients, 3–6 months) |
|---|---|---|---|---|
| Endocrine I/OGTT | | Preop = postop | New DM 29% | Preop = postop |
| | *K*-value | Postop $P < 0.01$ | Preop = postop | |
| | Insulin | Preop = postop | Preop = postop | |
| | C-peptide | Preop/postop NS | | Postop reduced $P < 0.05$ |
| | Glucagon | Preop/postop $P < 0.001$ | | Postop reduced $P < 0.05$ |
| | PP (AUC) | | | Postop reduced $P < 0.05$ |
| Exocrine | BT-PABA | | Postop reduced $P < 0.01$ | Postop reduced $P < 0.05$ |

I/OGTT, intravenous/oral glucose tolerance test; DM, diabetes mellitus; PP (AUC), pancreatic polypeptide (area under the curve); BT-PABA, pancreo-lauryl test.

**Table 58.4** Endocrine function and pain after DPPHR for chronic pancreatitis—results of long-term follow-up.

| | Preoperative | | Late postoperative | |
|---|---|---|---|---|
| | 1972–1998<br>504 patients | 1984 [35]<br>Median follow-up<br>2.0 years<br>56 patients | 1988 [36]<br>Median follow-up<br>3.6 years<br>109 patients | 1997 [37]<br>Median follow-up<br>5.7 years<br>303 patients |
| OGTT normal | 246 (49%) | 66 % | 48% | 39% |
| OGTT reduced | 134 (26%) | | 26% | 17% |
| IDDM | 124 (25 %) | – | 26% | 44% |
| Pain free[a] | | 92.8% | 89% | 91.3% |
| Continuing abdominal pain | | 7.2% | 11% | 8.7% |
| Abdominal complaints | | – | 12% | 12% |
| Rehospitalization, preoperative attacks of acute pancreatitis (100%; 2.7 hospitalizations/patient) | | 14% (8/57) | 11% (11/109) | |

[a] No or rare pain.
OGGT, oral glucose tolerance test; IDDM, insulin-dependent diabetes mellitus.

**Table 58.5** DPPHR versus pancreatoduodenectomy for chronic pancreatitis—results of a meta-analysis 2008 [44].

| | DPPHR (93 patients) | PD (91 patients) |
|---|---|---|
| Complete pain relief | | Equal |
| Blood transfusion | $P < 0.01$ | |
| Pancreatic fistula | | Equal |
| Delayed gastric emptying | $P < 0.01$ | |
| Overall postoperative morbidity | | Equal |
| Hospital stay | $P < 0.01$ | |
| Exocrine insufficiency | $P < 0.01$ | |
| Endocrine insufficiency | $P < 0.08$ | |
| Postoperative weight gain | $P < 0.01$ | |
| Occupational rehabilitation | $P < 0.01$ | |
| Quality of life | $P < 0.01$ | |

## The Frey Procedure—an Alternative Surgical Approach for all Patients with Chronic Pancreatitis?

In 1987, Frey et al. published a technique for chronic pancreatitis in six patients; the authors recommended a coring-out technique of ventral pancreatic head tissue combined with longitudinal pancreaticojejunostomy [45]. In 1994, Frey propagated a variation of the local resection–lateral pancreaticojejunostomy (LR–LPJ) procedure, extending the coring-out to the dorsal part of the pancreatic head, which results in a partial head resection, but leaves the intrapancreatic segment of the CBD predominantly embedded in pancreatic tissue. The Frey procedure, taking out some tissue ventrally from the pancreatic head, is a modification of the Partington–Rochelle duct drainage procedure.

When the Frey procedure is performed as a subtotal pancreatic head resection in chronic pancreatitis, the long-term outcome is similar to that for DPPHR [44]. However, in many institutions that perform a tissue-sparing resection in chronic pancreatitis, coring out the pancreatic head is performed as a partial ventral pancreatic head resection. With regard to the long-term outcome in pain control, ventral coring-out of pancreatic head tissue is found to result in the re-establishment of upper abdominal pain in approximately one-third of patients (HG Beger, unpublished data). An additional

risk of the Frey procedure is incomplete decompression of the CBD due to partial ventral coring-out of the pancreatic head tissue, leading to postoperative cholestasis, with attacks of cholangitis due to persistence or reappearance of duct compression by pancreatic tissue mass. Re-surgery after the Frey procedure is a well-documented indication for redo-surgery because of the persistence of biliary stenosis [46,47].

## Summary

Duodenum-preserving resection of the head of the pancreas is a low-risk procedure for patients with chronic pancreatitis, particularly for those who have developed an inflammatory mass in the pancreatic head. Subtotal resection of the pancreatic head does not result in a significant reduction of the exocrine and endocrine functions of the pancreas. Because of the limited nature of the intervention, hospital and late mortality rates are low. More than 80% of patients with chronic pancreatitis experience long-lasting relief of pain after duodenum-preserving head resection. For patients with stenosis of the intrapancreatic CBD, an internal biliary anastomosis establishes long-lasting normal bile flow. For patients with multiple duct stenosis in the left pancreas, duct stones, calcifications, and duct dilations, pancreaticojejunostomy, in addition to subtotal pancreatic head resection, relieves recurrent attacks of pancreatitis and restores pain-free survival and quality of life.

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# 59

# Major Pancreatic Resection

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## Overview

Chronic pancreatitis is a debilitating disease characterized by pain, local mechanical complications such as biliary or duodenal obstruction, and pancreatic endocrine/exocrine insufficiency that may lead to a poor quality of life in many patients [1]. Significant developments in the management of chronic pancreatitis have occurred over the past few decades, driven by advances in cross-sectional imaging, endoscopy, and innovative surgical approaches to this complex problem [2]. Surgical approaches may be broadly categorized into drainage, resective, and hybrid procedures, with the latter preserving the duodenum and biliary tree [3]. The focus of this chapter will be major resective procedures that include pancreatoduodenectomy, distal pancreatectomy, and total pancreatectomy with or without islet cell autotransplantation. In this chapter, we aim to: (i) define indications for major pancreatic resection for chronic pancreatitis, (ii) describe major resective procedures, and (iii) summarize short- and long-term expected outcomes from these procedures.

## Major Pancreatic Resection

### Indications and Contraindications

While surgical options to manage chronic pancreatitis have expanded, the indications for major pancreatic resection remain relatively constant, except for hemosuccus pancreaticus and pancreatic ascites, which may now be managed by interventional radiologic and endoscopic techniques, respectively (Table 59.1). Chronic, intractable pain, either intermittent or constant, is the most common indication for surgical intervention. Mechanical complications such as pseudocysts, pancreatic duct disruption (chronic fistula/leak, disconnection, stricture/obstruction), obstructive jaundice, intestinal obstruction (duodenal or colonic), hemorrhage, and portal venous obstruction are well-recognized sequelae of chronic pancreatitis that may be amenable to surgical, endoscopic, and/or radiologic intervention. Inability to distinguish an inflammatory mass from a neoplasm on cross-sectional imaging, especially in a patient population at greater risk than the average population for developing pancreatic malignancy, calls for a resective approach to surgical management in order to exclude and treat possible malignancy [4].

Contraindications to resective procedures include the inability for the patient to tolerate major pancreatic surgery, anatomic restraints, and degree of peripancreatic inflammation that would preclude safe resection (Table 59.1). Anatomic issues related to congenital or acquired vascular anomalies such as mesenteric arterial vascular disease or portal venous hypertension with extensive collateralization would be important to address preoperatively. The degree of peripancreatic inflammation should also be assessed, as chronic pancreatitis patients may present with cases of acute-on-chronic pancreatitis. Although narcotic dependence is not a contraindication to pancreatic resection at our institution, we insist patients be abstinent from toxic exposures known to contribute to the pathophysiology of chronic pancreatitis such as ongoing nicotine use or alcohol abuse [2,4].

In the case of any proximal pancreatectomy, celiac artery stenosis secondary to either atherosclerosis or median arcuate ligament syndrome may result in hepatic ischemia and resultant necrosis following division of the gastroduodenal artery, which interrupts retrograde arterial flow from the superior mesenteric artery (SMA) to the liver [5,6]. Although celiac axis stenosis may be

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 59.1** Indications and contraindications for surgical resection in chronic pancreatitis.

| | Indications | Relative contraindications |
|---|---|---|
| Any resection | Intractable pain | Patient fitness |
| | Inability to exclude malignancy/pancreatic mass | Comorbidities for which perioperative risk of pancreatic resection are high |
| | Hemorrhage (intracystic/ hemosuccus pancreaticus)[a] | |
| | Pancreatic ascites[b] | |
| Proximal pancreatectomy | Small-duct disease | Anatomic concerns |
| | Biliary obstruction | Celiac axis stenosis requiring revascularization (preoperatively or intraoperatively) |
| | Gastrointestinal obstruction | |
| | Pancreatic obstruction | Portal vein thrombosis/stenosis with venous collateralization |
| | Symptomatic pseudocyst | |
| Distal pancreatectomy | Disconnected duct | Degree of peripancreatic inflammation |
| | Symptomatic pseudocyst | Encasement/abutment of major vascular structures |
| Total pancreatectomy | Diffuse "small-duct" disease | Ongoing toxic exposures |
| | Symptomatic hereditary pancreatitis | Smoking/nicotine dependence |
| | | Alcohol abuse |

[a] Managed with interventional radiology procedures.
[b] If failed endoscopic management.

diagnosed from its typical triad of postprandial abdominal pain, weight loss, and abdominal bruit on auscultation, due to collateral formation, the vast majority of patients with this condition are asymptomatic [5,7]. Cross-sectional images in the arterial phase, particularly sagittal views, reliably demonstrate celiac artery stenosis, as evidenced by focal narrowing of the proximal celiac artery with post-stenotic dilation and prominent arterial collaterals around the pancreatic head [5]. Celiac axis stenosis may be addressed preoperatively by endovascular revascularization through balloon angioplasty with or without stenting or intraoperative decompression in the form of median arcuate ligament release, aorto-celiac bypass, or patch angioplasty [5,6,8].

Extrahepatic portal venous hypertension may be associated with chronic pancreatitis when there is mechanical entrapment, obstruction, or thrombosis of the portomesenteric vein [9,10]. Patients with such complications are often compensated without evidence of liver cirrhosis and are not clinically apparent [10]. However, preoperative imaging demonstrates portal/superior mesenteric vein (SMV) stenosis (from extrinsic compression) or chronic thrombosis (from intimal changes in veins secondary to surrounding fibrosis), usually with formation of multiple venous collaterals around the pancreas and other foregut structures [9]. Pancreatic resection in this setting may be complicated with massive intraoperative hemorrhage (due to inadvertent injury to parasitizing venous collaterals under relatively high pressure), postoperative hepatic portal venous ischemia (due to loss of mesenteric venous inflow to the liver), or mesenteric venous congestion (due to loss of venous outflow from collateral vessels) [9–11]. Operating time, intraoperative blood loss, blood transfusions, and overall complications are increased in patients with extrahepatic portal venous hypertension undergoing surgery for chronic pancreatitis compared to patients without portal venous hypertension [9,10].

Anatomic planes may be distorted or obliterated as a result of peripancreatic chronic inflammation with resultant fibrosis. Development of safe dissection planes between the pancreas and surrounding vascular structures may result in significant intraoperative hemorrhage. As with the evaluation of pancreatic neoplasms, planes between the pancreatic head and the SMV/SMA should be carefully evaluated with inflammatory encasement of surrounding visceral arteries precluding safe resection. Such situations may be better approached with hybrid procedures such as the Frey procedure or Beger procedure, which would involve resecting pancreatic parenchyma without extensive peripancreatic dissection of surrounding vasculature (see Chapter 58) [4]. Although such procedures may be performed with acceptable perioperative morbidity and mortality without significant derangements in pancreatic function, our institutional preference is for pancreatoduodenectomy when possible over duodenal-preserving pancreatic head resections, as this has been shown to provide durable pain relief in our experience [1,12–14].

We do not believe narcotic dependence to be a contraindication to major pancreatic resection, as neuropathic pain is often severe and progressive in patients

with chronic pancreatitis [15]. However, we insist chronic pancreatitis patients abstain from alcohol and smoking, known contributing factors to the pathogenesis of chronic pancreatitis [2]. Chronic pancreatitis patients referred for surgical management have generally exhausted all nonoperative management strategies for their pain management, including multimodal analgesia, pancreatic enzyme supplementation with nutritional support, or celiac plexus neurolysis. Pain management in the postoperative period should therefore include a dedicated pain consult service to assist with management of acute-on-chronic postoperative pain as well as a long-term strategy to wean patients off narcotics.

### Preoperative Investigations

High-quality cross-sectional imaging is critical in the surgical planning of pancreatic resection for chronic pancreatitis. Our preference is a pancreas protocol triple-phase (noncontrast, arterial, and venous phases), thin-slice (2 mm cuts) helical abdominal computed tomography (CT). This is used to evaluate the arterial and venous anatomy, the presence of vascular collaterals, and their relationship to any inflammatory process extending beyond the pancreas. As with pancreatic head resections for other indications, vascular anomalies such as a replaced or accessory right hepatic artery would be important to note to avoid inadvertent injury during hilar and uncinate process dissections. Additionally, abdominal CT allows for evaluation of the morphology of the pancreas with respect to irregularity of pancreatic contour, ductal dilation with or without pancreatolithiasis, gland atrophy or enlargement, parenchymal calcification, and the presence of any cystic or solid lesions. Mechanical complications such as biliary or gastrointestinal obstruction may be determined as well, which could prompt preoperative optimization with biliary drainage (endoscopic or percutaneous) and/or provisions for nutritional supplementation (such as a nasojejunal feeding tube preoperatively) [4].

Important adjuncts to CT include endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasound (EUS). ERCP is considered the gold standard in diagnosing and staging chronic pancreatitis with a reported sensitivity of 90% and specificity of 100%. Disadvantages of ERCP include cost and invasiveness with a 3–7% risk of post ERCP pancreatitis. MRCP has emerged as a noninvasive alternative to ERCP for mapping ductal anatomy as well as visualizing pancreatic parenchymal changes associated with chronic pancreatitis. Disadvantages of MRCP include inability to perform therapeutic maneuvers that could be done with ERCP, decreased accuracy in visualizing side-branches of the pancreatic duct compared to ERCP, and decreased sensitivity in detecting early stages of chronic pancreatitis compared to ERCP. EUS may be particularly useful in cases of chronic pancreatitis with suspected malignancy where fine-needle aspiration or core-needle biopsy may be performed. Autoimmune pancreatitis may be detected in rare circumstances, which is treated medically. With this said, a negative biopsy in the context of a pancreatic mass with underlying chronic pancreatitis does not exclude malignancy and pancreatic resection should still be pursued [2,16].

### Types of Pancreatic Resections

Pancreatic resections may be proximal, distal, or total and the choice of operation for patients with chronic pancreatitis should be tailored to location and extent of disease as well as morphologic characteristics of the pancreatic parenchyma (e.g., calcifications) and duct (e.g., dilation, stones, stricture/disconnection). Proximal resections include pancreatoduodenectomy with or without pylorus preservation. Concomitant splenectomy is typically performed for distal resections (distal and subtotal pancreatectomy) as splenic preservation in the setting of chronic pancreatitis is often difficult due to chronic inflammation around the tail of the pancreas. Moreover, sinistral hypertension secondary to splenic vein thrombosis from pancreatitis may be associated with upper gastrointestinal bleeding from gastric varices, the definitive treatment of which is splenectomy. Total pancreatectomy combines technical aspects of both proximal and distal resections and may be performed in conjunction with islet cell autotransplantation to avoid implications of managing brittle diabetes. The perioperative outcomes following such procedures for all indications are summarized in Table 59.2 [3,4].

## Pancreatoduodenectomy

### Patient Selection

Candidates for pancreatoduodenectomy include chronic pancreatitis patients with intractable pain, small-duct (<7 mm), head-dominant disease where perivascular tissue planes are relatively preserved and portal hypertension is absent. Pancreatoduodenectomy will address intractable pain with resection of the pancreatic head, mechanical complications such as biliary or intestinal obstruction, and suspicion of malignancy. Although improvements in cross-sectional imaging have enhanced diagnostic discrimination, the distinction between benign and malignant disease remains a dilemma in 6–8% of patients [24]. Modifications of pancreatoduodenectomy include reconstruction with a lateral side-to-side pancreaticojejunostomy rather than the standard

**Table 59.2** Results of pancreatoduodenectomy for chronic pancreatitis.

| Source | Patients (*N*) | Operative mortality (%) | Operative morbidity (%) | Pain relief (%) | Follow-up (years) |
|---|---|---|---|---|---|
| Stapleton and Williamson, 1996 [17] | 52 | 0 | 46 | 80 | 4.5 |
| Martin et al., 1996 [18] | 54 | 1.8 | 30 | 92 | 5.2 |
| Rumstadt et al., 1997 [19] | 134 | 0.7 | 18 | 88 | 8.3 |
| Traverso and Kozarek, 1997 [20] | 47 | 0 | NA | 100 | 3.5 |
| Sakorafas et al., 2000 [21] | 105 | 3.0 | 32 | 89 | 6.6 |
| Jimenez et al., 2000 [22] | 72 | 1.4 | 45 | 70 | 3.6 |
| Schnelldorfer et al., 2007 [23] | 97 | 1.0 | 51 | 34 | 4.9 |
| Croome et al., 2016 [1] | 166 | 1.8 | 30 | [a]7.9 ± 3.5 preop<br>1.6 ± 2.6 postop | 15 |

[a] Mean preoperative and postoperative (± SD) pain scores (on scale 1–10) in 54 of 81 surviving patients responding to survey median of 15 years following pancreatoduodenectomy for chronic pancreatitis ($P < 0.001$).
NA, not available.

end-to-side pancreaticojejunostomy. A circumstance for which a lateral side-to-side pancreaticojejunostomy may be considered is in the patient with large-duct, head-dominant disease with a pancreatic stone burden in the head that exceeds the ability to "core out" such parenchyma effectively in duodenal sparing pancreatic head resections [4].

## Technique

A midline incision is used unless patients are of obese body habitus or with a broad costal arch. In the latter, a bilateral subcostal is our preference. A fixed, upper abdominal retractor is placed to allow secure retraction of both costal margins in the cephalad direction for optimal exposure. The operation begins with abdominal exploration, freeing the omentum from the transverse colon in its avascular plane, take down of the hepatic flexure, and Kocher maneuver for pancreatic exposure and mobilization. Adhesions to the posterior stomach are taken down to completely open the lesser sac. The SMV is identified between the uncinate process and mesocolon at the level of the transverse duodenum and inferior border of the pancreas. The gastrocolic venous trunk is identified and divided. Blunt dissection is performed to develop a retropancreatic tunnel under the neck of the pancreas to the level of the SMV–portal vein confluence. This plane may be difficult to develop and attempts at creating a retropancreatic tunnel should be abandoned if persisting will lead to tearing or delamination of vein walls (Fig. 59.1).

The gastrohepatic ligament beneath the left lobe of the liver is incised avascularly, taking care to preserve the nerves that supply the pylorus. The common hepatic artery is traced distally. The gastroduodenal artery is divided as well as the right gastric artery. Prior to division of the gastroduodenal artery, a noncrushing clamp is placed temporarily to ensure adequate arterial flow to the liver, the absence of which would indicate celiac axis stenosis for which celiac revascularization would be necessary. After ligation and division of the gastroduodenal artery, a plane is developed between the superior border of the pancreas and the common hepatic artery to identify the portal vein. Blunt dissection is carried out underneath the neck of the pancreas to complete mobilization of the pancreatic neck from the portomesenteric vein, which is encircled with umbilical tape (Fig. 59.2).

Cholecystectomy is performed and the cystic duct is kept in continuity with its junction to the bile duct. The common bile duct is palpated posterior laterally to identify the presence of a replaced or accessory right hepatic artery. The bile duct is mobilized from surrounding hepatoduodenal ligament structures and isolated with umbilical tape. The right gastroepiploic and retroduodenal vessels are divided off the duodenum distal to the pylorus for approximately 3–4 cm (Fig. 59.3). Attention is then directed to the inframesocolic compartment. The ligament of Treitz is mobilized and the tissues to the right of the inferior mesenteric vein are incised, thereby communicating the inframesocolic dissection with the previously performed Kocher maneuver. The bowel is transilluminated approximately 20 cm beyond the ligament of Treitz and a mesenteric window is created. The proximal jejunum is stapled and transected. Mesenteric branches to the proximal jejunum are divided up to the fourth portion of the duodenum and uncinate process. The mobilized proximal jejunum is then passed beneath the SMA back into the supramesocolic compartment (Fig. 59.4).

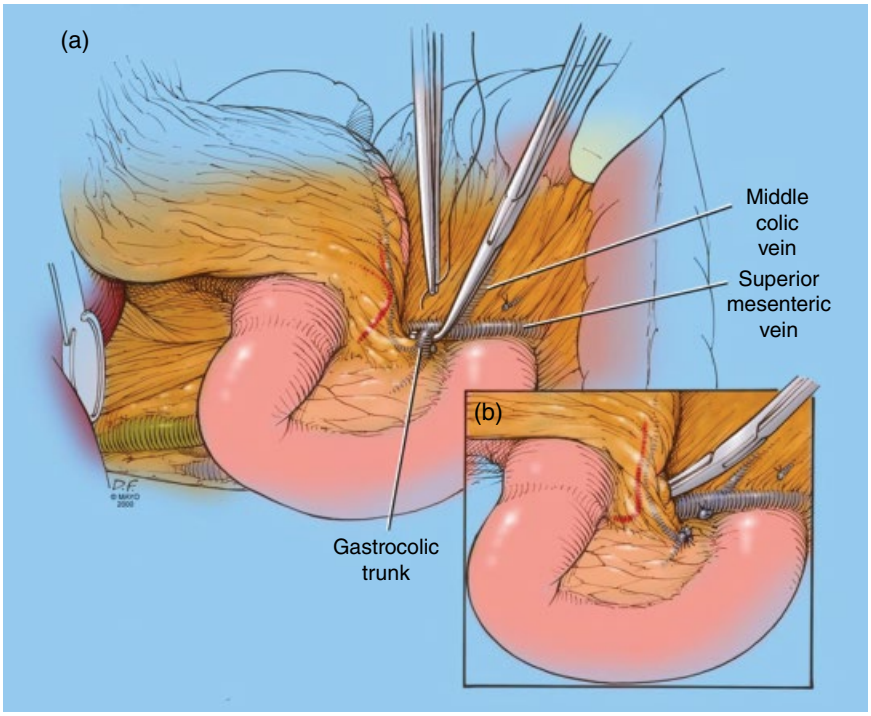


**Figure 59.1** (a) The superior mesenteric vein is identified beneath the neck of the pancreas and the gastrocolic venous trunk is divided. (b) A plane is gently developed between the neck of the pancreas anteriorly and the superior mesenteric vein/portal vein posteriorly using a blunt dissector. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

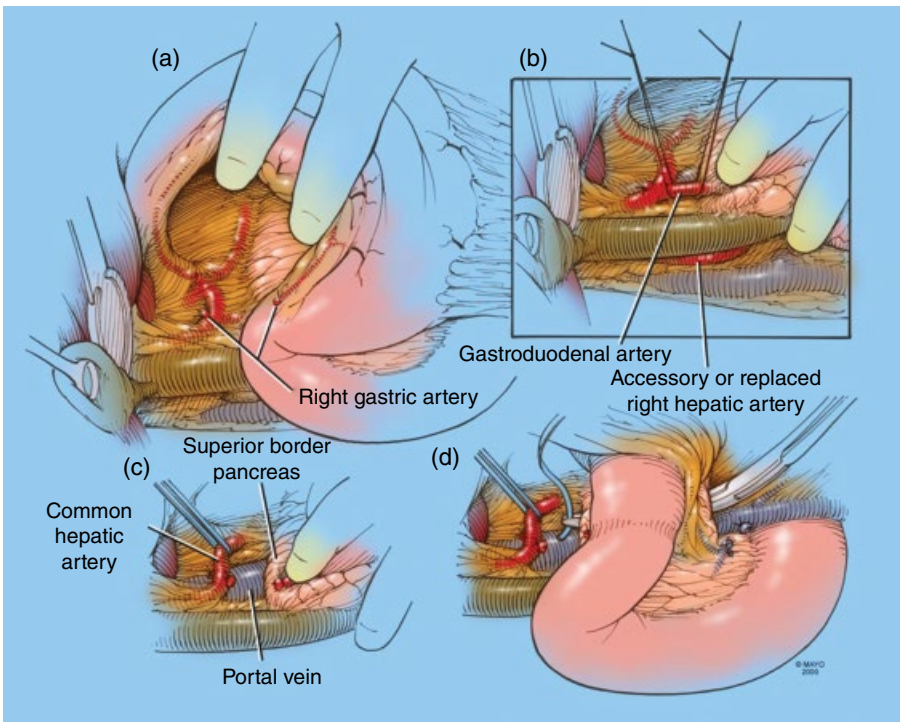


**Figure 59.2** (a) The right gastric artery is divided. (b) The common hepatic artery is identified and the gastroduodenal artery is divided; arterial pulsation posterior to the bile duct may represent a replaced or accessory right hepatic artery. (c) The portal vein is identified underneath the common hepatic artery at the superior border of the pancreas. (d) A retropancreatic tunnel is created at the neck of the pancreas from the superior mesenteric vein to portal vein and isolated with umbilical tape. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

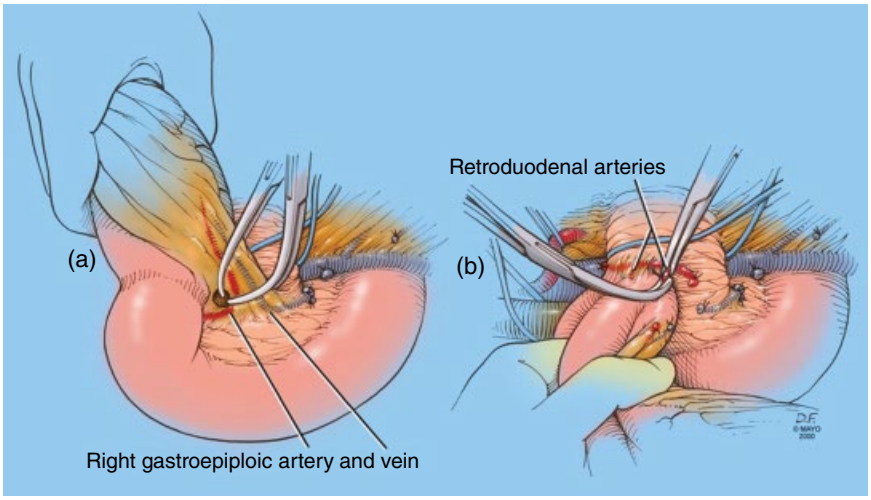


**Figure 59.3** (a) The right gastroepiploic artery and vein are divided. (b) Retroduodenal arteries are divided to mobilize the duodenum approximately 3 cm from the pylorus. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

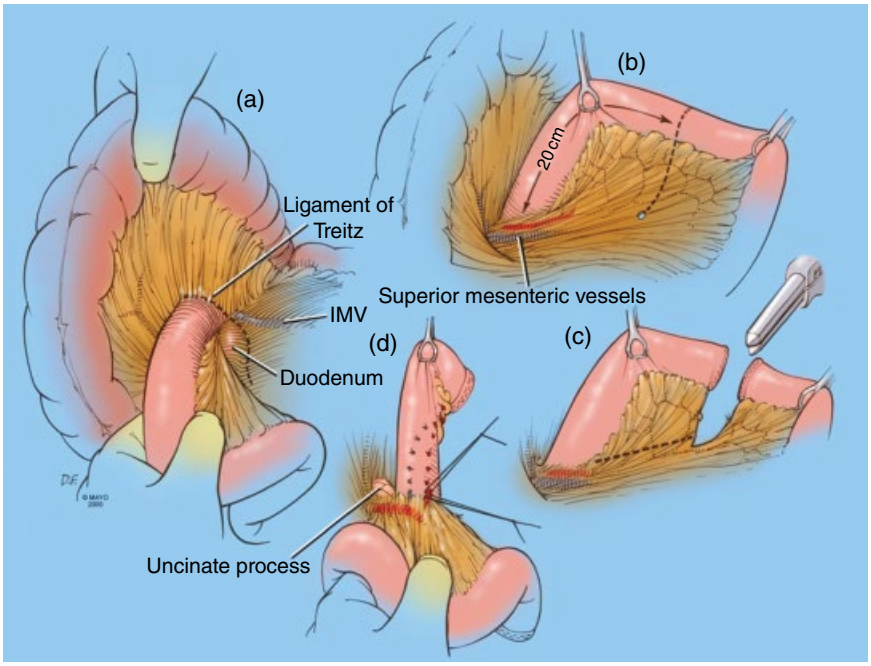


**Figure 59.4** (a) The ligament of Treitz is mobilized in the infracolic compartment with care taken to avoid injury to the inferior mesenteric vein (IMV). (b) The jejunum is divided approximately 20 cm from the ligament of Treitz. (c) The bowel is transected with a GIA stapler. (d) Mesenteric vessels are divided with either silk ties or an energy device until the uncinate process is visible. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

The duodenum is then transected approximately 3 cm beyond the pylorus. In preparation for division of the pancreas, hemostatic sutures are placed at the inferior and superior borders of the pancreas. The pancreas is divided with a scalpel to the left of the portomesenteric vein; this allows for centering of the pancreatic duct as it courses quite posteriorly more proximally. A bulldog clamp is placed on the common hepatic duct to minimize bile spillage and the bile duct is transected sharply. The uncinate process is then dissected off the surrounding mesenteric vessels. Vein retractors are placed and the portomesenteric confluence retracted to the patient's left. Venous tributaries are divided, which allows access to the anterior aspect of the SMA. Occasionally, the first jejunal vein will need to be ligated and divided if it courses to the right of the SMA to facilitate peri-adventitial dissection. Dissection is carried posteriorly on the right side of the SMA and pancreatoduodenal tributaries are controlled and divided. Posterolaterally, the inferior pancreatoduodenal artery will arise from the SMA and should be ligated and divided. The specimen is now removed from the operative field (Fig. 59.5).

Reconstruction is undertaken (Fig. 59.6). An opening is made in the mesocolon to the right of the middle colic vessels. The jejunum is passed through this opening. A two-layered, interrupted, duct-to-mucosa end-to-side pancreaticojejunostomy is fashioned over a temporarily placed silastic stent. We prefer using 4-0 silk for our

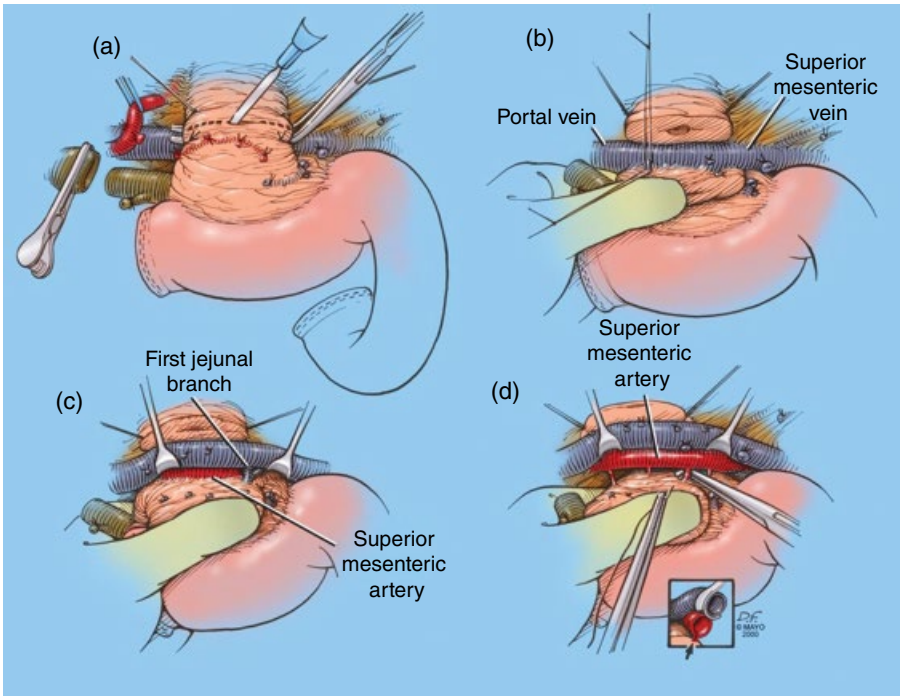


**Figure 59.5** (a) The common hepatic duct is divided sharply and a bulldog clamp placed to minimize bile spillage. The neck of the pancreas is divided sharply with electrocautery. (b) Venous tributaries from the portal vein are divided to free the portal vein. (c) The first jejunal branch is divided. (d) Periadventitial dissection of the superior mesenteric artery is performed. An energy device may be utilized; however, the inferior pancreaticoduodenal artery should be ligated and divided with silk ties. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

outer layer and 6-0 Vicryl suture for the inner layer. Approximately 8–10 cm distal to the pancreaticojejunostomy, an end-to-side hepaticojejunostomy is fashioned with technique dependent upon bile duct size. We prefer a running biliary enteric anastomosis in a single layer with two 5-0 polydiaxone sutures (PDS), one placed anteriorly and the other posteriorly to prevent purse-stringing of the anastomosis. Patients with small, thin-walled bile ducts are reconstructed with interrupted 6-0 PDS. The traversing jejunal limb is secured to the mesocolon with interrupted 3-0 silk. Distal to this biliary enteric anastomosis (by approximately 20–30 cm), an antecolic, end-to-side, two-layer duodenojejunostomy is constructed. The outer layer is formed with interrupted 3-0 silk sutures and the inner layer is formed with a running 3-0 Vicryl suture. Mesenteric defects are closed and hemostasis is attained. A closed suction drain is placed in the peritoneal cavity in Morison's pouch and the tip just beyond the underlying pancreaticojejunostomy. Closure is performed in layers in the usual fashion.

## Perioperative Outcomes

Our institutional experience at Mayo Clinic was recently reviewed to include 166 patients undergoing pancreatoduodenectomy for treatment of chronic pancreatitis from 1976 to 2013 (Tables 59.3 and 59.4). This was a longitudinal follow-up study to determine long-term outcomes following pancreatoduodenectomy and differences in practice with respect to chronic pancreatitis management [1]. This study suggested that alcohol was the most common underlying etiology (51%), while the most common clinical manifestation was abdominal pain (88%). Uncertainty or suspicion of malignancy prior to surgery was identified in 48% of patients. A low operative mortality (1.8%) was observed with no operative mortality reported since 1997. Rates of delayed gastric emptying (11%), postoperative pancreatic fistula (8%), and postpancreatectomy hemorrhage (5%) were low. Median length of hospital stay was 12 days. Trends in management of chronic pancreatitis were also evaluated and increasing nonsurgical management options such as endoscopic stenting as well as celiac plexus neurolysis increased over time ($P < 0.001$). This resulted in a doubling of time from presentation of chronic pancreatitis to surgery from 1 year to 2 years ($P = 0.017$).

## Long-Term Results

Long-term results following pancreatoduodenectomy for chronic pancreatitis were assessed with a short form (SF-12) questionnaire administered to all patients still

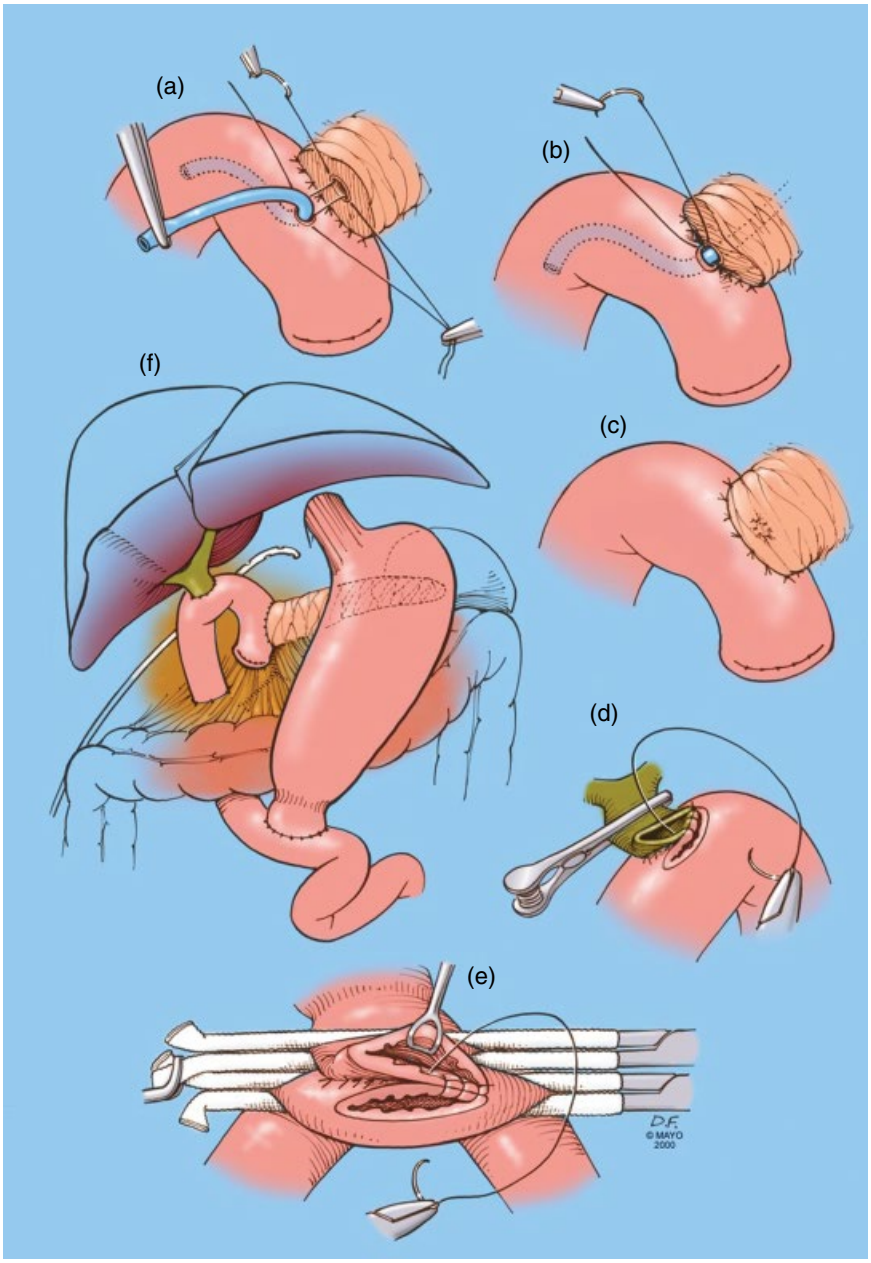


**Figure 59.6** (a) Duct-to-mucosa pancreaticojejunostomy is fashioned. (b) Silastic catheter is used as a temporary stent while completing the inner layer. (c) Completed two-layer pancreaticojejunostomy. (d) End-to-side hepaticojejunostomy with anterior and posterior suture layers. (e) End-to-side duodenojejunostomy is fashioned in two layers. (f ) Drain placement by anastomoses with tip beyond the pancreaticojejunostomy posteriorly. *Source:* By permission of Mayo Foundation for Medical Education and Research. All rights reserved.

alive and eligible for study. Results from the SF-12 survey demonstrated that the mean physical component score (PCS) was 43.8 ± 11.8 and mental component score (MCS) was 54.4 ± 7.9. Patients were significantly lower on the PCS ($P < 0.001$) and significantly better on the MCS ($P = 0.001$) than the general US population. Mean pain score out of 10 was significantly lower after surgery at 1.6 ± 2.6 than before surgery at 7.9 ± 3.5 ($P < 0.001$). In long-term follow-up, no pain medication was required in 66% of the cohort. With respect to long-term pancreatic function, new onset of diabetes since the time of surgery was present in 28% of patients and pancreatic enzyme supplementation was utilized by 43% of patients, with 15% of patients reporting frequent diarrhea (Table 59.5).

Long-term survival was also examined (Fig. 59.7). Compared to an age-matched US population, inferior

**Table 59.3** Trends in treatments prior to pancreatoduodenectomy from 1976 to 1997 versus 1998–2013.

| Intervention | All patients *N* = 166 | 1976–1997 *N* = 105 | 1998–2013 *N* = 61 | *P*-value |
|---|---|---|---|---|
| Previous pancreatic surgery | 4 (2%) | 2 (2%) | 2 (3%) | 0.58 |
| Previous stenting | 51 (31%) | 10 (10%) | 41 (67%) | <0.001 |
| Previous biliary surgery | 43 (26%) | 37 (35%) | 6 (10%) | <0.001 |
| Previous gastric surgery | 21 (13%) | 9 (9%) | 12 (20%) | 0.038 |
| Previous celiac plexus block | 14 (8%) | 5 (5%) | 9 (15%) | 0.026 |
| Time from presentation to surgery (years) | 1.56 | 1.13 | 2.09 | 0.017 |

**Table 59.4** Trends in postoperative complications from 1976 to 1997 and 1998–2013.

| Morbidity | All *N* = 166 | 1976–1997 *N* = 105 | 1998–2013 *N* = 61 | *P*-value |
|---|---|---|---|---|
| Mortality (30-day) | 3 (2%) | 3 (3%) | 0 (0%) | 0.18 |
| Delayed gastric emptying | 19 (11%) | 11 (10%) | 8 (13%) | 0.61 |
| Postoperative pancreatic fistula | 13 (8%) | 5 (5%) | 8 (13%) | 0.051 |
| Postpancreatectomy hemorrhage | 8 (5%) | 1 (1%) | 7 (11%) | 0.002 |
| Reoperation (30-day) | 10 (6%) | 6 (6%) | 4 (7%) | 0.83 |
| Length of stay (median, range) | 12 (4–82) | 14 (6–82) | 11 (4–70) | <0.001 |
| Intensive care unit days (median, range) | 0 (0–15) | 1 (0–15) | 0 (0–11) | <0.001 |

survival was noted in patients undergoing pancreatoduodenectomy for chronic pancreatitis. This observation is consistent with other studies and we speculate this phenomenon is due to the underlying chronic pancreatitis as well as comorbidities inherent in this population [21,25]. This is underscored by the large proportion of alcoholic pancreatitis observed and the deaths secondary to causes such as alcoholic cirrhosis seen in the follow-up period. Previous epidemiologic studies in patients with chronic pancreatitis have demonstrated frequent alcohol abuse and cigarette smoking with related deaths due to liver cirrhosis, cardiovascular disease, and malignancies of the mouth, esophagus, and lungs [25]. It should be noted, however, that survival curves become parallel between chronic pancreatitis patients and matched general population subjects beyond 10 years of follow-up. Thus, survival beyond 10 years in patients with chronic pancreatitis who undergo pancreatoduodenectomy approaches that of age-matched general population controls.

## Distal Pancreatectomy

Distal pancreatectomy is rarely indicated in patients with chronic pancreatitis. That said, patients experiencing intractable pain following acute necrotizing pancreatitis with associated "disconnected duct syndrome" secondary to critical stenoses or complete obliteration of the pancreatic duct may be candidates for distal pancreatectomy. In such patients, the pancreas to the right of the ductal stenosis may be uninvolved and distal resection may afford complete relief of symptoms. As with proximal pancreatectomies for chronic pancreatitis, these operations may be complicated by chronic inflammation with resultant fibrosis. Collateral damage to surrounding organs, such as the posterior wall of the stomach, left transverse colon, fourth portion of duodenum, left kidney, and adrenal gland, may occur during dissection away from these structures. With a similar operative incision, set-up, and exposure to proximal pancreatectomy, we begin our operation by dissecting the omentum from the colonic splenic flexure to enter the lesser sac. The omentum is divided at the transverse colon. Short gastric vessels are then serially divided up to the level of the gastroesophageal junction in order to mobilize the stomach. The splenocolic and splenorenal ligaments are divided. A plane is developed between the spleen and tail of the pancreas anteriorly and the left kidney and adrenal gland posteriorly. Dissection is then carried out medially where the splenic artery and vein are divided. The pancreas is then transected at the level of the disconnection. The stump is oversewn if there is

**Table 59.5** Long-term results (15 years) following pancreatoduodenectomy for chronic pancreatitis.

| Outcome | Result (*N* = 54) | *P*-value |
|---|---|---|
| SF-12 score | | |
| Physical (PCS) | 43.8 ± 11.8 | <0.001* |
| Mental (MCS) | 54.3 ± 7.9 | <0.001* |
| Pain (scale 1–10)[a] | | |
| Before | 7.9 ± 3.5 | <0.001** |
| After | 1.6 ± 2.6 | |
| Pain medication | | |
| None | 35 (65%) | |
| Non-narcotic | 9 (17%) | |
| Occasional narcotic | 3 (6%) | |
| Regular narcotic | 7 (13%) | |
| Endocrine insufficiency | | |
| Insulin | 17 (31%) | |
| Oral hypoglycemics | 2 (4%) | |
| Diet controlled | 2 (4%) | |
| New-onset diabetes | 15 (28%) | |
| Exocrine insufficiency | | |
| Pancreatic enzymes | 23 (43%) | |
| Frequent diarrhea | 8 (15%) | |
| Weight | | |
| Increased | 21 (39%) | |
| Decreased | 13 (24%) | |
| Same | 20 (37%) | |
| Alcohol consumption | | |
| Never | 34 (63%) | |
| Occasional | 16 (30%) | |
| Frequent | 4 (7%) | |
| Return to work | | |
| No | 10 (19%) | |
| Yes | 31 (57%) | |
| Not applicable | 13 (24%) | |
| Type of resection | | |
| Laparoscopic | 5 (9%) | |
| Open standard | 17 (31%) | |
| Open pylorus-preserving | 32 (60%) | |
| Reoperation related to pancreatoduodenectomy | 3 (6%) | |
| Readmission | 16 (24%) | |

[a] Mean pain score ± standard deviation on scale 1–10.
SF-12, 12-item short form health survey; PCS, mean physical component score on SF-12; MCS, mean mental component score on SF-12
* Significantly different compared to general population.
** Significantly different preoperatively compared to postoperatively.

incomplete disconnection, as shown by preoperative ERCP; if complete, the stump is not disturbed.

## Total Pancreatectomy

Total pancreatectomy with islet cell autotransplantation may be indicated in patients with intractable pain due to hereditary or idiopathic pancreatitis [26–28]. However, we would not recommend prophylactic total pancreatectomy in patients with hereditary pancreatitis in the absence of intractable pain. The operative exposure for total pancreatectomy is also similar to that of pancreatoduodenectomy. Spleen preservation may be attempted, but like distal pancreatectomy, may be difficult due to the degree of peripancreatic inflammation and fibrosis. Some technical points will be highlighted in this procedure that combines key steps of proximal and distal pancreatectomy. For total pancreatectomy with islet cell autotransplantation, preserving blood supply to the pancreas until

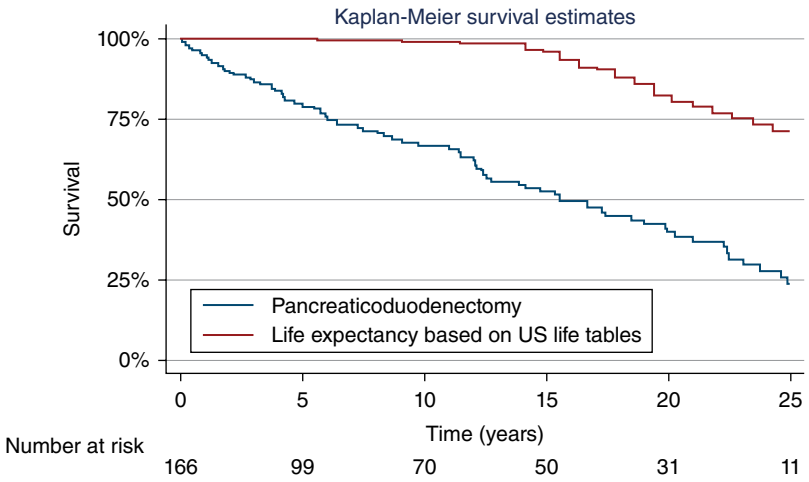


**Figure 59.7** Survival of patients with chronic pancreatitis treated by pancreatoduodenectomy compared to expected survival based on life tables.

terminal stages is advised by mobilizing the entire pancreas before taking its vascular supply. Venous drainage of the stomach deserves special mention, particularly in cases of total pancreatectomy with splenectomy. With the splenic vein, short gastric veins, right gastric and gastroepiploic veins taken during a total pancreatectomy with splenectomy, venous drainage of the stomach is dependent upon the left gastric (coronary) vein. To prevent venous congestion of the stomach, preservation of the left gastric vein is important. Should venous congestion of the stomach occur despite these preventative efforts, distal gastrectomy may be considered.

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# 60

# Laparoscopic Surgery

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## Introduction

The introduction of laparoscopy into abdominal surgical practice has revolutionized the approach to complex surgical conditions. The first laparoscopic procedure for chronic pancreatitis was reported in 1994 by Gagner and Pomp who successfully performed a pylorus-preserving pancreaticoduodenectomy on a 30-year-old woman [1]. In 1996, Cuschieri et al. described a series of five laparoscopic distal pancreatectomies (LDP) with splenectomy in patients with chronic pancreatitis, with good perioperative outcomes [2]. Due to concerns of excessive morbidity, the expansion of laparoscopic pancreatic surgery was initially met with resistance. However, over the past 10 years this approach has slowly been integrated into the repertoire of high-volume centers, with rates of mortality and morbidity equivalent to those of open procedures [3]. In addition, with the advent of robotic assistance, surgeons can now benefit from binocular three-dimensional vision, scaling, stabilization of tremor, reduced operator fatigue and improved ergonomics from the console–surgeon interface.

As the majority of surgical interventions for chronic pancreatitis are typically performed through an open approach, data on outcomes following minimally invasive procedures are scarce. Although there are many reports on laparoscopic versus open pancreas surgery in general, these data tend to combine both benign and malignant indications. Since only a few studies have focused solely on benign indications, it may be reasonable to infer that outcomes of larger laparoscopic and/or robotic series can be used to provide insight into the applicability of minimally invasive approaches to chronic pancreatitis. This chapter, therefore, will summarize the limited available data on the safety, feasibility, and efficacy of laparoscopic procedures for chronic pancreatitis, but also draw on the larger available existing reports of minimally invasive pancreatic surgery performed for other indications.

Broadly, surgical strategies for chronic pancreatitis can be categorized into resection type procedures, drainage type procedures, and combination type procedures involving resection and drainage (Table 60.1). In addition, laparoscopic surgery can be broadly defined as pure or robotic assisted.

## Resection Procedures

### Total Pancreatectomy with Islet Autotransplantation

Total pancreatectomy with islet autotransplantation (TPIAT) is a rare procedure that is performed in only a few specialized centers across the United States, with mortality and morbidity up to 16% and 70%, respectively [5]. As expected, the majority of such procedures are completed through an open approach, with laparoscopic or robotic-assisted approaches infrequently reported (Fig. 60.1). A single-center retrospective review of six patients with chronic pancreatitis who underwent fully robotic-assisted TPIAT reported a mean operative time of 712 minutes and mean estimated blood loss (EBL) of 630 mL and no mortality [4]. At 1 month follow-up, all five patients who initially presented with intractable chronic pain syndrome were in the process of weaning off narcotics.

The largest reported case series of robotic-assisted laparoscopic total pancreatectomy includes 10 patients with both benign and malignant pathology [5]. One of three

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 60.1** Clinical outcomes following laparoscopic treatment for chronic pancreatitis.

| Author | Study design Indication | Pts | Approach | Operating room time (min) | Open conversion | EBL (mL) | Complications | Mortality | LOS | Follow-up | Outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Resection** | | | | | | | | | | | |
| Total pancreatectomy with islet autotransplantation (TPIAT) | | | | | | | | | | | |
| Galvani et al., 2014 [4] | Retrospective CP | 6 | Robotic (1 with AIT) | 712 | 0 | 630 | 2 (33%) | 0 | 12.6 | 1 mo | All 5 patients weaning narcotics; 2 required splenectomy |
| Zureikat et al., 2015 [5] | Retrospective 3/10 CP | 10 | Robotic | 560 | 1 (10%) | 650 | 2 (20%)[a] | 0 | 10 | NR | 1 (10%) reoperation |
| Pancreaticoduodenectomy (PD–Whipple) | | | | | | | | | | | |
| Zureikat et al. (2013) [6] | Retrospective 8% Benign | 132 | Robotic | 527 | 11 (8%) | ~250 | 28 (22%)[a] | 1.5% | 10 | NR | 3% reoperation; 28% readmission |
| Boggi et al., 2015 [7] | Systematic review 17.% Benign | 746 | 52% PL<br>16% LA<br>31% robot<br>1% hand | 464 | 64 (9.1%) | 321 | 41% | 1.9% | 13.6 | NR | NR |
| Distal pancreatectomy (DP) | | | | | | | | | | | |
| Cuschieri et al., 1996 [2] | Retrospective CP | 5 | Lap | 240–360 | 0 | 400 | 1 (20%) | 0 | 6 | 3–22 mo | Substantial pain relief in all, complete in 2 patients |
| Fernandez-Cruz et al., 2002 [8] | Retrospective CP | 5<br>41 | Lap<br>Open | 240 | NR | 450 | 1 (20%)<br>20 (48%) | 0 | 4.5<br>12 | 13 mo<br>5 years | 100% lap patients pain free<br>80% open patients pain free |
| Venkat et al., 2012 [9] | Meta-analysis Benign + malignant | 780<br>1034 | Lap<br>Open | MD 10.2 | NR | MD 355* | OR 0.73* | OR 0.63 | MD 4.1* | NR | 2.1% reoperation in lap, 12.6% readmission |
| **Drainage** | | | | | | | | | | | |
| Lateral pancreaticojejunostomy (LPJ–Puestow) | | | | | | | | | | | |
| Khaled et al., 2011 [10] | Systematic review CP | 37 | Lap | 218 | 5 (13.5%) | NR | 5 (13.5%) | 0% | 5.5 | 5–84 mo | 89% pain free; 2.7% reoperation rate |
| Meehan et al., 2011 [11] | Case report CP | 1 | Robot | 390 | 0 | NR | NR | 0 | 8 | 2 yrs | Pain free |
| Khaled et al., 2014 [12] | Retrospective CP | 5 | Lap | 278 | 0 | 150 | 1 (25%) | 0 | 5 | 14 mo | 4/5 (80%) patients pain free |
| Cyst gastrostomy (CG) | | | | | | | | | | | |
| Khaled et al., 2014 [13] | Retrospective Sterile pseudocyst | 30<br>10 | Lap<br>Open | 62<br>95 | 0<br>- | NR | 3 (10%)*<br>6 (60%) | 0<br>1 (10%) | 6.2*<br>11 | 13 mo<br>18 mo | 97% resolution in lap<br>100% resolution in open |
| Worhunsky et al., 2014 [14] | Retrospective 2/3 sterile necrosis | 21 | Lap | 170 | 0 | 50 | 12 (57%) | 1 (5%) | 5 | 11mo | 10% reintervention<br>6% long term complications |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Khreiss et al., 2015 [15] | Retrospective<br>Sterile necrosis | 20 | 14 Robot<br>6 Lap | 167 | 0 | 30 | 4 (20%) | 0 (0%) | 7 | NR | 15% reintervention<br>0.42 months to resolution |
| Video-assisted retroperitoneal debridement (VARD) | | | | | | | | | | | |
| Horvath et al., 2010 [16] | Prospective | 9<br>25<br>6 | Perc<br>VARD<br>Open | 135 | 10 (40%) | NR | 0<br>9 (36%)<br>3 (50%) | 1 (11%)<br>0<br>0 | 48<br>64<br>54 | 6 mo<br>6 mo<br>6 mo | 11% pancreatic fistula<br>20% pancreatic fistula<br>33% pancreatic fistula |
| García-Ureña et al., 2013 [17] | Retrospective<br>Necrotizing pancreatitis (1 CP) | 7 | Lap | 63 | 0 | NR | 4 (57%) | 0 (%) | 50 | NR | 2 (29%) requiring second VARD |
| **Combination** | | | | | | | | | | | |
| Frey procedure | | | | | | | | | | | |
| Cooper et al., 2014 [18] | Case report<br>CP | 1 | Lap | NR | 0 | NR | 0 | 0 | 6 | NR | No narcotics on discharge |
| Tan et al., 2015 [19] | Case series<br>CP | 9<br>37 | Lap<br>Open | 323<br>NR | 2 (22%)<br>– | 57<br>293 | 1 (14%)<br>4 (11%) | 0<br>0 | 7<br>NR | 3 mo<br>NR | 100% lap patients had decreased VAS pain score |
| Beger procedure | | | | | | | | | | | |
| Khaled et al., 2014 [12] | Case report<br>CP | 1 | Lap | 285 | 0 | NR | 0 | 0 | 5 | 16 | Mild pain; 1/3 of preop opioid dose |

CP, chronic pancreatitis; AIT, auto-islet transplantation; Lap, conventional laparoscopy; robot, robotic approach; Pts, number of patients; LOS, length of stay, median days; NR, not reported; VAS, visual analog scale; PL, pure laparoscopy; LA, laparoscopic-assist; MD, mean difference; OR, odds ratio.

[a] Clavien–Dindo grades 3 or 4.

* $P < 0.05$.

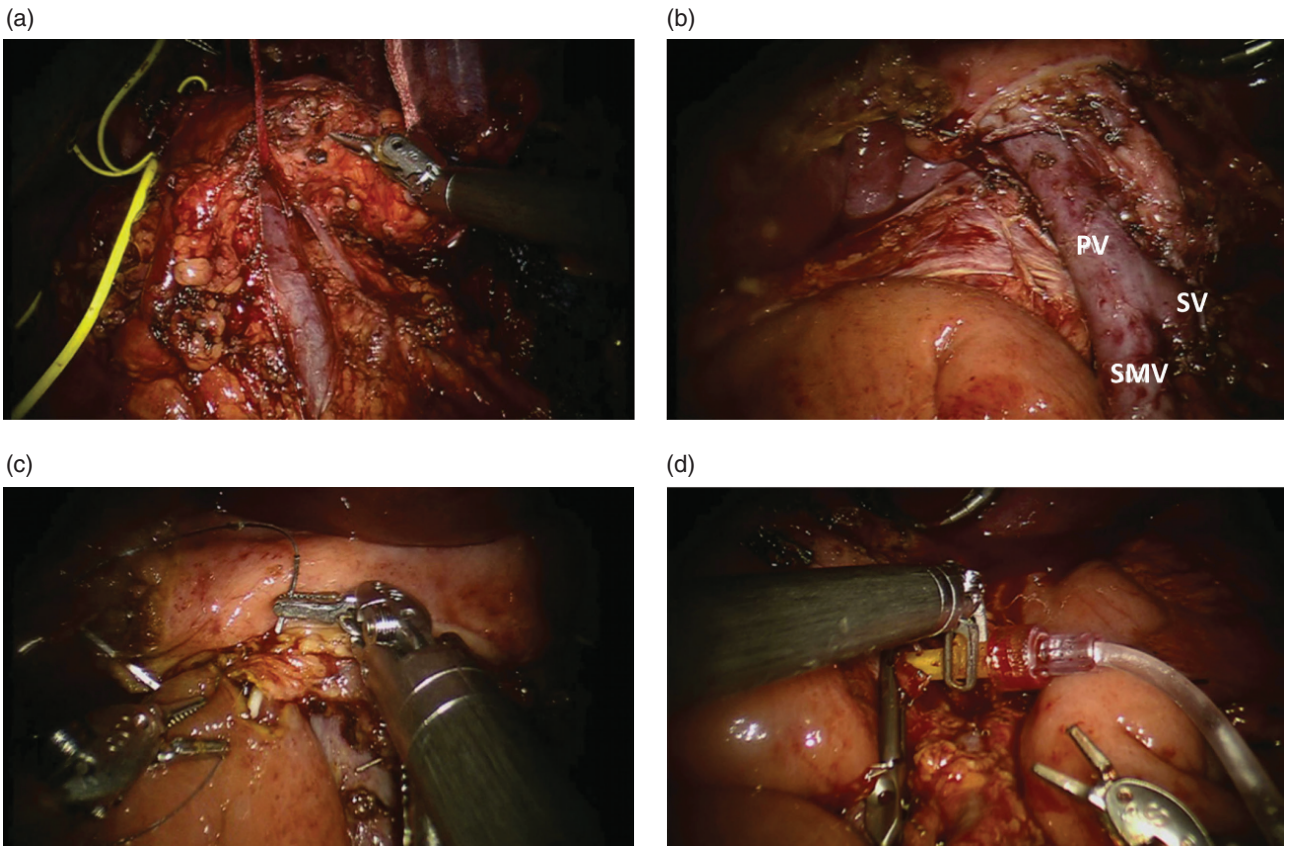


**Figure 60.1** Robotic-assisted total pancreatectomy with auto-islet transplantation. (a) Pancreatic neck is freed from the superior mesenteric vein (SMV), splenic vein (SV), and portal vein (PV). (b) Resection of entire pancreas from the retroperitoneum. (c) Creation of hepaticojejunostomy over a stent. (d) Angiocatheter introduced through the SV stump for islet cell infusion.

patients with chronic pancreatitis underwent AIT; seven patients had concomitant splenectomy while two were spleen-preserving. Median operative time was 560 minutes and median EBL was 650 mL. There was no 90-day mortality, and two Clavien–Dingo grade III complications were reported in two patients, including pleural effusion and fascial dehiscence. The median length of stay (LOS) was 10 days. These results are comparable to a recently published series of 12 TPIAT through an open approach [20].

## Pancreaticoduodenectomy (Whipple)

The last 10 years have witnessed an increasing number of single-institution reports of minimally invasive pancreaticoduodenectomy, but the efficacy of either laparoscopic or robotic pancreaticoduodenectomy for chronic pancreatitis still requires larger series and a more robust assessment of outcomes. It can be inferred from these studies that include benign and malignant indications that the minimally invasive pancreaticoduodenectomy is a safe and feasible procedure for select cases at high-volume centers. A recent systematic review, for example, comparing laparoscopic and open pancreaticoduodenectomy (17.5% for benign disease) found similar rates of postoperative morbidity [7]. The study included 25 articles encompassing 746 cases of laparoscopic pancreaticoduodenectomies: 386 (52%) were pure laparoscopy, 121 (16%) with laparoscopic assistance, 231 (31%) with robotic assistance, and 5 (1%) with hand assistance. Overall, open conversion was necessary in 9.1% of all cases. Mean operative time was 464 minutes and EBL 321 mL. The morbidity rate was 41%, including 22% patients developing pancreatic fistula, and mortality 1.9%. Mean LOS was 13.6 days. Pure laparoscopy was associated with shorter operative times, less blood loss, and lower rates of pancreatic fistula. Laparoscopic assistance had shorter operative times than robotic assistance, but higher rates of blood loss and pancreatic fistulas. The largest available single-institution review of robotic pancreaticoduodenectomy (132 cases) performed for various indications reported outcomes comparable to open historic controls [6].

## Distal Pancreatectomy

Similar to pancreatic head resections, the majority of studies comparing laparoscopic with open distal pancreatectomy do not stratify between benign and malignant indications. Specifically, data on minimally invasive

distal pancreatectomy for chronic pancreatitis are lacking and limited to a handful of small series such as that by Fernandez-Cruz et al., who reported a series of five chronic pancreatitis patients who underwent LDP with spleen preservation, compared to 41 open pancreaticoduodenectomies with or without splenectomy [8]. This early study suggested that LDP for chronic pancreatitis was feasible with acceptable outcomes.

LDP appears to be a safe and feasible approach for the treatment of left-sided pancreatic pathology. A systematic review of 18 studies by Venkat et al. (1814 patients) comparing laparoscopic (43%) and open (57%) distal pancreatectomies for all indications found that the laparoscopic technique was associated with decreased intraoperative blood loss by 355 mL, surgical site infections (3% vs. 8%), postoperative complications (34% vs. 44%), and decreased length of hospital stay by 4 days [9], with no differences in operative time, postoperative pancreatic fistula, or mortality. In addition, two single-institution retrospective series also suggest the robotic approach to distal pancreatectomy may have lower rates of open conversion, and higher rates of splenic preservation compared to conventional laparoscopy [21,22]; this latter benefit, however, may not be translatable in the setting of adhesive chronic pancreatitis.

## Drainage Procedures

### Lateral Pancreaticojejunostomy (Puestow)

The conventional open lateral pancreaticojejunostomy (LPJ) can be associated with high morbidity rates of up to 25% and a morality <5% [10]. Limited case reports of laparoscopic LPJ have shown it to be feasible, safe, and effective [10,12]. In 2014, Khaled et al. described five laparoscopic LPJ for chronic pancreatitis with a median operative time of 278 minutes and EBL of 150 mL with no mortality and 5 day LOS. At a follow-up of 14 months, four out of the five patients were pain free [12]. These results are comparable to a recent literature review of 37 laparoscopic LPJs that reports a mean operative time of 218 minutes, 0% mortality, and mean 5.5 day LOS. There was a 13.5% rate of open conversion and 13.5% complication rate. Importantly, at variable rates of follow-up between 5 and 84 months, 89% of patients were pain free [10].

A single-case report of a robotic-assisted LPJ in a 14-year-old child with idiopathic chronic pancreatitis was recently reported. Reported operative time and EBL were 390 minutes 8 days, and the patient remained asymptomatic and pain free at 2 years postoperatively [11].

### Cyst Gastrostomy

Complications of pancreatitis such as pseudocyst, walled-off necrosis (WON), and infected WON are increasingly being managed by minimally invasive techniques. Although WON have been traditionally treated with open cyst gastrostomy (or cyst jejunostomy if the WON is not retrogastric in location) and necrosectomy, the associated operative morbidity of this approach has spawned the application of endoscopic and minimally invasive surgical alternatives (Fig. 60.2) [13,15].

Deciding between an endoscopic versus minimally invasive approach to cyst gastrostomy and necrosectomy should take several factors into consideration. Endoscopic and laparoscopic cyst gastrostomy have been shown to have comparable mortality and morbidity, but the reintervention rate is usually higher using the endoscopic route [15]. Khreiss et al. compared 20 patients with sterile WON undergoing minimally invasive surgical drainage with 20 patients undergoing endoscopic drainage. In the laparoscopic group, the median operating room time was 167 minutes with 30 mL EBL. There were no open conversions, reoperations, or periprocedural mortality, and both groups had equal complication rates (20%). However 45% of the endoscopic patients required a reintervention for residual WON, compared to 15% in the minimally invasive surgical group. Despite a shorter LOS in the endoscopic group (2 days vs. 7 days), surgical patients had a faster time to resolution (mean 0.42 months vs. 3.6 months). The authors concluded that minimally invasive cystgastrostomy and debridement for WON can be advantageous, especially if a concomitant cholecystectomy is needed at the time of the WON drainage. A similar retrospective review of 21 patients with pancreatic necrosis (14/21 with sterile necrosis) by Worhunsky et al. reported that 19 of 21 patients (90%) were successfully debrided in a single operation without requiring additional interventions [14].

### Video-Assisted Laparoscopic Retroperitoneal Debridement

Video-assisted retroperitoneal debridement (VARD) is a minimally invasive technique that allows debridement of WON via a retroperitoneal route. The presence of a retroperitoneal drain—especially on the left side—is a requirement for a VARD procedure, since it provides a direct unimpeded route to the necrosum, thereby avoiding associated peritoneal inflammation and adhesions. Briefly, the procedure entails placing a laparoscopic port into the retroperitoneal cavity with the guidance of a percutaneous drain. Irrigation, suction, and direct debridement are gently conducted under direct visualization. A large sump drain is left in the cavity at the conclusion of the operation. Postoperatively, scheduled lavage using normal saline or dilute hydrogen peroxide is repeated until the effluent is clear.

Horvath et al. analyzed 40 patients with pancreatic necrosis across six tertiary care centers; 9 of whom were treated with drains alone, 25 with VARD, and 6 with

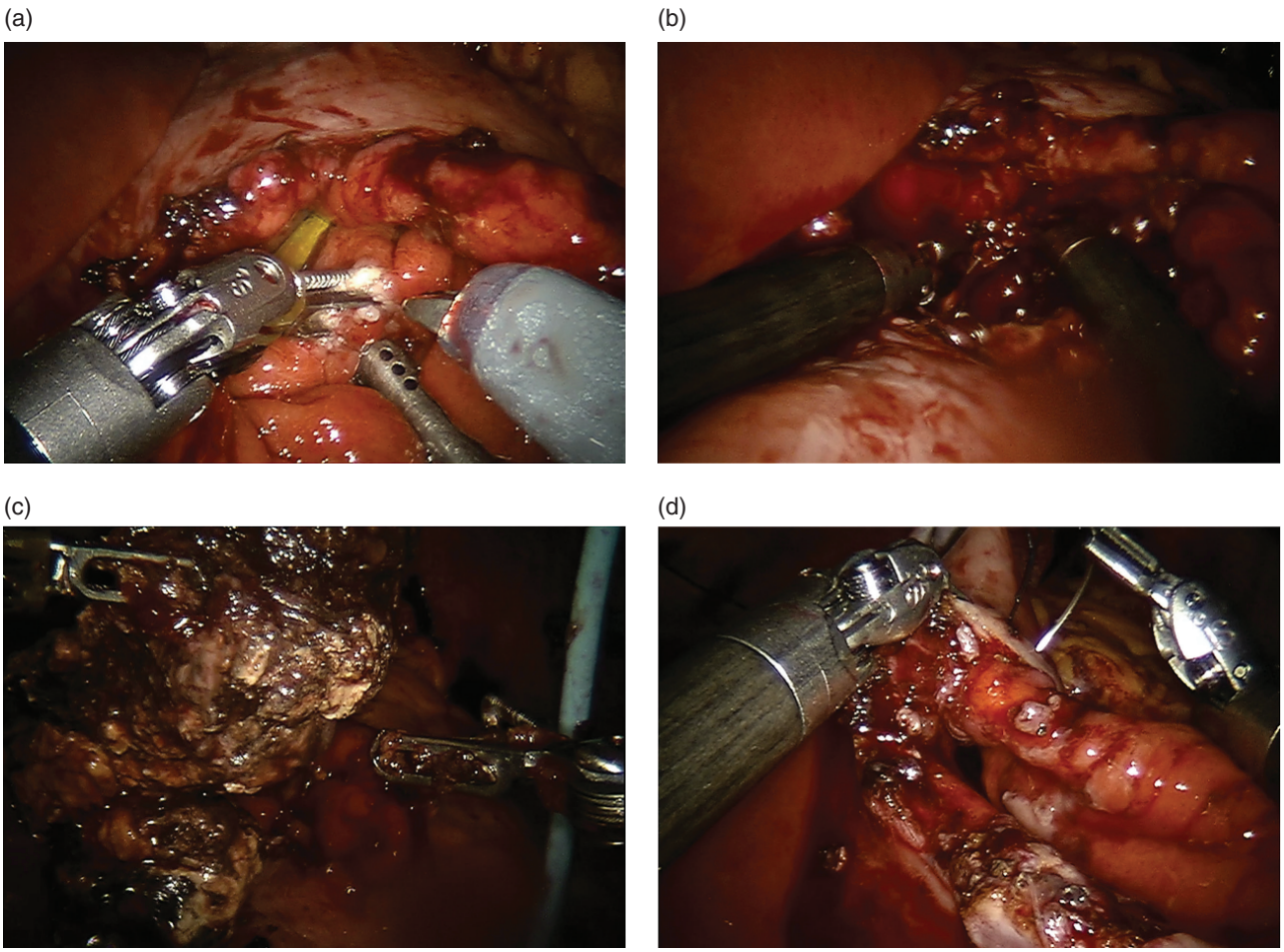


**Figure 60.2** Robotic-assisted laparoscopic cyst gastrostomy. (a) Anterior cyst gastrostomy. (b) Posterior cyst gastrostomy. (c) Pancreatic debridement. (d) Gastrostomy closure.

planned open surgery [16]. Patients already treated with a percutaneous drain were enrolled, and received an additional retroperitoneal drain (within 48 hours of enrollment) that was upsized every 3–4 days until a 20 F catheter was reached. Patients underwent a computed tomography (CT) scan on postdrain day 10–14; those exhibiting >75% reductions in collection size were treated with drains alone. Out of 25 patients requiring VARD, 10 (40%) required an open conversion and 19% required a second VARD. The most common cause of open conversion was a centromedial collection with extension into the mesenteric root that was not accessible from the flank. The mean operative time was 135 minutes. There were 4 (16%) primary VARD-related complications including bleeding and enteric fistula, and 9 secondary complications (pneumonia, deep vein thrombosis, respiratory failure, bacteremia, pseudocyst, pancreatic fistula). The median LOS was 64 days, and there were no 30-day mortalities, though there was 1 death (4%) between 3–6 months following discharge.

Overall, low reported rates of morbidity and mortality for VARD compare favorably to open necrosectomy. As 23% of 40 patients in the Horvath study were successfully treated with percutaneous drainage alone, and in accordance with the "step-up approach" [23], it is reasonable to begin with percutaneous or endoscopic drainage. Of note, 75% size reduction of the necrotic collection at 10–14 days on CT scan in the Horvath study predicted success of percutaneous drains alone with 100% accuracy. If patients fail to progress clinically, treatment may be escalated to additional drains, or a VARD.

## Combination Procedures (Resection and Drainage)

### Frey Procedure

The surgical tenets of the laparoscopic Frey procedure are closely modeled after the open technique, as depicted in Fig. 60.3. However, data from Europe and the United States on outcomes following laparoscopic Frey procedure for chronic pancreatitis are limited to case reports [18].

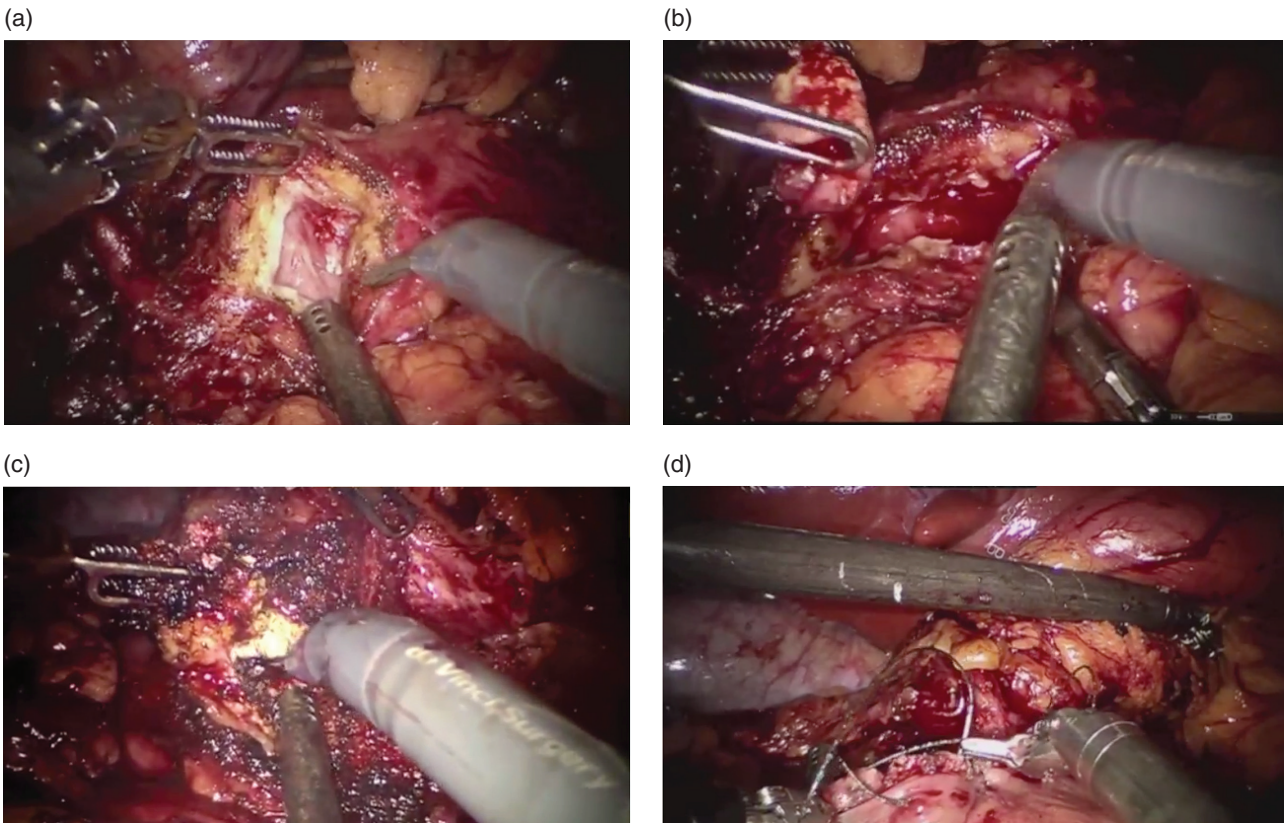


**Figure 60.3** Robotic-assisted Frey procedure. (a) Opening of pancreatic duct. (b) Removal of pancreatic duct stones. (c) Enucleation of pancreatic head. (d) Lateral pancreaticojejunostomy.

A single-institution experience in China described 9 laparoscopic and 37 open Frey procedures for chronic pancreatitis [19]. In 2 (22%) laparoscopic cases, open conversion was necessary due to inability to locate the pancreatic duct. In the 7 laparoscopic completions, mean operating room time was 323 minutes with 57 mL of blood loss. There was 1 postoperative complication of postpancreatectomy hemorrhage, with no mortality. Average LOS was 7 days. At 3-month follow-up, all seven patients had significantly decreased visual analog scale (VAS) scores for pain. Outcomes were comparable to the open cohort. The authors recommended a minimum pancreatic duct width of >8 mm for successful laparoscopic intervention.

### Beger Procedure

Available data on the laparoscopic Beger procedure is scarce. A case report of a laparoscopic Beger procedure with "Berne modification" in a patient with an inflammatory head mass causing an intrapancreatic common bile duct stricture documented [12] an operative time of 285 minutes. The patient was discharged after 5 days without complications and at 16-month follow-up reported mild pain, controlled with one-third of the preoperative oral opioid dose.

## Patient Selection

Laparoscopic pancreatic resection, drainage, or combination procedures offer the advantages of minimally invasive surgery to appropriately selected patients. For example, young adults with hereditary pancreatitis may benefit from less pain and psychological trauma that is associated with a laparotomy scar. The specific procedure of choice will depend on patient factors, as well as anatomic considerations such as the presence of a pancreatic head mass, peripancreatic fluid collection, dilated pancreatic duct, etc. Patient-related factors including age, comorbidities, body habitus, ability to tolerate pneumoperitoneum, prior pancreatic interventions, and abdominal surgeries are also important to consider when deciding on minimally invasive approaches to chronic pancreatitis. Importantly, given the infrequent indication for surgical interventions in chronic pancreatitis, minimally invasive pancreatic operations for chronic pancreatitis are best delivered at high-volume tertiary centers, by experienced pancreatic surgeons, in the context of multidisciplinary assessment. The operative approach to such patients (open, laparoscopic or robotic assisted) must be dictated by surgeon experience and comfort level.

## Conclusion

Although limited by small retrospective studies and case reports, laparoscopic approaches for chronic pancreatitis are safe and feasible in highly specialized centers. Analogous to the open approach, a myriad of resection, drainage, and combination type procedures can be performed. Further comparative studies on the efficacy of minimally invasive approaches and their impact on the quality of life of this patient subset are needed.

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# Management of Diabetes and Long-Term Outcome of Chronic Pancreatitis

## 61

## Chronic Pancreatitis: Long-Term Outcome After Medical and Surgical Treatment

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## Introduction

Both interventional and surgical approaches can be used to treat outflow disorders of the pancreatic duct or the common bile duct and pseudocysts due to chronic pancreatitis. The best procedure for symptom-oriented therapy has to be decided on according to the clinical appearance of the patient and the varying disease patterns on the one hand and the long-term outcome on the other hand. A primary aim is the provision of adequate pain therapy. Whereas Chapters 55–60 focus on interventional and surgical procedures for pseudocysts, pain due to chronic pancreatitis, and biliary and pancreatic duct obstructions, this chapter reports on long-term results and discusses the significance within the context of complex treatment of chronic pancreatitis.

## Outcomes of Interventional and Surgical Therapy for Pancreatic Pseudocysts

### Results of Interventional Therapy for Pseudocysts

The etiology of pseudocysts has to be considered during therapy planning. Internal drainage techniques have increasingly replaced percutaneous methods. Today, computed tomography (CT)- or ultrasound-guided percutaneous puncture and drainage is almost always restricted to emergency relief of infected or necrotic cysts. The reason for this development is the observation of recurrence in as many as 70% of patients and cutaneous fistulas in up to 20% of patients. An analysis in terms of the effectiveness of percutanously drained pseudocysts remains difficult because of inconsistencies in the nomenclature of pseudocysts in different studies. Moreover, there are no data on long-term surveillance.

Pancreatic pseudocysts can be drained safely by transgastric, transduodenal, or transpapillary routes using an endoscopic approach with placement of stents in the cyst cavity. However, there are no prospective data concerning the best time point for changing the stents and the duration of stent therapy. In the case of a transmural drainage of cysts the distance between cyst cavity and the wall of the hollow organ should be as small as possible to reduce the risk of stent dislocation. Endoscopic ultrasound (EUS)-guided puncture and drainage of a cyst is technically superior to the non-ultrasound-guided transmural drainage (success rate 94% vs. 72%), whereas no differences exist with regard to complication rate and short-term treatment outcome [1]. The long-term results from endoscopically inserted stent therapy are difficult to determine because of an inconsistent nomenclature and consideration of the etiology (acute vs. chronic) of the pseudocysts. Recent studies report symptom resolution, and therefore therapeutic effectiveness, of up to 91% and mortality of less than 1%, on the one hand, and a maximum recurrence rate of 18% in long-term follow-up (median 6–43 months), on the other hand [2–4].

### Results of Surgical Therapy for Pseudocysts

The aim of surgery is the eradication of the cyst. However, surgical therapy increasingly comes up against the complex pseudocysts frequently associated with chronic pancreatitis. These include huge pseudocysts, multiple pseudocysts, or those with simultaneous stone- or stricture-associated changes and truncation of the pancreatic duct [5]. The so-called internal and external drainage procedures can be expanded by a partial resection of the pancreas.

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External drainage surgery has no noteworthy status in the therapy of chronic pancreatitis. The long-term prospect of success is too low and these procedures are therefore at most performed to relieve infected pseudocysts in acute pancreatitis. There are no data on the long-term outcome of these procedures in chronic pancreatitis.

Internal drainage procedures include pseudocyst gastrostomy, pseudocyst duodenostomy, and pseudocyst jejunostomy. If possible, the anastomosis should be placed at the lowest part of the cysts to guarantee longstanding complete emptying. Depending on the localization of the pseudocysts and the underlying disease the technical feasibility ranges between 90% and 100%, with an average rate of recurrence of 12% in long-term follow-up. The procedure-associated mortality is 2.5% and the morbidity is approximately 16% [5]. Although there are no randomized trials, a center-specific overview suggests that pseudocyst jejunostomy is the preferred surgical procedure compared to pseudocyst gastrostomy.

Surgical procedures for drainage of pseudocysts have slightly higher success rates but also have a higher morbidity compared to endoscopic pseudocyst drainage into the duodenum or the stomach. Surgical resection procedures are mainly performed in cases of obstruction of the pancreatic duct or of the bile duct in the course of chronic pancreatitis.

Unfortunately, there are currently no randomized trials comparing surgical and endoscopic and interventional drainage procedures for pseudocysts. Comparison and evaluation of operative, interventional, and endoscopic drainage procedures is difficult because of the different accompanying morbidities in what is a very heterogeneous patient group.

Laparoscopic surgery has been established for pseudocyst jejunostomy, a combined laparo-endoscopic intragastric pancreatic pseudocyst gastrostomy, and pseudocyst gastrostomy via an anterior approach. Hitherto, the significance of the different procedures has not been finally classified because there are no prospective randomized trails. The perioperative complication rate is less than 10% and the long-term follow-up of some studies is longer than 6 years [6]. Thanks to a recurrence rate between 0% and 13% [7], the effectiveness and safety of the laparoscopic procedures can be compared with open surgery. Both the comorbidities of the patients and the nature and localization of the pseudocysts are very heterogeneous. All these aspects impact on the short-term course, but also have a particular effect on the long-term outcome of interventional, endoscopic, and surgical treatments of pseudocysts. Needless to say, the experience and expertise of the treating endoscopist, interventional radiologist, or surgeon play important roles. To achieve reliable statements in terms of therapeutic procedures and follow-up there is a need for clear definitions of pseudocysts and comprehensive consideration of the etiology of pancreatitis [8].

## Outcome of Pain Management in Chronic Pancreatitis

The morphologic correlates of recurrent pain in chronic pancreatitis are inflammatory cellular infiltration of the parenchyma and nerve sheaths, often associated with inflammatory pancreatic head enlargement or obliterating stones in the main pancreatic duct. The primary therapeutic step is the avoidance of triggering factors—most frequently a complete abstinence from alcohol and smoking—and adequate analgesia. In the case of persistent pain despite medical treatment, multidisciplinary therapy needs to be escalated by interventional or surgical methods [9]. This section focuses on the outcome of the therapeutic procedures presented in Chapters 51–54.

### Results of Medical Treatment for Chronic Pain

According to the World Health Organization (WHO) scheme for pain therapy and as explained in Chapters 41 and 51, peripherally acting analgesics are combined with tricyclic antidepressants, anticonvulsive agents, or opioids to achieve a positive effect in the therapy of chronic pain due to chronic pancreatitis [10]. In the next step, more potent opioids can be applied with close attention to both the patient's pain symptoms and the efficacy profile of the drug.

There are no reliable long-term results from well-designed randomized controlled trials that identify any opioid as being better than others with regard to both pain relief and side-effects [11]. With regard to the genesis of neuropathic pain in chronic pancreatitis, pregabalin has been tested for its potency in pain relief and was found to be significantly suited [10], although long-term results on both persistent pain relief and late drug-related side-effects in chronic pancreatitis are still not available.

### Results of Interventional Treatment Options for Chronic Pain

The so-called celiac plexus blockade can be performed endoscopically or under CT guidance. The aim is to interrupt pain sensations in sensory nerval fibers of the celiac ganglion region by either a mix of steroids and anesthetics (nerve block) or concentrated alcohol (50–90%) or phenol (neurolysis). In the short term, a

significant improvement should be found in the overall pain score. EUS-guided techniques seem to be safer, more effective, and more enduring compared to fluoroscopy-guided or CT-guided techniques [12–14]. The success rate of EUS-guided plexus blockade in terms of sufficient pain reduction was reported to be between 50% and 60% in two meta-analyses [12,13]. However, long-term data are rather sparse and the effect is only transient in most cases, as only 10% of the patients treated still enjoy persistent pain relief after 24 weeks [15].

Pain therapy includes treatment for pancreatic duct strictures and impacted stones, so lithotripsy, sphincterotomy, dilatation, or stenting of the pancreatic duct may become necessary. Pancreatic duct drainage hypothetically initiates decompression of the duct and reduced pressure in the segments behind, which consecutively leads to pain reduction or even freedom from pain. Nevertheless, it remains difficult to evaluate the individual impact of the changes on the character of pain. The clinical guideline of the European Society of Gastrointestinal Endoscopy (ESGE) recommends extracorporeal shock wave lithotripsy (ESWL) for first-line therapy in uncomplicated, painful chronic pancreatitis and (head)stones larger than 5 mm which obstruct the main pancreatic duct, followed by endoscopic removal of the fragments [16]. During a follow-up period of up to 77 months after this procedure, complete freedom from pain and partial freedom from pain were reported in 48% and 91% of patients, respectively [17]. However, only one randomized controlled trial exists comparing ESWL versus ESWL plus endoscopy in patients with obstructive chronic pancreatitis. Interestingly, both intensity and number of pain relapses were similar during a 2-year follow-up [18].

Evidence-based recommendations for endoscopic therapy of pancreatic duct strictures are lacking. Overall, the long-term pain relief of different studies varies between 52% and 90% over 14–69 months [19]. Multiple stenting was found to be successful in terms of freedom of pain and symptoms in more than 80% of the patients treated in an interval of 38 months [20]. However, prospective studies are necessary to investigate this therapeutic approach because single versus multiple stenting have not been compared to date.

## Results of Surgical Therapy for Chronic Pain

Direct comparison of surgical therapy (80% resections, 20% draining procedures) and endoscopic therapy with and without stenting revealed the superiority of the surgical approach for long-term pain and weight control in a prospective, controlled, randomized study. The results in terms of at least partial pain relief were still comparable (more than 90%) in both groups after 1 year. However, surgery aiming for freedom from pain turned out to be significantly advantageous in chronic obstructive pancreatitis after 3 and 5 years (surgery: 41% vs. endoscopic: 11% and surgery: 37% vs. endoscopic 14%, respectively) during further observation. In addition, the percentage of so-called "non-responders" (failure) was significantly higher in the interventionally treated group of patients. The monitoring of the course of the body weight of patients who received either surgery or intervention revealed similar results of superiority of the surgery group with an increase of body weight (surgery vs. endoscopy: 60% vs. 66% after 1 year but more than 50% and 27% after 5 years) [21].

Another prospective, randomized controlled study investigated approaches for refractory pain and compared endoscopical stenting and operative lateral pancreaticojejunostomy [22]. Patients from the surgical group reported partial or complete freedom of pain in 75% whereas only 32% of the patients of the interventionally treated group showed this improvement. The study had to be stopped prematurely because the advantage of the operative strategy was obvious and therefore continuing patient recruitment for study completion was ethically unacceptable. During the long-term follow-up of 79 months, another important finding was that patients who initially received surgical drainage reported markedly less pain and less frequently required additional therapy, either endoscopic or operative. However, surgical or interventional reintervention was required in almost 50% of the primarily endoscopically treated patients [23]. Moreover, physicians should bear in mind that early surgical therapy within the first 3 years after diagnosis apparently results in the best outcome in terms of pain reduction [24].

In a multicenter randomized trial initiated by the Dutch Pancreatitis Study Group the best time point for operative therapy after diagnosis is currently being investigated. The aim of this trial is to clarify whether early surgical intervention is better in terms of pain control and organ function compared to the step-up model of medical, endoscopic, and surgical treatment [25].

However, there are data indicating increased morbidity of salvage surgery after failed endoscopic treatment of pancreatic disease [26].

Taken together, the results of two randomized controlled clinical trials reveal the superiority of surgery compared to interventional endoscopy in the treatment of chronic pancreatitis. In addition to local pancreatic surgery, the efficacy of bilateral thoracoscopic transection of the splanchnic nerves has been shown to have long-lasting or even permanent positive effects in terms of pain control and quality-of-life improvement in chronic pancreatitis [27–29].

## Outcome of Therapeutic Options for Biliary and Pancreatic Ductal Stenoses

In association with inflammatory reactions and advancing glandular remodeling, stenoses of the pancreatic duct and the intrapancreatic biliary duct may develop. In addition to endoscopic methods, resective and operative drainage procedures must be evaluated. However, it should be remembered that the possibility of malignant lesions in the pancreatic tissue should be considered. After all, the cumulative risk for pancreatic cancer is considerably increased with an incidence of 4.6% after 5 years and 14% after 25 years in patients with chronic pancreatitis compared to disease-free controls [30].

### Results of Endoscopic Therapy for Ductal Stenoses

Different factors have relevant impacts on the success of endoscopically treated pancreatic duct strictures and stenoses. These are, for example, the number of impacted stones and/or strictures, the length of the latter, and the dilatation of the distal duct segment. Endoscopic therapy has been shown to be particularly effective in treating dominant strictures and dilatation of the pancreatic duct. In an overview including approximately 1500 patients, pain relief was reported in 31–100% during an observation time of 8–72 months [31]. A multicenter study concentrated on the long-term course after decompression of the pancreatic duct including strictures, stones, and the combination of both in more than 1000 individuals. During the follow-up period of up to 12 years, pain reduction, independently from the localization of the stricture and stone impaction, was achieved in 86% and in 65% in an intention-to-treat analysis. Over the long term (2–12 years; mean 4.9 years), surgical intervention was inevitable in a quarter of the patients [32]. Previous stent application was not rated as an obstacle during the subsequent operation.

The incidence of bile duct strictures in the context of chronic pancreatitis ranges between <5% and approximately 50% [33]. Both plastic and metal stents can be placed endoscopically. During a follow-up of nearly 5 years the disappearance of strictures was reported in 10–38% only [34]. Multiple stenting over 4 years resulted in a long-term resolution rate of 44% [35]. These results appear rather unsatisfactory with regard to effective treatment of bile duct obstructions in patients with chronic pancreatitis. Therefore, surgical options should be taken into consideration whenever other chronic pancreatitis-related complications such as duodenal stenosis or pain exist.

### Late Outcome of Resective Versus Draining Procedures

Operative strategies for chronic pancreatitis for both draining and resection should consider pathophysiology and the underlying morphologic changes. Details of the various surgical procedures mentioned in the next paragraph can be found in Chapters 56–60.

In brief, surgical drainage procedures are performed if the pancreatic head is not enlarged but the pancreatic duct shows congestion. The most common surgical technique is longitudinal pancreaticojejunostomy, according to Partington–Rochelle. In addition to a low morbidity of 21% and a mortality of less than 1%, sufficient and lasting pain-release has been reported in 80% for an observation period of 15–110 months [24,36].

The rationale behind a (limited) pancreatic head resection is the hypothesis that pain persists due to incomplete decompression of the duct in the pancreatic head by a drainage-only procedure. For long time classical pancreatoduodenectomy (Kausch–Whipple) was the first choice in surgical therapy of chronic pancreatitis with head-related complications. However, despite a low mortality (less than 5% in high-volume centers) more than half of the patients showed long-term gastrointestinal problems such as dumping, diarrhea, peptic ulcers, delayed gastric emptying, and diabetes. Alternatively, the pylorus-preserving modification according to Traverso was developed, but this modification was found to be no better than the classical Kausch–Whipple procedure with regard to morbidity, mortality, and adverse side-effects.

In patients with inflammatory enlargement of the pancreatic head and pancreatic duct dilatation a combination of both resection and drainage has been suggested. Several techniques have been developed, including the duodenum-preserving pancreatic head resection pioneered by Hans Beger from the early 1970s. The encouraging long-term outcome of this technique performed in 504 patients revealed 91% freedom from pain, 69% professional rehabilitation, and 72% of the patients had a Karnofsky index of 90–100% whereas only 9% had a recurrence of pancreatitis during up to 14-year follow-up [37].

Beger's original idea of performing organ-preserving surgery for chronic pancreatitis-related complications was subsequently modified by Frey, Büchler/Bern, and Farkas in the following years. Recently, the results from a randomized controlled trial comparing the Beger procedure and the Bern modification showed no difference in patient-relevant long-term outcome during a median 129 months follow-up [38].

In a first randomized trial investigating both short- and long-term outcomes, the superiority of duodenum-preserving pancreatic head resection compared to the classical Kausch–Whipple procedure was demonstrated

with regard to pain relief, gain of body weight, and time of hospital stay [39]. In addition to comparable results concerning morbidity, course of pain intensity, and endocrine function, a meta-analysis showed advantages of the duodenum-preserving procedures (Beger, Frey, Büchler/Bern procedures) concerning hospital stay, exocrine function, and quality of life [40]. However, especially with regard to effective long-term absence of pain and quality of life these results have to be treated with caution because a meta-analysis could not find a significant superiority [41]. In 2008 the long-term results (14-year follow-up) from a randomized clinical trial comparing pylorus-preserving resection and Beger procedure demonstrated no presence of the early advantages of the latter [42]. The results from the ongoing randomized multicenter study (ChroPac) comparing duodenum-preserving pancreatic head resection and classical pylorus-preserving duodenopancreatectomy with regard to the primary end-point "quality of life" 2 years after surgery will be available within the next few years. In 2013, the 15-year follow-up data from a randomized controlled trial on pylorus-preserving pancreatoduodenectomy versus Frey procedure in chronic pancreatitis was published [43]. Whereas pain control was comparable between both groups in the long-term follow-up, the authors reported better quality of life after Frey procedure and an increased long-term mortality after pylorus-preserving duodenopancreatectomy [43]. Furthermore, no correlation between endocrine and exocrine pancreatic function and pain could be identified. Taken together, this study clearly recommends duodenum-preserving pancreatic head resection in chronic pancreatitis whenever possible.

Another study investigated the differences between the Beger procedure and the Frey procedure but could not identify any superiority with regard to morbidity, quality of life, pain relief, and endocrine or exocrine function [44]. Recently, the data from a 16-year follow-up analysis after Beger and Frey procedure agreed with these findings [45]. Comparison of the two duodenum-preserving resections—"Beger procedure" and "Büchler/Bern procedure"—revealed a shorter operation time and a shorter hospital stay for the latter [38,46] but no differences with regard to quality of life, pain control, occupational disability, exocrine and endocrine pancreatic function, endoscopic interventions, and reoperations during the 10-year follow-up [38]. Finally, there are no published studies in the literature comparing the "Büchler/Bern procedure" and the "Frey procedure."

## Conclusion

Currently, surgeons and gastroenterologist do not always agree in terms of the right time point and indications for interventional or surgical therapy in patients with obstructive chronic pancreatitis. Even among surgeons there are different opinions concerning the respective operative procedures. Both individual experience and local or interdisciplinary expertise have crucial impacts on decision making. This inhomogeneity is caused by the weak evidence of existing analyses, which are small and underpowered in most cases. New comprehensive, randomized controlled trials should clearly be initiated to support or refute these data. Complex cases have to be discussed and planned in an interdisciplinary approach. Nevertheless, in the light of the currently existing data there should be some change in decision making in favor of earlier initiation of a surgical approach, because studies report better and more long-lasting pain control and maximum possible preservation of function after organ-sparing operations. Early surgery can also prevent damage to the parenchyma which leads to better postoperative function of the remaining pancreatic tissue and reduces the risk of malignant transformation.

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# 62

# Management of Pancreatic Diabetes Secondary to Chronic Pancreatitis

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## Introduction

Because of the close anatomic and functional links between the exocrine and endocrine pancreas, any pancreatic disease that involves one will inevitably affect the other. Chronic pancreatitis is characterized by pancreatic inflammatory and fibrotic injury that results in loss of pancreatic structure and both exocrine and endocrine functions, often leading to complications such as glucose intolerance and diabetes mellitus [1–5]. Diabetes secondary to pancreatic diseases is classified as pancreatic diabetes or type 3c diabetes in the current classification of diabetes [6]. Diabetes secondary to chronic pancreatitis differs both metabolically and clinically from other forms of diabetes, and usually occurs late in the course of chronic pancreatitis. Since the reduction in β-cell mass caused by chronic inflammation of the pancreas plays a major role, pancreatic diabetes is characterized by marked impairment of insulin secretion in response to ingestion of a meal. Secretion of counterregulatory hormones including glucagon and pancreatic polypeptide (PP) is simultaneously impaired. Managements of hyperglycemia with glucose-lowering agents and improvement of malnutrition status are very important.

## Definition and Prevalence of Pancreatic Diabetes

Type 3c diabetes is a complication of exocrine pancreatic disease, including pancreatitis of any etiology, pancreatic trauma, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis, and fibrocalculous pancreatopathy [6,7]. Type 3c diabetes accounts for 5–10% of all cases of diabetes in Western populations [4], but most of the cases have been misclassified as type 2 diabetes [8,9]. Distribution of those pancreatic diabetes based on 1922 hospitalized patients with diabetes consisted of chronic pancreatitis (76%), pancreatic neoplasia (9%), hemochromatosis (8%), cystic fibrosis (4%), and post-pancreatic resection (3%) [8]. Ewald et al. [10,11] showed that 9.2% of all patients with diabetes were classified as having type 3c diabetes, and in 78.5% of the patients with type 3c diabetes chronic pancreatitis was the underlying disease.

## Incidence of Diabetes in Chronic Pancreatitis

The reported incidences of diabetes in chronic pancreatitis have been in the approximately 40–60% range [1]. Several studies of large series of patients with chronic pancreatitis have been conducted in various countries [1,3,12–15]. The results of a recent national survey in Japan showed that 46.3% of patients with chronic pancreatitis had diabetes [16], and an Italian survey reported that 31% of patients with chronic pancreatitis had endocrine insufficiency [17].

There is a strong positive correlation between the duration of chronic pancreatitis and the incidence of pancreatic diabetes. In Italy, 41.5% of patients with chronic pancreatitis were found to have diabetes at the 15-year follow-up examination [13]; 23.6% were on insulin therapy and 17.9% were being treated with oral antidiabetic agents [13]. Ammann et al. [14] conducted a long-term study of 207 patients with alcoholic chronic pancreatitis and found that overt diabetes requiring treatment with oral hypoglycemic agents or insulin was present in approximately 20% at 6 years after the onset of chronic pancreatitis, and in nearly 50% 10 years after

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Companion website: www.wiley.com/go/beger/thepancreas

onset. A prospective cohort study of 500 patients with chronic pancreatitis revealed a cumulative rate of complication by diabetes of 83% at 25 years after the clinical onset of chronic pancreatitis, and 54% of the patients with diabetes required insulin [1]. Wang et al. [3] monitored patients with chronic pancreatitis for the development of diabetes over a 20-year period and reported cumulative rates of diabetes of 3.6% at 0 year, 7.5% at 1 year, 24.2% at 10 years, and 51.5% at 20 years after the clinical onset of chronic pancreatitis.

Autoimmune pancreatitis is a particular type of pancreatitis [18,19], and 83.3% of the patients have diabetes [20]. Steroid therapy has been reported to ameliorate both diabetes and exocrine dysfunction in patients with autoimmune pancreatitis complicated by diabetes [21,22].

## Risk Factors for Pancreatic Diabetes in Chronic Pancreatitis

### Alcohol Abuse

Alcohol abuse is a factor of chronic pancreatitis in the progression as well as in its etiology. Endocrine function is more impaired in alcoholic chronic pancreatitis than in nonalcoholic chronic pancreatitis. Koizumi et al. [12] reported an incidence of pancreatic diabetes in nonalcoholic and alcoholic cases of 36.1% and 53.7%, respectively. In a recent nationwide study in Japan, the largest causal factor of chronic pancreatitis with pancreatic diabetes was alcoholic consumption (77.3%) [16].

### Pancreatic Calcification

Pancreatic calcification is an indicator of longstanding and advanced chronic pancreatitis, and correlates well with pancreatic tissue loss. Both secretion of insulin and glucagon have been reported to be more severely impaired in calcified chronic pancreatitis than in noncalcified chronic pancreatitis [23]. There is a close correlation between the presence of pancreatic calcification and the development of pancreatic endocrine insufficiency [1,13]. In a prospective study by Malka et al. [1], the presence of pancreatic calcification was the clinical factor significantly associated with the risk of diabetes, and once calcification had developed, the risk of diabetes and insulin requirement increased by more than threefold. Ito et al. [24] reported findings that the risk of diabetes increased 1.32-fold after the onset of calcification. A recent report from China also identified pancreatic calcification as a risk factor for diabetes (HR 2.326) [3]. Kawabe et al. [25] reported findings that patients with pancreatic diabetes were more common in a calcified chronic pancreatitis group (74.4%) than in a noncalcified group (21.3%).

### Smoking

Smoking is known to increase the risk of pancreatic diabetes in chronic pancreatitis patients. Maisonneuve et al. [26,27] found that heavy smoking (>20 cigarettes/day) was associated with the development of diabetes (HR 2.3) in patients with alcoholic chronic pancreatitis. Wang et al. [3] identified smoking as an independent risk factor for diabetes (HR 2.859) in chronic pancreatitis in Chinese patients before any invasive therapy.

## Pathogenesis of Pancreatic Diabetes

### Pancreatic Histology and β-Cell Dysfunction

Histologically, in the advanced stages of chronic pancreatitis, the exocrine parenchyma is almost completely replaced by fibrosis. Alterations of the endocrine islets are rather modest in the early stages of chronic pancreatitis, and even in the advanced stages of the disease. Although histologic examination of the pancreas in advanced chronic pancreatitis shows that the pancreatic islets are embedded in fibrous tissue, they are relatively well preserved in comparison with the degree of acinar cell destruction. Many studies have shown that even though a decrease in the number of islets is observed in chronic pancreatitis patients, the residual islets are often enlarged because the islet cells have undergone hyperplasia [28–30].

The relation between pancreatic β-cell area and the clinical manifestation of pancreatic diabetes in chronic pancreatitis patients has been investigated [31,32]. Meier et al. [32] conducted a study of 82 patients who underwent pancreatic surgery. They found that the relative β-cell deficits at the onset of diabetes and impaired glucose tolerance were 64% and 21%, respectively, based on 2-hour glucose levels, and concluded that pancreatic diabetes probably develops after a reduction in β-cell area of ~65%. Islet morphology and physiology may be altered by inflammation and cytokine release [33,34], which led to islet dysfunction, and the subsequent development of fibrosis and sclerosis may impair pancreatic capillary circulation and diminish islet perfusion, and ultimately leads to islet destruction. Cyclooxygenase has also been found to play a major role in islet inflammation and in the pathogenesis of diabetes [35].

### Dysfunction of Other Hormones

#### Glucagon

Beta-cell dysfunction develops first in chronic pancreatitis patients, and is followed by impairment of α-cell function. Alpha cells appear to be more resistant to the effects of chronic inflammation. Basal glucagon levels have been

reported to be maintained in chronic pancreatitis patients, but their response to stimulation is weaker [36]. Another study showed lower basal glucagon levels in patients with calcific chronic pancreatitis than in patients with primary diabetes or healthy controls [23].

### Pancreatic Polypeptide

The number of PP cells is also decreased in chronic pancreatitis. Since the fasting and postprandial increases in PP have been shown to be much lower in patients with chronic pancreatitis [7,30,36], a diminished PP response can be used as an early marker of the development of endocrine insufficiency [37]. A recent consensus statement has proposed a weak or absent PP response to meal testing as a specific sign of pancreatic diabetes [38]. The impaired expression of hepatic insulin receptor that occurs in association with chronic pancreatitis may be caused by PP deficiency, because PP has been shown to have an effect on hepatic sensitivity to insulin [4,7,36,39]. Andersen [39] has demonstrated reversal of the decrease in hepatic insulin receptor in patients with chronic pancreatitis in response to PP administration, and a randomized placebo-controlled study has shown that PP administration enhanced insulin sensitivity and lowered the insulin requirements of the patients with type 1 and type 3c diabetes [40].

### Incretins

Glucose-dependent insulinotropic polypeptide and glucagon-like peptide 1 (GLP-1) are insulinotropic intestinal peptide hormones, also known as "incretin hormones." Incretins are responsible for up to 70% of the insulin secretion after glucose ingestion. Because incretin secretion is stimulated by nutrient digestion and absorption in the small intestine, pancreatic exocrine insufficiency results in decreased incretin release [41]. In fact, the incretin effect is strongly reduced in chronic pancreatitis patients with diabetes, suggesting that the incretin defect is a consequence of the diabetic state [42–44]. Several studies have shown that pancreatic enzyme supplementation increases the postprandial incretin response in patients with pancreatic exocrine insufficiency [42–44].

## Diagnosis of Type 3c Diabetes

The initial diagnostic evaluation of diabetes in patients with chronic pancreatitis is a fasting blood glucose and $HbA_{1c}$ analysis. A fasting blood glucose level >126 mg/dL or $HbA_{1c}$ value >6.5% may indicate the presence of diabetes based on the most widely used diagnostic criteria for diabetes [6,38]. Type 3c diabetes is more common than generally thought [10,11]. It is very important to recognize this type because failure to make the diagnosis would result in failure to implement appropriate therapy [8,45]. Ewald et al. [11,45] recently proposed new criteria for diagnosing type 3c diabetes (Box 62.1), but there is a degree of overlap between type 3c diabetes and other forms of diabetes, because longstanding type 1 and type 2 diabetes are also often associated with exocrine pancreatic failure. An absent PP response to a mixed-nutrient test meal appears to be the most reliable and specific indicator of type 3c diabetes (Table 62.1) [7,38].

**Box 62.1 Proposed diagnostic criteria for type 3c diabetes mellitus**

**Major criteria (must be present)**

- Presence of exocrine pancreatic insufficiency (monoclonal fecal elastase-1 test or direct function tests)
- Pathological pancreatic imaging (endoscopic ultrasound, MRI, CT)
- Absence of type 1 diabetes mellitus associated autoimmune markers

**Minor criteria**

- Absent pancreatic polypeptide secretion
- Impaired incretin secretion (e.g., GLP-1)
- No excessive insulin resistance (e.g., HOMA-IR)
- Impaired β-cell function (e.g., HOMA-B, C-peptide/glucose ratio)
- Low serum levels of lipid soluble vitamins (A, D, E, and K)

*Source:* Ewald, Hardt 2013 [11], Table 2. 

## Clinical Characteristics of Pancreatic Diabetes

The most common symptoms of pancreatic diabetes are the same as those of any other type of diabetes, but the alterations in glucose metabolism range from only mild impairment to a severe form characterized by frequent episodes of hypoglycemia, particularly after insulin administration, commonly referred to as "brittle diabetes." Glycemic control in type 3c diabetes is unstable because of the loss of the glucagon response to hypoglycemia, carbohydrate malabsorption, and/or inconsistent eating patterns as a result of concomitant pain and/or nausea or chronic alcohol abuse [11]. Unlike hypoglycemia, diabetic coma and diabetic ketoacidosis are relatively rare in pancreatic diabetes.

**Table 62.1** Islet cell hormonal response to mixed-nutrient meal testing.

| | Type 1 diabetes | Type 2 diabetes | Type 3c diabetes |
|---|---|---|---|
| C-peptide | Normal[a], low or absent | Elevated[b] or normal[a] | Normal[a], low or absent |
| Insulin | Normal[a], low or absent | Elevated[b] or normal[a] | Normal[a], low or absent |
| Glucagon | Normal[a] or elevated | Normal[a] or elevated | Normal[a], low or absent |
| Pancreatic polypeptide | Normal or low | Normal or elevated | Low or absent |

*Source:* Rickels et al. 2013 [38], Table 3. Reproduced with permission of Elsevier.
[a] Values in the normal range are inappropriate in the context of elevated glucose and indicate an impairment in β-cell mass or function.
[b] Elevated levels were calculated by comparing area under the curve for serum C-peptide and insulin responses to a liquid test meal for cases and controls.

## Complications of Pancreatic Diabetes

Prolonged hyperglycemia puts diabetes patients at increased risk of micro- and macrovascular complications, which cause high morbidity and mortality. The development of early microvascular complications in pancreatic diabetes is similar to that in other types of diabetes. Nakamura et al. [46] reported a high incidence (40%) of retinopathy in calcified chronic pancreatitis. The peripheral nerves in patients with alcoholic chronic pancreatitis have already been damaged as a result of long-term alcohol abuse, malnutrition, and vitamin malabsorption due to pancreatic exocrine insufficiency. A prevalence of neuropathy of 30% has been reported in patients with pancreatic diabetes, which is comparable to its prevalence in idiopathic diabetes [46]. A higher prevalence of peripheral neuropathy has been reported in patients with chronic pancreatitis due to alcohol abuse (44%) and in patients with pancreatic diabetes treated with insulin (79%) [12].

## Therapy of Pancreatic Diabetes

Management that maintains good glycemic control and good nutritional status is most important, because it can prevent long-term complications of diabetes in patients with pancreatic diabetes. The initial treatment of all patients with type 3c diabetes should begin with a concentrated effort to correct lifestyle factors, including weight control, abstinence from alcohol, and smoking cessation. The goal of treatment in pancreatic diabetes is to achieve an $HbA_{1c}$ level as close to normal as possible, while avoiding life-threatening hypoglycemia. Whether to choose insulin or noninsulin therapy for the initial treatment of pancreatic diabetes depends on the clinical presentation of the patient [4].

### Insulin Therapy

Insulin replacement therapy is the only effective treatment option for patients with advanced pancreatic diabetes who are markedly hyperglycemic (fasting glucose >10 mmol/L or 180 mg/dL, and $HbA_{1c}$ level >8.5%). Insulin therapy is often used as the treatment of first choice for patients with severe malnutrition and weight loss because the desired anabolic effects in such patients. Although patients with type 3c diabetes should be treated based on the general insulin dosing and regimen guidelines for type 1 and type 2 diabetes [47,48], the dose of insulin required to achieve and maintain glycemic control in type 3c diabetes may be significantly lower than in other types of insulin-dependent diabetes.

Insulin therapy for patients with type 3c diabetes is started with a bedtime 10 U or 0.2 U/kg dose of an intermediate-acting insulin or with a bedtime or monitoring dose of a long-acting insulin, with progressive dose increases based on the results of fasting and postprandial blood glucose determinations [4,47]. Intensive insulin therapy in combination with a preprandial dose of short- or ultra-short-acting insulin for postprandial hyperglycemia and a dose of long-acting insulin at bedtime for basal requirement is also recommended (Fig. 62.1) [25]. Since the long-acting insulin analogs are characterized by the absence of pronounced peaks and a 24-hour time–action profile, nocturnal hypoglycemia can be avoided.

Patients with pancreatic diabetes lack counterregulatory hormones, such as glucagon and PP, and thus are susceptible to hypoglycemia and other metabolic dysfunctions. Because of the lack of pancreatic enzymes and significant delay in digestion, there may be asynchrony between meal ingestion, delivery of exogenous insulin, and nutrient absorption.

### Therapy with Other Hypoglycemic Agents

The hypoglycemic agents typically used to treat type 3c diabetes are the same as used to treat type 2 diabetes [30,47,48]. They may be tried as a valid approach in patients with pancreatic diabetes with mild hyperglycemia and relatively early in the course of the disease [38].

When the hyperglycemia in pancreatic diabetes secondary to chronic pancreatitis is mild ($HbA_{1c}$ <8.0%) and concomitant insulin resistance is suspected, metformin is the preferred initial drug of choice for oral antidiabetic therapy because of improvement of insulin resistance

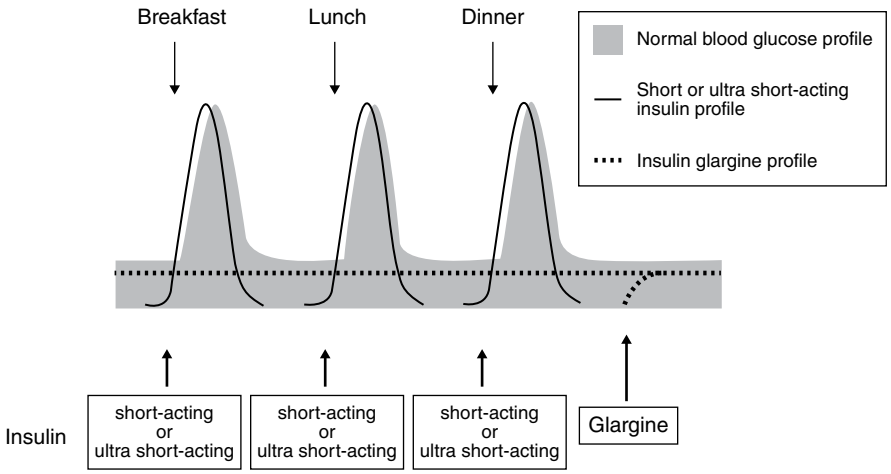


**Figure 62.1** Intensive insulin therapy in combination with pre-meal short- or ultra-short-acting insulin and long-acting insulin glargine for basal requirement. *Source:* Kawabe et al. 2009 [25], Fig. 6. Reproduced with permission of Springer.

and reduction in risk of malignancy in patients with chronic pancreatitis [38]. Insulin and insulin secretagogues therapy may increase the risk of malignancy in patients with chronic pancreatitis [49], whereas metformin therapy has been shown to reduce the risk of pancreatic cancer by as much as 70% [50]. Metformin should be continued if insulin therapy must be added to achieve adequate glycemic control [4,7,11].

Therapy with insulin secretagogues (sulfonylureas and glinides) may also be considered in patients with pancreatic diabetes in the early stages ($HbA_{1c}$ <8.0%) [38]. However, because the risk of hypoglycemia with these drugs may be greater in patients with impaired glucagon secretion, short-acting agents are preferable when meal ingestion is inconsistent. Sulfonylureas may increase the risk of severe and prolonged hypoglycemia.

Incretin-based therapies with GLP-1 analogs and dipeptidyl-peptidase-4 (DPP-4) inhibitors may be ineffective in pancreatic diabetes because natural incretin levels may already be high [41,42]. Moreover, the possible induction of pancreatitis and pancreatic cancer by incretin-based therapies has been widely debated [51], although a recent study reported a low incidence of pancreatitis among patients being treated with incretins and that the drugs do not increase the risk of pancreatitis [52]. It might be better to avoid their use in pancreatic diabetes patients until their safety is clearly confirmed.

Glitazones improve peripheral insulin resistance sensitivity, but are known to associate increased risk of fluid retention, congestive heart failure, and bone fracture. Fractures are a particular concern, because chronic pancreatitis patients are already at increased risk of osteoporosis. Alpha-glucosidase inhibitors (α-GI) specifically lower postprandial glucose excursions, but may aggravate diarrhea, bloating, and intestinal malnutrition. Such adverse effects may further impair intestinal digestion and absorption in patients with pancreatic exocrine dysfunction. The actions of sodium–glucose cotransporter-2 (SGLT-2) inhibitors are independent of insulin, but the weight loss should be considered, especially in patients with malnutrition. Thus, therapeutic effects of glitazones, α-GI, and SGLT-2 inhibitors on pancreatic diabetes have not been confirmed, and their use should generally be avoided [38].

## Pancreatic Enzyme Replacement Therapy

Many patients with chronic pancreatitis manifest some degree of fat malabsorption, regardless of the presence of symptoms. Since clinically apparent protein and fat malabsorption does not occur until over 90% of pancreatic exocrine function is lost, exocrine pancreatic insufficiency and maldigestion may remain undetected by patients and their physicians. Impaired absorption of fat-soluble vitamins (A, D, E, and K) should be a concern in patients with even mild fat absorption. A decrease in serum 25-hydroxyvitamin D level has been observed in >90% of patients with pancreatic diseases [53]. Oral pancreatic enzyme replacement protects against the failure to absorb of fat-soluble vitamins and prevents metabolic bone diseases [39].

Several studies have shown improvement in the incretin response to ingestion of nutrients after pancreatic enzyme replacement in patients with pancreatic exocrine insufficiency due to chronic pancreatitis [44,45] and cystic fibrosis [46]. Adequate oral pancreatic enzyme replacement therapy should therefore be added to glycemic control therapy to improve clinical symptoms of steatorrhea and prevent qualitative malnutrition and metabolic complications. Diabetes and malabsorption may impair the metabolism of trace elements and decrease plasma concentrations of zinc and selenium.

### Total Pancreatectomy with Islet Autotransplantation

Total pancreatectomy with islet autotransplantation (TPIAT) is a potential treatment option for select patients with severe painful chronic or recurrent acute pancreatitis. Bellin et al. [54] reported being able to isolate significant islet mass in 27 patients with chronic pancreatitis and diabetes who underwent TPIAT. Recommendations for TPIAT in chronic pancreatitis have recently been published by the PancreasFest working group [55]. Numerous areas of potential future research in regard to TPIAT remain.

## Prognosis of Pancreatic Diabetes

A long-term follow-up study of patients with chronic pancreatitis showed that 5.6% of them had died of diabetes [13]. The cause of death in half of the cases was hypoglycemia, and in the other half it was hyperglycemia. Another study reported finding that the major causes of death at an average of 5.5 years after the onset of diabetes were diabetic complications (about 48%), including cardiovascular and cerebrovascular diseases [12]. Ammann et al. (14) reported that the death rate in chronic pancreatitis was almost three times higher in a group that continued to abuse alcohol than in a group that decreased or ceased alcohol intake. An epidemiologic survey conducted in Japan revealed a mortality rate 2.3%, that hypoglycemia was the most frequent cause of death, and that many of the deceased patients had been treated with insulin but continued to consume alcohol [16]. Cessation of drinking and smoking may decrease the mortality rate from pancreatic diabetes.

Chronic pancreatitis, longstanding diabetes, and insulin therapy are known risk factors for pancreatic cancer [5,7,49]. Patients with diabetes secondary to chronic pancreatitis on insulin therapy are at very high risk of developing pancreatic cancer [4].

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# Section 5

# Autoimmune Pancreatitis

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# Epidemiology of Autoimmune Pancreatitis

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## Introduction

There are two histologic types of autoimmune pancreatitis (AIP): (i) lymphoplasmacytic sclerosing pancreatitis (LPSP), which is called type 1 AIP, and (ii) idiopathic duct-centric pancreatitis (IDCP), which is called type 2 AIP. Type 1 AIP has come to be recognized as a pancreatic manifestation of IgG4-related disease [1]. Since 2002, several sets of diagnostic criteria for AIP have been developed worldwide and international consensus diagnostic criteria (ICDC) were created to incorporate the diagnostic strategies used in the different criteria [2].

There have been three nationwide epidemiologic surveys of AIP in Japan [3–5], as well as three international multicenter surveys of AIP [6–8]. In this chapter, the epidemiology of AIP is described based on the findings of these surveys.

## Nationwide Survey of Autoimmune Pancreatitis in Japan

The first nationwide survey of AIP was conducted in Japan in 2002, and the estimated number of AIP patients was 900 [3]. This number increased 3.1 times to 2,790 in 2007 in the second Japanese nationwide survey [4]. This rapid increase in the number of AIP patients might be explained by the following: the focal type of AIP could not be diagnosed using the Japanese diagnostic criteria of 2002, and recognition of AIP increased in Japan.

The third nationwide survey in Japan was conducted in 2011 [5] using the Japanese diagnostic criteria of 2011 [9]. At that time, there were an estimated 5,745 AIP patients, and the overall prevalence rate was 4.6 per 100,000 population. The number of newly diagnosed AIP patients was estimated to be 1,808, and the annual incidence rate was 1.4 per 100,000 population. The male to female ratio was 3.2, and the patients' mean age was 66.3 years. Of the 936 patients, 86.4% presented with high serum IgG4 levels (≥ 135 mg/dL), while almost 50% of patients were found to have localized pancreatic enlargement. Pancreatic tissue was obtained in 45.4% of cases, and tissue samples were obtained by endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) in 63.8%. A total of 532 (57.9%) patients had extrapancreatic lesions: 153 had sialadenitis/dacryoadenitis, 95 hilar sclerosing cholangitis, 76 retroperitoneal fibrosis, and others. Steroid treatment was given to 761 (82.3%) patients and it was effective in 96.3%. Maintenance steroid treatment was given to 84.6% and the relapse rate was 22.2%. Overall, 109 (11.8%) patients had malignant tumors, including 7 patients with pancreatic cancer.

## First International Survey of Autoimmune Pancreatitis

The first international multicenter survey of AIP in 2009 involved 10 centers in 5 Asian countries (Japan, Korea, Taiwan, China, and India) [6]. A total of 327 AIP patients (258 males, 69 females; average age 60.0 years) who were diagnosed according to the Asian diagnostic criteria [10] were enrolled.

Obstructive jaundice was the most common initial symptom, followed by weight loss and abdominal pain. Diffuse swelling of the pancreas was common in Japan (64%) and Korea (81%), whereas segmental swelling of the pancreas was more commonly seen in Taiwan (70%)

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and China (72%) ($P < 0.01$). In Japan, Korea, and Taiwan, 58–100% of patients had increased serum IgG4 levels. Pathologically, almost all Asian AIP patients were diagnosed with LPSP. Steroid therapy was the major therapeutic strategy and it was effective, although the rate of resection or bypass surgery was higher in Taiwan and China ($P < 0.01$).

Due to their geographic proximity, the populations of Japan, Korea, Taiwan, and China appear to share a common genetic background. AIP patients had fundamentally similar characteristics, with most being type 1 AIP in these countries. Differences in the rates of recognition of this disease might account for the differences in the clinical and pathophysiological characteristics of AIP in these countries.

## Second International Survey of Autoimmune Pancreatitis

The second international, multicenter survey of AIP in 2010 involved 15 institutes from 8 countries (Japan, Korea, Taiwan, India, the United States, Germany, Italy, and the United Kingdom) [7]. A total of 731 AIP patients were enrolled; 204 cases were confirmed histologically to be LPSP, and 64 cases were confirmed to be IDCP. Various diagnostic criteria were used to diagnose AIP.

LPSP patients were approximately 16 years older than IDCP patients (61.6 years vs. 44.8 years), and there was no sex difference between the two groups. With respect to the initial presentation, obstructive jaundice was more common in LPSP than in IDCP (75% vs. 47%, $P < 0.01$), whereas abdominal pain (41% vs. 68%, $P < 0.01$) and acute pancreatitis (5% vs. 34%, $P < 0.01$) were more common in IDCP patients. LPSP patients were more likely than IDCP patients to have diffuse pancreatic swelling (40% vs. 25%, $P < 0.05$), increased serum IgG4 levels (63% vs. 23%, $P < 0.01$), retroperitoneal fibrosis (7% vs. 0%, $P < 0.05$), and salivary gland swelling (12% vs. 0%, $P < 0.01$), while they were less likely to have ulcerative colitis (1% vs. 16%, $P < 0.01$). Surgery was more commonly performed for IDCP patients (60% vs. 78%, $P = 0.01$). Both groups showed good therapeutic responses to steroid treatment, though the relapse rate was significantly lower in IDCP patients (36% vs. 5%, $P < 0.01$).

Among AIP patients whose diagnosis was not confirmed histologically, obstructive jaundice was the most frequent initial symptom in six countries, but it was less frequent in Italy (44%) and Germany (13%), while abdominal pain was the most frequent initial symptom in India (86%) and Germany (63%). Acute pancreatitis was common in Germany (66%) and Italy (32%). Overall, 85–100% of AIP patients had increased serum IgG4 levels in Japan, Taiwan, India, and the United States, while only 50–61% had increased serum IgG4 levels in other countries. Italian AIP patients often had ulcerative colitis (30%). Steroid treatment was given to 69–100% of AIP patients, with the initial prednisolone dose being 1 mg/kg/day in three countries, 0.6 mg/kg/day in two countries, and 30–40 mg/day in the remaining three countries. This dose was then tapered by 5 mg every 1–2 weeks. The time from initiation to cessation of steroid therapy ranged from 3 months to 2 years, and all patients responded well to steroid therapy, with a relapse rate of 15% to 64% in steroid-treated patients (Table 63.1).

The clinical profiles of patients in six countries were similar to those of LPSP patients. However, different clinical profiles that appeared to include a mixture of LPSP and IDCP were observed in Italian and German AIP patients.

## Third International Survey of Autoimmune Pancreatitis

The third international, multicenter survey of AIP in 2012 involved 23 institutes in 10 countries (Japan, Korea, Taiwan, the United States, Germany, Italy, the United Kingdom, Hungary, Sweden, and France) [8]. The patients were diagnosed using the ICDC [2], and the survey focused on long-term outcomes, including organ involvement, treatments, relapse frequency, and long-term sequelae.

The survey included 1,064 patients meeting the ICDC [2] for type 1 ($n = 978$) or type 2 ($n = 86$). The average ages of type 1 and type 2 patients were 61.4 and 39.9 years, respectively, and 77% of type 1 patients and 55% of type 2 patients ($P < 0.01$) were males. The proportion of patients diagnosed with type 2 AIP was lower in Asia (3.7%) than in both Europe (12.9%, $P < 0.01$) and North America (13.7%, $P < 0.01$) (Fig. 63.1).

In type 1 patients, jaundice was the most common presentation in 63%, followed by abdominal pain, but abdominal pain and inflammatory bowel disease were the most common in type 2 AIP. Most (74%) type 1 patients were initially treated with steroids, while only 62% of type 2 patients were treated with steroids ($P = 0.01$).

Almost all type 1 and 2 AIP patients achieved remission, while 302 (31%) type 1 patients had at least one disease relapse, compared to 8 (9%, $P < 0.01$) of type 2 patients. Most relapses in type 1 patients involved the biliary system or pancreas, while all relapses in type 2

**Table 63.1** Clinical, radiologic, and serologic features of nonhistologically confirmed AIP patients in the second international survey.

| Country | Japan | Korea | Taiwan | India | USA | Germany | Italy | UK |
|---|---|---|---|---|---|---|---|---|
| Number of pts | 127 | 86 | 33 | 36 | 28 | 38 | 87 | 28 |
| Average age, years | 64.7 | 59.0 | 66.4 | NA | 64.1 | 45.5 | 43.4 | 57.6 |
| Gender (% male) | 106 (83%) | 61 (71%) | 29 (90%) | 25 (69%) | 22 (79%) | 17 (45%) | 54 (62%) | 23 (82%) |
| Initial symptom | | | | | | | | |
| Jaundice | 77 (61%) | 43 (50%) | 23 (70%) | 20 (56%) | 22 (79%) | 5 (13%) | 38 (44%) | 18 (64%) |
| Abdominal pain | 16 (13%) | 20 (23%) | 6 (18%) | 31 (86%) | 14 (50%) | 24 (63%) | 17 (20%) | 5 (18%) |
| Acute pancreatitis | 3 (2%) | 11 (13%) | 6 (18%) | 8 (22%) | 7 (25%) | 25 (66%) | 28 (32%) | 0 |
| Diffuse pancreatic swelling | 74 (58%) | 73 (85%) | 13 (39%) | 15 (41%) | 16 (57%) | 18 (47%) | 32 (37%) | 5 (18%) |
| Elevation of serum IgG4 | 102/112 (91%) | 32/62 (52%) | 28/28 (100%) | 36/36 (100%) | 22/26 (85%) | 19/31 (61%) | 28/56 (50%) | 15/28 (54%) |
| OOI | | | | | | | | |
| Total involvement | 80 (63%) | 35 (41%) | (33%) | 11 (31%) | 21 (75%) | 17 (44%) | 13 (15%) | 23 (82%) |
| Proximal bile duct | 13 (10%) | 9 (10%) | (25%) | 7 (19%) | 13 (46%) | 10 (26%) | rare | 22 (79%) |
| Renal lesions | 11 (9%) | 9 (10%) | (4%) | 0 | 7 (25%) | 0 | 2 (2%) | 5 (18%) |
| Retroperitoneal fib. | 5 (4%) | 14 (16%) | (4%) | 2 (6%) | 4 (14%) | 0 | 2 (2%) | 2 (7%) |
| Salivary/lacrimal | 27 (21%) | 7 (8%) | (17%) | 1 (3%) | 2 (7%) | 1 (3%) | 4 (5%) | 3 (11%) |
| Extensive LN | 27 (21%) | 6 (7%) | (17%) | 1 (3%) | 2 (7%) | 0 | NA | 5 (8%) |
| Ulcerative colitis | 4 (3%) | 3 (3%) | 0 | 2 (6%) | 3 (11%) | 0 | 26 (30%) | 4 (14%) |
| Initial therapy | | | | | | | | |
| Steroid | 84% | 85% | 100% | 100% | 89% | 71% | 69% | 93% |
| Response rate | 100% | 100% | 100% | 100% | 100% | 100% | 100% | 100% |
| Relapse rate | 15% | 26% | 18% | 25% | 64% | 15% | 37% | 54% |

NA, not available; OOI, other organ involvement.
*Source:* Adapted from Kamisawa et al. 2011 [7]. Reproduced with permission of Wolters Kluwer Health.

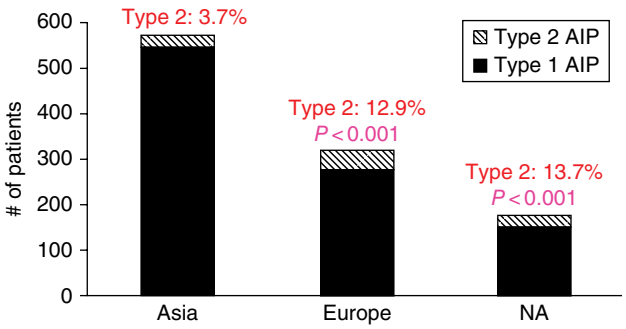


**Figure 63.1** Regional distribution of type 1 and 2 AIP based on the country of diagnosis. *Source:* Redrawn from Hart et al. 2012 [8]. Reproduced with permission of BMJ Publishing.

patients involved the pancreas. Several relapses occurred in type 1 AIP, but only one relapse occurred in type 2 AIP (Table 63.2). With or without alternative treatment, such as azathioprine, steroid retreatment remained effective for inducing remission.

## Conclusions

With increased recognition of the concept of AIP and the development of diagnostic criteria, the number of AIP patients has increased rapidly in Japan. The recent nationwide survey in Japan estimated that there were 5,745 AIP patients, with an overall prevalence rate of 4.6 per 100,000 population.

The international surveys of AIP highlighted regional and ethnic differences in the pathologic and clinical features of AIP, as well as the quite different profiles of type 1 and type 2 AIP patients. Further multinational collaborations are required to improve our understanding of this disease. Whether or not the prevalence of type 2 AIP, for which no blood test is currently available, is being underestimated and whether AIP in general is a risk factor for pancreatic cancer or merely a common differential diagnosis will also have be determined by careful epidemiologic surveys.

**Table 63.2** Initial treatment strategies and relapse in type 1 and type 2 AIP patients in the third international survey.

| | Type 1 AIP ($n=901$) | | Type 2 AIP ($n=85$) | |
|---|---|---|---|---|
| **Initial treatment:** | **Successful remission** | **Relapse rate** | **Successful remission** | **Relapse rate** |
| Steroids | 681/684 (99.6%) | 35.8% | 48/52 (92.3%) | 15.3% |
| Surgical resection | 125/127 (98.4%) | 30.2% | 17/25 (68.0%) | 0% |
| Palliative surgical bypass | 22/23 (95.7%) | | 1/2 (50.0%) | |
| Conservative | 37/67 (55.2%) | | 4/6 (66.7%) | |

| | Type 1 AIP ($n=724$) | Type 2 AIP ($n=53$) | *P* value |
|---|---|---|---|
| **Indications for steroid treatment:** | ***n*** | ***n*** | |
| Jaundice | 458 (63%) | 13 (25%) | <0.01 |
| Pancreatitis/abdominal pain | 198 (27%) | 34 (64%) | <0.01 |
| Inflammatory bowel disease | 1 (0.1%) | 23 (48%) | <0.01 |
| **Location of relapse following steroid treatment:** | ***n* = 245 episodes** | ***n* = 8 episodes** | |
| Biliary system | 124 (50.6%) | – | |
| Pancreas | 107 (42.9%) | 8 | |
| Salivary | 18 (7.3%) | – | |
| **Frequency of relapse per subject:** | | | |
| 1 relapse | 189 (77.1%) | 8 | |
| 2 relapses | 39 (15.9%) | – | |
| 3 relapses | 13 (5.3%) | – | |
| ≥4 relapses | 4 (1.6%) | – | |

*Source:* Adapted from Hart et al. 2012 [8]. Reproduced with permission of BMJ Publishing.

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# Pathogenesis of Autoimmune Pancreatitis

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## Introduction

Similar to many other immune-mediated conditions, a likely pathogenetic mechanism for autoimmune pancreatitis (AIP) is the exposure of genetically susceptible individuals to environmental or intrinsic factors that results in orchestral immune reactions. Among the two distinct subtypes of AIP, type 1 has been the main target of pathogenetic studies [1]. Therefore, this chapter focuses on the prototypic type of immune-mediated pancreatitis. Although the molecular features of type 2 AIP are currently unclear, recently obtained findings on the less common form of AIP are also briefly introduced in the last section.

## Type 1 Autoimmune Pancreatitis

### Genetic Predisposition

The strongest genetic risk is related to human leukocyte antigens (HLA), with the subtypes DRB1*0405 and DQB1*0401 known to increase the susceptibility of Japanese populations to type 1 AIP [2]. The absence of aspartic acid at HLA DQβ1 57 has also been correlated with disease relapse in Koreans [3]. Other potential disease-susceptible genes encode cytotoxic T lymphocyte-associated protein 4 (*CTLA4*), tumor necrosis factor-α (*TNFA*), Fc receptor-like protein 3 (*FCRL3*), and cationic trypsinogen (*PRSS1*) [4–7]. More comprehensive analyses including genome-wide association studies are required in order to obtain a better understanding of the genetic risks of this condition. Whether the associated HLA types identified in Asian patients are also associated with AIP type 1 in Caucasians is presently unknown.

### Autoimmune Nature

Clinical findings showing that antinuclear antibodies are present in ~40% of patients with type 1 AIP suggest the involvement of autoimmunity in disease initiation or progression [8,9]. Patients also frequently have autoantibodies against carbonic anhydrase II (CA-II), lactoferrin, pancreatic secretory trypsin inhibitor, and/or trypsinogens [8,10]. Although the presence of these autoantibodies may explain predominantly lobular injury and other organ involvement (some of these enzymes are also expressed in other organs) in type 1 AIP, some may simply be secondary to extensive acinar destruction. None of the autoantibodies identified in patients with type 1 AIP have been proven to be of the IgG4 subtype.

In a recent study, circulating IgG1 and IgG4 isolated from patients with type 1 AIP were subcutaneously injected into neonatal mice in order to elucidate the tissue reactivity of patient-derived immunoglobulins [11]. IgG1 and IgG4 both caused pancreatic injury, as evidenced by stromal edema, acinar necrosis, hemorrhage, and the infiltration of polymorphonuclear leukocytes, and histologic changes were more extensive with IgG1. Interestingly, tissue destruction induced by IgG1 was suppressed by the simultaneous injection of patient IgG4, suggesting that IgG1 is the primary autoantibody against the pancreas, while patient IgG4 may exert inhibitory effects on pancreatic injury [11]. The similar anti-inflammatory induction of IgG4 was

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previously reported in allergic individuals treated with desensitization therapy [12]. The underlying antigen of AIP type 1 remains currently unknown.

## T Cells, Cytokines, Chemokines

Among the T-cell subsets, Th2 cells and regulatory T cells (Tregs) are activated in this condition, with the Th1/Th2 balance shifting in favor of Th2 [13,14]. However, the Th1 reaction is not fully suppressed [15]. The expression of IFN-γ in the tissues of type 1 AIP is similar to that in those of primary sclerosing cholangitis and primary biliary cholangitis, while the expression of Th2 cytokines (e.g., IL-4, IL-5, IL-13, and IL-21) is markedly stronger in type 1 AIP, with a large number of IL-4+ lymphocytes infiltrating the pancreas (Fig. 64.1) [13]. The proportions of Tregs are also increased in both tissue-infiltrating lymphocytes and peripheral blood mononuclear cells [13,16].

Th2 cytokines such as IL-4, IL-5, and IL-13 supposedly contribute to tissue or serum eosinophilia and elevated serum IgE levels, which are sometimes observed in patients with type 1 AIP [17,18]. IL-10, a cytokine produced by Tregs, is also strongly expressed in type 1 AIP (Fig. 64.1) [13,14]. The combination of IL-4 and IL-10 may be relevant to the production of IgG4 because IL-4 induces the production of IgE and IgG4 from B cells and plasma cells, while IL-10 in addition to IL-4 suppresses the production of IgE, but selectively enhances that of IgG4 [19]. TGF-β, another regulatory cytokine, may play a central role in the fibrosing aspect of type 1 AIP.

The CCL1–CCR8 interaction appears to be crucial for the recruitment of Th2 cells and Tregs because 50% of Th2 lymphocytes and 60% of FOXP3+ Tregs express CCR8 [20]. CCL1 is expressed in the duct epithelium and endothelial cells, including those involved in obliterative phlebitis, in type 1 AIP [21]. CCL1+ sites are infiltrated by CCR8+ lymphocytes (Fig. 64.2). The CCL1–CCR8

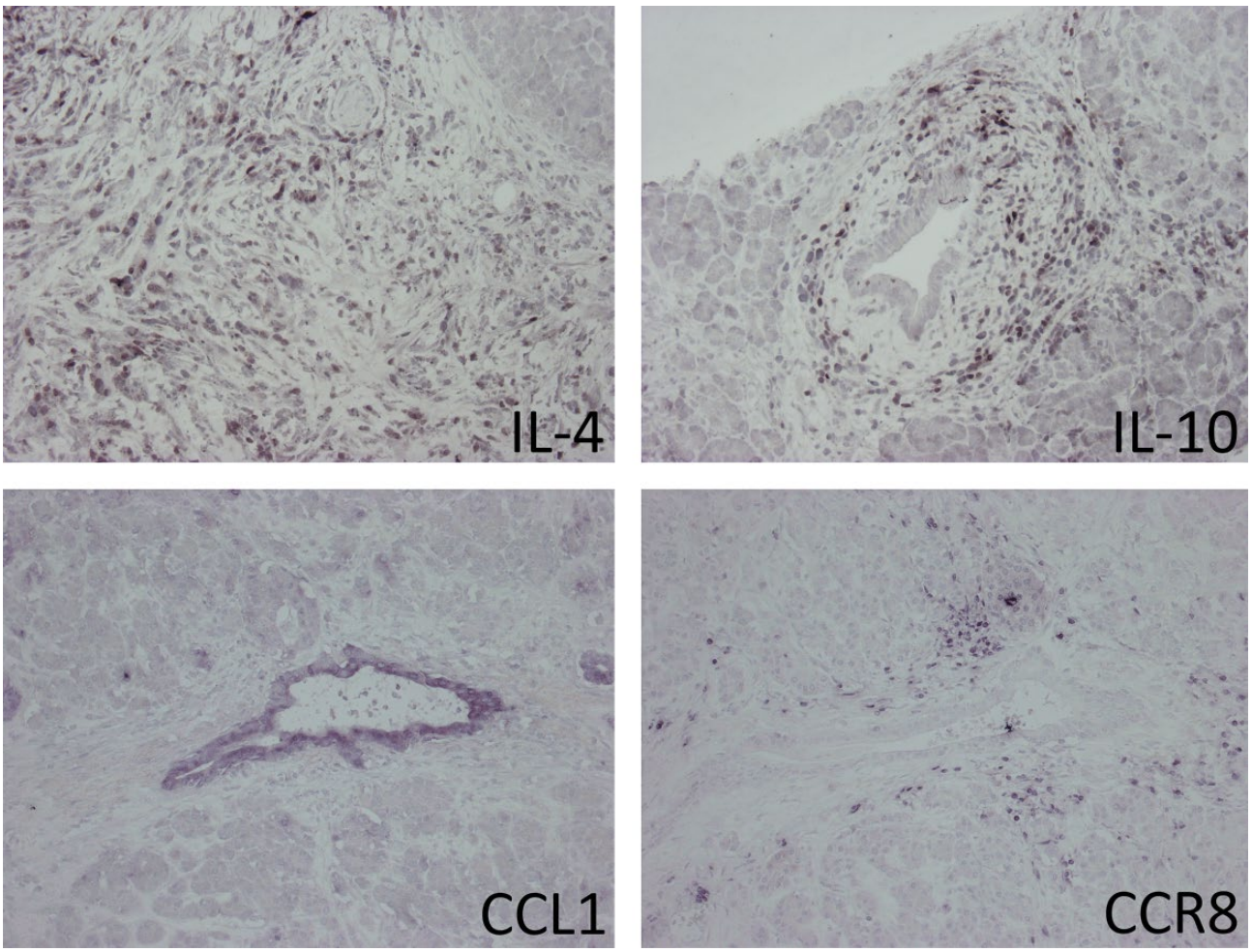


**Figure 64.1** Immunologic factors expressed in type 1 AIP (*in situ* hybridization). Lymphocytes expressing IL-4 or IL-10 are observed. The pancreatic duct positive for CCL1 is surrounded by CCR8+ lymphocytes. Sources: (Upper panels) Zen et al. 2007 [13]. Reproduced with permission of John Wiley & Sons. (Lower panels) Zen et al. 2013 [21]. Reproduced with permission of Elsevier.

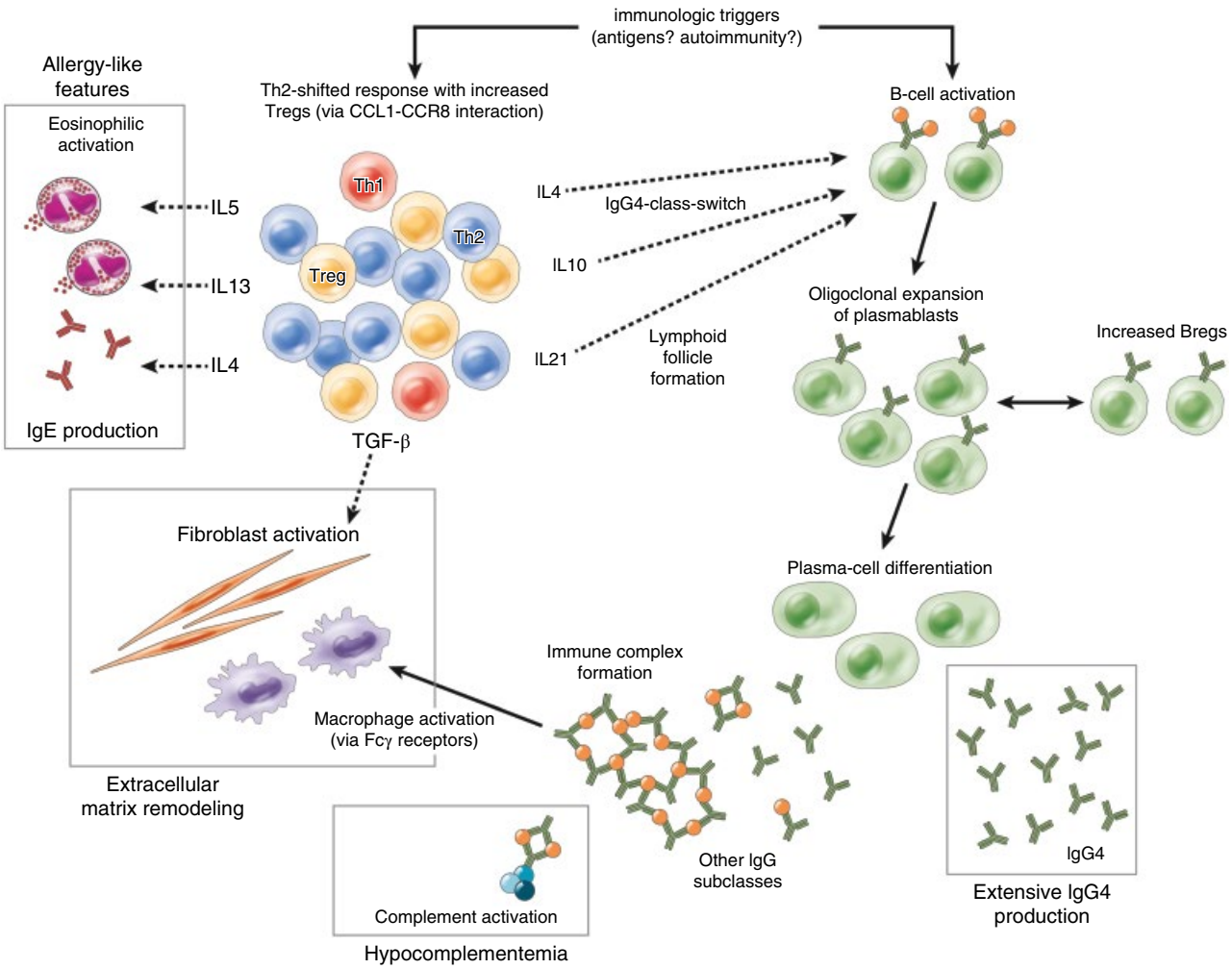


**Figure 64.2** Proposed immunologic interactions in type 1 AIP. Source: Hart et al. 2015 [1]. Reproduced with permission of Elsevier. 

interaction may create a microenvironment in which Th2 cells and Tregs are abundant, leading to the IgG4 class switch through IL-4 and IL-10. This immunologic reaction is also probably responsible for the characteristic histologic changes observed in type 1 AIP such as periductal inflammation and obliterative phlebitis.

## Expansion of B Cells and Plasmablasts

B-cell depletion therapy with anti-CD20 antibodies is effective for type 1 AIP, which highlights the crucial involvement of B cells in its pathogenesis [22]. The proportion of circulating plasmablasts increases in type 1 AIP, and decreases rapidly upon treatment. Expanded plasmablasts are mainly of the IgG4 type and oligoclonal in nature, with dominant clones varying among patients [23]. Similarly, tissue-resident and circulating IgG4-switched B cells in type 1 AIP are oligoclonal [24]. The oligoclonality of IgG4-switched B cells/plasmablasts and the diverse dominant clones across patients support the hypothesis that IgG4 is less likely to be a pathognomonic autoantibody in this condition.

## Roles of Plasma Cells

IgG4 is generally regarded as a noninflammatory antibody because of its relative inability to fix complement and its poor capacity to bind to Fc receptors [25]. This minor IgG subclass also has the unique ability to exchange a pair of heavy and light chains (the "Fab-arm exchange") [26]. This immunologic process causes IgG4 molecules to lose their antigen cross-linking ability, behave as monovalent antibodies, and become incapable of forming large immune complexes. Based on these anti-inflammatory aspects, IgG4 induction in type 1 AIP may be secondary in order to suppress inflammatory reactions, as suggested

in the study described earlier, in which patient IgG1 and IgG4 were injected into mice [11].

In a recent global proteomic study, a robust proteomic approach with phosphopeptide enrichment methods identified 4,870 proteins including 1,121 phosphoproteins in frozen bile duct tissue involved in type 1 AIP [27]. In the pathway analysis based on strongly expressed or highly phosphorylated proteins, the immunologic pathway activated most significantly in type 1 AIP than in primary sclerosing cholangitis was Fc-γ receptor-mediated phagocytosis [27]. This signal cascade occurring inside macrophages is initiated by the interaction between IgG molecules and Fc-γ receptors on the cell membrane. Since the capacity of IgG4 to bind to Fc receptors is poor [25], this signal pathway may be activated by IgG subclasses other than IgG4.

A similar discussion will also be applied to hypocomplementemia, which is observed in ~40% of patients, particularly those with renal involvement [28]. Among the three complement activation systems, the classical pathway is predominantly activated in type 1 AIP. Since IgG4 cannot efficiently activate the classical pathway, complement fixation may be activated by other IgG subclasses, particularly IgG1, which fix complements more efficiently.

To summarize, the activation and expansion of particular subsets of lymphocytes have been identified in type 1 AIP, with the T-cell–B-cell interaction also being relevant to its pathogenesis (Fig. 64.2). The roles of IgG4 molecules in this condition have not yet been elucidated in detail. Other IgG subclasses, particularly IgG1, supposedly drive the disease, while IgG4 may be secondarily induced in order to suppress extensive immune responses in this markedly inflamed condition.

## Type 2 Autoimmune Pancreatitis

The rarity of this condition as well as the lack of serologic and immunologic biomarkers has restricted our investigations on the pathogenesis of type 2 AIP. A single potential clue is that one third of patients have inflammatory bowel disease, particularly ulcerative colitis [29]. In our recent study, the immunopathologic features of type 2 AIP were compared with those of type 1 AIP and ulcerative colitis [30].

Quantitative PCR using mRNA extracted from pancreatic tissues revealed the markedly higher expression of IL-8 in type 2 AIP than in type 1 AIP. The expression of other cytokines (e.g., IFN-γ, IL-4, IL-10, and TNF-α) was similar in types 1 and 2 AIP or weaker in type 2 AIP. Immunostaining revealed that IL-8 was mainly expressed in the damaged duct epithelium, infiltrating neutrophils, and lymphocytes, with its expression being particularly strong around injured ducts (Fig. 64.3). This expression pattern of IL-8 was not observed in other forms of pancreatitis. Since IL-8 is a chemotactic factor for neutrophils, its aberrant expression in pancreatic ducts may underlie pathognomonic duct-centered, neutrophil-rich inflammation, known as granulocytic epithelial lesions (GELs), in type 2 AIP [31,32].

A similar expression pattern of IL-8 was also observed in colonic biopsies of active ulcerative colitis. IL-8 appeared to be aberrantly expressed in the crypt epithelium, particularly at sites of cryptitis and crypt abscesses [30]. The colonic epithelium was largely negative for this immunologic marker in infectious colitis, another form of neutrophil-rich enteritis. These findings indicate that IL-8 is one of the key molecules involved in the pathogenesis of type 2 AIP, and also suggest a pathogenetic link between type 2 AIP and ulcerative colitis.

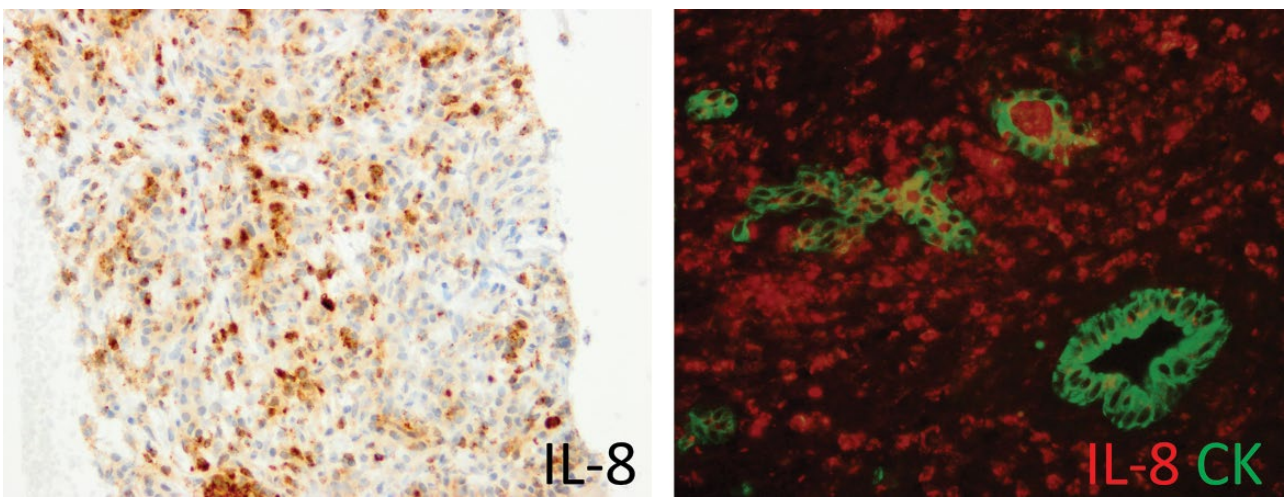


**Figure 64.3** IL-8 expression in type 2 AIP. Single immunostaining shows the extensive expression of IL-8 in pancreatic tissue. On double immunostaining, IL-8 (red) appears to be expressed in infiltrating inflammatory cells and pancreatic ducts that are also positive for cytokeratin (CK, green).

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# 65

# Histology of Autoimmune Pancreatitis

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## Introduction

Autoimmune pancreatitis (AIP) is a distinct form of chronic pancreatitis, often presenting as a pancreatic mass, and characterized by a set of unique histopathologic features, frequent elevation of immunoglobulin IgG4 in serum and tissue and swift response to steroids. Although no specific antibody has been identified, the autoimmune nature of this disease is strongly supported by the finding of clonally expanded B- and T cells [1,2]. Currently there are two histologically distinct variants of AIP recognized: type 1 AIP and type 2 AIP. Type 1 AIP is the pancreatic manifestation of IgG4-related disease. In contrast, type 2 AIP bears no histologic resemblance to IgG4-related disease [3–5].

## Type 1 Autoimmune Pancreatitis

Type 1 AIP (alternate names: lymphoplasmacytic sclerosing pancreatitis; IgG4-associated pancreatitis; AIP-lobulocentric) generally presents as an isolated tumefactive pancreatic lesion, and less commonly, as a synchronous or metachronous mass-forming lesion at other sites such as lymphadenopathy, sclerosing cholangitis, and pulmonary lesions. Grossly, the resected pancreas does not show a discrete mass, and is instead characterized by diffuse gland enlargement, invariably accompanied by fibrosis, creating a rock-hard pancreas. The pancreatic duct is narrow and multiple strictures may be seen; a dilated main pancreatic duct is distinctly unusual.

Type 1 AIP is characterized by the presence of three histologic features: (i) dense lymphoplasmacytic infiltrate, (ii) storiform fibrosis (Fig. 65.1), and (iii) obliterative phlebitis (Fig. 65.2). Notably, these histologic features are also characteristic of IgG4-related disease [6,7]. While all three features are readily observed on a pancreatectomy specimen, obliterative phlebitis is seldom seen on a needle biopsy. Storiform fibrosis, a hallmark of type 1 AIP, is characterized by a swirling pattern of fibrosis consisting of short fascicles of spindle cells (which are either fibroblasts or myofibroblasts) and interspersed collagen, intimately intermixed with the dense inflammatory infiltrate composed of lymphocytes and plasma cells. These spindle cells are usually positive for smooth muscle actin and negative for desmin. This fibroinflammatory infiltrate is most prominent in the interlobular septa of the pancreas, but could also involve the pancreatic lobules and extrapancreatic adipose tissue. These characteristic histologic features may not be seen in patients with long-standing disease, instead pancreatic calculi may be observed in the late phase of the disease.

Although the inflammatory infiltrate may surround pancreatic ducts, histologic evidence of ductal injury is seldom observed. This is in contradistinction to type 2 AIP where ductal infiltration with neutrophils and/or intraductal aggregates of neutrophils, the so-called granulocytic epithelial lesions (GEL), is a prominent and defining feature of this disease. Other histologic features that may be observed include nonobliterative phlebitis, obliterative arteritis, markedly increased number of eosinophils in the pancreatic stroma and prominent lymphoid follicles with or without germinal centers.

Immunostaining for IgG4 usually reveals abundant IgG4+ plasma cells (>10 cells/HPF in core biopsies or 50 cells/HPF in resection specimens) in most cases of type 1 AIP [8,9]. A diffuse infiltrate of IgG4+ plasma cells is the norm; in contrast, focal pockets of IgG4+ cells are

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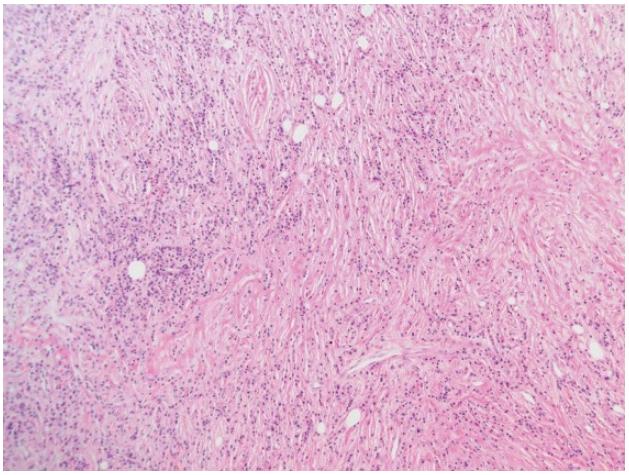

**Figure 65.1** Autoimmune pancreatitis type 1 with storiform type fibrosis.

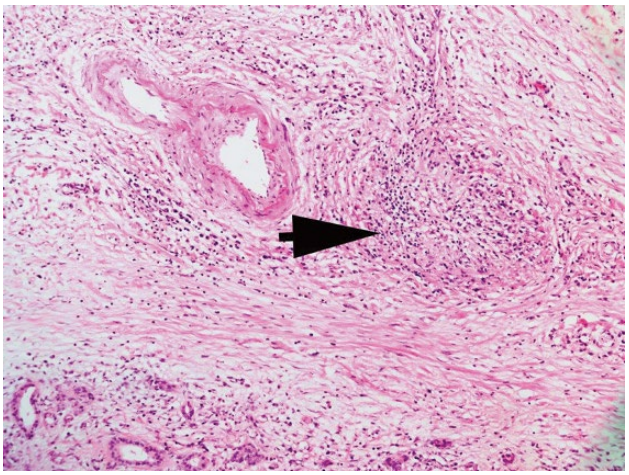

**Figure 65.2** Autoimmune pancreatitis type 1 with obliterative phlebitis. The arrow highlights an obliterated vein.

identified in other inflammatory and nonneoplastic diseases of the pancreas. It is important to emphasize that the histologic features are paramount, and neither tissue nor serum IgG4 are entirely specific for IgG4-related disease; this immunoglobulin subclass is also identified in a wide range of inflammatory and neoplastic entities including pancreatic adenocarcinoma [10]. In addition, rare examples of type 1 AIP negative for tissue and/or serum IgG4 have been reported [11,12]. An elevated IgG4 to IgG ratio of greater than 40% represents a more specific marker of type 1 AIP [8,13].

The overwhelming majority of lymphocytes are CD4+ T cells [9]. Aggregates composed of B lymphocytes are invariably identified. Macrophages are only obvious on special stains such as CD68 and CD163. The B- and T lymphocytes as well as plasma cell populations are polyclonal. It should be noted that plasma cells bearing other immunoglobulins—IgE, IgG1, IgG2, and IgG3—are also found within the inflammatory infiltrate, although IgG4-bearing plasma cells tend to dominate.

### Differential Diagnosis

The histologic features on a resected pancreas are highly characteristic and unlikely to be mistaken for other inflammatory and neoplastic diseases of the pancreas. However, the diagnosis on a core biopsy is far more challenging [14]. The closest histologic mimic is well-differentiated pancreatic adenocarcinoma, a disease that may be associated with elevated serum and/or tissue IgG4. However, careful attention to the clinical, imaging, and histologic features should assist in excluding malignancy. Nevertheless, a needle biopsy may not capture the diagnostic areas, and such nondiagnostic biopsies are not uncommon. The primary role of a fine needle aspiration biopsy is to rule out malignancy; however, in some cases the fibro-inflammatory nature of the process may also be discerned [15]. Other forms of chronic pancreatitis such as groove pancreatitis and type 2 AIP may also mimic type 1 AIP, although these diseases show few, if any, IgG4+ plasma cells [16].

One recently described variant of chronic pancreatitis, follicular pancreatitis, also deserves mention [17,18]. Although both AIP and follicular pancreatitis cases show dense lymphoplasmacytic inflammation, the latter is characterized by the presence of large and prominent lymphoid aggregates with germinal centers, typically located in the periductal region and may surround the main pancreatic duct. Notably, the main pancreatic duct is often dilated, a feature not seen in AIP. Follicular pancreatitis does not appear to represent an IgG4-related disease, and tissue IgG4+ cells are either absent or fewer than typically seen in type 1 AIP. Anecdotal evidence suggests that like type 1 AIP, follicular pancreatitis may respond to immunosuppressive therapy.

## Pancreatic Cancer and Autoimmune Pancreatitis

In recent years, a number of cases of pancreatic ductal adenocarcinoma (PDAC) arising in patients with AIP have been reported [19–24]. One study has also looked at the association between pancreatic intraepithelial lesions (PanIN) and AIP and found that the number of PanIN lesions are increased in AIP, with fewer such preneoplastic lesions in chronic pancreatitis [25]. Whether there is an increased risk of PDAC in patients with AIP remains an open question.

## Type 2 Autoimmune Pancreatitis

On macroscopic examination, type 2 AIP (alternative names: idiopathic duct-centric pancreatitis; AIP with GELs; AIP-ductal) is similar to type 1 AIP, although a discrete mass may be appreciable. Although the disease is localized to the pancreas, there appears to be a strong association between type 2 AIP and inflammatory bowel disease.

Type 2 AIP is a pancreas-centric disease characterized histologically by: (i) dense periductal lymphoplasmacytic inflammation, and (ii) periductal and/or intraluminal infiltration of small and medium-sized interlobular ducts by neutrophils resulting in variable degree of duct destruction (Fig. 65.3) [4,7,26]. Neutrophils within acini are a frequent feature, and may represent the only diagnostic clue on a biopsy. Notably absent in type 2 AIP are storiform fibrosis, obliterative phlebitis, and diffuse infiltrates of IgG4+ plasma cells, although occasional clusters of IgG4+ cells may be seen. Other notable but inconstant features include: nonobliterative phlebitis, tissue eosinophilia, lymphoid aggregates, and periductal granulomas.

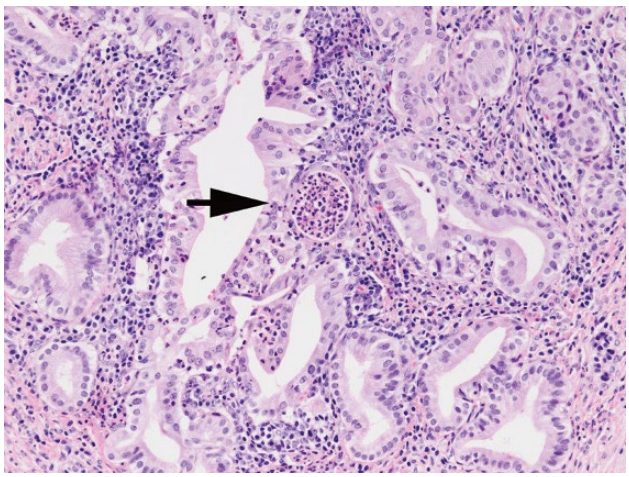

**Figure 65.3** Autoimmune pancreatitis type 2. The image shows a pancreatic duct surrounded by a lymphoplasmacytic inflammatory infiltrate. Intraductal neutrophils are identified (arrow), granulocytic epithelial lesions.

### Differential Diagnosis

Histologically, alcohol-related chronic pancreatitis may mimic type 2 AIP; however, both the presence as well as the severity of periductal inflammation and GELs is lower in alcohol-related pancreatitis. Additionally, alcohol-related pancreatitis shows characteristic histologic features, including dilated ducts containing inspissated proteinaceous material and calculi, features seldom seen in early-stage AIP. The differential diagnosis also includes groove pancreatitis, although GELs are uncommon in this disease.

## Unclassified Autoimmune Pancreatitis

In spite of general agreement regarding criteria pertaining to the histopathologic diagnosis of type 1 and type 2 AIP, a few cases such as examples of type 1 AIP with GELs defy classification, and these biopsies are best regarded as "unclassified AIP."

## Conclusions

The two forms of AIP are clinically, histologically, and immunologically distinctive (Table 65.1). The histologic diagnosis of AIP on a core biopsy relies on the coexistence of supportive clinical, laboratory, radiologic findings. In the absence of characteristic histologic features, the presence of elevated numbers of IgG4+ plasma cells is a relatively nonspecific feature and may be seen adjacent to a PDAC.

**Table 65.1** Histopathologic differences between type 1 and type 2 autoimmune pancreatitis

| Features | Type 1 AIP | Type 2 AIP |
|---|---|---|
| Storiform fibrosis in interlobular stroma | present | absent |
| Periductal lymphoplasmacytic infiltrate | usually mild | usually moderate to marked |
| Overt duct injury associated with infiltration by neutrophils (GEL) | usually absent | present |
| Lobular infiltration by neutrophils | usually absent | frequently present |
| Eosinophils in the stroma | common | rare |
| Lymphoid follicles in the stroma | can be present | rare |
| Phlebitis | present, usually obliterative in nature | uncommon; if present, nonobliterative in nature |
| Tissue IgG4 count | elevated, biopsy >10 per HPF, resection >50 per HPF | generally not elevated |
| IgG4/IgG ratio | >40% | <40% |

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# 66

# Clinical Manifestation of Type 1 Autoimmune Pancreatitis

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## Type 1 and Type 2 Autoimmune Pancreatitis

Professor Henri Sarles of Marseilles was first to point out that in some cases, autoimmunity may be involved in the pathogenesis of chronic pancreatitis [1]. In 1961, he investigated the pathology of 10 cases of noncalcifying chronic pancreatitis with poor prognosis showing unique clinical features such as fever, jaundice, abdominal pain, and emaciation. Pathologic findings, including the predominant appearance of inflammatory cells and severe fibrosis in the pancreas, the elevation of serum gammaglobulin, and the ineffectiveness of antibiotics, suggested the possible involvement of "self-immunization" in the pathogenesis.

The disease concept of autoimmune pancreatitis (AIP) was established in a case report by Yoshida et al. in 1995 [2]. The case was a 68-year-old female who presented with painless jaundice. After examining the patient in detail and comparing their findings with similar cases in the literature, Yoshida et al. proposed a new disease concept, which they coined AIP, characterized by the following: unique clinical finding of frequent onset of painless jaundice, the morphologic finding of diffuse enlargement of the pancreas with pancreatic duct narrowing, the serologic findings of elevated serum gamma-globulin levels and the appearance of autoantibodies, the histologic findings of abundant lymphocytes and severe fibrosis, the presence of other complicating diseases, such as other autoimmune diseases, and the therapeutic effectiveness of steroids. These clinical features coincide with those of the subsequently classified type 1 AIP. In 1991, Kawaguchi et al. had already reported a unique type of pancreatitis with a peculiar histology called "lymphoplasmacytic sclerosing pancreatitis (LPSP)," which is characterized by massive infiltration of lymphocytes with fibrosis and plasma cells centered around the pancreatic ducts, together with obliterative phlebitis [3]. LPSP is considered to be the current histopathologic definition of type 1 AIP. In 2001, Hamano et al. first reported the specific elevation of serum IgG4, the serologic feature of AIP [4], and subsequently confirmed the prominent infiltration of IgG4+ plasma cells in the affected tissues and organs [5]. These findings supported the view that most clinical features of AIP reported from Japan since the proposal of the disease concept by Yoshida et al. correspond to those of the later defined type 1 AIP [6].

Conversely, based on a pathologic re-evaluation of pancreatic tissues resected for suspected pancreatic cancer in Western countries, another type of pancreatitis involving immunologic mechanisms was proposed. In 2003, Notohara et al. reported the presence of inflammatory changes characterized by an infiltration of numerous granulocytes, chiefly around the inter- and intralobular ducts, with occasional destruction of duct epithelium and accumulation of granulocytes in the duct lumen in these pancreatic specimens. This finding subsequently became known as "idiopathic duct-centric pancreatitis (IDCP)" [7]. IDCP is considered to be a pathologic counterpart of "nonalcoholic duct-destructive chronic pancreatitis (NADCP)" previously reported by Ectors et al. [8]. Zamboni et al. also noticed an infiltration of granulocytes around ducts with occasional disruption of duct epithelium in a histologic examination of tumor-forming chronic pancreatitis, and pathologically defined this as "granulocytic epithelial lesions (GEL)" [9]. The pancreatitis characterized by GEL is understood to be a kind of AIP due to its histologic features involving the massive infiltration of inflammatory cells and fibrosis around

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ducts, as well as the occasional association with inflammatory bowel disease (IBD). However, this tends to develop in younger patients with acute episodes of pancreatitis, regardless of sex, and with no specific serum markers [9].

As described earlier, while the AIP proposed in Japan shows various clinical features and has a histologic definition of "LPSP," AIP proposed in Western countries is pathologically defined as "IDCP/GEL" and shows clearly different clinical features [10]. The Mayo Clinic assigned the nomenclature of "type 1 AIP" to the former and "type 2" to the latter [11]. The classification of AIP was discussed as a topic at a satellite symposium of the Japan Pancreas Society and the American Pancreatic Association Joint Meeting held in Honolulu in 2009, and an international consensus referred to as the "Honolulu Consensus" was reached. The "Honolulu Consensus" approved the classification of AIP into two subtypes, type 1 and type 2, pathologically defined as LPSP and IDCP/GEL, respectively, and proposed additional investigation into the clinical and pathologic features of these subtypes in order to further clarify their identities [12].

## International Consensus Diagnostic Criteria (ICDC) for Autoimmune Pancreatitis

With regard to the diagnosis of AIP, various criteria have been proposed from many countries, with the Japanese criteria in 2002 being the first [13]. These include the following: Japanese clinical diagnostic criteria (2002 [13], 2006 [14]); Korean diagnostic criteria (2006 [15], 2007 [16]); the HISORt criteria of the Mayo Clinic (2006 [17], 2009 [18]); Asian criteria (2008 [19]); Italian criteria (2006 [10], 2009 [20]); and Spanish criteria (2005 [21]). Since all of these had been devised before the Honolulu Consensus, different types of AIP were mixed in the cases diagnosed using these criteria.

The international consensus diagnostic criteria of AIP (ICDC) proposed in 2011 are at present the sole criteria for classifying AIP into type 1 and type 2 [12] and can diagnose both types separately [22]. The ICDC are common global criteria that were compiled by world experts after discussion at a consensus symposium during the 14th meeting of the International Association of Pancreatology (IAP) held in Fukuoka, Japan in 2010.

Using the ICDC, AIP can be diagnosed by a combination of the following five cardinal features: (i) parenchymal imaging (P); (ii) ductal imaging (D); (iii) serology (S); (iv) other organ involvement (OOI); and (v) histology of the pancreas (H), with response to steroids (Rt) as an optional criterion. In order to provide a degree of flexibility in the diagnostic process, respective features are categorized as level 1 and 2 findings depending on their diagnostic reliability (Table 66.1) [22]. In addition, by employing a combination-based framework, the ICDC enable the diagnosis of AIP in any situation and in any country, even if the practice patterns and priority of diagnostic modalities are different.

The strategy of the ICDC is to reduce the number of other cardinal features necessary for the diagnosis of typical cases showing diffuse enlargement of the pancreas, whereas for cases with focal enlargement or atypical appearance, a stricter approach using a combination of more specific findings is employed for differentiation from pancreatic cancer. In addition to pancreatic imaging, the following are used to diagnose type 1 AIP: (i) elevation of serum IgG4 for serology; (ii) histologic findings of extrapancreatic organs, imaging of bile duct, retroperitoneal fibrosis (RF), physical evidence of sialadenitis, and radiologic finding of renal involvement for other organ involvement; and (iii) LPSP for histology of the pancreas. To diagnose type 2 AIP, IBD was adopted for other organ involvement and IDCP/GEL for histology of the pancreas (Table 66.2). A definitive or probable diagnosis is given for both types of AIP depending on the number of findings and their reliability. The diagnosis of not otherwise specified (NOS) is made for cases that satisfy the imaging findings but lack other cardinal features and show response to steroids (Table 66.3). Although the ICDC seem somewhat complicated, they were reported to show superior sensitivity, specificity, and accuracy compared with any other diagnostic criteria for AIP proposed in the past [23].

## Clinical Features of Type 1 Autoimmune Pancreatitis

To strictly separate type 1 AIP cases and clarify their specific clinical features, the selection of cases with histologically confirmed LPSP or cases diagnosed with type 1 by the ICDC [22] or the ICDC-based criteria [24] is required. Here we summarize the clinical features of type 1 AIP that satisfy the above conditions from eight recent studies which had a relatively large number of patients (Table 66.4) [25–32].

### Patient Profiles and Symptoms

Type 1 AIP shows a tendency to develop in elderly men with painless jaundice [25–32]. The average age range at onset was 60.5–66.3 years, which is clearly higher than that of type 2 AIP (34–52.5 years). Roughly more than 70% (66.7–91.9%) of the type 1 AIP cases were male, which

**Table 66.1** Level 1 and level 2 criteria for type 1 AIP.

| | Criterion | Level 1 | Level 2 |
|---|---|---|---|
| P | Parenchymal imaging | Typical: Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement) | Indeterminate (including atypical[†]): Segmental/focal enlargement with delayed enhancement |
| D | Ductal imaging (ERP) | Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation | Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm) |
| S | Serology | IgG4, >2 × upper limit of normal value | IgG4, 1–2 × upper limit of normal value |
| OOI | Other organ involvement | a or b<br>a) Histology of extrapancreatic organs (any 3 of the following)<br>1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration<br>2) Storiform fibrosis<br>3) Obliterative phlebitis<br>4) Abundant (>10 cells/HPF) IgG4+ cells<br>b) Typical radiologic evidence (at least 1 of the following)<br>1) Segmental/multiple proximal (hilar/intrahepatic) or proximal and distal bile duct stricture<br>2) Retroperitoneal fibrosis | a or b<br>a) Histology of extrapancreatic organs including endoscopic biopsies of bile duct[‡] (Both of the following)<br>1) Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration<br>2) Abundant (>10 cells / HPF) IgG4-positive cells<br>b) Physical or radiologic evidence (at least 1 of the following)<br>1) Symmetrically enlarged salivary/lachrymal glands<br>2) Radiologic evidence of renal involvement described in association with AIP |
| H | Histology of the pancreas | LPSP (core biopsy/resection)<br>At least 3 of the following:<br>1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration<br>2) Obliterative phlebitis<br>3) Storiform fibrosis<br>4) Abundant (>10 cells/HPF) IgG4+ cells | LPSP (core biopsy)<br>Any 2 of the following:<br>1) Periductal lymphoplasmacytic infiltrate without granulocytic infiltration<br>2) Obliterative phlebitis<br>3) Storiform fibrosis<br>4) Abundant (>10 cells/HPF) IgG4+ cells |
| Response to steroid (Rt)* | Diagnostic steroid trial<br>Rapid (≦2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations | | |

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.
† Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative.
‡ Endoscopic biopsy of duodenal papilla is a useful adjunctive method because ampulla often is involved pathologically in AIP.
*Source:* Shimosegawa et al. 2011 [22]. Reproduced with permission.

appeared slightly higher than the ratio for type 2 (54.9–73.7%); however, this difference was not significant.

The most frequent initial symptom of type 1 AIP was painless jaundice, which occurred more frequently in type 1 (60–90%) than in type 2 (13–68.4%) AIP patients [25–32]. Meanwhile, abdominal pain showed a tendency to occur more frequently in type 2 (31.6–76.7%) than in type 1 AIP patients (10–58.3%). Acute pancreatitis (AP) was a rare initial symptom in type 1 AIP patients, whereas about 34–40% of type 2 AIP patients presented with AP. Diabetes mellitus (DM), mostly type 2 DM, was a complication in more than half (59.5–68%) of the type 1 AIP patients, which was considerably higher compared with the type 2 patients (14–26.7%) [28–31]. Among the patients with DM, 34.3% had DM before the onset of AIP, 56.9% developed DM concurrently, and only 8.8% developed DM after steroid treatment [33]. Mild to moderate exocrine dysfunction was frequently observed [34,35], and therefore caution should be exercised because 12–50% of type 1 AIP patients may experience weight loss [27,28,31].

## Imaging Findings

Characteristic imaging findings of AIP are diffuse or localized enlargement of the pancreas and narrowing of the main pancreatic duct (MPD). It is impossible to

**Table 66.2** Level 1 and level 2 criteria for type 2 AIP.

| | Criterion | Level 1 | Level 2 |
|---|---|---|---|
| P | Parenchymal imaging | Typical: Diffuse enlargement with delayed enhancement<br>(sometimes associated with rim-like enhancement) | Indeterminate (including atypical†):<br>Segmental/focal enlargement with delayed enhancement |
| D | Ductal imaging (ERP) | Long (>1/3 length of the main pancreatic duct) or multiple strictures without marked upstream dilatation | Segmental/focal narrowing without marked upstream dilatation (duct size, <5 mm) |
| OOI | Other organ involvement | | Clinically diagnosed inflammatory bowel disease |
| H | Histology of the pancreas (core biopsy/resection) | IDCP:<br>Both of the following:<br>1) Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation<br>2) Absent or scant (0–10 cells/HPF) IgG4+ cells | Both of the following:<br>1) Granulocytic and lymphoplasmacytic acinar infiltrate<br>2) Absent or scant (0–10 cells/HPF) IgG4+ cells |
| Response to steroid (Rt)* | | Diagnostic steroid trial<br>Rapid (≦2 wk) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations | |

* Diagnostic steroid trial should be conducted carefully by pancreatologists with caveats only after negative workup for cancer including endoscopic ultrasound-guided fine needle aspiration.
† Atypical: Some AIP cases may show low-density mass, pancreatic ductal dilatation, or distal atrophy. Such atypical imaging findings in patients with obstructive jaundice and/or pancreatic mass are highly suggestive of pancreatic cancer. Such patients should be managed as pancreatic cancer unless there is strong collateral evidence for AIP, and a thorough workup for cancer is negative.
*Source:* Shimosegawa et al. 2011 [22]. Reproduced with permission.

**Table 66.3** Diagnosis of definitive and probable type 1 and type 2 AIP, and AIP-NOS.

| Diagnosis | Primary basis for diagnosis | Imaging evidence | Collateral evidence |
|---|---|---|---|
| *Definitive type 1 AIP* | Histology | Typical/Indeterminate | Histologically confirmed LPSP (level 1 H) |
| | Imaging | Typical/Indeterminate | Any non-D level 1/2<br>Two or more from level 1 (+ level 2 D*) |
| | Response to steroid | Indeterminate | Level 1 S/OOI + Rt or Level 1 D + Level 2 S/OOI/H + Rt |
| *Probable type 1 AIP* | Histology | Indeterminate | Level 2 S/OOI/H + Rt |
| *Definitive type 2 AIP* | | Typical/Indeterminate | Histologically confirmed IDCP (level 1 H) or<br>Clinical IBD + level 2 H + Rt |
| *Probable type 2 AIP* | | Typical/Indeterminate | Level 2H/clinical IBD + Rt |
| *AIP-NOS* | | Typical/Indeterminate | D 1/2 + Rt (case with only D 1/2) |

* Level 2 D is counted as level 1 in this setting.
*Source:* Shimosegawa et al. 2011 [22]. Reproduced with permission.

differentiate type 1 from type 2 AIP solely by imaging findings [25–32]. Typical cases with a diffuse type show a prominently swollen hypoechoic pancreas referred to as a "sausage-like appearance" on ultrasound [36,37] (Fig. 66.1a). Delayed enhancement of the pancreas is a finding characteristic of AIP on dynamic computed tomography (CT) (Fig. 66.1b,c) and magnetic resonance imaging. In addition, some patients show a low-density rim-like structure referred to as a "capsule-like rim" that may reflect fibroinflammatory changes extending outside the pancreas [38] (Fig. 66.1d,e). The prevalence of a "capsule-like rim" is reportedly from 25–48.6% [27,28]. Since this finding is very specific to AIP, it is useful to differentiate AIP from pancreatic cancer [39]. A Korean report suggested a significantly higher rate of "capsule-like rim" in type 1 AIP compared with type 2 [28], whereas no difference was found in a report from North America [27].

MPD narrowing is another important finding of AIP, and the assessment should be done using endoscopic retrograde cholangiopancreatography imaging (ERCP) [36]

**Table 66.4** Comparison of clinical features of Type 1 and Type 2 AIP in eight recent reports.

| Diagnosis | | Type 1 AIP (LPSP) | Type 2 AIP (IDCP/GEL) |
|---|---|---|---|
| Mean age (y) | | 60.5–66.3 | 34–52.5 |
| Male ratio (%) | | 66.7–91.9 | 54.9–73.3 |
| Initial symptom | Jaundice (%) | 60–90 | 13–68.4 |
| | Abdominal pain (%) | 10–58.3 | 31.6–76.7 |
| | Acute pancreatitis (%) | 2.7–5 | 34–40 |
| Imaging | Diffuse swelling (%) | 15–75 | 16–73.3 |
| | Focal swelling (%) | 17.7–70 | 26.7–85 |
| Serology | Elevation of serumlgG4 (%) | 63–86.4 | 0–23 |
| | Elevation of serumlgG (%) | 54.1–56.4 | 0 |
| | ANA (%) | 18.2–33.5 | 0 |
| | RA (%) | 17.2–35 | 0 |
| Other organ involvement | Sclerosing cholangitis (%) | 10.3–42.9 | 0–23 |
| | Sialadenitis (%) | 8.1–22.2 | 0 |
| | Retroperitoneal fibrosis (%) | 1.6–11 | 0 |
| | Renal involvement (%) | 3.2–13.5 | 0–3 |
| | Lung involvement (%) | 1.6–4.1 | 0 |
| | Lymphadenopathy (%) | 8–26 | 0 |
| | Ulcerative colitis (%) | 1–3.2 | 15.7–33.3 |
| | Crohn's disease (%) | 0.2–1.6 | 2–3.9 |
| Steroid treatment | Response rate (%) | 92–100 | 100 |
| | Relapse rate (%) | 22.2–41.2 | 0–5 |

The data are the lowest and highest values shown in the 8 studies [Refs. 24–31].

(Fig. 66.2a). MPD narrowing with an irregular duct wall is characteristic of AIP, and branch ducts are often visible, even at the narrowed MPD [39]. Mild to moderate dilatation of ducts upstream of the narrowing is an important finding for differentiation from pancreatic cancer, because pancreatic cancer usually shows marked dilatation in the upstream section of the duct [39] (Fig. 66.2b,c). Magnetic resonance cholangiopancreatography (MRCP) is considered inadequate for the precise evaluation of narrowed ducts in AIP because of the insufficient resolution [40]. [$^{18}$F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) is useful for judging the response to steroids. FDG accumulates densely in the affected pancreatic and extrapancreatic lesions in AIP, but promptly improves in response to steroids [41] (Fig. 66.2d,e).

Enlargement of the pancreas and narrowing of MPD are findings seen in almost all cases of AIP, and they often provide a clue for suspected AIP. Although no specific tendencies have been observed in the proportion of diffuse and localized types between type 1 and 2 AIP (Table 66.4), special care should be taken regarding the differentiation of focal type AIP from pancreatic cancer. According to a report from Japan [32], enlarged pancreas can be observed in 92.9% of AIP cases, and the proportion of diffuse (more than two-thirds), segmental (one third to two-thirds), and focal (less than one third) involvement was 52.6%, 27.6%, and 17.7%, respectively, whereas atypical imaging such as a tumor-like appearance was only seen in 0.5%. Similarly, MPD narrowing was observed in 89.6% of AIP patients, and the proportion of diffuse narrowing (more than two-thirds the entire length of the MPD), segmental narrowing (one third to two-thirds), and focal narrowing (less than one third) was 44.5%, 31.4%, and 17.3%, respectively, with multiple narrowing seen in 3.7%.

## Blood Tests

Serum IgG4 is a biomarker with high specificity to type 1 AIP and is elevated in 63–86.4% of all type 1 AIP patients [25–32]. It is far superior to IgG and gamma-globulin in terms of sensitivity and specificity, and therefore, the ICDC adopted IgG4 as the lone serum marker of type 1

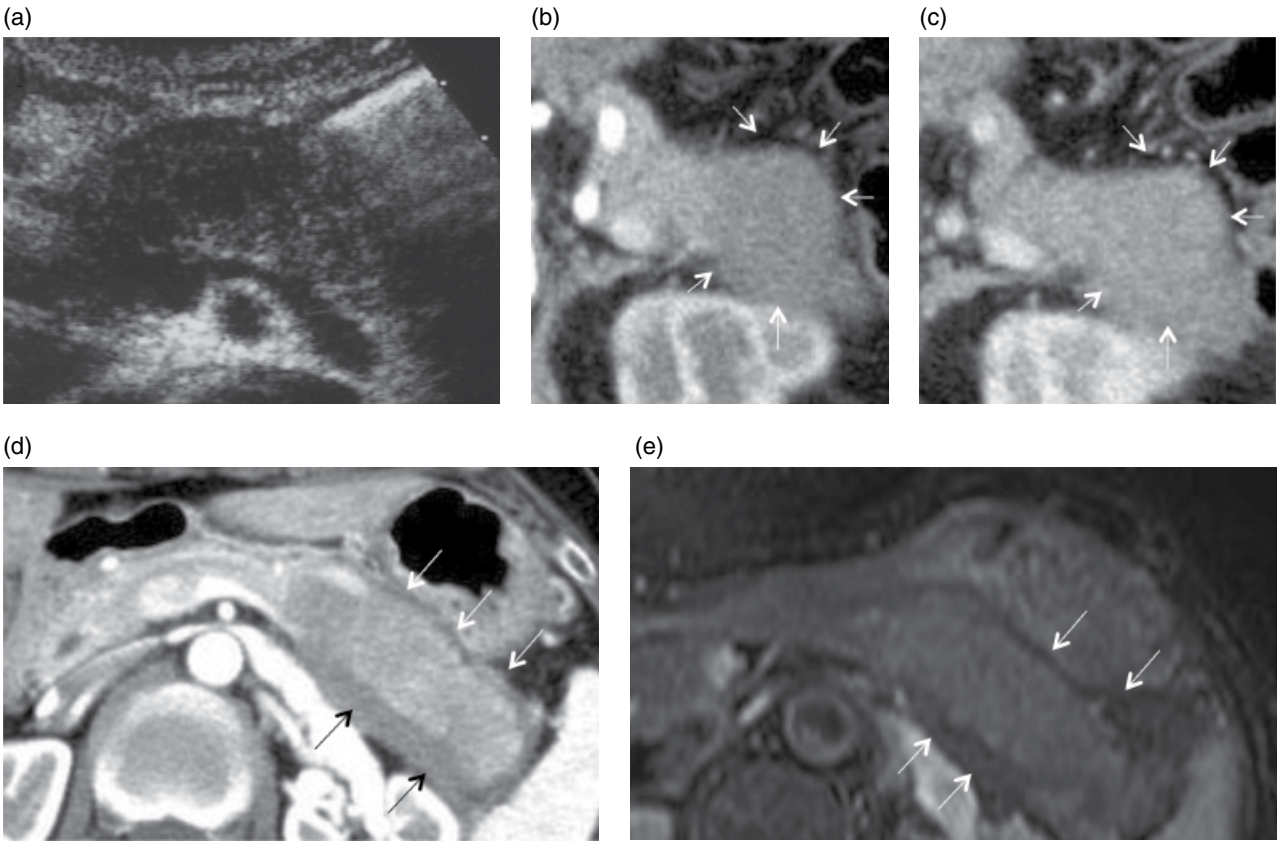


**Figure 66.1** Characteristic parenchymal imaging of type 1 AIP. (a) Diffuse enlargement of the pancreas called "sausage-like appearance" on US. (b,c) Delayed enhancement of the pancreatic lesion on the dynamic CT (arrows). The low-density area in the pancreatic tail (b) is enhanced in the late phase (c). (d) "Capsule-like rim" is shown in the body-tail region of the swollen pancreas (arrows) on the contrast-enhanced CT. (e) MRI T2WI imaging shows the "capsule-like rim" (arrows).

AIP [22]. Its elevation in blood is caused by an overproduction of polyclonal IgG4, and 135 mg/dL is usually employed as the cut-off value. However, since it is reported that up to 10% of pancreatic cancer patients may also show a value higher than the normal upper limit [42], the level 1 finding for serology in the ICDC set the cut-off at more than double the normal upper limit. The serum IgG4 level is considered to reflect disease activity, but the average value differs. For example, average IgG4 levels of 533 mg/dL and 241 mg/dL were reported in Japan [32] and Korea [28], respectively. The serum IgG level increases in 54.1–56.4% of type 1 AIP patients [25–32], and the prevalence of antinuclear antibody and rheumatoid factor are 18.2–33.5% and 17.2–35%, respectively [25–32]. In addition, there are some reports involving cases with excessive eosinophilia [43] and low serum complement levels with formation of IgG1 immune complex [44].

Other autoantibodies that may appear in AIP patients include anticarbonic anhydrase II antibody [45], antilactoferrin antibody [45], antipancreatic secretory trypsin inhibitor antibody [46], antiamylase α-2A antibody [47], and autoantibodies suspected of cross-activity with plasminogen-binding protein of *H. pylori* and ubiquitin-protein ligase E3 component n-recognin 2 [48], although their practical significance, usefulness, and specificity to AIP subtypes have not yet been clarified.

## Pathologic Findings of the Pancreas

LPSP is the histopathologic definition of type 1 AIP [11,12]. It consists of the following four items: (i) prominent infiltration of lymphocytes and plasma cells without granulocytes in the parenchyma and around ducts; (ii) storiform, that is, whirl-like fibrosis; (iii) obliterative phlebitis; and (iv) appearance of more than 10 IgG4+ plasma cells per a high-power field [22]) (Fig. 66.3a–d). In contrast to IDCP/GEL, which is characterized by a disruption of duct epithelium (Fig. 66.3e,f), the preservation of ductal lining is a distinct histologic feature of LPSP. The histologic diagnosis of type 1 AIP in the ICDC is categorized as level 1 when three or more of the four features are found, and categorized as level 2 when only two of four items are observed. Some rare cases

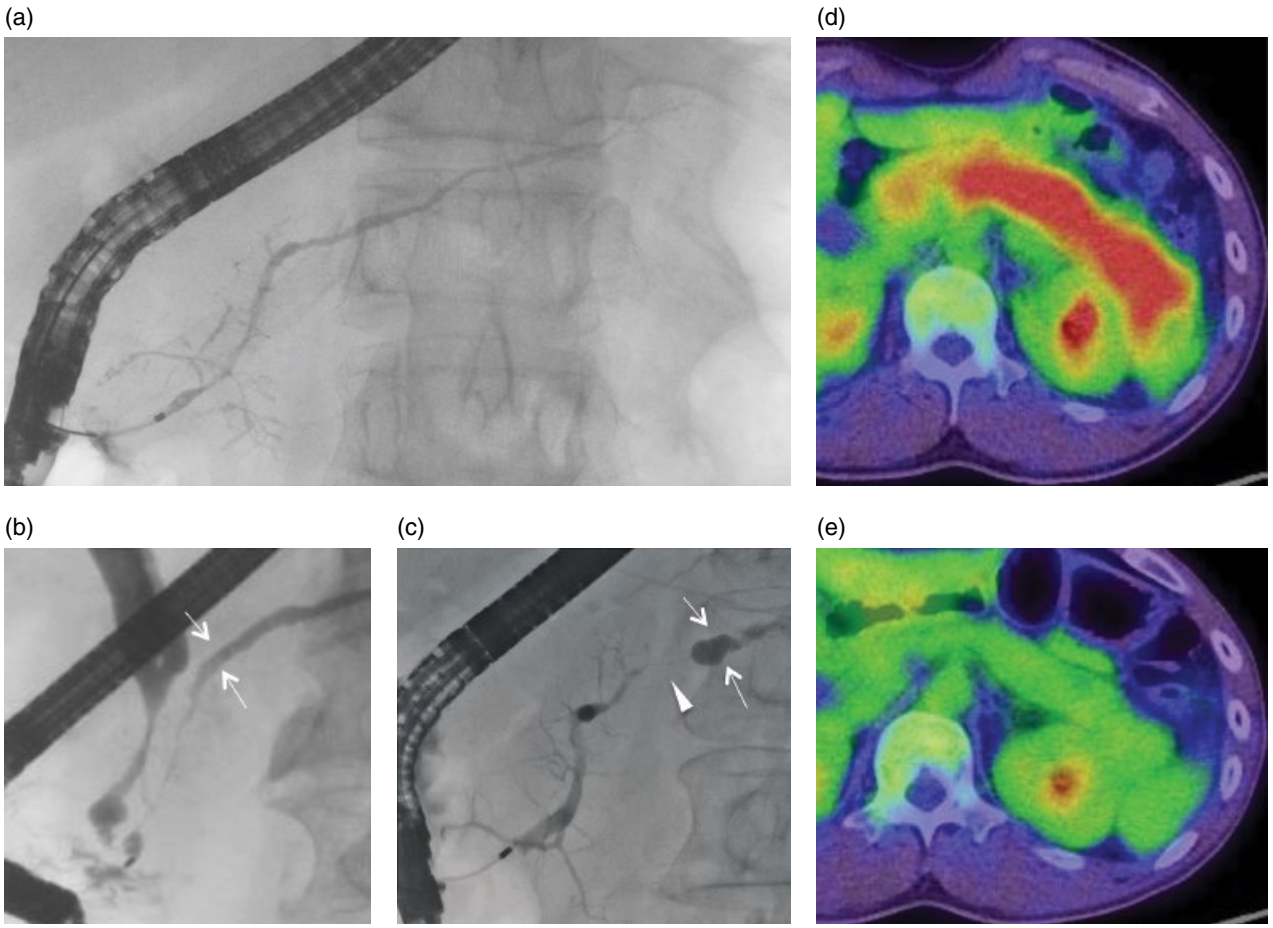


**Figure 66.2** (a) Characteristic ductal imaging of type 1 AIP on the ERCP. The main pancreatic duct (MPD) shows diffuse narrowing with irregular duct walls and visible branch ducts. (b) Focal narrowing of the MPD in the pancreatic head without association of remarkable upstream dilatation (arrows) in type 1 AIP. Intrapancreatic bile duct also shows severe narrowing. (c) Marked MPD dilatation (arrows) upstream of severe stenosis (arrowhead) by pancreatic cancer. (d,e) [$^{18}$F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging of the pancreas in a type 1 AIP patient. The pancreas showed diffuse and strong accumulation of FDG in the body and tail regions (d), which disappeared in response to steroid treatment (e).

showing LPSP with abundant eosinophils have been reported [49]. The use of resected or core biopsy specimens of the pancreas is the principle approach for pathologic diagnosis, because an adequate amount of pancreatic tissue is necessary for the correct diagnosis of type 1 and type 2 AIP [22].

## Extrapancreatic Lesions

Various extrapancreatic lesions appear synchronously and metachronously in about 45–80% of type 1 AIP patients [25–32]. Other than bile duct stenosis, these lesions are specific to type 1 AIP and are rarely seen in type 2. On the other hand, IBD such as ulcerative colitis and Crohn's disease are frequent complications, occurring at a rate of 15.7–33.3% in type 2 AIP, but at an extremely low rate in type 1 AIP (Table 66.4) [25–32].

The pathologic findings of extrapancreatic lesions are remarkably similar to those of the pancreas, which is the reason why type 1 AIP is regarded as the pancreatic manifestation of systemic IgG4-related disease [50]. Sclerosing cholangitis is the extrapancreatic lesion most frequently seen in type 1 AIP patients (10.3–42.9%) [25–32]. It appears as bile duct narrowing at the hepatic hilum and/or narrowing of the intrahepatic or intrapancreatic bile duct (Fig. 66.4a,b); however, proximal bile duct involvement is regarded as a more specific finding for sclerosing cholangitis in type 1 AIP [22,51–53]. Due to its prompt response to steroids and differences in imaging findings, sclerosing cholangitis occurring in type 1 AIP is a different pathologic condition from primary sclerosing cholangitis [51–53]. The second most frequent extrapancreatic lesion is sialadenitis, which appears in 8.1–22.2% of patients [25–32]. In typical cases, the bilateral lachrymal glands of the upper eyelids

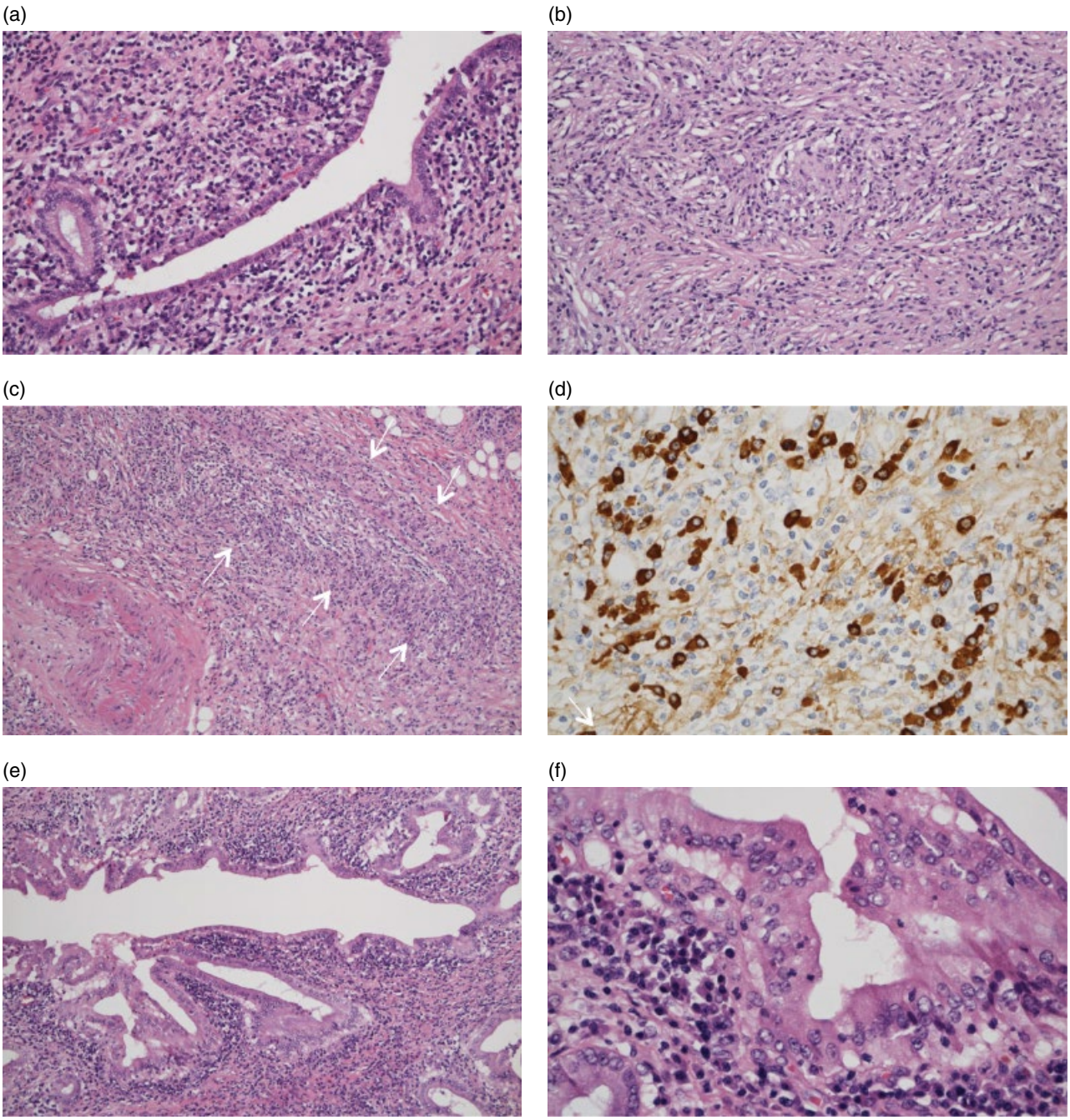


**Figure 66.3** LPSP (a–d) and IDCP/GEL (e,f). These images were kindly provided by Kenji Notohara (Department of Pathology, Kurashiki Central Hospital). (a) Numerous lymphocytes and plasma cells are seen around a duct with association of thick fibrosis. The ductal epithelium is preserved nearly intact. (b) Storiform fibrosis. (c) Obliterative phlebitis (arrows). (d) Immunostaining for IgG4 shows abundant IgG4+ plasma cells in the pancreas of type 1 AIP. (e) Massive infiltration of inflammatory cells with granulocytes around pancreatic ducts in the pancreas of type 2 AIP. (f) Granulocytes infiltrate into the duct epithelium and destroy the epithelial structure.

(Fig. 66.5a,b) and/or bilateral submandibular glands (Fig. 66.5c,d) swell symmetrically, becoming palpable, elastic hard, smooth surface nodules or tumors without tenderness that may correspond to Mikulicz disease [54] or Küttner tumor [55], and are considered to be clinical and pathologic entities distinct from Sjögren syndrome because the former involves predominantly submandibular glands, presents with milder dry mouth symptoms, shows negative SS-A/SS-B antibodies and infiltration of numerous IgG4-positive plasma cells, and shows good response to steroids. Retroperitoneal fibrosis (RF) occurs in about 10% (1.6–11%) of type 1 AIP patients and is

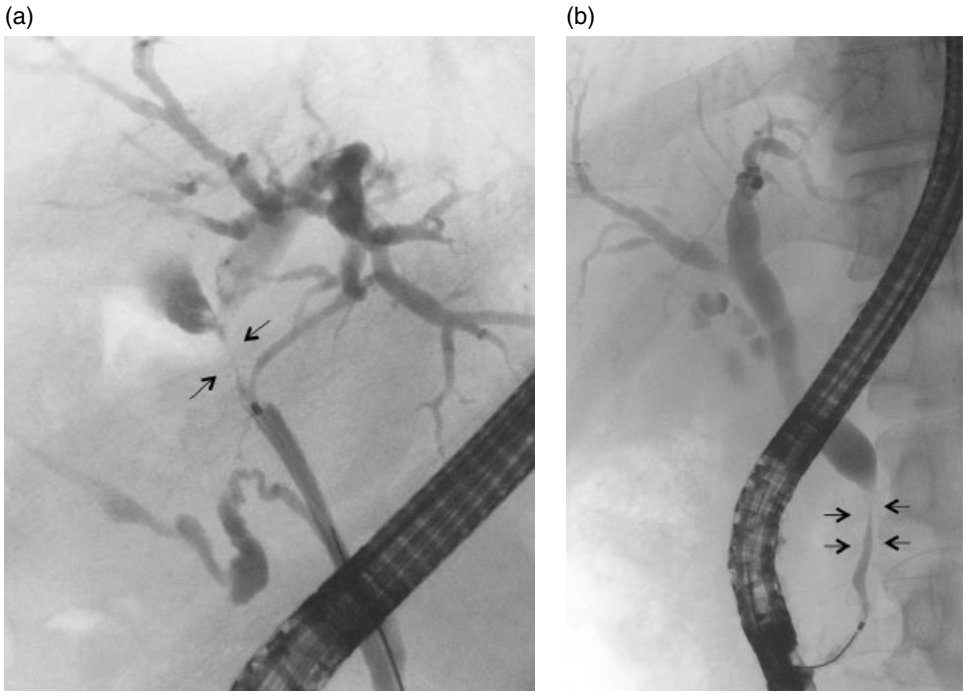


**Figure 66.4** Sclerosing cholangitis in type 1 AIP. (a) Severe stenosis (arrows) of the bile duct at the hepatic hilum. (b) Stricture of the intrapancreatic bile duct (arrows).

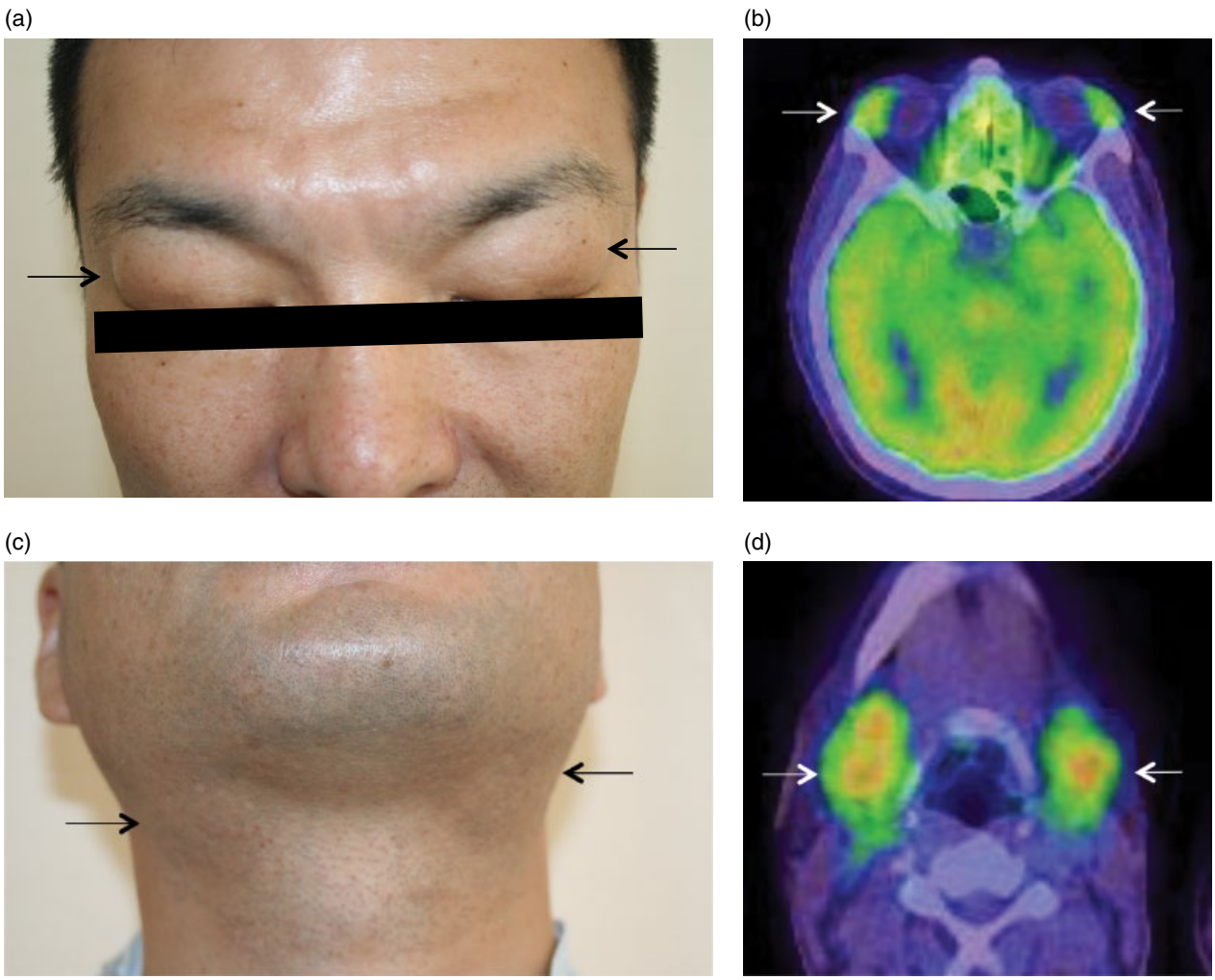


**Figure 66.5** Lachrymo-sialadenitis in type 1 AIP. (a) Bilateral lachrymal glands swell symmetrically (arrows). (b) FDG accumulation in the swollen lachrymal glands (arrows). (c) Bilateral submandibular glands swell symmetrically (arrows). (d) FDG accumulation in the swollen submandibular glands (arrows).

observed as a soft tissue band or mass in front of or around the abdominal aorta [5] (Fig. 66.6a). Renal involvement is seen as various imaging findings on contrast-enhanced CT such as tumor/nodule-like appearances and multiple perfusion defects in the renal cortex [56,57] (Fig. 66.6b,c). These findings are observed reportedly in 3.2–13.5% of AIP patients [25–32].

Other pathologic conditions suspected as extrapancreatic lesions of type 1 AIP include the following: inflammatory aortic aneurysm [58]; tubulointerstitial nephritis [59–61], swelling of the papilla of Vater [62–66] (Fig. 66.6d), hilar lymphadenopathy [67], chronic thyroiditis [68], inflammatory pseudotumors [69,70], prostatitis [71,72], interstitial lung disease [73] (Fig. 66.6e), hypophysitis [70] (Fig. 66.6f,g), autoimmune thrombocytopenia [74], hepatopathy [75], autoimmune neurosensory hearing loss [76], uveitis [77], and Schönlein-Henoch purpura [76].

## Response to Steroids and Relapse

The standard therapy for type 1 AIP is oral administration of prednisolone, which is effective in more than 92% of patients and shows nearly a 100% response rate [25–32] (Table 66.4). Response can be seen usually within 2 weeks after the initiation of steroid treatment, and improvements in swollen pancreas and extrapancreatic lesions are sometimes accompanied by a decrease in serum IgG and IgG4. Another important clinical feature of type 1 AIP is the high rate of relapse, which occurs in 22–41.2% of patients [25–32] (Table 66.4). It is reported that relapse occurs in the pancreas in 55.4% of type 1 AIP patients, in the bile duct in 28%, in the lachrymal and salivary glands in 8.3%, and as RF in 5.7% [32]. Type 2 AIP shows a significantly lower relapse rate (0–9%) than type 1 AIP [25–32].

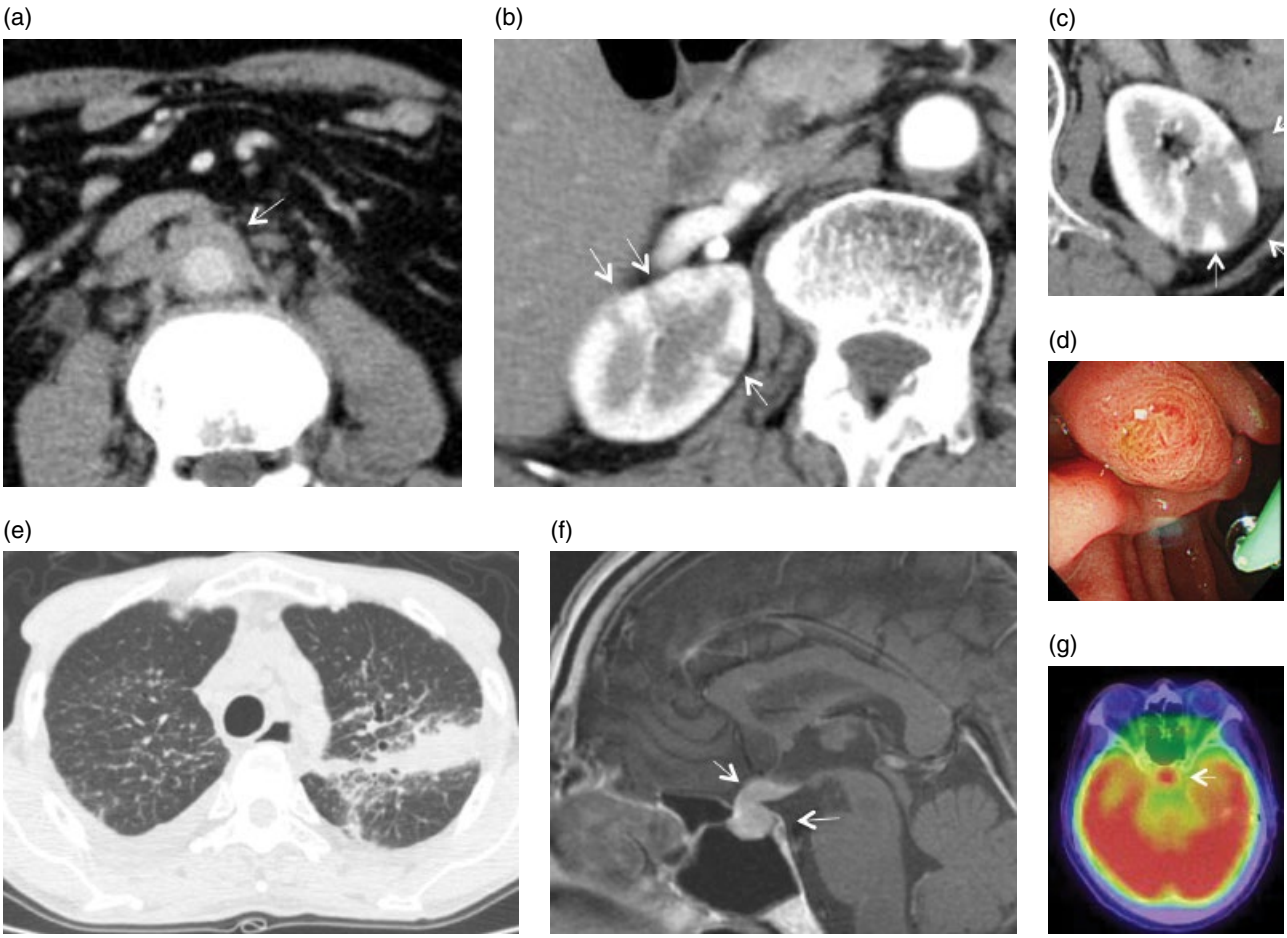


**Figure 66.6** Extrapancreatic lesions of type 1 AIP. (a) Retroperitoneal fibrosis can be seen as a soft tissue surrounding the abdominal aorta (arrow). (b,c) Low-density perfusion defects of the renal cortex on dynamic CT (arrows). (d) Swollen duodenal papilla Vater. (e) CT findings of the interstitial pneumonitis in type 1 AIP. (f,g) Hypophysitis associated with type 1 AIP. MRI imaging shows a remarkably swollen stalk and body of the pituitary gland (f, arrows). FDG-PET imaging shows an intense accumulation of FDG in the pituitary gland (g, arrow).

## IgG4-Related Disease (IgG4-RD)

Because type 1 AIP is considered to be a systemic fibrous disease characterized by an increased number of IgG4+ plasma cells with overproduction of IgG4 [50], in 2003, Kamisawa et al. proposed the new concept of "IgG4-related sclerosing disease" [78–80]. Various other names were proposed, including SHIPS (systemic IgG4-related plasmacytic syndrome) [81], with Mikulicz disease as one such representative, and IgG4-MOLPS (IgG4-related multiorgan lymphoproliferative syndrome) [82], from the viewpoint of IgG4+ plasma cell proliferative disease. The nomenclature was subsequently unified as IgG4-related disease (IgG4-RD) [83]. IgG4-RD includes sclerosing cholangitis (IgG4-SC), Mikulicz disease (IgG4-Mikulicz), tubulointerstitial nephritis (IgG4-nephropathy), RF, inflammatory pseudotumors, inflammatory aortic aneurysm, periaortitis, and periarteritis, among others [50,83].

Regarding the diagnosis of IgG4-RD, comprehensive diagnostic criteria for IgG4-RD were compiled in 2011 [84] and have been used for the screening of this disease. However, since the criteria are heavily based on histologic findings, other diagnostic criteria more specific to AIP [22], IgG4-SC [85], IgG4-Mikulicz [86], and IgG4-related kidney disease [87] should be applied to cases if tissue biopsy is difficult and/or confirmation of the respective diagnosis is necessary.

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# Clinical Manifestations of Type 2 Autoimmune Pancreatitis

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## Introduction

Over the last decade significant clinical and scientific attention has surrounded the concept and definition of autoimmune pancreatitis (AIP), a corticosteroid-responsive form of pancreatitis with two distinct histologic and clinical profiles. The focus of this chapter is the clinical manifestations of type 2 AIP, which incorporates idiopathic duct-centric pancreatitis (IDCP) and AIP with granulocytic epithelial lesions (GEL). The chapter includes a historical perspective on the discovery and terminology used to describe the condition, worldwide epidemiologic studies, demographics and clinical presentation, diagnosis, treatment, relapse, and clinical outcome.

## Search Criteria

We searched online literature databases including Pubmed, Medline, and EMBASE from January 1, 1961 until March 1, 2016. Search terms included "autoimmune pancreatitis type 2," "idiopathic duct-centric pancreatitis," "granulocytic epithelial lesions," and "duct-destructive pancreatitis." Publications were reviewed and high-quality original, review articles were included, predominantly from the last 10 years.

## Historical Perspective

A chronic inflammatory sclerosis of the pancreas was first described in 1961. Chronic pancreatitis with diffuse irregular narrowing of the entire pancreatic duct was later reported in 1992 [1], followed by the proposal of "autoimmune pancreatitis" (AIP) in 1995, to describe a corticosteroid-responsive disease associated with features of autoimmunity [2]. Nonalcoholic duct-destructive pancreatitis was later described in 1997 [3]. The clinical findings of elevated serum IgG4 levels and histologic evidence of abundant IgG4-bearing plasma cell infiltration in the pancreas were reported by Hamano et al. [4,5], and became important serologic and pathologic hallmarks for the diagnosis of AIP, now known as type 1 AIP or the pancreatic manifestation of IgG4-related disease. American and European pathologists highlighted two separate histopathology patterns in the pancreas in 2003, based on retrospective histologic assessments of resected specimens from patients who had mass-forming chronic pancreatitis [6], which were referred to as lymphoplasmacytic sclerosing pancreatitis (LPSP) and idiopathic duct-centric chronic pancreatitis (IDCP). The IDCP variant resembled duct-destructive pancreatitis, with neutrophil infiltration in the pancreatic duct epithelium [7], and was also termed AIP with granulocyte epithelial lesions [8]. These variants were shown to have distinct clinical profiles, and therefore two subtypes of AIP, called type 1 (LPSP) and type 2 (IDCP) AIP, were formally recognized [8,9]. This was later reinforced in the International Consensus Diagnostic Criteria (ICDC) for AIP in 2011 [10].

## Terminology

Several descriptive terms for type 2 AIP are used throughout the literature, and are listed in Table 67.1. The entity had been called "nonalcoholic duct destructive pancreatitis,"

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**Table 67.1** Terminology used to describe type 2 AIP

| Nomenclature | Reference |
|---|---|
| Type 2 autoimmune pancreatitis | 32 |
| Nonalcoholic duct-destructive pancreatitis | 3 |
| Idiopathic duct-centric chronic pancreatitis (IDCP) | 6 |
| Idiopathic duct-centric pancreatitis (IDCP) | 33 |
| AIP with granulocytic epithelial lesions (GEL) | 8 |
| GEL-positive pancreatitis | 7 |

"GEL-positive pancreatitis," and "IDCP" [3,9,11]. All three terms highlight the duct-centric nature of the disease. For the purpose of this chapter, type 2 AIP is used.

## Epidemiology

The epidemiology of type 2 AIP is incompletely defined. In particular, the necessity for histologic assessment has rendered diagnosis difficult, almost certainly leading to underrecognition of the disease. A nationwide population survey of all AIP patients in Japan in 2011 estimated the annual incidence as 1.4 per 100,000 and prevalence as 4.6 per 100,000 of the population [12]. In an international multicenter survey of 1,064 patients with AIP across 10 countries, only 8% were defined as type 2 AIP [13]. The proportion of type 2 AIP patients was lower in Asia (3.7%) than in both Europe (12.9%, $P < 0.0001$) and North America (13.7%, $P < 0.001$) [13]. This was supported by retrospective review of 26 original articles involving 706 AIP patients in China, suggesting the estimated proportion of type 2 AIP was 4.7% [14]. However, when assessing all histologically confirmed AIP patients in Korea, the proportion of type 2 AIP was 28.8 % (15/52), suggesting that this entity may not be as rare as originally thought [15].

## Demographics

Type 2 AIP has a young to middle-age disease onset (30–40 years) with no gender bias, in contrast to type 1 AIP which carries an elderly male predominance [16].

## Disease Associations

A coexistent history of other autoimmune diseases has been reported in up to 20% of patients with AIP [17]. Type 2 AIP is most often associated with inflammatory bowel disease (IBD), studies suggesting a frequency of 25–44% of cases (compared to 3% to 5% in type 1 AIP) [18–20]. In one study from the Mayo group, the diagnosis of IBD was most often made preceding or simultaneous to AIP [20]. Ulcerative colitis (UC) was more frequent than either Crohn's colitis or IBD-colitis type unclassified, and was pancolonic in distribution and clinically mild in severity [20]. There were no differences in clinical profiles between type 2 AIP patients with and without IBD.

Conversely, the overall prevalence of AIP in patients with IBD is low. A Korean study of 1,106 UC patients estimated the crude prevalence of AIP (any subtype) as 0.54% [19]. Furthermore, a Japanese study reported that type 2 AIP was found in 5 (0.5 %) of 961 patients with UC and 2 (0.3 %) of 790 patients with Crohn's disease [21]. However, in a study of 138 cases of pancreatitis with complicating IBD from Japan, 10.8% (15/138 patients) had histologic evidence of type 2 AIP [16]. This high rate is likely due to the recruitment of patients from centers specializing in AIP. In general, pancreatic diseases that complicate IBD consist mainly of acute pancreatitis due to gallstones, alcohol consumption, medications such as mesalazine and azathioprine, and duodenal lesions from Crohn's disease [22]. Furthermore, in patients consecutively evaluated for acute pancreatitis, irrespective of the presence of IBD, AIP (any subtype) explained less than 5% of cases [23].

## Clinical Symptoms and Signs

The clinical characteristics of type 2 AIP have been reported to be different from those of type 1 AIP [13,15,24]. Patients often present with abdominal pain, consistent with acute pancreatitis [16]. In one study, almost half of type 2 AIP patients ($n = 25$) had more than one episode of acute pancreatitis prior to a diagnosis of AIP, and after diagnosis episodes were less frequent and clinically mild [20]. Obstructive jaundice occurs less often than in type 1 AIP, likely due to a lower prevalence of pancreatic head swelling and lower bile duct stenosis [16]. In accordance with these observations, serum amylase concentrations are higher, but serum total bilirubin, biliary enzymes, and transaminases are lower when compared with type 1 AIP. Patients can experience diarrhea, particularly in those with complicating IBD and also due to exocrine pancreatic insufficiency [25].

No specific symptoms allow reliable differentiation of AIP from other causes of a pancreatic mass. The diagnosis may also be reached during the investigation of nonspecific abdominal symptoms in the setting of elevated amylase. Disease may be asymptomatic and can be found incidentally on cross-sectional imaging performed for another reason. Other cases are identified in a patient presenting with symptoms related to IBD.

## Diagnosis

Two of the greatest challenges to accurately diagnosing type 2 AIP are its misclassification and the need for histology (core tissue biopsy or resected specimen) to make a definitive diagnosis. The goal of defining diagnostic criteria in AIP focused initially on type 1 AIP (LPCP variant), and type 2 AIP received limited attention [23,26]. Recently, development of the International Consensus Diagnostic Criteria (ICDC) for AIP sought to provide alternative means for diagnosing type 2 AIP when definitive histologic features are not present, that is, small sample size, sampling error, or when tissue is unavailable [10]. The ICDC incorporate five cardinal features: imaging characteristics of the pancreatic parenchyma and pancreatic duct, serology, organ involvement, pancreatic histology, and the optional criterion of response to steroid therapy. Depending on diagnostic reliability, the evidence for each feature is characterized by category (level 1 or 2). The diagnosis of type 2 AIP can be definitive or probable, depending on the strength of supportive evidence, although occasionally the two types can be indistinguishable (AIP-not otherwise specified) [10].

For a diagnosis of type 2 AIP, the presence of granulocytic infiltration and absent or scant IgG4+ cells on histology (definitive diagnosis), or the presence of concurrent clinical inflammatory bowel disease (IBD) with either supportive histology (definitive diagnosis) or a response to steroid therapy (probable diagnosis) are required [10]. Limited clinical experience suggests these diagnostic categories are appropriate. One study, which compared patient and disease-related characteristics of definitive and probable type 2 AIP patients, using IBD as a valid supportive criterion for probable disease, concluded that both groups were representative of the same disease entity [20]. Furthermore, a controlled study that compared the ICDC to four other criteria in the diagnosis of AIP in a Japanese cohort found the ICDC to be the most sensitive (ICDC 91%; Korean 90.2%; Japanese 86.9%; Asian 83.6%, HISORt 83.6%) [27].

## Differential Diagnosis

Type 2 AIP should be differentiated from other benign and malignant conditions. In particular, other causes of acute pancreatitis, chronic pancreatitis, and pancreatic neoplasms [28]. One Korean study advocated a 2-week steroid trial after negative investigation for malignancy, in those with a high suspicion of AIP but not fulfilling diagnostic criteria, to differentiate this from pancreatic cancer [29]. However, this study included predominantly type 1 AIP patients and experience suggests that inflammatory changes surrounding malignant neoplasms can resolve with high-dose corticosteroids and mimic the resolution of AIP. This approach should only be adopted under close observation in centers with experience in managing the disease.

## Treatment

The aims of treatment in AIP are to alleviate symptoms, and prevent disease-related complications and irreversible fibrosis. Significant spontaneous improvement of type 2 AIP can occur, but further episodes of acute pancreatitis are seen [20,24]. Type 2 AIP is a corticosteroid-responsive disorder, and the symptoms and inflammatory changes respond rapidly to therapy [13]. Steroid use induces remission quicker, more consistently, and with a reduced relapse rate than a conservative approach [30]. Over three-quarters of type 2 AIP patients with jaundice require biliary stent placement [13].

There is an absence of randomized placebo controlled trials in the treatment of AIP. International consensus regarding initiation therapy with oral steroids has been reached [31], and a starting dose of prednisolone 30–40 mg daily for 4 weeks, before reducing by 5 mg every 2 weeks, depending on response, is recommended. During treatment, patients are reviewed regularly for evidence of steroid-induced side effects, biliary obstruction, and cholangitis/sepsis. Clinical, biochemical, and radiologic improvement should be seen within 4–6 weeks of starting treatment, and should be confirmed by repeat imaging. Remission, defined as complete resolution of pancreatic mass and/or normalization of biochemical tests, was reported in 92% of type 2 AIP patients in response to steroid therapy in one multicenter study [13]. Nonresponse may be representative of a less inflammatory burnt-out disease, a more fibrotic phenotype, or importantly an alternative diagnosis.

## Disease Relapse

Disease relapses in type 2 AIP are uncommon (<10%) [13,24], and appear to be much lower than in type 1 AIP. The cumulative relapse rate has been reported in one study as 7.9% at 6 months, 10,6% at one year, and 10.6% at 3 years (median follow-up 2.9 years) [20]. When relapses occur, they remain isolated to the pancreas and respond to corticosteroid retreatment. Hence, the benefit of steroid therapy to prevent future episodes of recurrent acute pancreatitis remains uncertain. Steroid

treatment can be reserved for those with imaging evidence of persistent inflammation of the pancreatic parenchyma following resolution of acute abdominal pain. The use of immunosuppressive maintenance therapy for type 2 AIP is usually unnecessary; however, may be used in the context of IBD [25]. Relapse-free survival was decreased in those initially presenting with acute pancreatitis or treated with steroids (compared with surgery) [20].

## Clinical Course and Outcome

Long-term outcome data in type 2 AIP is lacking. If diagnosed and treated early, steroid-responsive type 2 AIP appears to have a favorable prognosis [13,20,24]. Side effects and intolerance of corticosteroid therapy are the most troublesome. Long-term complications, including pancreatic insufficiency, pancreatic duct stones, and malignancy, seem to be uncommon in type 2 AIP. In the international multicenter study of 1,064 AIP patients meeting ICDC criteria, including 86 type 2 AIP patients, there were no pancreatic duct stones or pancreatic cancers in the type 2 AIP group [13].

## Summary

Type 2 AIP is a pancreas-specific disorder that is rare and challenging to diagnose. There are a variety of different clinical presentations including abdominal pain consistent with acute pancreatitis, diarrhea consistent with IBD, and/or exocrine insufficiency, and less frequently obstructive jaundice or an incidental pancreatic mass. Diagnosis is based upon the ICDC for AIP incorporating pancreatic imaging, histologic findings, presence of IBD, and response to steroid therapy. Although acute pancreatitis is a common presentation in those diagnosed with type 2 AIP, AIP itself remains a rare etiology of acute pancreatitis. The presence of IBD, especially in young patients, may be a clue in this context. Histologic sampling is often insufficient and leads to complexity in securing a solid diagnosis. Current therapy with corticosteroids follows expert consensus, but there is a lack of randomized controlled trials, which will require international collaboration. Disease relapse and complications are seemingly infrequent. Greater awareness of type 2 AIP and identification of more accurate noninvasive biomarkers will further refine our approach to diagnosis and management of this disease.

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# Laboratory Diagnosis of Autoimmune Pancreatitis

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## Introduction

Autoimmune pancreatitis (AIP) is an enigmatic disease, which has stirred up the fields of pancreatology and gastroenterology. After the rediscovery of an autoimmune form of pancreatitis in the 1990s, a pivotal paper described the presence of elevated IgG and IgG4 in this form of pancreatitis (then called "sclerosing" pancreatitis). From histology (see Chapter 65) it became clear that there are two forms of AIP and only the type 1 AIP was associated with IgG4, both in serum and tissue. It became further apparent that type 1 AIP is part of a larger syndrome that is now known as IgG-related diseases (IgG-RD). With two types of AIP that may look similar upon imaging (see Chapter 70), but differ in their response to treatment and complications, the need for further blood-based markers became obvious.

## Serum Markers

### Generic Markers

The conventional markers of inflammation, that is, erythrocyte sedimentation rate (ESR) and leucocytes (WBC), are of no use in establishing the diagnosis of AIP. Depending on the character of the respective disease form, stage, and time point, these may or may not be elevated.

### Pancreatic Enzymes

In 1929, it was stated that "elevated amylase has become a cornerstone in the diagnosis of pancreatitis" [1]. Although the specificity of both serum amylase and lipase for chronic pancreatitis is acceptable (in the range of 90 to 95%), their sensitivity is extremely low, oscillating at around 10%. As a consequence, serum markers cannot be used either for establishing the diagnosis of chronic pancreatitis or for the diagnosis of AIP. There are many possible reasons for elevated serum amylase and lipase levels and thus, elevated levels in patients with abdominal pain have a low specificity for chronic pancreatitis [2]. Serum elastase-1 is useful as a marker for acute pancreatitis [3] but has no better performance in diagnosing chronic pancreatitis or AIP than amylase and lipase [4].

Plasma trypsin-like activity has been claimed to be a sensitive and specific marker for early (mild) chronic pancreatitis; however, the only study in this patient population comprised 16 patients and had some methodological ambiguities [5]. Trypsinogen concentrations have also been suggested to be a good indicator for chronic pancreatitis [6].

While plasma trypsin-like activity and trypsinogen concentrations are elevated in a quarter of patients with established chronic pancreatitis, they seem to remain normal in early chronic pancreatitis. While we could not demonstrate significant differences for absolute values of cationic (PRSS1) and anionic trypsinogen (PRSS2) [7] in AIP, CP, and healthy controls, we found a change in the PRSS1–PRSS2 ratio: in healthy individuals (ratio 1:3) and in AIP (ratio 1:2) PRSS2 dominates [7]. In non-AIP CP [6] the ratio is shifted towards PRSS1 (ratio 2:1).

If one reflects on how amylase, like any other enzyme, reaches the circulation (serum) [8], its low specificity and sensitivity are not surprising. After massive damage of exocrine pancreatic tissue, that is, leakage through dead cells, serum levels rise significantly; however, this condition is not chronic (autoimmune)

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pancreatitis, but acute pancreatitis. Other promising markers such as pancreatic stone protein [9] and procarboxypeptidase B [10] have also not fulfilled their promise as sensitive markers for chronic pancreatitis and are of no use in diagnosing AIP.

Taken together, neither a generic marker nor serum levels of pancreatic enzymes can be used to establish the diagnosis of AIP.

## Markers of Autoimmunity

Generic markers of autoimmune disease are certain immune globulin classes, and some other markers. Elevated IgG, and especially IgG4, has been the first marker for AIP [11], later found to be elevated in the type 1 (lymphoplasmacytic sclerosing pancreatitis, LPSP) that was determined to be part of the IgG4 syndrome, IgG4-RD [12]. As a result of many studies in AIP, increased levels of both IgG and/or IgG4 have been determined to be defining for AIP type 1 in the International Consensus Diagnostic Criteria (ICDC) for AIP [13].

Approximately two-thirds of patients with AIP have elevated serum IgG4 levels [14]. However, mild elevations of serum IgG4 levels (1–2 times the upper limit of normal) have also been observed in 10–15% of patients with pancreatic cancer, cholangiocarcinoma, and primary sclerosing cholangitis (PSC) [15]. Even though higher elevations may improve specificity, the extremely low disease prevalence results in a low positive predictive value (10–15%) of elevated serum IgG4 levels for the diagnosis of AIP/IgG4-RD when the pretest probability of disease is low [15]. Thus, although elevated serum IgG4 levels are one characteristic of AIP type 1, they are helpful only for establishing a diagnosis of AIP in conjunction with other diagnostic findings [16].

Other measures of autoimmunity (i.e., nonspecific markers) that can be found are ANA (54–69%), RF (23–33%), and ASMA (15%) [16,17]. Measures such as ICA (3.8%), anti-DS (4.5%), and AMA (0–2%) are rarely found [16,17]. In an attempt to define a serum marker profile, we could not identify a specific set for AIP [18], even if this was successful for pancreatic cancer [19]. Taken together, autoimmune markers cannot establish the diagnosis of AIP.

Autoantibodies against specific target tissue-related antigens are the hallmark of any autoimmune disease. Autoantibodies can be divided into two categories: non-organ and organ-specific autoantibodies. Shortly after the initial description of IgG4, the first autoantibodies against pancreatic antigens were reported in AIP: against lactoferrin and carbonic anhydrase type II, the lead enzyme of the pancreatic duct epithelial lining producing bicarbonate [20]. However, only a small subset of patients seem to be positive [21] (Table 68.1). The third autoantibody described was directed against SPINK1 [17], a protein known to be disease-facilitating once mutated in some genetically determined forms of hereditary pancreatitis [22]. These autoantibodies against SPINK1 were confirmed in an independent patient group by other investigators [7].

Another autoantibody merits a mention because it could suggest a link to the possible etiology or causing agent/precipitating event: the ubiquitin protein ligase E3 component n-recognin 2 (UBR2), an enzyme highly expressed in acinar cells of the pancreas [23]. There is a certain degree of homology to the plasminogen-binding protein (PBP) of *Helicobacter pylori*—an agent that has been suggested to be linked to AIP for another homology between *Helicobacter pylori cag-A* and human carbonic anhydrase type II in a molecular mimicry fashion [24–26]. However, no confirmatory studies have been performed with URB2. We were also unable to detect *H. pylori* DNA in pancreatic tissue samples from AIP [27].

**Table 68.1** Disease-specific autoantibodies and immunoglobulins in autoimmune pancreatitis

| Antigen | % pos all AIP | AIP 1 | AIP 2 | Sensitivity | Specificity | % pos in PDAC | References |
|---|---|---|---|---|---|---|---|
| CA II | 53.8 | | | | | n.d. | 17, 20 |
| Lactoferrin | 73 | | | 73 | | 0 | 17, 20 |
| SPINK1 | 42 | | | 79* | | n.d. | 17, 7 |
| Trypsinogens | 79 | | | | | 0 | 7 |
| UBR2 | 95 | | | | | 10 | 23 |
| Amylase α2A | 79 | 67 | 75 | | | 0 | 28 |
| IgG, IgG4 | 40 | 80 | <5 | 41 | 99 | 10 | 11 |

CA-II, carbonic anhydrase II; *, SPINK1 and ALF together; n.d., not determined; PDAC, pancreatic ductal adenocarcinoma.

Recently, another antibody against the acinar compartment, amylase α2A, was described with good sensitivity and reasonable specificity [28] (Table 68.1).

None of the autoantibodies could be correlated with the expression levels of IgG or IgG4, and when investigated, the autoantibodies were not of the IgG4 class [16]. None of these antibodies were sufficiently disease-specific, and this is one of the distinct features of AIP compared to other GI and liver autoimmune disease, which are characterized by disease-specific autoantibodies such as AMA in PBC and anti-LKM1 in AIH [16].

Taken together, autoantibodies have been found against ductal (carbonic anhydrase type II) but mostly acinar (SPINK1, lactoferrin, trypsinogen, amylase α2A) antigens. There are no data indicating a correlation to subtypes of AIP. It is also of note that only the autoantibodies against SPINK1 together with carbonic anhydrase and lactoferrin could be confirmed by independent studies.

We propose a possible pathomechanism, based on the RNA expression profiling and proteomics data in conjunction with blood findings that explain the occurrence of these antibodies, at least against the acinar antigens (Fig. 68.1). This is based on the fine description of IgG-RD elsewhere [12].

## Other Markers

For the diagnosis of (chronic) pancreatitis, especially AIP, some other body fluids could be used. One option is pancreatic juice collected during ERCP or in the duodenum stimulated after secretin injection. In an attempt to describe markers from pancreatic juice samples, we could not detect any with high-resolution 2D-PAGE [29]. The cytologic analysis did not reveal anything diagnostically relevant for establishing the diagnosis of AIP.

Fecal elastase-1 (FE-1), a marker of pancreatic exocrine insufficiency (PEI), can also be measured. It is a rather crude marker, which if positive (below 200 μg/g) enables the diagnosis of PEI, and in so doing would confirm the diagnosis of any sort of chronic pancreatitis. In itself, however, FE-1 is not specific, either for chronic or autoimmune pancreatitis.

## Conclusion

The only clinical relevant possibilities for diagnosing AIP with blood-based assays are serum IgG and IgG4 when considered together with clinical findings. The only commercially available autoantibody assays exist for

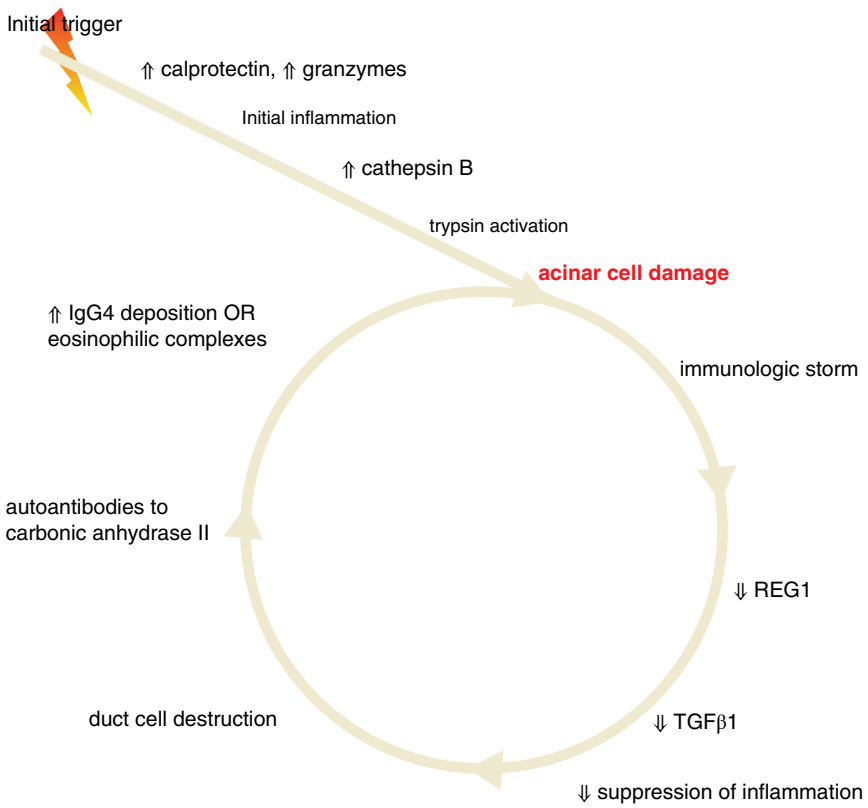


**Figure 68.1** Pathomechanism explaining the occurrence of autoantibodies in AIP. Expression profiling data from Löhr et al. 2010 [7].

autoantibodies against lactoferrin, carbonic anhydrase type II, and SPINK1, the latter only in Japan and not in Europe. These three autoantibodies have been shown to be of relevance in more than one study. Especially the newer autoantibodies against URB2 and trypsinogens require confirmation and the availability of commercial ELISA tests. So far, attempts to find novel markers have been unsuccessful.

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# 69

# What is the Evidence Measuring Immune Markers

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## Introduction

Autoimmune pancreatitis (AIP) is a distinct type of chronic pancreatitis that is presumed to be caused by autoimmune mechanisms. Although several immune markers have been identified for the purpose of AIP diagnosis, its differentiation from such mimicking conditions as pancreatic cancer, and the prediction of relapse during follow-up [1], immunoglobulin (Ig) G4 has been established as the most reliable [2]. This chapter will discuss the evidence measuring immune markers in AIP, with special reference to their usefulness in diagnosis, differentiation, and prediction of relapse. AIP has been restricted to type 1 in this chapter as the detailed clinical features of type 2 AIP remain unclear.

## Evidence of the Utility of Markers in Autoimmune Pancreatitis Diagnosis

In earlier paper electrophoresis assays, most patients with AIP were observed to display a polyclonal band in the rapidly migrating fraction representative of the now characteristic phenomenon of β-γ globulin bridging (Fig. 69.1). Immunoprecipitation trials revealed that this finding was due to high serum concentrations of IgG4 [2]. Comprising only 4–7% of total IgG, IgG4 represents a minor component of the four IgG subclasses whose serum elevation is observed only in specific disorders, such as various forms of atopy, parasitic infestations, and pemphigus. However, it has also been confirmed that serum IgG4 concentrations in patients with AIP were over 10-fold higher than those in healthy subjects. Moreover, approximately 90% of AIP patients exhibited increased serum IgG4 values, whereas few patients with other diseases, including pancreatic cancer, chronic pancreatitis, primary biliary cholangitis (PBC), primary sclerosing cholangitis, and Sjögren syndrome, showed such elevations (Fig. 69.2) [2]. In contrast, elevated total IgG and IgE were detected in 70% and 33% of AIP patients, respectively, both of which were also positive in a variety of other conditions, and the immune markers of antinuclear antibody and rheumatoid factor showed respectively low sensitivities of 40% and 30%. Disease-specific autoantibodies, such as anti-Sjögren syndrome A (SSA)/Ro, anti-Sjögren syndrome B (SSB)/La, and anti-mitochondrial antibodies, which have been useful in the diagnosis of Sjögren syndrome and PBC, were rarely also observed for AIP [1,3]. The aforementioned results strongly indicated that IgG4 was a particularly sensitive and specific biomarker for AIP diagnosis. The efficacy of IgG4 in the diagnosis of AIP has since become well recognized worldwide, showing an overall sensitivity, specificity, and diagnostic odds ratio (DOR) from seven representative studies [2,4–9] of 82%, 95%, and 63.9, respectively, and a favorable area under the receiver operating characteristic curve (AUROC) value of $0.920 \pm 0.073$ [10]. Another recent systemic review of 15 studies [2,7–9,11–19] demonstrated similar overall IgG4 results for sensitivity (74%), specificity (94%), DOR (62.91), and AUROC (0.953) [20]. Consequently, serum IgG4 measurement has been adopted as a key item in numerous diagnostic criteria systems for AIP [21–24], while the infiltration of IgG4-bearing plasma cells in affected pancreatic tissue has been established as a histologic hallmark of AIP for its pathologic diagnosis [25]. Most recently, the discovery of extrapancreatic involvement with IgG4-bearing plasma cell infiltration in various tissues has helped establish the new disease concept of IgG4-related disease. AIP has now been recognized as a pancreatic manifestation of this systemic disease, for which IgG4 seems to exert a major role in pathogenesis [3].

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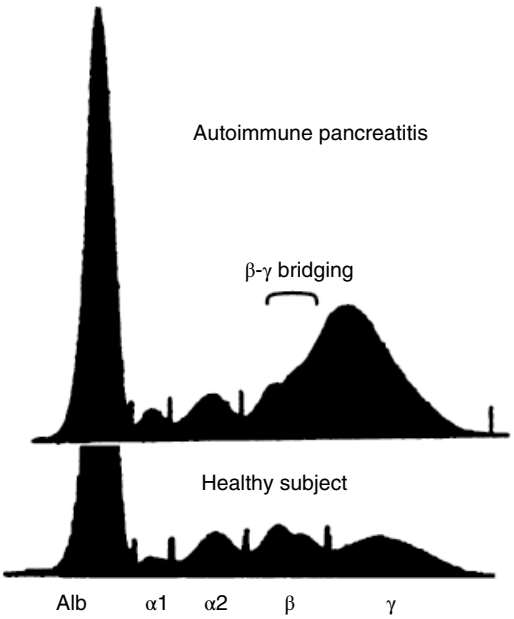


**Figure 69.1** Paper electrophoresis of serum from a patient with AIP and from a healthy subject displaying the β-γ globulin bridging routinely found in AIP. *Source:* From Tan to Sui 2001;22:603–608 [Japanese publication]. Reprinted with permission of Igaku-tosho Shuppan Co., Ltd.

Apart from IgG4, the serum values of several other immunoglobulins represent novel diagnostic markers of AIP. Taguchi et al. measured the serum levels of IgG, IgA, IgM, and IgG4 in individuals with AIP and other hepatopancreatic diseases and witnessed that IgM and IgA were markedly decreased in patients with untreated AIP, indicating a reciprocal correlation between IgM or IgA and IgG. Thereafter, the ratios of IgG to IgM and IgG to IgA in AIP were determined to be significantly higher than in other diseases, providing a diagnostic sensitivity and specificity for the differentiation of AIP from other hepatopancreatic conditions almost equivalent to those of IgG4 [26]. These ratios show promise as useful, low-cost markers that require only simple calculations based on routine immunoglobulin examinations.

## Evidence of the Utility of Markers in Differentiating Autoimmune Pancreatitis from Mimicking Conditions

AIP is characterized by the reported clinical features of elderly male preponderance, onset with obstructive jaundice, apparent pancreatic swelling in various imaging tests,

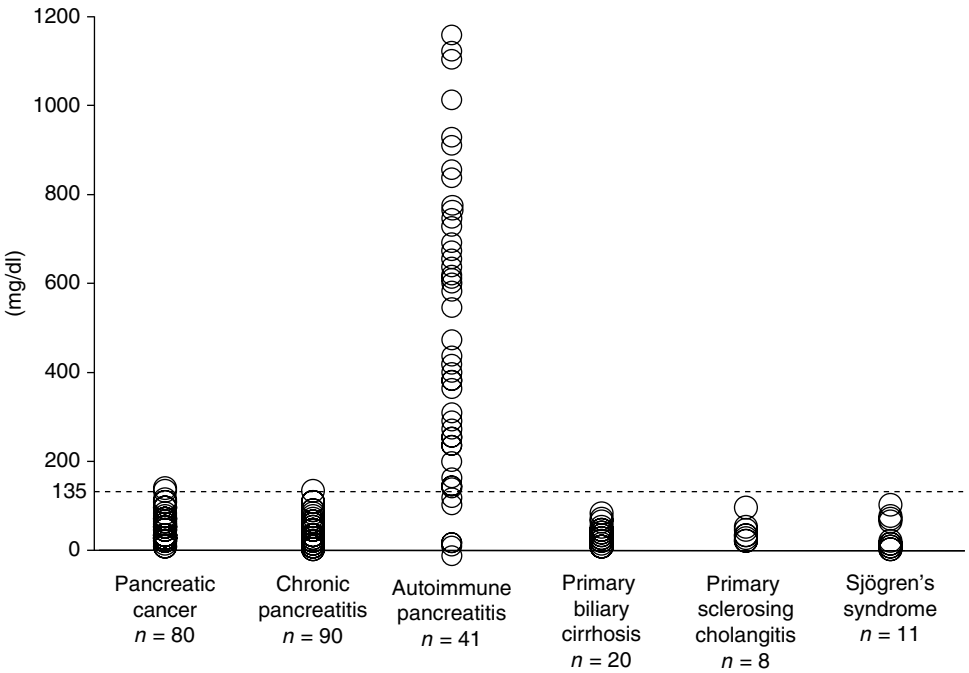


**Figure 69.2** Scattergram of serum IgG4 values in AIP and various other conditions. *Source:* Hamano et al. 2001 [2]. Copyright © 2001 Massachusetts Medical Society. Reprinted with permission.

irregular narrowing of the main pancreatic duct, and stenosis of the lower bile duct [1,3]. As these features mimic those of pancreatic cancer, extensive examination is needed for their proper differentiation; in fact, 2–3% of individuals who had undergone surgery based on a diagnosis of pancreatic cancer were later revealed to have AIP [27,28]. At a cut-off value of 135 mg/dL, IgG4 as a biomarker displayed a sensitivity of 90%, specificity of 98%, and accuracy of 95% in distinguishing between AIP and pancreatic cancer [2]. The efficacy of IgG4 in the differentiation of AIP and pancreatic cancer has since been supported worldwide, with an overall sensitivity, specificity, and DOR from four representative studies [2,7–9] of 82%, 95%, and 144.6, respectively, and a favorable AUROC value of 0.914 ± 0.191 [10]. A recent systemic review of 13 studies [2,7–9,11–13,15–17] showed comparable overall results of 73% sensitivity, 93% specificity, 60.61 DOR, and 0.926 AUC [20]. However, mild (<twofold cut-off value) elevations in serum IgG4 have also been seen in pancreatic cancer [8,19]. It must therefore be stressed that IgG4 elevation alone does not necessarily rule out the existence of malignancy since AIP complicated with pancreatic cancer has been reported as well [29,30].

AIP is histologically defined as lymphoplasamcytic sclerosing pancreatitis (LPSP) with abundant lymphoplasmacytic infiltration, storiform fibrosis, and obstructive phlebitis [31]. However, another type of AIP histologically identified as idiopathic duct-centric chronic pancreatitis (IDCP) [32] or AIP with granulocytic epithelial lesion (GEL) [33] that is characterized by granulocytic infiltration in the ductal epithelium has been reported mainly in Europe and America. Although both types of AIP share certain imaging finding similarities, IDCP/AIP with GEL has no correlation with IgG4 [32,34]. AIP is now classified as either type 1 or type 2 based on the pathologic subtypes of LPSP and IDCP/AIP with GEL, respectively [35]. In an international survey of AIP, type 2 AIP was observed in 8% of cases, with the proportion of this subtype being remarkably lower in Asian countries (3.7%) than in European (12.9%) and North American (13.7%) populations [36].

## Evidence of the Utility of Markers in Predicting Relapse

Although individuals with AIP usually respond well to corticosteroid treatment, relapse is a characteristic feature of AIP that occurs in an estimated 30–50% of patients based on several long-term follow-up studies [37–40]. Relapse may be a predisposition factor for pancreatic calcification, which in turn possibly triggers the transition to a chronic pancreatitis state with exocrine and endocrine dysfunction [41,42]. Accordingly, useful biomarkers that predict AIP relapse are needed for the establishment of effective prophylactic measures.

In a 3-year follow-up study, IgG4 seropositivity was found to be a significant independent factor of relapse prediction in AIP patients during maintenance corticosteroid treatment [43]. Other investigations have also reported significantly higher AIP relapse rates of approximately sixfold in AIP groups with elevated serum IgG4 levels than in those with normal IgG4 values [44,45].

In the clinical course of a 69-year-old woman with AIP who experienced two relapses, serum elevations of IgG4 and immune complex (IC) preceded the overt appearance of each clinical relapse by several months (Fig. 69.3)

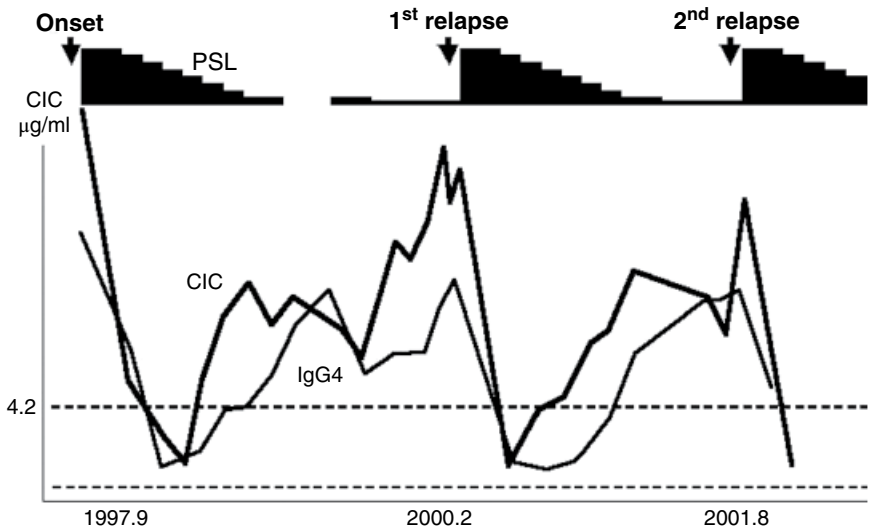


**Figure 69.3** Clinical course of a 69-year-old female patient with AIP demonstrating a correlation between two recurrences and preceding IgG4 and IC values. CIC, circulating immune complex; PSL, prednisolone. *Source:* Kawa and Hamano 2007 [46], Figs 4 and 5. Reproduced with permission of Springer.

[46], indicating that IgG4 and IC could sensitively predict relapse and represent disease activity. Elsewhere, persistently elevated serum IgG4 values were associated with AIP relapse and failure of disease control by steroid therapy [47], and Matsubayashi et al. reported that high serum IgG4 levels were related to severe clinical profiles that included jaundice, large pancreatic lesions, a high frequency of extrapancreatic lesions, and relapse [48].

While steroid therapy is generally effective for AIP, the incidence of relapse within 3 years after the start of treatment is relatively high [49]. Thus, it will be crucial to identify good predictors of relapse related to the eventual tapering or discontinuation of steroids. Shimizu et al. found that the rate of serum IgG4 decrease after the start of treatment was significantly higher in a non-relapse group than in a relapse one, suggesting that AIP patients responding to initial steroid therapy with a rapid drop in serum IgG4 are less likely to experience a relapse and thereby implicating the rate of IgG4 decrease as a predictor AIP recurrence [50].

Regarding other immune markers, IC value at treatment onset was significantly higher in a relapse group compared to a non-relapse group and displayed a good sensitivity (62%), specificity (70%), and accuracy (67%) at a cut-off value of 10 mg/dL. The probability of relapse was 60% at IC 10 mg/dL and 30% at IC 10 mg/dL [51]. Yet other activity immune markers of AIP are total IgG, complement C3 and C4, soluble interleukin-2 receptor, and β2-microglobulin, all of which may have use in the prediction of AIP relapse [1,3]. Especially since IgG and complement C3 and C4 are low cost and routinely measured, these parameters represent readily available means of predicting relapse in regular clinical practice and require further study.

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# 70

# Imaging Diagnosis of Autoimmune Pancreatitis

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## Introduction

The disease concept of autoimmune pancreatitis (AIP) was proposed in 1995 by Yoshida et al. [1], and subsequently this condition has been recognized as the pancreatic manifestation of IgG4-related disease (IgG4-RD) [2]. After several revisions of the concept, AIP is currently recognized as being classified into two distinct types [3,4]. AIP is subclassified according to the International consensus of diagnostic criteria (ICDC) for autoimmune pancreatitis as either type 1 (IgG4-related) or type 2 (GEL). Both types of AIP present with pancreatic swelling or mass formation often leading to obstructive jaundice. These features are similar to pancreatic cancer on the basis of the clinical and radiologic findings alone.

Histopathologic features of type 1 (IgG4-related) AIP, termed lymphoplasmacytic sclerosing pancreatitis, are characterized by abundant infiltration of lymphocytic and IgG4+ plasma cells, obliterative phlebitis, and fibrosis [3,5,6]. Type 2 AIP is characterized by granulocytic epithelial lesions (GEL) [5,7], histopathologically termed as idiopathic duct-centric chronic pancreatitis (IDCP) [8], and appears to be more common in Western countries than in Asian countries, whereas type 1 AIP accounts for the majority of cases in the world [9,10,11].

This chapter outlines pancreatic imaging based on current diagnostic criteria because of the particularly important role of these techniques in the diagnosis of AIP. Abdominal US, CT, and MR imaging are useful in the morphologic diagnosis of the pancreatic parenchyma. Magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde pancreatography (ERP) are useful in the morphologic diagnosis of the pancreatic duct. In addition, positron emission tomography (PET) may be useful in evaluating the response to steroid therapy and also extrapancreatic involvements. ERP has long been considered essential in Japan for potential AIP cases marked by localized pancreatic swelling [1]. However, in the ICDC and Japanese diagnostic criteria of 2011 it is stated that a possible diagnosis of AIP can be made without ERP if a fine needle aspiration under endoscopic ultrasonography excludes malignancy, and the patient responds to steroid treatment.

## Pancreatic Parenchyma Imaging

Diffuse swelling of the pancreas corresponding to a sausage-like appearance is highly characteristic for AIP. This feature can be demonstrated by US, CT, or MRI. However, localized (segmental or focal) swelling in AIP requires differentiation from pancreatic cancer. Concerning the definition of pancreatic swelling many investigators use the Haaga criteria (pancreatic head: ≥1 vertebral body, pancreatic body and tail ≥2/3 of a vertebral body define a pancreatic swelling and correspond to roughly a head of ≥3 cm and a body and tail of ≥2 cm) [12]. As the pancreas may be atrophic in the elderly a strict definition is difficult to achieve, but these criteria make it possible to recognize pancreatic swelling also in cases with shrinkage of the pancreas due to steroid treatment. Although "diffuse" and "localized" are not strictly defined, the ERP findings in the majority of cases with chronic pancreatitis are consistent with the Cambridge classification (2/3 diffuse, 1/3 segmental 2/3, focal 1/3) [13].

### Abdominal Ultrasonography (US) [5,11]

The typical US appearance of the pancreas in AIP shows a diffusely swollen organ that resembles a sausage. The swollen portion is hypoechoic with scattered hyperechoic spots. In cases with localized swelling, the differential

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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diagnosis between pancreatic cancer and mass-forming pancreatitis is problematic. Dilatation of the main pancreatic duct is frequently not detected by US, but delineation of the main pancreatic duct within the mass—known as the "duct penetration sign"—is helpful in differentiating AIP from pancreatic cancer [14]. However, the findings of only mild ductal dilatation or multiple hypoechoic masses within the pancreatic parenchyma make a differentiation between AIP and metastatic pancreatic tumors or lymphoma difficult.

## Abdominal CT Imaging [5,11]

The CT features are pancreatic swelling, a pattern of delayed contrast enhancement on dynamic CT, and a capsule-like rim surrounding the pancreas (Fig. 70.1) [15,16]. Most AIP patients are elderly and therefore tend to have some atrophy of the pancreas before the onset of AIP. This can obscure the presence of pancreatic swelling in the early stages of the disease. On the other hand, there are also cases in which pancreatic swelling can be judged to have been present at onset based on a decrease in the size of the pancreas following steroid therapy. Other cases are characterized by atypical findings of mild diffuse swelling alone of the pancreas, and/or partial dilatation of the MPD, cystic lesions, or, in rare cases, calcification of the pancreatic parenchyma.

### Pancreatic Swelling and Delayed Enhancement

Delayed enhancement is characteristic on the portal phase of dynamic CT, but the specific findings vary according to disease stage and activity. The enhancement effect can be altered by the degree of fibrosis. If the extent of fibrosis is only mild, the amount of enhancement may be difficult to distinguish from normal pancreas. Thus, the absence of delayed enhancement does not exclude AIP in the early stages of the condition, when extensive fibrosis is unlikely.

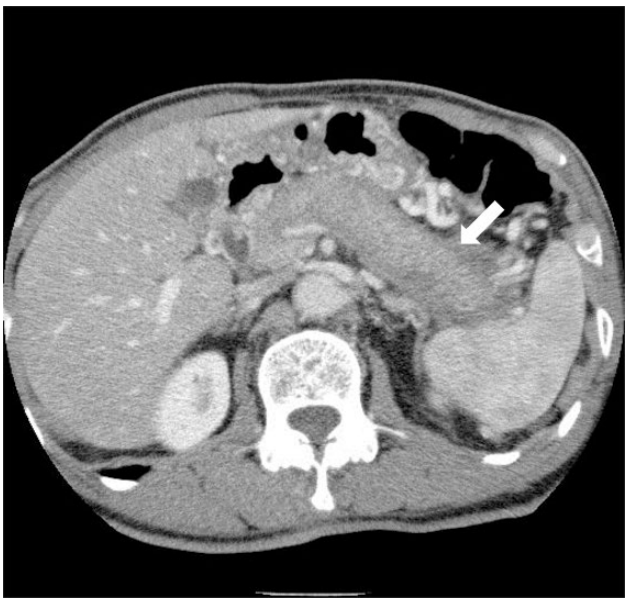

**Figure 70.1** Abdominal CT image of autoimmune pancreatitis (diffuse swelling) showing pancreatic swelling with delayed enhancement (sausage-like) and capsule-like low-density rim (arrow).

### Capsule-Like Low-Density Rim

The finding of a low-density, capsule-like rim around the pancreas is less common than delayed enhancement, but such a finding has a high specificity for AIP [15]. The capsule-like rim is thought to reflect fibrosis at the edge of the lesion, corresponding to the delayed pattern of enhancement observed on dynamic CT. A capsule-like rim is extremely helpful in differentiating AIP from pancreatic cancer. The absence of such a rim, however, by no means excludes AIP. Pancreas imaging alone cannot distinguish type 1 from type 2 AIP due to the similarity of their morphologic appearance.

## Abdominal MR Imaging [5,11]

### Pancreatic Swelling and T1/T2-Weighted Pancreatic Parenchyma Findings

Hypointensity on T1-weighted MR images and delayed enhancement on the portal phase of dynamic MRI are characteristic of AIP in addition to diffuse swelling. Because the normal pancreas is hyperintense relative to the liver on T1-weighted images, any relative hypointensity detected must be considered abnormal. However, hypointensity on MR is also found in both pancreatic cancer and chronic pancreatitis from other causes, and therefore does not distinguish AIP among these entities. Similar to CT, differentiation of the normal pancreas from cases of only mildly fibrotic AIP is challenging. Conversely, severe fibrosis can be associated with only slight hypointensity on T2-weighted images, because of the limited inflammation present at that point.

### Capsule-Like Rim

Both a capsule-like rim and a delayed enhancement pattern can be detected by MRI. Both of these findings reflect fibrosis and are highly characteristic for AIP. The capsule-like rim is visualized as a hypointense region on T2-weighted images. Dynamic MRI is the most effective means of demonstrating delayed enhancement.

## Nuclear Medicine Examinations

Gallium citrate (Ga-67) scintigraphy and fluorine-18 fluoro-deoxyglucose positron emission tomography (FDG-PET) [5,11].

Ga-67 and FDG accumulate in pancreatic lesions, making the differentiation from lymphoma difficult. Ga-67 and FDG accumulation is not limited to pancreatic lesions alone, but is also found at sites of extrapancreatic involvement, notably in the hilar lymph nodes of the

chest, the lacrimal glands, and the salivary glands. Such lesions frequently disappear rapidly after glucocorticoid administration [16–18]. However, the expense of these examinations further limits their clinical utility and has so far prevented them from entering routine practice.

## Pancreatic Duct Imaging

### ERCP Findings [5,11]

A characteristic irregular narrowing of the MPD constitutes strong evidence in favor of the diagnosis of AIP (Fig. 70.2a) [19]. Irregular narrowing of MPD refers to a situation in which the pancreatic duct diameter is thinner than usual and irregular. These lesions tend to affect greater lengths of the duct than do occlusive or stenotic lesions. In typical cases, irregular narrowing accounts for more than one third of the entire pancreatic duct length (~5 cm). Even in localized lesions marked dilatation of the main pancreatic duct upstream to the stenotic portion is frequently not observed. In cases with a short irregular narrowing pancreatic duct (roughly <3 cm), the differentiation from pancreatic cancer is difficult. Side branches arising from the narrow area of the MPD and skip lesions are useful signs in the differentiation from pancreatic cancer [20]. In the earlier diagnostic criteria

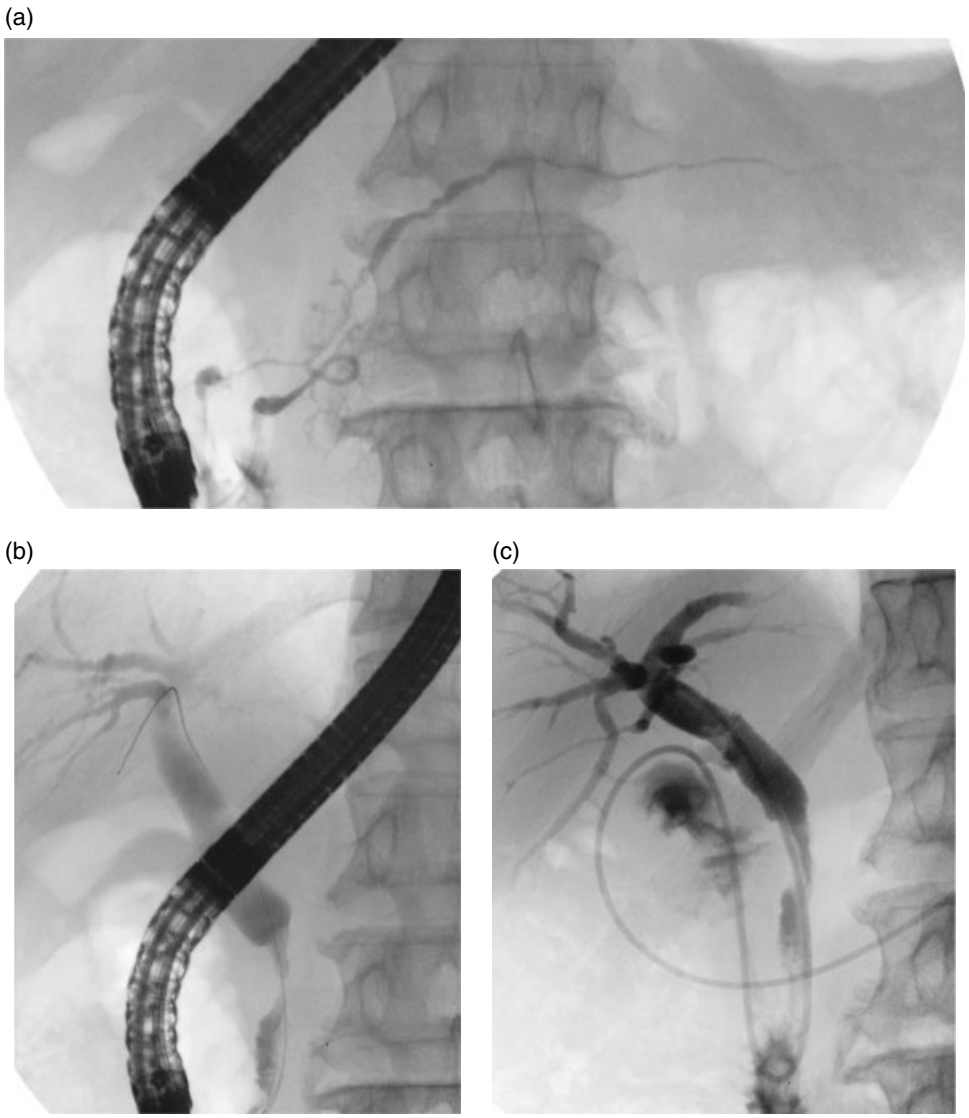


**Figure 70.2** ERCP images of autoimmune pancreatitis. ERP (a) shows irregular narrowing in the pancreatic head and tail. Side branches arising from the stenotic portion of the main pancreatic duct (MPD) in the pancreas head can be observed. Before steroid treatment, ERC (b) shows stenosis of the terminal common bile duct and improvement of stenotic change after steroids (c).

for AIP put forth in Japan, the finding of characteristic irregular narrowing within the MPD was considered to be an essential piece of diagnostic evidence [5,11]. In cases with focal irregular narrowing, the need to differentiate AIP from pancreatic cancer must be kept in mind. In AIP, bile duct stenosis is found in about 80% of cases. Bile duct stenosis is most common in the inferior bile duct (Fig. 70.2b,c), but may also develop in the extrahepatic and intrahepatic bile ducts.

### MRCP Findings [5,11]

When evaluating patients with possible AIP and other disorders that mimic it, delineation of the morphologic features of the MPD by ERP or another direct visualization method is essential. At present, MRCP does not delineate the pancreatic duct with sufficient accuracy for reliable diagnosis of AIP or the precise evaluation of irregular narrowing in the MPD. Its ability to demonstrate noncontinuity of the duct is helpful in making the diagnosis of AIP (Fig. 70.3), although the specificity of this finding is, in itself, imperfect. However, three-dimensional MRCP can now detail the main pancreatic duct within a normal pancreas and failure to identify the main duct suggests the presence of irregular narrowing. With the recently introduced 3.0 Tesla MR imagers, further enhancement of the image quality of MRCP is anticipated and MRCP may have a greater role to play in the assessment of the response of AIP to therapy and in follow-up observations.

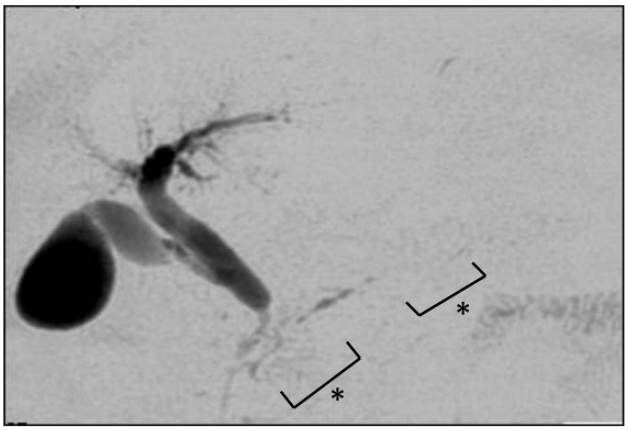


**Figure 70.3** MRCP findings of autoimmune pancreatitis. MRCP usually fails to identify the correct presence of irregular narrowing of the MPD. In this case, MRCP shows the segmented MPD (skip lesions), suggesting the possibility of autoimmune pancreatitis (*).

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# Medical Management of Autoimmune Pancreatitis

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## Introduction

In 1995, Yoshida et al. coined the term autoimmune pancreatitis (AIP) to describe a condition reminiscent of autoimmune hepatitis because it was corticosteroid-responsive and associated with elevated levels of autoantibodies and gamma globulins [1]. Earlier, Kawaguchi had described its histopathologic features and called it lymphoplasmacytic sclerosing pancreatitis (LPSP) [2]. Subsequently, this entity was shown to be part of a multiorgan disorder called IgG4-related disease (IgG4-RD).

A different disease entity was seen to share histopathologic and clinical features with LPSP and its histopathologic pattern was termed idiopathic duct-centric chronic pancreatitis (IDCP) [3]. The term AIP came to be used for both diseases with LPSP called type 1 AIP and IDCP as type 2 AIP. Here we will use the terms AIP and IDCP, respectively to describe the two entities.

## Management of Autoimmune Pancreatitis: An Overview

AIP is to be managed medically; surgical intervention, usually pancreatic resection or biliary bypass for "unresectable" disease, occurs when the condition is mistaken for pancreatic cancer. Like other autoimmune disorders, treatment of AIP includes induction of remission, treatment of relapse, and maintenance of remission. The cornerstone of medical management of AIP is the use of corticosteroids to target the inflammatory response in the affected organ. This provides symptom relief, often dramatic, which in some instances can be helpful for confirming the diagnosis. Although the early use of corticosteroids may delay progression to fibrosis, pancreatic parenchymal fibroatrophic changes that accompany the initial presentation of the disease are usually permanent. Steroid-sparing agents are mostly used for long-term maintenance of remission or in steroid-intolerant patients.

## Definitions

The consistent use of well-defined terms to describe treatment goals is an important component of the treatment algorithm of AIP. AIP is a fibroinflammatory disease and treatment targets the inflammatory component; the accompanying fibrosis may permanently alter organ structure and function. Currently, there are no therapies that specifically prevent or halt fibrosis.

"Remission" indicates the complete resolution of the inflammatory component of the disease with or without restitution of normal structure and function. The rapid and complete resolution of symptoms such as jaundice or abdominal pain after initiation of corticosteroids has diagnostic utility; persistent symptoms on high-dose steroids indicate an alternate diagnosis. Even with remission organs affected may never return to normal morphology and function due to fibrosis-related damage. Biochemical abnormalities in liver tests and pancreatic enzymes often resolve completely with disease remission. Confirmation of histologic remission after treatment, although ideal, is not feasible and is almost never needed in clinical practice. Normalization of serum IgG4 levels is not a reliable treatment target and does not correlate with disease remission.

"Recrudescence" is the worsening of disease or "flare" during treatment when the disease is still not in remission.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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This may happen in the setting of corticosteroid dose reduction or premature withdrawal.

"Relapse" refers to disease recurrence after complete remission has been achieved. This could be in the form of recurrent clinical, radiologic, or biochemical features of disease that often mimic the initial presentation. AIP being part of a multiorgan disease (IgG4-RD), relapse may occur in the organ being treated or in another, previously unaffected, organ. Abdominal pain as a standalone symptom is rarely a manifestation of relapse. Similarly, isolated "serologic relapse," that is, elevation of IgG4 without biochemical or radiologic change, is not indicative of disease relapse and should not be treated.

## Management of Initial Presentation

### Induction of Remission

Corticosteroids are the mainstay of initial treatment. High-dose induction therapy with 30–40 mg/day of prednisone or equivalent-dose corticosteroid is typically administered for 4 weeks. Clinical and radiologic response is assessed at the end of 4 weeks of high-dose therapy and in patients demonstrating remission or significant interval improvement in target organ inflammation, this is followed by a gradual corticosteroid taper using a decremental dose of 5 mg per week. Subsequent need for therapy is determined by treatment response. For patients with no previous history of AIP who have limited disease burden that rapidly resolves, steroid therapy is typically tapered to discontinuation at this stage.

While steroid-resistance is rare, therapeutic options are fairly limited in patients who are unable to be weaned off high-dose corticosteroids following induction therapy. Rituximab (RTX), a chimeric monoclonal antibody against CD20 antigen on B cells is the only currently known agent other than corticosteroids that has the ability to induce remission. Generally reserved for treatment of relapsing disease, it can be used as a first-line agent in select clinical scenarios where patients need high-dose steroids to maintain remission, or when steroids are contraindicated or poorly tolerated. The most commonly used induction regimen for RTX is 2 doses (1 gm each) 2 weeks apart. There is limited data and no consensus on the use of RTX as first-line treatment for AIP. In a Mayo Clinic series, complete remission was achieved in three out of three patients who were corticosteroid-naïve and were treated with RTX as the first-line agent [4]. However, experience from treatment of other manifestations of IgG4-RD and additional unpublished experience from our center suggests that RTX can be used as first-line and sole agent for induction and maintenance of remission, if necessary [5].

### Maintenance of Remission

In patients who achieve complete remission with induction therapy, there is considerable debate regarding the continued use of low-dose corticosteroid treatment for maintenance of remission. Several Asian centers favor the long-term continuation of low-dose corticosteroid therapy for several years and even indefinitely, whereas most centers in Europe and North America recommend weaning to discontinuation over 8–10 weeks after the initial 4 weeks of high-dose treatment. However, in a large study of 459 subjects with AIP from Japan who received maintenance corticosteroid treatment nearly one fourth relapsed (23%, 63/273). Though this was lower compared to patients in whom corticosteroids were discontinued after achieving remission (34%, 35/104; $P = 0.048$), the authors do not provide treatment alternatives for those who did relapse on steroids [6].

An alternative approach to steroid maintenance therapy is the use of immunomodulators as a steroid-sparing agent. The choice of immunomodulator does not impact treatment outcomes with 6-mercaptopurine, mycophenolate mofetil, and azathioprine all having similar efficacy. Intolerance to one agent can be managed by substituting one of the other agents. The optimal dose and duration of treatment is not well defined. However, for azathioprine, higher doses similar to those used in the management of inflammatory bowel disease (2.0–2.5 mg/kg), have a greater likelihood of preventing subsequent relapses compared to lower doses (1 mg/kg) [4].

Maintenance therapy is of greatest benefit to patients at the highest risk of relapse. This includes patients with proximal biliary tract disease, diffuse enlargement of the pancreas, elevated baseline IgG4, IgE, peripheral eosinophilia, and possibly those with persistent elevation of IgG4 at the end of induction therapy [7]. For patients who only have a partial response or in whom it is difficult to wean corticosteroids to a maintenance dose, early use of immunomodulators or RTX needs to be considered to avoid long-term high-dose corticosteroid use. However, immunomodulators do not induce remission; hence, if the disease is still active when steroids are withdrawn, there is a high likelihood of disease recrudescence, despite use of immunomodulators.

## Management of Relapse

Although the majority of patients with AIP have a dramatic response to corticosteroid treatment, relapse is common and up to 60% of patients experience a disease flare either during steroid taper or after discontinuation [6,8,9]. There are four treatment strategies that have

been variably implemented for the treatment of relapsing AIP. These include (i) high-dose corticosteroid for 4–6 weeks followed by gradual taper and either maintenance on low-dose steroids (2.5–10 mg daily) or discontinuation, (ii) high-dose corticosteroids for 4–6 weeks along with coadministration of immunomodulator followed by steroid taper and discontinuation, (iii) RTX induction therapy alone with either 4 weekly doses (375 mg/m2 BSA) or 2 doses (1000 mg each) administered 2 weeks apart, and (iv) RTX induction therapy followed by maintenance dose infusions (375 mg/m2 BSA) every 2–3 months for a 2-year period.

There is limited data comparing the relative efficacy of these different strategies. In our previously published experience of treating 51 patients for a first relapse, a subsequent relapse occurred in 9 out of 24 (38%) patients in the steroid monotherapy group and 8 out of 27 (30%) in the group treated with corticosteroids and an immunomodulator [4]. Relapse-free survival was not significantly different in the two groups.

In the same study, 12 patients who were resistant or intolerant to steroids and immunomodulators were treated with RTX induction and maintenance. Ten patients (83%) in this group achieved complete remission with no disease recurrence during a median follow-up of 10.6 months [4]. In a larger cohort of 60 patients with IgG4-RD (12 with pancreatic involvement) treated with RTX induction therapy alone (two infusions separated by 15 days), a clinical response was noted in 95% [7]. In this study, 21 patients (37%) experienced relapses following RTX treatment and the median time interval between RTX treatment and relapse was 244 days [7]. In our experience, relapses are distinctly uncommon in patients on RTX maintenance therapy. However, this needs to be confirmed in future studies comparing outcomes of RTX induction alone versus maintenance therapy.

## Follow-Up and Management of Disease-Related Sequelae

### Exocrine Insufficiency

Steatorrhea is uncommon in patients with AIP. A study using a diagnostic cut-off of FE-1 < 200 μgm/gm reported an abnormal test result in more than 80% of patients with AIP [10]. This is discordant with our clinical observations and it is unlikely that FE-1 values at that cut-off accurately reflect the true prevalence of exocrine pancreatic insufficiency in patients with AIP. Significant pancreatic parenchymal atrophy is seen in up to 25% patients after corticosteroid therapy and may contribute to the development of exocrine dysfunction over time [11]. The use of PERT should be limited to patients with clinical evidence of fat malabsorption.

### Endocrine Insufficiency

Risk factors for the development of new-onset diabetes in patients with AIP include extensive pancreatic parenchymal atrophy, long duration of disease, advanced age, smoking, and alcohol consumption. Periodic monitoring of glycemic status should be considered for early detection and timely intervention, especially in patients with the above-mentioned risk factors.

## Risk of Pancreatic Malignancy

There is conflicting evidence regarding the risk of pancreatic cancer in patients with AIP. Although some studies have shown increased risk, the vast majority have failed to establish an association. The risk of cancer appears to be highest in the first year after diagnosis of AIP [12]. In a recently published study of 107 AIP patients with a median follow-up of 74 months, none of the study subjects developed pancreatic cancer [13]. Interestingly, eight patients developed a non-pancreatic malignancy and the cancer risk in this study cohort was comparable to an age- and gender-matched reference population. The concomitant diagnosis of AIP and pancreatic cancer has also been reported [14]. Although this phenomenon is exceedingly rare, it highlights the importance of a detailed diagnostic work-up to exclude pancreaticobiliary malignancy before embarking on an AIP treatment protocol. Also, malignancy should be considered in the differential diagnosis of patients who do not respond to corticosteroid induction since primary nonresponse to steroid therapy is extremely unusual.

## Management of Medication Side-Effects

### Corticosteroids

Hyperglycemia and altered mood are the two most frequent and clinically relevant treatment-related complications linked to high-dose corticosteroid therapy. For those with a pre-existing mood disorder, careful assessment of mental health status, and if necessary medication dose adjustment should be considered prior to initiation of treatment. A baseline fasting plasma glucose should be obtained in all patients and those with a pre-existing diagnosis of diabetes mellitus closely monitored to modify steroid and insulin dosing. Less commonly encountered serious side-effects of high-dose

steroids include avascular necrosis, osteoporosis, hypertension, and worsening heart failure.

### Immunomodulators

Unfortunately, in most reported series up to a quarter of patients treated with immunomodulators have experienced treatment-limiting side effects [4]. The commonly encountered adverse effects that result in drug discontinuation include nausea, liver enzyme elevation, drug rash, myelosuppression, and bacteremia. A switch to a different immunomodulator is tolerated in about half of these patients.

### Rituximab

Rituximab treatment is fairly well tolerated. All patients should be screened for hepatitis B virus (HBV) prior to initiation of therapy since reactivation hepatitis B can potentially result in fulminant liver failure [15]. Common infusion-related adverse reactions include flu-like symptoms, pruritus, transient hypotension, and bronchospasm. Serious infusion reactions are rare, but near-fatal infusion reactions have been reported [16]. Other rare serious reactions that would necessitate discontinuation of therapy include toxic epidermal necrolysis and progressive multifocal leukoencephalopathy.

## Management of Idiopathic Duct-Centric Pancreatitis

IDCP is exquisitely steroid-responsive. The dose and duration of induction treatment with corticosteroids is similar to AIP. Clinical response is often dramatic and relapses are infrequent. A Mayo Clinic study of 31 subjects with a definitive diagnosis of IDCP reported a relapse rate of 10.6% at 12 months [17]. Initial presentation with acute pancreatitis predicted a lower relapse-free survival. Relapses almost always respond to retreatment with corticosteroids. In view of the relatively low relapse rate, maintenance therapy with steroids or immunomodulators is currently not recommended. Long-term disease related sequelae such as pancreatic duct stones, pancreatobiliary malignancy also appear to be less common compared to type 1 AIP.

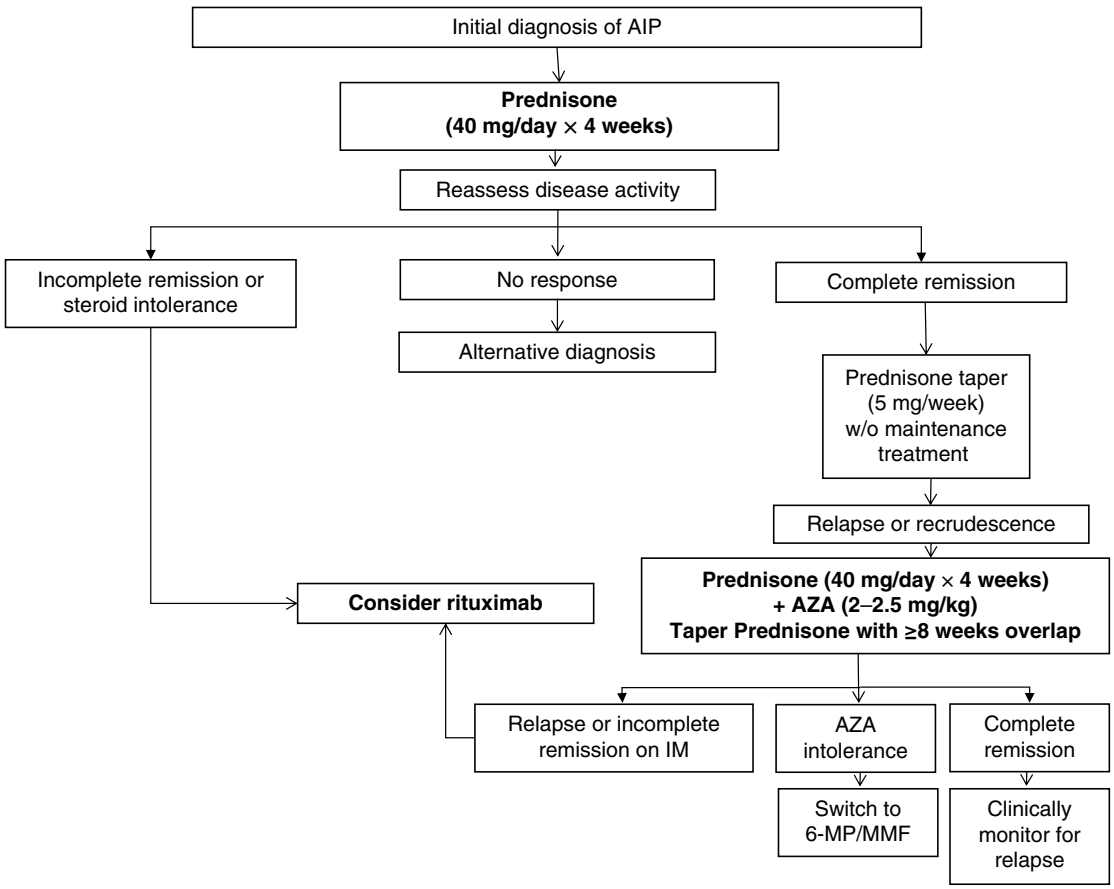


**Figure 71.1** Mayo Clinic treatment algorithm for management of initial presentation and subsequent disease relapses for patients with established autoimmune pancreatitis.*Source*: Adapted from Hart et al. 2013 [4]. Reproduced with permission of BMJ Publishing Group Ltd.

## Conclusion

In patients with a confirmed diagnosis of AIP the initial medical management is straightforward. Treatment of relapses and disease that does not respond or incompletely responds to high-dose corticosteroids requires a thoughtful approach with the judicious use of immunomodulators and B-cell depletion therapy (Fig. 71.1). Although, based on preliminary experience RTX appears to be the agent of choice for the treatment of patients with refractory disease, the optimum dosing regimen and duration of treatment continues to evolve and needs further study. Novel biomarkers that allow disease activity surveillance and predict relapse may facilitate more accurately tailored treatment regimens in the future.

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# Long-Term Outcome of Management of Autoimmune Pancreatitis

## 72

## Long-Term Outcome After Treatment of Autoimmune Pancreatitis

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### Introduction

Autoimmune pancreatitis (AIP) is a clinical entity that is well described in clinical and imaging findings at the onset of the disease [1]. The early phase is also known, in particular the outcome after steroid treatment, which represents a diagnostic criterion. However, the long-term outcome of patients suffering from AIP is still largely unknown. Many aspects are not yet fully clarified, particularly the need for and efficacy of treatment with nonsteroidal immunosuppressants (azathioprine) or biologics (rituximab (RTX)) in preventing disease relapse and progression toward chronic pancreatitis in terms of loss of pancreatic function (exocrine and endocrine insufficiency), onset of pancreatic calcifications, and the risk for pancreatic cancer. Since the term "autoimmune pancreatitis" was introduced in 1995 [2] and the disease was recognized as an entity, and thus early treatment has become the norm, the long-term clinical outcome of the disease has been modified by the use of steroids, nonsteroidal immunosuppressant drugs, and/or biologics (RTX). Therefore, while the natural history of the disease remains obscure, what can be observed nowadays is the long-term outcome of AIP after therapy.

An unanswered question is the fate of patients suffering from AIP before 1995 and appropriate immune suppressive treatment. We know that some of them underwent surgery because of the suspicion of pancreatic cancer. To answer this question may well lead to a better understanding of the natural history of AIP.

### Disease Relapse after Steroids and Treatment

Relapse of AIP may be symptomatic, evident on imaging, serology, and/or histology [3]. However, an AIP relapse may be clinically asymptomatic and detectable only on imaging [4]. The site of the relapse is mainly in the pancreas, but may involve extrapancreatic organs (kidney, salivary glands, biliary tree, and retroperitoneum) [4–7]. Relapse rates reported in the literature include symptomatic and asymptomatic patients with both, pancreatic and extrapancreatic involvement without distinction.

After a first course of steroids, disease relapse has been reported in between 13% and 64% of cases (Table 72.1) [6,8–16]. Disease relapse does not differ between patients who underwent surgery compared to those treated conservatively (Table 72.2) [6,9–13,15,17]. Furthermore, relapse rates are significantly higher and more frequently observed in AIP type 1 compared to type 2 [6,18,19]. Ikeura et al. [18] reported a 20% relapse rate of AIP NOS (not otherwise specified), lower than in type 1 (34%) and higher than in type 2 AIP (6%). High levels of serum IgG4 [6,7,9,12,19–22], intrahepatic biliary involvement [6,20,23], and other organ involvement [7], have all been identified as risk factors for relapse. These factors were all strictly correlated with type 1 AIP, which may therefore be considered as a more aggressive disease.

The treatment of choice for disease relapse is a new course of steroids (prednisolone) to induce remission [25]. This therapeutic approach is widely accepted, even if it is based only on cohort studies. The dosage of prednisolone is the same as that proposed after the diagnosis

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**Table 72.1** Frequency of relapse in patients suffering from AIP.

| Author | Year | Country | Patients N. | Relapse rate |
|---|---|---|---|---|
| Ryu et al. [8] | 2008 | Korea | 67 | 15% |
| Frulloni et al. [9] | 2009 | Italy | 87 | 25% |
| Raina et al. [10] | 2009 | USA | 26 | 57% |
| Maire et al. [11] | 2010 | France | 44 | 27% |
| Kubota et al. [12] | 2011 | Japan | 70 | 34.3% |
| Kamisawa et al. [13] | 2011 | Asia | 327 | 13.1% |
| Kamisawa et al. [14] | 2011 | Asia, Europe, USA | 731 | from 15% to 64% |
| Song et al. [15] | 2012 | Korea | 52 | 24% |
| Hart et al. [6] | 2013 | Asia, Europe, USA | 1064 | 29.1% |
| van Heerde at al. [16] | 2014 | Netherlands | 111 | 37% |

**Table 72.2** Frequency of relapse in patients suffering from AIP divided in those treated with steroids and who underwent surgery.

| Author | Year | Country | Steroids | Relapse rate | Surgery | Relapse rate |
|---|---|---|---|---|---|---|
| Frulloni et al. [9] | 2009 | Italy | 67 | 34% | 20 | 30% |
| Raina et al. [10] | 2009 | USA | 15 | 60% | 4 | 0% |
| Maire et al. [11] | 2010 | France | 26 | 31% | 12 | 33% |
| Kubota et al. [12] | 2011 | Japan | 42 | 9% | 20 | 17% |
| Kamisawa et al. [13] | 2011 | Asia | 231 | 21% | 42 | 12.5% |
| Song et al. [15] | 2012 | Korea | 27 | 40% | 11 | 10% |
| Hart et al. [6] | 2013 | Asia, Europe, USA | 736 | 33% | 141 | 25% |
| Yurci et al. [17] | 2013 | USA | 11 | 27% | 21 | 19% |
| **All studies** | – | – | **1155** | **30%** | **271** | **37%** |

of AIP (prednisolone, 30–40 mg/day or a weight-adjusted dose range from 0.5 to 1 mg/kg of body weight per day), which can be varied according to disease activity. After the induction of remission in relapsing AIP a maintenance regimen has been suggested. Long-term maintenance therapy with low-dose steroids (prednisolone, 5–10 mg/day) is used in Asian countries, but is still debated elsewhere. Steroid-sparing agents, in particular azathioprine (2–2.5 mg/kg/day), have been proposed for long-term treatment of relapsing AIP [20], even in the absence of controlled trials, but again their use is still being debated. However, experts recommend an add-on therapy with steroid-sparing agents for IgG4-related disease [26], to which AIP type 1 belongs.

RTX, an anti-CD20 antibody inducing B-cell depletion, seems to be effective in inducing specific serum IgG4 reductions and for better disease control in IgG4-RD, even in steroid refractory cases [27]. RTX would probably interfere with the immunologic processes underlying IgG4-RD, but the exact mechanism is still unknown. Since AIP type 1 is considered a manifestation of IgG4-RD, the use of RTX has been suggested for this subtype of AIP [26,28]. Some preliminary cohort studies seem to confirm the efficacy of RTX in AIP type 1 [29]. There is still no consensus regarding the dosage and the RTX schedule. A rheumatologic (intravenous infusions at a dosage of 375 mg/m$^2$ body surface area at time points 0 and 15 days, repeated after 6 months) rather than a hematologic schedule (intravenous 375 mg/m$^2$ body surface area four times at weekly intervals, then repeated infusions every 2–3 months up to 24 months) can be suggested, but randomized trials are needed to better understand the most appropriate protocol for AIP patients.

## Loss of Pancreatic Function and Evolution Toward Chronic Pancreatitis

The long-term outcome of AIP patients is described in only few studies, and limited to the first 10 years after clinical onset. The key points about the natural history of AIP are the deterioration of exocrine and endocrine function, the onset of pancreatic calcifications, and, more generally, the evolution toward "ordinary" chronic pancreatitis.

Exocrine pancreatic function is already reduced at clinical onset of the disease (Table 72.3) [5,9,11,30–32] and its improvement has been observed in a significant proportion, but not all, patients after steroids [32,33]. The exocrine pancreatic function evaluated by secretin-cerulein test is reduced at clinical onset of the disease in nearly all AIP patients, involving particularly enzyme production more than bicarbonate secretion [34]. After steroids, studies have shown that exocrine pancreatic insufficiency evaluated by PABA test [32] or fecal elastase-1 [33] improved, but severe pancreatic insufficiency remained in 33–50% of cases. However, pancreatic exocrine insufficiency remains present in a large portion of AIP patients (80%) in the long-term follow-up after steroids [30]. Therefore, evaluation of pancreatic function in AIP is recommended to identify patients who may benefit from pancreatic enzyme replacement therapy.

Similar data have been published for endocrine pancreatic function (Table 72.3) [5,9,11,30–32], and diabetes is quite common in AIP. Steroid-induced diabetes is frequently observed at clinical onset of the disease, particularly in older patients [33,35].

The results of long-term follow-up suggest that some patients with AIP could develop pancreatic calcifications, generally after several disease relapses [21,22,36].

Loss of pancreatic exocrine and endocrine function, onset of calcifications, and atrophy of the pancreatic gland seem to suggest that AIP can transform into "*ordinary*" chronic pancreatitis. This hypothesis, even if not completely supported by clinical data and imaging findings, could explain why AIP was not identified in the past and may have been confused with chronic calcifying pancreatitis in its advanced stage.

This hypothesis also implies that imaging is only typical for AIP in the early phase of the disease and the diagnosis can be more easily achieved. In the more advanced stage, the radiologic features are less suggestive for AIP, and it is highly probable that the diagnosis of AIP will be missed.

Fig. 72.1 shows a diagram of the postulated natural history of AIP.

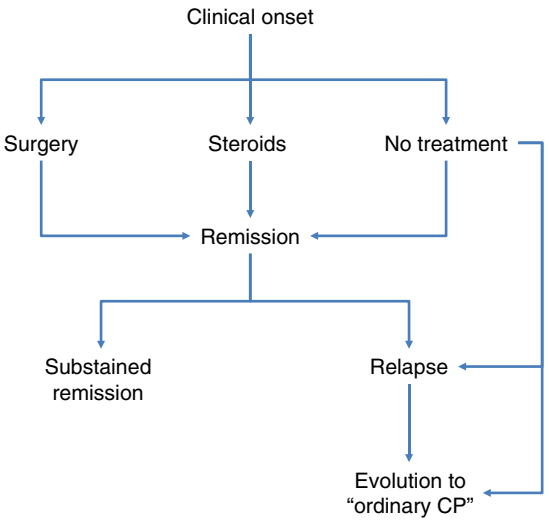


**Figure 72.1** Natural history of autoimmune pancreatitis hypothesized on the basis of evidence in the literature.

**Table 72.3** Frequency of pancreatic exocrine and endocrine insufficiency in patients suffering from AIP.

| Author | Year | Patients N. | Follow-up months | PEI | Diabetes |
|---|---|---|---|---|---|
| Kamisawa et al. [32] | 2003 | 12 | 41 | 67% | 83% |
| Frulloni et al. [9] | 2009 | 87 | 89 | 28% | 26% |
| Uchida et al. [31] | 2009 | 21 | 41 | 48% | 46% |
| Maire et al. [11] | 2010 | 44 | 41 | 34% | 37% |
| Bujis et al. [30] | 2015 | 68 | 74 | 82% | 57% |
| Lopez-Serrano et al. [5] | 2016 | 47 | 50 | 36% | 36% |

PEI, pancreatic exocrine insufficiency.

## Risk for Pancreatic and Extrapancreatic Cancer

A risk for pancreatic cancer in AIP has been reported [21,31,37–44], as for other chronic inflammatory gastrointestinal diseases, but studies are limited to case reports or small series. The risk for pancreatic adenocarcinoma is highest in the early phase of the disease, probably because the imaging features of AIP and pancreatic cancer can overlap, and lower in a more advanced phase. The clinical implication is therefore to exclude cancer at the clinical onset of the disease, and to monitor AIP patients by imaging techniques during follow-up, not only to diagnose the disease relapse, often asymptomatic, but also for an early diagnosis of cancer.

The incidence of extrapancreatic cancer within 5 years from diagnosis of AIP is high, ranging from 6.6% to 13.9% [6,45–47]. The increased risk for extrapancreatic malignancy has been reported for AIP type 1, but not for AIP type 2, which may be related to the patient's age more than the AIP subtype. It is still debated whether this incidence is increased compared to general population. In any case, physicians should be aware that 10% of patients could develop a cancer after diagnosis of AIP and, therefore, the use of immunosuppressant drugs and biologics should be carefully evaluated.

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## Section 6

## Neoplastic Tumors of the Exocrine Tissue: Benign Cystic Neoplasms of the Pancreas

73

# Epidemiology of Cystic Neoplasms of the Pancreas

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## Introduction

Pancreatic cystic lesions (PCL) can be histopathologically classified as nonneoplastic or neoplastic. Nonneoplastic cysts do not have any malignant potential and include pseudocyst, lymphoepithelial cyst, retention cyst, hydatid cyst, enteric duplication cyst, and mucinous nonneoplastic cyst. Neoplastic cysts, termed as pancreatic cystic neoplasms (PCN) have a potential to develop malignancy or are malignant at diagnosis. PCN are further classified as serous cystic neoplasm (SCN), mucinous cystic neoplasm (MCN), intraductal papillary mucinous neoplasm (IPMN) (including branch-duct and main-duct IPMN), solid-pseudopapillary neoplasm (SPN), and cystic change in an otherwise solid tumor (e.g., ductal adenocarcinoma or neuroendocrine tumor (CPNT)). The risk for developing malignancy in these cysts varies from <1% in SCN to >60% in main-duct IPMN [1–3].

PCL are being increasingly identified in asymptomatic patients on routine imaging studies [4]. While a neoplastic nature of PCL <5 mm in size is not always certain, the majority of larger, resected cysts are neoplastic [5]. However, the vast majority of PCL are not resected [6] and therefore, PCL >10 mm in size are presumed to be PCN and are managed accordingly. Studies based purely on imaging diagnosis of pancreatic cysts can provide information on incidence and prevalence of PCL in the general population [7,8]. However, these studies lack confirmatory histopathologic diagnosis. In contrast, surgical series cannot be used to determine the incidence and prevalence in the general population, but they provide information of the histopathologic spectrum of pancreatic cysts [5,6]. We use the term PCL in reference to data from imaging studies and PCN for data from surgical series. Although, some studies on PCL do make presumptive histopathologic diagnoses based on imaging and, when available, cyst fluid characteristics; however, preoperative diagnosis may be incorrect in nearly one third of PCL when correlated with surgical histopathology [9].

## Pancreatic Cyst Lesions

### Incidence

There is limited information on incidence of PCL in the general population. A study from Olmsted County, MN showed the prevalence of PCL suspected to be IPMN was 4.35 per 100,000 persons in 2005 [8] (Fig. 73.1). The age- and sex-adjusted incidence had risen 14-fold compared to 1985, when it was 0.31 per 100,000 (Fig. 73.1). This growing incidence was felt to be secondary to diagnostic scrutiny rather than a true increase in incidence over time. In this study, other non-IPMN pancreatic cysts such as SCN were excluded.

### Prevalence

In hospital-based studies, the prevalence of PCL has been reported to range between 0.2% and 41.6% [4,10–17]. Various risk factors affect the prevalence of PCL, including study-related factors and patient-related factors. Study-related factors include study design, imaging modality, and year of study. A recent study showed that incidental PCLs were documented in only 31% of radiology reports [11]. Thus, retrospective studies based on review of radiology reports rather than review of images underestimate the prevalence rates of PCL. Type of imaging modality also affects the prevalence rate, with increasing prevalence rates reported in studies using US,

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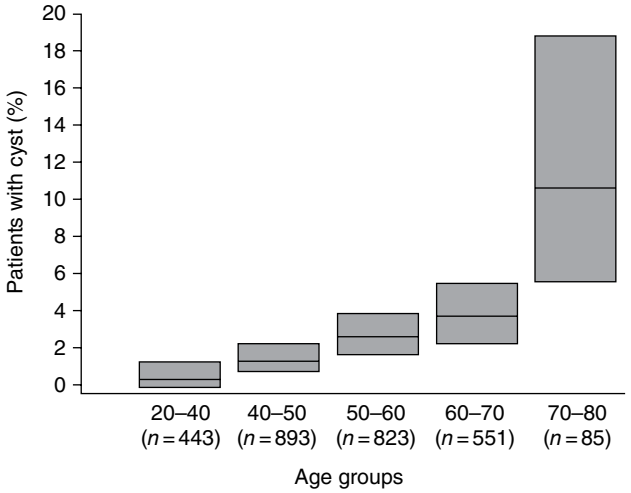


**Figure 73.1** Prevalence of pancreatic cysts per age group. The *black line* shows the prevalence and the *gray boxes* represent the CI. For patients older than age 80, see the text for more details. *Source:* de Jong et al. 2010 [14], Fig. 1. Reproduced with permission of Elsevier.

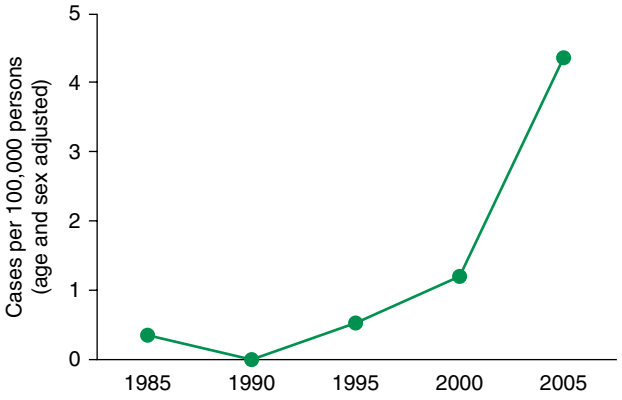


**Figure 73.2** Incidence of total IPMN per 100,000 person-years as reflected by the Rochester Epidemiology Project. *Source:* Klibansky et al. 2012 [8], Fig. 1. Reproduced with permission of Elsevier.

CT, MRI, and EUS, respectively [17,18]. Older studies report lower prevalence rates compared to newer studies. For instance, PCL were identified in 1.4% of abdominal scans in a study from 1980 [19], compared to 9.3% in a recent study from 2015 [7]. Higher prevalence in the newer studies is likely to be due to better quality of cross-sectional imaging hardware and software. In an interesting study by Moris et al., newer versions of MRI hardware and software were independently associated with higher PCL detection rates [4].

## Risk Factors

### Age

Older age is a risk factor for PCL (Fig. 73.2). In general, when study populations consist of older individuals the reported prevalence is high. For example, an autopsy series reported PCL prevalence of 24.3% in a population with a mean age of 79.3 years [16]. A study based on MRIs in asymptomatic individuals with a mean age of 51.1 years, the prevalence was 2.4% [14]. PCL are infrequent under the age of 40 years; the prevalence in this age group varies from 0–1.2%, depending on the imaging modality used to identify PCL [12,13]. However, in one study using single-shot fast spin-echo MRI sequence, the overall prevalence of PCL was 9.1% in this age group [20]. The risk rises gradually over age 40 years. In a large study the odds of a PCL being present increased by 1.06 for each additional year after age 40 [12]. In individuals over 70 years, up to 40% patients appear to have a PCL [11]. In older patients, not only does PCL prevalence increase, but also the size and number of cysts increases [11,20]. In addition, compared to younger patients, older patients have a greater likelihood of finding malignant pathology and also a greater probability of undergoing pancreatic surgery for PCL [21].

### Gender

Although one study showed greater prevalence of PCL in women [22], the majority of studies have not shown any difference in prevalence of PCL between the two sexes [11,12,14,15]. Most studies have not shown a difference in size of PCL between men and women [11,14,21], except one study, which showed larger cyst size in men compared to women [12]. There is no difference between rates of malignancy and number of PCL between the sexes [11,21].

### Race and Geography

There are limited data on prevalence of PCL based on racial background. Only one study showed that the cysts are 3.5 times more prevalent in Asians compared to non-Asians after controlling for age as a risk factor [12]. Although the prevalence was higher in Asians, cyst size, location, or number was not different compared to non-Asians.

In an autopsy study from Japan the prevalence was 24.3% [16]. By contrast, in an ultrasound-based study from Japan the prevalence was 0.21%. In a study from the Netherlands, MRIs done in asymptomatic individuals showed a prevalence of 2.4% [14]. In a recent study based on CT scans from San Marino, prevalence in asymptomatic individuals was 5.4% [7]. The estimated standardized population prevalence for the state of San Marino was 2.2% [7]. An MRI study from Brazil reported a prevalence of 9.3% [13]. Studies from the United States have shown a prevalence rate of 1.2–19.6% [11,12,20]. It is

unclear if this difference in prevalence is due to geographical factors, since various other factors that could impact prevalence, such as age and modality of imaging, were not adjusted.

#### Family History of Pancreatic Cancer

Based on a case-control study, PCL were reported to be nearly three times more common in individuals with a first-degree relative who had pancreas cancer [15]. A multicenter US screening study in high-risk individuals for pancreatic cancer, such as individuals from familial pancreatic cancer families, hereditary pancreatitis, familial atypical multiple mole melanoma, familial breast-ovarian cancer with breast-related cancer mutation and hereditary nonpolyposis colorectal cancer, and Peutz–Jeghers syndrome have shown a prevalence of 42% with multiple modalities—CT, EUS, and MRI [18]. The prevalence increased with age, as nearly 65% high-risk individuals over 70 years of age were noted to have a PCL. Another similar study from Sweden, showed a prevalence of 40% in such high-risk individuals undergoing MRI screening for pancreatic cancer [23].

In the authors' experience, 5–10% of patients with PCL have a family history of pancreatic cancer in first-degree relatives. Whether risk for pancreatic cancer is higher in this subgroup is not known.

#### History of Pancreatitis

PCN such as IPMN can cause acute pancreatitis. IPMN have also been reported in patients with chronic calcifying pancreatitis [24]. On the other hand, individuals with a history of pancreatitis can develop pseudocysts, which are often indistinguishable from PCN [25–27]. Given such issues, studies on the prevalence of PCL have typically excluded patients with a history of pancreatitis. Studies including patients with a history of pancreatitis have reported a prevalence of 16.6–42% [20,21]. However, whether these cysts represented pseudocysts or PCN was not known.

#### Miscellaneous

Recent studies have shown diabetes mellitus and insulin use as independent risk factors for PCL [15]. Presence of extrapancreatic cysts has also been strongly associated with PCL [4,14,20]. In a study, 70% patients with PCL had an extrapancreatic cyst [4]. The most frequent organs involved were kidneys (50%) and liver (50%). The presence of liver cysts is independently associated with PCL [14]. PCLs are seen in 11% of solid organ transplant recipients [28]. Fortunately, pancreatic cancer is rarely seen in this group of patients. Lifestyle factors such as cigarette smoking and alcohol consumption are not associated with development of PCL [11–14,20,21].

PCL are seen in association with autosomal dominant polycystic kidney disease (ADPKD). About 5% to 10% of individuals with ADPKD have PCL, based on ultrasound [29]. However, ADPKD is rarely seen in patients with pancreatic cysts (~1%) [20]. In contrast, pancreas involvement is frequently seen in patients with von Hippel–Lindau disease (VHL). In a large French multicenter study, 77.2% of patients with VHL had pancreatic involvement, mostly PCLs [30]. In 7.6% of these patients, the pancreas was the only organ involved. In this series, VHL patients with PCL had fewer pheochromocytomas than those without.

#### Cyst Size and Morphology

The majority of incidentally identified PCL are subcentimeter in size, the average cyst size being 8–10 mm [11–14,20]. However, cyst size increases gradually with age. For instance, in a study by Lee et al., the median cyst size in patients >90 years was 14 mm compared to 3 mm for those <39 years [11]. Large cysts (>3 cm) are infrequent, seen in <5% cases.

Among patients with incidentally identified cysts, almost half have more than one cyst [13,20]. Multifocal (>5) cysts have been reported in 10% to 40% of cases [13,14,20]. Cyst distribution is generally equal throughout the gland, with half the cysts located in the proximal part of gland (head, neck, or uncinate) and the other half in the distal part of the gland (body or tail) [11,14].

Morphologically, the majority of PCL (80–90%) identified incidentally are simple in nature without any wall thickening, septations, or mural nodules [11,14]. Communication with the main pancreatic duct is seen in 8% to 35% of cases [11,20].

## Pancreatic Cystic Neoplasms

As discussed in the preceding section, PCL are commonly seen, especially in older patients. Most of these are suspected to be PCN. The majority of these patients do not undergo surgery and therefore, their pathologic diagnosis is never known. In the few patients who undergo surgery, the histopathologic characteristics can be used to classify PCN. In one of the largest surgical series of 851 patients at Massachusetts General Hospital undergoing surgery for PCL, IPMN were the most common PCN, seen in 38% of cases [5] (Fig. 73.3). MCN were the next most common (23%), followed by SCN (16%), CPNT (7%), and SPN (3%). There was a trend towards an increasing number of surgeries for PCN in the recent time period—376 between 2005 and 2011, compared to 67 between 1978 and 1989.

IPMN are mucinous neoplasms arising from the pancreatic ducts. When they arise from the side branches,

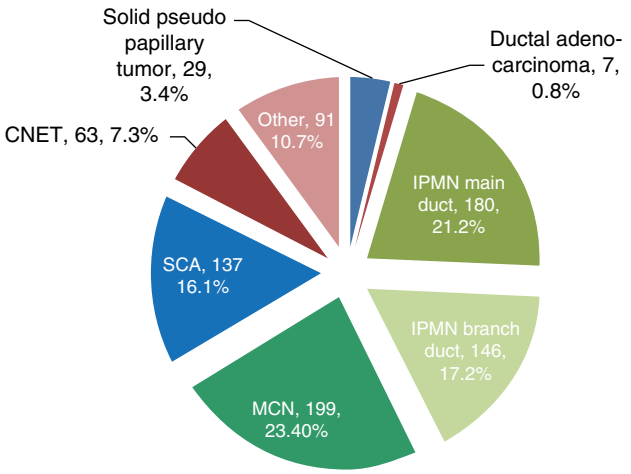


**Figure 73.3** Distribution of pathologic diagnoses in 851 resected cystic neoplasms of the pancreas. Lesions classified as "other" included pseudocysts, 25; benign epithelial cysts, 11; acinar cell cystadenomas and cystadenocarcinomas, 3; lymphoepithelial cysts, 5; choledochal cysts, 4; lymphangiomata, 4; hemangiomata, 2; and other unclassified epithelial cysts. *Source:* Valsangkar et al. 2012 [5], Fig. 1. Reproduced with permission of Elsevier.

they are referred to as branch-duct IPMN (BD-IPMN) and are called main-duct IPMN (MD-IPMN) if they involve the main pancreatic duct. Mixed-IPMN involve both branch and main ducts, but for practical purposes they are considered together with MD-IPMN.

The median age of surgery for BD-IPMN is about 65 years with an almost equal distribution between males and females [31]. However, studies from Asia have reported male sex predilection with a 3:1 ratio [32]. The median size of resected BD-IPMN varies between 2 to 3 cms [31,33]. BD-IPMN appear as a solitary cyst, multifocal cysts, or a cluster of cysts. They arise from the side branches of the pancreatic duct, although the communication with the main pancreatic duct may not always be visible. Almost 60% are located in the head of the pancreas and 40% in the body/tail region; 15–40% are multifocal [31,33]. Malignancy can be present in about 20% of cases [31,33]. About 12% have a history of pancreatitis and 35% have a history of smoking [31,33].

Similar to BD-IPMN, the median age for MD-IPMN is between 65 and 70 years [5]. They appear as dilation of the main pancreatic duct without any obstructing mass or stricture. The majority (64%) are in one location, most commonly in the head of the pancreas [3,5]. Among the 36% involving multiple locations, almost half have diffuse involvement of the entire pancreatic duct [3]. Malignancy can be seen in up to 60% of MD-IPMN, and is associated with older age, jaundice, and new-onset diabetes mellitus [3]. Mixed-IPMN have a similar risk for malignancy as MD-IPMN. One fourth of MD-IPMN have a history of pancreatitis. Most (50–60%) of MD-IPMN patients are smokers. Nearly 12% have a history of diabetes [3].

MCN are almost exclusively seen females (>95%) [34–37]. The median age is 40–50 years, and the majority of patients are <60 years [34–37]. The median size of MCN typically varies between 5 cms to 10 cms [34,37]. MCN with an associated invasive carcinoma are generally larger than benign MCN and an associated invasive carcinoma is rarely seen in those <4 cms [34,37]. They are solitary and often have septations and a thick wall. Wall calcification can be seen in about 25% of cases [35,36]. They are almost always (>90%) located in the body/tail region of the pancreas [34–37]. Less than 5% have communication with the main pancreatic duct [36]. An associated invasive carcinoma at the time of surgical resection is found in 10–20% [35–37]. Older age, larger cyst size, presence of mural nodules, and elevated CA-19-9 are associated with malignant transformation [34–37]. About 5–10% of patients with an MCN have a history of pancreatitis [35,36]. Nearly 30–40% are smokers [34,37] and 7% have a history of diabetes mellitus [34].

SCN are seen more commonly in females (75%) and the median age is 58 years [1]. Their median size is about 3 cms [38]. They are solitary, and generally appear as a cluster of multiple cysts separated by thin fibrous septae with a characteristic central scar seen in 30% of cases [39]. The pattern of cysts is microcystic in 45%, macrocystic in 32%, both microcystic and macrocystic in 18%, and solid in 5% of cases [1]. Cyst calcification is seen in about 15% of cases [1]. They are equally distributed in the pancreas with 40% in the head, 34% in the body, and 26% in the tail [1]. Malignancy is very rare (0.1%) [1]. They are seldom associated with pancreatitis and about 5% of cases have a history of diabetes [1].

SPN are mostly seen in females (>85%) [40,41] with a median age of 35 years [41]. They are generally very large at the time of diagnosis with an average size of 8.5 cms [40]. They are solitary, well encapsulated, round-oval, and have a variable amount of solid and cystic component, hemorrhage, and necrosis [41,42]. Cyst calcification can be seen in nearly half the cases [42]. They are equally distributed between the head, body, and tail of the pancreas [41]. Metastases can be seen in 15–20% of cases at surgery [41,42].

CPNT are seen at a median age of 55–60 years and are equally distributed between the sexes [43,44]. The mean size varies between 2 to 5 cms [43,44]. They are solitary cystic lesions with a varying degree of solid/cystic component. Most have arterial hyperenhancement of solid component, as is seen with other solid neuroendocrine tumors of the pancreas [43,44]. Nearly half of these have a characteristic hypervascular rim [43]. Calcification is rarely seen and 3% of cases have a history of pancreatitis [44]. They are associated with multiple endocrine neoplasia (MEN) syndrome in 6% of cases [43,44].

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# Histologic Classification and Staging of Cystic Neoplasms

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## Introduction

With the increased use of cross-sectional imaging in the work-up of numerous abdominal complaints, cystic lesions of the pancreas have been increasingly identified. The prevalence of incidental pancreatic cystic lesions in the adult population is high, and ranges from 2.6% to 19.6% [1]. Autopsy series report an increase in pancreatic cystic neoplasms prevalence with age: 8% in patients <70 years of age, up to 35% >90 years of age [2]. In clinical practice, only 5–15% of pancreatic cysts have been reported as neoplastic (Table 74.1) [3]. Recently most of pancreatic cysts are considered to be small intraductal papillary mucinous neoplasms (IPMN) or retention cysts. Cystic neoplasms, including serous cystic neoplasms (SCN), mucinous cystic neoplasms (MCN), intraductal papillary mucinous neoplasms (IPMN), solid pseudopapillary neoplasms (SPN), and some types of acinar cell neoplasms can be classified according to their malignant potential into benign, premalignant, and malignant [4]. It is important to recognize pancreatic cystic neoplasms before an invasive carcinoma develops, especially in MCN and IPMN. MCN and IPMN show ductal differentiation of the neoplastic epithelium; however, the differentiation of epithelial cells in SCN and SPN has not been fully recognized. The histopathologic classification and staging of major cystic neoplasms are discussed in this section.

## Serous Cystic Neoplasms

Serous cystic neoplasms (SCN) are almost always benign, and are indolent pancreatic neoplasms composed of innumerable small cysts lined by epithelial cells showing a clear cytoplasm and round, uniform nuclei. Patients are usually women (female/male ratio: 7:3) with a mean age at diagnosis of 60 years [5–7]. Approximately 40% of SCN are incidentally detected by imaging studies at routine physical examinations or for other diseases. Other patients complain of symptoms related to local mass effects, such as abdominal pain, palpable mass, nausea, and vomiting. Patients with von Hippel–Lindau (VHL) syndrome are at an increased risk for development of serous cystic neoplasms. SCN are observed in 15% of patients with this syndrome [8]. Sporadic SCN have been found to feature somatic mutations in the *VHL* gene in 50% of cases [8].

Macroscopically, SCN are multilocular, large cystic neoplasms and their cut surface typically shows a well-circumscribed, sponge-like appearance (called "microcystic type") with a central scar (Fig. 74.1a). The size of the cysts is variable, and there are several variants described in the following text. The cysts contain serous watery fluid. They usually do not communicate with the pancreatic larger ductal system.

Histologically, the cysts are separated from one another by thin fibrous septa and the internal surface of the cysts is covered by a monolayer epithelium (Fig. 74.1b). The lining epithelial cells have a clear cytoplasm and round, uniform, centrally located nuclei. Although a moderate nuclear pleomorphism is not unusual, necrosis and mitoses are not identified.

Because the cells contain large amounts of glycogen, they stain strongly with the periodic acid–Schiff (PAS) reaction, but only without diastase digestion. Immunohistochemically, the epithelial cells lining the cysts express cytokeratins (CK), such as CK7 and CK19, and epithelial membrane antigen (EMA), MUC6, inhibin alpha, and GLUT-1, but not CEA, trypsin, or chromogranin A [3,4].

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According to the current World Health Organization (WHO) classification, variants of serous neoplasms are classified into macrocystic serous adenomas, solid serous adenomas, VHL-related serous cystic neoplasms, and mixed serous neuroendocrine neoplasms [4]. The lining epithelium of these subtypes of SCN is the same as that of the common type (microcystic type) of SCN.

The most important differential diagnoses are with the two mucinous neoplasms, MCN and IPMN. Malignancy (serous cystadenocarcinoma) is defined by the presence of distant metastases because SCN with locally aggressive features, such as direct invasion into adjacent tissues, can rarely recur or even metastasize [5,6].

**Table 74.1** Classification of cystic lesions of the pancreas.

| |
|---|
| Cystic neoplasms – Epithelial |
| Serous cystic neoplasm |
| Mucinous cystic neoplasm |
| Intraductal papillary mucinous neoplasm |
| Solid pseudopapillary neoplasm |
| Acinar cell cystadenoma |
| Acinar cell carcinoma (intraductal papillary variant) |
| Mature cystic teratoma |
| Cystic neoplasms – Nonepithelial |
| Lymphangioma |
| Cystic degeneration of the nonepithelial neoplasms |
| Nonneoplastic cystic lesions |
| Pseudocyst |
| Retention cyst |
| Lymphoepithelial cyst |
| Mucinous nonneoplastic cyst |
| Congenital cysts |
| Enterogenerous cyst |
| Endometrial cyst |

## Mucinous Cystic Neoplasm

Mucinous cystic neoplasm (MCN) occurs almost exclusively in women (male/female ratio: 1:10–20), arises in more than 90% of cases in the body-tail of the pancreas, and has no, or very infrequent, communication with the pancreatic ductal system [9,10]. The mean age at diagnosis is approximately 45 years. Like the other cystic neoplasms of the pancreas, growing numbers of MCN are being detected in asymptomatic patients through imaging studies.

Macroscopically, MCN present as a round mass with a smooth, intracystic surface and a fibrous pseudocapsule with variable thickness and frequent calcifications. The tumor size ranges from 2 cm to 35 cm at greatest dimension. The cut surface shows unilocular or multilocular tumor cysts (so-called "cyst-in-cyst appearance") that contain mucus, watery fluid, or hemorrhagic-necrotic material (Fig. 74.2a). The internal surface can be smooth or may present with papillary projections and/or solid nodules. The presence of larger dimension papillary projections and/or mural nodules correlates significantly with malignancy.

Histologically, MCN is composed of the following two distinct components: a mucinous epithelium and a densely cellular ovarian-type stroma (OS) that represents the entity-defining feature (Fig. 74.2b). The epithelium frequently displays areas with pseudopyloric, gastric foveolar, and small and colonic intestinal differentiation. According to the recent international consensus, on the basis of the highest degree of dysplasia, noninvasive MCN are subcategorized into low and high grades [11]. Low-grade MCN are characterized by a minimally

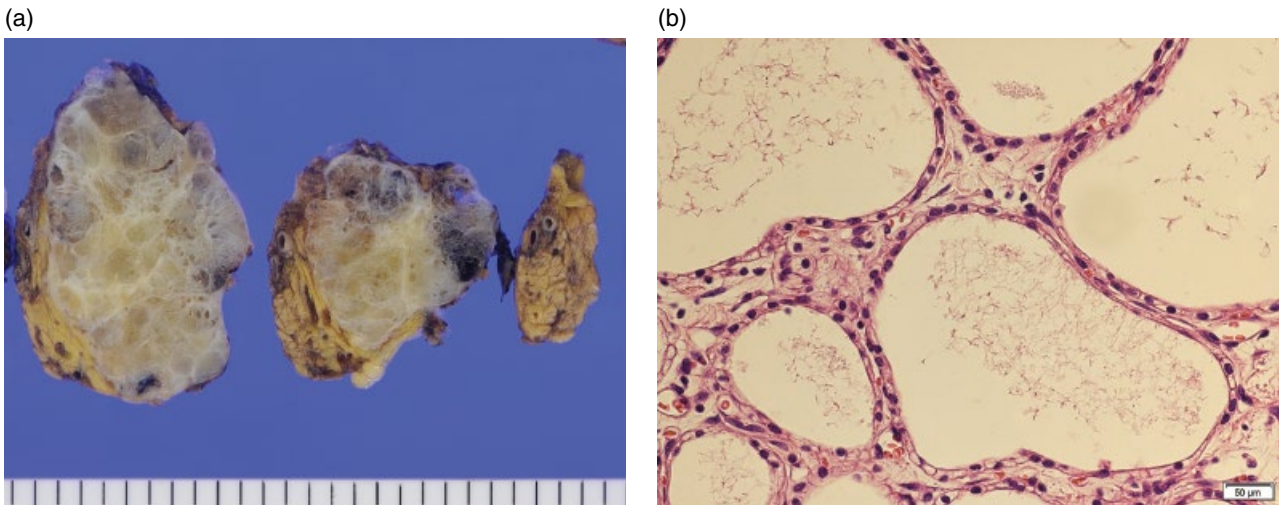


**Figure 74.1** (a) Macroscopic feature of serous cystadenoma (microcystic type). The cut surface shows the well-circumscribed sponge-like appearance with a central scar. (b) Histology of serous cystadenoma (microcystic type). The internal surface of the cyst is covered by a monolayer epithelium. The lining cells show clear cytoplasm and small, round nuclei.

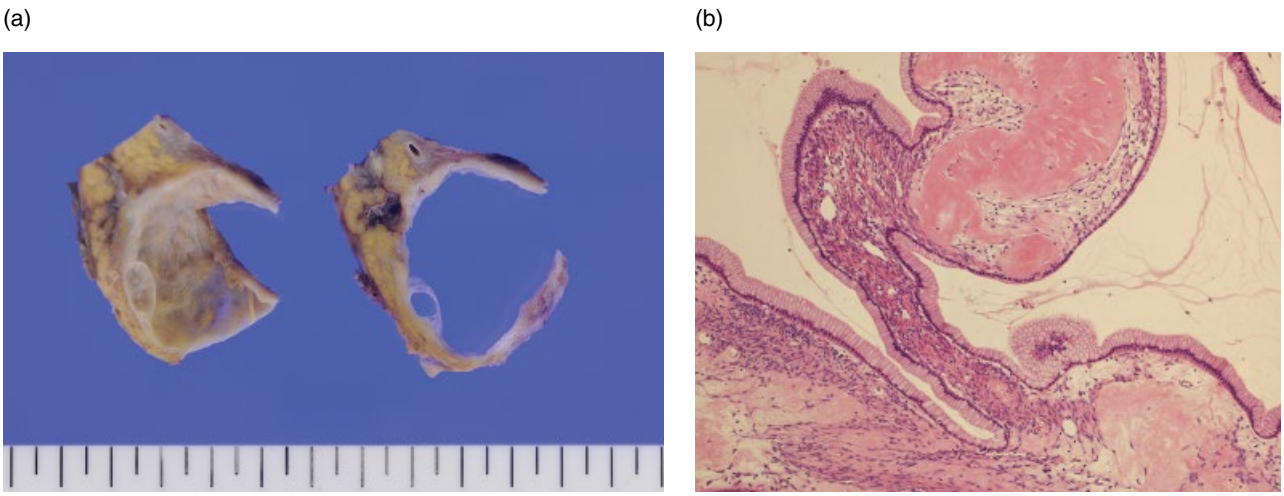


**Figure 74.2** (a) Macroscopic feature of mucinous cystic neoplasm. The cut surface shows a "cyst-in-cyst appearance." (b) Histology of mucinous cystic neoplasm. MCN is composed of a mucinous neoplastic epithelium and a subepithelial densely cellular ovarian-type stroma.

dysplastic epithelium, whereas the high-grade MCN (the equivalent of carcinoma *in situ*) show papillae with irregular branching, budding, severe nuclear atypia, and frequent mitosis. The epithelial cells frequently show immunoreactivity for gastric foveolar type mucin marker MUC5AC, whereas MUC2 is only present in the goblet cells and MUC1 is usually expressed in high-grade MCN and invasive carcinomas.

The OS is a compact layer of cellular stroma that underlines the mucinous epithelium. It is constituted by spindle cells that show immunoreactivity for vimentin, smooth-muscle actin, progesterone receptors (PR), and estrogen receptors (ER). Occasional plump, eosinophilic cells, resembling luteinized cells and expressing alpha-inhibin, may be present. The presence of OS, currently requested for the diagnosis of MCN, in some cases can be hard to identify, because the OS can be replaced by a hyalinized stroma, secondary to a long history and high pressure-related atrophy.

Up to one third of MCN are associated with an invasive carcinoma, which usually resembles the common ductal adenocarcinoma; colloid carcinomas are extremely rare [12].

The staging of the MCN with invasive carcinoma should be determined following the recent scheme proposed by Tanaka et al. [13]. The term "minimally invasive," that has been variably defined by different authors, should be avoided and replaced by the conventional staging protocols, including the AJCC/TNM. The overall size of the invasive carcinoma should be recorded and categorized as early (≤2 cm, pT1) and advanced (>2 cm, pT2, and beyond). pT1 tumors should be subcategorized into pT1a (<0.5 cm), pT1b (0.5–1 cm), and pT1c (>1 cm) [13].

The majority of MCN show an indolent clinical course. However, the survival of invasive MCN may vary from excellent [14] to 53% and 63% at 5 years [9,15]. Recently, Jang et al. [10], using the UJCC/TNM staging, reported an aggressive clinical course with 3- and 5-year survival rates of 44% and 26%, respectively, with a worse prognosis for pT2 than pTl invasive tumors. However, three of their pT1a patients died of the disease.

## Intraductal Papillary Mucinous Neoplasm

Intraductal neoplasms of the pancreas are a heterogeneous category of radiographically and grossly detectable lesions defined as cystic or mass-forming epithelial neoplasms with ductal differentiation that grow primarily within the ductal system, and that can progress to invasive carcinoma [4].

Recently, intraductal neoplasms were classified into IPMN and intraductal tubulopapillary neoplasms (ITPN) [4,16]. ITPN is an epithelial neoplasm proliferating within the pancreatic duct. The neoplastic epithelium shows nonmucinous and high-grade morphology. This neoplasm is an important entity in the differential diagnosis of IPMN; however, this is usually not recognized as a cystic lesion [16].

IPMN are more common in men than in women. The mean age is approximately 65 years. Most IPMN are solitary and located in the pancreatic head, although 20–40% are multifocal.

IPMN can be classified by several viewpoints, such as localizations (main duct or branch duct), histologic grading (low to high grade), histologic differentiation

(gastric, intestinal, oncocytic, or pancreatobiliary), and mucin hypersecreting or not.

Macroscopically, IPMN is an intraductal neoplasm usually showing flat to papillary epithelial proliferation within the dilated pancreatic ducts (>1 cm) by abundant mucus (Fig. 74.3a). IPMN can be classified into main-duct type IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN), and combined-type IPMN according to the ductal portion of tumor involvement [4,13]. MD-IPMN typically show diffuse dilatation of the main pancreatic duct with abundant mucus and villous neoplastic components. BD-IPMN show multiple cystic dilatations of pancreatic ducts called "grape-like appearance." They arise more often in the head and neck and frequently involve the uncinate process.

Histologically, the direction of differentiation of the neoplastic epithelial cells varies among IPMN, including gastric, intestinal, oncocytic, and pancreatobiliary types of differentiation. IPMN have varying degrees of cytologic and architectural atypia, and noninvasive IPMN can be categorized into low- and high grades with the same grading system as MCN. These various differentiations and grades of neoplasm are frequently mixed up within one neoplasm. Many intestinal type IPMN arise in the larger pancreatic ducts, such as the main pancreatic duct (MD-IPMN), and usually show villous or high papillary projections of neoplastic epithelium with abundant extracellular mucus (Fig. 74.3b). If they invade outside the pancreatic duct, invasive components often form a colloid (mucinous) carcinoma. Intestinal-type IPMN show MUC2, MUC5AC, and CDX2 on immunohistochemistry. Gastric-type IPMN frequently occur in branch ducts (BD-IPMN). Their inner surface is covered by low papillary or flat neoplastic epithelium with low-grade dysplasia. Many of these gastric-type IPMN have an indolent course. Gastric-type IPMN are immunoreactive with MUC5AC and MUC6 in some cases. Pancreatobiliary and oncocytic-type IPMN characteristically grow with arborized pattern. Pancreatobiliary-type and oncocytic-type IPMN are immunoreactive with MUC1, MUC5AC, and MUC6 in some cases. These different phenotypes can be observed together, with the IPMN classified according to the predominant type.

The 5-year survival rate for patients with a surgically resected IPMN without invasion is 90–95%. There are significant differences in the prevalence of invasive cancer between the MD-IPMN and the BD-IPMN. Carcinomatous transformation is reported in 30–50% of MD-IPMN or mixed-IPMN, whereas the BD-IPMN have a lower risk of carcinomatous transformation, with 24% of surgically resected BD-IPMN found to have high-grade dysplasia or invasive adenocarcinoma [13]. Most of the invasive carcinomas that arise in MD-IPMN are colloid carcinomas, whereas tubular-type adenocarcinomas, characterized by the presence of malignant glands similar to conventional pancreatic ductal adenocarcinoma (PDAC), are associated with both pancreatobiliary-type IPMN and, in a small percentage, with gastric type BD-IPMN. The type of invasive carcinoma has major prognostic implication: colloid carcinoma has a better prognosis than tubular adenocarcinomas, with the latter behaving like a conventional PDAC.

In contrast, approximately 10% of IPMN are concomitant with the conventional PDAC (histologically

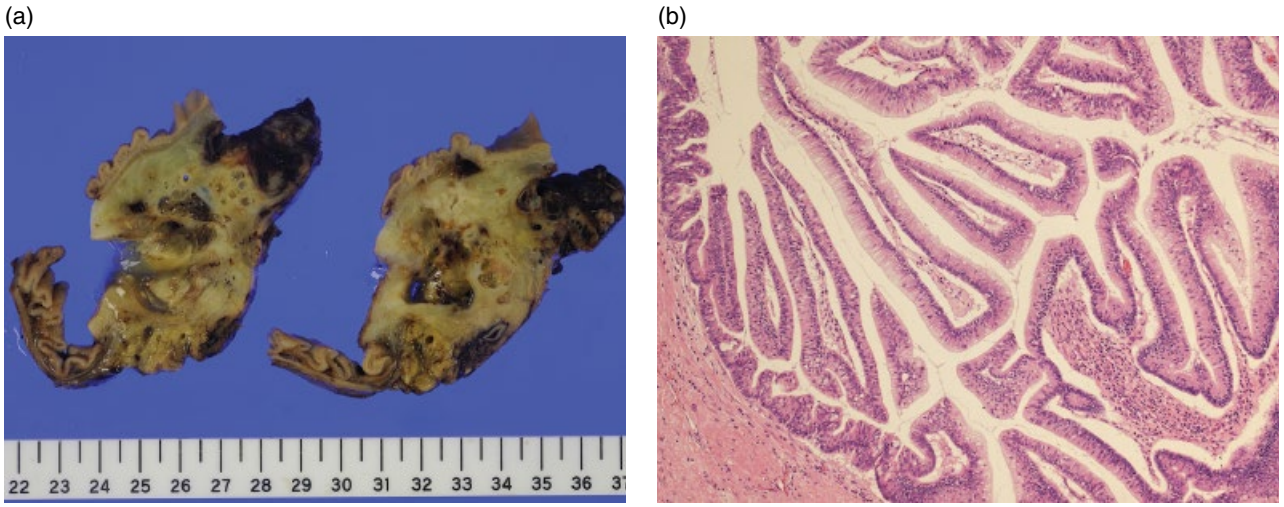


**Figure 74.3** (a) Macroscopic feature of intraductal papillary mucinous neoplasm (main-duct type). The cut surface shows intraductal papillary lesions within the dilated main pancreatic duct. (b) Histology of intraductal papillary mucinous neoplasm (intestinal type). Intestinal type IPMN shows villous projections of neoplastic epithelium.

separated from the IPMN) [17]. Although the identification of the concomitant carcinomas has biologic (GNAS mutations) and prognostic (worse prognosis) relevance, at times their correct identification can be hard to achieve. The most frequent molecular abnormalities of IPMN are either a *GNAS* or a *KRAS* mutation, and more than half IPMN have both mutations. The targeted genes found in PDAC, including *KRAS2*, *p16*/*CDKN2A*, *SMAD4*, and *TP53* genes, are found much less frequently [18,19].

The stage of the invasive carcinoma, similarly to invasive MCN, is one of the most important prognostic parameters, and should be determined following the criteria suggested by Tanaka et al. [13] and the recent recommendations of the Consensus at the Verona meeting on IPMN [20]. The UICC/AJCC staging protocol is suggested, with their subcategorization of pT1 into pT1a (<0.5 cm), pT1b (0.5–1 cm), and pT1c (>1 cm).

## Solid Pseudopapillary Neoplasm

Solid pseudopapillary neoplasm (SPN) of the pancreas is a low-grade epithelial neoplasm primarily occurring in girls and young women (20–40 years) and shows solid and cystic areas at macroscopy and pseudopapillary and poorly cohesive features at histology.

Macroscopically, SPN are frequently large, round, well-circumscribed masses and show variable proportions of solid and cystic areas filled with hemorrhagic fluid and necrotic debris (Fig. 74.4a). At the extreme ends of the spectrum of macroscopic appearances, some cases can be exclusively solid (usually the smaller lesions), whereas others (usually the larger tumors) may be entirely cystic.

Histologically, the tumors are composed of a mixture of solid and cystic areas, usually surrounded by a fibrous capsule. The tumor cells, collected in solid areas or lining pseudopapillae, are monomorphous with round to oval nuclei and eosinophilic, granular cytoplasms (Fig. 74.4b). PAS-positive globules, stromal myxoid degeneration, necrotic changes with foam cells, and hemorrhage are distinctive features of SPN. Mitotic figures are virtually absent.

The histogenesis of SPN remains unknown. The neoplastic cells show positivity for the endocrine markers CD56, NSE, and occasionally for synaptophysin, but the staining for chromogranin is always negative. Similarly, staining for acinar and ductal markers is consistently negative. Consistent positivity is present for vimentin, CD10, CD117, and progesterone receptors. Paranuclear dot-like immunostaining for CD99 is characteristic [21]. The most constant and diagnostically useful finding is the abnormal nuclear immunoexpression for β-catenin, which reflects the somatic point mutations in exon 3 of the β-catenin gene [22].

SPN are considered to be potentially malignant neoplasms, but most of the cases do not recur after complete resection of the tumor. Only 10–15% of cases progress aggressively, almost always involving the liver or the peritoneum. Even in such cases, the patients survive for many years. Only a few patients have died of a metastasizing tumor [23,24].

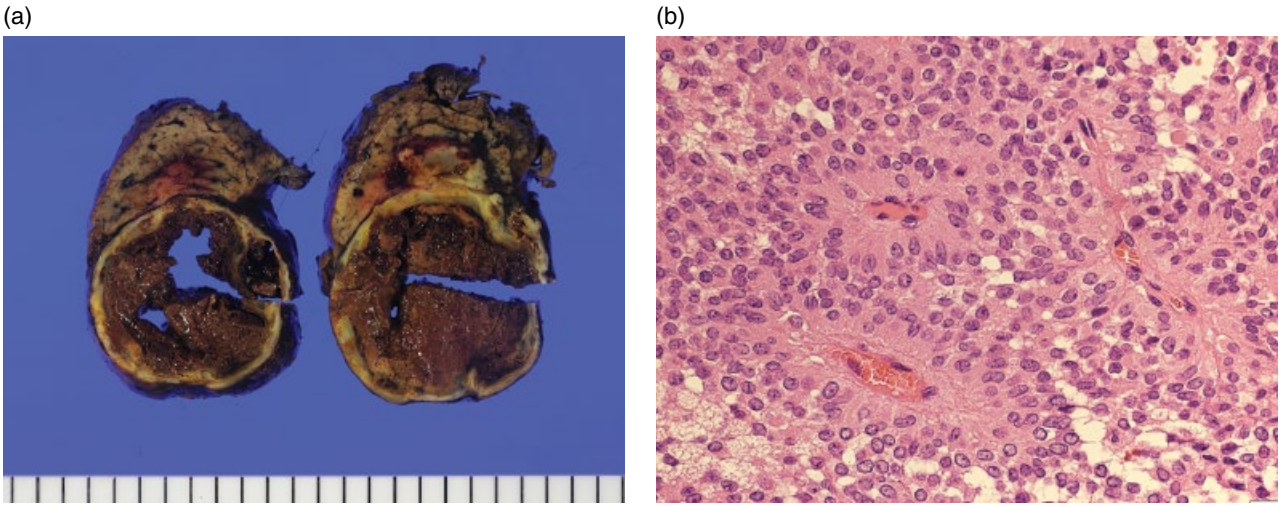


**Figure 74.4** (a) Macroscopic feature of solid pseudopapillary neoplasm. The cut surface shows round, well-circumscribed masses with hemorrhagic and degenerative material. (b) Histology of solid pseudopapillary neoplasm. Solid area of the tumor shows pseudopapillary structures composed of monomorphous cells with round to oval nuclei and eosinophilic, granular cytoplasm.

## Acinar Cell Cystadenoma

Acinar cell cystadenoma is a recently recognized cystic lesion lined by cells with acinar differentiation, and is believed to behave in a benign fashion. Many of these lesions, particularly those that diffusely involve the gland, are considered not neoplastic [25]. The lining cells of the cystic inner surface lack atypia, and transitions between the cysts and pre-existing acinar structures are often observed. Acinar cell carcinomas may rarely form intraductal papillary tumors.

## Mature Cystic Teratoma

Mature cystic teratomas, also known as dermoid cysts, are rare, benign cystic neoplasms commonly composed of multiple cell types derived from one or more of the three germ layers (ectoderm, mesoderm, and endoderm). These cystic neoplasms are filled with thick, yellow, sebaceous material. Histologically, the cysts are lined by a simple ciliated or stratified squamous epithelium and skin appendages and other tissues, such as cartilage, bone, and brain, can be seen

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# 75

# Molecular Mechanisms of Cystic Neoplasia

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## Introduction

Cystic neoplasms of the pancreas can pose significant clinical challenges. Some cystic neoplasms are precursors to invasive pancreatic cancer and they therefore are concrete opportunities to save lives through early detection and early treatment [1]. Other cystic neoplasms are, however, entirely benign, and will never progress to invasive cancer. These harmless cystic neoplasms, because they can be hard to distinguish clinically from high-risk cystic lesions, present a real risk for over-treating patients [2–4].

While enhancements in imaging and years of experience have improved the pre-operative clinical classification of cystic neoplasms, currently available imaging technologies still have relatively poor sensitivity and specificity in diagnosing cyst type, and there is still enormous room for improvement [5,6]. Simply put, too many pancreatic cysts are clinically misclassified, and when they are, patients can be harmed [2,3]. Preoperative misclassification of pancreatic cysts is the result of lack of accurate classifiers compounded by the fact that sometimes a cyst of one type can radiographically mimic a different cyst type (Table 75.1). A common consequence of misclassification of a cyst is surgery. The surgical resection of a benign pancreatic cystic lesion for the reason that it clinically mimics a potentially malignant tumor is a significant clinical problem, because pancreas surgery, even at high-volume centers, is associated with significant morbidity and a 1–2% risk of operative mortality [2].

A great deal of effort has therefore gone into defining the molecular alterations underlying the development of the different pancreatic cyst types, with the hope that knowledge of these alterations may be translatable into clinical tests to determine cyst type and the need for surgery preoperatively.

All of the major cystic neoplasms of the pancreas have recently been well-characterized at the molecular level, providing insights into the fundamental processes driving these tumors, and providing tools that can be used to classify them better preoperatively (Table 75.2) [7–9]. Importantly, studies in which both the cyst fluid and tissue form the same neoplasm were available showed excellent concordance between the genetic changes present in the cyst fluid and in the tissue, suggesting that the cyst fluid can be used preoperatively to identify genetic changes present in the neoplastic cells lining cysts.

In this chapter we will review the molecular mechanisms driving each of the major types of cystic neoplasms of the pancreas, with emphasis placed on translating this new knowledge to patient care.

## Serous Cystic Neoplasm

Serous cystic neoplasms (SCNs) are cyst-forming neoplasms composed of uniform cuboidal neoplastic cells containing abundant glycogen[10]. Although SCNs are benign and most can simply be observed clinically, many SCNs are surgically resected because they cannot be distinguished clinically from potentially malignant cystic neoplasms. For example, the oligocystic variant of SCN forms large cysts, and these large cysts can clinically mimic other cystic neoplasms of the pancreas, particularly mucinous cystic neoplasms [2,10]. Similarly, the solid variants of SCN can mimic pancreatic neuroendocrine tumors.

The exomes of a series of well-characterized SCNs have been sequenced [7,11]. SCNs contain an average of 10 intragenic somatic mutations per tumor, and the *VHL* gene on chromosome 3p is mutated in ~50% of SCNs [7]. These mutations are typically inactivating mutations. In

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 75.1** Identification of cyst type can be problematic.

| Cyst type | Clinical characteristic | Clinical management goal | Reason for misclassification |
|---|---|---|---|
| SCN | Benign | Surveillance | Cystic SCNs mimic MCNs; solid SCNs mimic PanNETs |
| IPMN | A fraction progresses to malignancy | Surgery for high grade; surveillance for low grade | Difficult to identify the grade |
| MCN | A fraction progresses to malignancy | Surgery for malignant; surveillance for the rest | Sometimes radiographically mimic SCN; hard to decipher malignant from nonmalignant |
| SPN | Malignant | Curative surgery | Cysts associated with SPNs can radiographically mimic other types of pancreatic cystic |

IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; PanNET, pancreatic neuroendocrine tumor; SCN, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm.

addition, the neoplastic cells of SCNs also often have loss of heterozygosity (LOH) on chromosome 3p at the *VHL* locus, providing a "second hit" that inactivates gene function [7]. Germline mutations in the *VHL* gene can lead to the development of serous cystadenomas, as patients with the von Hippel Lindau syndrome often develop serous cystadenomas of the pancreas [12]. As will be discussed later in the section on clinical implications, both *VHL* gene mutations, and LOH on 3p are detectable in cyst fluid and cyst fluid analysis for these markers can therefore be used to characterize a cyst as an SCN [11].

The *VHL* gene codes for a protein, VHL, which functions in the hypoxia-induced factor (HIF) pathway [13]. The VHL protein forms a complex with other proteins, and this complex has E3 ubiquitin ligase activity, functioning in the ubiquitination and subsequent degradation of hypoxia-inducible factor alpha (HIFα) [13]. HIFα is a transcription factor that functions to control gene expression in response to cellular oxygen levels. HIFα stabilization created by the inactivating mutations in *VHL*, among other things, promotes the expression of a number of genes including vascular endothelial growth factor (VEGF) which in turn promotes angiogenesis and ultimately tumorigenesis [13].

The role of the VHL in the HIF1 pathway led Yip-Schneider and colleagues to hypothesize that vascular endothelial growth factor A (VEGF-A) levels may be elevated in SCNs [14]. They therefore determined VEGF-A levels in cyst fluid samples obtained from surgically resected pancreatic cysts [14]. VEGF levels were determined by a simple enzyme linked immunosorbent assay (ELISA) test. Although the number of cases they examined was relatively small, they found that VEGF-A levels are significantly increased in cyst fluid from SCNs compared with cyst fluid from all other types of pancreatic cysts ($P < 0.0001$). They reported that VEGF-A has 100% sensitivity and 97% specificity as a biomarker for SCN [14]. Yip-Schneider and colleagues also found that the presence of a *VHL* mutation in the neoplastic cells of an SCN correlated with elevated cyst fluid VEGF levels. These studies nicely illustrate that gene and protein markers can both be useful clinically, and how genetic changes can be used to inform protein expression studies.

MicroRNA expression has not been well-studied in SCN.

## Intraductal Papillary Mucinous Neoplasm

Intraductal papillary mucinous neoplasms (IPMNs) are distinct mucin-producing neoplasms that are usually papillary and which, by definition and name, involve the pancreatic duct system [10]. IPMNs are common in the general population, especially in the elderly [15,16]. Imaging studies suggest that ~3% of the population has an IPMN [15,16]. A small fraction of IPMNs progress to invasive carcinoma, and it can be difficult to determine clinically which IPMNs need to be resected and which can be safely followed.

Intragenic somatic mutations have been reported in a number of genes in IPMNs. These genes include *KRAS, GNAS RNF43, PIK3CA, p16/CDKN2A, SMAD4*, and *TP53* [7,9].

*KRAS* (v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) gene mutations are present in ~80% of IPMNs [7,9]. These are almost always activating point mutations in codons 12, 13, or 61 of the *KRAS* gene. *KRAS* gene mutations activate a number of very complicated downstream pathways including the RAF (rapidly accelerated fibrosarcoma)/MAPK (mitogen activated protein kinase) and phosphoinositide 3′-kinase (PI3′K) pathways [17–19]. Activated KRAS also upregulates the GLUT-1 glucose transporter and alters the expression of enzymes involved in glucose utilization producing the so-called "Warburg effect" in the neoplastic cells [17–20]. In addition, activated KRAS signaling leads to constitutively high levels of autophagy [18]. All of these changes conspire to promote tumorigenesis.

**Table 75.2** Types of cysts with their major genetic alterations.

| | AVG # of intragenic mutations | *CTNNB1* | *GNAS* | *KRAS* | *PIK3CA* | *RNF43* | *SMAD4* | *TP53* | *VHL* |
|---|---|---|---|---|---|---|---|---|---|
| IPMN | 27 | | X | X | X | X | X (HGD) | X (HGD) | |
| MCN | 16 | | | X | X | X | X (HGD) | X (HGD) | |
| SCN | 10 | | | | | | | | X |
| SPN | 3 | X | | | | | | | |

HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; SCN, serous cystic neoplasm; SPN, solid-pseudopapillary neoplasm.

Activating point mutations in the *GNAS* (Guanine nucleotide binding protein (G protein), alpha stimulating activity polypeptide 1) gene, usually at codon 201 (R201C and R201H), are present in ~75 % of IPMNs [7–9]. *GNAS* mutations appear to be more common in IPMNs with "intestinal" differentiation than they are in IPMNs with "pancreatobiliary" or "gastric-foveolar" differentiation [9,21]. A *GNAS* mutation and/or a *KRAS* gene mutation are seen in >90% of IPMNs [8,9]. The *GNAS* gene codes for a protein which forms a protein complex that activates adenylate cyclase.

Several studies integrating *GNAS* and *KRAS* mutational analyses with tissue pathology have provided insight into IPMNs biology and clinical behavior. For example, IPMNs have historically been defined pathologically as lesions >1 cm, while smaller precursor lesions (<0.5 cm) are categorized pathologically as pancreatic intraepithelial neoplasia (PanIN) [22]. This leaves a large unclassified grey zone for lesions between 0.5 and 1.0 cm. PanINs have not been shown to harbor *GNAS* mutations, while IPMNs do. Matthaei and colleagues therefore examined 21 lesions in the size grey zone (0.5 cm–1.0 cm) for *KRAS* and *GNAS* mutations [23]. *GNAS* mutations were identified in seven (33%) of these lesions, helping to define them as small ("incipient") IPMNs rather than large PanIN lesions [23]. As a result the new pathologic classification system for precursor lesions in the pancreas now includes the new term "incipient IPMN" for lesions ≤1.0 cm with histologic or genetic features of a larger IPMN [24]. Matthaei and colleagues also used *KRAS* gene mutational and LOH analyses to establish that grossly multifocal IPMNs are, in some cases, genetically multiclonal, too [25].

The *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) gene codes for a protein that forms the catalytic subunit of the phosphatidylinositol 3-kinase (PI3K) enzyme. This enzyme activates a number of downstream functions that in turn promote cell proliferation and migration, and ultimately cell survival and tumorigenesis. *PIK3CA* gene mutations have been reported in 10% of IPMNs [9]. These mutations are, as was true for *GNAS* mutations, more common in IPMNs with intestinal differentiation.

Inactivating mutations in the *RNF43* gene are present in 30–70% of IPMNs [7,9]. The *RNF43* gene codes for a ubiquitin ligase protein that functions in the Wnt/β-catenin signaling pathway [26,27]. As will be discussed later in this chapter, the presence of genetic alterations of the *RNF43* gene in some IPMNs suggests that Wnt/β-catenin signaling is a potential therapeutic target for invasive carcinomas that arise from *RNF43* mutant IPMNs [26,28].

*SMAD4*, *p16/CDKN2A*, and *TP53* are all tumor suppressor genes that have been reported to be inactivated in IPMN [7,9]. The *p16/CDKN2A* gene, which encodes CDKN2A, an important regulator of the cell cycle, is inactivated by intragenic mutation, usually a deletion or an indel, of one allele coupled with LOH of the second allele in 10–30% of IPMNs, and in additional cases by hypermethylation of the gene's promoter [7,9,29]. Mutations in this gene can be seen in IPMNs with both low- and high-grade dysplasia. By contrast, *SMAD4* and *TP53* inactivation appear to be late genetic events, and are found in IPMNs with high-grade dysplasia and in invasive carcinomas that arose in association with an IPMN [7,9].

Studies of the genetic alterations present in the noninvasive and invasive components of IPMNs have shown that the invasive and noninvasive components virtually always harbor identical mutations [7,9]. This finding helps establish that invasive carcinomas can arise from IPMNs (they are not chance coincidental lesions).

The expression of a number of microRNAs is dysregulated in IPMN. These microRNAs may have important biologic functions in the neoplasms, and some may be useful clinical markers [30–34]. For example, Matthaei and colleagues compared the expression of 750 microRNAs in a series of microdissected IPMNs to their expression in normal ductal epithelium and identified a panel of microRNAs that have the potential of being used to distinguish IPMNs with low-grade dysplasia from IPMNs with high-grade dysplasia [30]. Similarly, Caponi and colleagues found that miR-21 and miR-155 are upregulated in IPMNs with an associated invasive carcinoma, as compared with IPMNs without an invasive carcinoma, and, conversely that miR-101 levels are higher in IPMNs without an invasive component than in IPMNs with an invasive component [34]. Going a step further, Matthaei and colleagues also identified a panel of microRNAs that could help distinguish IPMNs from other types of cysts in the pancreas [30]. Of note, microRNAs can be identified in cyst fluid samples, suggesting that quantifying microRNA levels in cyst fluid aspirated at the time of endoscopy could be used to improve the clinical classification of pancreatic cysts [30,32].

A number of alterations in protein and glycoprotein expression have also been reported in IPMNs [35–40]. As is true for microRNAs, several proteins and glycoproteins are differentially expressed in IPMNs with low-grade as compared to IPMNs high-grade dysplasia, and most are detectable in cyst fluids [35–37]. Pandey and colleagues have established a useful on-line resource that summarizes many of proteins whose expression is altered in invasive pancreatic cancer, and the expression of many of these proteins is also altered in IPMNs [38].

## Mucinous Cystic Neoplasm

Mucinous cystic neoplasms are mucin-producing and cyst-forming neoplasms that contain a characteristic ovarian-type stroma [10]. In contrast to IPMNs, the cysts of MCNs almost never communicate with the main duct system of the pancreas [10]. As is true for IPMNs, only a fraction of MCNs progress to invasive carcinoma.

Many of the genes targeted in IPMNs are also targeted in MCNs [7]. These genes include *KRAS*, *RNF43*, *PIK3CA*, *p16/CDKN2A*, *SMAD4*, and *TP53* [7,41]. The major difference is that, in contrast to IPMN, the *GNAS* gene is rarely, if ever, targeted in MCNs. The function of these genes is described in detail earlier in the section on IPMNs.

Just as the genetic alterations found in IPMNs have proven useful, so too have a number of groups attempted to use the genetic alterations in MCNs clinically. As noted earlier, oligocystic serous cystadenomas can mimic MCNs, and, as a result, some benign serous cystic neoplasms are surgically resected [10]. There is therefore a great clinical need to distinguish between these two entities. The initial clinical results using molecular approaches to distinguish between serous cystic neoplasms and MCNs are not as promising as they are with IPMNs [42]. For example, Singhi and colleagues tested 546 pancreatic cyst fluid samples obtained by fine-needle aspiration at the time of endoscopic ultrasound (EUS) for *KRAS* gene mutations and found that although *KRAS* mutations had a specificity of 100% and a sensitivity of 54% for mucinous differentiation (IPMNs and MCNs), the sensitivity was only 14% when limited to MCNs [42]. However, with improvements in methodology, addition of more genes, and new algorithms the sensitivity of detecting MCNs has increased significantly [7,11].

The patterns of microRNA expression in MCNs have been studied, and as is true for the genetic mutations, there is some overlap with IPMNs [32]. For example, mir-21 is elevated in MCNs [32].

## Solid-Pseudopapillary Neoplasm

Solid-pseudopapillary neoplasms are epithelial neoplasms composed of poorly cohesive, relatively uniform, neoplastic cells [10]. Although all SPNs are now classified as malignant, the vast majority(~90%) of patients with an SPN can be cured with surgical resection [10].

The exomes of a series of well-characterized SPNs have been sequenced, and, quite remarkably, virtually all SPNs harbor a *CTTNB1* (β-catenin) gene mutation, and practically no other genetic alterations [7,43,44]. The *CTTNB1* mutations observed prevent the degradation of the β-catenin protein, which is then translocated from the cytoplasm to the nucleus. In the nucleus β-catenin functions to activate the Wnt (int/Wingless) signaling pathway which in turn mediates gene expression through the lymphoid enhancer-binding factor 1 (LEF1)/T-cell factor transcription complex [45]. Indeed, Singhi and colleagues have shown that *CTTNB1* gene mutations strongly correlate with LEF1 nuclear overexpression in SPNs [45].

Of interest, SPNs are also characterized by alterations in e-cadherin expression, including loss of expression of the extracellular domain of the e-cadherin protein [46,47]. Recently Huels and colleagues have suggested that reduced e-cadherin expression has a synergistic effect with activating mutations in β-catenin in promoting tumorigenesis [48].

Little is known of the changes in microRNA and protein expression in SPNs [49–51]. In large part this is because the normal cell type that corresponds to the neoplastic cells of SPNs is not well defined. Therefore, expression studies are challenged by the absence of a good control tissue/normal cell type. Several immunohistochemical labeling studies using a candidate marker approach have shown that CD99 and CD10 are overexpressed in SPNs, that the β-catenin protein is abnormally localized to the nucleus, and that e-cadherin expression is lost (when antibodies to the extracellular domain are used) or abnormally localized to the nucleus (when antibodies to the intracellular domain are used) [52,53].

## Other Cystic Neoplasms of the Pancreas

For completeness sake we should mention that some typically solid neoplasms of the pancreas can present as cystic masses. For example, pancreatic neuroendocrine tumors (PanNETs) can be cystic, as can some ductal adenocarcinomas [10]. These cystic variants appear to have the same molecular alterations as the solid variants of these same tumors.

## Clinical Applications

Several clinical applications of our growing knowledge of the molecular events that drive the formation of cystic neoplasms of the pancreas have been mentioned earlier, and in this section we focus on what we believe to be the most promising clinical applications close on the horizon.

First, the genes mutated in IPMNs can be used clinically to distinguish IPMNs from other neoplasms, and in so doing prevent unnecessary surgeries [7,8]. For example, as noted earlier, serous cystic neoplasms virtually never harbor *KRAS* or *GNAS* mutations, while one or both of

these mutations is seen in 90–95% of IPMNs [11]. Since mutant DNA present in neoplastic cells is shed into the cyst fluid, endoscopic ultrasound (EUS) aspiration of cyst fluid coupled with sequencing of the fluid for *KRAS* or *GNAS* mutations can be used to distinguish serous cystadenomas from IPMNs [11,42]. Furthermore, the cysts of IPMNs communicate with the pancreatic duct system, suggesting that a similar approach can be taken with sequencing secretin-stimulated pancreatic secretions ("juice") obtained in the duodenum at the time of endoscopy [54,55]. It is hoped that additional markers, such as *SMAD4* and *TP53* gene mutations and patterns of LOH, will be useful in distinguishing IPMNs with low-grade dysplasia from IPMNs with high-grade dysplasia [11].

Second, some of the molecular alterations present in cystic neoplasms that progress to invasive carcinoma are potentially therapeutically targetable. As mentioned previously, a significant fraction of IPMNs and MCNs harbor *RNF43* gene mutations that are predicted to activate the Wnt signaling pathway [7,26,56]. A number of new agents, including selective inhibitors of the porcupine protein in the Wnt pathway, are being developed that could be effective in treating invasive pancreatic cancers that have *RNF43* mutations because they arose from a precursor IPMN with an *RNF43* mutation [26].

The *PIK3CA* gene functions in the mTOR pathway and *PIK3CA* is targeted in ~10% of IPMNs [9]. A number of agents targeting PIK3CA have been developed, and again, these agents could be effective in treating invasive pancreatic cancers that have *PIK3CA* gene mutations because they arose from an IPMN precursor with a *PIK3CA* gene mutation.

## Implications for Families

Several familial cancer syndromes are associated with an increased risk of developing a pancreatic cystic neoplasm. Perhaps the greatest risk is seen in patients with the Peutz–Jeghers syndrome (PJS) [57]. Patients with PJS have a 130-fold increased risk of developing invasive pancreatic cancer, and Su and colleagues have demonstrated that some of these invasive cancers arise from noninvasive IPMN precursor lesions [58]. This suggests that patients with PJS may benefit from screening for early curable pancreatic neoplasms (noninvasive IPMNs) [59–61].

Although not strictly a "familial genetic syndrome," the McCune-Albright syndrome is caused by *GNAS* mutations acquired very early during embryogenesis [62,63]. Affected individuals harbor mosaic *GNAS* mutations, and ~15% of individuals with the McCune-Albright syndrome, in addition to the characteristic skin and bone changes, develop IPMNs, some of which progress to invasive carcinoma [62,63]. Of note, Parvanescu and colleagues screened 272 patients operated on for an apparently sporadic IPMNs and found a patient with polyostotic fibrous dysplasia and café au lait spots suggestive of McCune-Albright syndrome [62].

Finally, as noted earlier, germline *VHL* gene mutations cause the von Hippel–Lindau syndrome (VHL), and patients with VHL frequently develop serous cystadenomas of their pancreas [12]. Fortunately, these are virtually always benign.

## Conclusions

It is clear that there is a clinical need to better classify cysts preoperatively. Current guidelines do not appear to be adequate [64]. Molecular analyses of cystic neoplasms of the pancreas have helped validate the existing histologic classification of these cysts, and have provided new opportunities to improve the clinical management of patients with a cystic tumor of the pancreas.

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# 76

# Clinical Presentation of Cystic Neoplasms

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## Introduction

Pancreatic cystic neoplasms comprise intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystic neoplasms (SCN), lymphoepithelial cysts, epidermoid cysts, and the cystic degeneration of solid tumors including solid-pseudopapillary neoplasms (SPN) and cystic pancreatic neuroendocrine neoplasms (cystic PanNET) [1,2]. The varied clinical manifestations of cystic neoplasms of the pancreas are important to recognize for several reasons. First, the clinical manifestations can be nonspecific, and if clinicians are not familiar with them, the symptoms caused by a clinically important cystic neoplasm can be misinterpreted as secondary to a benign etiology such as back strain. Second, the clinical manifestations of a cystic lesion in the pancreas can provide a clue as to the type of cyst. For example, some clinical manifestations such as those of pancreatitis, suggest the diagnosis of an IPMN over an SCN. Finally, some clinical manifestations, such as jaundice, are suggestive of an associated invasive carcinoma, and can help guide the management of a cystic lesion in the pancreas [3]. Therefore, accurate diagnosis is imperative as management is guided by symptoms and risk of malignancy. Here, we describe the clinical presentation of PCN.

## Classification

Fig. 76.1 shows a general classification of pancreatic cystic neoplasms. True cysts can be neoplastic or nonneoplastic. Neoplastic true cysts include SCN, MCN, and IPMN. Nonneoplastic cysts comprise cystic fibrosis, as well as retention, lymphoepithelial, and epidermoid cysts. Cystic degeneration of solid tumors, including cystic PanNET and SPN, can also produce cystic lesions, as can nonneoplastic pseudocysts.

Typical patient characteristics are shown in Table 76.1.

## General Clinical Presentation of Pancreatic Cysts

Most pancreatic cysts are asymptomatic, and the cysts are discovered incidentally on imaging for another indication. The symptoms of pancreatic cysts mainly depend on their size. Larger pancreatic cysts can cause abdominal discomfort (abdominal/back pain, loss of appetite, nausea, and vomiting). Pancreatic pseudocysts should be considered in patients with chronic pancreatitis and when a patient has persistent abdominal pain after an episode of acute pancreatitis. If pancreatic cysts, such as IPMN, communicate to the pancreatic duct, pancreatitis can be seen due to mucin or bleeding inside the cyst. If the pancreatic cyst has an associated invasive carcinoma, and begins to invade the surrounding tissues, it may lead to the same symptom as pancreatic ductal cancer.

## Clinical Presentation and Characteristics of Serous Cystic Neoplasms

Serous cystadenomas (SCA) account for about 16% of resected cystic tumors of the pancreas [3]. Four-fifths of SCN are asymptomatic and are found incidentally. Even when symptomatic, the symptoms are mostly vague and nonspecific nausea, abdominal discomfort, and weight loss. These symptoms are caused by mass effects or compression of the main pancreatic duct, resulting in

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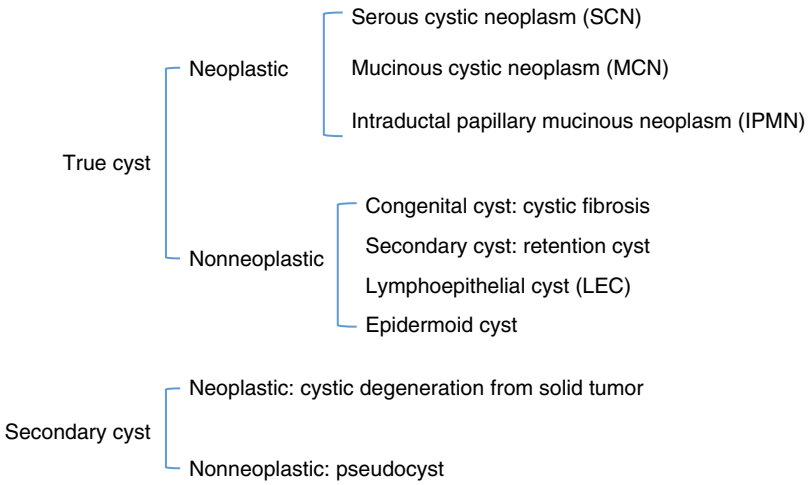


**Figure 76.1** Classification of pancreatic cystic lesions.

**Table 76.1** Characteristics of pancreatic cystic lesions

| | IPMN | MCN | SCN |
|---|---|---|---|
| Age | 50–70 | 40–60 | 50–70 |
| Gender | Male > Female | Female | Female > Male |
| Location | Head > Body/tail<br>Multifocal | Body/tail | Body/tail > Head |
| Symptom | Yes<br>Acute pancreatitis | Size dependent (mass effect) | Size dependent (mass effect) |
| Malignant potential | Yes | Yes | No (rare) |

obstructive pancreatitis. Clinical symptoms are observed more commonly in large(>4 cm) compared to smaller (<4 cm) SCN (72% vs.22%, $P < 0.001$) [4]. Jaundice is rarely seen in patients with an SCN, but may occur when an SCN located in the head of the pancreas has enlarged and occluded the common bile duct.

SCN occur in 35–75% of patients with von Hippel–Lindau(VHL) disease, and in these patients SCN are often multifocal and can diffusely involve the pancreatic gland [5]. Pancreatic cysts can be the first manifestation of VHL.

On imaging, the typical SCN is composed of many tiny microcysts with a honeycomb appearance lined by a cuboidal, glycogen-rich epithelium. Microcystic SCN typically appear on CT and MRI as isolated, lobulated multilocular lesions with well-defined margins in clusters of (usually >6) small cysts separated by a thin septum [6]. Each small cyst is usually <2 cm. Microcysts can occasionally appear as a solid mass on CT, but high signal intensity is evident on T2-weighted MRI. Microcyst structures can be further defined using endoscopic ultrasound (EUS). The septa are usually thin, and typical microcystic SCN have a calcified central fibrotic scar [7,8]. The macrocystic type of SCN without a microcystic component requires differentiation from MCN, or branch-type IPMN.

## Clinical Presentation and Characteristics of Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCN) are relatively uncommon neoplasms that comprise about 25% of all resected cystic neoplasms of the pancreas [3]. MCN arise in the distal pancreas (>95%) almost exclusively (>95%) in women with a peak incidence in the fifth decade [7]. In a Japanese multicenter study, only 1 of 156 patients with MCN had the tumor in the head of the pancreas, and the median age of diagnosis was between 45 and 48 (range, 16–84) years [8]. Unlike branch duct (BD)-IPMN, MCN are almost always solitary lesions [3]. They are often large, measuring 8–10 cm, but rare examples can be as large as 25 cm [9–11].

Most patients present either incidentally or with vague symptoms, and the clinical presentation depends on tumor size. Symptoms include a palpable mass in the upper abdomen reported 12% with MCN patients [3], and rarely general fatigue and weight loss. Ten (6.5%) of 153 patients in one series presented with acute pancreatitis. In patients with MCN, the presence of clinical symptoms (especially back pain, jaundice, or systemic

manifestations) should increase the suspicion for underlying associated invasive carcinoma [12]. Communication with the main pancreatic duct is very rare in MCN.

Sperti et al. [13] reported two patients with MCN whose first presentation was an acute attack of pancreatitis and pointed out the possibility of misdiagnosing MCN as a pseudocyst in such patients. MCN should be considered when acute pancreatitis has occurred in nonalcoholic women with no gallstones and has resulted in a cyst formation in the body and tail of the pancreas.

## Clinical Presentation and Characteristics of Intraductal Papillary Mucous Neoplasms

IPMN of the pancreas represent 60% of cystic pancreatic lesions and occur more frequently in elderly men [5]. They are classified as main-duct (MD-IPMN), or BD-IPMN arising from branches, or as mixed IPMN arising in both the main duct and side branches.

Of all the cystic neoplasms of the pancreas, IPMN most commonly produce clinical manifestations. Main-duct IPMN are more often symptomatic than are branch-duct IPMN. Some IPMN, especially those of the main duct, can produce copious amounts of mucin. This mucin may occlude the pancreatic duct, causing acute pancreatitis manifested as epigastric discomfort, episodes of severe pain, and hyperamylasemia. These symptoms can recur repeatedly for many years, but they become less frequent with time because of loosening of the papillary orifice caused by repeated passage of mucin, and as the pancreas itself atrophies from the damage caused by the repeated episodes of pancreatitis. Approximately 25% of patients reportedly have had symptoms of pancreatitis. The presence of symptoms is an independent risk factor for malignancy in multivariate analysis assessing the relationship between clinical features and malignancy [9,14,15].

## Clinical Presentation and Characteristics of Solid-Pseudopapillary Neoplasms

SPN are uncommon cystic lesions of the pancreas, accounting for <4% of resected pancreatic cystic lesions [3]. SPN are much more common in women than in men (>80%) and most occur in the third or fourth decades of life [16]. SPN can occur throughout the pancreas but usually occur in the pancreatic body or tail, and usually present with nonspecific symptoms such as abdominal discomfort, increased abdominal girth, and poor appetite and nausea from tumor compression of adjacent organs [16]. With the increased use of abdominal imaging, more and more SPN are being discovered incidentally [3]. In a recent systematic review of SPN, the most common presenting symptom was abdominal pain or discomfort, which was present in 65% patients. Patients also presented with a palpable abdominal mass, nausea or vomiting, and weight loss. Pancreatitis and jaundice were relatively rare, occurring in 5.0% and 10.3% of patients, respectively. Almost 40% of the patients were asymptomatic. In rare cases, the SPN can rupture producing an acute abdomen.

## Clinical Presentation and Characteristics of Cystic Pancreatic Neuroendocrine Neoplasms

Cystic pancreatic neuroendocrine neoplasms (CPanNET) account for approximately 8% of resected PCN [3,11] and 10–15% of resected pancreatic neuroendocrine tumors [3,11]. Most are found incidentally and are nonfunctioning. They occur equally in men and women, are usually diagnosed between 60 and 70 years of age [3], and are more prevalent in the body and tail of the pancreas [17]. CPanNET are more common in patients with multiple endocrine neoplasia type 1 (MEN-1), with one study finding MEN-1 to be 3.5 times more likely in CPanNET than in solid tumors [18].

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# 77

# Evaluation of Cystic Lesions Using EUS, MRI, and CT

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## Introduction

Pancreatic cysts are incidentally detected in 2.6% of computed tomography (CT) and 3–13% of magnetic resonance imaging (MRI) studies [1,2]. Pancreatic cysts represent a range of etiologies from benign cysts such as pseudocysts or serous cystadenomas, those with the potential for progressing to invasive carcinoma (IC), such as intraductal papillary neoplasms (IPMN), and mucinous cystic neoplasms (MCN), as well as those that are by definition malignant, including solid-pseudopapillary neoplasms (SPN) and cystic degeneration of a neuroendocrine tumor (NET). The four most common types of pancreatic cysts seen are pseudocysts, IPMNs, MCNs, and serous cystadenomas (SCAs), which account for over 90% of pancreatic cysts seen [3].

Imaging plays two critical roles. First to identify the type of cyst, and second to identify features associated with the presence of high-grade dysplasia (HGD) or invasive carcinoma (IC) in patients with IPMNs and MCNs, in whom surgical resection should be considered [4]. In this chapter, we review the imaging features of different types of pancreatic cysts using CT, MRI, and endoscopic ultrasound (EUS).

## Low-Risk Pancreatic Cysts

### Pseudocyst

Pancreatic pseudocysts are inflammatory collections related to trauma, acute or chronic pancreatitis. They are well defined, and found either within, or adjacent to the pancreas, and can be single or multiple. Initially the wall is thin but may thicken as the pseudocyst matures. Pseudocysts appear as low-attenuation fluid collection on CT. On T1 weighted (T1W) images, they have a hypointense center, with an enhancing wall. Blood products, necrotic or proteinaceous debris are commonly present in postnecrotic collections associated with necrotizing pancreatitis (walled-off pancreatic necrosis) and are seen as areas of increased signal on T1W images [5]. On T2 weighted (T2W) images pseudocysts appear hyperintense due to their fluid content. Similarly areas of decreased signal may be seen in postnecrotic collections or walled-off pancreatic necrosis due to the presence of debris [5]. In acute pancreatitis, peripancreatic fluid and stranding may be present, which correlates with the degree of inflammation present on the T2W fat-suppressed images [6]. On EUS, they appear as a well-defined, anechoic lesion. The wall may appear thickened, and debris can appear as irregular, echogenic material within the cyst (Fig. 77.1). Differentiating pseudocysts from IPMNs can occasionally be difficult, as highlighted by surgical series in which pseudocysts account for between 3–6% of resected cases, and cyst fluid analysis can be helpful in these cases [3,7]. A very low cyst fluid amylase of <250 U/L excludes 98% of pseudocysts [8]. A CEA of <5 ng/mL has a high specificity (98%), but low sensitivity (50%) for a pseudocyst [8].

### Serous Cystadenoma

SCAs are typically unifocal lesions, and can occur in any location in the pancreas. The exception to this rule is von Hippel–Lindau disease, in which multiple SCAs occur. Two-thirds occur in women, with a median age of presentation of 58 years [9]. They carry an exceptionally small risk (0.1%) of transformation into a cystadenocarcinoma [9]. Thus, differentiating these

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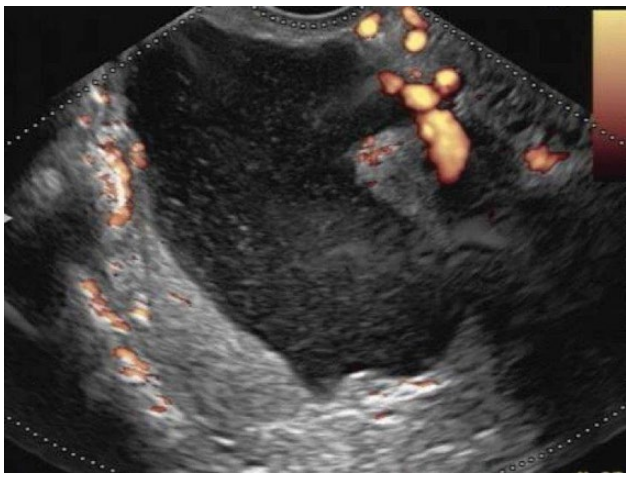

**Figure 77.1** Pseudocyst. The features of a well-defined pseudocyst seen on EUS, with hyperechoic material within the cyst consistent with debris. *Source:* Copyright AML, by permission of the author.

very low-risk cysts from other types of neoplastic cysts is extremely important for appropriate clinical management. Classical teaching is that SCAs have a non-dilated main pancreatic duct, which does not communicate with the cyst. However, 10% of pathologically proven SCAs had evidence of communication on ERCP on preoperative imaging, while main-duct dilation is found in between 11–50%, and a stricture identified in 37.5% [9,10]. The presence of a central scar, with or without calcification, is found in between 11–30% of SCAs and is very specific [10]. A microcystic, or honeycomb, appearance is found in 45–58% of SCAs, 32–35% have a macrocystic, 18–28% a mixed macro- or microcystic appearance, and 5–6% have a solid appearance (Fig. 77.2a–d) [9,10]. On CT, the most common appearance is a conglomeration of small cysts that are greater than six in number, measure up to 2 cm and may exhibit a central scar with or without calcification [11]. On MRI they have a low intensity on T1W

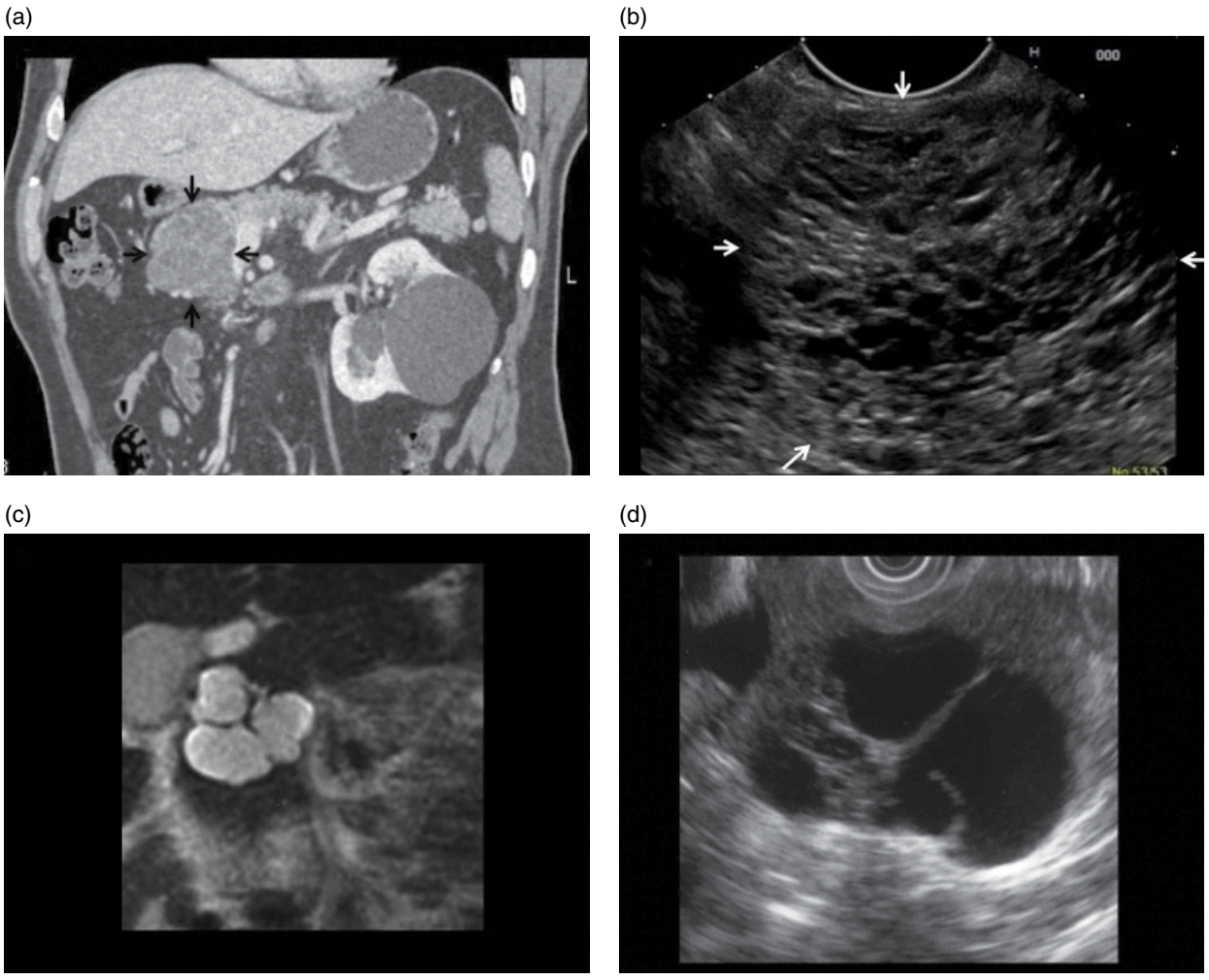


**Figure 77.2** Serous cyst. Serous cysts (arrows) have a range of appearances including microcystic (a,b), macrocystic (c), mixed macro and microcystic (d). They can occasionally have a solid appearance (e,f). In these cases MRI/MRCP is helpful in confirming the cystic, rather than solid nature of the cyst (g). *Source:* (a,b) Copyright AML, by permission of the author.

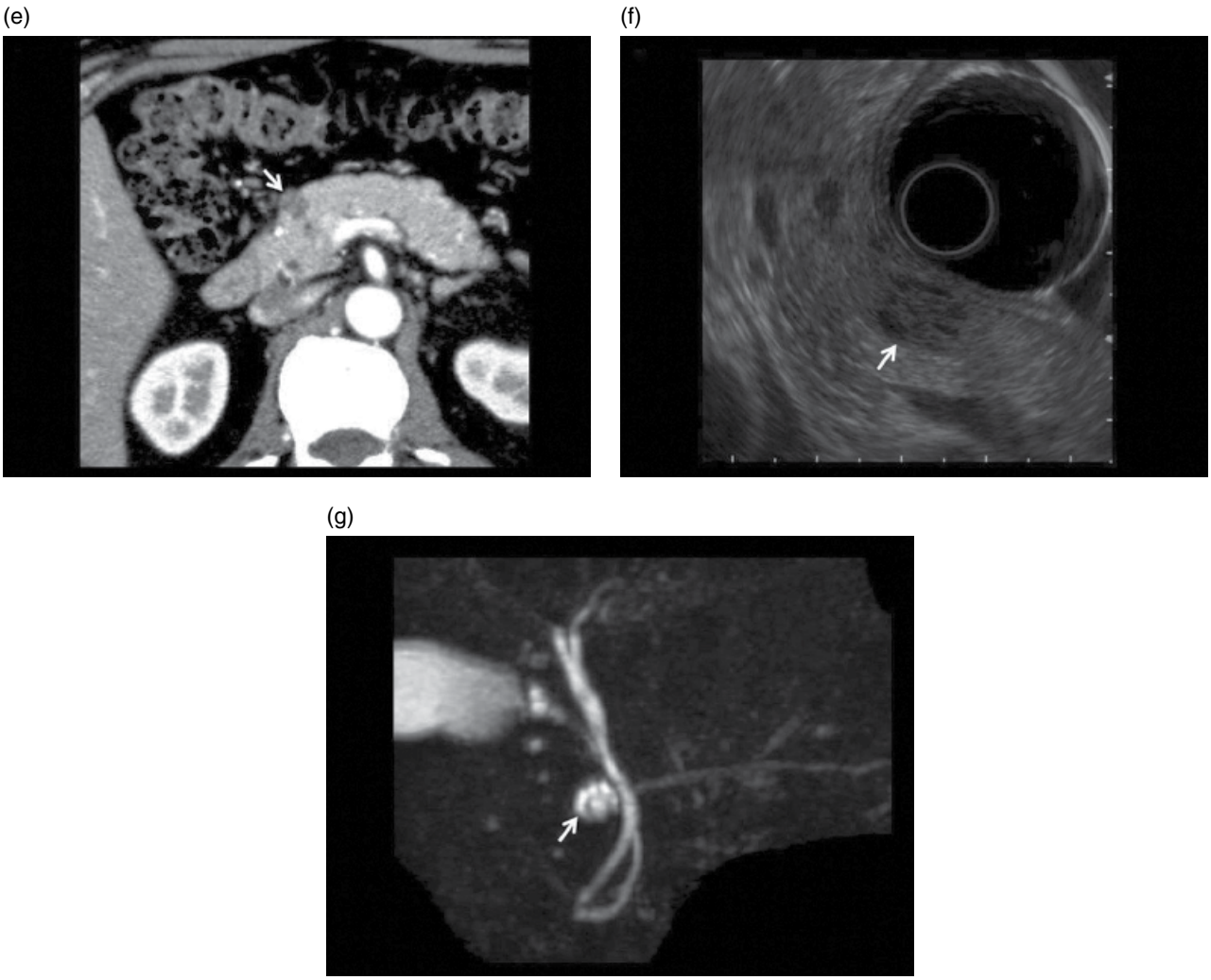


**Figure 77.2** (Continued)

imaging, high signal on T2W imaging, with enhancement of the septations on contrast-enhanced T1W imaging with or without a central scar. In solid appearing SCA, MRI and magnetic resonance cholangiopancreatography (MRCP) are useful for confirming the cystic, rather than solid nature of the cyst (Fig. 77.2g). EUS can be useful in these cases in which classic imaging features are absent. It is superior for identifying a classic microcystic appearance to either CT or MRI [10], while the vascular nature of SCAs is often seen with Doppler, or with contrast-enhanced EUS. A very low cyst fluid CEA, of <5 ng/mL, has 95% specificity, and 50% sensitivity for a SCA [8]. Almost 70% of SCA harbor a mutation in the Von–Hippel Lindau (*VHL*) gene or loss of heterozygosity (LOH) of chromosome 3 where the *VHL* gene is located. The presence of either of these findings, and the absence of mutations in *GNAS*, *KRAS*, or *RNF43* has 100% sensitivity and 91% specificity for a SCA [12].

## Lymphoepithelial Cyst

Lymphoepithelial cysts are rare, benign pancreatic cysts, which occur predominantly in middle-aged men (82%), with a mean age of presentation of 55 years [13]. They are single cysts, with almost 70% found adjacent, or outside of the pancreas [14]. Sixty percent are multilocular. The main pancreatic duct is normal, and unlike IPMNs or pseudocysts, there is no communication between the cysts and the duct. Lymphoepithelial cysts typically have a mixed solid and cystic appearance, with a purely cystic or mainly solid lesion occurring in only 14% and 16% of cases, respectively (Fig. 77.3a,b) [13]. Lymphoepithelial cysts are low-attenuation cystic lesions on CT. On MRI, they may be hyperintense on T1W imaging, and heterogeneous on T2W imaging due to the presence of fluid (high signal) and high keratin content (low signal) [13]. These features are not classically seen in other cysts and may be helpful in identifying these lesions [13]. On EUS

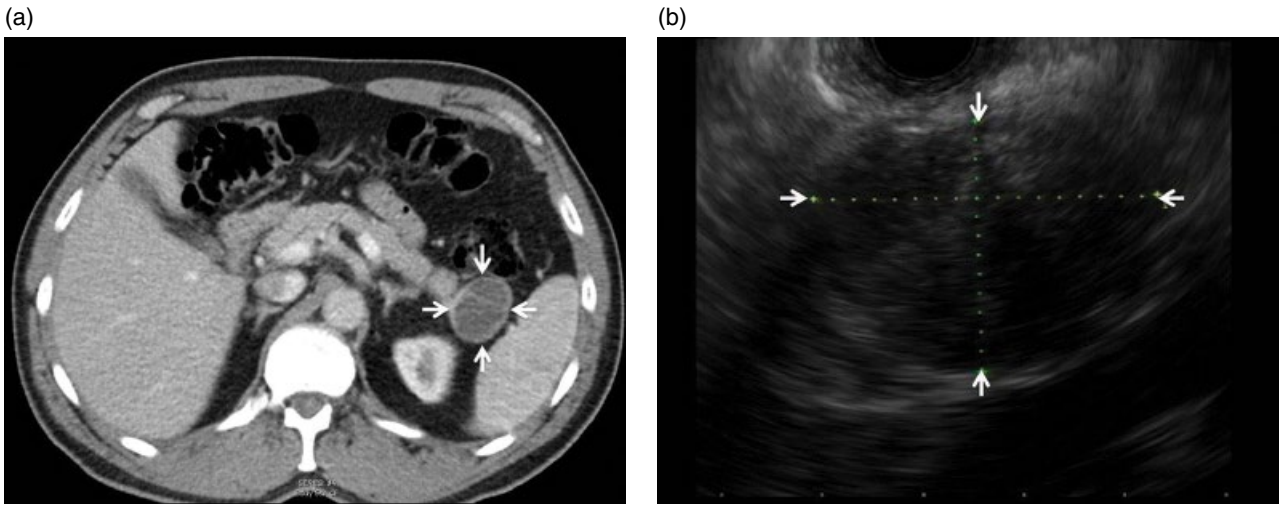


**Figure 77.3** Lymphoepithelial cyst. The CT (a) and EUS (b) appearance. *Source:* Copyright AML, by permission of the author.

they are a solid-appearing, hypoechoic, heterogeneous lesion with posterior acoustic enhancement and may have evidence of debris within the cyst [14]. Cytology can be useful and identified 22% of lymphoepithelial cysts in a large series of 117 patients [13]. Cyst fluid CEA is >192 ng/mL in a third of patients [13].

## Pancreatic Cysts with Malignant Potential

### Mucinous Cystic Neoplasm

Mucinous cystic neoplasms (MCNs) are unifocal lesions, which occur almost exclusively in women (20:1 ratio), with a mean age of presentation of 53 years [15]. Just over 90% of MCNs are located in the body or tail of the pancreas. Although MCNs do not involve the main pancreatic duct, abnormalities can be found. Main pancreatic duct dilation is found in 17% of MCNs, which increases to 43% in the presence of HGD/IC. The absence of communication between the cyst and the main pancreatic duct is a classic feature used to differentiate a MCN from an IPMN; however, a study of 156 MCNs found communication between the MCN and the pancreatic duct in 18% of cases [16]. Almost 40% of MCNs are multilocular, and may have slightly thickened septations. The classic appearance of a MCN is a thickened wall, which enhances on contrast-enhanced CT and MR imaging. This thick wall, or capsule, often has a "cyst within a cyst" appearance, which resembles an orange on CT or MRI (Fig. 77.4a,b). On EUS the cyst is unilocular with the "cyst within a cyst" seen within the wall (Fig. 77.4c). Calcification is located at the edge of the cyst creating an "eggshell" type appearance (Fig. 77.4d,e). In large surgical series between 15–25% of MCNs have a mural nodule, increasing to 54–100% in MCNs with HGD/IC [16,17]. This is seen on CT and MRI as intracystic enhancing soft tissue, or a hypoechoic, irregular area on EUS (Fig. 77.4f). Cyst fluid CEA (>192 ng/mL) and amylase are elevated. *KRAS* mutations are present in 50% of MCNs [12].

### Intraductal Papillary Mucinous Neoplasm

IPMNs can involve the main pancreatic duct (MD-IPMN), branch-duct (BD-IPMN), or both, in which case it is termed a mixed-type IPMN (Fig. 77.5a–c). This classification is important, as it determines the risk of malignant transformation, and the management of patients with IPMNs. IPMNs have an equal distribution in men and women, with a median age of presentation of 66 years [18]. They have a slight preponderance for the head of the pancreas, but can occur anywhere. Just over a third of individuals with IPMNs will have multifocal cysts [18]. One of the classic features used to identify BD-IPMNs from other types of cysts is the presence of communication between the IPMN and the main pancreatic duct (Fig. 77.5b). This is best assessed with either MRI or EUS, which have a 100% and 89% sensitivity, respectively [19]. MRCP with secretin has been shown to improve the detection of ductal communication in some, but not all, studies. Cysts are usually well defined, with thin walls, can be unilocular or multilocular, and calcification is rarely present. Main-duct involvement, which occurs in MD-IPMN or a mixed IPMN, is defined as focal or diffuse dilation of the main pancreatic duct to >5 mm. On endoscopy a gaping "fish-mouth" papilla extruding mucus is occasionally seen.

IPMNs have the potential to progress to HGD or IC. There are a number of imaging features that are

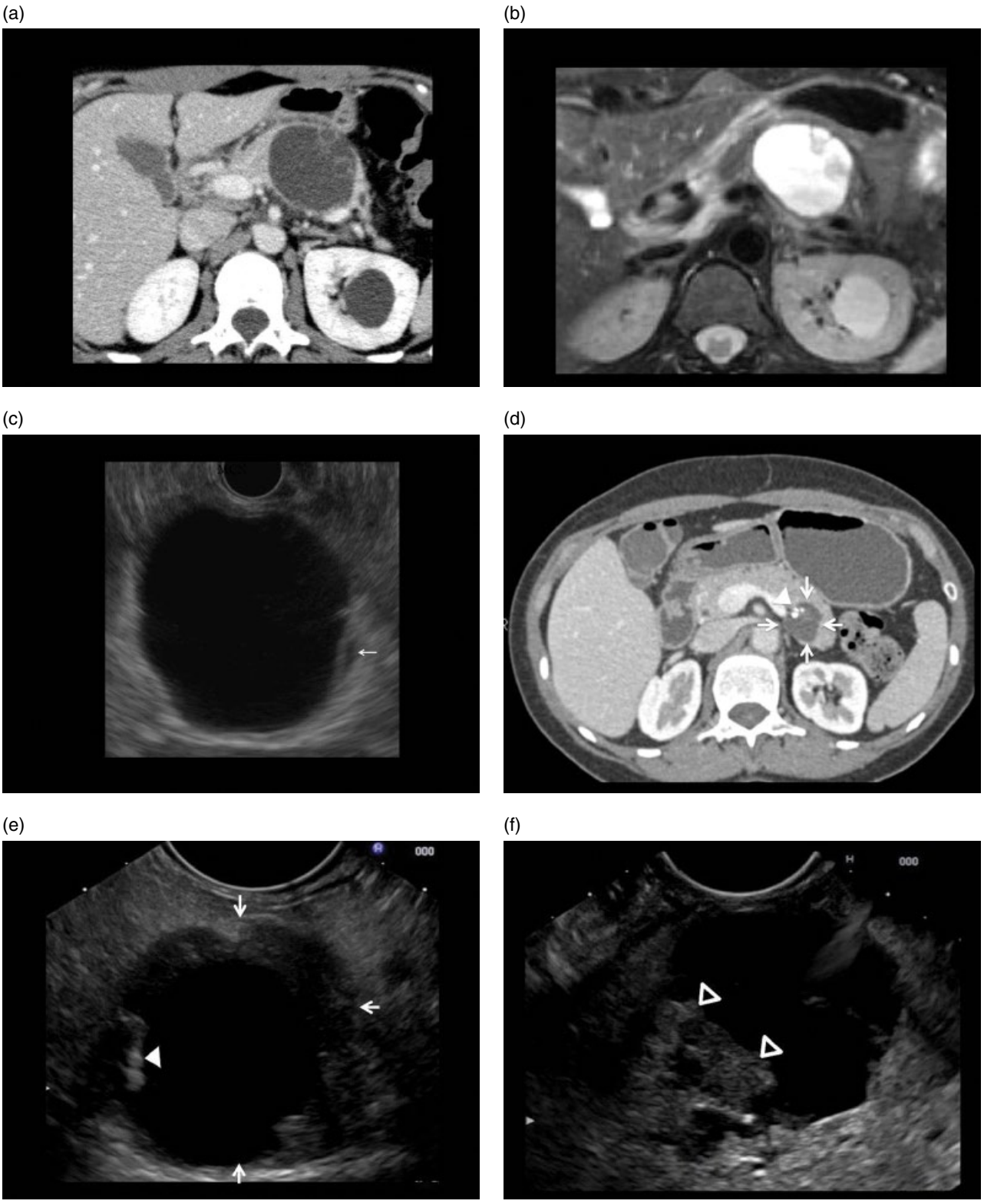


**Figure 77.4** MCN. Classic "cyst within a cyst" appearance of a MCN on CT and MRI (a,b). On EUS the cyst is unilocular, with the "cyst within the cyst" seen in the wall (c, arrow). A classic appearance of a MCN (a) with calcification at the edge (d, arrowheads). The EUS appearance showing calcification at the edge (e, arrowhead) with a thickened, irregular wall (f, arrowheads). *Source:* (c–f) Copyright AML, by permission of the author.

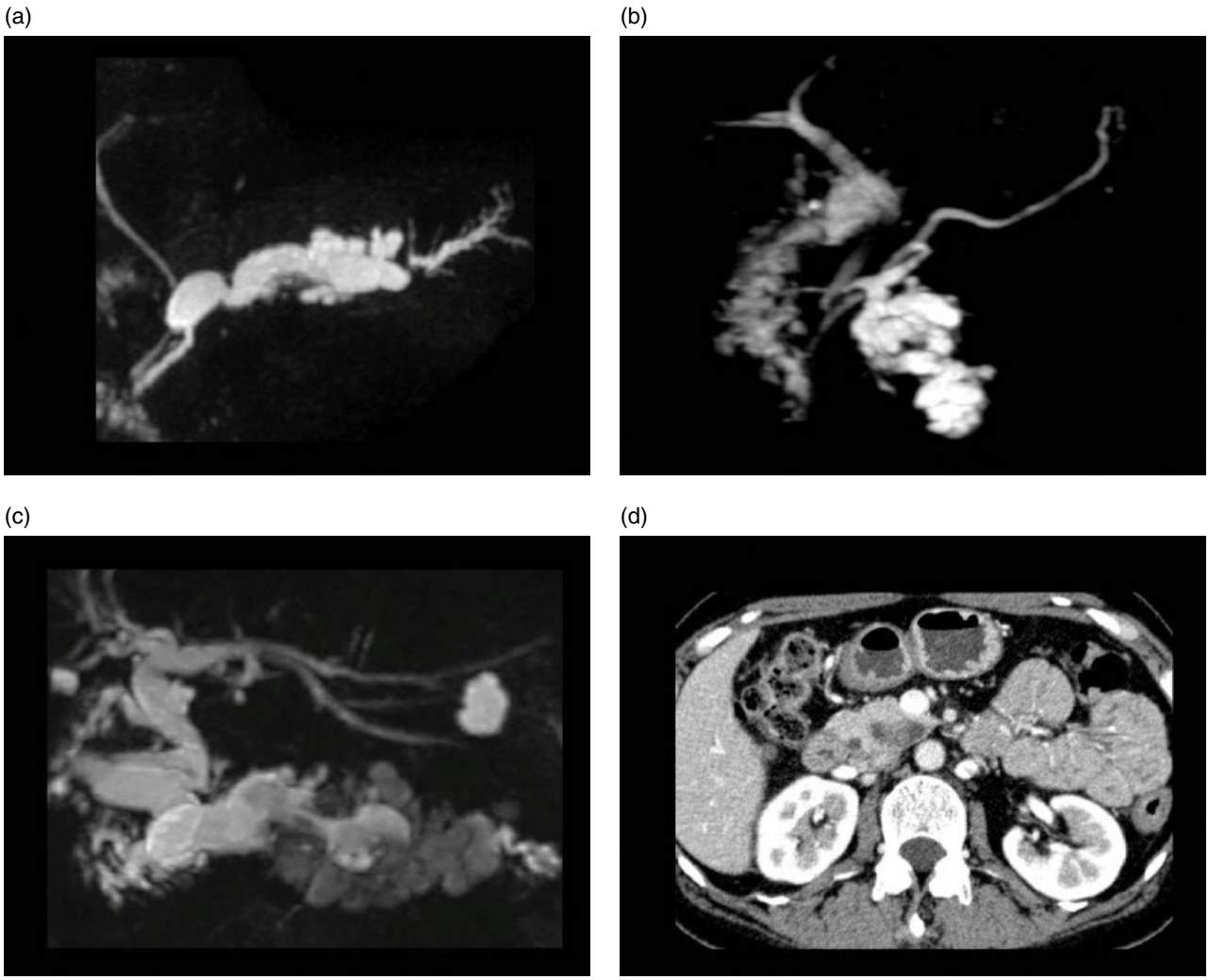


**Figure 77.5** IPMNs. The classic dilated main pancreatic duct seen in main-duct IPMN (a). In comparison there is a cyst but a normal pancreatic duct in a BD-IPMN (b,c), and a dilated main pancreatic duct and a cyst in a mixed-type IPMN (c). Mural nodules appear as soft tissue mass with contrast enhancement on CT and hyperechoic protruded lesion on EUS (d,e). Tissue harmonic echo (THE) shows a superior imaging compared with B-mode (f,g).

associated with an increased risk of HGD or IC including cyst size >3 cm (odds ratio (OR) 2.97), dilation of the main pancreatic duct (OR 2.4), and the presence of a solid component, or mural nodule (OR of 7.7) [20].

On CT and MRI, a mural nodule appears as a soft tissue nodule protruding into a mucin-filled dilated duct or cyst, with enhancement following administration of intravenous contrast. On EUS, a mural nodule appears as a hyperechoic, irregular lesion (Fig. 77.5d,e). The size of the mural nodule is associated with the risk of IC; however, the exact size is unclear and varies in studies from ≥3 mm to >10 mm, with the latter associated with IC in almost 90% of patients in one study [21,22]. Mucin appears as a hypoechoic lesion, with a hyperechoic, smooth rim on EUS, and is non-enhancing on CT or MRI. Contrast-enhanced EUS (CE-EUS) may demonstrate vascularity in mural nodules and is useful for differentiating a mural nodule from a mucin ball. A prospective study found that CE-EUS correctly identified 75% of mural nodules with HGD or IC. Tissue harmonic echo (THE) imaging is a further development in EUS. Preliminary studies appear promising, and show superior image visualization of mural nodules compared with normal B-mode imaging (Fig. 77.5f,g) [23]. Individuals with IPMNs can develop concomitant pancreatic adenocarcinoma in a region separate to the cyst, highlighting the importance of inspecting the entire parenchyma and not just the cyst. The cyst fluid analysis

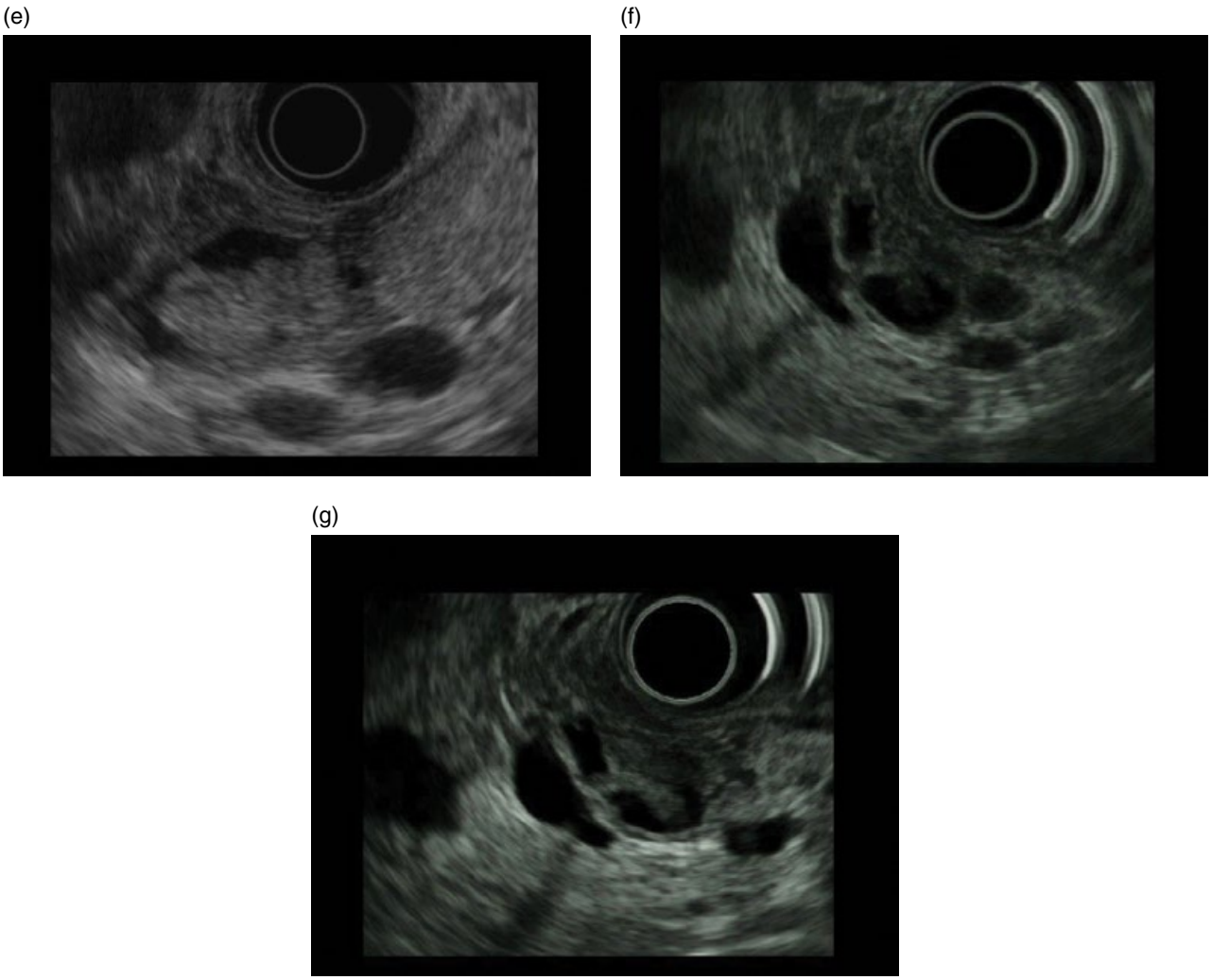


**Figure 77.5** (Continued)

shows a high CEA (>192 ng/mL), and high amylase. A *GNAS* or *KRAS* mutation is present in 91% of IPMN.

## Solid-Pseudopapillary Neoplasm

SPNs are single cysts, with 60% located in the body or tail of the pancreas. Almost 90% occur in women, presenting at a mean age of 29 [24]. The main pancreatic duct is normal, and does not communicate with the cyst. The cysts are well circumscribed, round or oval, with calcification present in almost half the cases [25]. In ~70% of cases, the imaging appearance is of a cystic and solid lesion, in 30% they are predominantly solid, and in rare cases are entirely cystic (Fig. 77.6a) [24,25]. The imaging appearance varies due to the cystic and solid nature of these neoplasms with areas of fluid appearing as low attenuation on CT and high signal on T2W imaging with weak enhancement within the solid components [26]. Areas of increased signal may be seen on the precontrast T1W imaging due the presence of hemorrhage within the lesions.

## Cystic Neuroendocrine Tumor

Cystic degeneration of neuroendocrine tumors is rare, occurring in less than 20% of cases [27]. There is an equal distribution between genders, with a mean age at presentation of 53 years. These cysts are predominantly solid, with the cystic component due to degeneration of the tumor. They are round, usually well defined, with a rim of tissue which enhances on the arterial phase CT and MR imaging. On EUS they appear as a well-defined, round, hypoechoic lesion, with an anechoic cystic area (Fig. 77.6b,c). They often have a vessel running around the edge of the lesion. Cyst fluid CEA and amylase levels are low.

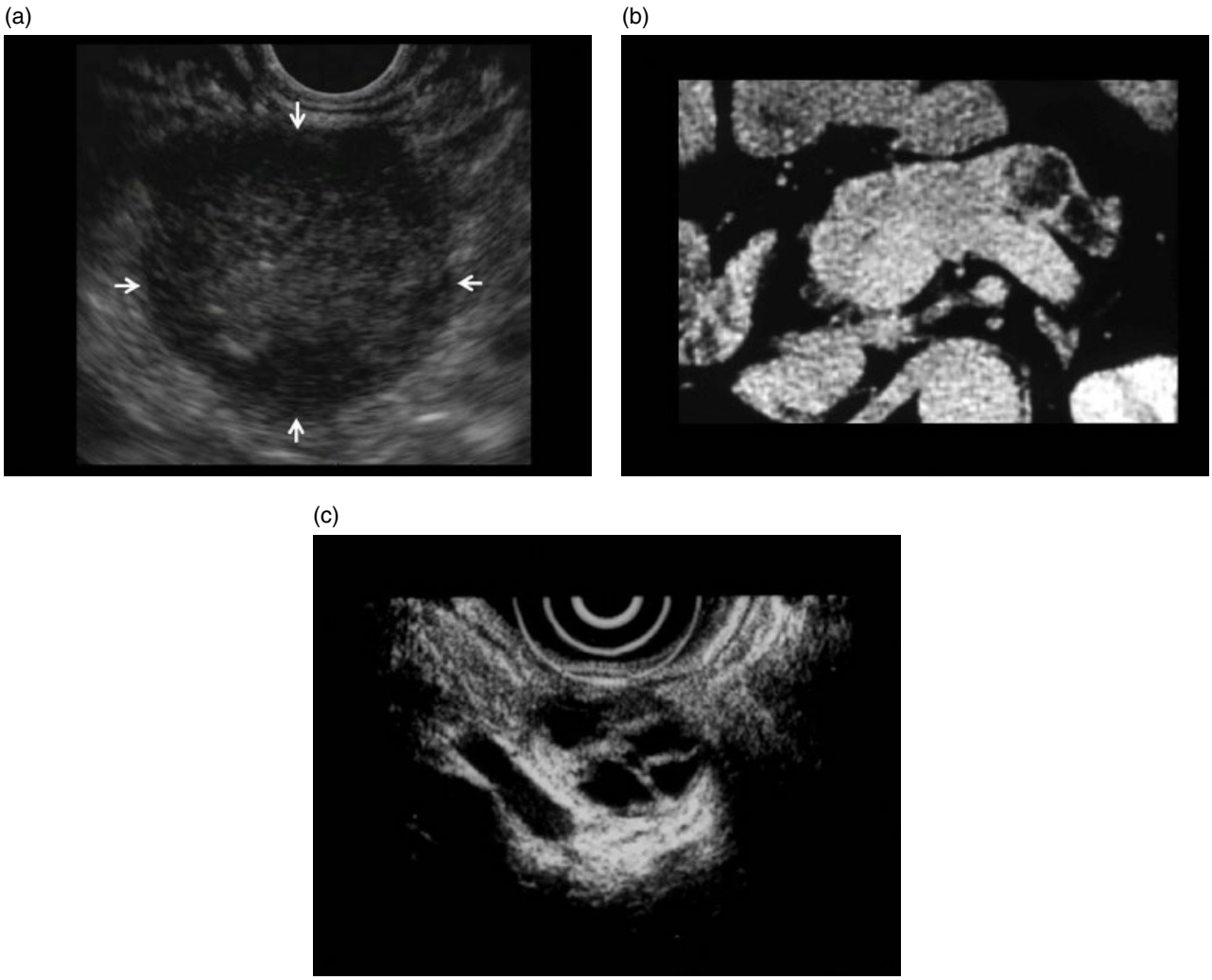


**Figure 77.6** SPN and PanNET. Solid appearing SPN (a). Cystic PanNET showing enhancement of the rim and septum on CT (b). On EUS the appearance is of a solid component with cystic areas (c). *Source:* (a) Copyright AML, by permission of the author.

## Future Technology

A number of promising new techniques have been developed to evaluate pancreatic cysts. Diffusion-weighted MRI imaging has shown promise in differentiating pancreatic cancer from mass-forming focal pancreatitis; however, its role in identifying cyst type is unclear, with conflicting results from different studies [28–31].

A new area under investigation are disease-specific ligands, such as antibodies. These have been developed and can be attached to a microbubble surface, or gadolinium (III)-containing micelles and liposomes, and then injected into a patient where they bind to their target and can be visualized with CE-EUS in the former, or MRI in the latter case. Preliminary studies in pancreatic cancer animal models have demonstrated feasibility and are promising [32–34].

Needle-based confocal endomicroscopy (nCLE) is a relatively new technology in which a very thin microscope is passed through a 19-gauge EUS-FNA needle into a cyst and creates a real-time optical biopsy of the cyst. Initial studies found that different types of cysts had specific imaging features, such as a superficial vascular network in SCAs, and identify cyst type with 59–80% sensitivity and 100% specificity [35,36]. A fiberoptic probe can also be passed through a needle into a cyst, with good or excellent visualization achieved in 70% of cases, and 71% sensitivity and 100% specificity for identification of IPMNs and MCNs in one study [36]. The initial results from both of these techniques are promising; however, there are limitations in the studies published to date and further larger, prospective studies are required to fully evaluate their potential and role.

## Acknowledgment

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# 78

# Cytologic Evaluation of Cystic Neoplasms

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## Introduction

The management of patients with a cystic lesion of the pancreas balances the benefits of surgically resecting a curable precursor lesion with the risks of overtreating a patient with an entirely benign lesion [1,2]. Cytohistology (fine needle aspiration biopsy with direct smears and cellblocks of small tissue fragments from needle rinsings and/or microbiopsies) is a critical tool in determining cyst type and the risk of malignancy. While cytology alone can be readily diagnostic, the diagnosis of cystic neoplasms often requires a multidisciplinary and multimodal approach for accurate interpretation [3,4]. Table 78.1 outlines the clinical, imaging, and cyst fluid characteristics of primary cystic neoplasms most commonly encountered in clinical practice.

## Cytology of Neoplastic Cysts

### Serous Cystadenoma

Aspirates of serous cystadenoma (SCA) produce variable amounts of cyst fluid depending on the size of the cysts. Microcystic SCA generally yield scant bloody specimens on fine needle aspiration (FNA) whereas macrocystic (oligocystic) variants often produce relatively abundant bloody or clear, thin, nonviscous fluid. Aspirates contain few cells and most cells do not survive the mechanical forces of direct smearing during slide preparation. Cyst fluids also rarely contain many intact cyst lining cells. As such, most FNAs are nondiagnostic.

When present, intact serous cells are small cuboidal cells with round, regular nuclear membranes and inconspicuous nucleoli [5,6] (Fig. 78.1a). Cytoplasm is scant, pale, and finely vacuolated, glycogen-rich and nonmucinous [5,7]. Given the high vascularity of the septae, which can bleed, hemosiderin-laden macrophages may be noted and these cells may serve as a surrogate marker for the diagnosis [5]. Microbiopsies may procure small diagnostic tissue fragments (Fig. 78.1b).

#### Ancillary Studies

The absence of thick mucin, mucinous epithelial cells, and high-grade cytologic atypia, coupled with low cyst fluid amylase and carcinoembryonic antigen (CEA) levels are characteristic findings that support the diagnosis. Periodic acid–Schiff (PAS) stain performed on formalin-fixed paraffin-embedded tissue will highlight the cytoplasmic glycogen and diastase will remove it (Fig. 78.2a,b). Molecular analysis may detect the *VHL* gene mutation or loss of heterozygosity on chromosome 3p, either of which would also support the diagnosis.

### Mucin-Producing Cysts

The distinction between intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN) as specific diagnoses is often not possible on cytology alone. Cytologic analysis may be able to ascertain that the cyst is mucin-producing, however, and determine whether there are any cells suggestive or diagnostic of malignancy [8].

The volume of fluid aspirated from mucinous cysts is highly variable, obviously dependent on the size of the cyst(s) accessible to the needle. Visibly "thick and viscous fluid" indicates a mucin-producing cyst. Smears of grossly thick, viscous mucin correlates with colloid-like, thick extracellular mucin, which is not characteristic of gastrointestinal contamination, and is a finding that supports the diagnosis of a mucin-producing cyst (Fig. 78.3). The presence of degenerated cells and debris floating in

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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**Table 78.1** Clinical, imaging, and cyst fluid characteristics of primary neoplastic cysts of the pancreas.

| | | | | Cyst fluid biochemistry | | |
|---|---|---|---|---|---|---|
| **Cyst type** | **Clinical features** | **EUS features** | **Cytologic findings** | **CEA[a]** | **Amylase[b]** | **Molecular analysis** |
| Serous cystadenoma | Abdominal pain; often asymptomatic; F>>M; 65 yrs | Spongy; soap-bubble appearance to multiseptated macrocysts; lobulated borders | Cuboidal, nonmucinous, glycogen-rich cells with benign appearing nuclei; hemosiderin-laden macrophages in the background | ↓↓ | ↓↓ | *VHL*, 3p25 deletions |
| Mucinous cystic neoplasm | Abdominal pain; often asymptomatic; F>>>M; 40–50 yrs. | Solitary, well circumscribed, septated, thick-walled; some calcifications; no connection with MPD; body/tail | Mucinous epithelial cells with usually low-grade dysplasia but can have intermediate and high-grade dysplasia as well as invasive carcinoma; +/-extracellular mucin | ↑↑↓ | ↓↓↑ | *KRAS*<br>*RNF43*;<br>HR supported by *TP53*, *SMAD4* loss |
| Intraductal papillary mucinous neoplasm | Abdominal pain; often asymptomatic with BD-IPMN; M>F; 65 yrs | MPD >10 mm is HR; 5–9 mm is worrisome; BD unilocular or septated, thin wall; enhancing nodule is HR; nonenhancing is worrisome | Mucinous epithelial cells with low-, intermediate- and high-grade dysplasia as well as invasive carcinoma; +/-extracellular mucin | ↑↑↓ | ↑↑↑ | *KRAS*<br>*GNAS*<br>*RNF43*;<br>HR supported by *TP53*, *SMAD4* loss |

[a] relative to 192 ng/mL
[b] relative to 1000 U/L
BD, branch-duct; CEA, carcinoembryonic antigen; HR, high risk; MPD, main pancreatic duct.

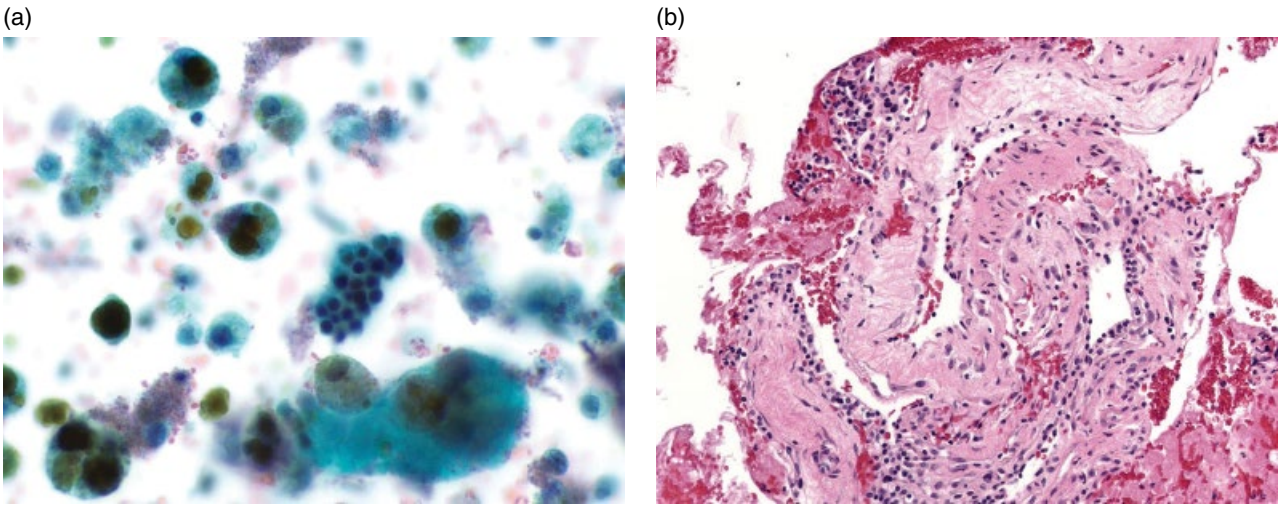


**Figure 78.1** Serous cystadenoma. Cyst lining cells are nonmucinous cuboidal cells with benign round nuclei and finely vacuolated cytoplasm rich in glycogen and many are associated with hemosiderin-laden macrophages, which is not an uncommon finding given the highly vascular septa of this neoplasm (a). Cellblock or core biopsy provides tissue for diagnosis and ancillary testing (b). ((a) SurePath preparation; Papanicolaou test; (b) cellblock, hematoxylin, and eosin).

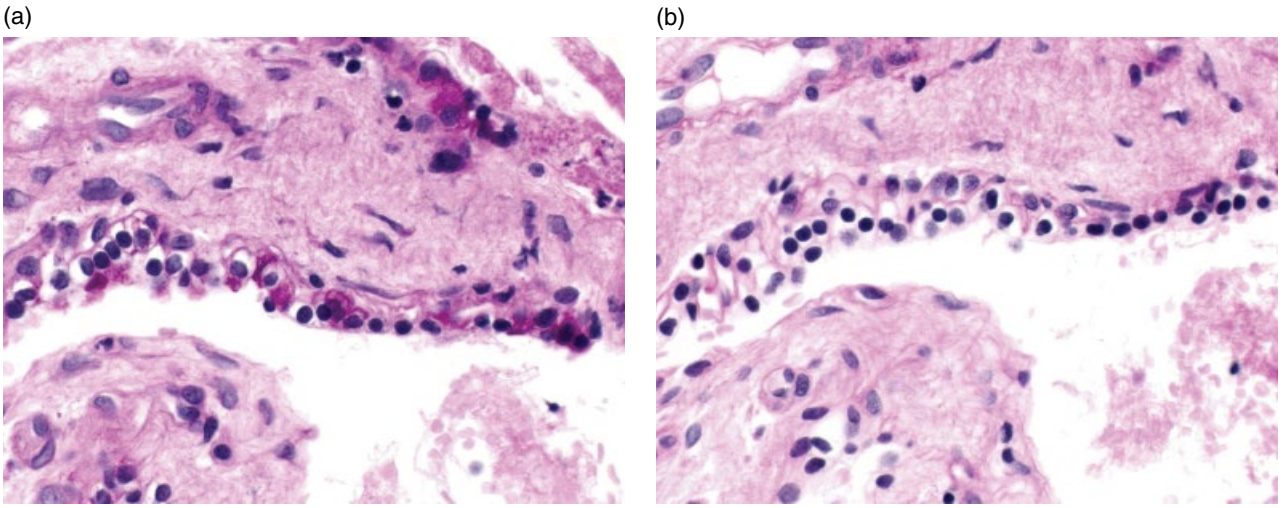


**Figure 78.2** Serous cystadenoma. The glycogen-rich cytoplasm of the cyst lining cells is highlighted by a PAS stain (a), which, in contrast to mucin, is removed with diastase (b). (Cellblock; (a) periodic acid–Schiff; (b) periodic acid–Schiff with diastase).

the mucin is a finding that also supports origin from the cyst rather than contamination. The absence of an epithelial component in colloid-like mucin should not lead to a nondiagnostic report, but instead, a report of a neoplastic mucin-producing cyst [9].

Cytologic features associated with various grades of dysplasia (low, intermediate, and high) have been described for IPMN [10–15]. These findings are similar for MCN, although most MCN are low grade even when quite large [16,17]. IPMN are associated with four distinct types of lining epithelium, but specifying the cell type is not necessary on cytology. The most important cytologic interpretation is to report whether the cells are low risk (low-grade or intermediate-grade dysplasia, e.g., low-grade atypia) or high risk (high-grade dysplasia or invasive carcinoma, e.g., high-grade atypia) for malignancy [9].

Cytologic features associated with grades of dysplasia are as follows:

- Low grade

*Low-grade dysplasia* (Fig. 78.4): Low-grade mucinous epithelial cells are gastric-foveolar type epithelial cells, which are columnar cells with basal nuclei and mucinous

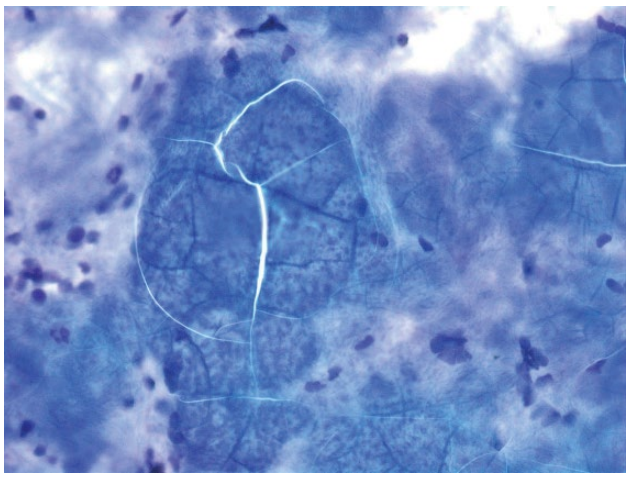

**Figure 78.3** Mucinous cyst. Thick, colloid-like extracellular mucin is not consistent with gastrointestinal contamination and supports the diagnosis of a mucinous cyst, regardless of the presence of an epithelial component. (Direct smear; Diff-Quik).

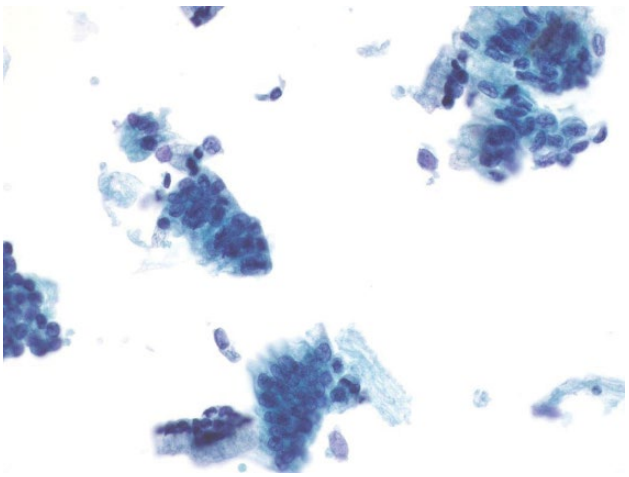

**Figure 78.5** IPMN with intermediate-grade dysplasia. Cells show stratification of the nuclei and moderate cytologic atypia with mild anisonucleosis and slight loss of polarity. (Cytospin; Papanicolaou).

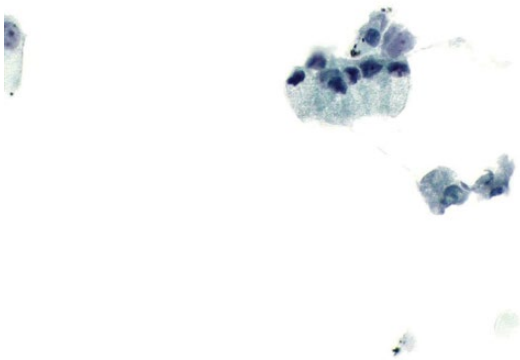

**Figure 78.4** IPMN with low-grade dysplasia. Columnar mucinous epithelial cells show abundant mucinous cytoplasm and minimal nuclear atypia. (Cytospin; Papanicolaou).

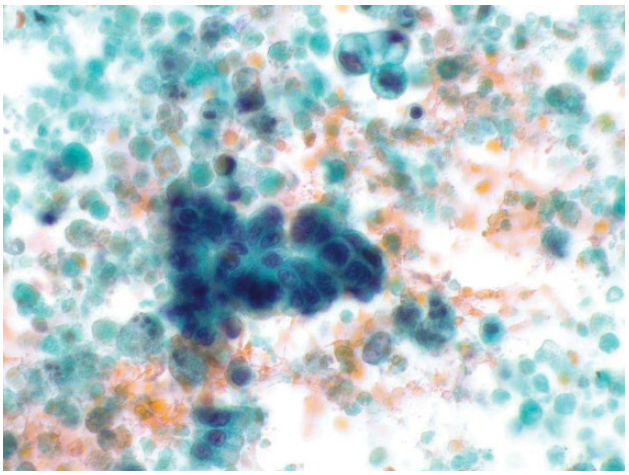

**Figure 78.6** IPMN with high-grade dysplasia. Cells are small (<12 micron duodenal enterocyte), often in small clusters and singly, with abnormal chromatin and typically associated with background necrosis. (Cytospin; Papanicolaou).

cytoplasm. Aspirated cells are present as two-dimensional cell groups, sheets of mucinous cells, and single cells.

*Intermediate-grade dysplasia* (Fig. 78.5): Intermediate-grade dysplastic cells are either intestinal type epithelial cells or gastric-foveolar type epithelial cells with stratification and tufting, crowding, and some loss of polarity. The cells demonstrate increased nuclear to cytoplasmic ratio and may also demonstrate mild nuclear atypia including inconspicuous nucleoli and membrane irregularity. Mucinous cytoplasm is still present in many but not all cells.

- High grade

*High-grade dysplasia* (Fig. 78.6): High-grade dysplasia may be pancreaticobiliary type, oncocytic type, or high-grade dysplastic gastric or intestinal type cells. High-grade atypical cells are noted in large to small bud-like clusters and single cells. These cells are usually smaller than a 12 μm duodenal enterocyte. They will have increased nuclear to cytoplasmic ratio, abnormal chromatin (hypochromasia or hyperchromasia), some have irregular nuclear membranes, and the cytoplasm is variably vacuolated. In addition, background necrosis is usually present [15].

*Adenocarcinoma* (Fig. 78.7): Cellular atypia diagnostic of malignancy (i.e., "positive" aspirates) is not very

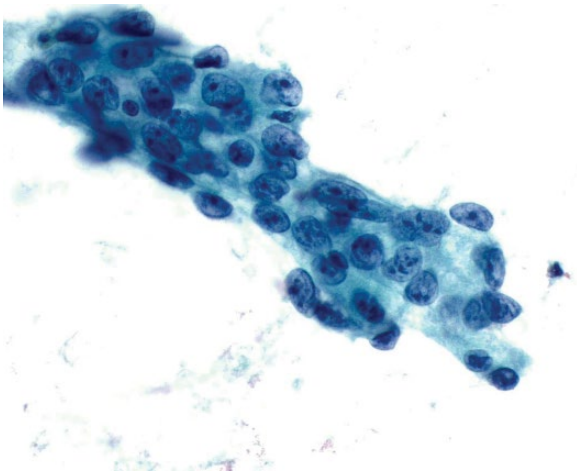

**Figure 78.7** IPMN with invasive carcinoma (adenocarcinoma). Cells show irregular spacing in a sheet with nuclear crowding and overlap, anisonucleosis of 4:1, and irregular nuclear membranes. (Cytospin; Papanicolaou).

common unless the imaging features are also those of a high-risk lesion. Cells are present in three-dimensional groups and single cells with variable anisonucleosis (variation in nuclear size) of at least 1:4 in a single sheet, irregular nuclear membranes, prominent nucleoli, and variably vacuolated cytoplasm, usually present in a background of necrosis [18].

#### Ancillary Studies

Establishing that the cyst is mucin-producing is accomplished by detection of extracellular mucin either grossly, microscopically, or with special stains, documentation of cyst fluid CEA elevation (generally above 192 ng/mL) [19,20], or molecular analysis documenting *KRAS, GNAS*, or *RNF43* mutations [21–24]. Grading atypia requires cytologic analysis of the cells. Detection of mutations known to occur late in progression to malignancy such as *TP53* or deletion of *SMAD4* supports malignancy [23,24].

### Secondarily Cystic Solid Neoplasms

Secondarily cystic neoplasms include solid-pseudopapillary neoplasm, neuroendocrine tumor, acinar cell carcinoma, and conventional ductal adenocarcinoma. These usually solid neoplasms may form complex cysts more often with the solid component greater than the cystic component. Rarely do typically solid neoplasms mimic primary cysts of the pancreas, but this does occur. Endoscopic ultrasound (EUS)-FNA targeting of the solid component produces cellular aspirates and should provide sufficient tissue for cellblocks, which is a goal of the FNA to ensure tissue for ancillary testing. The cytomorphologic characteristics recapitulate those of their solid counterparts. The two more commonly encountered neoplasms are described in the following section. The ancillary studies used to distinguish these neoplasms are outlined in other chapters specific to each neoplasm.

### Solid-Pseudopapillary Neoplasm

Solid-pseudopapillary neoplasms (SPN) produce cellular aspirates with many discohesive single cells as well as branching and papillary cell groups (Fig. 78.8a). The cells have a high nuclear to cytoplasmic ratio, bland nuclei with round to oval shape, even chromatin, and frequent nuclear grooves or indentations, which yields a "coffee bean appearance." The cytoplasm is typically scant and ill-defined but may show large clear perinuclear vacuoles or well-defined hyaline globules that are PAS positive (Fig. 78.8b) (both best highlighted on air-dried Romanowsky stain) [25–27]. Fibromyxoid stroma separates the cells from the vessels. Cellular smears and cellblocks of needle rinsing typically contain sufficient small tissue fragments to make a morphologic diagnosis (Fig. 78.8c).

### Cystic Neuroendocrine Tumors

The cytologic features of cystic pancreatic neuroendocrine tumors (PanNET) are similar whether the aspirate is from a solid tumor or a cystic lesion [28–31]. Cystic PanNET often produce yellow cyst fluid that has low CEA and amylase levels [31,32]. The neoplastic cells are usually small clusters or individual cells with coarse, stippled chromatin and a plasmacytoid appearance caused by the eccentrically located nucleus (Fig. 78.9). Nucleoli may be prominent.

## Summary

The cytopathologist plays a pivotal role in the management of patients with pancreatic lesions. It cannot be overemphasized that the accurate diagnosis of pancreatic cysts depends upon a multimodal team approach that combines the clinical and radiologic patient information with the cytologic impression and the results of ancillary studies. The gastroenterologist and pathologist must understand the optimal methods of tissue handling and processing of cyst fluid and the pathologist must be familiar with pancreatic histopathology and the nomenclature of pancreatic cytology for accurate diagnosis and consistent, standardized reporting [8,9,33].

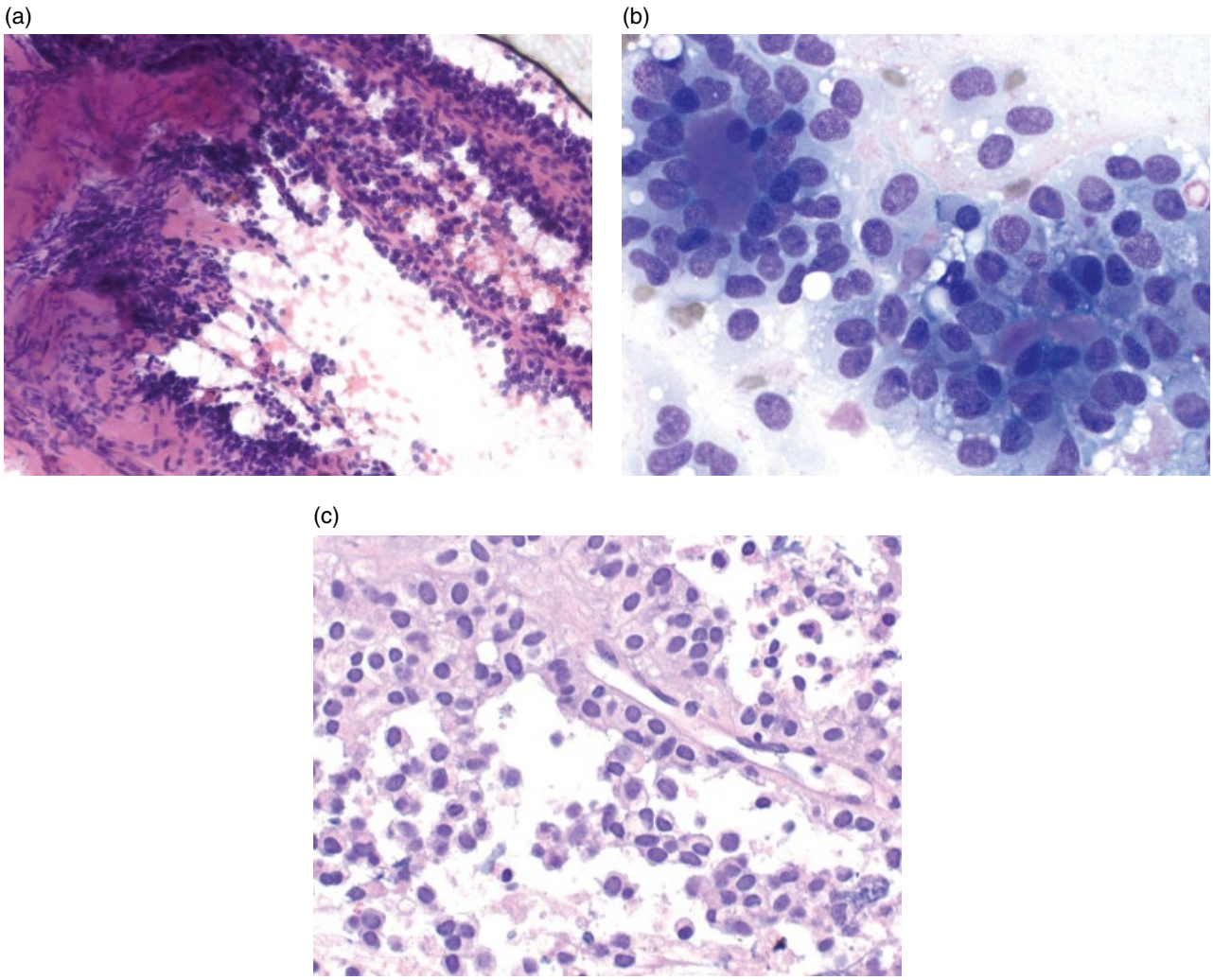


**Figure 78.8** Solid-pseudopapillary neoplasm. Smears are cellular with fibromyxoid stroma and thin, branching, papillary groups (a). The cells are bland with a high nuclear to cytoplasmic ratio, round to "coffee bean" shaped nuclei, and perinuclear cytoplasmic vacuoles or hyaline globules (b). Cellblocks provided tissue for morphology and ancillary studies ((a) Direct smear; hematoxylin and eosin; (b) direct smear; Diff-Quik; (c) Cellblock; hematoxylin and eosin).

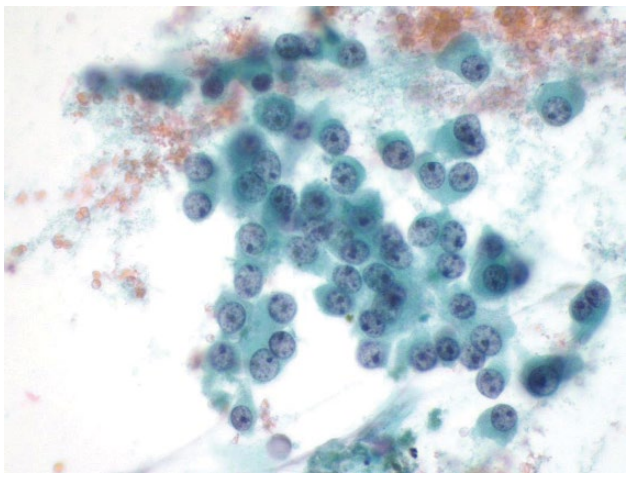

**Figure 78.9** Cystic neuroendocrine tumor. The neoplastic cells are typically individual cells with coarse, stippled chromatin and a plasmacytoid appearance typical of solid tumors. (Cytospin; Papanicolaou).

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79

# Natural History of Cystic Neoplasms: IPMN, MCN, SCN, and SPN

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## Introduction

In recent years, cystic lesions of the pancreas have been identified with rising incidence owing to the extended use of modern abdominal imaging modalities, and therefore have gained increasing awareness [1,2]. Any type of cystic lesion or pancreatic branch-duct alteration can be found frequently in the general population, increasing to a 50–70% prevalence in people aged >70 years [3,4].

For adequate diagnosis and management of cystic pancreatic lesions, it is crucial to correctly differentiate between pancreatic pseudocysts and pancreatic cystic neoplasms. In the past, inflammatory pseudocysts were considered to account for the majority of all cystic pancreatic lesions. With the increasing use of modern abdominal thin-slice imaging, it has become clear that neoplastic pancreatic cysts are far more common than pancreatic pseudocysts, particularly in patients without previous history of pancreatitis. While pseudocysts are benign residual lesions that occur after acute or recurrent chronic pancreatitis, pancreatic cystic neoplasms display a certain potential for malignant transformation. The most common cystic neoplasms of the pancreas are intraductal papillary mucinous neoplasms (IPMN), mucinous cystic neoplasms (MCN), serous cystic neoplasms (SCN), and solid-pseudopapillary neoplasms (SPN).

## Intraductal Papillary Mucinous Neoplasms

Intraductal papillary mucinous neoplasm is the most frequent entity of cystic pancreatic neoplasms comprising approximately 35% of all tumors. IPMN are characterized by the production of mucin as well as intraductal and papillary growth of the duct epithelium. According to their location in the pancreatic duct system, they can be subclassified into main-duct (MD), branch-duct (BD), or mixed-type IPMN, involving both the main duct and its major side branches [1,5]. To date, it remains controversial whether the mixed-type arises from the main pancreatic duct or from side branches, or whether it represents a distinct subtype of IPMN [6]. Beside pancreatic intraepithelial neoplasms (PanIN), IPMN are the best-described precursors to ductal adenocarcinoma of the pancreas [7].

MD- and mixed-type IPMN are characterized by a dilation of the main pancreatic duct >5 mm, segmentally or diffusely, without any sign of external obstruction [8]. The neoplastic epithelial cells produce abundant mucin with a high viscosity that cannot be sufficiently drained, which leads to an internal obstruction and secondary dilation of the affected parts of the duct system [9]. In contrast, BD-IPMN are characterized by cysts >10 mm communicating with the pancreatic main duct without its dilation (Fig. 79.1) [2]. Although most IPMN are fundamentally noninvasive, they progress over time following an "adenoma-carcinoma" sequence via four grades (low-grade, intermediate-grade, high-grade dysplasia, and invasive cancer).

Four major aspects determine the natural history of IPMN patients:

- morphologic type (MD-, BD-, or mixed-type IPMN);
- age at time of diagnosis and time course of the disease;
- histologic subtype (intestinal, pancreaticobiliary, oncocytic, gastric differentiation);
- grade of dysplasia (low-grade, intermediate-grade, high-grade dysplasia, invasive cancer).

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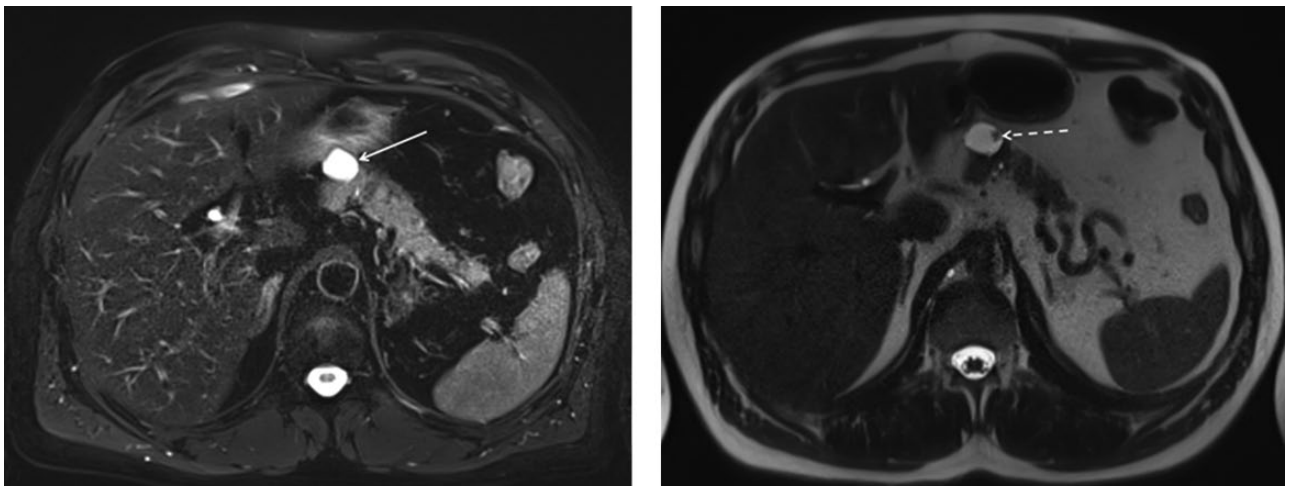

**Figure 79.1** Natural history of branch-duct IPMN. Fifty-four-year-old male patient with initial MRI finding of a BD-IPMN, serum CA 19-9 negative, no worrisome or high-risk features, diameter 22 mm (white arrow, left side). MRI control 8 months later with development of a mural nodule (broken white arrow, right side). Indication for laparoscopic distal pancreatectomy, histopathology: BD-IPMN, oncocytic subtype, pTis, N0 (0/12), R0.

## Morphologic Type (MD-, BD-, or Mixed-Type IPMN)

In a recent meta-analysis MD- and mixed-type IPMN have been identified as invasive carcinoma in about 43%, whereas the rate of invasive BD-IPMN is only about 17% [2]. Lesions with high-grade dysplasia (previously called carcinoma *in situ*) can also be regarded as "malignant" lesions because within a very short time they may progress to invasive cancer [10–12]. Together with high-grade dysplasia lesions, MD-IPMN harbor an ~60% risk of malignancy, whereas BD-IPMN show malignant transformation in around 20–25% of cases at the time of resection. Mixed-type IPMN seem to be associated with the highest risk of malignancy, estimated to be ~70% in larger study populations [2,13]. To date, the dynamic of progression for the different morphologic IPMN types is not completely understood, especially for MD- and mixed-type IPMN—which are generally resected by the time of diagnosis—and no reliable data are available (Fig. 79.2). Furthermore, radiologically defined findings of BD-IPMN may reveal as mixed-type lesions in the histologic workup when they are resected [14]. This underlines the difficulty in evaluating an individual patient's risk on the basis of morphologic characteristics.

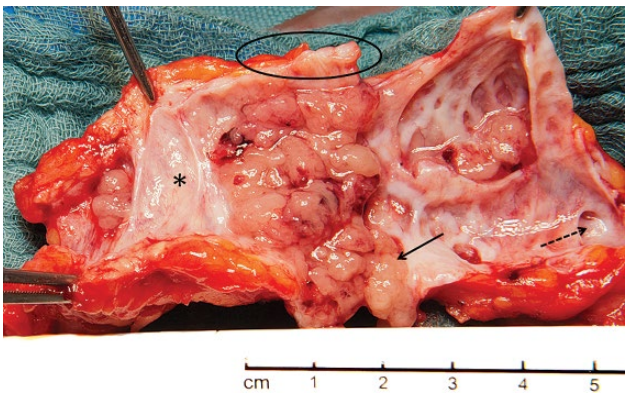


**Figure 79.2** Mixed-type IPMN of the pancreatic head and body (resection specimen) showing typical findings and stages of IPMN. Dilated main duct without dysplasia (black star), branch duct component (broken black arrow), papillary changes in the main duct with borderline dysplasia (black arrow), and progression to invasive cancer arising from the main duct component (black circle). Histopathology: IPMN with invasive cancer based on mixed-type IPMN, pT1, N0 (0/17), R0.

## Age at Time of Diagnosis and Time Course of the Disease

Significant differences in the median age of patients presenting with benign IPMN compared to malignant IPMN have been reported in cohort studies of 140 resected MD- and mixed-duct IPMN by Salvia et al. [15] as well as in another study by Sohn et al. with 136 resected MD-IPMN patients [16]. From both studies, the mean time of progression to invasive IPMN can be estimated at 5–6 years as patients with benign IPMN showed a median age of 61 and 63 years, compared to 67 and 68 years for patients with malignant findings [16]. This can be regarded as a surrogate parameter for an already longer subclinical course of preceding IPMN development by the time of diagnosis, which might be an indirect indicator for disease progression and malignant transformation over time [15,16]. Another corresponding observation is the correlation between duct diameter and the risk of malignancy in MD-IPMN, underlining

that a potentially longer course of the disease reflected by the increased duct size leads to a higher proportion of malignant findings [17].

Time-dependent progression rates in patients with BD-IPMN, who were mostly observed due to the lack of any worrisome features, have been reported in larger studies by Sahora et al. [18] and Maguchi et al. [19]. Among 411 and 349 patients respectively, signs of progression occurred in 18% during a median follow-up time of 26 months and 44 months, respectively. Malignant histologic features after resection were found in 9% and 15% of these patients. Furthermore, both studies demonstrated the development of "remote" lesions—both IPMN as well as separate and independent PDAC—distant from the index lesion during the observation. This underlines the hypothesis that IPMN-bearing pancreata may harbor a "field defect" of the entire gland [20]. Another aspect in this context is the synchronous occurrence of multiple BD-IPMN [21]. As patients with these multifocal lesions are generally older than those with solitary IPMN findings, the "field defect" theory seems reasonable and the progression from solitary to multifocal IPMN can be regarded as the natural course of this disease [21]. Although multiple lesions are likely to increase the long-term risk of malignant transformation, it remains controversial whether multifocal IPMN have a higher risk of malignancy compared to unifocal lesions [21]. The additional risk for IPMN patients of developing concomitant PDAC ranges between 3% and 9% over a 10-year period [22,23]. In what respect the IPMN might play an indirect promoting role in the development of PDAC remains unclear and prognosis of the long-term outcome of these patients is almost always determined by the PDAC component. It is supposed that some kind of pancreatic genetic field defect might lead to multifocal neoplastic changes over time.

## Histologic Subtypes

The differentiation of histologic subtypes (intestinal, pancreaticobiliary, oncocytic, and gastric type [24]) has a relevant prognostic impact. The intestinal subtype reveals a phenotype that resembles villous polyps of the colon with neoplastic epithelial cells expressing MUC2, MUC5AC, and CDX2. A recent study focused on 173 patients with MD-IPMN could show that most MD-IPMN were of intestinal type with invasive components in 50% and overall invasiveness of 39% [22]. Invasive carcinomas that arise in association with an intestinal-type IPMN are usually colloidal carcinomas and show a better median survival compared to patients with PDAC (107 vs. 20 months) [9,25,26]. The pancreatobiliary subtype is composed of branched papillary epithelia with high-grade atypia. In the immunohistochemical examination it is positive for MUC1 and MUC5AC, and 90% of all cases show an associated invasive component. The associated invasive tubular adenocarcinomas are very similar to PDAC in morphology and prognosis [9,27,28]. The oncocytic subtype is characterized by eosinophil cytoplasm, goblet cells, and complex branched papillary epithelia expressing MUC1 and MUC6. This subtype is rare as well as a malignant transformation into an oncocytic carcinoma, which shows a prognosis similar to patients with a colloid carcinoma [26–28]. BD-IPMN usually are of the gastric subtype. The typical morphology is multiple small cysts with foveolar gland epithelium, similar to the glands of the gastric antrum. A tubular adenocarcinoma can eventually arise from these IPMN and is associated with a rather poor prognosis with a mean survival of only 45 months [9,29].

## Grade of Dysplasia (Low-Grade, Intermediate-Grade, High-Grade Dysplasia, Invasive Cancer)

Data on outcome with referral to the grade of dysplasia are available from various larger cohorts of surgical patients [5,22,30]. As these results always reflect the grade of dysplasia at the time of resection, a valid estimation on the time intervals between the distinct grades remains difficult. Patients with resection of IPMN harboring noninvasive IPMN with a range of low-grade to high-grade atypia show an excellent overall and disease-specific survival prognosis of 95–100% in a follow-up of 10 years in both MD- and BD-IPMN [5,22]. In invasive IPMN poor prognosis is closely related to disease stage, positive resection margins for invasive IPMN, and N1 status [22,30]. While early stages including pT1 and pN0 show a much more favorable prognosis compared to sporadic PDAC, this advantage vanishes in more advanced stages (pT2–pT4), and also positive lymph nodes in any stage result in a prognosis that is similar to PDAC [30].

As all types of IPMN must be considered as a chronic and life-long disease—unless a total pancreatectomy has been performed—the natural course of these entities requires surveillance and postoperative follow-up. Surveillance and management strategies have been determined in the IAP consensus guidelines published in 2006 and updated in 2012 [2,8], as well as in the 2013 European guidelines [31] and the 2015 AGA guidelines [32]. These guidelines are partly conflicting not only with regard to surgical and nonsurgical management but also regarding surveillance, follow-up diagnostics, and intervals after resection of IPMN. Lately, published follow-up data from surgical IPMN patients showed that 17% of 381 patients after resection of invasive and noninvasive IPMN had a recurrence of IPMN after a median of 17 months [23]. Within this study, 33 patients had only

partial resection of the multifocal disease with mixed-type as well as BD-IPMN. The residual BD-IPMN with a median size of 10 mm at the date of resection grew within a follow-up of on average 5 years to a median size of 13 mm. In another cohort of 130 patients who had undergone partial pancreatic resections for noninvasive IPMN, He et al. showed that 17 % of the patients developed lesions suspicious for new or progressive IPMN within a median time of 46 months [33]. Within this disease progression cohort some patients developed high-grade dysplasia and invasive cancer. Another 12% of the cohort showed neither new IPMN nor progression in known residual IPMN. Although within the literature the recurrence rates vary between 8% and 57% [15,23,33,34], even patients with noninvasive IPMN might have an estimated average recurrence rate of 25% of remote IPMN and 7% for developing pancreatic cancer within 5 years after resection, which underlines the necessity of a structured and long-term follow-up.

## Mucinous Cystic Neoplasms

Mucinous cystic neoplasms (MCN) generally occur in perimenopausal women with a median age of 48 years. MCN are often located in the distal body or the tail of the pancreas (>90%) with a mean size of 6.5 cm in diameter at diagnosis. Macroscopically, MCN show a uni- or multicystic pattern with a thick wall and potentially solid components without any communication to the pancreatic duct system. An ovarian-like stroma is typical and pathognomonic for the histology of MCN [35,36].

Similar to IPMN, most MCN are noninvasive, but show a risk of an "adenoma-carcinoma" sequence over time. In 15–20 % of all resected cases, MCN harbor at least focally an invasive component [37]. As data show that patients with an invasive MCN are significantly older (median 3–10 years) than those with a noninvasive MCN, a time-dependent tumor-progression is suggested, comparable to that in IPMN [2,38,39]. It has been suggested that ectopic ovarian stroma in the pancreatic tail might release hormones and growth factors that stimulate endodermally derived epithelium to progress and form cystic pancreatic neoplasms [40]. This hypothesis is supported by the fact that rapid growth of pancreatic MCN was seen in women during pregnancy. It has been reported that mural nodules on imaging, lesion size >6 cm and calcification of the cyst wall are associated with the presence of a tubular-type invasive carcinoma very similar to PDAC [38,41–43]. Since nearly all reported MCN have been resected, the natural history of MCN is still unknown and recommendations are based on findings from resection specimens revealing the aforementioned malignancy rates. Once a MCN is diagnosed, a distal pancreatectomy is indicated in most cases due to the young age of the patients and the present inability to differentiate securely between a benign and a malignant lesion. For most patients with noninvasive MCN complete resection means curative therapy as these lesions are solitary and show no recurrence or second neoplasms [2]. A postoperative surveillance is not mandatory and would require life-long high-resolution imaging associated with high costs without any advantage to the patient [2,31]. In contrast, follow-up after resection of invasive MCN should be performed similar to PDAC [31]. The 5-year survival of patients presenting with invasive MCN has been described to be as high as 62%, being worse for elderly patients and for patients with more advanced tumor stages [44].

## Serous Cystic Neoplasms

Serous cystic neoplasms (SCN) are typically located in the pancreatic body and tail and show no significant potential for malignant transformation. The incidence of SCN is higher in women than in men with a peak at the age of 60 years. In abdominal imaging, SCN have a micro- or macro-cystic appearance with a spongy structure. In some cases, they also present with a solid growth pattern. On histopathology, they typically are composed of cysts lined by a single layer of cuboid epithelial cells filled with glycogen [36,45]. A preoperative distinction of SCN from MCN is feasible in most cases due to significant differences in imaging. SCN are usually sporadic, but some arise in patients with von Hippel–Lindau (VHL) syndrome. In patients with VHL syndrome, SCN are commonly multiple. These patients show a loss of heterozygosity of the *VHL* gene [46,47,48]. Sporadic SCN have a somatic mutation of the *VHL* gene in up to 50% with an inactivation of the VHL tumor suppressor protein [46–49] and often show a mutation in the *TBC1D3* gene, also known as PRC17, but no mutations in the genes typically mutated in mucin-producing neoplasms, such as KRAS, RNF43, or TP53 [47,49].

At time of diagnosis, micro- and macro-cystic SCN have a mean size of 4–6 cm and approximately 50% of all patients are asymptomatic [45,50]. Depending on the localization and size of the lesion, symptoms including abdominal pain, discomfort, jaundice, or fatigue are reported. Malignant transformation of SCN with the occurrence of a serous cyst adenocarcinoma is very rare and has only been described in a few case reports [51]. Thus, for asymptomatic patients with a SCN of <4 cm in diameter and without criteria for malignancy on preoperative imaging, surveillance is indicated instead of surgical resection. The natural course of SCN is characterized by a gradual increase in diameter (0.6 cm per year on average).

The growth rate seems to be dependent on initial tumor size as small SCN (<4 cm) show a significantly slower growth rate of 1–2 mm per year than larger lesions (>4 cm) in which annual growth rates of up to 2 cm can be observed [50]. Consequently, besides the size itself, growth rate during surveillance may have an influence on the decision for surgery to avoid local complications due to compression. Following resection, recurrence risk is extremely low and no structured follow-up is recommended [31].

## Solid-Pseudopapillary Neoplasm

The solid-pseudopapillary neoplasm (SPN), also known as Frantz tumor, was first described in 1959. SPN are rare cystic neoplasms that account for approximately 1–2% of all pancreatic tumors [52]. They usually occur in women with a median age of 30 years and are most frequently located in the tail of the pancreas. SPN are classified as malignant due to the potential of lymphatic spread, recurrence, and distant metastases [53]. As all reported series include mainly patients who underwent resection, the natural history of SPN without resection (i.e., growth dynamics) cannot be addressed sufficiently. Anecdotal reports on nonsurgical treatment have shown that both courses—long-term survival with locally limited tumor manifestation, and also aggressive systemic spread with short survival times—are possible [54].

At diagnosis, SPN have a mean size of 8 cm and are located in the body and tail of the pancreas in 60% of patients [53,55,56]. Their macroscopic morphology varies from pure solid to entirely cystic [57]. Tissue analysis of resection specimen has shown that characteristic mutations in exon 3 of the β-catenin gene occur in 83–100% SPN [58,59]. Moreover, especially the absence of other common mutations, such as KRAS, SMAD4, or TP53, distinguishes SPN from other neoplasms of the pancreas [59,60].

Following complete surgical resection, the long-term outcome of SPN is excellent although approximately 6% of the patients show locally advanced tumors (vascular involvement, lymph node metastases) and 8% present with distant metastases [53]. The most comprehensive review including 2.285 resected patients showed that 95.6% of the patients are disease-free during long-term observation. The time to recurrence in the remaining 4.4% of the patients is more than 4 years and final tumor-related mortality is 1.5% [53]. Despite this overall favorable prognosis, SPN must be considered as a tumor entity with a basically malignant course and complete surgical resection is indicated in all patients who qualify for a respective operation. Furthermore, a life-long follow-up (i.e., annually) is mandatory [31].

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# 80

# Surveillance or Surgical Treatment in Asymptomatic Cystic Neoplasms

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## Introduction

Our knowledge regarding cystic lesions of the pancreas has evolved tremendously over the last few decades, and currently we can offer a safe and individual approach to most patients. In cystic neoplasms, such as solid pseudopapillary neoplasms, mucinous cystic neoplasms, cystic neuroendocrine tumors, and main-duct intraductal papillary mucinous neoplasms (IPMN), the accepted approach is surgical resection if the patient is a suitable candidate [1,2]. Otherwise, observation of serous cystic neoplasms and branch-duct intraductal mucinous neoplasms has proved to be safe [3]. However, in a majority of patients with small lesions, identification of the cyst subtype is either not feasible or uncertain. Based on observational data, several treatment algorithms have been proposed for these unclassified cystic lesions, facilitating the decision whether to operate or observe [4–6]. Most of these recommendations are based on the presence of the patient's symptoms and morphologic cyst characteristics. Symptomatic patients per se should strongly be considered for surgery, while in the absence of symptoms, observation is recommended in lesions without suspicious morphologic features. Further aspects such as age, comorbidities, quality of life, and assumption of costs by the local healthcare system should also be considered when counseling a patient with an asymptomatic cystic lesion of the pancreas.

## Rationale for Surveillance or Surgery in Asymptomatic Cystic Neoplasms

After an early period of radical resection of all pancreatic cystic tumors, growing evidence from larger case series caused a transition towards a more selective and observational approach. The rationale behind the selective surveillance in asymptomatic patients with a pancreatic cyst is: (i) some cystic lesions, such as serous cyst-adenomas of the pancreas, never progress into malignant tumors; (ii) in others that can become malignant, an adenoma–carcinoma transformation takes many years; and (iii) cystic lesions with malignant potential normally exhibit suspicious features that can distinguish them from those that are benign. Overall, it can be assumed that the risk that a cystic lesion is malignant at the time of diagnosis is not exceeding 0.01% and for cystic neoplasm >2 cm the risk is a maximum of 0.21% [7]. Further estimation based on collective data from large case series suggests that the percentage of patients developing an invasive carcinoma is approximately 0.24% per year, with a lifetime risk of <1% if the cyst has no worrisome features at presentation [5]. While this direct relation between cyst size and the risk of malignancy has been investigated and described in numerous studies, the relative meaning of cyst size change over time has been given less attention. Certainly, rapidly growing cystic lesions should be generously resected in young patients or observed in very short intervals by EUS and/or MRI (3–6 months). Kang and colleagues showed in a cohort of patients with BD-IPMN that malignant cysts grew by a greater percentage (69.8% vs. 19.4%; $P = 0.046$) and at a greater rate (4.1 mm vs. 1.0 mm/year; $P = 0.001$) [8]. At our institution we strongly recommend surgery if cyst size changes more than 25% within one year. In the common scenario that a patient presents with multiple cystic lesions (25–41% of all BD-IPMN), overall no greater risk of malignancy has been described and decisions about resection or observation should be made on an individual lesion. If symptoms are present or the cystic lesion exhibits suspicious morphologic changes, resection should be recommended to all surgically fit patients.

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Ideally, patients should only be recommended pancreatic surgery if this is to prevent death from pancreatic cancer or if resection is required for relief of symptoms. In patients with a high comorbidity burden (measured by a Charlson comorbidity score of ≥7), an analysis from our institution demonstrated that the absolute majority of patients with unsuspicious cystic lesions, assumed to be branch-duct (BD)-IPMN, died from causes other than IPMN carcinoma [9]. Therefore, the question could be raised about whether further surveillance should be limited to those patients who would benefit from major pancreatic surgery if the lesion develops features that cause concern.

## Treatment Guidelines for Asymptomatic Cystic Neoplasms

Presently, the International Association of Pancreatology (IAP) guidelines for the management of IPMN and MCN of the pancreas [4,6] or the American Gastroenterological Association (AGA) guidelines on the management of asymptomatic neoplastic pancreatic cysts [5] have been adopted by most physicians. There are several differences between these proposed algorithms. Primarily the AGA guidelines have been designed for asymptomatic mucinous cysts in general, while the IAP algorithm focuses on the management of BD-IPMN. Both of them established a list of concerning or worrisome features on which further diagnostic workup, surveillance or surgery is recommended (AGA: main-duct dilation, size ≥3 cm, solid component, concerning cytology; IAP: main-duct dilation, size ≥3 cm, solid component, concerning cytology, thickened cyst wall, abrupt change of main-duct diameter). The IAP recommends further evaluation by endoscopic ultrasound (EUS) ± fine needle aspiration (FNA) if one of these features is present, while the AGA requires two or more of them. If a definitive mural nodule/solid component, and/or main-duct involvement is confirmed by EUS, surgery should be considered in all fit patients according to the IAP guidelines. These guidelines also recommend surgery if the EUS shows concerning features or the cytology shows high-grade dysplasia or more. The AGA guidelines, by contrast, only recommend surgery if two concerning features are present and the cytologic analysis of the fluid or cyst wall (obtained by EUS) is either malignant or suspicious for high-grade dysplasia. For further surveillance, the AGA proposed an annual interval once after diagnosis, followed by a two-year interval, and end of surveillance after 5 years. Diversely, the IAP surveillance frequency is based on cyst size: <1 cm, 2–3 years; 1–2 cm, yearly for 2 years, then longer if no change; 2–3 cm, EUS in 3–6 months, then longer interval alternating magnetic resonance imaging (MRI) with EUS as appropriate; ≥3 cm, close follow-up with EUS every 3–6 months. At the Massachusetts General Hospital, surveillance of asymptomatic cystic neoplasm of the pancreas is conducted according to the AIP guidelines. The flowchart in Fig. 80.1 shows our recommended approach at the Massachusetts General Hospital. Observing cystic lesions with a solid component carries an eightfold risk of harboring malignancy and for main-duct dilation we assume a similar probability. Therefore, in surgically fit patients we consider resection if a single worrisome feature is suspected by imaging studies and confirmed by EUS.

## Quality of Life, Surgery Versus Surveillance

The major objective in treating a patient with an asymptomatic und unsuspicious cystic neoplasm is preventing or detecting the development of an invasive pancreatic carcinoma. Repeating imaging studies, invasive diagnostic procedures and many-times major pancreatic surgery are indispensable requirements to maintain this aim.

Yet, the majority of case series and actual guidelines often neglect issues relating to quality of life, patient preference, or postsurgical functional status. In a unique analysis, Weinberg et al. used decision analysis with Markov modeling to compare competing management strategies in a patient with a pancreatic head cyst [10]. In their study they found that surgery remains the superior strategy for maximizing quality of life in patients who are between 65 and 75 years of age with cysts ≥3 cm, but concluded that patients >85 years have improved quality of life when managed with surveillance. They assume that poor quality of life experienced postoperatively often outweighs the minimal benefit derived from surgery in this population. Analogous consideration has been reported regarding prostate cancer in the elderly, where "watchful waiting" is often more appropriate than radical prostatectomy [11]. Van der Gaag et al. reported that, after cyst resection, long-term quality of life is equal to healthy references and concludes that the excellent long-term overall outcome justifies proceeding with surgery once an indication for resection has been made [12]. Equally, evaluation of Italian patients with BD-IPMN under observation revealed that their quality of life did not deviate from the normal population. Further psychological questionnaires conducted at basal evaluation and during the follow-up demonstrated that the majority of patients showed no signs of anxiety or depression [13].

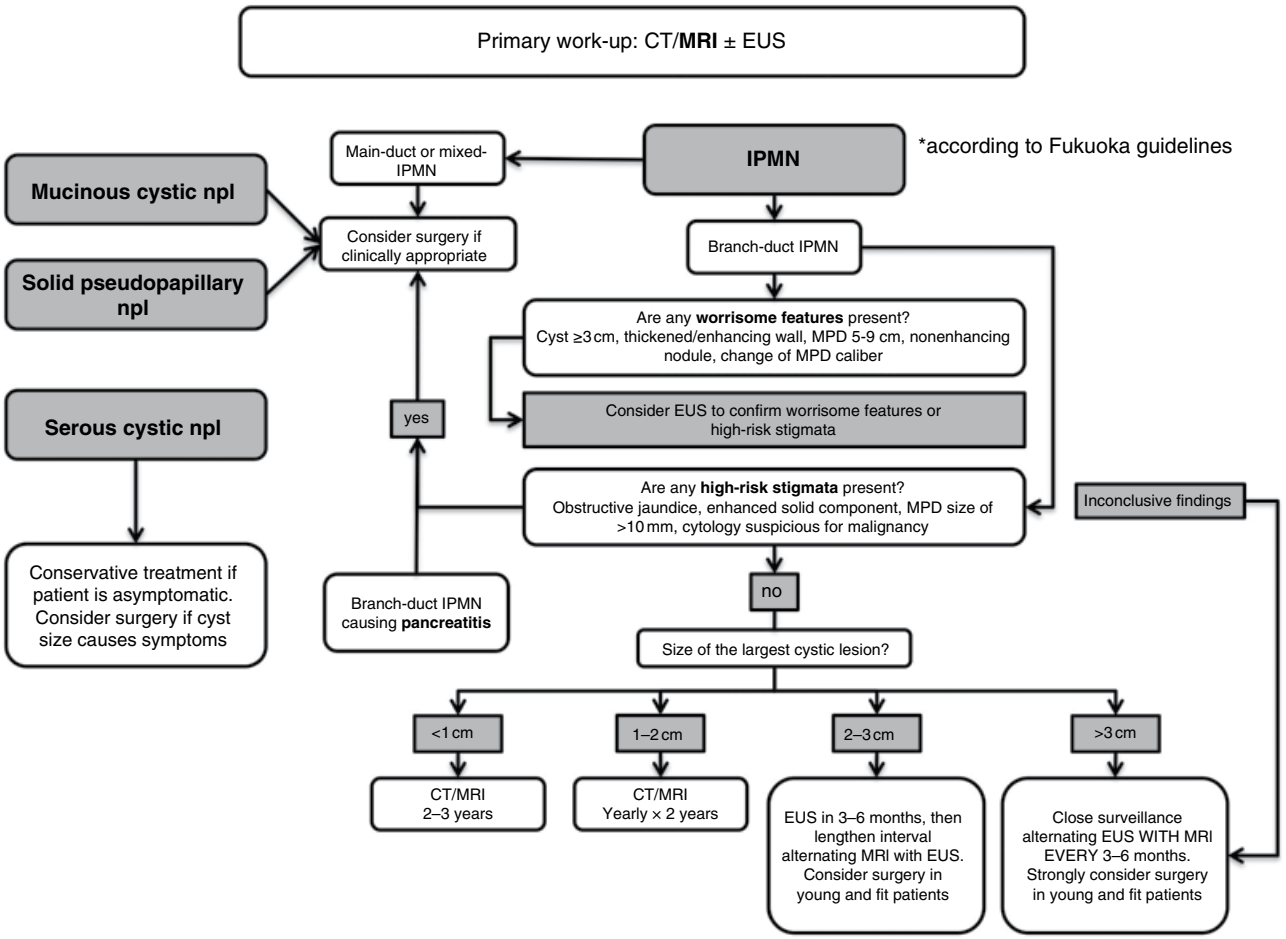


**Figure 80.1** Recommended approach in patients with cystic neoplasms. IPMN, intraductal papillary mucinous neoplasms; npl, neoplasm; EUS, endoscopic ultrasound; CT, computed tomography; MRI, magnetic resonance imaging.

## Cost-Effectiveness of Each Approach

In light of continuously increasing healthcare costs and a restrictive compensation policy by insurance companies, an optimal cost-effective management of asymptomatic pancreatic cystic neoplasm has become relevant. Repeated costly MRI imaging studies for patients under surveillance must be weighed against a more aggressive surgical approach and follow-up with any innervation or stop of surveillance in selected patients. Yet, only a few studies have focused on cost-effectiveness in the management of pancreatic cystic neoplasm. Das et al. used a Markov model with a third-party-payer perspective, comparing follow-up without any specific intervention versus an aggressive surgical approach and initial EUS with FNA with cyst fluid analysis for risk stratification and resection of all mucinous cysts [14]. The strategy based on risk stratification of malignant potential by EUS with FNA and cyst fluid analysis was the most cost-effective strategy and yielded the highest quality-adjusted life years. Researchers from our institution reviewed the cost-effectiveness of the IAP consensus guideline implementation in the management of BD-IPMN [15]. Three scenarios based on 60-year-old patients with branch-duct IPMN were analyzed: surveillance using consensus guidelines for surgical resection (surveillance strategy), surgical resection based on symptoms without surveillance (no surveillance strategy), and immediate surgery (surgery strategy). Surveillance according to the IAP guidelines is a cost-effective strategy in the management of branch-duct IPMN in the head of pancreas when compared to no surveillance and immediate surgery. However, given the large number of patients who are found to have incidental pancreatic cysts, and the lack of endpoint in surveillance, there is a clear need for additional triage strategies that hopefully will identify groups of patients with higher risk and those with negligible risk, where potentially surveillance could be stopped early on. These potential strategies include analysis of cyst fluid for

unique markers and identification of circulating tumor cells, exosomes, or free DNA. For example, mAb Das-1, a monoclonal antibody against a colonic epithelial phenotype investigated at our institution, showed high reactivity, both in EUS-FNA cyst fluid samples (sensitivity of 89%, specificity of 100%) and histologic specimens from resected high-grade IPMN (sensitivity of 85%, specificity of 95%) [16].

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# Local and Standard Surgical Treatment of Cystic Neoplasms

## 81

## Duodenum-Preserving Partial or Total Pancreatic Head Resection

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### Background

Standard surgical treatments for benign cystic neoplasm of the pancreas are presently multiorgan resections; pancreatoduodenectomy (PD) for tumors of the pancreatic head and a left-sided pancreatic resection, either spleen-preserving or with splenectomy, for tumors in the body and tail. Many of the cystic neoplasms are benign and small (tumor size <4 cm) at the time of diagnosis. The question arises, why a surgical treatment with radical resection of the tumor-bearing pancreas, unnecessarily sacrificing duodenum, pancreatic biliary and gastric tissue, is applied for a benign lesion? Although not performed as standard, parenchyma-sparing, local resection procedures for pancreatic tumors have the potential for low procedure-related postoperative morbidity and preservation of exocrine and endocrine pancreatic functions [1,2].

### Classical Pancreatoduodenectomy or Local Extirpation for Cystic Neoplasms of the Pancreatic Head?

The standard treatment for a benign cystic neoplasm in the pancreatic head is currently the Kausch-Whipple resection. PD is a multiorgan resection associated with considerable loss of functional pancreatic and extrapancreatic tissue, including the stomach, duodenum, and biliary tree. PD is associated with a considerable rate of severe postoperative complications, including pancreatic fistula, disruption of anastomosis, surgical side abscess, intra-abdominal hemorrhage, and a severe form of delay of gastric emptying, requiring reoperation and/or reintervention in 5–12% of cases [3,4]. Hospital mortality after PD in high-volume institutions ranges below 3–5%. However, 30-day mortality rates as high as 4–8% have been reported [4–6]. Postoperatively, new diabetes mellitus develops in 12–20% of patients after surgical resection of a benign or premalignant pancreatic lesion [7–11]. In total, 30–40% of the preoperative diabetic patients display postoperatively an escalation of the adjustment of diabetic glucose metabolism [11]. Following PD, the exocrine pancreatic functions are significantly reduced in 30–50% of cases [12]. The duodenectomy of the Kausch-Whipple operation induces long-lasting dysfunctions of secretion of gastrointestinal hormones and gastrointestinal motility disorders [13–16] (Table 81.1).

In contrast to the Kausch-Whipple resection, duodenum-preserving total pancreatic head resections for benign pancreatic head lesions are associated with low postoperative surgery-related morbidity and a very low hospital mortality [18]. A recently published meta-analysis on functional changes before and after DPPHR and PD revealed that exocrine and endocrine pancreatic functions following DPPHR were unchanged, in contrast to PD [8]. Despite the resection of pancreatic head tissue, total duodenum-preserving pancreatic head resection maintains endocrine functions as reflected by $HbA_{1c}$ levels, glucose tolerance testing, and the frequency of postoperative new-onset diabetes mellitus [8]. The same is true for exocrine pancreatic functions. DPPHR preserves the exocrine functions, whereas after PD there is often a significant decrease, requiring enzyme

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**Table 81.1** Short- and long-term metabolic and functional sequelae after pancreatoduodenectomy.

| | Results | | | |
|---|---|---|---|---|
| | Percentage | Number | Period of follow-up (years, months) | Reference |
| New-onset diabetes mellitus | 12.2% | 4/32 pts* | 2.8 y, median | J Gastrointest Surg 2012 [7] |
| | 16.4% | 28/171 pts** | 3–6 m | Pancreatology 2015 [8] |
| | 18% | 24/135 pts* | 25 m | J Gastrointest Surg 2015 [9] |
| | 16% | 28/178 pts* | <3 m | HBP 2016 [10] |
| | 17% | 17/76 pts* | 1 y | Br J Surg 2013 [11] |
| Impaired glucose tolerance | 47.4% | 36/76 pts* | 1 y | Br J Surg 2013 [11] |
| Postoperative escalation of diabetes mellitus | 48% | 21/44 pts* | 25 m, median | J Gastrointest Surg 2015 [9] |
| | 44.4% | 19/42 pts* | 2.8 y | J Gastrointest Surg 2012 [7] |
| Exocrine pancreatic insufficiency | 44% | 42 pts** | 3–6 m | Pancreatology 2015 [8] |
| | 43% | 94/214 pts* | <3 m | HBP 2016 [10] |
| Failure of biliary anastomosis | 14% cholangitis, jaundice, leak, stricture | 49/352 pts* | early, <3 m | HBP 2016 [17] |
| Reduced level of GI hormones | cholecystokinin | 51 pts* | 3–6 m | J Hep Bil Pancreat Sci 2000 [16] |
| | motilin | 9 pts* | 6 m | Surgery 1996 [14] |
| | secretin | 14 pts* | 6 m | Jpn J Gastroenterol Surg 1997 [13] |

*Of the 1044 patients who had pancreatoduodenectomy, 44% suffered a benign tumor and 56% a cancerous lesion.
**PD for benign tumors only.

supplementation. The probability of developing endocrine and exocrine pancreatic insufficiency 1 year and 5 years after PD was found to be 32% and 85%, respectively [19].

## Rationale for Local Pancreatic Head Resection

The rationale for a local resection of a benign tumor in the pancreatic head is based on: (i) preserving the duodenum, distal biliary duct, and gall bladder as well as distal stomach and pylorus; (ii) maintaining the functional integrity of the duodenum regarding coordination of digestive, metabolic, and motility functions of the pancreas, liver, and stomach, respectively; (iii) conserving a maximum of the pancreatic tissue; (iv) protecting the patient against metabolic and nutritional long-term persisting GI-tract disorders of glucose metabolism and disturbances of carbohydrate, fat, and protein digestion.

The goals of limited, parenchyma-sparing pancreatic head resection are: (i) application of a procedure with a low risk for surgery-related severe complications and hospital mortality, which are superior to the standard surgical procedure; (ii) maintenance of the quality of life of patients aged below 50 years when referred for surgical treatment in the case of IPMN, MCN, SCN, and pancreatic neuroendocrine tumors; (iii) prevention of fear of suffering pancreatic cancer.

## Duodenum-Preserving Total Pancreatic Head Resection With or Without Segmental Resection of the Peripapillary Duodenum and the Intrapancreatic Common Bile Duct

Tumor size and location, radio-morphologic type, and histopathology of the neoplasm being resected determine whether a total or partial pancreatic head resection should be undertaken (Table 81.2).The surgical technique of DPPHR is almost identical to the standard PD procedure except for dissection of the pancreatic head along the duodenal wall and the conservation of the intrapancreatic common bile duct (CBD), and in some instances resection of a 2 cm segment of the peripapillary duodenum. To preserve the duodenum and the intrapancreatic CBD, a total pancreatic head resection (DPPHR-T) entails complete resection of the pancreatic head, including the uncinate process (Fig. 81.1). Duodenum-preserving total pancreatic head resection with segment resection of the peripapillary duodenum (DPPHR-S) comprises total pancreatic head extirpation and resection of the segment of the peripapillary duodenum and the intrapancreatic CBD, while preserving the pancreatic neck (Fig. 81.2). Three anastomoses are to be performed to ensure postoperative GI integrity. An excluded jejunal loop or the stomach is used for anastomosis of the left pancreas. Partial

**Table 81.2** Indication for DPPHR for benign cystic neoplasms of the pancreatic head.

| | |
|---|---|
| DPPHR total<br>+ Segment duodenum + CBD | TM abutment to duodenal wall<br>TM involving CBD<br>TM location dorsal: ischemic lesion of peripapillary duodenum<br>Cystic neoplasm + carcinoma *in situ*/minimal invasive carcinoma (T1a, N0) |
| DPPHR total<br>Conservation of duodenum and CBD | TM extending to head + neck of pancreas, CBD not involved<br>TM extending in dorsal and ventral head segments, not involving duodenum + CBD |
| DPPHR with partial head resection | TM location in *processus uncinatus* (uncinectomy)<br>TM location in neck of pancreas<br>CBD not involved |

CBD, common bile duct; DPPHR-T, total pancreatic head resection; DPPHR-S, subtotal pancreatic head resect; TM, tumor.

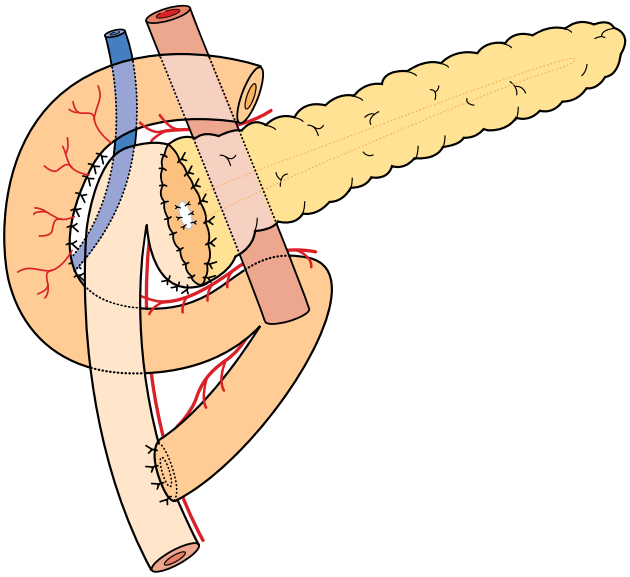

**Figure 81.1** Duodenum-preserving total pancreatic head resection conserving the duodenum and the CBD.

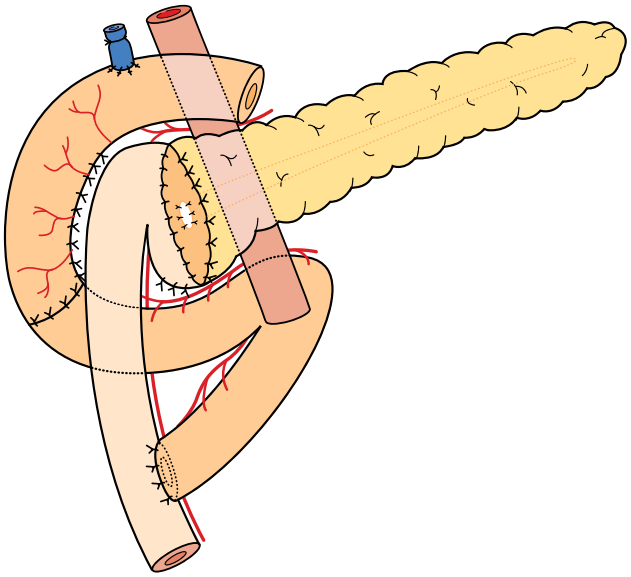

**Figure 81.2** Duodenum-preserving total pancreatic head resection including resection of peripapillary duodenum and CBD.

pancreatic head resection is performed by extirpating the tumor-bearing tissue from the pancreatic head or by resecting of the uncinate process (Fig. 81.3a,b). The application of a duodenum-preserving total pancreatic head resection with preservation of the peripapillary duodenum and the intrapancreatic CBD is associated with a higher frequency of local complications in the area of the peripapillary duodenum and the intrapancreatic CBD [18]. Two additional steps are needed to perform a lymph node (LN) dissection in association with DPPHR. Harvesting the anterior head LN is part of total head extirpation. The access to LN left of the superior mesenteric artery (SMA) and the LN along the hepatic and celiac arteries as well as in the hepatoduodenal ligament are performed in the same way as in the classical PD. Sampling the posterior head LN necessitates an additional step.

Duodenum-preserving total or subtotal pancreatic head resection has been applied in two-thirds of patients with a unifocal cystic neoplasm of the head of the pancreas (Table 81.3). Most total head resections have been performed for an IPMN, followed by SCA; in one third of cases a partial, subtotal head resection was performed, whereas in two-thirds of cases a total, parenchyma-sparing head resection was executed. Approximately 10% of the cystic neoplasms resected by local head resection have been reported to contain high-grade dysplasia or a minimal invasive cancer. The procedure-related morbidity includes: severe complications (Clavien-Dindo >3) 12.7%; POPF B + C 13.6%; reoperation 2.7%; rehospitalization 3.2%; 90-day mortality 0.4%. After a mean follow-up time of 62 months, a recurrence was observed in 2.9% of cases [18].

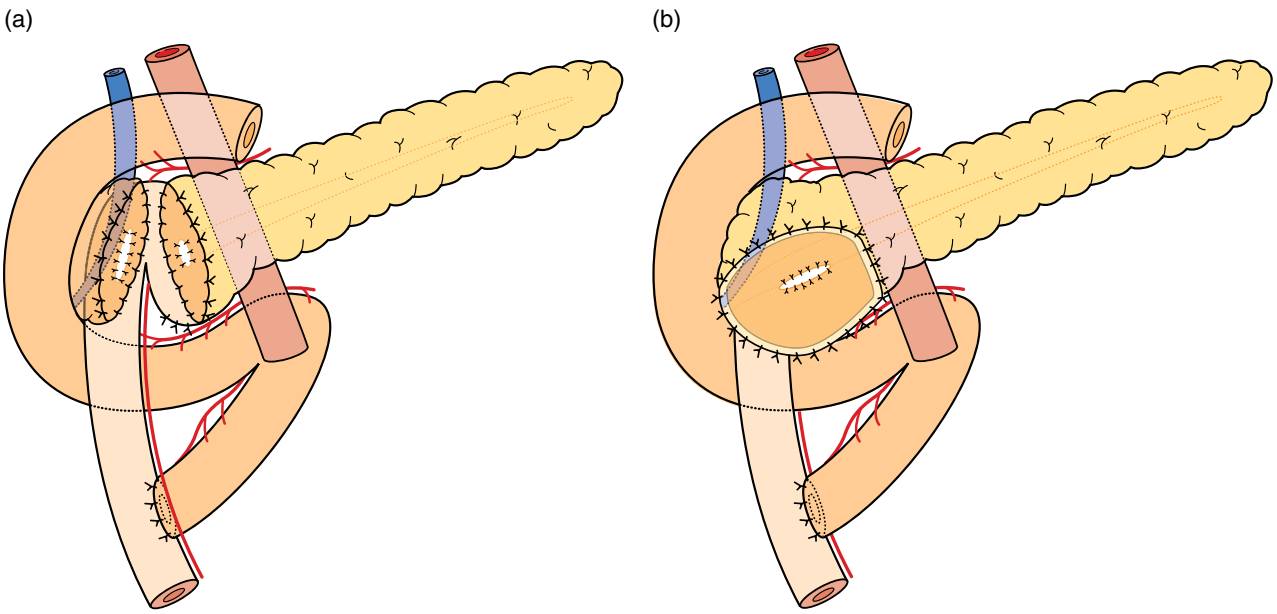


**Figure 81.3** (a) Duodenum-preserving partial pancreatic head resection. (b) Duodenum-preserving partial pancreatic head resection: uncinectomy.

**Table 81.3** Findings after local, parenchyma-sparing duodenum-preserving total or partial pancreatic head resection for cystic neoplasms of the pancreatic head.

| Total pts | Cystic neoplasms* Total no. of patients | Neoplasm with high-grade dysplasia | Minimal invasive cancer associated with the cystic neoplasm | Others** |
|---|---|---|---|---|
| 503 | 338/503 | 23/338 | 8/338 | 165/503 |
| 100% | 67.2% | 6.8% | 2.4% | 32.8% |

*IPMN 250 pts, MCN 30 pts, SPN 20 pts, SCA 38 pts.
**PNET, low-risk $T_1$ periampullary cancer, inflammatory/biliopancreatic malfunction.

## Conclusion

For surgical treatment of benign and low-risk cystic neoplasms of the pancreatic head, the application of a local, parenchyma-sparing head resection offers major benefits to the patient by maintaining the quality of life. The advantages of the duodenum-preserving total or partial pancreatic head resection compared to PD are a low surgery-related early postoperative morbidity and a very low hospital mortality. Local pancreatic head resections are associated with an almost complete conservation of the endocrine and exocrine pancreatic functions in contrast to the metabolic consequences following PD. The risk of recurrence after local head resection of cystic neoplasms, including high-grade dysplasia and minimal invasive carcinoma, is very low provided frozen section investigation is used to exclude an advanced cancer.

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# 82

# Pancreatic Middle Segment Resection

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## Introduction

Pancreatic middle segment resection (PMSR; the Dagradi-Serio-Iacono operation) is a parenchyma-sparing operation allowing the removal of benign and low-grade malignant lesions from the neck and the proximal body of the pancreas (Fig. 82.1) [1]. Compared to pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), PMSR is associated with a lower risk of postoperative diabetes and exocrine insufficiency. This operation also spares the spleen, with lower infective and thromboembolic complications, as well as the upper digestive and biliary tract, which is not possible in PD.

The first PMSR was performed in 1982 by Dagradi and Serio resecting a neuroendocrine tumor (insulinoma) located in the neck of the pancreas and was reported in the "*Enciclopedia Medica Italiana*" [2]. Subsequently, Iacono validated PMSR with endocrine and exocrine functional tests [3]. These findings were reported in several international reports demonstrating that there is almost no postoperative impairment of endocrine and exocrine functions when appropriate indications and technique are respected [2–4].

Furthermore, in the last decades, several authors have reported clinical series on patients who underwent PMSR demonstrating that this operation has become a standardized technique commonly applied in the surgical treatment of pancreatic diseases [2,4–9]. Currently, PMSR is performed worldwide either by traditional open surgery [2,4–9] or by using minimally invasive or robotic approaches [2,4,10–12].

## Indications

The prerequisites allowing PMSR include:

1) Benign lesions between 2 and 5 cm in size, when a simple enucleation entails risk of injury to the main pancreatic duct;
2) Cystic lesions not suitable for enucleation: symptomatic serous cystadenoma (Fig. 82.1), mucinous cystadenoma, solid cystic pseudopapillary tumors, selected cases of intraductal papillary mucinous neoplasm (IPMN);
3) Small tumors deeply located in the gland and therefore not eligible for simple enucleation (i.e., functioning endocrine tumors);
4) Focal chronic pancreatitis with isolated short stenosis of the pancreatic duct;
5) Solitary metastases in the pancreatic neck (i.e., from kidney cancer);
6) Metastatic pancreatic endocrine tumors in a multimodality program treatment.

## Contraindications

Contraindications include:

1) A distal pancreas stump of less than 5 cm in length;
2) Distal body–tail atrophy;
3) Malignant tumors (i.e., pancreatic ductal adenocarcinoma);
4) Neoplastic involvement from other organs (stomach, transverse colon);

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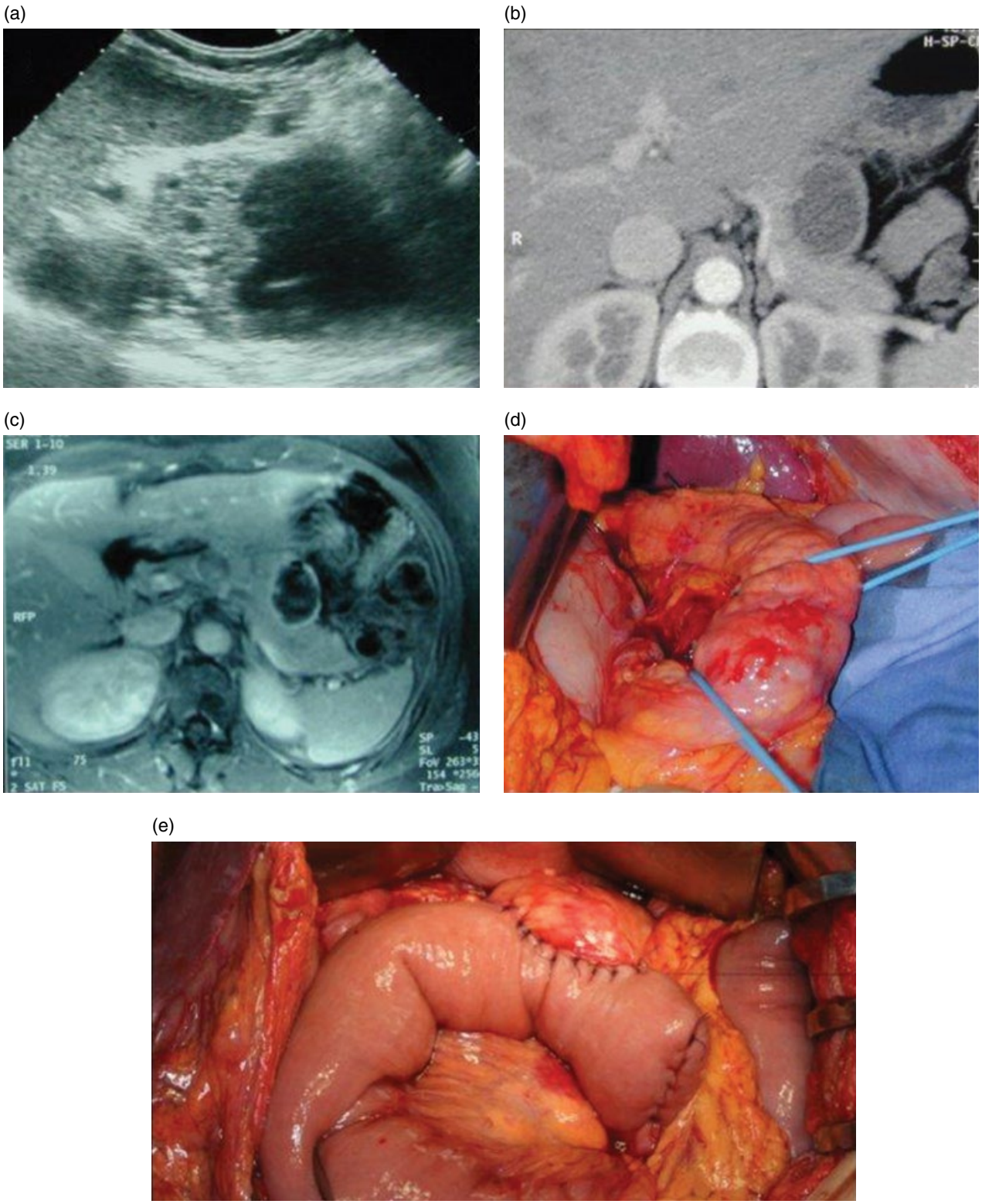


**Figure 82.1** A young patient with a symptomatic serous cystadenoma. Ultrasonograhy (a), computed tomography (b), and magnetic resonance imaging showing a cystic lesion at the neck of the pancreas (c). (d) Intraoperative aspect with evidence of the lesion localized at the pancreatic neck. (e) Final aspect of PMSR, the cephalic stump is sutured and the distal stump is anastomized by duct-to-mucosa pancreaticojejunostomy with a Roux-and-Y jejunal loop.

5) Diffuse or focal chronic pancreatitis not involving the central part of the gland;
6) When the arterial supply for the body–tail of the pancreas is exclusively from the transverse pancreatic artery (left branch of the dorsal pancreatic artery; type III according to Mellière and Moullé) [1].

## Technique

PMSR requires two steps, the first phase to resect the central pancreatic segment (isthmus, and/or proximal body) (Fig. 82.1d), followed by a second phase that includes reconstructive suture of the cephalic stump and performing digestive anastomosis with the distal stump (Fig. 82.1e) [1,3,13,14].

### Resection Step

PMSR requires a midline incision. Access to the lesser sac is achieved by division of the omentum from the transverse colon (the preferred procedure of the author) or of the gastrocolic ligament. The pancreatic gland is widely exposed by dividing the adhesions between the posterior surface of the stomach, retracted upward, and the pancreas.

This is followed by the intraoperative diagnostic workup performed with pancreatic ultrasonography to better identify the lesion or with fine needle biopsy for those cases with uncertain diagnosis.

Incision of the posterior peritoneum along the superior and inferior margin of the gland is carried out. The posterior surface of the pancreatic segment including the lesion is carefully dissected from the portomesenteric axis and the splenic vein and artery avoiding vessel injury.

This phase could be simplified by performing first a proximal dissection of the pancreas (mobilizing the pancreatic stump towards the left) and then exposing all the thin pancreatic veins, which can be more easily divided.

The identification of a large dorsal pancreatic artery might suggest that the left pancreatic blood supply is exclusively maintained by the transverse pancreatic artery. This vascular variation is, as previously mentioned, a clear contraindication to PMSR. Occasionally, it is necessary to isolate and mobilize the common hepatic artery to divide those branches originating from it (i.e., the dorsal pancreatic artery) that supply the central pancreas.

The extent of the resection of the central segment is limited on the right by the gastroduodenal artery and on the left so as to leave at least 5 cm of normal pancreatic remnant.

After stay sutures are placed in the superior and inferior pancreatic margins to indicate the proximal and distal limits of division, the pancreatic cephalic end is transected using either a scalpel or a stapler. For the distal side, the resection should be performed with a scalpel in order to avoid damage to the splenic artery or vein.

The resected pancreatic specimen is then sent to the pathologist to verify that the resection margins are adequate and to confirm the diagnosis by frozen sections. In the presence of malignancy, a PD or left splenopancreatectomy with lymphadenectomy should be performed.

Hemostasis of the two raw surfaces is achieved with interrupted 4/0 or 5/0 nonabsorbable stiches, and the integrity of the main pancreatic duct on the distal stump is preserved by the insertion of a small catheter.

In the presence of IPMN, a pancreatoscopy might be performed just after the resection of the main pancreatic duct in both stumps to rule out other ductal lesions.

### Reconstructive Step

When not stapled, the duct of Wirsung of the cephalic stump is sutured selectively with figure-of-eight nonabsorbable stitches; a row of interrupted, overlapping stitches of the mattress type is placed through the entire length of the stump and tied.

The distal stump is reconstructed using several techniques commonly applied in PD, which include an end-to-end telescopic or invaginated pancreaticojejunostomy (PJ), end-to-side PJ anastomosis, double PJ for both stumps, side-to-side PJ, duct-to-mucosa, using a Roux-en-Y jejunal loop isolated and brought up through the mesocolon; and pancreaticogastrostomy.

In the author's original report, a telescopic PJ with a double-layer suture was performed, while subsequently, an end-to-end invaginated PJ was carried out with a single layer of interrupted stitches. The posterior and anterior parts of the anastomosis was closed with stitches that were tied one after another. To avoid any damage to the duct of Wirsung, a small catheter was introduced before the stitches were inserted and was removed just prior to the stitches being tied. Currently, the author prefers to perform a duct-to-mucosa with a plastic transanastomotic catheter (Fig. 82.1e).

The operation is concluded with the construction of an end-to-side jejunojejunostomy with a double layer of absorbable stitches, about 50 cm distal to the pancreatic anastomosis. Finally, two soft drains are placed close to the head pancreatic stump and the pancreatic digestive anastomosis and pulled through the right and left flanks.

In a recent systematic review, the distal stump was usually dealt with by a PJ in about two-thirds of cases and by a pancreaticogastrostomy in another third of cases.

In the majority of patients, the proximal stump was closed by sutures with or without specific ligation of the main pancreatic duct [4].

## Results

Iacono et al. reported that between 1988 and 2010, 94 studies described 963 patients who underwent PMSR; among these a minimally invasive approach (laparoscopic or robot-assisted) was performed on 30 patients. In a sensitivity analysis considering only studies involving more than 10 patients, short-term postoperative morbidity was recorded in 45.3/% of patients, pancreatic fistula was the most frequent complication in about 40% of patients with only a minority of patients (~10%) presenting with a grade C fistula according to the International Study Group on Pancreatic Fistula (ISGPF) classification [4]. Other surgical complications were intraperitoneal abscess and fluid collections (often related to pancreatic fistulae), splenic vein thrombosis with secondary infarction of the spleen, abscess, pancreatitis, delayed gastric emptying, wound infection, and intestinal obstruction. Less than 5% of patients had an early reoperation for abdominal bleeding, pancreatic fistula, intra-abdominal collections, pancreatitis of the distal stump, or intestinal obstruction [4].

The in-hospital mortality rate was less than 1% and causes of death were heart disease, pancreatic fistula associated with portal vein thrombosis, hepatic failure, respiratory failure, and delayed hemorrhage.

Exocrine and endocrine insufficiencies were observed in about 10% and 5% of patients, respectively.

Disease recurrence after PMSR was about 3%, mainly because of IPMN or inappropriate indications; when the correct indications were respected the rate of local recurrence was almost zero [4].

More importantly, in a meta-analysis comparing PMSR to DP, PMSR was associated with longer operating times and hospital stay but less blood loss during the surgical procedure. Nearly half of the patients who underwent PMSR suffered from postoperative morbidity, in contrast to less than one third of those who underwent DP. Overall morbidity was significantly higher after PMSR, as was the incidence of pancreatic fistula. Despite increased morbidity, PMSR was associated with a significant reduction in the risk of reoperation and with similar in-hospital mortality rate. Interestingly, the incidence of long-term complications was lower after PMSR than DP for both endocrine and exocrine failures [4].

## Conclusions

PMSR assures that the functional parenchyma is preserved as much as possible, and avoids the infective and thrombotic complications commonly associated with splenectomy. Despite the high risk of pancreatic fistula, PMSR has demonstrated low rates of postoperative reoperation, and endocrine and exocrine insufficiency. Following precise anatomic and pathologic indications, PMSR is a consistent and precise surgical technique for the treatment of benign and low-grade malignant pancreatic disease, especially in young patients.

The open approach is still the standard for CP, but minimally invasive surgery, especially the robotic approach, has an emerging role in experienced centers.

It is the author's opinion that PMSR should be included in the technical skills of a modern pancreatic surgeon, but to achieve safety and good results, adherence to the proper indications and experience in pancreatic surgery are recommended.

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# 83

# The Indications For and Limitations of Tumor Enucleation

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## Introduction

Cystic neoplasms of the pancreas are increasingly diagnosed due to improvements in modern imaging modalities [1]. Nearly 3% of all patients undergoing abdominal computed tomography (CT) will have an incidentally detected pancreatic cystic lesion. This number varies significantly according to the size of the cyst and the threshold of radiologists to report them. While some of these cysts are benign, most carry some risk of malignancy, and all have the potential to cause symptoms. Diagnosis is often unclear despite multiple strategies including CT, endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and fine needle aspiration (FNA) with cytology and cyst fluid biochemical and DNA analysis. A definitive diagnosis may be difficult without surgical resection. Treatment of these lesions must therefore balance the diagnostic and therapeutic benefit against the significant morbidity and potential mortality of surgical resection. If patients require surgical treatment, techniques associated with lower morbidity must be considered. In select cases, cyst enucleation is an effective option with lower morbidity and mortality than pancreatic resection [2–6].

## Indications

A major challenge of pancreatic cyst enucleation is appropriate patient selection. Careful characterization of the cyst is necessary to determine if an indication exists for enucleation. Selection can be done with thorough preoperative evaluation. The first step is cross-sectional imaging (CT or MRI-MRCP with thin slices). Additional diagnostic tests may help in diagnosis and oncologic risk stratification, including EUS with FNA for cyst fluid cytology and biochemical/DNA analysis. Fig. 83.1 shows MRCP of a branch-duct intraductal papillary mucinous neoplasm (BD-IPMN) eligible for cyst enucleation. Radiographic and biologic workup must take place in order to rule out malignancy [6], vascular involvement, and metastases [7], as these are all contraindications to enucleation.

Many lesions amenable to resection also may be amenable to enucleation. Patients who are symptomatic or have signs of malignant/premalignant pancreatic lesions generally should undergo surgical resection. Symptomatic pancreatic cysts should be resected, not only to alleviate symptoms, but also because of the increased risk of malignancy associated with symptomatic lesions [8]. If evidence strongly suggests the lesion is malignant, an oncologic resection should be performed without consideration of enucleation. Findings consistent with malignancy include lymphadenopathy, distant metastases, mural nodules, and solid components [6]. Lesions with uncertain diagnosis or lesions that are premalignant may be appropriate for cyst enucleation. When no oncologic need exists for traditional pancreatic resection, enucleation can avoid unnecessary sacrifice of pancreatic parenchyma minimizing the risk of pancreatic exocrine and endocrine insufficiency [9,10].

Although pancreatic neuroendocrine tumors (PanNET) are the most common lesion removed via cyst enucleation, many other cysts types also are suitable for this method of resection [11]. These cysts include, but are not limited to, mucinous cystic neoplasms (MCN), BD-IPMN [12], serous cystic neoplasms (SCN), and

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

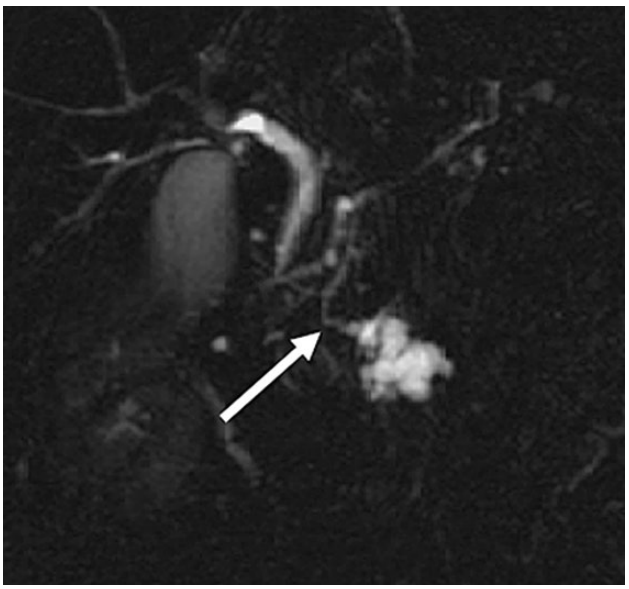

**Figure 83.1** MRCP of a BD-IPMN of the uncinate process eligible for cyst enucleation. The arrow identifies the communicating duct. *Source:* Turrini et al. 2011 [2]. Reproduced with permission of Elsevier.

**Table 83.1** Indications for pancreatic cyst enucleation.

| Pathology | Criteria |
|---|---|
| Nonfunctional PanNET | <2 cm, N0M0 |
| Functional PanNET | if technically feasible |
| MCN | if likely benign; <4 cm; no mural nodules |
| BD-IPMN | rapidly increasing size; high-grade atypia; mural nodules |
| SCN | only if symptomatic |
| SPN | if technically feasible and no evidence of malignancy |

solid-pseudopapillary neoplasms (SPN) [5,13]. Table 83.1 lists criteria for enucleation based on specific pathology. Cyst enucleation is considered the procedure of choice for most functional PanNET as long as technically feasible [6,14]. The prohibiting factor is often size, defined as greater than 3–4 cm by multiple authors [15,16]. Nonfunctional PanNET may be enucleated if less than 2 cm and are N0M0 radiographically [6,16,17]. If lymph node involvement is suspected, oncologic resection should be performed. Nonfunctional lesions less than 1 cm may be observed under a structured surveillance program. Some authors argue that size is not prognostic as up to one quarter of nonfunctional PanNET less than 2 cm will have lymph node metastases [18]. This risk may be unacceptably high indicating a need for lymph node sampling in all nonfunctional PanNET [19]. Conversely, other authors have shown no prognostic value of nodal status in an analysis of 3,851 patients with PanNET [20].

The Sendai and Fukuoka guidelines address indications for surgical resection of MCN and BD-IPMN [8,21]. MCN should be removed and may be enucleated if they appear benign on imaging, are less than 4 cm, and do not contain mural nodules. The indications for resection of BD-IPMN are more controversial. These lesions are often observed, but may require resection if high-risk features exist such as rapidly increasing size, high-grade atypia, associated main-duct dilation (early main-duct involved IPMN) and mural nodules. Because SCN carries a very low risk of malignancy, they are generally only resected if the diagnosis is in doubt or if symptomatic. However, if allowed to grow, enucleation may no longer be technically possible. Thus, the decision for surgical management should be made on an individual basis.

If surgical resection is indicated, assessment of patient fitness must be undertaken. This assessment includes evaluation of comorbid conditions, nutritional status, and psychosocial health. Patients should be assessed for fitness for both enucleation and formal resection since the operation may convert to resection based on intraoperative findings. Fitness is not only an important factor in determining patient tolerance of the procedure, but also in determining life expectancy. Patients with limited life expectancy may be more likely to die of alternate causes than cyst-related causes. In this case, a surgical procedure would not extend their life and would put them at undue risk of surgical complications.

## Contraindications

Table 83.2 lists the major contraindications to pancreatic cyst enucleation. Patients with known or suspected malignancy should not undergo enucleation and instead should have an oncologic resection with negative margins and lymph node dissection [11,22]. This includes lesions with high risk of progression to malignancy such as main-duct IPMN (MD-IPMN). Diagnosis of malignancy is based on symptoms, radiographic images, cytopathology, and DNA profile. Despite these multiple diagnostic tools, a definitive diagnosis of malignancy is often difficult to achieve preoperatively. In those cases, consultation with experts and the patient are necessary to determine the best course of action. The surgeon may elect to begin the operation as a parenchymal-sparing enucleation until he/she encounters evidence of malignancy intraoperatively. Malignant cysts can be difficult to dissect due to adherence to surrounding parenchyma. Whether or not the surgeon suspects malignancy,

**Table 83.2** Contraindications to pancreatic cyst enucleation.

| Contraindications |
|---|
| Suspected malignancy or high-risk lesions (i.e., MD-IPMN) |
| Pancreatic duct involvement/close proximity |
| Location in tail |
| Large size |
| Multifocality |
| Poor patient fitness |

intraoperative frozen section pathology confirmation of invasive cancer necessitates conversion to formal pancreatic resection.

The lesion's proximity to the main pancreatic duct is an important technical consideration for enucleation. If the cyst involves the main duct, enucleation cannot be achieved without transection of the duct and, therefore, is contraindicated [17,23]. Additionally, cysts involving the main duct, specifically main-duct IPMN (MD-IPMN), are at a greater risk of conversion to invasive cancer and, thus, require formal resection [8]. Enucleation also may be contraindicated based on the cyst's close proximity to the main duct. Risk of injury and subsequent pancreatic fistula is greatly increased (60%) when the cyst is within 2 mm of the duct [23,24]. Distance of 2–3 mm between the cyst and the main pancreatic duct is safe for cyst enucleation and can be determined with preoperative imaging such as MRCP and EUS [3,25]. During surgery, this safe distance is confirmed with intraoperative ultrasound (IOU). Location of the cyst within the pancreas is also important when considering enucleation. If located in the tail of the pancreas, enucleation does not save much parenchyma compared to distal pancreatectomy and thus, would offer no benefit.

The mean size of enucleated pancreatic cysts is 2.4 cm [11]. This relatively small size is due to the relationship between larger size and higher likelihood of malignancy [26]. Enucleation of larger cysts also may sacrifice too much pancreatic parenchyma for this procedure to be beneficial over formal resection. The size at which enucleation may be safely performed is controversial and differs based on pathology. Four centimeters is arguably the cut-off at which enucleation should be performed due to increased risk of recurrence of lesions greater than 4 cm [3,11,17,23]. Data suggest that this size limit may be increased to 6 cm in SCN and MCN without increasing recurrence, morbidity, or mortality [27]. Multifocality is a relative contraindication due to incremental risk of pancreatic fistula with each enucleation. Similar to size, multifocality of cysts also requires a larger amount of parenchymal resection without benefit over formal resection. Depth of the cyst is a relative contraindication for enucleation. More extensive dissection is required for deeper lesions making their dissection more tedious and at times, making formal resection the more appropriate choice [4,5,22].

## Surgical Technique

Pancreatic cyst enucleation can be performed minimally invasively (laparoscopically/robotically) or open and is based on surgeon preference. Currently, enucleations are being performed minimally invasively in approximately one quarter of cases, and are associated with shorter recovery times and similar morbidity and mortality as open enucleations [11,28,29]. The steps of the procedure remain the same regardless of whether minimally invasive or open techniques are used. After entrance into the abdomen, the liver, hemidiaphragms, and all peritoneal surfaces are surveyed for occult metastatic disease. IOU is used to identify intraparenchymal metastases, thus completing the survey of the liver. The pancreatic cyst is then exposed using the Kocher maneuver for head lesions, and entrance into the lesser sac for body and tail lesions. Ultrasound can aid in both location and careful characterization of the cyst [30]. The distance between the cyst and the main pancreatic duct is calculated to determine safety of performing enucleation. Concerning features such as mural nodules and solid components are identified with IOU. After ultrasound evaluation, enucleation may be aborted due to suspicion for malignancy or duct proximity.

Superficial lesions with extrapancreatic components are the most amenable to cyst enucleation, as significantly less dissection is required to free them from surrounding parenchyma. Ultrasound guidance can assist in locating deeper lesions. Overlying parenchyma is dissected away until the lesion is identified. Frozen section pathology is always performed; and if invasive disease is discovered, lymph nodes must be retrieved and negative margins must be achieved for maximal survival benefit. Parenchyma sparing must be balanced against but never compromise oncologic principals. BD-IPMN have communicating ducts that must be identified and ligated to prevent leaks (Fig. 83.2). After removal of the cyst, the cavity is searched for small vessels and ducts, which are ligated with clips, ties, or tissue coagulation devices. Thermal injury can result from cautery and should be avoided when the main duct is near. Main pancreatic duct integrity can then be evaluated with ultrasound and secretin stimulation. Some surgeons close the pancreatic parenchyma with absorbable suture [31] and many routinely leave surgical drains.

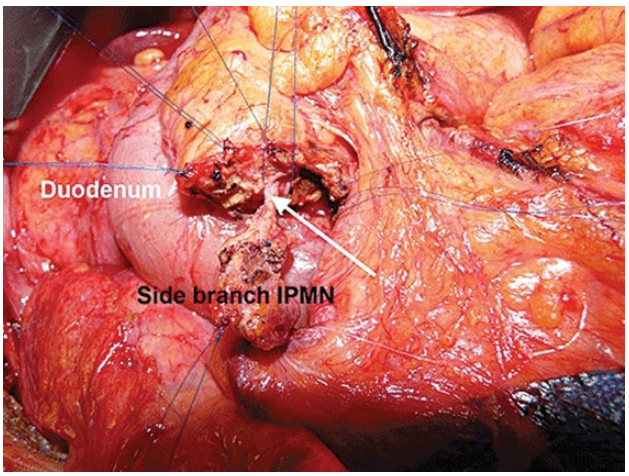


**Figure 83.2** Intraoperative photograph of a BD-IPMN. The arrow identifies the communicating duct. *Source:* Turrini et al. 2011 [2]. Reproduced with permission of Elsevier.

## Postoperative Management

Postoperative management of patients following cyst enucleation is the same as any pancreatic resection. If surgical drains are placed intraoperatively, drain amylase should be followed. Drain amylase should be measured on postoperative day one (POD #1) [6]. Drain amylase elevated greater than three times the serum level indicates a pancreatic fistula [32]. Growing evidence suggests that in patients with low POD #1 drain amylase levels, drain removal by POD #3 dramatically reduces the incidence of a pancreatic fistula [27,28,30,31].

Management of pancreatic fistulas depends on grade and surgeon preference. No standardized management plan exists due to lack of strong evidence. Treatment of diet ranges from continued normal diet, to nothing by mouth with total parenteral nutrition [6]. Other management options include endoscopic pancreatic sphincterotomy. This method has been practiced in patients with prolonged pancreatic fistula and may lead to improved healing time due to the decreased duct pressure [33].

Parenteral octreotide may be used in the immediate postoperative period to decrease the rate of pancreatic fistula [6,12,34]. A Cochrane review revealed decreased rate of fistulas, but no decrease in mortality, hospital stay, or rate of reoperation [35]. Those prescribing prophylactic octreotide endorse 7 days of use. Authors of the Cochrane review recommend routine use in patients undergoing pancreatic resection because the potential benefit outweighs the low risk and low cost of the medication.

## Complications

Pancreatic fistula is the major morbidity following enucleation and occurs in 18–61% of cases (see Table 83.3). However, the majority of the fistulas are Type A without clinical significance. Postoperative pancreatic fistulas can be difficult to treat because of their many associated problems. Intra-abdominal infection and/or hemorrhage, delayed gastric emptying, increased hospital stay, increased readmission, and the need for reintervention have all been associated with pancreatic fistula [4,22]. Specific risk factors for development of pancreatic fistula include soft pancreatic texture with absence of fibrosis, main pancreatic duct (MPD) diameter of less than 3 mm, cyst distance less than 2 mm from the duct, and cyst depth of greater than 3 mm (see Table 83.4) [3,25,33]. New York Heart Association class II or III and procedure time greater than 180 minutes were also recently found to be independent risk factors for fistula formation following enucleation [4]. Multiple studies have attempted to identify methods for decreasing risk of fistula. In addition to the previously described prophylactic octreotide, a study by Kiely et al. demonstrated a decreased fistula rate (50% to 27%) by adding intraoperative ultrasound and closure of the space after cyst removal [31]. Preoperative nasopancreatic stenting is another approach that allows surgeons to palpate and directly visualize the duct, thereby avoiding MPD injury and fistula formation [4,5,36–38]. If injury to the MPD is suspected, a jejunal Roux-en-Y onlay technique can be used to decrease the risk of pancreatic fistula development. This technique can also be used in management of inadequate branch-duct ligation.

## Outcomes

Table 83.3 displays contemporary pancreatic cyst enucleation outcomes from studies conducted since 2007. Six case-control and eight case series reported overall morbidity and mortality of cyst enucleation to be 12–67% and 0–1% (with one 7% outlier), respectively. Although recent, small case-control studies ($n$ = 7–127) show no difference in morbidity and mortality as compared to formal pancreatic resection, a larger analysis by Parikh et al. employing the American College of Surgeons National Quality Improvement Program (ACS NSQIP), reported lower morbidity and mortality of cyst enucleation [39]. Compared to pancreatoduodenectomy and distal pancreatectomy, enucleation had 0.1 and 0.17 times the odds of mortality, respectively. Pancreatic fistula occurs at a similar rate in both enucleation and formal resection. Despite the same number of fistulas, some

**Table 83.3** Pancreatic cyst enucleation case-control/case series studies from 2007–current. Contemporary case-control and case series studies from the last decade are displayed. Outcomes of case-control studies show both the rate of occurrence and an arrow indicating comparison of cyst enucleation to formal resection.

| Author | Year | Cyst type | Morbidity | Mortality | Fistula | Endo. insuf. | Exo. insuf. | OR time/ blood loss | Recurrence | 5 yr survival |
|---|---|---|---|---|---|---|---|---|---|---|
| **Crippa** | 2007 | 38 NET, 5 pseudocyst, 5 SCN, 3 MCN, 3 SPN, 7 other | 43% | 0% | 38% | 3% | 0% | | 0% | |
| **Pitt** | 2009 | 37 NET | 49% ↔ | 0% ↔ | 38% ↔ | | | ↔ | 0% ↔ | 94% ↔ |
| **Ge** | 2009 | 8 MCN, 3 SCN | 36% ↔ | 0% ↔ | 18% ↔ | 0% | 0% | ↓ | 0% ↔ | |
| **Turrini** | 2010 | 7 BD-IPMN | 43% ↔ | 0% ↔ | 43% ↑ | | | ↓ | | |
| **Casadei** | 2010 | 15 NET | 47% ↔ | 7% ↔ | 33% ↔ | | | | 0% ↔ | 93% ↔ |
| **Cauley** | 2011 | 21 NET, 10 MCN/IPMN, 10 SCN, 4 other benign | 56% ↔ | 0% ↔ | 33% ↔ | 4% ↓ | 2% ↓ | ↓ | | 93% ↔ |
| **Brient** | 2012 | 35 NET, 6 MCN, 2 SCN, 10 other | 37% | 0% | 27% | 0% | 0% | | 2% | |
| **Crippa** | 2012 | 106 insulinoma | 47% ↔ | 0% ↔ | 38% ↔ | 1% ↓ | ↔ | ↓ | 2% ↔ | 100% ↔ |
| **Zhang** | 2013 | 90 NET, 2 MCN | 67% | 0% | 61% | 3% | 0% | | 1% | |
| **Heeger** | 2014 | 50 NET, 1 MCN | 65% | 0% | 52% | 0% | | | 0% | |
| **Sauvanet** | 2014 | 44 BD-IPMN | 55% | 0% | 47% | | | | | |
| **Zhang** | 2015 | 17 NET, 5 MCN, 4 SCN, 11 other | 43% | 0% | 38% | 3% | 8% | | 0% | |
| **Song** | 2015 | 24 NET, 9 MCN, 7 IPMN, 3 SPN | 12% | 0% | 20% | 2% | | | 0% | |
| **Faitot** | 2015 | 47 NET, 38 BD-IPMN, 26 MCN, 16 other | 63% | 1% | 57% | 8% | | | 7% | 93% ↔ |

Endo. insuf., pancreatic endocrine insufficiency; Exo. insuf., pancreatic exocrine insufficiency.

**Table 83.4** Risk factors for pancreatic fistula following cyst enucleation.

| Pancreatic fistula risk factors |
|---|
| Soft texture |
| Pancreatic duct diameter <3 mm |
| Distance of cyst from pancreatic duct <2 mm |
| Cyst depth >3 mm |
| NYHA class II or III |
| OR time >180 min |

studies suggest that fistulas after enucleation are less severe and require less intervention than fistulas following formal resection [17]. Patients undergoing enucleation also utilize less healthcare resources. Although length of hospital stay may be comparable between groups, ICU stay, operative time, and pancreatic insufficiency are decreased in cyst enucleation patients. Additionally, oncologic outcomes for premalignant lesions are no different between enucleation and formal resection. This fact is demonstrated by the similar rates of recurrent tumor and 5-year overall survival between groups [17,40].

## Contraindications

Appropriate patient selection is one major challenge in pancreatic cyst enucleation. This procedure is beneficial for a very select group of patients. Indications for enucleation versus close observation or nonparenchymal-sparing pancreatic resection are specific and exclusive. Table 83.1 displays the limited criteria for performing enucleation in contrast with Table 83.2, which lists several excluding factors. Poor outcomes are often attributed to improper patient selection. Pancreatic fistula results in patients with risk factors listed in Table 83.4. Unfortunately, it is often difficult to definitively categorize patients as appropriate for cyst enucleation prior to pathologic evaluation of the surgical specimen. If the evaluation reveals malignancy, the patient must then undergo additional surgical treatment.

## Cyst Ablation

Pancreatic cyst ablation is an alternate treatment option in which cysts are lavaged with ethanol or a chemotherapy solution. Potential candidates for cyst ablation are high-risk surgical candidates or those who refuse surgery [8]. Ablation may also be used as a bridge to surgery when patients are already receiving EUS with FNA for indeterminate lesions [41]. Patients with coagulopathies should not undergo ablation as passage of the needle into the cyst may cause bleeding. Most endoscopists use the cut-off of international normalized ratio (INR) less than 1.5 and platelets greater than 50,000 [41,42].

The procedure begins with a complete endoscopic ultrasound exam. The cystic lesion is located and characterized. Cysts must be greater than 2 cm in order to safely target. Multiple septations are another barrier to ablation. If the cyst contains multiple septations in which not all compartments communicate, complete drainage will not be possible. Unilocular or oligolocular cysts with two to six compartments are therefore the preferred lesion [41]. The MPD should be carefully evaluated to confirm absence of communication with the cyst. The ablative agent will be lost though the communicating duct if the cyst is connected to the main duct [42]. Some authors advocate preoperative ERCP to determine the cyst's ductal relationship [41]. IOU can also serve as a final opportunity to diagnose overt cancers with peripancreatic invasion. Ablation may then be aborted.

Following a complete IOU examination, a 22-gauge needle is passed transduodenal or transgastric into the cyst. This passage is done under direct ultrasound guidance. The cyst is then aspirated until collapse. If the cyst fluid is thick and mucinous, the clinician may be unable to complete cyst aspiration [41]. Formal resection must be considered if ultrasound characterization or cyst fluid analysis is consistent with invasive cancer. With the cyst collapsed, 99% ethanol is injected into the cyst, which is then lavaged for 3–5 min [42–44]. Following lavage and removal of ethanol, some endoscopists advocate the use of paclitaxel injection into the cysts as an additional ablative agent [41]. The volume of paclitaxel used is equal to that of the cyst fluid aspirated. If the cyst is in communication with the main pancreatic duct as previously described, the ablative solution will not remain in the cyst during this time. Acute pancreatitis is a major complication of pancreatic cyst ablation. The ablative agent may trigger acute pancreatitis by extravasation into the parenchyma or exposure of the ductal system via cyst communication.

Existing literature is heterogeneous with varying rates of cyst resolution, 33–79% [41,42,44,45]. Data suggest a higher rate of resolution with the combined use of ethanol and chemotherapy agents. Oh et al. found 62% complete resolution of pancreatic cysts using this method [41]. Additional studies have shown greater decrease in size and higher rates of cyst resolution with multiple ablation sessions [43]. Resolution is most often based on radiographic evidence as shown in Fig. 83.3 [42]. Resolution may be dependent upon cyst type, with mucinous cysts having much lower rates of resolution [45]. Other predictive features include cyst size, fluid volume,

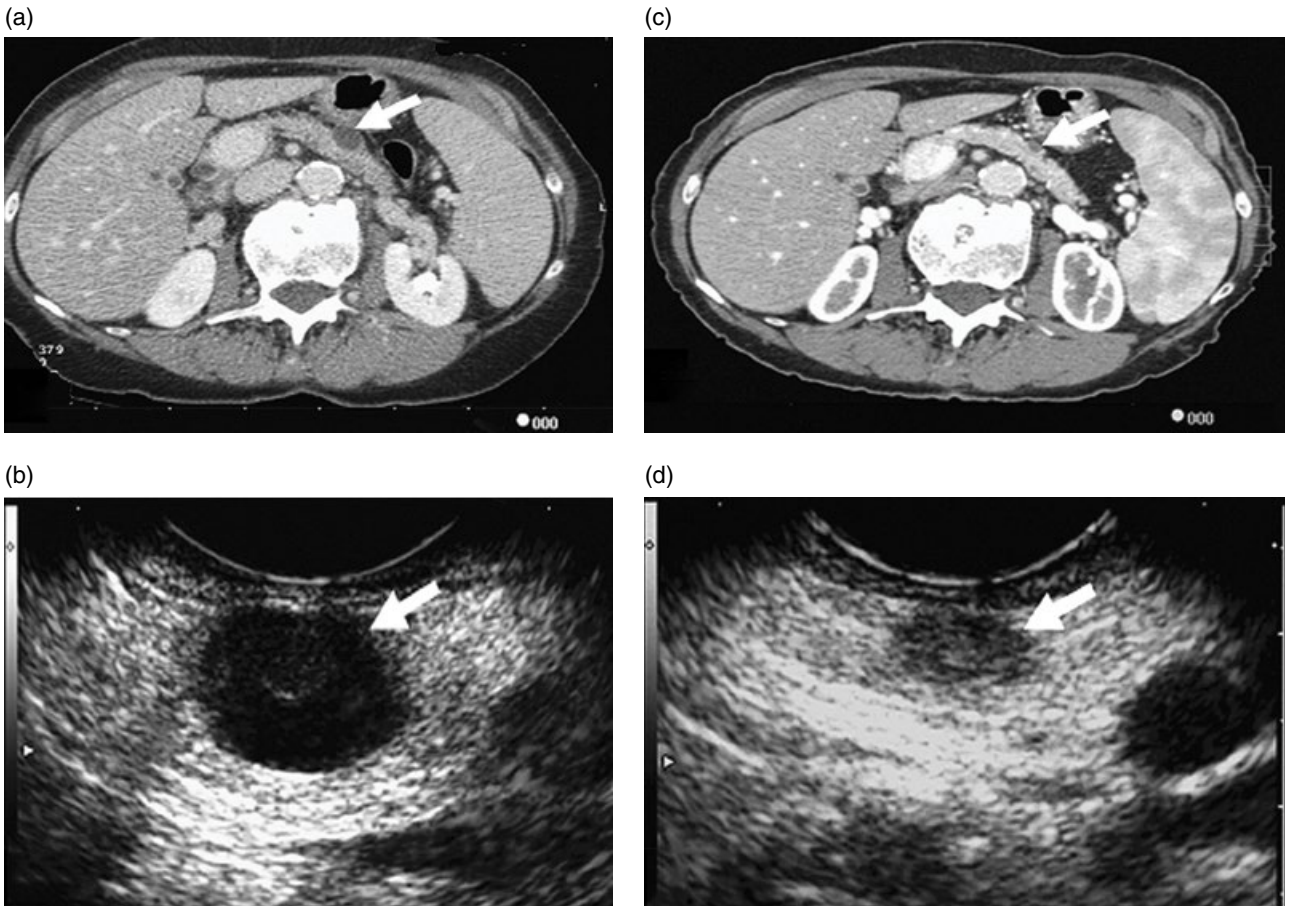


**Figure 83.3** Radiographic evidence of cyst ablation after ethanol lavage. (a) CT scan of the abdomen showing a 13 mm cyst in the body of the pancreas (white arrow). (b) Ultrasound of the same pancreatic cyst. (c) and (d) CT scan and ultrasound of the same patient 3 months after ablation. The cyst measures 8 mm. *Source:* DeWitt et al. 2009 [42]. Reproduced with permission of Elsevier.

locularity, and presence of mural nodules. Less than 14 mL of cyst fluid and less than 3.5 cm diameter on ultrasound examination were specifically shown to be predictive of cyst resolution in recent published data [41]. Of those patients who do achieve complete cyst resolution, data are even less clear as to which patients will have recurrence of their cyst. A small prospective study followed patients 13–39 months after ablation and found no recurrence in any patient who had complete radiographic cyst resolution [46]. Additional studies are needed to better quantify cyst recurrence. Although uncommon, multiple complications have been reported including fever, abdominal pain, and acute pancreatitis. Abdominal pain is reported in up to 20% of patients, and acute pancreatitis occurs in 4.5–10% of cases. Intracystic hemorrhage, bowel perforation, and severe acute pancreatitis are even less commonly reported [41,42,45].

Cyst ablation is considered an experimental therapy and should be performed in a very select group of patients. Additional studies are required to further characterize the utility of this procedure and appropriate surveillance of patients following the procedure. Although multiple studies have shown complete or partial resolution of cyst radiographically, far fewer cysts have been resected post-ablation for pathologic evaluation [42,44,45]. It is therefore unclear as to whether these cysts reach true histopathologic resolution.

## Conclusions

Pancreatic cyst enucleation is an alternate surgical option for small, low-risk cystic lesions. Several factors make each pancreatic cyst more or less optimal for enucleation. Main-duct involvement or close proximity increases the rate of postoperative fistula development. Enucleation of large, multifocal, or tail cysts does not yield significant parenchymal preservation and therefore, is not beneficial to perform. Patients considered for enucleation must receive appropriate preoperative evaluation and must be adequately fit. Postoperative pancreatic fistula is the major morbidity of enucleation

but occurs at the same rate as in formal resection with fewer grade B or C fistulas. Enucleation is associated with less utilization of healthcare resources and similar or lower morbidity and mortality without compromising local recurrence rates or long-term survival. Lastly, cyst ablation is an alternate technique that may be employed in patients unwilling or unable to tolerate enucleation or resection.

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# Standard Surgical Management of IPMN, MCN, SPN, and SCN Lesions: Open Approach

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## Introduction

Pancreatic cystic neoplasms (PCN) were previously considered rare. With the increased use and improved sensitivity of cross-sectional imaging, PCN are identified more frequently and often diagnosed incidentally [1]. The prevalence of incidental pancreatic cystic lesions identified by multidetector computed tomography and magnetic resonance imaging ranges from 2.4% to 13.5% in asymptomatic patients and increases with age [2–4]. Despite the improved detection of these pancreatic cysts, radiologists fail to document their presence 69% of the time in the radiology report [4]. This underreporting may explain the discrepancy between the current prevalence of pancreatic cysts and an autopsy study reporting that 24.3% of people harbor pancreatic cysts at time of death [5].

The most common subtypes of PCN are intraductal papillary mucinous neoplasm (IPMN), mucinous cystic neoplasm (MCN), serous cystic neoplasm (SCN), and solid-pseudopapillary neoplasm (SPN). These PCN comprise a diverse group of tumors with a wide range of malignant potential, making the management quite challenging. The management of pancreatic cysts is driven by the presumed cyst subtype, which is based primarily on age at presentation, gender, imaging cyst characteristics, and cyst fluid analysis. While together this information is not fully diagnostic, the pancreatic cyst subtype is accurately diagnosed the majority of the time, guiding management of the cystic lesion [6].

The decision between operative resection and surveillance imaging of a PCN involves weighing the risk of surgical resection against the risk of malignant progression (or presence of malignancy). Although pancreatic resection has become safer with a low risk of mortality at high-volume centers, postoperative morbidity continues to remain high at roughly 40% [1,7,8]. While all PCN should be evaluated, surgical resection should only be recommended when appropriate. Most pancreatic cysts are asymptomatic, small (<2 cm), and benign in nature. In these lesions, the risk of surgical resection is generally greater than the risk of malignant progression, making routine surveillance appropriate. In lesions that are symptomatic, have malignant potential, or are concerning for frank malignancy, surgical resection is recommended. In this chapter, we will discuss the standard, open surgical management of each of the PCN subtypes.

## Pancreatic Cystic Neoplasm Subtypes, Surgical Indications, and Operative Intervention

PCN can be broken down into four subtypes: IPMN, MCN, SCN, and SPN. PCN are further classified by the type of cystic fluid they produce: mucin-producing versus nonmucinous. While SCN and SPN are nonmucinous cystic lesions, IPMN and MCN are considered mucinous cystic lesions. Approximately 10% of SPN have metastatic potential and both IPMN and MCN can be precursor lesions to invasive pancreatic cancer or harbor an invasive component. With an increase in the proportion of incidentally discovered PCN over time, the number of pancreatic resections for PCN has also increased. IPMN is the most common pancreatic cystic lesion resected (38%) followed by MCN (23%), SCN (16%), and SPN (3%) [1]. More importantly, the proportion of resected malignant neoplasms has decreased over time, likely reflecting earlier diagnosis and surgical resection of these premalignant lesions [1].

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## Intraductal Papillary Mucinous Neoplasm

IPMN is an intraductal mucin-producing neoplasm and precursor lesion to invasive pancreatic cancer, accounting for the majority of PCN resected at roughly 38% [1]. IPMN has a male predominance with a median age of presentation at 67 years old [9]. IPMN is thought to be a precursor lesion to invasive pancreatic cancer, progressing from low-grade dysplasia to high-grade dysplasia to invasive cancer. In addition, IPMN is a "field defect" with the entire pancreatic duct at risk of developing IPMN or pancreatic ductal adenocarcinoma. IPMN can be categorized as main-duct (MD-IPMN), branch-duct (BD-IPMN), or mixed IPMN, which behaves in a similar way to MD-IPMN. The risk of malignancy is much higher with main pancreatic duct involvement, making the classification between MD-IPMN, BD-IPMN, and mixed IPMN clinically significant. MD-IPMN or mixed IPMN are associated with 62.2% and 57.6% risk of high-grade dysplasia and 43.6% and 45.3% risk of invasive cancer, respectively [6,10]. BD-IPMN is associated with a lower risk of high-grade dysplasia (24.4%) and invasive cancer (16.6%) [6,10].

Based on the Fukuoka International Consensus Guidelines 2012, the presence of "high-risk stigmata," including obstructive jaundice in a patient with a cystic lesion in the head of the pancreas, enhancing solid component on cross-sectional imaging, or main pancreatic duct ≥10 mm, warrant surgical resection. The presence of "worrisome features," including cysts ≥3 cm, thickened enhanced cystic walls, nonenhanced mural nodules, main pancreatic duct size 5–9 mm, abrupt change in the main pancreatic duct caliber with distal pancreatic atrophy, and lymphadenopathy, warrant further evaluation with endoscopic ultrasound (EUS) [10]. If EUS identifies a definite mural nodule, main duct features suspicious for involvement, or cytology suspicious or positive for malignancy, pancreatectomy should be performed in patients fit for surgery. If no "worrisome features" are present, no further workup is recommended, but surveillance is required [10].

In the setting of surgical resection for IPMN, pancreaticoduodenectomy (PD) is performed the majority of the time (71%) followed by total pancreatectomy (15%), distal pancreatectomy (12%), and central pancreatectomy (2%) [9]. Operative intervention for IPMN can be complex at times. In the setting of MD-IPMN, if invasive pancreatic cancer is identified at the time of resection, a partial pancreatectomy should be performed to resect only the invasive cancer, as it will dictate survival. If no invasive component is identified, pancreatectomy to resect the main duct component should be performed with intraoperative frozen section to achieve margins free of high-grade dysplasia. Additional margins should be taken if the frozen specimen returns as high-grade dysplasia until achieving at least moderate-grade dysplasia. Occasionally, achieving an adequate margin may require performing a total pancreatectomy. In a younger and relatively healthy patient, a total pancreatectomy should be considered if the MD-IPMN seems to involve the entire gland, as the risk of the remnant developing pancreatic cancer may be quite high. In the setting of BD-IPMN, segmental pancreatectomy should be performed to resect the lesion with the highest oncologic risk, especially in the setting of multifocal BD-IPMN [10]. Unfortunately, clinically significant IPMN recurs in at least 20% of patient undergoing surgical resection [11]. Hence, close postoperative surveillance with cross-sectional imaging is imperative, as surgical intervention may be required in the future.

## Mucinous Cystic Neoplasm

Accounting for 23% of resected PCN, MCN is a mucin-producing cystic lesion of the pancreas and precursor lesion to invasive pancreatic cancer [1]. MCN occurs almost exclusively in females (95%) with the median age of diagnosis in the mid-40s [12–17]. MCN are precursors to invasive pancreatic cancer with carcinoma *in situ* identified in 3.9–6% of resected lesions and invasive cancer present in 4.4–16% of resected lesions [12–15,18]. Malignant transformation from MCN to mucinous cystic neoplasm with an associated invasive component is concerning with older age, larger lesions (≥4 cm), presence of mural nodule, cyst wall irregularity and thickening, and elevated cancer antigen (CA) 19-9 in cyst fluid [10,13,14,18–20]. Malignant transformation is rarely present in MCN <4 cm without mural nodules.

Given the unknown natural history of MCN and the young age of those affected by MCN, surgical resection is currently recommended to prevent progression to invasive pancreatic cancer in patients who are appropriate surgical candidates. The great majority of MCN is located in the pancreatic tail, making distal pancreatectomy with or without splenectomy the most common surgical resection performed for MCN [12,13,15–17]. In patients with small lesions and low risk of malignancy, spleen-preserving distal pancreatectomy is a reasonable option as well [13]. Of note, great care should be taken to prevent rupture of the cyst during surgical resection in order to prevent tumor seeding and spread. The 5-year disease-specific survival for noninvasive MCN is excellent at 100% and lower at 26–76% for those with invasive cancer [12–15,18]. Postoperative surveillance with cross-sectional imaging is not necessary for patients with benign MCN [6]. On the other hand, those with mucinous cystic neoplasm with an associated invasive

component will require routine surveillance with cross-sectional imaging similar to that of patients with pancreatic ductal adenocarcinoma [6].

### Serous Cystic Neoplasm

SCN are benign PCN and have an extremely low risk of malignant transformation to serous cystadenocarcinoma, accounting for roughly 16% of resected PCN [1,21–23]. SCN or serous cystadenomas occur predominantly in females (70–75%) and in the seventh decade of life (mean age 61 years old) [22–24]. While they rarely undergo malignant transformation, SCN can be locally aggressive in nature. Tumor diameter and tumor location in the head of the pancreas have been demonstrated to correlate with a locally aggressive behavior of SCN [23,24]. Large SCN (≥4 cm) are more likely to be symptomatic and have an accelerated rate of growth at 1.98 cm per year compared to lesions <4 cm with a growth rate of 0.12 cm per year [22]. Furthermore, the growth rate of SCN has been demonstrated to increase after the first 7 years of baseline evaluation (0.1 cm per year during the first 7 years after baseline evaluation to 0.6 cm per year after the first 7 years) [25].

Given the benign nature of SCN, surgical resection should be considered when the cystic lesion causes symptoms or is difficult to differentiate from a mucin-producing cystic lesion [26,27]. While SCN can affect any portion of the pancreas, surgical resection largely depends on the location of the lesion, attempting to preserve as much pancreas and pancreatic function as possible. In several large series, patients with SCN underwent PD with similar frequency as distal pancreatectomy with or without splenectomy [22–24]. Surgical resection is considered curative with no postoperative surveillance required.

### Solid-Pseudopapillary Neoplasm

SPN are rare, indolent pancreatic neoplasms with the potential to metastasize, accounting for roughly 3% of resected PCN [1]. SPN occur predominantly in young females (85%) with median age at presentation in the third and fourth decades of life [28–32]. SPN are usually indolent in nature but have the potential for metastatic spread. Approximately 10% of patients with SPN will have locoregional or metastatic spread involving the liver, portal/mesenteric vessels, lymph nodes, or spleen [28,29,31,32]. Tumor size >5 cm, focal discontinuity of tumor capsule on cross-sectional imaging, and Ki-67 positivity have all been noted to be suggestive of metastases [29,33,34].

Surgical resection with negative margins (R0 resection) is recommended for all patients with SPN given the metastatic potential of these tumors. SPN are usually located in the pancreatic tail or body, requiring a distal pancreatectomy and splenectomy [28,29,31,32,35]. Although incomplete gross resection (R2) or incomplete microscopic resection (R1) are associated with a worse outcome, it may still benefit the patient, and long-term prognosis with complete surgical resection of SPN is excellent with 5-year survival at 95% [32]. At times, locally advanced tumors are technically not resectable. However, metastases should not preclude resection as good long-term outcomes can still be achieved with aggressive surgical resection of the primary tumor and metastatic lesions [32].

## Pancreatectomy

The surgical approach to each of these PCN subtypes is dependent primarily upon the location of the cystic lesion. Preoperative evaluation, operative considerations for each of the major pancreatic resections, and postoperative management will be discussed in this section.

### Preoperative Evaluation

Prior to operative intervention, the patient should be evaluated and assessed regarding the medical risks of undergoing a major abdominal operation. Given that PCN range widely in malignant potential, the benefits of surgery should be weighed heavily against the risks, such as patient medical comorbidities, before proceeding to the operating room. In addition, patients should be assessed and treated for pancreatic insufficiency preoperatively, which occasionally occurs in the setting of PCN and requires pancreatic enzyme replacement. When total pancreatectomy is considered preoperatively, the patient should be evaluated by an endocrinologist prior to surgery, both to establish care and set expectations regarding the management of brittle diabetes. Establishing this relationship preoperatively allows for close diabetes management postoperatively.

### Pancreaticoduodenectomy

PD (also known as a Whipple procedure) is performed for PCN involving the head or neck of the pancreas. Given the integral relationship between the head of the pancreas, distal common bile duct, and duodenum, resection of all three en bloc is generally required for a lesion involving the head of the pancreas. A small portion of the distal stomach, the entire duodenum, and the first portion of the ileum just distal to ligament of Treitz (LOT) are resected en bloc with the specimen, referred

to as a classic PD. Alternatively, the pylorus can be left intact also leaving behind a small segment of the first portion of the duodenum, referred to as pylorus-preserving PD.

The reconstruction generally involves using a loop of proximal jejunum to create a pancreaticojejunostomy (PJ), hepaticojejunostomy (HJ), and gastrojejunostomy (GJ). The proximal jejunal loop is passed retrocolic through the transverse colon mesentery or the LOT defect to complete the PJ and HJ anastomoses. The PJ can be performed in a variety of ways with numerous methods described, primarily in an effort to decrease the pancreatic fistula rate [36]. This not only indicates the complexity of the anastomosis but also the lack of a gold standard method for reconstruction. The two most common PJ anastomoses are the duct-to-mucosa anastomosis and the invagination technique. A plastic biliary stent may also be placed with one end partially in the duct of the pancreas and the other end partially in the jejunal limb, in essence creating a controlled fistula. The second anastomosis downstream to the PJ is the HJ, performed as a single-layer anastomosis. The third anastomosis is the GJ, which can be performed in an antecolic or retrocolic fashion. At the conclusion of the operation, the surgeon may choose to place drains near the PJ and HJ.

When performing a PD, special anatomic situations should be taken into consideration. Aberrant anatomy, such as a replaced right hepatic artery, should be noted on preoperative cross-sectional imaging if possible to avoid injuring the aberrant anatomy intraoperatively. However, aberrant anatomy is not always evident on preoperative imaging, and the surgeon should always be cognoscente of the potential for aberrant anatomy at the time of surgical intervention. Another special anatomic consideration to be noted on preoperative cross-sectional imaging is the presence of celiac artery stenosis (CAS) [37]. During a pancreaticoduodenectomy, the gastroduodenal artery (GDA) is ligated in order to resect the head of the pancreas. In the setting of CAS, the proper hepatic artery may be receiving retrograde flow from the GDA via collateral vessels supplied by the superior mesenteric artery. Thus, ligating the GDA during a PD can lead to liver failure and potentially death. The treatment of this is based on the etiology of CAS: atherosclerotic disease or median arcuate ligament (MAL) syndrome. If the etiology of CAS is atherosclerotic disease, preoperative stenting of the celiac artery may be attempted. If the etiology is MAL syndrome, releasing the MAL intraoperatively and reassessing proper hepatic arterial flow is appropriate. This should be done routinely by clamping the GDA prior to ligation and assessing hepatic flow with palpation and/or Doppler signals. If in the rare chance celiac artery stenting or MAL release do not restore proper hepatic arterial flow via the common hepatic artery, a proper hepatic artery bypass may be necessary at the time of PD [37].

## Distal Pancreatectomy

Distal pancreatectomy is performed for PCN involving the tail, body, or even the neck of the pancreas. Splenectomy should be performed in conjunction with distal pancreatectomy when the lesion has malignant potential in order to assess the lymph nodes, which reside in the splenic hilum. While SPN has metastatic potential requiring splenectomy at the time of distal pancreatectomy, splenic preservation can be considered for patients with small MCN lesions, SCN, and BD-IPMN and low risk of malignancy. Spleen-preserving distal pancreatectomy can be technically more difficult than a distal pancreatectomy and splenectomy given the integral relationship between the pancreas and the splenic vessels.

Surgical considerations during a distal pancreatectomy include the method of pancreatic transection and early splenic artery ligation when a splenectomy is also being performed to decrease blood loss during splenic mobilization. Transection of the pancreas can be done with a scalpel or electrocautery, oversewing the pancreatic remnant. Alternatively, the pancreas can be transected with a stapler with or without an absorbable mesh staple-line reinforcement. Regardless of the method, the surgeon may choose to place a drain near the pancreatic remnant.

## Total Pancreatectomy

A total pancreatectomy is rarely performed in any PCN other than IPMN. Given IPMN is a "field defect," occasionally total pancreatectomy is considered in the appropriate patient if the entire gland is involved. While total pancreatectomy can be technically straightforward requiring a PD and distal pancreatectomy/splenectomy with HJ and GJ reconstruction, postoperative brittle diabetes is the major concern in performing a total pancreatectomy. With the entire pancreas removed, the patient no long has autogenous insulin production or, more importantly, autogenous glucagon production. The lack of glucagon puts the patient at risk of life-threatening hypoglycemia. Total pancreatectomy is generally considered for younger patients with extensive IPMN who have a lifetime risk of developing pancreatic cancer and those with IPMN and a strong family history of pancreas cancer. Equally important, total pancreatectomy should only be offered to patients who will be able to reasonably manage their brittle diabetes given the real risk of life-threatening hypoglycemia.

## Central Pancreatectomy

In select patients with a centrally located PCN, central pancreatectomy may be an appropriate surgical option. Central pancreatectomy involves resecting a central portion of the pancreas and reconstructing with either a pancreaticogastrostomy to the posterior stomach or a Roux-en-Y retrocolic PJ to the distal pancreas. The major benefit of central pancreatectomy is preservation of pancreatic endocrine and exocrine function. However, due to two potential sources of pancreatic leak from the proximal pancreatic remnant and the pancreatic-enteric anastomosis, central pancreatectomy has a higher risk of pancreatic fistula ranging 36% to 63% [38–40]. While most of these centrally located PCN can be resected with an extended PD or extended distal pancreatectomy, central pancreatectomy should be considered for young and healthy patients to prevent long-term sequela of pancreatectomy, such as pancreatic insufficiency and diabetes. These patients will also medically tolerate a pancreatic leak or fistula better than an elderly patient or a patient with multiple medical comorbidities.

## Alternative Procedures

An alternative to pancreatectomy is enucleation of the PCN. Enucleation involves removing the lesion in a nonanatomic fashion, preserving as much functional pancreas as possible. Enucleation should be considered only for PCN that have a low risk of malignancy, such as SCN and small MCN. The entire cyst wall should be resected, taking care to prevent rupture of the cystic lesion. The main disadvantage of enucleation is the increased risk of pancreatic fistula, based on proximity of the lesion to the pancreatic duct.

An alternative to open surgical resection for PCN is minimally invasive surgery, including laparoscopy and robotic surgery. Laparoscopic distal pancreatectomy with or without splenectomy has become a standard operation in many institutions. Minimally invasive surgery for PD or total pancreatectomy can be considered for smaller PCN and extensive IPMN with absence of vascular involvement. Minimally invasive surgery for pancreatectomy is currently evolving and increasing in use, but it should be recommended in the appropriately selected patient by a surgeon who is comfortable performing minimally invasive pancreatectomies.

## Postoperative Management

Postoperative, patients undergoing pancreatectomy are slowly advanced on their diets until tolerating a regular diet. While the risk of perioperative mortality is low, the risk of postoperative morbidity is roughly 40%. The major risks associated with pancreatectomy include pancreatic fistula, delayed gastric emptying, diabetes, pancreatic insufficiency, anastomotic leak or stricture, and postoperative bleed.

The most common complication after major pancreatectomy is a pancreatic fistula with rates reported around 10–28% [41,42]. While numerous studies have investigated various operative techniques and pharmacologic measures to reduce the pancreatic fistula rate, no single measure has been demonstrated to be superior across institutions [43–45]. Recently, a somatostatin analog pasireotide administered in the perioperative period has been demonstrated to show significant reduction in the risk and severity of postoperative pancreatic leak and fistula after PD and distal pancreatectomy [46]. Furthermore, in an effort to prevent uncontrolled pancreatic leaks, some surgeons will place drains around the PJ or pancreatic remnant at the time of surgery. The drain output is then checked postoperatively for amylase levels as a marker of pancreatic leak. Drain amylase level <600 U/L on postoperative day one has been reported to be indicative of <1% risk of pancreatic fistula, with recommendations for early drain removal in these situations [47]. In those with high-output pancreatic fistulas, intravenous nutrition and limiting oral intake along with somatostatin analog may be considered. After a distal pancreatectomy, an endoscopic stent may be placed into the pancreatic duct to divert flow of pancreatic fluid from the remnant back through the ampulla and into the bowel.

Delayed gastric emptying (DGE) is another common complications following a PD, ranging from 14% to 61% [7,48]. DGE is diagnosed with an oral contrast study demonstrating delay in emptying contrast from the stomach after a PD. While the pathogenesis of DGE remains unclear, several factors have been studied, such as pylorus-preservation versus classic PD, antecolic versus retrocolic GJ, and the presence or absence of a pancreatic fistula [48,49]. However, none of these factors have been demonstrated to consistently contribute to DGE. DGE is often managed with replacement of nasogastric tube, subsequent removal with decrease in daily output, and slow advancement of diet. Rarely, a patient must have a percutaneous endoscopic gastrostomy tube with a jejunal feeding limb placed to provide enteral nutrition until gastric function returns to normal.

A late post-PD bleed can be a life-threatening complication. An early postoperative bleed (within first 5 days of surgery) indicates a surgical bleed requiring operative intervention. A late postoperative bleed, however, (5 days after surgery or more) occurs most commonly as a pseudoaneurysm bleed in the setting of a pancreatic fistula. Delayed post-PD bleed will present as blood in the

drains, bleeding through the midline incision, gastrointestinal bleed, and/or hemodynamic instability. A delayed bleed requires interventional radiology to embolize the bleeding vessel and rarely surgical intervention. A delayed post-PD bleed significantly increases mortality to 16% and should be addressed immediately [50].

## Conclusion

As a result of the increased use and improved sensitivity of cross-sectional imaging, more people are undergoing pancreatic resection for cystic neoplasms than in the past [1]. Furthermore, the proportion of resected malignant neoplasms has decreased over time, reflecting earlier diagnosis and resection of these premalignant lesions [1]. However, the morbidity of pancreatectomy remains high despite pancreatic resections becoming safer at high-volume institutions over time [1,7,8]. In addition to the immediate perioperative period, some endure the long-term sequelae of pancreatic resection, such as diabetes mellitus or pancreatic exocrine insufficiency.

The wide range of malignant potential between the various subtypes of PCN as well as the lack of ability to accurately characterize all lesions continue to make the management of PCN significantly challenging. Continued efforts are being made to improve accuracy in diagnosis, determine the true malignant potential of each subtype of PCN, and understand the natural history of each of these PCN. With improved knowledge regarding each of these areas, surgical resection can be reserved for highly selective patients harboring PCN that are symptomatic or have the greatest risk of developing pancreatic dysplasia or malignancy in the future.

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# Surgical Treatment of Cystic Neoplasms: Laparoscopic Approach

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## Introduction

Surgical approaches to abdominal disease have undergone a sea change in the past three decades driven by the increased use of laparoscopy and other minimally invasive techniques. While Cushieri first reported laparoscopic distal pancreatectomy (LDP) in 1994, adoption of minimally invasive techniques in pancreatic surgery has been slow [1,2]. Barriers to use include a high degree of operative complexity, the high rate of perioperative morbidity in pancreatic surgery, and concerns about oncologic efficacy.

These barriers have started to break down for pancreatic surgery, in part due to work highlighting superior operative outcomes with preserved cost-effectiveness for LDP performed in a variety of healthcare settings [3–16]. With a broad literature review confirming superiority, consensus is growing that a laparoscopic approach to distal pancreatectomy is preferable, particularly in the setting of benign disease [17]. A recent comprehensive meta-analysis even suggests that splenic preservation (with or without vessel preservation), when safe and of negligible oncologic effect, is perhaps best [18]. The increasing utilization of the laparoscope for left-sided resections has led to the adoption of a laparoscopic approach to other procedures, including enucleation, central pancreatectomy, pancreaticoduodenectomy, and total pancreatectomy [19].

The indications for a laparoscopic operation in cystic disease of the pancreas are identical to those for an open operation. The most commonly cited guidelines for resection are derived from consensus opinion of the 14th meeting of the International Association of Pancreatology [20]. Specifically they include: intraductal papillary mucinous neoplasm (IPMN) of the main pancreatic duct, endoscopically visualized dilated papilla with mucin extrusion, or branch-duct IPMN rapidly increasing in size, with mural nodularity, or with high-grade atypia on tissue sampling. Guidelines also recommend resection for mucinous cystic neoplasms, with a stated preference for a laparoscopic approach in those lesions without mural nodularity and less than 4 cm in size. Rarely, other diagnoses may be encountered that are best managed by extirpative therapy, including symptomatic enteric duplication cysts [21] and intrapancreatic accessory spleen with associated epithelial cysts [22,23]. Notably, the presence of a potentially malignant cystic neoplasm should not, in isolation, be viewed as a contraindication to a laparoscopic approach and will be discussed further in this chapter.

## Specific Surgical Considerations and Procedures

Key operative landmarks in pancreatic surgery include the superior mesenteric-portal vein (SMV-PV) confluence (representing the standard margin of transection), the gastroduodenal artery (representing the landmark for selecting resection of the uncinate/head with the lesion versus body/tail) and the splenic vessels (with either preservation or controlled ligation as indicated by disease and operative planning). When possible during a partial pancreatectomy, the site of gland transection is the pancreatic neck [24]. When pathology is located close to the SMV-PV confluence, the site of transection may vary from the neck and recent data demonstrates this is associated with an elevated rate of postoperative pancreatic fistula (POPF). This increased risk for POPF is hypothesized to be due to the increase in gland

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Companion website: www.wiley.com/go/beger/thepancreas

diameter to either side of the SMV-PV confluence [24]. The specific method chosen for pancreatic transection can vary based on procedure and will be covered in more detail later.

The most commonly performed laparoscopic procedure for cystic lesions is distal pancreatectomy (LDP) [25]. Historically, cystic lesions are overrepresented in retrospective reviews of LPD as compared to open DP, with the proportion of cystic lesions in many LPD series approaching 60% of diagnoses [8,17]. This proportion is higher than those reported in open DP and is most likely biased by concerns about oncologic efficacy [26].

When evaluating patients for distal pancreatectomy, selective splenic preservation can be entertained in the presence of benign etiology [18,27]. In many high-volume centers, LDP for benign indications, such as mucinous cystic neoplasms, serous cystic neoplasms, or branch-duct IPMN, is commonly carried out with preservation of the spleen. When cystic lesions are overtly malignant or carry a higher risk of malignancy (i.e., main-duct or mixed-type IPMN), an en-bloc splenectomy as dictated by standards of lymphadenectomy in pancreatic tail malignancy should be performed [28]. From a technical point of view, there are two commonly employed methods for splenic preservation in the setting of distal pancreatectomy. The first involves careful dissection and preservation of the splenic artery and vein with ligation of the short branches to the distal pancreas. The second involves ligation and resection of the splenic artery and vein along its course near the distal pancreas with careful preservation of the short gastric branches towards the hilum (Warshaw technique) [18,29]. Both techniques for splenic preservation have been demonstrated to be safe, with no clear randomized data for superiority of either. Dissection of the pancreatic body and tail out of its retroperitoneal position can be safely performed using an ultrasonic dissector or vessel-sealing device. A recent meta-analysis comparing ultrasonic to conventional dissection in DP suggests superiority of the ultrasonic approach in terms of postoperative morbidity [30]. The most common method of parenchymal transection during LDP is the application of a stapling device (Fig. 85.1), as sharp transection with suture closure is technically challenging laparoscopically and rates of POPF for staple and suture closure appear similar [31].

Operative morbidity most frequently involves POPF. Reported rates of POPF following LDP range between 20% and 65%, with clinically relevant rates (ISGPS grade B or C) ranging between 10% and 25% [3–16,32]. Efforts to reduce POPF often focus on modifications to stapling techniques, including staple line reinforcement with a bioabsorbable synthetic fabric or glue. Currently, there are no reproducible, high-quality data to recommend any specific modification to a stapled pancreatic transection [33–35]. As rates of POPF remain high, intraoperative drain placement at the resection margin is routine in many centers. Data quantifying blood loss, pain, and speed of postoperative recovery all favor LDP over open DP and suggest that LDP should be the procedure of choice for cystic lesions located in the pancreatic body and tail.

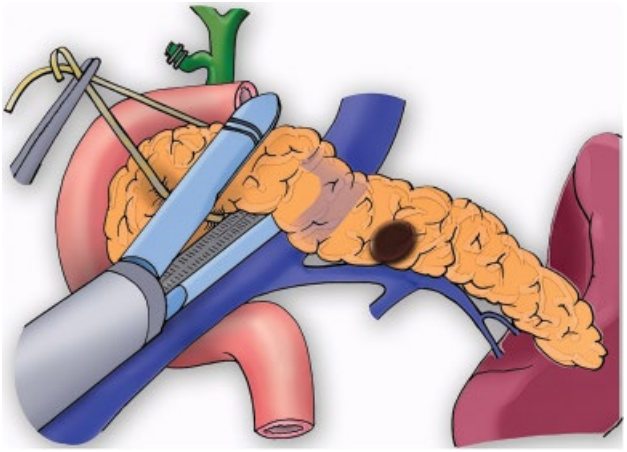

**Figure 85.1** Laparoscopic transection of the pancreas. The technologic refinement of laparoscopic stapling devices allows for simple, safe, and effective transection of the neck of the gland during distal pancreatectomy. Following circumferential dissection of the pancreas at the neck, a stapling device is inserted and closed gently across the gland. The contents in the stapler are inspected from both the left and right sides to ensure there are no inadvertent structures grasped prior to transection. Following staple deployment and transection, hemostasis can be achieved by a combination of electrocautery, suture ligature, and application of clips.

Enucleation of cystic lesions for benign disease, enabling parenchymal preservation, can also be performed laparoscopically. Though the collective experience is not as vast as with LDP, enucleation of cystic lesions in either the pancreatic head or tail is a safe and effective approached in selected pathologies. Importantly, enucleation is associated with significant oncologic limitations that prevent its use in diseases such as IPMN, where diffuse involvement of the ductal system may be associated with small foci of invasive disease. Literature demonstrating the technical feasibility and perioperative safety of enucleation is dominated by case series data and most commonly limited to 5–30 patients [36–38]. Dissection into the pancreas risks two major complications: hemorrhage and postoperative leak. Typically, an electrosurgical or ultrasonic device is used during the gland dissection and care must be taken to ensure adequate hemostasis at the conclusion of the case. Additionally, a gross inspection (at a minimum) of the pathologic specimen after enucleation is required prior to abdominal closure to ensure that it includes the lesion of interest. While a minimally invasive approach to

enucleation may have several potential advantages, it is burdened by a high rate of POPF. Case series data would suggest that these POPF are generally uncomplicated and most frequently not of clinical relevance [36–38]. Operatively placed drains are frequently used after enucleation to mitigate the morbidity that may arise from an uncontrolled pancreatic fistula.

Central pancreatectomy (CP) is another parenchymal-sparing procedure that is often considered for nonmalignant cystic lesions located in the pancreatic body. Originally developed in the 1950s, this operation was first described laparoscopically in 2003 [39]. Similar to LDP, the pancreas is divided at the SMV-PV confluence by stapler and the pancreatic body is mobilized towards the tail with preservation of the splenic vessels. After resection of the pathology-bearing segment, pancreaticoenteric anastomosis of the tail is required. Both pancreaticojejunostomy and pancreaticogastrostomy have been reported in the literature, with pancreaticogastrostomy often favored due to apparent ease in a laparoscopic setting [40–42]. Methods for pancreatoenteric anastomosis vary according to surgeon preference, with the two most common techniques being a duct-to-mucosa or an invagination style. Similar to LDP, the most frequent complication of CP is POPF. As CP leaves the patient with two cut surfaces across the gland, rates of POPF are high in reported series (40–60%). Most of these leaks remain clinically minor and can be managed conservatively with prolonged peritoneal drainage [40–42].

One major advantage to parenchymal preservation (both enucleation and CP), compared to LDP, is maintenance of pancreatic exocrine and endocrine function in the perioperative period. This is highlighted by literature documenting a very low risk for postoperative diabetes mellitus in parenchymal preserving operations as compared to distal pancreatectomy [19,43]. Therefore, when location and extent of cystic pathology lend themselves to a parenchymal-sparing procedure it should be seriously considered. In all laparoscopic approaches, intraoperative ultrasound can be an important tool used to confirm the location of pathology and choose a suitable surgical strategy. Additionally, intraoperative frozen section analysis of both the lesion and the surgical margins should be routinely performed to avoid a return to the operating room due to unanticipated disease or margin involvement.

Though the use of laparoscopy and robotics in pancreaticoduodenectomy (PD) is increasing, it has yet to become routine in most centers. Similar barriers to widespread adoption exist for PD today as they did for distal pancreatectomy 20 years ago, including operative complexity, patient safety, and concerns about oncologic efficacy. Despite these barriers, there are several high-volume centers demonstrating that minimally invasive PD can be achieved safely [44–46]. Typically, four to six ports are required for laparoscopic PD and the approach to the dissection can vary by surgeon preference. Key points in the dissection are identical to those during an open procedure and include mobilization of the duodenum and pancreatic head, confirmation of resectability by assessment of disease spread, isolation and transection of the gastroduodenal artery, development of a retropancreatic tunnel to facilitate safe gland transection, and careful uncinate dissection. Though the key points in dissection are similar, the techniques for exposure and visualization are unique when the head of the pancreas is approached laparoscopically. For liver retraction, for example, both the falciform and the gallbladder can be used as "handles" to manipulate positioning. During laparoscopy, the angle of the operating table can also facilitate bowel "retraction" by allowing it to fall away into the pelvis by gravity alone. Reconstructive techniques in a minimally invasive PD are also similar to those done in an open procedure. For pancreatoenteric reconstruction, for example, both duct-to-mucosa and invagination techniques can be performed. Reports demonstrating similar outcomes for minimally invasive PD and open procedures are now commonplace [44,45,47]. In highly selected patients, outcomes for a laparoscopic approach can even be superior to an open approach [44]. The expansion of minimally invasive PD away from high-volume centers must be approached with caution, however, as data is emerging that suggests mortality may be increased when utilized in low-volume settings [47].

## Future Perspectives

The use of laparoscopy in the setting of pancreatectomy is likely to continue to expand along with advancements in technology, technique, and the understanding of tumor biology. As discussed earlier, recent data is challenging two long-standing barriers to rapid adoption of minimally invasive surgery: technical safety and oncologic effectiveness. The technical challenges are being progressively overcome and the list of relative contraindications to laparoscopy is decreasing as published experience grows with large tumors and tumors located in technically challenging positions [42,48]. Historically, the view that a laparoscopic approach may compromise oncologic effectiveness of resections involving biopsy-proven malignancy is also being challenged. For example, a recent retrospective analysis from French healthcare databases suggests that a laparoscopic approach does not compromise long-term oncologic outcomes in left-sided pancreatectomy [49]. Many thought leaders in surgical oncology are now calling for a large, randomized trial focusing on oncologic effectiveness, defined end-points,

and cost-effectiveness of a laparoscopic approach to pancreatic malignancy [17,26].

As experience with laparoscopic distal pancreatectomy has increased, there has been a shift in patient selection to sicker patients with more proximal tumors and yet similar perioperative outcomes can be achieved [50]. Despite these data, as the use of minimally invasive techniques expands it is important to remember that patient safety must remain paramount. For laparoscopic pancreatectomy, this means that accurate patient selection is a critical component to any surgical practice. Supporting this view, a recent series documented that those patients requiring conversion from laparoscopic to open pancreatectomy were found to have increased rates of perioperative morbidity and pancreatic leak than the cohort with an initial approach via laparotomy [5]. There are several identified risk factors for failure of a laparoscopic approach and increased perioperative morbidity (including body mass index and extent of pancreatic resection) that can help guide surgeons in accurate preoperative assessment [5,51]. In one series, the adoption of a robotically assisted minimally invasive approach to distal pancreatectomy reduced the risk of conversion to an open resection while maintaining equivalent safety outcomes [52].

Descriptions of a laparoscopic-robotic hybrid or purely robotic approaches to pancreatectomy are increasing in the literature. Touted for superior 3-dimensional visualization and hinged instrumentation, the robot may provide a technologic platform for safe completion of more technically demanding operations. Though conceptually familiar to surgeons learning laparoscopy, there is a definite learning curve evident with the adoption of robotic technology [53]. In experiences that extend beyond the period of surgeon learning, the outcomes for robotic and laparoscopic approaches appear to be similar [46,52,54]. Thus, in the face of data suggesting equivalency, it is becoming increasingly apparent that future surgical decision making will be driven in part by patient and surgeon preference for operating platform (open, laparoscopic, or robotic).

Finally, there is increasing awareness of healthcare expenditures both in the United States and abroad. The adoption of novel technologies requires an initial investment by healthcare systems to enable practitioners to offer procedures such as laparoscopy and robotics. From a global health perspective, this initial investment remains beyond the reach of many hospitals and systems. Once acquired, however, the utilization of resources (as measured by cost) may in fact be decreased by the adoption of minimally invasive approaches to pancreatectomy. Similar to other studies of MIS in pancreatectomy, the most mature data to support this view comes from analysis of cost data in LDP. Retrospective reviews of data in both the United States and Britain document an overall cost advantage to MIS pancreatectomy as compared to an open technique [55,56]. One distinct limitation in both these studies is the inability to account for the initial investment costs required to procure the instruments needed to successfully perform these advanced procedures.

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# Management of Recurrence of Cystic Neoplasms

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## Introduction

In an era of improved cross-sectional imaging, pancreatic resection has been increasingly performed for cystic neoplasms, with intraductal papillary mucinous neoplasms (IPMN) representing more than half of resected cystic neoplasms [1,2]. The natural history of IPMN varies widely, depending on a host of variables including pattern of duct involvement and epithelial subtypes, amongst others [3]. In 2012, the International Association of Pancreatology (IAP) established an updated consensus guideline addressing the appropriate indications of resection based on predictors of malignancy [4]. The follow-up and surveillance strategy for patients after they have had an IPMN resected, however, remains a matter of debate, with no formal evidence-based gold standard. This is in part due to imprecise use of the terms "recurrence" and "progression" in studies attempting to characterize these patterns to inform surveillance strategies.

The term "recurrence" has historically been used in the context of malignancy and implies the return of disease as a result of descendant cells of the original resected lesion on account of residual microscopic disease, mainly in IPMN with an associated invasive cancer. In regard to the natural history of the occurrence of a new IPMN in the pancreatic remnant following resection of noninvasive IPMN, the term "recurrence" when used in this manner only accounts for a subset of disease. In most cases, patients have multifocal disease and have residual IPMN separate from the index lesion not meeting criteria for resection in their remnant gland, or they develop new metachronous lesions that either remain stable or progress. These "recurrences" should be analyzed as a distinct process, as the former (IPMN with an associated invasive cancer) has an overwhelming risk of systemic and local recurrence akin to conventional pancreatic ductal adenocarcinoma [5,6]. With the practice of parenchymal-sparing pancreatectomy for IPMN [7,8], it is ever more important to characterize the progression or development of new lesions in the remnant pancreas to inform postoperative surveillance strategies. In this chapter, we will be focusing on reviewing the current literature that analyzes the natural history of the remnant pancreas after resection of noninvasive IPMN. Mucinous cystic neoplasms are predominantly solitary and complete resection is often curative [9]. Thus, the postoperative surveillance strategies are not applicable and will not be the focus of the chapter.

## Fate of the Pancreatic Remnant

IPMN is a disease associated with a "field defect," with rates of synchronous disease reported to be as high as 83% [10], and risk of developing clinically significant metachronous lesions being about 8% [11]. This field defect predisposes the remnant gland to developing significant neoplasia, even after resection of a primary lesion. Kang et al. reported a recurrence rate of 5.4% in the remnant gland after resection of 298 noninvasive IPMN [12]. More importantly, 10 of the 298 recurred as an invasive lesion. In the largest series to date, Marchegiani analyzed close to 300 patients with noninvasive IPMN and similarly reported a 9% risk of recurrence after resection of a noninvasive IPMN, with six representing invasive recurrences [13]. This is in line with the literature, which reports a recurrence rate ranging from 1% to 20%, and an invasive recurrence

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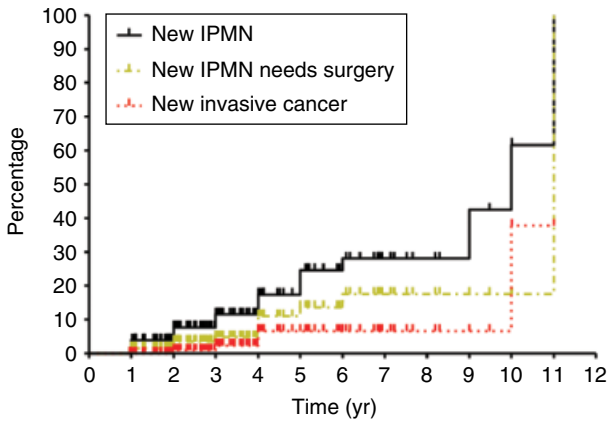
**Table 86.1** Studies reporting recurrence rates after resection of benign IPMN.

| 1st author, year | *n* | Median follow-up, months | Recurrence rate, % | Recurrence rate with invasion, % | Time to recurrence, months | 5-year survival, % |
|---|---|---|---|---|---|---|
| Chari, 2002 [14] | 60 | 37 | 8.3 | 3.3 | 40 | 85 |
| Sohn, 2004 [15] | 84 | – | 8.3 | 5.9 | – | 77 |
| Wada, 2005 [16] | 75 | – | 1.3 | 0 | – | 100 |
| Salvia, 2006 [17] | 80 | 31 | 1.0 | 0 | – | 100 |
| Raut, 2006 [18] | 28 | 34 | 0 | 0 | – | 100 |
| White, 2007 [19] | 78 | 40 | 7.7 | 5.1 | 22 | 87 |
| Fujii, 2010 [20] | 103 | – | 9.7 | 7.8 | – | – |
| Miller, 2011 [21] | 191 | – | 20 | 2 | 35 | 83 |
| He, 2013 [22] | 130 | 38 | 17 | 4 | 46 | 81 |
| Kang, 2014 [12] | 298 | 44 | 5.4 | 2.3 | 47 | – |
| Marchegiani, 2015 [13] | 316 | 58 | 9 | 5 | 48 | – |

IPMN, intraductal papillary mucinous neoplasm.

rate of 2% to 7.8% [14–22]. Despite this, 5-year survival has been reported to be favorable, ranging from 77% to 100%. The median time to recurrence has been described to range from 22 months to 46 months, suggesting that long-term surveillance is necessary as recurrence can occur up to 4 years after resection of a benign IPMN (Table 86.1).

Perhaps the most comprehensive analysis specifically investigating the natural history of the pancreas remnant after resection of a noninvasive IPMN is that from the Johns Hopkins group. In an analysis of 130 patients who underwent resection of noninvasive IPMN, He et al. reported that the 1-, 5-, and 10-year risks of developing a new IPMN are 4%, 25%, and 62%, respectively, with the subsequent chances of requiring surgery being 1.6%, 14%,and 18%, respectively [22]. Even more importantly, the risk of developing invasive cancer at 1-, 5-, and 10-years is 0%, 7%, and 38%, respectively (Fig. 86.1) [22]. At a median follow-up of 60 months, all patients who were found to have invasive carcinoma on completion pancreatectomy remained alive with no evidence of recurrent disease. This study has two very important implications: (i) after resection of noninvasive IPMN, indefinite surveillance is necessary because of these long-term risks; (ii) management of recurrent IPMN in line with the same resection criteria as the primary IPMN set by the IAP is safe. It is important to point out that there is a possibility that the invasive cancer recurrences could represent concurrent ductal adenocarcinoma that was undetected at the time of surgery instead of the metachronous development of a new invasive adenocarcinoma. Regardless, the implication is that patients who had a noninvasive IPMN resected still require long-term surveillance.




| | 1yr | 5yr | 10yr |
|---|---|---|---|
| New IPMN | 4% | 25% | 62% |
| New IPMN requiring completion pancreatectomy | 2% | 14% | 18% |
| New invasive cancer | 0% | 7% | 38% |

**Figure 86.1** Cumulative recurrence curve for patients undergoing resection of noninvasive IPMN. IPMN, intraductal papillary mucinous neoplasm. *Source:* Adapted from He et al. 2013 [22]. Reproduced with permission of Elsevier.

## Predictors of Recurrence

A better understanding of the risk of recurrences can guide resource allocation and maximize the efficiency of postoperative surveillance. The Johns Hopkins series found that patients with a family history of pancreatic cancer were significantly more likely to develop recurrence after resection of a noninvasive IPMN (23% vs. 7%, $P < 0.05$), and family history was the only independent preoperative predictor of recurrence (OR 4.2, 95% CI

1.3–14.1, $P = 0.02$) [22]. The Massachusetts General Hospital group reported an increased incidence of concurrently occurring ductal adenocarcinoma (11.1% vs. 2.9%, $P = 0.02$) and extrapancreatic malignancies (35.6% vs. 20.1%, $P = 0.03$) in patients with a family history of pancreatic cancer [23]. Taken together, patients with a family history of pancreatic cancer represent a high-risk cohort that should not only be followed more intensely after resection of their index lesion, but also encouraged to pursue general age-appropriate cancer screening. Some have even proposed that younger patients with preexisting diabetes and a family history of pancreatic cancer may benefit from total pancreatectomy given that their cumulative risk would be higher, carefully balancing this strategy against potential debilitating metabolic derangements from an apancreatic state.

The impact of surgical margin at the time of surgical resection on recurrence risk, however, is still debated, with conflicting outcomes reported by different centers. The Johns Hopkins (27% vs. 22%, $P$ = ns) [22] and Seoul National University groups (16.7% vs. 10.2%, $P = 0.421$) [12] reported no difference in recurrence rates when margin positive patients were compared with margin negative patients. Conversely, the Memorial Sloan Kettering group reported that dysplasia of any degree at the resection margin was a risk factor for recurrent disease at the remnant gland (OR 2.9, $P = 0.02$), but not for recurrent disease at the resection margin itself [24]. Similarly, the Massachusetts General Hospital group reported a significantly higher rate of recurrence in patients with positive margins (25% vs. 14%, $P = 0.008$), and they found that margin status was one of the most important predictors of survival on multivariate analysis (HR 2.6, $P = 0.0046$) [25]. The discrepant findings are likely to be a result of the retrospective nature of underpowered studies in trying to analyze a small, specific subcohort of patients. The current IAP guidelines recommend that, when present, a low- and intermediate grade IPMN at the resection margin does not require re-resection, whereas high-grade dysplasia or invasive foci are indications for further pancreatectomy to reduce risk of recurrences [4].

High-grade dysplasia in the primary lesion has also been shown to pose a higher risk of recurrence in the remnant pancreas. He et al. reported that 17% of patients with high-grade dysplasia discovered in their primary resected IPMN developed new or progressive disease in their pancreatic remnant [21]. Similarly, the Indiana group reported that 10% of patients with an IPMN with high-grade dysplasia developed a subsequent de novo invasive IPMN despite negative surgical margins [22]. In an analysis of 140 patients, the Johns Hopkins group reported that patients with high-grade dysplasia in their primary resected IPMN were more than eightfold more likely to subsequently develop an invasive cancer (OR 8.82, 95% CI 2.56–30.43, $P = 0.001$) [26]. This specific cohort should be categorized as high risk for recurrence and should undergo close surveillance as well.

## Low-Risk Lesions Left Behind in Remnant

Approximately 7–20% of patients have synchronous IPMN, one or more of which did not meet criteria for resection at the time of index surgery, and were therefore left behind [7,21,27]. The Indiana group reported a 5-year progression-free survival of 88% for these patients, which was no different from the survival of patients who did not have any residual lesion after resection of a noninvasive IPMN (82%, $P > 0.05$) [21]. Similarly, in an analysis of 203 patients who underwent resection, Moriya et al. reported that 14 patients had residual lesions after resection, with no incidence of progression at a median follow-up of 40 months [27]. These patients are not at any higher risk for recurrence or progression, justifying current practices of only operating on IPMN that meet criteria for resection. However, surveillance is still necessary given the similar non-negligible risk of progression and will be discussed in the next section.

## Postoperative Surveillance Strategy

As opposed to conventional adenocarcinoma, early diagnosis of a recurrent IPMN might lead to early surgical intervention that can improve long-term survival. Currently, no published guidelines exist for the management of patients who had a noninvasive IPMN resected. A better understanding of the patterns and mechanisms of recurrence will aid in the development of useful guidelines for follow-up strategies. As noted earlier, several factors appear to correlate with recurrence—family history, a positive resection margin, and high-grade dysplasia in the primary lesion. In these individuals close observation is necessary since the risk of subsequent high-risk lesions or malignancy is high. Moreover, as previously mentioned, the long time periods to recurrence after resection of a noninvasive IPMN implies a lifelong surveillance strategy for these patients, especially in younger patients and high-risk cohorts, that is, patients with high-grade dysplasia at the surgical margin or in the primary lesion, and those with a family history of pancreatic cancer. We feel that the current IAP guidelines recommending history/physical examination and magnetic resonance cholangiopancreatography (MRCP)

surveillance performed at 2- and 5-years following resection, with a gradual lengthening in follow-up interval once there is a pattern of stability may not be sufficient [4]. This is particularly true for patients with risk factors for recurrence. It should be noted that in the He et al. study, the risk of developing a clinically significant lesion is estimated to be over 30% at 10 years. Taken together, these observations argue against reducing the frequency of surveillance once "stability" is determined. In this regard it would appear that the risk of clinically significant lesions increases with time. That said, patients who undergo resection for noninvasive BD-IPMN without the aforementioned risk factors have a very low risk of recurrence, and when they do recur, are rarely invasive [13]. For selected elderly or frail patients with significant comorbidities in whom life expectancy is short or who cannot tolerate a pancreatectomy, follow-up after resection of BD-IPMN could potentially be avoided altogether.

## Conclusions

The recurrence rate after resection of noninvasive IPMN ranges from 1% to 20%, with a little less than half of the recurrences being invasive diseases. The cumulative 10-year risk of developing indications for resection or invasive cancer after resection of a noninvasive IPMN are 18% and 38%, respectively. Because early detection of recurrence or IPMN progression has a positive impact on long-term survival, patients undergoing resection for noninvasive IPMN should be closely surveyed postoperatively. Family history, grade of disease, and resection margins are the only predictors of recurrences after resection, and total pancreatectomy may be contemplated in a highly selected cohort of young patients with preexisting diabetes. Clinical judgment should dictate the need for further surveillance in older patients who have undergone resection for low-grade, noninvasive BD-IPMN.

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# Long-Term Outcome of Management of Cystic Neoplasms

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## Long-Term Outcome After Observation and Surgical Treatment: What is the Evidence?

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### Introduction

Many aspects related to the natural history and outcome of pancreatic cystic neoplasms are poorly understood, because the vast majority of the data are retrospective and uncontrolled, and long-term follow-up is limited. Selective resection of cystic neoplasms seems to be appropriate, balancing the risk of malignancy with those of operation, and—over the years—initial management evolved towards fewer patients undergoing operative resection and fewer benign lesions being resected [1,2]. Patients managed nonoperatively are enrolled in radiologic surveillance protocols, with the aim of finding signs of possible malignant degeneration. Surveillance protocols require periodic cross-sectional imaging and/or endoscopic ultrasound, at a high economic cost for the community. Furthermore, there is no ideal test to diagnose transformed pancreatic cystic neoplasms, and there is not general agreement on the optimum method and timeframe to follow up for these lesions. Long-term results of surveillance protocols have begun to be reported in the literature, especially for lesions amenable to initial observation, such as serous cystic neoplasms and BD-IPMN [3,4].

In patients undergoing resection, either at the time of diagnosis or after observation, the chance of cure, the incidence of tumor recurrence, and disease-specific or overall survival depend on the cyst type and the presence of an invasive component, although long-term data are limited. This chapter describes long-term outcomes after observation of surgical resection of pancreatic cystic neoplasms.

### Serous Cystic Neoplasms

The almost invariably benign nature of serous cystic neoplasms, combined with the morbidity and potential mortality of pancreatic resections, led to a management strategy weighted towards surveillance. The safety of a periodic surveillance program and the generally slow growth rate of these lesions have been recently demonstrated by different institutions, including the authors' own [3,5]. The optimal interval between follow-up imaging tests in pancreatic serous cystic neoplasms is still unclear. Many institutions recommend imaging on a semi-annual or annual basis for all cystic neoplasms. According to the most recent data, cystic lesions presumed to be benign can be safely observed on a 2-year basis [6]. Clearly, surveillance can be tailored on the basis of cyst morphology (i.e., unclear discrimination between serous and mucinous lesions), patient's age, sex, and tumor location. As a matter of fact, most of the patients currently undergoing resections for a serous cystic neoplasm are misdiagnosed with another pancreatic neoplasm [5]. In patients managed operatively, complete surgical resection ensures cure, and serous cystic neoplasms do not recur. Therefore, a regular radiologic follow-up program is unnecessary, thereby saving cost. Follow-up outpatient visits should be better focused on quality of life. Malignant serous cystic neoplasms (serous cystoadenocarcinomas) are exceptionally rare, with less than 40 cases being published. Synchronous or metachronous liver metastases have been frequently noted (36%). Mean survival was 36 months among the few cases with follow-up; the prognosis seems to be favorable also in patients with metastatic disease [7].

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## Mucinous Cystic Neoplasms

Mucinous cystic neoplasms generally require surgical resection, although small lesions without mural nodules, especially in elderly patients with comorbidities, may be observed. Such patients are, however, very uncommon. Because most patients with mucinous cystic neoplasms are middle-aged women with a long life expectancy, non-operative management of low-risk lesions based on periodic imaging would require years of radiologic follow-up at high cost [8].

Radical resection of noninvasive neoplasms ensures cure. These neoplasms do not recur and—as already pointed out for serous cystic neoplasms—outpatient follow-up should be focused on quality of life, because regular radiologic postresection surveillance is probably unnecessary.

Minimally invasive mucinous cystic neoplasms (invasion limited to the ovarian stroma), but without tissue invasion, have an excellent prognosis. On occasion, undocumented foci of invasive carcinoma may exist within a presumed noninvasive proliferative MCN; this emphasizes the importance of a careful histopathologic analysis of the entire lesion. In such cases, recurrence and metastases can be observed. In general, these patients should undergo a radiologic follow-up protocol, despite the fact that minimally invasive adenocarcinomas arising in mucinous cystic neoplasms can be virtually cured by surgery, particularly if the neoplasms are completely examined histologically [9].

Five-year survival of patients with invasive mucinous cystic neoplasms (true cystadenocarcinoma) appears to be quite poor, ranging from 15% to 35%, albeit somewhat better than the survival rate for patients with typical ductal adenocarcinoma of the pancreas. The extent of invasion is the most significant prognostic factor in malignant mucinous cystic neoplasms. Some authors have suggested that patients with resected mucinous cystadenocarcinoma should be carefully followed on a 6-month basis with cross-sectional imaging, matching the interval to follow-up of ductal adenocarcinoma [10]. However, proof that surveillance imaging improves the prognosis compared with a strategy based on symptom recurrence is lacking.

## Intraductal Papillary Mucinous Neoplasms

### Outcome of IPMN Managed Nonoperatively

The decision to follow an IPMN is based on multiple factors, namely the neoplasm type (main-duct/mixed *versus* branch duct), patient age, family history, symptoms, comorbidities, perceived pancreatic cancer risk, and patient preference [2,11]. Initial follow-up is generally proposed only to patients with BD-IPMN devoid of malignant features (Sendai-negative), in which the risk of invasive cancer appears to be low. The majority of papers confirm this policy to be relatively safe, although robust long-term data are lacking. In a cohort of 170 patients from MSKCC initially selected for surveillance, after a median follow-up period of 40 months, 97 underwent delayed resection because of endoscopic or radiologic changes, concern about premalignant conditions, or suspicious cytology. Of these, 79 had a noninvasive disease, 18 had an invasive IPMN. High-grade dysplasia or invasive IPMN were larger (median diameter of 3 cm), and were more likely to have main pancreatic duct involvement. Overall survival after delayed resection was 142 months for noninvasive disease and 126 months for invasive disease. Interestingly, 5 patients initially selected for surveillance developed a pancreatic ductal adenocarcinoma in a region remote from the lesion being monitored (median time from diagnosis to resection for invasive disease was 20 months). In spite of an active surveillance program, no patient had stage I disease [4]. Another multi-institutional series from Japan analyzing 349 follow-up BD-IPMN patients who had no mural nodules at initial diagnosis (median follow-up of 3.7 years) showed that 62 patients (17.8%) exhibited disease progression during follow-up. Twenty-two underwent surgery, leading to a pathologic diagnosis of invasive disease in 9 and adenoma in 13. A pancreatic ductal adenocarcinoma developed in 7 patients (2.0%). Of these, only 4 were resectable [12]. In two smaller series from France limited to low-risk BD-IPMN the follow-up period was longer. The former series included 49 patients. After a mean follow-up period of 77 months, 77.5% of patients remained symptom-free. Five patients were operated on because of recurrent pancreatitis and/or an increase in size of either cysts or the main duct (mean time delay after diagnosis was 20 months). Pathologically, none of these patients had malignancy [13]. In the latter series, analyzing 53 patients with follow-up ≥60 months (median 84 months), crossover to surgery was necessary in 3 patients, none of whom ultimately had an invasive disease. However, an invasive advanced carcinoma occurred in 2 patients, both after 84 months follow-up [14]. The same concept was reported by a Japanese series of 103 BD-IPMN patients conservatively followed up for ≥2 years (median 59 months). The 5-year actuarial rate of development of pancreatic cancer was 2.4% [15].

Interestingly, in a series of IPMN meeting criteria for resection (Sendai-positive) and not operated because of age and comorbidities, the outcome was relatively good (overall median disease-specific survival of 55 months),

especially in the BD-type. The authors proposed that a conservative approach in patients who are not surgically fit is also reasonable [16]. The most robust data in this setting come from a recent multi-institutional series of "Sendai-positive" IPMN that were managed conservatively. Of note, those presenting with "worrisome features" and not recommended for surgery mainly because of comorbidities had a 96% 5-year DSS. Conversely, the presence of "high-risk stigmata" was associated with a 40% risk of IPMN-related death [17]. In this regard, a conservative approach for individuals presenting with "worrisome features" seems appropriate, particularly in elderly patients. On the contrary, some authors claim that even Sendai-negative BD-IPMN and MD-IPMN with a main pancreatic duct of less than 1 cm have significant malignant potential (24.6–60 %), and propose a more liberal operative policy [18,19].

In general, there is little evidence in the literature to guide the frequency and type of surveillance for IPMN managed nonoperatively. Some authors propose that surveillance can be safely spaced at every 2 years or even discontinued after long-term stability in low-risk lesions. However, concern over the development of pancreatic ductal adenocarcinoma in the pancreas harboring IPMN prompts a continuation of active life-long surveillance at short intervals [2]. Undoubtedly, surveillance results in significant utilization of cross-sectional imaging, endoscopic ultrasound, and economic investment. Research is focusing on fluid cyst biomarkers able to distinguish invasive from noninvasive cysts.

## Outcome After Resection of IPMN

The outcome after resection of IPMN depends on different factors, including:

- Presence of an invasive component
- Epithelial histologic subtype
- Type of invasive component
- Duct involvement
- Resection margin
- Lymph node status (in invasive IPMN).

The prognosis of patients with noninvasive IPMN is excellent, and the 5-year survival rate is reported to be >70% in most series. Some series have even suggested a 5-year survival in excess of 90% after resection. Conversely, the 5-year survival rate for invasive IPMN (carcinoma arising in the background of IPMN) ranges from 34% to 62%. The outcome of invasive IPMN is therefore poor in comparison with noninvasive IPMN, but appears to be better than pancreatic ductal adenocarcinoma, which exhibits a 5-year survival ranging from 9% to 21%. Whether this is due to a stage-shift with earlier diagnosis of IPMN, or because of a truly less aggressive behavior of invasive IPMN remains controversial [20]. Disease recurrence may arise either in the pancreatic remnant or in peripancreatic or extrapancreatic sites.

Recent data indicate that invasive IPMN is a heterogeneous disease, because it can exhibit different histologic patterns, namely colloid (colloid carcinoma), tubular (tubular adenocarcinoma), or oncocytic (oncocytic carcinoma). According to reports by Furukawa et al. and by Mino-Kenudson et al., colloid carcinoma derives from intestinal-type IPMN, and is associated with a particularly indolent behavior [21]. Tubular adenocarcinoma correlates with gastric and pancreatobiliary epithelial subtypes, and is associated with a dismal prognosis, similar to that of pancreatic ductal adenocarcinoma. Oncocytic carcinoma derives from the uncommon oncocytic subtype, and has a significantly better outcome than ductal adenocarcinoma, even though it can present with very late tumor recurrence (up to 7 years after surgical resection) [20–22].

It is well established that the type of duct involvement, branch versus main duct, is associated with the risk of invasive cancer. Because the type of duct involvement correlates with epithelial subtypes of IPMN, it may also identify the likely histologic subtype of cancer. In particular, MD-type are mainly of intestinal and oncocytic type, whereas BD-type are often associated with gastric epithelial type. The association BD-IPMN/gastric subtype/tubular adenocarcinoma seems paradoxical, because gastric-type BD-IPMN most often harbor low-grade dysplasia and absence of invasion. In the series by Mino-Kenudson et al., 15.6% of surgically resected gastric-type IPMN gave rise to tubular adenocarcinoma [20]. According to these findings, the final pathologic report of resected invasive IPMN should indicate the histologic pattern of the invasive component and the background histologic subtype. This is of essential prognostic significance.

The clinical implications of surgical resection margin (frozen section of the pancreatic cut surface) are controversial, and the results in the literature are mixed on this topic [23]. In general, not all studies found a strong correlation between margin status and risk of recurrence. There have been reports of invasive carcinomas in association with only mild or moderate dysplasia (adenomas or borderline lesions) within the IPMN in the remnant pancreas. A recent meta-analysis showed that the recurrence rate in patients with noninvasive IPMN was 3.72% with negative margins, and 9.56% with positive margins. The same meta-analysis showed that recurrence after surgical resection of invasive IPMN occurred in 33.8% of patients with negative margins and in 53.6% of patients with positive margins [24]. This data is reinforced by a recent series from the MGH, stating that resection margin is indeed an independent predictor of tumor recurrence for invasive IPMN [25].

Because recurrence in the remnant stump may be due to the presence of multifocal disease or to the development of a metachronous IPMN rather than due to the progression of margin-positive disease, the margin should be used as a marker of residual disease throughout the remnant.

Lymph node status is another factor affecting long-term outcome in invasive IPMN. The 5-year survival of patients with positive lymph nodes ranged from 20% to 30%, while N0 patients lived much longer, in the range from 80% to 85%. Lymph node ratio >0.2 has been shown to be associated with worse prognosis [26]. Data from a meta-analysis demonstrated that nearly 77% of lymph node positive patients recurred, while disease recurrence occurred in only 30.8% of patients with negative lymph nodes [24].

## Solid Pseudopapillary Neoplasms

More than 95% of patients with solid pseudopapillary neoplasms limited to the pancreas are cured by complete surgical excision. Local invasion or resectable liver and lymph node metastases are not contraindications for resection, and some patients with advanced tumors can survive for more than 10 years after the operation [27]. During the follow-up period, recurrence of the disease in the liver or lymph nodes is uncommon, at 6.6%. Prognosis for solid pseudopapillary neoplasms with treated liver metastases usually surpasses 5 years. Conversely, from a recent internal review of the Verona case series, other factors such as presence of capsular invasion and pancreatic parenchyma invasion correlated with the likelihood of tumor recurrence after complete surgical excision. Overall, 2-year survival rate (with metastases or not) was 97%, and 5-year survival around 95%. In the few unresectable cases in which radiotherapy or chemotherapy were used, results were encouraging [28].

## Final Remarks

The natural history of pancreatic cystic neoplasms is largely unknown in the long term, and data beyond 5 years are virtually lacking. Because it seems that survival is clearly favorable in comparison with pancreatic ductal adenocarcinoma, it will be of great importance to understand how these neoplasms behave, with respect to the time to degeneration, the risk of developing a new IPMN or additional malignancy, and the risk of disease-specific mortality. Accurate surveillance, either pre- and post-operatively seems mandatory in the majority of cystic neoplasms, since most have the potential to become malignant or to recur. For those that become malignant, it may take perhaps as long as 10 years or more for that evolution. So early reports with limited length of follow-up are just the beginning, and are not long enough to really capture the natural history of these neoplasms.

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# Section 7

# Neoplastic Tumors of Exocrine Tissue: Pancreatic Cancer

# 88

# Epidemiology of Pancreatic Cancer

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## Incidence, Mortality Trends, Survival Prognosis

In 2012, worldwide, there were approximately 380,000 individuals diagnosed with pancreatic cancer and approximately 331,000 individuals died from their disease making pancreatic cancer the seventh most common cause of cancer death [1]. Pancreatic cancer is strongly associated with increased age, with the majority of cases occurring after age 60. In the United States, from 2009–2013 the incidence of pancreatic cancer in Whites increased from less than 5 per 100,000 before age 45, to 30.0 per 100,000 in individuals aged 60–64, and 93.7 per 100,000 in individuals aged 80–84 [2]. Incidence is approximately equal in men and women. The disease burden is strongest in developed countries compared to developing countries [1]. This difference is likely driven, in large part, by differences in the age structure as well as access to medical care necessary for the diagnosis of pancreatic cancer [3].

In developed countries the overall incidence of pancreatic cancer is expected to continue to increase with the general aging of the population, particularly in high-income countries [4,5]. Pancreatic cancer is projected to become the second leading cause of cancer death in the United States by 2030 [6]. However, other countries have seen a recent decrease in the incidence of pancreatic cancer that seems to reflect patterns in cigarette consumption. As discussed later, cigarette smoking is a major risk factor for pancreatic cancer and never smoking or smoking cessation is strongly associated with a decrease in risk. In contrast, increased body mass index (BMI) and diabetes mellitus are both associated with a greater risk of pancreatic cancer and the increasing prevalence of these risk factors is projected to lead to a rise in incidence of pancreatic cancer.

Pancreatic cancer is associated with an extremely poor prognosis with an estimated average 1-year relative survival rate of ~20%, and a 5-year rate of ~8% [4]. Survival rates have increased only slightly since the mid-1970s from 4–5% to around 8% in the United States [2]. The low survival rates are mainly due to advanced stage at diagnosis with only ~20% of patients presenting with local disease [2]. Among patients who undergo surgical resection, the 5-year survival rate is ~15–25% [7]. Outcomes after surgical resection of the pancreas are highly dependent on the experience of the surgeon and the hospital; mortality rates are 70% lower among high-volume surgeons compared with low-volume surgeons, and hospitals with a high patient volume compared with low-volume hospitals [8].

## Cigarette Smoking

Of modifiable risk factors, the relationship between active cigarette smoking and pancreatic cancer risk is well established. Approximately, 20% of all pancreatic cancers are attributable to cigarette smoking [9–11]. Numerous studies have explored the relationship between smoking and pancreatic cancer. A meta-analysis of 82 epidemiologic studies published between 1950 and 2007 [9] reported a 1.74-fold (95% CI: 1.61–1.87) increased risk of pancreatic cancer among current smokers and a 1.2-fold (95% CI: 1.11–1.29) increased risk of pancreatic cancer among former smokers when compared with never smokers. Pooled analysis of individual-level data from the nested case-control studies within the Cohort Consortium (PanScan) [11] as well as analysis of data from 12 case-control studies in the Pancreatic Cancer Case-Control Consortium (PanC4)

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[10] showed that smokers have a 75–120% increased risk of pancreatic cancer compared with never smokers, and the risk persists for 10–20 years after smoking cessation [10,11]. Risk also increased according to the number of cigarettes consumed per day; smokers of more than 35 cigarettes per day have a threefold (95% CI: 2.2–4.1) increased risk of pancreatic cancer compared with never smokers [10]. Quitting smoking is associated with a reduced pancreatic cancer risk with a decreased odds ratio in former smokers when compared with active smokers. Studies suggest that the risk in former smokers returns to that of never smokers 15–20 years after smoking cessation [10,11].

## Diabetes

The relationship between diabetes and pancreatic cancer is quite complex; many newly diagnosed pancreatic cancer patients report a recent onset of diabetes, and those with long-standing diabetes report a recent worsening of diabetes. Thus, it is generally considered that while long-standing diabetes is a risk factor for pancreatic cancer, diabetes can also result as a consequence of pancreatic cancer.

There is considerable variability when estimating the prevalence of diabetes and/or glucose intolerance among newly diagnosed pancreatic cancer patients [12]. It has been estimated that up to 80% of newly diagnosed pancreatic cancer patients have glucose intolerance or diagnosed diabetes [13]. Studies that rely on patient or medical records of reported diabetes show lower prevalence estimates, including a large Mayo Clinic case-control study where 40% of patients reported diabetes [14]. Over 75% of pancreatic cancer patients who develop diabetes, do so within the 2 years preceding their pancreatic cancer diagnosis [15]. Thus, there is considerable interest in examining populations of newly diagnosed diabetics to determine whether this might enable earlier detection of pancreatic cancer. It has been shown that up to 1% of newly diagnosed diabetics develop pancreatic cancer within 3 years of their diabetes diagnosis [16].

While many pancreatic cancer patients develop diabetes as a consequence of their disease, there is considerable support from numerous population-based studies that long-standing diabetes (>3 yr) is associated with a modest increase in the risk of pancreatic cancer. Overall, the risk of pancreatic cancer in long-standing diabetes ranges from 1.5- to 2.4-fold [17–20]. However, as the duration of diabetes increases the association between diabetes and pancreatic cancer weakens, with some studies showing only modest or no increase in pancreatic cancer risk 15–20 years after diagnosis with diabetes [20,21]; however, some studies still support an association with diabetes of 20 years or more [19].

In patients with new-onset diabetes who undergo surgical resection, diabetes often resolves after removal of the pancreatic cancer. In contrast, diabetes does not resolve in patients with long-standing diabetes after surgical removal of their cancer [22].

## Body Mass Index

In addition to diabetes, increased weight or BMI has consistently been associated with increased risk of pancreatic cancer. The World Health Organization (WHO) defines overweight individuals as those with a BMI of 25.0–29.9 $kg/m^2$ and obese individuals as those with a BMI >30.0 $kg/m^2$.

Over the past 15 years many studies have demonstrated an increased risk of pancreatic cancer among obese individuals. In 2001, Michaud et al. reported a relative risk of pancreatic cancer of 1.72 (95% CI: 1.19–2.4) for individuals with a BMI >30 $kg/m^2$ compared with individuals with a BMI <23 $kg/m^2$ after controlling for the effect of age, smoking, and diabetes among participants of the Health Professionals Follow-Up Study and the Nurses' Health Study. Many subsequent studies have confirmed this finding; a pooled analysis of data from 13 prospective cohort studies reported an OR for pancreatic cancer of 1.33 (95% CI: 1.12–1.58) when comparing individuals in the lowest quartile of BMI with those in the highest quartile after controlling for the effects of age and smoking. Adjusting for the effect of diabetes, attenuates this association slightly (OR = 1.21, 95% CI: 1.01–1.44) [23].

## Alcohol

Numerous studies have examined the association between alcohol consumption and risk of pancreatic cancer. The results of these studies have been inconsistent, with some studies showing an association and others showing no relationship. One challenge to these studies is the strong relationship between smoking and heavy alcohol use, making it difficult to assess the independent association between alcohol use and pancreatic cancer risk. However, several recent large-scale studies that have pooled data across several studies, either using data from prospective cohort studies or retrospective case-control studies, have demonstrated that high levels of alcohol intake are associated with an increased risk of pancreatic cancer. These studies consistently report a ~20–45% increased risk of pancreatic cancer among heavy drinkers (defined as three drinks/day or ≥30 grams/day of alcohol), compared with non- or occasional

drinkers [24–26]. In addition, in a pooled analysis of data from the Pancreatic Cancer Case-Control Consortium [27], the risk increases up to 60% among extremely heavy alcohol drinkers (≥9 drinks /day). Heavy alcohol consumption is associated with pancreatitis, an established risk factor for pancreatic cancer. Furthermore, acetaldehyde is an established carcinogen. Thus the association between alcohol and pancreatic cancer risk could be either via alcohol-induced pancreatitis or as a direct effect of acetaldehyde.

## Pancreatitis

The relationship between pancreatitis and pancreatic cancer has been well established. Individuals with hereditary pancreatitis, a rare inherited condition, have a remarkably high lifetime risk of pancreatic cancer of 40% [28]. The risk is further increased by cigarette smoking [29]. Quantifying the association between pancreatitis and pancreatic cancer is challenging given the difficulties in diagnosis and differentiation between chronic and acute pancreatitis [30]. In addition, like diabetes, pancreatitis is both a risk factor and a manifestation of pancreatic cancer. The inflammation and damage of long-standing pancreatitis can lead to the development of pancreatic cancer. However, individuals with pancreatic cancer also experience pancreatitis as a consequence of their cancer. A recent large-scale study of 5,048 cases of ductal pancreatic adenocarcinoma and 10,947 controls from 10 case-control studies within the Pancreatic Cancer Case-Control Consortium examined the association between pancreatic cancer and pancreatitis. Overall, 6% of pancreatic cancer patients reported a history of pancreatitis compared to 1% of control individuals. The association between a recent diagnosis of pancreatitis (<1 yr) and pancreatic cancer was remarkably high (OR = 21.35, 95% CI: 12.03–37.86) [31]. In contrast, the association between a pancreatitis diagnosis of >2 years and pancreatic cancer was estimated to be (OR = 2.71, 95% CI: 1.96–3.74) [31]. The association between pancreatitis and pancreatic cancer persisted after controlling for other risk factors including smoking, alcohol consumption, BMI, and diabetes. Interestingly, there was evidence of effect modification by age, with a stronger association between pancreatitis and pancreatic cancer in patients diagnosed before the age of 65 [31].

## Dietary Factors

Given the generally late age of onset of pancreatic cancer and the complexity of lifetime dietary factors, identification of dietary factors that are consistently associated with pancreatic cancer risk has been remarkably challenging. Several studies have suggested a diet rich in fruit and vegetables may protect against pancreatic cancer with risk reduction in the order of 30–40%, when comparing the highest intake to the lowest intake of fruits and vegetables [32–34]. While a diet rich in fruit and vegetables may protect against pancreatic cancer, several studies have demonstrated an increased risk of pancreatic cancer among individuals who are frequent consumers of smoked or processed meats [35]. A meta-analysis including 6,643 pancreatic cancer cases from 11 prospective studies, reported that eating at least one serving of processed meat a day was associated with a 19% increased risk of pancreatic cancer [35].

## Gastrointestinal Microbiome

In recent years, the importance of the microbiome in human health and disease has gained recognition. Several studies have shown that periodontal disease and tooth loss is associated with pancreatic cancer risk [36]. In 2007, a study among males participating in the Health Professionals Follow-up Study reported that individuals with a history of periodontal disease had a HR of pancreatic cancer of 1.54 (95% CI: 1.16–2.04) compared with those without such a history [37]. A recent study examined the association between specific oral pathogens and pancreatic cancer risk using prospective samples collected within the PLCO trial. This study found that individuals circulating antibodies to *Porphyromonas gingivalis* and *Aggregatibacter actinomycetemcomitans* had higher odds of pancreatic cancer (OR = 1.60, 95% CI: 1.15–2.20, and OR = 2.20, 95% CI: 1.16–4.18, respectively), compared with noncarriers [38].

While some studies have shown an association between pancreatic cancer risk and *Helicobacter pylori* infection not all studies have shown a positive association. One possible explanation for these inconsistent results is that the relationship may vary between CagA-positive and CagA-negative infections; CagA-negative infection is positively associated with disease and CagA-positive infection potentially has a protective effect. A recent meta-analysis found an overall association of OR = 1.13, 95 % CI: 0.86–1.50 for *H. pylori* infection and pancreatic cancer risk. The association was OR = 0.78, 95% CI: 0.67–0.91, and OR = 1.30, 95 % CI: 1.02–1.65 for CagA-positive and CagA-negative strains, respectively [39].

## Allergy

Individuals with a history of allergies, including hay fever, allergic rhinitis, atopic dermatitis, and atopic asthma may have a lower risk of developing pancreatic

cancer. A meta-analysis published in 2005 reported an overall association between allergies and pancreatic cancer risk of RR = 0.82, 95% CI: 0.68–0.99). A stronger protective effect was reported in atopic allergies (RR = 0.71, 95% CI: 0.64–0.80) and no association was reported for asthma or food allergies [40]. A recent pooled analysis of data from the Pancreatic Cancer Case-Control Consortium reported a protective effect of hay fever and animal allergies (OR = 0.74, 95% CI: 0.56, 0.96, and OR = 0.62, 95% CI: 0.41, 0.94, respectively), and no association with asthma [41]. In contrast, a recent case-control study from Spain reported a protective effect of both allergy and asthma (OR = 0.66, 95% CI: 0.52–0.83, and OR = 0.64, 95% CI: 0.47–0.88, respectively) [42].

## Family History

One of the strongest risk factors for pancreatic cancer is having a family member with pancreatic cancer. The clustering of pancreatic cancer in families was first reported in the 1970s. Large-scale observational studies have consistently estimated an increased risk of pancreatic cancer among those with a family history of pancreatic cancer [43–51]. A recent pooled analysis of data from one case-control and six cohort studies estimated the odds of pancreatic cancer to be 1.76 higher (95% CI: 1.19–2.61) among individuals who had at least one first-degree relative with pancreatic cancer compared with those with a family history of pancreatic cancer [51]. Risk is even higher in familial pancreatic cancer kindreds (defined as a having at least one pair of first-degree relatives with pancreatic cancer) with a 6.79-fold increased risk of pancreatic cancer among first-degree relatives. Mutations in the following genes have been associated with a markedly increased risk of pancreatic cancer: *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *CDKN2A*, *STK11*, *PRSS1*, *MSH2*, *MLH1*, *MHS6*, and *PMS2* [52–58].

## Conclusions

Pancreatic cancer is a leading cause of cancer mortality in developed countries. Unlike other cancers, the incidence of pancreatic cancer has increased in recent years. Major modifiable risk factors include cigarette smoking, diabetes, obesity, alcohol intake. Nonmodifiable risk factors include age and family history of pancreatic cancer.

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# Smoking, a Risk for Pancreatic Cancer: Experimental and Clinical Data

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## Introduction

Epidemiologic data clearly indicates that cigarette smoking is a risk factor for developing pancreatic cancer—in fact, cigarette smoking is the most important modifiable risk factor for these patients. While clear epidemiologic associations exist between inhaled cigarette smoke and pancreatic disease, our ability to delineate this association remains limited. Of note, no similar association has been demonstrated between smokeless tobacco and pipe or cigar smoking and pancreatic cancer.

## Experimental Data Regarding Smoking: A Risk Factor for Pancreatic Cancer

Due to the large number of chemicals in cigarette smoke, the effect of cigarette smoke on the pancreas is likely multifactorial and complex. Several of these chemicals display toxic, carcinogenic, or pharmacologically active properties, of which many have not yet been identified, contributing to our incomplete understanding of the effects of cigarette smoking on the pancreas. However, two mechanisms of action have been identified. First, chemicals such as polycyclic aromatic hydrocarbons have obvious carcinogenic properties that damage genomic DNA. Second, chemicals such as nicotine exert pharmacologic effects on cells, contributing to neoplasia.

During carcinogenesis of pancreatic cancer, genetic alterations in 12 signaling pathways are found in over 67% of patients [1]. Some of these pathways include integrin signaling, apoptosis, DNA damage control, and regulation of the G1/S phase, to name a few. Carcinogens derived from cigarette smoke are likely contributing to genetic alterations such as these. Following inhalation, carcinogens travel through the blood stream to the pancreas where they are taken up by acinar or ductal cells. Once carcinogens reach their target tissue, they then begin to exert their toxic properties. For example, 80 days of oral 2-aminoanthracene intake, a member of the anthracene family, was found to induce pancreatic acinar cell necrosis with formation of duct-like structures [2]. Other carcinogens have to be metabolized to more active compounds before they exert their toxic properties. Especially nitrosamines, nitroaromatic hydrocarbons, and aromatic and heterocyclic compounds, which are metabolized to reactive electrophiles. These reactive electrophiles are then able to interact with DNA to exert their genotoxic carcinogenic effects [3,4].

Several enzymatic systems are available for pancreatic carcinogen metabolism of which the cytochrome P450 system, glutathione S-transferases, and the UDP-glucuronosyltransferases are the most important ones. NNK (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone), the most abundant and best studied carcinogen in cigarette smoke, undergoes CYP 450 dependent oxidation to form NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol) whose S-enantiomer shows high adduct formation with pancreatic DNA [5]. This results in the creation of DNA adducts to either thymidine or guanine [6]. It can be postulated that these DNA adducts induce mutations and act as key steps in pancreatic cancer development if these mutations are randomly formed in critical gene loci such as *KRAS* or *P53*. In addition to DNA mutations in critical

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loci, a disturbance of epigenetic regulation of gene expression can be induced by cigarette smoke through aberrant DNA methylation by benzo[a]pyrene, shown to be present in significantly high concentrations in cigarette smoke. This effect of aberrant DNA methylation has been previously demonstrated in the pancreas of mice treated with benzo[a]pyrene [7]. The carcinogen-induced DNA methylation can interfere with the expression of a variety of crucial genes in the pancreas.

Apart from their carcinogenic properties, compounds such as nicotine or NNK, NNN (N-nitrosonornicotine), and (N-nitrosdiethylamine) exert pharmacologic effects by functioning as ligands for cell surface receptors. These substances contained in cigarette smoke at high concentrations interact and activate nicotinergic acetylcholine receptors (nAChR). These receptors are expressed not only on normal acinar and ductal cells but also on pancreatic cancer cells [8]. Each substance can be found in different concentrations in cigarette smoke with nicotine demonstrating the highest concentration, followed by NNK and NNN. In addition to the varying quantities of these chemicals, substantial discrepancies in binding affinities also exist. NNK preferentially binds to α7nAChR while NNN has a higher affinity for α2-α6nAChR [9]. This activation of nAChR contributes to cigarette smoke-induced pancreatic carcinogenesis [8].

Independent of pancreatic carcinogenesis, nicotine is associated with the development of pancreatic inflammation. The inflammatory effects of nicotine on acinar cells are thought to occur in a calcium-dependent mechanism. In isolated acinar cells, nicotine activates nAChR, promoting the influx of calcium into the acinar cell and enhancing the secretion of digestive enzymes [10,11]. This appears to be a key event in the development of cigarette smoke-associated acute and chronic pancreatitis since pancreatic acinar cell damage can be observed experimentally following prolonged nicotine treatment [12]. While the mechanism is not well described, the influence of nicotine on calcium signaling also promotes tumor cell viability, even after the development of pancreatic cancer [13].

Apart from calcium signaling, nicotine also exerts its effects through other pathways. Of note, treatment of pancreatic ductal epithelial cells and pancreatic cancer cells with nicotine previously resulted in a dose-dependent secretion of adrenaline and noradrenaline, contributing to cellular proliferation. This nicotine-induced autocrine catecholamine loop was mediated by 3α, 5α, and 7α nAChR [14]. In addition, pancreatic ductal cells and pancreatic cancer cells secrete the neurotransmitter GABA following combined stimulation with nicotine and catecholamines. GABA can also act as a potent tumor suppressor, mitigating the damaging effects of chronic nicotine exposure in cells co-incubated with GABA [15]. Interestingly, nicotine is able to reduce GABA secretion in a time-dependent manner. This is thought to be mediated by a downregulation of the GABA synthesizing enzymes GAD65 and GAD67 in a 4α nAChR-dependent manner, abrogating the GABA-induced growth inhibition [15].

In addition to its effects on cellular proliferation, nicotine also influences the ability of tumor cells to migrate, invade surrounding tissues, and metastasize. In pancreatic cancer cell lines, cigarette smoke extracts and nicotine induce the expression of MUC4 in an α7 nAChR-dependent manner [16]. MUC4 is a mucin that promotes tumorigenesis and tumor progression [17]. Additionally, MUC4 is aberrantly expressed in pancreatic cancer and its expression is upregulated in progressively worsening PanIN lesions [18,19].

Nicotine has also been found to stimulate pancreatic cancer growth, invasion, and metastasis by inducing the expression of osteopontin, a secreted molecule expressed in many cancers. Following nicotine-dependent activation of nAChR, osteopontin confers tumorigenicity to cells, resulting in increased cell survival, cell motility, tumor growth, and metastasis [20,21]. This effect is mitigated in the presence of nAChR antagonists, preventing nicotine-induced osteopontin expression [22].

These pathways represent only a fraction of the pathways involved in cigarette smoke-associated pancreatic damage. The carcinogenic effects that are conveyed to many different types of cancer are not specific to the pancreas. Therefore, pancreas-specific effects of cigarette must be involved, rendering the pancreas susceptible to damage from cigarette smoke. These effects are also mediated by the activation of nAChR that regulate the secretory function of the pancreas. This is evident when CCK-stimulated acinar cells are treated with nicotine, resulting in a reduction of CCK-stimulated amylase secretion [23]. Additionally, it has been shown that chronic nicotine treatment not only reduces the secretion of amylase, but also increases the intracellular amylase content in pancreatic acinar cells [24]. Somewhat similar observations were made by cigarette smoke inhalation over a period of 12 weeks. Cigarette smoke inhalation induced a dose-dependent increase in trypsinogen expression while cigarette smoke inhalation did not influence the expression of genes associated with pancreatic ductal cells [25]. These secretory alterations were associated with focal inflammatory lesions detected throughout the pancreas [26]. When nicotine treatment was performed over a prolonged period in mice carrying a constitutively active *KRAS* gene, comparable effects were observed in the pancreas. Nicotine

treatment in conjunction with active *KRAS*-induced pancreatic acinar cell damage leading to higher grade PanIN lesions and increased acinar-to-ductal metaplasia [27]. This was associated with a loss of *GATA6* expression, which could be reversed by metformin. After full transition to pancreatic cancer cells, nicotine induced a cancer stem cell phenotype by interacting with α7-nAChR and further induced epithelia-mesenchymal transition, promoting cell migration. Similarly, these effects were also reversible with *GATA6* overexpression [27]. These pathways appear to be crucial steps in cigarette smoke-induced pancreatic damage. Another mechanism by which nicotine induces pancreatic cancer progression and metastasis is by inducing MUC4 expression in a dose-dependent manner [16]. Even though pancreatic inflammation and acinar-to-ductal metaplasia are very likely to be associated with pancreatic carcinogenesis, nicotine alone is not the sole factor in pancreatic tobacco-associated carcinogenesis but enhances it occurrence. Acinar cell stimulation plays an important role in these mechanisms since the stimulation of acinar cells by CCK also significantly increased the rate of pancreatic cancer formation indicating that nicotine may enhance the fatal action of carcinogens by altering the secretory function of acinar cells [28].

Other carcinogens are also able to induce acinar to ductal metaplasia. This has been demonstrated in rodent models of ductal adenocarcinoma in which 7,12-dimethylbenz(a)anthracene(DMBA) crystals are surgically implanted in the pancreatic tissue [29]. In this model, histologic alteration of the exocrine pancreas was observed and described as tubular complexes, representative of acinar-to-ductal metaplasia [30].

In summary, experimental evidence of cigarette smoke-induced pancreatic carcinogenesis can be placed into two categories (Fig. 89.1). The first is that carcinogens can induce genetic or epigenetic changes resulting in DNA damage. Second, carcinogens mediated their pharmacologic effects through nACh receptors. The latter can be further subcategorized. The first subset of nAChR-dependent mechanisms centers on the enhancement of pro carcinogenic events mediated by a variety of substances. The second subset of nAChR-dependent mechanisms involves alterations in acinar cell secretory function, contributing to the development of pancreatic inflammation [31,32].

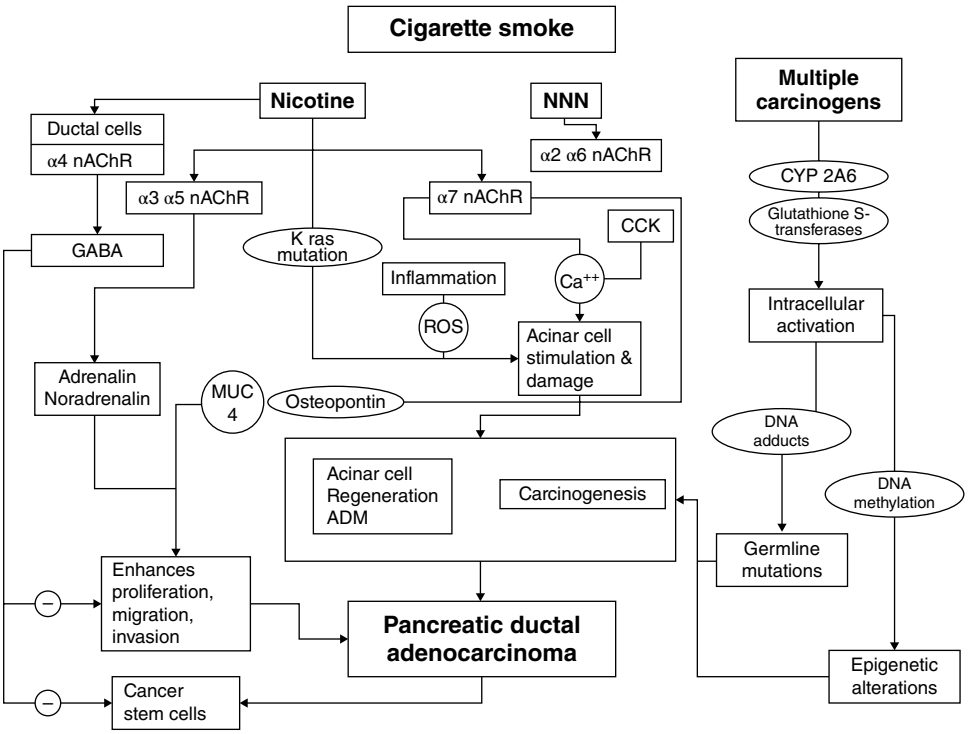


**Figure 89.1** Summary of experimental and clinical data on the effects of cigarette smoking on pancreatic carcinogenesis. The pharmacologic activity of cigarette smoke on the pancreas is mediated by nicotinergic acetylcholine receptors (nAChR) and induces pancreatic acinar cell damage and mediates a variety of adverse events. In addition to that, the carcinogenic action is induced after the intracellular activation of carcinogens by cytochrome P450 enzymes. Glutathione transferases seem to be involved in the intracellular detoxification.

## Clinical Data Supporting the Experimental Findings

Clinical data on cigarette smoke-induced pancreatic damage largely consists of the epidemiologic correlations between smoking, pancreatic inflammation, and cancer. Some of the key elements such as carcinogen accumulation and interference with the regulation of pancreatic enzyme secretion have been confirmed in clinical studies. Prior research has demonstrated that carcinogens do accumulate in pancreatic juice of smokers. In these studies, NNK was detectable in 83% of smokers [33]. Previous studies have also demonstrated that inhaled carcinogens are delivered to the pancreas and that enzymes metabolize these compounds into active electrophiles [34], at which point, they can exert their genotoxic properties within the pancreas [35,36]. As an example of the clinical relevance, the phenotypic variation of carcinogen metabolizing enzymes, such as CYP450 2A6, influenced the pathogenesis of pancreatic cancer. In an adjusted categorical analysis, subjects in the uppermost quartile of CYP2A6 activity carried an 80% greater risk of acquiring pancreatic cancer [37]. Similar observations have been made for glutathione S-transferases (GST), a family of phase II isoenzymes believed to protect cells from reactive chemical intermediates [38]. In this study, the adjusted odds ratios of pancreatic cancer for heavy smokers with the GSTT1-null genotype were 5.0 (95% CI: 1.8–14.5) for women and 3.2 (95% CI: 1.3–8.1) for men, indicating that the combination of heavy smoking and a deletion polymorphism in GSTT1 is associated with an increased risk of pancreatic cancer.

Tobacco-derived carcinogens are undoubtedly involved in the carcinogenesis of pancreatic cancer. $^{32}$P-postlabeling analysis indicates a specific adduct pattern in smokers, increased adducts in pancreatic DNA were observed in smokers but an association with BMI was also observed [39]. No clear association of DNA adducts in the pancreas with the individual smoking history utilizing chromatography has yet been established [40]. This could be due to the relatively limited amount of DNA adducts present or this quantity being below the limit of detection [41]. Independent of detection methods, non-smokers must be also exposed to many environmental carcinogens inducing the formations of DNA adducts similar to those observed in smokers [42].

Similar to experimental observations, cigarette smoke exerts widespread pharmacological effects on the human pancreas which are mediated by nicotine and other tobacco derived carcinogens displaying pharmacologic activities. In the 1970s, the relationship of cigarette smoking with the pancreatic secretion was discovered [43,44]. In a clinical experiment, smoking induced immediate and reproducible effects on the pancreatic secretion in volunteers. After smoking cigarettes, the fluid and bicarbonate secretion was immediately altered and returned to normal within 30–60 minutes. This effect directly correlated with the serum nicotine concentration. In accordance with this observation, cotinine, a derivate of nicotine with a longer half-life, was detected in the pancreatic juice of active smokers with an average concentration of 129 ηg/mL [33]. The concentration of these compounds has not been measured in pancreatic tissue, but the differential expression of nAChR receptors has been demonstrated on human pancreatic acinar and ductal cells [8,14].

The effects of cigarette smoke on pancreatic exocrine function is thought to be responsible for the induction of pancreatic acinar cell damage and has been shown to have a clear association with both acute and chronic pancreatitis [31,45,46]. While a small subset of patients experience inflammation of the entire gland, in most patients, the cigarette smoke induced pancreatic damage is only present in small focal areas of the pancreas where remodeling is occurring at the same time as sample acquisition. Similar to experimental data, an increase in small inflammatory foci with ongoing pancreatic regeneration was observed in humans as well. In this context, focal acinar cell dysplasia has been described at the time of autopsy and in surgical specimens. These acinar cell lesions were found to be acquired and correlated to history of smoking. Additionally, they were detectable in 83% of heavy smokers [47,48]. Acinar cell lesions are also associated with simple and atypical ductal hyperplasia, indicating that either the cigarette smoke induced damage leads to ductal lesions as well, or it can be speculated that these ductal lesions are the result of acinar to ductal metaplasia [49].

## Summary

Evidence today for cigarette smoke-induced pancreatic disease remains incomplete, but available experimental and clinical data proposes potential pathomechanisms of cigarette smoke-induced pancreatic carcinogens that remain to be further investigated in both experimental and clinical studies. The pancreas is susceptible to the effects of carcinogens found in cigarette smoke partly as a result of acetylcholine receptor mediated events, or by mutations, for example, of tumor suppressor genes [50]. These contribute to the induction proliferative signaling pathways and pancreatic inflammation. These events provide a fertile environment for pancreatic ductal adenocarcinoma to develop, at which point the smoking history appears to have no impact on the clinical course [51]. However, patients who continue to smoke following surgical resection of a ductal adenocarcinoma have decreased survival compared to individuals who refrain from smoking [52].

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# 90

# Molecular Understanding of Development of Ductal Pancreatic Cancer

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## Introduction

Pancreatic cancer is predicted to be the second leading cause of cancer death by the year 2030 [1]. A fundamental understanding of the molecular underpinnings of pancreatic cancer will not only provide insight into the pathophysiology driving this neoplasm, but will also provide new tools that can be used to detect early curable pancreatic neoplasms and to treat advanced cancers.

The groundwork for our understanding of the genetic drivers of ductal adenocarcinoma was laid decades ago, but this knowledge has exploded in recent years. The first gene identified as targeted in ductal adenocarcinoma was the *KRAS* oncogene in the mid-1980s [2–4]. It took almost another decade before the *TP53* tumor suppressor gene was shown to be inactivated in most of these cancers [5,6]. In the 1990s a team led by Scott Kern extensively characterized the allelic losses in a series of ductal adenocarcinomas and in so doing identified a number of recurrent genetic alterations, including homozygous deletions on chromosomes 9p, 13q, and 18q, in these cancers—these loci correspond to three additional tumor suppressor gene loci that drive ductal adenocarcinoma [7–9]. The homozygous deletion identified on chromosome 9p proved to target the *p16*/*CDKN2A* tumor suppressor gene, the deletion on 13q led to the discovery of the *BRCA2* gene, and the homozygous deletion on 18q led to the discovery of *SMAD4* (*DPC4*) [10,11]. Thus, by the mid-1990s the four genes most frequently targeted in ductal adenocarcinomas had been discovered (*KRAS*, *TP53*, *SMAD4*, *p16*/*CDKN2A*), as had one of the major familial pancreatic cancer genes (*BRCA2*). Over the ensuing decade, a number of additional genes were found to be targeted in ductal adenocarcinomas, often using candidate gene approaches [12–14]. Most of these proved to be low prevalence genes (altered only in a small fractions of the cancers), such as *BRAF* and *FBXW7* [14].

The completion of the draft map of the human genome was completed in 2001, providing a foundation for dramatically changing the pace of gene discovery in ductal adenocarcinomas [15]. Jones and colleagues used the draft map of the human genome to Sanger sequence the complete exomes of a series of 24 well-characterized ductal adenocarcinomas, providing a first complete catalogue of protein-coding mutations in this cancer type [16]. This work had several important results: the oncogene *KRAS* and the tumor suppressor genes *TP53*, *SMAD4*, and *p16*/*CDKN2A* were confirmed to be the most commonly targeted "mountains" in ductal adenocarcinoma (Table 90.1), and a number of "hills" with less prevalent mutations were also identified (Table 90.2). In addition, the Jones study led to the discovery of a familial pancreatic cancer gene (*PALB2*) [16–18]. For the first time, a comprehensive understanding of the genetic drivers of pancreatic tumorigenesis was possible. A number of large-scale studies followed, and in recent years several groups, including the International Cancer Genome Consortium (ICGC), The Cancer Genome Atlas (TCGA), and a team at Baylor University, have extended Jones' whole exome sequencing study by sequencing the exomes and even genomes of additional ductal adenocarcinomas [19–22]. The time is now ripe to translate this understanding into patient care.

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**Table 90.1** "Mountains" of pancreatic tumorigenesis

| Gene | Chromosome | Gene type | Function | Mechanism of alteration |
|---|---|---|---|---|
| *KRAS* | 12 | Oncogene | MAPK signaling | Point mutation (hotspots) |
| *P16/CDKN2A* | 9 | Tumor suppressor | Cell cycle regulation | Point mutation/LOH, homozygous deletion, methylation |
| *TP53* | 17 | Tumor suppressor | DNA damage response | Point mutation/LOH |
| *SMAD4* | 18 | Tumor suppressor | TGFβ signaling | Point mutation/LOH, homozygous deletion |

LOH, loss of heterozygosity; MAPK, mitogen-activated protein kinase; TGFβ, transforming growth factor β.

**Table 90.2** Well-defined "hills" of pancreatic tumorigenesis

| Gene | Chromosome | Function |
|---|---|---|
| *AKT2* | 19 | PI3K signaling |
| *ARID1A* | 1 | Chromatin remodeling |
| *ATM* | 11 | DNA repair |
| *BRAF* | 7 | MAPK signaling |
| *BRCA2* | 17 | DNA repair |
| *CDK6* | 7 | Cell cycle regulation |
| *FBXW7* | 4 | Cell cycle regulation |
| *GATA6* | 18 | Transcription factor |
| *KDM6A* | X | Chromatin remodeling |
| *MAP2K4* | 17 | MAPK signaling |
| *MET* | 7 | Growth factor signaling |
| *MLL3* | 7 | Chromatin remodeling |
| *MTAP** | 9 | Polyamine metabolism |
| *MYC* | 8 | Cell cycle regulation |
| *ROBO2* | 3 | Axon guidance |
| *SLIT2* | 4 | Axon guidance |
| *SMARCA4* | 19 | Chromatin remodeling |
| *TGFBR1* | 9 | TGFβ signaling |
| *TGFBR2* | 3 | TGFβ signaling |

* Gene often included in p16/CDKN2A homozygous deletions; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; TGFβ, transforming growth factor β.

## Genetic Alterations: The Four Mountains

### *KRAS*

The *KRAS* oncogene is activated in >90% of ductal adenocarcinomas, usually by a point mutation at codon 12, 13, or 61 [23]. *KRAS* gene mutations activate a complex cascade of downstream signaling pathways including the mitogen-activated protein kinase and phosphoinositide 3′-kinase pathways [24–27]. *KRAS* gene mutations also contribute to the "Warburg effect" and increase autophagy in the neoplastic cells [24–26]. The resultant changes caused by *KRAS* gene mutations combine to promote tumorigenesis.

*KRAS* wild-type ductal adenocarcinomas can have other distinctive genetic alterations [14,28]. Some *KRAS* wild-type tumors harbor *BRAF* mutations, and others, as will be discussed in greater detail later, are microsatellite unstable [14,19,28].

### *p16/CDKN2A*

The *p16/CDKN2A* tumor suppressor gene on chromosome 9p is inactivated in 90% of ductal adenocarcinomas [7,29]. In ~40% of the cancers the gene is inactivated by an intragenic mutation in one allele coupled with loss of the second allele (loss of heterozygosity, LOH). In another 40% the *p16/CDKN2A* gene is inactivated by homozygous deletion, and in 10–15% of the cancers it is inactivated by hypermethylation of the *p16/CDKN2A* gene promoter [29,30]. Loss of p16 protein function leads to the loss of a major regulator of the cell cycle. The *MTAP* gene on chromosome 9p is often included in the homozygous deletions that target *p16/CDKN2A* [31]. As will be discussed later, the deletion of *MTAP* has potential therapeutic implications.

### *TP53*

The *TP53* tumor suppressor gene on chromosome 17p is inactivated, usually by an intragenic mutation in one allele coupled with LOH in the remaining allele, in ~75% of ductal adenocarcinomas [16,32]. Loss of p53 function disrupts a number of critical tumor suppressive pathways including response to DNA damage, apoptosis, cell cycle arrest and senescence [33]. Aberrant protein expression patterns, as seen on immunohistochemical assays, are correlated with gene mutation—these include strong diffuse nuclear expression (Fig. 90.1) as well as complete absence of expression.

### *SMAD4*

The *SMAD4* tumor suppressor gene on chromosome 18q is inactivated in ~55% of ductal adenocarcinomas [11]. As noted earlier, *SMAD4* was discovered by Scott

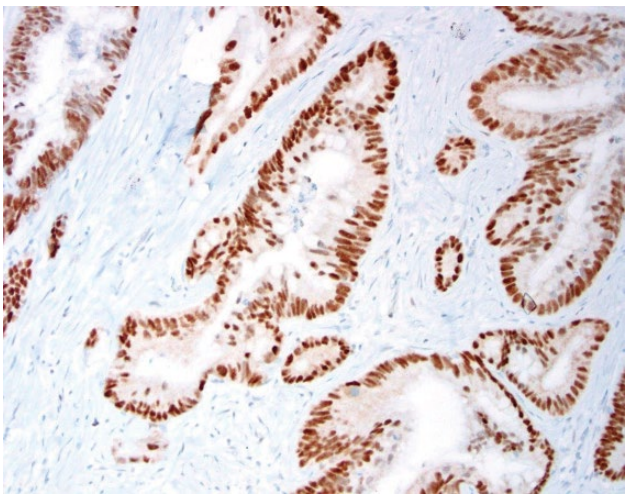

**Figure 90.1** Aberrant p53 protein expression in *TP53* mutant ductal adenocarcinoma. Immunohistochemistry for p53 shows strong diffuse nuclear labeling, which is strikingly different from the occasional weak nuclear labeling seen in the nonneoplastic stromal cells.

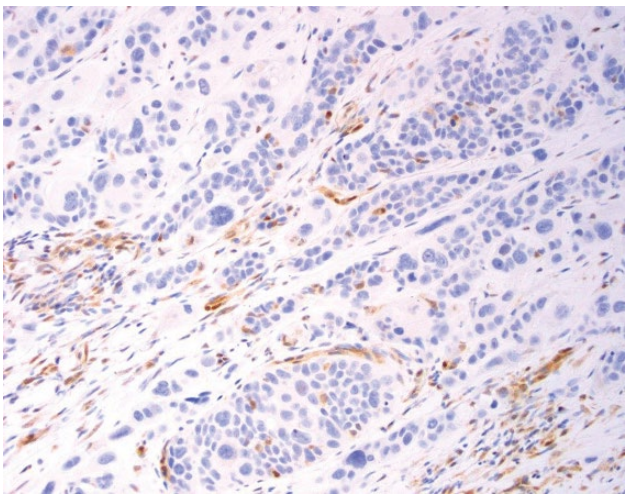

**Figure 90.2** Loss of SMAD4 protein expression in *SMAD4* mutant ductal adenocarcinoma. Immunohistochemistry for SMAD4 shows loss of protein expression in malignant cells, while retained expression in nonneoplastic stromal cells serves as an internal control.

Kern and colleagues as a recurrent homozygous deletion identified using a panel of microsatellite markers [11]. Subsequently, *SMAD4* has been shown to encode a protein that functions in the transforming growth factor-beta (TGF-β) pathway. Immunolabeling for the Smad4 protein is a good surrogate marker for *SMAD4* gene inactivation, as inactivating mutations in *SMAD4* are associated with loss of Smad4 protein expression (Fig. 90.2) [34].

## Genetic Alterations: The Hills

In addition to the four mountains, the four genes targeted in >50% of pancreatic cancers, a growing number of genes have been found that are altered in only a small fraction (usually <10%) of ductal adenocarcinomas (Table 90.2) [16,19–21]. For example, Biankin and colleagues sequenced the exomes of close to 100 ductal adenocarcinomas and reported that genes coding for embryonic regulators of axon guidance, including *ROBO* and *SLIT*, are targeted in a minority of these cancers [20]. Sausen and colleagues report uncommon mutations in chromatin regulating genes (such as *MLL3* and *ARID1A*) that are associated with improved survival [35]. Others have reported focal gene amplifications in ductal adenocarcinomas, including amplification of *MYC*, *GATA6*, *BRAF*, *CDK6*, and *MET* [21,36–38].

## Chromosome Instability

In addition to the specific genes noted earlier that are targeted by focal chromosomal alterations, ductal adenocarcinomas of the pancreas are also characterized by larger chromosome abnormalities [21,39,40]. These larger chromosome abnormalities were first noted in karyotyping studies of pancreatic cancer [39]. Subsequently, the exact loci involved could be defined better in whole genome sequencing studies [21]. These latter studies also showed that chromosome instability is associated with the inactivation of DNA maintenance genes (*BRCA1*, *BRCA2*, or *PALB2*) and a DNA damage repair deficiency mutational signature [21].

## Microsatellite Instability

A small fraction (2–3%) of pancreatic cancers have microsatellite instability, with defective DNA repair pathways leading to a large number of point mutations [28,41,42]. Some pancreatic cancers with microsatellite instability (also known as MSI-high cancers) arise in association with intraductal papillary mucinous neoplasms (IPMN) and others have a characteristic medullary histology that includes poor differentiation, a syncytial growth pattern, and pushing tumor borders (Fig. 90.3) [41]. These carcinomas are important to recognize because, despite their poor differentiation, they are associated with a good prognosis [41,42]. In addition, as will be discussed later, MSI-high pancreatic cancers may be particularly sensitive to immunotherapies [43].

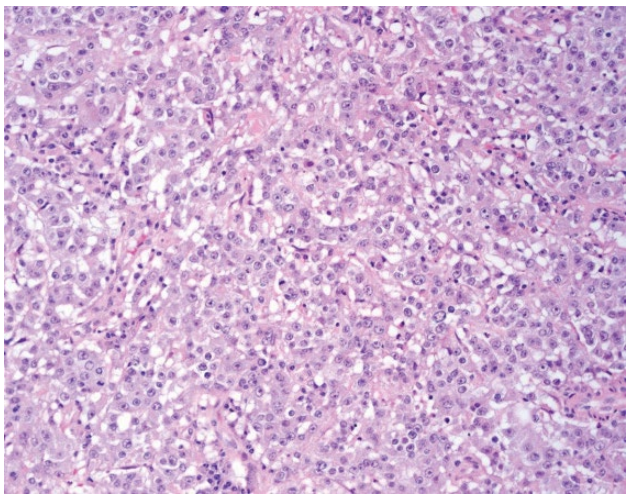

**Figure 90.3** Medullary carcinoma. The characteristic morphology of medullary carcinoma (poor differentiation, syncytial growth, pushing borders) is frequently seen in tumors with microsatellite instability.

## Mitochondrial Gene Mutations

Although we tend to focus on the nuclear genome, eukaryotic cells also have a mitochondrial genome. Jones and colleagues sequenced the mitochondrial genome (mtDNA) of a series of pancreatic cancers and homoplasmic mtDNA somatic mutations were identified in nearly all of the cancers [44]. While it could not be determined whether any of these mtDNA mutations were driving the neoplastic process, Jones and colleagues were able to show that mtDNA is greatly (six- to eightfold) increased in ductal adenocarcinoma cells relative to normal cells. This finding suggests that mtDNA mutations may be easier to detect than nuclear mutations, and that mtDNA mutations may be useful in screening tests [44,45].

## Expression Changes

A number of genes are overexpressed in ductal adenocarcinomas relative to normal nonneoplastic pancreatic ductal cells [46–52]. Many of these overexpressed genes were identified at the mRNA level using techniques such as serial analysis of gene expression (SAGE) and expression microarrays, and then protein overexpression was confirmed using Western blotting or immunohistochemical labeling [46–52]. Other overexpressed proteins were discovered using mass spectrometry and other proteomic approaches [53]. The list of genes and proteins overexpressed in ductal adenocarcinomas is long, and includes mesothelin, claudins, annexins, S-100-related proteins, and others [48,54–59]. Pandey and colleagues have reviewed the literature and established a centralized resource for the collection and sharing of these overexpressed genes [60,61]. As discussed later, differentially expressed genes may be useful targets for developing early detection tests and for novel therapies. The technologies to distinguish quantitatively among peptides are now so refined that normal proteins can be distinguished from mutant proteins created by some of the DNA mutations discussed earlier [62].

In addition to the overexpressed genes, a number of genes are downregulated in ductal adenocarcinomas. Promoter hypermethylation often accounts for this downregulation [63]. Genome-wide analyses of DNA methylation in ductal adenocarcinomas have identified over 1,000 genes that are differentially methylated in pancreatic cancer relative to normal pancreatic ductal cells, and many of these differentially methylated genes are differentially expressed at the protein level [63,64].

MicroRNA are small noncoding RNA that have emerged as important regulators of a number of cell functions, and the expression of a number of microRNA is dysregulated in ductal adenocarcinomas of the pancreas [65]. These microRNA include miR-21, miR-101, miR-155, miR-192, miR-193, miR-194, miR-196, miR-210, and miR-335 [65,66]. Some of these microRNA have been proposed as prognosticators and others as potential therapeutic targets in ductal adenocarcinomas [67].

## Precursor Lesions

Most invasive ductal adenocarcinomas of the pancreas are widely metastatic and incurable at the time of diagnosis [68]. We believe that early detection is one of the best hopes to impact the dismal prognosis associated with these cancers. An understanding of the biology of the precursor lesions that give rise to invasive carcinoma is therefore essential.

Three precursor lesions are currently recognized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMN), and mucinous cystic neoplasms (MCN) (Table 90.3). A number of studies have examined the genetic alterations and gene expression changes in these precursors, and increasing degrees of dysplasia are associated with the accumulation of genetic alterations and changes in gene expression [66,69–71]. Lesions with high-grade dysplasia have many of the same changes that are found in invasive ductal adenocarcinomas [66,69–71]. For example, most of the microRNA overexpressed in invasive ductal adenocarcinoma are also overexpressed in precursor lesions with high-grade dysplasia. These findings suggest that gene mutations and changes in expression may be useful markers for the early detection of pancreatic neoplasms [66].

**Table 90.3** Precursors to ductal adenocarcinoma

| Precursor | Abbreviation | Location | Size | Key genetic alterations |
|---|---|---|---|---|
| Pancreatic intraepithelial neoplasia | PanIN | Head = Tail | <0.5 cm | Early: *KRAS*, *CDKN2A* Late: *TP53*, *SMAD4* |
| Intraductal papillary mucinous neoplasm | IPMN | Head > Tail | ≥1 cm | Early: *KRAS*, *GNAS*, *RNF43*, *CDKN2A* Late: *TP53*, *SMAD4* |
| Mucinous cystic neoplasm | MCN | Tail > Head | Broad range | Early: *KRAS*, *RNF43*, *CDKN2A* Late: *TP53*, *SMAD4* |

## Neoplasms with Acinar Differentiation

Although the vast majority of "pancreatic cancers" are ductal adenocarcinomas, malignancies with acinar differentiation do occur, and these cancers are clinically and molecularly unique [72]. Acinar cell carcinomas form solid masses in older adults and have a poor prognosis. Recent whole exome sequencing studies have revealed that acinar cell carcinomas exhibit striking genomic stability, commonly having either microsatellite instability or chromosomal instability [72]. There is striking heterogeneity in the genes altered in individual tumors, with no single gene mutated in >30% of cancers [72]. Uncommon mutations occurred in well-characterized drivers of ductal adenocarcinoma (*SMAD4*) and pancreatic cystic neoplasms (*GNAS*), as well as genes commonly altered in other tumor types (*APC*, *BRAF*). Pancreatoblastoma, the most common pancreatic tumor in childhood, can contain a variety of cell types but at a minimum contains an acinar component and squamoid nests. These neoplasms contain far fewer somatic mutations than acinar cell carcinomas, and alterations in the Wnt pathway (*APC*, *CTNNB1*) as well as loss of a highly imprinted region on chromosome 11p are the most common genetic alterations [72,73].

## Clinical Applications

These are exciting times. We are on the cusp of translating our growing understanding of the underlying biology of pancreatic cancer into patient care. We anticipate that in the near future, new molecular approaches will be developed to enhance the early detection, diagnosis, treatment, and monitoring of pancreatic cancer. Let us give examples of each of these.

Early detection is one of the most promising areas for the translation of molecular genetics into patient care. For example, mutant *GNAS* shed from noninvasive IPMN can be detected in secretin-stimulated pancreatic secretions (pancreatic juice) collected at the time of endoscopic ultrasound (EUS) [74]. Similarly, mutant *KRAS* shed from early stage (operable) ductal adenocarcinomas of the pancreas is detectable in the blood [75]. Panels of new biomarkers such as tumor-specific genetic mutations, applied to the right biosamples, will provide exciting new opportunities for the early detection of curable pancreatic neoplasms.

Molecular genetics can also be used to supplement tissue diagnoses. For example, in patients with a known pancreatic cancer it can be difficult to determine if an adenocarcinoma in a distant site, such as the lung, represents a metastasis or a new primary. In these instances, the loss of Smad4 expression, as determined by immunohistochemical labeling, supports the diagnosis of a metastasis from a pancreatic primary over a second lung primary (Fig. 90.2) [34].

Notable advances have also been made in the application of molecular genetics to personalized therapy of ductal adenocarcinomas. Five examples include: (i) Approximately 2–3% of pancreatic cancers are microsatellite unstable (MSI-high), and these cancers appear to be remarkably sensitive to immunotherapy, particularly with PD-1 blocking agents [43]. (ii) Most pancreatic cancers overexpress mesothelin and a number of anti-mesothelin specific vaccines have been developed [76,77]. (iii) Pancreatic cancers with a mutation signature indicative of DNA damage repair deficiency (including those with *BRCA2* mutations) are likely to respond to specific chemotherapeutic regimens, including platinum agents and poly(ADP ribose) polymerase (PARP) inhibitors [78,79]. (iv) *KRAS* wild-type ductal adenocarcinomas often harbor *BRAF* mutations, and these *BRAF* mutant cancers are highly sensitive to targeted BRAF inhibition [19]. (v) As mentioned earlier, the *MTAP* gene on chromosome 9p is homozygously deleted with *P16/CDKN2A* in 30–40% of pancreatic cancers. This gene codes for the enzyme methylthioadenosine phosphorylase (MTAP), and MTAP-deficient cells may be differentially sensitive to methylthioadenosine (MTA, the substrate for the MTAP enzyme) and to small molecular inhibition of protein arginine methyltransferase 5 (PRMT5, an enzyme upstream from MTAP) [80,81].

Finally, a molecular genetics approach can be used to monitor patients for response to therapy. Neoplasms release mutant DNA into the circulation (circulating

tumor DNA, ctDNA) and this ctDNA can be quantified [35,75]. Velculescu and colleagues have shown that monitoring ctDNA can be used to quantify the response of a neoplasm to therapy.

## Summary and Conclusions

These are the best of times. Hundreds of ductal adenocarcinomas of the pancreas have been sequenced, and the fundamental drivers of tumorigenesis in the pancreas are now defined. These drivers give us new tools for the early detection of pancreatic neoplasms, and it is hoped that these early detection efforts will save lives, especially when applied to high-risk populations such as individuals with a deleterious germline mutation in a familial pancreatic cancer gene. Despite our best efforts at early detection, we recognize that most patients will still be diagnosed with an invasive carcinoma, and new approaches to personalized therapies are needed. These may include immunotherapy for MSI-high cancers and PARP inhibitors for *BRCA2* mutant cancers. In the near future we will also be able to follow the effectiveness of new therapies using novel approaches such as monitoring circulating tumor DNA (ctDNA). The future is bright!

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# Familial Pancreatic Cancer

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## Introduction

Pancreatic cancer, like all cancers, is fundamentally a genetic disease driven by both acquired and inherited genetic changes. Having a family history of pancreatic cancer is one of the strongest risk factors for the development of pancreatic cancer [1,2].

## Familial Pancreatic Cancer

Familial pancreatic cancer is defined as a kindred in which a pair of first-degree relatives have been diagnosed with pancreatic cancer (i.e., a parent and child or a pair of siblings). Observational studies suggest that having at least one single family member with pancreatic cancer increases the risk of pancreatic cancer 1.5- to 13-fold [1,3–11]. Prospective studies within the National Familial Pancreatic Tumor Registry have shown that first-degree relatives of familial pancreatic cancer patients (individuals with at least two family members with pancreatic cancer) have a 6.79-fold, 95% CI: 4.54–9.75 increased risk of pancreatic cancer [1].

Unlike other inherited cancer syndromes where there is a profound difference in the mean age of onset between the familial and sporadic forms of the disease, the age of onset of pancreatic cancer in patients with a family history of pancreatic cancer is at most 6 years younger than those with sporadic disease [12,13], with other studies showing no age difference [9,14].

In addition to higher pancreatic cancer risk, relatives of familial pancreatic cancer patients have a higher risk of other cancers. Relatives of familial pancreatic cancer patients have a significantly increased risk of dying from breast (wSMR 1.66, 95% CI: 1.15–2.34), ovarian (wSMR 2.05, 95% CI: 1.10–3.49), and bile duct cancers (wSMR 2.89, 95% CI: 1.04–6.39). Relatives of sporadic pancreatic cancer patients are at higher risk of bile duct cancer (wSMR 3.01, 95% CI: 1.09–6.67) [15]. Other studies also showed pancreatic cancer patients are more likely to report a family member with prostate cancer (OR 1.45, 95% CI: 1.12–1.89) [11] or liver carcinoma (SIR 2.70, 95% CI: 1.51–4.46) [16].

## Pathology of Familial Pancreatic Cancer

The pathologic phenotype of cancers that develop in individuals with a hereditary cancer syndrome can differ from the phenotype of cancers that develop in patients with apparently sporadic disease, such as mismatch repair deficient cancers among Lynch syndrome patients [17,18], or an excess of triple-negative breast cancers among *BRCA1* mutation carriers [19]. In contrast, familial and apparently sporadic pancreatic cancer appear remarkably similar. A review, blinded to family history, of 519 familial and 651 sporadic pancreatic cancers [20] reported no statistically significant differences in histologic subtypes between familial and apparently sporadic invasive pancreatic cancers. Additionally, among resected tumors there were no significant differences in mean tumor size, location, perineural invasion, angiolymphatic invasion, lymph node metastasis, or pathologic stage. The somatic genetic profile of familial pancreatic cancer does not differ from that of apparently sporadic cancer [12]. In combination, these data further support the finding that the etiology of familial and sporadic pancreatic cancer is very similar.

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In contrast, there is evidence supporting an increased prevalence of pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasia in the pancreata of individuals with familial pancreatic cancer compared to those with sporadic disease. Familial pancreatic cancer patients had a significantly higher rate of PanIN per square centimeter 2.75 (95% CI: 2.05–3.70; adjusted for age) than patients with sporadic pancreatic cancer. The precursor lesions observed in familial patients were more advanced than those observed in patients with sporadic disease, relative rate of PanIN-3 lesions 4.20 (95% CI: 2.22–7.93) and the observation of high-grade IPMN was limited to familial cases [21].

## Predisposition Genes

The ability to understand the inherited genetic variation that increases risk of pancreatic cancer is hindered by its underlying genetic heterogeneity [22]. Advances in both genotyping and sequencing technology has led to the identification of several new high-penetrance mutations associated with pancreatic cancer risk [22–24] and common genetic variation associated with an increase in pancreatic cancer risk [25–28]. However, mutations in the high-penetrance genes that are firmly associated with pancreatic cancer explain only about 20% of the familial clustering of pancreatic cancer and the causative mutations have yet to be identified in ~80% of familial pancreatic cancer kindreds. This 80% is likely due to a combination of high-penetrance mutations, polygenic effects, and environmental effects. For the 20% of familial pancreatic cancer kindreds where a causative mutation has been identified, knowledge of the precise genetic mutation can help guide therapeutic decisions for those who develop pancreatic cancer and early detection screening choices for at-risk relatives. Examples include: early detection screening clinical trials using imaging techniques for patients who have a strong family history of pancreatic cancer and/or carry germline mutations in established familial pancreatic cancer genes [29–33], increased sensitivity of *BRCA2* or *PALB2* deficient cancers to Parp inhibitors (PARP) or Mitomycin C [34–37], and improved survival of pancreatic cancer patients with a family history of breast, ovarian, or pancreatic cancer when treated with platinum-containing agents [38].

### *BRCA2*

Of the individuals who undergo germline genetic testing of pancreatic cancer, mutations in *BRCA2* account for the largest proportion of individuals with identifiable mutations [39]. Mutations in the *BRCA2* gene are best known for predisposing to breast and ovarian cancers yet carriers are also at increased risk of prostate and pancreatic cancer. The first report of an increased frequency of *BRCA2* mutations in pancreatic cancer was by Goggins et al., who reported deleterious *BRCA2* mutations in 7% of pancreatic cancer patients, unselected for family history [40]. *BRCA2* mutation prevalence has been shown to vary somewhat by family history with prevalence estimates as high at 16% for pancreatic cancer patients reporting three or more family members with pancreatic cancer [41], 12% in German pancreatic cancer patients from families with a least two pancreatic cancers [42], and 6% among US and Canadian pancreatic cancer patients with a first- or second-degree relative with pancreatic cancer [43]. Like the initial report by Goggins et al., more recent studies have also demonstrated that a substantial fraction, up to 3.6%, of pancreatic cancer patients, unselected for family history, carry deleterious mutations in *BRCA2* [44]. While some families found to have deleterious *BRCA2* mutations report a family history of breast and/or ovarian cancer, many do not [40,41]. Deleterious *BRCA2* mutations have also been reported in 4.6% of resected Ashkenazi Jewish pancreatic cancer patients, irrespective of family history of cancer [45]. Studies of the lifetime risk of pancreatic cancer among *BRCA2* carriers are limited to families ascertained based on a history of breast/ovarian cancer, and suggest a 3.51- to 5.79-fold increased risk of pancreatic cancer [46,47].

### *BRCA1*

Individuals who carry deleterious mutations in *BRCA1* have also been shown to be at increased risk of pancreatic cancer. However, risk of pancreatic cancer in *BRCA1* carriers is thought to be less than that of *BRCA2* carriers. Studies of the lifetime risk of pancreatic cancer in *BRCA1* carriers are limited to families ascertained based upon a history of breast and/or ovarian cancer. Risk estimates range from 2.26- to 4.11-fold [47,48]. While not all studies report an excess of *BRCA1* mutations among patient with pancreatic cancer [45,49], other studies have reported a prevalence of 1.2% in patients with familial pancreatic cancer [39]. As with *BRCA2*, the lack of a reported family history of breast and/or ovarian cancer does not rule out the presence of a deleterious *BRCA1* mutation.

### *PALB2*

Mutations in the *PALB2* gene, a binding partner of *BRCA2*, have also been associated with pancreatic cancer risk. While the initial reports suggested that up to 3% of FPC patients carry deleterious *PALB2* mutation [23], subsequent studies suggest the prevalence may be closer to 1% [39,50,51].

### *ATM*

Recently, mutations in the DNA repair gene *ATM* have also been associated with familial pancreatic cancer. Approximately 2.6–3.4% [22,24] of patients with familial pancreatic cancer harbor deleterious mutations in *ATM*. Mutations in *ATM* have also been reported in apparently sporadic pancreatic cancer patients [52].

### *CDKN2A*

Germline *p16/CDKN2A* mutations have been reported in 2.5% of patients with familial pancreatic cancer [39] and are associated with a 38-fold increased risk of pancreatic cancer [53]. Mutation carriers have a lifetime risk of pancreatic cancer of 17% [54,55].

### Lynch Syndrome

Individuals with Lynch syndrome have been shown to have a 3.68% (95% CI: 1.45–5.88) risk of pancreatic cancer by age 70 [56].

### Peutz–Jeghers

Individuals with Peutz–Jeghers syndrome have a remarkably high risk of 11–32% [57] of developing pancreatic cancer [58,59].

### Hereditary Pancreatitis

The risk of developing pancreatic cancer is extremely high among individuals with hereditary pancreatitis, risk by age 70 is 30–40% [60,61]. Individuals with hereditary pancreatitis who smoke develop the disease 20 years prior to non-smokers [61]. A portion of patients with hereditary pancreatitis have inherited mutation in the *PRSS1* genes [62–64].

## Common Genetic Variants

In addition to mutations in high-penetrance genes, several recent genome-wide association studies have identified common variants in the following regions as also significantly associated with pancreatic cancer risk: 9q34(*ABO*), 13q21, 1q31(NR5A2), 5p15.33 (*CLPTM1L* and *TERT*)), 7q32.3, 16q23.1 (*BCAR1/CTRB1/CTRB2*), 13q12.12 (*PDX1*), 22q12.1 (*ZNRF3*), 2p13.3 (near *ETAA1*), 3q29 (*TP63*), 7p13 (*SUGCT*), 17q25.1 (*LINC00673*) [25–28,65]. Individually, these variants have only a small effect on pancreatic cancer increase with per-allele odds ratios ranging from 1.1 to 1.3. Many of these same variants have also been shown to have a similar association with familial pancreatic cancer [66].

## Summary

Inherited genetic variants play an important role in pancreatic cancer risk. Individuals with a family history of pancreatic cancer have been shown to be at increased risk of developing pancreatic cancer as well as other cancers. The genetic underpinnings of the familial clustering of pancreatic cancer is highly heterogeneous. However, an understanding of the causative genetic mutations can help inform early detection screening in at-risk individuals and treatment decisions for those who do develop pancreatic cancer.

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# 92

# Pathology of Exocrine Pancreatic Tumors

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## Introduction

The bulk of the normal pancreas is composed of acinar cells, yet the majority of neoplasms of the pancreas have ductal differentiation. The classification of exocrine neoplasms of the pancreas is based on more than a century of integrating gross and microscopic findings with patient outcome. The recent introduction of molecular genetics and gene expression technologies has supported this gross and histologic classification: most pathologically defined neoplasms of the pancreas have distinct genetic and gene expression profiles [1,2].

The purpose of this chapter is to describe the pathologic features of exocrine neoplasms of the pancreas, with emphasis on clinical correlates.

## Ductal Adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC), commonly known as "pancreatic cancer," is defined as a malignant gland-forming epithelial neoplasm of the pancreas [3]. Despite many years of study, the 5-year survival rate remains at a dismal 8% [4,5]. This high mortality rate is in large part due to widespread local and metastatic disease at the time of diagnosis, combined with the poor response of most PDACs to existing therapies [6].

Endoscopic ultrasonography (EUS) can be used to define the local extent of disease and to biopsy lesions by fine-needle aspiration (FNA), a technique that has a high sensitivity for diagnosis of PDACs when performed by experienced endoscopists [7]. Because only 15–20% of PDACs are resectable at diagnosis, FNA is often the only way for most patients to receive a definitive diagnosis prior to treatment [6].

### Gross

PDACs are grossly white or gray sclerotic lesions that form firm, ill-defined masses that subtly infiltrate the normal soft, lobulated yellow pancreatic parenchyma (Fig. 92.1). These carcinomas may invade or obliterate the common bile duct, the main pancreatic duct, or both, which results in upstream dilatation of the affected duct and fibrous atrophy of the pancreatic parenchyma. The majority of PDACs occur in the pancreatic head, followed by the body and tail; there are even rare case reports of PDAC arising in heterotopic pancreas [3,8].

Careful gross examination of pancreaticoduodenectomy (Whipple) specimens is critical for margin assessment and for accurate grading and staging of the tumor. Margins to investigate include the common bile duct (usually taken parallel to the margin as a "shave" section), the pancreatic neck/distal pancreatic margin (shave), the proximal and distal bowel margins, and the uncinate/retroperitoneal/superior mesenteric artery margin (radial). The pancreatic neck and retroperitoneal margins are important in distal pancreatectomies. Patients with no residual tumor (R0) have a better prognosis than those with microscopically positive margins (R1) [9,10]. Adequate sampling of the primary tumor is important for grading of the carcinoma because overall grade depends on the highest grade component of the tumor. Finally, assessment of at least 12 pancreatic lymph nodes is important for staging, although in general, the more lymph nodes that can be examined, the more accurate the prognosis given to the patient [11,12].

### Histology

PDACs are characterized by haphazardly arranged glands and duct-like structures embedded in dense desmoplastic stroma (Fig. 92.2a). The cells lining the glands may be

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

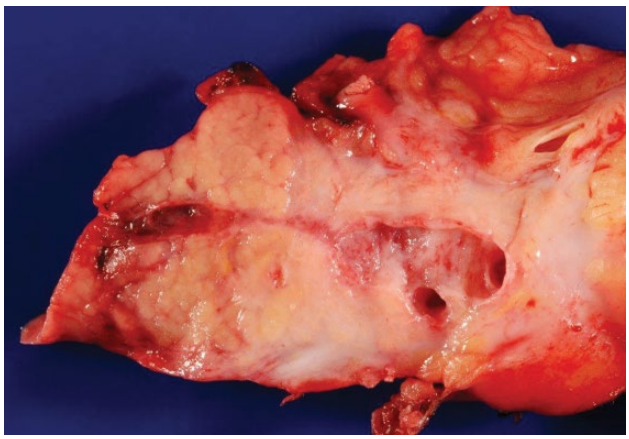

**Figure 92.1** Pancreatic adenocarcinoma. This photograph of a pancreatic specimen demonstrates the obstruction caused by pancreatic adenocarcinoma. The pancreatic duct is patent at its most proximal end (left) and is surrounded by normal tan-yellow, lobulated pancreatic parenchyma. Moving distally (right), the duct narrows and is surrounded by pale tan-white tissue, a mixture of adenocarcinoma and desmoplastic stroma. The obstruction has caused significant dilation of distal ducts, which are completely surrounded by the white fibrotic tissue of chronic pancreatitis.

cuboidal or columnar and often have intracytoplasmic mucin. Two histologic features stand out in PDAC. First, the neoplastic cells are extremely infiltrative. Perineural and intravascular invasion are present in practically all cases (Fig. 92.2b). The perineural invasion may explain some of the pain experienced by patients with PDAC, and nerves also serve as pathways for neoplastic spread beyond the pancreas [13]. Vascular invasion often leads to widespread dissemination of the neoplastic cells to other organs, particularly the liver. PDAC can grow into the lumina of vessels in a very distinctive way. Instead of forming a tumor thrombus, the neoplastic cells of PDAC can flatten out and grow along the endothelial surface of a vessel, mimicking the appearance of a duct (Fig. 92.2c) [14]. PDAC can also grow into pre-existing pancreatic ducts in a similar fashion. This extension of the malignancy along ducts is referred to as "cancerization" of a duct. An abrupt transition from benign to malignant cytology favors cancerization (Fig. 92.2d) [15]. A second striking feature of PDAC is the dense, desmoplastic stroma. This stroma explains the firm consistency of PDAC, and it has been suggested that the stroma may impede the delivery of chemotherapy to the neoplastic cells [16–18].

Histologic grading of PDAC takes into account both cytologic and architectural features of the malignancy. PDACs that resemble normal pancreatic ducts are designated "well differentiated," while those that do not form glands, or which form poorly-formed glands, are designated as "poorly differentiated." When more than one grade is present in a tumor, the highest/worst grade should be given; this grade drives prognosis [19,20]. Well-differentiated PDAC can be quite bland by histology with well-formed ductular structures and relatively uniform nuclei. Well-differentiated PDAC can be histologically distinguished from the reactive glands of chronic pancreatitis using "architectural" features: loss of normal lobular architecture, incomplete ductules, and the presence of ducts next to muscular arteries. Other helpful features include necrosis within glandular lumina, perineural invasion, and vascular space invasion [16]. A particularly tricky histologic variant of well-differentiated PDAC is the "large duct" variant, which can mimic cystic neoplasms grossly and histologically. The glands of the large duct variant form irregular dilated structures lined with a mucinous epithelium. Again, the clues to the diagnosis of an invasive PDAC are primarily architectural: loss of lobular organization and large ducts that dissect through a desmoplastic stroma [21].

Moderately differentiated PDAC has greater variation in cytologic appearance and increased numbers of mitotic figures. Poorly differentiated PDAC is defined by the presence of solid sheets and/or individual neoplastic cells that range in morphology from small cells with scant cytoplasm to larger bizarre cells with abundant eosinophilic cytoplasm. Histologic grading is important because the prognosis of a poorly differentiated PDAC is significantly worse than that of a well or moderately differentiated one [3,20].

Gene expression in PDAC is important for multiple reasons. First, the protein products can be interrogated for diagnostic purposes. These include keratins 7 and 19, carcinoembryonic antigen (CEA), mesothelin, and mucin 1 (MUC1). Second, several genes are known to be mutated as part of pancreatic carcinogenesis. These provide potential pathways for therapeutic targets and include *KRAS, SMAD4/DPC4*, and *p16/CDKN2A*. Finally, genetic information from PDAC has allowed for advances in the understanding of and screening for familial PDACs.

## Histologic Variants of Ductal Adenocarcinoma

Several morphologic variants of PDAC with distinct clinical features have been described.

### Adenosquamous Carcinoma

Adenosquamous carcinoma is, as the name suggests, an adenocarcinoma with a significant component with squamous differentiation (at least 30%). If no adenocarcinoma component can be found on extensive sampling, a metastasis from a primary squamous cell carcinoma from another organ must be considered. Patients with adenosquamous carcinoma of the pancreas have a worse prognosis when compared to patients with PDAC, but recent studies have reported that some adenosquamous carcinomas respond to platinum-containing chemotherapies [22,23].

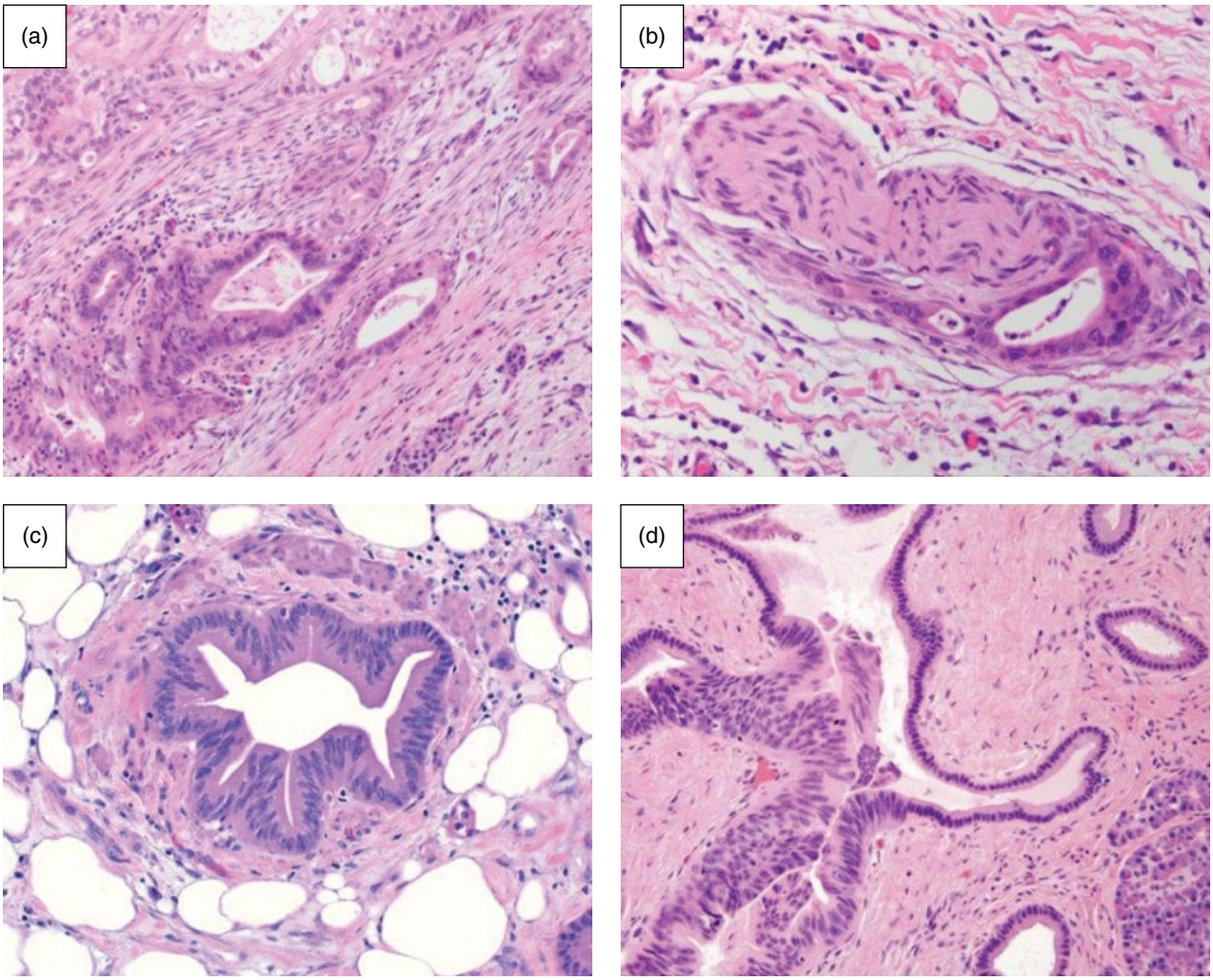


**Figure 92.2** Pancreatic adenocarcinoma (a) demonstrates tubular or glandular formation on histology. The nuclei are enlarged (compare to residual endocrine cells in bottom right corner of the photomicrograph) and hyperchromatic. The cytoplasm of PDAC is often eosinophilic but may also have a cleared appearance. The presence of desmoplastic stroma may be helpful to diagnose invasion in small biopsies. Perineural invasion (b) is a commonly seen feature of PDAC and may explain the pain experienced by patients. Vascular invasion (c). Cancerization of ducts is another interesting growth pattern of PDAC in which the adenocarcinoma tracks along and replaces existing ductal epithelium (d).

#### Colloid Carcinoma

Colloid, or mucinous noncystic, carcinoma is a variant of PDAC associated with intestinal-type intraductal papillary mucinous neoplasms (IPMNs, discussed later). In this subtype pools of mucin dissect through stroma, and associated neoplastic epithelium either lines the mucin pools or floats within the mucin. Care must be taken not to overcall a ruptured cyst with mucin extruded into the stroma with a truly invasive colloid carcinoma. Malignant epithelium must be seen with the mucin for a diagnosis of invasion [24].

#### Medullary Carcinoma

Like its counterpart in other organs, this variant is characterized by the syncytial growth of poorly differentiated epithelioid neoplastic cells with large nuclei. Medullary carcinomas also have "pushing" rather than infiltrating borders, and there is often a brisk inflammatory infiltrate of predominately lymphocytes surrounding and infiltrating into the tumor, but fibrous stroma is scant [25]. Medullary carcinomas are important to recognize for three reasons. First, despite their poor differentiation, they are associated with a good prognosis [26]. Second, patients with a medullary carcinoma are more likely to have a family history of cancer [25]. Third, medullary carcinomas are more likely than ductal adenocarcinomas to have the genetic change of microsatellite instability (mismatch repair defect) [27]. Not only may these mismatch repair deficient PDAC be the first presentation of Lynch syndrome [28,29], but new treatment options such as PD-1 inhibitors may be effective in mismatch repair deficient malignancies [30].

#### Undifferentiated Carcinoma

Undifferentiated carcinomas are composed of predominantly spindled cells or bizarre large cells without a clear direction of differentiation. A lower grade component of conventional PDAC can often be found in these neoplasms, but the histologic grade and prognosis are defined by the undifferentiated "grade 4" component [3,31]. Undifferentiated carcinomas are less cohesive than typical PDAC, a feature that can be demonstrated by loss of e-cadherin expression and which may contribute to the extremely poor prognosis of this variant: the mean survival is less than 1 year [32].

#### Undifferentiated Carcinoma with Osteoclast-Like Giant Cells

Undifferentiated carcinoma with osteoclast-like giant cells is a distinctive neoplasm characterized by the presence of numerous intratumoral multinucleated nonneoplastic giant cells. Admixed with these giant cells are undifferentiated spindled or bizarre malignant cells that often, but not always, label with antibodies to keratins by immunohistochemistry. The giant cells express histiocytic markers, such as CD68. Genetic analyses of single cells microdissected from these carcinomas have shown that the multinucleated giant cells are not neoplastic, but that the undifferentiated cells in between the giant cells are [33]. As is true for undifferentiated carcinomas, the prognosis of patients with an undifferentiated carcinoma with osteoclast-like giant cells is poor, with mean survival of less than 1 year [34,35].

#### Uncommon Variants

The hepatoid and signet ring cell variants of PDAC are unique in that they can resemble metastases from other organs to the pancreas. As the name suggests, the hepatoid variant consists of polygonal eosinophilic cells that mimic a hepatocellular carcinoma and that may even label with hepatocyte antigens, such as Hep-Par and α-fetoprotein [36,37]. Metastasis to the pancreas from the liver must be ruled out before a diagnosis of primary hepatoid PDAC is rendered [3].

The signet ring variant of PDAC is characterized by cells that contain intracytoplasmic mucin with indented and displaced nuclei. The neoplastic cells grow as single, infiltrating cells rather than in well-formed glands or sheets [38]. This carcinoma most closely mimics lobular breast carcinoma or diffuse gastric carcinoma, both of which should be considered in the differential for a malignancy of this morphology.

#### Ductal Malignancies with Mixed Differentiation

Carcinomas of the pancreas can rarely have multiple different directions of differentiation. These include mixed ductal-neuroendocrine carcinoma and mixed ductal-neuroendocrine-acinar carcinoma. Diagnosis of a "mixed" carcinoma requires that at least one third of the malignancy be composed of each neoplastic component. The prognosis for patients with a mixed carcinoma is generally driven by the worst component, in these cases, the PDAC [39,40].

#### Staging

The staging of PDAC and its variants by the WHO and the American Joint Committee on Cancer, 7th edition, takes into account the size of the malignancy, the extent of local direct spread, regional lymph node involvement, and distant metastases (the TNM system) [3,41]. Questions often arise when attempting to differentiate a T2 (tumor limited to the pancreas), from a T3 (tumor in peripancreatic tissue). Because there is no clear histologic demarcation of the edge of the pancreas, and because bouts of malignancy-induced pancreatitis distort the relationship between the pancreas and surrounding adipose tissue, the 8th edition AJCC T staging places greater emphasis on size of the neoplasm.

## Cystic Neoplasms

### Intraductal Papillary Mucinous Neoplasm

The intraductal papillary mucinous neoplasm (IPMN) is a mucin producing, duct-based, usually papillary neoplasm that, by definition, is greater than 1.0 cm [15,42]. IPMN may arise in the main pancreatic duct or within a branch duct. Main-duct IPMNs are more likely to be symptomatic and to progress to invasive carcinoma [43]. IPMNs are often multifocal, and patients are at risk for synchronous and metachronous disease. Genetic analyses have suggested that this multifocality can be caused by intraductal spread of neoplastic cells or by genetically distinct and physically separate neoplasms. Because of this multifocality, patients who undergo partial pancreatectomy for IPMN remain at risk for additional neoplastic cysts and even PDAC in their remnant pancreas [44]. EUS-guided biopsy with sampling of cystic fluid for cytology and molecular studies can be important for preoperative diagnosis and planning [45,46].

#### Gross

Main-duct IPMNs diffusely dilate the main pancreatic duct. Long finger-like papillae can often be seen projecting into the duct, and the duct typically contains thick, tenacious mucin. Branch-duct IPMNs, by contrast, more often appear as a small group of cysts, often compared to a cluster of grapes, adjacent to but not involving the main duct. Many IPMNs are mixed and involve both main and

branch ducts [42]. Foci of dense sclerosis adjacent to an IPMN suggest the possibility of an associated invasive adenocarcinoma. For this reason, and because invasion can be focal, the general rule for pathologic examination of IPMNs is very extensive, if not complete, submission for histology [47].

**Histology**

Histologically, the dilated ducts of IPMNs are lined by columnar mucin-producing neoplastic epithelial cells that may have intestinal, gastric, biliary, or oncocytic type differentiation (Fig. 92.3a–d). A single IPMN may have mixed differentiation, making the correlation between subtype and prognosis all the more complicated [42].

Intestinal-type IPMNs have interspersed goblet cells, typical of intestinal epithelium, and immunolabel with antibodies to MUC2, MUC5AC, and CDX-2 [42]. Of interest, many intestinal-type IPMNs have been found to harbor *GNAS* gene mutations [48]. Early somatic *GNAS* mutations are the underlying genetic defect in McCune-Albright syndrome, and IPMNs are known to be associated with this disorder [49].

Gastric-type IPMNs have small nuclei with an apical, eosinophilic mucin cap similar to foveolar cells of the stomach, and these IPMNs label with antibodies to

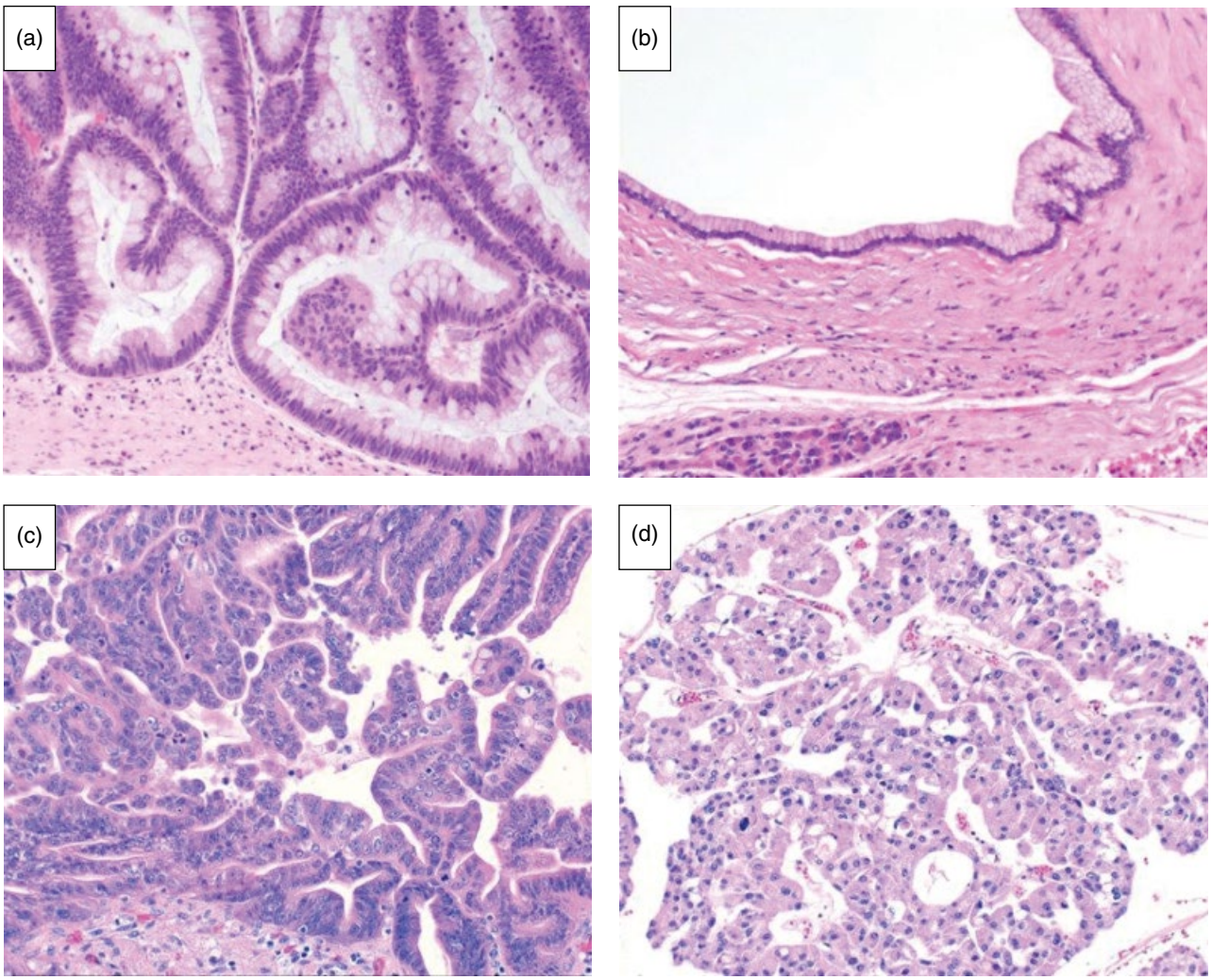


**Figure 92.3** IPMN subtypes. The intestinal subtype (a) occurs most often in the main duct and consists of columnar cells with cigar-shaped nuclei and goblet cells. The gastric subtype (b) is usually a low-grade neoplasm that occurs in branch ducts. The lining is again columnar, but the nuclei are small and basally oriented with a mucin cap reminiscent of the foveolar mucin in the stomach. The pancreatobiliary subtype (c) is typically a high-grade lesion that can involve both main and branch ducts. The lining cells are cuboidal with enlarged, hyperchromatic, round nuclei that are pseudostratified. The cytoplasm is amphophilic rather than mucinous, and the architecture is complex and branching. The oncocytic subtype (d) appears as a high-grade lesion with complex branching architecture and pseudostratified, hyperchromatic nuclei in columnar cells with abundant eosinophilic cytoplasm.

MUC5AC. Pancreatobiliary-type IPMN are composed of cuboidal cells with increased nuclear : cytoplasmic ratio and minimal intracytoplasmic mucin, and they immunolabel with antibodies to MUC1 and MUC5AC. The oncocytic variant of IPMN, known as the IOPN, is composed of an eosinophilic, multilayered epithelium with large nuclei and prominent nucleoli; this variant immunolabels with antibodies to MUC6. Despite the marked atypia in oncocytic IPMN, invasive carcinoma is not common in this subtype [47].

IPMNs are graded as having low-, intermediate-, or high-grade dysplasia based on the degree of architectural and cytologic atypia. Low-grade dysplasia is defined as a single layer of cells with small, uniform nuclei growing along cyst walls with well-formed papillae. Intermediate-grade dysplasia has the beginning of nuclear stratification, pleomorphism, and micropapillae formation. High-grade dysplasia is characterized by loss of nuclear polarity with nuclear hyperchromiasia and pleomorphism along with architectural irregularities including irregular papillae and cribriform growth. Most gastric IPMNs are low- to intermediate grade, while pancreatobiliary and oncocytic IPMNs are usually high grade. Intestinal-type IPMNs may have low-, intermediate-, or high-grade dysplasia [3,42,43]. IPMNs with low-grade and IPMNs with intermediate-grade dysplasia can be combined under the umbrella designation "low-grade IPMN."

Approximately one third of surgically resected IPMNs have an associated invasive PDAC. The risk is greater with main-duct IPMNs, if a mural nodule is present, and with increasing grades of dysplasia. High-grade intestinal-type and pancreatobiliary-type IPMNs are the most likely to have an associated invasive adenocarcinoma of colloid (mucinous noncystic) and tubular type, respectively [47]. Genetic analyses have shown that the carcinomas that arise in direct anatomic association with IPMN usually arose from the IPMN [50].

## Mucinous Cystic Neoplasm

Mucinous cystic neoplasms (MCNs) are mucin-producing epithelial neoplasms of the pancreas that typically do not involve the duct system, and which, by definition, have a characteristic ovarian-type stroma (Fig. 92.4a). MCNs, like IPMNs, also can progress to invasive adenocarcinoma. MCNs are most often located in the tail of the pancreas, and the vast majority arise in women.

### Gross

Gross examination of MCNs shows a well-demarcated multilocular cystic lesion. The cysts can be filled with mucin, or in some instances blood-tinged fluid. The cysts can have a smooth lining or papillary projections may protrude into the lumina. The latter finding often corresponds to high-grade dysplasia and increased risk for invasive carcinoma.

### Histology

Histologically, MCN is lined by columnar mucin-producing epithelium that may have intestinal or gastric differentiation with varying degrees of dysplasia that is graded similarly to IPMN as low-, intermediate-, or high grade. The key diagnostic feature for MCN is the specialized "ovarian-type" spindle-cell stroma seen underlying the epithelium. Immunohistochemical stains for smooth muscle actin and progesterone receptor can be used to highlight the ovarian stroma [3,51].

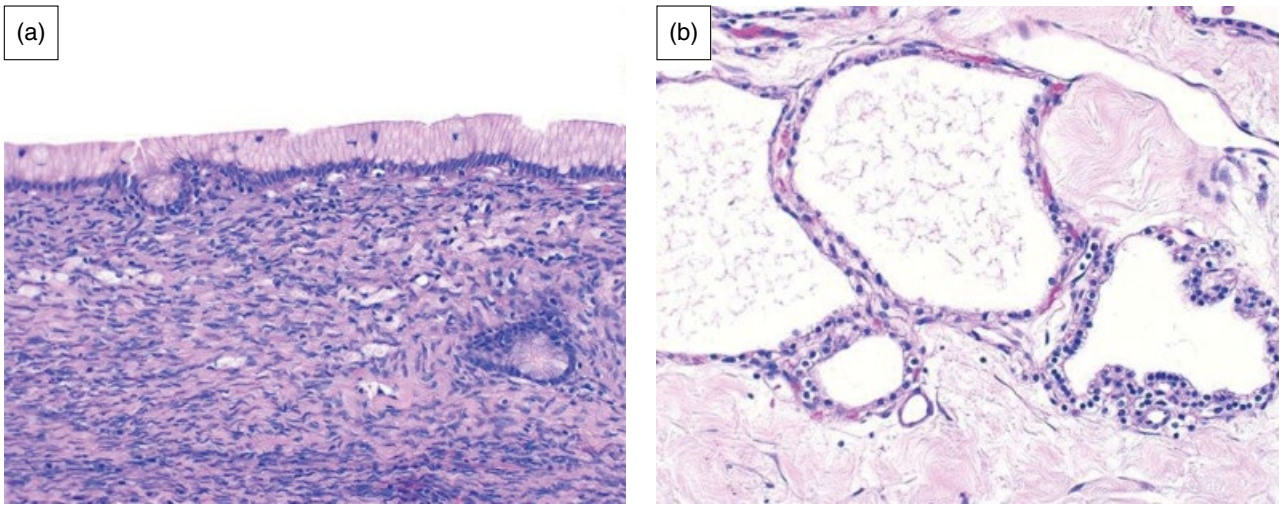


**Figure 92.4** Other cystic neoplasms. A mucinous cystic neoplasm is defined by its ovarian-type stroma made up of spindled cells. Even when these cysts have attenuated mucinous lining (a), the presence of progesterone receptor positive stroma is diagnostic for this neoplasm. A serous cystadenoma generally has very little stroma, and instead demonstrates back to back tubules lined by epithelial cells with clear cytoplasm and small, dark nuclei (b).

Because MCNs are unifocal lesions, surgical resection of an MCN without invasive carcinoma is considered curative; however, up to 30% of MCNs have an associated invasive adenocarcinoma. The invasive component is usually a typical PDAC rather than a colloid carcinoma [3,51]. The depth and extent of invasion of the carcinoma have proven to be important prognosticators [52].

### Serous Cystadenoma

Serous cystadenomas (SCAs) are cystic neoplasms of the pancreas composed of multiple cysts lined by glycogen-rich cells (Fig. 92.4b). The cyst fluid is watery or serous rather than mucinous.

#### Gross

The most common form of SCA is the microcystic SCA. Microcystic SCAs have innumerable small (millimeter) cysts, often surrounding a central scar. The macrocystic variant of SCA consists of one or at most a few large cysts. This latter variant can mimic an IPMN or MCN on imaging. Multiple SCAs throughout the pancreas suggest the von Hippel-Lindau (VHL) syndrome, as do mixed serous-neuroendocrine tumors [53]. The solid serous adenoma is a variant of SCA that, as the name suggests, grossly appears to be solid. Because solid serous adenoma remains well circumscribed, the differential diagnosis on both imaging and gross examination includes a neuroendocrine tumor [54].

#### Histology

All SCA variants are lined by a serous epithelium made up of cuboidal cells with clear to eosinophilic cytoplasm and small, centrally placed uniform nuclei. Transformation to a malignant serous cystadenocarcinoma (as defined by the presence of metastatic disease) is rare; therefore, asymptomatic patients do not require surgery, and in symptomatic cases surgical resection of an SCA is considered definitive therapy [3,55,56].

### Solid-Pseudopapillary Neoplasm

The solid-pseudopapillary neoplasm (SPN) is a neoplasm of uncertain histogenesis and low malignant potential [57,58]. SPNs occur with equal frequency in the pancreatic head, body, and tail.

#### Gross

On imaging and gross examination, SPNs are often large and heterogeneous but well demarcated. On cross-section, the tumor may be predominantly solid or cystic, and is often filled with hemorrhagic and necrotic material (Fig. 92.5a).

#### Histology

By light microscopy SPNs are composed of loosely cohesive monomorphic epithelial cells with clear cytoplasm and round to oval grooved nuclei growing in pseudopapillae (Fig. 92.5b). Hyaline globules are often seen within the epithelial cytoplasm (Fig. 92.5c), and foreign-body giant cells may be present. Touch preparations at the time of intraoperative consultation can beautifully demonstrate the branching vascular architecture, cellular uniformity, and poor cohesion of the neoplastic cell population (Fig. 92.5d). SPNs label with beta-catenin (nuclear), which reflects the underlying β-catenin gene mutation in this neoplasm, and with CD10 [57,59].

All SPNs are classified as malignant. Although the majority of SPNs are indolent and cured by resection, cases of widespread metastatic disease are reported [3,60,61].

## Acinar Cell Lesions

### Acinar Cell Cystadenoma

This lesion is the subject of case series due to its rarity, and the reactive versus neoplastic nature is disputed because these lesions have not been found to harbor clonal mutations commonly associated with pancreatic neoplasia [62,63]. On gross examination, the cysts are well circumscribed and filled with clear, nonmucinous fluid. Histologic examination reveals an epithelial lining composed of cells with acinar differentiation and granular two-toned cytoplasm. There have been no reports of malignant transformation of this lesion [3,62].

### Acinar Cell Carcinoma

Acinar cell carcinoma (ACC) of the pancreas is also quite rare, making up less than 2% of resected pancreatic neoplasms. ACCs have been reported in children as well as adults [64,65], and this malignancy usually harbors a high number of mutations [66].

#### Gross

ACCs are well circumscribed but bulky, fleshy, and often hemorrhagic neoplasms that may resemble the more common pancreatic neuroendocrine tumor (PanNET).

#### Histology

Histologic review shows a predominantly cellular neoplasm that is composed of a monomorphic population of cells with granular cytoplasm, large nuclei, and single prominent nucleoli (Fig. 92.6a). Several architectural patterns can be seen, from the formation of well-defined acini to solid sheets of cells. Desmoplastic stroma is not a prominent feature of ACC [65].

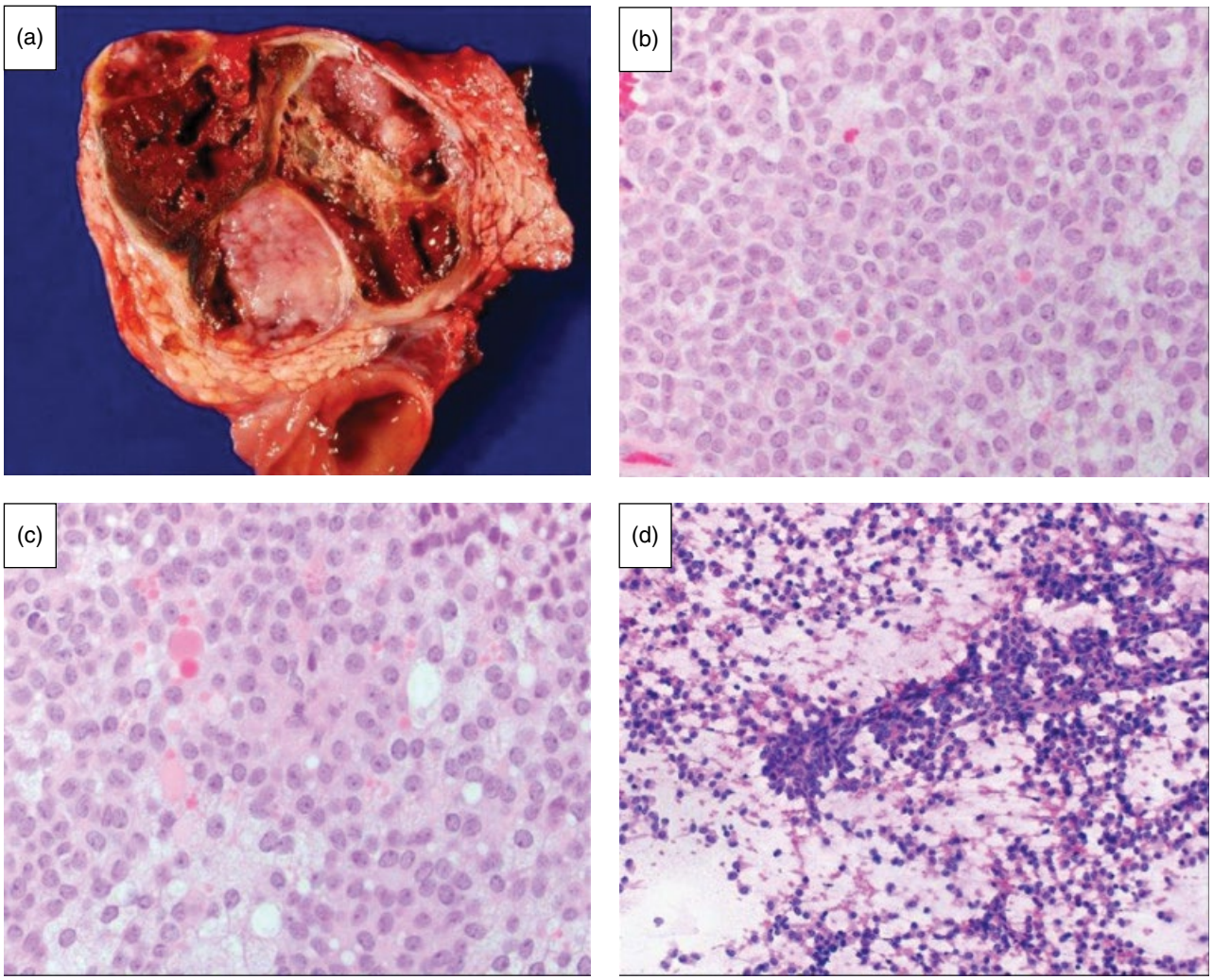


**Figure 92.5** Solid-pseudopapillary neoplasm. On gross examination, a solid-pseudopapillary neoplasm is heterogenous with solid areas as well as evidence of hemorrhage and cystic degeneration (a). The nuclei are relatively monomorphic and may have grooves (b) and cytoplasmic hyaline globules (c). A touch preparation made during the intraoperative consultation demonstrates the delicate branching architecture (d).

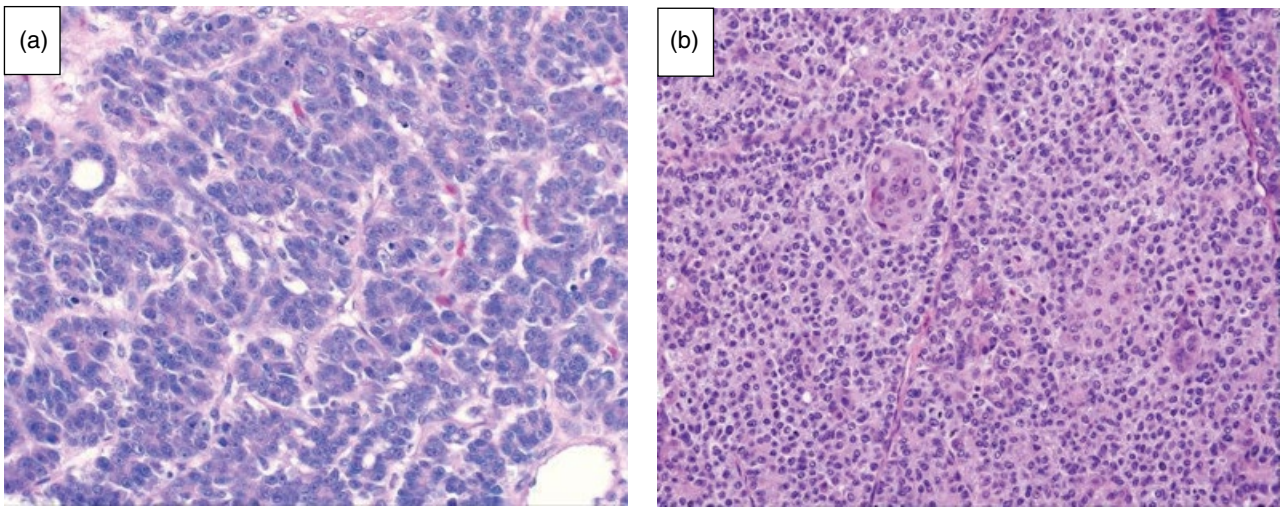


**Figure 92.6** Acinar lesions. Acinar cell carcinomas are typically very cellular with scant stroma (a). The classic cytologic features of this carcinoma are round nuclei with prominent nucleoli and granular eosinophilic cytoplasm. Various architectural patterns, including acinar and solid, may be observed. Pancreatoblastoma has the acinar features of an acinar cell carcinoma, however, the presence of squamoid nests are diagnostic of this neoplasm (b). Endocrine and heterologous mesenchymal elements may also be seen in pancreatoblastoma.

Ancillary stains are usually necessary to definitively diagnose an acinar cell carcinoma. Immunolabeling with antibodies to the pancreatic enzymes trypsin and chymotrypsin will highlight the cells, although a simple periodic acid–Schiff with diastase (PAS-D) can also highlight the enzymatic granules [65]. Another helpful immunostain is BCL-10, which labels the nuclei in 85% of acinar cell carcinomas [67]. Up to one third of acinar cell carcinomas will show patchy labeling with neuroendocrine markers, specifically chromogranin A [65]. To diagnose a true mixed acinar cell/neuroendocrine carcinoma, however, at least 25–30% of the neoplastic cells need to have definitive neuroendocrine differentiation in addition to the cells with definitive acinar differentiation [68]. Mixed acinar/ductal adenocarcinomas have also been described [40]. The prognosis in mixed tumors is driven by the most aggressive component [40,68]. In pure acinar cell carcinoma, the prognosis is better than that of stage-matched PDAC, with a 25–50% 5-year survival rate. Staging of acinar cell carcinoma follows the rules of PDAC [3].

### Pancreatoblastoma

Pancreatoblastomas are more common in childhood [69,70]. Although most are nonsyndromic, pancreatoblastomas have been reported in infants with Beckwith-Wiedemann syndrome and in older children/young adults with familial adenomatous polyposis [71,72]. Cases in adult patients can occur, but with even less frequency than in children [73].

#### Gross

On gross examination fleshy lobules of tumor, fibrosis, necrosis, and calcifications all may all be present in a single neoplasm [74].

#### Histology

On histologic review, pancreatoblastomas are composed of neoplastic cells with acinar cell differentiation admixed with squamoid nests (Fig. 92.6b). Squamoid nests are aggregates of cells with spindled to epithelioid morphology. Squamoid nests differentiate pancreatoblastoma from pure acinar cell carcinoma. Cells with neuroendocrine differentiation are also usually present, and rarely heterologous elements or small cell features may be seen within a pancreatoblastoma [64].

Like an acinar cell carcinoma, pancreatoblastoma is reactive for PAS-D, trypsin, chymotrypsin, and BCL-10; and scattered neuroendocrine markers may be expressed across the tumor. Abnormal, often patchy, nuclear labeling with antibodies to beta-catenin is seen in a subset of pancreatoblastoma.

Surgical resection is considered first line of treatment, and patients with nonresectable disease have a dismal prognosis. Even with resection, the 5-year survival rate for pancreatoblastoma is only 65% [70,75].

## Conclusions

Exocrine malignancies of the pancreas include benign lesions as well as some of the deadliest malignancies known. The importance of accurate pathologic diagnosis and staging for patient prognosis and treatment cannot be overstated, especially when dealing with the complicated area of cystic neoplasia. A new understanding of the molecular drivers of pancreatic neoplasia supports the current gross and histologic classification presented here. We hope that this chapter has provided the tools for confident gross examination histologic diagnosis of exocrine pancreatic lesions.

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# 93

# Pancreatic Cancer: Precancerous Lesions

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## Introduction

Different precursor lesions can give rise to pancreatic ductal adenocarcinoma (PDAC). The initial basis for the current classification of these lesions was established in an international consensus meeting in 1999 [1]. Since then, three additional consensus meetings have been held [2–4]. At present, four precursor lesions are recognized: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), intraductal tubulopapillary neoplasm (ITPN), and mucinous cystic neoplasm (MCN) [4]. These precursors exhibit a unique multistep morphologic and genetic progression to invasive carcinoma [5].

## Pancreatic Intraepithelial Neoplasia

### Clinical Features

Pancreatic intraepithelial neoplasia (PanIN) is the most common precursor lesion of PDAC and it is believed that most PDAC arise from PanIN [6,7]. Hulst (Boerhaave Laboratory, Leiden, The Netherlands) was the first to describe this microscopic lesion a century ago as a lesion in between (*Zwischenform*) normal tissue and invasive carcinoma [8]. These lesions were shown to be more common in pancreata with an invasive carcinoma than in pancreata without cancer. PanIN can be found in 82% of pancreata with invasive carcinoma, in 60% of pancreata with chronic pancreatitis, and in 16% of normal pancreata [9].

Both sexes are equally affected and their incidence tends to increase with age [9–12]. In patients with a family history of pancreatic adenocarcinoma, PanIN typically occur multifocally [13–15].

Because of their small size (by definition <0.5 cm), it is impossible to detect PanIN on noninvasive imaging. Only nonspecific findings such as lobular atrophy and fibrosis can suggest their presence [13]. PanIN are not associated with specific clinical signs or symptoms and are typically found incidentally in resections or biopsy specimens [10,16,17]. Most studies show that PanIN are more common in the head of the gland than in the tail [9,10,18].

### Pathologic Features

PanIN are noninvasive, microscopic, epithelial neoplasms and by definition involve pancreatic ducts less than 0.5 cm in diameter [1,4,7]. Initially, it was thought PanIN arose only from ductules or small ducts [1,19,20]. However, several case reports have suggested that some PanIN can arise from larger ducts, including the main duct [16,19,21]. Some PanIN may cause obstruction and retrograde dilatation. This can make the differential diagnosis with an intraductal papillary mucinous neoplasm (IPMN) difficult. PanIN are characterized by cuboid-to-columnar cells with varying amounts of apical cytoplasmic mucin and varying degrees of cytologic atypia. PanIN almost always show gastric-foveolar differentiation and have a micropapillary or flat architecture [4].

Since the first classification of the precursor lesions in 1999, three grades are discriminated in the progression of PanIN, based on the increasing degree of epithelial atypia and architectural complexity: PanIN-1, PanIN-2, and PanIN-3 (see Fig. 93.1) [1]. PanIN-1 lesions are characterized by minimal nuclear atypia, inconspicuous nucleoli, and absent mitotic figures, and can be further subdivided into flat (PanIN-1A) and micropapillary types with slight nuclear stratification

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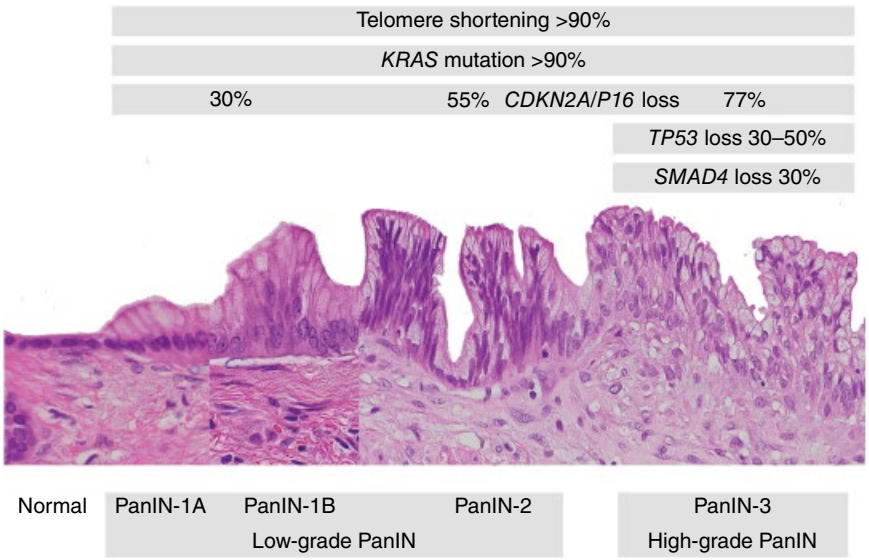


**Figure 93.1** The progression of PanIN is associated with an increase in cellular and architectural atypia and accumulation of genetic mutations. PanIN-1 shows minimal nuclear atypia. PanIN-1A has a flat growth pattern, while PanIN-1B shows formation of micropapillae. PanIN-2 shows moderate nuclear atypia and pseudostratification. PanIN-1 and PanIN-2 are both grouped as low-grade PanIN. PanIN-3 or high-grade PanIN has the most severe nuclear and architectural atypia.

(PanIN-1B). Because of the absence of nuclear atypia and presence of mucin, which is not normally observed in pancreatic ductal cells without histochemical staining, these lesions were previously designated as "mucinous metaplasia" or "mucous cell hypertrophy" [22,23]. Moderate nuclear atypia, pseudostratification, loss of polarity, hyperchromasia, and rare mitotic figures are features of PanIN-2. PanIN-3 lesions have marked atypia, contain (atypical) mitotic figures, show loss of polarity and have a papillary, micropapillary, or occasional flat architecture. Cribriform structures, necrosis, and tufting of epithelial cells in the lumen may be present. PanIN-3 is almost exclusively found in association with invasive PDAC [9,10]. This feature is so striking that, in pancreata without a PDAC, a PanIN-3 lesion may serve as a surrogate marker for invasion elsewhere [9,24]. When PDAC is present, PanIN-3 is very hard to differentiate from the infiltrating carcinoma, growing into preexisting pancreatic ducts (i.e., ductal cancerization). Indications for this phenomenon of so-called ductal cancerization are a close proximity of an invasive carcinoma to a ductal lesion, an abrupt transition from highly atypical epithelium to normal ductal epithelium, luminal obstruction, and ductal destruction [1,7,25].

Of note, the presence of PanIN lesions of any grade at the surgical margin of pancreata resected for invasive PDAC, does not influence patient prognosis and additional surgery is not required [26].

Recently, an expert panel advised to use a two-tiered grading system with low-grade PanIN (former PanIN-1(A/B) and PanIN-2) and high-grade PanIN (former PanIN-3). The reason for this advice was the poor interobserver agreement between PanIN-1 and PanIN-2 [27]. Moreover both PanIN-1 and PanIN-2 show very limited progression to PDAC [9,28].

There are some descriptions of rare morphologic variants of PanIN, without any further biologic or clinical significance [26]. These variants are: *foam gland type*, which is associated with the foam gland subtype of pancreatic carcinoma and is characterized by foamy cells; *oncocytic type* with granular, eosinophilic cytoplasm and round nuclei with evident nucleoli; and *intestinal type* with goblet cells and pseudostratified nuclei [26,29]. However, intestinal type and oncocytic type PanIN could be early manifestations of IPMN.

PanIN show an increased expression of MUC1/EMA and the gastric foveolar mucin, MUC5AC in higher grades of dysplasia [30–33]. The opposite is seen for the pyloric gland mucin MUC6, showing reduced expression in higher grades of dysplasia [31,34].

## Molecular Features

The lowest grade PanIN lesions with minimal cytologic atypia were not originally regarded as neoplastic, but instead were interpreted as hyperplasia or metaplasia [18,35]. After finding activating *KRAS* mutations, these lesions were considered neoplastic and the term "pancreatic intraepithelial neoplasia" was proposed [1,22–24,35,36]. Another early event, frequently found in PanIN, is telomere shortening [37]. In 10% of the lesions that meet the criteria for PanIN, *GNAS* mutations were found, frequently as early events [38]. Since *GNAS* mutations are found in 60% of intraductal papillary mucinous neoplasms (IPMN), these lesions could also represent early IPMN [39,40]. Further in the progression of PanIN, genetic and epigenetic inactivation of *CDKN2A/P16* is seen [41–43]. Mutations in *TP53* and *SMAD4* are considered transitional events in the progression of PanIN to invasive ductal carcinoma, changing TGFβ and BMP signaling from tumor suppressive to tumor promoting (see Fig. 93.1) [5,33,44–47a].

## Intraductal Papillary Mucinous Neoplasm

### Clinical Features

The first description of what is now known as an intraductal papillary mucinous neoplasms (IPMN) of the pancreas, probably dates back to 1936 [48,49]. Haban et al. described a pancreatic lesion with "aneurysma-like" cyst formation, papillary growth of the epithelium, and mucin production. Until 1994, these tumors had various names, each emphasizing a different morphologic feature of the tumor. In 1994, all these entities were grouped together under the term "intraductal papillary mucinous neoplasm" [50,51].

Initially, IPMN was considered a disease of older, cigarette-smoking men. However, a meta-analysis showed that there are geographic differences in the gender of patients with an IPMN. In Asia, main-duct (MD-IPMN) and branch-duct (BD-IPMN) type IPMN affect more men than women. In the United States and in Europe, MD-IPMN affect more men, while BD-IPMN affect more women [52]. Worldwide, the mean age of patients at the time of an IPMN diagnosis is 60–66 years [53–57]. Only a minority develop a PDAC from an IPMN. The mean age of diagnosis of patients with an IPMN with PDAC is 3–6 years older than the mean age of patients at the time of an IPMN diagnosis [53–57]. IPMN are seen more frequently in patients with a family history of pancreatic cancer, Peutz–Jeghers syndrome, familial adenomatous polyposis (FAP), Lynch syndrome, Carney complex, and McCune-Albright syndrome [14,58–64].

Due to the widespread implementation of cross-sectional abdominal imaging techniques, macroscopic, pancreatic cysts like IPMN are relatively common findings. Epidemiologic studies show great variety in the prevalence of pancreatic cysts due to the use of different imaging techniques and different study populations [65–74]. If only cysts larger than 0.5 cm in patients imaged for other indications than pancreatic pathology and without a history of pancreatic pathology are considered, the prevalence is 10–21% [66,67]. A younger and partially healthy population scanned at a center for preventive medicine, had a much lower prevalence of 2.4% [75]. Of course, not all pancreatic cysts are IPMN. About one third of resected asymptomatic pancreatic cysts appear to be an IPMN [76,77].

Most people diagnosed with IPMN are asymptomatic. Only few patients experience nonspecific symptoms [78]. Main duct involvement is more often associated with acute pancreatitis than an IPMN involving only the smaller pancreatic ducts [53,56,77,79,80]. On endoscopy, a classic patulous papilla extruding mucus can be seen in 25% of patients with IPMN. This is also called a "fish-eye" or "fish-mouth" and is virtually diagnostic for the presence of an IPMN [81,82].

IPMN are most frequently located in the proximal pancreas (the pancreatic head and the processus uncinatus). Based on the involvement of the different pancreatic ducts on radiologic and pathologic examination, IPMN are classified as MD-IPMN, BD-IPMN, or mixed-type IPMN [83]. However, there is considerable discrepancy between the radiologic and the histopathologic assessment of the involved ducts. Studies have shown that the main duct often shows some degree of involvement, even in IPMN that were classical BD-IPMN by radiologic imaging [84,85]. These BD-IPMN with minimal involvement of the main duct were very similar to pure BD-IPMN with regard to clinicopathologic features as well as clinical outcome [84].]

Data from multiple studies showed that invasive carcinoma was present in 43.6% of MD-IPMN, in 45.3% of mixed-type IPMN, and in 16.6% of BD-IPMN [86].

### Pathologic Features

IPMN have been defined in a consensus meeting as: "*grossly visible, predominantly papillary or rarely flat, noninvasive mucin-producing epithelial neoplasm arising in the main pancreatic duct or branch ducts.*" By definition, an IPMN is at least 1.0 cm in diameter [1,4,7]. An intraductal neoplastic precursor lesion, larger than a PanIN ($\geq$ 0.5 cm), but smaller than a true IPMN (<1.0 cm) can be either a large PanIN or a small IPMN. Features that occur predominantly in the setting of an IPMN, like the differentiation towards intestinal-, pancreatobiliary- or oncocytic-type epithelium or a mutation specific for IPMN (such as a *GNAS* mutation), are clues for a small IPMN [4,40,87]. If one of these features is present, the lesion can be called "incipient IPMN" [40]. Gastric-type differentiation can be seen in both PanIN and IPMN, making it a nondistinctive feature. Gastric-type lesions of at least 0.5 cm but smaller than 1.0 cm should be documented descriptively [4]. In the past, other features have been used to make the distinction between both lesions: MUC2, although insensitive, is a specific marker for IPMN, IPMN has taller and more complex papillae and IPMN produces more luminal mucin [7].

Similarly to PanIN, a consensus meeting recommended to replace the current three-tiered grading system with a two-tiered grading system, for better reproducibility and risk assessment. The former "IPMN with low-grade dysplasia" and "IPMN with intermediate-grade dysplasia" become "IPMN, low-grade." The former "IPMN with high-grade dysplasia" become "IPMN, high-grade" [4].

IPMN are subtyped by their direction of differentiation as gastric, intestinal, pancreatobiliary, or oncocytic [87].

Gastric-type IPMN is characterized by cells that resemble the foveolar epithelium of the stomach. The epithelium consists of a monolayer of columnar cells

with basally oriented nuclei and abundant mucinous cytoplasm (see Fig. 93.2a). The growth pattern can be flat, papillary, or tubular. The tubular growth pattern can sometimes predominate. The tubular-predominant, gastric-type IPMN was previously considered as an intraductal tubulopapillary neoplasm (ITPN) with low-grade cytonuclear features. In the past, this entity was called "intraductal tubular adenoma, pyloric gland type" or "pyloric gland adenoma" [88–96]. Later, the high-grade cytonuclear features of true ITPN were acknowledged and they were called "intraductal tubular carcinomas" (ITC), to differentiate them from "intraductal tubular adenomas" (ITA) (see Table 93.1). Eventually, immunohistochemical and molecular studies showed that ITA have more features in common with gastric-type IPMN than with ITPN [97]. Gastric-type IPMN typically involve the branch ducts [98].

The pancreatobiliary-type IPMN is lined by mucin-depleted cells with nuclei with marked variation in size and shape and these nuclei have irregular contours and prominent nucleoli (see Fig. 93.2b). The histologic features of pancreaticobiliary-type IPMN and what some people consider high-grade, gastric-type IPMN, are very similar [2]. For this reason, some people consider these as the same entity but with different grades of dysplasia, with gastric-type IPMN being the low-grade dysplastic variant and pancreatobiliary-type the high-grade dysplastic variant [99,100]. Gastric-type IPMN is rarely

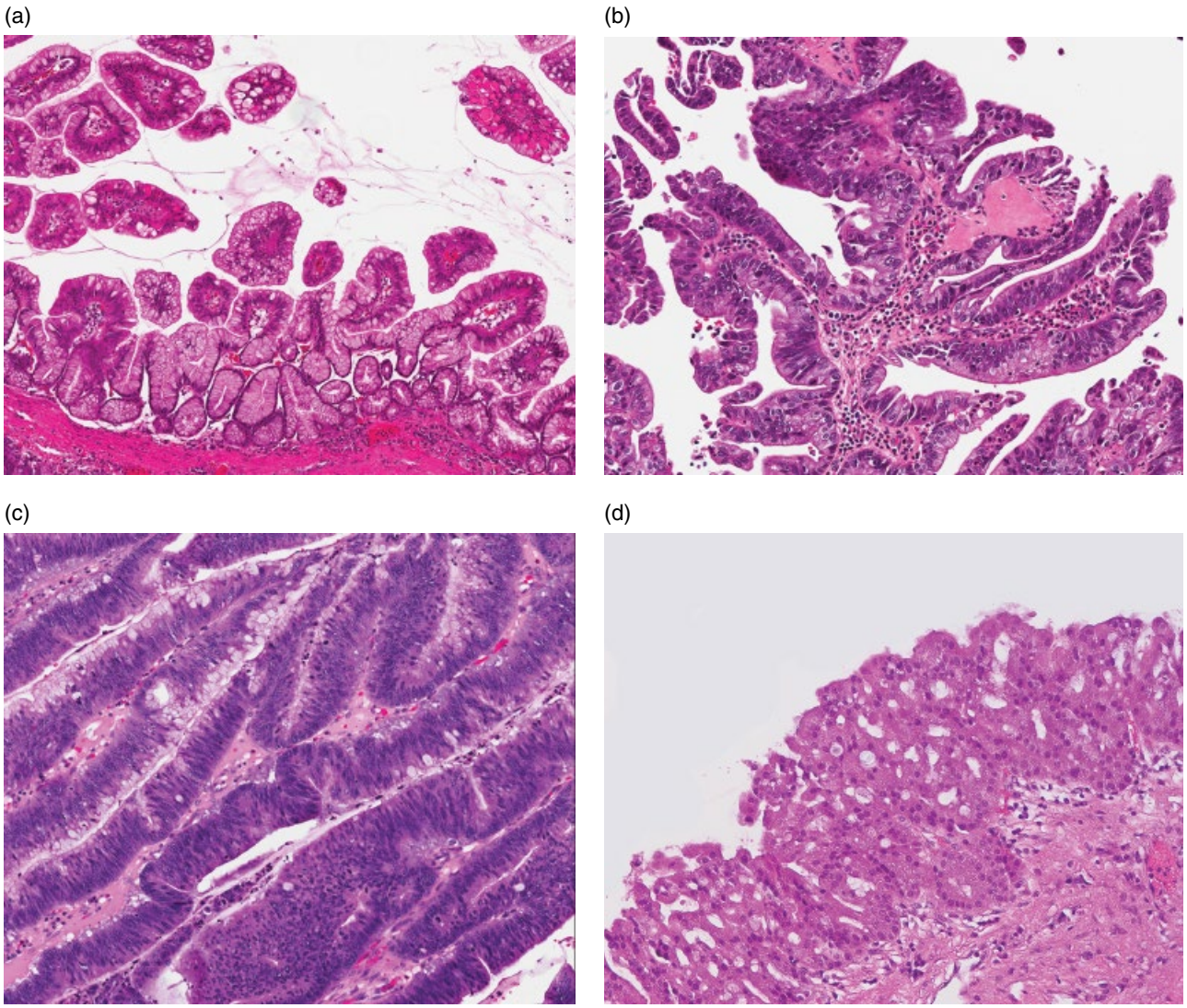


**Figure 93.2** The different subtypes of IPMN. (a) Gastric-type IPMN with a flat architecture and a single layer of gastric foveolar-type epithelium. (b) Pancreatobiliary-type IPMN lined by cells with marked atypia and prominent nucleoli. (c) Intestinal-type IPMN with scattered goblet cells. (d) Oncocytic-type IPMN, composed of cells with abundant eosinophilic cytoplasm, reflecting the accumulation of mitochondria.

**Table 93.1** Nomenclature of the entities, now known as tubular-predominant, gastric-type IPMN and ITPN and previously considered as (different grades of) the same entity

| Current name | Former names |
|---|---|
| Gastric-type IPMN with extensive tubular growth | Intraductal tubular adenoma, pyloric gland type; pyloric gland adenoma; intraductal tubular adenoma (ITA) |
| Intraductal tubulopapillary neoplasm (ITPN) | Intraductal tubular adenoma, pyloric gland type; pyloric gland adenoma; intraductal tubular carcinoma (ITC) |

associated with high-grade dysplasia and has the lowest risk of invasive carcinoma, while pancreatobiliary-type IPMN has the most aggressive behavior [98,101].

The intestinal-type IPMN is morphologically similar to a colonic villous adenoma. The nuclei of the cells are hyperchromatic, elongated, show some degree of pseudostratification and contain variable amounts of intracellular mucin. Dispersed goblet cells can be observed. The papillae are typically long and occasionally branching (see Fig. 93.2c). This subtype most frequently involves the main duct [98].

Oncocytic-type IPMN is a rare entity, characterized by cells with abundant eosinophilic cytoplasm, due to the accumulation of mitochondria. The nuclei of these oncocytic cells contain a single, prominent, eccentric nucleolus. The growth pattern of these oncocytic-type IPMN is distinctive, consisting of arborizing papillae, lined by one to five layers of cuboidal cells. A specific feature is the punched-out spaces in the epithelium (see Fig. 93.2d).

The 2010 World Health Organization classification of tumors of the digestive system provided an immunohistochemical aid for subtyping these IPMN based on mucin glycoprotein-stains. All IPMN stain positive for MUC5AC, while intestinal-type IPMN also show positivity for MUC2 and CDX2, and pancreatobiliary-type for MUC1/EMA. Oncocytic-type IPMN show more positivity for MUC6 than for MUC5AC [2,87,100,102,103]. However, several studies have shown that some IPMN are unclassifiable due to their uncharacteristic morphology and immunophenotype [104–108]. Mixed epithelial differentiation makes subtyping impossible in 25% of cases. Because of these reasons and the moderate interobserver agreement for morphologic subtyping of pancreatic IPMN, subtyping of IPMN has a poor reproducibility [109]. The fact that studies have reported differences in prognosis between the various subtypes of IPMN, despite the poor reproducibility, suggests that associations between histologic type and prognosis may be even stronger than reported [98,101,105,109–112].

### Molecular Features

Whole exome sequencing of IPMN revealed an average of 26 mutations per IPMN [39]. *KRAS* and *GNAS* are the most frequently mutated genes in 50–80% and 40–60% of IPMN, respectively [39,113]. Moreover, *RNF43*, an E3 ubiquitin-protein ligase acting as a negative regulator of the Wnt-signaling pathway is also frequently mutated in IPMN [39]. In addition, *TP53* and *SMAD4* mutations can be found in high-grade dysplasia.

Several studies suggest the existence of two distinct molecular progression pathways in IPMN [32,114]. These two distinct pathways are a reflection of the observation that IPMN can progress into a tubular carcinoma or a colloid carcinoma. Tubular carcinomas are more associated with a pancreatobiliary-type IPMN with a mutation profile resembling conventional PDAC with frequent *KRAS* mutations [114–116]. In contrast, colloid carcinomas are associated with intestinal-type IPMN and harbor frequent *GNAS* mutations [117].

These different pathways are also reflected in a different immunophenotype with colloid carcinomas being MUC1 negative (0%) and MUC2 positive (100%), while tubular carcinomas are typically MUC1 positive (63%) and MUC2 negative (1%) [32]. Colloid carcinomas have a less aggressive behavior and a better prognosis than tubular carcinomas [105,106]. In gastric-type IPMN, *KRAS* and *GNAS* mutations are identified equally. This suggests that gastric-type IPMN are a heterogenic group of early lesions [114].

Oncocytic-type IPMN is genetically distinct from other IPMN subtypes and does not contain *KRAS* or *GNAS* mutations [117a].

## Intraductal Tubulopapillary Neoplasm

### Clinical Features

Intraductal tubulopapillary neoplasms (ITPN) are rare intraductal neoplasms of the pancreas. Together with IPMN, they are grouped as “intraductal neoplasms” [118]. They occur equally in men and women. The presenting symptoms are nonspecific. About 50% of these neoplasms involve the head of the pancreas, 15% are localized in the tail of the pancreas and 30% of the cases involve the pancreas diffusely [118,119]. As much as 40% of cases harbor an associated invasive carcinoma. With a 5-year survival of more than 30%, prognosis of an ITPN-associated invasive tumor is significantly better than the prognosis of conventional PDAC. Recurrence or metastasis to lymph nodes or to the liver is seen in about one third of cases. Even these patients sometimes experience a protracted clinical course over >2 years, which is unusual for conventional PDAC [119].

### Pathologic Features

ITPN is characterized by densely packed tubules that frequently lie back to back, forming large sheets. Tubulopapillary growth is sometimes seen. The cells are cuboidal with modest amounts of eosinophilic cytoplasm and do not contain apparent mucin. There is moderate nuclear atypia and increased mitotic activity. Extracellular mucin production is not prominent and cyst formation is less evident than in IPMN. Comedo-like necrosis is sometimes present [120].

In contrast to IPMN, immunohistochemistry for MUC5AC is typically negative in ITPN [44,120]. MUC1 and MUC6 are positive in 100% and 60% of cases, respectively [120]. Because of similar morphology and shared positivity for MUC6 with gastric and duodenal pyloric gland adenomas, ITPN has previously been described as "intraductal tubular adenomas, pyloric gland type," "pyloric gland adenoma", or "intraductal tubular carcinomas" (ITC) (see Table 93.1) [88,96].

### Molecular Features

ITPN differ from IPMN on a molecular level: *KRAS* mutations are found in only 7% of ITPN. *GNAS* mutations have never been observed in ITPN [121–123]. *PIK3CA* mutations are the single, most frequently observed mutations in ITPN (21–27%) [121,124].

## Mucinous Cystic Neoplasms

### Clinical Features

The vast majority of mucinous cystic neoplasms (MCN) occur in perimenopausal women [76,118,125–129]. The mean age of presentation of patients with a noninvasive MCN is 44 years. The mean age of presentation of patients with an MCN with associated adenocarcinoma is 55 years [12]. Only a few, rare cases have been described in men [130]. MCN are commonly found in the pancreatic body and tail. Because of the close proximity of the female gonad to the pancreatic tail during embryologic life and the fact that similar lesions occur in the other side of the body, it has been hypothesized that the pancreatic MCN develops from a remnant of endodermal immature gonadal stroma, stimulated by female hormones [125,131]. This is reflected in the ovarian-type stroma surrounding the cyst [132]. Similar lesions are found in neighboring organs: mucinous cystadenomas of the hepatobiliary tree, mesentery and retroperitoneum, and the mixed epithelial and stromal tumor (MEST) of the kidney [133–136].

The prognosis after surgical resection is excellent if the neoplasm is noninvasive or if invasive carcinoma is confined to the ovarian-type stroma of the septa [128,129,137,138]. The prognosis of patients with an MCN with an associated invasive carcinoma after resection is better than that of patients with conventional invasive ductal adenocarcinoma not arising in an MCN; the 5-year survival rate of the MCN patients with an associated invasive carcinoma is up to 50% [125,128].

### Pathologic Features

MCN usually do not communicate with the pancreatic duct system and show a "cyst-in-cyst" growth pattern, by the formation of septae. Microscopically, MCN are defined as having two components: the cyst is lined by neoplastic, mucinous, columnar epithelial cells, surrounded by a nonneoplastic, ovarian-type stroma (see Fig. 93.3). The epithelium can harbor varying degrees of architectural and cytologic atypia [118]. The atypia is graded in a two-tiered system, as recommended by the latest consensus meeting. This two-tiered system replaces the three-tiered system: "MCN with low-grade dysplasia" and "MCN with intermediate-grade dysplasia" are now both classified as "MCN, low-grade" [4].

Ovarian-type stroma may be only focally present or not obvious due to fibrosis or hypocellularity [125,139]. Sometimes, nests of epithelioid cells are seen in the stroma suggesting luteinization. Rarely, a corpus luteum can be seen in the stroma. The cells of the ovarian-type stroma frequently express progesterone and estrogen receptor, inhibin, caldesmon, alpha-SMA, and desmin [133,140].

When an MCN evolves into an invasive carcinoma, this is typically a tubular adenocarcinoma. MCN rarely evolve into a colloid carcinoma, although 51% of MCN

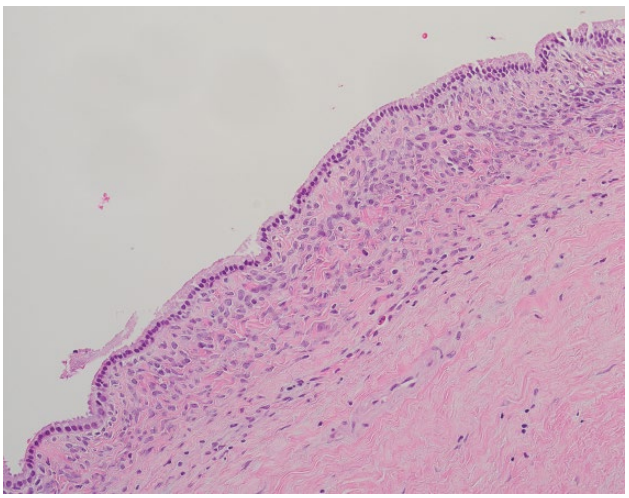

**Figure 93.3** MCN with mucinous epithelium with low-grade dysplasia and characteristic ovarian-type stroma.

show intestinal differentiation by immunostaining for CDX2 [141,142]. MCN with malignant, sarcomatous stroma have been reported but are more likely spindle cell carcinomas rather than true mesenchymal neoplasms, since the ovarian-type stroma of the MCN is nonneoplastic [143–146].

### Molecular Features

Whole-exome sequencing of the MCN showed on average 16.0 ± 7.6 nonsynonymous somatic mutations and relatively few "loss of heterozygosity" events, compared with IPMN [39]. This could explain the lower frequency of progression towards an invasive carcinoma in MCN, since there is a correlation between aneuploidy and a poor prognosis [147]. Only one region on chromosome 17q, containing the gene *RNF43*, was lost in more than one tumor. In three MCN, intragenic mutations were found in the *RNF43* gene. Further analysis showed mutations in the four main pancreatic cancer genes *KRAS*, *CDKN2A*, *TP53*, and *SMAD4* [39].

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# Clinical History and Risk Factors of Pancreatic Cancer

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## Introduction

It does not matter which way you look at it or by what means you endeavor to access the extensive field of pancreatic carcinoma—whether as a nonspecialist but interested reader, or as an oncology expert, or even as an afflicted patient—and no matter the angle of view or the basic discipline you use to acquaint yourself with pancreatic carcinoma—whether by pathology, internal medicine, or surgery—the catchy introductory phrase is almost always followed by the stereotypical statement: "The diagnosis of pancreatic carcinoma most frequently implies an unfavorable prognosis." This monotonous introduction to pancreatic carcinoma is clear evidence of the lack of effective therapeutic options, especially in the case of an unresectable tumor. There are multiple reasons, but undoubtedly the relatively long period of freedom from symptoms greatly contributes to the fact that only around one fifth of patients are diagnosed early enough to consider a curative approach. Moreover, numerous widespread, but rarely specific, factors exist that often cannot be influenced but may increase the likelihood of developing pancreatic carcinoma. Although it should be noted that phenomena such as pancreatitis or diabetes tend to be part of the clinical appearance of the tumor disease rather than risk factors. This chapter aims to make a connection between current knowledge in terms of relevant risk factors and the clinical appearance and symptoms of pancreatic carcinoma. Finally, by raising the reader's awareness, it is hoped to improve early detection and intervention as a basis for a more effective therapeutic approach and thus a better prognosis for the patient.

## Clinical History of Pancreatic Cancer

Probably the greatest hindrance to the prompt diagnosis of pancreatic carcinoma is the lack of early disease-specific symptoms. On the one hand, it is difficult to distinguish these from other nonspecific symptoms, and on the other hand, afflictions that possibly indicate malignant disease can often be explained otherwise and may be misinterpreted. This problem was demonstrated in a groundbreaking study during the 1970s: in 57% of the patients with respective symptomatic complaints, the authors found concurrent reasons, including malignant diseases in 13% and nonpancreatic, nonmalignant diseases in 44%, respectively [1]. Moreover, symptoms may vary significantly depending on the tumor's location in the pancreas.

### Functional Impairment of the Pancreas

Increasing loss of exocrine function is one potential tumor-related symptom. The absence of important digestive enzymes in the functionally complex interaction of intestinal digestion causes an inadequate fragmentation of carbohydrates, proteins, and fats. Therefore resorption across the intestinal wall into the portal system is insufficient, the major portion of the undigested fat remains in the gut, which causes so-called *fatty stools* (*steatorrhea*). This may lead to considerable *diarrhea*, *flatulence*, and *abdominal cramps*.

Furthermore, the tumor may noticeably compromise the endogeneous function of the pancreas by destroying insulin-producing cells. Several studies have proved that *diabetes* frequently predates a diagnosis of pancreatic carcinoma. This particularly applies when diabetes is first

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diagnosed during or beyond a patient's sixth decade and without familial disposition [2]. A retrospective analysis of 736 patients with pancreatic carcinoma revealed diabetes prior to the malignant disease in approximately 40% of cases, whereas only 19% were identified in a control group. In the majority of these cases, diabetes was noticed between several months and up to 2 years prior to the diagnosis of pancreatic cancer. However, the authors add that in most cases this was type 2 diabetes but not a pancreatic carcinoma-associated diabetes [3]. It is therefore likely that the mechanism of diabetes development in pancreatic carcinoma is probably not only due to B-cell destruction because even pancreatic carcinomas that involve only small parts of the organ are already associated with diabetes. In molecular analyses of sera from patients with pancreatic carcinomas, for example, peptides were identified that are able to induce diabetic effects [4].

## Invasion into Intra- and Extrapancreatic Nerve Plexus

Rapid *loss of weight* and reduced general state of health in afflicted patients are frequently triggered by *pain symptoms* in the upper abdomen and the back. Pain in the upper abdomen can be found in approximately 70% of patients with pancreatic carcinoma. Symptoms usually start intermittently and after a distinct period of time develop into continuous pain. Inside the pancreas specific changes in neural structures occur as tumor cells are able to perform intra- and extrapancreatic perineural invasion. This phenomenon is known as *neuropathic pain*, which, in contrast to *nociceptive pain*, develops in the absence of any stimulus. The continuous spread of the tumor cell and the consecutive degree of severity of neural invasion increase both the risk of neural metastatic spread into the adjacent extrapancreatic nerve plexus and the spread of pain. The morphologically detectable changes in intrapancreatic nerve integrity culminate in the destruction of the whole nerve plexus. Noticeably, patients with severe abdominal pain show a higher degree of neural invasion and increased nerve hypertrophy compared with patients who are pain free [5, 6].

The development of neuropathic pain is not only effected by neurons but also by immune cells, Schwann cells, and glial cells of the central nervous system [7]. Current research is investigating the genesis of neuropathic pain with the aim of developing adequate pain management.

## Tumor Cell Ingrowth into Adjacent Organs and Nearby Vessels

Whereas a tumor located in the head of the pancreas characteristically causes both pain-free *jaundice* and intra- and extrahepatic cholestasis, lesions in the panceatic corpus and caudate rarely give rise to these symptoms [8]. Jaundice of sclerae and skin and the accompanying troublesome *pruritus* is caused by intrapancreatic biliary obstruction with consecutive storage of bile acids and bilirubin in the tissue. The tumor causes constriction of the common bile duct that passes through the pancreatic head and then leads to the major duodenal papilla and the duodenum together with the pancreatic duct. In case of constriction of the pancreatic duct, *acute pancreatitis* may develop. Patients usually also report *discoloration of feces and urine*. As a consequence of the impaired biliary excretion via the bowel, feces become light and clay-colored. The accumulated bilirubin in the serum is then compensatorily excreted by the kidneys, turning the urine brown.

Furthermore, local tumor growth and infiltration of adjacent organs may cause gastric emptying disorders or duodenal obstructions, resulting in *nausea*, *loss of appetite*, *a sensation of pressure in the upper abdomen*, and *increasing emesis*. Because of the close anatomic proximity of the pancreas to adjacent vessels (portal vein, celiac trunk, and superior mesenteric artery) even relatively small tumors may invade vessels. However, the so-called *paraneoplastic syndromes*—especially thromboses of the major femoral and lower leg veins with respective clinical appearance—are independent of local tumor growth.

## Clinical Symptoms of Neuroendocrine Tumors of the Pancreas

Apart from the afore-mentioned nonspecific and sometimes nondirective symptoms of pancreatic carcinomas, neuroendocrine tumors (NET) of the pancreas often secrete hormones into the bloodstream. Various types of NET produce different hormones, which in turn cause varying clinical symptoms. However, not all NET of the pancreas are hormonally active.

***Gastrinomas*** are functionally active NET that produce the hormone gastrin, which causes increased secretion of gastric acid. Typically, gastric and intestinal ulcers resistant to medication develop in up to 95% of afflicted patients over time or rapidly reoccur after end of treatment. Subsequently, *intense abdominal pain* and/or *intestinal bleeding* may appear. A smaller number of patients (~60%) develop pathologic *gastroesophageal reflux* with *pyrosis* or *dysphagia*. Over 30% of patients suffer from *diarrhea* and/or *steatorrhea*.

***Insulinomas*** are the most frequent type of functionally active NET of the pancreas. These tumors typically release insulin, which depresses blood glucose levels and provokes symptoms of *hypoglycemia* such as *trembling*, *ravenous appetite*, and *confusion*.

***Glucagonomas*** may cause nonspecific *loss of capability* or *body weight*. Hyperglycemia caused by release of glucagon and *necrotizing dermatitis* are characteristic symptoms of glucagonomas.

***Somatostatomas***, ***VIPomas***, and ***PPomas*** are rare hormone-producing NET. A list of specific and nonspecific symptoms are shown in Table 94.1, together with symptoms of the afore-mentioned tumors.

## Risk Factors for Pancreatic Cancer

The triggers for development of a pancreatic carcinoma can be difficult to identify retrospectively. Comprehensive observational studies have detected predisposing factors but they may not be found in all patients; conversely, not all individuals who have one or more risk factors will inevitably develop a pancreatic carcinoma.

### Smoking

The etiology of numerous diseases can be attributed to inhalation of tobacco. This mainly applies to respiratory organs, the cardiovascular system, and malignant tumors. Smoking is an unambiguous risk factor for development of pancreatic cancer. A meta-analysis of 82 cohorts and case-control studies reports on a relative risk of 1.7 (95% CI: 1.6–1.9) for smokers and 1.2 (95% CI: 1.1–1.3) for ex-smokers independent of gender and region. The investigation of cigar smokers and pipe smokers ascertains a pooled risk of 1.5 (95% CI: 1.02–2.3) and 1.4 (95% CI: 0.94–2.0), respectively [9]. Another pooled analysis studied the impact of cigar and pipe tobacco and smokeless tobacco on pancreatic cancer risk. The results principally confirm an association between cigarette smoking (odds ratio [OR] = 1.5, 95% CI: 1.4–1.6) and cigar smoking (OR = 1.6, 95% CI: 1.2–2.3) and pancreatic carcinoma. However, any impact of pipe smoking on later occurence of pancreatic carcinoma could not be demonstrated [10]. Data on smokeless tobacco use (mainly snus) is rare. Here the authors show results consistent with a respective meta-analysis, which does not show any excessive risk of pancreatic carcinoma in several case studies [11]. Conversely, another meta-analysis refers to

**Table 94.1** Clinical symptoms of pancreatic carcinoma.

**By functional impairment of the pancreatic gland**

Digestive difficulties (diarrhea, abdominal pain, flatulence)

Changes in stools

Development of diabetes

Loss of weight

**By intra- and extrapancreatic nerval invasion**

Pain in the upper abdomen and the back

**By infiltrative tumor growth into adjacent organs and vessels**

Jaundice

Nausea and vomiting

Inappetence

Sensation of pressure in the upper abdomen

Acute pancreatitis

Thromboses (including paraneoplastic syndromes)

**By specific hormones of neuroendocrine pancreatic tumors**

| Type of tumor | Hormone | Symptoms |
|---|---|---|
| Gastrinoma | gastrin | Acid reflux, burning abdominal pain, excess fat in stool, weight loss |
| Glucagonoma | glucagon | High blood glucose, anemia, weight loss, swelling/irritation of skin |
| Insulinoma | insulin | Low blood glucose, perspiration, confusion, shakiness, accelerated heartbeat |
| Somatostatinoma | somatostatin | Nonspecific symptoms like diabetes, gallstones, diarrhea, weight loss |
| VIPoma | vasoactive intestinal peptide | Watery diarrhea, fatigue, nausea |
| PPoma | pancreatic polypeptide | Belly pain, enlarged liver, watery diarrhea |

VIPoma, vasoactive intestinal peptide-releasing tumor; PPoma, pancreatic polypeptide-producing tumor.

an association between smokeless tobacco and pancreatic carcinoma [12]. However, the consumption of smokeless tobacco in particular has not been proven to be a distinct risk factor because of the marked heterogeneity of ingredients.

The risk seems to increase according to both quantity of tobacco use and length of exposure to cigarette smoke. However, the elevated risk of pancreatic cancer diminishes after complete cessation of smoking. Due to the high prevalence of smoking worldwide experts assume that as many as 25% of pancreatic carcinomas can be attributed to cigarette consumption [13].

## Diabetes Mellitus

As stated in the introduction to this chapter, risk factors and early symptoms of pancreatic cancer can be difficult to distinguish. A comprehensive study revealed a threefold increased risk of pancreatic cancer in patients with type 2 diabetes (OR = 3.22, 95% CI: 3.03–3.42) [14]. These results can be supported by results from an earlier meta-analysis that also identified diabetes type 2 as a risk factor for pancreatic carcinoma (OR = 1.82, 95% CI: 1.66–1.89) [15]. Individuals who were diagnosed with diabetes <4 years previously showed a 50% higher risk of tumor disease compared with patients with a diagnosis of diabetes >5 years previously (OR = 2.1 vs. 1.5). These findings again support the theory that the onset of diabetes may be an early symptom of pancreatic cancer (as outlined in the earlier section "Functional impairment of the pancreas"), because otherwise an increasing risk could be expected over the ongoing length of time of diabetes disease. However, the authors hint at the fact that in most of the included studies there was no distinction between type 1 and type 2 diabetes. Nevertheless, it could be assumed that most individuals had type 2 diabetes, which is the most frequent type of diabetes in the elderly [15]. In a meta-analysis of three cohorts and six case-control studies the investigators took this factor into account and analyzed 39 patients with type 1 diabetes and young-onset diabetes (interpreted as type 1). Type 1 diabetes could be identified as a risk factor for pancreatic carcinoma with a relative risk of 2.00 (95% CI: 1.37–3.01) but the authors urgently call for confirmation by further studies because of the low number of patients [16]. A prospective cohort study was initiated to determine the independent association between postload plasma glucose concentration and the risk of pancreatic cancer development among patients without self-reported diabetes. After an observation period of 25 years and after adjusting for age, race, cigarette smoking, and body mass index (BMI), the relative risk of pancreatic cancer mortality was 1.65 (95% CI: 1.05–2.60, for postload plasma glucose levels between 6.7 and 8.8 mmol/L). The authors concluded that factors associated with abnormal glucose metabolism have a significant impact on the development of pancreatic cancer [17]. Furthermore, another study reported a positive association between pancreatic cancer and elevated baseline fasting serum concentrations of glucose and insulin, and insulin resistance, respectively [18].

## Overweight and Obesity

The World Health Organization (WHO) defines overweight and obesity by use of the BMI calculated as weight in kilograms divided by height in meters squared. Thereby, underweight (BMI < 18.5 $kg/m^2$), normal weight (1.5–24.9 $kg/m^2$), and overweight (>25 $kg/m^2$) can be differentiated. In several cohort studies and case-control studies an up to threefold increased risk for development of pancreatic carcinoma was found for overweight individuals. Next, it was shown that overweight (OR = 1.67, 95% CI: 1.20–2.34) and obese individuals (OR = 2.58, 95% CI: 1.70–3.90) had an elevated risk for pancreatic carcinoma independent of concomittant diabetic disorders [19]. An interesting aspect of this study was the finding that overweight and obesity during early adulthood increased the risk of developing pancreatic cancer and that it usually develops 2–6 years earlier than average (between 20 and 49 years). This was the first report of an association between excess body weight across an individual's life span and the risk of pancreatic cancer, which emphasizes the importance of these findings with regard to public health [19]. These results were confirmed in a recently published pooled analysis of 20 prospective cohort studies. This analysis determined an association between increased pancreatic cancer mortality and BMI during early adulthood in individuals who are overweight or obese [20]. Along with other studies, it was concluded that there is an increased risk of obesity-associated pancreatic cancer in males [19]. These findings raise the question whether those (rather few) individuals who manage to reduce their body weight significantly and approach normal weight during their life can thereby reduce the risk of pancreatic cancer development. Therefore, an important prevention measure is body weight control at younger ages.

## Chronic Pancreatitis and Consumption of Alcohol

The positive correlation between chronic pancreatitis and development of pancreatic carcinoma was proven in a precedent-setting cohort study [21]. Including 2,000 patients with chronic pancreatitis, the authors demonstrated an increased lifetime risk of approximately 4% in this population group in terms of development

of pancreatic carcinoma. Population-based prospective surveys assume a standardized incidence ratio of 4.8, which approximates to a risk of 0.6% after 20 years. Amongst approximately 1,500 patients who were observed for a period of at least 2 years, the percentage distribution of pancreatitis was alcohol-induced in 77%, idiopathic in 17%, hereditary in 1.9%, and of different origin in 4.1%, respectively. Even though the relation may have turned slightly towards a higher rate of hereditary pancreatitis during the last two decades, this study identified chronic pancreatitis to be a risk factor, which is independent of age, region, and underlying origin. Numerous other reports suggest that chronic pancreatitis is a risk factor for pancreatic carcinoma; however, the relative risk varies considerably in the literature (range: 2.3 [22] and 18.5 [23]). Most likely these variations can be attributed to methodologic concerns and the retrospective design of many studies. In a prospective analysis of 373 patients with proven chronic pancreatitis and a follow-up of at least 2 years, a significantly increased risk for pancreatic cancer was validated compared with the general population [24].

The true impact of alcohol as a direct risk factor for pancreatic cancer is under debate and different mechanisms are postulated. Inducing different cascades of inflammation, alcohol might indirectly induce carcinogenesis via both chronic pancreatitis and diabetes, respectively [25]. However, one point of criticism of the partially inconsistent studies is the fact that analyses were performed without considering the relationship of doses and pattern of alcohol exposure. Heavy alcohol consumption was associated with an increased risk for development of pancreatic cancer in males in a population-based study. According to dose, duration, and pattern of alcohol abuse the OR was increased 1.5-fold to sixfold [26].

### Environmental Factors

A range of environmental factors has hitherto been identified to have a possible association with pancreatic carcinoma development. Table 94.2 shows an excerpt of these ubiquitously present and numerous triggers. Aromatic amines seem to be the substrate of the carcinogenic effect of both smoking and consumption of cooked meat and fish. The same applies to occupations with comparatively high exposure to these amines.

### Hereditary Factors

A positive family history of pancreatic carcinoma has repeatedly been shown to be a risk factor for its cumulative appearance. These aspects and the respective tumor predisposition syndromes are the subject of Chapter 91.

**Table 94.2** Risk factors for pancreatic adenocarcinoma.

| | |
|---|---|
| **Demographic factors** | |
| Age | [27] |
| Black race | [28] |
| Blood group | [29] |
| **Environmental factors** | |
| Smoking | [9] |
| Alcohol | [30] |
| Aromatic amines (cooked meat, cigarette smoke) | [31] |
| Obesity, high-fat diet | [32] |
| Occupations (chemists, petrochemical worker …) | [33] |
| **Preexisting diseases** | |
| Chronic pancreatitis | [21] |
| Diabetes mellitus | [14] |
| Insulin resistance | [18] |
| Gastrectomy | [34] |
| *Helicobacter pylori* infection | [35] |
| **Genetic factors** | |
| Positive family history | |
| Tumor predisposition syndromes (see Chapters 45 and 91) | |

## Conclusion

The identification of early symptoms of pancreatic cancer and the subsequent timely start of diagnostics in daily clinical practice remain highly demanding. In contrast, several specific and nonspecific risk factors of pancreatic carcinoma have been identified with more or less certainty so far, which can be proved by respective studies. If possible, abstinence and avoidance should be practiced to the greatest extent to prevent development of pancreatic cancer. With regard to numerous predisposing factors and especially a positive family history this cannot be performed satisfactorily. An early diagnosis is the only possibility to improve a patient's survival. Therefore, every worrisome finding should be investigated and resected in case of doubt.

Finally, particular attention must be drawn to the group of cystic pancreatic tumors with their numerous and different entities and distinct clinical and morphologic characteristics. These neoplastic and nonneoplastic, mucinous, and serous cystic lesions can be detected even earlier and at a smaller stage because of continuing improvements in imaging methods. Nowadays, these tumors can be

investigated by a highly precise risk stratification, which results in distinct therapeutic recommendations. Based on several clearly defined criteria, the pancreatic cystic tumors should be either observed or resected. This strategy allows for early resection of precancerous lesions or even pancreatic cancer with the chance of cure.

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# 95

# Pancreatic Cancer Within the Uncinate Process: Radiologic and Clinical Characteristics

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## Embryology of the Pancreas

The pancreas is a two-headed organ in two respects: origin and function. It develops from two separate primordia at the foregut–midgut junction. The following sections provide an overview of its organogenesis.

The development of the pancreas begins approximately 5 weeks after gestation in common with the development of other endoderm-derived organs in the region of the foregut (for development of the pancreas, see Chapter 1). It originates from two pouches of the endodermal lining of the duodenum, which will form the ventral and dorsal pancreas. These pouches initially grow and differentiate independently, but later fuse to form a single organ. They occur on the ventral and dorsal surfaces of the primitive digestive tube forming the ventral and dorsal pancreatic bud. The dorsal bud will develop into the tail of the pancreas, the body, the isthmus, and the accessory pancreatic duct as well as a part of the head. The much smaller ventral bud gives rise to the other part of the pancreatic head, the uncinate process forming the lower portion of the pancreatic head and the main pancreatic duct. The ventral pancreatic primordium forms in the interspace between the liver and the gall bladder primordia (also endoderm-derived) and the primitive gut.

In contrast to the ventral bud, the dorsal bud grows more rapidly. An asymmetric growth of the duodenum causes its rotation together with the ventral pancreas, annexed to the primordium of the common bile duct, towards the dorsal pancreas. This moves the originally ventral part to a dorsal location. Finally, the ventral and dorsal parts merge and the ductal systems fuse, forming a single organ and the main pancreatic duct so that secretions of the dorsal part enter the shared ductal system of the ventral part and the common bile duct (Fig. 95.1). The region of the primary duct of the ventral pancreas proximal to the duodenum fuses with the primary duct of the dorsal pancreas and becomes the primary drainage into the duodenum, entering the duodenum immediately adjacent to the common bile duct.

## Radiologic Characteristics

Over the past few years, there have been significant technical developments in the area of cross-sectional imaging. This draws imaging into focus with regard to the diagnosis of pancreatic cancer. In case of suspicion, multidetector computed tomography (MDCT) and/or magnetic resonance imaging (MRI) are deployed. MDCT and MRI are of equal value with respect to the diagnosis of pancreatic cancer. When it comes to the diagnosis of liver metastases, there is a slight advantage in using MRI in combination with a hepatobiliary contrast agent. Despite the higher accuracy of endoscopic ultrasound examination, in daily practice, it is used in cases of unclear results or when there is an urgent clinical suspicion and in combination with imaging.

Cross-sectional imaging plays a central role in the diagnosis and staging of pancreatic tumors. The methods are useful to assess the response of a therapy and for early detection of recurrence. The increasing use of high-resolution cross-sectional imaging will facilitate more frequent discovery of prior unknown tumors of the pancreas [1–4]. This concerns primarily cystic lesions, which are usually benign, but also solid tumors that are malignant in most cases. For general screening of pancreatic cancer, these methods are not yet appropriate and early detection measures are confined to high-risk groups [2].

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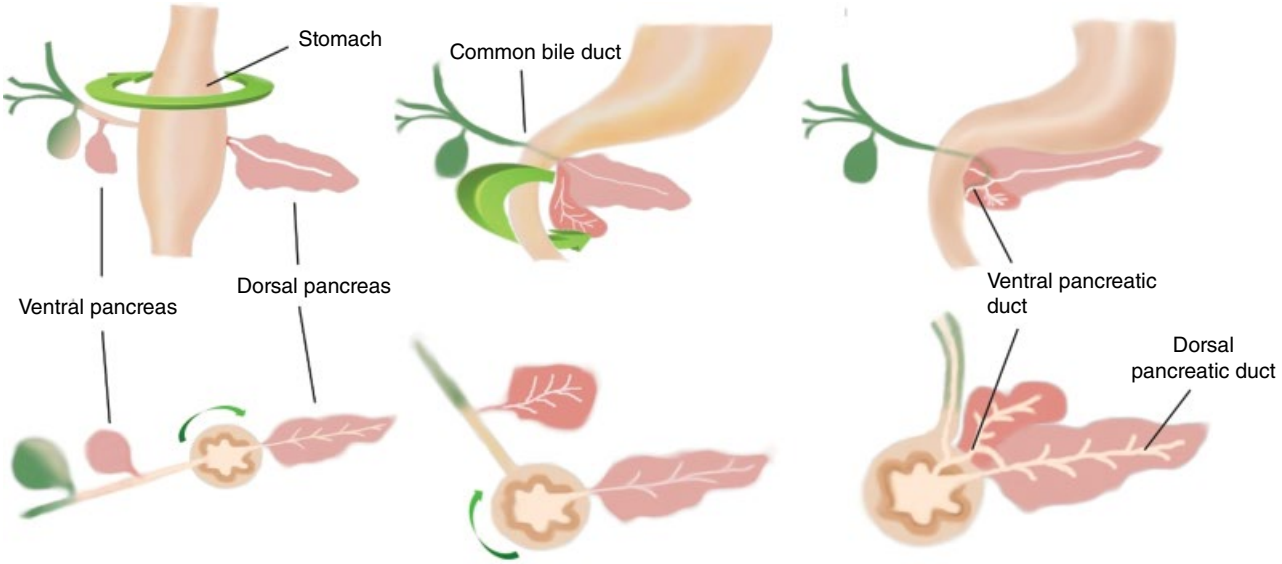


**Figure 95.1** Fusion process of the ventral and dorsal pancreatic bud.

Following the recent recommendation by the American Joint Committee on Cancer, the staging of pancreatic cancer is based on the assessment of resectability by a spiral CT.

Tumor imaging of the pancreas has three objectives:

- Detection and characterization of tumors
- Differentiation of ductal carcinomas and other forms of tumors or chronic pancreatitis (which is often not possible with absolute certainty)
- Staging and evaluation of resectability.

## Clinical Characteristics of the Uncinate Process Pancreatic Cancer (UPDAC)

Because of the embryologic and anatomical uniqueness of the uncinate process, the clinical presentation of patients with UPDAC varies. In contrast to the literature concerning ductal adenocarcinoma of the pancreas, there is a lack of data regarding UPDAC. Only a handful of published series of UPDAC exist. It is therefore difficult to quantify the incidence of UPDAC (the literature data vary from 2.5% to 11%) [5,6].

By tradition, UPDAC are considered to have a lower resection rate and a poorer prognosis than comparable cancers of the pancreatic head. The reason is the immediate positional relation of the mesenteric vessels and the retroperitoneum. The overall resectability (31.7% for UPDAC vs. 46.2% for non-uncinate process pancreatic head cancer; $P = 0.003$), the rate of curative resection (24.8% vs. 41.8%; $P < 0.001$), and R0 resection rate (22.3% vs. 35.6%; $P = 0.003$) are significantly lower for UPDAC. UPDAC is more often unresectable (68.3% vs. 53.8%; $P = 0.003$) [7]. The percentage of vascular (SMV/PV and/or SMA) invasion at the time of diagnosis is significantly higher in the case of UPDAC than in patients with non-UPDAC (58.2% vs. 38.1%; $P = 0.019$) [8]. The rate of isolated PV or SMV encasement is also significantly higher (45.5% vs. 20.0%; $P = 0.001$ and 54.5% vs. 36.2%; $P = 0.026$, respectively). The rates of PV-resection and consecutive reconstruction do not differ significantly (11.8% vs. 11.1%; $P = 0.885$) [7].

In the uncinate process, because one part of the head extends posteriorly and medially to lie dorsally of the portal vein, the superior mesenteric artery (SMA), and the superior mesenteric vein (SMV), it is closer to the SMA and set back from the courses of the common bile duct or pancreatic duct compared with the remaining part of the head. This peculiarity [6,7,9–12] may result in distinct clinical features and the key anatomical position of the uncinate process makes its separation from the SMA, SMV, and the retroperitoneum or even partial vessel resection (SMV and/or PV), of surgical importance in achieving R0 resection in case of uncinate cancer.

Clinical symptoms of UPDAC often appear late in the course of the disease. In contrast to cancer arising in the head of the pancreas, there is a lack of jaundice as a presenting symptom (Tables 95.1 and 95.2). The literature provides only scanty data on UPDAC [5]. Described clinical symptoms are abdominal pain (74%), weight loss (69%), jaundice (28%), and duodenal obstruction (9%). The cumulative resectability lies between 16.7% and 31%.

**Table 95.1** Clinicopathologic findings of patients with UPDAC: an overview of the reported series.

| Author | Suzuki et al. [11] | Yamaguchi [13] | Birk et al. [10] | Li et al. [12] | Ye et al. [7] | Kang et al. [8] |
|---|---|---|---|---|---|---|
| *n* | 6 | 3 | 39 | 10 (resected cases) | 59 (deemed resectable) | 161 |
| Sex (m:f) | 2:1 | 2:1 | 1.17:1 | 1.5:1 | 1.95:1 | 1.88:1 |
| Age | 57.7 ± 7.1 | 63 ± 6.97 | 63.3 (range 48–79) | range 50–61 | 60.2 (range 53–84) | 62 ± 10.6 |
| **Symptoms (%)** | | | | | | |
| Nausea | n/a | n/a | 51.28 | n/a | n/a | n/a |
| Diarrhea | 0 | n/a | 61.54 | n/a | n/a | n/a |
| Abdominal pain | 83.3 | 66.57 | 82.05 | 100 | 67.8* | 62.3 |
| Lumbar pain | 66.67 | n/a | n/a | n/a | * | n/a |
| Jaundice | 16.67 | 0 | 12.82 | 20 | 40.68 | 45.3 |
| Palpable mass | 33.3 | n/a | n/a | n/a | 0 | n/a |
| Weight loss | 100 | n/a | 87.18 | n/a | 57.63 | 46.8 |
| Duration of symptoms (months) | 5 | n/a | 5.5 | n/a | 12 | 1.9 ± 2.1 |
| **Resection (%)** | 16.67 | 66.67 | 30.77 | 100 | 89.83 | 31.7 (22.3 % R0) |
| Venous resection | 0 | 0 | 25 | 70 | 30.19 | 11.8 |
| Overall survival (months) | 4.05 | 4.67 | 5 | 17 | 12.1 | 21 (median) |
| 3-year survival rate (%) | n/a | n/a | n/a | n/a | n/a | 5.9 |

* mostly associated with lumbar pain.

**Table 95.2** Comparison of clinicopathologic findings of uncinate process (UPDAC) and non-uncinate process cancer (non-UPDAC) [8].

| | UPDAC (161) | Non-UPDAC (292) | *P* |
|---|---|---|---|
| Age | 62.0 ± 10.6 | 61.1 ± 10.9 | 0.710 |
| Sex (m:f) | 1.88:1 | 1.89:1 | |
| Symptoms | | | |
| Abdominal pain | 62.3% | (51.7%) | 0.032 |
| Weight loss | 46.8% | 35.8% | 0.022 |
| Jaundice | 45.3% | 56.2% | 0.027 |
| Duodenal obstruction | 8.7% | 4.8% | 0.099 |
| Symptom duration (months) | 1.9 ± 2.1 | 1.7 ± 1.8 | 0.189 |
| Operation | 42.2% | 58.6% | 0.001 |
| Resection | 31.7% | 46.2% | 0.003 |
| curative intended | 24.8% | 41.8% | <0.001 |
| R0 resection | 22.3% | 35.6% | 0.003 |
| Recurrence after R0 resection | 66.7% | 65.4% | 0.889 |
| Median survival after R0 resection (months) | 21 | 26 | 0.018 |

Despite advances in the treatment of many surgical malignant entities the outcome of surgery for uncinate process pancreatic cancer remains poor. The 1- and 3-year survival rates are 71% and 5.9%, respectively (Fig. 95.2). The median overall survival after R0 resection is lower for UPDAC than for non-UPDAC (15 months vs. 19 months; $P = 0.036$) [6].

The invariably final part of removing the resectate during a pancreatoduodenectomy is the division of the uncinate process and the retroperitoneal separation. This approach is made more difficult when the cancer emerges in the uncinate process. In this case, vascular and nodal as well as margin involvement and thus reduced survival are more likely. However, there is still a lack of evidence of increased venous and nodal involvement and a higher rate of either macroscopic or microscopic positive resection margins in UPDAC. Despite improvements in chemotherapy and surgical techniques for treating UPDAC (Tables 95.1 and 95.2) in recent decades, the short-term prognosis remains poor and further investigations of this entity are highly desirable.

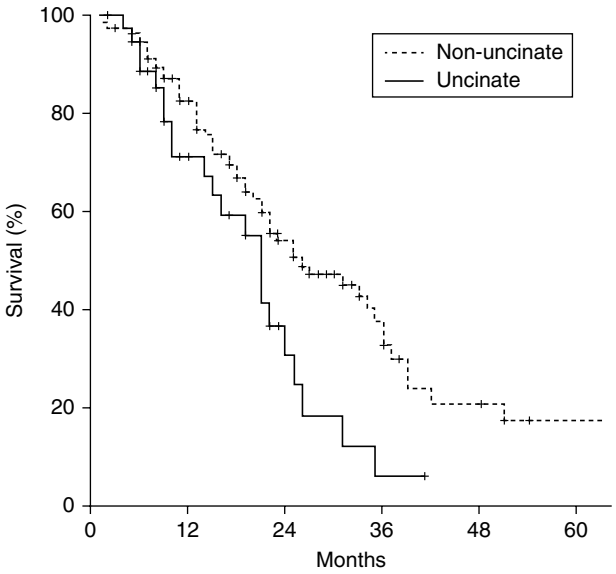


**Figure 95.2** Kaplan-Meier curve for overall survival in patients after R0 resection according to the tumor location.

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# 96

# The Role of EUS in the Diagnosis and Differential Diagnosis of Neoplastic Lesions

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## Introduction

Imaging modalities such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS), have remarkably improved the visualization of small lesions. Although these modalities can detect pancreatic lesions <2 cm, differentiating benign from malignant lesions based on morphologic appearance alone remains challenging. Therefore, a safe, accurate, and straightforward method of tissue sampling is required. Minimally invasive EUS was developed during the 1980s to visualize and collect tissues from embedded organs such as the pancreas.

Among various methods of sampling pancreatic lesions, EUS-FNA has become indispensable [1]. This section describes EUS and EUS-guided FNA (EUS-FNA) for evaluating and differentially diagnosing pancreatic disorders.

## Characteristics of Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is the most popular endoscopic technique used to diagnose and evaluate pancreatic masses [2]. High-resolution images of the pancreas can be generated by placing a high-frequency probe in close proximity to the pancreas [3].

The EUS equipment includes probes for various imaging procedures (Fig. 96.1): radial probes allow 360° imaging perpendicular to the long axis, and convex probes allow imaging along a plane parallel to the long axis of the instrument (Table 96.1). The former allows only diagnostic imaging, whereas the latter was developed for fine-needle aspiration (FNA) [4,5]. Pancreatic masses can be detected by EUS with 93–100% sensitivity and a negative predictive value approaching 100%, particularly when combined with FNA [6]. Small masses (<2 cm) that can be detected by EUS, may be identified as occult according to other imaging modalities and for patients with previous indeterminate findings.

The National Comprehensive Cancer Network (NCCN) guidelines for pancreatic adenocarcinoma state that patients without a pancreatic mass evident on cross-sectional images should undergo further evaluation with EUS and/or endoscopic retrograde cholangiopancreatography (ERCP) as clinically indicated [7]. Another advantage of EUS is that pancreatic masses can be detected and characterized without intravenous contrast, which is of particular importance when patients have renal dysfunction or other contraindications.

## New Screening Modality Comprising Contrast EUS and Elastography

Conventional EUS sometimes cannot detect pancreatic tumors in patients with chronic pancreatitis, diffusely infiltrating carcinoma, or a recent episode of acute pancreatitis [8]. Contrast enhanced (CH)-EUS and EUS elastography may help to improve the diagnostic accuracy of EUS.

Parenchymal perfusion and the pancreatic microvasculature can be visualized without artifacts by CH-EUS [9], and it is useful in the differential diagnosis of pancreatic cancer, especially when tumors are small [10,11]. Fusaroli et al. [12] reported that pancreatic tumor visualization is more precise by CH-EUS than by conventional EUS. A recent meta-analysis of 1,139 patients found that the sensitivity and specificity of CE-EUS for a differential diagnosis of pancreatic cancer were 94% and 89%, respectively [10].

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Radial scope

Convex scope

**Figure 96.1** Radial and convex EUS. Radial EUS image is 360° perpendicular to the long axis. Convex EUS image is along a plane parallel to the long axis of the instrument.

**Table 96.1** Advantages and disadvantages of EUS imaging modalities.

| | Radial scope | Convex scope |
|---|---|---|
| Advantages | • Scanning range is 360°<br>• Pancreas is easily seen as a longitudinal and continuous image | • Histologic diagnosis is possible<br>• Junction between the pancreatic head and body can be seen from the stomach |
| Disadvantages | • Histologic diagnosis is impossible<br>• Operator-dependent | • Scanning range is 180°<br>• Images of the body and tail of the pancreas become cross-sectional images |

The higher sensitivity of CH-EUS allows it to identify targets of EUS-FNA [12–14] and might also help to avoid puncturing necrotic and inflammatory areas of malignant masses or hard and scirrhous areas of inflammatory masses, thus reducing the need for repeated FNA assessments.

Another emerging technology is EUS elastography, which can visualize tissue stiffness in real time. It is based on the premise that compression causes less strain on hard, than on soft tissues [15]. The results of recent investigations using EUS elastography for diagnosing pancreatic focal lesions are promising [16–18]. As malignant lesions are generally harder than normal adjacent tissue, measuring strain might help to classify pancreatic masses. Two meta-analyses recently found high pooled sensitivity (95–97%) and low pooled specificity (67–76%), for a differential diagnosis of solid pancreatic masses [19,20]. However, CH-EUS and EUS elastography are not widely available and have yet to be widely tested as screening tools for pancreatic cancer [21,22].

## EUS-FNA for Solid Pancreatic Lesions (Figs 96.2 and 96.3)

### Indications

A fundamental principle of EUS-FNA is that the information obtained should have the potential to affect patient management [23,24]. In addition, the indications for EUS-FNA should be guided by its diagnostic accuracy, cost-effectiveness, and patient comfort and safety [23–26]. EUS-FNA is indicated for cytopathologic diagnoses of lesions of the gastrointestinal tract (and adjacent tissue) and of lymph nodes in their vicinity when less invasive or other sampling methods have failed.

### Contraindications

When the risks associated with the procedure outweigh the expected benefits of the diagnostic information obtained, EUS-FNA is contraindicated. Contraindications would include all conditions where the FNA findings would not affect patient management, when the lesion cannot be clearly visualized or a tumor mass or vessel is interposed between the needle-to-target path, when a patient is susceptible to bleeding or has a risk of tumor seeding [23–26].

## Diagnostic Yield and Safety of EUS-FNA for Solid Pancreatic Lesions

The reported sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of EUS-FNA for detecting pancreatic cancers are 79–98%, 71–100%, 96–100%, 33–85%, and 82–98%, respectively [26–31]. False negative and false positive

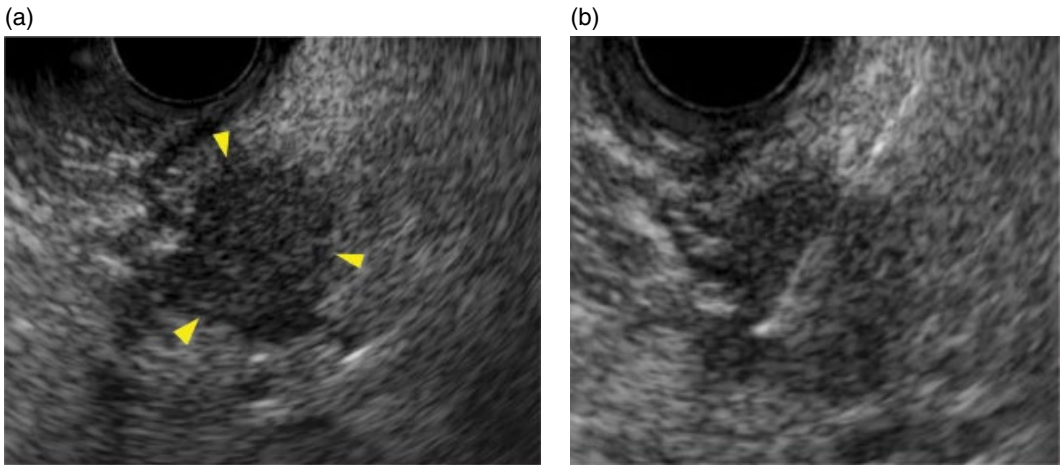


**Figure 96.2** Representative EUS findings of an adenocarcinoma. (a) Convex EUS shows a 12 mm low echoic mass with unclear margin in the uncinate process. (b) EUS-FNA proceeded using a 22G FNA needle.

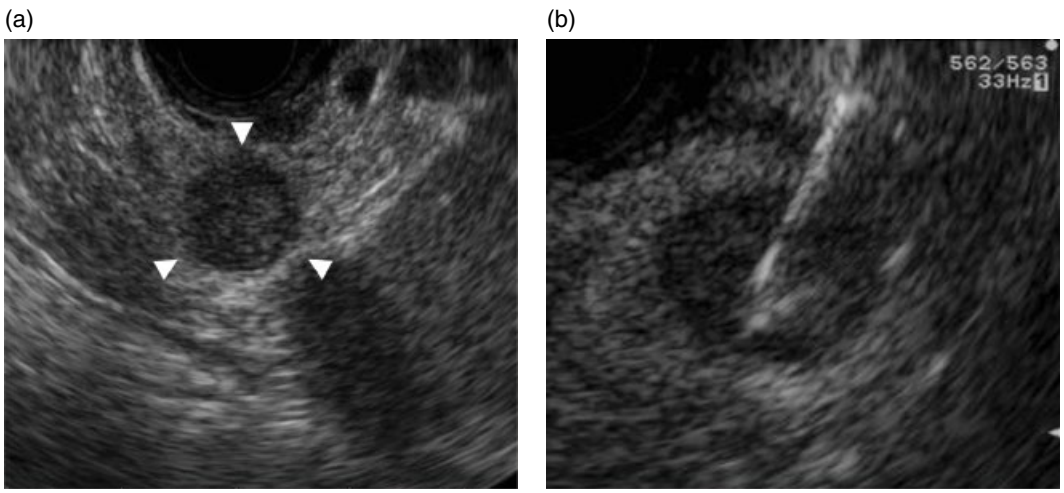


**Figure 96.3** Representative EUS findings of a neuroendocrine tumor. (a) EUS shows 6 mm low echoic mass with clear margin in the tail. (b) EUS-FNA proceeded using a 22G FNA needle.

rates are 12–14% and 0–5% [27,32–34], respectively. Although invasive, EUS is generally safe, as the range of total complication rates of EUS-FNA in a published series was 0–13% [35,36].

Complication rates determined in a multicenter study in the United States and a more recent prospective study were 0.28% [37] and 0.85% [35], respectively. The occurrence of complications was not definitively associated with the type and size of pancreatic lesions, number of passes, or history of chronic pancreatitis. The most frequent complications are bleeding (1–4%), pancreatitis (1–2%), and perforation (0.03%) [38]. Peritoneal tumor seeding is a rare complication that occurs less frequently after EUS-FNA than percutaneous biopsy [39]. Tumor seeding is a late complication that might be induced by EUS-FNA, and several case reports have indicated gastric and/or peritoneal dissemination in patients with cancer at the pancreatic body and tail [40–42]. However, several retrospective studies have not found definitive evidence that EUS-FNA increases levels of dissemination or worsens survival [43–45]. For example, Ngamruengphong et al. [43] analyzed data from 498 (24%) of 2,034 patients with surgically resected pancreatic cancer listed in the US Surveillance Epidemiology and End Results (SEER) medical database who underwent EUS-FNA between 1998 and 2009. The results revealed a marginally improved prognosis for the patients who underwent EUS-FNA compared with those who did not, even when the data were adjusted for the tumor site.

## Factors Affecting EUS-FNA Procedures

Most studies have shown that having a rapid on-site evaluation (ROSE) by a cytopathologist is beneficial, although this may be difficult in smaller hospitals [1,46]. The yield, accuracy, and complication rates do not differ among needle sizes including 19G, 22G, and 25G [1,46]. However, the 25G needle remains popular due to its flexibility in accessing the head of the pancreas and uncinate lesions [47]. Core biopsy needles do not appear to confer an advantage over 22G or 25G FNA needles except for reducing the number of passes required for an adequate sampling [1,46]. Furthermore, the use of stylets, suction, and various sampling techniques have not consistently increased the yield of FNA [1,46].

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# 97

# Radiologic Diagnosis of Pancreatic Cancer: CT, MRI

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## Introduction

Despite the large variety of advances in the surgical and oncologic treatment of pancreatic cancer over the course of the last decade, pancreatic adenocarcinoma still carries an extraordinarily poor prognosis with a high mortality, representing the fourth leading cause of cancer-related mortality in the United States. Fewer than 20% of patients are considered to be candidates for curative resection at the time of presentation, and unfortunately, even in patients considered to be candidates for curative resection, the overall survival rate is less than 15% [1,2]. Despite these poor numbers, it is worth remembering that imaging plays an extraordinarily important role in the evaluation of patients with pancreatic cancer, particularly when surgical resection is still considered a potential option. Not only does modern imaging (particularly CT and MRI) play an important role in identifying these aggressive malignancies in their earliest stages (when they are still potentially resectable), these imaging modalities also play a critical role in terms of properly staging these tumors and providing the information necessary to determine whether a patient is truly capable of undergoing an R0 surgical resection (i.e., complete surgical resection with negative tumor margins) [1,2].

This chapter will detail the two most important imaging modalities in the preoperative evaluation of pancreatic cancer, namely multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI). MDCT is currently the most important modality for the evaluation of pancreatic cancer, playing a vital role in the initial identification of tumors and subsequently, allowing optimal staging of a tumor's local extension (including vascular involvement) and identifying the presence/absence of distant metastatic disease. MRI, alternatively, may allow the identification of tumors in difficult cases where tumors may be small or isodense to the pancreatic parenchyma on CT (and thus not adequately visualized), and can also be helpful in terms of staging distant metastatic disease in equivocal cases, particularly when evaluating indeterminate liver lesions [3]. This chapter will discuss standard protocol options for both MDCT and MRI, the typical imaging findings of pancreatic cancer on each of these two modalities, and the strengths and weaknesses of each of these modalities both in terms of lesion identification and tumor staging.

## Multidetector Computed Tomography

### Technique

The MDCT evaluation of the pancreas and biliary system makes the administration of intravenous (IV) contrast absolutely critical, as noncontrast images make adequate visualization of small tumors nearly impossible (with the vast majority of small pancreatic cancers appearing invisible on noncontrast imaging). Typically, roughly 100–120 cc of intravenous contrast media are administered through a peripheral IV, and a small amount of water (roughly 500–750 cc) is ingested by the patient immediately prior to the scan in order to distend the stomach and duodenum and allow the radiologist to distinguish duodenal or gastric pathology from a true pancreatic mass. Most standard pancreaticobiliary CT protocols employ a dual-phase technique, with the acquisition of both arterial and venous phase images. Arterial phase images are typically acquired at roughly 30 to 40 seconds, often using bolus tracking software, while venous phase images are typically acquired between 60 to 70 seconds, typically using a fixed delay.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

Noncontrast and delayed images have little utility in the evaluation of pancreatic cancer and are usually not acquired as a part of these protocols [1,2].

Images on the most recent generation of CT scanners can be acquired with extremely thin collimation (0.625–0.75 mm), and these thin collimation images can subsequently be reconstructed into thicker axial images (3–5 mm) for standard radiology review, and facilitate the reconstruction of high-quality coronal and sagittal reformations directly at the CT scanner. In addition, the evaluation of pancreatic cancer is one instance where 3D reconstructions can be very helpful, particularly when evaluating vascular involvement by tumor. Thin collimation images are typically sent to an independent workstation where the radiologist can use advanced 3D visualization software to create 3D images in real time. The two most important 3D reconstruction algorithms being used widely today in clinical practice include maximum intensity projection imaging (MIP), a 3D technique that entails the acquisition of the highest attenuation voxels in a data set and their projection into a 3D image (a very important technique when seeking to evaluate a tumor's involvement of the adjacent vasculature), and volume-rendered imaging (VR), a complex computational algorithm that assigns a specific color and transparency to each voxel in a data set. Which of these two techniques is most useful will depend on the individual radiologist's preferences, the specific tumor being imaged, and the imaging feature being evaluated [1,2,4–6].

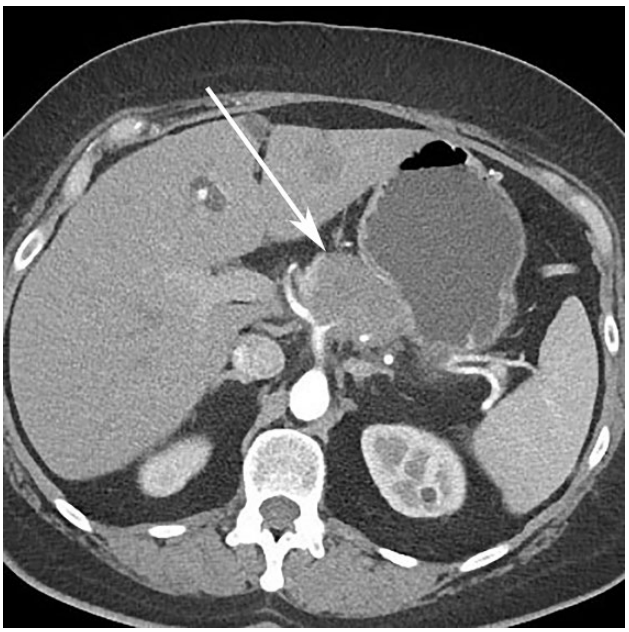

**Figure 97.1** Axial contrast enhanced CT image demonstrates a hypodense mass centered in the pancreatic body (arrow), with infiltrative, poorly defined margins, classic for pancreatic adenocarcinoma. Note that the tumor involves the celiac artery, hepatic artery, and splenic artery, and abuts the adjacent stomach.

## Diagnosis

Pancreatic adenocarcinoma appears as an infiltrative, hypodense, poorly marginated mass with frequent extension posteriorly into the retroperitoneum to involve critical vascular structures (Figs 97.1, 97.2, 97.3, and 97.4) [7–10]. The literature has shown that MDCT is an excellent modality for the identification of pancreatic cancer, with sensitivity rates well over 95%, and it is very likely that this underestimates the true sensitivity of CT, particularly given the rapid improvements in both temporal and spatial resolution seen with the most recent generation of CT scanners over the last several years. Much of the data we have regarding the efficacy of MDCT for pancreatic cancer is based on early generation scanners in the early multidetector era, and it is undoubtedly true that modern CT scanners have many additional features and improvements that have added to the efficacy of the imaging modality. In most cases, pancreatic cancer is most apparent in the venous phase, with the hypodense tumor nicely juxtaposed against the enhancing pancreatic parenchyma, although there are some cases where the tumor may be slightly more conspicuous on the arterial phase (as compared to the

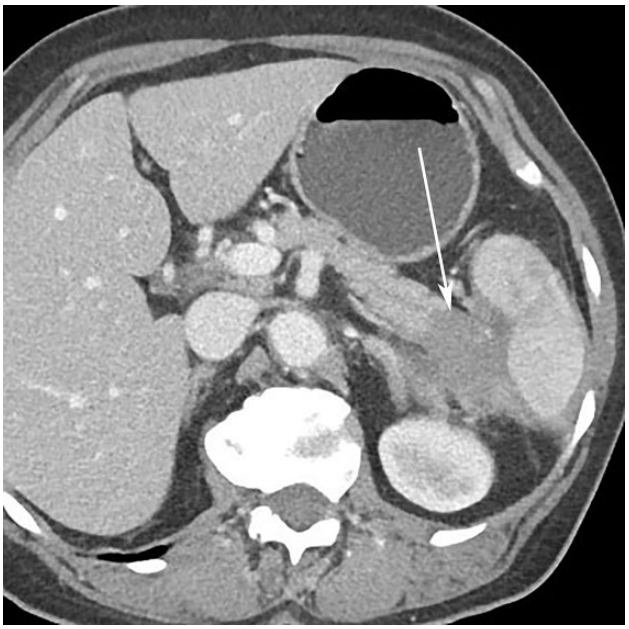

**Figure 97.2** Axial contrast enhanced CT image demonstrates a poorly defined hypodense mass (arrow) centered in the pancreatic tail, compatible with pancreatic adenocarcinoma. The tumor in this case is markedly infiltrative, involving not only the adjacent spleen but also extending to involve the adjacent left adrenal gland.

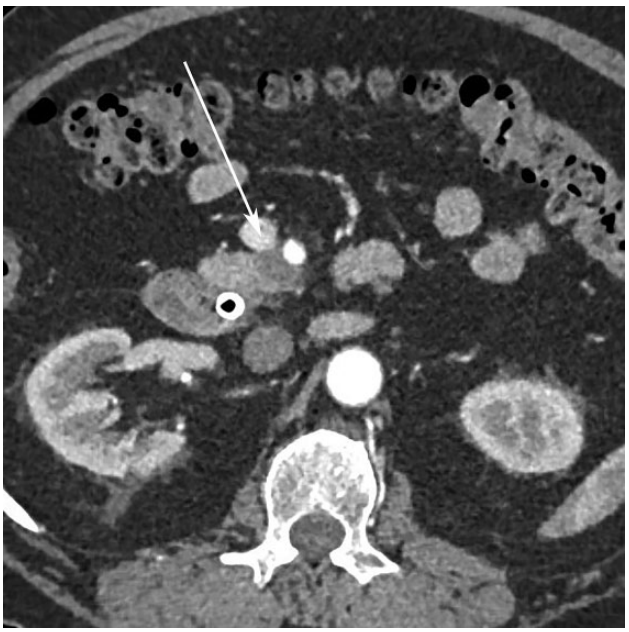

**Figure 97.3** Axial contrast enhanced CT demonstrates a subtle hypodense mass (arrow) in the uncinate process, a location in which pancreatic tumors are commonly missed on CT.

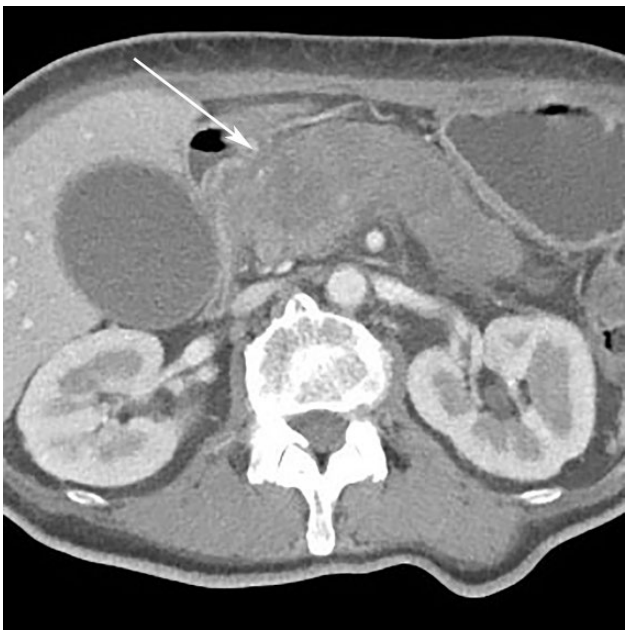

**Figure 97.4** Axial contrast enhanced CT demonstrates a large hypodense infiltrative mass (arrow) involving nearly the entirety of the pancreas, found at resection to represent pancreatic adenocarcinoma.

venous phase). Accordingly, the acquisition of images using a dual-phase technique does improve sensitivity, particularly when seeking to identify subtle or small tumors [11–13]. Nevertheless, it is worth remembering that there are small subcentimeter tumors (probably

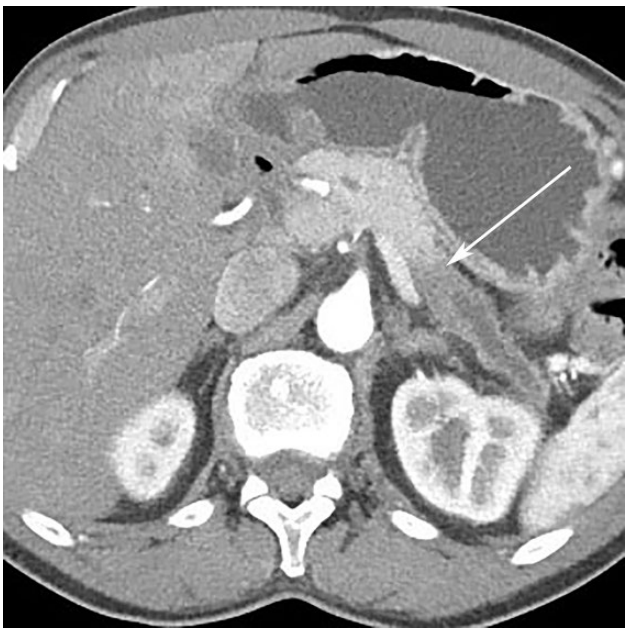

**Figure 97.5** Axial contrast enhanced CT demonstrates a very subtle hypodense mass (arrow) in the pancreatic body segment, representing pancreatic adenocarcinoma. Noticeable is severe atrophy with a dilated pancreatic duct in the upstream pancreas, features that are highly suggestive of an underlying malignancy. The presence of a dilated pancreatic duct with pancreatic atrophy, even in the absence of a discretely visualized mass, should raise strong concern for an occult tumor.

representing less than 5% of all lesions) that are isodense to the pancreatic parenchyma on all phases of imaging, and can thus be very difficult to identify in the absence of secondary signs of malignancy [14].

Even if the primary tumor is not clearly visualized, secondary signs of malignancy can be extraordinarily helpful in terms of identifying subtle or small lesions. In particular, the most important secondary signs of malignancy include focal or upstream pancreatic atrophy, pancreatic ductal dilatation/obstruction with abrupt cut-off of the pancreatic duct, biliary ductal obstruction (especially with pancreatic head malignancies), and an abnormal contour of the pancreas [15,16]. In our own experience, many of the missed cases of pancreatic cancer that we have seen in our practice (or referred into our practice from outside institutions) have been due to one or more of these secondary signs of malignancy being ignored or disregarded. Of these secondary signs, by far the most important is the presence of a dilated pancreatic duct: A dilated pancreatic duct with abrupt cut-off should always be considered suspicious for an occult obstructing mass/tumor, even if the primary lesion is not clearly visible on CT, and should prompt further evaluation with another modality, usually endoscopic ultrasound (Figs 97.5 and 97.6) [17].

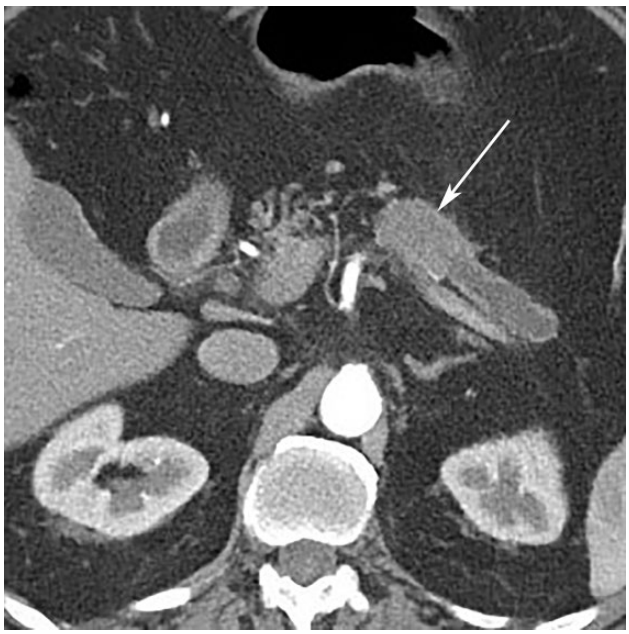

**Figure 97.6** Axial contrast enhanced CT demonstrates a hypodense pancreatic mass in the body (arrow) resulting in severe upstream pancreatic atrophy and abrupt obstruction of a dilated pancreatic duct.

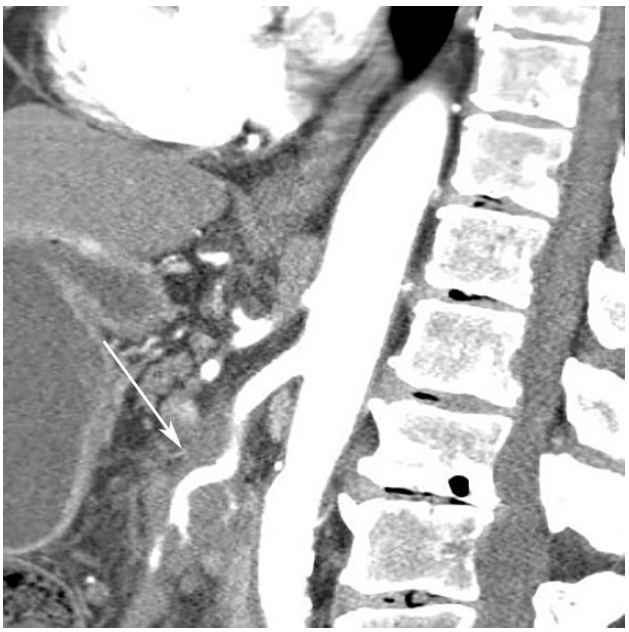

**Figure 97.7** Sagittal contrast enhanced CT demonstrates a hypodense pancreatic mass, representing a pancreatic adenocarcinoma, resulting in 360° encasement of the superior mesenteric artery, a feature that makes this patient's tumor unresectable.

## Staging

CT currently represents the best modality for the local staging of pancreatic adenocarcinoma, including a tumor's involvement of adjacent retroperitoneal vascular structures and other organs. In particular, a tumor's involvement of several critical retroperitoneal vascular structures plays a crucial role in terms of determining whether a patient is capable of undergoing an R0 surgical resection. The five vessels that are most important in determining a patient's resectability include three major arteries (i.e., celiac artery, superior mesenteric artery, and hepatic artery), and two major veins (portal vein, superior mesenteric vein, and portal/SMV confluence). It should be noted that only these five major vessels are important in terms of dictating a patient's resectability, while smaller vascular structures (such as the gastroduodenal artery or inferior mesenteric vein) do not have the same presurgical significance.

When evaluating the central mesenteric arterial vasculature using CT, tumoral involvement is typically stratified using a quantitative system, with tumoral involvement delineated as either involving <180° or >180° of the vessel circumference. The ability of CT to distinguish such subtle degrees of vascular involvement by tumor has become increasingly critical, as the line between "resectable" and "unresectable" tumors has increasingly become blurred. At one time, tumors that demonstrated *any* significant involvement of the celiac, SMA, or hepatic artery were considered "unresectable," while a tumor was considered "resectable" only if it did not involve any of these major mesenteric arteries. Increasingly, however, it is possible to have some mild degree of arterial involvement and be considered "borderline resectable," and still undergo surgical resection following preoperative neoadjuvant chemoradiation [18]. However, placing the patient into this "borderline resectable" category requires very careful evaluation of tumoral involvement of the vessel, and making quite subtle distinctions between <180° and >180° involvement of the vessel, although these distinctions have become slightly easier given improvements in image quality on the latest generation of scanners (Figs 97.7, 97.8, 97.9, and 97.10).

Involvement of the central mesenteric venous vasculature has recently become less of a hindrance for complete surgical resection because of the increasing utilization of modern vascular surgical reconstruction techniques (such as interposition grafts or other vein reconstruction procedures). Accordingly, a strict numerical descriptor of tumoral involvement of the portal vein or SMV is less important than providing the surgeon with enough information to determine whether a surgical reconstruction of the vein is feasible (when involved by tumor). In other words, the radiologist's report should provide information regarding the length and degree of venous involvement and whether there is sufficient normal portal vein above or normal SMV below the tumor to allow an interposition graft to be placed (Fig. 97.11).

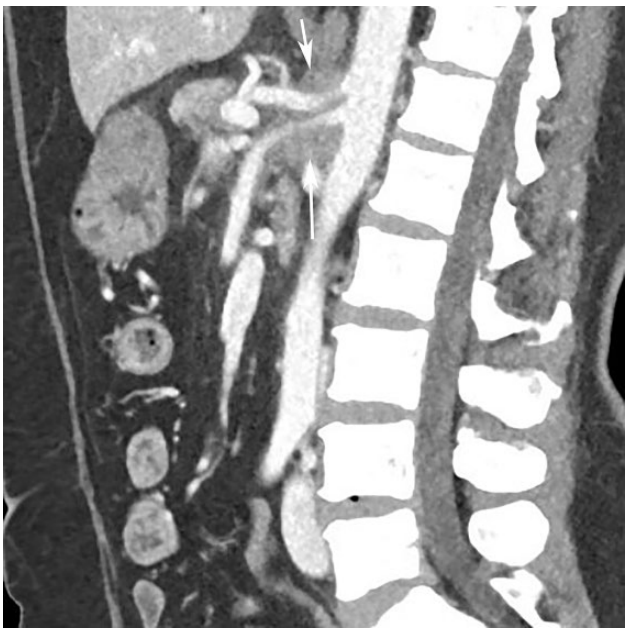

**Figure 97.8** Sagittal contrast enhanced CT demonstrates a poorly marginated hypodense pancreatic mass (arrows) resulting in 360° encasement of both the celiac artery and the superior mesenteric artery at their origins from the aorta.

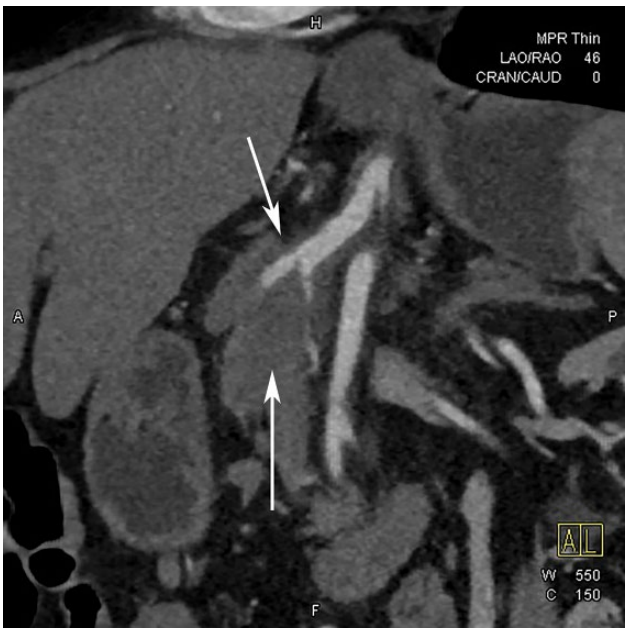


**Figure 97.10** Coronal contrast enhanced CT demonstrates a hypodense infiltrative pancreatic mass (arrows) resulting in 360° encasement of the distal celiac artery and the hepatic artery.

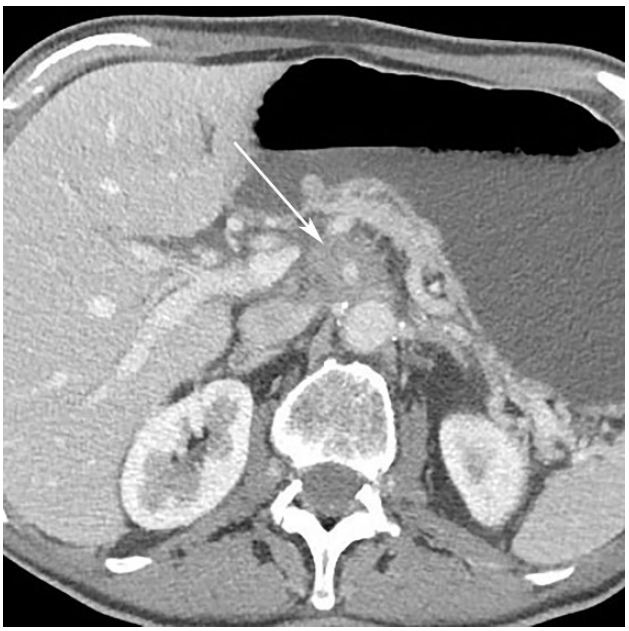

**Figure 97.9** Axial contrast enhanced CT demonstrates an infiltrative hypodense mass (arrow) arising from the pancreatic uncinate process resulting in 360° encasement of the celiac artery.

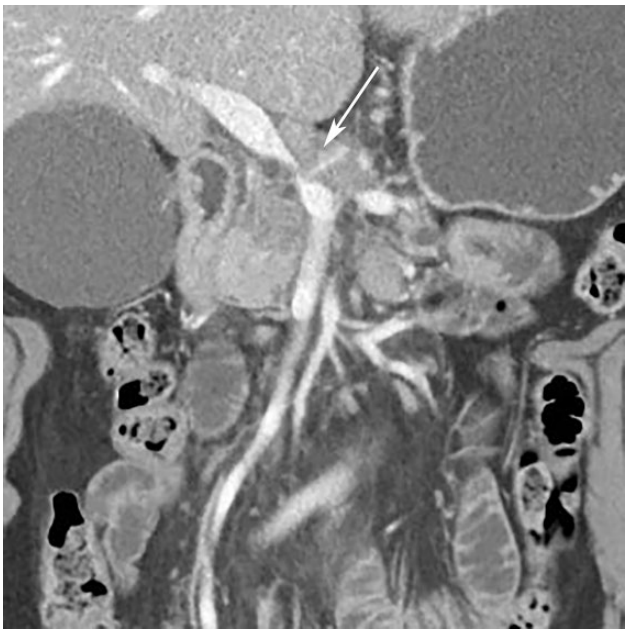

**Figure 97.11** Coronal contrast enhanced CT imaging the venous phase demonstrates a hypodense pancreatic adenocarcinoma (arrow) resulting in narrowing of the distal main portal vein near the portal/SMV confluence.

## Metastatic Disease

The most common sites of distant metastatic disease in patients with pancreatic cancer include locoregional lymph nodes, liver, and peritoneum, with metastatic disease to the lungs and bone relatively less common. As with many other malignancies in the abdomen/pelvis, the assessment of peripancreatic and retroperitoneal lymphadenopathy using CT is relatively limited, particularly given that CT

relies only on size criteria when delineating a node as "normal" or "suspicious." As one can imagine, normal size nodes can often harbor metastatic disease, while alternatively, enlarged nodes may be reactive and be histologically normal on surgical resection [19,20]. Accordingly, several studies looking at the sensitivity and specificity of CT for metastatic lymphadenopathy have shown that CT is relatively limited, with accuracy rates under 60% [1,2,21]. Fortunately, the accuracy of MDCT for metastatic lymphadenopathy is not of significant consequence, as locoregional lymph node metastases do not typically preclude a patient from undergoing surgical resection.

However, distant metastatic disease is critical in determining the patient's resectability, as the presence of distant metastases (most often to the liver or peritoneum) preclude surgical resection, making radiation or chemotherapy the only palliative options. The liver is, by far, the most common site of distant metastatic disease in patients with pancreatic cancer, and in virtually all cases, is the first site of distant metastatic disease (prior to the development of peritoneal, lung, or osseous metastatic disease). While the arterial phase of imaging may have some utility in the identification of liver metastases (demonstrating peripheral hyperenhancement around a lesion or perfusion abnormalities near a metastasis), the venous phase images are absolutely the most critical for the identification of liver lesions (Fig. 97.12). The overall sensitivity of CT for liver metastases is relatively good for lesions that measure over 1 cm, with sensitivity rates ranging above 75%. However, regardless of the type of primary tumor, the sensitivity of CT for smaller lesions (particularly lesions measuring under 1 cm in size) is relatively limited, probably with sensitivity rates under 50% [22]. In particular, part of the problem when assessing small liver lesions is accurately differentiating small benign lesions (such as cysts or hemangiomas) from truly malignant lesions, as standard imaging criteria can be very difficult to utilize for tiny too small to characterize liver foci. Nevertheless, the vast majority of these tiny nonspecific liver lesions (in the absence of clear morphologic features of malignancy) are benign, and MRI may be an additional helpful tool if it is absolutely necessary to further characterize these small lesions [23,24].

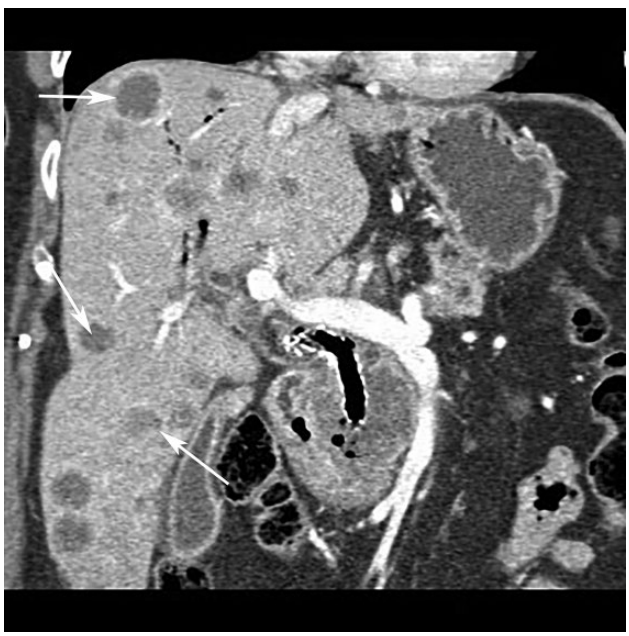

**Figure 97.12** Coronal contrast enhanced CT imaging a patient with a pancreatic head adenocarcinoma demonstrates multiple hypodense lesions (arrows) in the liver, some of which demonstrate peripheral enhancement, compatible with extensive metastatic disease to the liver.

The second most common site of distant metastatic disease in patients with pancreatic cancer is peritoneal carcinomatosis, and regardless of the primary tumor, CT is well known to struggle in the identification of early peritoneal metastatic disease. The overall sensitivity of CT for peritoneal disease is well under 50%, and the imaging appearance can be quite subtle in the earliest stages. The imaging appearance of peritoneal metastases can range from a subtle micronodular pattern (with tiny nodular foci in the omentum and adjacent stranding/induration) to the development of frank confluent omental soft tissue with an "omental caking" pattern. In most cases, peritoneal carcinomatosis is accompanied by the presence of ascites, so the presence of free fluid in a patient with pancreatic cancer should prompt a very careful, thorough search of the omentum and peritoneal cavity for tumor implants (Figs 97.13 and 97.14) [25].

## Magnetic Resonance Imaging

### Technique

While CT protocols for pancreatic imaging are relatively standardized across institutions (with some exceptions), there is a considerable variability in the types of MRI protocols utilized in different departments, in addition to a considerable amount of variation in the types of scanners being utilized at different institutions. Our own protocol for pancreatic imaging includes axial T2 FSE images with chemical fat saturation, coronal HASTE T2-weighted images, coronal T2 FIESTA images, magnetic resonance cholangiopancreatography (MRCP) images (both thick slab HASTE images and 3D volumetric T2 images), diffusion-weighted images (with ADC map), gradient echo sequences with in and out of phase imaging, as well as pre- and post-gadolinium T1-weighted images (with arterial, venous, and delayed phase acquisitions). One of the advantages of MR is that individual protocols can be tailored to the exact indication for the study and additional sequences can be added as necessary.

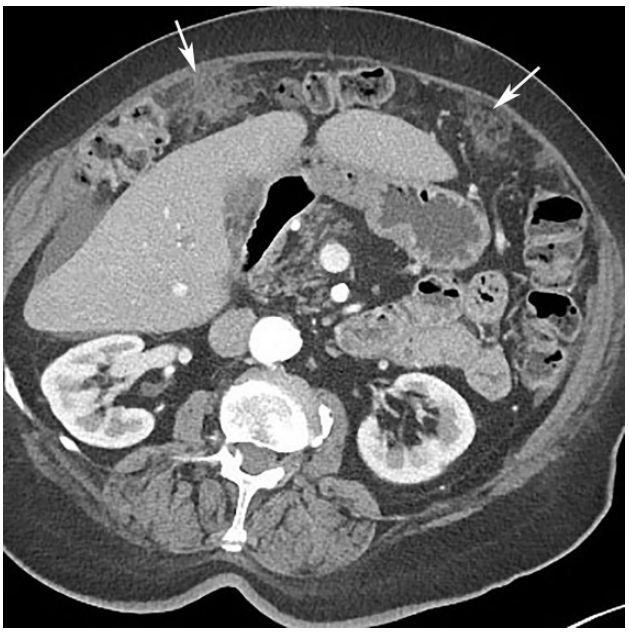

**Figure 97.13** Axial contrast enhanced CT imaging of a patient with known peritoneal carcinomatosis demonstrates a small amount of ascites, as well as ill-defined soft tissue and nodularity in the omentum (arrows), compatible with peritoneal carcinomatosis.

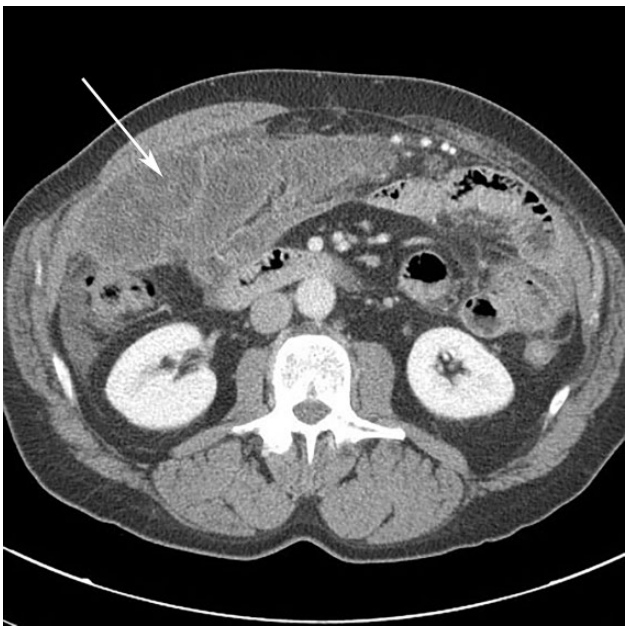

**Figure 97.14** Axial contrast enhanced CT demonstrates extensive hypodense soft tissue throughout the omentum, compatible with peritoneal carcinomatosis and "omental caking" in this patient with underlying pancreatic cancer.

## Lesion Identification

In most of the other organs of the abdomen, T2-weighted images are of critical importance, and often pathology will appear conspicuous as a result of its T2 hyperintensity. However, the pancreas is somewhat unique, given that its intrinsic T2 signal intensity can be quite variable depending on the age of the patient and the degree of fatty infiltration, and accordingly, pancreatic adenocarcinoma is often relatively inconspicuous on standard T2-weighted images. Alternatively, the pancreatic parenchyma contains a large amount of acinar protein, and in the absence of underlying chronic pancreatitis (which can reduce the T1 intensity of the pancreatic parenchyma), the pancreas is typically relatively T1 bright (roughly equal in signal intensity to the liver parenchyma). As a result, pancreatic cancers, which are usually relatively T1 hypointense and fibrotic, are often conspicuous when juxtaposed against the intrinsically T1 bright pancreatic parenchyma. T1-weighted images can, therefore, be relatively useful for lesion identification in patients who cannot receive gadolinium as a result of renal dysfunction or allergy. The pancreas upstream from the mass often appears atrophic and abnormally T1 hypointense as a result of fibrosis, and the upstream dilated/obstructed pancreatic duct is often nicely accentuated on T2-weighted images (Figs 97.15, 97.16, 97.17 and 97.18) [3,26,27].

Pancreatic adenocarcinoma on post-gadolinium images typically demonstrates an imaging appearance comparable to CT, appearing hypodense, infiltrative, and poorly marginated. While not reliably seen in all cases,

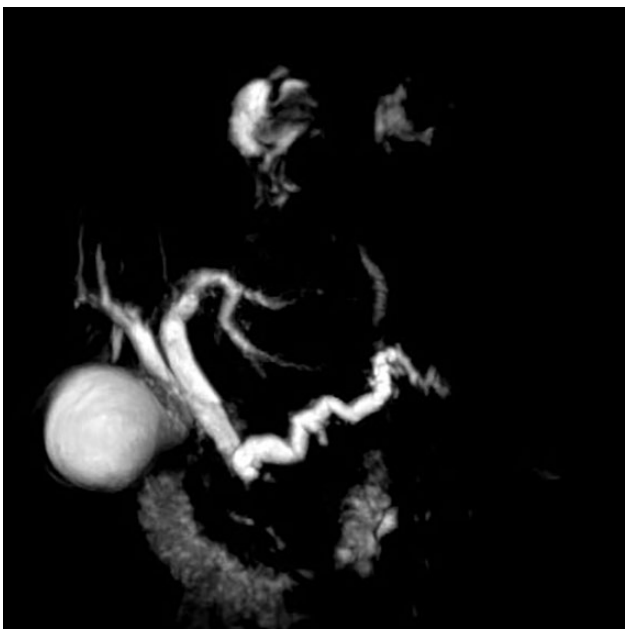

**Figure 97.15** Coronal MRCP images with maximum intensity projection reconstruction demonstrates a classic double duct sign of pancreatic adenocarcinoma, with marked dilatation of both the biliary tree and the pancreatic duct to the level of the pancreatic head, at the site of the patient's known pancreatic adenocarcinoma

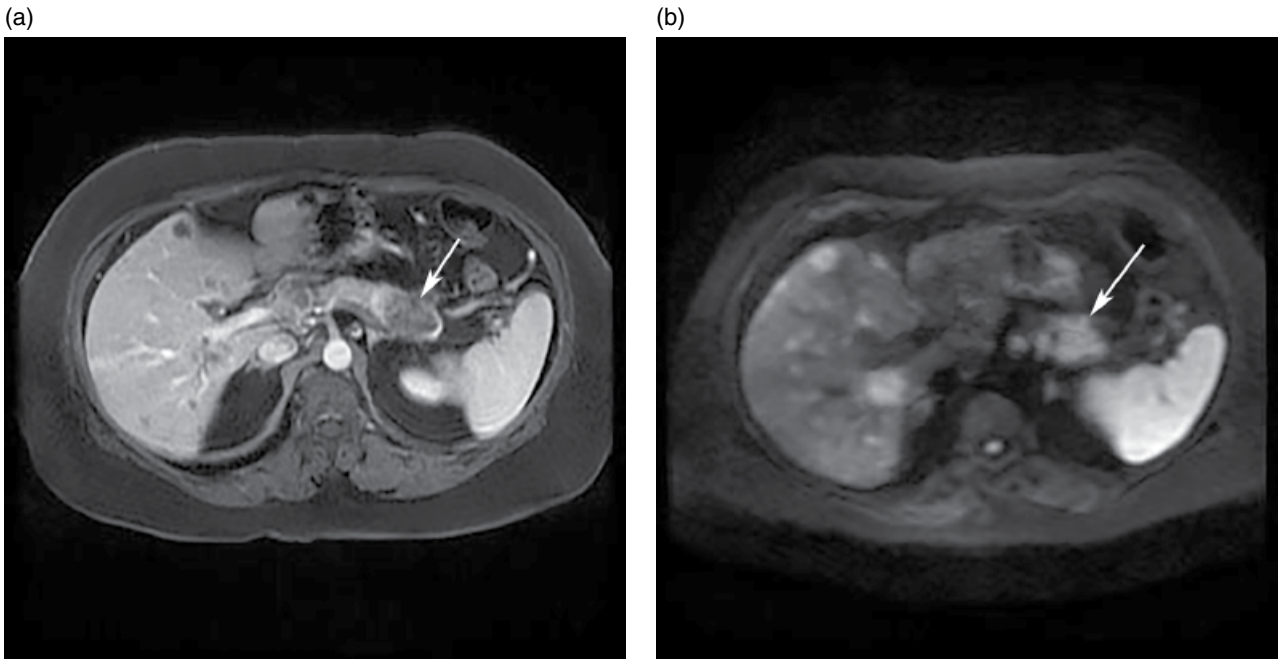


**Figure 97.16** Axial post-gadolinium T1-weighted image (a) and axial DWI (b) demonstrate a mass in the pancreatic tail (arrows), which demonstrates hypoenhancement on the post-gadolinium image and demonstrates restricted diffusion (i.e., bright on the DWI image). Notice the multiple metastases in the liver, which also demonstrate hypoenhancement and restricted diffusion.

many of these tumors do demonstrate restricted diffusion, offering another means of identifying subtle or small tumors that may be relatively inconspicuous on standard imaging sequences [3,26,28–32].

In most cases, MRI is not utilized for the initial screening or diagnosis of these tumors (although many sources suggest that it can be quite accurate when asked to do so), but rather as a troubleshooting tool to be used when a tumor is not adequately visualized on MDCT. In particular, MRI can be quite valuable in those cases where a primary tumor is strongly suspected on the basis of secondary signs (such as a dilated duct), but where the tumor is not seen on MDCT because it is too small or isodense to the pancreatic parenchyma.

## Tumor Staging

There is little doubt that MRI is generally inferior to multidetector CT in the local staging of pancreatic adenocarcinoma, and in particular, in evaluating a tumor's involvement of the critical retroperitoneal mesenteric vasculature. In general, CT is better for evaluating involvement of the mesenteric arteries and veins because of its superior temporal resolution, as CT images are much less likely than MRI to be plagued by motion artifacts or other technical artifacts that might make subtle determinations of vascular involvement difficult. Some authors have recently argued that technical advancements in MRI protocols and scanners may have made this gap less than was previously thought, but our own experience still argues for the superiority of CT in terms of staging vascular involvement [33,34].

MRI suffers from many of the same problems as CT in terms of evaluating locoregional lymph nodes, as MRI also largely relies on size criteria for the differentiation of benign from malignant lymph nodes. In some cases, as with CT, a lymph node can be delineated as abnormal based on morphologic characteristics (such as abnormal shape or central necrosis), but this is relatively comparable to CT. Unfortunately, while diffusion-weighted imaging was originally thought to hold some promise in terms of differentiating benign from malignant lesions, it is now clear that there is a significant overlap in the ADC values of benign and malignant lesions (including normal and abnormal lymph nodes), and the presence or absence of restricted diffusion within a lymph node is of little value in terms of making an absolute judgment as to whether or not a lymph node is infiltrated by tumor.

However, one area where MRI does have some clear advantages over CT is in the evaluation of indeterminate liver lesions. In particular, while CT struggles in terms of definitively characterizing lesions under 1 cm, this is an area where MRI may be a helpful troubleshooting tool, as multiple MRI pulse sequences can be used in conjunction together to make a more specific diagnosis, even in those cases where a lesion is under 1 cm, such as tiny cysts (which demonstrate a fluid signal on T2-weighted images) or small hemangiomas (which also demonstrate

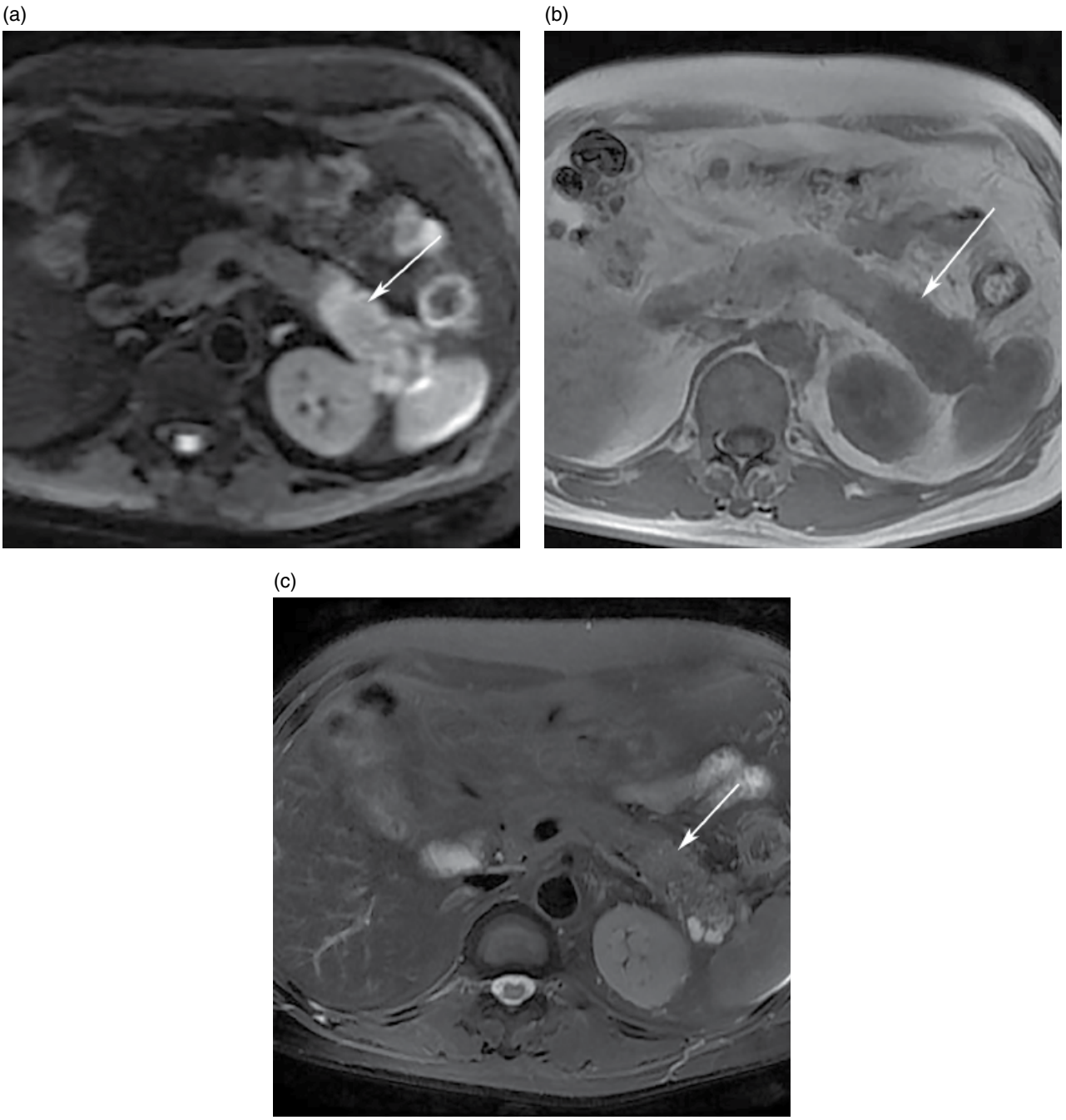


**Figure 97.17** Axial DWI (a), axial T1 without gadolinium (b), and axial T2 FSE with fat saturation (c) demonstrate a pancreatic adenocarcinoma (arrow) in the tail. Notice how the mass is relatively conspicuous on the pre-gadolinium T1-weighted images, juxtaposed against the T1 bright pancreatic parenchyma, and is also quite conspicuous on the DWI images as a result of restricted diffusion. However, as with many pancreatic adenocarcinomas, the mass is relatively inconspicuous on the T2-weighted images.

marked T2 hyperintensity). While not every patient with pancreatic adenocarcinoma requires evaluation of the liver with MRI, MRI may be a helpful tool in those few patients where an indeterminate liver lesion on CT may make a critical difference in terms of whether a patient is, or is not, a surgical candidate.

## Conclusion

There is little doubt that MDCT is currently the most important imaging modality for the identification of tumors, local tumor staging (including a tumor's involvement of adjacent retroperitoneal vasculature and

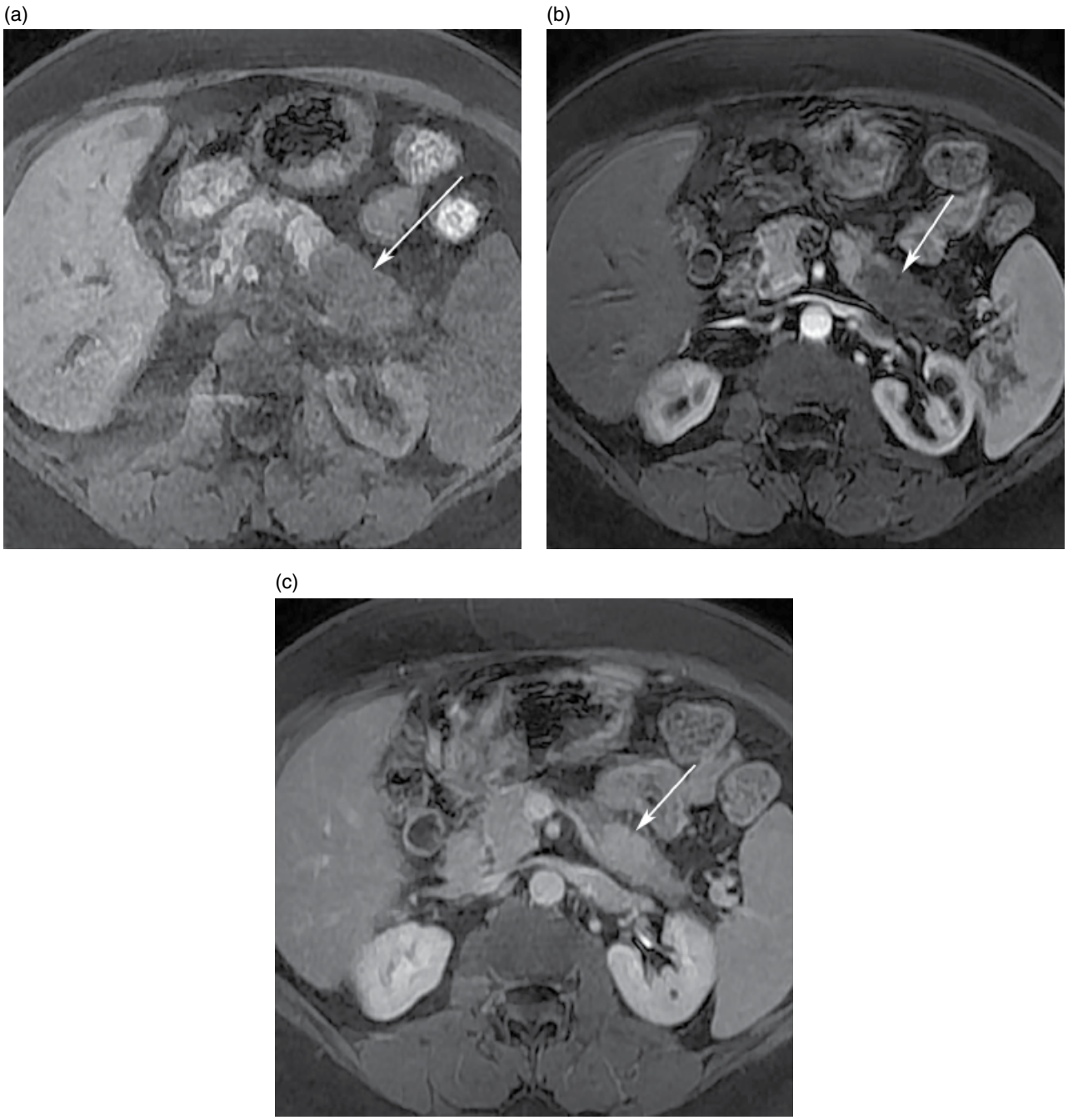


**Figure 97.18** Axial T1 without gadolinium (a), axial T1 post-gadolinium in the arterial phase (b), and axial T1 post-gadolinium in the delayed phase (c) demonstrate a hypodense mass (arrows) in the pancreatic tail, conspicuous on both the pre- and post-gadolinium images. The mass does demonstrate evidence of delayed enhancement, a relatively common feature with these tumors.

other organs), and the identification of distant metastatic disease (most commonly the liver and peritoneum). Every generation of CT scanners has brought additional improvements in terms of both temporal and spatial resolution, and it is likely that every new generation of CT scanners will allow us to better identify and stage these aggressive tumors [35]. While no one would argue that MRI should be a first-line modality in the identification and staging of pancreatic cancer, MRI does have a great deal of utility in terms of identifying lesions that may be occult or subtle on CT, and moreover, as a troubleshooting tool that might help provide more definitive answers when confronted with an indeterminate liver lesion on CT.

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# Screening of Patients with Hereditary Pancreatic Cancer

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## Pancreatic Cancer Risk and Pancreatic Screening

Pancreatic cancer is expected to be the second leading cause of cancer-related deaths in the USA by 2030 [1]. In the USA, the average lifetime risk of developing pancreatic cancer is ~1.4%. Since the long-term benefits of pancreatic screening are not known, screening is only offered to those individuals whose risk of pancreatic cancer is sufficiently high that the potential benefits are estimated to be greater than the potential risks of screening. Experts consider that pancreatic screening may be justified if the lifetime risk of developing pancreatic cancer is at least 5%, which is equivalent to a ~fourfold increased relative risk [2]. Estimating an individual's future cancer risk is an important step in deciding whether an individual should be considered for pancreatic screening.

The main tool used to quantify pancreatic cancer risk is the family history. A detailed cancer family history will determine whether or not individual is a first-degree relative of one or more subjects with pancreatic cancer and at what age pancreatic cancer developed in the family [3,4]. The estimates of pancreatic cancer risk in families have been achieved by following families long term in pancreatic cancer family registries [5]. Familial pancreatic cancer has been defined as kindred having two first-degree relatives with pancreatic cancer [6], although pancreatic cancer often runs in families who do not meet this definition. The risk of developing pancreatic cancer in first-degree relatives increases with the number of affected relatives [7]. This risk has been estimated to be 6.4-fold greater in individuals with two affected first-degree relatives (lifetime risk ~8–10%) and 32-fold greater in individuals with three or more first-degree relatives with pancreatic cancer (lifetime risk ~40%) [7]. Among kindred with familial pancreatic cancer, the risk of pancreatic cancer is higher in those with a young-onset pancreatic cancer (age <50 years, relative risk [RR] = 9.3) in their family compared to those without a young-onset case [4]. The increased risk of developing pancreatic cancer in pancreatic cancer families identified through prospective studies points to inherited factors, although it is suspected that in some families shared environmental factors plays a role in pancreatic cancer susceptibility.

Since the risk of developing hereditary pancreatic cancer is likely to be influenced by the same factors that influence the development of sporadic forms of the disease, in principle, pancreatic cancer risk factors such as smoking, obesity, diabetes, and pancreatitis history could be used to refine estimates of cancer risk [8–10]. However, to date these risk factors do not confer sufficient risk on their own to be useful in clinical practice [11].

Most patients with a family history of pancreatic cancer do not have an identifiable pancreatic cancer susceptibility gene mutation. However, identifying a cancer susceptibility gene mutation in a family can help identify which members of a family are at most risk of developing pancreatic cancer. Many pancreatic cancer susceptibility genes increase cancer risk at other organs and so knowledge of the genetic basis of a family's pancreatic cancer risk can help guide a patient's overall cancer surveillance. Gene testing to look for pancreatic cancer susceptibility genes is best performed on an affected individual with pancreatic cancer from a familial pancreatic cancer kindred. However, germline mutations in the known pancreatic cancer susceptibility genes explain only about 10% of the familial susceptibility to pancreatic cancer so most individuals with a family history of multiple pancreatic cancers who undergo gene testing will not have an identifiable susceptibility gene mutation.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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The genes known to cause hereditary forms of pancreatic cancer when mutated in the germline include *BRCA2*, *ATM*, *PALB2*, *CDKN2A (p16)*, *STK11*, *PRSS1* [12–16], and the hereditary nonpolyposis colon cancer (Lynch) syndrome [17] susceptibility genes, which are associated with a significantly increased risk of developing pancreatic cancer. In addition, recent genome sequencing of ~600 pancreatic cancer families identified the pancreatitis susceptibility gene, *CPA1*, as a candidate pancreatic cancer susceptibility gene (deleterious mutations were found in 4/598 families) [18]. Among familial pancreatic cancer kindred, *BRCA2* is the gene most likely to have deleterious germline mutations (usually found in ~5–10% of such families [21–23]). Approximately 1% of individuals of Jewish ancestry have a deleterious founder mutation in *BRCA2* [24–26]. Approximately 10% of individuals with pancreatic cancer and Jewish ancestry carry the founder *BRCA2* gene mutation (even in the absence of a family history) [27,28]. Therefore, all such individuals should be considered for genetic counseling and testing [29,30]. The average lifetime risk of developing pancreatic cancer in *BRCA2* gene mutation carriers is estimated to be ~5% [31–34]. In contrast to *BRCA2*, the risk of developing pancreatic cancer among germline *BRCA1* gene mutation carriers is modest (RR 2.3-fold increased risk), which suggests that *BRCA1* mutation carriers generally do not warrant pancreatic screening [35].

Germline *ATM* mutations are the second most common known cause of hereditary pancreatic cancer [12,18]. Individuals with germline *ATM* mutations are at increased risk of developing multiple types of cancer. The protein product of *ATM* functions in DNA repair pathways and undergoes somatic mutation in a variety of cancers [36]. In a large multicenter study of familial pancreatic cancer kindred the prevalence of *ATM* mutations was ~2% [18]. The lifetime risk of pancreatic cancer among *ATM* mutation carriers has not yet been determined. Germline *CDKN2A (p16)* gene mutations cause familial atypical melanoma mole syndrome (FAMMM syndrome) [37,38]. The lifetime risk of developing pancreatic cancer among *CDKN2A* mutation carriers is estimated to be ~20% [39–41]. Germline *PALB2* (partner and localizer of Brca2) mutations are found in <1% of patients with familial forms of pancreatic cancer [42–46]. The risk of developing pancreatic cancer among *PALB2* gene mutation carriers is not known but given the similar functions of *BRCA2* and *PALB2*, the risk may be similar. Kindred of hereditary nonpolyposis colorectal cancer (Lynch syndrome), which arises from germline mutations in mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) gene mutations, have an estimated lifetime risk of pancreatic cancer of 3.7% [17,47]. The pathologic features of pancreatic cancers with mismatch repair defects can be characteristic [48]. The significance of identifying Lynch syndrome families with cancer is more important than ever, since not only are such mutation carriers targets for cancer prevention strategies, cancers with mismatch repair defects (which also occur in sporadic cancers) are more likely to respond to immunotherapy with checkpoint inhibitors [49].

It is known that long-standing chronic pancreatitis predisposes to the development of pancreatic cancer [9,10,15,50–52]. This is best illustrated by the ~40% average pancreatic cancer risk associated with hereditary recurrent acute pancreatitis [15], a risk that is even higher for smokers with hereditary pancreatitis [15]. The gene most commonly implicated in hereditary chronic pancreatitis is *PRSS1* [53], and affected individuals typically develop pancreatitis in their teens and have many decades of pancreatitis that often results in pancreatic insufficiency [54]. Pathologically, the pancreas of *PRSS1* mutation carriers undergoes progressive lipomatous atrophy with increasing age [55]. While other genes such as *CPA1* that have been identified as pancreatitis susceptibility genes are now suspected to be causes of hereditary pancreatic cancer [18], this has not been shown to be true for carriers of the pancreatitis modifier genes, *SPINK1* and *CFTR* [56] that increase the likelihood of developing pancreatitis [18]. Patients with long-standing chronic pancreatitis from hereditary causes likely benefit from pancreatic screening but the detection of pancreatic neoplasia in such individuals is often more challenging because of the effects of pancreatitis [57].

Patients with Peutz–Jeghers syndrome (PJS) (who generally carry germline *STK11* gene mutations) have a very high risk of developing pancreatic cancer (cumulative lifetime risk 11–36%) [58,59].

Other low-penetrance genetic variants associated with pancreatic cancer susceptibility have been identified through genome-wide association studies (GWAS) [60–62]. Thus, carriers of non-O blood groups have an approximately 1.4-fold elevated risk of developing pancreatic cancer relative to O-blood group carriers [64–66]. GWAS have also identified variants *PDX1*, *TERT*, and other loci as being associated with pancreatic cancer risk [60–64].

Many patients with germline susceptibility genes that predispose to pancreatic cancer do not present with evidence of familial cancer syndromes. Instead, incomplete or low penetrance is common [16,18–20]. For example, most patients with familial pancreatic cancer who carry germline *BRCA2* mutations do not have extensive histories of breast or ovarian cancer [30]. Indeed, germline mutations in pancreatic cancer susceptibility genes are not infrequently detected in patients with apparently sporadic pancreatic cancer [19,20,67].

## At What Age Should Pancreatic Screening Begin and End?

Although the lifetime risk of developing pancreatic cancer for many individuals undergoing pancreatic screening is 5–10%, the age-specific incidence of pancreatic cancer is much lower than the lifetime risk. Pancreatic screening protocols attempt to screen individuals over the period starting a few years before their peak incidence of pancreatic cancer (age 55–80) [2]. The average age of individuals at diagnosis for those with familial/inherited forms of pancreatic cancer is 68 [4], similar to sporadic pancreatic cancer although pancreatic cancer is thought to emerge at a younger age among hereditary pancreatitis gene mutation carriers [15]. For this reason, most screening programs recommend pancreatic screening at age 55, although many screening programs initially start screening patients from age 50 or earlier [68,69]. The Cancer of the Pancreas Screening program at Hopkins and collaborating centers initiates pancreatic screening at age 55 for individuals who are first-degree relatives of at least one person with pancreatic cancer and another first- or second-degree relative (clinicaltrials.gov NCT02000089). One reason for beginning pancreatic cancer screening a decade or more before the average age of pancreatic cancer diagnosis was to provide an opportunity to identify and manage the precancerous lesions in affected individuals [69]. For those individuals who are known pancreatic cancer susceptibility gene mutation carriers, the screening recommendations are tailored depending on the gene mutation. For germline *CDKN2A (p16)* mutation carriers and subjects with Peutz–Jeghers syndrome, pancreatic screening is generally initiated at age 50 or earlier [68]. *BRCA2* mutation carriers are generally recommended to undergo pancreatic cancer screening if they have at least one blood relative with pancreatic cancer. For individuals with a young-onset blood relative with pancreatic cancer in their family (age <55) who meet other family history or gene mutation criteria for screening, it is often recommended to begin pancreatic screening 10 years before the youngest pancreatic cancer in the kindred. Pancreatic screening guidelines developed from available evidence and expert opinion [2] are summarized in Table 98.1. Consensus guidelines developed in 2011 did not agree on when pancreatic screening should be discontinued in pancreatic cancer families [2]. Pancreatic screening often continues beyond age 75 in subjects who have pancreatic cysts but it is probably appropriate to discontinue pancreatic screening by age 75 or 80 in high-risk individuals without any evidence of pancreatic precancerous lesions on prior screening.

**Table 98.1** Pancreatic cancer screening guidelines [2].

| Family history | Germline mutation/cancer syndromes |
|---|---|
| • ≥ 1 pair FDR w/ PC, at least 1 FDR to patient | • Peutz–Jeghers syndrome (PJS)<br>• FAMMM<br>• *BRCA2*/*PALB2* or *ATM* mutation carrier + 1 FDR or SDR with PC<br>• HNPCC mutation carrier + 1 FDR or SDR with PC |
| ***At what age should pancreatic screening begin?***<br>• For most individuals with a family history of pancreatic cancer: age 55 or 10 years younger than the youngest relative with pancreatic cancer.<br>• For *CDKN2A* germline mutation carriers, age 50.<br>• Peutz–Jeghers syndrome, age 40.<br>Surveillance: Annual surveillance is recommended unless concerning lesions are identified. | |

*Source*: Canto et al. 2013 [2]. Published under the terms of a Creative Commons licence. FAMMM, familial atypical melanoma mole syndrome; FDR, first-degree relative; PC, pancreatic cancer; SDR, second-degree relative.

## Pancreatic Screening Tests

Currently, pancreatic screening utilizes pancreatic imaging tests. In a head-to-head blinded comparison of pancreatic endoscopic ultrasound (EUS), MRI/MRCP and pancreatic protocol CT performed as part of the CAPS3 study of high-risk individuals, EUS had the highest rate of detection of pancreatic cysts, followed closely by MRI/MRCP [69]. MRCP provides the best visualization of cyst communication with the main pancreatic duct to determine the nature of the pancreatic cyst [70]. EUS has the advantage that it can identify subcentimeter solid lesions better than MRI, but it is more operator-dependent [71]. Pancreatic-protocol CT is currently less sensitive at detecting subcentimeter cysts [69] and also has the disadvantage of giving a low-dose of radiation, although the technology continues to improve. Pancreatic-protocol CT is also an excellent test to use to evaluate selected patients undergoing screening and surveillance when lesions of uncertain significance are identified.

## Lesions Identified by Pancreatic Screening

Pancreatic cysts are commonly identified in pancreatic screening cohorts. In the CAPS3 study the average age of the study population was 56 and over one third of the

study population had at least one pancreatic cyst with the prevalence increasing with advancing patient age [69]. Multiple other pancreatic screening studies of high-risk groups have reported a high prevalence of pancreatic cysts [68,69,72–80]. With improved pancreatic imaging in recent years, it is clear that pancreatic cysts are very prevalent in the general population, particularly among subjects in their 70s and older [81]. The high prevalence of pancreatic cysts in the general population and the recognition that most of these individuals are not going to develop pancreatic cancer has also raised questions as to the significance of pancreatic cysts in high-risk individuals. Although most pancreatic cysts identified in the screening population are branch-duct intraductal papillary mucinous neoplasms (IPMN), most of these are subcentimeter in diameter and the majority will not progress to invasive cancer [82]. To date, the number of pancreatic cancers detected by pancreatic screening in the literature is quite low (~1–5% of subjects under surveillance) [2], which is consistent with the expected age-specific incidence of pancreatic cancer of those undergoing screening.

Some patients who undergo pancreatic screening will have suspicious pancreatic cysts or solid lesions detected that are found at pancreatic resection to be nonneoplastic or of minimal malignant potential (such as serous cystadenomas, pancreatic neuroendocrine tumor, or lobulocentric parenchymal atrophy associated with PanIN) [80,83].

## Pancreatic Pathology not Detected by Current Screening Tests

Pancreatic cysts can be detected by pancreatic imaging even when they are quite small (~2 mm). But in the resected pancreata of patients who undergo pancreatic resection for pancreatic cysts, the most common neoplasm detected is the pancreatic intraepithelial neoplasia (PanIN) [83]. These lesions are generally too small (<5 mm diameter by definition) to be identified by current imaging modalities [84]. Although EUS can detect subtle changes like microcysts and hyperechoic foci that are often associated with the presence of PanIN, these EUS changes are not specific for PanIN [83,85]. PanIN-1 lesions are common in the population and have very low malignant potential [86], whereas PanIN-3 lesions are thought to have a significant risk of progressing to invasive cancer [84]. Most pancreatic cancers are thought to arise from PanIN and although pancreatic cysts (IPMN) are common in patients with hereditary forms of the disease, it is thought that most of the cancers that arise in these patients arise from PanIN [84,87–89]. Evidence for this comes from multiple sources. A blinded histologic review of hundreds of familial and sporadic pancreatic cancers found no significant differences in the histologic features of familial and sporadic cases, including no difference in the number of IPMN-associated cancers) [90]. Second, the genetic profiles of pancreatic ductal adenocarcinomas are similar to PanIN [91,92]. Finally, although ~66% of IPMN harbor *GNAS* mutations, *GNAS* mutations are not typically found in the pancreatic ductal adenocarcinomas of patients with a family history of pancreatic cancer [93–95].

## Surveillance

Because of the malignant potential of pancreatic cysts, their presence has been used to guide surveillance intervals. In recent years, surveillance recommendations for high-risk individuals have generally followed the recommendations used for subjects with pancreatic cysts without a familial susceptibility to pancreatic cancer [96] even though these recommendations were created from experience following patients with incidentally identified "sporadic" pancreatic cysts. However, the recognition that most pancreatic cysts (including those identified as IPMN) have low malignant potential [45,73,74,76,78] poses particular challenges in the high-risk setting. One the one hand, the cumulative cost and personal burden of annual pancreatic imaging tests is high. At the same time, it is understood that most pancreatic cancers arise from PanIN and it can be difficult to detect small pancreatic cancers. Indeed, among subjects that have had screen-detected pancreatic cancers, many have Stage II disease despite regular surveillance [97]. The recommendation that high-risk individuals undergo frequent (typically annual) surveillance reflects the underlying biology of pancreatic cancer and the limitations of current pancreatic imaging tests. Studies estimating the time to progression of pancreatic cancer predict that a cancer can progress from Stage I disease to Stage IV disease within approximately 1 year [98]. It may be appropriate to have longer surveillance intervals (several years apart) when the risk of pancreatic cancer is lower (such as for subjects in their 50s) increasing it to annually for older subjects, but more evidence is needed.

The choice of surveillance test is often influenced by practical considerations such as patient preference and insurance. Surveillance protocols often alternate EUS and MRI to provide complementary imaging and limit the burden of annual EUS [68]. Subjects who have large pancreatic cysts, pancreatic duct abnormalities, or solid lesions undergo fine-needle aspiration of any focal concerning lesion(s) and close surveillance.

## Surgery for Lesions Identified by Pancreatic Screening

As clinicians have gained experience with pancreatic screening, the indications for pancreatic resection in the screening setting have become more defined. Pancreatic resections are usually undertaken once there is evidence that a pancreatic cyst has features concerning for invasive cancer or for a cancerous solid mass or suspicious mass. Most patients are likely to develop their cancer from PanIN that will grow into a solid mass and not a cystic lesion. The strategy of waiting for the emergence of a cancer risks missing opportunities for cure as most patients who present with resectable cancers will not be cured, but operating on subjects with IPMN without a cancer or strong suspicion of cancer often results in overtreatment (the detection of PanIN-1 and low-grade dysplasia in IPMN). The rationale for performing pancreatic resection for high-risk patients with multiple medium-sized pancreatic cysts that do not individually meet criteria for resection is that some of these patients have PanIN-3 in their resected pancreata [80,83].

The choice of operation for high-risk patients with lesions identified by pancreatic screening can be challenging since some patients will have concerning cysts or other lesions in both the head and the tail of the pancreas. However, total pancreatectomy is only occasionally undertaken in this setting because of the potential morbidity associated with diabetes after total pancreatectomy. Instead, patients usually undergo partial pancreatectomy for screen-detected lesions and are then recommended to continue surveillance postoperatively. These cases are evaluated on a case-by-case basis preferably by an experienced multicenter team and at a high-volume center [99,100].

## Developing Better Pancreatic Screening Tests

The limitations of currently available pancreatic screening tests highlight the need for better tests. The most optimal test would be a simple blood test able to detect Stage I pancreatic cancers with high diagnostic accuracy. A screening test that performs well at detecting more advanced pancreatic cancers (even resectable cancers) would not have a major impact on survival since the median survival of patients with Stage II pancreatic cancer is less than 2 years [101,102]. Many candidate blood markers of pancreatic cancer have been developed, and most are not sufficiently useful for pancreatic screening. Screening blood tests need to have very high diagnostic performance since they can generate a lot of downstream testing with the risks of complications, worry, and cost. Serum CA19-9 has good performance characteristics but among patients with resectable pancreatic cancers only ~60% of these have elevated CA19-9 [103]. Some studies have identified elevated CA19-9 levels in a small fraction of prediagnostic blood samples from patients who subsequently develop pancreatic cancer [104,105]. Overall, it is the occasional false-positive elevations of CA19-9 that have limited its potential as a screening test [106]. Perhaps the best test identified to date is circulating *KRAS* mutations, but less than half of patients with resectable pancreatic ductal adenocarcinoma have detectable circulating tumor DNA [107,108]. Other markers such as glypican-positive exosomes and thrombospondin-2 have been reported to be potential markers of pancreatic cancer, but further evaluation of these markers is needed [109,110]. Most other circulating markers that have been reported as potential pancreatic cancer markers do not have the diagnostic characteristics that would make them suitable for pancreatic screening [111,112].

The inability of current pancreatic screening tests to detect PanIN-3 lesions means that we cannot identify patients most likely to progress to cancer. If this could be done reliably, screening intervals could be shortened for those with PanIN-3 and lengthened for those without PanIN-3. Approaches that have been used to identify PanIN by pancreatic screening include pancreatic juice analysis and molecular imaging. Analysis of secretin-stimulated pancreatic juice collected endoscopically from the duodenum of patients enrolled in the CAPS trials revealed that *KRAS* mutations are often detected in the pancreatic juice of high-risk individuals without pancreatic cysts or pancreatic cancer; these mutations are thought to arise from small PanIN lesions [113]. Similarly, *GNAS* mutations are detected in the pancreatic juice of over half of patients with evidence of IPMN (close to what would be expected if one directly analyzed their IPMN) [82,114,115]. Next-generation sequencing analysis of pancreatic juice can be used to detect low-abundance mutations affecting multiple genes (such as *KRAS*, *TP53*, *SMAD4*, *GNAS*, *CDKN2A*, and *RNF43*) from the pancreata of patients with pancreatic ductal adenocarcinoma [97]. Improvements in how pancreatic juice is collected may be needed to improve the diagnostic yield of this sample [114].

Molecular imaging offers the possibility to detect these lesions in the future [116], but the molecular targets and imaging approaches needed are still under investigation (such as more IPMN-associated cancers) [117].

## Evaluating the Long-Term Outcomes of Patients who Undergo Pancreatic Screening

Large multicenter studies involving patients followed for many years will be required to prove the benefit of pancreatic screening. The goal of pancreatic screening is to demonstrate it can reduce the risk of pancreatic cancer death. Although such trials are needed, it is clear we still do not have optimal screening tests so such large studies probably need to await for better screening tests. Such studies need to await improvements in our ability to identify individuals at most risk of developing pancreatic cancer. For now, surrogate endpoints (such as the detection of Stage I pancreatic cancer, resectability rate, PanIN-3 lesions, and IPMN with carcinoma *in situ*) are used to define the success of pancreatic screening. Since most patients who have their pancreatic cancer diagnosed by screening will have advanced disease, and since the 5-year survival of patients with Stage I pancreatic cancer is considerably higher than for those with advanced disease, the detection of Stage I pancreatic cancer is a good surrogate endpoint [118,119]. Treating Stage I pancreatic cancer is likely to improve patient outcome for most patients, although lead-time bias could also cause this. In one prospective screening study of high-risk germline *p16* mutation carriers using MRI/MRCP, nine invasive pancreatic cancers were detected and treated in 79 patients followed for a median of 4 years. The number of patients who needed to be screened to detect and treat one patient's pancreatic cancer in this cohort was 11 [76]. A more recent study from this group found that pancreatic screening resulted in downstaging (more resectable cancers) and improved 5-year survival (24%) compared with patients who present with symptomatic pancreatic cancer [120].

## Summary

Pancreatic screening of subjects who have an inherited predisposition to develop pancreatic cancer frequently detects pancreatic neoplasms in these individuals, but the long-term benefits of screening remains to be determined. Pancreatic cancers are detected in a very small percentage of patients and the early detection of these cancers provides an opportunity to improve patient outcome. Similarly, resecting precancerous neoplasms in patients who have high-grade dysplasia (PanIN-3 or high-grade dysplasia in IPMN) is likely to be beneficial in preventing cancer in many cases. Managing concerning but indefinite pancreatic lesions identified by screening is best done by experienced multidisciplinary teams. There are major unanswered questions about pancreatic screening. There is a need to better define pancreatic cancer risk so as to improve the targeting of individuals who most need pancreatic screening. There is also a need to develop better screening tests. Current pancreatic imaging tests do not reliably detect PanIN, which are the most common precursor lesion. With the development of more accurate blood tests it may ultimately be possible to detect small potentially curable Stage I pancreatic cancers.

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# The Role of PET in Diagnosis of Pancreatic Cancer and Cancer Recurrence

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## Introduction

Positron emission tomography (PET) is a noninvasive functional imaging technique that is used to observe metabolic processes in the body. The patient is given a radioactive glucose analog carrying a positron emitter. During the radioactive decay of the so-called radiotracer positrons are emitted. The positrons next collide with electrons, which cause the release of photon pairs. Detectors arranged in a circle around the patient then can record the latter. Thereby, PET can analyze both the localization and the intensity of the radioactive tracer in the patient's body. Compared with morphologic imaging, PET therefore provides functional data of the investigated tissue, which can also be measured quantitatively. Different radiotracers can be applied depending on the clinical problem. Currently, the radiotracer 2-[$^{18}$F]-fluoro-2-deoxy-D-glucose (FDG) is most commonly used. Its uptake reflects glucose metabolism in the cells which is significantly increased in malignant tumors. However, FDG is not a cancer-specific agent and its uptake has been described in a number of nonneoplastic inflammatory lesions as well. Thanks to consequent technical improvements, integrated PET-computed tomography (PET-CT) was introduced in 1999 [1]. These PET-CT scanners provide a simultaneous acquisition of both high-resolution anatomic CT data and high-resolution metabolic PET information. However, as PET-CT is still a cost-intensive diagnostic tool with limited availability, reliable data evaluating the actual benefit of PET and PET-CT is of crucial importance. Therefore, this chapter gives an overview on currently available data of PET and PET-CT imaging in pancreatic cancer, summarizing its value and possible indication in the setting of primary diagnosis, staging, detection of tumor recurrence, and therapy monitoring. Finally, the potential value of recently introduced integrated whole-body PET-magnetic resonance imaging (MRI) into clinical practice is outlined.

## The Role of PET and PET-CT in Primary Tumor Diagnostic of Pancreatic Carcinoma

Despite excellent registration of anatomic and pathologic structures, morphologic imaging is unable to distinguish malignant from benign processes unconditionally. The sensitivity of multidetector CT (MDCT) has improved over the past few years. According to data from the literature, sensitivity of MDCT in pancreatic carcinoma was reported to be between 75% and 100% in so-called multiphase scans with a specificity of 70% to 100%. However, concerning lesions smaller than 2 cm, the sensitivity reaches values of no higher than 77% [2,3], which demands for complementary histopathologic investigation of suspicious lesions. MRI appears to be of outstanding impact in detection and assessment of tumor lesions of the pancreas, which cannot be directly depicted in CT imaging because of isoenhancing [4]. Concerning magnetic resonance cholangiopancreaticography (MRCP) in primary tumor diagnostics, Fusari et al. demonstrated sensitivity, specificity, accuracy, and positive and negative predictive values (describing the probabilities of FDG-positive lesions to be malignant and of negative lesions not to be malignant) to be 100%, 88%, 98%, 97%, and 100%, respectively [5]. For comparison purposes, sensitivity and accuracy of endo-ultrasound for lesions smaller than 2 cm are reported to be as high as 100% and 95%, respectively [3].

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Companion website: www.wiley.com/go/beger/thepancreas

Tumor detection and assessment of tumor dignity with FDG-PET encounter problems of a different nature. As FDG-PET displays areas of increased glucose metabolism within the body, those tissues with a high metabolism by nature and all hypermetabolic processes are depicted regardless of its dignity. This might lead to false-positive diagnosis in, for example, inflammation. The differentiation of pancreatic lesions is complicated, whenever a local pancreatitis is present at the time of FDG-PET examination [6]. The glucose oxidation of activated leukocytes in inflammatory sites is highly increased, which causes an intense FDG uptake in this area as well. Additionally, within autoimmune pancreatitis an increased FDG uptake can be demonstrated in up to 100% of the cases [7]. Contrary, in patients with chronic pancreatitis without active inflammatory components, PET shows a FDG uptake in only 13% of the patients [8]. Therefore, the pancreatic carcinoma can be distinguished from chronic pancreatitis, because most pancreatic adenocarcinomas show a relatively high FDG uptake (Fig. 99.1). However, recent studies prove difficulties in the differentiation between metastasis-free pancreatic carcinoma and mass-forming pancreatitis because of an overlap of the maximum standardized uptake value of both diseases [9]. Further, FDG uptake in tumor tissue and normal tissue is influenced by the dietary state, as FDG is a glucose analog. The investigator has to ensure a well-controlled serum glucose concentration in the examined patient to allow for adequate PET diagnostics. This is especially important in diabetic patients, because glucose concentrations above 8.4 mmol/L significantly reduce the detection rate of pancreatic carcinoma [6].

Kauhanen et al. reported on a higher diagnostic accuracy of PET-CT compared to conventional MDCT and MRI in primary diagnosis of pancreatic cancer [10]. In their analysis including 38 patients the pooled sensitivity and specificity turned out to be 85% and and 94%, respectively. For comparison, sensitivity and specificity were 85% and 92% for MDCT, and 85% and 72% for MRI. In two prospective studies on primary diagnostics of pancreatic cancer the sensitivity of PET-CT (89%) turned out to be comparable to both CT [11] and endo-ultrasound [12]. However, no homogeneous consent has been reported so far concerning any superiority of PET or PET-CT compared with MDCT and MRI, respectively. A 2014 published meta-analysis including 35 studies reports on a pooled sensitivity (SN), specificity (SP), positive predictive value, and negative predictive value of 90%, 76%, 90%, and 76% for PET and 90%, 76%, 89%, and 78% for FDG-PET-CT, respectively. In contrast, sensitivity and specificity of CT and MRI are 91% and 85% versus 84% and 82%. Therefore, Rijkers and colleagues could not derive any superiority or additional benefit of both FDG-PET and FDG-PET-CT in primary diagnosis of pancreatic carcinoma [13]. These data therefore support the current guidelines of the NCCN, which do not recommend PET-CT for standard primary diagnostics in patients with pancreatic carcinoma. Taken together, PET-CT is a useful diagnostic method *in addition* to conventional imaging procedures, especially when the results are inconclusive or show cystic and complex lesions in the pancreas [14]. Therefore, currently, the role of PET and PET-CT in diagnostics of primary pancreatic carcinoma cannot be finally rated.

## The Role of PET and PET-CT in Oncologic Staging of Pancreatic Carcinoma

Whereas primary diagnostics exclusively aim for the detection and proof of a pancreatic carcinoma, TNM-staging focuses on gathering information on the oncologic extent of the primary tumor and its potential metastases, which is essential for the individual evaluation of therapeutic options. Regarding tumor resectability and reasonableness of surgical procedures both local tumor infiltration of vessels and detection of distant metastases have crucial impact on the therapeutic

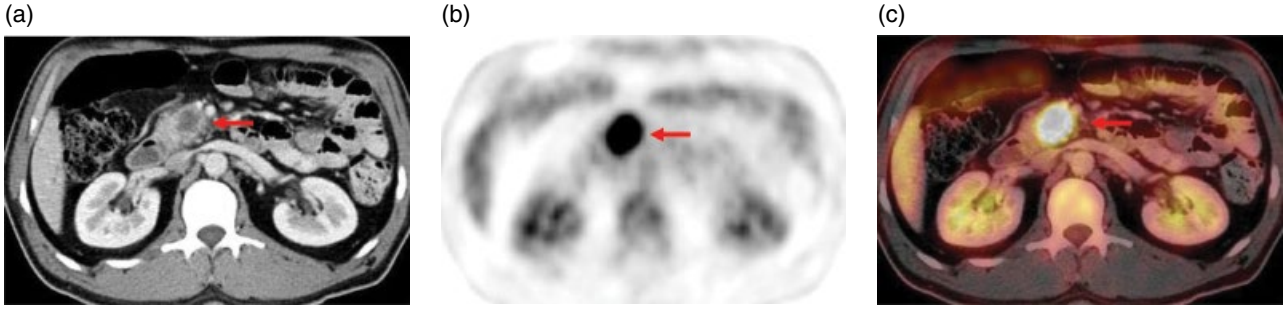


**Figure 99.1** (a–c) FDG PET-CT examination of a patient with primary diagnosis of pancreatic cancer presenting with an intense, focal FDG uptake in the pancreatic head.

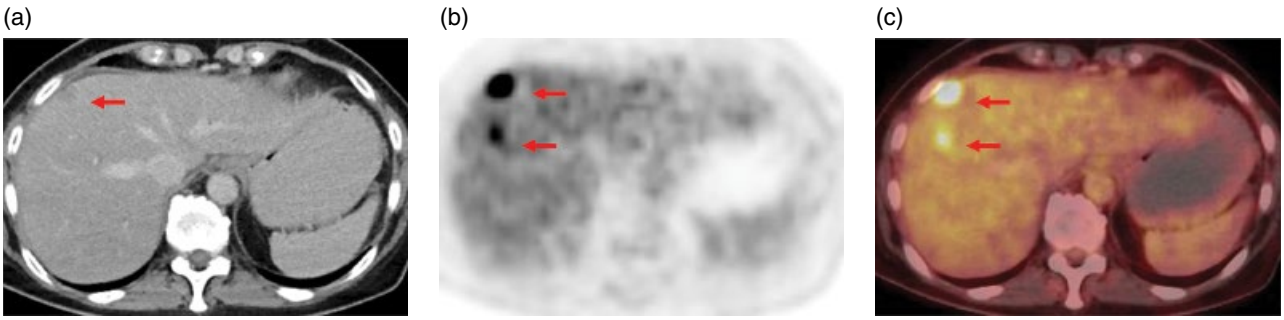


**Figure 99.2** FDG PET-CT of a patient presenting with two liver metastases of pancreatic cancer with high, focal FDG uptake (b,c). However, note, that only one of them was visible with diagnostic CT (a).

strategy. As a result of high surgical standards and improvements in downstaging of pancreatic carcinomas, the classification of *resectable*, *borderline resectable*, *locally advanced/irresectable*, and *metastasized* tumors has just recently gained increasing attention. MDCT and MRI are the most commonly used methods in staging of pancreatic carcinomas. Here, T-staging is of special importance because unresectability of pancreatic cancer is defined morphologically as infiltration of the superior mesenteric artery and/or the celiac trunk. The preference of either method depends on both the local availability and the experience of the investigator. The NCCN practice guides support both contrast-enhanced pancreatic CT and MRI and the International Study Group of Pancreatic Surgery (ISGPS) recommends the investigation of the pancreas by use of contrast-enhanced CT imaging. Nevertheless, the assessment of local resectability remains difficult even with these tools. In ambiguous cases the decision has to be forwarded to a pancreatic surgery reference center. A study of Strobel et al. revealed that the use of enhanced FDG PET-CT as a 1-stop-shop imaging protocol for assessing the resectability of pancreatic cancer is feasible and accurate. In their study, enhanced PET-CT was significantly superior to PET alone and although not being significant, there was a trend for enhanced PET-CT to be superior to unenhanced PET-CT [15]. Therefore, PET-CT should always include a diagnostic contrast-enhanced CT as unenhanced PET-CT has limited value in T-staging.

During the last years combined FDG PET-CT made distinct progress in terms of staging of malignant pancreatic tumors. The advantage of this whole-body examination especially concerns the M-staging where its specificity reaches up to 100%, for example in the detection of lung and bone metastases [15]. Heinrich et al. could prove that in patients with known metastatic spread more metastases became visible by PET compared with CT scan alone [11]. In addition, the authors evaluated the oncologic impact of PET-CT on further therapeutic decision making. In 16% of the patients investigated the detection of metastasis prompted the physicians to refrain from surgical therapy. This is concordant with the results of Bang et al. who revealed that PET scan increased the tumor stage in approximately a quarter of the investigated patients because metastases had not been visible with CT imaging alone [16]. Another study demonstrated the superior sensitivity of FDG-PET (88%) compared to MDCT (38%) and MRI (38%) regarding the detection of liver metastases. This study also reports a change of therapeutic strategy in 29% of the patients as the then palliative situation made surgical procedures unnecessary [10]. These results could be augmented by a recently published meta-analysis, which reports an increased sensitivity of PET-CT compared to PET alone (82% vs. 67%) regarding the detection of liver metastases [17]. The sensitivity of PET-CT in the detection of lymph node metastases has been reported to be as low as 21% to 38% [10,11]. Conversely, other studies underline the role of PET-CT in staging of locoregional and distant lymph node metastases. Here, PET-CT has been reported to be more accurate than CT or PET alone with regard to locoregional N-staging. However, the differences turned out to be rather small (85.3% vs. 83.8% and 79.4%) [18]. Because of the contrary results published in the literature, the value of PET-CT regarding N-staging has to be questioned. In summary, PET seems to be more sensitive in detection of distant metastases but has not achieved significance in routine staging and has not given proof of cost-effectiveness yet [19] (Fig. 99.2).

## Therapy Control and Diagnostics of Malignant Pancreatic Tumor Recurrence by PET and PET-CT

The impact of FDG-PET and PET-CT in terms of response prediction after neoadjuvant chemotherapy in patients with pancreatic adenocarcinoma is promising. They are particularly expected to allow for decision

making in tumors that were initially described as a borderline situation. Both the depiction of metabolic processes and the morphologic evaluation of lesions are highly difficult because of neoadjuvant chemotherapy-induced regional alterations around the tumor. Katz and co-workers demonstrated imposingly, that the resectability of a tumor could be predicted on the basis of imaging procedures in only 0.8% of the investigated patients after intended downstaging. However, tumors actually turned out to be resectable in 66% of the patients during surgical exploration [20]. The ISGPS consecutively postulates the explorative laparotomy in all patients without proof of metastatic spread or other indicators of tumor progress after neoadjuvant therapy.

FDG-PET and PET-CT show a significant advantage compared with CT and MRI in the detection of local recurrence after initially performed surgical resection of pancreatic carcinoma. Tumor recurrence could be approved in 96% of the patients by use of FDG-PET but in only 39% when CT or MRI imaging were performed [21]. In another study proof of tumor recurrence by FDG-PET was successful in 96.8%, whereas CT scan was accurate in only 55.6% of the cases [22]. Therefore, PET gains some significance in monitoring of surgical patients after resection of pancreatic cancer.

However, pancreatic tumors are often unresectable when diagnosed. FDG-PET served as therapy control of pancreatic carcinoma in several investigations. Advantages of PET-CT compared with CT scan could be demonstrated in terms of decreasing standardized uptake values in case of a tumor response in both follow-up monitoring after radiotherapy [23] and after chemotherapy [24], respectively. These findings allow for some prognostic assessment concerning survival of every single patient. Nevertheless, the correlations between metabolic response and prognosis remain under debate because of very heterogeneous results. However, new therapeutic agents and their effectivity can be tested and validated by use of FDG PET-CT within studies.

## Potential Value of PET-MRI in Patients with Pancreatic Cancer

With the recent introduction of integrated whole-body PET-MRI into clinical practice, a novel metabolic–anatomic imaging technique is now available with the opportunity to perform multiparametric oncologic imaging that reflects different aspects of tumor biology (tumor diffusion, perfusion, and glucose metabolism). Hereby it also combines the strengths of PET (metabolic imaging) with the advances of MR (soft-tissue contrast, functional imaging, e.g., using diffusion-weighted imaging and dynamic contract-enhanced imaging) (Fig. 99.3).

This multiparametric approach allows for noninvasive phenotyping of tumor biology which, by combining

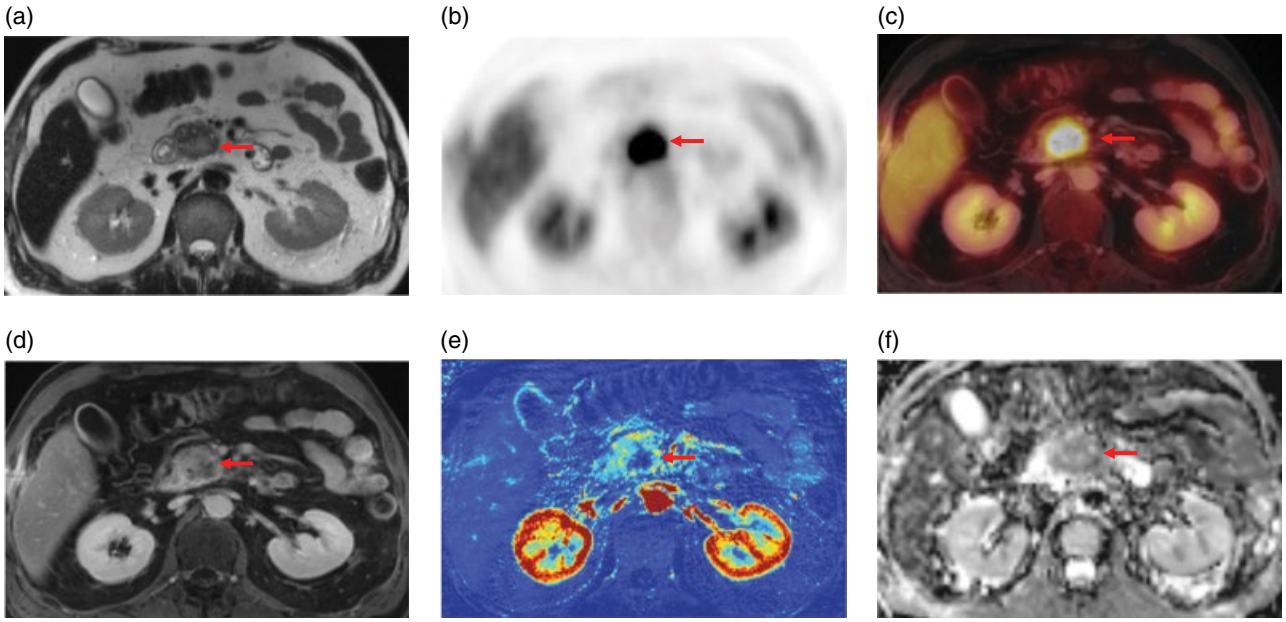


**Figure 99.3** Multiparametric FDG PET-MRI of a patient with primary diagnosis of pancreatic cancer. The MR image shows an inhomogeneous, hypointense tumor in the pancreatic head (a) with a high, focal FDG uptake (b,c). Dynamic contrast-enhanced (DCE) MRI shows peripheral hypervascularity (d) and the parametric map of iAUC60 (initial area under the DCE-MRI contrast agent concentration-time curve after 60 s) confirmed a high wash-in rate (e). Corresponding diffusion-weighted imaging presents low ADC values within the tumor indicating low cellularity (f).

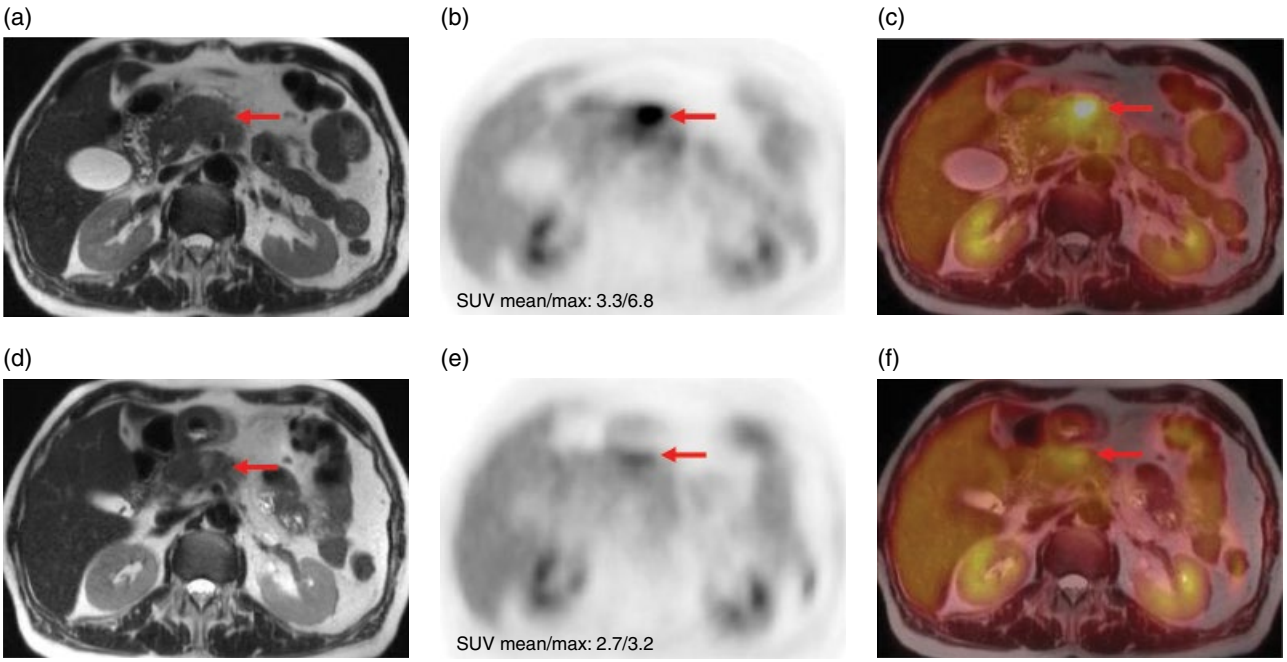


**Figure 99.4** FDG PET-MRI of a patient with pancreatic cancer before (a–c) and 6 weeks after beginning of chemotherapy (d–f). Note the decrease of SUV values (b,e) after chemotherapy indicating a tumor response (decrease of SUV mean/max 18% and 53%).

different functional and molecular imaging methods, might lead to a higher accuracy for tumor detection and differentiation as well as response (Fig. 99.4).

First studies suggest that PET-MRI seems to be highly accurate in T-staging of tumor entities for which MRI has traditionally been favored, such as squamous cell carcinomas of the head and neck [25]. By adding functional MRI to PET, PET-MRI may further improve diagnostic accuracy in the differentiation of scar tissue from recurrence of tumors such as rectal cancer. With regard to N-staging, PET-MRI does not seem to provide a considerable benefit as compared with PET-CT but provides similar N-staging accuracy when applied as a whole-body staging approach [25]. M-staging will benefit from MRI accuracy in the brain and the liver and allows visualization of the biologic heterogeneity of tumors. However, regarding M-staging it has to be noted that the detection rate of small lung lesions in PET-MRI is still inferior compared with PET-CT with diagnostic CT of the chest [26]. For neuroendocrine tumors in the pancreas a first preliminary study has shown an added value of PET-MRI compared with PET-CT [27].

However, organ-specific data on the diagnostic performance of PET-MRI in pancreatic cancer are not available yet. There is only one study evaluating retrospective FDG PET-MRI fusion to PET-CT in various pancreatic tumors (96 cancers and 23 benign lesions) showing a significantly improved accuracy (96.6% vs. 86.6%) [28]. Therefore, the simultaneous acquisition of multiparametric MRI and PET data is awaited to create new options in molecular tumor imaging by improving tumor detection and delineation as well as biologic characterization.

## Conclusion

The final appraisal of the patient-relevant benefit of PET and PET-CT with regard to primary diagnostics, diagnostics of tumor recurrence, or staging cannot be based on a comparison with the standard methods only. In fact, the major matter of interest is the question of the impact of an improved diagnostic tool on therapy and therefore patient morbidity, mortality, and quality of life, respectively. Randomized studies have to be initiated to investigate the impact of findings from PET and PET-CT in all those cases where they indicate different results or tumor stages compared with standard methods. At the moment there are no studies that allow for any statement concerning PET and PET-CT in this respect. However, many studies validate the quality of PET and PET-CT by scrutinizing the improvement in primary diagnostics, diagnostics of tumor recurrence, and tumor staging of pancreatic carcinoma compared with the standard methods without PET. The current literature does not obligatorily recommend the use of PET-CT within primary diagnostics of pancreatic carcinoma, but it is considered to be a useful modality. However, PET-CT

plays a promising role in the assessment of borderline resectable tumors and locally advanced tumors. Furthermore, the additional use of PET scanners demonstrated auspicious results within the staging of locally resectable lesions with synchronous CT- and MRI-morphologically occult metastases. Nevertheless, the sensitivity concerning the detection of lymph node metastases is rather low. The impact on therapeutic consequences in tumor therapy will play a relevant role in future socioeconomic concerns, however, while sparing patients unnecessary surgical procedures. Finally, PET-CT already plays an important role in detection of tumor recurrence after surgical resection and therapeutic monitoring in unresectable pancreatic cancer.

PET-MR is a new and increasingly used multimodal imaging technique, which is expected to improve diagnostic performance especially in oncology patients. The combination of PET and MR in hybrid whole-body PET-MRI systems has the potential to combine excellent morphologic, functional, and biologic information in one imaging session with precise image co-registration. Contrary to PET-CT, the MR part of PET-MRI provides superior soft-tissue contrast and imposes no ionizing radiation. So far, studies evaluating the performance of PET-MRI in pancreatic cancer are pending; therefore, the potential benefit of PET-MRI in comparison to PET-CT and conventional imaging modalities has still to be validated.

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# 100

# Tumor Markers in Pancreatic Malignancies

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## Conventional Tumor Markers for Pancreatic Cancer

### CA 19-9

There are several tumor markers for pancreatic cancer. The usefulness and efficacy of these markers for clinical decision making are well established, but several pitfalls need to be kept in mind. CA 19-9 is a sialyl-Lewis A antigen, which is recognized by a mouse monoclonal antibody NS 19-9 established by Koprowski et al. [1]. Indispensable roles of CA 19-9 are described in recent clinical guidelines for pancreatic cancer, such as NCCN Guidelines for Patients®, Pancreatic Adenocarcinoma, Version 1.2013, or ESMO-ESDO Clinical Practice Guidelines [2,3]. Currently, the clinical usefulness of CA 19-9 is mainly for follow-up after surgery, assessment of chemotherapy effect, and prognosis. Patients with a low postoperative CA 19-9 value have a better prognosis [4]. Similarly, patients with low CA 19-9 before surgery or adjuvant chemotherapy also have a better prognosis [4]. Another study reported that decrease of CA 19-9 during gemcitabine-based chemotherapy could predict better median survival, suggesting the possibility as a determinant factor of chemotherapy continuation [5]. Based on this line of evidence, measurement of CA 19-9 before and after surgery or during chemotherapy is strongly recommended. However, CA 19-9 is not a suitable marker for "early" detection of pancreatic cancer in the general population. According to a recent meta-analysis, the pooled diagnostic sensitivity of CA 19-9 was around 80% [6]. In addition, the diagnostic sensitivity of CA 19-9 was only 55.6% in Stage I [7].

False-positive and false-negatives of CA 19-9 should also be taken into consideration. Elevation of CA 19-9 is observed in several conditions besides pancreatobiliary cancers. Obstructive jaundice causes CA 19-9 elevation, regardless of the etiology of the biliary stricture. Adequate biliary drainage then leads to a decrease of CA 19-9 [8], and NCCN Guidelines recommend measurement of CA 19-9 after the normalization of serum bilirubin by biliary drainage [2]. Patients with liver cirrhosis sometimes have nonspecific elevation of CA 19-9 [9]. Synthesis of CA 19-9 sialyl-Lewis A epitope requires α-1,4-fucosylation of sialyl-Lewis C precursor, which is regulated by the *Le* gene encoding fucosyl transferase [10]. Individuals lacking this enzymatic activity are unable to synthesize CA 19-9 epitope, therefore CA 19-9 levels become undetectable. Measurement of CA 19-9 is performed in patients with suspicious lesions for pancreatic cancer found by imaging. Initial measurement of CA 19-9 will identify Lewis-negative individuals. After a definitive diagnosis of pancreatic cancer, changes in CA 19-9 value will be monitored after surgery or during chemotherapy. Continuous elevation after surgery suggests tumor spread or resistance to chemotherapy, needing additional imaging studies to detect progression of the initial lesion or the development of new lesions. The algorithm for CA 19-9 measurement is summarized in Fig. 100.1. Measurement of CA 19-9 in high-risk individuals might have some benefit for early diagnosis of pancreatic cancer. Intraductal papillary mucinous neoplasm (IPMN) of the pancreas may progress to pancreatic cancer in a small proportion of individuals. Elevated CA 19-9 in patients with branch-duct IPMN may be associated with concomitant pancreatic cancer [11].

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### DU-PAN-2 and SPan-1

DU-PAN-2 is a sialyl-Lewis C antigen, which is a precursor of CA 19-9. Mouse monoclonal antibody against DU-PAN-2 was established by immunizing mice with the HPAF human pancreatic cancer cell line [12]. Since Lewis-negative individuals can synthesize this antigen [10], DU-PAN-2 becomes an alternative marker of pancreatic cancer in patients with low levels of CA 19-9 (typically less than 2.0 KU/L). SPan-1 is recognized by a monoclonal antibody raised against mucins purified from the SW1990 pancreatic cancer cell line [13], which therefore recognizes both sialyl-Lewis A and C antigens [14]. False-positives for DU-PAN-2 and SPan-1 can also be seen in patients with obstructive jaundice, liver cirrhosis, or chronic hepatitis [15,16].

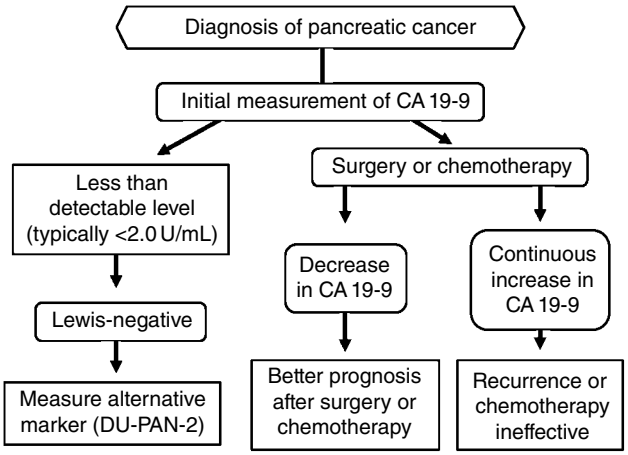



**Figure 100.1** Clinical flow-chart for CA 19-9 measurement in patients with pancreatic cancer.

## Other Markers for Pancreatic Malignancies

### Markers for Rare Pancreatic Malignancies

Acinar cell carcinoma is a rare type of pancreatic cancer. Elevation of alpha-fetoprotein (AFP) has been reported in cases of acinar cell carcinoma, and a decrease of serum AFP levels after therapeutic intervention has also been described [17,18]. Measurement of AFP in patients with pancreatic tumor suggestive of acinar cell carcinoma by imaging studies or pathologic diagnosis will be beneficial for follow-up after surgery and during and after chemotherapy.

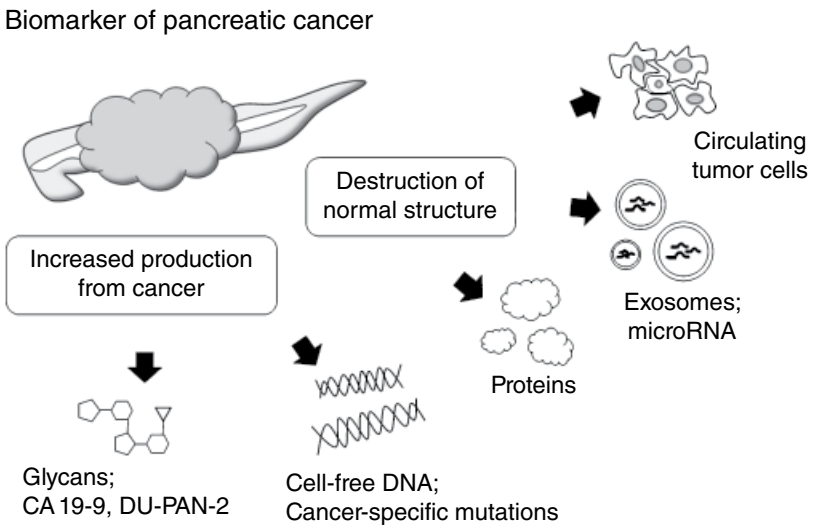
Production of granulocyte colony-stimulating factor (G-CSF) has been reported in various types of cancer, such as gastric cancer or hepatocellular carcinoma [19,20] and also pancreatic cancer with a poor prognosis [21,22].

## Novel Markers for Pancreatic Cancer

### New Candidates for Pancreatic Cancer Marker

Currently, conventional markers of pancreatic cancer are not suitable for early detection or screening so novel markers are being investigated (summarized in Fig. 100.2). Circulating tumor cells (CTC) are detectable in blood samples from some patients with pancreatic cancer, especially in patients with advanced disease and a poor prognosis after surgery [23]. Cell-free DNA sequencing by next-generation sequencer (NGS) may identify cancer-specific gene in some cases [24]. Mass-spectrometry-based proteomics has identified serum

**Figure 100.2** Current biomarker of pancreatic cancer and future candidates for novel biomarker.



LAMC2, a constituent of basement membrane, as a potential marker of CA 19-9 [25].

MicroRNA, which are normally protected from degradation by nucleases by extracellular vesicles such as exosomes, are detectable in various body fluids [26]. Elevated expression of miR-21 in pancreatic cancer tissues has been correlated with clinical outcome and gemcitabine resistance [27]. Stool detection of miR-21 may differentiate patients with pancreatic cancer from those with chronic pancreatitis patients and from healthy controls [28]. A 70% diagnostic sensitivity and specificity for pancreatic cancer was found for elevated miR-3679-5p and miR-940 levels in salivary samples [29]. Urinary miR-143, miR-223, and miR-30e are elevated in patients with pancreatic cancer of which miR-143 could differentiate Stage I pancreatic cancer patients from healthy controls, with sensitivity of 83.3% [30].

### Markers for Personalized Medicine

The expression levels of deoxycytidine kinase was correlated with progression-free survival in patients who have received gemcitabine therapy after surgery [31]. Severe neutropenia is a limitation in using FOLFIRINOX [32] and may be linked to a specific genotype of *UDP-glucuronyltransferase 1A1* (*UGT1A1*) that is required for elimination of active metabolite of irinotecan [33]. A blinded analysis of the human equilibrative nucleoside transporter 1 (hENT1) levels was undertaken in microarrays from 434 patients randomized to chemotherapy in the ESPAC-3 trial plus controls from the ESPAC-1 and ESPAC-3 trials [34]. Multivariable analysis confirmed hENT1 expression as a predictive marker in gemcitabine-treated but not 5-fluorouracil-treated patients [34]. Prospective validation, is now underway to evaluate the roles of hENT1 expression in the use of gemcitabine versus gemcitabine-based regimens.

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# 101

# The Role of Laparoscopy and Peritoneal Cytology in the Management of Pancreatic Cancer

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## Introduction

Pancreatic cancer is either systemic or local disease and in approximately 90% of patients, it is complicated by systemic disease according to previous autopsy studies [1,2]. However, about 40% of patients with pancreatic cancer are diagnosed as having local disease only at the time of initial diagnosis [3,4]. The discrepancy in the ratio of local versus metastatic disease between the autopsy and initial diagnosis suggests that some local disease may progress toward metastatic disease after the initial diagnosis and that others may harbor "occult" metastatic disease. In the active treatment of pancreatic cancer, surgery and/or radiation therapy in combination with chemotherapy may be used for local disease, while chemotherapy is currently the choice of treatment for systemic disease [5,6]. Therefore, it is of vital importance to define the disease as systemic or local before initiation of active treatment. In patients complicated by peritoneal metastasis, cancer cells may be disseminated as a number of small nodules in the peritoneal cavity that are often not visible even with state-of-the-art multidetector CT. Moreover, small metastasis on the surface of the liver is also hard to detect with the present imaging technologies. To identify such metastatic disease, efforts by means of staging laparoscopy and peritoneal cytology have been made. The role of laparoscopy and peritoneal cytology in the management of pancreatic cancer is described in this chapter.

## Laparoscopy

The usage of laparoscopy for pancreatic cancer dates back to 1970s. Cuschieri et al. started to use laparoscopy in patients with suspected pancreatic cancer in 1973 and found "metastatic deposits elsewhere in the abdomen" in 2 of 15 patients with obstructive jaundice [7]. Ishida et al. have used a two-channel laparoscope in patients with pancreatic cancer and pancreatitis since 1976 and succeeded in obtaining biopsy specimens of the pancreatic tissue [8]. Observation of the peritoneal cavity by a laparoscope provided physicians with information about peritoneal dissemination and superficial liver metastasis, both of which are determinant factors for staging of the disease. Thus, diagnostic laparoscopy became widely called staging laparoscopy or laparoscopic staging. One of the advantages of staging laparoscopy is detection of peritoneal dissemination and superficial liver metastasis, which are not detectable with CT and other imaging studies. This advantage has contributed to avoiding unnecessary laparotomy as demonstrated in many retrospective studies [9–13]. However, the development of high-resolution imaging technologies such as multidetector CT has led to a decline in the role that staging laparoscopy should play. Nevertheless, small nodules, for example, those <0.5 cm, are often invisible even with state-of-the-art CT and there is a role for staging laparoscopy in selected patients. Selection criteria vary among the previous reports partly because of the diverse accuracy of imaging studies in different eras. In general, high value of serum CA 19-9, large tumor, location in the body-tail, and any suspected metastatic lesions on imaging support the use of staging laparoscopy [14,15]. Moreover, staging laparoscopy is widely used in the setting of neoadjuvant chemoradiation therapy in order to rule out metastatic disease. Recently, advantages of "extended" staging laparoscopy over standard staging laparoscopy have been advocated [16]. By simply observing the peritoneal cavity without intracorporeal surgical manipulation, it is impossible to explore the lesser cavity

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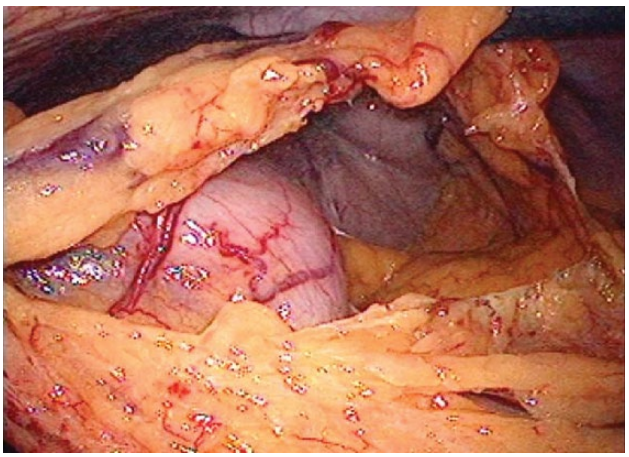

**Figure 101.1** Observation of the lesser sac through a division of the gastrocolic ligament during "extended" staging laparoscopy.

and some parts of the liver surface in dead angles. Since the early era, the lesser sac has been explored by using various techniques [7,8]. In order to explore the lesser cavity during staging laparoscopy, surgeons have to divide the gastrocolic ligament with surgical instruments such as ultrasonic coagulation dissectors or bipolar vessel sealing systems (Fig. 101.1). To visualize the liver surface more thoroughly, the liver must be retracted medially and caudally by retractors and/or atraumatic forceps and the superior, posterior, and lateral surface of the right lobe can be visualized with an angled laparoscope of 30° or 45° or a flexible videoscope. For these maneuvers during "extended" staging laparoscopy, three or four trocars for a laparoscope and laparoscopic surgical instruments are needed [15], while only one or two trocar(s) are used for standard staging laparoscopy. Cytologic examination of peritoneal washing with saline can be done during staging laparoscopy [16] and the role of peritoneal cytology is described later. For the purpose of evaluating tumor involvement around major vessels and detecting subsurface lesions of the liver, laparoscopic ultrasonography is utilized by some surgeons [17]. Furthermore, some interventional procedures can be carried out in conjunction with staging laparoscopy. As examples of interventional staging laparoscopy, a radiographic marker, Visicoil® fiducial, for target tracking radiation therapy can be implanted [18] and the common hepatic artery can be ligated laparoscopically to ensure collateral blood flow from the superior mesenteric artery to the proper hepatic artery via the gastroduodenal artery before a distal pancreatectomy with celiac artery resection for a locally advanced tumor [19] (Fig. 101.2).

## Peritoneal Cytology

Peritoneal cytology is a method of pathocytologic examination to collect spread cells in the ascites or in the liquid after peritoneal cavity lavage with saline and to make a diagnosis of potential spread of cancer cells (Fig. 101.3). In patients with cancers of abdominal organs including the ovary, stomach, and pancreas, peritoneal cytology has been used as a prognostic indicator. Peritoneal cytology can be performed either by laparotomy or laparoscopy [20]. In the Classification of Pancreatic Cancer by the Japan Pancreas Society, it is recommended to gently irrigate the pelvic cavity with 100 mL of saline for peritoneal

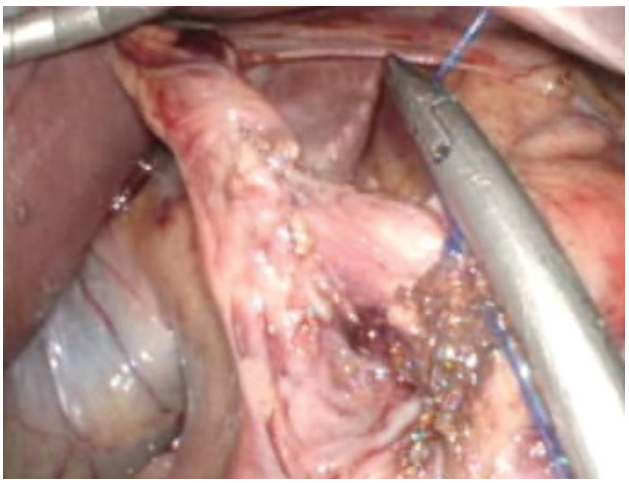

**Figure 101.2** Ligation of the common hepatic artery during interventional staging laparoscopy.

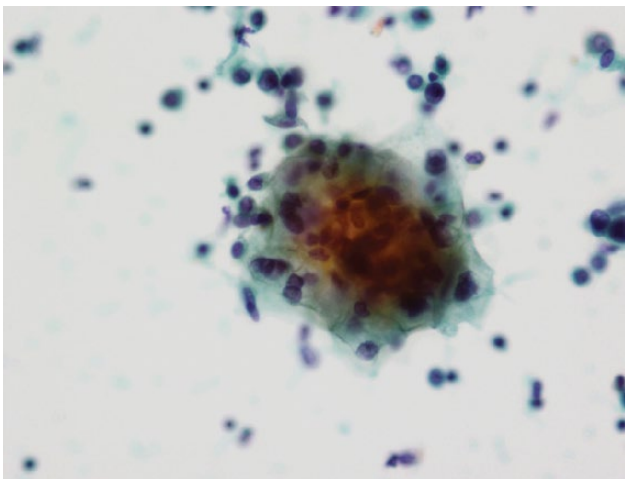

**Figure 101.3** Example of a cell cluster in peritoneal washing fluid. The cluster consists of atypical cells with remarkable nuclear dysplasia and mucin in the cytoplasm, suggesting intraperitoneal spread of cancer cells. (Papanicolaou stain, original magnification × 400)

cytology [21]. Positive peritoneal cytology of pancreatic cancer indicates spread of cancer cells in the peritoneal cavity and is associated with higher incidence of invasion into the anterior pancreatic capsule [22,23]. Accordingly, large tumors are risk factors for positive cytology. It has been well demonstrated that positive cytology is a significant negative prognostic factor [24] and, in the National Comprehensive Cancer Network (NCCN) guidelines, it is stated that positive cytology from washings obtained at laparoscopy or laparotomy is equivalent to M1 (metastatic) disease. However, there are debates about whether or not all positive cytology patients are complicated by peritoneal metastasis. In a cohort of 134 patients who underwent surgical resection after cytologic examinations of peritoneal washings, Yachida et al. have shown that there were no significant differences in cumulative survival rates between patients with negative cytology ($n = 114$) and those with positive cytology but no macroscopic peritoneal metastasis ($n = 19$) [22]. In another cohort of 523 patients with pancreatic cancer including 390 who underwent resection, Yamada et al. demonstrated that multivariable analysis of 12 clinical pathologic parameters including peritoneal cytology identified tumor size, portal vein invasion, plexus invasion, and lymph node metastasis as independent predictive factors but not peritoneal cytology as such [23]. While patients with positive cytology tended to develop peritoneal metastasis, the correlation was not statistically significant and the first site of tumor recurrence in some patients with positive cytology was other than peritoneal metastasis [23]. Thus, positive peritoneal cytology does not directly predict peritoneal metastasis. Besides, there are many long-term survivors who underwent surgical resection despite positive cytology [22,23]. Positive peritoneal cytology may not be a contraindication of surgical resection if the patient can tolerate surgery. Nevertheless, those patients with positive cytology are complicated by more advanced disease and likely to develop systemic metastasis. Therefore, adjuvant treatments for systemic disease are strongly recommended. In the setting of neoadjuvant chemotherapy and neoadjuvant chemoradiation therapy, the significance of peritoneal cytology should be further studied.

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# Clinical Assessment and Staging of Advanced Pancreatic Cancer

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## Introduction

Pancreatic adenocarcinoma (PDAC) is now the fourth leading cause of cancer deaths in the United States, with 5-year survival of 7%. Recent data suggests that incidence and mortality rates are increasing [1,2]. Some predict that PDAC will surpass colorectal cancer to become the second leading cause of cancer death by 2020. Unfortunately, because of the vague symptoms at presentation, fewer than 10% of patients will be diagnosed in the earliest stages when tumors are resectable [1].

This chapter serves to highlight the clinical assessment and staging of those who are diagnosed with PDAC with a focus on those diagnosed with advanced cancers.

## Clinical Presentation

The dismal prognosis associated with PDAC is partly related to a lack of symptoms until late in the disease course. The earliest symptoms may be associated with tumor location such as painless jaundice for tumors arising in the head of the pancreas and obstructing the biliary and pancreatic ducts. Earlier signs of biliary obstruction include choleuria, acholic stools, and pruritus. Chronic obstruction of the pancreas can result in exocrine and endocrine insufficiency, manifested by steatorrhea and new/worsening diabetes. Body and tail lesion tumors more commonly result in nonspecific symptoms of abdominal pain that may radiate, appetite loss, weight loss, nausea, and possibly vomiting and consequently, are more likely to be diagnosed at a later stage [3].

Examination can confirm signs of biliary obstruction with scleral icterus and jaundice. For obstructing right-sided tumors, a distended and palpable gallbladder may be appreciated. The presence of ascites, confirmed with a distended abdomen and fluid wave, raises suspicion for peritoneal disease. Involved supraclavicular (Virchow's node) or umbilical (Sister Mary Joseph node) nodes or peritoneal implants found in the pelvic cul de sac on rectal exam (Blummer's shelf lesions) are consistent with metastatic disease.

## Evaluation for Pancreatic Cancer

### Serologic Evaluation

Serologic workup may include a comprehensive metabolic panel inclusive of liver function tests, complete blood count, amylase, lipase, coagulation studies, and albumin. Right-sided tumors may result in biliary obstruction with a conjugated hyperbilirubemia. Elevations in transaminases may be absent or mild. For those who are newly diabetic, hemoglobin $A_{1c}$ ($HbA_{1c}$) may be grossly elevated or demonstrate a rapid rate of rise, similar to those with type 1 diabetes [4].

CA 19-9 is the only FDA-approved serologic tumor marker for PDAC. Initially described in colon cancer, the test is based on a sialyl-Lewis A antigen ($Le^A$) produced by epithelial cells on the surface of erythrocytes and in the mucin produced by pancreatic cancer cells [5]. The sensitivity and specificity is up to 81% and up to 90%, respectively. There is an approximately 10% risk of a false negative (i.e., Lewis-negative patients). False positives occur in the setting of biliary obstruction and pancreatitis [6].

In secretors of the antigen, this marker can serve as a marker of tumor burden to guide management. Studies have demonstrated that preoperative CA 19-9 levels correlate with stage of disease and oncologic outcome. Ferrone et al. suggested that postoperative reduction in

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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CA 19-9 and a postoperative CA 19-9 < 200 U/mL were strong predictors of survival [7]. Evaluation of postresection CA 19-9 within the setting of the phase III trial, RTOG 9704, also supported this finding, reporting a 72% reduction in risk of death in patients with a postresection CA 19-9 < 180 [8]. Others have proposed that a preoperative CA 19-9 130 U/mL is a predictor of unresectability and should prompt a diagnostic laparoscopy [9].

CEA and CA-125 have a limited role in the management of PDAC, though may have utility in patients whose tumors do not secrete the Lewis antigen [10]. Recently published work suggests that panels based on microRNA expression (miR-145, miR-150, miR-223, miR-636, miR-26b, miR-34a, miR-122, miR-126, miR-505, miR-885.5p) were significantly different in patients with PDAC compared to normal controls [11]. Other potential screening tests involve promoter DNA methylation of *BNC1* and *ADAMTS1* [12]. However, no serologic markers beyond CA 19-9 have been approved for PDAC management.

## Radiologic Evaluation

Abdominal ultrasound is the first diagnostic tool commonly employed for a patient with obstructive jaundice and abdominal pain. The study may demonstrate intra- and/or extrahepatic biliary ductal dilation, pancreatic dilation, and possibly a pancreatic mass. However, it has only a limited role in the diagnosis and staging of advanced PDAC except to guide percutaneous biopsy of liver metastases.

A dedicated pancreatic computed tomography (CT) using a multidetector CT with angiography and with thin, axial sections is the preferred method to diagnosis and stage PDAC [1,13]. These scans assess arterial and venous phases using water as the oral contrast agent (Fig. 102.1). CT has a high predictive value for unresectability (up to 100%) but a lower predictive value for resectability, primarily because small liver lesions and peritoneal implants may be missed [14]. The presence of ascites can be an indicator of peritoneal metastases.

Magnetic resonance cholangiopancreatography (MRCP) may be particularly useful in assessing soft tissue contrast and ductal structures, particularly for early tumors that may not be visible on a CT [15]. Additionally, MRCP may better detect small tumors and/or evaluate focal fatty infiltration, a hypertrophied pancreatic head, and isoattentuating pancreatic cancer [16]. MRI may also be used to characterize CT-indeterminate liver lesions or in the setting of patients with an iodinated intravenous contrast allergy.

The utility of positron emission tomography (PET) with [$^{18}$F]-fluoro-2-deoxy-D-glucose (FDG) in assessing stage and resectability for PDAC is unclear. Studies

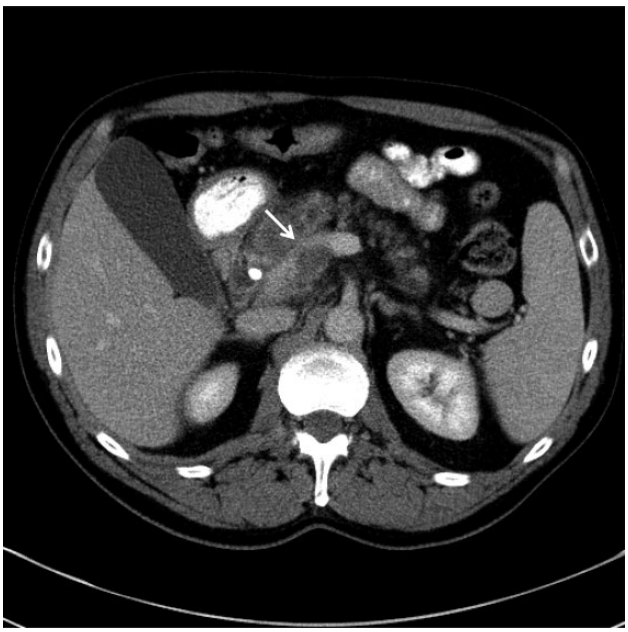

**Figure 102.1** CT pancreatic protocol, with representative venous phases, demonstrating encasement of the portal vein (arrow). This patient's carcinoma was deemed locally advanced as it had not only encasement of the portal SMV, but also nonreconstructable encasement of the hepatic artery.

demonstrate that PET has a lower specificity and positive predictive value compared to CT and MRI [17]. However, it demonstrates a sensitivity and specificity that is superior to that of CT and MRI for evaluation of metastatic disease [17,18]. One may consider PET in specific situations: to assess those at high risk for distant metastatic disease (i.e., large regional lymph nodes, large primary tumors, a markedly elevated CA 19-9, or borderline resectable or locally advanced disease) [19] and to assess response to treatment [20].

## Endoscopic Evaluation and Treatment of Advanced Pancreatic Cancer

Endoscopic techniques, such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasound (EUS), are increasingly utilized for diagnosis and to complement imaging. Historically, ERCP allowed for cytology via brushings. ERCP has been largely replaced by EUS with fine-needle aspiration (FNA) for diagnostic purposes as it offers an opportunity to obtain specimens for histopathology diagnosis, with a sensitivity and specificity of 87% and 96%, respectively [21]. EUS is considered one of the most accurate means by which to diagnose small, focal tumors of the pancreas and is associated with a lower risk of complications, particularly in those with obstructive jaundice, compared to ERCP [20].

Endoscopic procedures remain a mainstay of management for PDAC, particularly for its role in palliating symptoms, such as obstructive jaundice. Endoscopic stenting, with either plastic or metallic stents, is commonly employed at diagnosis to relieve jaundice and pruritus and to permit treatment with neoadjuvant therapy in locally advanced PDAC. Endoscopic stenting has been thoroughly studied in the palliative setting. Studies have demonstrated that in patients presenting with obstructive jaundice due to malignant obstruction and who require palliative decompression, palliative biliary stenting, compared to surgical bypass, is associated with no difference in technical or therapeutic success, fewer total complications, lower procedure-related mortality, greater quality of life scores, and lower total cost. While there are more reocclusions in those stented, total hospital days are reduced in whom stents are employed [22–26]. A recent randomized controlled trial evaluated the cost efficiency of self-expandable metal stents (SEMS) compared to those with plastic stents for palliation. The study demonstrated that while the up-front costs of SEMS are greater than plastic stents, SEMS have a longer functional time and no significant difference in cost at 1 year [27]. Advances in endoscopic technology with regard to approach (transgastric, transduodenal) and techniques (rendez-vous, hepaticogastrostomy, and choledochoduodenostomy) lead to success rates approaching 100% [28]. In the event of failure, hepaticojejunostomy or radiologically placed percutaneous biliary drainage may be considered.

Symptoms attributable to gastric outlet obstruction (GOO) can also be addressed particularly in patients with advanced PDAC. This has been reported to occur in up to 25% of patients with unresectable disease [29]. Mehta et al. found no difference in survival for patients with malignant GOO undergoing laparoscopic gastrojejunostomy versus endoscopic duodenal stent placement. In that study, patients who underwent endoscopic stenting had fewer complications and shorter length of stay, suggesting that duodenal stenting may be preferable to surgical bypass [30].

Lillemoe et al. originally reported that intraoperative celiac plexus neurolysis (CPN), compared to placebo in patients with unresectable PDAC considerably reduced mean pain scores and led to a substantial survival improvement in those patients with significant preoperative pain [31]. With modern imaging, CPN is now more commonly performed endoscopically or radiologically. A recent randomized trial of early EUS-guided CPN demonstrated that early EUS-CPN provided improved pain control for patients with inoperable PDAC with pain and may avoid progressive increase in morphine use [32].

Emerging data is now available evaluating the role of EUS-guided radiofrequency ablation, intratumoral drug delivery, and radiation therapy. Larger studies are needed to determine the safety and impact on survival of these techniques but may serve as future endoscopic options available to patients with advanced PDAC.

### Surgical Evaluation and Treatment in Advanced Pancreatic Cancer

The principal role of surgical evaluation for advanced PDAC is the further assessment of resectability and palliation. Staging laparoscopy with peritoneal washings may be employed prior to neoadjuvant therapy or embarking upon a laparotomy to attempt resection. The presence of positive peritoneal cytology is considered M1 disease.

Surgical bypass with either hepatojejunostomy and/or gastrojejunostomy have been surgical mainstays for palliation of advanced tumors in the head of the pancreas. The incidence of these procedures has decreased in recent years with the emergence of endoscopic stenting. Nevertheless, laparoscopic or open bypass remains a viable palliative option, particularly when endoscopic stenting is not feasible, or when an attempted resection is aborted well into the dissection. Limited data suggest that laparoscopic gastrojejunostomy is feasible and successful, including in situations in which duodenal stenting fails [33]. Laparoscopic gastrojejunostomy seems to be associated with a reduction in time to oral intake and a trend toward reduced delayed gastric emptying and length of stay compared to open operation [34].

Up to 33% of patients who appear resectable by radiologic criteria will be found to have metastatic or unresectable disease at the time of exploration [29]. Early studies suggested that prophylactic bypass at the time of laparotomy reduced the risk of late GOO [35–37]. Contemporary studies suggest prophylactic bypass may not be necessary due to dismal overall survival [38,39]. However, celiac plexus blockade done prophylactically at this time can both improve quality of life and survival [31].

Operative biliary bypass and CPN have been discussed previously.

## Staging for Advanced Pancreatic Cancer

The American Joint Cancer Committee (AJCC) TNM Staging System, Seventh Edition, is a commonly employed staging system for PDAC. The staging system incorporates status as it relates to tumor size (T), regional lymph nodes (N), and the presence/absence of distant metastatic disease (M). The staging correlates with overall survival and, to some extent, with treatment guidelines (Table 102.1).

While the AJCC TNM staging correlates with prognosis (Table 102.1), it does not correlate with treatment guidelines as well since it does not satisfactorily define tumor resectability. It is well established that surgical resection provides the only opportunity for long-term survival for patients with PDAC.

Pancreatologists commonly employ a surgical and radiologic staging system that more properly defines whether tumors are resectable. Originally described by MD Anderson, with modification from the NCCN most recently in 2017, tumors are defined as resectable, borderline resectable, and unresectable, based on relationships to the relevant vascular structures (Table 102.2; Fig. 102.1) [4,19,40,41].

While there is some controversy about the role of neoadjuvant therapy for resectable tumors, patients with borderline resectable PDAC are frequently treated with neoadjuvant chemotherapy and/or chemoradiation followed by restaging and assessment for resection, often requiring a vascular resection and reconstruction [4].

**Table 102.1** Summary of AJCC Staging, 7th edition, with correlation to overall survival.

| TNM staging | Median survival (mo) |
|---|---|
| Stage IA T1N0M0 | 10.0 |
| Stage IB T2N0M0 | 9.1 |
| Stage IIA T3N0M0 | 8.1 |
| Stage IIB T1-3N1M0 | 9.7 |
| Stage III T4N0-1 M0 | 7.7 |
| Stage IV T1-4 N0-1 M1 | 2.5 |

*Source:* Modified from [2,42].

A tumor staged as "locally advanced" in the MD Anderson/NCCN system is unresectable even if not metastatic. There is no role for surgery beyond that for palliation unless the tumor responds dramatically to chemotherapy or chemoradiotherapy. This degree of response occurs less than 10% of the time. The role of radiation in this setting is unclear. The LAP-07 trial evaluated patients with locally advanced PDAC with stable or responsive disease after 4 months of chemotherapy (gemcitabine ± erlotinib). Patients were randomized to chemoradiotherapy compared to ongoing chemotherapy. There was no difference in overall survival reported [43]. Recently multidrug regimens (FOLFIRNOX and gemcitabine-*nab*-paclitaxel) have produced favorable responses in the locally advanced setting, similar to what is seen in the Stage IV disease [44]. These chemotherapy regimens are now considered the standard for systemic treatment of Stage IV PDAC because they have improved median survival as well as quality of life and global health status, compared to best supportive care and gemcitabine [45,46].

An understanding that a tumor is locally advanced or metastatic may also appropriately lead to management decisions involving palliative care. Temel et al. published a landmark randomized study evaluating patients with newly diagnosed nonsmall cell lung cancer and demonstrated that early palliative care resulted in significant improvements in quality of life, mood, and survival (in spite of less aggressive interventions) [47]. While there are no studies of its kind evaluating the role of early palliative care in the setting of advanced PDAC, some institutions do employ an early palliative care approach, particularly in the locally advanced and metastatic settings to achieve a balance of quality of life and survival.

## Conclusion

In spite of extensive research in PDAC, it remains a highly lethal malignancy in part due to the high percentage of patients presenting with advanced tumors at diagnosis.

**Table 102.2** Surgical staging system of NCCN and MD Anderson.

| Stage | Superior mesenteric artery (SMA) | Celiac axis (CA) | Hepatic artery (HA) | Superior mesenteric vein (SMV)/portal vein (PV) |
|---|---|---|---|---|
| Resectable | No contact | No contact | No contact | No contact with SMV/PV or ≤180° contact without irregularity |
| Borderline resectable | ≤180° | ≤180° or >180° and amenable to modified Appleby procedure | + Contact with common HA without extension | IVC involvement, SMV/PV involvement >180° or ≤180° with irregularity/ thrombosis but + reconstructable |
| Unresectable* | >180° or contact with 1st jejunal SMA branch | >180° or with CA + aorta contact | | Unreconstructable SMV/PV |

*Source:* Modified from [4,19,40,41].
*Criteria as noted or with distant metastases.

Management of these patients involves a comprehensive clinical, radiologic, and endoscopic approach to define the tumor and stage. Treatment involves a multidisciplinary approach, and many times, the tools employed for clinical workup, as summarized here, can also be extrapolated for palliative care of symptoms in the advanced setting.

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# Surgical Treatment of Pancreatic Cancer

## 103

## Pancreatic Cancer: Indications for Resection

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## Introduction

Pancreatic cancer has the worst prognosis of all gastrointestinal neoplasms. An estimated 39,590 people will die of pancreatic cancer during 2014 in the United States [1]. This type of cancer is the fourth most common cause of death among the malignant neoplasms in the United States and Japan. The prognosis of pancreatic cancer is still poor, despite developments in surgical techniques and chemotherapy. Surgical resection offers the only possibility of a cure. The morbidity and mortality of pancreaticoduodenectomy (PD) were high about 30–40 years ago. However, the morbidity and especially the mortality of PD have been greatly reduced, and operative mortality rates had fallen to 2.8% in 2014 in Japan [2].

## Clinical Criteria for Resection

### Age and Concomitant Diseases

The peak incidence of pancreatic cancer occurs in the seventh and eighth decades of life. In our experience and that of high-volume centers, the morbidity and especially the mortality of pancreatic resection have been greatly reduced, and there is no difference in mortality rates between patients >70 years of age and those <70 years of age [2,3]. Patient age, comorbidity, performance status, and frailty are all topics for discussion during multidisciplinary review. One of the few medical contraindications for PD is liver cirrhosis with ascites and portal hypertension.

### Diagnosis and Staging

Diagnosis of pancreatic cancer will be discussed in another chapter. Preoperative staging is usually performed with multidetector computed tomography (MDCT) [4,5]. Endoscopic ultrasound (EUS) is also sometimes used in staging and diagnosis of pancreatic cancer. Laparoscopy is another potentially valuable diagnostic tool for cancer staging.

### Biopsy

Confirmation of the malignancy by biopsy is considered necessary before proceeding with surgical resection. Histologic diagnosis of adenocarcinoma of the pancreas is often made using fine-needle aspiration biopsy with either CT or EUS guidance. Pancreatic ductal blushing or biopsies can also be obtained at the time of endoscopic retrograde cholangiopancreatography. However, histologic or cytologic diagnosis of the malignancy is not required before surgical resection when the clinical suspicion of pancreatic cancer is high.

### Tumor-Associated Antigens

Tumor-associated antigens, such as carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, DU-PAN-2, and SPan-1 have been studied in connection with pancreatic adenocarcinoma. CA 19-9 1000 U/mL may correlate with distant metastasis or unresectable tumor in pancreatic cancer [6].

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## Surgical Criteria for Resection

### Preoperative Staging for Extent of Disease

There are no universally accepted criteria for resection. However, it is clear that patients with hepatic, peritoneal, and pleural metastases derive no benefit from resection. Therefore, preoperative staging to assess the extent of disease is important. The initial staging procedure is MDCT with contrast imaging [4,5]. This technique is reported to predict a high resectability rate. Factors contraindicating resection are extrapancreatic disease, obstruction of portal or superior mesenteric veins, and direct tumor extension to the celiac axis and superior mesenteric artery (SMA), which are assessed by MDCT. It is generally convenient to consider a clinical staging system based on whether the disease is resectable or borderline resectable, locally advanced unresectable, or disseminated. The criteria defining resectability status according to National Comprehensive Cancer Network (NCCN) Guidelines (Table 103.1) are generally used [7]. EUS is believed to be complementary to CT, providing additional information for patients in whom CT shows no lesions, or who have questionable involvement of major vessels or lymph nodes. Laparoscopy can reveal peritoneal or hepatic metastasis that might be missed even with the use of MDCT.

## Surgery for Pancreatic Cancer

The ideal operation for pancreatic cancer is isolated pancreatectomy. "Isolated" means en bloc resection using a non-touch isolation technique. It is easy to perform isolated distal pancreatectomy for cancer of the pancreatic body or tail compared with isolated PD. Isolated PD is difficult because of the complex vascular anatomy of the pancreas head region. However, isolated PD is also possible using a mesenteric approach [8], and catheter bypass of the portal vein [9] if necessary. Indication for

**Table 103.1** Criteria defining resectability status.

| Resectability status | Arterial | Venous |
|---|---|---|
| Resectable | No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]). | No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity. |
| Borderline resectable | Pancreatic head/uncinate process:<br>• Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction<br>• Solid tumor contact with the SMA of ≤180°<br>• Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning.<br>Pancreatic body/tail:<br>• Solid tumor contact with the CA of ≤180°<br>• Solid tumor contact with the CA of ≥180° without involvement of the aorta and intact and uninvolved gastroduodenal artery (some members prefer this criteria to be in the unresectable category). | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.<br>• Solid tumor contact with the inferior vena cava (IVC). |
| Unresectable | • Distant metastasis (including nonregional lymph node metastasis).<br>*Head/uncinate process*:<br>• Solid tumor contact with SMA >180°<br>• Solid tumor contact with the CA >180°<br>• Solid tumor contact with the first jejunal SMA branch.<br>*Body and tail*:<br>• Solid tumor contact of >180° with the SMA or CA<br>• Solid tumor contact with the CA and aortic involvement. | *Head/uncinate process*:<br>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)<br>• Contact with most proximal draining jejunal branch into SMV.<br>*Body and tail*:<br>• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus). |

total pancreatectomy or PD in pancreatic head cancer is one of the key problems in pancreatic cancer surgery. Recent studies using histopathologic and immunohistochemical analysis of total pancreatectomy specimens have clarified that carcinoma development from head to body or tail of the pancreas is continuous [10–12]. Therefore rapid intraoperative histopathologic diagnosis using frozen sections is important for diagnosis of intrapancreatic carcinoma development, for PD for pancreatic head cancer as well as distal pancreatectomy for pancreatic body or tail cancer [13]. Pylorus-preserving PD was intended to improve delayed gastric emptying and provide nutritional benefit [14]. However, no consistent data suggest that pylorus preservation leads to better quality of life or nutritional status after resection [15]. The superiority of laparoscopic or robotic surgery compared with open surgery for pancreatic cancer has not yet been clarified surgically and oncologically.

## Local Invasion

Invasion of the distal bile duct, duodenum, stomach, or mesocolon can often be dealt with by en bloc resection. The retroperitoneal margin, which includes the connective tissues behind the pancreas and those adjacent to the SMA, which are composed of extrapancreatic nerve plexuses, is often involved with a tumor. The mesenteric approach is ideal to obtain surgical free margins at this location. A negative margin is an important prognostic factor in survival [16,17].

## Extrapancreatic Nerve Plexus Invasion

Pancreatic carcinoma often invades the extrapancreatic nerve plexus [18–20]. There is no clear explanation for invasion of the extrapancreatic nerve plexus in the Union for International Cancer Control classification [21]. In the Japan Pancreas Society classification [22], the precise anatomy of the extrapancreatic nerve plexus is explained (Fig. 103.1). The grade of intrapancreatic neural invasion correlates with extrapancreatic nerve plexus invasion, and the manner of neural invasion has no relationship with lymph node metastasis [20]. In pancreatic head carcinoma, complete dissection of the extrapancreatic nerve plexus, especially the second portion of pancreatic head nerve plexus, is necessary to obtain a carcinoma-free surgical margin (Fig. 103.2). However, complete resection of the nerve plexus around the SMA causes severe diarrhea after surgery, and the prognosis for pancreatic carcinoma invading the extrapancreatic nerve plexus is poor [16]. The main cause of carcinoma-positive surgical margins is

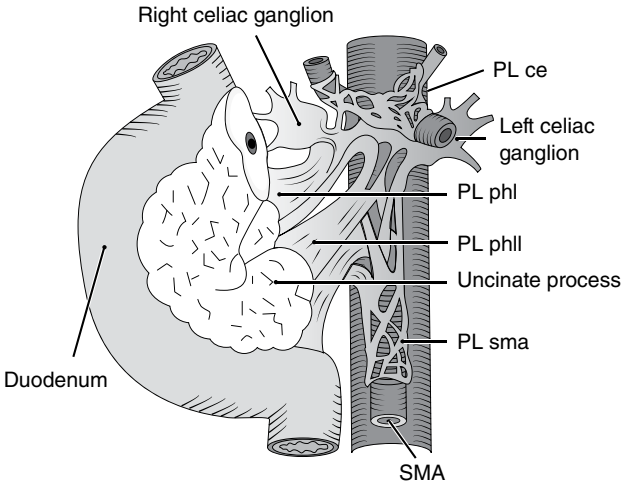


**Figure 103.1** Extrapancreatic nerve plexus (Japan Pancreas Society, Classification of Pancreatic Carcinoma, 3rd English edn, 2011). PL ce, celiac plexus; PL phI, first portion of pancreatic head nerve plexus; PL phII, second portion of pancreas head nerve plexus; PL sma, nerve plexus around the superior mesenteric artery; SMA, superior mesenteric artery.

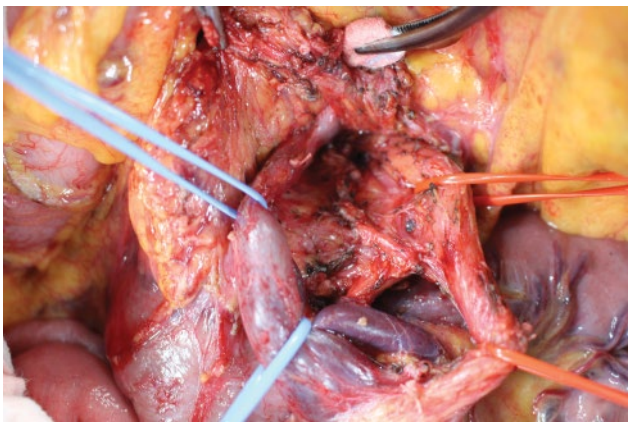

**Figure 103.2** Exposure of the mesopancreas (second portion of the pancreatic head nerve plexus) using the mesenteric approach. The nerve plexus around the superior mesenteric artery is completely preserved in this case.

extrapancreatic nerve plexus invasion [16,18,20]. The term mesopancreas has been used recently [23]. However, it is better to use the second portion of pancreatic head nerve plexus (PLphII) instead of mesopancreas (Fig. 103.3).

## Vascular Invasion

Cancer invasion of the superior mesenteric and portal veins is common in pancreatic head cancer. Over the past 35 years, the operative mortality rate of PD combined with portal vein resection has decreased, and portal vein resection in pancreatic cancer surgery has become a safe procedure [24].

From 1981 to 2014, 463 patients with pancreatic carcinoma underwent tumor resection in our department, and vascular resection was performed in 297 (64.1%) of these. Arterial resection with portal vein resection was undertaken in 16 patients. Operative mortality was 2.4% (11/463) in resected patients, 0.6% (1/166) in patients without vascular resection, 1.8% (5/281) in patients with portal vein resection without arterial resection, and 31.3% (5/16) in patients with portal plus arterial resection. Survival in patients is shown in Fig. 103.4 [24]. The combined portal and arterial resection group had a high operative death rate, more advanced stage, and high incidence of positive carcinoma invasion on the dissected peripancreatic margin. Carcinoma invasion to the SMA, celiac artery, and common hepatic artery is a contraindication for resection [25]. One of the exceptions is pancreatic body cancer that invades the celiac axis. This cancer should be resected by distal pancreatectomy with celiac axis resection [26]. Vascular resection is indicated when carcinoma-free surgical margins are necessary. There is no indication for extended resection in patients in whom surgical margins will become cancer positive if such an operation is done.

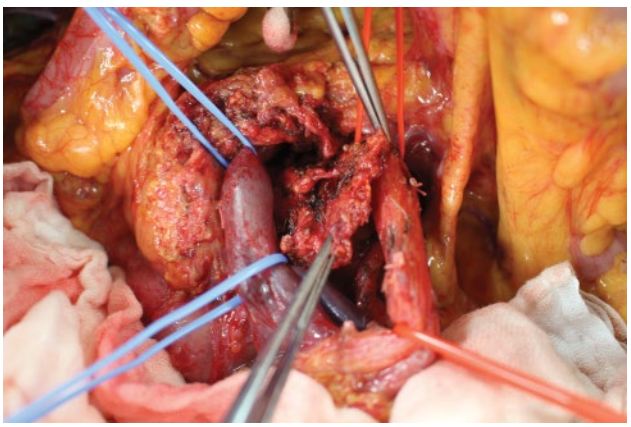

**Figure 103.3** Total mesopancreas excision along the superior mesenteric artery.

## Lymph Node Metastases

Lymph node dissection is one of the important components in pancreatic cancer surgery. The high incidence of 56–77% [27–30] in resected specimens of pancreatic cancer is the reason for extensive dissection of lymph nodes in pancreatic cancer surgery. There are few reports about para-aortic lymph node metastasis: the incidence of para-aortic lymph node metastasis in pancreatic head carcinoma is reported to be 16% [29] and 26% [30], while that in pancreatic body and tail carcinoma is reported to be 13% [31] and 17% [32], respectively. Although the efficacy of extended lymph node dissection in pancreatic cancer surgery was suggested, this issue was not clarified in recent prospective controlled studies [33–37] for pancreatic cancer surgery. The extended dissection of lymph nodes, including para-aortic lymph nodes, should not be considered as a routine part of PD, and although it does not contribute to survival, it does allow accurate staging.

## Peritoneal Metastases

Peritoneal dissemination is frequent in pancreatic cancer and is one of the contraindications for resection. Peritoneal metastases are too small to diagnose by CT or ultrasound, if the patients have no ascites. Therefore, diagnosis of peritoneal dissemination is done by direct visualization using laparoscopy or at the time of surgical exploration. Using conventional staining, the incidence of cancer cells ranges from 0% to 17% [38–42]. However, high incidences of 58% [43], 39% [44], and 22% [42] have been reported by immunocytochemical staining using monoclonal antibodies against tumor-associated antigens and cytokeratins. Controversy exists about prognosis with regard to positive and negative cytology [45]. Further study is necessary to determine whether positive cytology without macroscopic dissemination from washings

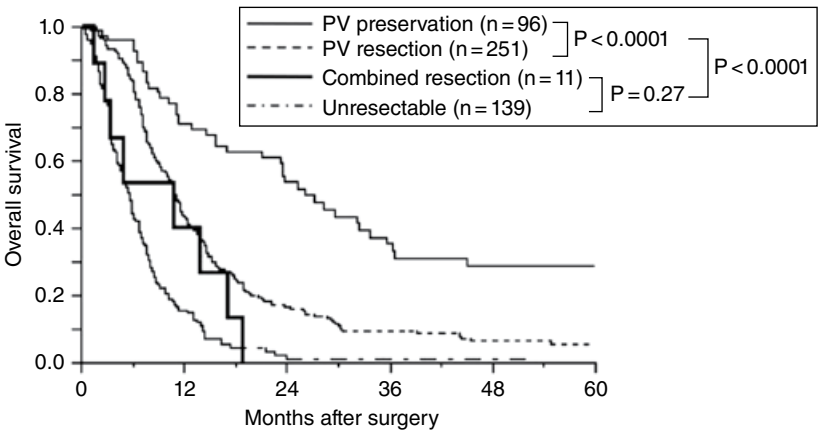


**Figure 103.4** Cumulative survival rates of the portal vein (PV) preservation and resection groups. Combined resection means the group with both portal vein and artery resection. *Source:* Nakao et al. 2012 [24]. Reproduced with permission of Wolters Kluwer Health.

obtained at laparoscopy or at the time of surgical exploration is a contraindication for resection.

## Liver Metastases

Liver metastases are also common in pancreatic cancer, and survival is so short that resection of the primary tumor is contraindicated. Metastases are usually multiple, and there are no data showing longer survival by pancreatectomy, with or without resection of liver metastases.

## Other Distant Metastases

Occasional distant metastases to the lungs, bone, and supraclavicular lymph nodes are also contraindications for resection of a primary tumor.

## Effect of Clinical Volume

Several studies have reported the effect of institutional volume on patient outcomes. In 1995, Lieberman et al. [46] assessed 1972 pancreatectomies, including total pancreatectomy, from 184 institutions in New York State. High-volume centers with >40 cases per year had significantly less mortality than low-volume centers (4% vs. 12.3%). Several other studies have also reported decreased mortality, length of hospital stay, and overall cost at high-volume compared with low-volume centers [47–49]. Furthermore, negative margin status and 5-year survival rates are higher in high-volume centers [50]. The definition of high and low volume varied among all these studies. The NCCN Panel recommendation is that pancreatic resections should be done at institutions that perform at least 15–20 cases of pancreatic resections annually [7].

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# Pancreaticoduodenectomy for Pancreatic Cancer, Short- and Long-Term Outcomes After Kausch–Whipple and Pylorus-Preserving Resection

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## Introduction

Dr. William Stewart Halsted performed the first successful resection of a periampullary tumor in 1898 [1,2]. The first successful regional resection of the head of the pancreas was performed by Kausch and was reported in 1912 [3]. The operative procedure of pancreaticoduodenectomy was popularized by Whipple, when he presented three patients to the American Surgical Association in 1935 [4,5]. During this era, and extending into the 1970s, pancreaticoduodenectomy was performed only infrequently because of a hospital mortality in the range of 25% [6]. Beginning in the 1980s, and extending up until the present, pancreaticoduodenectomy has become a safe procedure, performed in virtually any age group in high-volume centers, with a hospital mortality rate less than 5% [2,7,8]. The 30-day mortality in our hospital has been below 1% over the last decade [9].

Pancreatic cancer (PDAC) is a common cause of cancer death and is difficult to treat because of late presentation, disease heterogeneity, and treatment resistance. Long-term overall survival remains poor with a 5-year survival rate of 5% and virtually unchanged over the last three decades. For PDAC in the head of the pancreas, pancreaticoduodenectomy with curative intent is the only treatment modality that offers a chance of cure. With the development of effective neoadjuvant chemotherapy and significantly reduced surgery-related mortality, more patients with PDAC will have a chance for pancreaticoduodenectomy.

An accurate diagnosis of PDAC is required before any treatment plan. High-resolution computed tomography (CT) with pancreas protocol is the choice of imaging. Tissue diagnosis is necessary if neoadjuvant chemotherapy is part of the treatment plan. This can be achieved by endoscopic ultrasound (EUS) guided fine-needle aspiration (FNA).

The definition of resectability is categorized in Table 104.1. PDAC without visible distant metastasis is classified as resectable, borderline resectable (BRPC), or locally advanced cancer (LAPC) based on the preoperative CT imaging.

Several randomized studies have shown equivalent outcome between pylorus-preserving pancreaticoduodenectomy and the classic Whipple procedure [10,11]. In this chapter, we will discuss the short- and long-term outcomes after pancreaticoduodenectomy (classic and pylorus-preserving) for pancreatic cancer.

## Short-Term Outcome

Approximately 20% of patients with PDAC present with resectable disease. Surgery with curative intent should achieve an R0 resection with negative margins. The 5-year overall survival rate for all-comers after a successful resection is approximately 20% and is higher for those with negative nodes and margins [9].

Whether patients with borderline resectable pancreatic cancer (BRPC) will benefit from neoadjuvant chemotherapy remains controversial [12]. Konstantinidis et al. showed that patients undergoing an R1 resection have an improved survival compared with patients with locally advanced unresectable pancreatic cancer. Survival after resections with a 1 mm margin or less (169 patients) was similar to R1 resections (157 patients) [13]. There are currently two Alliance trials on the topic of the benefit of neoadjuvant chemotherapy and/or radiation therapy (A201101 and A201501). We are expecting results of these randomized clinical trials in a few years. These hopefully will settle the controversy over neoadjuvant treatment for patients with BRPC.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 104.1** Definition of resectability of pancreatic cancer.

| | Resectable | Borderline resectable | Locally advanced |
|---|---|---|---|
| **MD Anderson** | SMV/PV abutment or encasement w/o occlusion; No abutment of SMA/CHA/celiac | SMV/PV short segment occlusion; Abutment of SMA/CHA/celiac | SMV/PV not reconstructible; Encasement of SMA/CHA/celiac |
| **NCCN** | SMV/PV no abutment; SMA/CHA/celiac no abutment | SMV/PV abutment, short segment occlusion but reconstructible; Abutment of SMA/CHA; No abutment of celiac | SMV/PV not reconstructible; Encasement of SMA/CHA/celiac |

CHA, common hepatic artery; NCCN, National Comprehensive Cancer Network; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
Abutment: less than 180° of vascular circumference.
Encasement: more than 180° of vascular circumference.

Locally advanced pancreatic cancer (LAPC) is often treated with systemic neoadjuvant chemotherapy with the hope of a surgical resection. Case reports [14] and small series have been published showing the feasibility of surgical resection of LAPC after neoadjuvant chemotherapy. Faris et al. reported 22 patients with LAPC treated with FOLFIRINOX (5-fluorouracil [5-FU], oxaliplatin, irinotecan, and leucovorin). Five patients (23%) subsequently underwent R0 resections. Although the chemotherapy was associated with a 23% conversion to resectability, 3 of these 5 patients had distant metastasis by 5 months [15]. Ferrone et al. reported 40 patients with BRPC/LAPC who received FOLFIRINOX and surgery. Although 19 patients still had LAPC after FOLFIRINOX, 35 patients (92%) had R0 resections. The short-term outcomes such as length of stay, readmission, and mortality rate were similar when compared with patients with no neoadjuvant FOLFIRINOX [16]. Bickenbach et al. reported 36 resected patients with LAPC who received neoadjuvant chemotherapy. Their median overall survival was similar to those who presented with resectable PDAC [17]. Kadera et al. summarized their experience of 49 patients with LAPC. After a median of 7 months of neoadjuvant chemotherapy, 37 of 49 patients were lymph node negative (75.5%) and 42 (85.7%) had negative resection margins. They reported 45.8% with a complete pathologic response, the highest in the literature [18]. In a systemic review of 57 studies (median BRPC/LAPC patients per study = 27), Gillen et al. reported that 33.2% of patients were resected after neoadjuvant therapy. Resection after neoadjuvant chemotherapy or chemoradiation appears to give patients similar overall survival rates as those with resectable PDAC [19].

Regardless of the indications for pancreaticoduodenectomy as discussed earlier (resectable vs. BRPC vs. LAPC), factors affecting the short-term surgical outcome include patient age, history of neoadjuvant therapy, vessel resection and reconstruction, extension of lymph node dissection, and methods of reconstruction. These factors will be discussed here:

- Compared with age <80 years, patients aged 80 or over are associated with higher morbidity (55% vs. 44%) and hospital mortality (4% vs. 1%) [2]. Younger patients (<45 yrs) have fewer complications after curative resections and better survival compared with older patients (over 70 yrs) [20].
- History of neoadjuvant therapy has been associated with lower operative morbidity. Ferrone et al. reported no pancreatic fistula in her series of 40 patients with BRPC/LAPC who received FOLFIRINOX and surgery [16]. Motoi et al. reported a large series of 388 patients who received neoadjuvant therapy. There were no significant differences in postoperative morbidity rate between the neoadjuvant and no neoadjuvant groups [21].
- Resection of the portal vein/superior mesenteric vein is occasionally necessary to achieve an R0 resection. Riediger et al. reported their experience in 53 patients with vein resection. Thirty-two percent were segmental resections; 40% had no tumor infiltration of the vein on final pathology. Compared with patients without vein resection, patients with vein resection had similar morbidity rates (23 vs. 35%) [22].
- Arterial resection and reconstruction after neoadjuvant chemotherapy may be required to achieve an R0 resection. The most common resected artery during pancreatectomy is the celiac axis. The procedure came to be known as the modified Appleby procedure where a distal pancreatectomy and splenectomy with en bloc celiac axis resection is performed, and arterial perfusion of the liver is maintained by retrograde collateral blood flow from the superior mesenteric artery (SMA) via the gastroduodenal artery (GDA). Numerous small series have shown the safety and feasibility of this surgery [23–28]. The short-term outcome including postoperative morbidity of the modified Appleby procedure is similar to that of distal pancreatectomy.
- Hepatic artery and SMA are infrequently resected during pancreaticoduodenectomy because of the technical challenge of arterial reconstruction and poor

short-term outcome. Rehders et al. reported their experience with arterial vascular resection for PDAC and argued that arterial vascular involvement is an indicator of unfavorable topography, instead of adverse tumor biology. They claimed vascular resection is warranted if an R0 resection can be achieved by experienced surgeons [29]. Although a few small series have shown the safety of an en bloc resection of the hepatic artery or SMA [30], the benefit has not been proved by any large study or meta-analysis [31].

- Extended lymphadenectomy is not widely utilized as many randomized trials and systemic reviews have shown no benefit and more postoperative complications [32–36].
- After resection, pancreaticojejunostomy is preferred at our hospital. Postoperative pancreatic fistula (POPF) can be significantly reduced by meticulous anastomosis with optimization of blood supply at the pancreaticojejunostomy [37].

In our recent series of pancreaticoduodenectomy for 1,687 patients with PDAC, the overall complication rate was 41%, with the most common complications including delayed gastric emptying (DGE) (16%), wound complications (11%), and POPF (6%) (Table 104.2) [9]. DGE and wound complications are often related to POPF. In the absence of POPF, the management of DGE is mainly supportive. A nasogastric tube is often used to decompress the stomach. Parental nutrition support is necessary. Patients with DGE might benefit from prokinetics such as metoclopramide and erythromycin. The antecolic location of gastrojejunostomy has been shown to reduce the incidence of DGE in several publications [38,39]. In a recent series of 160 pancreaticoduodenectomies, Nakamura et al. showed a side-to-side anastomosis of gastrojejunostomy on the greater curvature could significantly reduce the incidence of DGE (2.5% vs. 21% from end-to-side anastomosis) [40]. It seems that an antecolic side-to-side gastrojejunostomy has the lowest chance of DGE in our practice.

**Table 104.2** Trends of the three most common postoperative morbidities after Whipple for pancreatic cancer.

| | POPF | DGE | Wound complications |
|---|---|---|---|
| 1980s ($n$ = 66) | 0 (0%) | 2 (3%) | 1 (2%) |
| 1990s ($n$ = 507) | 18 (4%) | 74 (15%) | 33 (7%) |
| 2000s ($n$ = 1115) | 75 (7%) | 190 (17%) | 151 (14%) |
| Total ($n$ = 1688) | 93 (6%) | 266 (16%) | 185 (11%) |

DGE, delayed gastric emptying; POPF, postoperative pancreatic fistula.

## Long-Term Outcome

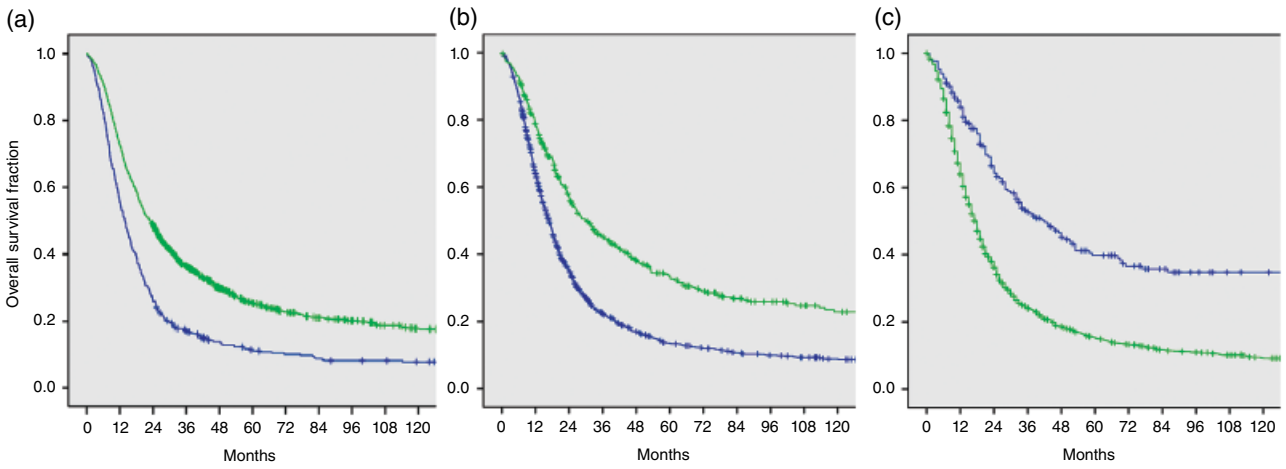
Long-term overall survival after Whipple surgery for patients with PDAC is not optimistic. Although the 30-day mortality after Whipple surgery has been low at 1% since the 1990s, the median survival for PDAC remained at 19 months in our recent analysis of PDAC patients from 1981 to 2011 [9]. In this series of 1,687 patients with PDAC, resection margin status and lymph node positivity were associated with overall survival (Fig. 104.1). For those patients with negative resection margin and negative lymph node metastasis, the estimated overall survival was 42 months compared with 18 months for patients with either positive margin or nodal metastasis.

The commonly used prognostic factors for 5-year survival include tumor size, lymph node status, margin status, tumor differentiation, lymphovascular and perineural invasion, and adjuvant chemotherapy. Whether these factors can predict the 10-year survival rate remains unknown. We reviewed the clinicopathologic characteristics of patients who underwent pancreatectomy for PDAC at the Johns Hopkins Hospital between 01/2000 and 12/2010. The estimated disease-specific survival at 5 and 10 years was 20.4% and 15.1%, respectively. Using the Aalen's linear hazards model to study time-varying effect, the commonly used prognostic factors for 5-year survival were not important for survival after 5 years. Among 119 patients who survived >5 years, 30 (25%) had positive margins, 13 (11%) had tumor size >4 cm, 8 (7%) had >5 positive nodes, 36 (30%) had poor tumor differentiation, 38 (32%) had lymphovascular invasion, and 95 (80%) had perineural invasion. Among 27 patients who survived >10 years, 8 (30%) had positive margins, 4 (15%) had tumor size >4 cm, 2 (7%) had >5 positive nodes, 12 (44%) had poor tumor differentiation, 6 (22%) had lymphovascular invasion, and 24 (89%) had perineural invasion. The reported prognostic factors for PDAC are time-dependent and restricted to the first 5 years following pancreatectomy.

Completion of the full course of adjuvant chemotherapy was an independent prognostic factor for survival, but time to treatment initiation after surgery was not [41].

Neoadjuvant chemotherapy has significantly increased the chance of resection of PDAC. Although no phase 3 trial data has been published about the use of neoadjuvant chemotherapy in PDAC, neoadjuvant chemotherapy and/or chemoradiation therapy is widely used especially for patients with BRPC/LAPC [15,16,42].

A meta-analysis of more than 4,000 patients with PDAC showed that 32% of patients with locally advanced disease would have surgical resection after neoadjuvant chemoradiation therapy. The survival rate is similar to patients with resectable disease [19]. The most commonly




| | Margin positive ($n=440$) | Margin negative ($n=1247$) | Node positive ($n=1277$) | Node negative ($n=410$) | Margin/Node negative ($n=214$) | Other ($n=1473$) |
|---|---|---|---|---|---|---|
| Median overall survival (months) | 14 | 23 | 17 | 30 | 42 | 18 |

(a) Overall survival of PDAC patients with margin negative resection (green line) vs. margin positive resection (blue line). (median survival 23 vs. 14 months, $P<0.001$)
(b) Overall survival of PDAC patients with negative lymph node metastasis (green line) vs. positive lymph node metastasis (blue line). (median survival 30 vs. 17 months, $P<0.001$)
(c) Overall survival of PDAC patients with negative lymph node metastasis and negative margin (blue line) vs. other (green line). (median survival 42 vs.18 months, $P<0.001$)

**Figure 104.1** Overall survival curve of patients with PDAC.

used regimen for neoadjuvant chemotherapy is FOLFIRINOX if the patient has good performance status. The rationale to use FOLFIRINOX is based on the data extrapolated from the metastatic setting where FOLFIRINOX showed better improvements in both median progression-free survival (PFS) (6.4 months vs. 3.3 months; $P<0.001$) and median overall survival (11.1 months vs. 6.8 months; $P<0.001$) compared to gemcitabine [43].

Another regimen for neoadjuvant chemotherapy is gemcitabine and nab-paclitaxel. This is also based on the data extrapolated from the metastatic setting where the combination of both drugs improved overall survival (8.7 months vs. 6.6 months; $P<0.0001$; HR, 0.72) and PFS [44].

Several national trials are enrolling patients with resectable PDAC (SWOG S1505), BRPC (Alliance A201101 and A201501), or LAPC (RTOG 1201) to determine the benefit of neoadjuvant chemotherapy and/or radiation. A phase 2 study of FOLFIRINOX plus a short course of radiation therapy is being explored in the neoadjuvant setting to determine the rate of R0 resection (NCT01591733). We are expecting level 1 evidence in the next few years regarding the benefit of neoadjuvant chemotherapy and/or radiation therapy.

Recently, stereotactic body radiotherapy (SBRT) has been used for patients with BRPC/LAPC in both neoadjuvant and adjuvant settings [45]. SBRT can deliver a high dose of radiation to the tumor area while sparing radiation damage to surrounding tissue [46]. SBRT targeting of the tumor bed outlined by surgical clips is being explored in a prospective single-arm clinical trial in combination with a pancreatic tumor cell vaccine and FOLFIRINOX in the adjuvant setting (NCT01595321) [45]. Chuong et al. reported the combination of gemcitabine, docetaxel, and capecitabine (GTX) and SBRT in 57 patients with BRPC. Of these patients, 32 (56.1%) underwent successful surgical resection, with a 96.9% rate of R0 resection, a 9.4% rate of pathologic complete response, and a median overall survival (OS) of 19.3 months [47]. Whether the benefit of using SBRT to achieve better local control can be translated into longer overall survival is still unknown.

Other surgical factors affecting the long-term outcome of pancreaticoduodenectomy may include margin status and vessel resection/reconstruction. Data have shown if an R0 resection is obtained with vein excision, overall survival appears similar to those with R0 resections without venous involvement, with no significant increase in morbidity and mortality [48]. Venous involvement is an

indicator of tumor location rather than aggressive tumor biology. Kelly et al. reported the experience of 71 patients with vein resection. The long-term outcome is not worse for patients with Whipple and vein resection compared with patients who had Whipple without vein resection (overall survival 12 vs. 19 months; $P = 0.05$) [49]. Tseng et al. reported a similar experience of 110 patients who underwent Whipple with vein resection. Median survival was 23.4 months in the group that required vein resection and 26.5 months in the group that underwent standard Whipple surgery ($P = 0.177$) [50].

Although retrospective studies have shown that in selected patients Whipple with vein resection can achieve low mortality and median survival of 2 years, aggressive resection with both arterial and venous resection and reconstruction does not lead to long-term survival [31,51].

Although data are rare, prospective data are being collected for patients with limited liver metastasis (less than 3) and response to a full course of neoadjuvant chemotherapy (6 months). The outcome of these patients who are treated with diagnostic laparoscopy and then surgical resection is pending.

## Future Trends

Minimal invasive pancreaticoduodenectomy including total laparoscopic [52,53] or robotic-assisted approach [54,55] has shown promising short-term outcomes such as shorter hospital stay and faster recovery. This could be translated into timely adjuvant chemotherapy. Total laparoscopic approach has also been shown to have a longer PFS compared to that of open pancreaticoduodenectomy. Early detection, minimal invasive surgery, and more effective chemotherapy will lead to a better outcome for patients with PDAC in the future.

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# 105

# Left Pancreatectomy for Body and Tail Cancer

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## Introduction

Patients with cancer of the pancreatic body and tail typically present in a more advanced stage, because of the initial lack of symptoms. By the time clinical signs occur, disease is usually present outside of the pancreatic parenchyma and infiltration of adjacent vascular structures or organs is often observed [1]. Moreover, lymphatic metastasis in locoregional lymph nodes and dissemination to distant organs may also be present at the time of diagnosis, leading to less than 15% of body and tail located malignant tumors being resectable at initial presentation [2].

Treatment modalities are optimally decided by a multidisciplinary team, based on imaging studies, cancer biomarker values, and patient performance status. Surgical resection of the malignant lesion is the treatment of choice and provides the highest chance of cure. Patients who are eligible for surgery undergo a left pancreatectomy (LP), also known as distal pancreatectomy [3]. It is a standardized surgical procedure that has been performed with improved postoperative outcomes over the years [4]. LP involves resection of the distal portion of the pancreas, to the left of the superior mesenteric vessels, and the spleen when malignancy is involved. Resection of adjacent organs, such as the ipsilateral adrenal gland or the stomach may be necessary, due to local advancement of the tumor or inflammatory adhesions [5].

The combination of advanced disease and technical challenges, such as extensive retroperitoneal surface area, has led to increased rates of postoperative morbidity and positive margin resections accompanying the procedure [6].

## Tumor Staging and Resection Eligibility

Multidisciplinary consultation at a high-volume center for pancreatic surgery is optimal for diagnosis, assessment of resectability, and management of left-sided pancreatic cancer [7]. High-quality imaging studies are essential in evaluating the extent of the disease at presentation and should include a pancreas protocol multidetector CT or an MRI (Fig. 105.1). Radiologic findings and laboratory values of cancer biomarkers (CA 19-9) allow the categorization into resectable, locally advanced, and metastatic disease. Additional diagnostic modalities, such as endoscopic ultrasound and fine-needle aspiration biopsy (EUS-FNA), are utilized when radiologic and clinical findings are suggestive of additional differential diagnosis apart from pancreatic solid tumor [8]. Proof of malignancy via biopsy is not required in candidates for surgical resection and a diagnostic biopsy should not delay definitive treatment, when clinical findings indicate high probability of pancreatic cancer [9]. Resectability status criteria for solid tumors of the pancreatic body and tail are shown in Table 105.1.

## Surgical Technique

### General Considerations

Left pancreatectomy is performed as an oncologic procedure with the goal to achieve R0 resection and regional lymph node dissection. Detailed knowledge of the anatomy, including anatomic spaces and major vascular structures is mandatory. The pancreatic body and tail lie

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

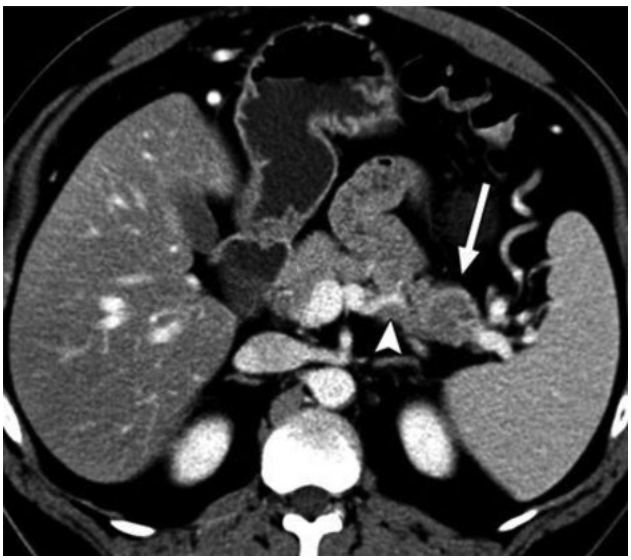

**Figure 105.1** Computed tomography of a patient with adenocarcinoma of the pancreatic tail (white arrow) and concomitant splenic vein thrombosis (arrowhead). *Source:* Reprinted with permission from the American Journal of Roentgenology.

**Table 105.1** Resectability criteria for pancreatic body and tail cancer.

| | |
|---|---|
| **Borderline resectable** | • Tumor contact with the celiac artery of ≤180°<br>• Tumor contact with the celiac artery of >180°, without involvement of the aorta and with intact gastroduodenal artery<br>• Tumor contact with the inferior vena cava<br>• Tumor contact with the superior mesenteric vein or portal vein of >180° or ≤180° with contour irregularity or vein thrombosis |
| **Unresectable** | • Tumor contact with the superior mesenteric artery or celiac artery of >180°<br>• Tumor contact with the celiac artery and aortic involvement<br>• Unreconstructable superior mesenteric vein or portal vein due to occlusion |

in the retroperitoneum in an oblique position behind the lower portion of the gastric greater curvature; in the same left anterior pararenal space in which the duodenum, the root of the mesocolon, and the splenic flexure also lie. Medially, the pancreatic body relates to the superior mesenteric artery, the celiac artery, and the portal-splenic-superior mesenteric vein confluence; all surrounded by connective tissue. Therefore, development of malignant tumors in the left part of the pancreas can penetrate the pancreatic capsule and invade any of the afore-mentioned surrounding structures.

A combined pancreatosplenectomy is usually performed, since spleen preservation is generally not indicated in pancreatic adenocarcinoma. When the tumor involves adjacent organs beyond the spleen, a wider en bloc resection is indicated. Direct tumor invasion to the splenic vessels constitutes a T3 pathologic stage (extension beyond the pancreas); further vascular involvement increases the probability of unresectability.

Patients who are eligible for surgery should undergo diagnostic laparoscopy at the beginning of the operation to exclude possible distant metastases (liver) or carcinomatosis, missed by the imaging studies [10]. In the presence of metastatic disease, a lesion biopsy is performed.

## Retrograde Left Pancreatosplenectomy

After initial laparoscopy, a long midline skin incision from the xiphoid to 8–10 cm below the umbilicus is created; in patients with normal weight this incision provides satisfactory exposure for mobilization of the pancreatic body and tail. Alternatively, a left subcostal incision is suitable in obese patients.

Exposure of the pancreatic body and tail follows after a thorough exploration of the abdominal cavity for signs of metastatic disease. Initially, the omentum is detached from the transverse colon, and the peritoneal layer that surrounds the pancreas is incised along the inferior border, starting from the tail. Care must be taken to avoid injury to the inferior mesenteric vein that lies deep in the peritoneal layer. Palpation of the left-sided pancreas allows a precise evaluation of tumor extension. Ligation of the splenic artery follows, close to its point of origin from the celiac artery; palpation of the hepatoduodenal ligament prior to ligation secures that the hepatic artery has not been occluded.

The traditional retrograde approach continues with mobilization of the spleen, by incision of the splenorenal and splenocolic ligaments with electrocautery or Metzenbaum scissors. The spleen can now be elevated away from the ipsilateral adrenal gland and kidney. Division of the short gastric and the left gastroepiploic vessels allows the detachment of the spleen from the greater curvature of the stomach and the free inspection of the posterior pancreatic surface (Fig. 105.2). The splenic vein is identified and ligated distal to the confluence with the inferior mesenteric vein with two 2-0 silk ligatures.

The final step involves the division of the pancreatic parenchyma. This can be accomplished by numerous methods. Traditionally, the pancreas is divided sharply or with electrocautery followed by the placement of figure of eight sutures to occlude the superior and inferior pancreatic arteries. Once hemostasis is achieved, the pancreatic duct is identified and oversewn with a fine

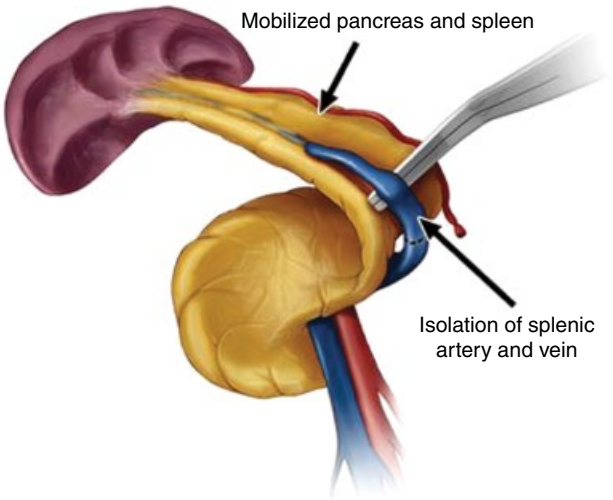


**Figure 105.2** Mobilization of the pancreatic body and tail and visualization of the posterior pancreatic surface. *Source:* Reprinted with permission from the American Journal of Roentgenology.

absorbable suture. This is followed by the placement of mattress sutures over the entire transection line. Alternatively, a more modern approach is to use a 48–55 mm linear stapler that is applied across the pancreatic transection line. Prior to closure, closed suction drains are usually placed near the transection margin.

### Radical Antegrade Modular Pancreatosplenectomy

In 2003, Strasberg et al. described a modification of LP for malignant tumors that relied on early control of major blood vessels, improved visualization of the posterior resection margin, and extensive lymph node dissection [11]. In radical antegrade modular pancreatosplenectomy (RAMPS) the dissection takes place in an antegrade fashion (from right to left). The parenchyma is dissected first at the pancreatic neck using a stapler and the underlying vascular structures are exposed. The splenic vessels are ligated and extended dissection of celiac and superior mesenteric artery nodes follows. The final resection plane is decided based on tumor extension. The anterior renal fascia is always excised; if the pancreatic lesion invades the ipsilateral adrenal gland or further, the resection plane extends towards the anterior surface of the kidney, behind the perinephric fat (posterior RAMPS) [4].

Improved 5-year survival has been reported in patients with pancreatic adenocarcinoma of the left pancreas who underwent RAMPS [12,13]. Modifications of the surgical procedure can also be found in the literature [4,14]. Randomized trials comparing standard LP and RAMPS will be needed to support the improved oncologic outcome of the latter.

### Distal Pancreatectomy with en Bloc Celiac Artery Resection

Vascular involvement of the celiac axis in pancreatic cancer is considered an indicator of unresectability. In the last decade, a modified Appleby procedure has been adopted for resection of locally advanced tumors of the pancreatic body [15]. The operation is a left pancreatectomy with en bloc splenectomy and resection of the celiac axis. In the modified Appleby procedure, once the celiac trunk and common hepatic artery are resected, the liver receives adequate blood supply from the superior mesenteric artery via retrograde flow, through the inferior pancreaticoduodenal artery, the arcade within the pancreatic head, and finally the gastroduodenal artery to the proper hepatic artery.

Few small series of patients who underwent a modified Appleby operation have been published [16–18]. Appropriate patient selection is necessary and consideration on anatomic variations of hepatic circulation must be given. Neoadjuvant chemotherapy or chemoradiation is necessary in stage III borderline patients [19]. The procedure has a postoperative morbidity rate similar to LP [20]. The median overall survival of these patients is improved, compared with chemotherapy or chemoradiotherapy alone, and is similar to that of stage I/II patients, who undergo resection [21].

## Minimally Invasive Left Pancreatectomy

Laparoscopic and robotic surgery of the distal pancreas has developed rapidly over the last few years. The first laparoscopic LP was reported in a patient with chronic pancreatitis, early in the development of laparoscopic surgery [22]. Utilization of laparoscopic technique in dissection of malignant tumors of the pancreatic body and tail progressed slower. The surgical principles remain the same as in the open pancreatectomy: margin-negative resection and an adequate lymphadenectomy. Both the standard retrograde [23] and the RAMPS technique [24–26] are amenable to the laparoscopic approach. Although operating time is reported to be longer on average, several publications demonstrated a lower estimated blood loss compared to open LP [27–29]. Additionally, R0 resection and number of dissected lymph nodes in laparoscopic LP are similar to the open approach [30,31], which leads to comparable long-term oncologic outcomes. Moreover, the reported overall survival was similar in the open and laparoscopic approach [30,32,33]. Interestingly, some have suggested that postoperative complication rates are improved compared to the open approach, including hemorrhage and pancreatic fistulas

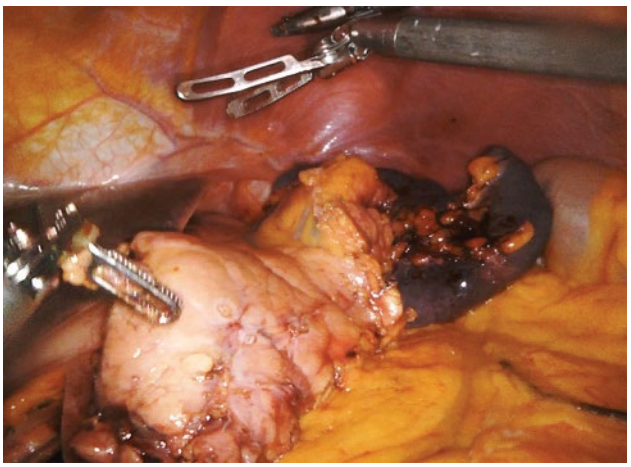

**Figure 105.3** Robotic left pancreatectomy for pancreatic adenocarcinoma.

[34,35]. Others have reported that shorter length of stay, lower postoperative costs, and shorter time for initiation of adjuvant therapy are observed in patients who undergo laparoscopic LP [35–37].

Robot-assisted resections were the next step in minimally invasive pancreatic surgery. In 2003, three cases of robot-assisted laparoscopic LP for adenocarcinoma were reported by Giulianotti et al. [38]. Since then, utilization of robotic surgical systems (Fig. 105.3) has increased significantly and major case series have been published [39–44]. Main comparisons are made against the laparoscopic resection. A recent systematic review and meta-analysis found no statistically significant difference in blood loss, operative time, and conversion rates between the two approaches; postoperative morbidity was also similar [45]. It appears that robot-assisted laparoscopic LP is as feasible and safe as the laparoscopic approach.

The advantages of laparoscopic and robot-assisted LP are evident: smaller incisions, decreased blood loss, less postoperative pain, shorter length of hospital stay, and faster recovery. However, reported conversion rates of 10–15% [46] indicate that these operations are feasible in well-selected patients and substantial surgeon experience in minimally invasive techniques is required [46,47]. Randomized controlled trials are recommended to evaluate further the feasibility and long-term outcomes of these approaches.

## Postoperative Considerations

### Postoperative Pancreatic Fistula

Postoperative pancreatic fistula (POPF) is the most common major complication of left pancreatectomy with a reported incidence of 20–30% [48,49]. The impact of the closure technique on POPF rates following LP has been extensively studied. Multiple prospective studies and randomized trials have compared the suturing and stapling technique [50–53] and a trend favoring use of stapler for remnant closure is observed. However, Bilimoria et al. reported that identification and direct ligation of the main pancreatic duct is associated with reduced pancreatic leak rates in left pancreatectomy [54]. The most recent meta-analysis identifies lower overall POPF incidence with use of stapler, but no difference in clinically relevant POPF [53]. Other risk factors for development of pancreatic fistula include size of the pancreatic gland [55], location of parenchymal transection [56], and extensive lymphadenectomy [57].

Placement of a postoperative drain on the surgical bed and time of its removal is an ongoing debate. The goal of drain placement is to recognize a pancreatic leak early and allow controlled drainage of the pancreatic fluid, which invariably resolves within 3–4 weeks. However, drains have been associated with retrograde intra-abdominal infections, peripancreatic vessel and hollow viscera erosion, and increased possibility of promoting pancreatic fistula formation, especially with closed suction drainage [58–60]. Utilization of drains is highly dependent on the surgeon's preferences and clinical experience.

Pancreatic fistula diagnosis is clinical; nonspecific symptoms such as anorexia, nausea, and abdominal discomfort or pain are usually present. Secondary delayed gastric emptying can also be observed, and mildly elevated WBC count and C-reactive protein levels should raise clinical suspicion for POPF. Definitive diagnosis is placed with an abdominal CT, where a peripancreatic collection is seen. In the vast majority of cases, management of POPF is a combination of support with enteral nutrition [61,62] and image-guided percutaneous drainage of peripancreatic fluid collection [63]. Recent studies indicate that utilization of somatostatin analogs in POPF does not provide significant advantage in fistula closure rate [64].

### Postoperative Diabetes Mellitus

New-onset pancreatogenic diabetes (type 3c) is a complication of a varying rate between 5% and 50%, depending on preexisting pancreatic disease and extension of parenchyma resection [65,66]. With the improved survival achieved after resection of body and tail adenocarcinoma, postoperative diabetes can become a lifelong complication. In a recent meta-analysis, the cumulative risk for new-onset diabetes after LP for malignancy is 7–28%, with an increased chance of insulin dependency [67]. Patients who will be submitted to LP should be informed preoperatively about the possibility of developing diabetes.

## Conclusions

Patients diagnosed with cancer of the pancreatic body and tail usually present with locally advanced or metastatic disease. In those cases where the tumor is manageable surgically, a left pancreatectomy with negative margins provides the best chance for curative treatment. Postoperative morbidity rates are relatively high, but the majority of them are self-limited and the surgical mortality remains low. Utilization of laparoscopic and robotic techniques allows faster recovery and timely initiation of adjuvant therapy.

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# 106

# Total Pancreatectomy: Indications and Limitations

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## Total Pancreatectomy

Total pancreatectomy (TP) was first described by Rockey in 1943 [1], and the popularity of this procedure increased during the 1960s [2]. The rationale for TP was to avoid pancreatic anastomosis-related complications and to optimize oncologic surgery in pancreatic cancer patients. After the initial enthusiasm for TP, results of large series of TP for pancreatic cancer were published in the late 1980s and 1990s [3–8]. They showed that TP could not improve the rates of R0 resections for pancreatic cancer, had perioperative mortality rates similar to or higher than partial pancreatic resections (13–27%), and no survival advantage was found [3–8]. Furthermore, TP was complicated by permanent pancreatic endocrine and exocrine deficiencies [9]. These results led surgeons largely to abandon TP and no longer consider it as a viable option for pancreatic disease.

However, recent advances in surgical techniques, perioperative management, and the development of high-volume surgical centers demonstrate that TP can be performed with lower mortality rates than in the past [10–13]. Furthermore, improvements in long-acting insulin formulations and high-quality enzyme replacement formulations for managing brittle diabetes mellitus and malabsorption from exocrine insufficiency enable more effective control of these conditions after TP [10–14].

In this chapter, recent indications and limitations of TP are considered, based on short- and long-term outcomes after TP reported in the literature.

## Elective Total Pancreatectomy and Salvage Completion Pancreatectomy

TP can be classified into elective TP and salvage completion pancreatectomy for complications after partial pancreatectomy [12,15,16].

An elective TP includes primary TP and two-stage TP after previous partial pancreatic resections. Primary elective TP is performed in cases of central tumor location in the pancreas or multifocal tumors with preoperatively planned TP, the intraoperative finding of an extended tumor other than preoperative imaging finding, or tumor positive intraoperative frozen pancreatic transection margin with the need for extension of the pancreas. Two-stage elective TP is performed in cases of tumor recurrence or of new tumors developing in the remnant pancreas after partial pancreatic resection.

Salvage completion pancreatectomy is indicated in the clinical situation of a patient with a severe complication after a pancreatic resection, such as pancreatic fistula or abdominal hemorrhage, and when conservative treatment strategies have been exhausted [12,16].

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Companion website: www.wiley.com/go/beger/thepancreas

## Perioperative Outcomes After Total Pancreatectomy

### Elective TP

High perioperative mortality and morbidity rates after TP have long been reported [3–8]; however, a dramatic decrease has been achieved in recent years due to improvements in surgical techniques and postoperative management [10–13,15,16]. Recent single-institution series have reported perioperative mortality rates ranging from 3% to 12.5%, and perioperative morbidity rates ranging from 25% to 54% (Table 106.1) [10,12,15–20]. Advanced age (>70 years), the presence of comorbid conditions, lengthy operative time (>420 min), high blood loss (>2,000 mL), and/or arterial resections were reported as independent risk factors for mortality following TP [20,21].

Surgical complications after TP include delayed gastric emptying, intra-abdominal abscess, abdominal hemorrhage, anastomotic leakage, and wound infection. Several studies report that rate of delayed gastric emptying is the most frequent perioperative complication following TP [12,19,20], and that the relationship between delayed gastric emptying and surgical technique (i.e., with or without preservation of the pylorus ring of the stomach) was unclear [12,20].

Although mortality rates following TP have decreased, perioperative morbidity rates remain high. Therefore, careful patient selection, surgical procedure, and postoperative management are essential to decrease morbidity rates after this procedure.

### Salvage Completion Pancreatectomy

High mortality rates after emergent complete pancreatectomy have been reported, ranging from 39% to 48%, and morbidity rates were also high, ranging from 79% to 91% [12,16]. Furthermore, the postoperative outcomes after salvage completion pancreatectomy, including complications, hospital stay, and survival, were significantly worse than those after elective TP [12,16]. The poor outcomes are associated with conditions such as severe abdominal sepsis or hemorrhage after partial pancreatectomies, when conservative treatment strategies have been exhausted.

With advances in interventional radiology techniques, including drainage of pancreatic fistula or intra-abdominal abscess, and arterial embolization for abdominal hemorrhage, complications from salvage TP after partial pancreatectomies should become more avoidable [22,23].

## Long-Term Outcomes After Total Pancreatectomy

With the increasing number of long-term survivors after TP [20,25,26], management of late complications and evaluation of quality of life (QOL) are important, although there have been few reports about long-term outcomes [10,12,15,18–20,24,27]. Late complications after TP include anastomotic ulcer at gastrojejunostomy and hepatic steatosis as well as diabetes mellitus and malabsorption caused by endocrine and exocrine insufficiency. Furthermore, long-term QOL may be associated with postoperative symptoms, such as diarrhea, inappetence, and weight loss [10,12,20,27].

### Diabetes Mellitus After Total Pancreatectomy

Diabetes mellitus after TP is caused by a complete lack of endogenous insulin and glucagon, leading to frequent and deep states of hypoglycemia and hyperglycemic episodes that can be difficult to control (brittle diabetes) [9].

**Table 106.1** Perioperative mortality and morbidity rates after an elective total pancreatectomy reported in the main literature.

| Author | Period of time | Total number | Disease PDAC | IPMN | Others | Mortality rate (%) | Morbidity rates (%) |
|---|---|---|---|---|---|---|---|
| Billings et al. [10] (2005) | 1985–2002 | 99 | 33 | 26 | 40 | 5% | 32% |
| Müller et al. [12] (2007) | 2001–2006 | 124 | 67 | 18 | 39 | 4.8% | 24% surgical<br>14.5% nonsurgical |
| Stauffer et al. [17] (2009) | 2002–2008 | 47 | 10 | 31 | 6 | 2% | 37% |
| Casadei et al. [18] (2010) | 2006–2009 | 20 | 7 | 8 | 5 | 5% | 25% |
| Crippa et al. [15] (2011) | 1996–2008 | 65 | 19 | 31 | 15 | 0% | 38.5% |
| Barbier et al. [19] (2013) | 1993–2010 | 56 | 4 | 39 | 13 | 3.6% | 45% |
| Hartwig et al. [20] (2015) | 2001–2012 | 434 | 289 | 75 | 70 | 7.8% | 37.3% surgical<br>37.6% nonsurgical |
| Almond et al. [16] (2015) | 1987–2013 | 98 | 45 | 12 | 41 | 12.5% | 46% |

**Table 106.2** Long-term outcomes after total pancreatectomy reported in the main literature.

| Author | Total number | $HbA_{1c}$ | Diabetes | Weight loss % of patients | Digestive symptoms |
|---|---|---|---|---|---|
| Billings et al. [10] (2005) | 27 | 7.4% (5.0–11.3%) | Three deaths owing to hypoglycemia | 70% | – |
| Müller et al. [12] (2007) | 67 | Malignant: 7.5%<br>Benign: 6.7% | No death related to diabetes; 8.3% readmission for diabetes control | 41% | Diarrhea 41%<br>Abdominal pain 15% |
| Casadei et al. [18] (2010) | 13 | 8% (5.2–10.3%) | No death related to diabetes; 23% readmission for glycemic control | 85% | – |
| Crippa et al. [15] (2011) | 45 | 7–9% in 56% of patients, >9% in 11% of patients | No death related to diabetes | 45% | Abdominal pain 22%<br>Diarrhea 13%<br>Steatorrhea 27% |
| Barbier et al. [19] (2013) | 25 | 7.8% (6.3–10.3%) | One death owing to hypoglycemia; one death owing to ketoacidosis | 60% | 28% with night stools |

$HbA_{1c}$, hemoglobin $A_{1c}$.

Recently, new levels of diabetes management using well-established long-acting insulin formulations [10] and specialist nurse-led diabetic care have dramatically improved diabetic outcomes following TP [20,24]. Several reports have shown that hemoglobin $A_{1c}$ ($HbA_{1c}$), as a long-term marker of blood glucose concentrations, can be kept within a tolerable range (median $HbA_{1c}$, ranging from 6.5% to 8.0%, Table 106.2) [10,12,15,18–20]. However, the potential morbidity associated with endocrine deficiency must not be underestimated, because there have been several reports of deaths due to hypoglycemia and hyperglycemia after TP [10,19]. Preoperative referral to a department of endocrinology and advice on postoperative management and use of insulin formulations as well as postoperative education by specialists on the treatment of diabetes mellitus are therefore essential for patients undergoing TP.

## Exocrine Insufficiency After Total Pancreatectomy

Exocrine insufficiency is an important late complication after TP [9]. It can cause diarrhea, steatorrhea, weight loss, osteopathy and osteoporosis, and hepatic steatosis (Table 106.2). Diarrhea and/or steatorrhea contribute to the loss of fat-soluble vitamins, especially vitamin D, magnesium, and trace elements, leading to malnutrition-related complications such as osteopathy and osteoporosis, as well as to hepatic steatosis [28]. Increasing attention has been given to the development of hepatic steatosis after pancreatectomy, because postoperative hepatic steatosis may be progressive and lead to life-threatening hepatic decompensation [29–31]. However, the etiology and pathogenesis remain largely unknown. Malnutrition resulting from a lack of pancreatic enzyme formulations is one hypothesis [30,31], and female sex and early postoperative nutritional status have been reported to be independent risk factors for hepatic steatosis after TP [29].

Pancreatic exocrine enzymes break down ingested food into micronutrients for absorption [28,32]. Disruption of this process leads to severe diarrhea and steatorrhea with subsequent nutritional deficiencies [28]. Nutritional interventions, such as low-fat diets and pancreatic enzyme replacement therapy, are used to improve clinical symptoms. Pancreatic enzyme replacement therapy, including ingestion of 40,000–50,000 units of lipase per day, is standard therapy for pancreatic exocrine insufficiency, because it significantly improves absorption of fat and nitrogen [29,33,34]. Special attention should therefore be given to patient education with regard to exocrine insufficiency and available treatment after TP.

## Anastomotic Ulcer After Total Pancreatectomy

An anastomotic ulcer at gastrojejunostomy can occur both in the early postoperative course and in the long term after TP [19,35]. This complication can be severe, resulting in reoperation or even death. An anastomotic ulcer may be observed after TP with or without preservation of the pylorus ring of the stomach, indicating that this complication cannot be prevented technically [19]. However, it has been reported that routine administration of a proton pump inhibitor (PPI) may prevent this complication [19]. Life-long treatment with a PPI may therefore be necessary for patients who have undergone TP.

## Long-Term QOL After Total Pancreatectomy

There have been several reports evaluating long-term QOL following TP [10,12,20,27]. Overall QOL was considered to be acceptable; however, patient reports varied with regard to the scale of symptoms, with a decrease in

QOL focusing mainly on fatigue and diarrhea, and healthcare satisfaction scores were poor [10,12,20,27]. It is therefore important to provide sufficient information to patients before and after TP to help improve postoperative QOL.

## Indications for Total Pancreatectomy

TP is a reasonable procedure for some cases of pancreatic disease, because perioperative mortality is low and the long-term consequences are now better managed, with an acceptable morbidity rate and postoperative QOL [10–13,15,16,18–20]. Therefore, TP should no longer be generally avoided for patients in whom complete removal of the pancreas is required for oncologic prophylactic reasons. Furthermore, with the extension of resection criteria in pancreatic malignant or premalignant disease, and more advanced knowledge of specific disease entities of the pancreas that can affect the whole pancreas and require TP, the number of cases requiring the procedure have been increasing. Diseases that might require TP include extensive pancreatic head or body cancers, recurrence or new tumors developing in the remnant pancreas after previous partial pancreatic resection, diffuse or multifocal intraductal papillary mucinous neoplasms (IPMN), renal cell metastases, multifocal neuroendocrine tumors and inherited neoplastic disease, including multiple endocrine neoplasia 1 (MEN1) syndrome, history of familial pancreatic cancer, and hereditary chronic pancreatitis. In addition, TP may also be performed to avoid pancreatic-enteric anastomotic-related complications or salvage complete pancreatectomy for severe complications after partial pancreatectomies [12,20], although these indications are controversial.

### Pancreatic Ductal Adenocarcinoma

The frequency of TP in patients with pancreatic ductal adenocarcinoma (PDAC) varies from 3–9%, according to previous reports [16,26,36,37]. Less than 1 year of median overall survival time was reported in the 1980s–1990s [6,37,38]; however, recent reports have described more than 1-year overall survival after TP, ranging from 12 months to 18 months [20,25,26,36], due to improvements in surgical techniques and postoperative management, and advanced adjuvant therapies. Hartwig et al. reported that poor tumor grading, higher stage cancers according to the American Joint Committee on Cancer tumor staging system, age >70 years, and an R1 resection were independent risk factors for poor survival of patients who had undergone TP [20]. Satoi et al. reported that the rate of completion of adjuvant therapy was lower and the frequency of postoperative liver metastasis was higher in PDAC patients undergoing TP, compared with patients who had a pancreaticoduodenectomy; however, overall survival was similar between the TP and pancreaticoduodenectomy matched-pairs groups [36]. Schmidt et al. reported that among PDAC patients with a positive pancreas margin pathologically, the surgical results were compared between patients undergoing subsequent TP after pancreaticoduodenectomy and R1 patients undergoing only pancreaticoduodenectomy. The authors showed that mortality and morbidity rates were similar between the two groups, although conversion of pancreaticoduodenectomy to TP was associated with survival benefits [25]. However, it was unclear whether radical oncologic surgery, including extended lympadenectomy and increased soft tissue clearance around the pancreatic gland by TP, improved survival, when compared with partial pancreatectomies [20,24,26,36]. Based on these results, TP seems to be a powerful strategy for patients who have a positive margin of transected pancreas after pancreaticoduodenectomy to achieve an R0 resection; completion of adjuvant therapies after TP is necessary to improve survival, as with other pancreatectomies. As discussed earlier, adequate control of endocrine and exocrine pancreatic insufficiency is essential to improve survival of PDAC patients who have undergone TP.

### Intraductal Papillary Mucinous Neoplasm

According to international consensus guidelines for the management of IPMN [39], main-duct IPMN is an indication for surgical resection, because of the risk of malignancy. Diffuse main-duct IPMN or multifocal branch-duct or mixed-type IPMN sometimes require TP, and long-term outcomes for these cases are favorable [20,22]. Therefore, these types of IPMN are a good indication for TP, although careful preoperative diagnosis of malignancy [16,40] and patient selection are necessary to obtain survival benefits.

### Inherited Diseases

Patients with a family history of hereditary pancreatic cancer and patients suffering from hereditary chronic pancreatitis are at increased risk of developing pancreatic cancer during their lifetime [22,41]. Therefore, TP is a prophylactic measure for patients at high risk of developing pancreatic cancer, although the timing and extent of surgery are still controversial.

### Tumor Recurrence or New Tumor Developing in the Remnant Pancreas After Previous Partial Pancreatic Resection

Tumor recurrence or new tumor, such as PDAC or IPMN, developing in the remnant pancreas without distant metastasis is sometimes found, and several reports have shown survival benefits of a two-stage completion pancreatectomy with low rates of mortality and morbidity [12,15,20,42]. A tumor developing in the remnant of the pancreas is therefore an indication for two-stage complete pancreatectomy.

### Conversion From Partial Pancreatectomy to Total Pancreatectomy Because of Avoidance of Pancreatic-Enteric Anastomosis-Related Complications

Pancreatic-enteric anastomotic leakage, called pancreatic fistula, after partial pancreatectomy can cause life-threatening complications, and conversion to TP from pancreaticoduodenectomy is sometimes performed intraoperatively. Hartwig et al. reported that in 20% of cases, intraoperative conversion to TP was performed because of the morphology of the remaining pancreas, including extremely soft or lipomatous pancreas that might be associated with high risk of postoperative pancreatic fistula, and combined arterial reconstruction during pancreatectomy [20]. However, the indication for conversion to TP from pancreaticoduodenectomy to avoid postoperative pancreatic fistula, but with resulting endocrine and exocrine insufficiency, remains controversial.

### Salvage Complete Pancreatectomy for Complications After Partial Pancreatectomies

As described earlier, the mortality and morbidity rates of salvage TP for severe complications after partial pancreatic resections are extremely high; therefore, this procedure should be avoided, if possible [12,16]. The significant decline in the use of salvage complete pancreatectomy relative to a pancreaticoduodenectomy reflects a shift in the management of pancreatic fistula and postoperative hemorrhage, with radiologic drainage and arterial embolization now readily available and preferred to re-laparotomy [23,43].

## Limitations of Total Pancreatectomy

Although mortality rates after TP have dramatically decreased, the perioperative morbidity rates remain high [10–13,15,16], particularly in the case of salvage completion pancreatectomy for severe complications after partial pancreatectomies [12,16]. This procedure should therefore be avoided, if possible. Furthermore, postoperative endocrine and exocrine insufficiency after TP can cause life-threatening complications [10,12,15,18–20]. Careful patient selection while considering the balance between clinical benefit and postoperative risk, and providing information about postoperative management before and after TP are necessary to improve survival and QOL in patients who undergo TP.

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# Laparoscopic and Robotic Resection for Pancreatic Cancer

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## Introduction

Minimally invasive techniques (MIS) have begun to revolutionize the surgical management of benign and malignant pancreatic disease. Both laparoscopic and robot-assisted approaches to pancreatic surgery have been shown to be safe and feasible in high-volume centers of excellence [1–3]. Additionally, the MIS approach demonstrates improvement in the traditionally high morbidity rates associated with these procedures [4].

The pancreaticoduodenectomy was described and popularized in 1935 by Allen O. Whipple as a two-stage procedure, which was refined into the single-stage procedure we recognize today [5,6]. Since its inception, pancreatic surgery has resulted in high morbidity and mortality, which prevented widespread implementation for many years.

Though the laparoscopic approach to the pancreaticoduodenectomy was initially met with skepticism because of the long operative times when first performed in 1994, it has now been established as safe and feasible when performed by select high-volume surgeons at experienced centers [7]. The robotic pancreaticoduodenectomy (RPD), first performed in 2007, is now being increasingly utilized for pancreatic malignancies due to perceived benefits of stereotactic vision, magnification, platform stability, and favorable ergonomics [8]. We present a review of the minimally invasive techniques for pancreaticoduodenectomy (PD) and distal pancreatectomy (DP), focusing on current data on metrics of technique, safety, morbidity, and oncologic outcomes.

## Patient Selection and Indications for the MIS Approach to Pancreaticoduodenectomy

Determining the resectability of pancreatic adenocarcinoma (PDA) of the head of the pancreas depends primarily on the involvement of the mesenteric vessels. Preoperative assessment of presence of metastatic disease and vascular involvement is critical in determining whether a patient is a candidate for an open versus MIS pancreaticoduodenectomy or whether they are a surgical candidate at all [9]. Given that minimally invasive approaches, including laparoscopic and robotic techniques, do not allow for palpation of the tumor intraoperatively, patients undergo triphasic CT scanning and EUS prior to any surgical planning since both modalities have been found to be useful in predicting which patients can undergo an R0 resection [10]. In our institution, resectable and borderline resectable tumors are offered RPD. The only strict exclusion criterion is the need for a long segment vein resection with conduit for reconstruction.

## Laparoscopic Pancreaticoduodenectomy

### Technique of LPD

Zureikat et al. previously described a total LPD (TLPD), which involves complete laparoscopic mobilization of the pancreas and duodenum [11]. After gaining access to the abdomen using an optical-separator device in the left

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Companion website: www.wiley.com/go/beger/thepancreas

upper quadrant, seven ports are placed in a semilunar shape around the xiphoid process. A right lower quadrant utility incision is used for specimen extraction. The inferior border of the pancreas is dissected in order to identify the superior mesenteric vein prior to the Kocher maneuver. Once the hepatic flexure is mobilized and the duodenum is kocherized, the porta hepatis is dissected. The retropancreatic tunnel is then created between the pancreatic neck and the portal vein, and the pancreas is divided using bipolar electrocautery.

Reconstruction proceeds with an end-to-side duct to mucosa pancreaticojejunostomy using a two-layered closure technique with running absorbable monofilament. A running 4-0 absorbable monofilament suture is used for the hepaticojejunostomy. A stapled technique is utilized for the gastrojejunostomy, and drains are left around the pancreaticojejunostomy prior to closure [11].

### Outcomes of LPD

The initial report of 10 LPD in 1997 by Gagner and Pomp revealed a high conversion rate from the laparoscopic approach to open technique for the pancreaticoduodenectomy (OPD) without noting any significant benefits [12]. However, many reports have emerged subsequently describing the safety and oncologic efficacy of the LPD, and some have directly compared it to the OPD to determine benefits of the minimally invasive technique. Some of the key publications to summarize LPD outcomes are shown in Table 107.1 [12–21].

Palanivelu and colleagues described the largest series of laparoscopic pancreaticoduodenectomies to date, including 130 LPD performed for malignant indications [13]. This report demonstrated the advantages and feasibility of the MIS approach when performed by highly skilled surgeons. Mean operative time for the entire cohort was 310 ± 34 minutes, mean blood loss (EBL) was 110 ± 22 mL, with one conversion to open surgery, and an average hospital stay of 8 ± 2.6 days. The overall postoperative morbidity was 29.7%, with a pancreatic fistula (POPF) rate of 8.46%. Overall mortality rate was 1.53%. In regard to oncologic outcomes, resected margins were positive in 9.23% of cases, and mean number of retrieved lymph nodes was 18.15 ± 4.73. The overall 5-year actuarial survival was 29.42%, and the median overall survival was 33 months [13].

Numerous other case series are outlined in Table 107.1 delineating LPD outcomes, including Kim et al.'s series of laparoscopic pylorus-preserving PD with 100 cases, which held an overall morbidity rate of 25%, including postoperative hemorrhage in five patients, only one of whom required reoperation, and delayed gastric emptying (DGE) in two patients. Another series of 62 LPD (45 patients with malignant disease) by Kendrick and Cusati, had a mean hospital stay of 7 days and overall morbidity rate of 42%, including DGE in nine patients and PF in 18% of patients. Reoperation was required in three (5%) patients for POPF (1), control of hemorrhage following percutaneous drain placement (1), and revision of a biliary leak (1).

Several comparative effectiveness studies have also been performed, comparing laparoscopic pancreaticoduodenectomy to the open approach (Table 107.2) [11,22,23]. Croome and Kendrick et al. focused on the oncologic effectiveness of the minimally invasive distal pancreatectomy (MIDP) in another review, comparing 108 patients who underwent LPD to 214 patients who underwent OPD for PDA [22]. They found a significantly higher proportion of patients in the OPD group (12%) who had a delay of greater than 90 days or who did not receive adjuvant chemotherapy at all compared with the TLPD group (5%; $P = 0.04$). There was no significant difference in overall survival between the two groups, but a significantly longer progression-free survival was seen in the TLPD group ($P = 0.03$), revealing a possible oncologic advantage to the laparoscopic approach over the open technique [22]. Another comparative study by Asbun et al. included 215 and 53 patients who underwent OPD and LPD, respectively [23]. Significant differences favoring LPD were seen in intraoperative blood loss ($P < 0.001$), transfusions ($P < 0.001$), length of hospital stay ($P < 0.001$), and length of ICU stay ($P < 0.001$). Operative time was significantly longer for LPD ($P < 0.001$). There were no differences in overall complications, POPF, or DGE. Oncologic outcomes demonstrated no significant differences in resection margins, size of tumor, or T/N stages. There were significant differences in number of lymph nodes retrieved ($P = 0.007$) and lymph node ratio ($P < 0.001$) in favor of LPD [23].

## Robotic Pancreaticoduodenectomy

### Technique of RPD

As described by Zeh et al., the first step in the robot-assisted approach to the pancreaticoduodenectomy was previously achieved laparoscopically and included mobilization of the right colon and kocherization of the duodenum along with mobilization of its third and fourth portions [24]. Our institution now performs the entire procedure robotically, docking the robot immediately upon gaining access to the abdomen (Fig. 107.1). We start with a near total Cattell-Braasch maneuver followed by an extended Kocher maneuver where the ligament of Treitz is dissected and the jejunum is pulled into the right upper abdomen. The jejunum is transected about 10 cm distal to the uncinate using a linear stapler and then dissection of the posterior stomach from the

**Table 107.1** Case series of laparoscopic and robotic pancreaticoduodenectomies.

| Author | Year | Technique | *N* (total)/*N* (malignant) | EBL (mL) | Operative time (min) | Fistula rate (Grade C) | Mortality rate | Oncologic outcomes (R0 rate, LN) |
|---|---|---|---|---|---|---|---|---|
| Gagner [12] | 1997 | Lap | 10/8 | – | 510 | 10% | 0% | 100%, 7 |
| Dulucq [19] | 2006 | Lap | 22/21 | 107 | 295 | 4.5% | 4.5% | 100%, 18 |
| Pugliese [21] | 2008 | Lap | 19/18 | 180 | 461 | 0% | 0% | 100%, 11 |
| Kendrick and Cusati [15] | 2010 | Lap | 62/45 | 240 | 368 | 18% | 1.6% | 89%, 15 |
| Corcione [18] | 2013 | Lap | 22/22 | – | 392 | 9% | 4.5% | 100%, 15 |
| Kim [14] | 2013 | Lap | 100/12 | – | 474 | 6% | – | 100%, 13 |
| Lee [16] | 2013 | Lap | 42/20 | 374.5 | 404 | 2.4% | 2.4% | – |
| Palanivelu [13] | 2015 | Lap | 130/130 | 110 | 310 | 8.5.% | 1.5% | 90.8%, 18 |
| Wang [17] | 2015 | Lap | 31/30 | 260 | 515 | 3.2% | 0% | 100%, 13 |
| Liu [20] | 2015 | Lap | 21/18 | 240 | 368 | 4.8% | 0% | 100%, 12 |
| Guilianotti [30] | 2010 | Robot | 60/45 | 394 | 421 | 31.6% | 3% | 90%, 18 |
| Zureikat [31] | 2013 | Robot | 132/106 | 300 | 527 | 3.7% | 1.5% | 87.7%, 19 |

Lap, laparoscopic; EBL, estimated blood loss; LN, median lymph nodes retrieved.

anterior surface of the pancreas is performed. The stomach is divided with a linear stapler.

The porta dissection begins with removal of the hepatic artery lymph node, facilitating delineation of the common hepatic artery, gastroduodenal artery (GDA), and portal vein (PV). After the borders of the common bile duct and PV are fully exposed, the GDA is transected and periportal lymphadenectomy is completed, taking care to identify an aberrant right hepatic artery. The SMV is dissected off the inferior border of the pancreas and a tunnel is created over the portal vein. After completion of the tunnel, the neck of the pancreas is divided with electrocautery, reserving sharp robotic scissor transection for the pancreatic duct. The first jejunal branch is identified and preserved where possible. The SMV-PV is reflected medially and the SMA is identified. Dissection proceeds along the SMA by clearing all the tissue around the anterior, right side, and posterior surface of the SMA [25].

Reconstruction is started with a two-layered end-to-side duct to mucosa pancreaticojejunostomy in a modified Blumgart fashion. The choledochojejunostomy is then performed in a running fashion. An anticolic hoffmeister end-to-side gastrojejunostomy had been sewn in two layers for the first 5 years, and most recently stapled with the common enterotomy sewn in two layers [24].

## Outcomes of RPD

To date, one of the largest series of open PD was reported by Winter et al. from Johns Hopkins in 2006 [25]. Their review of 1,432 cases for PDA, demonstrates a high-volume historic control for comparison when describing new technology. The authors reported a mean operative time of 380 minutes for the procedure, a mean blood loss of 800 mL, 58% R0 resection, and a mean length of stay of 9 days. They described a 5% POPF (pre-ISGPF criteria) and a 2% mortality rate.

Both LPD and RPD outcomes are similar, and are not inferior to OPD in large single institutional series (Table 107.2 and Table 107.3). One challenge of national administrative databases is that many of these report small-volume centers performing their first and possibly only case. They do not represent a mature series of surgeons who have surpassed their learning curve. Tseng et al. demonstrated that the OPD has an inherent learning curve. After 60 cases, surgeons achieved significantly decreased EBL, operative time, and hospital stay, and carried out more margin-negative resections. Improvement in measured outcomes continues during the operative career [26]. A recent publication showed that minimally invasive PD may be associated with a higher 30-day mortality using the National Cancer Database (NCDB) [27]. These reports need to be evaluated with some caution, as the same group published another report 6 months later also using NCDB data demonstrating no differences in 30-day mortality [28]. Surgeon volume and experience need to be taken into account and large national databases are not granular enough to do so. Outcomes for the RPD have been comparable, with certain parameters even showing superiority to historic series.

Our institution has performed over 365 RPD to date, 43.5% of which were completed for PDA. Our experience

**Table 107.2** Comparative effective analyses of laparoscopic to open pancreaticoduodenectomies.

| Author | Year | *N* (LPD/OPD) | Cancer (*n*) | LOS (days) | OR time (min) | EBL (cc) | Mortality 30 d (%) | Morbidity (%) | Fistula rate (Grade C) | R0, LN |
|---|---|---|---|---|---|---|---|---|---|---|
| Zureikat [11] | 2011 | 14/14 | 12/11 | 8/8.5 | 456/372 | 300/400 | 7/0 | 21/7 | 0/7.1 | 100, 18.5/91.7, 19.1 |
| Asbun [23] | 2012 | 53/215 | 40/68 | 8/12.4 | 541/401 | 195/1032 | 5.7/8.85 | 24.5/24.7 | 7.1/6 | 94.9, 23.4/83, 16.8 |
| Croome [22] | 2014 | 108/214 | 108/214 | 6/9 | 380/388 | 492/866.7 | 1/2 | 5.6/13.6 | 11/12 | 77.8, 21.4/76.6, 20.1 |

LPD, laparoscopic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LOS, length of stay; OR time, operative time; EBL, estimated blood loss; R0, negative margins; LN, median lymph nodes retrieved.

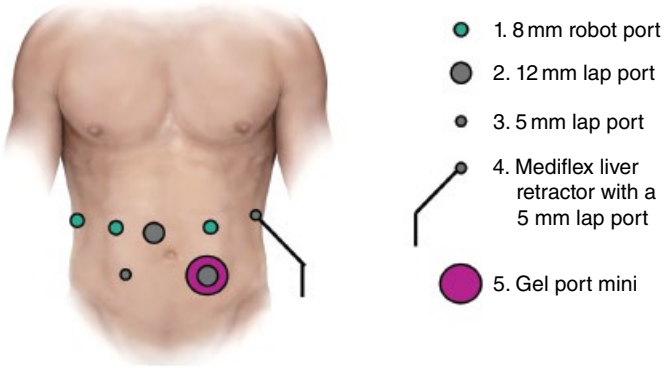


**Figure 107.1** Port configuration for robotic pancreaticoduodenectomy.

has shown that not only is RPD feasible, but that it can be performed safely with a 30- and 90-day mortality of 1.4% and 2.9%, respectively. Median EBL was 300 cc, with a conversion rate of only 5%, superior to most open series and laparoscopic series, respectively. Despite an overall median time in excess of 404 minutes, the first 80 within our learning curve had a median operative time of 569 minutes and were performed primarily by attendings. The last 80 cases have seen a reduction to a median time of 362 minutes even with the integration of the trainee into the operative team. The conversion rate and blood loss metrics have also improved with increased experience. Morbidity remains a considerable factor with any new technology, but showed comparable grade 3 and 4 complication rates of 10.6% and 12%, respectively to the open approach. With increased experience, POPF rate was 17.9% (grade C = 3%), comparing favorably with the most recent large analysis by Denbo et al. of over 2,700 OPD (18% POPF, grade C ≤ 5%) [29]. Several case-control studies and case series evaluating outcomes of RPD have been performed and have shown that EBL and length of stay is significantly better in the RPD with no increase in operative mortality compared to the open cohort (Table 107.1 and Table 107.3) [30–36]. None of the studies to date have demonstrated an improvement in overall morbidity, POPF rate, or operative time.

### Summary

Laparoscopic and robotic platforms seem to be advantageous to OPD with respect to blood loss, shorter hospital stay, and potentially complications. Our personal opinion is that the robotic approach will prove to be the more robust and durable MIS platform with the shortest learning curve for surgeons. Larger studies are still needed to confirm this hypothesis.

## Indications for the MIS Approach to the Distal Pancreatectomy

The minimally invasive approach to the distal pancreatectomy is now considered by many to be the preferred method of resection for malignant tumors of the distal pancreas. Several studies have been performed, collectively supporting that LDP and RDP can be performed with superior results to the open approach in patients with malignant disease [37,38]. Specifically, the minimally invasive approach results in shorter hospital stay, reduced EBL, and decreased complication rates [39]. Similar oncologic resections can be accomplished in terms of lymph node dissection and resection margins, although larger reports of long-term survival are still lacking.

## Laparoscopic Distal Pancreatectomy

### Technique of LDP

As previously described, the peritoneum is accessed via an optical separator technique inserted in the left subcostal area to induce pneumoperitoneum, which is followed by placement of four additional trocars. Dissection begins with division of the gastrocolic ligament in order to enter the lesser sac. The splenic flexure of the colon is then mobilized inferiorly, the inferior border of the pancreas is dissected, and the pancreas is mobilized out of the retroperitoneum at the site of transection by creating a subpancreatic tunnel. Early identification of the splenic vessels and dissection of the vein and artery off the superior-posterior aspect of the pancreas allows safer pancreatic transection. Once the vessels have been mobilized, the pancreatic parenchyma is divided using a linear stapler or harmonic scalpel, which is followed by division of the splenic

**Table 107.3** Comparative analyses of robotic to open pancreaticoduodenectomies.

| Author | Year | *n* (RPD/OPD) | Cancer (*n*) | LOS (days) | OR time (min) | EBL (cc) | Mortality 30 d (%) | Morbidity (%) | Fistula rate (Grade C) | R0, LN |
|---|---|---|---|---|---|---|---|---|---|---|
| Buchs [32] | 2011 | 44/39 | 33/27 | 13/14.6 | 444/559 | 387/827 | 4.5/2.6 | 36.4/48.7 | 2.3/5.1 | 90.9, 16.8/81.5, 11 |
| Zhao [36] | 2011 | 8/8 | 8/8 | 16.4/24.3 | 718/420 | 153/210 | 7/7 | 25/75 | 12.5/12.5 | 100, –/83.3, – |
| Lai [34] | 2012 | 20/67 | 15/53 | 13.7/25.8 | 247/774 | 247/774 | 0/3 | 50/49.3 | 5/1.5 | 73.3, 10/64.1, 10 |
| Chalikonda [35] | 2012 | 30/30 | 14/14 | 9.79/13.3 | 485/775 | 485/775 | 4/1 | 30/43 | 3.3/10 | 100, 13.2/87, 11.7 |
| Bao [33] | 2014 | 28/28 | 19/26 | 7.4/8.1 | 100/300 | 100/300 | 7/7 | 28/28 | 10.7/7.1 | 63, 15/88, 20 |

RPD, robotic pancreaticoduodenectomy; OPD, open pancreaticoduodenectomy; LOS, length of stay; OR time, operative time; EBL, estimated blood loss; R0, negative margins; LN, median lymph nodes retrieved.

vessels using a stapling device or clips. The spleen is then mobilized by sectioning the suspending ligaments, and the specimen is then placed in a large bag and brought through an access incision [39].

### Outcomes of LDP

Since the first LDP was described by Cushieri for chronic pancreatitis disease in 1996, there have been a number of series reporting on LDP. In 2008, a large multi-institution study was performed by Kooby et al. evaluating laparoscopic distal pancreatectomy to the open approach in a 3:1 matched comparison (Table 107.4) [39–41]. They demonstrated that the laparoscopic approach was associated with a lower blood loss, shorter length of hospital stay, increased splenic preservation, less overall morbidity without an increase in POPF rates.

Two methodologic problems complicate prospective studies of surgical technique for distal PDA: (i) only 20.8% of PDA arise in the distal pancreas; and (ii) the 1,640 distal pancreatic resections performed annually in the United States are distributed among 1,743 hospitals according to 1998–2003 data in the Nationwide Inpatient Sample, an average annual case volume of one per hospital [42]. As a result, most comparative effectiveness research has been retrospective and confined to single institution data [43]. Several case series have demonstrated the advantages of the laparoscopic approach to the distal pancreatectomy (Table 107.4) [39–41].

Our institution performed a retrospective case series comparing clinicopathologic and long-term oncologic outcomes after MIS and ODP for PDA in 62 consecutive patients at a single institution [37]. Intention-to-treat analysis demonstrated no evidence for inferiority of MIDP compared with ODP in terms of postoperative outcomes or long-term survival.

## Robot-Assisted Distal Pancreatectomy

### Technique of RDP

After the peritoneum is accessed in a similar fashion to that obtained in the laparoscopic approach, additional trocars are placed, and the robot is docked (Fig. 107.2) [31]. The splenic artery is isolated at its take off from the celiac trunk, and divided with a vascular stapler. A lymphadenectomy is then carried out starting from the left side of the SMA laterally, taking the posterior pancreatic fascia en bloc, and a comprehensive celiac lymphadenectomy is completed. With large tumors, involving the fourth portion of the duodenum or colon, the robot allows meticulous en bloc resections with reconstructions performed in a similar fashion to the open technique [31].

### Outcomes of RDP

At the University of Pittsburgh, we compared outcomes of LDP and RDP in a retrospective matched comparison [38]. Patients undergoing RDP and LDP demonstrated equivalent age, gender, ethnicity, ASA score, and tumor size. They noted a statistically significant decrease in the conversion rate to open with RDP compared to LDP; 0% versus 16% [38]. A more recent updated series of 100 RDP demonstrated a persistently low conversion rate of 2% [31]. This may be secondary to the surgeon at the console's ability to control large vessels and manage unexpected bleeding via intracorporeal suturing more readily with the robot than using laparoscopy. The authors minimized patient selection bias in that the easier cases may have been chosen for the newer robotic technique by relegating the LDP control cohort to a period when robotic surgery was not available. In this comparison, a 35% margin-positive rate was observed in the LDP group compared to zero in the RDP group,

**Table 107.4** Case series of laparoscopic and robotic distal pancreatectomies

| Author | Year | Technique | N (total)/N (malignant) | EBL (mL) | Operative time (min) | Fistula rate (Grade C) | Mortality rate | Oncologic outcomes (R0 rate, LN) |
|---|---|---|---|---|---|---|---|---|
| Fernandez-Cruz [40] | 2007 | Lap | 82/13 | 370 | 222 | 7% | 0% | 77%, 14.5 |
| Kooby [39] | 2008 | Lap | 142/54 | 357 | 230 | 26% | 0% | 93%, NR |
| Jayarman [41] | 2010 | Lap | 107/16 | 150 | 193 | 16% | NR | 97%, 6 |
| Kang [45] | 2011 | Robot | 20/18 | 372 | 348 | NR | 0% | NR, NR |
| Zureikat/Zeh [31] | 2013 | Robot | 83/60 | 150 | 256 | 36% | 0% | 97%, 16 |
| Daouadi [38] | 2013 | Robot | 30/22 | 212 | 293 | 13% | 0% | 100%, 18.6 |

Lap, laparoscopic; OPD, open pancreaticoduodenectomy; LOS, length of stay; OR time, operative time; EBL, estimated blood loss; R0, negative margins; LN, median lymph nodes retrieved.

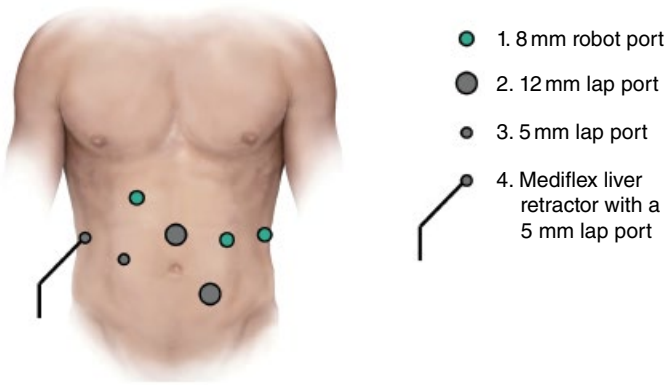


**Figure 107.2** Port configuration for robotic distal pancreatectomy.

which was statistically significant ($P < 0.05$), suggesting that the laparoscopic approach may be inferior to the robotic approach in this matched comparison. It has been shown that patients having undergone RDP as opposed to LDP or ODP have shorter hospital stays given decreased wound complications and increased rates of splenic preservation [44]. As further experience with the robot-assisted approach is gained, additional advantages may be realized. Several case series have been performed demonstrating the benefit of the robotic approach to the distal pancreatectomy (Table 107.4) [31,38,45]. Comparative studies of robotic and laparoscopic distal pancreatectomies have shown a decreased blood loss in the robot group as well as shorter hospital stays and decreased wound complications [46,47].

The oncologic outcomes between the MIS and open approaches for distal pancreatectomy have been shown to be equivalent. Our institutional experience demonstrated that despite a higher percentage of adenocarcinoma in the robotic group (43% vs. 15%, $P < 0.05$) and a similar median tumor size of approximately 3 cm, RDP was associated with improved R0 resection rates (100% vs. 64%, $P < 0.05$), and median lymph node count (19 vs. 9, $P < 0.01$) when compared to laparoscopy [38].

### Summary

The minimally invasive approach to the distal pancreatectomy has proven advantages over the open approach. The robotic approach does appear to offer benefits over the laparoscopic technique in regards to blood loss as well as splenic preservation.

## Adopting the MIS Pancreatectomy: The Learning Curve

A recent RPD analysis from the University of Pittsburgh confirmed that outcomes are optimized after an initial steep learning curve of approximately 80 cases. In-depth analysis of this learning curve revealed that blood loss and conversions were optimized after 20 cases (600 vs. 250, $P < 0.05$, and 35% vs. 3%, $P < 0.05$ respectively), incidence of POPF after 40 cases (27% vs. 14%, $P < 0.05$), and operative time after 80 cases (582 min vs. 417 min, $P < 0.05$) [48]. Complication rates, length of hospital stay and readmissions also improved but the sample size was underpowered to detect a significant difference. In the last 100 cases, we found a POPF rate of 6%, a 90-day mortality rate of 3%, and a median length of stay of 8 days. Importantly, a two attending approach was employed throughout the learning curve period to ensure patient safety and procedural efficacy [48]. Additionally, the laparoscopic platform for the PD has also been shown to have a learning curve. Speicher et al. demonstrated that the initial 10 cases represent the biggest hurdle with respect to operative times, but for an experienced teaching center using a staged and team-based approach, LPD appears to offer meaningful reductions in operative time and blood loss within the first 50 cases [49]. This data suggests that meaningful comparative effectiveness studies of minimally invasive and open PD should take into consideration the impact of the learning curve before any outcomes are assessed.

The learning curve for the distal pancreatectomy appears to be somewhat shorter. A study by Braga et al. described 30 patients who underwent LDP between 2009 and 2010. Overall conversion rate was 23.3%, but it dropped significantly after the first 10 patients ($P = 0.01$) [50]. Mean operative time progressively declined from 254 min in the first subgroup of 10 patients to 206 min in the second ($P = 0.09$ vs. first), and 183 min in the third subgroup ($P = 0.006$ vs. first). No significant difference was found for operative blood loss, postoperative morbidity rate, and length of hospital stay in the different subgroups. Both conversion rate and operative time dropped after the first 10 patients who underwent LDP. The robotic approach to distal pancreatectomy has also been demonstrated to have a learning curve of about 10 cases as well, as shown by Napoli et al. [51].

In today's age of increased outcome scrutiny, learning curves may not be feasible. Fong et al. wrote about this concern in a recent editorial, reflecting on the importance of performing these operations in high-volume centers in a somewhat centralized fashion [52]. We have developed a detailed curriculum for surgical oncology fellows that maximizes the mastery of basic and advanced robotic skills outside of the operating room. After adoption of this curriculum we have successfully integrated these trainees into the operative team with no increase in operative times.

## Conclusion

The safety and feasibility of MIS pancreatic resections have now been established by the early adopters. Preliminary comparative effectiveness studies of high-volume providers suggest some advantage. However, dissemination and decreasing the learning curve for new centers is critical for success and sustainability of MIS pancreatectomies.

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# 108

# Extended Radical Surgery for Pancreatic Cancer

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## Introduction

In only 15–20% of patients suffering from pancreatic ductal adenocarcinoma (PDAC), surgery is possible at time of diagnosis, which offers the chance of long-term survival in 20–25% when combined with adjuvant chemotherapy [1, 2]. With the ongoing development of specialization and centralization for pancreatic surgery since the late twentieth century, not only has postoperative mortality considerably decreased but also the borders of resectability have been extended [3–7]. This has led to the development of so-called "extended resections," which exceed the standard historic approaches of partial pancreatoduodenectomy and distal or total pancreatectomy. In particular, extended lymphadenectomy, resection of adjacent vessels (superior mesenteric and/or portal vein, celiac axis, superior mesenteric artery) and organs have been performed and were investigated in a large number of studies [8–18]. These developments raised the need for a definition and standardization of local resectability to better compare publications on this topic and to establish pathways for the diagnostic and therapeutic management of these patients. Today, the only situation that represents a clear contraindication for surgery is the finding of systemic spread, especially peritoneal carcinomatosis or diffuse liver metastases [19, 20]. Regarding limited metastatic PDAC (i.e., single liver metastasis), resections are technically possible and several small case series have been reported [21]. Despite some encouraging results in these studies, surgery in metastatic PDAC remains a highly individual concept and the oncologic outcome is unclear to date [21].

The definition of "extended resection" in PDAC is closely correlated with the definition of "resectability." The critical anatomic structures to evaluate local resectability in PDAC are the arterial and venous vessels located close to the pancreatic head and body, namely the superior mesenteric (SMV)/portal vein (PV) and the celiac axis (CA) as well as the superior mesenteric artery (SMA).

Resectability is defined as (i) primary resectable PDAC, (ii) borderline resectable (BR-PDAC), or (iii) irresectable PDAC according to the criteria published by the International Study Group of Pancreatic Surgery in 2014 [22], which are mainly based on the recommendations of the NCCN (National Comprehensive Cancer Network) [19]. Besides these two recently published definitions, two other classifications are in clinical use, namely the definition of the AHPBA/SSO/SSAT published in 2009 [23] and the MD Anderson criteria, which were published in 2006 [24].

All of these definitions are similar with regard to resectable PDAC. This implies that the tumor does not involve any vascular structures (no distortion of SMV or PV and clearly preserved fat planes towards CA and SMA).

BR-PDAC is characterized by a distortion/narrowing or occlusion of the respective veins but there is a technical possibility of reconstruction on the proximal and distal margin of the veins (Fig. 108.1). PV involvement according to the MD Anderson definition does not include contact or narrowing of the vein, but gives occlusion as the criterion for BR-PDAC. Regarding arterial structures, all definitions describe a semicircumferential abutment (<180°) of the SMA or an attachment at the hepatic artery without contact toward the CA as borderline resectable.

Unresectable PDAC is defined as a more extended involvement of the SMA, CA, aorta, or inferior vena cava as well as an SMV/PV venous involvement without a possibility for surgical reconstruction of the venous tract because of the lack of a suitable luminal diameter of the feeding and/or draining vein. This situation is most likely associated with tumor-related portal cavernous transformation.

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

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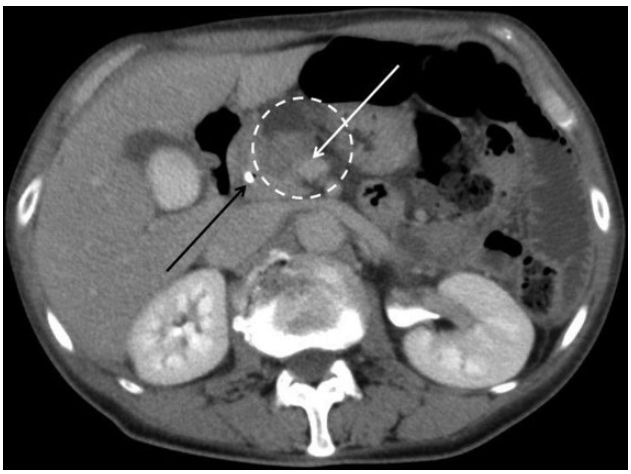

**Figure 108.1** Contrast-enhanced CT scan (transversal, venous phase) showing a hypointense PDAC (white circle) with PV contact (white arrow); borderline resectability according to the ISGPS criteria. Stent inserted in common bile duct (black arrow).

Beyond the topic of vascular tumor involvement, the involvement of an adjacent organ, that is, mesocolon, colon, stomach, adrenal gland, or kidney may require extended radical resection approaches. There is international consensus that these extended approaches are feasible in terms of surgical and oncologic outcome and organ involvement should not be considered an obstacle for resection as long as a radical tumor removal is possible [22].

## Surgical Procedures and Outcomes

### Lymphadenectomy

Lymph node spread is one of the most important prognostic factors for long-term outcome after PDAC resection. The extent of lymphadenectomy during PDAC surgery is well defined and included in national guidelines and international consensus statements [25]. In partial pancreatoduodenectomy, the lymph nodes of the hepatoduodenal ligament, those along the common hepatic artery, portal vein, and the cranial portion of SMV as well as right-sided lymph nodes of the celiac trunk and along the SMA [25]. In distal pancreatectomy for tumors of the body and the tail of the gland, tumor spread involvement is mainly observed in the lymph nodes attached to the pancreas [26]. Further frequent metastatic sites are the nodes along the splenic artery, the para-aortic area, and along the inferior margin of the pancreas as well as along the SMA. These lymph nodes should be routinely removed [27, 28]. Lymphadenectomy during total pancreatectomy can be regarded as a combination of the approaches of lymph node dissection in partial pancreatoduodenectomy and distal resection. It includes the dissection of the hepatoduodenal ligament, the lymph nodes along the hepatic artery, both sides of the celiac trunk, the splenic artery as well as the inferior pancreatic margin. This procedure will usually result in approximately 30–50 lymph nodes included in the resected specimen. The most commonly reported extended approach in lymphadenectomy is the dissection of inter-aortocaval and para-aortic lymph nodes, especially when these are macroscopically suspicious during exploration [14–18]. Although there are differences between the studies with regard to the total number of harvested lymph nodes and outcome of certain subgroup analyses, there is no evidence that extended lymphadenectomy results in a better oncologic outcome or survival. This is confirmed by a recent meta-analysis including 13 studies and demonstrating that positive para-aortic lymph nodes are associated with significantly worse survival [29]. Furthermore, extended lymphadenectomy is associated with a significantly increased surgical morbidity (i.e., chyle leakage and fluid collections) and decreased quality of life (QOL) (i.e., diarrhea and intestinal discomfort) in the postoperative follow-up [18]. Consequently, the concept of extended lymphadenectomy during PDAC resection is not recommended as an uncertain oncologic value is achieved at the price of a high postoperative morbidity.

### Vascular Resections

Historically, major vessel involvement has been a contraindication for PDAC resection. In 1973, Fortner described a surgical approach of regional pancreatectomy with en bloc resection of peripancreatic soft tissue, regional lymph nodes, and PV resection (type I), or resection and reconstruction of a major artery (type II) [30]. These initial extended resections, which were associated with a high morbidity (67%) and mortality (23%) as well as low survival rates (3-year survival rate 3%), discouraged generalized adoption of major vessel resection and reconstruction [30]. However, major advances in radiologic and surgical techniques improved preoperative staging and reduced surgical morbidity and mortality [2, 3, 31].

### Venous Resections

Resection of the PV and/or SMV during PDAC surgery can be performed without an increased perioperative morbidity or mortality and with good oncologic outcome compared to standard resections [6–9, 11, 12, 31]. This has been demonstrated in a large number of studies and meta-analyses and has consequently been implemented in national guidelines and consensus recommendations [19, 20, 32].

Venous resection can be done either by a tangential or a segmental resection [6–9]. A small defect can be closed by direct suture if the vein is not relevantly narrowed as this may cause thrombosis in the postoperative course. If a tangential resection defect needs to be augmented, this is possible by an autologous peritoneal patch [33]. In case of segmental resection, the reconstruction requires an end-to-end anastomosis (Fig. 108.2). Depending on the length of the resection, either a direct suture is possible or an autologous venous/prosthetic graft must be inserted. For this purpose, autologous grafting (e.g., renal vein, saphenous vein, internal jugular vein) is possible but requires a venous harvesting before clamping and resection [34, 35]. Alternatively, a synthetic graft, that is, a 10–12 mm ringed GORE-TEX® prosthesis, can be chosen to bridge the resected vein segment [36]. When a resection of the venous confluens is required during partial PD, the splenic vein should be reinserted by an end-to-side anastomosis as long as this does not create any lateral tension on the anastomosis. This avoids left-sided portal hypertension and restores free drainage of the stomach. In case of total pancreatectomy with splenectomy, stomach drainage is an important topic as well. In this situation, the gastric coronary vein may be preserved or reinserted, if necessary [37]. Another important aspect during PV/SMV resection is the diameter of the distal venous vessel especially in tumors located in the uncinate process. The presence of a SMV branch of a sufficient diameter has to be confirmed before resection as otherwise it may be impossible to restore small bowel drainage afterwards, which may be a technical limit for resectability. Furthermore, for all attempts of venous resection, the mesenteric root should be mobilized completely by resolving the attachment of the right hemicolon to the retroperitoneal adhesions (Cattell-Braasch maneuvre [38]). This enables long distances to be bridged after resection of the vein, and graft interposition can often be avoided by this approach. When other surgical outcome parameters are considered, it has been demonstrated that both—resection with a direct anastomosis or the interposition of a graft—can be performed safely. Numerous authors have reported a mortality rate below 5% in patients undergoing venous resection with PD, similar to that of standard PD [6–9, 34–36]. A systematic review [8] of outcome of synchronous PV/SMV resection during pancreatectomy included 52 studies encompassing 1,646 patients undergoing venous resection mainly together with partial PD (71%) or total PD (24%). The median morbidity rate for patients undergoing PD with venous resection was 42 %, and the mortality rate was 6% with a median survival of 13 months and 1-, 3-, and 5-year overall survival rates of 50%, 18%, and 8%, respectively. Another more recent meta-analysis [9] included 19 studies and compared 661 patients with and 2,247 patients without venous resections. Both groups showed similar surgical outcomes without any difference in overall survival. Furthermore, in terms of oncologic results, no difference in overall survival between both patient collectives was found, resulting in a 5-year survival rate of 12.3%, certainly superior to palliative treatment. This demonstrates that resection of the PV or SMV is potentially curative and the involvement of the SMV or PV seems to be rather a consequence of the tumor located close to these structures than a reflection of an uncommonly aggressive tumor biology.

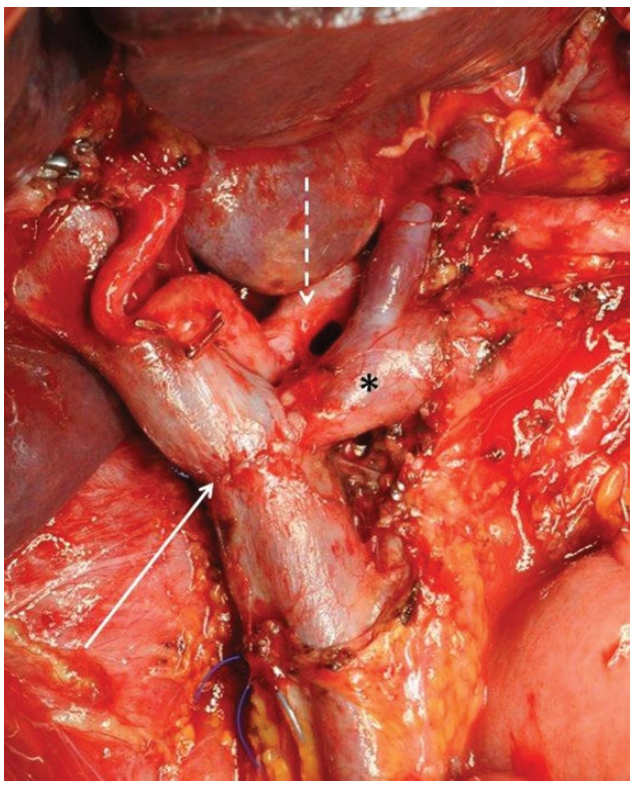


**Figure 108.2** Intraoperative situs after PV confluens resection. End-to-end anastomosis (white arrow) between SMV and PV. Splenic artery (broken white arrow); splenic vein (black star) has been reinserted under preservation of the gastric coronary vein.

## Arterial Resections

Arterial resection during PDAC surgery has remained an area of controversy since Fortner first introduced the concept as part of regional pancreatectomy. Many authors regard the invasion of hepatic artery and celiac axis of the SMA as a contraindication for surgery because of the high morbidity and mortality rates associated with arterial resection and reconstruction as well as assuming a rather poor oncologic outcome [11–13, 39]. Recently, with the introduction of effective neoadjuvant and adjuvant therapies, attention is being refocused on the

potential benefit of removing the primary tumor, even in the setting of complex arterial abutment or encasement, when this is the only site of disease [40–46]. Although in some patients arterial invasion is considered as borderline resectable according to the ISGPS consensus statement, an upfront resection is rarely recommendable, even if it can technically be performed [32]. Furthermore, arterial invasion usually predicts extensive involvement of the mesenteric neural plexus with an inability to achieve a negative resection margin even with radical extended surgery. However, there is growing evidence that patients after neoadjuvant therapy should be subjected to surgical exploration as long as no signs of systemic tumor spread are present. Using this approach, in 33–50% of all primarily unresectable patients, a radical resection might be possible and R0 resection rates comparable to standard resections can be achieved [40–45]. With the use of FOLFIRINOX as the most effective neoadjuvant chemotherapy regimen, this rate can even be increased to more than 60% of all patients who undergo a successful resection after being initially staged as locally advanced and unresectable [46].

An artery-first approach with evaluation of the SMA and celiac axis should be routinely used early during surgical resection in order to explore arterial as well as retroperitoneal tumor invasion [47–50]. Various artery-first approaches during PD can be carried out, either through a right-sided route after Kocher maneuver or through a left-sided route after lowering the duodenojejunal flexure or by an infracolic route [47]. These techniques offer several oncologic benefits, such as facilitating interaortocaval lymphadenectomy at the origin of the SMA and checking resectability at the retroperitoneal margin. The most comprehensive meta-analysis on arterial resections included 26 studies with 366 patients undergoing arterial resection and 2,243 patients without arterial resection [39]. Then analysis showed a median perioperative morbidity of 54% and mortality of 12%, respectively. Survival analysis did not show a benefit compared with patients who underwent only venous resection. However, compared with patients who underwent only palliative treatment, the 1-year survival was favorable being threefold greater for patients with arterial resection.

Regarding SMA resection, only a few studies are available, including a total number of less than 50 patients. All studies show that the resection is technically possible and grafting with the saphenous vein is the most commonly used method for reconstruction. However, morbidity of this approach remains high and the oncologic outcome is not convincing from the limited evidence to date. Celiac axis or hepatic artery resection is performed more often. Current literature includes approximately 200 patients on this topic [39]. Surgical morbidity is up to 40% and mortality in PD with arterial resection ranges from 0–35%, showing the inconsistent data basis of this approach. Overall outcomes following PD with arterial resection seem to justify the approach especially in DP and were comparable to previous reports of major cancer operations commonly performed regarding long-term survival and oncologic results. From the technical point of view, after celiac axis or hepatic artery resection reconstruction can be carried out either by direct anastomosis, by interposition of a venous graft (i.e., reversed saphenous or internal jugular vein) or with a prosthesis. The celiac axis might be resected down to its aortal orifice in PD as well as in DP or total pancreatectomy. As long as the proper hepatic artery can be preserved, a reconstruction is possible. An arterial graft (i.e., splenic artery) can also be used [51].

Regarding DP, celiac axis resection without revascularization (modified Appleby procedure) is an option for tumor removal as long as the proper hepatic artery is preserved and a sufficient arterial inflow via the gastroduodenal artery is present (Fig. 108.3). Numerous case series have described this procedure with reasonable results in terms of surgical and oncologic outcome, which seem to be nearly equal to the standard approaches [52–59]. According to the larger series in the literature, including more than 10 patients, these procedures can be carried out with mortality rates of 0–7% and an average overall morbidity of ~50%. Median survival in these reports ranges between 10 and 25 months, in the majority of publications ~20 months can be achieved. According to these retrospective studies, the modified Appleby procedure seems to be a considerable option in terms of postoperative and long-term outcome; however, no high-level evidence is available to support these findings.

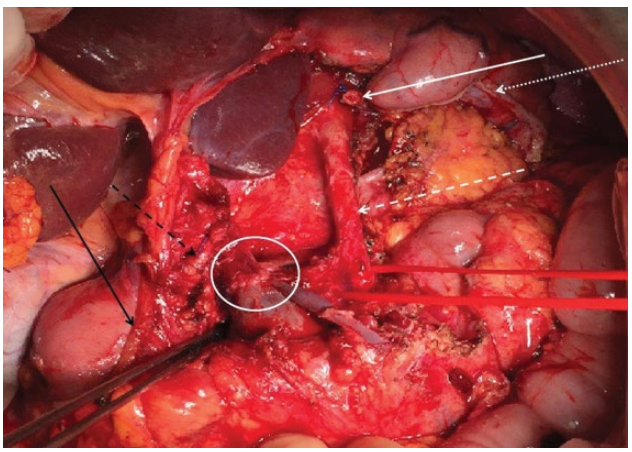

**Figure 108.3** Intraoperative situs after modified Appleby resection for PDAC of the pancreatic body combined with PV resection (white circle). Cut CA basis (white arrow), dissected SMA (broken white arrow), subcardial cut margin of the stomach (dotted white arrow), cut margin of the duodenum (black arrow), preserved gastroduodenal artery for hepatic perfusion (broken black arrow).

### Combined Vascular Resections

Data on combined vascular procedures (venous and arterial resection) are scarce. There is only very limited literature published on this topic, no conclusive evidence with regard to perioperative morbidity and oncologic outcome is available. The approach is technically feasible, but is not recommended as a standard procedure and must be based on individual decisions.

### Multivisceral Resections

If adjacent organs are affected by locally advanced PDAC (i.e., colon, stomach, left adrenal gland, small bowel, or left kidney), complete tumor removal requires partial or total resection of these organs, which also fulfils the criteria of "extended resections" defined by the ISGPS in 2014 [32]. A neoadjuvant treatment is not indicated if technically a complete resection can be achieved based on the preoperative cross-sectional imaging. In larger series, between 20 and more than 270 patients are included and the most commonly resected organs are the colon and stomach [5, 10, 60–62]. In many patients also PV/SMV resections are often performed synchronously reflecting the local extension of the tumor and the close anatomic relationship of these venous structures. Multivisceral resections have been investigated in large patient collectives and are associated with an increased postoperative morbidity predicted by a long operation time and a resection of two or more additional organs [10, 60–62]. Postoperative mortality is not increased unless patients show a relevant preoperative comorbidity. Regarding oncologic outcome, survival is similar to standard resections and in ~10–15% of these patients 5-year survival can be achieved, which is clearly superior to any palliative treatment option. These results underline that extended surgery is a feasible approach if patients are accurately selected for these procedures as certain subgroups seem to have a much greater benefit from surgery than others. For this purpose, common cross-sectional imaging is not sufficient and other markers need to be defined in the future. Tumor markers, especially CA 19-9, are used in the clinical practice. A cutoff value of 400 U/mL has been identified as the threshold for a poor oncologic outcome and may help to stratify patients preoperatively [63].

### Metastases Resection

According to international guidelines and clinical practice, Stage IV PDAC patients are generally referred to palliative treatment by chemotherapy [2, 19, 20]. With the administration of modern chemotherapy regimens, a median survival of 11 months can be achieved in a palliative setting [64]. However, these regimens are often associated with severe side effects that can impair patients' QOL and no long-term survivors have been reported. Although it remains unquestionable that PDAC with diffuse tumor spread to the liver, peritoneum, or the lung is a situation in which surgery is not indicated, the approach of a surgical resection or liver-directed therapies in oligometastatic situations has been performed in a limited number of studies in the past with partly conflicting results [65–69]. An older meta-analysis published in 2007 [21] showed no clear benefit for resection of metastases; however, the study was based on a small case series and, therefore, the evidence was highly limited. A recent study showed more encouraging results with a median survival of 12 months [70], which is clearly superior to recently reported survival times of 6–7 months following palliative standard chemotherapy (i.e., gemcitabine). Although this survival time may be expanded by modern chemotherapy regimens (i.e., FOLFIRINOX), this is achieved at the price of high toxicities with a considerable impairment of quality-adjusted life-time. An additional resection of liver metastases may not have an influence on postoperative morbidity resulting in reduced QOL. In addition and most importantly, in contrast to the palliative setting, the combination of surgery and adjuvant chemotherapy can give the perspective of a long-term survival with 5-year survival rates of 10%, which is impossible without surgery in Stage IV PDAC. This underlines the importance of a comprehensive multimodal approach and a proper patient selection of surgical candidates with Stage IV PDAC. Besides synchronous resection in an oligo-metastatic situation, also metachronous approaches to liver metastases have been reported [66–68, 70]. In this context, the interval between the initial and the consecutive operation or liver-directed therapy may be useful as an additional criterion for patient selection, and probably best reflects the tumor biology and potential prognosis of the individual patient. In general, from the clinical experience a time interval of 12 months can probably be regarded as a reference, although not based on high-level evidence. As this observation period cannot be used for synchronous resection of liver metastases, the decision for surgery in this situation remains even more challenging and additional studies and markers are warranted for prognostic patient stratification and evaluating these approaches in the future.

## Postoperative Outcome of Extended Surgical Approaches

The outcome after extended resections has to be differentiated between short-term postoperative morbidity and mortality and the long-term consequences for the respective patients in terms of metabolism, nutritional status, and QOL.

As mentioned earlier, extended lymphadenectomy procedures are associated with a considerable rate of postoperative complications, although in-hospital mortality is not increased [14–18]. A major—and often long-lasting—problem is the occurrence of chyle leaks, which are observed after 1.3–10.0% of all pancreatic resections [71–73]. In extended approaches, especially when dissection of para-aortic lymph nodes has been performed, this rate may increase and require total parenteral nutrition, percutaneous interventions or even surgical leak closure [74]. As also severe diarrhea can impair patients' QOL and no survival benefit has been shown for extended lymphadenectomy, this approach is not recommended and has mostly been abandoned [14–17, 75].

Postoperative morbidity after extended PDAC surgery including vascular and multivisceral resection is increased compared to standard approaches. In large series, the most important complications comprise bleeding with the need for transfusion, POPF, and DGE [10, 60–62, 76, 77]. Moreover, the rate of re-laparotomy, the length of ICU stay and—in some studies—also in-hospital mortality (up to 9%) is increased [60, 76]. With regard to the oncologic benefit of these procedures compared to palliative treatment, however, these approaches are recommendable and established in high-volume centers around the world.

Long-term QOL after extended pancreatectomies is dependent on the performed resection. The most invasive resection is total pancreatectomy, which inevitably leads to a complete endocrine and exocrine failure with the need for insulin and high-dosage enzyme replacement. Especially within the first 12 months postoperatively, these changes occur with a body weight loss of ~10% [78–80]. Even under good glycemic control, which can be achieved in most patients with $HbA_{1c}$ levels between 6.4–7.0%, the occurrence of fatty liver disease is observed within this time period in up to 75% of patients [80]. Despite these problems, it has to be emphasized that in most patients undergoing total pancreatectomy for PDAC, in the long term QOL is not determined by postoperative changes but by the underlying disease itself, as within 2–3 years local recurrence or metastatic disease are frequently observed. Therefore, chemotherapy and tumor progression may impair QOL to a much greater extent than pathophysiology of glycemic and nutritional status. Furthermore, in case of actual long-term survival, it has been shown that QOL continuously improves up to 4 years postoperatively and patients can reach a functional scale level of up to 90% compared to healthy controls with regard to physical, social, emotional, and role functioning [78]. For PD or DP combined with extended procedures, QOL impairment is generally less pronounced than after total pancreatectomy. In a 105 patient cohort of patients after PD, a similar overall QOL was observed when standard and extended PD was evaluated [81]. In all subscale scores (physical, social, emotional, and functional well-being) results between both groups were comparable after a median follow-up of 2.2 years. These results imply that no negative long-term QOL outcomes are associated when extended resections instead of standard procedures are required during PDAC surgery. Yet, it seems reasonable to subject patients to a structured follow-up postoperatively to recognize potential metabolic and nutritional problems early and initiate or optimize the required therapeutic measures [82].

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# Palliative Pancreatoduodenectomy: Benefits and Limitations

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## Introduction

While surgical removal of the tumor remains the only curative treatment option for patients suffering from pancreatic ductal adenocarcinoma (PDAC), only a minority of diagnosed cases receive surgery. This is due to frequent diagnosis of PDAC in locally advanced stages, distant metastatic disease [1], and sometimes delayed referral to a pancreas center [2]. When possible, resection of the primary pancreatic tumor is the treatment of choice and is considered potentially curative. However, rates of margin-positive resection (R1) are exceptionally high (>70%), according to recent data using a revised pathology classification [3,4]. Thus, the term "palliative resection" should be used with caution and be reserved for obvious R2 situations. This is particularly true, because in both the margin-negative (R0) and -positive (R1) groups of patients, long-term survivors are found [5]. However, planned "palliative resections," for example debulking procedures, have been shown to have no effect on survival and should thus generally not be attempted [6–9]. For palliation of symptomatic advanced PDAC, interventional bile duct stenting and/or bypass surgery without tumor removal are the treatment of choice [10,11].

## Definition of Palliative Resection

One of the greatest clinical challenges in making treatment decisions for patients with PDAC is the pretreatment stratification of tumors deemed to be either locally confined or locally advanced. Metastatic disease is usually found before treatment is initiated. Because of the lack of biomarkers to stratify the heterogeneous group of PDAC preoperatively, the treating physician's most important tool of diagnosis is cross-sectional imaging. The diagnostic accuracy of computed tomography (CT) and magnetic resonance imaging (MRI) has considerably improved over the last decades. However, the exact dimensions of the tumor and its relationship to surrounding structures and organs are frequently difficult to determine. While putative invasion of the superior mesenteric/portal vein axis can be managed surgically to achieve margin-negativity (at least at the vein margin), tumor extension towards the superior mesenteric artery is at times hard to determine in preoperative scanning and may even intraoperatively be only detected in the final pathology specimen. Similarly, the medial margin (the so-called "mesopancreas"), is frequently at risk but can mostly only be judged on when the resection has been performed. Thus, exploratory laparotomy followed by dissection of the superior mesenteric artery axis (and/or the celiac axis) is sometimes necessary to determine exactly local resectability.

## Review of the Literature

The advent of higher resolution in cross-sectional imaging and the advance in surgical techniques have led to the expansion of the spectrum of patients receiving surgery. A cohort study including over 16,000 patients receiving pancreatic resection identified an in-hospital mortality of 5% [12] illustrating both the risk of pancreatic surgery and the rising standard of intraoperative and postoperative treatment. However, it is important to notice that pancreatic surgery is a field where great expertise of the surgeon and the whole team is required to reduce patient risk to a minimum. This is especially true for initial assessment of operability, which paves the way for the further course.

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## Imaging and Staging

Contrast-enhanced helical computed computer tomography (tri-phasic pancreatic-protocol CT) and/or magnetic resonance imaging of the abdomen and pelvis represent the essential cornerstones of preoperative tumor staging and assessment of resectability [13,14]. Involvement and invasion of major abdominal vessels including the superior mesenteric artery (SMA), superior mesenteric vein (SMV), portal vein, and celiac axis are crucial determinants of local operability and the possible extension of surgery beyond classical procedures such as the Whipple's operation. While venous and/or portal vein involvement are no strict contraindication for a potentially curative approach [15], tumors with advanced arterial involvement are regarded as locally incurable [16]. It is generally accepted that in these cases R0 resection is practically impossible to achieve, and extension of surgery, that is, major arterial resection, may increase morbidity and mortality without a proven benefit for survival and therefore should only be performed in selected cases within clinical studies. As described later, recent multimodality treatment strategies using polychemotherapy as a neoadjuvant therapy are valid options in such a setting.

In recent years special attention has been drawn to the SMA, as the adherent posterior resection margin is the most common location of microscopic tumor remains (R1 situation) [4]. While neither of the cross-sectional imaging modalities provide high accuracy in predicting SMA involvement, surgical exploration remains the only reliable diagnostic means. During a classical pancreatoduodenectomy the medial and posterior resection margins can only be reliably assessed after transection of the pancreas has been performed. These findings have led to the so-called posterior artery-first approach for locally advanced tumors [17], which allows for precise intraoperative assessment of the SMA before transection of the pancreas.

In addition to palpation and visual control, intraoperative ultrasonography (IOUS) has further increased the accuracy of resectability assessment [18,19]. This illustration of the diagnostic process, which in many cases only begins at the time of laparotomy, suggests that only specialized surgeons in high-volume centers should perform operations on malignomas of the head of the pancreas labeled as borderline resectable.

## Perioperative Multimodal Therapy

Due to highly invasive growth and the tendency to metastasize in early tumor stages, PDAC can be considered a systemic disease. While surgery is the only curative option in early tumor stages, the systemic nature of advanced disease PDAC justifies the need for a multimodal therapeutic approach.

If local unresectability is confirmed intraoperatively, surgery is terminated and chemotherapy or chemoradiation may be initiated. Because FOLFIRINOX-based chemotherapy regimens have recently been shown to be effective with considerable response rates (at least when compared with classical chemoradiation) [20–23], we advocate administrating four to six cycles of FOLFIRINOX before restaging, followed by pancreas CT-staging. If there is no local growth, no distant metastasis, preferably a decrease in CA 19-9, and if the patient's general health status allows, re-exploratory laparotomy is performed and resectability judged again. This approach has shown considerable local response to chemotherapy with margin negativity. However, intraoperative judgment is complex because of the remaining local fibrotic response, which cannot be differentiated from the presence of remaining cancer cells, resulting in a longer, more demanding operation compared to surgery without neoadjuvant treatment [24]. A recent publication by Katz et al. [25] even suggests surgery in the setting of local tumor growth during restaging, as long as distant metastases are excluded, due to the lack of adequate predictive value of imaging in this setting. If the tumor had primarily been unresectable, resection rates after neoadjuvant therapy can be up to 40–50% [26,27]. Several studies demonstrated that the rate of margin-negative resections in this setting is comparable to the rate in initially resectable patients [26,27]. Intraoperative frozen tissue sampling may be helpful in distinguishing the fibrotic tissue from viable tumor.

Intraoperative radiotherapy (IORT) is a treatment option when an intraoperatively obtained frozen tissue section shows margin positivity. A recent systematic review on the topic suggests possible survival benefits for selected patients, without reaching statistical significance [28].

## Novel Classification of Margin Status

Recently, Verbeke et al. demonstrated that after application of a novel, standardized pathology protocol, a significantly higher amount of patients (85%) had a positive margin [3]. Esposito et al. presented similar data and showed that most pancreatoduodenectomy specimens (operated on with curative intent) in their series of 111 patients had a locally incomplete resection (76% R1 resections) [4]. This led the authors to the assumption that a standardized protocol on tissue workup rather than the extent of surgery predominantly determines the

R1 status. An intriguing but difficult-to-prove hypothesis is that R1 status in resected PDAC may be linked to the underlying biologic phenotype. A more aggressive biologic tumor phenotype in R1 resected tumors with an elevated lymph node ratio and more microvascular invasion compared with R0 resected tumors was identified in a recent study by Kimbrough et al. [29]. This underlines the urgent need for a diagnostic approach reaching beyond macroscopic and microscopic description of the cancer towards a biologic model allowing for individualized, tumor-adapted treatment.

### Palliative Surgery

In patients with jaundice and/or gastric outlet obstruction who suffer from a tumor labeled as unresectable, bypass surgery is a viable option (see Chapter 110) to ensure symptomatic relief. Because debulking is sometimes inevitable, there are a few studies evaluating outcomes after debulking procedures.

A recent systematic review performed by Gillen et al. [7] includes four patient cohorts with a total of 399 patients. Of these patients, 138 received pancreatic resection (R2 status), whereas the others underwent surgical bypass (biliary and/or enteral). Operation time, morbidity and mortality were significantly increased in the resection group, whereas overall survival was only minimally extended. Similar results were obtained by Tachezy et al. who included 22 patients in their study and also reported significantly higher rates of complications in the resection group [6]. Both authors conclude that in the context of locally advanced carcinoma intentional incomplete pancreatoduodenectomy is not justified [30].

## Management of Preoperatively Under-Staged Patients

Because of the limitations of contemporary diagnostic methods and the resulting vagueness in preoperative imaging, some patients are also discovered to have locally advanced tumors during operation in our institute. Nevertheless, routine staging laparoscopy is not employed because of the reported limited detection rate and the likely absence of a large gain after switching from surgical to endoscopic palliation [31].

In patients without any evidence of distant metastasis and when the tumor is clearly locally unresectable, the operation is terminated and neoadjuvant therapy is planned [20–23]. Palliative bypass (biliary and gastric) operations in such patients depend on the tumor extent and on the patient's symptoms. For example, in patients with functional biliary stents, bypass operations are not undertaken. However, if the patient has biliary obstruction, biliary and gastric bypass operations are performed. After completion of neoadjuvant therapy, patients are reevaluated. All patients without clear evidence of distant metastasis are offered surgical exploration. The exploration is terminated if metastatic disease is detected during laparotomy. All patients without metastasis may receive—if available in the institution—another boost of IORT (15 Gy) regardless of resection status, and all tumors deemed resectable after neoadjuvant treatment are removed.

In patients without any evidence of distant metastasis, when the tumor appears to be locally resectable, a resection is carried out. When a resection is only achieved with a likelihood of a tumor-positive margin, the patients may receive intraoperative radiation to the resection bed, if available.

In any event, when a positive SMA and/or celiac trunk margin is verified by frozen section after resection of the pancreas is performed, a careful and meticulous surgical attempt is made to convert an R2 resection into an R1/R0 resection (it can also be argued that once tumor integrity is disturbed, it is no longer possible to achieve an R0 resection). However, it should be emphasized that such an attempt could create a domino effect that may ultimately necessitate the ligation of major vessels or re-arterialization of the liver or the bowels. Therefore, it should be kept in mind that such procedures can potentially increase the morbidity and mortality rates, and should not be attempted outside of referral centers.

## Conclusions

True palliative pancreatoduodenectomy in PDAC (e.g., with macroscopically positive margins) is generally regarded as obsolete and should not be performed electively. Nevertheless, with the currently limited diagnostic modalities, it is unavoidable in approximately 10% of patients. Under such circumstances, most R2 resections can be converted to R1 resections with meticulous surgery. It should be emphasized that such an attempt is not based on evidence and should only be performed as part of a scientific study in tertiary referral centers. Aggressive surgical approaches are justified, since resection provides the only chance of cure for some, and the best palliation for most, of the patients. Further research to preoperatively stratify the patient cohorts is necessary to delineate groups that benefit from extended resections from those who do not.

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# 110

# Bypass Surgery for Advanced Pancreatic Cancer

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## Introduction

Complete surgical removal is the only curative therapy for pancreatic cancer [1]; however, fewer than 20% of patients present with resectable disease at the time of diagnosis. Among them, fewer than 10% receive a margin-negative resection (according to the latest pathology standards) and overall 5-year survival rates remain at less than 5% [2]. Palliative therapy to reduce or to prevent symptoms is needed in many patients not eligible for resectional surgery [3]. Different from the situation with a potentially resectable tumor, histologic confirmation should be obtained in potentially palliative cases in order to guide further management. Palliative therapy primarily aims to reduce pain, obstructive jaundice, and duodenal obstruction. The latter two are most frequently palliated using endoscopic/interventional methods, but can also be treated with bypass surgery. However, the potential benefit of a surgical procedure must be weighed carefully against perioperative morbidity and length of hospital stay. This holds particularly true for patients with a presumed very limited overall survival. The decision to perform a surgical bypass procedure is made either in patients in whom the tumor was initially deemed resectable, in those where endoscopic/interventional bypass is impossible, or in select cases with a potentially relatively good prognosis (e.g., over 1 year of expected survival). This chapter focuses on the indications for endoscopic/interventional versus surgical bypass procedures and the respective operative techniques and approaches.

## Background

Before the mid-1980s, palliation of biliary and/or duodenal obstruction was provided primarily through surgical bypass [4]. In some series, up to 57% of the patients with unresectable pancreatic cancer underwent surgical bypass [5]. Palliative surgical bypass of the gastrointestinal and biliary tracts has been the standard course of therapy in many of these cases [6]. Due to great improvements in interventional and endoscopic therapies, palliation of jaundice and/or gastric outlet obstruction is nowadays mostly performed nonsurgically.

## Symptoms

Biliary obstruction with jaundice most frequently emerges as a result of carcinomas of the pancreatic head and is the most frequent presenting symptom [7]; it occurs in about 80% of patient with tumors of the pancreatic head. In patients with a carcinoma of the body or tail of the pancreas, it occurs in late course of the disease and thus only rarely requires palliative bypass procedures. Because obstructive jaundice causes malaise, malabsorption and anorexia, severe and resistant pruritus, and impaired liver function leading to liver failure, its palliation is clinically important. Mechanical gastric outlet obstruction, however, occurs in less than 5% of all patients with pancreatic carcinoma at time of presentation and in only approximately 10–30% in cases of advanced disease [7]. Importantly, nausea and vomiting

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Companion website: www.wiley.com/go/beger/thepancreas

occur in the majority of pancreatic cancer patients without suffering from duodenal obstruction. This is attributed to retroperitoneal infiltration of autonomic nerve plexus leading to gastric dysfunction and cannot be palliated by a bypass procedure [8].

## Endoscopic or Interventional Biliary Decompression

Endoscopic stenting through endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the standard palliative treatment for patients with malignant biliary obstruction (current studies comparing covered and uncovered stents are summarized in Table 110.1). Through a minimally invasive procedure, endoscopic stenting relieves biliary obstruction within a short period of hospitalization. Compared to surgical methods, it is associated with a lower short-term complication rate (also see later). However, it frequently necessitates redo procedures, mainly because of stent occlusion or stent migration. Alternatives to endoscopic stenting are the percutaneous transhepatic cholangio-drainage (PTCD) or the surgical bypass.

Palliative endoscopic transpapillary drainage was first described in 1980 [9] and today endoscopic decompression has a 90% success rate and low morbidity and mortality [10]. Endoscopic endoprostheses need to be changed approximately every 4–6 months, while self-expanding metal stents (SEMS) have longer patency rates [11]. SEMS have been enhanced with different kinds of walls promising better patency and stent migration rates but definitive data favoring one special type of stent over another are missing [12–14]. However, a recent publication demonstrated that covered SEMS were not inferior to multiple plastic stents [15], with the restriction that this study was carried out on patients with a benign biliary stricture.

Although endoscopic stenting is the preferable method for treating bile duct obstruction, it is technically unfeasible in some patients; particularly, when there is an occlusion that cannot be bridged endoscopically (e.g., complete obstruction) [16]. In such cases, PTCD—which was initially described in 1974 [17]—is a valid option, despite the higher risk of major complications (i.e., bleeding, biliary fistula, liver abscess) and its conflicting therapeutic success rate [18,19].

## Surgical Bypass: Techniques

Despite the success of endoscopic treatment of biliary obstruction, surgery continues to be an important alternative option for select patients. Surgery was historically the first option as a bypass procedure and the initial techniques have been described as cholecystojejunostomy by Monastyrski in 1887, as choledochoduodenostomy by Sprengel in 1891, and as hepaticojejunostomy by Dahl in 1909 [20]. Cholecystojejunostomy is a relatively simple procedure but has low long-term patency rates with 8–11% of recurrent jaundice compared to 0–3% after choledochojejunostomy [5]. In a large cohort study of 1,919 patients, cholecystoenterostomy was significantly inferior to other bypass procedures [21]. Occlusion of the cystic duct might explain the lack of long-term patency since the hepatocystic junction was located most frequently within 1 cm distance from the biliary obstruction. Because of this anatomic situation, cholecystojejunostomy was thus found to be frequently inadequate for the permanent relief of recurrent obstruction [22]. We believe that this procedure is only an option in cases where dissection of the porta hepatis is technically challenging, for example because of local variceal conversion due to portal hypertension/portal vein thrombosis. Recently, hepaticocholecystojejunostomy has emerged as a potentially viable alternative to hepaticojejunostomy. Here, similar functional results have been shown, whereas the construction of the bypass was technically less demanding than a hepaticojejunostomy [23,24]. While laparoscopic biliary decompression would be feasible in principle, laparoscopy does not commonly allow for judging resectability at the same extent as open surgery. It is thus infrequently used [25,26].

## Endoscopic Versus Surgical Bypass

In general, surgical bypass has been linked with a higher risk of morbidity and mortality [27]. In 2007, Moss et al. published a meta-analysis comparing surgery with plastic stent deployment [27]. However, no differences in technical success, therapeutic success, quality of life, or length of survival were found. Similar results were obtained by two previous meta-analyses using the same data and methods [28,29]. Maosheng and co-workers reported a retrospective study comparing biliary bypass with SEMS in treating biliary obstruction caused by unresectable pancreatic cancer [30]. Here, there was no significant difference in procedure success rate, early complication, and survival between the surgical and stenting groups, though patients receiving surgery had a lower prevalence of late complications (mainly due to recurrent biliary obstruction). In line with these data, the incidence of recurrent jaundice in surgical patients is consistently lower than that in stented patients despite the fact that surgery itself tends to be associated with a higher early complication rate [31–33]. Apart from the biliary bypass, two randomized controlled trials

**Table 110.1** Selected studies on endoscopic biliary stenting.

| | Year | Type of stent | Patient number | Mean stent patency | Mean patient survival | Cumulative stent patency rate at 6 months | Cumulative stent patency rate at 12 months | Complications rate (early, late) | Stent occlusion (%) |
|---|---|---|---|---|---|---|---|---|---|
| Lee | 2014 | SEMS | 20 | 413 | 359 | 74% | 63% | (0%, 20%) | 20% |
| Lee | 2014 | CSEMS | 20 | 207 | 350 | 49% | 25% | (5%, 50%) | 50% |
| Ung | 2014 | SEMS | 34 | 127 | 157 | – | – | (0%, 17%) | 17% |
| Ung | 2014 | CSEMS | 34 | 153 | 154 | – | – | (6%, 13%) | 13% |
| Kitano | 2013 | SEMS | 60 | 132 | 222 | 60% | 43% | (3%, 37%) | 37% |
| Kitano | 2013 | CSEMS | 60 | 187 | 285 | 82% | 63% | (3%, 23%) | 23% |
| Krokidis | 2011 | SEMS | 40 | 166 | 203 | 70% | 70% | (10%, 30%) | 30% |
| Krokidis | 2011 | CSEMS | 40 | 234 | 247 | 92% | 87% | (12.5%, 10%) | 10% |
| Kullman | 2010 | SEMS | 191 | – | 174 | 78% | 56% | (10%, 23%) | 23% |
| Kullman | 2010 | CSEMS | 188 | – | 116 | 74% | 50% | (7%, 24%) | 24% |
| Telford | 2010 | SEMS | 61 | 711 | 239 | 90% | 55% | (26%, 18%) | 18% |
| Telford | 2010 | CSEMS | 68 | 357 | 227 | 87% | 47% | (33%, 29%) | 29% |

demonstrated that an additional prophylactic gastrojejunostomy (e.g., double bypass) is effective in preventing the development of potential gastroduodenal obstruction without increasing surgery-related morbidity and mortality [6,34]. However, surgery itself is more extensive and may significantly affect the quality of life of patients with a short life expectancy. Advantages of surgical bypass increase with longer survival of the patient, avoiding frequent readmissions and recouping initial higher costs with less future management costs than in nonsurgical patients [35]. Thus, surgical bypass is a good option for those patients in whom unresectable cancer during surgery for planned tumor resection is found, and also occasionally for patients who have a relatively long life expectancy [6,36]. Several factors were found to predict early mortality following palliative bypass: presence of distant metastatic disease, poor tumor differentiation, severe preoperative nausea and vomiting, and lack of previous placement of a biliary stent [37]. These factors may be helpful in selecting appropriate interventions for this group of patients undergoing a palliative bypass procedure. Nevertheless individual clinical judgment is still important when discussing the options with the patient. Importantly, the recent increases in survival even in Stage IV disease using polychemotherapy [38] may render surgical bypass a more frequently used procedure in the (near) future.

## Gastric Decompression

Placement of a nasogastric tube or percutaneous gastrostomy are options for palliative gastrostomy that reduce quality of life substantially and do not give nutritional support for the patient. The endoscopic method to bridge malignant stenosis with a metal stent has been proven to be an alternative to surgical bypass in retrospective studies and small randomized control trials with a technical success rate of over 90%, a stent-obstruction rate of about 10% within 15 weeks, and a stent migration rate of less than 3%; however, data on long-term outcomes are scarce [39]. Thus, in cases with true gastric outlet obstruction, surgical gastrojejunostomy remains the standard of care [40].

## Surgical Technique

Surgical gastric bypass was initially described by Wölfler and Wosler in 1881 in an antecolic way. Retrocolic gastrojejunostomy was performed first by Courvoisier in 1883 with the patient not surviving the operation while von Hacker performed it successfully in 1885. After years of debate about the value of gastrojejunostomy due to high morbidity and mortality, the results of gastroenterostomy have improved significantly [40]. Today's standard side-to-side gastrojejunostomy can be performed in antecolic or retrocolic fashion, but delayed gastric emptying is still a relevant clinical issue after this procedure [34]. Laparoscopic gastric bypass procedures are a viable option and recently gained more attention [25,41].

## Comparison of Surgical Gastric Decompression with Nonsurgical Management

Prophylactic retrocolic gastrojejunostomy at diagnosis of unresectable disease during explorative laparotomy was studied by Lillemoe et al. [6] and showed an increase in operation length, no differences in blood loss or transfusion, or in postoperative morbidity and mortality including delayed gastric emptying rate, length of hospital stay, and mean survival (8.3 months) compared with no gastric bypass. About 80% of the patients received additional hepaticojejunostomy. Late gastric outlet obstruction appeared more frequently in the control group (19% vs. 0%, $P = 0.01$) after a median of 2 months. Therefore the authors concluded that prophylactic gastrojejunostomy should be performed routinely in patients with unforeseen unresectable periampullary cancer. This was confirmed in a recent meta-analysis and systematic review [40]. Van Heek et al. [34] compared double bypass (hepaticojejunostomy and retrocolic gastrojejunostomy) to single bypass finding no significant differences in terms of postoperative morbidity including delayed gastric emptying, length of hospital stay, survival, and quality of life. Gastric outlet obstruction occurred significantly more often in the single bypass group, leading to an increased rate of repeat gastrojejunostomy. A longitudinal analysis of quality of life after double bypass by the same authors showed that quality of life can be preserved for a considerable time [42]. Fig. 110.1 shows a CT scan of a pancreatic cancer with distal infiltration of the duodenum and the mesenteric root with consequent local unresectability. A surgical biliary and duodenal bypass procedure was performed after multiple, unsuccessful attempts at endoscopic/interventional bypass.

## Our Approach

Given these data, we perform prophylactic gastrojejunostomy and hepaticojejunostomy as our standard approach in patients with unforeseen unresectable pancreatic

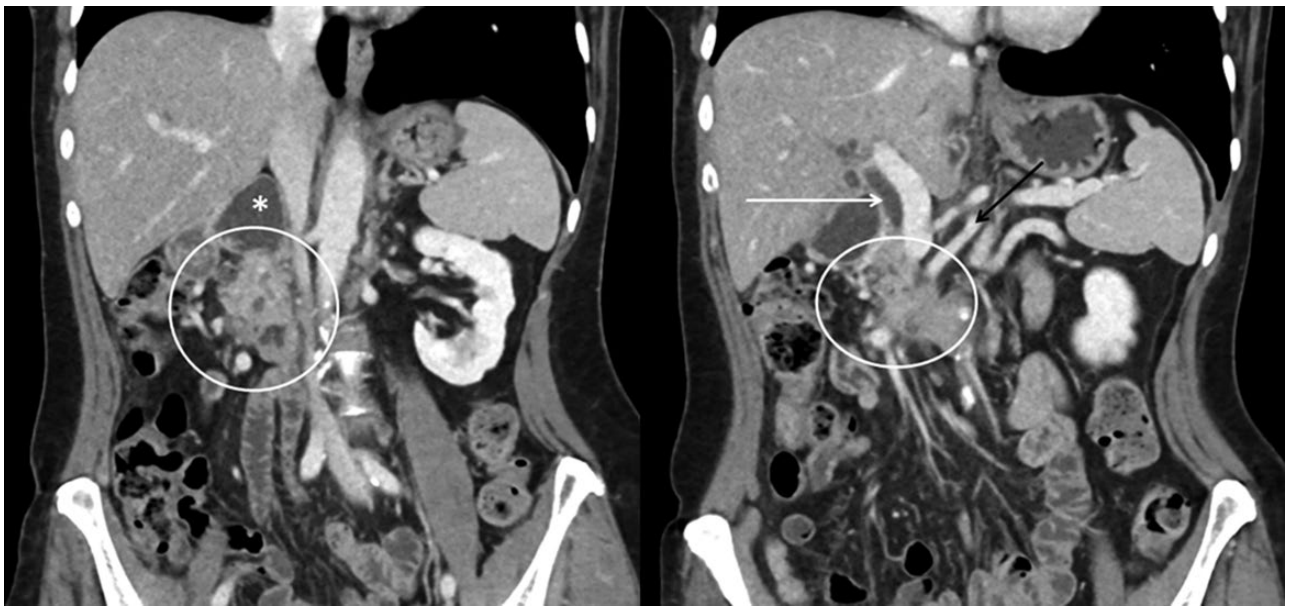

**Figure 110.1** Locally advanced pancreatic cancer with invasion of the duodenum and obstruction of the bile duct. Left side: tumor (white circle) with complete duodenal obstruction (white star). Right side: infiltration of the superior mesenteric artery (black arrow) by the tumor (white circle) and obstruction of the bile duct (white arrow).

cancer to reach palliation of symptoms in one definite procedure [43]. Patients with primarily unresectable disease but a presumed favorable survival time may receive surgical bypass in select cases. Laparotomy includes cholecystectomy and obtainment of histopathologic diagnosis. After double fenestration of the transverse mesocolon and isolation and division of the bile duct followed by running suture closure of the distal bile duct stump, division of the jejunum with a linear intestinal stapler is conducted 60–80 cm distal to the ligament of Treitz. Retrocolic end-to-side hepaticojejunostomy is conducted with the distal jejunal part before an isoperistaltic side-to-side gastrojejunostomy of about 6 cm length to the first jejunal loop and an end-to-side jejunojejunostomy at least 40 cm distal to the hepaticojejunostomy is performed. Routine nasogastric tube is only used in cases of gastric dilatation. Oral feeding is started and removal of the intra-abdominal drains is performed on the first postoperative day. This standardized approach is associated with minimal morbidity and mortality. However, constant improvement in preoperative staging in the last years has led to a significant reduction in the number of such bypass procedures. As described earlier, recent progress in multimodality treatment may considerably increase survival time for many more patients, which in turn may again increase the number of surgical bypass procedures.

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# Nonsurgical Palliation of Pancreatic Cancer

## 111

## Endoscopic and Interventional Palliation of Pancreatic Cancer

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## Introduction

The number of cases of pancreatic cancer has been increasing worldwide. The latest data show that the number of cases of pancreatic cancer has increased to more than 50,000 in the United States [1]. Most pancreatic cancers are in their advanced stage when they are detected with more than 80% of patients not surgically resectable [2]. Most patients with advanced pancreatic cancer show resistance to adjuvant therapies such as chemotherapy, resulting in a mortality of more than 40,000 in the United States [1]. Unresectable pancreatic cancers cause various complications, such as obstructive jaundice, gastric outlet obstruction, abdominal pain, main pancreatic duct obstruction, and pancreatitis, which will delay the start of palliative chemotherapy. Surgical intervention such as hepatojejunostomy and gastrojejunostomy are invasive procedures and delay recovery compared with nonsurgical intervention by interventional endoscopy (IVE) and interventional radiology (IVR). Intervention by endoscopic ultrasonography (EUS) supplements therapeutic endoscopic retrograde cholangiopancreatography (ERCP).

## Biliary Obstruction

Malignant biliary obstruction, particularly in the extrahepatic bile duct, is one of the most common symptoms in patients with advanced pancreatic cancer. The progression of biliary obstruction causes cholestasis and jaundice, and sometimes acute cholangitis, leading to fat malabsorption, malnutrition, and cachexia. Absence of therapy for obstructive jaundice leads to exacerbation of liver dysfunction and eventually liver failure. Thus, biliary drainage has been traditionally performed to improve the quality of life of patients. For resectable pancreatic cancer with jaundice, preoperative biliary drainage (PBD) has been preferred to improve the postoperative morbidity and mortality rates. However, recent high-quality studies [3,4] have suggested that PBD should not be performed routinely. There are a number of drainage methods including percutaneous transhepatic biliary drainage (PTBD), endoscopic drainage by ERCP, and combined procedures, and various types of endoscopic stents including small and large bore plastic stents. PBD using a large-bore metal stent is now the preferred technique as a bridge to surgery with a low adverse event rate [5–7].

Traditionally, biliary decompression in patients with unresectable pancreatic cancer has been conducted by ERCP and PTBD as nonsurgical and palliative interventions. The choice of the drainage method depends on the preference of the physician and the presence of skilled ERCP endoscopists and interventional radiologists in each institution. Endoscopic ultrasonography-guided biliary drainage (EUS-BD) has emerged as a salvage therapy in cases of failed ERCP [8].

### Palliation of Obstructive Jaundice by ERCP (Table 111.1)

#### Conventional ERCP

Endoscopic plastic stent placement by ERCP is the most common procedure for biliary decompression since the first report by Soehendra and Reynders-Frederix in 1980 [9]. Early randomized controlled trials (RCT) have revealed that endoscopic plastic stent placement in the palliation of biliary obstruction has a similar outcome in terms of technical success, morbidity, and mortality to surgical intervention [10,11], and is the preferred option

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 111.1** Typical technique of nonsurgical biliary decompression.

| |
|---|
| I) Endoscopic retrograde cholangiopancreatography (ERCP) |
| 1) External drainage (naso-biliary drainage) |
| 2) Biliary stenting |
| II) Endoscopic ultrasonography (EUS) |
| 1) Hepaticogastrostomy |
| 2) Choledochoduodenostomy |
| 3) Antegrade biliary stenting |
| 4) Rendezvous |
| III) Percutaneous transhepatic biliary drainage (PTBD) |
| 1) External drainage |
| 2) Internal drainage |
| 3) Internal–external drainage |
| 4) Rendezvous |

to reduce morbidity and mortality [12]. Plastic stents are usually used at the initial biliary drainage because they are less expensive and can be removed easily while the pancreatic lesion is evaluated. Self-expandable metal stents (SEMS) with a larger bore stent (8–10 mm) allow a longer stent patency, reducing the number of reinterventions compared with small-bore plastic stents (7-Fr to 10-Fr) [13,14]. Plastic stent occlusion occurs within 4 months compared to about 9–12 months with SEMS. A Cochrane review concluded that SEMS were preferable to plastic stents with an additional patency period of more than 4 months, a lower stent failure rate, a lower risk of acute cholangitis, a decreased total hospitalization period, and overall lower costs [15]. Davids et al. [16] showed that the initial use of SEMS results in a 28% decrease in the interventions compared with the initial use of plastic stents. SEMS also appear preferable in patients with borderline resectable pancreatic cancer undergoing neoadjuvant therapy, with fewer preoperative complications [3,17]. Endoscopic metal stent placement has a similar outcome for biliary obstruction compared with surgical bypass [18].

Two meta-analyses have shown equivocal advantages of covered compared to uncovered SEMS [19,20] but a more recent RCT demonstrated a superiority for covered SEMS [21]. Evaluation between stent types is challenging because of the clinical setting and disease heterogeneity and differences in stent engineering such as stainless versus nitinol metals, braded or laser cut, fully or partially covered, and with or without an antimigration system.

One of the most critical issues of endoscopic stenting is reintervention owing to stent blockage. Although a plastic stent can be exchanged with a new stent, removal of a SEMS, particularly an uncovered SEMS, is much more difficult. A stent-in-stent technique inserting a new stent within the existing occluded metal stent can be performed using a plastic stent or an uncovered/covered SEMS. Plastic stent placement may be as effective as a second SEMS placement [22]. Removal of an occluded covered SEMS seems to be an even better option [23–25].

#### Balloon Enteroscopy-Assisted ERCP

ERCP in patients with a Roux-en-Y (RY) reconstruction including a RY gastrectomy and a RY gastric bypass is always a challenging procedure. Conventional endoscopy has a success rate of less than 50%. Single-balloon (SBE) and double-balloon enteroscopy (DBE) have improved success rates in RY reconstructions [26–29]. In patients following a Whipple resection, malignant or benign stenosis of the hepaticojejunostomy can be treated by balloon dilation and/or stent placement using BE-assisted ERCP [30].

### Palliation of Obstructive Jaundice by EUS

Selective biliary cannulation by ERCP for biliary decompression is not always successful because of intradiverticular papillae, surgically altered anatomy, or gastroduodenal obstruction. In the case of failed ERCP but EUS-BD using transmural approaches such as the EUS-rendezvous technique (EUS-RV), EUS-guided choledochoduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS) (Fig. 111.1), and EUS-guided antegrade stenting (EUS-AS) are options [31]. Technical and clinical success rates are around 80–90% with moderate adverse event rates of 10–30% such as bile leakage, bleeding, and stent migration although the severity of most adverse events are mild or moderate [32]. Covered SEMS reduce unexpected adverse events such as bile leakage for biliary decompression, although there is no difference between plastic stents and covered SEMS in the EUS-HGS procedure [33]. Of the EUS-BD procedures, EUS-RV appears to achieve minimum invasive drainage because ERCP and BE-assisted ERCP can be performed. EUS-CDS can be an effective and safe alternative to PTBD with a similar success rate, complication rate, cost, and patient quality of life [34].

### Palliation of Obstructive Jaundice by IVR

PTBD can be achieved by external drainage, internal–external drainage, and internal drainage. A 7-Fr to 8-Fr percutaneous tube is used, which allows sufficient drainage for the therapy of obstructive jaundice. Internal drainage appears to be the most efficacious. Percutaneous SEMS placement using a small-caliber (approximately 6-Fr to 7-Fr) delivery system allows good efficacy, with few complications and reduced pain [35]. Percutaneous covered SEMS placement provides long stent patency compared with percutaneous uncovered SEMS [36]. Endoscopic stenting, however, has a significantly higher

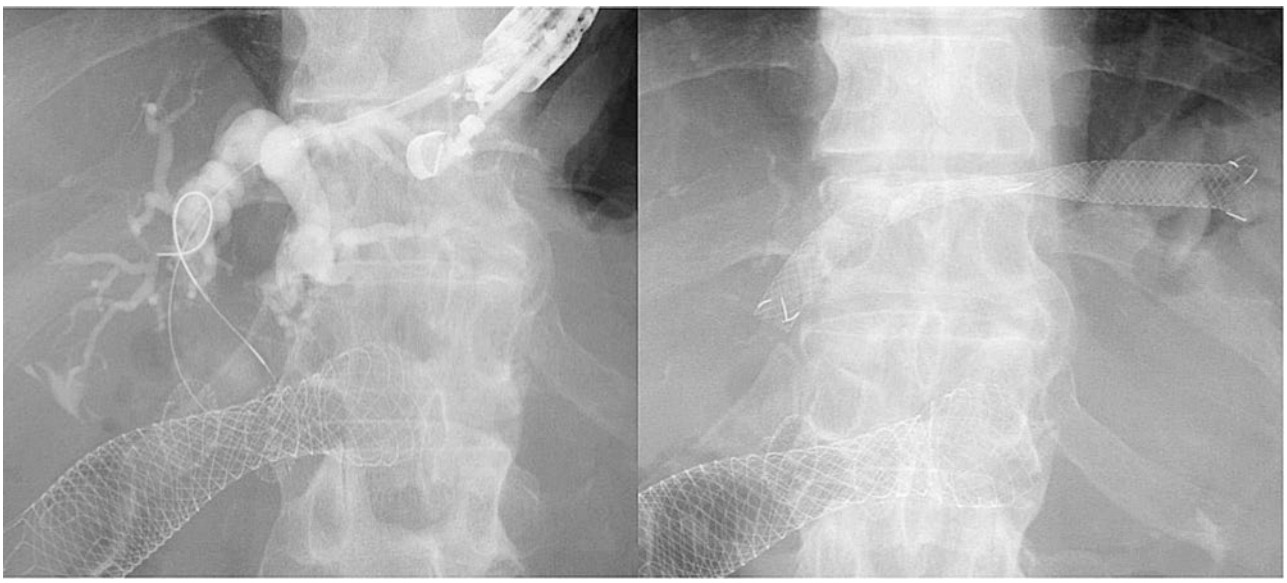

**Figure 111.1** EUS-guided hepaticogastrostomy. Metal stent delivery system was inserted in the intrahepatic bile duct (left). Hepaticogastrostomy was completed using a metal stent.

success rate than percutaneous stenting in relieving jaundice with a lower 30-day mortality from complications associated with liver puncture [37,38]. The success rate of needle puncture in a nondilated bile duct is lower than that in a dilated bile duct (63% vs. 86%) [39]. PTBD remains a salvage therapy [40,41].

## Malignant Gastric Outlet Obstruction

Surgical gastrojejunostomy (GJ) by laparotomy or laparoscopy, provides good palliative treatment for malignant gastric outlet obstruction MGOO, but has a relatively high morbidity and mortality [42,43].

### Duodenal Metal Stent Placement

Duodenal stent placement is undertaken using a 20–22 mm diameter SEMS under fluoroscopic guidance, or endoscopically using a thinner 10-Fr delivery system as an alternative to surgical GJ because the stent can be inserted through the accessory channel with a high technical success rate and less invasiveness [42–47]. A systematic review [42] has revealed that the initial clinical success rate was higher after stent placement than after surgical GJ (89% vs. 72%, respectively) with fewer minor complications (9% vs. 33%, respectively). However, recurrent obstructive symptoms were more frequent after stent placement (18% vs. 1%, respectively) owing to tumor ingrowth, preventing the patient from being able to eat soft solid food or a full diet. Endoscopic stenting might be preferable in patients with a relatively short life expectancy, whereas surgical GJ might be preferable in patients with a longer expected survival (>2 months) [42,43]. Endoscopic stent occlusion often occurs during longer follow-up periods owing to tumor ingrowth. In this cohort, an additional stent is often placed within the original stent, which can lead to early stent occlusion or stent-related adverse events such as perforation. One study has demonstrated that EUS-guided GJ using a dedicated double balloon and a fully covered lumen-apposing SEMS (15 mm in diameter) had a high technical and clinical success without causing serious adverse events (Fig. 111.2) [48].

### Duodenal and Biliary Stent Placement: Double Stenting

In patients with unresectable pancreatic cancer, progression of the cancer is accompanied not only by MGOO but also by biliary obstruction, which is usually a late manifestation. In such patients, both biliary stent placement and duodenal stent placement, so called "double stenting" is often required. The methods and ease of the procedure vary according to the site and timing of the duodenal obstruction. In particular, the duodenal obstruction site appears to be more important in terms of planning the biliary stenting strategy. The duodenal obstruction site is classified in relation to the position of the major papilla, namely, Type I where the obstruction site is at the entrance from the principal papilla, Type II where the obstruction site is somewhat convoluted with the papilla present in the second portion, and Type III where the obstruction site is

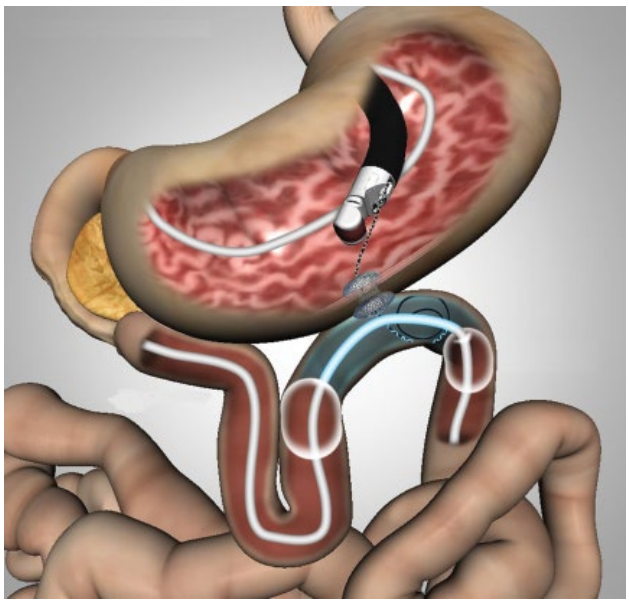

**Figure 111.2** EUS-guided gastrojejunostomy. Lumen-apposing metal stent was placed over the wire using a dedicated double-balloon tube.

closer to the anal side than to the major papilla [49]. In double stenting, biliary drainage with or without the rendezvous technique is performed using three kinds of approaches: the percutaneous transhepatic approach, an ERCP approach, and the EUS approach. In double stenting by ERCP, if the duodenal obstruction site is convoluted around the major papilla (Type II), the treatment is most complicated. Even if the balloon is stretched or the duodenal stent is placed first, cancer invasion makes it difficult to identify the major papilla and confirm the distance from the scope. In addition, it is very difficult to pass the biliary stent through the mesh gap of the duodenal stent. Thus, in case of Type II, the traditional percutaneous transhepatic approach including biliary drainage and rendezvous appears more preferable for double stenting than the ERCP approach. The EUS approach has allowed biliary drainage including EUS-HGS, EUS-CDS, EUS-AS, and EUS-RV even in Type I and Type II MGOO. In Type I and Type II MGOO, EUS-HGS and EUS-AS appear to be suitable drainage techniques for the treatment of obstructive jaundice and can replace the percutaneous transhepatic approach because of the minimum invasive procedures involved [50].

## Pain Management Derived from Cancer

Pain due to cancer invasion of the celiac plexus is a major manifestation of pancreatic cancer occurring in approximately 70% of patients with unresectable pancreatic cancer [51]. At present, pain is comparatively well controlled by opioid analgesics, IVE, and/or IVR. Celiac plexus neurolysis (CPN) is most often performed by injecting a local anesthetic followed by absolute alcohol into the celiac plexus neural network of ganglia with the intention to ablate the tissue transmitting pain from the pancreas and adjacent visceral organs. Currently, there are two CPN approaches, namely, EUS-CPN and percutaneous CPN.

### Endoscopic Ultrasonography-Celiac Plexus Neurolysis (EUS-CPN)

Standard EUS-CPN is performed using a 19-gauge to 25-gauge EUS-guided fine-needle aspiration (EUS-FNA) needle [52]. A needle is advanced anterior to the lateral aspect of the aorta at depiction of the celiac trunk. Then, after confirming the absence of backflow of blood, absolute alcohol is injected following local anesthetic injection. A meta-analysis has demonstrated that pain was reduced in 80% of the patients following EUS-CPN for pancreatic cancer [53]. Although most adverse events of EUS-CPN are mild and include transient hypotension, diarrhea, constipation, and pain exacerbation, serious and fatal adverse events can occur [53]. Unilateral neurolysis is conducted by a single injection into the base of the celiac artery takeoff. In contrast, bilateral neurolysis is performed by injecting into both sides of the celiac plexus. Bilateral injection is superior to central injection for pain reduction (86% vs. 46%, respectively) [53]. An RCT comparing the two approaches in pancreatic cancer among 50 patients showed no significant difference in terms of pain control or adverse events [54]. An RCT comparing EUS-guided celiac ganglia neurolysis (EUS-CGN) in which alcohol is injected directly into the celiac ganglia (detection rates of 80–90%) by EUS showed greater pain relief than in the EUS-CPN group (73.5% vs. 45.5%, respectively) with similar adverse events [55].

### Percutaneous CPN

Percutaneous CPN, which is performed using a 22-gauge needle mostly by anesthesiologists and radiologists under transabdominal ultrasound (US), fluoroscopy, or computed tomography (CT), is also an option [52]. A meta-analysis has shown that percutaneous CPN improves pain in patients with upper abdominal cancer, with a decrease in opioid consumption and side effects although it is unclear whether there is any change in the quality of life [56]. US-guided CPN (US-CPN), using a unilateral paramedian needle-insertion technique is comparable with a bilateral paramedian needle-insertion technique with regard to pain relief and side effects [57]. Another open randomized comparison of clinical effectiveness of

protocol-driven opioid analgesia, celiac plexus block, or thoracoscopic splanchnicectomy for pain management in patients with pancreatic and other abdominal malignancies showed no significant difference [58].

## Anticancer Therapy

Although EUS-guided or percutaneously guided intratumoral TNFerade biologic with 5-fluorouracil and radiotherapy as first-line treatment for locally advanced pancreatic cancer is feasible, it is not effective [59]. EUS-guided interstitial implantation of $^{125}I$ seeds might improve pain, but without any survival benefit [60]. EUS-guided radiofrequency ablation of unresectable pancreatic cancer is also technically feasible and safe but without any proven therapeutic efficacy demonstrated [61]. EUS-guided cryothermal ablation therapy [62] and EUS-guided dendritic cell injection therapy [63,64] are also being evaluated.

## Miscellaneous

ERCP stent placement has been used to relieve pain thought to be due to pancreatic duct (PD) obstruction and then EUS-guided PD stent placement if this fails. EUS-guided PD stent placement can also be used for symptomatic anastomotic stricture (pain or intermittent acute pancreatitis) of the pancreatojejunostomy after pancreatoduodenectomy. Acute pancreatitis due to pancreatic cancer is rare but is observed in some patients. Pancreatic fluid collections including walled-off necrosis and pseudocyst, require EUS and/or percutaneous drainage. Furthermore, endoscopic necrosectomy may be required to remove the infected necrotic tissue.

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# Medical Treatment of Pancreatic Cancer

## 112

## Neoadjuvant Treatment of Pancreatic Cancer: Downstaging Results

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### Introduction

In order to appreciate the evolution of therapy for localized pancreatic cancer, a brief overview of clinical results in resectable pancreatic cancer is required. For years, the standard approach to resectable pancreatic cancer has been upfront surgical resection followed by adjuvant therapy [1,2]. Over time, it has been established that the completeness of surgical resection has prognostic implications. Better survival has generally been observed for patients undergoing complete resection with microscopically negative surgical margins compared with patients left with gross or microscopic residual disease at the completion of surgery [2–5]. It is now broadly accepted that all pancreatic resections should be classified according to residual disease status, termed "R" factor: R0, no gross or microscopic residual disease; R1, microscopic residual disease (microscopically positive surgical margins with no gross residual disease); and R2, grossly evident residual disease. This designation was previously used to describe the completeness of resection in rectal cancer in which margins of resection also have prognostic implications [6]. The United States definition defines an R1 margin as one or more cancer cells at any surface margin but this differs from that used in Europe, which shares this part of the definition with the US but also states that one or more cancer cells up to 1 mm from any surface also counts as an R1. If one or more cancer cells is not at any surface margin but is less than 1 mm from any surface the US definition would refer to this as an R0, not an R1 as in Europe [7].

Reports from single institutions and from large multicenter adjuvant trials have shown that R1 resections occur quite frequently in pancreatic adenocarcinoma and are generally associated with worse survival [2,8–11]. While high-quality cross-sectional imaging has been quite reliable in predicting the surgeon's ability to remove all gross tumor [12], the diffusely infiltrating nature of pancreatic adenocarcinoma and the very narrow space from the tumor to the mesenteric vessels, portal vein, and celiac trunk make achievement of an R0 resection a therapeutic challenge [13]. Thus, some centers have focused on preoperative or neoadjuvant therapy as a means to sterilize the tumor's periphery, which is very close to vasculature that cannot be sacrificed.

### Neoadjuvant Therapy for Resectable Pancreatic Cancer

The rationale for delivering preoperative treatment to patients with potentially resectable tumors is based on: (i) the early treatment of micrometastatic disease, which is present in the majority of patients; (ii) providing a sufficient time interval to assess the underlying tumor biology thereby selecting patients for surgery who have the highest likelihood to benefit from it; (iii) delivering "adjuvant" therapy in a "neoadjuvant" setting, when it is expected to be better tolerated since surgical recovery will not complicate the timely delivery of treatment; and (iv) the potential to sterilize the periphery of the tumor, thereby improving the chances of an R0 resection. In several trials of preoperative therapy utilizing chemoradiation, high R0 resection rates have been reported with antitumor treatment effect demonstrated in resected specimens ranging from minimal killing to occasional complete pathologic responses [14–17].

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### Early Results in Downstaging Pancreatic Tumors

As neoadjuvant therapy for resectable pancreatic cancer was being studied, publications from the 1990s to 2000s reported on the potential to downstage initially unresectable pancreatic cancer with neoadjuvant therapy. One of the earliest trials reported modest success using infusional 5-fluoruracil (5FU) with external beam radiation (EBRT) in 16 patients with locally advanced disease [18]. While only two (12.5%) were able to undergo surgery with curative intent, the survival of these two patients was comparable to patients with resectable pancreatic cancer treated with upfront surgery and adjuvant therapy. In a larger trial, the group at Duke University reported on 111 patients treated with preoperative chemoradiation from 1995 to 2000 and included patients with resectable ($n$ = 53) or locally advanced disease ($n$ = 58) [17]. The overall resection rate was superior for patients defined as having resectable disease (53%) compared with the rate for patients with locally advanced disease (19%) with an overall R0 resection rate of 70%.

Importantly, during this time frame an appreciation for the distinction between tumors that would now be considered borderline or marginally resectable was emerging [19]. For example, one of the earliest reports utilizing preoperative therapy to downstage what is now known as borderline resectable disease was conducted at Stanford University and reported by Mehta et al. [20]. The investigators reported on 15 patients they described as having "marginally resectable adenocarcinoma of the pancreas" defined as tumors having "PV, SMV, or artery involvement." These patients were treated with infusional 5-FU and EBRT to doses ranging from 50.4–56 Gy. Nine patients (60%) underwent surgical resection with negative surgical margins and 2 of 9 (22%) had a complete pathologic response to preoperative treatment. Furthermore, there was a striking difference in overall survival between those patients who did undergo surgical resection and those who did not (30 vs. 8 months, respectively).

These and other reports have suggested that for a subset of patients with pancreatic cancer not initially considered resectable, neoadjuvant therapy could provide sufficient tumor destruction or "downstaging," to proceed with surgical resection. However, the resection rates reported after neoadjuvant therapy have varied widely from as low as 1% to 60%, with most studies reporting resection rates ranging between 20–40% [21–24]. Patients reported in these studies likely represented a heterogeneous population comprised of some having tumor with complete vascular encasement and others having some degree of tumor-vessel contact without encasement.

## Emerging Recognition of Borderline Resectable Pancreatic Cancer

Broadly defined, borderline resectable tumors represent a subset of localized pancreatic cancers that have a high risk of R1 resection with upfront surgical intervention based on a tumor's intimate proximity to surrounding vascular structures [25]. A number of factors have led to the recognition of the entity now known as borderline resectable pancreatic cancer. First, it has been increasingly appreciated that high-quality cross-sectional imaging is now capable of characterizing the tumor/vessel interfaces as having clearly interposed fat planes (potentially resectable), having tumor abutment (<180°) without encasement of a vessel or vessels (borderline resectable), or having tumor encasement of critical vascular structures (locally advanced). Second, most experts agree that an R1 resection puts the patient at risk for poor survival. Third, as discussed earlier, neoadjuvant therapy is capable of producing some local tumor destruction and appears to increase the chances of achieving an R0 resection for patients with resectable disease. While this should not be considered downstaging per se, microscopic downstaging is likely occurring as a result of neoadjuvant therapy in this setting. Fourth, studies from a number of institutions suggests that a subset of patients who are defined as having borderline resectable disease may ultimately undergo surgical resection with curative intent after a period of neoadjuvant therapy [26]. For these patients, median overall survival has been encouraging.

Recognition of borderline resectable disease is increasingly appreciated and provides a framework for better defined, more homogeneous, and reproducible subsets of patients for entry onto clinical trials investigating neoadjuvant therapy as a downstaging strategy. This allows for three separate categories of localized pancreatic cancer: potentially resectable, borderline resectable, and locally advanced, and reports are now emerging on the role of neoadjuvant therapy for these three distinct subsets.

## Downstaging Borderline Resectable Disease with Neoadjuvant Therapy

In addition to the report by Mehta et al., other centers have reported on results with neoadjuvant therapy for borderline resectable disease. For example, we performed a retrospective analysis and classified 160 patients as having borderline resectable disease (based on our previously published definition) [22]. Among those patients, all of whom were treated with neoadjuvant therapy, approximately 40% had some combination of clinical, laboratory (i.e., drop in tumor marker), or radiographic

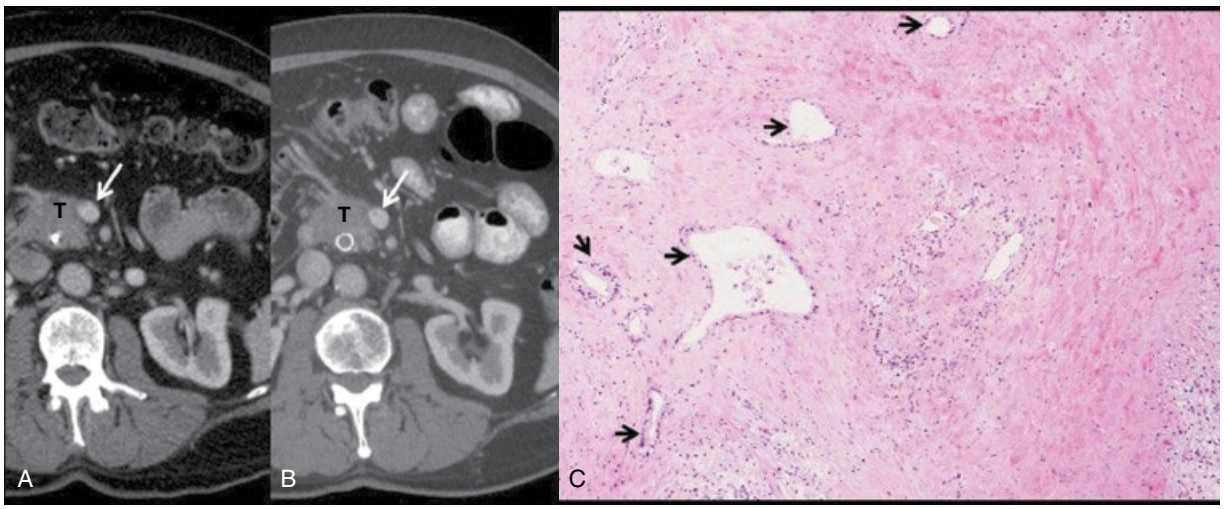


**Figure 112.1** A. Pre-treatment CT image of a borderline resectable pancreatic cancer. B. Post-treatment CT image of tumor after induction FOLFIRINOX followed by gemcitabine-based chemoradiation. T depicts tumor mass; white arrow depicts SMV. Note no overall change in tumor. C. Photomicrograph of resected specimen. Black arrows show small residual nests of viable tumor glands with large areas of fibrosis and necrosis. Tumor estimated to be 85% nonviable.

response to therapy to justify surgery. For the patients that ultimately underwent resection, the R0 resection rate was 94% with a median overall survival of 40 months. Of note, the survival of patients who did not undergo surgery was consistent with patients having locally advanced disease and managed with nonoperative therapy (13 months). A number of other institutions are beginning to publish their resection rates after neoadjuvant therapy for borderline resectable tumors with several reporting resection rates between 40–60% and some having rates around 80% [26]. Recently, Katz et al. have reported on results of a multi-institutional trial of 5FU, folinic acid, irinotecan, and oxaliplatin (FOLFIRINOX) followed by capecitabine-based chemoradiation, for patients with borderline resectable disease. Among the 23 patients enrolled, 68% underwent surgery with curative intent; the R0 resection rate was 93% [27]. Taken together, these reports have led some groups to recommend against upfront surgical resection in the setting of borderline resectable disease, while others do not [28–31]. Currently, a randomized trial of surgery versus preoperative chemoradiation followed by surgery, is being conducted among patients with resectable and borderline resectable disease [31].

## Challenges of Neoadjuvant Therapy in Borderline Resectable and Locally Advanced Pancreatic Cancer

Despite keen interest, questions remain about tumor downstaging using a neoadjuvant approach. First, what is the optimal duration of therapy prior to considering surgery resection? Second, what is the relative contribution of systemic therapy and radiotherapy to tumor downstaging? Third, and perhaps the most difficult question is what response criteria can identify patients most likely to benefit from surgical resection after neoadjuvant therapy? Recent publications describe the inability of repeat cross-sectional imaging to reliably identify tumor downstaging [32,33]. It is widely known that the tumor microenvironment of pancreatic cancer can have a dense desmoplastic and fibrotic component which prevents overall tumor shrinkage to be demonstrated despite significant tumor cell destruction (Fig. 112.1). In general, radiographic evidence of a stable or shrinking tumor mass, with evidence of clinical improvement, decrease in tumor marker levels, and no interval development of metastatic disease are indications for surgery. Furthermore, normalization of CA 19-9 in response to neoadjuvant therapy is associated with long-term survival in resected patients [34].

## Future Directions

The complex biology of the microenvironment of pancreatic adenocarcinoma, with stromal elements that may act to both sequester malignant cells and protect them from cytotoxic therapy or immunologic attack, is steadily being elucidated. Future interventions that lead to stromal changes with agents such as hyaluronidase, vitamin D analogs, or other immunomodulating agents are certain to be investigated as strategies to enhance downstaging in localized pancreatic cancer [35–37]. Further,

other locally destructive techniques are being explored for their potential to enhance local tumor killing while sparing normal surrounding structures. Investigations of irreversible electroporation are being conducted as a way to improve treatment of locally advanced pancreatic cancer and to enhance complete tumor destruction at the margin of resection in borderline resectable disease [38]. Stereotactic body radiation and proton beam therapy are also being evaluated as alternatives to conventional EBRT [39,40].

Lastly, based on some improvements in systemic therapy now available, more attention to local control strategies to include aggressive surgical intervention is certain to develop. At present, venotomy with primary repair, or en bloc venous resection with reconstruction are commonly performed in pancreatic cancer centers of excellence with some renewed interest in arterial resections and reconstruction [41]. Thus, more aggressive surgical approaches coupled with active neoadjuvant therapy may allow for even greater numbers of patients to undergo surgery with curative intent.

## Summary

Neoadjuvant therapy is a rational approach to therapy for nonmetastatic pancreatic cancer. Tumor downstaging is not required in the setting of resectable pancreatic cancer, but it may lead to microscopic downstaging and improve the likelihood of an R0 resection. In borderline resectable disease, which by definition places the patient at high risk for an R1 resection, treatment with neoadjuvant therapy is sufficiently active in 40–60% of patients to ultimately allow for surgical resection. For those with locally advanced pancreatic cancer, although the chances of subsequently undergoing surgery with curative intent are only 20%, newer drug therapies and locally destructive techniques may expand the proportion of these patients who can undergo surgery. Lastly, the recognition of and formalized definitions for borderline resectable disease that is intermediate in the spectrum of resectable and locally advanced/unresectable pancreatic cancer will allow for more reliable comparison of results in clinical trials of various neoadjuvant regimens.

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# 113

# Adjuvant Chemotherapy in Pancreatic Cancer

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## Introduction

Pancreatic ductal adenocarcinoma remains the most common malignancy of the pancreas, and is the fourth highest cause of cancer death in the developed world. An estimated 367,000 new cases were diagnosed worldwide in 2015, and it is likely to become the second leading cause of cancer mortality within the next decade [1].

The majority of patients with pancreatic cancer present with advanced disease. Surgery remains the only potentially curative option, but even in specialized centers just 10–15% of patients are suitable for resection [2]. The mortality associated with major pancreatic surgery has reduced considerably in recent years, and is now routinely reported as less than 5% [3]. Following surgery alone, prognosis remains dismal with a median survival of around 13 months and only 10% surviving for 5 years [4]. Increasingly radical resections that include extended lymphadenectomy or total pancreatectomy have been employed in an attempt to improve long-term outlook, but prospective trials comparing these more radical resections with classical surgical techniques have failed to demonstrate any survival benefit, with significant disadvantage in terms of postoperative quality of life [5].

Around 70% of patients undergoing curative intent surgery succumb to distant metastases rather than local recurrence [6] and so attention has turned to additional therapies that may delay or prevent the development of recurrence in an effort to improve long-term outcome. Adjuvant therapy is used with the aim of reducing these occult micrometastases and the results from contemporary randomized studies provide the most compelling evidence so far to support its use after surgery for pancreatic cancer. This chapter aims to provide a summary outline of key trials in adjuvant therapy, as well as to highlight potential future avenues to improve outcomes in this deadly disease.

## Rationale for Adjuvant Therapy

The first randomized assessing the role of adjuvant treatment for pancreatic cancer was the small 1985 Gastrointestinal Tumour Study Group (GITSG) study, where 43 resected patients were randomized to receive either 5-FU concurrent with radiation (50 Gy) followed by maintenance 5-FU, or observation alone. Such was the nihilistic approach to pancreatic cancer at that time, the trial closed prematurely because of failure to recruit. Despite these problems, median survival was considerably longer for the adjuvant therapy arm (20 months vs. 11 months, $P = 0.04$) (see Table 113.1) [7]. However, it was impossible to tell whether it was systemic chemotherapy or radiotherapy that led to this improvement.

Subsequent to this, a larger European study (EORTC 40891) assessed concurrent 5-FU and radiation (40 Gy) versus observation alone for 120 patients with resected pancreatic head cancer and periampullary tumors but demonstrated no difference in median [8] or long-term [9] survival, even when the pancreatic head group was evaluated independently.

The European Study Group of Pancreatic Cancer (ESPAC)-1 trial [10,11] provided a further challenge to the value of chemoradiation and suggested that chemotherapy alone provided the primary survival benefit seen in GITSG. The study used a $2 \times 2$ factorial design to stratify patients undergoing curative intent surgery for pancreatic adenocarcinoma by center, type of tumor, and resection margin status. Patients were then randomized to one of four arms: (i) chemoradiation (50 Gy split

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**Table 113.1** Summary of major trials of adjuvant therapy for pancreatic cancer.

| Trial | Year | Regimen | Median survival (months) | P | 5-year survival (%) | P |
|---|---|---|---|---|---|---|
| GITSG [7] | 1985 | Observation | 11 | 0.04 | 13.6 | NR |
| | | 5-FU/50 Gy | 20 | | 4.7 | |
| EORTC 40891 [8,9] | 1999 | Observation | 19 | 0.2 | 22 | NS |
| | | 5-FU/40 Gy | 25 | | 25 | |
| ESPAC-1 [10,11] | 2001 | Chemotherapy (Bolus 5-FU) | 20.1 | 0.009 | 21 | 0.009 |
| | | No chemotherapy | 15.5 | | 8 | |
| | | Chemoradiotherapy (50 Gy) | 15.9 | 0.05 | 10 | 0.05 |
| | | No chemoradiotherapy | 17.9 | | 20 | |
| CONKO-001 [12] | 2007 | Gemcitabine | 13.4 | <0.001 | 20.7 | 0.01 |
| | | Observation | 6.7 | | 10.4 | |
| ESPAC-3 [14] | 2010 | 5-FU/leucovorin | 23.0 | 0.39 | 15.9 | NS |
| | | Gemcitabine | 23.6 | | 17.5 | |
| ESPAC-4 [18] | 2016 | Gemcitabine | 25.5 | 0.03 | 28.8 | 0.032 |
| | | Gemcitabine/capecitabine | 28.0 | | 16.3 | |
| JASPAC-01 [15] | 2016 | S1 | – | – | 44.1 | <0.0001 |
| | | Gemcitabine | – | | 24.4 | |
| EORTC 40013 [22] | 2010 | Gemcitabine | 24.4 | NS | – | – |
| | | Gemcitabine/50.4 Gy | 24.3 | | – | |

NS, nonsignificant; NR, not reported; –, data not available.

course), (ii) 6 months of systemic chemotherapy (bolus 5-FU), (iii) combination chemotherapy and chemoradiotherapy, or (iv) observation. A total of 289 patients from across Europe were randomized. At a median follow-up of 47 months, 5-year survival was significantly higher for those receiving chemotherapy versus those who did not (21% vs. 8%, $P = 0.009$). Median survival for those treated with chemotherapy was 20.1 months compared to 15.5 months for those without ($P = 0.009$). Median survival was also significantly longer in the group who did not receive chemoradiotherapy (17.9 vs. 15.9 months, $P = 0.05$), which translated to an estimated 5-year survival rate of 10% for those treated with chemoradiation compared to 20% for those who did not ($P = 0.05$) (see Fig. 113.1). The survival rates for patients treated with chemoradiation in ESPAC-1 were broadly in keeping with those from other series, and the superior outcomes seen after systemic chemotherapy led to a move away from adjuvant radiotherapy in favor of systemic chemotherapy across Europe.

The promising results of ESPAC-1 led other researchers to question whether the use of more active systemic chemotherapies would translate to improved long-term outcome. The Charité Onkologie (CONKO)-001 trial compared six cycles of systemic gemcitabine with observation alone in 368 patients who had undergone resection, and found a significant improvement in median disease-free survival (13.4 vs. 6.7 months, $P < 0.001$) [12], which also translated into improved 5-year survival (20.7% vs. 10.4%, $P = 0.01$) [13]. This benefit was consistent irrespective of tumor stage, nodal status, and margin status although patients with a postoperative CA 19-9 level >92.5 KU/L were excluded from trial entry and so the patient population included a prognostically more favorable group.

Both ESPAC-1 and CONKO-001 therefore confirmed the role of adjuvant therapy as standard of care after curative resection, and led to an almost doubling in the 5-year survival after surgery.

ESPAC-3 built on these findings by randomizing 1,088 patients to observation, bolus 5-FU/leucovorin, or bolus gemcitabine for 6 months after surgery [14]. The observation arm was closed when the final results of ESPAC-1 were published. Final analysis at a median follow-up of 34.2 months demonstrated equivalence in median survival (23.0 months for 5-FU/leucovorin vs. 23.6 months for gemcitabine, $P = 0.39$) (see Fig. 113.2) but significantly lower grade 3/4 toxicity in the gemcitabine arm (7.5% vs. 14%, $P < 0.001$). These results defined gemcitabine as the optimal adjuvant monotherapy for patients who had undergone curative resection.

The Japan Adjuvant Study Group of Pancreatic Cancer (JASPAC)-01 trial assessed S-1 (a 5-FU analog with marked efficacy in the Japanese population) versus

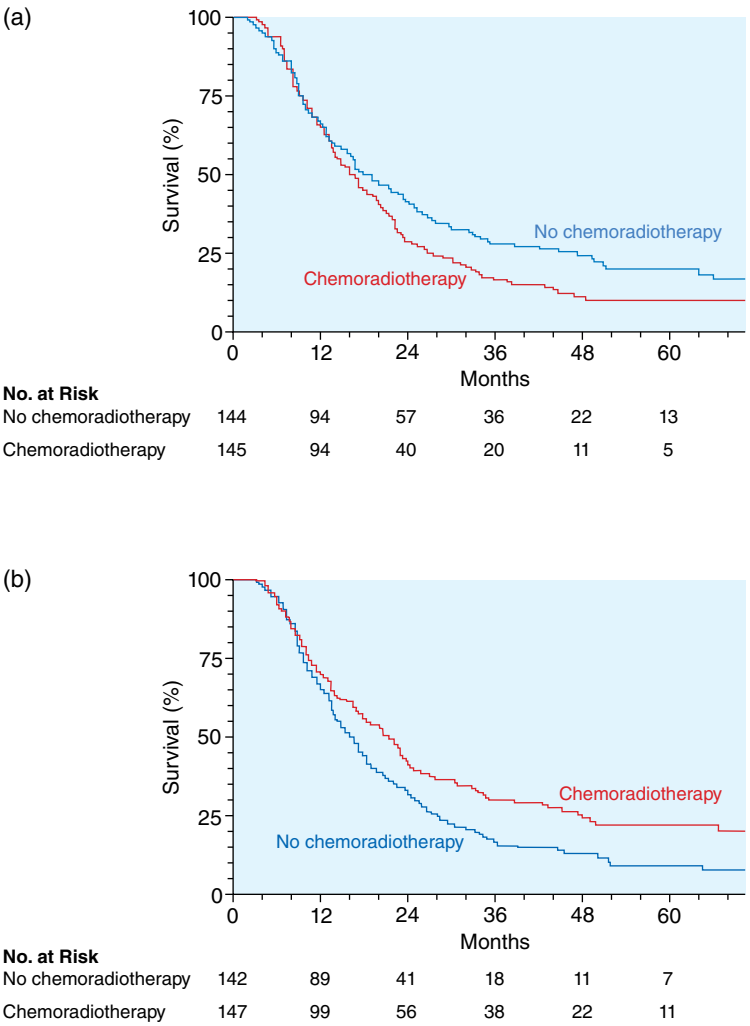
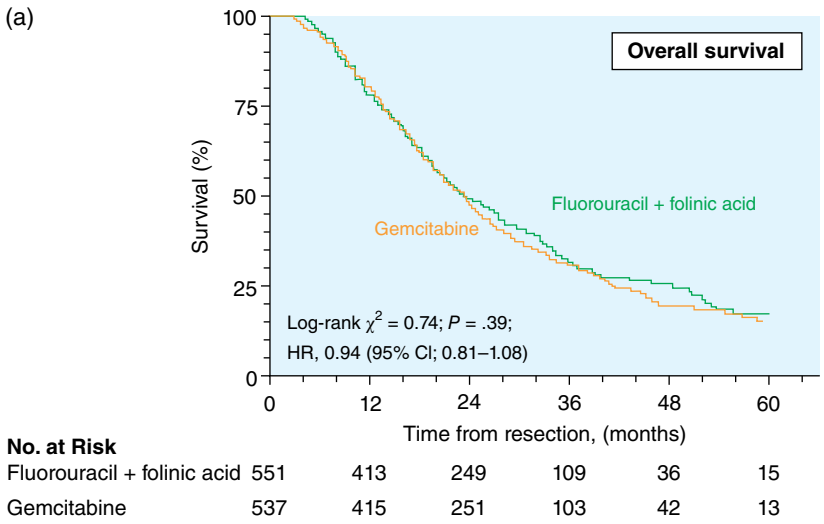



**Figure 113.1** Overall survival from the ESPAC-1 trial [11]. *Source:* New England Journal of Medicine, Neoptolemus JP et al., A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer, Vol. 350. Copyright © 2004 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

gemcitabine in the adjuvant setting. This noninferiority study randomized 385 Japanese patients, and found overall survival at 2 years of 70% for the S-1 group compared with 53% for the gemcitabine group, with a 5-year overall survival of 24.4% in the gemcitabine group and 44.1% in the S-1 group ($P < 0.0001$ for noninferiority, $P < 0.0001$ for superiority) [15]. While these results are impressive, it remains unclear whether they are applicable to a non-Japanese population with different S-1 metabolism where efficacy is lower and toxicity higher. In addition, randomized patients were a prognostically favorable group with only 13% having an R1 resection and only 21% having a raised CA 19-9. As such, the results may have limited applicability in a real-world Western population.

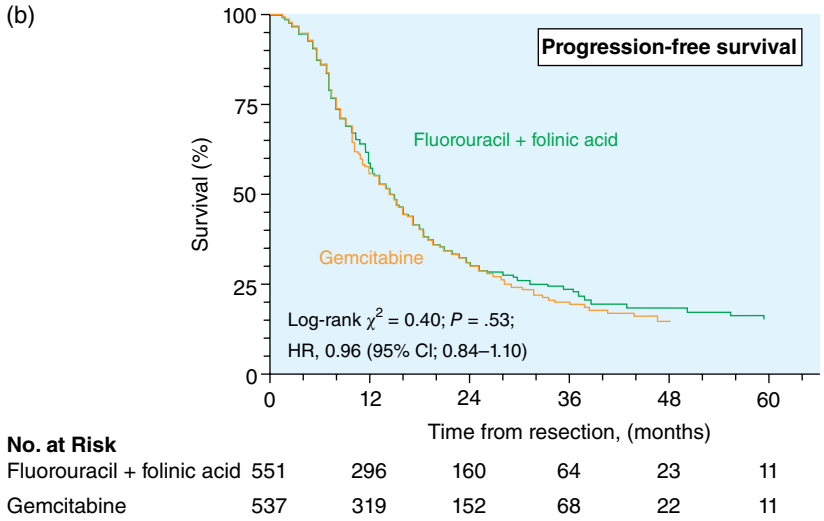
Combination therapy with gemcitabine and capecitabine has become increasingly common in the palliative treatment of metastatic pancreatic cancer, with good response rates and acceptable toxicity [16,17]. The ESPAC-4 study therefore assessed whether these improved response rates translated to improved overall survival in the adjuvant setting. A total of 732 patients were randomized to six cycles of intravenous gemcitabine with or without oral capecitabine. Median survival was slightly longer in the combination therapy arm (25.5 vs. 28.0 months, $P = 0.03$). However, the 5-year survival rates were considerably higher for patients receiving dual therapy rather than gemcitabine alone (28.8% vs. 16.3%) (see Fig. 113.3) [18]. Severe toxicities were similar, and both regimens were well tolerated. It is also important to note that ESPAC-4 recruited a wider variety of patients than other studies (see Table 113.2). For example, patients with raised postoperative CA 19-9 and without immediate preadjuvant imaging were eligible for inclusion. These findings suggest that combination therapy with gemcitabine/capecitabine should now be considered standard of care after curative resection, with a proven benefit in real-world patient population.

The overwhelming evidence supporting adjuvant therapy is reflected in the recent 2016 American Society of




**No. at Risk**

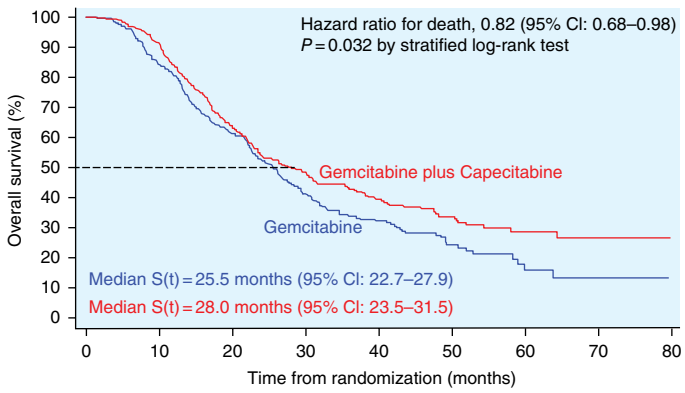
| | | | | | | |
|---|---|---|---|---|---|---|
| Fluorouracil + folinic acid | 551 | 413 | 249 | 109 | 36 | 15 |
| Gemcitabine | 537 | 415 | 251 | 103 | 42 | 13 |




**No. at Risk**

| | | | | | | |
|---|---|---|---|---|---|---|
| Fluorouracil + folinic acid | 551 | 296 | 160 | 64 | 23 | 11 |
| Gemcitabine | 537 | 319 | 152 | 68 | 22 | 11 |

**Figure 113.2** Overall survival from the ESPAC-3 trial [14]. *Source:* Reproduced with permission from JAMA 2012;308(2), Fig. 2. Copyright © 2012 American Medical Association. All rights reserved.




**No. at Risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Gem | 366 | 302 | 207 | 109 | 61 | 27 | 9 | 3 | 0 |
| GemCap | 364 | 328 | 219 | 139 | 83 | 50 | 19 | 10 | 1 |

**Figure 113.3** Kaplan-Meier plot for overall survival in the ESPAC-4 trial.

**Table 113.2** Comparison of patient populations in JASPAC-01, CONKO-01, and ESPAC-4 trials.

| Prognostic factor | JASPAC-01 [15] (*n* = 377) | CONKO-01 [12] (*n* = 368) | ESPAC-4 [18] (*n* = 730) |
|---|---|---|---|
| WHO PS 0 | 68.7% | – | 42.2% |
| PS 1 | 31.3% | – | 54.9% |
| PS 2 | 0.0% | – | 2.9% |
| Grade 3 | – | 35.9% | 40.4% |
| LN positive | 62.9% | 67.9% | 80.4% |
| R1 positive | 13.0% | 16.6% | 60.3% |
| Postop CA 19-9 > 37 KU/L | 21.0% | – | 31.7% |
| Postop CA 19-9 > 92.5 KU/L | – | 0.0% | 17.1% |

Clinical Oncology (ASCO) Clinical Practice Guidelines for Potentially Curable Pancreatic Cancer [19], which recommend that all patients with resected pancreatic cancer should have 6 months of adjuvant chemotherapy with gemcitabine and capecitabine and either gemcitabine or fluorouracil plus folinic acid if patients are only suitable for mono-chemotherapy.

## Adjuvant Chemoradiotherapy

The data presented from the CONKO-001, JASPAC-1, and ESPAC-1, -3, and -4 trials provide compelling evidence to support systemic chemotherapy for 6 months after surgical resection as standard of care. The role of additional adjuvant chemoradiotherapy remains less clear, with no randomized trial providing clear benefit in terms of overall survival.

Although the previously described GITSG and EORTC 40891 trials provide some evidence, these trials do not allow direct comparison of chemotherapy versus chemoradiotherapy. Concerns about the long-term survival benefit of additional adjuvant radiotherapy are supported by retrospective reviews and meta-analyses. Merchant et al. [20] performed a pooled analysis of 646 patients from seven high-volume centers, 299 of whom were treated with surgery followed by chemoradiation and 347 with surgery alone. Median overall survival was 20 months for the adjuvant chemoradiation arm, versus 14.5 months for surgery alone ($P = 0.001$). The investigators found a significant survival advantage only in patients with lymph node-positive disease. Somewhat surprisingly, the authors also identified reduced disease-free survival in patients with lymph node-negative disease who received adjuvant chemoradiotherapy (14.5 months vs. 18.6 months, $P = 0.034$). These findings were further supported by another large retrospective series that compared 1,130 patients treated with surgery, with or without adjuvant chemotherapy or chemoradiotherapy at eight major US centers over 10 years. They identified reduced local recurrence after chemoradiation, but no impact on distant recurrences (in contrast to systemic chemotherapy) and therefore no impact on overall survival [21].

The first attempt to directly compare systemic chemotherapy with systemic chemotherapy and additional radiotherapy was the 2010 EORTC 40013 study, which randomized 90 patients to four cycles of gemcitabine versus gemcitabine with concurrent chemoradiation (50.4 Gy). Median overall survival was the same for both arms at 24 months, with comparable toxicity profiles. Eighty-seven percent of patients treated with gemcitabine alone completed all planned treatments, compared to 73% undergoing combination therapy [22]. Supporting previous retrospective series, local recurrence as site of first progression was 24% for the chemotherapy arm compared with 11% in the chemoradiotherapy arm. However, this did not translate into a long-term survival benefit.

In 2005, Stocken et al. [23] performed a meta-analysis assessing the impact of adjuvant chemoradiation and chemotherapy on survival and included patient level data from five randomized trials of adjuvant therapy. Individual patient data was available in four out of the five studies (94% of patients). Analysis demonstrated a 25% reduction in the risk of death (HR 0.75; 95% CI: 0.64–0.90, $P = 0.001$) with chemotherapy compared to no chemotherapy but no significant difference between chemoradiation and no chemoradiation (HR 1.09; 95% CI: 0.89–1.32, $P = 0.43$). On subgroup analysis, chemoradiation was more effective and chemotherapy less effective in patients with positive resection margin.

In 2013, Liao et al. [24] performed an updated meta-analysis of adjuvant 5-FU versus gemcitabine versus

chemoradiation with 5-FU or gemcitabine, and showed that chemotherapy alone with either 5-FU (HR 0.65; 95% CI: 0.49–0.89) or gemcitabine (HR 0.59; 95% CI: 0.41–0.83) was associated with significant overall survival benefit. By contrast, adjuvant chemoradiation was associated with worse overall survival when compared with 5-FU (HR 1.69; 95% CI: 1.12–2.54) and gemcitabine (HR 1.86; 95% CI: 10.4–3.23) as monotherapy with significant additional toxicity.

The role of adjuvant chemoradiotherapy therefore remains unclear, with benefit seeming to be limited to patients with margin positive disease where it may have a role in reducing local recurrence.

## Future Directions in Adjuvant Therapy

Increasingly, biologically active palliative regimens are now being considered as adjuvant therapies. FOLFIRINOX (5-FU, leucovorin, irinotecan, oxaliplatin) demonstrated an increase in overall survival compared to single agent gemcitabine (6.8 months to 11.1 months) in the metastatic setting [25]. The same group has now developed the PRODIGE 24/ACCORD 24 trial comparing gemcitabine monotherapy with modified FOLFIRINOX (without infusional 5-FU) following resection of pancreatic adenocarcinoma. This regimen has been associated with significant toxicities, and so trial entry is only open to patients with good performance status who have fully recovered from surgery. With a target recruitment of 490 patients, the trial is due to mature in 2020.

Nab-paclitaxel (albumin-bound paclitaxel) has demonstrated synergistic clinical activity when delivered alongside gemcitabine [26], and so the 2013 MPACT trial compared nab-paclitaxel/gemcitabine with gemcitabine alone in the palliative setting with an improvement in median survival from 6.7 months in the gemcitabine monotherapy group to 8.5 months in the nab-paclitaxel/gemcitabine group (HR 0.72; 95% CI: 0.62–0.83, $P < 0.001$) [27]. The US-led ABI-007-PANC-003 trial aims to compare the same regimen in the adjuvant setting, with a trial reporting date somewhere in 2020.

As well as attempting to use increasingly active regimens, targeted adjuvant therapies offer great appeal. Whole genome sequencing of large numbers of tumors has led to the identification of frequently mutated genes in pancreatic cancer [28], as well as identifying distinct molecular subtypes [29]. Unfortunately, the four most commonly mutated genes (*KRAS*, *CDKN3A*, *TP53*, and *SMAD4*) are not currently actionable, with druggable mutations occurring with much lower frequencies. Although the reducing cost of whole-genome sequencing means that precision therapy based on identifiable and actionable mutations on a case-by-case basis is a possibility, its mainstream use remains some way in the future.

To overcome some of these limitations, targeted agents with wider mechanisms of action have been investigated. Erlotinib is an oral tyrosine kinase inhibitor that has demonstrated improvements in overall survival when added to gemcitabine in the palliative setting [30]. CONKO-005 therefore randomized 436 resected patients to receive gemcitabine or gemcitabine/erlotinib. However, there was no difference in disease-free survival (11.6 months for both) or overall survival (24.6 months for combination therapy vs. 26.5 months for gemcitabine alone) [31].

Immunotherapy has shown great promise in other cancer types. Around 90% of pancreatic cancers contain an activating mutation in *KRAS*. A small phase II trial therefore assessed the use of a novel *KRAS* vaccine in the adjuvant treatment of 23 patients with resected pancreatic cancer. The researchers found an immune response in 85% of patients, with a median survival of 28 months [32]. However, these results have not been replicated by other groups [33].

During repeated rounds of DNA replication, the telomeric ends of DNA become progressively shortened leading to eventual cell death. Reactivation of telomerase, the telomere-repair enzyme, is a crucial event in oncogenic transformation and occurs in nearly all pancreatic cancers. The TELOVAC trial therefore compared gemcitabine/capecitabine with or without a novel telomerase peptide vaccine (GV1001) in the palliative setting, but demonstrated no significant survival benefit, suggesting further ways to enhance the immune response are required for clinical efficacy [34].

As well as trialing novel agents, there are increasing efforts to improve the patient stratification for existing treatments. Penetration of gemcitabine into dense pancreatic stroma appears to be highly variable. Koay et al. [35] demonstrated widely variable incorporation of gemcitabine into tumor DNA despite consistent serum pharmacokinetics. They also identified and validated a series of novel radiomic markers that would allow preoperative assessment of gemcitabine efficacy. However, this issue was further confused by the demonstration of widely varying incorporation of gemcitabine even within individual tumors [36], suggesting intratumoral heterogeneity may pose a problem not only for novel targeted agents but also for existing cytotoxic regimens.

Biomarkers to predict response to treatment also offer significant potential to improve the stratification of treatment. Human equilibrative nucleoside transporter 1 (hENT1) is a cell surface protein that bidirectionally transports gemcitabine across pancreatic cell membranes.

Greenhalf et al. [37] assessed hENT1 expression in 434 patients from the ESPAC-3 trial, of whom 176 received gemcitabine. Median survival for patients treated with gemcitabine was 17.1 months for those with low hENT1 expression compared to 26.2 months for those with high hENT1 expression ($P = 0.002$), suggesting hENT1 may predict response to gemcitabine chemotherapy. However, this finding was not confirmed in the prospective LEAP (Low hENT1 Adenocarcinoma of the Pancreas) trial in patients with metastatic disease [38] where there was no difference in overall survival following treatment with gemcitabine in the hENT1 high and low groups. However, hENT1 status was determined from metastatic tissue and so inherent differences between the patient population in this trial and the adjuvant cohort cannot be excluded.

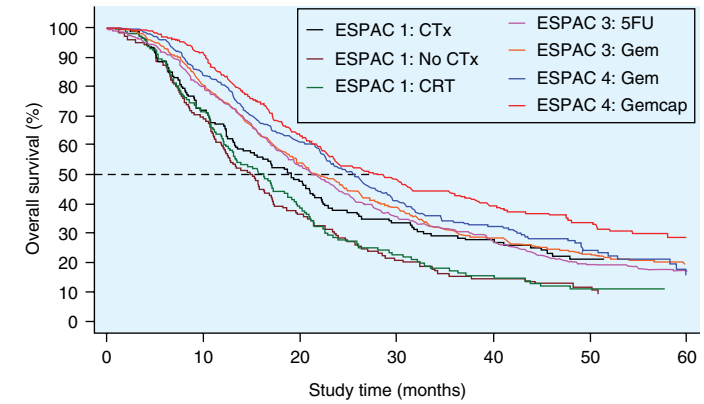
The GATA6 transcription factor has also been proposed as a predictive biomarker of response to adjuvant therapy. Martinelli et al. [39] assessed the expression of GATA6 in 313 patients treated with adjuvant 5-FU/leucovorin or gemcitabine, and found that in the 5-FU group patients with high GATA6 expression survived significantly longer than those with low expression. This finding did not hold true in the gemcitabine arm, suggesting GATA6 may be a predictive biomarker for response to adjuvant 5-FU.

## Timing and Duration of Adjuvant Therapy

The optimal timing of adjuvant therapy after surgery remains unclear. Patients need sufficient time to recover from the physiologic insult, whilst treatment needs to commence soon enough to prevent the establishment of micrometastatic deposits. Valle et al. [40] assessed the optimal timing to start of therapy in the ESPAC-3 trial. A total of 985 patients were included, of whom 486 received gemcitabine, 675 (68.5%) received all six planned cycles of adjuvant therapy, and 457 (46.4%) started treatment within 8 weeks of surgery. Overall survival was much better in those who received the full six cycles of treatment (28 months vs. 14.6 months) (HR 0.516; 95% CI: 0.443–0.601, $P < 0.001$) whilst time to start of treatment did not predict overall survival (HR 0.985; 95% CI: 0.956–1.015, $P = 0.99$). However, for the subgroup of patients who did not complete all six cycles of treatment the time to initiation of therapy was important, with overall survival better in those who waited more than 8 weeks (HR 0.92; 95% CI: 0.86–0.97, $P = 0.004$). These findings suggest that completion of a full course of treatment is more important than early initiation, and suggest that allowing patients to fully recover from surgery may lead to better tolerability of therapy and an increased likelihood of completing treatment.

## Conclusions

The last 20 years have seen a paradigm shift in the management of pancreatic cancer. The routine use of adjuvant treatment has led to significant increases in median and 5-year overall survival. The recently reported results of ESPAC-4 are likely to define 6 months of treatment with combination gemcitabine/capecitabine as standard of care, with growing recognition of the importance of patients receiving the full planned treatment course (see Fig. 113.4).




| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| E1–CTx | 149 | 105 | 68 | 46 | 34 | 19 | 16 |
| E1–No CTx | 143 | 99 | 50 | 28 | 17 | 10 | 8 |
| E1–CRT | 145 | 103 | 54 | 30 | 19 | 10 | 8 |
| E3–Gem | 539 | 422 | 283 | 187 | 126 | 93 | 64 |
| E3–5FU | 551 | 430 | 283 | 180 | 131 | 81 | 56 |
| E4–Gem | 366 | 302 | 207 | 109 | 61 | 27 | 9 |
| E4–GemCap | 364 | 328 | 219 | 139 | 83 | 50 | 19 |

**Figure 113.4** Kaplan-Meier plots for overall survival in the ESPAC-1 (E1), ESPAC-3 (E3), and ESPAC-4 (E4) trials.

Future directions for adjuvant therapy include the use of more active regimens, as well as better stratification of patients to existing therapies. Novel agents have shown some promise in the palliative setting, but this has not translated to improved outcomes after resection. Immunotherapy and targeted therapies offer great promise, but many technical challenges remain before these approaches enter routine clinical practice.

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# Immunotherapy for Pancreatic Cancer

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## Introduction

Pancreatic ductal adenocarcinoma (PDAC) comprises only 3% of all cancers diagnosed in the United States, yet it is the third leading cause of cancer-related deaths in men and women [1]. The only current chance of cure remains surgical resection but <30% of patients who present with PDAC are candidates for curative resection. The majority of those who undergo surgical resection will ultimately relapse and die from their disease [1]. While cytotoxic chemotherapy has been shown to improve survival in those with metastatic disease [2,3], the 5-year survival rate for these patients remains dismally poor. PDAC is notoriously resistant to chemotherapy and radiation therapy but there have been positive advances made by harnessing the immune system to help combat this disease.

## Immunology of Pancreatic Cancer

The tumor microenvironment (TME) of pancreatic tumors is renowned for its stromal density and heterogeneity, containing numerous cellular components including fibroblasts, pancreatic stellate cells, blood vessels, and immune cells [4].

The immune system is classically activated in response to foreign antigens, whereas cancer cells can express tumor-associated antigens as well as neoantigens that occur in response to the tumor's continuously changing molecular composition. In both cases, the immune system can be activated to recognize these tumor antigens. However, tumor cells are more likely to interact with the immune system and lose antigen recognition through the process of immunoediting [5]. This dynamic process consists of three phases: elimination, where the immune system successfully destroys the tumor cell; equilibrium, where the system controls tumor growth but does not destroy the tumor cell; and escape, where the tumor cell overcomes the immune system and progresses to a clinically detectable disease state.

The innate immune system consists of immune cells (e.g., macrophages, granulocytes, dendritic cells) that serve as "first responders" of the immune response and are attracted to regions of inflammation or infection within minutes or hours. The adaptive immune system comprises B- and T-cell lymphocytes which respond to foreign invasion of cells typically by infectious agents. Professional antigen presenting cells (APC, e.g. dendritic cells and macrophages) are alerted and take up foreign proteins for processing and triggering B- and T-cell responses. B lymphocytes are responsible for mounting a long-term response to a foreign antigen by producing an antibody-secreting effector cell. T lymphocytes, categorized according to cell surface markers, and the cytokines/chemokines they produce, have many distinct effector functions. CTL (cytotoxic T lymphocytes) express CD8 and kill cells by secreting molecules that induce apoptosis. When an APC expresses an antigen on major histocompatibility class II (MHCII), a $CD4^+$ T cell (helper T cell, Th) becomes activated and differentiates into distinct effector subtypes mediating the immune response through the secretion of specific cytokines (Fig. 114.1). A specific subtype of $CD4^+$ T cells, Treg, suppress T-cell activation thereby protecting the body from autoimmune reactions. $CD4^+$ T cells comprise the majority of T cells in PDAC and are associated with metastasis and negatively associated with survival [6,7].

The protective role of the immune system in cancer is demonstrated by the observation that increased amounts

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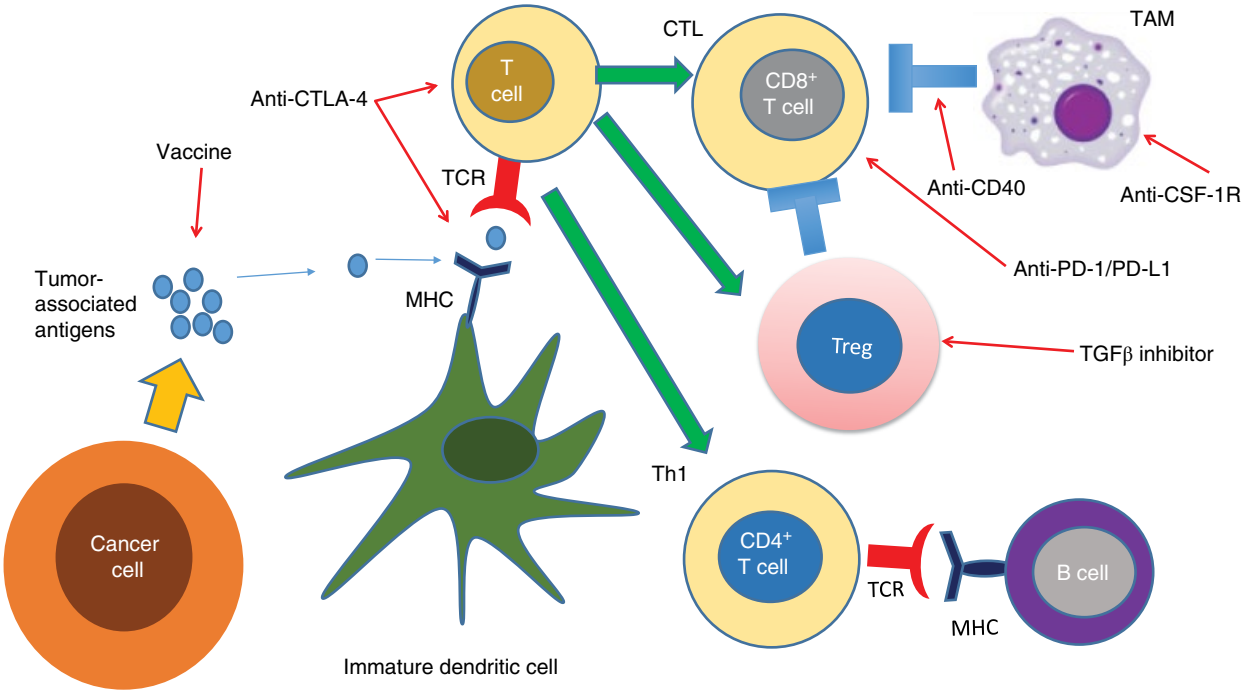


**Figure 114.1** Components of immunotherapy in pancreatic cancer. Tumor cells express specific antigens which can activate antigen-presenting cells by binding to MHC molecules on their cell surface which in turn bind to T-cell receptors (TCR) on T cells. Anti-CTLA-4 therapy directly targets this interaction. This results in T-cell activation and differentiation into various T-cell subtypes including CD8+ cytotoxic T lymphocytes (CTL), regulatory T cells (Treg), and Th1 (T helper cells). CTL activity can be eliminated by tumor-associated macrophages (TAM) resulting in tumor progression. Pharmacologic inhibition of CSF-1R (colony-stimulating factor-1 receptor) and CD40 can reduce this effect. Treg can also suppress CTL, an effect which can be negated by targeting TGFβ (transforming growth factor β). Th1 cells induce B-cell activation, which results in antibody production and activation of humoral immunity.

of tumor-infiltrating lymphocytes (TIL) correlate favorably with survival in many tumor types including melanoma and PDAC [8,9]. The complexity of the immune system results in certain immune components promoting immune suppression such as myeloid-derived suppressor cells (MDSC) and tumor-derived macrophages (TAM) [10,11]. Preclinical models, which faithfully recapitulate the progression of precursor pancreatic lesions in their development from preinvasive PanIN (pancreatic intraepithelial neoplasia) to invasive PDAC, show that immunosuppressive cells dominate the TME, even during the early stages of tumor development [12]. These cells, which include MDSC, Treg, and TAM, result in reduced T-cell development and infiltration (specifically effector T cells), which indirectly drives tumor promotion. This has led to efforts to directly target these immunosuppressive cells, for example targeting colony-stimulating factor 1 (CSF-1R), which regulates the differentiation and survival of TAM [13].

The procarcinogenic inflammatory response found in most tumors is highly regulated by the progressive genetic alterations that occur with cancer development and progression. For example, the *KRAS* proto-oncogene is mutationally activated in 90% of PDAC and results in constitutive activation of *KRAS* and its downstream signaling pathways. *KRAS* activation results in driving cancer cell migration and metastasis [14]. Preclinical models have shown that *KRAS* inactivation results in the high expression of granulocyte-macrophage colony-stimulating factor (GM-CSF) [15,16]. GM-CSF has been shown to result in the accumulation of Gr-1$^+$ CD11b$^+$ cells (MDSC) by inducing the proliferation and differentiation of precursor c-kit$^+$ stem cells, which leads to the suppression of CD8$^+$ T-cell-mediated antitumor immune responses thereby permitting tumor growth.

T cells express a number of stimulatory and inhibitory signals depending on the type of inflammation they encounter. Whether a T cell becomes activated or deactivated depends on the sum of the signals that are engaged. Two T-cell inhibitory signals have already been shown to have clinical relevance in cancer. CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) acts as an immune checkpoint striving to maintain immune homeostasis by downregulating T-cell function once CD28 binds to its ligand B7, therefore inducing T-cell cycle arrest (Fig. 114.2) [17]. Due to its role as a negative

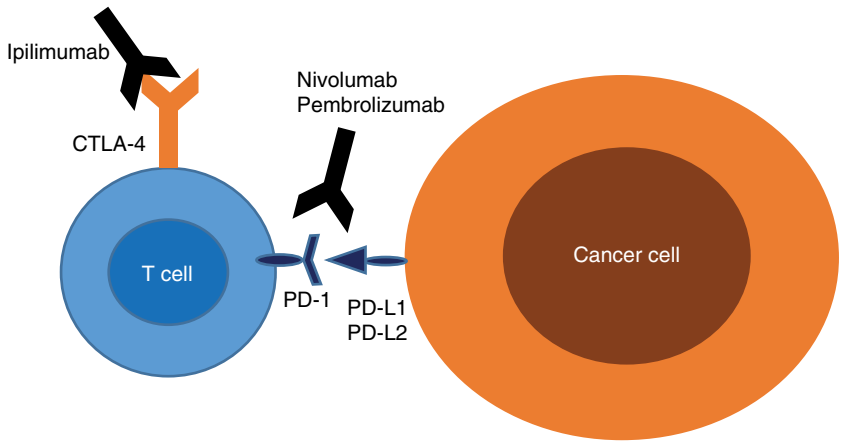


**Figure 114.2** Checkpoint inhibitors in pancreatic cancer. T cells express CTLA-4 (cytotoxic T lymphocyte associated-4) antigens on their cell surfaces which downregulate T-cell function. Anti-CTLA-4 antibodies (e.g., ipilimumab) can bind to CTLA-4 receptors on T cells and reverse immunosuppressive T-cell functions. PD-1 (programmed death-1) receptors on T cells bind to PD-L1 and PD-L2 ligands on cancer cell surfaces. Anti-PD-1 antibodies bind to PD-1 receptors preventing interactions with its ligands.

regulator of immunity, it was the first checkpoint to be targeted after preclinical models showed that antibody blockade of CTLA-4 leads to antitumor immunity [18,19]. PD-1 (programmed death-1) is also an immune checkpoint which negatively regulates T-cell activity when it interacts with its ligands, PD-L1 and PD-L2 [20]. PD-1 is expressed on many immune cells and inhibits effector T-cell function [21]. Antagonist antibodies that inhibit these molecules have recently become standard of care for cancers that naturally attract effector T cells into their tumor. However, PDAC patients have failed to respond to these single agent immune modulators. However, combinatorial immune-based approaches are currently under development to target multiple immune suppressive pathways and are showing promise in PDAC patients.

## Therapeutic Vaccines

Cancer vaccines are used to generate a humoral/cellular immune response to stimulate the immune system as a defense mechanism against tumor cells. Therapeutic vaccines deliver specific pancreatic tumor antigens systemically with the aim of stimulating the patient's immune system to recognize minor differences in the antigen that exists between normal and tumor cells. These vaccines are generally well tolerated because of their antigen specificity. Therapeutic vaccines can be broadly categorized into whole-cell vaccines and antigen-specific vaccines.

### Whole-Cell Vaccines

Polyvalent vaccines are derived from whole cells or cell lysates and have the capacity to allow the targeting of multiple antigens.

The allogeneic whole cell pancreatic tumor vaccine GVAX developed by Jaffee et al. [22] was derived from two human pancreatic cancer cell lines stably transfected to produce the human cytokine GM-CSF. GM-CSF has the capacity to overcome tumor-induced suppression and promote the recruitment and maturation of APC resulting in upregulation of MHC class II co-stimulatory molecules and cytokine production. GMC-CSF-producing tumor cells are subsequently irradiated and administered to patients intradermally. The phase I study comprised 14 patients with Stages I–III pancreatic cancer who received multiple administrations of vaccine with concentrations ranging from $1–50 \times 10^7$ cells after surgical resection and standard adjuvant therapy. This study found that three patients who received $\geq 10 \times 10^7$ vaccine cells developed increased delayed-type hypersensitivity (DTH) responses and that these patients remained disease free for over 10 years [22]. GVAX was well tolerated without any local or systemic dose-limiting toxicities observed. The most common adverse effects were self-limiting skin reactions (erythema, induration, pain) at the sites of immunization.

The phase II study involved administering $5 \times 10^8$ GM-CSF-secreting cells to 60 patients with resected PDAC [23]. Patients received five doses of vaccine in addition to 5-FU-based chemotherapy. The median disease-free survival was 17.3 months (95% CI: 14.6–22.8) and the median survival was 24.8 months (95% CI: 21.1–31.6). The addition of immunotherapy to chemotherapy did not result in additional toxicities and the development of mesothelin-specific $CD8^+$ T cells in HLA-$A1^+$ and HLA-$A2^+$ patients was correlated with improved disease-free survival.

Based on preclinical data that giving cyclophosphamide (Cy) prior to immunotherapy could enhance the intended immune responses by inhibiting $CD4^+/CD25^+$ Treg cells [24–27], Laheru et al. designed a clinical study comparing the effects of administering Cy prior to GVAX vaccine in patients with advanced PDAC [28]. Fifty patients received Cy one day prior to the vaccine or the vaccine alone and minimal toxicities were observed in

both arms. Survival data from this nonrandomized study suggested that adding Cy prolonged median survival (130 vs. 69 days). This study also found that mesothelin-specific immune responses were detected in this cohort of patients with advanced disease.

PDAC has traditionally been regarded as a nonimmunogenic cancer compared with melanoma and lung cancer. A neoadjuvant and adjuvant clinical trial was designed to test whether GVAX ± Cy could convert the relatively nonimmunogenic TME of PDAC into an immunogenic tumor with infiltrating effector lymphocytes [29]. Two weeks prior to surgical resection, 39 patients were randomized to receive either GVAX alone, GVAX preceded by a single intravenous Cy dose, or GVAX with daily Cy on alternate weeks. Examination of the resected PDA showed that vaccines induced intratumoral tertiary lymphoid aggregates in 85% of patients. Further analysis of these aggregates showed that they consisted of organized T- and B-cell zones with predominance of $CD68^+$ and $CD163^+$ cells indicating that they represented adaptive immunity. Specific gene expression signatures were found in these intratumoral aggregates including those showing a suppressed Treg pathway and enhanced Th17 pathway, which were associated with improved survival. Consistent with prior studies, there was an association between those who developed an immune response/lymphoid aggregates and improved survival. This study also showed that the expression of immune checkpoint signaling, such as PD-1 and PD-L1, was induced by vaccination, suggesting that GVAX therapy could play a role in priming patients to combat the lack of response to anti-PD-1 therapies seen in PDAC. Current studies are testing the combination of vaccine to induce PDAC-specific immunity together with immune checkpoint antibodies that unleash the full potential of the vaccine-induced immune response.

Algenpantucel-L is the other whole-cell vaccine that has had promising clinical data in PDAC. It consists of two live, irradiated human PDAC cell lines that express murine α-1, 3-galactosyltransferase, an enzyme responsible for the synthesis of α-galactosylated (α-gal) epitopes on cell surface proteins. Binding of anti-α-gal antibodies to α-gal activates the classic complement pathway, and noncomplement fixing antibodies also induce cell-mediated cytotoxicity to generate hyperacute rejection of allografts in humans. Hardacre et al. conducted a phase II study of the algenpantucel-L vaccine in addition to chemoradiation therapy in 70 patients in the adjuvant setting after resected PDAC [30]. The 12-month disease-free survival rate and 12-month overall survival rate were 62% and 86%, respectively. Toxicities were limited to injection site reactions and fatigue. These results have led to a phase III clinical trial for borderline resectable or locally advanced unresectable PDAC, which has completed accrual (NCT01836432).

## Antigen-Specific Vaccines

Antigen-specific vaccines take advantage of inherent defects in the genetics of PDA and translate these into functional targets of immunotherapy. As *KRAS* mutations are universal in PDAC and are known for their role in driving the PDAC development [31,32], they are an obvious target for immunotherapy. Early studies involving administering synthetic KRAS peptides to patients with unresectable PDAC showed that it was safe and induced an immune response in two out of five patients [33]. Another phase I/II trial coadministered mutant KRAS peptides with GM-CSF in a study involving 48 patients with PDAC [34]. Immune responses were elicited in 58% of patients and in those with advanced disease, a peptide-specific immune response was associated with improved survival. A further study evaluated the administration of patient-specific *KRAS* mutations (codon 12) with a 21-mer epitope containing the patient's mutation and GM-CSF in patients with resected PDAC [32]. They demonstrated median recurrence-free survival and overall survival of 8.6 months and 20.3 months, respectively. However, there were low rates of immunogenicity with a single patient developing a detectable mutation-specific immune response and 13% of patients developing a nonspecific DTH.

Interest first arose in mesothelin, a tumor-associated antigen overexpressed in most PDAC, as a target for immunotherapy in PDAC based on the observation that mesothelin-specific responses were associated with improved disease-free survival after GVAX therapy [28]. This led to the development of CRS-207, a recombinant live-attenuated, double-deleted strain of *Listeria monocytogenes* (LADD-Lm), which was engineered to secrete mesothelin into the cytosol of infected APC, which ultimately are processed and presented as major histocompatibility complex molecules. The phase I study involving CRS-207 demonstrated that multiple administrations were well tolerated and sufficient to induce mesothelin-specific T-cell responses [35]. Preclinical data suggested that a heterologous prime/boost strategy combining GVAX and LADD Lm-expressing mesothelin induced a synergistic T-cell induction and antitumor effect. A phase II study randomized patients with previously treated metastatic PDAC to receive Cy/GVAX followed by CRS-207 versus Cy/GVAX alone [36]. Overall survival for all patients was higher in the Cy/GVAX + CRS-207 group (6.1 vs. 3.9 months). For those patients who received at least three doses, overall survival for the Cy/GVAX + CRS-207 group was 9.7 months compared with 4.6 months for the Cy/GVAX-alone group. Enhanced mesothelin-specific $CD8^+$ T-cell responses were associated with longer survival in both treatment groups. Multicenter follow-up studies are ongoing to determine the survival benefit from vaccine alone and from vaccine given with the immune modulating agent nivolumab.

Patients with PDAC receiving GVAX who developed antibody responses to AnnexinA2, a novel pancreatic cancer antigen that may play a role in early metastasis, were observed to have prolonged disease-free survival [37–39]. A listeria-based vaccine targeting AnnexinA2 is currently in development.

### Neoantigen-Based Vaccines

Somatic gene mutations occurring in individual tumors can generate novel epitopes or "neoepitopes" that serve as targets for immune responses [40]. The technology to recognize individual neoepitopes now exists, which can scan the entire cancer exome (coding regions), but for neoepitopes to be functional, their mutant peptides must be processed by MHC molecules and T cells must recognize this peptide-MHC complex. An added complexity lies in the fact that these epitopes must have been tolerated by the immune system to permit the tumor to grow. This tolerance appears to be mediated by immune checkpoints, for example PD-L1 [41]. It is unsurprising that these tumor types are typically sensitive to immune checkpoint inhibition since they induce effector T-cell infiltration that resembles untreated melanomas [42].

Unlike tumors typically associated with high rates of mutations, for example melanoma, PDAC characteristically harbors fewer mutations although neoepitopes do exist [43]. Notwithstanding the challenges of identifying tumor neoantigens suitable for immunization, determining the number of neoantigens required for targeting and the challenges of producing personalized vaccines, future efforts should concentrate on developing neoantigen-based vaccines [44].

## Non-Vaccine Immunomodulators Used in Pancreatic Cancer

### CTLA-4

Ipilimumab is a fully human IgG1κ antibody that recognizes CTLA-4 and blocks its interaction with B7-1 and B7-2 on APC. This results in prolonged T-cell activation and amplification of T-cell-mediated immunity [45]. Ipilimumab has received FDA approval for use in Stages III–IV melanoma due to improved recurrence-free survival (adjuvant setting) [46] and overall survival (metastatic setting) [47].

A phase II study evaluated single-agent ipilimumab for patients with locally advanced or metastatic PDAC [48]. Twenty-seven patients received ipilimumab 3 mg/kg every 3 weeks for a maximum of eight doses. There were no responders by RECIST (response evaluation criteria in solid tumors criteria) although one subject experienced a delayed response after initially being diagnosed with progressive disease. The concept of pseudoprogression is a recognized phenomenon in immunotherapy whereby tumors may initially increase in size during treatment with immune checkpoint inhibitors only to produce delayed clinical responses which may be durable [49]. This phenomenon has prompted the inclusion of immune-related response criteria as a means of objectively assessing tumor response to immunotherapy [50].

### PD-1

A number of FDA-approved antibodies disrupting the PD-1 axis have been developed including pembrolizumab and nivolumab. These drugs target PD-1 and block its interaction with PD-L1 and PD-L2. They demonstrated durable response rates in phase I studies including patients with melanoma, lung cancer, and renal cell cancer [51,52]. The phase I study of pembrolizumab included a single patient with PDAC and involved a dose escalation study up to 10 mg/kg every 2 weeks [53]. Pembrolizumab was well tolerated with no dose-limiting toxicities observed. Two patients experienced complete responses (melanoma, merkel cell carcinoma) with the majority of patients experiencing disease stability. However, in contrast to other tumors, PDAC is not associated with high density of tumor-infiltrating lymphocytes, the principal targets of PD-1 therapy [54]. Although immune checkpoint inhibition is associated with impressive durable response rates in other tumor types, there is no current method to reliably predict response. PD-L1 expression measured by immunohistochemistry has been postulated as a potential predictive biomarker but this is limited by the lack of standardized assessment of PD-L1 expression by immunohistochemistry [55,56].

Another pharmacologic approach to targeting the PD-1 axis involves targeting either of the ligands, PD-L1 and PD-L2. PD-L1 is expressed on the cell surface of many tumor cells and is likely to be involved in tumor cell immune evasion [21]. There are several commercially available monoclonal antibodies targeting PD-L1 which have entered clinical trials. Brahmer et al. evaluated BMS-986559 in a phase I study involving patients with advanced cancer and found that it induced durable tumor regression (objective response rate 6–17%) and prolonged disease stabilization (12–41% at 24 weeks) [57]. MEDI4736 (AstraZeneca) has been tested in a phase I study (NCT01693562) where it has been reported to be safe and has preliminary evidence of clinical activity. Another antibody, MPDL3280A has shown response rates of 36% with patients with melanomas having the highest response rates [58].

## Targeting Tumor-Associated Macrophages

Tumor-associated macrophages (TAM) alter their functional subtypes based on signals in the TME in an attempt to maintain immune homeostasis [59]. Higher density of TAM in pancreatic tumors is associated with worse survival due to their tumor-promoting effects [60]. The cell surface molecule CD40 is expressed on numerous immune cells, for example, B cells and dendritic cells, and its signaling results in activation of antigen-presenting cells and T cells [61]. CD40 activation using agonist antibodies can reverse immune suppression and induce tumoricidal CD40-activated TAM [62]. Antibody blockade of CSF-1 (colony-stimulating factor-1) and its receptor CSF-1R expressed on macrophages, has the capacity to improve antitumor T-cell responses and improve responses to checkpoint inhibitor therapy [63,64].

## Combination Immunotherapy

Current efforts focus on trying to overcome the inherent resistance to checkpoint inhibition in PDAC by combining immunotherapeutic strategies. Due to the relative absence of TIL, strategies that can induce further infiltration of effector T cells have the potential to prime the pancreatic TME to become more sensitive to immune checkpoint inhibition.

GVAX is known to have the capacity to induce the development of tertiary lymphoid structures in PDAC alongside the upregulation of the PD-1 pathway [29]. In addition, Soares et al. demonstrated that relatively nonimmunogenic tumors, such as PDAC, can be sensitized to PD-1 blockade with the aid of cancer vaccines [65]. Pancreatic tumors demonstrate weak membranous PD-L1 staining but treatment with GVAX significantly upregulates PD-L1 expression. They subsequently demonstrated that combination treatment with GVAX and PD-1 or PD-L1 blockade improved survival in a preclinical PDAC model with an increase in IFNγ-producing $CD8^+$ tumor-specific TIL indicating the recruitment of cytotoxic T cells to the TME.

These studies provided the rationale for combinatorial immunotherapy in PDAC. Le et al. reported the results of administering ipilimumab 10 mg/kg (anti-CTLA-4) with or without GVAX in patients with advanced PDAC [66]. During this phase II study, patients received induction doses every 3 weeks for a total of four doses followed by maintenance dosing every 12 weeks. Median overall survival was longer in those who received ipilimumab/GVAX compared with ipilimumab alone (5.7 vs. 3.6 months, $P = 0.072$). However, the rate of adverse events was high in both arms of this study (73% for ipilimumab, 80% for combination therapy) leading investigators to consider using alternate forms of immunotherapy.

A currently recruiting phase II trial (NCT02243371) is enrolling patients with previously treated metastatic PDAC to receive Cy/GVAX followed by nivolumab/CRS-207 versus vaccine alone. Combination immunotherapy is also being used outside of the metastatic setting in a study that involves Cy/GVAX with or without nivolumab in the neoadjuvant and adjuvant settings (NCT02451982).

## Conclusion

Pancreatic cancer has notoriously poor survival rates that are not dramatically improved with the use of traditional cytotoxic chemotherapy. Immunotherapy has the potential to produce durable remissions, which has been demonstrated in other tumor types. Cancer vaccines have shown the ability to reverse the relatively nonimmunogenic phenotype associated with PDAC and induce subsets of immune cells which can, in turn, be sensitized to immune checkpoint inhibition [29,65]. The future success of treating PDAC with immunotherapy likely lies in the use of combinatorial regimens. There is also potential for optimizing these regimens with alternative strategies including epigenetic modulation, radiation therapy, and T-cell transfer therapies, which have the added advantage of targeting other cell types in the TME. Given the marked heterogeneity in tumor genetics, there is also a need to discover biomarkers that can reliably predict which subsets of patients are likely to respond to immunotherapy.

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# Targeted Therapies for Pancreatic Cancer

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## Introduction

Despite a continuously evolving understanding of the tumorigenesis and biology of pancreatic ductal adenocarcinoma (PDAC), current therapeutic strategies have only achieved modest improvements in patient outcomes. With FOLFIRINOX and gemcitabine-based therapies being the main arbiters in our armamentarium, intrinsic and acquired chemoresistance has prevailed as the rule rather than the exception in this disease. However, novel therapeutic options have begun to gain traction through the development and understanding of new targeted therapies and modulation of the tumor microenvironment through immunotherapies. Recent large-scale efforts in next generation sequencing (NGS) technologies have allowed us to interrogate the genomic landscape of PDAC and with it, the ability to tailor therapeutic options while exploiting molecular abnormalities. In this chapter, we describe how these efforts have given us insight into how we may be able to begin applying these therapies with the hope of curtailing this aggressive disease.

## Genomic Landscape of PDAC

Significant efforts through the International Cancer Genome Consortium (ICGC) and The Cancer Genome Atlas (TCGA) have allowed us to make meaningful progress in deciphering the genomic landscape of PDAC. Among the earliest events in PDAC pathogenesis is the activating point mutation in the *KRAS* oncogene, which is present in more than 90% of these tumors. Progression of this disease then follows a sequential model of loss of function mutations in *TP53*, *SMAD4*, and *CDKN2A*. Aside from these four key oncogenic drivers, it is important to note several low-frequency mutations that have been identified that converge on core signaling tumorigenic pathways including regulation of apoptosis, DNA damage, cell cycle, *KRAS* signaling, invasion, and transforming growth factor-B signaling [1–4] (Fig. 115.1). By identifying and understanding how these altered genes and pathways can affect tumorigenesis, we begin to interrogate how targeting these key nodes can be exploited for therapeutic stratification.

## Molecular Subtypes Reveal Therapeutic Vulnerabilities

In 2015, Waddell and colleagues reported whole genome sequencing and copy number variation analysis of 100 PDAC which revealed the presence of chromosomal rearrangements leading to genetic aberrations [4]. By classifying these structural variation profiles, four subtypes were identified and termed as: stable, scattered, unstable, and locally rearranged. Those classified as unstable were found to have widespread structural rearrangements and were characterized as having high levels of genomic instability secondary to defective DNA repair pathways (e.g., due to *BRCA1*, *BRCA2*, *PALB2*, and possibly, *ATM* aberrations). Described as having a "BRCA mutation signature," these tumors are more likely to have high sensitivity to DNA damaging agents such as

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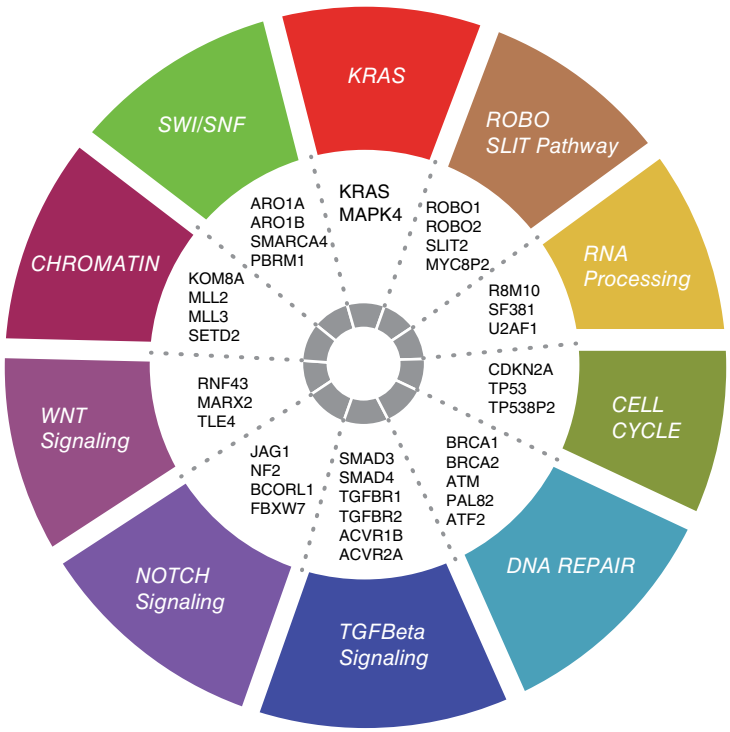


**Figure 115.1** Core signaling tumorigenic pathways in pancreatic cancer. Aberrant signaling pathways with associated genes enriched in pancreatic cancers based on NGS. Targeting these key nodes rather than specific gene mutations provides novel therapeutic strategies in treating pancreatic cancer. *Source:* Bailey et al. 2016 [2]. Reproduced with permission of Nature Publishing.

platinum-based therapies, mitomycin C, and PARP-1 (poly [ADP-ribose] polymerase 1) inhibitors. Another structural variant of interest is described as the locally rearranged subtype, which has the presence of intrachromosomal rearrangements leading to chromothripsis or breakage-fusion-bridge cycles, but more importantly contains regions of gains/amplifications in known oncogenes with therapeutic targets including *ERBB2*, *MET*, *CDK6*, *PIK3CA*, and *PIK3R3*.

In 2016, Bailey and colleagues performed the most comprehensive genomic analysis to date in PDAC involving 456 tumors, combining whole genome and exome sequencing, copy number analysis, and RNA expression profiles [2]. This identified four subtypes of PDAC based on differential gene expression signatures described as: squamous, pancreatic progenitor, immunogenic, and aberrantly differentiated endocrine exocrine (ADEX). Each subtype is associated with distinct histopathologic characteristics, with molecular features that infer different mechanisms of evolution. Among these, it is important to note the striking molecular similarities between subtypes across cancers rather than to subtypes within a single cancer. The implications of this now allow us to broaden our therapeutic options based on what has been effective in similar subtypes within other cancer types. For example, the squamous subtype of PDAC is more closely related to other so-called "basal" cancers seen in head and neck, bladder, lung, and triple negative breast cancers rather than the other three PDAC subtypes described; thus allowing us to expand clinical actionability based on these other tumor types.

Other identified actionable mutations include those in genes related to RNA splicing such as *SF3B1*, which is also found in myelodysplastic syndrome, breast and lung cancer, and infers potential targetability with the SF3b complex inhibitor spliceostatin A [5]. Aberrations in the oncogene *CCNE1*, involved in cell cycle regulation, were also found. *CCNE1* mutations in ovarian, breast, and lung cancers have dictated poor survival with resistance to platinum-based therapies, but may represent a therapeutic vulnerability to CDK inhibitors [6].

Another subset of sequencing efforts was performed by Witkiewicz et al., where they attempted to increase the purity of the tumor being profiled and thus mutation calling by using 109 micro-dissected PDAC [7]. Several frequently mutated pathways were identified and stratified based on genetic actionability, including:

1) Cell cycle progression (*RB*, *CDKN2A*, *CDKN2B*, or *CDK4*): CDK4/6 inhibitors (PD-0332991).
2) Beta-catenin (*RNF43*, *AXIN1/2*, or *APC*): porcupine and tankyrase inhibitors (LGK974 and XAV939).
3) NOTCH pathways: gamma-secretase inhibitors (MK0752).
4) MYC amplifications: CDK9 inhibitors or BET-bromodomain inhibitor (PHA767491 and JQ1) [7].

Identification of biomarkers with direct implications for the molecular biology of PDAC such as those

presented has the potential to influence treatment approaches with improvement in clinical outcomes for a subset of these patients.

## Targeting RAS

*KRAS* is among the most common oncogenic drivers in human cancers, making it the most obvious choice for targeted therapies. Activation of the RAS protein is the result of growth factor receptor signaling, which induces cycling of a GTP-bound (ON) and a GDP-bound (OFF) state that regulates downstream effectors. Within the protein lies an intrinsic GTPase, which allows RAS proteins to hydrolyze GTP to GDP and inactivate itself. Point mutations in *KRAS* effectively inhibit this interaction of RAS with GTPase-activating proteins resulting in the inability to hydrolyze GTP to GDP allowing for a constitutively active protein. Unfortunately, RAS has received notoriety as an "undruggable" target due to its high affinity to GTP and the smooth surface of the protein, prohibiting binding of therapeutic molecules [8]. Efforts at drugging RAS have involved direct inhibition, impairing localization, inhibiting downstream effectors, and exploiting synthetic lethality strategies.

Several direct *KRAS* inhibitors have been synthesized, but have yet to be clinically effective [9–11]. Among the most promising involves the development of a covalent inhibitor that targets the mutant form G12C, found mostly in lung and colorectal cancers but not typically observed in PDAC. This compound effectively increases the affinity of *KRAS* G12C for GDP over GTP leading to the accumulation of the GDP bound state, but suitable pharmacokinetics and pharmacodynamics remain to be optimized before use in the clinic.

Targeting intracellular trafficking of RAS has been a conceptually interesting alternative. Some of the earliest efforts at Ras targeting had focused on blocking its ability to attach to the plasma membrane for signal transduction using farnesyltransferase inhibitors, but these failed in phase II and III clinical trials [12–14].

Another strategy involves exploiting oncogene addiction wherein the cancer cells are dependent on Ras for survival and propagation. This is done through an approach known as synthetic lethality where defects in two genes leads to cell death, whereas a defect in one gene alone allows the cell to remain viable. By targeting genes activated by *KRAS* for tumor maintenance, several candidate synthetic lethal interactions have been identified.

Corcoran et al. performed a genome-wide screen using RNAi where they identified genes that cooperate with MEK inhibition leading to the identification of *BCL-XL*, an antiapoptotic gene [15]. When the MEK inhibitor, selumetinib, and the Bcl family inhibitor navitoclax were combined, researchers saw an induction of apoptosis in *KRAS* mutant cells. This combination therapy is currently in clinical trials for *KRAS* mutant cancers (NCT02079740). Another candidate target was found when researchers discovered that *KRAS*-mutant NSCLC requires CDK4 for survival and proliferation. Treatment with CDK4 inhibitors induced senescence and decreased tumor growth rates in mouse models, leading to a currently established clinical trial (NCT02022982) [16–18]. Although a clear effective drug for *KRAS* remains to be discovered, the novel strategies used by these described studies to identify viable candidates hold promise as we move forward.

While *KRAS* mutations are nearly ubiquitous in PDAC, it is important to note the oncogenic nature of wild-type *KRAS* PDAC. Recent studies have shown that these tumors still exhibit aberrations in RAS effector pathways, including mutations in *BRAF* and *PIK3CA* [7]. Particularly, *BRAF* mutations were found to be mutually exclusive of *KRAS* mutations and these cases might be sensitive to the FDA-approved BRAF inhibitor vemurafenib. This small subset of cases thus presents an opportunity for targeted therapies using BRAF and PI3K inhibitors.

## MEK/ERK Inhibition

A potential strategy to circumvent the "undruggability" of *KRAS* is to target its downstream effectors, which include the RAF/MEK/Erk and PIK3/AKT pathways. MEK and PI3K inhibitors, as well as combined inhibition of MEK and AKT pathways have shown promising effectiveness in the preclinical setting [19,20]. A phase I clinical trial on the safety and efficacy of the dual targeting strategy of the PI3K/AKT and RAF/MEK/ERK pathways showed the potential for favorable efficacy, but with associated increase in toxicity [21]. In phase II clinical trials, MEK inhibition in combination with gemcitabine did not demonstrate improved response rate or overall survival when compared to gemcitabine alone [22]. However, a noteworthy insight that came from this study was the prospect of increased effectiveness, although not statistically significant, in those patients with wild-type *KRAS* tumors. This demonstrates how molecular information may play a critical role in patient stratification for clinical trials.

## Epidermal Growth Factor Receptor Inhibition

Ligand binding to epidermal growth factor receptor (EGFR) with subsequent activation of downstream effector pathways (RAS/RAF/MEK, PIK3/AKT, and JAK/

STAT) involved in cell survival and proliferation is another potential target in PDAC [23]. Preclinical models have demonstrated the need for EGFR signaling in *KRAS* mutated pancreatic cancer initiation and progression [24,25]. Although initial phase III clinical trials demonstrated only modest improvement in overall survival for a subset of patients (<10%) using the tyrosine kinase inhibitor (TKI) erlotinib, other studies are under way testing additional anti-EGFR monoclonal antibodies and dual EGFR/HER2 targeting strategies (NCT00871169, NCT01204372, NCT01728818) [26]. Of particular interest are those patients with wild-type *KRAS* tumors who may find therapeutic potential with these TKI [27,28].

## Insulin Growth Factor-1 Receptor

Synonymous to EGFR signaling, insulin growth factor-1 receptor (IGFR) activation leads to effector pathways involved in survival and proliferation. Of note, clinical trials, including the phase III GAMMA trial, involving the monoclonal antibody against IGFR, AMG-479 (ganitumab), did not demonstrate any statistically significant improvement in overall survival, underscoring the complexity of signaling pathways in this disease.

## Pancreatic Stroma

PDAC is well known to be associated with a profuse desmoplastic stroma composed of fibroblasts, immune cells, endothelial cells, pericytes, and a complex extracellular matrix (ECM). Initial studies have demonstrated how various stromal elements can promote cancer cell proliferation, invasion, and immune suppression while decreasing drug perfusion, leading to the paradigm that the stroma acts as a tumor promoter [29–31]. However, recent work has challenged this model. Rhim et al. have shown that inhibiting the sonic hedgehog (SHH) pathway, which promotes the desmoplastic reaction, results in poorly differentiated tumors with increased vascularity and mortality in mouse models [32]. Ozdemir et al. demonstrated similar results, where depletion of aSMA+ pancreatic myofibroblasts and type 1 collagen led to cancer cells acquiring an EMT state, stem cell-like phenotype, and poor survival in genetically engineered mouse models [33]. This evolution in understanding the functional role of tumor stroma has led to several approaches in therapeutic targeting.

By following the route of the tumor stroma as a barrier to chemotherapy delivery, a SHH inhibitor, IPI-926, was used to decrease myofibroblastic proliferation and tumor collagen deposition. Although preclinical studies showed promise with this strategy, clinical trials with IPI-926 + gemcitabine in advanced PDAC failed to demonstrate survival benefit when compared to gemcitabine alone [34].

Hyaluronic acid is an ECM protein that induces a high interstitial pressure and vascular collapse within the PDAC stroma resulting in impaired perfusion. A strategy to overcome this barrier to perfusion involves the use of hyaluronidase, an enzyme that degrades hyaluron, and thus permits delivery of gemcitabine by lowering the stromal interstitial pressure. Clinical trials using gemcitabine and nab-paclitaxel ± PEGylated hyaluronidase have demonstrated significantly improved progression-free survival in advanced PDAC patients with high hyaluronic acid (HA) expression in preliminary results [35], and a phase III trial of front-line therapy with PEG-PH20 is being planned.

Another study has emphasized the role of "stromal reprogramming" in order to restore the normal function and homeostasis of the tumor stroma. Pancreatic stellate cells (PSC) are a stromal component of the pancreas, which when activated by cytokines, growth factors, oxidative or metabolic stress, transdifferentiate to myofibroblast-like cells that synthesize ECM proteins, contributing to fibrosis and tumor progression [36]. By activating the vitamin D receptor (VDR) present on these cells with an analog ligand, researchers were able to revert these activated PSC to a quiescent state where tissue homeostasis is restored, leading to increased drug delivery, reduced tumor volumes, and increased overall survival in preclinical models [37]. Synthetic Vitamin D priming as an adjuvant to chemotherapy is the subject of ongoing clinical trials in advanced pancreatic cancer patients.

Effective approaches to the tumor stroma remain to be fully elucidated considering the potential dual role that it can play in tumor progression or suppression. Still, it is important to note the heterogeneity of populations that exist within this microenvironment and how their divergent roles are likely a function of a dynamic process that is constantly changing and adapting to the conditions within the tumor.

## Enabling Targeted Therapies in Pancreatic Cancer

As detailed earlier, targeted therapies in the era of precision medicine are an exciting field considering the significant efforts made through the ICGC and TCGA. But an important caveat revolves around the fact that without having the ability to find the target, precision medicine becomes a futile endeavor. This is especially true for

patients with *de novo* or recurrent metastatic PDAC, where tumor tissue is rarely sampled apart from a fine-needle aspiration or a core-needle biopsy performed for diagnosis. Aside from only perfunctory molecular assays, such as immunohistochemistry and limited sequencing, the ability to discover actionable mutations remains a limitation to currently employed techniques [38]. Liquid biopsies involving three compartments: circulating tumor DNA (ctDNA), circulating tumor cells (CTC), and microvesicles referred to as exosomes have thus been used as an alternative for tumor profiling. These compartments represent tumor material that is released by primary and metastatic sites and can theoretically capture a full representation of tumor heterogeneity [39].

Sausen et al. have demonstrated the ability to detect somatic mutations in ctDNA of PDAC patients during subclinical, residual, and recurrent disease [40]. San Lucas et al. profiled tumor DNA contained within exosomes, identifying multiple actionable mutations including alterations in *NOTCH1* and *ERBB2* [41]. Of particular significance was the identification of a *BRCA2* mutation in a patient with exceptional response to a platinum-containing adjuvant regimen, underscoring the clinical applicability of the information stored within these exosomes. Genomic characterization of CTC has also demonstrated promise in guiding therapy options by predicting chemotherapy response and resistance [42]. Although preliminary, the collection of this data supports the utility of liquid biopsies in the context of targeted therapies by noninvasively monitoring tumor evolution and identifying emerging actionable mutations in real time.

## Summary

Much has been learned in the past three decades about the molecular mechanisms driving pancreatic carcinogenesis; allowing for therapeutic options to be expanded beyond just chemotherapies. Studies such as those performed by the TCGA and ICGC have highlighted the genetic heterogeneity within PDAC, but have also given an insight into strategies to overcome it. The likelihood of effectively treating PDAC using a single target is low. By tailoring therapeutic strategies to target multiple genetic aberrations or key nodal signaling pathways, we may find success in overcoming the inevitable resistance seen in this disease. Patient stratification into clinical trials based on molecular biomarkers remains an objective of utmost importance in order to more effectively discover and validate targeted therapies that may prove beneficial to these patients.

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# Palliative Chemotherapy for Advanced Pancreatic Cancer: Survival Benefit and Side Effects of Treatment

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## The Clinical Burden of Advanced Pancreatic Cancer

In the Western world, pancreatic cancer remains one of the poorest prognostic malignancies with 5-year survival of ~10% [1]. Due to its relatively asymptomatic nature until at an advanced stage and the absence of validated screening techniques, more than 80% of pancreatic cancer cases continue to be diagnosed at an advanced stage, precluding potentially curative treatment [2]. Furthermore, with a projected rise from being the fifth to the second most common cause of cancer mortality (after lung cancer) in 2030, the role of optimal management of advanced pancreatic cancer will increase in significance [3]. Pancreatic cancer comprises two major groups of malignancies, the carcinomas and the neuroendocrine cancers. While carcinomas contribute more than 95% of cases and are often treated with chemotherapy, the neuroendocrine cancers (<5%) are often treated with hormonal and molecular targeted therapies, with chemotherapy reserved for the rare high-grade variant (<1%) [4]. This chapter will focus on the benefits and side effects of chemotherapy for advanced pancreatic carcinomas.

## The Management of Advanced Pancreatic Carcinoma

Advanced pancreatic carcinoma is often associated with significant disease-related morbidity, typically emerging during the weeks to months preceding its diagnosis. Prior to the establishment of a role for palliative chemotherapy, the median survival for advanced pancreatic cancer was universally poor at ~6 weeks with best supportive care alone [5]. The importance of optimal supportive care as a prerequisite to commencement of cancer-directed therapeutic measures cannot be overemphasized. In this respect, it is noteworthy that all clinical trials demonstrating benefit from treatment with systemic chemotherapy have only shown this benefit in conjunction with best supportive care. Furthermore, most patients of WHO performance status (PS) 3 and those of PS4 do not survive long enough to potentially benefit from chemotherapy. Thus, disease complications such as pain, obstructive jaundice, malnutrition (due to factors such as anorexia, pancreatic exocrine insufficiency, gastric outlet obstruction), diabetes, and psychosocial issues should be optimally managed alongside initiation of systemic chemotherapy treatment. Given the relatively similar manner of presentation, chemotherapy was initially approached in the same way across the entire spectrum of advanced pancreatic cancer. However, patients with locally advanced (LA) disease (locoregional vascular involvement precluding resectability) are now known to have a better prognosis than those with metastatic disease (distant spread) concomitant with advances in locoregional treatment approaches [6]. Therefore, surgical and locoregional ablative approaches are emerging for indolent or chemosensitive forms of LA disease such that its management approach may diverge from that of metastatic disease in the future. In this chapter, we will discuss the treatment of advanced pancreatic cancer with palliative chemotherapy. We will then discuss more recent chemotherapy regimens validated to be beneficial for metastatic disease and their role in LA disease including potential integration with locoregional treatment approaches. A schematic diagram of the approach to the treatment of advanced pancreatic

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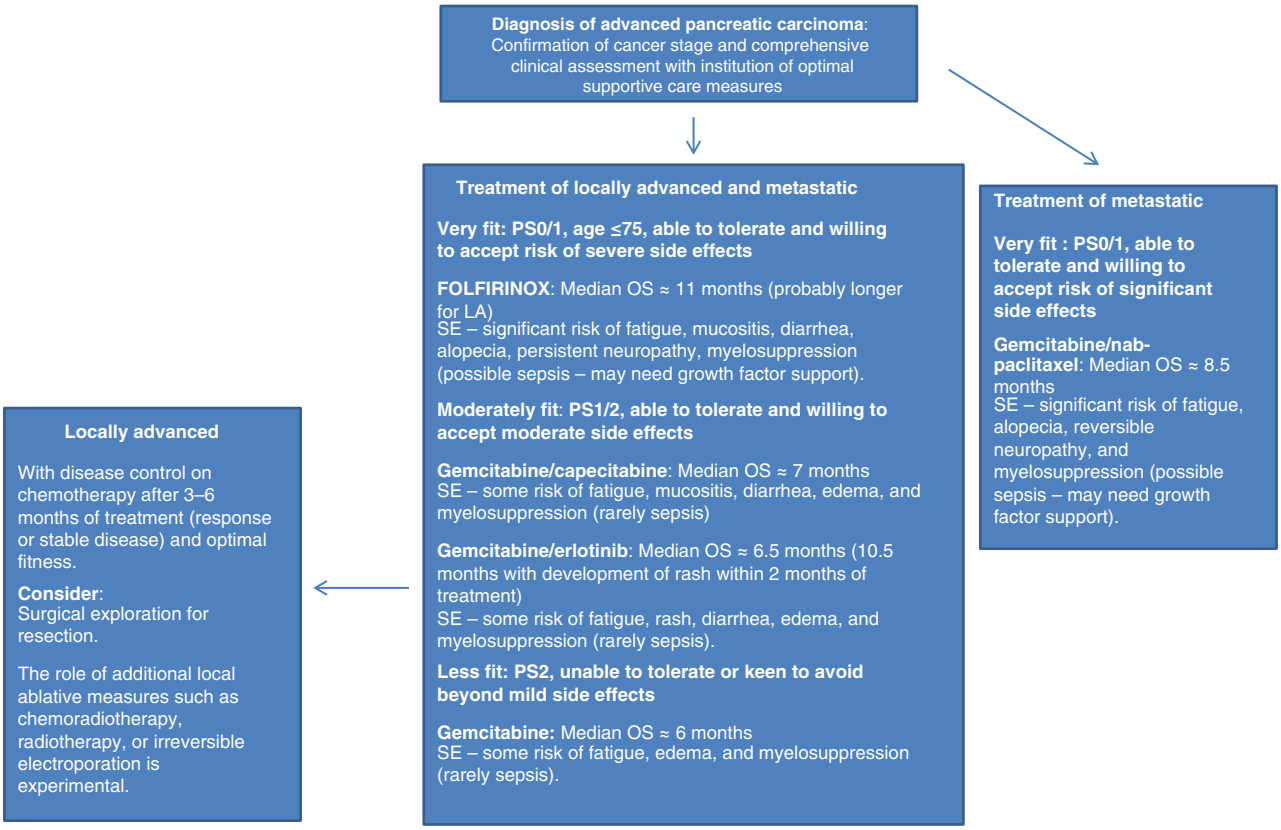


**Figure 116.1** Schematic diagram of the potential benefit and common side effects of chemotherapy treatment options for advanced pancreatic carcinoma. The broad selection criteria for different treatment options are also highlighted. LA, locally advanced; OS, overall survival; PS, WHO performance status; SE, side effects.

cancer including survival benefit and the potential adverse effects associated is shown in Fig. 116.1.

## First-Line Chemotherapy Treatment for Advanced Pancreatic Carcinoma

A multitude of chemotherapy regimens have been evaluated in advanced pancreatic carcinoma palliation over the past few decades. In trials, chemotherapy response rates have been low (5–32%) but rates of disease control (stabilization or response) have been higher (40–70%). Unfortunately, responses are not durable (median time to progression: 3–7 months) with a modest survival benefit (median: 6–11 months). The nucleoside analog gemcitabine became the standard of care for advanced pancreatic two decades ago based on marginally improved survival and quality of life compared with another nucleoside analog 5-fluorouracil (5-FU) [7]. In a population with KPS performance status (PS) ≥50 (76% metastatic), the response rate to gemcitabine was 5% with 45% disease stabilization rate and a median survival of 5.7 months. The gemcitabine control arms of several recent clinical trials have consistently reported similar survival benefit even in fitter populations. Gemcitabine is given as a 30 min one day a week infusion for 3 weeks in a 4-week cycle. Compared with many other chemotherapy regimens, it is relatively well tolerated with few common side effects, which tend to be cyclical including nausea, a flu-like feeling, rash, fatigue, and edema due to fluid retention [7]. Anti-emetics and supplementary steroids are routinely given with the regimen to ameliorate some of these, while diuretics as necessary can help with fluid retention. Myelosuppression can be observed, the risk of thrombocytopenia is significant but very rarely results in bleeding. Neutropenia is somewhat less common with low risk of febrile neutropenia. Anemia at times necessitating transfusion or treatment with erythrocyte colony-stimulating factor can be observed. Dose or regimen adjustments as well as periodic breaks of a few weeks can help with significant side effects despite optimal supportive care, particularly on protracted treatment. Pneumonitis is a very rare and idiosyncratic side effect for which high-dose steroid therapy and intensive care support may be necessary [8]. Hemolytic uremic syndrome (HUS) is another rare side effect [9]. It is very rare for HUS to be severe enough to

necessitate measures such as temporary transfusion support and renal replacement therapy. The optimal duration of a course of palliative gemcitabine treatment for advanced pancreatic cancer is not defined. However, treatment was continued as tolerated until progression in clinical trials due to the low response rate and risk of rapid clinical deterioration with progression off treatment. Consequently, many practitioners abide by this strategy in routine practice.

The survival benefit from 5-FU treatment was only marginally inferior to that of gemcitabine [7]. However, gemcitabine is generally preferred due to relatively improved quality of life. This may be due to less mucositis, diarrhea, and palmar-plantar erythrodysesthesia than 5-FU. Furthermore, 5-FU treatment (as currently administered) requires longer chemotherapy ward attendances for a few hours of bolus infusions twice-weekly, venous access lines, and an indwelling infusion pump for 2 days afterwards. Therefore, there are the additional risks of vascular access occlusion, thrombosis, and sepsis with 5-FU regimens. Consequently, despite the more frequent but brief hospital visits for gemcitabine administration, the burden of 5-FU treatment administration is greater overall, which becomes more of an issue for patients benefitting from long-term therapy. Capecitabine has been developed as a conveniently administered oral fluoropyrimidine that is bioequivalent to 5-FU [10]. However, there has not been direct trial comparison of the benefit of gemcitabine or capecitabine treatment for advanced pancreatic cancer.

Among various gemcitabine-containing chemotherapy doublets evaluated in populations of WHO PS1 and 2 with advanced pancreatic cancer, only two were reported to yield a marginal survival increment relative to single-agent gemcitabine treatment. In the Gem-Cap trial (gemcitabine-capecitabine combination) a significantly higher (19% vs. 12%) response rate was observed with the combination. Despite significantly longer time to progression, longer survival (log rank analysis hazard ratio [HR]: 0.86; median: 7.1 vs. 6.2 months) was not statistically significantly higher than for single-agent gemcitabine treatment [11]. However, pooled analysis with two similarly designed trials suggested that the marginal survival benefit was consistent and significant [10]. The main additional side effect on the combination arm was a higher rate of myelosuppression (but not sepsis). Diarrhea, mucositis, and palmar-plantar erythrodysesthesia, which are typically associated with fluoropyrimidines, were not significantly higher in the combination arm. In contrast, in the Gem-Erlotinib trial (gemcitabine-erlotinib combination [erlotinib is an oral epidermal growth factor receptor tyrosine kinase inhibitor]), combination treatment yielded relatively similar response rates to single-agent gemcitabine treatment (8%). However, a less than 2-week increment in median survival to 6.2 months (HR: 0.82) was statistically significant [12]. When the additional side effects of erlotinib therapy in the form of fatigue, diarrhea, rash, and a higher rate of rare pneumonitis are taken into consideration, the clinical significance of this marginal survival benefit is doubtful. Furthermore, the additional cost of erlotinib treatment (at the present time) for this marginal benefit has been prohibitive in most healthcare settings. Nevertheless, of particular interest was the observation that the subset of patients who develop a rash early on erlotinib treatment had longer median survival of 10.5 months, compared with 5.3 months in patients who did not develop a rash [12]. Therefore, some practitioners have adopted the development of a rash within 2 months of treatment with the regimen as a clinical biomarker of potential benefit from erlotinib. It is worth emphasizing that ~30% of patients had locally advanced disease in both the Gem-Cap and Gem-Erlotinib trials. Even though balanced between arms, their inclusion may have inadvertently masked survival differences between treatment arms due to their longer prognosis.

## Recent Advances in Chemotherapy Treatment for Metastatic Pancreatic Carcinoma

The most clinically meaningful survival increment for a gemcitabine-based combination treatment for advanced pancreatic cancer emerged in a trial on a relatively fit (KPS PS ≥ 70) metastatic patient population reported in 2013. Compared with gemcitabine alone, the addition of nab-paclitaxel (a modified taxane) was associated with higher response rates (23% vs. 7%), disease stabilization rate of ~50% with a longer time to progression, and longer survival (HR: 0.72; median: 8.5 vs. 6.7 months) [13]. Significant additional toxicity on this regimen include: fatigue, a higher rate of myelosuppression (including risk of neutropenic sepsis), and reversible peripheral neuropathy. These may necessitate temporary cessation of nab-paclitaxel therapy and dose adjustments. Alopecia, which rarely occurs with gemcitabine alone, is also common with the addition of nab-paclitaxel. Thirty-one percent of patients who received gemcitabine/nab-paclitaxel in this trial received second-line fluoropyrimidine treatment [14].

The role of fluoropyrimidine combinations in improving survival for advanced pancreatic cancer was uncertain until 2011, when FOLFIRINOX the combination of 5-FU with folinic acid (vitamin potentiator), irinotecan (a topoisomerase-1 inhibitor), and oxaliplatin (a platinum derivative) was evaluated in a trial on a fit (WHO PS ≤ 1) metastatic patient population. Compared with gemcitabine, a higher response rate (32% vs. 9%), disease stabilization rate of ~70%, with longer time to

progression and longer survival (HR: 0.57; median: 11.1 vs. 6.8 months) was reported [15]. Consequently, the longest median survival reported for metastatic pancreatic cancer chemotherapy treatment to date has been with the FOLFIRINOX regimen. FOLFIRINOX is administered as an alternate weekly infusional regimen with similar venous access requirements to 5-FU/FA, but with longer bolus infusions. Side effects such as nausea and vomiting are usually more severe than for gemcitabine regimens necessitating more effective antiemetic therapy. The risk of myelosuppression particularly neutropenic sepsis is ~50%, such that prophylactic granulocyte colony-stimulating factors are commonly used with the regimen. Furthermore, oxaliplatin cold-induced neurosenstivity is common, usually during the first few days of the cycle, relieved by avoiding cold stimuli and applying warm dressing if required. Perhaps of more clinical significance is the cumulative oxaliplatin-induced neuropathy, which is less readily reversible than neuropathy observed with nab-paclitaxel. As a result, most patients require dose adjustments or cessation of oxaliplatin after some months on the regimen. Mucositis, palmar-plantar erythrodysesthesia and diarrhea are common as for fluoropyrimidine regimens in general, which are managed symptomatically [15]. Alopecia is also common. While supportive care measures can help reduce the significance of such side effects, most patients require dose adjustment for side effects or significant fatigue on the regimen within the first few cycles. Indeed, many centers start with an attenuated regimen to reduce the risk of intolerable side effects (typically with omission of the 5-FU bolus). Some retrospective studies have suggested preservation of efficacy with attenuated forms of the regimen [16,17]. In the FOLFIRINOX trial, 47% of patients received second-line chemotherapy with gemcitabine after progression. However, outcomes for this subset were not reported. In a study of outcomes for selected patients fit enough to receive gemcitabine/nab-paclitaxel treatment after progression on FOLFIRINOX, median overall survival from starting FOLFIRINOX treatment was 18 months. However, rates of myelosuppression and neurotoxicity were significant [18].

There has not, as yet, been any reported comparison between first-line FOLFIRINOX and gemcitabine/nab-paclitaxel for metastatic pancreatic cancer such that the optimal first-line chemotherapy regimen for the treatment of metastatic pancreatic cancer in fit patients is yet to be fully defined. While nominally, FOLFIRINOX would appear to be superior, cross-trial comparison of survival for studies conducted in different settings is inadequate. Therefore, for fitter patients, the consensus in the medical community appears to be selecting either regimen in consultation with patients on a case by case basis after due consideration of comorbidities, discussion of potential benefit, potential side effects, administration requirements, and patient preference. For frailer patients (PS2 and selected patients of PS1, with particular comorbidities, or who choose to avoid the burden of toxicity associated with combination chemotherapy), gemcitabine remains an appropriate standard of care. However, infusional 5-FU/capecitabine may be substituted as necessary.

In the adjuvant setting, predictive biomarkers are showing promise in stratifying patients for the most appropriate form of chemotherapy. For example, expression of human equilibrative nucleoside transporter-1 (hENT1), which is required for active transport of gemcitabine into cells, detected by immunohistochemistry may predict benefit from adjuvant gemcitabine [19]. However, to date such predictive markers have not been validated for use in the palliative setting. Ongoing clinical trials may elucidate the utility of hENT1 and other biomarkers, in this context.

## First-Line Chemotherapy Treatment for Locally-Advanced Pancreatic Carcinoma and Locoregional Treatment Strategies

While the most efficacious regimens for advanced pancreatic cancer have, at the present time, undergone trial evaluation mainly in the metastatic population, FOLFIRINOX efficacy in particular has been extrapolated to LA disease. Its nominally higher rates of response and disease control have made it the regimen of choice particularly when potential downstaging of disease to resectability is a consideration. Even with FOLFIRINOX, low response rates and the extent of such responses assessed radiologically has made regression from LA disease to freedom from vascular invasion and resectablity possible only in a minority of cases [20]. However, a recent report suggests that residual local vascular invasion after FOLFIRINOX for a median of 6 months reflects a preponderance of stromal disease rather than active malignant tissue. With laparotomy and exploration in the absence of disease progression on FOLFIRINOX treatment, approximately 60% had resectable disease. Median survival (postoperatively) was 16 months (3-year survival of 28%) for patients who had surgical resection compared with 8.5 months in patients who did not undergo surgical resection [21]. Means to clearer identification of cases with resectable disease after chemotherapy are now required. In the meantime, more routine exploration to determine the nature of residual disease after chemotherapy would seem to be warranted.

The role of local ablative therapies to improve resectability and long-term survival with LA disease is

uncertain and remains largely experimental at the present time. What seems to be clear is that the proclivity of pancreatic cancer to early occurrence of micrometastatic disease even at the earliest stage precludes attempts at upfront locoregional treatment to the exclusion of chemotherapy for the control of systemic disease [22]. However, the role of interruption of chemotherapy for local ablative therapies in patients with responding or stable disease as well as those with mild local progression alone is unclear. Chemoradiation (CRT) has been the most widely investigated form of treatment in this setting with improved tolerability of capecitabine-based CRT compared with gemcitabine-based CRT regimens [23]. Nevertheless, in a study of an initial 4 months of gemcitabine ± erlotinib therapy followed by randomization to either continuation of chemotherapy or switching to high-dose capecitabine CRT, there was no survival benefit from CRT [24]. CRT is associated with gastrointestinal side effects and fatigue, which are worse than on chemotherapy and could lead to deterioration in quality of life for at least a 6-week period around such treatment [25]. Conversely, the short-term nature of CRT is such that a break from treatment with observation for a successful local ablative effect can be instigated whereas the continuous nature of chemotherapy may present a more long-term toxicity burden. A recent meta-analysis suggested that first-line FOLFIRINOX treatment for LA disease with subsequent local ablative treatment and/or surgery as appropriate, yielded median duration of disease control and overall survival of 15 and 24 months, respectively, which are nominally higher than for metastatic disease [26].

At the present time, further chemoradiotherapy trials utilizing the more recently validated chemotherapy regimens for better overall disease control, with optimization of radiotherapy doses and method of delivery are in progress. Furthermore, the role of alternative local ablative therapies such as stereotactic radiotherapy (SABR) and irreversible electroporation (IRE) are areas of clinical investigation beyond the scope of this chapter. Molecular predictors of propensity to localized rather than metastatic disease are also of interest to possibly help select between chemotherapy and local ablative treatment for LA disease. Loss of *SMAD4* has been proposed as one such predictor of metastases [27]. However, clinical data are conflicting and studies in genetically engineered mice suggest a complex role for *SMAD4* mutation in contributing to metastasis and rate of tumor proliferation. Heterozygous mutations attenuated metastatic potential whilst loss of heterozygosity promoted metastasis, such that its use in clinical practice at the present time cannot be recommended [22]. Other mouse models have suggested that Aldh1a3 expression may identify an aggressive subtype with a higher rate of distant metastases [28]. A subset of metastatic pancreatic ductal adenocarcinomas depends quantitatively on oncogenic Kras/Mek/Erk-induced hyperactive mTOR signaling [28]. This now warrants investigation in human resected cohorts as a potential predictor of early recurrence.

## Second-Line Palliative Chemotherapy for Advanced Pancreatic Carcinoma

With median time to progression on treatment of few to many months, patients with advanced pancreatic cancer require close monitoring to identify symptoms of progression with prompt radiologic assessment as necessary prior to clinical deterioration precluding further treatment. Furthermore, re-evaluation of supportive care needs will be crucial prior to initiation of further cancer-directed therapy. For patients who took a break after initially achieving disease control on first-line chemotherapy or completed CRT, retreatment with the first-line regimen for its proven benefit would be advisable, particularly with good tolerance. For patients with disease resistant to initial regimens, second-line chemotherapy treatment may be considered.

The best clinical trial evidence for second-line chemotherapy in advanced pancreatic cancer is in patients progressing on first-line gemcitabine treatment. A combination of 5-FU/FA and oxaliplatin increased the median survival after progression on first-line chemotherapy to 4.8 months from 2.3 months with best supportive care alone [28]. The adverse effect profile of the combination is as discussed for fluoropyrimidines in first-line treatment with additional fatigue, nausea/vomiting, and neuropathy from oxaliplatin treatment. Justification of the additional toxicity of oxaliplatin is debatable in this setting as its additional survival benefit is contentious [29]. Whether capecitabine can be substituted for 5-FU/FA for the convenience of oral administration with no detriment to survival is unknown. The most recent advancement in second-line therapy was from a trial suggesting that the addition of liposomal irinotecan to 5-FU/FA led to increment in median survival to 6.1 months compared with 4.2 months on 5-FU/FA alone with a slightly increased risk of diarrhea, fatigue, and neutropenia with the combination [30]. Therefore, fluoropyrimidine-containing regimens are potentially beneficial following progression on gemcitabine. However, clinical decisions on the exact regimen for individual patients are made taking into consideration their fitness levels to cope with combination treatment and (current) funding constraints for expensive novel treatment such as liposomal irinotecan for its marginal benefit.

There are to date no reported clinical trials to guide optimal second-line chemotherapy after progression on

FOLFIRINOX or gemcitabine/nab-paclitaxel treatment. However, the limited evidence to guide second-line treatment (gemcitabine-based regimens for FOLFIRINOX and fluoropyrimidine-based regimens for gemcitabine/nab-paclitaxel) have been discussed earlier.

### Strategies to Improve Survival Outcomes with Chemotherapy for Advanced Pancreatic Carcinoma

With median survival still under a year even for the fittest patients receiving the most efficacious chemotherapy regimens for metastatic pancreatic carcinoma, it is quite clear that the benefit from chemotherapy remains suboptimal. It is difficult to conceive further improving survival by adding extra chemotherapy agents to the established components of the FOLFIRINOX or gemcitabine/nab-paclitaxel regimens because of the potential additional toxicity from such. However, trials of modified nucleoside analogs to override cancer resistance mechanisms without increasing toxicity are an area of interest. Furthermore, the addition of appropriate cancer microenvironmental modulators to currently effective chemotherapy regimens is emerging as an attractive alternative strategy to improve on outcomes without adding significant toxicity. With improved understanding of the molecular and genetic basis of pancreatic cancer, treatment targeted at specific molecular alterations driving cancer progression and treatment guided by predictors of response to currently proven agents is also of immense interest [31–33]. However, the diverse nature of such abnormalities of variable functional significance has generated a significant hurdle which translational oncologists are working on surmounting.

In conclusion, despite its notoriously poor prognosis, advanced pancreatic carcinoma is in an era of expanding treatment options that have modestly improved survival outcome with tolerable adverse effects. Optimal utilization of currently proven chemotherapy agents discussed here will be crucial, while research effort may further enhance management of the increased burden of the disease anticipated over the coming decades.

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# Management of Pain in Pancreatic Cancer

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## Anatomy and Physiology of Pancreas Cancer Pain

The pancreas, an organ that is uniquely both endocrine and exocrine in function, can be visualized as being divided into four main segments because it extends from the midline laterally: the head (including the uncinate process), neck, body, and tail. While pancreatic cancer pain varies by tumor location [1,2], extension [3], and stage [4], it is typically abdominal and can be referred to the epigastric region, upper abdominal quadrants, less frequently to the lower abdominal quadrants, or it can be diffuse in nature [5]. Back pain in the T10-12 region, often misattributed due to its prevalence in the age group most affected by pancreatic cancer [6], is not only very common but is also the presenting symptom in many cases [7].

Visceral nociceptive signals generated by tissue damage, inflammation, ductal obstruction, and glandular infiltration associated with pancreatic cancer are transmitted along afferent sympathetic fibers to the celiac plexus (T12-L2) where they synapse with the splanchnic nerves on their way to the T5-T12 dorsal root ganglia [8]. Metastatic disease reaching other upper abdominal solid organs shares these pathways. Tumor extension into non-organ surrounding tissues such as the peritoneum, retroperitoneum, and bones results in localized somatic pain [9]. Neuropathic pain may also be present as the result of perineural invasion (PNI) of cancer cells into the lumbosacral nerve plexuses, intrapancreatic nerve fiber destruction, and epidural spinal cord compression [10,11].

A variety of physiologic factors contribute to the generation and continuation of pancreas cancer pain. Histologically, cancer of the pancreas is characterized by extensive infiltration of inflammatory cells [12,13]. This inflammatory state, particularly the increased presence of macrophages, is associated with upregulation of nerve growth factor (NGF), the overexpression of which is correlated with both the extent of PNI and pain intensity [14,15].

Additionally, in the early stages of pancreatic cancer, NGF induces sprouting of calcitonin gene-related peptide (CGRP) expressing sensory fibers, which increase in density with disease progression [16]. In later stages of disease, the central pancreas, now densely innervated with new sensory fibers, gradually becomes necrotic [17]. This results in the destruction of the distal ends of the sensory and sympathetic nerve fibers that had innervated the now necrotic tissue, resulting in a significant neuropathic pain state [2].

## Pharmacologic Pain Management

The principal philosophy behind chronic cancer pain management focuses on maximizing analgesia while minimizing unnecessary risk and patient side effects. In order to achieve this balance, a gradual, stepwise approach is recommended, beginning with escalating pharmacotherapeutic treatments before progressing to more invasive interventions. The succession is paused for as long as satisfactory pain control is achieved. As 70–80% of cancer patients can be successfully managed with pharmacotherapy alone: analgesic medications, predominantly nonsteroidal anti-inflammatory drugs (NSAID) and opioids, are considered to be the first line of chronic cancer pain management [18–20].

In 1987, the World Health Organization (WHO) published guidelines for the pharmacologic treatment of cancer pain [21]. These guidelines, updated in 1997 [22] and validated by multiple prospective studies [23–26]

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have served as the foundation upon which cancer pain pharmacotherapy has been based for nearly four decades. The guidelines outline a treatment strategy that is based upon five principles:

1) "By mouth": oral (least invasive) administration of analgesic medications should be chosen whenever possible.
2) "By the clock": analgesics should be given at regular intervals, titrated against the patient's pain such that pain is relieved by a given dose and does not return before the next dose is due. Additional rescue dosing may be given for incident and breakthrough pain.
3) "By the ladder": analgesics should be prescribed according to pain intensity as evaluated by a standardized scale.
4) "For the individual": while there are toxicity-limited doses for some medications, there are no standard doses for opioid class medications, and doses should be tailored to the individual needs of each patient.
5) "Attention to detail": each patient's medication regimen should be meticulously planned out over a 24-hour period and written out in full for the patient/family.

Principle three, "by the ladder," proposes that the first medication used in the treatment of cancer pain be a non-opioid (see Fig. 117.1) [22]. Though not specified, "non-opioid" has been interpreted to mean acetaminophen, acetylsalicylic acid (ASA), or an NSAID. These medications have the advantage of being widely available, familiar to patients, efficacious for a wide variety of etiologies, and easy to administer. Disadvantages of these medications include adverse side effects such as hepatotoxicity with acetaminophen and gastrointestinal bleeding and renal toxicity with NSAID. The latter two can largely be avoided with the use of selective cyclooxygenase (COX)-2 inhibitors.

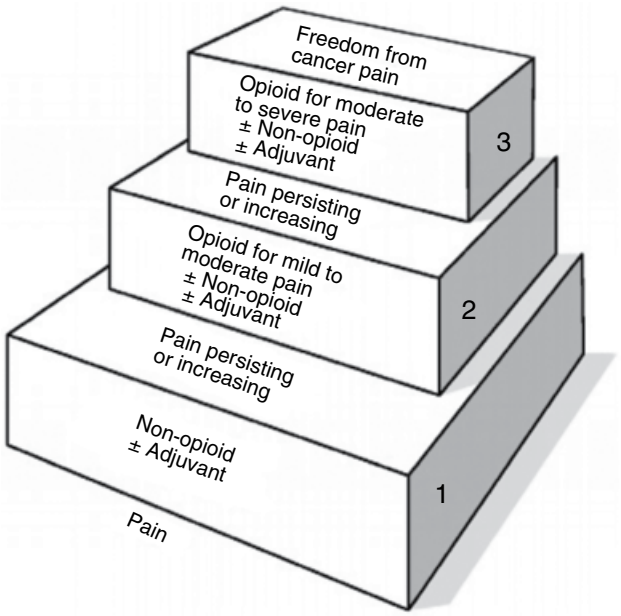


**Figure 117.1** The WHO three-step analgesic ladder. *Source:* World Health Organization 1997 [22].

If pain is not adequately controlled with one of these medications, an opioid for mild to moderate pain should be added. This step has been controversial insomuch as disagreement exists as to whether the addition of a "weak" opioid (with "ceiling" effects) to an NSAID decreases the necessary dose of either medication. The utility of this step seems to exist when either the ceiling effect or maximum safe dose of the nonopioid medication has been reached.

If satisfactory pain control has not been achieved with the addition of a weak opioid, step three recommends the addition of a strong opioid (morphine, hydromorphone, oxycodone). The WHO guidelines state that only one drug from each group should be used at the same time.

Despite or perhaps as a result of its widespread use, the WHO analgesic ladder has been the source of much debate [27]. Multiple adaptations have been proposed to include the elimination of the second level [28,29], adaptations of the analgesic scale to account for acute and chronic non-cancer pain [30,31], and the inclusion of a fourth step representing interventional treatments [32] (see Fig. 117.2) [33]. Though imperfect, when combined with sound clinical judgment, such a guideline for the pharmacologic treatment of cancer pain can serve as a foundation for the initial management of pancreatic cancer pain.

## Chemical Ablation of the Splanchnic Nerves or Celiac Plexus

Systemic analgesic therapy, per the WHO guidelines, is widely regarded as the standard of care for treating cancer pain. Unfortunately, not all cancer pain patients will achieve a satisfactory outcome by adhering to this algorithm, which has prompted some to challenge the clinical framework of the WHO guidelines for cancer pain [34]. A subset of patients with unresectable pancreatic cancer will suffer from medically refractory pain or develop intolerable side effects from opioids, which preclude their usage [22]. For these patients, a variety of minimally invasive techniques have been developed since the early twentieth century, the majority of which involve ablation of either the splanchnic nerves or celiac plexus, as these structures play a key role in the transmission of visceral pain from the pancreas.

A discussion of various technical approaches to either the splanchnic nerves or celiac plexus is beyond the

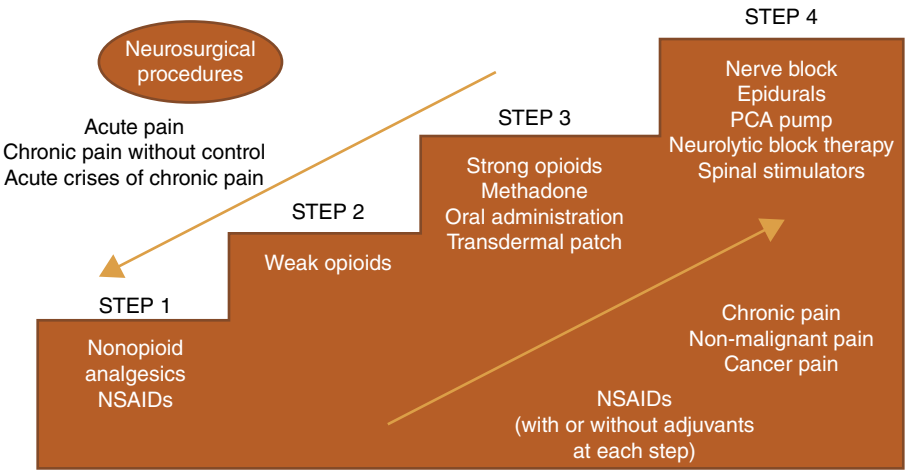


**Figure 117.2** New adaptation of the analgesic ladder. *Source:* Vargas-Schaffer 2010 [33], Fig. 2. Copyright © the College of Family Physicians of Canada.

scope of this chapter. These procedures can be subdivided into endoscopic and percutaneous techniques, with the latter consisting of anterior and posterior approaches. A common theme in all of these approaches is image-guided placement of one or more needles in close proximity to the targeted nerves and the use of a neurolytic solution, either phenol or concentrated alcohol. The former destroys nerves via protein denaturation, whereas the latter induces Wallerian degeneration; in either case, the nerves will ultimately regenerate but this process takes several months [35]. In the interim, patients can experience profound pain relief and markedly reduced side effects from systemic opioids.

Regardless of the technical approach, chemical ablation of these nerves tends to be quite effective in the setting of pancreatic malignancy. In the most recent systematic analysis of the literature by the Cochrane Group, the pooled experimental data on celiac plexus neurolysis reveals statistically significant reductions in reported pain scores, a difference that persists for at least 8 weeks postprocedure, and markedly reduced overall opioid consumption, which persists until the day before death. As a corollary to the observed reduction in systemic opioid usage, patients randomized to celiac plexus neurolysis tended to experience far fewer opioid-induced side effects such as constipation. Of note, the overall likelihood of a successful neurolysis is variable, but the published success rates generally range from 70% to 90% [36,37].

Although on meta-analysis, ablation of the celiac plexus is clearly effective regardless of the technical approach, the approach with the highest efficacy and lowest risk of patient harm remains quite controversial, especially with the advent of newer, endoscopic approaches to the celiac plexus (EUS-CPN) [34,38–41]. Endoscopic ultrasound celiac plexus neurolysis (EUS-CPN) is theoretically safer than posterior percutaneous approaches, as it allows more targeted deposition of the neurolytic agent in the vicinity of the celiac ganglia, real-time visualization of arterial vasculature in the targeted areas via Doppler, and potentially a reduced risk of anterior spinal artery syndrome. However, these theoretical advantages have not been definitely established in the medical literature as there are very limited data comparing endoscopic to percutaneous approaches for benign abdominal pain, and no experimental data thus far comparing the two approaches for treatment of pancreatic cancer pain. Randomized controlled trials are needed to determine the relative efficacy and safety of endoscopic versus percutaneous approaches in the treatment of severe pain due to pancreatic cancer [40,42].

The indications for chemical ablation of the celiac plexus (or splanchnic nerves) for pancreatic cancer pain are relatively straightforward. Given the palliative efficacy of surgical resection and the risks associated with chemical ablation of the splanchnic nerves or celiac plexus, traditionally these procedures have been reserved for a subset of pancreatic cancer patients with unresectable disease: more specifically, patients with neoplasm-related pain that is either (a) unresponsive to systemic analgesic medications or (b) associated with intolerable opioid-induced side effects [43–45].

Uncorrectable coagulopathy, lack of adequate resources for patient resuscitation, localized infection in

the anticipated trajectory of the needle(s), and sepsis are absolute contraindications. Markedly impaired cardiac reserve or inability to lie in the prone position are relative contraindications, as these conditions could increase the risk of ischemic or direct chemical injury to the spinal cord, respectively. Another key consideration is anatomic distortion from the pancreatic malignancy. In some cases, the distortion is so pronounced that certain approaches are not feasible. In other cases, severe tumoral invasion or displacement of the celiac plexus may increase the risk of a technical failure [46,47]. For this reason, a cross-sectional imaging study is recommended prior to the procedure itself.

There are a variety of complications associated with neurolysis of the splanchnic nerves or celiac plexus, but major complications from these procedures are rare. Temporary back pain, abdominal pain, hypotension, and diarrhea are fairly common occurrences, but are generally self-limited and respond quite well to supportive measures. Injury to the kidneys or ureters may occur, which can result in hematuria. Given the close proximity of various approaches to the diaphragmatic crura, pneumothorax is a described complication. There are some case reports in the medical literature of rare complications from celiac plexus neurolysis, including hemorrhagic gastritis/duodenitis, gastroparesis, and aortic dissection. These reported complications are so rare that the actual incidence of them remains unknown [48–50]. The most feared complication from celiac plexus neurolysis is permanent neurologic injury. The incidence of permanent paraplegia with posterior approaches is 0.15%. Bowel and bladder incontinence can also occur. Although one would expect inadvertent posterior migration of the alcohol into the spinal canal to result in permanent neurologic injury, with the advent of image guidance these mechanisms of neurologic injury can be avoided. Some have posited that the neurologic injury stems from alcohol-induced vasospasm of arteries feeding the spinal cord, resulting in an infarction of the spinal cord, a theory supported in part by basic science research involving the direct effects of alcohol and local anesthetics on vasomotor tone. If, in fact, neurologic injury from celiac plexus neurolysis stems from a vasospasm phenomenon, this risk would be nearly impossible to prevent [50–55].

## Surgical Options for Treatment of Pancreatic Cancer

Options for surgical treatment of refractory pancreatic cancer pain include thoracoscopic splanchnicectomy as well as intrathecal drug delivery.

### Thoracoscopic Splanchnicectomy

This procedure consists of the surgical interruption of the sympathetic chain via a thoracoscopic approach. Kang described 21 patients with unresectable upper abdominal malignancy and pain refractory to opioid analgesics who underwent bilateral thoracoscopic splanchnicectomy [56]. Baseline Karnofsky Performance Scale was greater than 60, and 71% of patients suffered from pancreatic cancer. NRS pain scores decreased from an average of 8.5 preoperatively to 1.7, while patients required bilateral chest tubes for an average of 3 days postprocedure.

Johnson reported 65 patients with unresectable upper abdominal malignancy who required opioid analgesia (58 with pancreas cancer) and were randomized to medical management, celiac plexus block, or thoracoscopic splanchnicectomy [57]. No significant differences were appreciated between the groups in pain scores or opioid consumption at 2 months. Limitations of the study include a failure to identify the presence of carcinomatosis in patients, use only of a fall in systemic blood pressure to identify a successful celiac plexus block, and a change in sample size from a calculated 324 necessary for analysis to only 65 due to slow recruitment.

### Intrathecal Drug Delivery Systems

IDDS (intrathecal drug delivery systems, i.e., intrathecal pumps) are an option for the treatment of patients with moderate to severe chronic refractory pain, and their use has led to improved quality of life, reduced pain, and increased satisfaction in those who have failed with other therapeutic options. IDDS have been shown to provide significant pain relief and statistically significant control of analgesic toxicity in cancer patients in a randomized study when compared with standard analgesic therapy, as well as a trend toward increased survival at 6 months [58].

The Polyanalgesic Consensus Conference (PACC) last issued guidelines on intrathecal (IT) analgesia use in 2012 [59]. Algorithms for nociceptive as well as for neuropathic pain (cancer pain may involve both) were issued, as well as recommended starting dose ranges, bolus trial ranges, and maximum daily dose and concentration ranges. Available IT analgesic medications for infusion include opioids, local anesthetics, clonidine, and ziconotide. IT therapy at the end of life is best weighed against surgical and infectious risk, as well as compared with home or institutional nursing care of externalized systems for those with a very limited life expectancy. Concentration and daily dose limitation is important to help prevent the development of an intrathecal granuloma at the catheter tip. Additional potential complications of IT therapy include respiratory depression and peripheral edema.

Trialing of IT analgesic medication has been described by both bolus dosing and continuous infusion [60], although some have argued a bolus trial is less representative of the long-term effects of IT therapy. Decrease in pain score by greater than or equal to 50% is a commonly used criterion for success of the trial. There exists debate regarding whether to continue, decrease, or eliminate existing systemic opioids in advance of IT trial. Typically, trials last between 3 and 7 days, with catheters placed at a spinal level corresponding with the vicinity of the patient's pain. Trials may consist solely of an opioid, but there is also the practice of adding an adjuvant agent such as bupivacaine and/or clonidine to the trial. Some have advocated the possibility of forgoing a trial in cancer patients due to the reported high success rates of cancer patients with IT therapy.

Complications may occur with implantation or pump management, drug reactions or side effects, device malfunction, and human error in programming or refilling the pump [61]. Use of IDDS is based on analysis of safety, efficacy, a goal of economic neutrality, and appropriateness for the patient. High concentrations of opioid or high daily dose predisposes to the risk of intrathecal granuloma, while the addition of adjuvant agents may lessen the risk by an opioid-sparing effect. Additional risks include infection, respiratory depression, peripheral edema, pump failure, and catheter obstruction or migration.

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# Role of Radio and Proton Beam Therapy for Pancreatic Cancer

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## Introduction

Amidst recent technological advances in radiation oncology, the role and optimal application of radiation therapy (RT) for pancreatic cancer (PCA) remains highly controversial. The origins of this controversy arise from key landmark trials with conflicting results regarding the relative merits of radiation. However, the manner in which these data should be applied to RT as delivered in the modern day using contemporary techniques is unclear. Nevertheless, fluency in the clinical literature exploring the role of RT for PCA across the disease's stages is critical. Equally important is an understanding of the way in which conformal radiation techniques and charged particle therapy can be used to improve the therapeutic window. Knowledge of these topics will yield both an appreciation of the value of modern RT for patients with PCA and an ability to better customize treatment regimens to individual patients. Herein, we review the role of RT in the adjuvant and neoadjuvant settings and discuss advanced modalities including proton beam therapy (PBT) and stereotactic body radiation therapy (SBRT).

## Radiation in the Adjuvant Setting

The optimal adjuvant management strategy for patients with resected PCA continues to generate considerable debate. Appreciation of the potential that modern RT may have for resected PCA requires a historical understanding of clinical trials that have explored the value of adjuvant chemoradiation (CRT). Early institutional reports demonstrated high rates of local failure (>50%) after surgical resection of PCA [1]. Predicated on these findings, the Gastrointestinal Tumor Study Group (GITSG) designed a randomized trial comparing adjuvant 5-fluorouracil (5-FU)-based chemoradiation with observation following Whipple resection. Patients in the CRT arm experienced improved 2-year OS (42% vs. 15%, $P = 0.03$), sparking adoption of adjuvant CRT in the United States [2]. However, this survival benefit could not be replicated in subsequent trials by the European Organisation for Research and Treatment of Cancer (EORTC) and the European Study Group for Pancreatic Cancer (ESPAC), with the latter trial suggesting improved survival with chemotherapy alone and inferior survival with CRT [3,4]. Importantly, key pitfalls of all of these trials must be acknowledged, including slow accrual and poor trial adherence. Perhaps most importantly, the radiation techniques employed in all three of these trials were antiquated by modern standards, including suboptimal doses, nonconformal techniques, and split-course schedules. As a result, the latter two trials failed to demonstrate decreased rates of local control in the CRT arms [3,4]. Nevertheless, European trials for patients with resected PCA have since focused on defining the optimal adjuvant chemotherapy-alone regimen. Indeed the Charité Onkologie (CONKO)-001 trial and subsequently the ESPAC-3 trial have established gemcitabine as the preferred adjuvant chemotherapeutic agent over bolus 5-FU, and the ESPAC-4 trial (ISRCTN96397434) is currently exploring adjuvant gemcitabine versus adjuvant capecitabine [5,6].

In the United States, outcomes with more conformal radiation techniques using higher doses without split-course schedules have been explored in both the nonrandomized and randomized settings. A pooled matched-paired analysis from the Mayo Clinic and Johns Hopkins demonstrated a survival benefit of adjuvant

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CRT when delivered to a median dose of 50.4 Gy compared to observation [7]. Moreover, Radiation Therapy Oncology Group (RTOG) 9704, which randomized patients to initial chemotherapy with either 5-FU or gemcitabine, followed by 5-FU-based chemoradiation to 50.4 Gy, followed by additional chemotherapy with 5-FU or gemcitabine, resulted in fewer local recurrences in both arms (25–30%) [8]. This local failure rate compared favorably with historical controls despite a predominance of patients with risk factors for local recurrence, including 35% with positive margins, 66% with positive lymph nodes, and 75% with advanced T-stage. Importantly, RTOG 9704 was the first trial to evaluate whether radiation field design influenced outcomes [9]. Failure to adhere to specified RT guidelines was associated with reduced survival and, for patients receiving gemcitabine, a trend toward increased nonhematologic toxicity. In fact, nearly 50% of the RT plans deviated from protocol guidelines. Consensus panel guidelines are now available for clinical target volume design, but the subset analysis of RTOG 9704 underscores the importance of appreciating the quality of radiation delivered when interpreting results from clinical trials [10].

Despite improved results seen in RTOG 9704, reported acute toxicity was still substantial, with 70.5% patients experiencing any grade ≥3 toxicity and 59% experiencing grade ≥3 nonhematologic toxicity [8]. To this end, a more focused form of RT termed "intensity modulated RT" (IMRT) may be helpful in sparing organs at risk (OAR) and minimizing toxicity. Yovino et al. compared toxicity between a cohort of 46 patients treated with adjuvant capecitabine-based CRT to a dose of 50.4 Gy using IMRT and a cohort of patients treated per RTOG 9704 with conventional CRT; grade ≥3 acute nonhematologic was significantly lower in the cohort of patients treated with IMRT [11]. With reduced toxicity, IMRT may allow for dose escalation and improved local control. In fact, low rates of acute nonhematologic toxicity have been reported in patients treated with IMRT to doses ≥55 Gy. As an example, Abelson et al. reported an 8% rate of acute nonhematologic grade ≥3 toxicity in 47 patients treated with up to 56 Gy with IMRT. In another study, Ben-Josef et al. reported a 7% rate of acute nonhematologic grade ≥3 toxicity in 15 patients treated with IMRT up to 55 Gy [12,13]. Beyond allowing for dose escalation, less toxicity associated with IMRT allows for incorporation of more aggressive concurrent chemotherapy or targeted therapies. As an example, an early phase trial exploring the combination of adjuvant RT with the EGFR inhibitor gefitinib caused dose-limiting diarrhea, but the combination of capecitabine-based IMRT with erlotinib was subsequently proven to be tolerable for most patients [14,15]. Given the potential merits of IMRT, it was incorporated into the RTOG 0848 trial, which is currently examining whether gemcitabine plus erlotinib produces superior survival results when compared to gemcitabine alone and whether radiation to 50.4 Gy with 5-FU improves outcomes beyond gemcitabine chemotherapy alone. IMRT with volumetric arc therapy allows for more rapid treatment of therapy and further sparing of adjacent normal tissues including bowel, stomach, and kidneys. Whether these advances translate into clinically meaningfully outcomes for patients requires further study [16].

SBRT is another technique being evaluated in the adjuvant setting. In a pilot study, 19 patients were treated with adjuvant SBRT, a pancreatic vaccine (GVAX), and FOLFIRINOX [17]. While preliminary, the study suggests that SBRT can be safely utilized in the adjuvant setting with minimal acute or chronic side effects. The combination of these therapies also resulted in a favorable progression-free survival (19 months) and OS (median not met) despite a high proportion of patients having margin- and node-positive resections. Multicenter studies are needed to determine whether SBRT should be more widely used in this setting.

## Radiation in Borderline Resectable and Locally Advanced Disease

While standard fractionation CRT appears to be a promising method to safely achieve local control and achieve margin-negative resections [18], hypofractionated regimens have increasingly gained traction in the field of radiation oncology. In a malignancy as aggressive as pancreatic adenocarcinoma, timing is critical; therefore, pancreas stereotactic body RT (SBRT) is particularly attractive due to the short treatment course (3–5 days in comparison with 25–28 days in standard fractionation regimens), which limits the delay of full-dose chemotherapy and subsequent surgery.

In patients with borderline resectable (BRPC) and locally advanced PCA (LAPC) specifically, pancreas SBRT has evolved to become standard of care option per the newly developed National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines v.1.2016 and American Society of Clinical Oncology (ASCO) LAPC Clinical Practice Guideline [19]. Seminal studies of pancreas SBRT involved 1- and 3-fraction regimens in LAPC [20–30]. Early Phase I/II studies using single-fraction SBRT (25 Gy in 1 fraction) demonstrated excellent freedom from local progression (FFLP) at 1 year (>90%) and minimal acute toxicity, but high rates of late grade 2–4 gastrointestinal toxicity were reported. A single-arm Phase II multi-institutional study evaluated whether gemcitabine with fractionated SBRT (in 5 fractions of 6.6 Gy, total 33.0 Gy) could achieve reduced late grade

2–4 gastrointestinal toxicity compared with a historical cohort of patients treated with gemcitabine and a single 25 Gy-fraction of SBRT [26]. Forty-nine LAPC patients received up to three doses of gemcitabine (1,000 mg/m$^2$) followed by a 1-week break and SBRT (33.0 Gy in 5 fractions). Following SBRT, patients continued gemcitabine until progression or toxicity. Rates of acute and late (primary endpoint) grade ≥2 gastritis, fistula, enteritis, or ulcer toxicities were 2% and 11%, respectively. QLQ-C30 global quality of life scores remained stable from baseline to after SBRT (67 at baseline, median change of 0 at both follow-ups; $P$ 0.05 for both). Patients reported a significant improvement in pancreatic pain ($P < 0.001$) 4 weeks after SBRT on the QLQ-PAN26 questionnaire. Median serum CA 19-9 was reduced following SBRT (median time post-SBRT 4.2 weeks, 220 vs. 62 U/mL, $P < 0.001$). Median OS was 13.9 months (95% CI: 10.2–16.7). FFLP at 1 year was 78%. Four patients (8%) with LAPC at diagnosis were taken to surgery and underwent margin- and node-negative resections; a fifth patient was deemed resectable after multidisciplinary review but denied surgery.

Neoadjuvant SBRT has recently been studied in patients with BRPC in order to increase the likelihood of a margin-negative resection. A retrospective study included 73 patients with localized PCA (57 BRPC, 16 LAPC) who received induction chemotherapy followed by 5-fraction SBRT (25–30 Gy) at Moffitt Cancer Center was published in 2013 [31]. Most patients received induction GTX (66%) or gemcitabine alone (25%) whereas only 5% received induction FOLFIRINOX. Among the patients with BRPC, 56% underwent surgery with 97% achieving a margin-negative (R0) resection and 9% a pathologic complete response. Median OS in the patients who underwent a R0 resection was significantly higher than in unresected patients (19.3 vs. 12.3 months; $P = 0.03$). Furthermore, this approach was well tolerated with no acute grade ≥3 toxicity reported and only 5.3% late grade ≥3 toxicity. More recently, this single-institution series was updated to include a total of 159 patients (110 BRPC, 49 LAPC) [27]. Among the BRPC patients, 51% underwent surgery with 97% achieving a R0 resection and 7% a pathologic complete response. Median OS in the resected BRPC patients was 34 months. Acute grade ≥3 toxicity was 2% and late grade ≥3 toxicity was 5%.

Johns Hopkins reported on 88 patients (14 BRPC, 74 LAPC) who received induction chemotherapy followed by 25–33 Gy SBRT [28]. The majority (76%) of patients received gemcitabine-based chemotherapy as opposed to 5-FU (specifically, FOLFIRINOX)-based chemotherapy. Of the 19 patients (22%) who underwent surgery following SBRT, 84% had a R0 resection and 16% of patients had a pathologic complete response. Median OS of resected patients was 20.2 months versus 12.3 months in unresected patients ($P = 0.07$). Of note, 89% of resected patients had LAPC.

With the consideration that patients originally deemed unresectable may be taken to the operating room, a shift towards neoadjuvant therapy in LAPC has recently emerged. Of the 49 LAPC patients who were treated with induction chemotherapy and SBRT at Moffitt, 5 (10%) were resected with a 100% R0 resection rate. LAPC patients survived a median of 13.2 months [27]. Johns Hopkins reported 15 of 74 (20%) LAPC patients who went to surgery, with an 80% R0 resection rate and 13% pathologic complete response rate. Median OS in LAPC patients was favorable at 18.4 months [28].

## Proton Beam Therapy

The pancreas is adjacent to several radiosensitive organs including the duodenum, stomach, and small bowel. While IMRT can minimize the high doses received by these organs and therefore decrease the likelihood of adverse effects compared to 3D-CRT, pancreatic RT remains compromised by the proximity of these normal tissues [11,32,33]. Therefore, some have looked to proton beam therapy (PBT) as a means to improve the therapeutic ratio for PCA patients with encouraging early results.

Protons have an inherent advantage over photons in that they deliver the vast majority of their dose at a specified depth beyond which there is no dose to normal tissues. Because proton beams have no exit dose, as few as two beams are needed to create highly conformal dose distributions (Fig. 118.1). Therefore, PBT can significantly minimize or even completely eliminate radiation dose from large volumes of normal tissue.

Dosimetric studies have illustrated that PBT for PCA can significantly reduce dose to normal tissues compared to photon therapy, importantly without sacrificing target volume coverage. Nichols et al. compared IMRT and passive scattering PBT prescribed to 50.4 Gy for 8 patients with resected pancreatic head tumors [34]. PBT plans had significantly lower doses to adjacent structures such as the right kidney V18 Gy (27.3 vs. 50.5%; $P = 0.0156$), small bowel V20 Gy (15.4 vs. 47%; $P = 0.0156$), and stomach V20 Gy (2.3 vs. 20%; $P = 0.0313$). Ding et al. evaluated 3D-CRT, IMRT, passive scattering PBT, and a more conformal proton delivery technique called modulated scanning for 11 resected PCA patients [35]. Similar to the study by Nichols and colleagues, PBT (specifically the modulated scanning plans) had the lowest right kidney V18 Gy, stomach V20 Gy, and small bowel V15 Gy. A more recent comparison of 3D-CRT, IMRT, and passive scattering protons in resected patients from Loma Linda also had

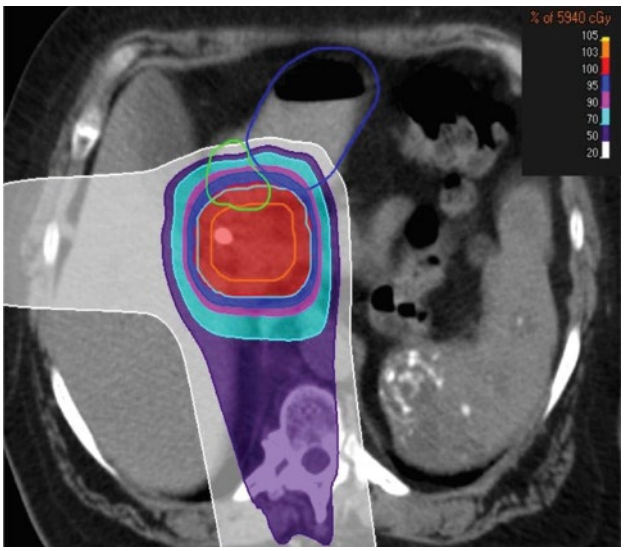


**Figure 118.1** PBT treatment plan illustrating the delivery of a highly conformal dose (to 59.4 Gy) to the tumor while minimizing dose to surrounding normal tissue.

similar results [36]. Proton plans delivered lower mean kidney dose, lower mean liver dose, lower maximum spinal cord dose, and lower small bowel dose (V15 Gy, V50 Gy). These findings are likely to be clinically relevant, especially with respect to reducing the volume of small bowel that receives lower doses. The small bowel is a major dose-limiting structure for pancreatic RT. In fact, a dose–volume relationship between small bowel dose and gastrointestinal toxicity has been described; it has been suggested that limiting the volume of small bowel that receives at least 15 Gy should be a priority [37,38]. The kidneys, liver, and stomach are also negatively affected by lower doses and thus the ability to spare these organs using PBT would likely add to the clinical significance of the dosimetric data presented earlier.

In addition to reducing toxicity, PBT may offer a means to safely escalate tumor dose for patients with LAPC and BRPC. Although higher tumor doses have been associated with improved treatment outcomes, the prescription dose for unresectable patients is limited to 50–54 Gy so that small bowel and stomach constraints can be achieved [39,40]. Hsiung-Stripp et al. compared passive scattering proton and 3D-CRT plans for patients with LAPC using 45 Gy for gross disease plus elective nodes followed by a 14.4 Gy boost to gross disease only for a total of 59.4 Gy [41]. Proton plans delivered lower dose to the spinal cord ($P = 0.003$), left kidney ($P = 0.025$), right kidney ($P = 0.059$), and liver ($P = 0.061$); small bowel was not evaluated. Bouchard et al. compared 3D-CRT, IMRT, and passive scattering PBT using a prescription dose of 72 Gy in 36 fractions and concluded that PBT could be beneficial, especially when treating tumors with anteriorly located small bowel [42]. Furthermore, PBT plans resulted in lower stomach V15 Gy (5 vs. 48%; $P < 0.0001$) and small bowel V15 Gy (9 vs. 61%; $P < 0.0001$). A group from the University of Pennsylvania recently published a comparison of IMRT, passive scatter PBT, and pencil beam scanning (PBS) PBT for 13 LAPC patients who were prescribed 55 Gy in 25 fractions [43]. Because PBS is the most conformal proton technique, it is not surprising that PBS resulted in less dose to some critical structures and was isoeffective with respect to others when compared to passive scattering; the clinical significance of this remains to be seen.

While the published clinical experiences using PBT for PCA are limited, the outcomes from these studies are encouraging (Table 118.1). Investigators from Massachusetts General Hospital (MGH) published outcomes of a Phase I trial that evaluated neoadjuvant hypofractionated PBT with concurrent capecitabine for resectable PC [44]. A total dose of 25 Gy delivered in 5 consecutive fractions was well tolerated; no dose-limiting toxicities occurred. There were no unexpected postoperative complications. In a similar trial, MGH compared neoadjuvant protons and photons with 5 Gy × 5 given with concurrent capecitabine. The study was closed early due to an unexpectedly high incidence of surgical complications seen in the photon group [45]. A subsequent MGH Phase I/II trial of neoadjuvant PBT (25 Gy in 5 fractions) with capecitabine for resectable PCA enrolled 50 patients with 35 being treated in the Phase II portion [46]. Grade 3 toxicity occurred in only two patients (4.1%). Of the 37 patients who had a pancreaticoduodenectomy, 81% had positive lymph nodes and 16% had positive margins. It is important to note that the lack of tumor downstaging was likely related to a 1-week break between RT and surgery. With median follow-up of 38 months for all patients, median progression-free survival was 10 months and median survival was 17 months.

The initial results of a Japanese Phase I/II trial of PBT with concurrent gemcitabine for LAPC were reported in 2012 [47]. Fifty patients were enrolled and were prescribed an aggressive treatment regimen; gemcitabine was given at 800 mg/m$^2$ weekly for 3 weeks concurrent with PBT and 80% of patients were prescribed 67.5 Gy in 25 fractions. With median follow-up of 12.5 months, outcomes were encouraging and included a grade 3 toxicity rate of ~10%. However, a subsequent publication that included 91 patients had a nearly 50% incidence of radiation-induced ulceration in the stomach and duodenum [48]. While margin expansions up to 5 mm were permitted during treatment planning to account for respiratory motion, no specific description of motion management usage was described in the manuscript. Therefore, the aggressive nature of the treatment regimen, and not PBT itself, is likely responsible for this high complication rate. Furthermore, this should serve as a reminder that despite

**Table 118.1** Summary of prospective studies evaluating the role of proton beam therapy in pancreatic cancer.

| Author | Study type | N | Resectability | Prescribed Dose | Elective Nodal Irradiation | Concurrent chemotherapy | Median Follow up (mos) | LRC | PFS | OS | Grade ≥3 Toxicity |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hong et al. [44]** | Phase 1 | 15 | Resectable | **Level 1**: 3 Gy(RBE) × 10<br>**Levels 2-4**[*]: 5 Gy(RBE) × 5 | Yes | Capecitabine 825 mg/m$^2$ BID | 12 | 93% | Median 10 months | Median not reached | Level 4: biliary obstruction ($n = 1$) |
| **Hong et al. [46]** | Phase 1/2 | 50 | Resectable | 5 Gy(RBE) × 5 | Yes | Capecitabine 825 mg/m$^2$ BID | 38 | 84% | Median 10.4 months | Median 17.3 months | Colitis ($n = 1$), chest wall pain ($n = 1$) |
| **Terashima et al. [47]** | Phase 1/2 | 50 | Unresectable | **P-1**: 2 Gy(RBE) × 25 (5 patients)<br>**P-2**: 2.7 Gy(RBE) × 26 (5 patients)<br>**P-3**: 2.7 Gy(RBE) × 25 (40 patients) | Yes | Gemcitabine 800 mg/m$^2$ | 12.5 | 1-year 81.7% | 1-year 64.3% | 1-year 76.8% | **P-3**: gastric ulcer/ hemorrhage ($n = 4$) |
| **Sachsman et al. [50]** | Phase 2 | 11 | Unresectable | 1.8 Gy(RBE) × 33 | No | Capecitabine 500 mg/m$^2$ | 14 | 1-year 86% | 1-year 55% | Median 18.4<br>1-year 61% | None |

LRC, locoregional control; PFS, progression-free survival; OS, overall survival; RBE, relative biologic effectiveness.
*Levels 2 and 3 treated on nonconsecutive days; level 4 treated on consecutive days.

the dosimetric advantages of PBT, we must remain vigilant about limiting dose to normal tissues and that motion management should always be considered.

The University of Florida also published early clinical outcomes of PBT for PC. Nichols et al. reported outcomes of 22 patients with resected and unresected PCA treated with PBT ranging from 50.4 to 59.4 Gy and concurrent capecitabine 1,000 mg twice daily [49]. With median follow-up of 11 months, no patient had any grade 3 toxicity. In fact, when proton treatment plans were altered to reduce bowel and stomach dose (posterior and right lateral beams were used instead of anterior and left lateral beams), no patient experienced grade ≥2 gastrointestinal toxicity. This beam arrangement was used by the same group to later treat unresectable patients using 59.4 Gy in 33 fractions and concurrent capecitabine and again there was no report of grade ≥2 gastrointestinal toxicity [50]. Despite the short follow-up and small patient numbers, these clinical data are certainly promising that the dosimetric advantages of protons may translate into clinically meaningful benefit.

These dosimetric and clinical outcomes suggest that PBT may be poised to have an expanded role in the management of PC. The reduction in normal tissue dose achieved by PBT could potentially transform the paradigm of PCA management perhaps through radiation dose escalation and/or novel combinations of PBT and multi-agent systemic chemotherapeutic regimens. While future studies will undoubtedly evaluate such uses of PBT, attention should also be paid to identifying patient subsets that are most likely to benefit from PBT as well as better understanding the effects of motion on PBT for abdominal targets.

While there is much potential to improve the therapeutic ratio for PCA patients with PBT, some practical proton planning and delivery considerations should not be overlooked. Proton dose deposition is strongly influenced by tissue densities within the beam path and changes in these densities such as from respiratory motion, setup errors, and even bowel peristalsis can potentially lead to underdosing of target and overdosing of normal tissues. As such, motion management strategies like respiratory gating, breath hold, or abdominal compression for targets in the upper abdomen should be used. Beam angles are selected in large part based on how reproducible the target and normal tissues will be within each beam on a daily basis. For example, beams that traverse large amounts of bowel are not ideal because the bowel shape and filling can be highly variable. Finally, image guidance for PBT is currently limited to only kV imaging at the majority of proton centers. This is not ideal for soft tissue assessment in PCA patients and therefore larger margins are typically used due to setup uncertainty. Cone beam CT (CBCT) has only recently become available at a few select proton centers and is expected to become more widely available over the next several years. CBCT will enable more selective margins to be used thereby further reducing normal tissue dose.

## Future Directions

Perhaps most critical to the appropriate use of radiation in patients with resected PCA is appropriate patient selection. Identifying those patients at greatest risk for local versus distant progression can help determine selective administration of RT and/or surgery. Development of predictive biomarkers that can identify those patients at greater risk for local failure is needed. One autopsy series of consecutive patients who succumbed to PCA demonstrated that roughly 30% of patients most likely died from locally destructive disease, highlighting the importance of achieving better local control [51]. In these patients, expression of Smad4 was highly associated with a locally destructive phenotype, findings which have also been replicated in a Phase II study of chemoradiation for LAPC [52].

As we await identification of more biomarkers, clinical investigation into treatment dose and fractionation may allow the benefit of time to understanding an individual patient's biology and risk of local failure. In addition to biomarkers, imaging modalities such as positron emission tomography (PET) may soon allow clinicians to further guide management decisions and practice personalized care. Historically delivered using photons, SBRT combined with PBT may have large clinical implications for patients with PCA. Future investigation will provide insight into the combination of SBRT and PBT as well as incorporation of SBRT and PBT with targeted therapy.

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# 119

# Management of Cancer Recurrence

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## Introduction

Management of pancreatic ductal adenocarcinoma (PDAC) recurrence is a very relevant topic because even after resection with curative intention in combination with adjuvant therapy this cancer recurs in the majority of cases. Most patients eventually die from local, metastatic, or combined tumor recurrences resulting in median survival and 5-year survival rates of only 20–25 months and 20% after resection, respectively [1]. Several reasons are thought to contribute to the high recurrence rate and poor prognosis. An obvious reason for local recurrences is insufficient resection margin clearance reflected by the high rate of R1 resections identified by stringent margin assessment [2–5]. However, more importantly most patients succumb to early development of metastatic recurrence and the existence of undetectable micrometastatic disease at the time of resection is thought to be the main reason for this systemic failure. While this provides a clear rationale for the administration of systemic neoadjuvant or adjuvant therapies (see Chapters 112 and 113), results from randomized controlled trials show that systemic therapy can significantly delay but not prevent recurrence (see Table 119.1). Aggressive tumor biology and high chemoresistance are thought to be main reasons for the lack of efficacy of most currently available chemotherapy regimens.

With significant improvements in the surgical therapy and in accompanying (neoadjuvant or adjuvant) systemic treatment options the long-lasting controversy on the role of surgery in resectable PDAC has been resolved [1]. High-volume centers have reported actuarial survival rates after resection of 20% overall and of up to 60% in patient subgroups with a favorable combination of prognostic factors [5–8]. There is clear evidence that surgical resection in combination with systemic treatment remains the only chance of cure in patients with PDAC.

In contrast, although PDAC recurrence is a pressing problem affecting the majority of patients, its management remains poorly studied, highly controversial, and is far from being evidence-based. A part of the underlying problem is a certain therapeutic nihilism towards PDAC recurrence that is reflected by the fact that current treatment guidelines do not even clearly endorse structured surveillance programs after resection due to a lack of evidence for effective treatment options or a survival benefit by regular follow-up examinations [9,10].

This chapter aims to give an overview of current treatment options for PDAC recurrence with a focus on isolated local recurrence. We also give an overview of several aspects that are relevant in this context, including incidence and pattern of recurrence after resection, and the potential value of structured surveillance after resection.

## Incidence, Timing, and Pattern of Recurrence

Due to the lack of structured surveillance programs after resection for PDAC our knowledge of the true incidence, timing, and pattern of PDAC recurrence is limited. The best information is available from randomized controlled trials on resection and adjuvant therapy (Table 119.1; [11–18]), from autopsy series [19,20], and from some observational studies dedicated to the topic of recurrence [21].

Data from randomized controlled trials (RCT) give the best reference with respect to the "clinical" pattern of recurrence that we would expect to see based on

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**Table 119.1** Incidence, timing and pattern of recurrence after potentially curative resection for pancreatic cancer in selected RCTs on adjuvant therapy.

| Reference & name of study | Study arms | *n* | Overall survival (median & survival rates) | Disease-free survival (median & survival rates) | Incidence and pattern of recurrence | Follow-up (median) |
|---|---|---|---|---|---|---|
| Neoptolemos et al. 2004 [11]<br>ESPAC-1 | 4 × 4 factorial design:<br>- CRT (20 Gy + FU)<br>- Chemotherapy: FU<br>- Chemotherapy + CRT<br>- Observation | 73<br>75<br>72<br>69 | 13.9 months, 5YSR: 7%<br>21.6 months, 5YSR: 29%<br>19.9 months, 5YSR: 13%<br>16.9 months, 5YSR: 11% | Chemotherapy:<br>15.3 months<br>No chemotherapy:<br>9.4 months | Local only: 35%<br>Local and systemic: 27%<br>Systemic only: 34% | Survivors:<br>47 months |
| Smeenk et al. 2007*<br>[12]<br>EORTC 40891<br>(long-term results) | CRT (40 Gy + FU) | 110 | 21.6 months<br>5YSR: 25%, 10YSR: 17% | 18 months<br>5YSR: 21%, 10YSR: 16% | Total: 68%<br>Initially local only: 20%<br>Local and systemic: 29%<br>Initially systemic: 48% | Overall: 11.7 years<br>Survivors:<br>9.8 years |
| | Observation | 108 | 19.2 months<br>5YSR: 22%, 10YSR: 18% | 14.4 months<br>5YSR: 20%, 10YSR: 17% | Total: 70%<br>Initially local only: 21%<br>Local and systemic: 30%<br>Initially systemic: 46% | |
| Oettle et al. 2007<br>[13]<br>CONKO-001 | Gemcitabine | 179 | 22.1 months<br>2YSR: 47.5%, 5YSR: 22.5% | 13.4 months<br>2YSR: 30.5%, 5YSR: 16.5% | Total: 74.3%<br>Local ± systemic: 34%<br>Systemic only: 56% | 53 months |
| | Observation | 175 | 20.2 months<br>2YSR: 42%, 5YSR: 11.5% | 6.9 months<br>2YSR: 14.5%, 5YSR: 5.5% | Total: 92.0% | |
| Ueno et al. 2009<br>[14]<br>JSAP-02 | Gemcitabine | 58 | 22.3 months<br>2YSR: 48.3%, 5YSR: 23.9% | 11.4 months<br>2YSR: 27.2% | Total: 76%<br>Local: 23%<br>Systemic: liver 30%, peritoneal 18%, other 27% | 60.4 months |
| | Observation | 60 | 18.4 months<br>2YSR: 40.0%, 5YSR: 10.6% | 5.0 months<br>2YSR: 16.7% | Total: 88%<br>Local: 32%<br>Systemic: liver 30%, peritoneal 13%, other 23% | |
| Regine et al. 2008<br>[15]<br>RTOG 97-04 | FU - CRT (FU, 50.4 Gy) - FU | 230 | 16.9 months, 3YSR: 22% | NA | Total: 85.7%<br>Local: 28%, regional: 8%<br>Systemic: 71% | Overall:<br>1.5 years<br>Survivors:<br>4.7 years |
| | Gemcitabine - CRT (FU, 50.4 Gy) - Gemcitabine | 221 | 20.5 months, 3YSR: 31% | NA | Total: 83.3%<br>Local: 23%, regional: 7%<br>Systemic: 71% | |
| Neoptolemos et al. 2010<br>[16]<br>ESPAC-3 | FU + Folinic acid | 551 | 23.0 months, 2YSR: 48.1% | 14.1 months, 2YSR: 30.7% | Total: 63%<br>(local, systemic, or both) | Survivors:<br>34.2 months |
| | Gemcitabine | 537 | 23.6 months, 2YSR: 49.1% | 14.3 months, 2YSR: 29.6% | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Van Laethem et al. 2010** [17] | Gemcitabine (4 cycles) | 45 | 24.4 months, 2YSR: 50.2% | 10.9 months | Local only: 24%<br>Local and systemic: 13%<br>Systemic only: 40% | 33.3 months |
| EORTC-40013-22012/ FFCD-9203/GERCOR | Gemcitabine, (2 cycles) + Gem.-based CRT | 45 | 24.3 months, 2YSR: 50.6% | 11.8 months | Local only: 11%<br>Local and systemic: 20%<br>Systemic only: 42% | 30.7 months |
| Schmidt et al. 2012 [18] CapRI | Chemoradioimmuntherapy (FU, Cisplatin, Interferon, 50 Gy) | 64 | 32.1 months | 15.2 months | Total: 67%<br>(local, systemic, or both) | Overall: 42.7 months |
| | FU + Folinic acid | 68 | 28.5 months | 11.5 months | | |

*only T1/2, N0-1a pancreatic or T1-3, N0-1a periampullary cancers included.

**only R0-resections included.

ESPAC, European Study Group for Pancreatic Cancer; EORTC, European Organization for Research and Treatment of Cancer; CONKO, Charité Onkologie; RTOG, Radiation Therapy Oncology Group.

YSR, Year survival rate; FU, Fluorouracil; NA, data not available.

structured follow-up programs with assessment of patient history, physical examination, cross-sectional imaging (usually contrast-enhanced computed tomography), and serum values of tumor markers, especially carbohydrate antigen 19-9 (CA 19-9). The follow-up results of selected RCT published since 2000 are summarized in Table 119.1 and allow several important conclusions on incidence, timing, and pattern of recurrence after resection for PDAC. Data on disease-free survival from RCT comparing adjuvant therapy versus observation show that without adjuvant therapy 50% of patients develop clinically detectable cancer recurrence within 5–10 months [11,13,14] and chemotherapy with gemcitabine or 5-fluorouracil [5-FU] monotherapy can delay this to 11–15 months. With patient selection based on known prognostic factors recurrence is observed later, at 14.4 months without and at 18 months with adjuvant therapy [12]. Even in the more recent RCT the median disease-free survival remains at 12–15 months [16,18]. Up to 90% of patients without and still about 70% with adjuvant therapy develop PDAC recurrence within a follow-up time of 30–50 months. While reporting on the pattern of recurrence in different RCT is heterogeneous, 20–30% of patients appear to first develop isolated local recurrence, while the majority of patients present with systemic progression. In summary, the data on recurrence from RCT show that even with adjuvant therapy most patients develop recurrence within 1.5 years after resection. The data also suggest that based on structured surveillance programs it may be possible to identify a subgroup of 20–30% of patients who first develop isolated local recurrence.

A multicenter observational study in 1,130 patients undergoing resection between 2000 and 2010 reported a median actuarial overall survival of 25.9 months (median follow-up 18 months) [21]. In this study the local recurrence rate was 22% and the distant recurrence rate was 41% based on radiographic evidence, pathologic confirmation, and/or tumor marker elevation, confirming the observations from RCT. The most relevant risk factor associated with local recurrence in this study was positive lymph node status. This suggests that many patients with "local recurrence" may in fact have progression of preexisting lymph node metastases and may be good candidates for re-resection.

While the RCT and observational clinical studies give us an indication of the clinically detectable pattern of recurrence, the few available autopsy series demonstrate the "true" pathologic pattern of recurrence and the relevance of the sites of recurrence for death. In a Japanese autopsy study in 24 patients who died after resection of pancreatic cancer 75% of patients had local recurrence, 75% had distant metastases (50% hepatic), and the local recurrence was the cause of death in 17% of patients [19]. Another autopsy study in patients with PDAC included 22 patients after resection [20]. At autopsy, 2 patients (9%) had died of unrelated causes and had no evidence of recurrence, 3 (14%) had isolated local recurrence, 4 (18%) had only metastatic recurrence, and 13 (59%) had both local and systemic recurrence. In this study, expression of DPC4 in the tumor was highly correlated with metastatic but not with localized disease [20].

These autopsy studies confirm that after resection and adjuvant therapy for pancreatic cancer most patients die of systemic disease, but a subgroup of patients develop and die from isolated (or predominantly) local recurrence. Molecular properties of the tumor appear to contribute to the pattern of recurrence [20].

It will be interesting to see how the neoadjuvant or adjuvant administration of more aggressive chemotherapy regimens such as FOLFIRINOX and advances in radiation oncology will affect incidence, timing, and pattern of PDAC recurrence [22]. Translational studies characterizing the molecular properties of PDAC in the context of the pattern of disease may identify biomarkers for the prediction of the pattern of recurrence that may be useful for decision making as a step towards precision oncology.

## Surveillance After Resection for Pancreatic Cancer

Current evidence-based clinical guidelines on PDAC therapy do not clearly endorse structured surveillance programs after resection and completion of adjuvant treatment, mainly because there is no available data showing that earlier detection and treatment of recurrence lead to better patient outcomes [9,10]. Population-based or single high-volume center studies from the United States demonstrated no significant survival benefit but increased costs from regular surveillance computed tomography (CT) scans [23,24]. While the German guidelines do not recommend a structured follow-up at all [10], the American NCCN guidelines recommend history and physical examination every 3–6 months for 2 years, then annually and, as category 2B recommendations (lower-level evidence), CT scans and CA 19-9 measurements every 3–6 months for 2 years after surgical resection based on the consensus that earlier detection of recurrence may facilitate patient eligibility for investigational studies or other forms of treatment [9].

It has to be acknowledged that such clinical guidelines have to be based on current evidence and have to include socioeconomic considerations and that there is currently little evidence for any of the treatment options for pancreatic cancer recurrence discussed later (Table 119.2). But how should such evidence ever be generated if not

**Table 119.2** Treatment options for recurrent pancreatic cancer.

| Treatment | Potential indications | Intention | Comments |
|---|---|---|---|
| **Chemotherapy** | Any recurrence<br>Systemic recurrence | Palliation | Most frequently used for pancreatic cancer recurrence irrespective of pattern.<br>No evidence based on RCT in the setting of recurrence.<br>Choice for best regimen has to be based on previous chemotherapy, performance status, etc. (see Chapters 113 & 116). |
| In multimodal setting with re-resection | Isolated local recurrence | Medium- to long-term control<br>Potential "cure" | Similar rationale as for neoadjuvant and adjuvant therapy in primary pancreatic cancer.<br>No evidence based on RCT.<br>Data from retrospective studies in selected patients with recurrence available (see Table 119.3b) |
| **Chemoradiation** | Isolated local recurrence | Palliation<br>Local control<br>Pain therapy | Preferred for isolated local recurrence in many centers, especially in a setting of unresectable perivascular recurrence.<br>No evidence from RCT.<br>Data from retrospective studies in selected patients with recurrence available (see Table 119.3a) |
| In multimodal setting with re-resection | Isolated local recurrence | Medium- to long-term control<br>Potential "cure" | May be used in a "neoadjuvant" setting and in a multimodal concept involving external and intraoperative radiotherapy.<br>Data from observational studies in selected patients with recurrence available (see Table 119.3b) |
| **Surgery**<br>- *Local re-resection*<br>In multimodal setting with chemotherapy or chemoradiation | Isolated local recurrence | Medium- to long-term control<br>Potential "cure" | Performed by only a few specialized surgical centers,<br>No evidence from RCT.<br>Data from retrospective studies in selected patients with recurrence available (see Table 119.3b) |
| - *Metastasectomy*<br>In combination with chemotherapy | Oligometastatic systemic recurrence | Medium- to long-term control | Literature restricted to case reports and small retrospective studies with mixed cohorts including synchronous metastases.<br>Several small series with favorable survival after resection of isolated lung metastases. |
| **Locally ablative therapies** | Isolated local recurrence (in combination with chemotherapy) | Palliation<br>Local control | Different modalities (radiofrequency ablation, irreversible electroporation, etc.) are currently evaluated in some centers.<br>Literature restricted to case reports and retrospective studies with mixed cohorts of primarily unresectable tumors and local recurrences. |

based on structured surveillance for early detection of PDAC recurrence?

Even with the limitations of cross-sectional imaging and serum levels of tumor markers in detecting metastatic disease known from the primary diagnosis of pancreatic cancer, the aforementioned data from RCT suggest that a structured follow-up program based on these tools would allow for earlier detection of localized recurrence.

In our center we offer a structured follow-up program to all patients with PDAC resection and we assess its potential value for early detection of recurrence and its impact on the clinical management of patients. Heye et al. [25] demonstrated that the comparison of sequential follow-up CT scans allows for early detection of local recurrences by observation of subtle but progressive changes at typical predilection sites for perivascular and lymphatic local recurrences (Fig. 119.1).

In an analysis of 940 postoperative follow-up visits of 618 patients over a 1-year period recurrence was detected in 74 (40%) of 184 patients after PDAC resection, of whom only 26% had symptoms [26]. In all of these patients a cancer-directed therapy was initiated. Of 16 patients with isolated local recurrence 12 (75%) were without symptoms and 11 were referred for re-resection.

These data have important implications, because they show that most recurrences are at first asymptomatic, will

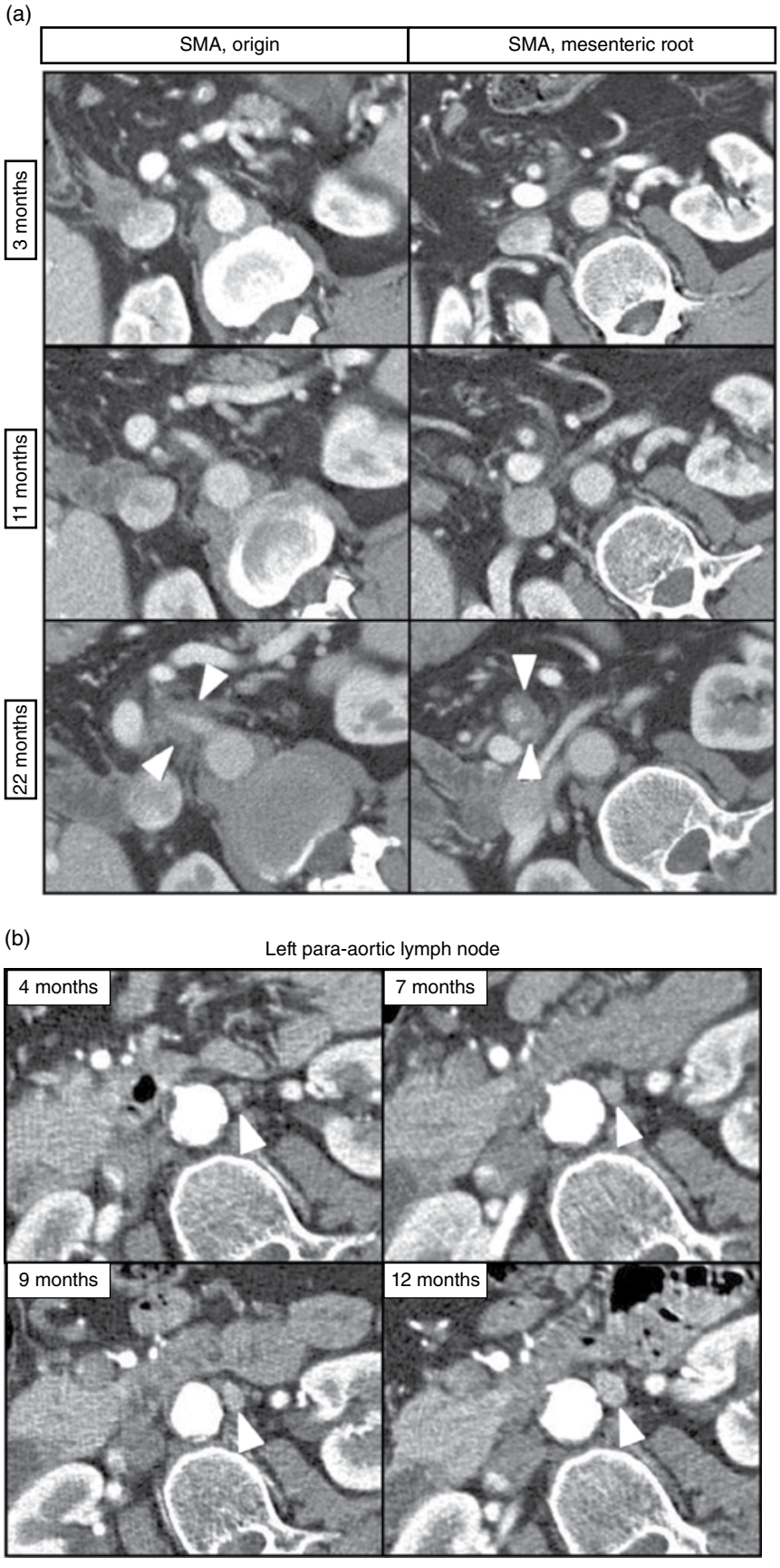


**Figure 119.1** Typical findings of local recurrence during sequential CT scans for surveillance after pancreatic resection for cancer. (a) Perivascular recurrence around the superior mesenteric artery (SMA) at different time points after pancreatoduodenectomy for pT3pN1 adenocarcinoma in a 69-year-old patient. Unsuspicious findings after 3 months, gentle density around the SMA at 11 months, development of dense tissue incasing the SMA as evidence of recurrence after 22 months. (b) Lymph node recurrence in a left para-aortic lymph node at different time points after pancreatic left resection for cancer. Gradual increase in lymph node size from 9 mm at 4 months to 16 mm at 12 months. *Source:* Modified from Heye et al. 2011 [25]. Reproduced with permission of Baishideng Publishing Group.

be detected earlier with regular surveillance including cross-sectional imaging, offering the opportunity for earlier initiation of oncologic therapy. While it appears logical that earlier detection of recurrence and initiation of therapy may result in better outcomes, future studies will have to assess how the treatment options discussed later affect survival and quality of life of patients with PDAC recurrence.

With advances in treatment options and diagnostic tools, the potential of structured surveillance programs will have to be reevaluated in the future. Novel analytic targets such as exosomal markers and cell-free DNA that are currently being evaluated in the early detection of PDAC may also be promising tools for postresection surveillance [27,28].

## Treatment of Systemic Recurrence of Pancreatic Cancer

The treatment options for PDAC recurrence after resection are based on little evidence. The literature is restricted to mostly small retrospective studies in selected patients and in multiple case reports, suggesting a considerable publication bias. Table 119.2 provides an overview of available treatment options for PDAC recurrence. Based on common sense the appropriate treatment options depend on multiple parameters including the pattern and localization of recurrence, the clinical performance status and comorbidity of the patient, previous treatment, and timing (i.e., interval between resection and recurrence).

Clearly, systemic chemotherapy is the appropriate palliative therapy for the majority of patients with PDAC recurrence, because they present with systemic disease. There is little evidence from the literature as to the best regimen in this situation. However, this is a palliative situation and depending on the time of recurrence (during or after adjuvant therapy), previous therapy, and performance status, the same principles as outlined for second-line adjuvant and palliative chemotherapy (Chapters 113 and 116) may be recommended. While metastastectomy for systemic PDAC recurrence is highly controversial, favorable survival has consistently been reported after resection of the rare cases of isolated lung metastases [29–31]. With respect to quality of life, adequate pain therapy and supportive care are very important aspects of palliative therapy in patients with PDAC recurrence (Chapter 117).

## Treatment of Isolated Local Recurrence of Pancreatic Cancer

While the current NCCN guidelines recommend inclusion in a clinical trial (preferred), chemoradiation (if not previously performed), switch to an alternative systemic chemotherapy, or best supportive care for local recurrence [9], the German S3 guidelines recommend the evaluation of local therapy options for isolated local recurrence based on the retrospective studies available [10].

Available treatment options for local recurrences include chemoradiation, re-resection, and locally ablative therapies (Table 119.2). In the following we will focus on chemoradiation and re-resection. While feasibility and safety of different locally ablative therapies are currently being tested for locally advanced PDAC, little is known on efficacy and long-term outcome [32] and data on locally ablative therapies for local recurrence are restricted to case reports.

## Rationale for "Local" Therapy Options

PDAC is a systemic disease and most patients will eventually die from metastatic disease. This notion has led to a long-lasting debate as to the value of resection even in resectable PDAC. Based on good evidence and with advances in both surgery and systemic therapy, resection in combination with systemic therapy has now been established as the only therapy with the potential for long-term survival or cure [1]. With further advances the limits for surgery are today being pushed towards extended resections and resections after aggressive neoadjuvant therapies with promising results for locally advanced PDAC [22,33]. Strategies of neoadjuvant treatment have the advantage that patients with early systemic progression who have no benefit of surgical resection are selected out before surgery. Together with the pattern of recurrence and survival, data from molecular studies suggest that patients with isolated local recurrence may have biologically distinct PDAC subtypes of a less aggressive phenotype with slower systemic progression [20,34]. This notion provides a good rationale to test localized treatments such as re-resection and chemoradiation in this biologically selected subgroup of patients. However, the majority of patients presenting with suspected isolated local recurrence may also have micrometastatic disease and develop systemic progression later. Therefore, as for primary pancreatic cancer, local therapies for recurrence have to be embedded in multimodal treatment strategies that include systemic chemotherapy.

## Chemoradiation for Isolated Local Recurrence

Chemoradiation is discussed by many as the main alternative to merely palliative chemotherapy for treatment of local recurrence. The evidence for chemoradiation is based on retrospective series of limited size (Table 119.3a).

**Table 119.3(a)** Retrospective series of chemoradiation for local recurrence of pancreatic cancer.

| Author | Year | *N* included | Radiotherapy | Chemotherapy | Oncologic ouctomes |
|---|---|---|---|---|---|
| Wilkowski [38] | 2006 | 18 | 45 Gy | 5-FU (*n* = 4)<br>5-FU, Gem (*n* = 6)<br>Cis, Gem (*n* = 8) | OS: 17.5 months<br>PFS: 14.7 months<br>CR: *n* = 6 (33%) |
| Wild [37] | 2013 | 18* | SBRT<br>25 (20-27) Gy | 28% (*n* = 5) | OS: 8.8 months |
| Habermehl [35] | 2013 | 41 | 39.6–54 Gy<br>+ IORT (15 Gy) in *n* = 15 | Gem (90%)<br>5FU or Cap (10%) | OS: 16.1 months<br>PFS: 6.9 months<br>CR: *n* = 6 (15%) |
| Nakamura [36] | 2014 | 30 | 54 (39–60) Gy | Gem (*n* = 18)<br>S-1 (*n* = 7) | OS: 15.9 months<br>PFS: 6.9 months |

Included are studies with >5 patients undergoing chemoradiation.
*Study includes *n* = 3 patients after definitive chemoradiation (no resection) for locally advanced disease.
SBRT, stereotactic body radiation therapy; OS, overall survival; PFS, progression-free survival; CR, complete remission (clinical).

**(b)** Retrospective series of re-resection for local recurrence of pancreatic cancer.

| Author | Year | *N* operated | *N* resected | Resection rate | Mortality | Other cancer-directed therapy | Oncologic outcome |
|---|---|---|---|---|---|---|---|
| Kleeff[#] [39] | 2007 | 30 | 15 | 50% | 1 (7%) | Chemoradiation: *n* = 7<br>Radiation: *n* = 1<br>Chemotherapy: *n* = 9<br>2nd re-resection: *n* = 6<br>None: *n* = 4<br>NA: *n* = 9 | Resection:<br>OS: 17.0 months<br>Exploration:<br>OS: 9.4 months |
| Lavu [40] | 2011 | NA | 8 | NA | 0 | NA | OS: 17.5 months |
| Thomas[$] [31] | 2012 | NA | 7 | NA | 0 | NA[$] | OS: NA[$]<br>DFS: 9 months |
| Strobel[#] [34] | 2013 | 97 | 41 | 42.3% | 1 (1.8%) | In cases with re-resection:<br>Chemoradiation: *n* = 22<br>IORT: *n* = 22<br>Chemotherapy: *n* = 21<br>NA: *n* = 4 | Re-resection:<br>OS: 26.0 months<br>Exploration (ILR):<br>OS: 10.8 months<br>Exploration (mets.):<br>OS: 9.4 months |
| Boone[$] [41] | 2014 | NA | 10 | NA | 0 | NA | OS: 31.8 months |
| Miyazaki [42] | 2014 | NA | 11 | NA | 0 | Chemotherapy: *n* = 8<br>None: *n* = 3 | Resection:<br>OS: 25.0 months<br>No re-resection:<br>OS: 9.3 months |
| Shima [43] | 2015 | NA | 6 | NA | 0 | Chemotherapy: *n* = 1 | OS: 27.5 months |

Included are studies with >5 patients undergoing re-resection.
[#]The cohort by Kleeff et al. is from the same center and included in the follow-up study by Strobel et al.
[$]Mixed cohort of local and distant recurrence. Only data of patients with local recurrence included here.
OS, overall survival; DFS, disease-free survival; ILR, isolated local recurrence without evidence of systemic disease confirmed by surgical exploration.

The actuarial overall median survival reported for chemoradiation is around 16–18 months, with median progression-free survival of 6.9 months in the two larger out of four studies [35–38]. A poorer median overall survival of only 8.8 months in the only series with a low reported rate of systemic therapy (28%) [37] supports the notion that any local therapy for recurrence has to be accompanied by systemic chemotherapy in order to achieve favorable survival results.

## Re-resection for Isolated Local Recurrence

The evidence for re-resection for the treatment of local PDAC recurrence is also based on retrospective series of limited sample size (Table 119.3b; [31,34,39–43]). However, the reported outcome with median overall survival rates of 25 to >30 months after re-resection in the most recent series [34,41–43] appear to be superior to the outcome reported after chemoradiation. It should be noted that these differences may in part be explained by selection bias due to the exclusion of patients with radiologically undetectable metastatic disease in the resection series. While most series did not report on resection rates, the series from Heidelberg initially reported a resection rate of 50%, which dropped to 42.3% in the larger series, mainly due to intraoperative diagnosis of metastases [34,39]. Disease-free survival after resection was not consistently reported. However, the summarized results demonstrate that re-resection was safe with 0–2% mortality and associated with very encouraging survival outcome at least in the selected patients who underwent re-resection. It should be emphasized that these results originate from specialized referral centers for pancreatic surgery and may not be commonly applicable.

We have reported our initial experience with re-resection in 2007 [39] and the so far largest series on surgery for isolated local PDAC recurrence in 2013 [34]. Analysis in this series allowed for several relevant observations. Of 97 patients with preoperatively suspected isolated local recurrence and histologic proof of recurrence, 57 (59%) had isolated local recurrence by surgical exploration, while distant metastases were identified in 40 (41%) patients. This again highlights the necessity of better diagnostic tools to detect small metastatic deposits, a problem known from primary PDAC staging. Of 57 isolated local recurrences, 41 (72%) were resected while 16 (28%) were locally unresectable. Median postoperative survival was 16.4 months in isolated local recurrence versus 9.4 months in metastatic recurrence, confirming the better prognosis of isolated recurrence that had been described previously [44]. Importantly, median survival in isolated local recurrence was significantly longer after resection (26.0 months) versus exploration for local unresectability (10.8 months). This observation in isolated local recurrence points to a potential survival benefit from re-resection. R0 re-resection was achieved in 18 patients and resulted in 30.5 months median survival.

While a true benefit of re-resection can only be demonstrated by RCT, these results suggest that selected patients with suspected isolated local PDAC recurrence may benefit from re-resection.

## Selection of Patients for Local Therapy

Several studies have identified the disease-free interval between primary tumor resection and recurrence to be associated with survival after re-resection or chemoradiation with different cutoffs from 9 to 20 months [31,36,39,41]. In the largest available series disease-free interval was not associated with prognosis while CA 19-9 was predictive for survival [34].

While exact cutoff values remain to be defined, early recurrence versus prolonged disease-free survival may be indicators for rapidly progressing versus less aggressive tumors and should be considered in decision making.

As in primary pancreatic cancer, CA 19-9 appears to be associated with survival in cancer recurrence. As discussed earlier, novel diagnostic tools and biomarkers may improve patient selection in the future [20,27,28].

## Conclusions

Pancreatic cancer recurrence is a pressing concern affecting the vast majority of patients even after resection and completion of systemic therapy. While the majority of patients develop metastatic recurrence, a significant subgroup of 20–30% of patients first develop isolated local recurrence. These patients may have tumors of less aggressive subtypes with slower systemic progression and may, therefore, benefit from a multimodal treatment strategy that includes local therapy. As most recurrences are at first asymptomatic structured follow-up programs are needed to identify these patients. Although the literature provides little evidence with respect to the management of PDAC recurrence, both chemoradiation and surgical re-resection have been suggested to be safe and effective by several retrospective series. The best "standard" management for cancer recurrence can only be determined based on RCT, which will be difficult to conduct for this indication. More likely, the therapy for PDAC recurrence will remain a matter of interdisciplinary, personalized

decision making. Novel effective treatments for PDAC therapy and novel biomarkers for early diagnosis will hopefully also advance the fields of surveillance after resection, and result in earlier detection and more effective management of isolated and systemic PDAC recurrence.

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# Long-Term Outcome After Treatment of Pancreatic Cancer

## 120

## Survival and Late Morbidity After Resection of Pancreatic Cancer

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### Introduction

Pancreatic cancer is currently the third leading cause of cancer death in the United States [1]. In light of the decreasing trend in cancer deaths from other common cancer types, pancreatic cancer deaths are expected to become second only to lung cancer within the next decade. Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal cancer with an overall 5-year survival for affected patients estimated to be only 7% [1]. Approximately 20% of patients with PDAC have localized and resectable disease at diagnosis. This subgroup has the best long-term outcome. In this chapter, we will review the survival of patients with resected PDAC, and highlight trends in survival over time. We will examine advances in prognostic markers, which can inform survival projections. As increasing numbers of patients achieve prolonged survival after resection for PDAC in the future, an understanding of late morbidity after pancreatic resection will become increasingly important. We will summarize the literature on delayed complications, although this body of work is relatively sparse and generally limited to studies of patients who underwent resections for benign disease.

### Survival after Resection for Pancreatic Cancer

Reported long-term survival outcomes after pancreatic resection for PDAC vary based on the specific characteristics of the patient cohort under investigation. Frequently, oncologists quote survival data from highly cited randomized, large, multi-institution adjuvant trials that include patients who have undergone a resection with curative intent, such as ESPAC-3 [2], RTOG 9704 [3], and CONKO-001 [4] (these trials are detailed elsewhere in this book). The reported median overall survivals in these studies were 23.2, 20.0, 22.8 months, respectively. In the ESPAC-1 trial the median survival was 14.0 months with no adjuvant chemotherapy [5] while in the recent CONKO-001 trial the no-treatment arm had a median survival of 20.2 months.

These results might be favorably skewed, however, compared with patients treated outside clinical trials because they are confounded by rather strong selection and entry biases related to strict eligibility criteria. For instance, these studies typically exclude patients with the most unfavorable cancers that are associated with either early recurrence at the time of eligibility screening, or in the case of CONKO-01 markedly elevated postoperative serum CA 19-9 levels. In addition, patients with significant medical comorbidities, or patients who recover poorly after pancreatectomy (including those who suffer a perioperative death), are excluded from these studies. Indeed, the ability to receive adjuvant therapy after resection for PDAC may be an important prognostic marker that is independent from the potential therapeutic benefits of such therapy (about 80–90% of patients in most high-volume centers in the United States receive adjuvant treatment). Population-based (nonrandomized) studies that suggest a strong benefit to adjuvant therapy should take this point into consideration [6].

Taken together, adjuvant trials reveal that modern single-agent adjuvant chemotherapy confers an average median survival advantage of perhaps 3–5 months over best supportive care [7,8]. Recurrences typically occur around 13 months after resection for patients who receive adjuvant therapy, as compared with around 7 months for patients off therapy [4]. Unfortunately, this difference (around 6 months) merely approximates the

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Companion website: www.wiley.com/go/beger/thepancreas

time patients spend on adjuvant therapy in many cases, suggesting that modern treatments often fail to provide a durable benefit that lasts beyond completion of therapy. In other words, in many cases the disease is kept at bay only while patients are receiving treatment.

Retrospective single-institutional experiences provide real-world survival data compared with prospective clinical trials, even though follow-up of these patients may be less rigorously collected. In contrast to prospective adjuvant trials, these retrospective studies are usually not confounded by the same degree of selection bias, as they generally include all patients who are candidates for resection at a given institution. Thus the results may be more generalizable. As would be expected, long-term survival outcomes reported by these studies tend to be worse. In a large, single-institution study of 1,175 PDAC resected at the Johns Hopkins Hospital (JHH) over 25 years, the median survival was just 18 months; 1-year, 2-year, 3-year, and 5-year overall survival rates were 65%, 37%, 27%, and 18%, respectively [9]. The overall survivals in a series of 555 resected patients from the Memorial Sloan Kettering Cancer Center (MSKCC) (1983–2000) were virtually identical [10].

In recent years, the results of retrospective studies of patients undergoing resection *after* neoadjuvant therapy have been reported and outcomes are often impressively long in comparison to historical retrospective data of patients who received adjuvant therapy following resection. However, there is a strong selection bias in these cohorts that should be acknowledged (just as with prospective, randomized adjuvant trials). A substantial portion of patients in the intent-to-treat neoadjuvant group fail to undergo resection, either due to disease progression or poor performance status. As a result, the neoadjuvant treatment model enriches the study cohort (i.e., patients undergoing subsequent resection) with the most favorable patients. Christians et al. recently published results from a retrospective analysis of 69 patients with resectable PDAC treated with neoadjuvant chemoradiotherapy from 2009 to 2013 at a single institution [11]. The reported median survival from this relatively small cohort was an astounding 44.9 months for patients who completed the neoadjuvant course and successfully recovered from pancreatic resection. However, the intent-to-treat analysis for the whole cohort was 13.5 months shorter (31.5 months), albeit still impressive. The survival of the 9 patients (15%) who failed to advance to surgical resection was just 8.1 months, and on a par with patients having advanced disease. Importantly, patients included in this study satisfied strict inclusion criteria of having "resectable" PDAC, which comprised a relatively favorable group when compared with large institutional series of patients receiving adjuvant therapy. In an earlier prospective, and nonrandomized study by Evans et al. published in 2008, 86 patients with resectable PDAC received preoperative neoadjuvant chemoradiotherapy [12]. Median survival was 34 months for patients who completed neoadjuvant chemotherapy and underwent a resection (64 patients). In the intent-to-treat group, overall survival rates were comparable with studies of patients who get resection first (22.7 months). In this study, a larger proportion of patients failed to undergo resection (25%) than the more recent report by Christians et al., suggesting improved patient selection in the later study. It is difficult to conclude from single-institution studies of neoadjuvant therapy such as these that the treatment is the principal driver of superior reported outcomes for resectable PDAC, because most of the patients only received gemcitabine or 5-FU-based monotherapy (marginally effective therapies). Tumor biology and patient selection likely play a more predominant role. As chemotherapy improves, the rationale for a neoadjuvant approach will probably gain greater traction, as the need for early systemic control is likely critical for improved survival in many patients. Randomized trials are needed to better assess the value of the neoadjuvant approach. We eagerly await such studies, including the ongoing German NEOPA trial, which varies the sequencing of gemcitabine and resection in patients with resectable PDAC [13]. Neoadjuvant treatment has become the standard approach for borderline resectable disease at most centers. A meta-analysis of 18 studies of patients undergoing neoadjuvant therapy for borderline resectable disease revealed that the resection rate is 65%, and the median survival is 26 months in the patients who achieve this result (18 months for the whole group [14]).

## How Commonly are Patients Cured of PDAC by Resection?

While many patients with localized disease may not be helped by resectional therapy (as 25% of patients die within a year after resection for PDAC [9,15]), there is no question that this surgical intervention provides the best opportunity for long-term survival for many patients. A randomized, patient-blinded study of 42 patients from Japan compared the effect of resection with that of chemoradiation without resection for patients with resectable PDA. The study revealed just a 3-month *median* survival benefit (which is comparable to the meager median survival benefit of adjuvant therapy) [16]. However, the *mean* survival advantage was an impressive 12 months, revealing that a significant proportion of favorable outliers received a substantial benefit from resection. In fact, there were no long-term survivors (>2 years) in the no-surgery group (vs. 35% in the surgery group), just as there are seldom any long-term survivors in historical studies of patients with advanced disease.

**Table 120.1** Five- and 10-year survival rates for patient with pancreatic cancer after surgical resection.

| | Study period | N | 5-year survival | 10-year survival |
|---|---|---|---|---|
| CONKO-001 (Adjuvant Group) | 1998–2004 | 168 | 20.7% | 12.2% |
| Shimada et al. [18] | 1990–2013 | 229 | 17% | 10% |
| Kimura et al. [19] | 1988–2012 | 149 | 13.40% | 3.60% |
| Ferrone et al. [20] | 1985–2006 | 499 | 19% | 10% |
| Dusch et al. [21] | 1972–2004 | 360 | 19.20% | 6.10% |
| Schnelldorfer et al. [22] | 1981–2001 | 357 | 18% | 13% |
| Adham et al. [23] | 1983–2000 | 30* | – | 30% of 5 yr survivors had ≥10 yr survival |
| Riall et al. [17] | 1970–1999 | 564 | 17% | 9% |

This and other outcome studies raise the question of cure rates associated with resection for PDAC. A handful of studies shed light on this question with survival outcomes reported to 10 years and beyond (Table 120.1). Similar to studies with shorter follow-up, 5-year survival rates are consistently around 18–20%. Reproducibly, the data also indicate that overall survival 10 years after resection is roughly half this rate, or 10%. The largest study to date on this subject was published by Riall et al., where the authors reported on the long-term survival of 564 patients with PDA [17].

Our own unpublished analysis of the publically available data from the Surveillance, Epidemiology, and End Results (SEER) cancer database (1975–2012) yields further insight into this question [24]. These data show that patients have roughly a 50% chance of doubling their own survival throughout their lifetime (starting at the 1 year point). For example, an individual who survives 4 years has a 50% chance of living another 4 years. This observation has several implications. First, the longer an individual lives, the greater their chance of surviving a further year. On the other hand, the data indicate that a 10-year survivor still carries a real risk of late recurrence. In an analysis of 30 five-year survivors, Adham et al. observed survival at 10, 15, and 20 years to be 30%, 13%, and 7% respectively. These outcomes are substantially worse than would be predicted from age-matched life tables, where a 65-year-old individual would be expected to have a 50% survival at 20 years. Ferrone et al. [20] analyzed a cohort of 499 patients resected at the Massachusetts General Hospital for PDAC (in a study entitled "Pancreatic ductal adenocarcinoma: long-term survival does not equal cure"), and also observed a number of recurrences beyond 10 years. Moreover, some cases of long-term survival on further pathologic review have been attributed to an incorrect diagnosis at the index resection, as exemplified by a patient on the CONKO-001 trial found later to have a neuroendocrine cancer [25]. While a patient can never be fully assured that they are free of recurrence risk, our analysis of life expectancy tables [26], superimposed with historical PDAC survival data after resection, suggests that the survival curves overlap after patients have lived for roughly 13 years after resection (~8% of patients achieve this outcome, with a median projected 19-year overall survival in this subgroup). After this time point, patients are just as likely to die from nonpancreatic cancer causes. Practically speaking, these patients then are "cured" of their disease. Therefore, we believe that the "cure rate" of pancreatic resection for PDA can be estimated to be around 8% for most patients.

## Survival Trends Over Time

A large, single-institution study from the Memorial Sloan Kettering Cancer Center [15] revealed that short (30-day) and intermediate (1-year) survivals after resection for PDAC have improved between the 1980s and 2000s. The authors concluded that over time, surgery had become safer with fewer perioperative deaths (i.e., early mortality); additionally, the authors hypothesized that patient selection had improved, perhaps as a result of modern imaging techniques used to stage patients with fewer early recurrences (i.e., intermediate mortality). However, there was no improvement observed in long-term mortality in this study, particularly when these other survival determinants (perioperative mortality and patient selection) were excluded from the analysis by focusing just on patients who survived at least 1 year. A subgroup analysis of SEER pancreatic cancer relative survival data over the past 40 years [24] also indicates that there has been no improvement in the survival of pancreatic cancer patients when we evaluated all patients with pancreatic cancer who survived at least 1 year (Fig. 120.1). Our review of pancreatic cancer survival statistics from a separate large data set, published

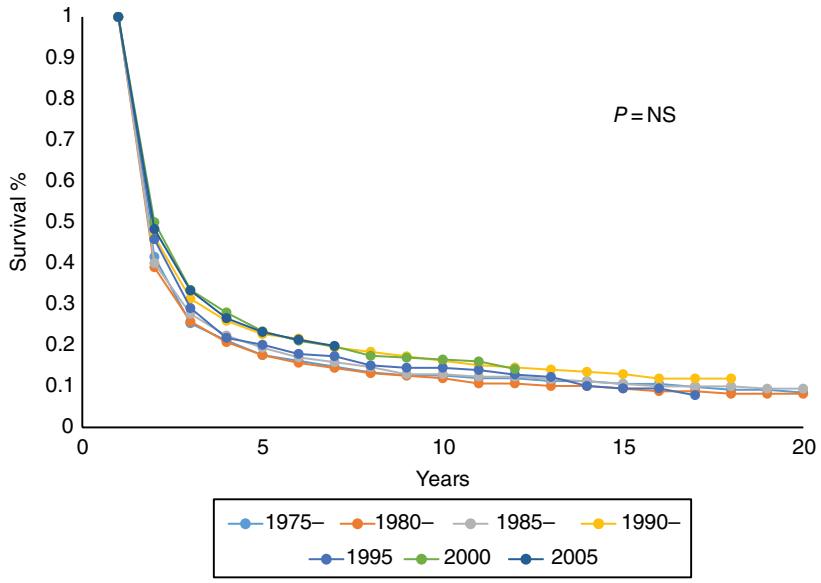


**Figure 120.1** Conditional relative survival for PDA patients surviving ≥1 year. Data from SEER database. Note the minimal change in relative conditional survival (≥1 year) over 30-year period compared with conditional survival in 1975–1979. NS, nonsignificant.

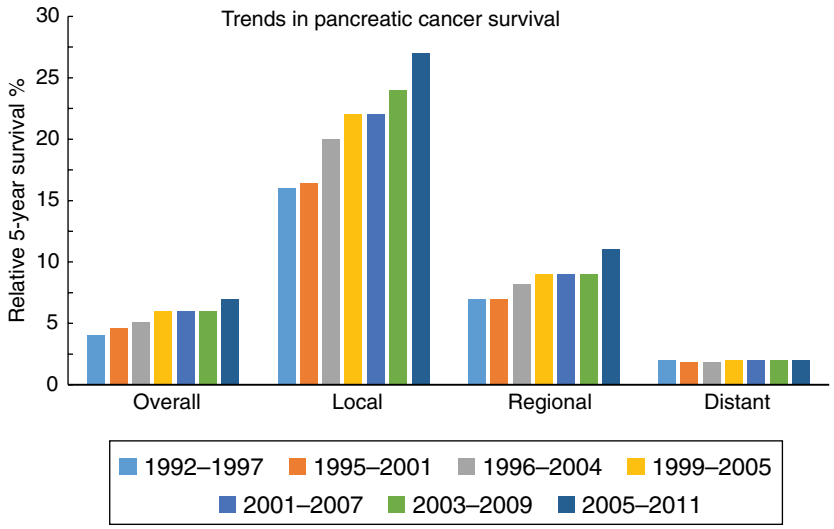


**Figure 120.2** Trends in 5-year survival of pancreatic cancer (1992–2011). American Cancer Society (ACS) published data. (Note the overlap in the time periods.)

by the American Cancer Society (ACS) between 1992 and 2011, adds further support to these observations [27]. The overall cancer 5-year survival (i.e., including all patients) rose from 4% in the period between 1992 and 1997, to just 7% between 2005 and 2011 (Fig. 120.2). Notably, there was virtually no improvement for metastatic disease, and only minimal improvement for regional disease. The greatest increase in survival was apparent for patients with localized disease (16% to 27% over the time interval). Again, the absence of any significant and widespread advances in chemotherapy over this time frame points to progress outside the domain of cancer therapeutics (e.g., safer surgery and patient selection) as principal drivers for positive change. Greater access to care (surgery and chemotherapy) may also have played an important role.

## Prognostic Risk Factors

Prognostic factors are key aspects to any discussion of survival, mainly due to the information they provide regarding the natural history of the disease. On occasion, prognostic information can be used to guide treatment decisions. Certain prognostic features have been consistently validated in patients with PDAC. However, it is important to note and discuss with patients that these factors are marginal at best at forecasting outcome. Patients with unfavorable features often achieve long survival after resection, while many with favorable features suffer an unfortunate early recurrence and death.

Pathologic features that are reproducibly found to be associated with worse long-term survival include increased tumor diameter, regional lymph node

metastases (including alternative metrics of lymph node burden such as lymph node ratio) [28–34], poorly differentiated histology, positive resection margin, and perineural invasion [17,35–37]. In multivariate models, each of these has associated hazard ratios below 2, reflecting their weak prognostic capabilities, and their limited utility for treatment-related decisions. Indeed, in a study that contrasted 137 patients with short survival (<12 months, $n = 58$) and long survival (>30 months, $n = 79$) after resection for PDAC, no pathologic features proved to be significant predictors for the survival group. Interestingly, 65% of the long-term survivors and 17% of the short-term survivors had regional lymph node metastases, respectively [38]. Aside from conventional pathologic features, the only other validated prognostic marker is the serum-based carbohydrate antigen 19-9 (or CA 19-9). This protein is a secreted sialylated Lewis A (sialyl $Le^A$) antigen that is produced in high amounts by pancreatic cancer cells. Elevated post-resection levels are associated with early recurrence and worse overall survival [39–41]. In fact, an ad hoc analysis of patients enrolled in the RTOG 9704 adjuvant trial [3,39] revealed that a level >180 U/mL is associated with an adjusted hazard ratio of 3.6 (which is substantially more powerful than conventional pathologic features). This finding has been replicated in multiple studies [40–43].

Scientists have tried to identify molecular prognostic markers that can enhance conventional staging strategies, although none have been validated to date. Winter et al. determined that high MUC1 and mesothelin (*MSLN*) expression were both associated with early cancer-specific mortality in a comparative analysis of short- and long-term survivors after resection for PDAC [38]. These immunohistochemical markers showed a greater prognostic ability compared to conventional pathologic features such as tumor size, regional lymph node metastases, resection margin status, and histologic grade [38]. Smith et al. performed a meta-analysis of several immunohistochemical prognostic markers (P16, SMAD4, VEGF, EGFR, bax, and bcl-2) in resected pancreatic cancer patients (11 eligible studies) and found vascular endothelial growth factor (VEGF) to be the most informative prognostic marker [44].

A separate study by Stratford et al. analyzed gene expression data in resected samples, and compared the profile to metastatic deposits found at autopsy. The authors identified a six-gene signature as prognostic for advanced disease. This gene cluster (*FOSB*, *KLF6*, *NFKBIZ*, *ATP4A*, *GSG1*, and *SIGLEC11*) proved to be predictive of worse outcome in a small validation cohort of patients with resected PDA, with an adjusted hazard ratio of 4.1 [45]. Recently, Chen et al. [46] described a prognostic 15-gene signature in early stage PDAC (hazard ratio 3.26), which was also validated in the Stratford cohort [45].

## Long-Term Morbidity

Studies on postoperative morbidity after pancreatectomy have historically focused on early complications after resection (addressed elsewhere in this book). Along these lines, the International Study Group of Pancreatic Surgery has published a series of consensus papers on various complications. *Late morbidity* after pancreatic surgery, however, has been considerably less studied. Relevant studies have naturally focused on patients undergoing resection for benign disease, since larger numbers of patients remain alive at long-term follow-up. The most common late complications that have been observed include gastrectomy-associated complications (e.g., dumping syndrome, bile reflux gastritis, marginal ulcers, bleeding, and gastric remnant cancer), bile duct strictures, pancreatic duct strictures, pancreatogenic diabetes mellitus, pancreatic exocrine insufficiency, nonalcoholic fatty liver disease (NAFLD), incisional hernia, and pyogenic liver abscess.

### Gastrectomy-Associated Complications

A classic pancreaticoduodenectomy (to include a distal gastrectomy) may carry a risk of delayed complications typically associated with a distal gastrectomy. These include afferent limb syndrome, bile reflux gastritis, marginal ulcers (associated with bleeding, stricture, or perforation), dumping syndrome, and gastric remnant cancer (Table 120.2).

Some early studies suggest that the rates of reflux gastritis, marginal ulcers, and dumping syndrome may be lower with a pylorus-preserving pancreaticoduodenectomy as compared with those after a classic pancreaticoduodenectomy [47,48]. Other studies, however, have shown no clear difference in the risk for marginal ulcers or reflux gastritis [49]. The principle etiology of afferent limb syndrome after pancreaticoduodenectomy is tumor recurrence, followed by radiation-induced stricture [50], and should be equally prevalent with either reconstruction technique.

The risk of gastric remnant cancer in patients undergoing a classic Whipple is a theoretical one, because the

**Table 120.2** Gastrectomy-associated complications for patients post-pancreatoduodenectomy.

| Complication | Prevalence |
|---|---|
| Alkaline reflux gastritis | 11–25% [49,51] |
| Marginal ulcer | 1–9% [49,51,52] |
| Afferent loop syndrome | 13% [50] |
| Dumping syndrome | 10% [47] |

supporting evidence is an extrapolation of literature based on prior gastrectomy for peptic ulcer disease. The incidence is believed to be around 7% [53–55], and the average latency is about 20 years [55]. Most gastric remnant cancers occur at or near the prior anastomosis, and the cause is believed to be related to combined reflux of bile and pancreatic secretions. While a similar risk has not been documented after a classic pancreaticoduodenectomy, the purported mechanism of pancreatobiliary reflux is nonetheless exacerbated when the pylorus is resected. The relevance of this complication is probably low with the present survival rates for PDAC (roughly 5% of patients, or less, will survive to 20 years), but will likely become an increasingly common issue for the current generation of hepatobiliary surgical trainees as treatments improve. Data from patients undergoing gastric resections for peptic ulcer disease suggest that surveillance should be performed in appropriately selected patients starting 5 years after their distal gastrectomy [53].

As a case in point, Dr. James J. Mezhir (1973–2016) suffered this very fate. He was an accomplished pancreatic surgeon and scientist, and in fact reported the largest series of gastric remnant cancers as a surgical oncology fellow at Memorial Sloan Kettering [53]. He underwent a pancreaticoduodenectomy as a teenager for the management of non-Hodgkin lymphoma causing bile-duct obstruction [56,57]. Sadly, he developed an aggressive gastric remnant cancer 25 years after the index operation, and recently died after a 2-year battle with the disease [56].

### Biliary Anastomotic Strictures

Biliary strictures occur in 3–8% of patients following pancreaticoduodenectomy [58–60], with the median time to stricture formation being just over 1 year. This complication is best managed initially, when possible, by nonoperative interventions including endoscopic or percutaneous balloon dilatation and biliary stents. Surgical revision is appropriate in cases where these interventions fail (approximately 5–24% of the time). Reported risk factors for biliary strictures include small bile-duct diameter at the time of the index resection (<5 mm) [60], preoperative biliary stenting, and postoperative biliary stenting [58].

### Pancreatic Anastomotic Strictures

Pancreatic anastomotic strictures occur at an almost similar rate (roughly 2–3% after pancreaticoduodenectomy) [59,61]. This complication typically presents as abdominal pain in the setting of pancreatitis, and manifests an average of 4 years after the index operation. MRCP or CT provide visual images to secure the diagnosis [61]. Pancreatic anastomotic strictures may be managed initially by endoscopic stenting (guided by ERP or EUS) in selected cases [62,63]. However, a definitive operative revision is at times required. Effective options include a revision of the pancreaticoenterostomy or a lateral pancreaticojejunostomy [61].

### Pancreatogenic Diabetes Mellitus

Pancreatogenic diabetes mellitus (Type 3c) is a subtype of secondary diabetes (Type 3) and refers to any diabetogenic process that results from damage or loss of pancreatic tissue. Notably, this form of diabetes is unique in that glucagon (α-cells), pancreatic polypeptide-producing cells, and exocrine acinar cells are also lost. Diabetes mellitus (DM) and PDAC have a close "reverse causality" relationship [64]; while diabetes mellitus has been associated with increased risk for pancreatic cancer, PDA has also been associated with inciting new-onset DM both through pancreatic tissue destruction (Type 3c), as well as through a paraneoplastic phenomenon that results in the inhibition of insulin secretion and the exacerbation of peripheral insulin resistance (Type 2-like DM) [65].

Table 120.3 shows the reported prevalence of new-onset pancreatogenic diabetes after pancreatectomy across multiple studies. Exacerbation of existing diabetes is also observed in a large proportion of these patients. The occurrence of new-onset DM may be slightly higher after distal pancreatecomy, as compared to pancreaticoduodenectomy. Paradoxically, resection of the pancreatic tumor may also lead to resolution of diabetic symptoms of DM in a small number of patients (although etiology is unclear, this may be related to the nearly universal weight loss of 10–15% after pancreatectomy) [66,67]. Due to the high frequency of new-onset or worsening of diabetes after pancreatic resection, this complication should be specifically addressed with patients prior to resection, via education and discussion.

### Pancreatic Exocrine Insufficiency

Pancreatic exocrine insufficiency occurs in roughly half of patients undergoing pancreaticoduodenectomy [70,73,74]. The mechanism of parenchymal loss is similar to pancreatogenic diabetes, and in fact, exocrine insufficiency is one of the major criteria used to make the diagnosis of Type 3c DM [64]. Symptoms may include abdominal pain and bloating; pasty, floating, and foul-smelling stools; and fat-soluble vitamin deficiency (vitamins A, D, E, and K). Reported risk factors for post-pancreaticoduodenectomy exocrine insufficiency include preoperative pancreatic endocrine impairment, preoperative decreased pancreatic parenchymal thickness, hard gland texture, postoperative imaging showing decreased pancreatic parenchymal

**Table 120.3** Prevalence of pancreatogenic diabetes mellitus after pancreatectomy.

| | N | Pancreaticoduodenectomy | Distal pancreatectomy |
|---|---|---|---|
| Burkhart et al. [68] | 267 | New onset: 18% (*n* = 135)<br>Exacerbation of DM: 48% (*n* = 44) | New onset: 31% (*n* = 55)<br>Exacerbation of DM: 26% (*n* = 23) |
| Hirata et al. [69] | 167 | New onset: 22% (*n* = 58)<br>Exacerbation of DM: 57% (*n* = 42) | New onset: 27% (*n* = 33)<br>Exacerbation of DM: 77% (*n* = 34) |
| Wu et al. [66] | 3,914 | New onset: 16% (*n* = 3914) | |
| Fang et al. [70] | 42 | New onset: 12% (*n* = 42) | |
| White et al. [71] | 100 | New onset: 11% (*n* = 79) | New onset: 9.5% (*n* = 21) |
| DiNorcia et al. [72] | 49 | | New onset: 37% (*n* = 38)<br>Exacerbation of DM: 82% (*n* = 11) |

Percentage of patients with pancreatogenic diabetes mellitus, total study population size in parenthesis. DM, diabetes mellitus.

**Table 120.4** Prevalence of post-pancreatectomy pancreatic exocrine insufficiency.

| | N | PPPD-PG | PPPD-PJ | Risk factors identified |
|---|---|---|---|---|
| Lemaire et al. [76] | 19 | 16/17 (94%) | | Decreased postoperative pancreatic parenchymal thickness, postoperative dilatation of the main pancreatic duct |
| Rault et al. [79] | 33 | 12/23 (52%) | 8/10 (80)% | Type of pancreatic reconstruction (PEI in PJ > PG) |
| Fang et al. [70] | 42 | 12/19 (63%) | 10/23 (43%) | |
| Nakamura et al. [73] | 61 | 38/61 (62%) | | Preoperative endocrine impairment, hard gland texture, postoperative dilatation of the main pancreatic duct |
| Nakamura et al. [75] | 52 | 34/52 (65%) | | Decreased pancreatic parenchymal thickness (preoperative and postoperative) |
| Hirono et al. [74] | 199 | 59/90 (66%) | 38/99 (38%) | Type pancreatic reconstruction (PEI in PJ > PG), hard gland texture |

PPPD, pylorus-preserving pancreatoduodenectomy; PEI, pancreatic exocrine insufficiency; PG, pancreatogastrostomy; PJ, pancreatojejunostomy.

thickness, and postoperative dilatation of the main pancreatic duct [73–76]. A summary of reported rates and risk factors of pancreatic exocrine insufficiency is provided in Table 120.4. This complication, although not fatal or debilitating, has been shown to be associated with a significant reduction in the quality of life [77]. The treatment consists of oral pancreatic enzyme replacement with meals. Recommended doses are in the range of 18,000 to 30,000 USP units of lipase. Of note, gastric pH should be maintained above 4.0 to prevent enzyme inactivation [78].

## Nonalcoholic Fatty Liver Disease

Increased hepatic fat deposition is a newly reported complication after pancreaticoduodenectomy [80], and in some cases it can progress to nonalcoholic fatty liver disease (NAFLD). NAFLD attributable to pancreaticoduodenectomy is defined as hepatic steatosis (proven by imaging or by histology) without other causes for secondary hepatic fat accumulation, such as significant alcohol intake, steatogenic medications or genetic disorders [81]. As this chronic condition progresses, the functional reserve of the liver diminishes and hepatic insufficiency may ensue [82]. This may assume increased relevance in patients with PDAC who receive chemotherapy, which itself carries an independent risk of hepatotoxicity [83,84]. The prevalence of post-pancreaticoduodenectomy NAFLD has been estimated at between 8% and 40% [85–88], although the exact mechanism of this complication remains unknown. Sato et al. evaluated postoperative imaging studies in 110 patients who underwent a pancreaticoduodenectomy over a 6-month period, and observed that decreased pancreatic volume was associated with NAFLD. Tanaka et al. [88], studied the physical and biochemical profiles in patients with NAFLD after pancreaticoduodenectomy, and noted a low BMI, decreased insulin resistance [89], and decreased serum levels of cholesterol, apolipoprotein B, and albumin. Since these findings are consistent with pancreatic exocrine insufficiency, an increased dosage of oral pancreatic enzyme supplements was evaluated as a possible therapy, and the intervention indeed reversed these biochemical abnormalities in a number of patients. Additionally, associated imaging findings of steatohepatitis improved. The findings were reproduced by Nagai et al. in a separate study [90]. Therefore, it may be advisable to initiate or

augment oral pancreatic enzyme supplementation in patients with post-pancreaticoduodenectomy NAFLD. Future studies are needed to determine if enzyme supplementation should be recommended indefinitely in all patients (or only those at highest risk) in order to prevent this complication.

### Incisional Hernia

Available literature regarding the incidence of incisional hernia post-pancreatic surgery is scarce, yet in our experience, the complication is frequently encountered. The risk can be extrapolated from the overall abdominal surgical literature. A meta-analysis of 14,618 patients (56 studies) undergoing a wide variety of surgical procedures reported a prevalence rate of 12.8% [91] at approximately 2 years after the index procedure. Risk factors for incisional hernia after abdominal surgery include obesity, history of smoking, previous abdominal surgery, and postoperative wound infection [92–94]. The incisional rate would be expected to improve substantially when a minimally invasive approach is utilized [95,96].

### Pyogenic Liver Abscess

Biliary-enteric anastomoses result in chronic colonization of the biliary tract with enteric flora (bactibilia) due to the absence of the sphincter of Oddi. This is generally of no clinical consequence, because of continuous biliary drainage and decompression. However, colonized bile ducts place patients with infarcted, injured, or necrotic liver parenchyma at risk for pyogenic liver abscesses. This can occur due to liver infarction from a retractor injury at the time of a pancreaticoduodenectomy, or as a result of parenchymal injury related to liver-directed therapies used to treat hepatic metastases, such as hepatic arterial embolization or ablative procedures. Of note, these therapies are rarely performed for patients with conventional PDA at this time, and are more relevant for patients with metastatic neuroendocrine carcinoma. In a large study from Memorial Sloan Kettering Cancer Center, the liver abscess rate in patients undergoing hepatic arterial embolization was 33% for patients with prior biliary-enteric anastomosis, but just 0.05% in other patients [97]. The risk of a liver abscess with any liver-directed therapy after pancreaticoduodenectomy was observed to be around 10% in a separate large multi-institution study [98]. Patients found to have zones of infarct identified after pancreaticoduodenectomy, either from retractor injury or typically accessory hepatic arterial ligation should be vigilantly monitored for the development of potentially life-threatening liver abscesses that can develop with immunosuppression related to adjuvant chemotherapy. Extra caution is necessary for patients who develop liver abscesses in the early postoperative period. Most liver abscesses can be managed effectively with antibiotics and percutaneous drainage if diagnosed in a timely manner.

## Conclusions

Long-term survival has only marginally improved after resection for pancreatic cancer, but this progress cannot be attributed to significant advances in pancreatic cancer medical therapy. The possibility of recurrence persists, even after many years. Novel effective therapies will likely emerge from ongoing innovative basic and translational work in the near future. As patients experience improved survival, the aforementioned late complications will become increasingly important. Pancreatic surgeons should be mindful of the rates and risks of each of these complications and discuss them with their patients. Future studies aimed at reducing these risks are therefore needed.

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## Section 8

## Neoplastic Tumors of the Endocrine Pancreas: Neuroendocrine Tumors of the Pancreas

# 121

# Epidemiology and Classification of Neuroendocrine Tumors of the Pancreas

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## Introduction

Neuroendocrine tumors (NET) of the pancreas are a heterogeneous group of epithelial neoplasms with a highly variable clinical presentation, malignant potential, and prognosis. Pancreatic NET (PanNET) range from small, slow-growing, incidentally detected nonfunctional and/or functional tumors to frank aggressive malignancies. These lesions were earlier described as "islet-cell tumors" based on the belief that they originate from the cells in the islets of Langerhans. They were later considered to be "pancreatic endocrine tumors" when evidence suggested that they might originate from pluripotent cells in the ductal epithelium [1,2]. The latest World Health Organization (WHO) 2010 classification system [3] recommended the use of the term "neuroendocrine" to describe these tumors as they are now considered to arise from cells that are part of the diffuse neuroendocrine cell system of the gastrointestinal tract and pancreas; these cells share certain unique biochemical (capability to synthesize, store, and secrete a number of amines and peptides) and immunohistochemical properties (documentation of markers of neuroendocrine differentiation, mainly expression of antigens commonly expressed by neuronal elements such as chromogranin A and synaptophysin, together with neuron-specific enolase) [4].

## Epidemiology of Pancreatic Neuroendocrine Tumors (Table 121.1)

Data on the epidemiology of PanNET is limited. Variations in coding and classification over time, and between different countries, have resulted in difficulties in precisely understanding the true epidemiology of these tumors. Moreover, various national, regional, and institutional cancer or NET registries, with their inherent deficiencies in data collection, happen to be the major sources of epidemiology of PanNET. The PanNET are rare tumors that possibly constitute <3% of all pancreatic tumors [5], and approximately 4–8% of all neuroendocrine tumors [6]. The annual incidence rate of PanNET is reportedly less than one per 100,000 person-years in population studies [5]. The absolute annual incidence rate of PanNET varies among registries in various countries, with PanNET ranging from the most common to the second most common site among gastroenteropancreatic NET.

The incidence of PanNET is higher in autopsy studies, ranging from 0.1 to 10% [5]. Grimelius et al. in Sweden reported 13 pancreatic "islet cell adenomas" at autopsy among 1366 adults (0.8%) [7]. Kimura et al. in Japan found 20 "endocrine tumors of the pancreas" among 800 autopsy cases (mean age 78.7 years); the incidence of tumors was higher among the 60 randomly selected cases that had 5 mm thick sections of the pancreas; six (10%) of them were found to have an endocrine tumor as opposed to only 12 out of 738 cases (1.6%) that had histologic studies of three random sections of the pancreas [8]. Lam and Lo in Hong Kong found 13 cases (0.1%) of "pancreatic endocrine tumors" among 11472 autopsies performed from 1972 to 1995 [9].

There has been a rise in the incidence and prevalence of PanNET over the past few decades; this could either reflect a true increase in incidence or be the result of an increased awareness of these tumors together with availability of more sensitive imaging techniques leading to their increased detection [10,11]. The PanNETs are most

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Companion website: www.wiley.com/go/beger/thepancreas

**Table 121.1** Incidence of pancreatic neuroendocrine tumors in selected autopsy series after the 1970s.

| First author | Year published | Country | Number of autopsies | Number of "islet cell tumors" | Percentage |
|---|---|---|---|---|---|
| Grimelius L | 1975 | Sweden | 1366 | 11 | 0.8 |
| Kimura W | 1991 | Japan | 800 | 20 | 2.5 |
| Kimura W | 1991 | Japan | 60 (5 mm sections) | 6 | 10 |
| Lam KY | 1997 | Hong Kong | 11472 | 13 | 0.1 |

*Source:* Adapted from Halfdanarson et al. 2008 [5].

common between ages 60 and 80 years, with an earlier age of onset in patients with multiple endocrine neoplasia type 1 (MEN1).

## Classification

The classification of PanNET has changed periodically since the first attempts at classification of these tumors were made in the early 1960s. They can be classified based upon:

I) Functionality as "functional or nonfunctional."
II) Association with inherited syndromes as "sporadic or syndromic."
III) Tumor biology and morphologic features.
IV) Evaluation of spread as "tumor–node–metastasis (TNM) classification."

### I. Functional Versus Nonfunctional PanNET (Table 121.2)

"Functional PanNET" are associated with a hormone-secreted clinical syndrome. The clinical presentation of these tumors is dominated by the metabolic effects of the excess hormone(s) secreted by the tumor, and they are classified based upon the predominant clinical syndrome produced by the hormone secreted by the tumor. There is a poor correlation between peptide expression on immunohistochemical staining of the tumor and the circulating levels of the respective secretory products; thus, the mere presence of positive immunohistochemical staining is not a defining criterion for a "functional" PanNET. The European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines for the management of functional PanNET syndromes divides functional PanNET into "most common functional PanNET syndromes," "established rare functional PanNET syndromes," and "possible rare functional PanNET syndromes" [12]. Of the many established and possible functional PanNET, the two that are more commonly seen in clinical practice are insulinomas and gastrinomas.

"Nonfunctional PanNET" do not produce any specific hormone-secreted clinical syndromes. They are either detected incidentally during imaging or present with symptoms attributable to the mass effect due to tumor bulk or distant metastases. Although some of them do not produce any amines or peptides, most do secrete substances such as chromogranin, pancreatic polypeptide, neurophysin, neuron-specific enolase, alpha subunit of human chorionic gonadotropin, and other peptides that do not result in any specific clinical syndrome.

Earlier reports suggested a preponderance of functional PanNET as they presented with recognizable clinical syndromes and were thus easier to identify. However, over the past two decades, nonfunctional PanNET have become the more common PanNET as a result of improvements in imaging techniques and increased detection rates [10,11].

The differentiation of PanNET based on functionality does not shed light on their biological behavior or help predict their long-term prognosis in the majority of situations; the one exception is insulinoma, which in the majority of cases runs an indolent course. As such, the biological behavior of functional PanNET should also be classified as one would classify a nonfunctional PanNET, including the grade and stage of the tumor. However, it is essential to identify and classify functional PanNET because they produce classic hormone-secreted clinical syndromes that require dedicated investigations, therapeutic interventions, and structured long-term follow-up.

### II. Sporadic Versus Syndromic PanNET (Table 121.3)

Less than 10% of PanNET are associated with inherited disorders. The four common inherited disorders that manifest a PanNET are multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (von Reclinghausen disease) (NF1), and tuberous sclerosis complex (TSC) [13].

Approximately 80–100% of patients with MEN1, 10–17% of patients with VHL, up to 10% of patients with NF1 and 1% of patients with TSC will develop a PanNET within their lifetime [13]. The PanNET associated with inherited disorders are frequently multifocal. As with functional PanNET, the association of these tumors with a specific

**Table 121.2** Functional pancreatic neuroendocrine tumors.

| Tumor type | Endocrine hormone secreted | Approximate incidence (patients per million per year) | Likelihood of malignancy (%) |
|---|---|---|---|
| **More common** | | | |
| Insulinoma | Insulin | 2 | <10 |
| Gastrinoma | Gastrin | 1 | >50 |
| **Less common** | | | |
| Glucagonoma | Glucagon | 0.05 or more | >50 |
| VIPoma | Vasoactive intestinal peptide | 0.05 | >50 |
| Somatostatinoma | Somatostatin | Rare | >50 |
| ACTHoma | Adrenocorticotrophic hormone | Rare | >50 |
| GRFoma | Growth hormone-releasing hormone | Rare | >50 |
| "Classical" carcinoid syndrome | Serotonin | Rare | >50 |
| PTHrPoma | Parathyroid hormone-related peptide | Rare | >50 |
| **Rare** | | | |
| Calcitoninomas | Calcitonin | Very rare | >50 |
| **Others (may be mixed)** | | | |
| Hormones | "Big IGF-II," erythropoietin, luteinizing hormone, renin | Very rare | Unknown |

*Source:* Adapted from Jensen RT et al. Neuroendocrinology 2012;95:100.

**Table 121.3** Pancreatic neuroendocrine tumors associated with hereditary syndromes.

| Syndrome | Gene location | Incidence (%) | Tumor type | Location |
|---|---|---|---|---|
| MEN1 | 11q13 | 80–100 | Nonfunctional, gastrinoma, insulinoma | Pancreas Duodenum |
| VHL | 3p25 | 12–17 | Nonfunctional | Pancreas |
| NF1 | 17q11 | 6 | Somatostatinoma | Pancreas |
| TSC | 9q34 (TSC 1) 16p13.3 (TSC 2) | <5 | – | Pancreas |

*Source:* Adapted from Chen M et al. J Gastrointest Oncol 2012;3:184.

inherited syndrome does not help predict their biological behavior or long-term prognosis. However, it is important to recognize a syndromic PanNET not only to help initiate a diligent search in the index patient to identify the multifocal pancreatic and extrapancreatic tumors but also to allow early and periodic surveillance of family members.

## III. Based on Tumor Biology and Morphologic Features (Tables 121.4–121.8)

Over the years, the classification of this rare group of tumors has evolved and a number of earlier classification systems exist. Most classification systems do make a clear and sharp distinction between well-differentiated PanNET and poorly differentiated neuroendocrine carcinoma (PD-NEC) that have an aggressive course with poor prognosis. Morphologic features of the tumor, extent of local/distant spread, and aggressiveness of the tumor are common to most classification systems. It should be emphasized that almost all PanNET are potentially malignant, and can metastasize, even after many years.

The salient classification systems proposed over the years for PanNETs include the following:

1) Capella classification system 1995 [14].
2) Armed Forces Institute of Pathology (AFIP) classification system 1997 [15].
3) Memorial Sloan Kettering classification system 2002 [16].
4) WHO classification system 2004 [17].

**Table 121.4** WHO classification of pancreatic neuroendocrine tumors (2004).

| Factor | Well-differentiated endocrine tumor: benign behavior | Well-differentiated endocrine tumor: uncertain behavior | Well-differentiated endocrine carcinoma | Poorly differentiated endocrine carcinoma | Mixed exocrine and endocrine tumors |
|---|---|---|---|---|---|
| Biological behavior | Benign behavior | Uncertain behavior (benign or low-grade malignant) | Low-grade malignant | High-grade malignant | |
| Infiltration/ metastases | Confined to the pancreas | Confined to the pancreas | Invasion of adjacent organs and/or metastases | Gross local invasion and/or metastases | |
| Tumor size | <2 cm | ≥2 cm | | | |
| Vascular/ perineural invasion | No vascular invasion<br>No perineural invasion | Vascular invasion<br>Perineural invasion | | | |
| Mitoses | <2 mitoses per 10 HPF | 2–10 mitoses per 10 HPF | | | |
| Ki-67 labeling index (%) | <2 | >2 | | | |
| Functionality | Insulinoma or nonfunctional | Functional or nonfunctional | Functional or nonfunctional | - | |

*Source:* Adapted from Klöppel et al. 2004 [17].

**Table 121.5** ENETS 2006 grading proposal for pancreatic neuroendocrine tumors.

| Grade | Mitotic count per 10 HPF[a] | Ki-67 labeling index (%)[b] |
|---|---|---|
| Grade 1 (G1) | <2 | ≤2 |
| Grade 2 (G2) | 2–20 | 3–20 |
| Grade 3 (G3) | >20 | >20 |

[a] 10 HPF = 2 $mm^2$, at least 40 fields (at 40× magnification; evaluated in areas of highest mitotic density).
[b] MIB1 antibody; percentage of 2000 tumor cells in areas of highest nuclear labeling.
*Source:* Rindi et al. 2006 [18], p. 399. Reproduced under the terms of the Creative Commons Attribution Noncommercial License.

**Table 121.6** WHO 2010 classification and grading of pancreatic neuroendocrine tumors.

| Classification/grade | Mitotic count (per 10 HPF) | Ki-67 labeling index (%) |
|---|---|---|
| Neuroendocrine tumor – grade 1 | <2 | <3 |
| Neuroendocrine tumor – grade 2 | 2–20 | 3–20 |
| Neuroendocrine carcinoma – grade 3 | >20 | >20 |

*Source:* Adapted from Rindi et al. 2010 [3], p. 13.

5) ENETS TNM staging and grading system 2006 [18].
6) WHO classification 2010 [3].
7) Union for International Cancer Control (formerly International Union Against Cancer)/American Joint Cancer Committee and WHO (UICC/AJCC/WHO) TNM classification 2010 [19].

We shall restrict ourselves in this chapter to describing in detail the WHO 2004 classification system [17], the WHO 2010 classification system for GEP-NET [3], the ENETS TNM staging and grading classification system proposed in 2006 (ENETS 2006 TNM) [18], and the UICC/AJCC/WHO 2010 TNM classification [19]. It will become evident that although considerable efforts have been made to arrive at a consensus, no single classification system has gained universal acceptance.

#### WHO Classification of PanNET 2004 (Table 121.4)

The WHO 2004 classification system divided PanNET into well-differentiated endocrine tumors with benign behavior, well-differentiated endocrine tumors with uncertain behavior, well-differentiated endocrine carcinomas (WDEC), poorly differentiated endocrine carcinomas (PDEC), and mixed exocrine and endocrine tumors [17]. Unlike the earlier 1995 Capella classification system [14], apart from staging parameters (such as tumor size, invasion of adjacent structures, and metastases), grading parameters (such as the aggressiveness of the tumors, as assessed by the mitotic activity, and/or Ki-67 labeling index) were introduced to refine prognostication. Unlike the earlier 2002 Memorial Sloan Kettering classification system [16], which included presence of necrosis for grading, the WHO 2004 classification was based solely on the proliferative rate of the tumor as reflected by the mitotic activity and/or Ki-67 labeling index for grading. This classification was tested clinically and was found to have prognostic relevance [20].

The WHO 2004 classification system for PanNET was a hybrid of staging and grading; an attempt at classification of PanNET was made based not only on staging parameters but also on the grade of the tumor. However,

**Table 121.7** TNM classification and disease staging for endocrine tumors of the pancreas (ENETS 2006).

| Definition | ENETS TNM |
|---|---|
| T definition | Primary tumor |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Limited to the pancreas and size <2 cm |
| T2 | Limited to the pancreas and size 2–4 cm |
| T3 | Limited to the pancreas and size >4 cm or invading duodenum or bile duct |
| T4 | Invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery) |
| – | For any T, add (m) for multiple tumors |
| N definition | Regional lymph nodes |
| Nx | Regional lymph node cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| M definition | Distant metastasis |
| Mx | Distant metastasis cannot be assessed |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Stage definition | |
| Stage I | T1, N0, M0 |
| Stage IIa | T2, N0, M0 |
| Stage IIb | T3, N0, M0 |
| Stage IIIa | T4, N0, M0 |
| Stage IIIb | Any T, N1, M0 |
| Stage IV | Any T, any N, M1 |

*Source:* Rindi et al. 2006 [18], p. 399. Reproduced under the terms of the Creative Commons Attribution Noncommercial License.

**Table 121.8** TNM classification and disease staging for endocrine tumors of the pancreas (UICC/AJCC/WHO 2010).

| Definition | UICC/AJCC/WHO 2010 TNM |
|---|---|
| T definition | |
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| T1 | Limited to the pancreas and ≤2 cm in greatest dimension |
| T2 | Limited to the pancreas and >2 cm in greatest dimension |
| T3 | Beyond the pancreas; without involvement of the celiac axis or the superior mesenteric artery (SMA) |
| T4 | Involvement of celiac axis or the SMA (unresectable tumor) |
| N definition | Regional lymph nodes |
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Regional lymph node metastasis |
| M definition | Distant metastasis |
| M0 | No distant metastasis |
| M1 | Distant metastasis |
| Stage definition | |
| Stage Ia | T1, N0, M0 |
| Stage Ib | T2, N0, M0 |
| Stage IIa | T3, N0, M0 |
| Stage IIb | T1–T3, N1, M0 |
| Stage III | T4, any N, M0 |
| Stage IV | Any T, any N, M1 |

*Source:* Adapted from Sobin et al. 2009 [19].

tumor stage and grade have independent prognostic significance. Moreover, the WHO 2004 classification system did not allow for the application of the grading system to advanced stages of the disease; an advanced PanNET need not necessarily be very aggressive; this is evident especially in metastatic PanNET, wherein, depending upon tumor grade, some metastatic diseases remain indolent for prolonged periods whereas others progress rapidly.

#### ENETS TNM Staging and Grading System 2006 (Tables 121.5 and 121.7)

In 2006, the ENETS proposed a TNM staging system of foregut NET (including PanNET), which also included a grading system [19]. The ENETS 2006 TNM classification system effectively separated staging from grading. It was realized that unlike poorly differentiated endocrine carcinomas (PDEC), where the behavior of the tumor is more aggressive and predictable, it was difficult to predict the behavior of well-differentiated PanNET, which could range from being indolent to the more aggressive forms. It was therefore decided to subdivide well-differentiated PanNET into two grades to help prognosticate them better based on proliferation markers of mitoses and Ki-67 labeling index. They proposed that mitoses should be counted in at least 40 high-power fields (HPF) in areas where they are most frequent, and expressed as number of mitoses per 10 HPF (2 $mm^2$). Only clear-cut mitotic figures should be counted. For Ki-67 protein assessment, they recommended that the labeling index should be assessed in 2000 tumor cells in areas where the highest nuclear labeling is observed. Ki-67 is a nuclear protein expressed in dividing cells closely associated with the nucleolus and heterochromatin. The monoclonal MIB-1 antibody is used for labeling.

Pancreatic NET were divided into three tumor categories: grade 1 (G1), grade 2 (G2), and grade 3 (G3) based on the number of mitoses seen per 10 HPF and/or the percentage of tumor cells that stain for Ki-67. In general, G1 and G2 refer to well-differentiated PanNET and G3 indicates poorly differentiated neuroendocrine carcinoma.

#### WHO Classification 2010 (Table 121.6)

The updated WHO 2010 classification aimed to standardize the classification system for GEP-NET [3]. It uses a proliferation-based grading system together with the classical histologic features-based classification. It emphasizes the malignant potential of PanNET.

It divides PanNET into "neuroendocrine tumors" (NET), which include low to intermediate-grade, well to moderately differentiated PanNET, and "neuroendocrine carcinomas" (NEC), which include high-grade, moderately to poorly differentiated PanNET. The WHO 2010 classification endorsed the grading system proposed by the ENETS 2006 TNM staging and grading system; based on the proliferative rate of the tumor (mitotic count per 10 HPF and/or Ki-67 labeling index), PanNET were divided into three grades, G1–G3. Grade 1 (G1) and grade 2 (G2) tumors referred to NET, whereas NEC were all uniformly high-grade tumors (G3). In cases of discordance between mitotic count and Ki-67 labeling index in assessing proliferation rate, the WHO 2010 classification system recommends using the higher grade of either mean.

Unlike the WHO 2004 classification, the updated WHO 2010 classification system separated grading from staging. Classification is based primarily upon the proliferative rate of the tumor rather than stage-pertinent features such as size of tumor, regional invasion, or distant metastases. Instead, the WHO recognized the need for a

separate staging system and, in 2010, together with the AJCC, endorsed the TNM staging system developed in 2009 by the UICC (UICC/AJCC/WHO 2010 TNM) [19]. This separation of grading from staging, which was earlier proposed by the ENETS in the 2006 TNM classification system, allows for prognostication of PanNET even when sufficient information is not available for staging, a not too infrequent scenario in clinical practice, when only small biopsy specimens are available for assessment of the grade of the tumor but detailed clinical assessment, including size and invasion, is lacking.

#### TNM Staging System (Tables 121.7 and 121.8)

The TNM staging system is an instrument for prognostication, allowing death-risk assessment at diagnosis, and guiding therapy. The ability to stratify patients into different stages at diagnosis reflecting increasingly worsening prognosis allows for planning of progressively more aggressive therapy. The success of the TNM staging system depends to a large extent on its ability to reflect the biology and natural history of the cancer. Well-differentiated PanNET, which are much more common than the more aggressive poorly differentiated PanNET, are biologically different from adenocarcinoma of the pancreas: they are larger in size, more indolent, late to metastasize, run a long course despite widespread metastases, and overall have a much better prognosis than adenocarcinoma of the pancreas.

A TNM staging system for PanNET was first proposed in 2006 by ENETS [18]. Subsequently, in 2009, the UICC released the seventh edition of the TNM classification of malignant tumors, which included a TNM staging system for well-differentiated PanNET [19]; this staging system was subsequently endorsed by both the AJCC and the WHO (UICC/AJCC/WHO TNM 2010). Tumor definition and the derived stages differ slightly between the two staging systems; as a result, although both systems use identical TNM terminology, they refer to slightly different extents of disease.

The ENETS TNM 2006 staging system has subsequently been validated by a number of series reporting on PanNET [21,22]. Since its introduction over 10 years ago, it has been widely used in Europe, with good prognostic discriminatory power among the various stages of PanNET. In contrast, the UICC/AJCC/WHO TNM 2010 staging system was introduced more recently; although a number of centers in the United States have been mandated to use this system, independent validation of this system is currently limited [23].

Overall, both TNM staging systems are predictive of patient outcome and, when combined with classification based on histologic and proliferative features, help stratify PanNET into groups of increasing malignant potential. However, a comparison between the two TNM staging systems, analyzing 891 patients from eight European centers, found the ENETS 2006 TNM staging system to be superior and more accurate than the UICC/AJCC/WHO 2010 TNM staging system [24]. However, this used a retrospective dataset and the management of PanNET was not standardized amongst the eight participating centers. Further modifications of the TNM staging system should be undertaken only after carefully analyzing the ability of the two existing systems in prognosticating PanNET, which should be assessed by collecting data using uniform protocols in a prospective manner. Until the adoption of such a unified TNM staging system, when reporting one should clearly mention which of the two systems was used for TNM staging. Since the discrepancy between the two staging systems is primarily limited to "tumor" staging, it is important to record the features that contributed to the "tumor" staging (tumor size and extent of invasion) to allow comparison between reported series using the alternative TNM staging system.

## Conclusions

Pancreatic NET should be classified based upon the WHO 2010 classification system into NETs (G1 or G2) and NECs (G3). Grading should be assessed using both the number of mitoses per 10 HPF and also the Ki-67 labeling index; however, if the specimen size is small, such as a biopsy specimen, with insufficient HPF for examination for mitoses, then grading can be based solely on the Ki-67 labeling index. In the rare event of discordance between the two markers of proliferation rate, the higher grade should be used. PNET should also be staged, whenever possible, using one of the two existing TNM staging systems (ENETS 2006 or UICC/AJCC/WHO 2010 TNM staging system). When reporting, care should be taken to mention the TNM staging system used, and details of the tumor size and extent of spread should be clearly recorded. The WHO 2010 classification and a TNM staging system should be applied to all PanNETs irrespective of whether they are functional or nonfunctional, syndromic or sporadic.

Future refinements in classification can be expected because the current existence of two parallel TNM staging systems that describe different extents of disease while using the same TNM terminology is confusing. Moreover, the current classification systems do not allow a clear separation of tumors, fortunately few in number, that predominantly exhibit features of a well-differentiated NET with low proliferative rates but have a few regions that have a much higher proliferative rate and increased cytologic atypia. Recently, it has also been noted that the clinical behavior of a small subset of

PanNET that are G2 by mitotic count (<20 mitoses per 10 HPF) but G3 by Ki-67 labeling index (>20%) is intermediate between that of G2 and G3 PanNET [25]. It would therefore seem that G3 PanNET as defined by the WHO 2010 classification are heterogeneous and need better delineation; they not only include a small subset of tumors that are well differentiated but have a higher proliferation index, but also another subset of tumors that are G3 but have a Ki-67 labeling index between 20 and 55% that seem to survive longer than those with Ki-67 index >55%. Moreover, currently it remains unclear whether well-differentiated G1 and G2 NET can transform and evolve into poorly differentiated NEC.

Collection of prospective data using unified management protocols over the coming years should lead to refinement of the classification system in the future and, it is hoped, the emergence of a unified TNM staging system. However, until that time, the WHO 2010 classification system, together with the use of either one of the two TNM staging systems, should remove much of the earlier controversy surrounding the classification of these rare endocrine tumors of the pancreas, allowing proper prognostic stratification, guiding appropriate stage- and grade-specific therapy, and enabling evaluation of new therapies and comparison of results of published therapeutic trials on PanNET.

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# 122

# Pathology of Neuroendocrine Neoplasms

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## WHO Classification and TNM Classification

The World Health Organization (WHO) classification published in 2017 divides pancreatic neuroendocrine neoplasms (PanNENs) into well-differentiated and poorly differentiated neuroendocrine neoplasms. The former is further subclassified into neuroendocrine tumor (NET) G1, NET G2, and NET G3, based on the mitotic and Ki-67 indices (NET G1: mitoses<2/10 HPF (high-power view) and Ki67 index <3%; G2 NET: mitoses 2–20/10 HPF or Ki67 index 3%–20%; NET G3: mitoses >20/10 HPF or Ki67 index >20 %) (Table 122.1) [1]. NET G3 is a newly introduced tumor category in the 2017 WHO classification that retains well-differentiated histology but presents high proliferative activity. The latter is high-grade pancreatic neuroendocrine carcinoma (PanNEC) presenting high proliferative activity (mitoses >20/10HPF or Ki67 index >20%), and categorized as NEC G3. NEC G3s are subtyped into small cell and large cell NEC based on the cell size and cellular feature. Both NET G3 and NEC G3 demonstrate high proliferative activity (Ki67 index>20%) but the clinical presentations of patients with NET G3 are more indolent than those with NEC G3 [2–4]. The morphological and immunohistochemical characteristics of the two high-grade neoplasms will be discussed in the Immunohistochemistry and Differential Diagnosis section. Nuclear labeling of Ki-67 should be counted in 500–2000 tumor cells. The Ki-67 index is usually higher than the mitotic index for identical tissues. Because the determination of the Ki-67 index of the tumor is highly significant for the estimation of aggressiveness and determination of therapeutic strategies, optimal evaluation methodologies, including automated counting, have been discussed [5,6]. Despite the high expected reproducibility of automated digital evaluation, it does not seem to be a realistic tool for routine diagnosis because of the low cost–benefit and its operator-dependent acquisition of morphology and/or color of the image [5]. Manual counting on the printed image may improve an "eyeball estimate" under microscopic observation. Based on the original proposal published by the European Neuroendocrine Tumor Society (ENETS), the mitotic index is defined as the total mitotic counts per $2\,mm^2$. Mitosis may distribute heterogeneously; therefore, it is recommended to observe a wider area (50 HPF) and select areas with the highest density of mitosis.

Mixed tumors of endocrine and exocrine components are categorized as a unique entity of mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN), which was termed mixed adenoneuroendocrine carcinoma (MANEC) in the previous classification [7]. MiNEN comprises at least 30% of both endocrine and exocrine components. The histology of NENs and MiNENs is further described in the Microscopy section.

In the 8th edition of TNM classification for malignant tumors by Union for international cancer control (UICC TNM), the TNM classification systems for PanNETs (NET G1, G2, G3) and PanNECs were separately stated. However, the differences between the two classifications were limited, only seen in pT1, pN1, and pM1 categories (Table 122.2) [8].

## Macroscopy

The macroscopic features of PanNENs are variable. Well-circumscribed tumors displaying a whitish tan to yellowish cut surface are most commonly encountered (Fig. 122.1a). The tumor size at the time of surgery varies

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

from <1 to 20 cm in diameter. Insulinomas are generally detected as small lesions (<2 cm), whereas nonfunctioning PanNET are usually detected as larger lesions. Cystic degeneration is often associated with glucagon production by the tumor cells (Fig. 122.1b) [9]. PanNECs usually exhibit unclear boundaries (Fig. 122.1c). Necrosis is not uncommon in PanNECs (Fig. 122.1c).

**Table 122.1** WHO 2017 classification of pancreatic neuroendocrine neoplasms [1].

| | Mitotic index (per 10HPF) | Ki-67 index (%) |
|---|---|---|
| Well-differentiated NENs | | |
| NET G1 | <2 | <3 |
| NET G2 | 2–20 | 3–20 |
| NET G3 | >20 | >20 |
| Poorly differentiated NENs | | |
| NEC G3 | >20 | >20 |

## Microscopy

Initially, morphologic observation is used to determine histopathologic differentiation, which should be further confirmed by immunohistochemistry.

G1 and G2 NET display well-differentiated morphology. Tumor cells of well-differentiated NENs are uniform in size and shape, having round to oval nuclei, with a coarsely granular (so-called salt-and-pepper) chromatin pattern (Fig. 122.2a). Nucleoli may be observed but are mostly inconspicuous (Fig. 122.2a). The cytoplasm of the tumor cells is mostly granular and appears to be slightly eosinophilic. The tumor cells form characteristic architectural patterns, such as anastomosing ribbon-like nests (Fig. 122.2b), trabecular nests (Fig. 122.2b), a glandular pattern (Fig. 122.2c), and a gyriform or solid growth pattern (Fig. 122.2d). Capillary or fibrocapillary stroma intervenes within tumor cell nests (Fig. 122.2a–h). The extent of fibrosis or hyalinosis varies among cases. Amyloid-like deposition of islet amyloid polypeptide is a characteristic feature of functioning NEN, especially

**Table 122.2** Two TNM classification of pancreatic neuroendocrine neoplasms listed in the 8th edition of Union for International Cancer Control (UICC) TNM classification for malignant tumors. The two different TNM classifications, one for well-differentiated tumor (NET G1, G2, G3), the other is for poorly differentiated neuroendocrine carcinoma and other pancreatic neoplasms [8].

| | Well-differentiated neuroendocrine tumors | Poorly differentiated neurondocrine carcinoma |
|---|---|---|
| Primary Tumor (T) | | |
| TX | Cannot be assessed | Cannot be assessed |
| T0 | Not evident | Not evident |
| T1 | Limited to the pancreas, <2 cm | T1a Limited to the pancreas, 0.5 cm or less |
| | | T1b Limited to the pancreas, 0.5 cm ≤, < 1 cm |
| | | T1c Limited to the pancreas, 1 cm ≤, < 2 cm |
| T2 | Limited to the pancreas, 2-4 cm | Limited to the pancreas, 2-4 cm |
| T3 | Limited to the pancreas, >4 cm, or invasion of duodenum or bile duct | Limited to the pancreas, >4 cm, or invasion of duodenum or bile duct |
| T4 | Invading adjacent organs (stomach, spleen, colon, adrenal grand) or the wall of large vessels (celiac axsis or the superior mesenteric artery) | Invading adjacent organs (stomach, spleen, colon, adrenal grand) or the wall of large vessels (celiac axsis or the superior mesenteric artery) |
| Regional Lymph Node (N) | | |
| NX | Cannot be assessed | NX Cannot be assessed |
| N0 | No regional lymph node involvement | N0 No regional lymph node involvement |
| N1 | Regional lymph node involvement | N1 Metastasis in 1–3 regional lymph nodes |
| | | N2 Metastasis in 4 or more regional lymph nodes |
| Distant Metastasis (M) | | |
| M0 | No distant metastasis | M0 No distant metastasis |
| M1 | M1a Only hepatic | M1 Distant metastasis |
| | M1b Extrahepatic metastasis | |
| | M1c Hepatic and extrahepatic | |

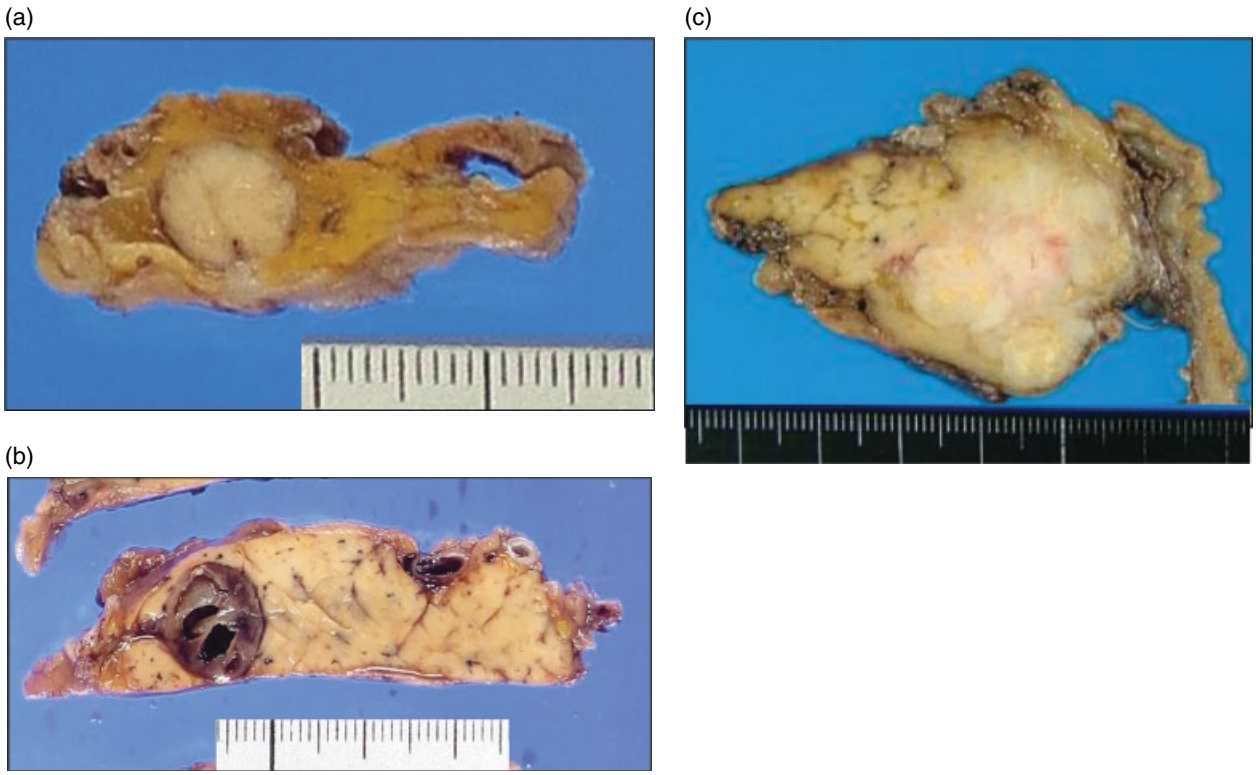


**Figure 122.1** Macroscopic images of pancreatic neuroendocrine neoplasms (PanNENs). (a) A round to oval-shaped, well-circumscribed tumor with a whitish tan cut surface observed in NET G1. (b) A well-demarcated tumor with cystic changes observed in G1 PanNET NET G1. (c) A tan–white and focally yellowish tumor with unclear boundaries observed in large-cell neuroendocrine carcinoma (large cell NEC G3).

insulinoma (Fig. 122.2e). Psammomatous calcification may be identified in gland-like small cavities of the tumor nests. Psammomatous calcifications suggest somatostatin production by the tumor cells, which is more frequently observed in the duodenum than in the pancreas. Tumor cells exhibiting abundant eosinophilic cytoplasm are regarded as an oncocytic variant of PanNEN, which is caused by abnormal mitochondrial accumulation. Oncocytic NENs tend to display larger nuclei and conspicuous nucleoli (Fig. 122.2f). This variant has been reported to be associated with a higher incidence of lymph node metastasis; however, the biological implication of this particular variant remains unknown [10]. The differential diagnosis of oncocytic NENs and acinar cell carcinoma (ACC) is described in the Differential diagnosis section. A PanNEN characterized by abundant clear cytoplasmic vacuoles or foamy microvesicular cytoplasm is known as a clear cell or lipid-rich variant of NEN (Fig. 122.2g). Nuclei are pushed by lipid vacuoles and appear to be polygonal and pyknotic; therefore, characteristic round or oval nuclear features are not necessarily recognized. The association of this variant with von Hippel–Lindau syndrome (VHL) has been described. It is important to note that the morphology of this variant is similar to those of other pancreatic neoplasms displaying clear cytoplasm, such as a serous cystic neoplasm (SCN), clear cell variant of solid pseudopapillary neoplasm (SPN), and metastasis of clear cell renal cell carcinoma, or foamy cytoplasm, such as adrenocortical neoplasm (see Differential diagnosis section). The tumor that presents large and hyperchromatic nuclei with marked pleomorphism, without high proliferative activity or necrosis, is known as a pleomorphic variant of PanNEN (Fig. 122.2h). It is important to distinguish this variant from highly aggressive neoplasms, such as anaplastic carcinoma or large-cell NEC.

The heterogeneity of histologic and clinical presentations of PanNENs that present high proliferative activity (NET G3 and NEC G3) has been a contentious subject [2–4,11,12]. NET G3s morphologically remain well-differentiated neuroendocrine patterns, but often present larger nuclei and more conspicuous nucleoli than NET G1/G2s. NET G3s also often demonstrate large solid nests and necrosis. These morphologic features can result in difficulty in differentiating them from NEC G3s. Tumor cells of NEC G3 comprise cells with a high degree of nuclear pleomorphism, nuclear enlargement, and high nuclear–cytoplasmic ratio. Necrosis is abundant in most cases of PanNECs. Characteristic architectural patterns are less evident and mostly comprise diffuse growth patterns or large nests (Fig. 122.3a, b). Based on cell size, PanNECs are further divided into small-cell NEC

(Fig. 122.3a) and large-cell NEC (Fig. 122.3b). Because of the rarity of these high-grade neoplasms, the biological, molecular, and clinical differences between small- and large-cell NEC have not been fully established; however, small-cell NEC seems to display a higher proliferative index and has a more aggressive clinical course than large-cell NEC. Proliferative activity, especially the Ki-67 index of small- and large-cell NEC, is extremely high, mostly exceeding 50%. A possibility of transformation from PanNET to PanNEC has also been suggested [11]. Given the difficulty of defining absolute cut-off values of proliferative indices, it is reasonable to expect that NET G2 and NET G3 share common biological mechanisms and clinical presentations.

MiNEN is a heterogeneous neoplasm comprising both endocrine and exocrine components in which either component must represent at least 30%. Endocrine components of MiNEN can be present as either NET or NEC, and its exocrine components can also vary, for example, tubular adenocarcinoma, poorly differentiated adenocarcinoma, or ACC. Histogenesis of MiNEN in the pancreas is still not clear. Currently, the following two theories have been hypothesized: (i) multiple components arise independently and (ii) heterogeneous components originate from common multipotent progenitor cells. The clinical course of the tumor is generally defined by the most aggressive component of MiNEN; in most cases, the endocrine component is the most aggressive.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant tumor syndrome characterized by multiple endocrine tumors arising in the

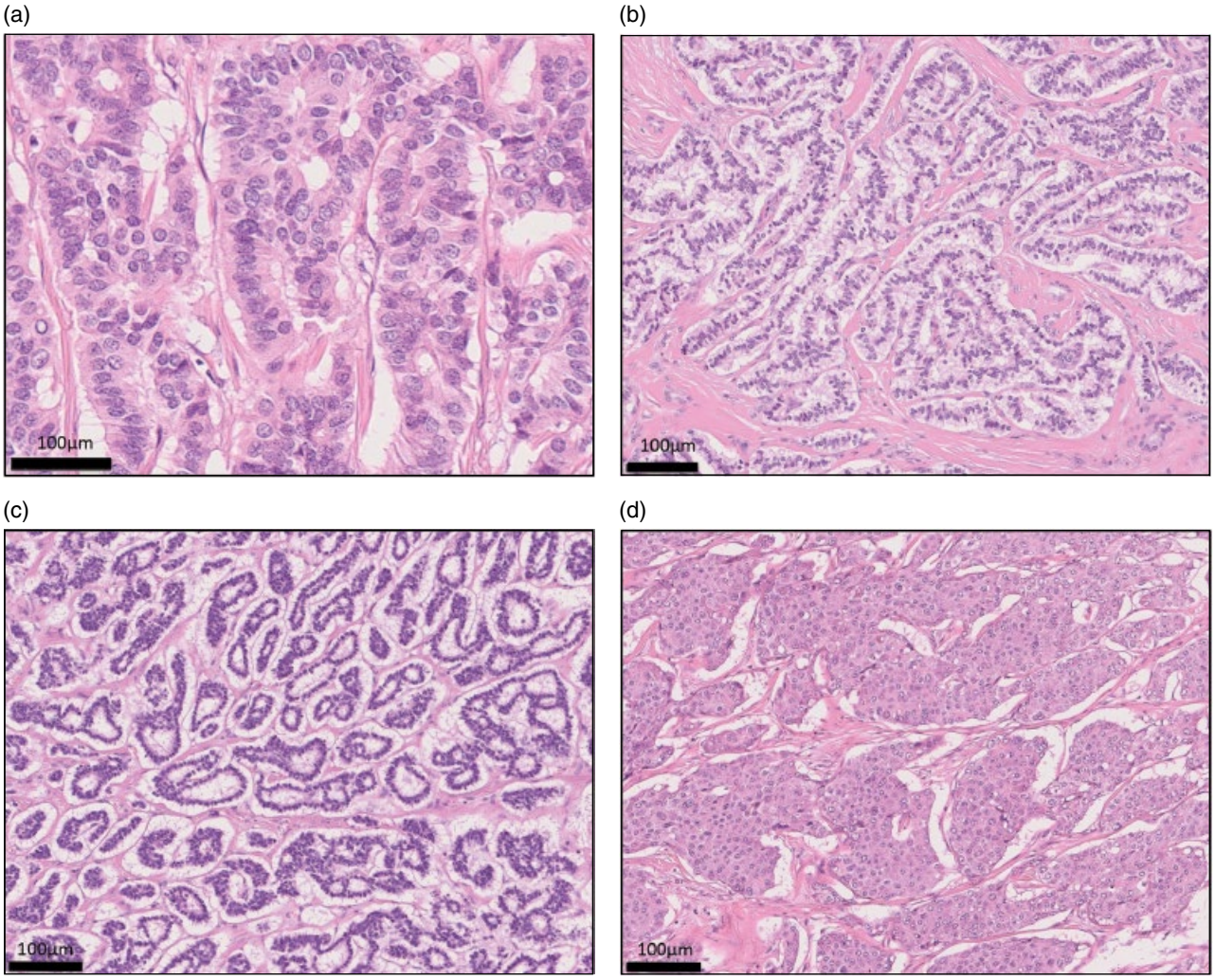


**Figure 122.2** Microscopic images of well-differentiated pancreatic neuroendocrine neoplasms (PanNENs) (NET [neuroendocrine tumor] G1 and G2). (a) Tumor cells display round to oval-shaped nuclei with coarsely granular so-called salt-and-pepper chromatin distribution. Tumor cells arranged in (b) anastomosing ribbon-like nests, (c) gland-like features, or (d) solid cell nests. (e) Marked amyloid-like deposition in insulinoma detected by direct Fast Scarlet staining. (f) An oncocytic variant of PanNEN. (g) A lipid-rich variant of PanNEN. (h) A pleomorphic variant of PanNEN. Abundant capillary or fibrocapillary stroma observed within tumor cell nests (a–h).

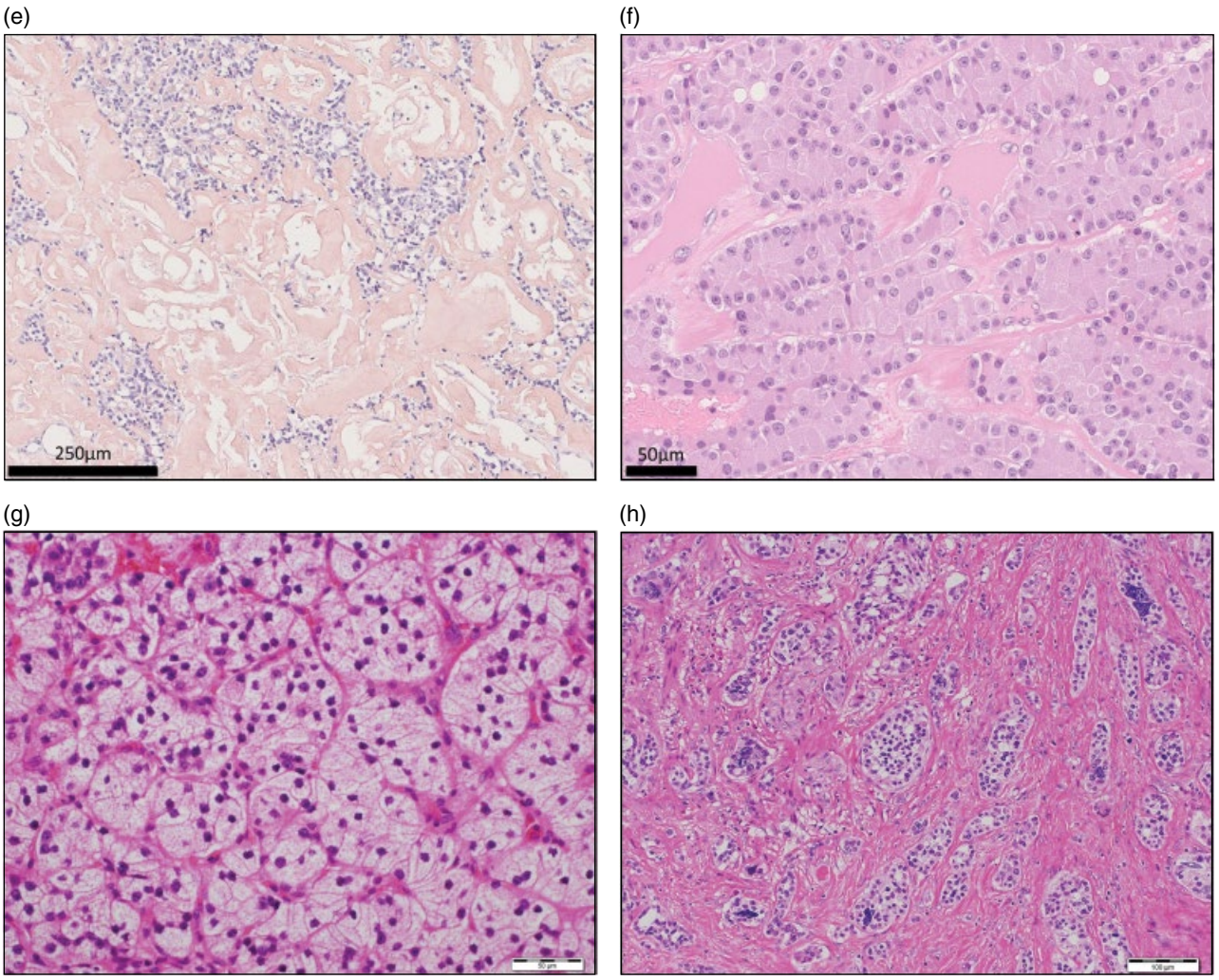


**Figure 122.2 (Cont'd)**

parathyroid, gastrointestinal tissue, pancreas, anterior lobe of the pituitary gland, and adrenal cortex. The histopathology of pancreatic lesions in patients with MEN1 is characterized by multiple microadenomas (microadenomatosis usually accompanied by macronodules) [13]. The multiple tumors observed in identical tissues of patients with MEN1 may produce variable hormones. Microadenomatosis of the pancreas is also associated with patients with VHL [13].

## Cytology

Owing to the development of the endoscopic ultrasound-guided fine-needle aspiration technique, cytology assessments have become a standard pathologic diagnostic tool for PanNEN. Cytology is one of the most powerful tools to determine the diagnosis of endocrine tumors, especially because of the characteristic nuclear morphology. Nuclei of tumors display a monotonous appearance; they are uniformly round to oval shaped, with a salt-and-pepper chromatin pattern or, often, plasmacytoid epithelial cells (Fig. 122.4a, b). Tumor cells of PanNETs are observed as variably sized, loosely cohesive clusters. Single cells are also frequently observed (Fig. 122.4a). Tumor cells surrounding and loosely attached to capillary vessels are frequently seen (Fig. 122.4b). A rosette-like arrangement is highly specific to PanNET, but similar arrangements may also be observed in ACC. Small- and large-cell NEC apparently exhibit higher nuclear pleomorphism and enlargement, often showing a necrotic background. PanNECs show low intercellular cohesiveness.

## Immunohistochemistry and Differential Diagnosis

Neuroendocrine differentiation of PanNEN is mostly suggested by morphologic assessment, but it must be further confirmed by immunohistochemistry. Chromogranin A

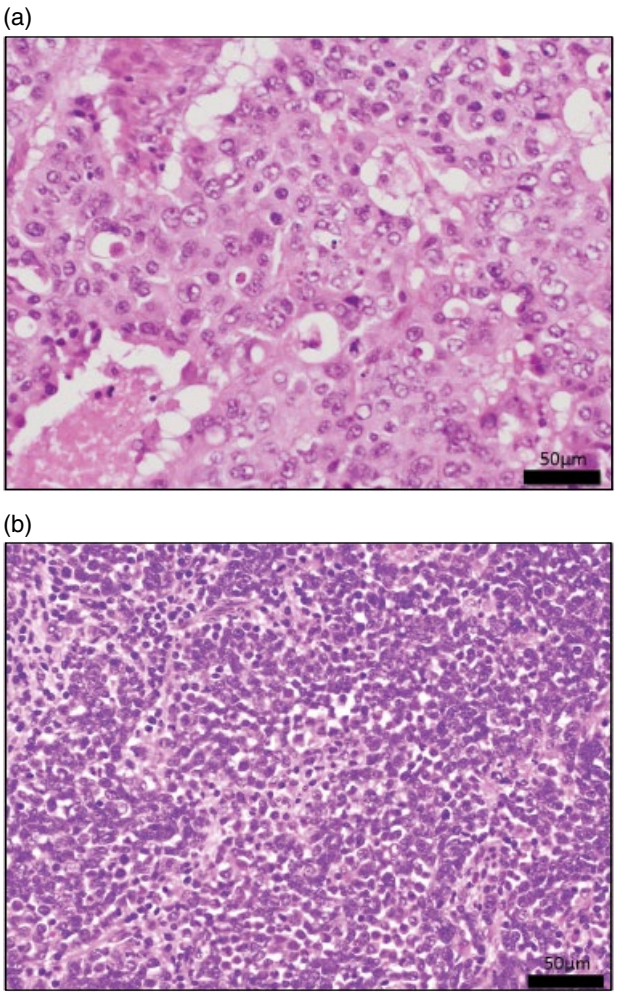


**Figure 122.3** Microscopic features of poorly differentiated neuroendocrine carcinoma (PanNEC). (a) Large-cell NEC displaying highly pleomorphic tumor cells showing a diffuse growth pattern. Necrosis is also observed. (b) Small-cell NEC composed of small, round tumor cells with a high nuclear–cytoplasmic ratio.

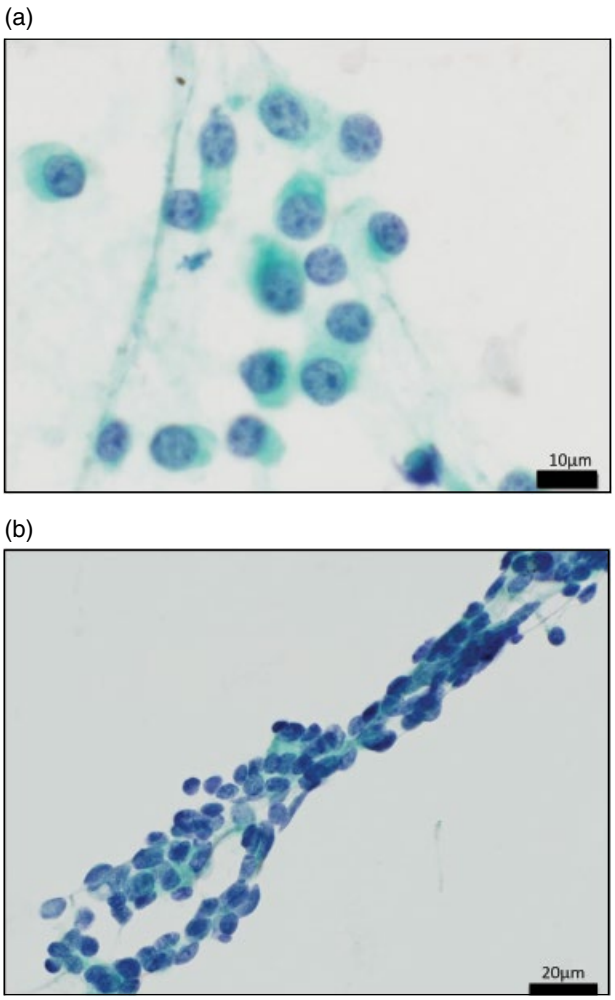


**Figure 122.4** Cytology images of pancreatic neuroendocrine tumors. (a) Loosely cohesive plasmacytoid epithelial cells with round to oval-shaped nuclei showing a salt-and-pepper chromatin pattern. (b) Tumor cells surrounding capillary vessels.

shows the highest specificity among neuroendocrine markers. The sensitivity of chromogranin A is also high in PanNETs, but its expression in PanNEC is usually weak and focal. Synaptophysin is a highly sensitive neuroendocrine marker, but its expression is also observed in non-neuroendocrine tumors, such as SPN, SCN, paraganglioma, and ACC; therefore, a panel immunohistochemical evaluation is useful to exclude the possibility of these tumors. CD56 and neuron-specific enolase (NSE) are not recommended for determination of PanNEN because of their limited specificity. PanNETs produce hormones, which are better revealed via clinical rather than pathologic analysis/examination. Consequently, clinical information should be considered in the pathologic evaluation. PanNETs usually do not demonstrate abnormal TP53 expression or loss of retinoblastoma 1 protein (RB1) by immunohistochemistry [12]. In contrast, PanNECs usually do not produce hormones, without showing abnormal TP53 expression or loss of Rb1 [12].

Positivity for cytokeratins, including CK8, CK18, CK AE1/AE3, and CAM5.2, observed in PanNENs is helpful to exclude the possibility of paraganglioma, mesenchymal neoplasms, or hematopoietic malignancies.

Low-grade cellular atypia and intervening capillary structures of SPN are common features of PanNET, although SPN is usually composed of heterogeneous growth architectures. Variable stromal changes, such as fibrosis, hyalinosis, cystic degeneration, and calcification, can be observed in both SPN and PanNET, but marked myxoid degeneration or solid and large calcification suggest the possibility of SPN rather than PanNET. Nuclear features of SPN are distinct from those of PanNET; chromatin is finely stippled, the salt-and-pepper pattern is not evident, and nuclear grooves may be observed in SPN. It is probably difficult to distinguish

these two neoplasms on small biopsy specimens, unless "pseudo-papillary structures" of SPN are finely observed. Nuclear expression of β-catenin is highly specific for SPN, whereas it is expressed only in the cell membrane of tumor cells of PanNET. It should be noted that SPN may express synaptophysin, but chromogranin A expression is mostly negative or very limited.

The architectural pattern of ACC is variable; an acinar growth pattern is most commonly observed, but solid, trabecular, and diffuse growth patterns may also variably intermingle. Tumor cells of ACC present hyperchromatic nuclei and higher pleomorphism than PanNET. Eosinophilic granular cytoplasm, because of zymogen granules, can be similar to the cellular features of the oncocytic variant of PanNET. Acinar differentiation should be defined by immunohistochemistry, for example, trypsin, lipase, and BCL10. ACC may also focally coexpress chromogranin A and synaptophysin. ACC, of which neuroendocrine expression is observed in more than 25% of all tumor cells, is regarded as mixed acinar-neuroendocrine carcinoma. The clinical and histopathologic features of mixed acinar-neuroendocrine carcinoma are more closely associated with ACC than PanNENs; therefore, mixed acinar-neuroendocrine carcinoma is considered to be a histologic subtype of ACC [14].

Pancreatic neoplasms that exhibit clear cytoplasm, such as clear-cell variant of SPN, metastasis of clear-cell renal cell carcinoma, and solid type of serous cystic neoplasm, can be mimics of the clear-cell variant of PanNET. Tumor cells that contain abundant lipid vacuoles appear to be mimics of adrenocortical neoplasm.

Ewing sarcoma is composed of small, round-shaped hyperchromatic tumor cells, and is histologically similar to small-cell NEC. It should be noted that Ewing sarcoma occurring in the pancreas often expresses cytokeratin and may be positive for neuroendocrine markers, such as synaptophysin, CD56, or NSE [15]. Malignant lymphoma is also composed of small, round-shaped tumor cells but it can be distinguished by immunohistochemical expression of leukocyte common antigen.

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# Molecular Genetics of Neuroendocrine Tumors

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## Introduction

Low-grade pancreatic neuroendocrine tumors (PanNETs) are the second most common malignancy of the pancreas, accounting for approximately 2% of newly diagnosed pancreatic malignancies. The increased diagnosis of patients with this disease has mainly been due to better imaging and diagnostic tools and a larger number of incidental findings [1–4]. Although PanNETs are not as lethal as pancreatic ductal adenocarcinoma (PDAC), more than 50% of patients have distant disease at diagnosis and the 10-year survival rate is about 40% [5]. High-grade neuroendocrine carcinomas (NECs) of the pancreas are extremely rare and highly lethal [6–9].

Well-differentiated PanNETs are classified as functional or nonfunctional, with the latter group being most common [10]. Functional PanNETs produce syndromes with systemic effects related to the hormones that they secrete. The most common functional PanNETs are insulinomas, and glucagonomas, gastrinomas, somatostatinomas, VIPomas, and some PanNETs of mixed histology comprise the rest of this group. Nonfunctional PanNETs do not secrete clinically significant hormones; rather, they grow silently, and patients often present with either an asymptomatic abdominal mass or abdominal pain resulting from compression due to a large tumor. Surgery can be curative in the case of primary cancers and some cases of metastasis, but many patients present with unresectable tumors or extensive metastatic disease.

Most of PanNETs are sporadic; however, they can also arise in patients with familial syndromes, most commonly in patients with multiple endocrine neoplasia type 1 (MEN1), followed by von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and tuberous sclerosis complex (TSC) [11–13]. As a result, the genomes of patients with PanNETs with the syndromes mentioned have germline mutations in the gene(s) that are responsible for the predisposition to the familial syndromes.

High-grade neuroendocrine carcinomas, defined as neuroendocrine neoplasms with proliferation rates >20%, are highly malignant neoplasms, and include entities previously defined as "small-cell" and "large-cell" neuroendocrine carcinomas [6–9]. There are some neoplasms that technically have proliferation rates >20%, but which retain an otherwise well-differentiated morphology, and these neoplasms likely have genetic alterations similar to well-differentiated PanNETs, and not those of the high-grade NECs [14,15].

We now know that cancer takes many years to develop, and is caused by the sequential alteration of a small number of genes that affect a smaller number of cellular processes [16]. The genomic landscapes of many tumor types have been determined, and although not everything is yet understood, these studies have provided sufficient information for developing effective approaches for reducing cancer morbidity and mortality. For similar reasons, much progress has been made in understanding the genetic alterations that underlie PanNET and NEC tumorigenesis. This chapter describes what is known about the genetic landscape and epigenetics of PanNET and NEC, and their clinical applications.

## Genetics of Sporadic PanNET

In order to gain insight into the genetic basis of PanNETs, whole-exome sequencing (WES) was performed in 10 clinically homogeneous nonfunctional PanNETs [17]. Then, the most commonly mutated genes were analyzed for mutations in 58 additional nonfunctional PanNETs. The most commonly mutated genes identified encode

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Companion website: www.wiley.com/go/beger/thepancreas

proteins that are involved in chromatin modification. *MEN1* had inactivating mutations in 44% of the samples. *ATRX* and death domain-associated protein (*DAXX*) genes had mutually exclusive inactivating mutations in 18 and 25% of the samples, respectively, resulting in the inactivation of the ATRX/DAXX complex in 43% of the PanNETs. Approximately 14% of the samples had mutations that should result in the activation of the mammalian target of rapamycin (mTOR) pathway. Tuberous sclerosis complex 2 (*TSC2*) was inactivated in 9% of the samples, and phosphatase and tensin homolog (*PTEN*) was inactivated in 7% of the samples. In addition, there was an activating mutation in *PIK3CA*, which encodes the p110 alpha catalytic subunit of PI3K. *TP53* was inactivated in only 3% of the PanNETs (Table 123.1). Overall, there were about 8–23 mutations per tumor with a mean number of 16 mutations, which is low compared with other solid tumors. Mutations in oncogenes are rare in most solid tumors, so it was not unexpected that only one sample had an activating oncogenic mutation [16]. This lack of activating mutations in oncogenes underlies the overall challenge for developing targeted therapies for PanNETs. As a result, understanding the pathways involved in the development and progression of cancers has become pivotal for developing therapeutics. A good example is the mTOR pathway. Existing therapeutic agents that inhibit this pathway do not target commonly mutated genes in the pathway; rather, they target mTORC1 as a shared downstream effector in the pathway.

Although the WES study greatly increased our understanding of the genetic alterations underlying PanNET tumorigenesis, it had its limitations. For example, the study did not identify chromosomal rearrangements, copy number variations, or foreign sequences. Comparative genomic hybridization studies have shown that PanNETs, much like other solid tumors, have a number of chromosomal gains and losses [18,19]. Some studies have reported that the number of chromosomal gains and losses is larger in metastatic lesions compared with the primary tumor from the same individual [18]. However, it remains unclear if these additional gains and losses are drivers, or just passengers, representing the continuous accumulation of genetic lesions in the advanced lesions.

Another limitation of WES studies is the difficulty in identifying large deletions in tumor suppressor genes. As will be discussed later, inactivating mutations in *ATRX* and *DAXX* correlated with the alternative lengthening of telomeres (ALT) phenotype. In fact, protein expression studies in 68 PanNETs indicated that all samples with *ATRX* or *DAXX* inactivating mutations exhibited the ALT phenotype [20]. Interestingly, tumors negative for nuclear staining of either ATRX or DAXX also showed the ALT phenotype, indicating that *ATRX* or *DAXX* genes were inactivated either by a rearrangement such as large deletions not identifiable by exome sequencing, or via epigenetic mechanisms. This study indicated that inactivation of *ATRX* or *DAXX* occurred in approximately 60% of the PanNET samples, of which 43% were caused by exomic mutations and the remaining cases most likely resulted from large deletions or epigenetic gene inactivation.

Mutations in the regulatory regions of genes were also not identified in the WES study. The best-studied mutations of these types are those in the telomerase reverse transcriptase (*TERT*) promoter. Two nucleotides account for almost all of the *TERT* promoter mutations that have been associated with human carcinogenesis [21,22]. These mutations result in changes in the chromatin state of the promoter, which, in turn, allow binding of transcription factors that promote TERT expression [23]. This expression is derived from the allele with the mutation, while the other allele remains silent [24]. In glial tumors, *ATRX* inactivating mutations and *TERT* promoter mutations are mutually exclusive, presumably because each type of mutation results in preservation of a the telomeric length appropriate for cell growth [25]. To evaluate the possibility of this occurring in PanNET, the samples analyzed for *ATRX* and *DAXX* mutations were also evaluated for *TERT* promoter mutations. None of the 68 PanNETs had *TERT* promoter mutations at the hot spots were shown to be mutated in many other tumor types; therefore, we presume that TERT is expressed in these tumors.

The exome of sporadic functional PanNET has only been sequenced in insulinomas. In a set of ten insulinomas, the most commonly mutated gene was the transcription factor Yin Yang 1 (*YY1*) [26]. Sequencing of *YY1* in an additional 103 insulinomas identified a hot spot mutation in 31 of them. Overall, 30% (34/113) of the insulinomas possessed the T372R mutation [26]. A more recent study focusing on the Caucasian instead of the Asian population, identified a much lower prevalence (13%) of *YY1* mutations in sporadic insulinomas. In the Caucasian population, the T372R mutation appeared to stratify with women and older age [27].

## Pathways Altered in PanNETs

### ATRX/DAXX Pathway

Approximately half of PanNETs have inactivating mutations in *ATRX* or *DAXX*. *ATRX* is located on chromosome X, and only the active copy needs to be inactivated to result in total loss of the ATRX protein. On the other hand, *DAXX* is located on chromosome 6, and both copies need to be inactivated for DAXX protein loss. The mutations that occur in the *DAXX* gene include single nucleotide base substitutions and indels that create frameshifts,

**Table 123.1** Comparison of commonly mutated genes and their prevalence in PanNET and other pancreatic neoplasms.

| Gene | Nonfunctional PanNET (%) | Syndromic microadenomas (%) | NEC (%) | PDAC (%) | Insulinomas (%) | Intracellular pathway | Clinical application | Future opportunity |
|---|---|---|---|---|---|---|---|---|
| *MEN1* | 44 | 100 | 0 | 0 | 2.50 | Chromatin methylation | Not available | Synthetic lethality |
| *ATRX* | 18 | 0 | 0 | 0 | 2.50 | Chromatin remodeling—ALT | Prognostic/diagnostic | Synthetic lethality |
| *DAXX* | 25 | 0 | 0 | 0 | 0 | Chromatin remodeling—ALT | Prognostic/diagnostic | Synthetic lethality |
| *TSC2* | 9 | Not tested | Not tested | 0 | 0 | mTOR | Target treatment—mTOR inhibitors | Improved mTOR inhibitors |
| *PTEN* | 7 | Not tested | <10 | 0 | 0 | mTOR | Target treatment—mTOR inhibitors | Improved mTOR inhibitors |
| *PIK3CA* | 1 | Not tested | Not Tested | 0 | 0 | mTOR | Target treatment—mTOR inhibitors | Improved mTOR inhibitors |
| *TP53* | 3 | Not tested | 95 | 85 | 0 | TP53 | Not available | Synthetic lethality |
| *KRAS* | 0 | Not tested | 30 | 100 | 0 | KRAS | Not available | Target therapy |
| *CDKN2A* | 0 | Not tested | 50 | 25 | 0 | Cell cycle | Not available | Synthetic lethality |
| *SMAD4* | 0 | Not tested | 10 | 27 | 0 | TGFβ | Not available | Synthetic lethality |
| *RB1* | 0 | Not tested | 74 | 0 | 0 | Cell cycle | Not available | Synthetic lethality |
| *YY1* | 0 | Not tested | 0 | 0 | 13–30 | Transcription | Not available | Target therapy |

larger deletions of single or multiple exons, and loss of heterozygosity. All of the mutations in both *ATRX* and *DAXX* lead to inactivation of the respective gene and lack of nuclear protein immunolabeling in PanNETs, in accordance with them being tumor suppressors. The mutations are also mutually exclusive, consistent with the two genes working within the same pathway [17,20].

ATRX is a chromatin remodeling protein that interacts with DAXX and together they function as a histone chaperone complex that deposits the histone variant H3.3 into pericentric, telomeric, and ribosomal repeat sequences [28–31]. Although the mechanism underlying the action of ATRX remains unclear, recent progress has been made. ATRX is thought to be recruited, perhaps by interacting with histones, to G-quadruplex DNA, where it is involved in chromatin remodeling, with consequences on gene expression, and relief of replication fork stalling [31,32]. Consequently, its absence can impair both nonhomologous end joining DNA repair and formation of protein complexes, resulting in changes to the epigenetic state of the DNA [33–35].

Perhaps more intriguing is the connection between the lack of ATRX or DAXX protein expression with the ALT phenotype [36]. There is telomere length attrition with every cell division resulting in telomeric lengths that are not compatible with further growth. Cancer cells must circumvent this issue. Telomeric length is usually maintained by TERT [37]; however, TERT is not always active. Cells with the ALT phenotype have very long telomeres whose lengths are maintained by recombination instead of the enzymatic action of TERT [38]. Mutations in *ATRX* or *DAXX* that abolish protein expression in PanNETs correlated with ALT [20,25,39]. *ATRX* inactivating mutations concomitant with ALT have also been identified in extra-pancreatic tumor types including glial tumors, neuroblastomas, and sarcomas, in cancer cell lines, and also in *in vitro* immortalized ALT cell lines [25,40]. Furthermore, loss of wild-type ATRX expression in somatic cell hybrids segregated with ALT, whereas ATRX expression led to inhibition of ALT [41,42]. A greater understanding of how ATRX loss may result in the ALT phenotype and its connection to increased chromosomal instability was provided by a study that showed that loss of ATRX in cancer cells lines can promote sister telomere cohesion associated with increased recombination between sister telomeres [43].

*ATRX* was first identified to cause an X-linked hereditary syndrome [44]. The germline mutations did not result in an increased cancer incidence in these patients, and cells from these patients did not demonstrate the ALT phenotype. This could be because the spectrum of mutations in these individuals was mostly missense, and even some of the presumably inactivating mutations retained expression of the protein. In alpha-thalassemia myelodysplastic syndrome (ATMDS), *ATRX* mutations are also mostly missense [45]. It is possible that because individuals with myelodysplastic syndrome tend to be older, some or most of the mutations are passenger mutations. In contrast, all of the mutations identified in solid tumors, including PanNETs, CNS tumors, and sarcomas, are inactivating and all correlate with ALT.

PanNETs are also unique in that *DAXX* mutations are predominant over *ATRX* mutations, even though *DAXX* mutations are extremely rare in other tumor types with ALT, which almost exclusively have *ATRX* mutations [17,46]. The differences in the spectrum of *ATRX* mutations in various diseases, and the preferential inactivation of *DAXX* in PanNETs, provide fertile ground for understanding the intricacies of this pathway and its tumor-specific ALT phenotype, with the hope that a deeper understanding will lead to the therapeutic targeting of the pathway.

### MEN1 Pathway

*MEN1* is the most frequently somatically mutated gene in PanNET [17,47]. This gene encodes the transcriptional regulator menin, which recruits the H3K4me3 histone methyltransferase mixed-lineage leukemia (MLL) complex [48,49]. Menin interacts with many proteins and regulates gene expression and intracellular cell signaling and it is associated with numerous cellular processes including the regulation of SMAD3 to inhibit TGFβ1-mediated inhibition of proliferation, and repression of JunD activity, regulation of homeodomain gene expression, and repression of telomerase expression [50–53]. Mutations in PanNETs inactivate both alleles either by inactivating mutations or by a combination of mutation coupled with loss of heterozygosity. Thus, by definition, *MEN1* is a tumor suppressor.

It appears that tumorigenesis in PanNETs is driven by alterations in both histone modification and chromatin remodeling as the overlap of *MEN1* with *ATRX/DAXX* mutations is significant (74%). *MEN1* and *ATRX/DAXX* are epigenetic drivers of cancers, resulting in a plethora of epigenetic changes in the cell. Hence it is important to determine which epigenetic alterations are the key drivers of PanNET tumorigenesis, which has obvious implications for therapeutic exploitation of the associated pathways.

### mTOR Pathway

The mTOR signaling pathway integrates environmental signals to regulate growth and homeostasis. mTOR is an atypical serine/threonine protein kinase that interacts with several proteins to form two key complexes in the pathway, named mTOR complex 1 (mTORC1) and 2 (mTORC2), each of which mediates different upstream inputs and which have different downstream outputs. A number of tumor suppressors and oncogenes commonly

mutated in cancers are upstream of mTORC1, including the PTEN/PIK3CA pathway, the RAS/RAF pathway, TSC1/2, NF1, and LKB1. Sequencing of PanNET revealed mutations in *TSC2*, *PTEN*, and *PIK3CA* genes in 16% of samples, all which activated the mTOR pathway, consistent with its pro-growth effects on cells. Downstream effectors of the pathway involve 4E-BP1, which in turn regulates hypoxia-inducible factor 1 (HIF1a), a target of VHL, and S6K1, resulting in increased proliferation signals, regulation of metabolism, and increased protein synthesis (reviewed in [54]). Inhibitors of the mTOR pathway have shown benefit in patients with different tumor types, including PanNET; however, correlations between pathway mutations and the observed benefits have not yet been established [55]. Based on results from other tumor types, we hypothesize that patients with tumors with mTOR pathway mutations will respond better to therapies targeting this pathway [56]. However, in clinical trials, the number of patients with PanNETs that benefited from treatment with everolimus, which targets the mTOR pathway, was larger than the number of PanNETs with mutations in the mTOR pathway [17,55]. However, this is an extrapolation as the PanNETs from the patients included in the study were not tested for mutations. It is worth noting that for such a complicated pathway, there could be other means of activation besides mutations. Related to this, expression studies resulted in the observation that expression of genes in the mTOR pathway are upregulated in PanNETs [57]. Nevertheless, a good study to test the companion diagnostic potential of the mutational status of the pathway would be important.

## High-Grade Neuroendocrine Carcinomas

In contrast to well-differentiated PanNETs, the *DAXX/ATRX* and *MEN1* genes are not targeted in most high-grade NECs [6,58,59]. Instead, the *RB1* and *TP53* genes are commonly somatically mutated in NECs [6]. Yachida et al. extensively studied a series of pancreatic NECs (PanNECs) (small- and large-cell neuroendocrine carcinomas), and found that the p53 expression was altered in 95% and Rb in 74% of the NECs [6]. Abnormal immunolabeling of p53 and Rb proteins correlated with the intragenic mutations in the *TP53* and *RB1* genes. By contrast, DAXX and ATRX labeling was intact in virtually all of these same carcinomas. These genetic differences indicate that the biology and process of tumorigenesis are distinct in PanNET and PanNEC, and the poorly differentiated PanNECs do not result from the progression of the well-differentiated PanNETs to a less differentiated state.

Genetic analyses, when integrated with histopathology and clinical outcomes, have helped further dissect the neoplasms lumped together as "grade 3 NEC" in the 2010 World Health Organization (WHO) classification. The nuclear morphology of some NEC with proliferation rates only slightly above 20% are very similar to that of the well-differentiated PanNETs, while the nuclear morphology of neuroendocrine neoplasms with very high proliferation rates (i.e., >50%) has a small- or large-cell appearance. The former group (those with nuclear features similar to those of well-differentiated PanNET) appear to have genetic changes closer to those of the well-differentiated PanNETs, whereas the latter neoplasms (those with proliferation rates >50%) are those of NECs, with *RB1* and *TP53* targeted. This has led some to propose a new four-tier classification system in which lesions previously lumped together as grade 3 NEC are now separated into two groups—those with proliferation rates slightly over 20% and with mutations seen in well-differentiated PanNETs (*DAXX/ATRX*, *MEN1*) and those with very high proliferation rates and *RB1/TP53* mutations [6–9,60,60b].

## Comparison of the PanNET Genetic Landscape with Other Pancreatic Neoplasias

The genetic landscape of well-differentiated PanNET is fundamentally different from that of the more aggressive pancreatic adenocarcinoma (PDAC) (Table 123.1). *KRAS* mutations that are not found in neuroendocrine tumors are present in almost 100% of PDACs. In addition, PDAC have a high rate of mutations in *SMAD4*, *CDKN2A*, and *TP53* genes, but no mutations in *DAXX*, *ATRX*, or *MEN1* [61,62].

The genetic alterations found in PanNETs are also distinct from those found in the other neoplasms of the pancreas. Serous cystic neoplasms are characterized by *VHL* gene mutations, solid-pseudopapillary neoplasms by *CTTNB1* mutations, intraductal papillary mucinous neoplasms by alterations in *KRAS*, *GNAS*, *RNF43*, *p16/CDKN2A*, and *TP53*, mucinous cystic neoplasms by mutations in *KRAS*, *RNF43*, *p16/CDKN2A*, and *TP53*, and acinar cell carcinomas by multiple complex alterations including mutations in *JAK1*, *BRAF*, and *APC*, among others [61,63,64].

The distinct mutational profile of each tumor type of the pancreas suggests that mutational analyses may be used to help classify tumor type in the future [65].

Finally, among neuroendocrine tumors, the targeting of the *ATRX/DAXX* pathway and ALT is relatively specific for those tumors that arise in the pancreas. This suggests that ALT status could be used to clarify the organ of origin in metastatic neuroendocrine tumors of unknown primary site [66].

## Familial Syndromes

The majority of PanNETs are sporadic; however, they can occur in individuals who are predisposed to certain syndromes. Most syndromic PanNETs occur in patients with MEN1, followed by those with VHL and NF1, and occasionally with TSC [7–9]. Perhaps not surprisingly, germline mutations that predispose individuals to these syndromes are in genes related to pathways that are somatically mutated in sporadic PanNET.

MEN1 is an autosomal dominant syndrome caused by germline mutations in *MEN1* gene on chromosome 11, which is the gene most frequently mutated in sporadic PanNETs [67]. As mentioned previously, *MEN1* is a tumor suppressor gene that follows the two-hit paradigm. The first hit in individuals with MEN1 is an inactivating inherited mutation. The second hit, which is an inactivating somatic mutation or loss of heterozygosity of the remaining wild-type allele, occurs in the tumors. Tumors of the pancreas are the second most common manifestation of the MEN1 syndrome. Most of the PanNETs in patients with MEN1 are nonfunctional, although about 10% of them are insulinomas. They typically appear as multiple microadenomas (<0.5 cm); however, in many cases, like the sporadic PanNETs, they can grow larger and even spread to other organs [11,68,69]. Study of the genetics of PanNET in the context of the MEN1 syndrome has shown that *MEN1* inactivation precedes *ATRX/DAXX* inactivation and the concomitant appearance of ALT [39]. In this study, 109 well-differentiated PanNETs from 28 patients with MEN1 syndrome were tested for the expression of ATRX and DAXX and for the presence of ALT by immunostaining as a proxy for the genetic inactivation of the genes that encode for these proteins. The lesions included 47 neuroendocrine microadenomas (<0.5 cm), 50 pancreatic neuroendocrine tumors (>0.5 cm), and 12 pancreatic neuroendocrine tumor lymph node metastases. All of the lesions had loss of function of the MEN1 protein by definition, since they were present in patients with MEN1 syndrome; hence this was the first and presumably the initiating event in these tumors. ATRX/DAXX expression was intact in all of the 47 microadenomas, which were also negative for ALT. On the other hand, ATRX/DAXX expression was lacking in 6% of the PanNETs, but all losses were in tumors larger than >3 cm. These tumors were also ALT positive, which is consistent with the already documented role of ATRX/DAXX loss in the development of ALT. In addition, in the samples with concurrent metastases, the genetic alterations in the primary and metastatic tumors were the same. The progression from *MEN1* inactivation to *ATRX/DAXX* inactivation and appearance of ALT as the tumor size and the risk of metastasis increased, which was observed in the MEN1 syndrome-associated PanNET, most likely also exists in the sporadic PanNET. However, *ATRX/DAXX* inactivation in sporadic pancreatic neuroendocrine microadenomas was much higher [70].

VHL is caused by germline mutations in the tumor suppressor *VHL* on chromosome 3. The VHL protein controls the degradation via ubiquitination of HIF1, and loss of VHL leads to tumor growth and angiogenesis. HIF1 regulation also has been proposed to be downstream of the mTOR pathway. Patients with VHL develop a number of different benign and malignant neoplasms, and approximately 12–15% of them develop nonfunctional PanNETs. Most of these tumors are well differentiated, but some are aggressive and they can metastasize [71,72].

PanNETs also arise, albeit less frequently, in patients with NF1 and TSC syndromes [12,13]. NF1 is caused by germline mutations in *NF1*, whereas TSC results from germline mutations in *TSC1/TSC2.* Both of these genes are tumor suppressors and are associated with the extensive mTOR pathway [73,74]. NF1 acts more distally upstream of the mTORC1 regulating the KRAS arm of the pathway. The TSC1/TSC2 complex inhibits mTORC1 activation. Mutations in *TSC2* were the most common mTOR pathway mutations observed in sporadic PanNETs.

If indeed the initiating event of PanNET development is a germline mutation that predisposes individuals to NF1 or TSC syndrome, it is likely that more than one route to PanNET tumorigenesis exists. It is possible that the mutations in *VHL*, *TSC2*, and *NF1* genes affect the mTOR pathway. The prevalence of PanNETs in these syndromes is in accordance with the presence of the affected pathways in sporadic PanNETs, with *MEN1* mutations occurring in 44% and mTOR only occurring in 16% of PanNETs [17]. Further studies on the genetic changes in syndromic PanNETs will provide an understanding of the pathways that drive PanNET tumorigenesis.

In a recent study, whole-genome sequencing of 102 presumed somatic PanNETs revealed the presence of rare germline mutations in *MUTYH* and even more rarely in *CHEK2* and *BRCA2* genes [75].

## Epigenetics

PanNETs can be classified into three groups according to their RNA profiles: well-differentiated islet cell tumors/insulinomas, poorly differentiated tumors, and gene mutation-enriched subtypes. The first two classification groups are not surprising as PanNET and NEC are two different tumor types. The differences between well-differentiated and gene mutation-enriched groups are intriguing in that they could reflect groups with different clinical behaviors. The well-differentiated and poorly differentiated groups were also seen in the RIP1-TAGs mouse model, in which PanNETs are induced by

expression of the SV40 T-antigen oncogenes in insulin-producing islet β cells, suggesting that this model may mimic a subset of human PanNET development [76].

Genome-wide methylation analysis of 53 PanNET identified significant differences in methylation profiles between tumors of different grade and between tumors with or without *ATRX*/*DAXX* mutations. However, this clustering was not perfect as some tumors with mutations in these genes clustered with normal controls. Interestingly, there were significant differences in the methylation profiles between PanNETs with *ATRX* mutations and those with *DAXX* mutations [46].

## Clinical Implications

The genetic landscape reflects the different biology and clinical manifestations of the pancreatic neoplasms, and has clinical ramifications. First, genetics can be used to classify the different lesions unambiguously. Second, the differences in the genetics suggest different types of treatments. Unfortunately, treatments are not available that can target the most common mutations in PanNETs, *MEN1* and *ATRX/DAXX* mutations. The relationship between loss of *ATRX/DAXX* with ALT, recombination, and DNA repair suggests that synthetic lethality could be feasible with agents that interfere with these pathways. However, this has not yet been proven.

*ATRX/DAXX* mutations in PanNETs have been associated with prognosis. In a study of 142 well-differentiated PanNETs, loss of ATRX and DAXX and presence of ALT correlated with higher tumor stage and a worse prognosis, perhaps a reflection of *ATRX/DAXX* mutations being a late event in PanNet tumorigenesis [77]. However, when only the subset of metastatic patients was considered, loss of ATRX and DAXX was associated with longer survival [77]. This latter observation is in accordance with the initial observation that patients with metastatic PanNETs harboring *MEN1*, *ATRX*, and *DAXX* mutations showed better prognosis and longer survival [17]. Similarly, in an independent study of 43 patients with liver metastasis managed with resection, loss of ATRX/DAXX was associated with better overall survival [66]. One interpretation of this is that tumors with *ATRX/DAXX* inactivating mutations demarcate a subgroup with a different clinical presentation than the PanNETs without inactivation of these genes.

Furthermore, as noted earlier, in a comparison between metastatic lesions in the liver from patients with PanNETs or gastrointestinal carcinoid tumors, the presence of ALT in the metastatic lesion was a useful biomarker to predict that the site of origin of metastatic lesions to the liver is a neuroendocrine tumor of the pancreas in cases where the primary site is unknown [66].

Of all the mutations identified in PanNETs, those in the mTOR pathway show promise as therapeutic targets, as it is thought that PanNETs with mTOR pathway mutations upstream of mTORC1 will derive benefits from mTOR inhibitors. However, this has yet to be proven in clinical trials. A recent trial has been described that will test this hypothesis [78]. It is worth noting the mTOR pathway is complex, hence mutations in other genes or via epigenetic mechanisms may activate this pathway in PanNETs. Even so, not only people with the described mTOR pathway mutations will show benefit from the therapies, but also people with "cryptic," at least for now, alterations of the mTOR pathway.

Everolimus is indicated as a treatment in several solid tumors, including hormone receptor-positive HER2-negative breast cancer and advanced renal cell carcinoma. Recent data from the BOLERO-1 and BOLERO-3 trials suggest that patients with human epidermal growth factor receptor 2-positive advanced breast cancer, having tumors with *PIK3CA* mutations, *PTEN* loss, or hyperactive PI3K pathway, could derive progression-free survival benefit from everolimus treatment [56].

Everolimus was approved by the US Food and Drug Administration in 2011 for use in patients with advanced PanNETs, based on the results of the RADIANT III trial [55]. In this trial, single therapy with everolimus was compared with the best supportive care for advanced PanNETs. The majority of patients had previously been treated with different therapies. Compared with placebo, everolimus led to increased progression-free survival (11 versus 4.6 months).

## Conclusions

Over the last several years, the studies mentioned in this chapter have increased our understanding of the genetic alterations and intracellular pathways that drive PanNET tumorigenesis. Although much remains to be determined, for example, identification of the driver genes in PanNETs that do not have mutations in *MEN1*, *ATRX*, or *DAXX*, we have sufficient information to develop clinical applications based on the genotype of these tumors (Table 123.1) [79]. Future studies should clarify which companion diagnostics should be available for therapies, such as everolimus, as many patients do not respond to this drug. In those who are responsive, the overall increase in survival is months not years. New therapies are needed for the management of patients with PanNETs. Therefore, efforts should be invested in understanding and therapeutically targeting the ATRX/DAXX and MEN1 pathways. It is clear that molecular genetics have provided new opportunities to improve the clinical management of patients with PanNETs.

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# 124

# Clinical Manifestation of Endocrine Tumors of the Pancreas

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## Introduction

"Neuroendocrine tumor" (NET) is a collective term for tumors originating in nerve and endocrine cells that are widely distributed in the body; these tumors develop in various organs such as the pancreas, digestive tract, lungs, and pituitary gland. As such, they are generally called gastroenteropancreatic neuroendocrine tumors. This chapter focuses on pancreatic neuroendocrine tumors (i.e., pancreatic NET or PanNET). Although PanNET represent a relatively rare disease with slow progression, it is important to treat them as malignant tumors in the clinical setting owing to their capacity to metastasize. These tumors are broadly categorized into functional PanNET, which are associated with excessive hormone secretion, and nonfunctional PanNET, which do not involve hormone secretion. Functional PanNET present with specific clinical symptoms because of the excessively produced and secreted hormones. This chapter describes the clinical manifestations of PanNET.

## Epidemiology of PanNET

In the West, PanNET represent 1–2% of all pancreatic tumors, and the annual prevalence is reported to be less than one per 100,000 individuals. According to the American SEER (Surveillance, Epidemiology, and End Results) database, more than 60% of tumors registered between 1973 and 2004 were gastrointestinal NET in which the ileum and rectum were sites of high incidence; 3.6% of these tumors were PanNET [1]. However, the incidence of NET has been increasing in the West [2, 3]. Epidemiologic surveys for PanNET were also conducted in Japan in 2005 and 2010 [4–6]. It was reported that approximately 2845 Japanese PanNET patients were treated in 2005 whereas 3379 patients were treated in 2010; the number of PanNET patients per 100,000 people was approximately 2.23 in 2005 and 2.69 in 2010. Moreover, the number of new patients per 100,000 people was estimated to be approximately 1.01 in 2005 and 1.27 in 2010. Hence the number of NET patients is definitely rising in Japan also.

## Clinical Symptoms of PanNET

As mentioned, PanNET is broadly categorized into functional and nonfunctional PanNET. The clinical symptoms of functional PanNET are caused by excessively secreted hormones.

### Functional PanNET

Two aspects must be taken into consideration when treating functional PanNET. First, multiple symptoms can be present because of the excessive levels of various hormones autonomously secreted by the tumors (Table 124.1), possibly causing deterioration of the patient's quality of life or development of a life-threatening situation. Therefore, appropriate treatments for alleviating hormone symptoms are critical. Second, malignant NET may grow rapidly and can frequently metastasize to other organs during the course of the disease. Therefore, a multidisciplinary approach, including chemotherapy, is of utmost importance.

#### Insulinoma

Insulinoma is characterized by hypoglycemic symptoms induced by excessive autonomous insulin secretion, and

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**Table 124.1** Symptomatic gastroenteropancreatic neuroendocrine tumors.

| Tumor | Cause | Site | Incidence of metastases (%) | Symptoms |
|---|---|---|---|---|
| Insulinoma | Insulin | Pancreas | <10 | Hypoglycemia (sweating, tremor, dizziness, unconsciousness, convulsion) |
| Gastrinoma | Gastrin | Pancreas | 100 | Refractory/recurrent ulcers, reflux esophagitis, duodenum |
| Glucagonoma | Glucagon | Pancreas | 80 | Necrolytic migratory erythema, glucose intolerance, hypoaminoacidemia, hypoalbuminemia, weight loss, anemia |
| VIPoma | VIP | Pancreas | 50 | WDHA syndrome (watery diarrhea, hypokalemia, achlorhydria) duodenum |
| Somatostatinoma | Somatostatin | Pancreas | 100 | Diabetes, fatty stool, gallstones, duodenum |

is categorized according to symptoms of the central nervous system (CNS) and those of the autonomous nerve system. CNS symptoms include headache, dizziness, disturbance of consciousness, and convulsions; they are sometimes mistaken for epilepsy or mental disease.

During hypoglycemic conditions, sympathicotonia can occur, followed by autonomic symptoms such as hunger, sweating, and tremors. As hypoglycemia improves upon consumption of food, a patient may tend to overeat, resulting in weight gain or obesity. Persistence of this condition can lead to memory disturbances or the development of intellectual impairment; such cases are sometimes regarded as dementia or cerebrovascular disorders. Some patients may fall into a coma without presenting with any autonomic symptoms beforehand; therefore, a cautious approach is necessary. Meanwhile, fasting hypoglycemic events are not the primary symptoms in some insulinoma patients; instead, excessive insulin secretion is noted after glucose loading (i.e., after eating a meal).

#### Gastrinoma

Gastrinoma is caused by excessive gastric acid secretion due to autonomic excessive gastrin release by the tumor, possibly leading to refractory/recurrent ulcers and reflux esophagitis. These conditions are well known as Zollinger–Ellison syndrome. Abdominal pain, heartburn, nausea/vomiting, gastrointestinal bleeding, and gastrointestinal perforation may occur, and are symptoms of refractory ulcers or excessive gastric acid. Digestion–absorption disorder may also occur because gastric acid is not neutralized in the duodenum, and pancreatic digestive enzymes are inactivated. As a result, fatty diarrhea, weight loss, and other symptoms may be observed.

#### Glucagonoma

Necrolytic migratory erythema, a well-described rash caused by glucagonoma, frequently occurs on the face, perineum, and limbs, causing itchiness and pain and exhibiting chronic healing/recurrence cycles. Excessive secretion of glucagon induces glucose intolerance, hypoaminoacidemia, hypoalbuminemia, weight loss, anemia, glossitis, angular cheilitis, venous thrombosis, mental symptoms, and other conditions.

#### VIPoma

Secretion of electrolytes and water from the intestine is accelerated by autonomic excessive secretion of VIP (vasoactive intestinal polypeptide) from the tumor, resulting in severe watery diarrhea and hypokalemia and also metabolic acidosis induced by massive excretion of bicarbonate ions. Owing to the secretin-like action of VIP, gastric acid becomes hypoacidic or anacidic. Various symptoms occur, including severe dehydration, weight loss, vasodilatation-caused skin flushing, hypercalcemia caused by accelerated bone resorption, and glucose intolerance.

#### Somatostatinoma

In addition to abdominal pain and weight loss, diabetes, gallstones, and fatty stool are also observed. Somatostatinoma is sometimes discovered during detailed examination of these symptoms.

### Nonfunctional PanNET

No specific symptoms are present in patients with nonfunctional PanNET. As the tumor grows, nonspecific symptoms appear that include abdominal distension, abdominal pain, anorexia, and weight loss. Nonfunctional PanNET is often discovered following compression or invasion by the primary tumor or a distant metastasis. In the case of advanced liver metastasis, hepatic dysfunction and jaundice are observed.

According to the results of an epidemiologic study in Japan, approximately 22 months passed between the appearance of PanNET symptoms and disease diagnosis in symptomatic cases, on average [5,6]. Although PanNET is not often encountered in actual clinical practice, it is important to consider it during differential diagnosis.

## Diagnosis of PanNET

When repetitive hypoglycemic events or refractory gastrointestinal ulcers are investigated, differential diagnosis for functional PanNET is required, including insulinoma and gastrinoma. If functional PanNET is suspected on the basis of the clinical symptoms, measurement of basal hormone levels in the blood and various loading tests are required to detect the presence of a hormone-producing tumor. If such a tumor is confirmed, its location should be accurately identified using imaging modalities; this is important for deciding the subsequent therapeutic strategy. Even if the presence of a tumor is first detected via imaging, as in the case of nonfunctional PanNET, the hormone-producing ability of the tumor and also the presence or absence of metastasis should be investigated in detail. PanNET is often associated with multiple endocrine neoplasia type 1; therefore, serum calcium and potassium levels should be determined upon initial examination to rule out excessive parathyroid hormone production.

### Diagnosis of Tumor Presence

#### Insulinoma

In the past, Whipple's triad (i.e., loss of consciousness on fasting combined with blood glucose levels <50 mg/dL, where symptoms improve upon consuming glucose) and Fajan's index for insulinoma (the ratio of plasma insulin concentration to fasting blood glucose >0.3) have been observed; however false-negative findings should be ruled out. For definitive diagnosis, a 72-hour fasting test is recommended.

#### Gastrinoma

Measurement of fasting serum gastrin and gastric acid secretion, and/or a 24-hour gastric pH monitoring test, are essential for diagnosis. It is important to inquire about the patient's medication history, as serum gastrin levels may increase owing to oral administration of proton pump inhibitors or $H_2$ blockers. For definitive diagnosis, a secretin or calcium stimulation test is useful, as gastrin secretion is increased by intravenous injection of secretin or calcium.

### Localization Diagnosis

Many PanNET are plethoric with inner uniformity; therefore, diagnosis is not difficult in typical cases. However, in atypical cases involving oligemia or cyst formation, it may be difficult to distinguish PanNET from a pancreatic ductal cancer or cystic pancreatic tumor on differential diagnosis. Furthermore, insulinoma and gastrinoma are often small in diameter, and accurate localization is important for surgery. Therefore, various imaging modalities are employed during actual examination.

#### Abdominal Ultrasonography (US)

The more uniform the inside of tumor, the more likely the mass can be visualized on US. When the tumor is large, an irregular shape that reflects internal bleeding, necrosis, or cystic degeneration is sometimes observed. Abdominal US is easy to perform, and is the least invasive among imaging modalities. However, its diagnostic accuracy is low (Fig. 124.1a).

#### Abdominal Computed Tomography (CT)

When contrast medium is used, typical PanNET are highly enhanced in the arterial phase (Fig. 124.1b). As contrast enhancement is weak in oligemic pancreatic ductal tumors, a CT image may be critical in distinguishing between PanNET and pancreatic ductal cancer. However, plethoric pancreatic tumors present the same contrast enhancement as PanNET, metastatic pancreatic tumor, and especially renal cancer; therefore, differential diagnosis should be carefully conducted. The diagnostic accuracy of CT is approximately 80% [7, 8].

#### Abdominal Magnetic Resonance Imaging (MRI)

A T1-weighted MRI scan of a PanNET shows low intensity, whereas a T2-weighted scan shows high intensity (Fig. 124.1c and d) [8, 9]. On MRI, a tumor is visualized similarly to CT; however, the diagnostic accuracy of this method is approximately 70%, which is slightly lower than that of CT. On the other hand, for the detection of hepatic metastases from PanNET, enhanced MRI is more sensitive than enhanced CT (Fig. 124.2) [10].

#### Endoscopic Ultrasound-Guided Fine-Needle Aspiration (Fig. 124.3)

PanNET is visualized on endoscopic ultrasonography (EUS) as a hypoechoic mass with border regularity and inner uniformity. EUS can screen the entire pancreas and detect lesions smaller than 1 cm. With a diagnostic accuracy of approximately 80–95%, this method is superior to CT and MRI and is therefore a very useful testing modality [11–13]. Furthermore, concurrent use of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) permits histopathologic diagnosis, which is critical for deciding the therapeutic strategy [14–16].

#### Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) can determine the position of the tumor in relation to the pancreatic duct. Additionally, ERCP allows pancreatic juice cytology, making it a critical test to employ during diagnosis.

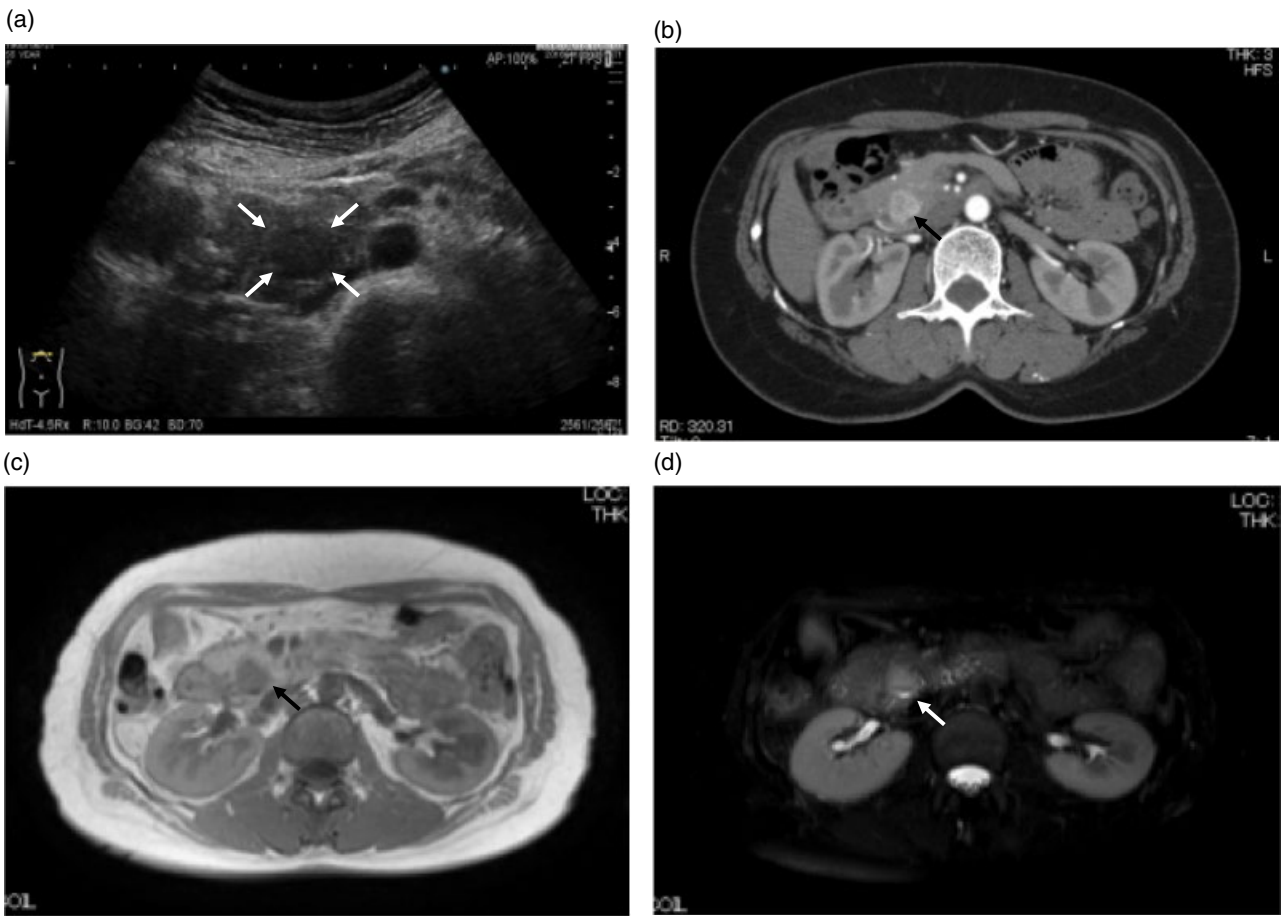


**Figure 124.1** Clinical imaging studies in a 55-year-old female patient with a nonfunctional neuroendocrine G1 tumor (white and black arrows) in the pancreatic head lesion: (a) US; (b) CT; (c) T1-weighted MRI; (d) T2-weighted MRI.

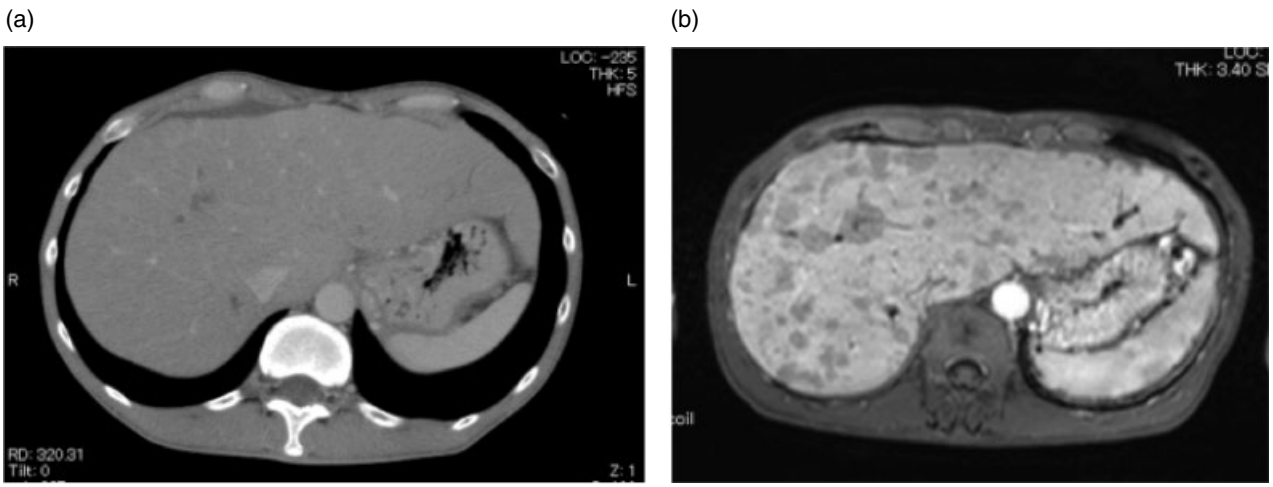


**Figure 124.2** Hepatic screening images in a 43-year-old male patient with pancreatic nonfunctional neuroendocrine tumors. An enhanced CT image shows no obvious metastases (a) whereas an enhanced MRI image clearly shows multiple liver metastases (b).

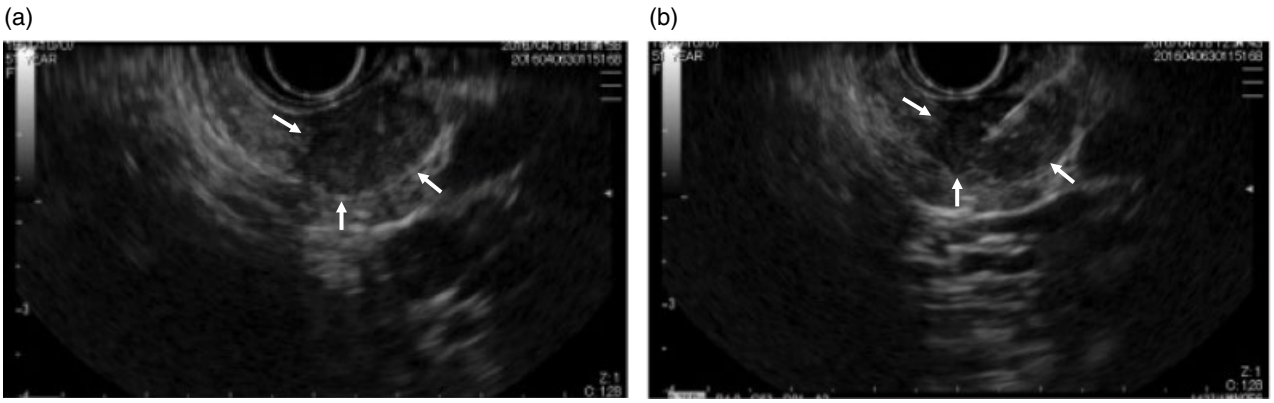


**Figure 124.3** EUS-FNA images in a 51-year-old female patient with a nonfunctional neuroendocrine G2 tumor (white arrows).

#### Selective Arterial Secretin/Calcium Injection Test

At the time of abdominal arteriography, a catheter is placed in the hepatic vein for secretin/calcium infusion into the feeding artery of each pancreatic region. The level of gastrin/insulin in the hepatic venous blood is then measured. The tumor's location is determined based on the increase in gastrin concentration (more than twofold). As the supply vessel for the tumor is identified, localization becomes possible for those tumors that are difficult to visualize by imaging modalities. This technique is especially useful as a preoperative test for gastrinoma and insulinoma [17, 18].

#### Somatostatin Receptor Scintigraphy

In well-differentiated PanNET, somatostatin receptor (SSTR) is highly expressed on the cell membrane. The somatostatin mimetic octreotide, which is metabolically stable and has a strong affinity for SSTR, is labeled with a radioisotope and then injected, whereupon it binds to SSTR and emits a gamma ray. This ray is then detected by single photon emission CT or positron emission tomography. Somatostatin receptor scintigraphy is useful for searching the entire body for PanNET, including metastatic lesions [19].

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# 125

# Evidence of Hormonal, Laboratory, Biochemical, and Instrumental Diagnostics of Neuroendocrine Tumors of the Pancreas

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## Introduction

The term "pancreatic neuroendocrine tumors" (PanNET) covers a variety of heterogeneous pancreatic tumors, originating from neuroendocrine cells. Many synthesize and secrete a variety of unique molecules and overexpress somatostatin receptors (SSTR) on their cell surface. Functional PanNET secrete one, or more than one, active hormone, resulting in classical symptoms and signs (see Chapter 124). Nonfunctional PanNET do not secrete any active hormones. The investigation of PanNET requires specialized biochemical investigations of specific hormones. Serum DNA and serum RNA are emerging as promising investigative tools. However, as PanNET are still rare, there is a lack of standardization of the various investigations and assays. This may cause difficulties in the interpretation of many of the laboratory-based investigations. Imaging with conventional computed tomography (CT), magnetic resonance imaging (MRI), and radionuclide scans is an essential part of the localization and assessment of PanNET. Imaging investigations based on the unique specific expression of cell surface receptors and unique metabolic features are particularly important in the detection of PanNET.

There has been rapid progress in many of the investigations for PanNET, with more serum-based measurements, better dynamic enhanced CT and MRI techniques, and a number of radioisotope-linked ligands and molecules becoming available for nuclear imaging. This chapter describes serum-based laboratory investigations followed by various conventional and more PanNET-specific radionuclide imaging investigations.

## Serum-Based Laboratory Investigations

Pancreatic neuroendocrine tumors often secrete hormones. However, as there may be incomplete or defective processing, the hormones may not be functionally active. Some of these incomplete hormones may still be identified in immunochemistry and be measurable in the serum in many commercial assays, and cause confusion if nonspecific symptoms and signs are present as to whether they are "functional" or not. Measurement of the relevant hormone, functional or not, if elevated, remains useful for diagnostic and prognostic purposes.

In addition to these hormonal secretions, some common molecules are secreted by many PanNET. The most established is chromogranin A (ChA). Many others have been reported, including chromogranin B, human pancreatic polypeptide, and neuron-specific enolase (NSE), but these markers generally have low specificity and sensitivity [1]. Finally, the rapidly advancing field of serum DNA and RNA identification, in particular patterns and clusters ("signatures"), is being studied for its usefulness as diagnostic and prognostic markers in PanNET.

All these serum-based investigations should be carried out with the appropriate precautions because of the difficulty in the interpretation of many of them. Endocrine hormones may be affected by their own dynamic regulation, and also by many commonly prescribed drugs. A recent consensus concluded that all the available biomarkers for neuroendocrine tumors (NET) had significant limitations and suggested a "multianalyte" approach [2].

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Table 125.1 gives a list of the more common functional PanNET for which specific hormonal and other investigations are useful.

## Insulinomas

Insulinomas are the most frequent functional PanNET. However, insulinomas are unlike other PanNET and rarely secrete ChA or overexpress SSTR. Insulinomas almost always originate from the pancreas, and may be sporadic or be associated with multiple endocrine neoplasia type 1 (MEN1), where they present as multiple tumors (see Chapter 126). Diagnosis of an insulinoma requires the clear demonstration of inappropriately elevated serum insulin concentrations in the presence of venous hypoglycemia, and exclusion of other causes. They are usually benign at the time of diagnosis.

The gold standard for diagnosis is the supervised prolonged fast (72 hours) with regular venous blood sampling every 4–6 hours for glucose, insulin, and C-peptide. The fast is terminated if there is hypoglycemia (glucose <2.5 or 3.0 mmol/L) with symptoms and signs. The presence of inappropriately elevated serum insulin and C-peptide concentrations (even within the normal range) is diagnostic. An elevated insulin level with low C-peptide indicates surreptitious exogenous insulin use. Absolute cut-off values given in some reports [3] have to be interpreted within the context of the laboratory, as both insulin and C-peptide assays are not standardized internationally.

A 48- or 24-hour fast, followed by vigorous exercise, with or without the aid of continuous glucose monitoring, has been reported to be as good in making a conclusive diagnosis [3,4]. An elevated plasma proinsulin-to-insulin ratio may be helpful. Provocative tests with infusion of arginine, calcium, and glucagon are now rarely performed.

In addition, urine or plasma sulfonylurea should be measured, as both insulin and C-peptide are elevated in patients taking these drugs surreptitiously. In East Asians, anti-insulin autoantibodies should also be measured to exclude insulin autoimmune syndrome [5]. Care should also be taken in the interpretation of elevated insulin levels if there has been previous bariatric surgery.

Imaging investigations should proceed after establishing a laboratory diagnosis (see later).

## Gastrinomas

Gastrin-secreting PanNET can occur sporadically and in association with MEN1 (one in four in some series). They are often multiple, malignant, and are present in the duodenum in addition to the pancreas at diagnosis. The hypergastrinemia causes severe gastric hyperacidity, with abdominal pain, increased gut motility, and diarrhea. Fasting serum gastrin is usually markedly elevated. However, there is no standardization of the assays or agreed normal population ranges. Commonly prescribed acid-suppressing drugs will elevate serum gastrin. These have to be stopped (7 days for proton-pump inhibitors [PPI], 2 days for others) and the fasting serum gastrin remeasured. Other causes of elevated fasting serum gastrin are chronic kidney disease, atrophic gastritis, and short bowel syndrome. Finally, several molecular forms of gastrin may be secreted that may or may not be accurately measured by many of the available commercial assays [6]. Therefore, care must be exercised in the preparation of the patient before taking measurements and in the interpretation of the results. Most patients with gastrinomas are *Helicobacter pylori* negative, and the presence of multiple peptic ulcers in such patients should raise the index of suspicion.

The secretin stimulation test has been reported to be useful in some patients, especially when hyperacidity symptoms are too severe to permit withdrawal of acid-suppression drugs. A 2 U/kg bolus of secretin is administered intravenously after an overnight fast and serum gastrin is measured at 0, 2, 5, 10 and 15 min. An increase in serum gastrin of >200 pg/mL is considered as diagnostic. However, false-positive results may still occur and care has to be taken in the interpretation of these tests [7].

Imaging studies should proceed if there is clear suspicion from the presence of severe hyperacidity or if gastroscopy shows the presence of multiple peptic ulcers (see later). SST-based positron emission tomography (PET)/CT may be necessary if other imaging modalities are negative.

## Glucagonomas

Glucagon-secreting PanNET are very rare and originate from the pancreas. They are usually sporadic but may be associated with MEN. The classical clinical syndrome of diarrhea, weight loss, hyperglycemia, and necrolytic migratory erythematous rash is usually recognized late, when the PanNET is large and liver and other metastases are already present (see Chapter 124). Mild anemia and recurrent venous thromboembolism are common. The grossly elevated concentrations of fasting serum glucagon and imaging findings will give a clear diagnosis. However, glucagon measurements in the absence of clinical signs are difficult to interpret. Secretion of glucagon is affected by many factors, and many smaller glucagon-like molecules are present in the blood and may give falsely elevated results [8].

Elevated fasting glucagonemia may be found in liver cirrhosis, chronic kidney disease, acromegaly, and hypercortisolism.

**Table 125.1** Investigation of pancreatic neuroendocrine tumors (see text for details).

| Suspected PanNET | Differential diagnosis | Pancreatic origin (versus other locations) (%) | Confined to pancreas at diagnosis | Laboratory investigations | Imaging investigations | Other special investigations |
|---|---|---|---|---|---|---|
| Insulinoma | Factitious; autoimmune disease | >90 | Often | Prolonged fast with insulin and C-peptide measurements | EUS | Selective intra-arteriolar calcium infusion; other radionuclide imaging (non-SSTR) |
| Gastrinoma | Acid-suppressing medications (proton pump inhibitors) | <50 | Very rarely | Fasting serum gastrin;secretin test; ChA | | SSTR imaging |
| Glucagonoma | | >90 | Very rarely | Serum glucagon<br>ChA | | Conventional CT/MRI usually adequate |
| VIPoma | | <50 | Rarely | Serum VIP;<br>ChA | | SSTR imaging |
| ACTH | Nonpancreatic ectopic ACTH tumor | <10 | If pancreatic, very often | Dexamethasone suppression test, CRH stimulation test | EUS | SSTR imaging |
| Somatostatinoma | | <50 | Very rarely | Serum somatostatin;<br>ChA | | Unknown |
| "Classical carcinoid syndrome" | | <10 | Rarely | 24-hour urine 5HIAA<br>ChA | | SSTR imaging |
| Nonfunctioning PanNET | | | Increasingly as "incidentalomas" | ChA, NSE, human pancreatic polypeptide, serum DNA signatures | Dynamic CT or MRI | SSTR imaging |

For abbreviations, see text.
SSTR imaging: includes PET/CT with [$^{68}$Ga]DOTA-TOC, DOTA-TATE and DOTA-NOC.
Non-SSTR radionuclides are not widely available and include PET/CT with [$^{68}$Ga]DOTA-exendin 4 and PET with [$^{18}$F]dopamine.

### Vasoactive Intestinal Peptide (VIP)

VIPomas are rare, sporadic, and usually occur in the distal pancreas. They are, like gastrinomas and glucagonomas, diagnosed late with established metastatic spread at diagnosis. The classical presentation is that of severe watery diarrhea, hypokalemia, and occasionally facial flushing. Serum VIP is often grossly elevated. However, in the early stages when secretion is episodic, levels may fluctuate and blood samples should be collected when the patient is having diarrhea. It is also important to use a reliable tested assay as elevated VIP may also be found in chronic kidney disease, short bowel syndrome. and radiation enteritis.

Imaging studies with SST analogs may be helpful in this rare PanNET.

### ACTH (and CRH)-Secreting PanNET

The diagnosis of Cushing syndrome due to ectopic adrenocorticotropic hormone (ACTH) secretion is often difficult. The initial screening test for hypercortisolemia is the 1 mg overnight dexamethasone test; wherein an adequate suppression of serum cortisol excludes hypercortisolemia. In the event of uncertainty, hypercortisolemia should be confirmed with a formal 3-day low-dose dexamethasone suppression test. The plasma ACTH should then be measured to distinguish between an adrenal cause or an ACTH-dependent hypercortisolic state. If the ACTH level is inappropriately elevated, then further investigations are necessary to distinguish between a pituitary tumor and an ectopic ACTH tumor. This may include a corticotrophin hormone test and inferior petrosal sinus sampling, or a combination of the two. In patients with ectopic Cushing syndrome, imaging and localization studies for the NET will include the pancreas, lung, and thymus. Imaging of the pancreas with fine-cut CT may reveal an ACTH-secreting PanNET. Rarely, PanNET may secrete corticotropin-releasing hormone (CRH). Measurements for serum CRH are not widely available, and interpretation is difficult.

Imaging with SST analogs is useful if conventional CT or MRI does not reveal a tumor.

### Other Functional PanNET (Somatostatin, Ghrelin, Serotonin)

Other PanNET have been reported to secrete endocrine hormones, including somatostatin (SST), ghrelin, growth hormone (GH), and parathyroid hormone (PTH). Other hormones have been reported, often as single case reports, and will not be discussed further.

SST-secreting PanNET are very rare, sporadic, and usually arise from the pancreas, but are found also in the duodenum. Symptoms are usually mild and nonspecific and include hyperglycemia, weight loss, abdominal pain, gallbladder stasis, and diarrhea. Liver and other metastases are usually present at diagnosis. Elevated SST levels are diagnostic but, like the other rarely measured hormones, available assays vary considerably in characteristics and ranges. Elevated SST may be found in medullary thyroid tumors, small-cell lung tumors, pheochromocytomas, and paragangliomas.

Ghrelin, growth hormone-releasing hormone (GHRH), and GH-secreting PanNET are very rare, and originate in the lung and pancreas. They may be sporadic or, rarely, associated with MEN1. Both ghrelin and GH cause classical acromegaly, which presents to the endocrinologist. There should be suspicion of this rare NET if there is elevated GH in the presence of a generally enlarged pituitary gland without a defined pituitary adenoma. Ghrelin and GHRH assays are not standardized and not widely available.

Serotonin (5-hydroxytryptamine, 5-HT)-secreting PanNET are very rare, as these classical "carcinoid tumors" are more frequent in the hindgut and other locations. When found as a PanNET, they are usually large and malignant, with metastases present at diagnosis. Urinary 5-hydroxyindoleacetic acid (5HIAA) is the investigation of choice and is elevated in most patients with the classical symptoms of facial flushing, diarrhea, and right heart failure.

Other functioning PanNET reported (as case reports) include the following: PTH and PTH-related polypeptide (PTH-rP)-secreting PanNET causing hypercalcemia, renin-secreting PanNET causing hypertension, erythropoietin (EPO)-secreting PanNET causing polycythemia, and calcitonin, cholecystokinin, and neurotensin. It is likely that there will be more reports when more assays become available and our understanding of the various rare hormones improves.

### Nonspecific Biochemical Markers in PanNET

Many PanNET secrete other molecules, which, if present, may be useful as biomarkers for diagnosis and prognosis [9,10]. These are useful in establishing a diagnosis of a PanNET in incidentalomas of the pancreas, or where a nonfunctioning PanNET is suspected. These include ChA, other chromogranins [11], human chorionic gonadotrophin (hCG), synaptophysin, NSE [12], pancreatic polypeptide, and, more recently pancreastatin (a derivative of ChA) [13]. Of these, only ChA has proved consistently useful as a marker for diagnosis and prognostication for most functioning and nonfunctioning PanNET, except for insulinomas. It is important to remember that ChA may also be elevated in other nonpancreatic endocrine tumors and in liver and kidney

disease. NSE is useful mainly in poorly differentiated PanNET, and pancreatic polypeptide may be useful in nonfunctioning PanNET.

Imaging with SST analogs is useful in identifying and distinguishing a PanNET from other tumors (except for insulinomas).

### Serum RNA and DNA Measurements in PanNET

Recent advances in measurements of serum DNA and RNA have led to studies of their usefulness as biomarkers in PanNET. Studies on serum DNA, together with fresh tissue from patients with NET, have been reported to identify similarities in the patterns of DNA expression and secretion into the circulation. Serum RNAs, including microRNAs (miRNA) and long non-coding RNAs (lcRNA) have been measured in various PanNET. Various patterns ('signatures') have been reported as potentially useful in distinguishing NET from other pancreatic tumors [14].

Some groups have reported promising results with serum DNA signatures [15]. Studies with serum RNA signatures are less promising, as RNA degradation in serum is more rapid and variable, and further studies will be necessary to establish their usefulness [2,16]. With the increasing availability of these techniques and the decrease in costs, it is possible that they may be useful in the future as biomarkers for PanNET.

## Instrumental and Invasive Investigations

Conventional ultrasound (US) scans are widely available and inexpensive, but have high operator dependency. Transabdominal US may be sufficient for large PanNET, but is generally less suitable for obese patients.

Insulinomas most frequently require invasive instrumental investigations because the diagnosis is made early with biochemical investigations when the tumor is very small. Insulinomas are almost always confined to the pancreas, rarely secrete ChA, and are not detectable on SST radionuclide imaging. In this context, endoscopic ultrasound (EUS) may be helpful in the localization of a small biochemically proven insulinoma [17]. Selective venous sampling, selective arterial injection of calcium, and intraoperative US (with direct contact with the pancreas during surgery) may all be useful. If all of these fail to reveal the tumor, then progressive partial pancreatectomy may be necessary, and that may find single or multiple tiny insulinomas or diffuse nesidioblastosis. Recent advances in dynamic CT (see later) and radionuclide receptor ligands may reduce the need for such invasive preoperative investigations for insulinomas in the future [18]. Other functioning PanNET are usually detectable as large tumors at diagnosis.

EUS, combined with guided fine-needle aspiration cytology and/or core biopsy, may be useful in diagnosing small nonfunctioning PanNET.

## Imaging

### Conventional CT and MRI

Conventional CT and MRI are useful for most functioning larger PanNET (around 1 cm in diameter or larger). Recent developments in multiphase contrast-enhanced CT and dynamic MRI have reported good results for earlier detection and characterization of smaller and nonfunctioning PanNET [19,20], and even for histologic staging [21]. Pancreatic NET are usually densely hypervascular and therefore appear as well-circumscribed masses with early strong enhancement from the arterial to pancreatic phase. Diffusion-weighted imaging MRI (DWI) has also been reported to be useful, alone or in conjunction with SST-based radionuclide imaging, in some PanNET [22]. Pancreatic NET usually appear as low-intensity images on T1 and high intensity on T2, with clear gadolinium enhancement. These findings may be adequate when sophisticated and expensive specialized radionuclide SST and other PET/CT imaging facilities are unavailable.

### Conventional PET Scans

Conventional scintigraphic scans are not helpful in the investigation of PanNET. The classical PET scan (including single-photon emission computed tomography [SPECT] and PET/CT) uses the uptake of [$^{18}$F]fluoro-2-deoxy-D-glucose (FDG) to identify tumor cells with high glucose utilization, and is useful in identifying aggressive PanNET with higher mitotic rates. More indolent PanNET are not identified using this scan.

To identify slower growing PanNET, other radionuclides have been studied based on the metabolic characteristics of normal pancreatic islet cells. Dopamine-based radionuclide studies have been reported using [$^{18}$F]fluorodopamine ([$^{18}$F]DOPA) and [$^{11}$C]-L-dopamine ([$^{11}$C]-L-DOPA), and [$^{11}$C]-5-hydroxytryptophan ([$^{11}$C]-5-HTP) for insulinomas [23]. However, all of these are available only at specialized centers and have been reported to be of use only in PanNET with negative or minimal SSTR expression (see later).

### Somatostatin and Other Peptide Receptor-Based Radionuclide Imaging

Most differentiated PanNET (except insulinomas), functional and nonfunctional, have the unique property of overexpression of cell-surface SSTR. This has led to the

development of radionuclides linked to SST analogs. Endogenous SST has a very short half-life of a few minutes and the synthetic analog octreotide, with a longer half-life, has been shown to be very useful in NET. Initially this was linked to iodine-123 and subsequently with indium-111 (commercialized as Octreoscan) and technetium-99 m. Detection rates were reportedly good in many PanNET and correlated with prognosis and response to treatment. More recently, these have been superseded by PET/CT scanning with gallium-68-linked octreotide analogs. The chelating molecule DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid) is used and three main DOTA compounds have been extensively studied and compared in large numbers of PanNET in several centers: DOTA-TOC (DOTA-Tyr-octreotide), DOTA-TATE (DOTA-Tyr-octreotate) and DOTA-NOC (DOTA-Nal-octreotide). These have proven much better at identifying both functioning and

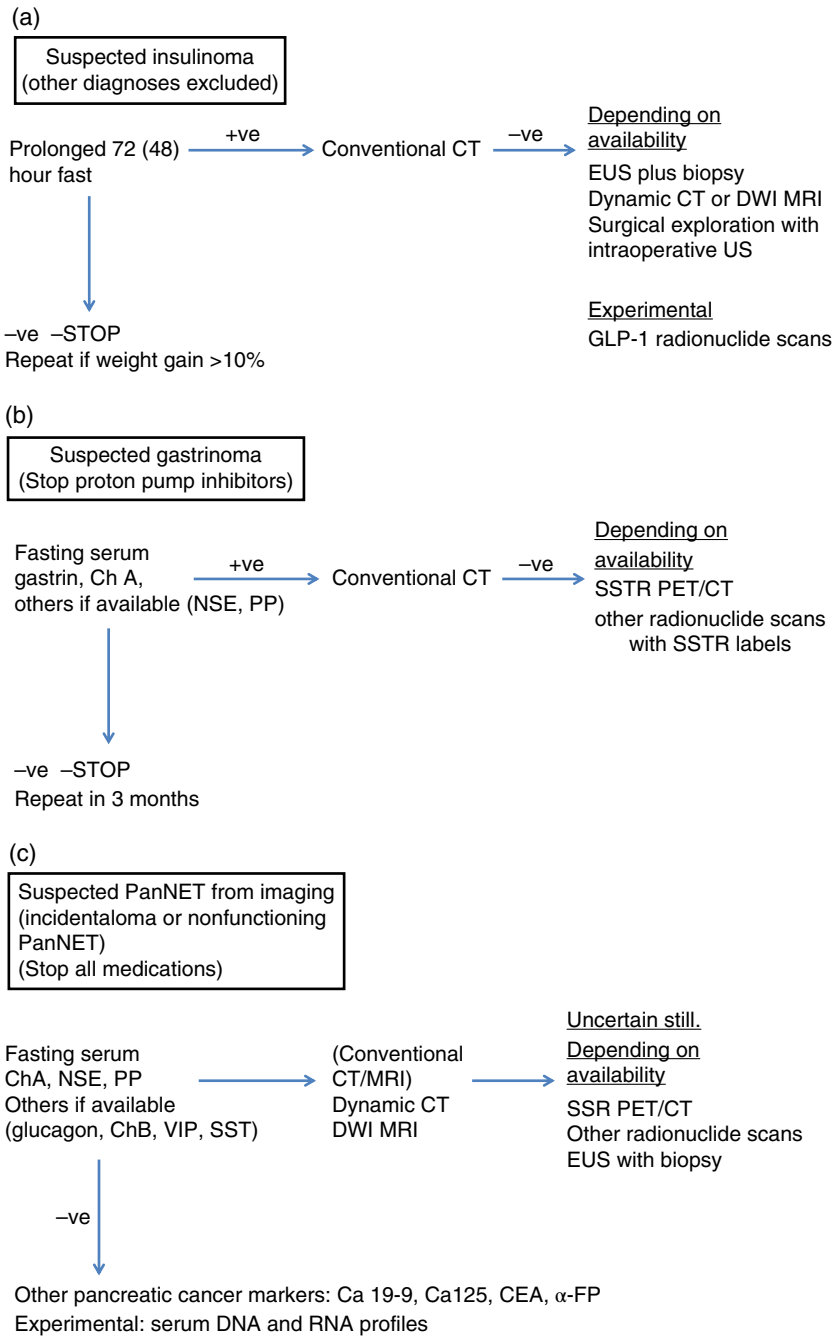


**Figure 125.1** Suggested flow chart for investigations in suspected PanNET.

nonfunctioning PanNET and their metastases. The specificity and sensitivity are high (>80%) and the differences reported in different PanNET of differing histologic stages are minor and may be the result of the different study populations [20].

There are five SSTR subtypes. Octreotide binds strongly only to the SSTR-2, and less to SSTR-5. Recent studies have investigated the newer SSTR analogs lanreotide and pasireotide. Lanreotide has similar binding as octreotide, but pasireotide has higher binding to SSTR-3 and -5 and similar binding to SSTR-2 compared with octreotide. Newer [$^{68}$Ga]DOTA radionuclides linked to pasireotide are being developed and studied actively in PanNET.

Other peptide receptors have been identified in PanNET and attempts have been made to utilize these for imaging (and therapy) in the less common NET with less overexpression of SSTR. These would have the greatest potential in insulinomas where the glucagon-like peptide 1 (GLP-1) receptor and the glucose-dependent insulinotropic peptide (GIP) receptor are abundant. The GLP-1 radioligand [$^{68}$Ga]DOTA-exendin 4 is already available with a promising report [24]. Other peptide receptors are being actively investigated at present and may have potential in pancreatic and other NET, including cholecystokinin-2/gastrin, gastrin-releasing peptide, and neuropeptide-Y [25].

### Combined Multitracer Radionuclide Scans

A recent multitargeted approach, using a cocktail of three different radioligand peptide receptors at the same time, targeting the SSTR, GLP-1, and GIP receptors, suggested better results than with single radioligand imaging [26]. Although this approach would save time, the costs will invariably be much higher. Moreover, interpretation may be difficult as normal tissues have different levels of expression of these peptide receptors, hence false-positive and -negative rates will have to be confirmed in other centers. In addition, in peptide receptor radionuclide therapy (PRRT) (see Chapter 128), information is necessary on the relative abundance of single receptor types, as the therapeutic doses of the therapeutic radioisotope, most commonly lutetium-177 or yttrium-90 (Y90), are bound to single analogs. This information will be lost if a cocktail of radionuclides is utilized for imaging.

## Conclusions

A suggested flow chart for investigations in suspected PanNET is presented in Figure 125.1.

Pancreatic NET are rare and heterogeneous tumors. Biochemical investigations are necessary and essential, but may be difficult to interpret because of the use of nonstandardized assays. However, rapid advances are emerging with an increase in the understanding of their distinguishing properties and behavior. The unique overexpression of SSTR in most PanNET has made this an essential imaging modality for the diagnosis and assessment of most PanNET.

Advances in both serum-based and imaging investigations of PanNET will need to be carefully evaluated for both diagnosis and management.

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# Pancreatic Neuroendocrine Tumors in Multiple Neoplasia Syndromes

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## Introduction

Neuroendocrine tumors, including pancreatic neuroendocrine tumors (PanNET), are on the rise and, probably owing to improved imaging techniques and better awareness, especially localized disease is more often diagnosed [1]. Although most of these tumors are sporadic, in 10–15% of PanNET there is a hereditary background with multiple endocrine neoplasia type 1 (MEN1) being the most relevant family cancer syndrome for PanNET. Early diagnosis of the hereditary syndrome is of diagnostic and therapeutic relevance for the patient and his or her kindreds. Diagnostic procedures, follow-up, and treatment should be managed by a multidisciplinary team with experience in the management of MEN1 [2].

MEN1 should always be suspected in patients with PanNET with multiple lesions, a positive family history, a second MEN1 typical manifestation such as hyperparathyroidism or pituitary tumor, or in cases of gastrinoma/Zollinger–Ellison syndrome (ZES) even in the absence of a positive family history. In addition to the classical "three-P triad" of **p**arathyroid tumor (90–100% of cases), **p**ituitary tumor (20–60%), and **p**ancreatic tumor (60–80%), patients with MEN1 may also develop adrenocortical tumors, lipomas, carcinoid tumors, including thymic, gastric, and lung carcinoids, facial angiofibromas, collagenomas, and meningiomas and may also have an increased risk for other nonendocrine malignant tumors such as lymphoma, myeloma, melanoma, renal cell cancer, ovarian tumors, and sarcoma [3]. This chapter focuses on the management of PanNET in MEN1.

## Epidemiology

With an estimated prevalence of 0.02–0.2 per 1000 inhabitants, MEN1 is one of the most common familial cancer syndromes; in an old autopsy study, the reported incidence was 0.25% [4,5]. Duodenopancreatic neuroendocrine tumors are the second most frequent manifestation of MEN1. Older studies probably underestimated the prevalence of PanNET in MEN1 syndrome and with more sensitive diagnostic tools about 70–80% of patients are found to develop PanNET [2,6]. PanNET have an earlier age of onset in patients with MEN1 than in patients without MEN1. These tumors are typically multiple and can present with hormone syndromes or be nonfunctioning [7]. The most common hormone-active duodenopancreatic tumors are gastrinomas, followed by insulinomas, whereas vasoactive intestinal peptide-releasing tumors (VIPomas) and glucagonomas are rare. Approximately 20–30% of all patients with ZES will have MEN1 [2,8].

## Genetics

MEN1 is an autosomal dominant inherited syndrome with high penetrance; 90% of persons with germline MEN1 mutation will develop symptoms of MEN1 during life. In 1988, the MEN1 gene locus was first mapped to the long arm of chromosome 11 (11q13) [9] and in 1997 the gene was identified and cloned [10]. It acts as a tumor suppressor gene and codes for the 610 amino acid protein

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

menin, which is involved in transcription regulation, genome stability, and proliferation [2,10]. In about 10% of MEN1 cases, the germline mutation arises *de novo* and the family history is negative [2].

More than 1300 inactivating mutations involving all locations of the gene have been identified so far and in about 90% of clinically diagnosed MEN1 cases the mutation in the MEN1 gene can be detected [2]. About 70% of the mutations are non-sense and frame-shift mutations, resulting in truncation of the protein. In contrast to the MEN2 syndrome, there is no clear genotype–phenotype correlation and even in one family the manifestations may vary [11,12]. The diversity of mutations makes mutational analysis in MEN1 difficult and complete sequencing of the whole gene is necessary. In contrast, if the mutation of an index case in the family is known, family members only have to be analyzed to determine whether the known mutation is present or absent.

## Diagnosis

Three diagnostic criteria for MEN1 exist, each individually establishing the diagnosis of MEN1 [2]:

1) identification of a germline MEN1 mutation in the individual, or
2) diagnosis of a MEN-associated tumor in a person who has a first-degree relative with known MEN1, or
3) occurrence of two or more primary MEN1-associated endocrine tumors.

The diagnosis of a PanNET may result either from symptoms (e.g., hypoglcycemia in a patient with insulinoma) or from biochemical (elevated levels of pancreatic polypeptide, gastrin, insulin, glucagon, vasoactive intestinal polypeptide [VIP]) or morphologic screening (identification of pancreatic lesions in computed tomography [CT], magnetic resonance imaging [MRI], endoscopic ultrasound, somatostatin receptor imaging).

In a patient with MEN1 syndrome, at least annual biochemical and morphologic screening for PanNET is recommended [2]. There is no clear recommendation regarding the method of morphologic screening, but endoscopic ultrasound (EUS) is more sensitive for small pancreatic lesions than CT or MRI [13]. It also could be demonstrated that precise documentation of the growth behavior of these small pancreatic lesions can be achieved using EUS [14]. In patients with gastrinoma, upper gastrointestinal endoscopy is indicated. Typically gastrinomas in MEN1 are small, multiple, and located in the duodenum, where the sensitivity of EUS is inferior compared with pancreatic lesions. In recent publications, a role for [$^{68}$Ga]DOTA-TOC (DOTA, 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; DOTA-TOC, DOTA-Tyr-octreotide) positron emission tomography (PET)/CT or DOTA-TATE (DOTA-Tyr-octreotate) PET/CT for screening and surveillance of patients with MEN1 has been suggested (Fig. 126.1) as this method has a higher sensitivity than somatostatin receptor scintigraphy and CT, especially for detecting small metastases and extra-abdominal disease [15,16]. Insulinomas express the somatostatin receptor subtype 2a in only

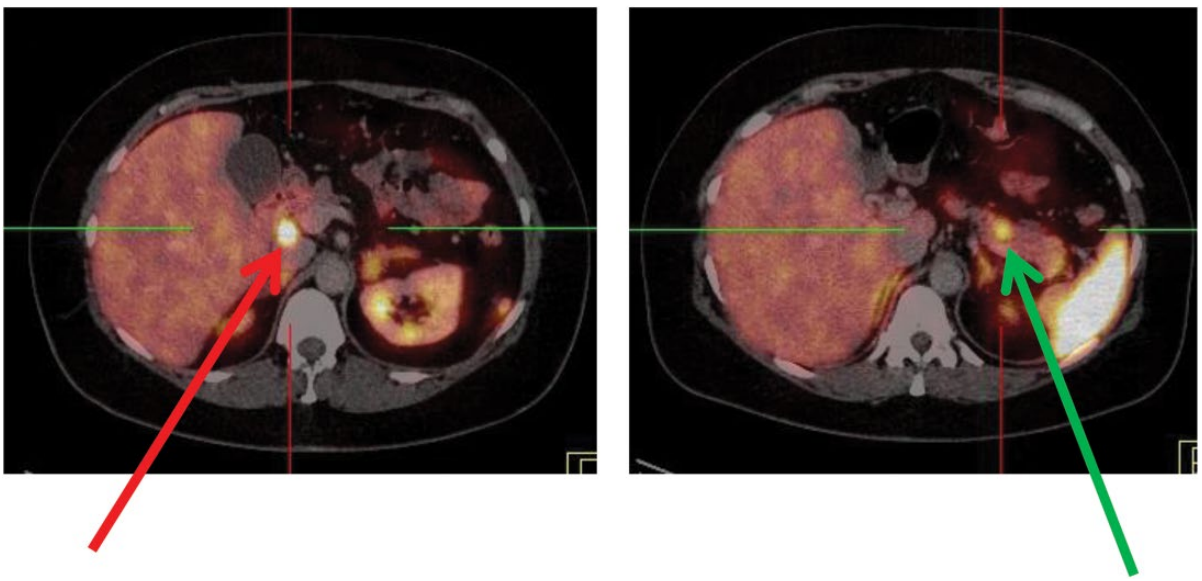

**Figure 126.1** [$^{68}$Ga]DOTA-TOC PET/CT in a 41-year-old patient with known MEN1 syndrome. She had undergone parathyroidectomy because of hyperparathyroidism 10 years earlier. At present she is diagnosed with hypergastrinemia without clinical manifestation of ZES. Red arrow, duodenal lesion. Green arrow, additional pancreatic lesion; no evidence of metastases.

about 50% of cases and therefore are often not detected in somatostatin receptor-based imaging. Recently, glucagon-like peptide 1 (GLP-1)-based scintigraphy or PET/CT has been shown to localize insulinoma with high sensitivity [17,18].

## Clinical Presentation

*Nonfunctioning PanNET* are usually asymptomatic. In cases of advanced disease, they can cause unspecific tumor-associated symptoms such as abdominal or back pain, jaundice, or weight loss.

*Gastrinomas* cause the *Zollinger–Ellison syndrome* (ZES) with a clinical manifestation resulting from gastric acid hypersecretion such as severe peptic disease (peptic ulcerations), gastroesophageal reflux disease, and diarrhea. Peptic ulcer bleeding may be the presenting symptom in some patients. The use of proton-pump inhibitors (PPI), however, may mask the symptoms of ZES and delay diagnosis. Concomitant hyperparathyroidism may enhance hypergastrinemia-associated symptoms. With biochemical screening in patients with a known diagnosis of MEN1, hypergastrinemia can be detected early before a clinically relevant ZES develops. Patients with MEN1 with ZES present at an earlier age (mean 32–35 years) than patients with sporadic gastrinomas.

*Insulinomas* present with symptoms of hypoglycemia (headache, diplopia, confusion, dizziness, abnormal behavior, amnesia, rarely seizures and coma) and symptoms resulting from the counter-regulation of the autonomic nervous system (sweating, weakness, hunger, tremor, anxiety, and palpitations). Patients often gain weight. The presence of a Whipple triad remains useful in suspecting underlying insulinoma [19]. The triad consists of symptoms of hypoglycemia, plasma glucose level <40 mg/dL, and relief of symptoms with administration of glucose. Insulinomas in patients with MEN1 often occur at young age (many <20 years), whereas sporadic cases generally occur in patients aged >40 years [2].

A *glucagonoma syndrome* is found in <5% of patients with MEN1 and is characterized by the presence of a necrolytic migratory erythema (a characteristic skin rash), weight loss, anemia, and glucose intolerance or diabetes. In clinical practice, the glucagnoma syndrome is rare and more often pancreatic lesions stain positive for glucagon with slightly increased glucagon serum levels, although without the clinical syndrome [2].

The *Verner–Morrison syndrome*, also called pancreatic cholera or WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria) is caused by hypersecretion of VIP. Patients suffer from excessive diarrhea with electrolyte and pH disturbances and dehydration. Less than 1% of patients with MEN1 present with Verner–Morrison syndrome [2].

In a patient with MEN1, more than one hypersecretion syndrome can develop over the years.

## Surgical Treatment

A proven organic hyperinsulinism is an indication for surgical treatment. Whereas in sporadic cases an enucleation is often appropriate, in patients with MEN1 who often have multiple tumors impeding the clear identification of the insulinoma, a left pancreatic resection with enucleation of tumors in the pancreatic head is regarded as the standard procedure by most surgeons. Excision of all macroscopically detectable tumors may be an alternative. Routine lymphadenectomy is not indicated. Intraoperative ultrasound and the determination of the insulin/glucose ratio have been suggested for assessing the success of the removal of the insulinoma [20].

In patients with glucagonomas and VIPomas, the primary tumor is often located in the pancreatic tail and surgical removal with curative intention (left pancreatectomy with lymph node resection) is the treatment of choice. In metastasized cases, interdisciplinary discussion of operative debulking, medical treatment, and hepatic artery embolization or combinations thereof is necessary.

The role of surgery in treating patients with MEN1-associated gastrinomas is controversial. About 90% of patients with MEN1 have multiple tumors in the duodenum and a favorable long-term prognosis if only small tumors (<2 cm) or no tumors are present on preoperative imaging examination [21]. In a French study, gastrinomas >3 cm demonstrated liver metastases in 40% of cases compared with only 4.8% when the tumors were <3 cm. Surgical treatment was associated with a significantly reduced risk for the development of liver metastases compared with medical treatment; however, the only significant prognostic factors for overall survival were the diagnosis of ZES before 1980 and age [22]. Thompson et al. proposed subtotal left pancreatectomy with preservation of the spleen, enucleation of tumors of the pancreatic head, duodenotomy with excision of duodenal tumors, and lymphadenectomy as the standard procedure for surgical treatment of ZES in MEN1 [23]. Most patients can be rendered eugastrinemic with this approach but cure is rare. Therefore, some centers suggest a more aggressive surgical approach with partial pancreaticoduodenotomy to provide a higher rate of cure [24]. The increased likelihood of cure has to be weighed against an increased operative mortality and long-term morbidity in each individual case and the patient's preference must be considered.

Nonfunctioning PanNET also harbor the risk of malignant transformation and there is an ongoing debate

regarding the correct timing and extent for surgical intervention. Thakker et al. suggested in their guidelines that surgery should be considered for tumors larger than 1 cm and/or demonstrating a significant growth over 6–12 months [2]. In the ENETS guidelines [25] and also in the French multicenter trial, a conservative approach is suggested unless the tumor exceeds 2 cm or is rapidly growing [7] because the risk of metastasis is low in this group and surgery may not prevent the development of metastases unless a total pancreatectomy is performed. However, total pancreatectomy is usually not recommended because of the significant long-term morbidity. Most authors suggest left pancreatectomy with enucleation of tumors of the pancreatic head with lympadenectomy, but sole enucleation and also more aggressive approaches have also been proposed.

## Medical Treatment

The principles of medical treatment of PanNET in MEN1 are identical with those in sporadic cases as studies especially for MEN1 are very limited.

### Medical Treatment in Functioning Tumors

In patients with gastrinoma, treatment with PPI is indicated to suppress hyperacidity. The recommended starting dose is equivalent to omeprazole 40–60 mg b.i.d. in MEN1/ZES [21]. Long-acting somatostatin analogs such as octreotide-LAR or lanreotide autogel also control acid secretion and can be added to PPI, which is the basic treatment of choice because of its effectiveness and the ease of oral intake.

In patients with insulinoma, prior to mostly curative surgery, intravenous glucose administration in addition to frequent small carbohydrate meals may be necessary. Additional medical treatment is mainly indicated in the rare metastatic cases and includes diazoxide (in combination with diuretics), somatostatin analogs (which should be started in the hospital to exclude worsening of hypoglycemia, which also has been reported), and the mammalian target of rapamycin (mTOR) inhibitor everolimus [26].

In patients with VIPomas and glucagonomas, long-acting somatostatin analogs can control the hypersecretion syndrome.

### Medical Treatment for Tumor Control

Medical treatment with antiproliferative intention is usually started in patients with nonresectable or metastatic disease. Nevertheless, one recent study suggested that early octreotide treatment in patients with MEN1 syndrome and duodenopancreatic manifestation may delay tumor progression [27].

Long-acting somatostatin analogs can be administered for antiproliferative purposes in patients with metastatic PanNET showing a slow tumor growth. The CLARINET trial has proven the efficacy with respect to progression-free survival (PFS) in somatostatin receptor-positive (sporadic) gastroenteropancreatic neuroendocrine tumors with a proliferation rate Ki-67 not exceeding 10% [28].

In patients with a high tumor load or rapid tumor growth, chemotherapy with streptozotocin and 5-fluorouracil or temozolomide and capecitabine is indicated [29]; in patients with liver-predominant disease, chemoembolization is an alternative. In recent years, two molecular-targeted treatments have become available for metastatic PanNET: the multikinase inhibitor sunitinib and the mTOR inhibitor everolimus. In placebo-controlled trials, both drugs demonstrated a doubling of PFS compared with placebo [30,31] and were approved for progressive metastatic PanNET. Although the studies included mainly non-MEN patients (two patients with MEN1 in the sunitinib trial; in the everolimus trial MEN status was not provided), it seems plausible that the results also apply for PanNET in MEN1 syndrome.

### Follow-up

Patients with MEN1 syndrome or MEN1 gene carriers should be offered a program of combined clinical, biochemical, and radiologic screening and follow-up as summarized in Table 126.1 [2]. The program should be individualized according to clinical judgment of the patient's history and actual situation and also the patient's preferences. A critical assessment of the screening program at our center demonstrated that most tumors were found at initial staging and concluded that an extension of the screening interval to 3 years may be appropriate [32], whereas others recommend CT or MRI every 1–2 years, especially to detect thymic, bronchial, and pancreatic NET early as these tumors are the leading cause of death in patients with MEN1 [3].

## Prognosis

Despite the fact that life expectancy in patients with MEN1 has increased in recent decades, still 50–70% of patients with MEN1 will die of causes directly related to MEN1 [33,34]. The mean age at death is 55–60 years [3]. Whereas in early series patients often died as a result of complications of hormonal effects of the tumors such as upper gastrointestinal bleeding resulting from ZES or renal complications as a consequence of hyperparathyroidism, today there is a shift toward death from

**Table 126.1** Suggested program of combined clinical, biochemical, and radiologic screening and follow-up.

| Examination | Interval | Extent |
|---|---|---|
| Clinical evaluation | Annually | Extensive history of symptoms of tumor manifestations and physical examination |
| Biochemical screening | Annually | Ca, parathyroid hormone, gastrin, fasting glucose, insulin, ChA, glucagon, VIP, prolactin, IGF-1 |
| Functional testing | No routine investigation, suspicion of gastrinoma | Gastric pH, secretin test, or Ca infusion test |
| | Suspicion of insulinoma | Fasting test |
| Abdominal imaging | Annually | EUS, MRI, or CT (or [$^{8}$Ga]DOTA-TOC PET/CT) |
| Imaging of the chest | Every 1–2 years | CT or MRI (or [$^{68}$Ga]DOTA-TOC PET/CT) |
| Imaging of the pituitary gland | Every 3 years | MRI |

ChA, chromogranin A; IGF-1, insulin-like growth factor 1; for other abbreviations, see text.

malignancy. PanNET and especially the more aggressive thymic carcinoid tumors are associated with an increased risk of death [34] and the risk of dying from a malignant nonendocrine tumor is also elevated [3]. Early diagnosis and surgical resection in cases with significant growth or diameter >2 cm to prevent metastatic spread provide a more favorable outcome in patients with MEN1 with nonfunctioning PanNET compared with sporadic cases. In patients with ZES, prognosis in patients with MEN1 is also better than in patients with sporadic ZES: the 15-year survival in patients with MEN-1 was 93% compared with 68% in sporadic patients [35].

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# 127

# Nonfunctioning Pancreatic Neuroendocrine Tumors: Diagnosis and Management Principles

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## Definition

Among pancreatic neuroendocrine tumors (PanNET), nonfunctioning PanNET (NF-PanNET) are defined as tumors exhibiting no specific symptoms arising from an excess of hormonal secretion. Therefore, PanNET exhibiting a high level of serum hormone or a positive result for a specific hormone on immunohistochemical assessment, while no specific symptoms are observed, are managed as NF-PanNET.

## Pathology

According to the World Health Organization (WHO) classification 2010 [1], neuroendocrine tumors (NET), including PanNET, are graded as G1, G2, and G3 using the mitotic count and/or the Ki67 labeling index. G1 (mitotic count <2 per 10 high-power fields [HPF] and/or ≤2% Ki-67 index) and G2 (mitotic count 2–20 per 10 HPF and/or 3–20% Ki-67 index) are compatible with well-differentiated NET, and G3 (mitotic count >20 HPF and/or >20% Ki-67 index) is compatible with poorly differentiated neuroendocrine carcinomas (NEC). Positive staining for specific neuroendocrine markers, such as chromogranin A and/or synaptophysin, is necessary to make a definitive diagnosis of the NET. Of note, there are some NF-PanNET that show positive staining for several specific hormones, including glucagon, pancreatic polypeptide, or serotonin, on immunohistochemical assessment.

## Mechanism of Tumorigenicity

Neoplastic cells of PanNET are considered to originate from neuroendocrine stem cells in the islet of Langerhans or pancreatic ductal epithelium; however, the mechanism of the progression to a PanNET has not been well documented. Several genetic alterations, which may be associated with the tumorigenicity of PanNET, have been reported. Jiao et al. [2] showed that alterations of *DAXX/ATR*, *MEN1*, and mammalian target of rapamycin (mTOR) pathway genes are frequently observed in well-differentiated PanNET. It is well known that NF-PanNET are often accompanied by hereditary diseases, including multiple endocrine neoplasia type 1 (MEN1), von Hippel–Lindau disease, von Recklinghausen disease, and tuberous sclerosis. However, poorly differentiated pancreatic NEC (PanNEC) are reported to have alterations in *p53*, *Rb*, and *bcl-2* and therefore are considered to have a different mechanism in terms of tumorigenicity from well-differentiated PanNET [3].

## Clinical Findings

PanNET account for about 2% of all pancreatic neoplasms, and NF-PanNET are the most common PanNET (40–60%), followed by insulinomas (~20%) and gastrinomas (~10%). In a recent Japanese nationwide survey [4], the estimated prevalence of PanNET in 2010 was 2.69/100,000 with an annual onset incidence of 1.27/100,000, including 65.5% of NF-PanNET. Most of

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the NF-PanNET are solitary, and sometimes multiple, especially in hereditary diseases. Well-differentiated NF-PanNET grow slowly; however, owing to the large size of NF-PanNET, they have the potential to metastasize to lymph nodes and the liver. Of note, NF-PanNET sometimes acquire hormonal production and the relevant symptoms with their progression [1]. However, poorly differentiated PanNEC show a fairly high malignant behavior, and most of the PanNEC are determined as unresectable because of distant metastases at the time of diagnosis. The frequency of PanNEC among NF-PanNET was 2–10%, and the associated MEN1 was observed in 4–30% of NF-PanNET. These distributions differ among races [4].

## Symptoms

Most of the patients with NF-PanNET do not have any specific symptoms, and the number of the patients who are diagnosed as having an asymptomatic small NF-PanNET at the time of medical examination or during surveillance for other diseases has recently been increasing. The patients with a large NF-PanNET often present with symptoms such as abdominal pain, discomfort, distension, weight loss, nausea, or a palpable mass. Involvement of the bile duct or pancreatic duct leads to jaundice, obstructive pancreatitis, or diabetes mellitus.

## Diagnosis

Typical radiologic findings in well-differentiated NF-PanNET are a well-demarcated homogeneous hypoechoic lesion from ultrasonography, a well-demarcated enhanced solid tumor from the early phase of enhanced computed tomography (CT) (Fig. 127.1a), and a low-intensity tumor in the T1-weighted image and a high-intensity lesion in the T2-weighted image from magnetic resonance imaging (MRI). The large-sized NF-PanNET often exhibit cystic changes or calcification, which are reflected in the radiologic findings (Fig. 127.1b and c). The lesions, which should be discriminated from well-differentiated PanNET because of the similarity of these radiologic findings, include acinar cell carcinoma, solid and pseudopapillary neoplasm, solid-type serous cystic neoplasm, metastatic pancreatic tumor from renal cell carcinoma, and accessory spleen. Somatostatin receptor scintigraphy is applied for the detection of metastatic lesions, and enhanced MRI is also useful for detecting small hepatic metastases. The serum chromogranin A concentration is used to assess the disease control during chemoradiotherapy or to detect recurrence after curative resection.

However, a pancreatic PanNEC has various radiologic findings and sometimes shows an irregular low-density solid lesion from the enhanced CT (Fig. 127.1d), which is similar to the findings for a pancreatic ductal adenocarcinoma.

For a definitive diagnosis, cytologic assessment under endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) is mandatory, and histologic grading can also be evaluated if a sufficient amount of neoplastic cells (usually over 2000 cells) can be obtained [5].

Table 127.1 presents a brief summary of the diagnostic issues.

## Surgical Treatment for Localized Lesions

Curative resection should be considered as the first treatment in all cases of localized well-differentiated NF-PanNET. However, the National Comprehensive Cancer Network (NCCN) guidelines [6] recommend that asymptomatic small-sized well-differentiated NF-PanNET (<10 mm in diameter), which are occasionally observed by imaging, can be determined without resection depending on consideration of the patient's general condition and the expected invasiveness of the operation. Operations for localized well-differentiated NF-PanNET range from enucleation to organ-preserving pancreatectomy, and standard pancreatectomy with regional lymph node dissection, and the surgical treatment strategy is determined based on the tumor size, the invasiveness, and the presence of regional lymph node metastases from imaging studies. Histologic grading by EUS-FNA is not usually included for these strategies in the guidelines [6–8], because this technique cannot always be performed in every institution worldwide, and a high sensitivity to determine accurately the histologic grade in the resected specimen has only been reported by a high-volume center. The rate of lymph node metastases in a small well-differentiated NF-PanNET remains unclear, hence sampling of the regional lymph node is always necessary even in enucleation or organ-preserving pancreatectomy for small NF-PanNET. In several guidelines [6–8], small NF-PanNET are considered as those with a tumor size of <2 cm and with no sign of invasiveness or lymph node metastasis. There is no evidence showing a benefit of neoadjuvant therapy before operation or adjuvant therapy after curative resection for well-differentiated NF-PanNET, therefore such adjuvant therapies are not recommended.

The surgical treatment for resectable PanNEC is standard pancreatectomy with regional lymph node dissection, and adjuvant therapy using platinum-based chemotherapy, in proportion to the regimen for small-cell carcinomas of the lung, is recommended [6].

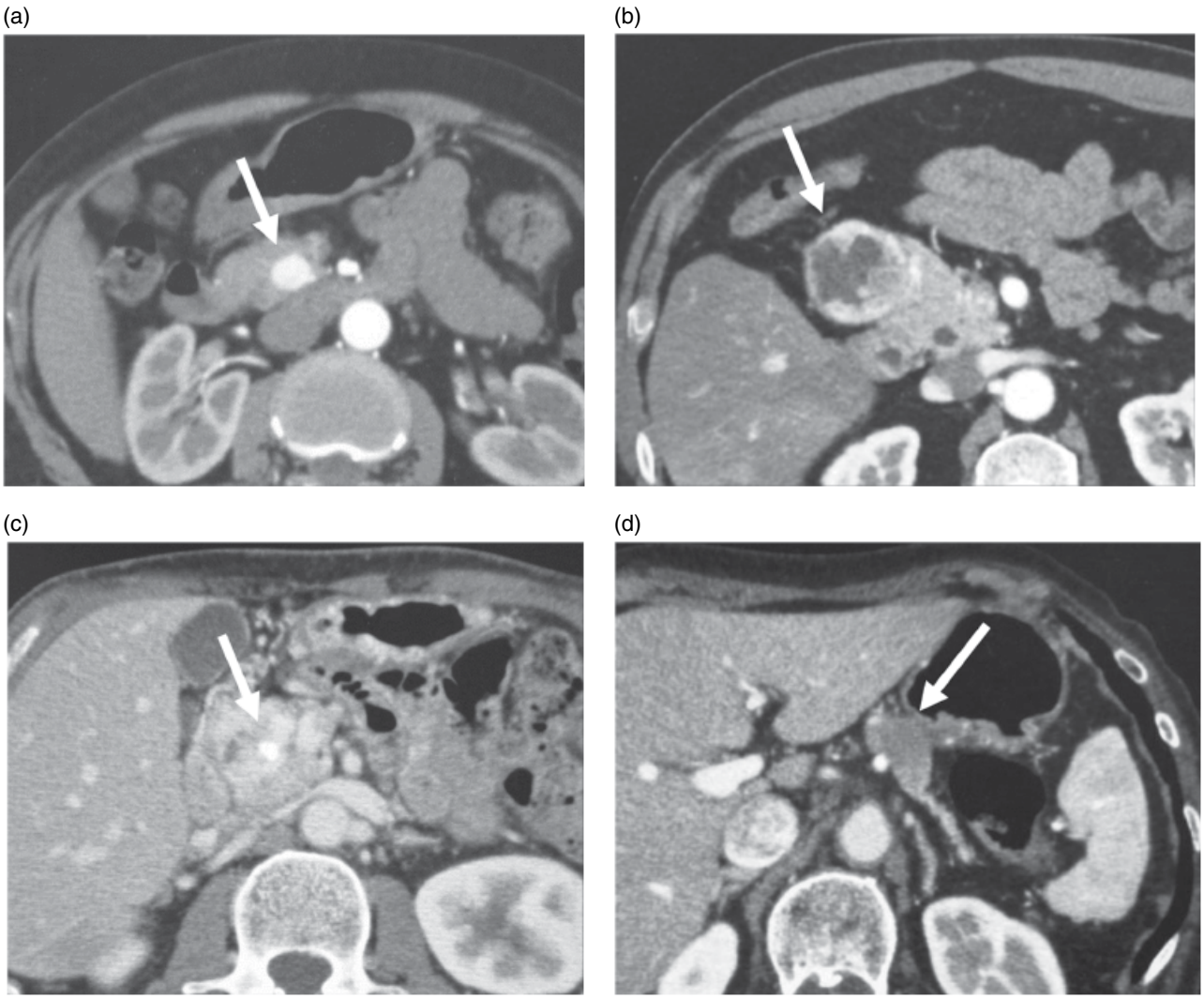


**Figure 127.1** Computed tomography of NF-PanNET. (a) Well-demarcated enhanced lesion in the pancreas head (arrow, 15 mm, G1); (b) enhanced lesion with cystic change in the pancreas head (arrow, 45 mm, G2); (c) enhanced lesion with calcification in the pancreas head (arrow, 35 mm, G2); (d) low-density lesion in the pancreas body with atrophy of the distal part of the pancreas (arrow, 25 mm, G3). *Source:* Parts (a)–(c) provided by Dr Tetsuhide Ito, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University.

PanNET are clinically observed in 50–60% of patients with MEN1, and all autopsy cases of MEN1 have PanNET, although they are microlesions [9]. Most cases involve multiple lesions, and the most frequent type is NF-PanNET. The presence of a PanNET is an important prognostic factor in patients with MEN1 [10]. Surgical treatment for multiple NF-PanNET in patients with MEN1 is complicated. Several guidelines [6–8] recommend removing only functioning PanNET and high-risk NF-PanNET (>1–2 cm in diameter) to avoid total pancreatectomy, for example, using distal pancreatectomy with enucleation of the PanNET in the proximal part of the pancreas, or pancreatoduodenectomy with enucleation of the PanNET in the distal part of the pancreas.

Prognosis of NF-PanNET after resection depends on the histologic grade, and 5-year survival rates are 80–100% in G1, 50–70% in G2, and 0–30% in G3 [11]. Some patients experience recurrences more than 10 years after operation, and therefore postoperative surveillance over a long duration is necessary.

## Multidisciplinary Treatment for Metastatic Lesions

The most frequent site for the distant metastases of PanNET is the liver, and 70% of hepatic metastases are diagnosed as multiple lesions at the time of initial

assessment [7]. In the recurrent cases after resection, some patients experienced hepatic metastasis more than 10 years after curative operation, as described above. Hepatic metastases are usually classified as simple (unilobar or limited), complex (bilobar), and diffuse pattern, according to the European Neuroendocrine Tumor Society (ENETS) guidelines [7]. Simple and complex patterns without extrahepatic metastases are usually treated by operation with or without regional ablation therapies such as radiofrequency ablation and transarterial chemoembolization. A diffuse pattern is basically a contraindication for surgical treatment; however, aggressive multidisciplinary treatment, including surgical debulking, might lead to a 5-year survival rate of over 50% if over 90% of the lesions can be removed [12–14]. Asymptomatic and slow-growing unresectable small-volume metastatic NF-PanNET can be observed without any treatment until the signs of growth or symptoms are apparent [1]. Liver transplantation for unresectable hepatic metastases from PanNET is not recommended because of unsatisfactory outcomes [15].

The necessity for resection of primary lesions in cases of synchronous unresectable hepatic metastases remains controversial. One report [8] claimed that the resection of the primary lesion would lead to a definitive diagnosis of PanNET with accurate histologic grade and also subsequent application of specific therapies for hepatic metastases such as transarterial chemoembolization and radiofrequency ablation. However, another report [16] showed that there were no differences in survival

**Table 127.1** Summary of diagnosis and treatment principles for nonfunctioning pancreatic neuroendocrine tumors.

1) Well-differentiated PanNET (G1, G2)
   a) Diagnosis
      Typical radiologic findings of primary lesion
         Ultrsonography; well-demarcated, homogeneous, hypoechoic lesion
         Computed tomography; well-demarcated enhanced lesion in early phase
         Magnetic resonance imaging; T1 low intensity, T2 high intensity
         Other findings: cystic change, calcification, etc.
      Differential diagnosis
         Acinar cell carcinoma, solid-pseudopapillary neoplasm, accessory spleen, etc.
      Definitive diagnosis
         Endoscopic ultrasound-guided fine-needle aspiration
      Detection of metastatic lesion
         Systemic; computed tomography, somatostatin receptor scintigraphy
         Liver; enhanced magnetic resonance imaging
   b) Treatment
      Primary
         <2 cm: enucleation or organ-preserving pancreatectomy (positive-node sampling)
         ≥2 cm: standard pancreatectomy with node dissection
         In multiple tumors of MEN1, remove only functioning tumor and high-risk
         nonfunctioning tumor (>1–2 cm in diameter) to avoid total pancreatectomy
      Metastases
         Resection, if possible, or multidisciplinary treatment including debulking surgery,
         regional ablation therapy, systemic chemotherapy, molecular-targeted therapy, somatostatin receptor agonist, etc.
2) Poorly differentiated PanNEC (G3)
   a) Diagnosis
      Radiologic findings of primary lesion
         Ultrasonography; irregular hypoechoic
         Computed tomography; irregular low density
         Magnetic resonance imaging; T1 low intensity, T2 high intensity
      Differential diagnosis
         Pancreatic ductal adenocarcinoma, etc.
      Definitive diagnosis
         Endoscopic ultrasound-guided fine-needle aspiration
      Detection of metastatic lesion
         Computed tomography, magnetic resonance imaging
   b) Treatment
      Resectable primary
         Resection + adjuvant chemotherapy using platinum-based regimen
      Unresectable primary or metastases
         Chemotherapy using platinum-based regimen

between patients with synchronous unresectable hepatic metastases who underwent resection of primary PanNET and those without primary resection. Owing to recent advances in the EUS-FNA technique for the definitive diagnosis of PanNET with histologic grade, and the development of new drugs, including molecular-targeted drugs, various types of somatostatin receptor analog, and radionuclide-labeled peptide targeting the somatostatin receptor, resection of the primary tumor is not always necessary in cases with synchronous unresectable hepatic metastases of PanNET.

Surgical indication for extrahepatic metastases is limited, because most of these cases also have hepatic metastases, and indication depends on the status of the hepatic metastases.

Treatment principles for NF-PanNET are summarized in Table 127.1. Medical treatment for PanNET includes chemotherapy (streptozocin, dacarbazine), molecular-targeted therapy (everolimus, sunitinib), and somatostatin receptor analog therapy, including radionuclide therapy, and details of these therapies are described elsewhere.

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# 128

# Medical and Nucleotide Treatment of Neuroendocrine Tumors of the Pancreas

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## Introduction

Pancreatic neuroendocrine tumors (PanNET), although relatively rare, are increasingly being diagnosed following the introduction of newer sensitive imaging techniques. Although a number of PanNET are capable of synthesizing and secreting biochemically active substances leading to distinct clinical syndromes (functioning tumors), the great majority are nonfunctioning [1] (Table 128.1). Surgical resection is the best means of removing the tumorous tissue, but this is not always feasible as a significant number of patients with PanNET present with unresectable disease. Even in such instances, surgery may be of benefit in cases of difficult-to-control secretory syndromes or when a substantial proportion of the tumor load can be removed [1]. However, for a significant number of patients, additional medical treatment will be required to deal with the symptoms related to secretory syndromes and existing tumor load and also prevent further tumor growth.

Before treatment initiation, a number of parameters need to be considered in order to choose the most appropriate treatment for each patient (Table 128.2). In the past, chemotherapy has been the main therapeutic approach substantiated by few well-controlled but mostly retrospective studies [2,3]. Similarly, long-acting somatostatin (SST) analogs have been used for the control of symptoms secondary to clinical syndromes, also achieving a mainly stabilizing effect on tumor growth [1]. Recent Phase III studies have introduced new therapeutic approaches and a number of retrospective studies have provided good-quality data on the efficacy of new and previously utilized treatments. Several international societies have established guidelines to aid in dealing with PanNET, but there are still some unresolved issues regarding the choice of first-line therapy, estimation of response, and selection of further treatment options following disease progression [4–6].

As every distinct clinical syndrome attributable to a specific functioning PanNET may require more complex and specific treatment, the syndromes will be discussed separately first, followed by a discussion of treatment against tumor growth, which will be similar for both functioning and nonfunctioning PanNET.

## Nonsurgical Treatment of the Secretory Syndromes

Treatment of common and relatively rare secretory syndromes secondary to functioning PanNET is shown in Table 128.1.

### Insulinoma

The most appropriate treatment for insulinomas is surgical resection, which is associated with a greater than 95% success rate. Medical treatment may be necessary in patients with unresectable disease who remain symptomatic despite administration of frequent meals. The use of medications, such as diazoxide, which exerts a direct inhibitory effect on insulin secretion, has been shown to be efficacious in approximately 60% of cases [5]. Diazoxide is usually well tolerated and can be given in doses of 3–8 mg/kg divided throughout the day; however, almost half of the patients on diazoxide therapy may develop fluid retention, hirsutism, and gastrointestinal upset [5]. As the majority of PanNET express on

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**Table 128.1** Treatment of PanNET according to their secretory component.

| PanNET | Syndrome | Secretory component | Treatment |
|---|---|---|---|
| Nonfunctioning | NF-PanNET | None | |
| Gastrinoma | Zollinger–Ellison syndrome (ZES) | Gastrin | PPI (rarely H2R antagonists, SST analogs) |
| Insulinoma | Endogenous hyperinsulinism | Insulin | Frequent meals, IV glucose, diazoxide, SST analogs, everolimus, pasireotide |
| VIPoma | Verner–Morrison syndrome, WDHA | VIP | SST analogs (rarely glucocorticoids, sunitinib) |
| Glucagonoma | Glucagonoma | Glucagon | SST analogs |
| Somatostatinoma | Somatostatinoma | Somatostatin | SST analogs |
| ACTHoma | ACTH | ACTH | SST analogs, cabergoline, pasireotide, adrenolytic treatment |
| GRFoma | GRF | GRF | SST analogs, pasireotide, cabergoline, pegvisomant |
| PanNET causing carcinoid syndrome | Carcinoid syndrome | Serotonin, tachykinins | SST analogs, terlotristat |
| PanNET causing hypercalcemia | PTHrPoma | PTH-rP | SST analogs, bisphosphonates, cinacalcet, calcitonin |
| Rare PanNET | LH, rennin, GLP-1, IGF-2, erythropoietin, CCK, enteroglucagon | Various hormones | Refer to relevant syndrome |

ACTH, adrenocorticotropic hormone; CCK, cholecystokinin;; GLP-1, glucagon-like peptide 1; GRF, growth hormone-releasing factor; IGF-2, insulin-like growth factor 2; LH, luteinizing hormone; PTH-rP, parathyroid hormone-releasing polypeptide; VIP, vasoactive intestinal polypeptide; WDHA, watery diarrhea, hypokalemia, and achlorhydria.

**Table 128.2** Factors that need to be considered in order to select the most appropriate treatment among the currently available nonsurgical treatments for PanNET.

| |
|---|
| Functioning tumor |
| Grading |
| Extent of disease (liver or other metastases) |
| Extent of liver involvement |
| Tumor growth rate |
| SRS uptake |
| Patient performance status |
| Presence of a familial syndrome |
| Local availability |

SRS, somatostatin receptor scintigraphy.

their surface somatostatin receptors (SSTR), the administration of long-acting synthetic SST analogs exerts an inhibitory effect on the secretory components of most functioning PanNET [1]. However, as more than half of insulinomas do not express enough SSTR (particularly SSTR2), the administration of long-acting SST analogs should be treated with caution, as it may worsen hypoglycemia owing to the inhibition of counter-regulatory hormone secretion [5]. This can be avoided by prior demonstration of avidity of the tumor to SSTR using somatostatin receptor scintigraphy (SRS) or by administering short-acting octreotide demonstrating that it is not associated with hypoglycemia [5]. Long-acting SST analogs are effective in approximately 35–50% of patients. For unresectable and metastatic cases, the mammalian target of rapamycin (mTOR) inhibitor everolimus has been shown to exhibit a specific capability to increase blood glucose levels [7]. Pasireotide, a long-acting somatostatin analog that binds to all SSTR except SSTR4, and can be associated with high glucose levels, could also be an additional option, but has not been specifically evaluated in insulinomas. In cases of extensive disease not responding to medical treatment, cytoreductive techniques, such as (chemo)embolization therapy using radiolabeled somatostatin analogs or surgical debulking, are employed, aiming at decreasing the tumor load and thus the amount of insulin secreted.

## Gastrinoma

Medical treatment of gastrinoma is directed against the gastric acid hypersecretory state, and also at the treatment of various endocrinopathies that may develop in patients with gastrinomas associated with multiple endocrine neoplasia type 1 (MEN1) syndrome (which accounts for approximately 25% of all gastrinomas). Proton-pump

inhibitors (PPI) are the drugs of choice because of their potency and long duration of action, and also their ability to be administered intravenously in the acute state. Histamine H2 antagonists (H2-R blockers) are also effective but need to be administered more frequently and at higher doses. Patients with difficult-to-control Zollinger–Ellison syndrome (ZES) may require higher doses of PPI, more frequent administration of PPI, or a combination of PPI with H2-R blockers. Long-term treatment with PPI has been shown to be safe. The potential side-effects are PPI-induced achlorhydria, which may lead to vitamin B12 deficiency, and there is a suggestion of an increased incidence of bone fractures [5].

### Other Functioning PanNET

In patients with vasoactive intestinal peptide-releasing tumors (VIPomas), meticulous control of high-volume fluid loss is mandatory, as these tumors may lead to severe electrolyte abnormalities and dehydration. Long-acting SST analogs achieve control of the diarrhea in the majority of such patients; medications such as glucocorticoids, clonidine, and loperamide, which were previously used, have now been surpassed by SST analogs. Similarly to VIPomas, SST analogs can control necrolytic erythema in 50–90% of patients with glucagonomas, although diabetes mellitus may not improve substantially; parenteral nutrition is required to help improve concomitant cachexia, hypoaminoacidemia, and weight loss [5]. SST analogs have also been shown to be efficacious in the few cases of apparent somatostatinomas described in the literature. Higher doses of SST analogs can be used in patients with suboptimal control of the secretory syndromes using conventional doses of the drugs. Patients who experience exacerbation of symptoms toward the final week of each treatment cycle may benefit from an increased frequency of administration. Supplemental doses of short-acting octreotide may also be used, offering an additive effect in such cases. Rarer syndromes related to the unique ability of these tumors to synthesize and secrete compounds that traditionally originate from different tissues, leading to so-called paraneoplastic syndromes, necessitate the administration of additional more specific treatment [8].

## Nonsurgical Treatment Directed Against Tumor Growth

### Treatment of PanNET with Somatostatin Analogs

The majority of PanNET (with the exception of insulinomas) express on their surface SSTR2 and -5, which aids in their diagnosis by use of SRS and in treatment with use of long-acting SST analogs (octreotide and lanreotide). SST and its synthetic analogs not only exert an inhibitory effect on the secretory components of most functioning PanNET (except insulinomas) but also show an antiproliferative activity mainly manifested as disease stabilization [1]. Following the findings of an earlier prospective Phase III study, which demonstrated that octreotide long-acting release (LAR) improves the median time to progression in patients with carcinoid tumors compared with placebo, a subsequent Phase III study, CLARINET, evaluated the efficacy of the other SST analog, lanreotide, in a variety of nonfunctioning gastrointestinal (GI)-NET, including PanNET [9,10]. In that study, 91 patients with nonfunctioning PanNET, who had no tumor progression in the 3–6 months before randomization, were studied. All patients had grade 1 or grade 2 tumors and a Ki-67 value of up to 10%, whereas a significant number of them had a hepatic tumor load of >25%. Patients were randomized to receive either lanreotide 120 mg monthly (without dose adjustment) or placebo, and were followed for 96 weeks [10]. After a median follow-up period of 14 months, the progression-free survival (PFS) in the lanreotide-treated patients was not reached (the predefined 50% progression rate among patients treated with lanreotide was not obtained) whereas that of the placebo group was 12.1 months, resulting in a hazard ratio of 0.58 (CI 0.32–1.04, $P = 0.0657$) [10]. This finding implies that patients treated with lanreotide had an almost 50% chance of remaining stable in respect of tumor progression compared with those treated with placebo, who experienced disease progression. Tolerance to treatment was consistent with that in previous studies [10]. The beneficial effect of lanreotide in respect of PFS was documented even in patients with a >25% hepatic involvement by the tumor and in those with grade 2 tumors (Ki-67 values up to 10%) [10]. CLARINET was the first study to provide good-quality data on the antiproliferative effect of SST analogs on PanNET; however, the data on the effect of this treatment on overall survival (OS) are still emerging. Recent preclinical and clinical studies have evaluated the effect of the more potent SST analog pasireotide, which binds to all SSTR except SSTR4, in PanNET. In a Phase II study, 28 patients with GI-NET were treated (including six with PanNET) and the most favorable effect was observed in patients with low hepatic tumor burden, normal baseline chromogranin A levels, and high tumorous SSTR5 expression; the best radiographic response was stable disease in 17 patients (60%). However, pasireotide was associated with a 79% rate of hyperglycemia, including 14% hyperglycemia of grade 3, raising concerns regarding its suitability as a first-line systemic agent [11].

Based on these findings, it has been suggested that patients with grade 1 and grade 2 tumors with a Ki-67

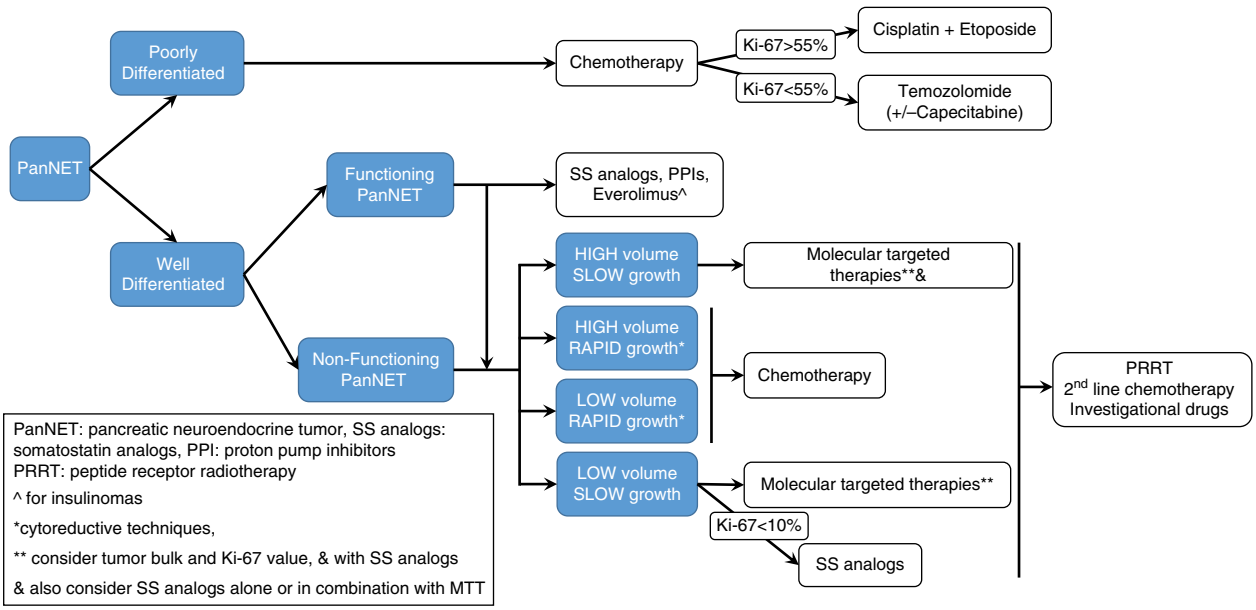


**Figure 128.1** Suggested algorithm for the nonsurgical management of PanNET.

value of up to 10% could be treated with SST analogs [10;11]. However, there are still a number of unresolved issues as to whether treatment should be initiated immediately following diagnosis or after a period of monitoring to access tumor growth rate, the effect that lower doses of SST analogs could exert, should treatment be intermittently discontinued, and data regarding their effect on OS are still pending [6]. In the presence of extensive disease involving the majority of the liver or in the presence of extrahepatic disease, other therapies should also be considered aimed at effectively reducing the tumor load (Fig. 128.1).

## Treatment with Chemotherapeutic Agents

In contrast to other GI-NET that are typically chemoresistant, well-differentiated (grade 1/2) PanNET appear to be sensitive to alkylating agents, including streptozotocin, dacarbazine, and temozolomide, and also fluoropyrimidines. Previous studies have shown that the combination of streptozotocin and fluorouracil (5FU) resulted in a response rate of 63% compared with streptozotocin monotherapy [2]. Furthermore, the combination of streptozotocin and doxorubicin appeared to be more efficacious than that of streptozotocin and 5FU, exhibiting a response rate and time to progression of 69% and 20 months compared with 45% and 6.9 months, respectively [2]. However, a more recent retrospective study of 84 patients with PanNET, which evaluated the response rate of the combination of streptozotocin, 5FU, and doxorubicin, demonstrated a 39% response rate whereas the median response duration was 9.3 months [12]. These later findings most probably represent more realistic figures, as the evaluation of response to therapy was performed with modern and more robust radiologic means compared with the earlier studies. Because streptozotocin has a relatively high toxicity profile and can cause myelosuppression and renal impairment, alternative chemotherapeutic regimens have recently emerged. Following the findings of a Phase II study that showed a 45% response rate for the combination of temozolomide and thalidomide in a small cohort of 11 patients with PanNET, a subsequent retrospective study evaluated the combination of temozolomide (oral derivative of dacarbazine) and capecitabine (oral derivative of 5FU) in 30 chemonaïve patients with PanNET and found a 70% radiologic response whereas the median PFS was 18 months [13–15]. Another antiangiogenic-based combination, temozolomide (given at 150–200 mg/m$^2$ for 14 days or as a metronomic daily dose) and bevazicumab, exhibited response rates ranging from 33 to 64% in 49 treated patients, 22 of whom had a PanNET. Temozolomide has also been coadministered with everolimus, exhibiting increased response rates [13]. The majority of these studies have limitations, including relatively small numbers of patients studied, differences in regimens used, and variable response rates obtained. However, temozolomide has gained popularity owing to its convenient mode of administration and favorable side-effect profile. Currently, chemotherapy is recommended in patients with a high tumor burden when tumor shrinkage is required, a rapidly progressive tumor

in subsequent follow-up suggestive of a more aggressive course, and when the Ki-67 labeling index is relatively high (>10%).

The role of chemotherapy is also well established in patients with pancreatic neuroendocrine carcinomas (PanNEC). These high-grade malignancies are locally advanced or metastatic at presentation, only rarely express SSTR, and are not associated with secretory syndromes. First-line systemic chemotherapy with a platinum-based agent (cisplatin or carboplatin) and etoposide is recommended for most patients with metastatic-stage disease, whereas sequential or concurrent chemoradiation is recommended for patients with locoregional disease [16]. Response rates ranging from 42 to 67% have been described but are usually of short duration; the median survival ranges from 15 to 19 months [16]. Based on the response, usually 3–4 cycles of chemotherapy are administered but, following relapse or nonresponse, second-line options are limited [16]. A recent retrospective study suggested that patients with PanNEC and Ki-67 values of less than 55% may respond better to temozolomide-based regimens than cisplatin combinations [17].

## Treatment with Molecular-Targeted Agents and Angiogenesis Inhibitors

Targeting a number of pathways thought to be involved in the pathogenesis and/or progression of PanNET has recently resulted in the availability of further therapeutic options. The tyrosine inhibitor sunitinib, which targets vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3, platelet-derived growth factor receptor (PDGFR), and tyrosine protein kinase Kit (c-Kit), was evaluated in a Phase III study at a dose of 37.5 mg versus placebo in 171 patients with grade 1/2 PanNET. A statistically significant improvement in PFS was found in the sunitinib arm (11.1 versus 5.5 months), with a response rate of 9.3%; however, data on its effect on OS are lacking. Sunitinib is currently approved for the treatment of metastatic PanNET; common toxicities include gastrointestinal, hypertension, palmar–plantar erythrodysesthesia, and cytopenias [18]. The mTOR inhibitor everolimus has also been evaluated in PanNET in a Phase III study (RADIANT 3) in which 410 patients with grade 1/2 PanNET were assigned to either 10 mg of everolimus or placebo. The median PFS was 11.0 months with everolimus compared with 4.6 months with placebo, representing a 65% reduction in the estimated risk of progression or death. Drug-related adverse events were mostly grade 1 or 2, including stomatitis, rash, diarrhea, fatigue, atypical infections, and rarely pneumonitis. Grade 3 or 4 events encountered more frequently with everolimus than placebo included anemia (6 versus 0%) and hyperglycemia (5 versus 2%). Everolimus is also currently approved for the treatment of PanNET, and it has been suggested that it should be widely used as its efficacy is not affected by previously administered therapies such as chemotherapy [19]. Although there have been no comparative studies between these two agents, they are usually the preferred second-line therapeutic options following progression after treatment with SST analogs (Table 128.3). Bevacizumab, a monoclonal antibody against vascular endothelial growth factor A (VEGF-A), has also been used in combination with temozolomide and biological treatments exhibiting clinically useful responses [13]. Recently, combinations of molecular-targeted therapies with chemotherapeutic agents or bevacizumab have also been employed in small series and observational studies, the findings of which require further validation.

**Table 128.3** Comparison of the findings of Phase III trials of molecular-targeted therapies.

| Study | Patients | Active treatment (mg/day) | PD at entry | ORR | PFS (months) | Safety |
|---|---|---|---|---|---|---|
| Sunitinib | 171 (86 sunitinib, 85 placebo) PanNET | 37.5 | Yes | Sunitinib: CR 2.3%, PR 7%, SD 62.8%<br>Placebo: CR 0%, PR 0%, SD 60% | Sunitinib: 11.4<br>Placebo: 5.5 | Most common adverse effects >30%: diarrhea, nausea, asthenia, vomiting, fatigue<br>Grade 3–4 neutropenia and hypertension 10–12% |
| Everolimus | 410 (207 everolimus, 203 placebo) PanNET | 10 | Yes | Everolimus: PR 5%, SD 73%, PD 14%<br>Placebo: PR 2%, SD 51%, PD 42% | Everolimus: 11.04<br>Placebo: 4.6 | Most common adverse effects: stomatitis 64%, rash 49%, diarrhea 34%, fatigue 31%, infections 23%<br>Severe side-effects: pneumonitis 12%, interstitial lung disease 2% |

CR, complete response; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

### Treatment with Radionuclides

Radiolabeled SST analog therapy (peptide receptor radionuclide therapy [PRRT]), aims at delivering potentially toxic radioactivity through radionuclides that bind to PanNET bearing SSTR. As the majority of PanNET are grade 1/2 tumors, they express on their surface somatostatin receptors, and can therefore be selected for treatment with PRRT on the basis of the intensity of tumorous tissue uptake during SRS. Treatment is restricted to tumors showing considerable uptake, and tumors demonstrating uptake higher than that of the liver are the ones that exhibit the best therapeutic response. Two radionuclides, namely $^{90}$Y-DOTA-TOC (DOTA-Tyr-octreotide) and $^{177}$Lu-DOTA-TATE (DOTA-Tyr-octreotate), have been extensively used in the treatment of functioning and nonfunctioning PanNET. A large nonrandomized study, which included 310 patients with GI-NET (91 PanNET) showed an overall 30% radiologic response that was more pronounced in patients with PanNET; the median time to progression was 40 months [20]. A similar study evaluated more than 1000 patients with NET (342 PanNET) treated with $^{90}$Y-DOTA-TOC; 34.1% of them experienced a radiologic response, 15.5% a biochemical response (a >50% reduction in tumor markers), and 29.7% a clinical response (improvement of symptoms of either a clinical syndrome in the case of a functioning tumor or of symptoms of mass effect to surrounding structures in the case of a nonfunctioning tumor). Patients who experienced any response had a much better survival than nonresponders after a median follow-up of 23 months [21]. In a recent analysis of 810 patients with various NET treated with these radionuclides, either singly or in combination, permanent nephrotoxicity occurred in 1.5% (mostly with $^{90}$Y), whereas myelodysplasia and leukemia occurred in 2.35 and 1.1%, respectively [22].

Studies combining different forms of medical treatments are currently emerging in an attempt to increase their efficacy and reduce potential side-effects.

## Conclusions

Treatment of PanNET has evolved significantly over the last decade following the introduction of newer therapeutic agents and the accumulation of good-quality information regarding the efficacy and safety of a number of therapies. As the majority of symptoms related to functioning PanNET are responsive to SST analogs, attention has mainly focused on control of tumor growth. SST analogs can be used for tumor growth control, mainly resulting in disease stabilization. For progressive tumors, or tumors with a relatively high Ki-67 labeling index (>10%), molecular-targeted agents can result in disease stabilization, but without achieving significant tumor shrinkage. Temozolomide- or streptozotocin-based chemotherapy is used in patients with rapidly progressive tumors and/or significant tumor bulk. PRRT can also be applied to tumors exhibiting significant uptake to SRS. High proliferative grade 3 PanNEC are treated with cisplatin-based chemotherapy but exhibit an overall worse prognosis. There is a clear need for the development of tumor markers that could help in individualization of treatment. Several societies have proposed therapeutic algorithms based on the findings of recent studies and acquired cumulative experience, as the one suggested (Fig. 128.1). However, several issues still remain unresolved, and it is hoped that these will be addressed by the findings of a number of ongoing prospective multicenter studies.

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# 129

# Interventional Radiology in the Treatment of Pancreatic Neuroendocrine Tumors

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## Type of Interventional Radiology Treatment

Interventional radiologic therapy is indicated as a treatment for hepatic metastases only from a well-differentiated pancreatic neuroendocrine tumor (PanNET). This is compatible for grade 1 and 2 tumors, according to the World Health Organization classification [1], but not for those from poorly differentiated pancreatic neuroendocrine carcinomas (grade 3). The reasons for this preference are that well-differentiated PanNETs show morphologically well-demarcated lesions and are relatively slow growing, even in the metastatic sites, and over 90% of the blood supply to the metastatic lesions in the liver is reported to be provided by the hepatic artery [2] (Fig. 129.1). Therefore, as is the case for hepatocellular carcinomas, transarterial embolization (TAE), transarterial chemoembolization (TACE), and radiofrequency ablation (RFA) are applied for metastatic PanNET in the liver. Microwave coagulation therapy, laser interstitial thermotherapy, and cryotherapy have recently been incorporated as potential advances in the various effective treatment options for unresectable PanNET.

Hepatic metastases from PanNET are morphologically classified into three patterns according to the European Neuroendocrine Tumor Society (ENETS) guidelines [3]: simple (unilobar or limited), complex (bilobar), and diffuse pattern. Simple and complex patterns without extrahepatic metastases are usually treated by curative resection, and the diffuse pattern is treated by multidisciplinary treatment including systemic medication and surgical debulking with regional ablation therapies such as TAE/TACE and RFA. Owing to recent advances in surgical techniques and the development of systemic medication using anticancer agents, molecular-targeted drugs, and peptide receptor analogs, the roles of TAE/TACE and RFA have been limited to providing relief of the hormonal symptoms caused by the rapid growth of the tumor or the adjuvant therapy during or after operation [3–7].

## TAE/TACE

TAE/TACE are involved in the multidisciplinary treatment of unresectable hepatic metastases from well-differentiated PanNET. Therefore, the effects of TAE/TACE alone on survival remain unclear; however, TAE/TACE are reported to provide a decrease of 50–90% in the symptoms caused by hormonal hypersecretion, with a prolonged effect of 6–53 months, and a time to progression of 10–19 months [2]. The reported 5-year survival rate of patients treated with TAE/TACE ranges widely from 0 to 80%, because the conditions, such as the range of tumor spread, timing of the TAE/TACE during multidisciplinary treatment, and other treatments subsequently performed after TAE/TACE, differ among the reports [2].

In TAE, histoacryl, in conjugation with lipiodol, forms particles with or without lipiodol, poly(vinyl alcohol) foam, and microspheres using glass or resin, which are used as embolic agents [2]. Several chemotherapeutic drugs, such as doxorubicin, streptozocin, dacarbazine, adriamycin, cisplatin, and mitomycin C, are used in conjugation with lipiodol during TACE [2,7]. A recent trend in transarterial techniques is radioembolization using a

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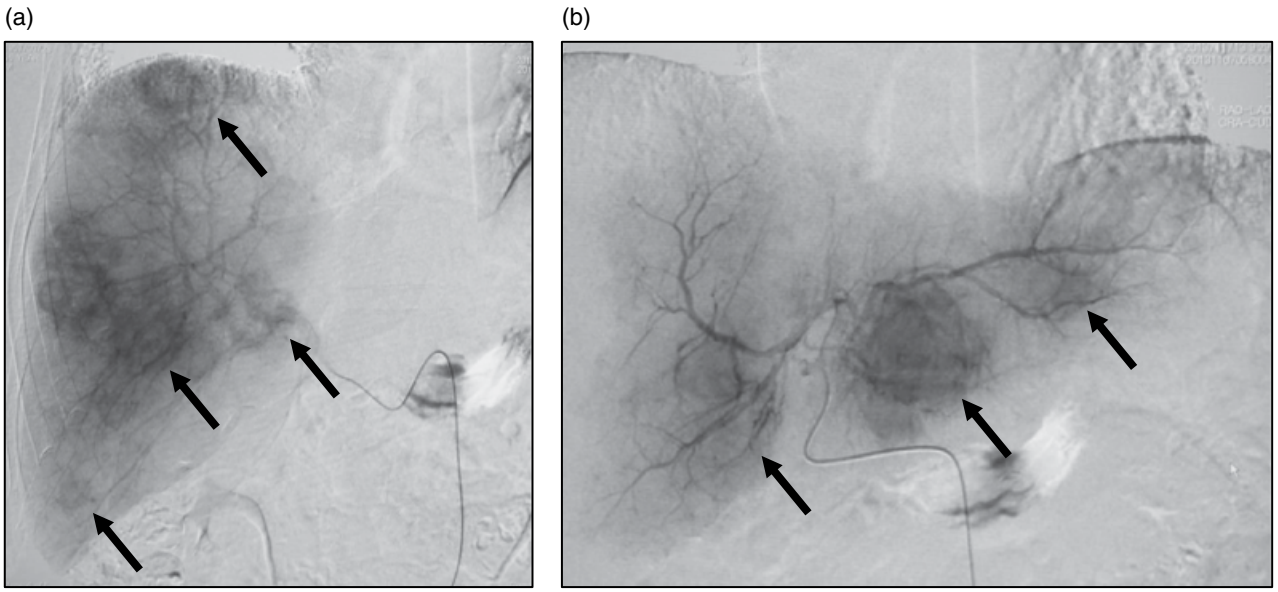


**Figure 129.1** Staining of hepatic metastases during angiography. Results of tumor staining during angiography from the right hepatic artery (a) and the left hepatic artery (b) in patients with VIPoma. Arrows indicate tumor staining. *Source:* Parts (a) and (b) provided by Dr Tetsuhide Ito, Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University.

radioconjugated somatostatin analog. Radioembolization using [$^{90}$Y]lanreotide provides a radiologic response of 22.5–63% and median survival times of 22–70 months [7]. The regional concentration of chemotherapeutic drugs by TACE is reported to be 10–20 times higher than that by systemic chemotherapy; however, the additional effect of chemotherapeutic drugs on TAE alone remains unclear [2]. Repeat TAE/TACE would lead to the disruption of the arterial endothelium and then acceleration of the collateral formation, resulting in difficulties with further TAE/TACE.

Morbidity and mortality after TAE/TACE are reported to be 0–28% and 0–5.6%, respectively [2]. Complications in relation to TAE/TACE include hepatic abscess, hepatic dysfunction (sometimes hepatic failure arising from infarction), pleural effusion, and gastric ulcer. Many patients experience post-TAE/TACE syndrome symptoms, including transient fever elevation, leukocytosis, and increase in hepatic enzymes, most of which are improved within a few days after TAE/TACE. Regional chronic infection in the biliary tree is a risk factor for hepatic abscess after TAE/TACE because the biliary system has a blood supply exclusively from a hepatic artery, and TAE/TACE would lead to biliary ischemia. Therefore, this technique should be avoided in patients who have a history of biliary intervention, including those after pancreatoduodenectomy or endoscopic sphincterotomy. In addition, patients who have portal neoplastic thrombus or hepatic ascites are also contraindications for TAE/TACE because of the high risk of post-TAE/TACE hepatic failure.

## RFA

RFA can be performed during open surgery and also laparoscopic operation, or by computed tomography or ultrasound-guided percutaneous techniques. One report [8] demonstrated that RFA alone for hepatic metastases from well-differentiated PanNET can provide a favorable prognosis comparable to that with hepatic resection; however, the indicated cases were limited to patients who had a relatively small size and small number of metastatic lesions. At present, RFA is being performed for persistent viable lesions as an adjuvant therapy during or after hepatic resection, or after TAE/TACE [3–7] (Fig. 129.2). Adverse events related to RFA include pneumothorax, hepatic abscess, perforation of the gastrointestinal tract, and skin burn; however, major and fatal complications are rarely observed [7]. RFA for patients who have a history of biliary intervention should be avoided for the same reason as mentioned for TAE/TACE, where there is a risk of fatal hepatic abscess.

Use of RFA for primary PanNET has recently been reported. An Italian group [9] described their experience with 10 patients, seven patients having their tumor in the proximal part of the pancreas and three in the distal part of the pancreas, with a mean tumor diameter of 16 mm (range, 9–29 mm). All the lesions were completely ablated by the percutaneous route in seven cases, under laparotomy in two cases, and under laparoscopy in one case. Mild pancreatitis occurred in three patients, all of whom were cured within 2 days. No recurrence was observed during the median surveillance period of

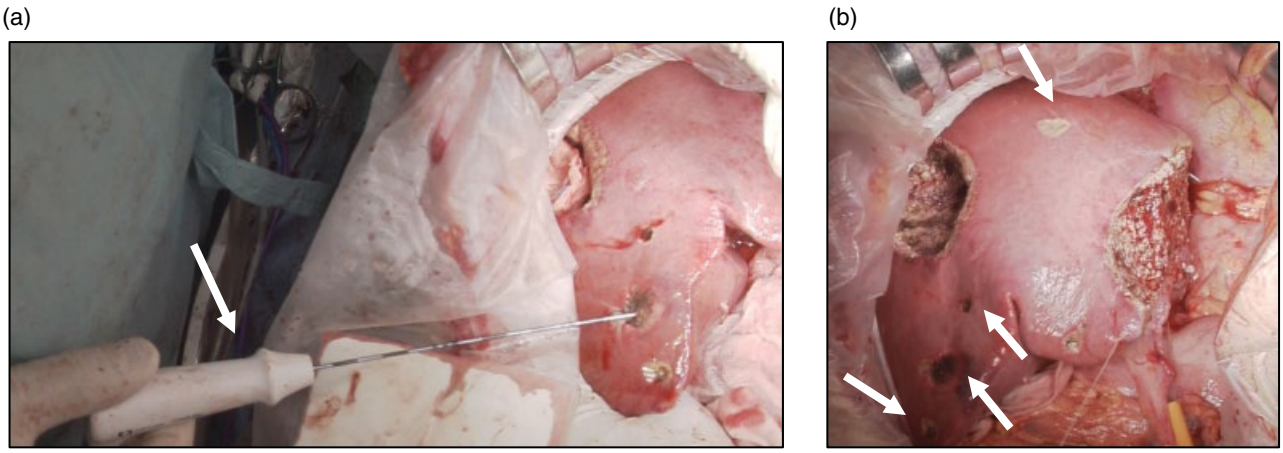


**Figure 129.2** Surgical debulking using radiofrequency ablation for hepatic metastases from pancreatic neuroendocrine tumors. (a) Radiofrequency ablation using a tip device (arrow). (b) Completion of the debulking operation. Arrows indicate the trace of the tip device for radiofrequency ablation. The patients are the same as those in Fig. 129.1.

30 months (range, 12–60 months). Although this intervention can be applicable for relatively small-sized primary PanNET in patients who are in generally poor condition, further investigations using a larger study population and with long-term surveillance are needed to determine the adequacy of this procedure.

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# Surgical Management of Endocrine Tumors of the Pancreas

## 130

## Surgical Treatment of Endocrine Tumors: Enucleation

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### Introduction

The history of pancreatic surgery is closely connected to pancreatic neuroendocrine tumors (PanNET), namely surgery for malignant and benign insulinoma [1,2]. Although not evidence based at the time, enucleation used to be preferred over resection because the endocrine tumor was almost always cured and the patient developed few and mostly minor surgical complications [3]. Some 90 years of surgical experience with small, clinically benign PanNET later, the important role of enucleation is still uncontroversial. However, the growing number of pancreatic incidentaloma, unearthed by advanced imaging techniques [4–10], has multiplied the challenge of managing these tumors appropriately. Risk stratification, using proliferation markers such as frequency of mitosis and the Ki-67 index in the tumor [11–14], informs clinical treatment plans such that the therapy selected is commensurate with the risk profile of the tumor at hand. Interventions range from expectant observation in the absence of hormone excess to enucleation, and ultimately to pancreatic resection.

### Observation Versus Surgery for Small Sporadic, Benign-Appearing, Nonfunctioning Pancreatic Neuroendocrine Tumors

Incidental small, nonfunctioning PanNET feature less aggressive growth patterns on histopathology compared with symptomatic PanNET [15]. Primary tumor size, reflecting a biological continuum, positively correlates with tumor grade [16], Ki-67 index [17], and the presence of lymph node and distant metastases [17–19]. The smallest tumors with lymph node metastases measured 12–19 mm in greatest dimension [17,18]. For PanNET smaller than 2 cm, disease-related mortality in most studies was close to zero [17,19–21]. Without surgical intervention, 13% [20] and 16% [17] of these sporadic nonfunctioning PanNET enlarged by more than 20%, yielding an estimated tumor growth of 0.12 mm per year [20]. In carefully selected groups of patients with nonfunctioning PanNET who were managed without surgery, no disease progression was seen after 18 [20], 45 [21], and even 283 months [17]. Provided that there is no clinical evidence of metastases and tumor growth, sporadic, incidentally detected nonfunctioning PanNET smaller than 15 mm are good candidates for expectant observation.

### Preoperative Imaging and Assessment of Proliferative Tumor Activity

In patients with small PanNET, preoperative imaging using endoscopic ultrasonography [22–25], cross-sectional (computed tomography [CT]; magnetic resonance imaging [MRI]) or functional (octreoscan; [$^{18}$F]fluoro-2-deoxy-D-glucose positron emission tomography [FDG-PET]/CT) imaging [26–30] informs the approach to the surgical target (laparoscopic versus conventional open surgery) and the method of tumor clearance (enucleation versus pancreatic resection). Unlike nonfunctioning PanNET, some functioning tumors, specifically very

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**Table 130.1** Indications for enucleation of PanNET.

Small nonfunctioning PanNET 1–2 cm, or insulinomas up to 2 cm in greatest dimension and

- benign appearing and low grade, based on standard and functional imaging, and, if performed, Ki-67 immunocytology
- without suspicious lymph node enlargement or distant metastases
- without wide and deep involvement of the pancreas
- without attachment to the main pancreatic duct on intraoperative ultrasonography.

Enucleation can be performed as a standalone procedure, or in combination with pancreatic resection for multiple MEN1-associated PanNET.

For PanNET located in the posterior head of the pancreas, both enucleation and head dorsal pancreatectomy may be considered.

Pancreatic gastrinomas should be treated preferentially by standard pancreatic resection irrespective of size because as many as 80–90% may be malignant and node-positive.

small insulinomas, may evade standard imaging. In this scenario, selective arterial stimulation is indicated to narrow down the location of the hormone-producing pancreatic tumor [31]. Small tumors residing in the anterior pancreatic head and the pancreatic body and tail usually qualify for enucleation unless they are situated deep down inside the pancreas and involve the main pancreatic duct (Table 130.1; Figs 130.1, 130.2, and 130.3). Conversely, deep-seated pancreatic tumors and tumors adherent to, or invading, the main pancreatic duct (Figs 130.1 and 130.3) necessitate pancreatic resection, with partial or complete resection of the pancreatic head, body, or tail depending on the situation. Preoperative imaging, whatever technique is being used, cannot exclude tumor involvement of the main pancreatic duct. It is crucial in this setting that intraoperative ultrasonography be used to identify the pancreatic duct and to rule out multifocal lesions before deciding on whether to embark on enucleation or pancreatic resection [32].

Preoperative risk stratification is performed by endoscopic ultrasound-guided fine-needle aspiration cytology to establish the diagnosis and allow tumor grading, supported by Ki-67 immunocytology to determine the proliferative tumor activity [32–35]. To make that determination correctly, the cytopathologist must be sufficiently experienced and cognizant of the methodologic limitations [33]. There is also a paucity of data about the prognostic significance of preoperative grading and Ki-67 immunocytology for small pancreatic tumors so that the benefits of enucleation versus pancreatic resection based on these findings remain unclear.

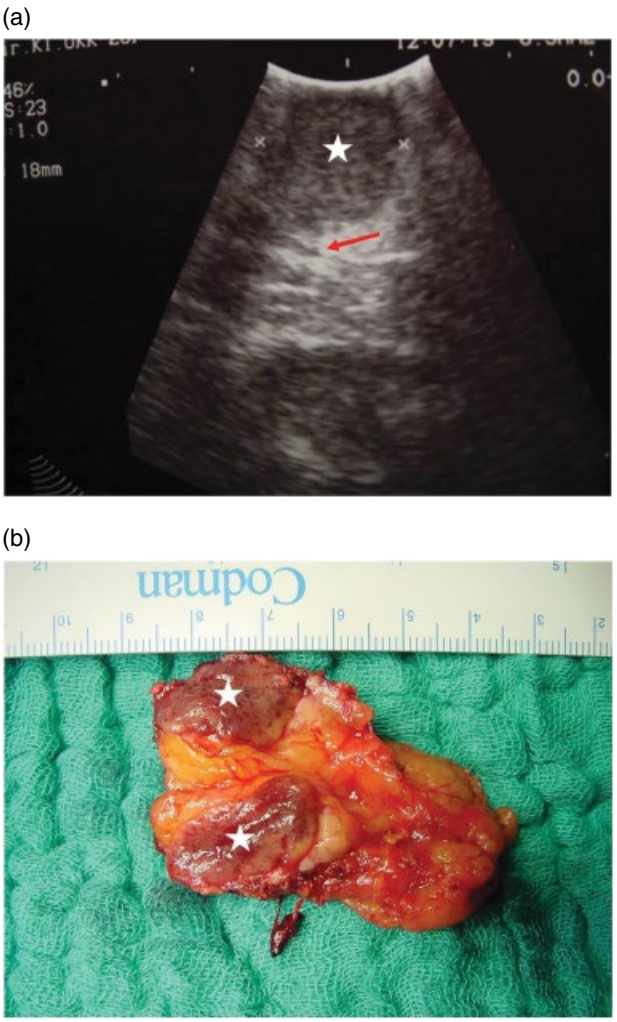


**Figure 130.1** Adherence of a pancreatic body insulinoma (asterisk) to the main pancreatic duct (arrow) (a) that was laparoscopically resected, instead of enucleated, because of this fact (b).

## Surgical Technique of Enucleation

Enucleation is the surgical technique of choice for small, benign-appearing or low-grade functioning and nonfunctioning PanNET without clinical evidence of metastases or involvement of the main pancreatic duct [36–46]. Unless the tumor is situated in the posterior part of the pancreatic head [47], enucleation of tumors from the head, body, and tail of the pancreas is technically feasible. The key advantage of enucleation is reduced surgical trauma, with better postoperative endocrine and exocrine pancreatic function. Major disadvantages include the considerable risk of pancreatic fistula and the fairly low risk of late recurrence and metastases if pancreatic tumors should turn out to be malignant and no lymph node dissection was carried out at the time.

Enucleation of the PanNET is performed after ultrasonographic evidence that the main pancreatic duct is

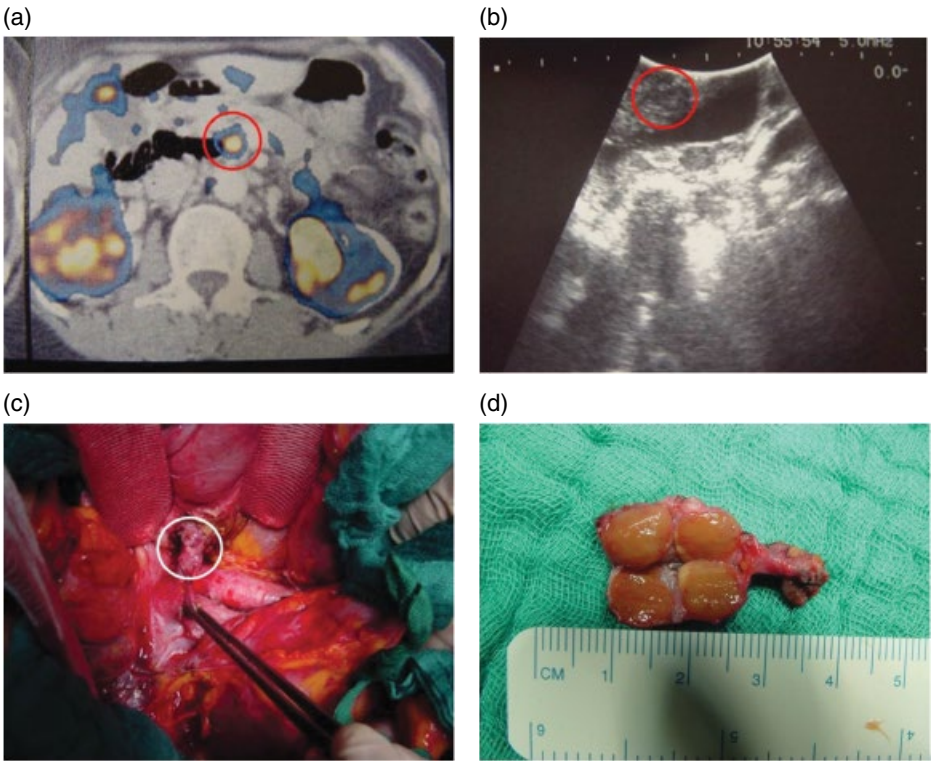


**Figure 130.2** Enucleation of a multiple endocrine neoplasia type 1 (MEN1)-associated insulinoma (encircled) in the uncinate process of the pancreas enucleated via open relaparotomy. (a) Preoperative [$^{18}$F]DOPA PET/CT; (b) intraoperative ultrasonography; (c) intraoperative view showing tumor enucleation; (d) surgical specimen.

clear. Particular care must be taken to dissect the pancreatic parenchyma around the tumor capsule meticulously, without opening it or resecting adjacent pancreatic tissue (Figs 130.2 and 130.3). Great emphasis is laid on closing small pancreatic ducts and vessels using fine sutures or clips. Upon confirmation that the surgical margins of the enucleated tumor specimen are clear on frozen section, the pancreatic capsule is closed using atraumatic absorbable single or running 5-0 or 6-0 sutures. Surgical drains are routinely placed and subsequently removed depending on the amount of, and the enzyme concentrations in, the fluid drained. When the main pancreatic duct has been inadvertently opened, it may be safer not to attempt to over-sew the leak but to convert the planned enucleation into a segmental (pancreatic body) or distal (pancreatic tail) resection or fashion a Roux-en-Y jejunal loop onto the pancreatic defect to drain the leak [46].

## Short- and Long-Term Outcomes After Enucleation

In a recent systematic review and meta-analysis of enucleation versus standard pancreatic resection for small, mainly (69%) neuroendocrine tumors [48], enucleation was performed laparoscopically in 9% of operations. Enucleation was superior to standard pancreatic resection, leading to shorter operations ($P < 0.001$) with fewer blood loss incidents ($P < 0.001$), inferior regarding the overall fistula rate (33 versus 20%) and comparable in the length of hospitalization, postoperative mortality, and the percentage of reoperation. Grade B/C fistula, as defined by the International Study Group [49], was slightly less frequent after enucleation than after standard pancreatic resection (44 versus 50%). Major contributors to postoperative pancreatic fistula included deep enucleations [38] and enucleation of PanNET from the head and uncinate process of the pancreas [36,37], but not surgical (laparoscopic versus open) approach [38].

With respect to long-term oncologic outcome, enucleation was not inferior to standard pancreatic resection when the tumor was low grade, surgical margins were clear on definitive histopathology, and locoregional or distant metastases were absent [48,50,51].

After enucleation of <2 cm nonfunctioning PanNET, late recurrences and metastases were found in 8% of patients [52]. The need to dissect regional lymph nodes in addition to clearing these tumors from the pancreas has sparked a lot of debate [53–59] because lymph node metastasis may have a negative prognostic impact on survival [53–57]. Lymph node metastases can be present in up to 25% of patients with nonfunctioning

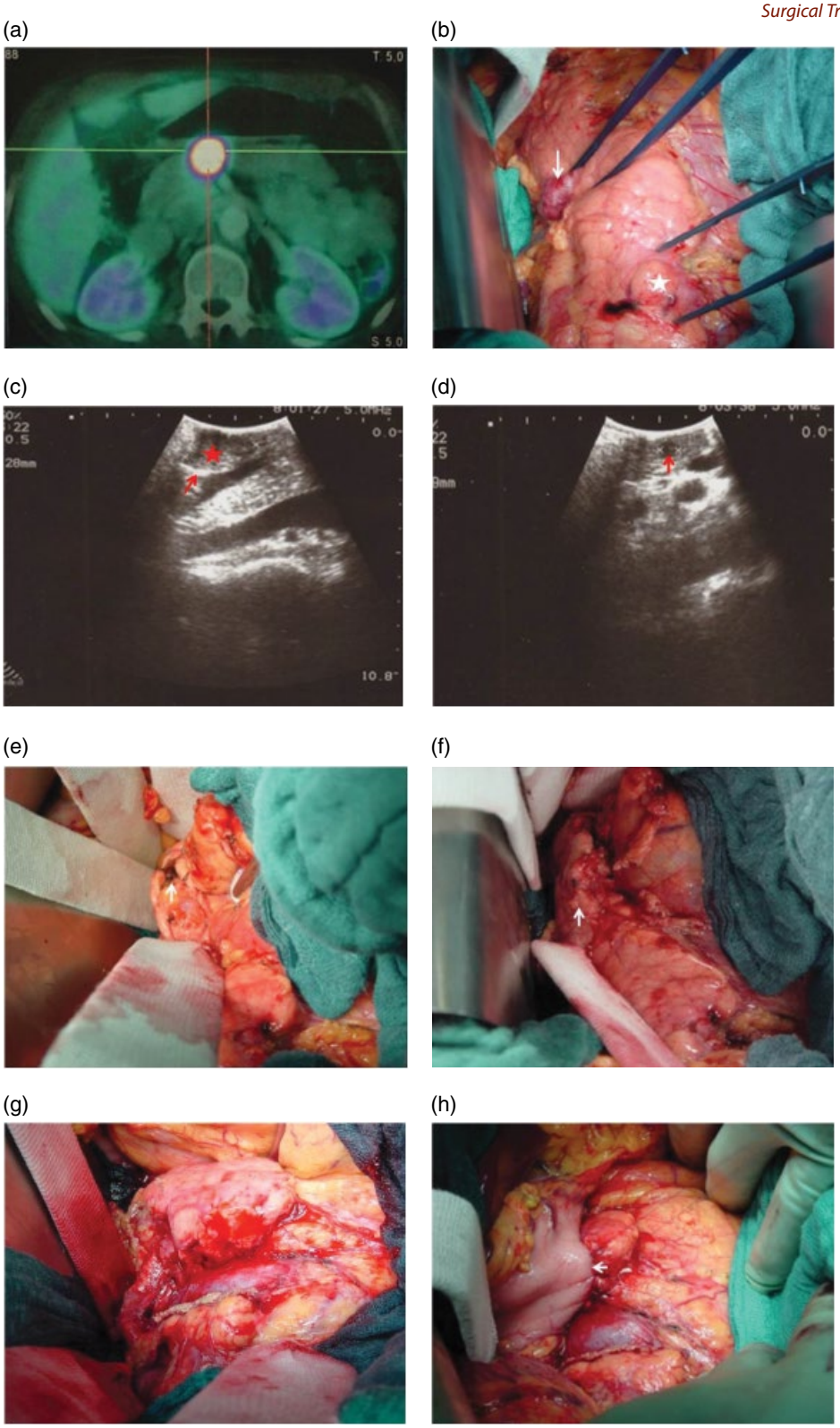


**Figure 130.3** Combined pancreatic tail enucleation and central pancreatectomy for multiple MEN1-associated nonfunctioning neuroendocrine pancreatic tumors. (a) Preoperative [$^{68}$Ga]DOTA-NOC (DOTA-Nal-octreotide) PET/CT showing a PanNET in the body of the pancreas adjoining the posterior pancreatic vascular axis; (b) intraoperative view picturing a PanNET at the body (asterisk) and another PanNET at the tail of the pancreas (arrow); (c) intraoperative ultrasonography revealing close proximity of the 25 mm pancreatic body PanNET (asterisk) to the mesenterico-portal vein and the main pancreatic duct (arrow); (d) intraoperative ultrasonography delineating the 6 mm PanNET in the pancreatic tail (arrow); (e) intraoperative situs of the pancreatic tail after enucleation (arrow); (f) intraoperative view of the closed pancreatic defect (arrow); (g) Intraoperative situs after central pancreatectomy; (h) intraoperative view of the pancreas reconstructed by pancreatogastrostomy (arrow).

PanNET no larger than 2 cm [53–55]. Preoperative identification of involved lymph nodes continues to be challenging [58], and concomitant lymph node dissection can drive up surgical morbidity. Balancing the benefits against the risks, it becomes immediately apparent that the recommendation for or against lymph node dissection must be individualized considering the circumstances of the case. There is evidence to suggest that patients with small non-grade 1 grade tumors and clinically suspicious lymph nodes [56] benefit more from standard pancreatic resection and lymph node dissection than from enucleation alone. Otherwise, enucleation, preserving more pancreatic parenchyma, caused fewer endocrine (1 versus 11%) and exocrine (0 versus 25%) pancreatic failures than standard pancreatic resection [48].

## Outcome After Laparoscopic Enucleation

The technical feasibility of laparoscopic enucleation of PanNET, alone or in conjunction with lymph node dissection, is widely recognized [60–66]. Prospective randomized controlled trials comparing laparoscopic with open enucleation have not been performed [60]. Retrospective studies hint at a higher risk of pancreatic fistula after laparoscopic enucleation than laparoscopic resection [64]. Enucleations of tumors from the pancreatic head are associated with more pancreatic leaks than left-sided enucleations [63], regardless of whether laparoscopic or conventional open enucleation has been carried out [65]. There is a dire need for more research to clarify the long-term oncologic and functional outcome after laparoscopic enucleation.

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# Local Treatment of Endocrine Tumors: Duodenum-Preserving Partial or Total Pancreatic Head Resection and Pancreatic Middle-Segment Resection

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## Background

Pancreatic neuroendocrine tumors (PanNETs) are increasingly more frequent, accounting for 10% of all benign tumorous lesions of the pancreas and 2% of all pancreatic neoplasms [1]. Hormonally active and inactive PanNETs develop from the islet cell parenchymal compartment, which constitutes 2–10% of the pancreatic tissue. owing to the systematic use of sensitive imaging modalities, the incidence of nonfunctional pancreatic neuroendocrine adenomas has increased more than twofold in the last 16 years and of small nonfunctional PanNETs (<2 cm) more than sevenfold [2]. The natural history of asymptomatic nonfunctioning adenomas of <2 cm is poorly understood. In contrast to most hormonally active PanNETs, functionally inactive endocrine tumors produce signs only late in the clinical course, which are mostly unspecific. In addition to well-established radiologic and endoscopic ultrasound (EUS) investigations, the measurement of specific hormones in the peripheral blood, somatostatin-receptor scintigraphy, and positron emission tomography (PET) are diagnostic measures that establish in most patients the diagnosis, type, and location of the tumor. Multifocality of PanNETs is well known, particularly in hereditary syndromes, including multiple endocrine neoplasia type 1 (MEN1) and von Hippel–Lindau syndrome. Neoplasms of ≤5 mm have been defined as microadenomas. These are mostly nonfunctioning, rarely grow, and are reported in autopsy studies in up to 10% of cases [3]. Two major staging systems have been proposed. In 2006, the European Neuroendocrine Tumor Society (ENETS) developed a tumor–node–metastasis (TNM) classification [4]. In 2010, the American Joint Commission on Cancer (AJCC) introduced a new classification of endocrine pancreatic tumors with adapted criteria from the staging of exocrine pancreatic adenocarcinoma [5]. Low-risk neuroendocrine carcinomas (NECs) are classified as T1N0, tumor grade 1/2, mitotic rate <20, and Ki-67 > 5% [3–5].

## Surveillance or Treatment of Neuroendocrine Tumors of the Pancreas?

Neuroendocrine neoplasms of the pancreas are a heterogeneous entity and display an unpredictable biological behavior [6]. The progress in diagnostic accuracy of small neoplastic lesions of the pancreas has led to a challenging setting of whether to observe or to operate. All gastroenteropancreatic neuroendocrine tumors are considered to be potentially malignant [7,8]. Only surgical treatment of benign PanNETs and low-risk NECs offers the chance of a cure. Up to 70% of all PanNETs are insulinomas, which most frequently display functional activity. Insulinomas are benign in approximately 90% of cases, independently of the symptoms. Functionally inactive adenomas account for 30–50% of all PanNETs, usually detected late in the clinical course. The risk evaluation focuses on signs of proliferative activities of the lesion. A mitotic count <2, 2–20, >20, Ki-67 index <2, 3–20, >20%, tumor growth, presence of enlarged lymph nodes, and distant metastases are established criteria of malignant transformation [7,8]. Lymph node metastases have been observed in up to 25% of patients with nonfunctioning PanNETs with a tumor diameter of <2 cm [9]. Tumor growth in small, nonfunctioning PanNETs was measured as 0.12 mm/year [10]. Long-term observation of patients with nonfunctioning PanNETs exhibited no disease progression after 45 and 283 months [9,10].

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After a median follow-up of 34 months, the mean tumor growth of small, sporadic, nonfunctioning PanNETs has been estimated to be 0.01 mm/year [9]. Nonfunctional PanNETs of <10 mm without clinical signs of tumor growth have a low risk of cancerous transformation; an annual monitoring protocol is recommended [11]. A risk–benefit analysis for surveillance or surgical management is recommended for each individual patient. For local advanced and metastatic NECs, an oncologic resection, balanced with cytoreductive and/or antihormonal medication and/or ablative treatment, is suggested.

## Indication for Surgical Treatment of PanNETs

Approximately 50–60% of PanNETs are located in the pancreatic head and neck, being predominantly nonfunctional PanNETs [12], and 40% in the body and tail. Pathomorphologically, endocrine tumors of the pancreas occasionally demonstrate cystic changes, calcification, and intralesional bleeding. The most import criteria for surgical decision making are clinical symptoms, tumor size >2 cm, and a risk calculation for malignancy. A neoplasm of >2 cm, positive nodule status, and a grading of mitoses >20 and Ki-67 index >3% are considered criteria for surgical management [13] (Table 131.1). Of prognostic significance are local infiltration and a neoplasm size >4 cm. For nonfunctional PanNETs, irrespective of tumor size, the Japanese National Comprehensive Cancer Network Guidelines recommend surgical resection, including that of regional lymph nodes. Lymph node metastases have been observed in patients with PanNETs of a maximal size <20 mm [9,14,15]. However, PanNETs with tumor size <2 cm with a histologic grading of G3 and a Ki-67 index >20% have a high probability of developing a neuroendocrine cancer. Sporadic gastrinoma, glucagonoma, and VIPoma of the pancreas display malignancy in >60–80% of cases, irrespective of tumor size. Approximately 10% of sporadic hormone-active insulinomas are malignant. MEN1-associated insulinoma infrequently shows signs of malignancy.

## Parenchyma-Sparing Local Resection of Neuroendocrine Tumors of the Pancreatic Head

A pancreatoduodenectomy (PD) of the Kausch–Whipple type is currently the surgical standard for neuroendocrine tumors of the pancreatic head. However, this multiorgan resection is associated with a considerable risk for early procedure-related complications and late outcome reduction of endocrine and exocrine pancreatic functions [16,17]. To maintain the quality of life of the patients, in recent years, local, parenchyma-sparing tumor extirpation techniques for benign neoplasm of the pancreas have been increasingly used. For small PanNETs up to a maximum diameter of 2 cm, a tumor enucleation is the favored option (see Chapter 130). However, deep enucleation of pancreatic head lesions is associated with increased morbidity regarding postoperative pancreatic fistula (POPF) grades B + C [18]. The limitations of enucleation of neuroendocrine neoplasms are a tumor size >3 cm, close proximity of the lesion to the pancreatic main ducts (PMD), and a high frequency of risk of POPF grades B + C [19].

## Duodenum-Preserving Total or Partial Pancreatic Head Resection

For benign tumors of the pancreatic head, parenchyma-sparing, local head resections are increasingly applied to avoid a classical Kausch–Whipple resection. Duodenum-preserving total or subtotal pancreatic head resection have the potential for a local tumor extirpation associated with a low procedure-related postoperative morbidity

**Table 131.1** Surveillance or local, parenchyma-sparing pancreatic resection of benign PanNETs and low-risk NECs.

| Diagnosis | Symptoms | Treatment |
|---|---|---|
| PanNETs | Clinical symptomatic adenomas | Surgery |
| | Functional adenomas | Surgery |
| | Hormone-active tumors >2 cm | Surgery |
| | Tumors with signs of growth and/or Ki-67 > 3% | Surgery |
| | Small non-G1 adenomas <2 cm and enlarged lymph nodes | Surgery |
| | Nonfunctioning adenomas <10–15 mm | Surveillance |
| MEN1 | All adenomas >2 cm | Surgery |
| Gastrinoma | | Classical resection |
| Malignant adenoma | Local advanced stage ± metastases | Oncologic resection including hepatic metastases |

*Sources:* [4,7,14,15].

and preservation of the exocrine and endocrine pancreatic functions compared with the preoperative status [16]. The advantages of duodenum-preserving total head resection (DPPHR) are underlined by randomized clinical trials comparing duodenum-preserving local resection with PD in patients with inflammatory head tumor (see Chapter 58). The size and location determine the application of a partial or total head resection. Of 431 patients who underwent a local tumor resection applying a DPPHR, 11% suffered a PanNET [17] (Table 131.2). The mean tumor size was 3.1 cm. In a subtotal pancreatic-head resection for tumors located in the pancreatic head but remote from the duodenal wall and the intrapancreatic CBD, a careful dissection of the pancreatic tissue from the portal vein is surgically demanding (Fig. 131.1a). When a PanNET is located in the uncinate process, a partial pancreatic-head resection resecting the anatomical uncinate process is recommended, using a jejunal loop for reconstruction (Fig. 131.1b). The surgical technique of total head resection with dissection of the pancreatic tissue from the peripapillary duodenum and preservation of nutritive arterial arcades is well established (Figs 131.2 and 131.3). Dissection of regional lymph nodes is standardized and readily executable. The low frequency of surgery-related complications of 12% and a POPF grades B + C rate of 13% compares favorably with the published figures for early postoperative morbidity after a PD. DPPHR was associated with a very low 90-day mortality of 0.5% [16] (Table 131.3). The major advantage of duodenum-preserving total and subtotal pancreatic head resection in the long-term outcome is the preservation of the exocrine and endocrine pancreatic functions. Long-term measurements showed an almost complete preservation of the exocrine and endocrine pancreatic functions after DPPHR for neoplastic tumors. Recurrence after DPPHR was low.

## Pancreatic Middle-Segment Resection

Pancreatic middle-segment resection of 912 patients was applied to 31% of patients suffering a neuroendocrine tumor [20] (Table 131.2). The mean tumor size was 2.9 ± 0.98 cm. Pancreatic middle-segment resection is an alternative to a pancreatic left resection for benign lesions of the pancreas. Pancreatic left resection results in a significant reduction in insulin production, leading to a deficit in insulin secretion, and thus to new-onset diabetes mellitus

**Table 131.2** Local surgical treatment of neuroendocrine pancreatic tumors and other neoplasms: frequency of extirpation procedures DPPHR and pancreatic middle segment resection (PMSR) for PanNETs.

| Treatment | Patients | PanNETs | Cystic neoplasms | Others | Tumor size (cm) |
|---|---|---|---|---|---|
| Duodenum-preserving partial or total head resection | 431<br>100% | 10.8% | 70% | 20% | 3.1 ± 0.75 |
| Pancreatic middle-segment resection | 912<br>100% | 31% | 63% | 7% | 2.9 ± 0.98 |

*Source:* Modified from Beger et al. [20].

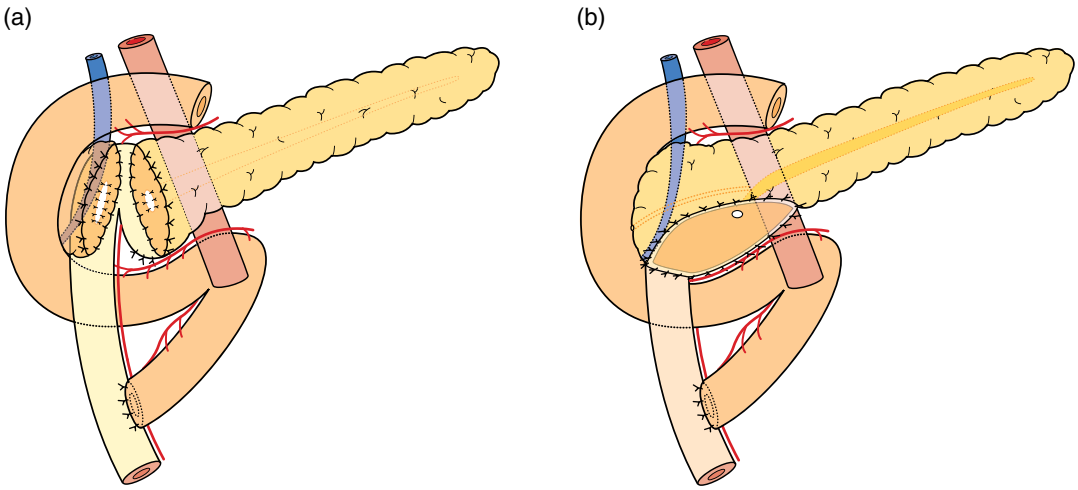


**Figure 131.1** (a) Partial, segmental pancreatic head resection for neuroendocrine tumor; (b) resection of the uncinate process for benign neuroendocrine tumor.

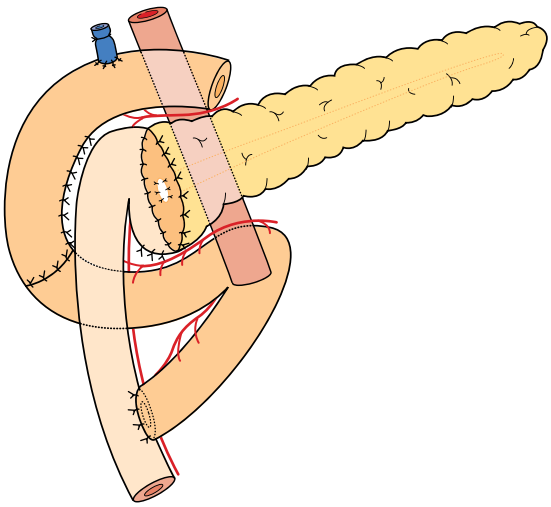

**Figure 131.2** Total pancreatic head resection preserving the duodenum and intrapancreatic common bile duct.

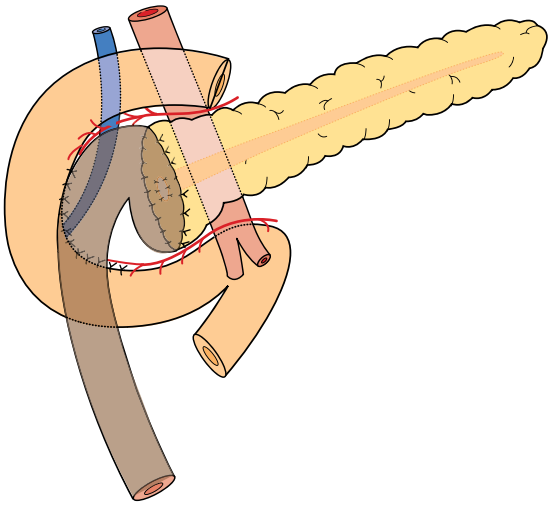

**Figure 131.3** Duodenum-preserving total pancreatic head resection for large PanNETs and low-risk NECs with segment resection of the peripapillary duodenum and the intrapancreatic common bile duct.

in 20–40% of cases and in 50% of the patients to a persistent exocrine insufficiency. The frequency of severe postoperative procedure-related complications was 16%. In 35% of cases, a fistula developed, of which 66% were of grades B + C and 5% displayed local hemorrhage, which required reoperation, involving reintervention and blood transfusion (Table 131.3). The crucial point of pancreatic middle-segment resection is surgical handling of the proximal pancreatic stump. Whereas the left pancreas is secured by a pancreaticojejunostomosis or an anastomosis with the stomach, the proximal pancreatic stump is mostly handled by a simple closure. The frequency of postoperative hemorrhage is caused by a surgical lesion of the splenic artery or vein during the resection process. After an extended middle-segment resection of a large pancreatic segment, the risk increases for a permanent endocrine and exocrine insufficiency in the long-term outcome.

## Conclusion

Neuroendocrine neoplasms of the pancreas are an increasingly more frequent entity of benign pancreatic tumors. Surgical extirpation is the only treatment modality to cure the patients with symptomatic adenoma and tumors at risk for malignancy. Local, parenchyma-sparing tumor resection is associated with a low level of postoperative complications, very low hospital mortality, and preservation of pancreatic functions. Duodenum-preserving pancreatic head resection for tumorous lesions in the pancreatic head and pancreatic middle-segment resection for body and tail tumors are recommended.

## Acknowledgment

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**Table 131.3** Local surgical treatment of neuroendocrine and cystic neoplasms of the pancreas: frequency of surgery-related complications after DPPHR and PMSR.

| | | Postoperative morbidity (%) | | | | | |
|---|---|---|---|---|---|---|---|
| **Treatment** | **Patients** | **Overall** | **Severe** | **Hemorrhage (%)** | **Fistula (%)** | **Hospital mortality (%)** | **Recurrence (%)** |
| DPPHR-P/T | 431 | 42 | 12 | – | 20 | 0.5[a] | 3 |
| PMSR | 912 | 48 | 16 | 5 | 35 | 0.8 | 4 |

[a] 90-day mortality.
*Source:* Modified from Beger et al. [20].

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# 132

# Surgical Treatment of Endocrine Tumors: Major Oncologic Resection

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## Introduction

Over the past two decades, pancreatic neuroendocrine tumors (PanNET) in general, not just small tumors <2 cm in greatest dimension, have become more frequent at the population level worldwide [1–6]. Among large PanNET, 90% of tumors are nonfunctioning [2], and about 20% have spread to distant organs at the time of diagnosis [1]. Whereas patient age is by and large comparable in patients with small and large sporadic tumors, greater primary tumor size correlates positively with lymph node and distant metastases, lower histopathologic grading, and extrapancreatic extension [1,5–7]. Although resection of the primary tumor, even when metastases are present, may prolong survival, the considerable morbidity inherent in major pancreatic resection limits the net benefit of extended surgery for locally advanced and metastasized PanNET [8–10].

## Clinical Workup of Advanced PanNET for Major Oncologic Resection

Unlike functional PanNET that present with signs and symptoms of hormone excess, such as insulinoma, gastrinoma, and the rare glucagonoma, vasoactive intestinal peptide-releasing tumor (VIPoma), or somatostatinoma, nonfunctioning PanNET rather manifest with symptoms caused by tumor expansion, invasion, or metastatic disease. Nonfunctioning PanNET often reside in the pancreatic head, mimicking pancreatic adenocarcinoma, and compress adjacent organs, giving rise to jaundice, abdominal pain, weight loss, nausea and vomiting, back pain, and occasionally pancreatitis [2]. About 10% of PanNET are inherited in the context of multiple endocrine neoplasia type 1 (MEN 1), von Hippel–Lindau syndrome (VHL), neurofibromatosis type 1 (NF1), and the tuberous sclerosis complex (TSC). Patients with hereditary PanNET typically are younger than patients with sporadic PanNET, have multiple lesions scattered throughout the pancreas, and often yield a positive family history. MEN1-associated PanNET often comprises functioning and nonfunctioning tumors [11,12], necessitating more customized treatment plans than are required for solitary sporadic PanNET (Fig. 132.1) [13,14].

Diagnosis and extent of PanNET are established by cross-sectional (computed tomography [CT]; magnetic resonance imaging [MRI]) [15–17] and functional imaging (somatostatin receptor scintigraphy) in conjunction with [$^{18}$F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) [18,19] and percutaneous or endoscopic ultrasound (EUS)-guided biopsy [20–23]. Because treatment concepts for metastatic exocrine and endocrine cancers differ tremendously, biopsy of the primary tumor or its metastasis takes center stage in differentiating pancreatic adenocarcinoma from PanNET. Clinical staging and grading of the PanNET afford stratification of patients into prognostic subgroups and facilitate individualized treatment concepts [24–26]. Ki-67 immunocytology, using World Health Organization (WHO)-defined categories of 0–3% (grade 1), 3–20% (grade 2), and >20% (grade 3) [27], helps estimate the patient's risk of recurrence and survival [28–30]. For WHO grades 1, 2, and 3, 5-year overall survival has been estimated at 85, 78, and 9%, respectively [28]. With a Ki-67 score of <2%, the likelihood is remote that the cancer extends beyond the pancreas, invades great

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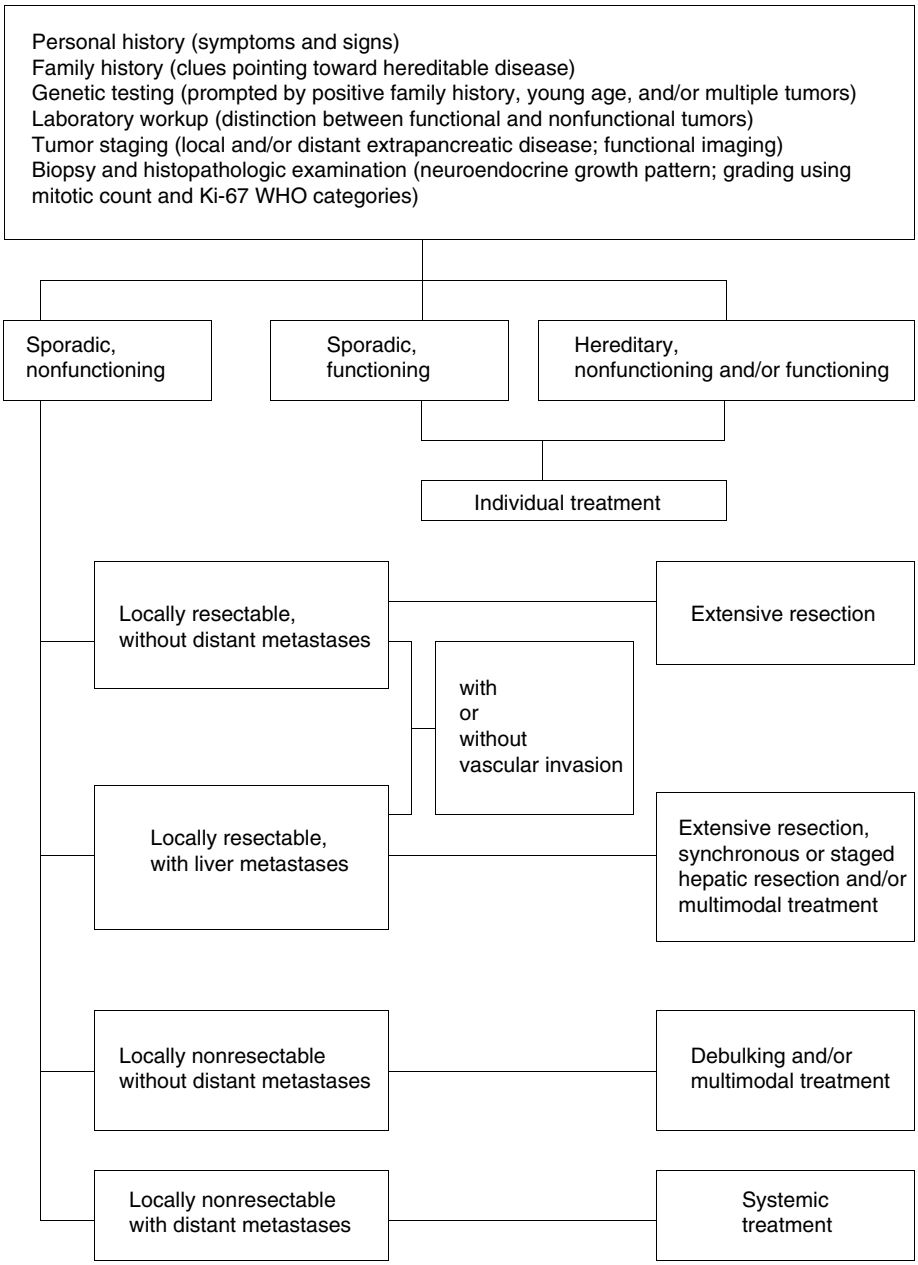


**Figure 132.1** Algorithm for clinical workup and surgical treatment of advanced PanNET.

vessels, is metastatic, or will recur [28]. Most studies support the notion that poor tumor differentiation, WHO grade 3, and distant metastases are closely connected to PanNET-specific mortality [28,31–35].

## Surgical Approach to Locally Advanced Nonfunctioning PanNET Without Clinical Evidence of Distant Metastases

Based on preoperative imaging and intraoperative exploration, locally advanced nonfunctioning PanNET are defined as large tumors frequently invading parapancreatic organs such as the stomach, spleen, colon, kidney, or adrenal gland, and/or great vessels, namely the mesentericoportal vein, superior mesenteric artery, or celiac trunk. Lymph node metastases may evade imaging [36,37], but if clinically apparent often herald systemic disease. Although lymph node metastasis is not a prognostic factor for survival in its own right [38], regional lymph node dissection has become an integral element of surgery for advanced disease reducing the risk of local recurrence.

Given the unavailability of equally effective nonsurgical treatment options, resection of a locally advanced nonfunctioning PanNET at institutions experienced in

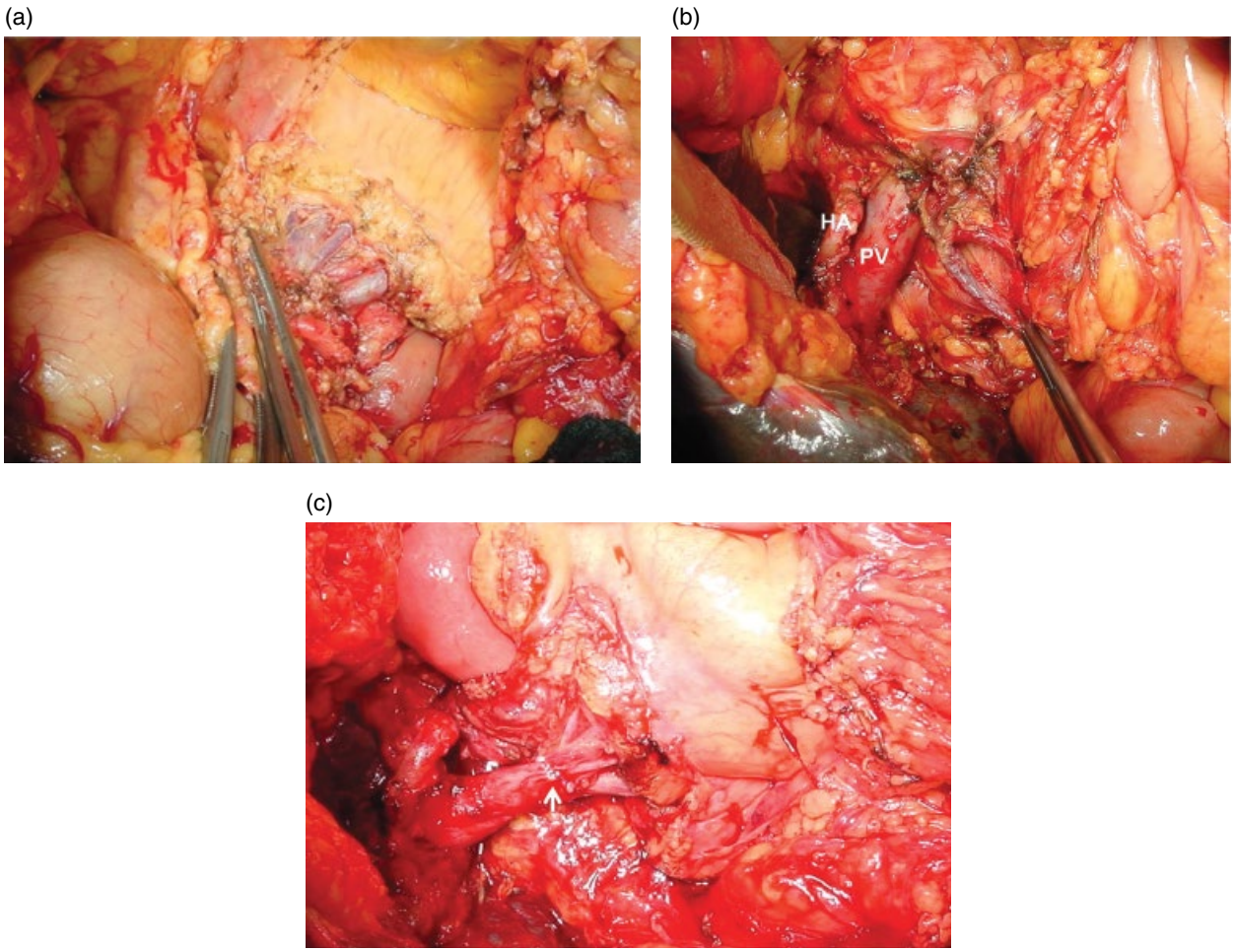


**Figure 132.2** Neuroendocrine carcinoma of the pancreatic uncinate process invading the mesentericoportal vein. (a) Infrapancreatic clamping of the superior mesenteric vein; (b) dissection of the portal vein (PV) and hepatic artery (HA); (c) end-to-end anastomosis of the mesentericoportal vein (arrow).

pancreatic surgery is the method of choice [29,36,39]. Provided that clear surgical margins are achievable, resection of neighboring organs and great vessels seems worthwhile [36,39]. Resection of the mesentericoportal axis is almost always feasible (Fig. 132.2) and requires only rarely the use of an autologous vein, or prosthetic material for reconstruction [40–46]. Conversely, arterial resection and reconstruction (Figs 132.3, 132.4, and 132.5) is much more complex [47–51] and associated with incremental surgical morbidity and mortality [52,53]. The decision to embark on the resection of great arteries needs to be pondered carefully, jointly taking into account patient age and comorbidity, stage and grade of the PanNET, extent of invasion of the artery by the tumor (celiac/hepatic artery and/or superior mesenteric artery without or with invasion of the mesentericoportal vein), and the condition of the artery itself (presence or absence of arteriosclerosis). However, systematic clinical outcome studies after resection and reconstruction of one, two, or more major vessels invaded by PanNET (Fig. 132.5) are unavailable because of the rarity of the condition [47,49]. In the absence of evidence-based information, best judgment should be exercised to determine, on a highly selective basis, whether to resect major arteries invaded by nonfunctioning locally advanced PanNET.

To clarify resectability, the greatest tumor extension outside the pancreas needs to be explored first. For invasion of the mesentericoportal axis below the pancreas, the infrapancreatic/infracolonic approach (Fig. 132.6) is a natural choice. When major branches of the superior mesenteric vein are invaded, complete resection of the tumor is unfeasible and should not be attempted. Major arteries invaded by tumor, such as the superior mesenteric or hepatic artery, are best resected toward the end of pancreatic surgery to allow immediate arterial reconstruction, keeping ischemia time to a minimum. Arterial reconstruction is accomplished directly, or with the use

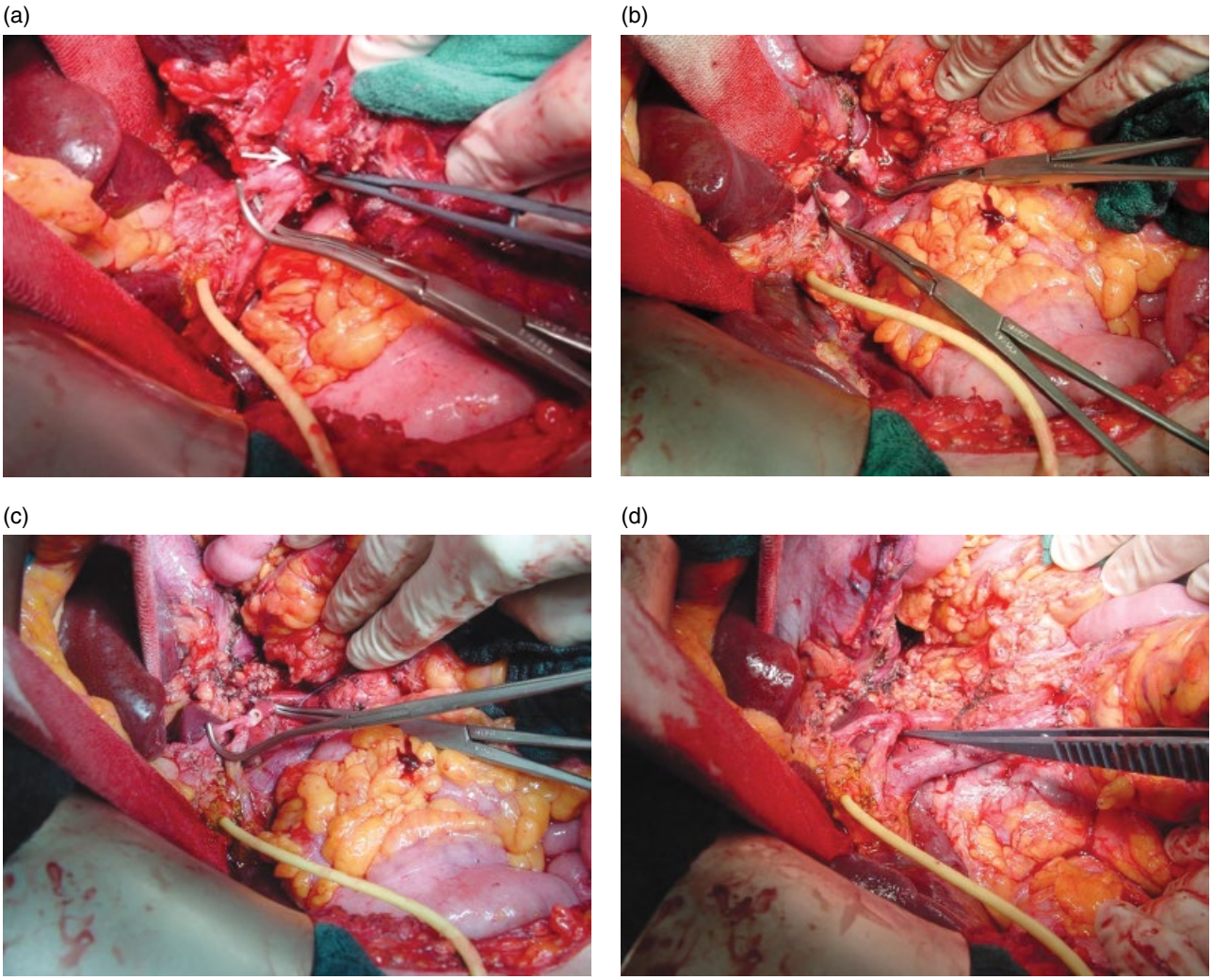


**Figure 132.3** Neuroendocrine carcinoma of the pancreatic head invading the hepatic artery. (a) Operative view of the invaded hepatic artery (arrow); (b)–(d) resection of the invaded hepatic artery segment and reconstruction by end-to-end anastomosis.

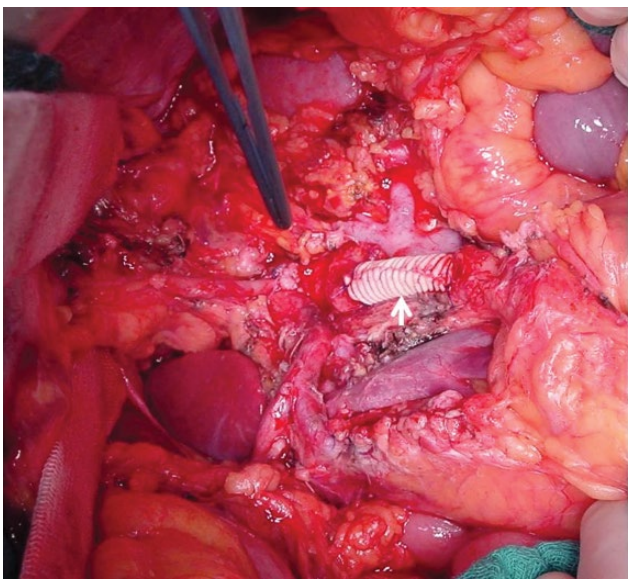

**Figure 132.4** Neuroendocrine carcinoma of the pancreatic body invading the superior mesenteric artery: operative situs after resection and prosthetic reconstruction (arrow).

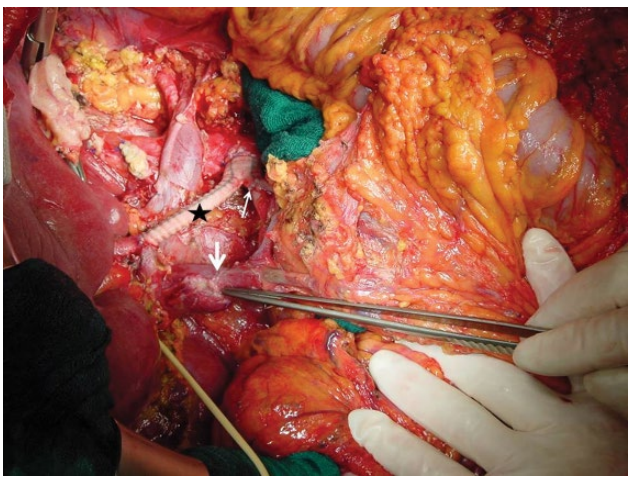

**Figure 132.5** Neuroendocrine carcinoma of the pancreatic body encroaching onto pancreatic head and tail and invading the superior mesenteric artery, superior mesenteric vein and the hepatic artery: operative situs after total pancreatectomy, three-vessel resection, end-to-end-reconstruction of the superior mesenteric vein (thick arrow) and arterial reconstruction using a Y-shaped prosthesis connecting the hepatic (asterisk) and superior mesenteric (thin arrow) arteries with the aorta.

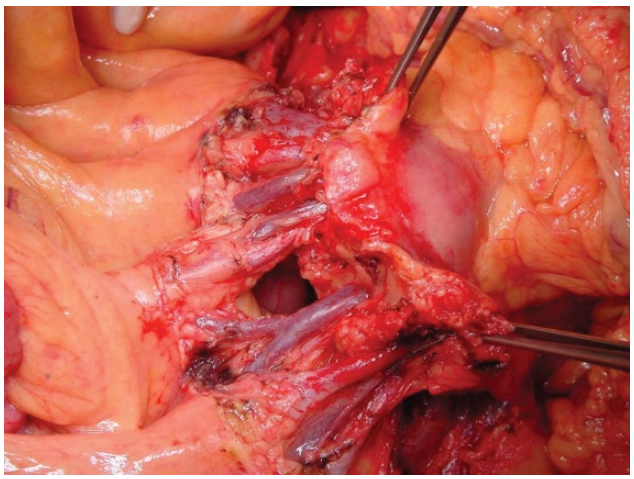

**Figure 132.6** Infracolonic dissection of the superior mesenteric vein and its branches, fenestrating the transverse mesocolon to gain access to a locally advanced PanNET of the pancreatic head.

of autologous or prosthetic material. Resection of the splenic vein alone does not warrant reconstruction [54]. In one study, segmental portal hypertension was not associated with increased mortality or severe morbidity after surgery for advanced PanNET [55].

## Locally Advanced Nonfunctioning PanNET with Clinical Evidence of Distant Metastases

Larger primary PanNET are often associated not only with invasion of adjacent organs and major vessels and more frequent lymph node metastasis, but also with liver metastases [7]. Extensive surgery for locally advanced PanNET with liver metastases, even though it may prolong survival, is controversial regardless of whether the metastases are resectable or not [56–63]. Clinically, PanNET present in more than 50% of patients with liver metastases as the only systemic manifestation, which are unresectable in 80% of patients [56].

For locally advanced PanNET without or with liver metastasis alone, or with liver metastasis as only one manifestation of systemic disease, there are no systematic outcome studies regarding the benefit of resection of the primary tumor so that the role of surgery remains to be defined for a wide range of clinical settings: symptomatic versus asymptomatic PanNET, with or without liver or other remote resectable or unresectable metastases; number and size of liver metastases; location of the primary tumor within the pancreas (head versus body or tail); and tumor grade and differentiation.

In light of the current literature, and subject to interdisciplinary consensus taking into account the circumstances of the case, it may be reasonable to suggest the following courses of action:

- For patients with *locally advanced PanNET with resectable liver metastases*, resection of the primary tumor should be considered, especially when the tumor is symptomatic. The issue of whether liver resection should take place in the same surgical session or whether a staged approach should rather be pursued depends on the extent of resection and the patient's condition [57,59,61]. A recent meta-analysis found that liver resection improved symptom relief and survival compared with nonsurgical therapy [63].
- Patients with *unresectable liver metastases of locally advanced PanNET* also may benefit from resection of the primary tumor. In a single-center study of 43 patients with PanNET and unresectable liver metastasis, the 5-year disease-specific survival was 82% in the operative group compared with 50% in the nonsurgical group ($P = 0.027$). On multivariate analysis, not only removal of the primary tumor but also younger patient age, a lower Ki-67 index, and a liver tumor burden <25% were associated with better disease-specific survival [56].
- Patients with *locally advanced PanNET and liver metastases as only one manifestation of systemic disease* are candidates for surgery only in exceptional circumstances, even when the liver metastases should be resectable. In these highly selected patients, the limited clinical effects of resection need to be carefully balanced with the benefits of nonsurgical treatment options [39,64,65].

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# 133

# Management of Insulinoma

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## Introduction

Insulinomas are neuroendocrine neoplasms (NEN) originating from the pancreatic Langerhans β cells [1–5]. As symptoms of hyperinsulinemic hypoglycemia are varied and nonspecific, diagnosis of insulinoma is sometimes difficult. Therefore, a cautious diagnostic approach is taken to detect the presence of insulinoma and to localize the tumors [1,2,5]. Most insulinomas are benign, and surgical resection can bring about complete cure. However, in incurable cases, hormonal symptoms are difficult to control, requiring multidisciplinary therapy tailored to each patient [1,4,5].

## Clinical Features of Insulinomas

Insulinoma is a very rare disease, developing in 1–4 individuals per 1 million population per year [1–5]. Insulinoma presents characteristically in the fifth decade of life, and has a predilection for women (41% male, 59% female) [1–4]. Among functional NEN, insulinomas occur most frequently. Over 99% of insulinomas occur in the pancreas [1–3] and the majority of these tumors are sporadic, solitary, and small in size (≤2.0 cm) [1–3,6]. About 4–12% of cases are associated with multiple endocrine neoplasia type 1 (MEN1), and MEN1-associated insulinomas are often multiple [6–9]. About 90% of insulinoma are benign, and surgical resection can bring about complete cure [2,3,6]. The remaining 10% are malignant insulinomas with distant metastasis at the time of diagnosis; prognosis is poor, with a median survival of less than 2 years [1,3,5]. Hypoglycemic symptoms in insulinomas are divided into two major categories: neuroglycopenic symptoms, such as confusion, visual changes, amnesia, and coma, and adrenergic symptoms, such as sweating, weakness, and tremors (Table 133.1) [4,9–11]. Hypoglycemic symptoms occur most frequently in the fasting state; however, they may occur in both the fasting and postprandial states in 21% of patients, and only in the postprandial state in 6% of patients [12]. Classical diagnosis of insulinoma is the Whipple triad (presence of hypoglycemic symptoms, blood glucose level under 50 mg/dL at the time of symptom onset, improvement of symptoms after glucose intake) [1–5]. Although insulinoma is the most frequent cause of adult hypoglycemia, there are other various hypoglycemia-causing diseases that require differentiation and, therefore, cautious diagnosis is important [1–4,7–9].

## Diagnosis of Insulinomas

When excessive endogenous insulin secretion is observed during hypoglycemia, insulinoma is suspected [1–4,10,13]. When spontaneous hypoglycemia is observed, the blood is drawn to measure plasma glucose (PG), serum levels of immunoreactive insulin (IRI), proinsulin, C-peptide, and β-hydroxybutyrate (BHOB) [12–18]. According to the guidelines of the European Neuroendocrine Tumor Society (ENETS), the diagnosis of insulinoma is confirmed by hypoglycemic symptoms and the following six diagnostic criteria [1]: (1) documented blood glucose levels ≤2.2 mmol/L (≤40 mg/dL), (2) concomitant insulin levels ≥6 U/mL (≥36 pmol/L; ≥3 U/L by immunochemiluminometric assay), (3) C-peptide levels ≥200 pmol/L, (4) proinsulin levels ≥5 pmol/L, (5) BHOB levels ≤2.7 mmol/L, and (6) absence of sulfonylurea (metabolites) in the plasma and/or urine. When spontaneous hypoglycemia is not observed, the

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**Table 133.1** Clinical symptoms and frequencies in patients with insulinoma.

| Symptoms | | Frequency (%) |
|---|---|---|
| Neuroglycopenic symptoms | | |
| | Confusion | 67–80 |
| | Visual changes | 42–59 |
| | Amnesia or coma | 47 |
| | Altered consciousness | 16–38 |
| | Seizures | 16–17 |
| | Headache | 7 |
| Adrenergic symptoms | | |
| | Sweating | 30–69 |
| | Weakness | 28–56 |
| | Tremors | 12–24 |
| | Hyperphasia | 14 |
| | Palpitations | 5–12 |
| | Anxiety | 12 |
| Obesity | | <50 |

following tolerance tests are conducted to induce hypoglycemia, and the above parameters are measured.

### Fasting Test

The 72-hour fasting test (Table 133.2) is the gold standard for the diagnosis of insulinoma [1–4,7,9,12,19]. In recent years, various insulin surrogates have become measurable, and some reports have indicated that the fasting period can be shortened to 48 hours [16,20]. For the fasting test, a patient needs to be hospitalized for blood collection every 4–8 hours under close medical supervision, for measurement of PG, IRI, proinsulin, and C-peptide [1,2,17–21]. PG ≤45 mg/dL with hypoglycemic symptoms is considered a positive response. Positive results are obtained within 12 hours in 33–42.5%, within 24 hours in 65–66.9%, within 48 hours in 93–94.5%, and within 72 hours in 98.4–99% of cases [16,19]. As hypoglycemic symptoms are often unnoticeable in patients with insulinoma, those symptoms should not be overlooked [16,22]. After the fasting test, serum levels of BHOB and free fatty acids are measured as supplementary data [12–16]. In rare insulinoma cases, positive results are not produced in the fasting test, and insulin is excessively secreted in response to glucagon or glucose loading, according to previous reports [21,23,24]. After the fasting test, glucagon 1.0 mg is injected intravenously and PG is measured at 10, 20, and 30 minutes. When ΔPG, defined as the difference between the maximum and baseline levels, is ≥25 mg/dL, insulinoma may be considered [2,14,21].

**Table 133.2** Fasting test instructions.

1) Meal is eaten at 18:00 and the fasting test is started:
   - Medication is minimized, and unnecessary medicines are suspended. No-calorie decaffeinated drinks can be taken. The patient is instructed to engage in daily activities.
2) Blood is drawn every 6 hours:
   - Blood tests include plasma glucose (PG), immunoreactive insulin, and C-peptide.
   - After PG is lowered to 60 mg/dL or below, blood is drawn every 1–2 hours.
3) Judgment is made as to whether the fasting test should be terminated:
   - PG ≤45 mg/dL and emergence of hypoglycemic symptoms are taken as a positive result for the fasting test, and the test is terminated.
   - When the result is negative, the test is terminated at 72 hours.
   - As PG ≤45 mg/dL may occur during fasting in healthy people (females in particular), the test should not be terminated only with PG decrease.
   - Even if PG ≤45 mg/dL is not achieved, the test can be terminated if hypoglycemic symptoms are severe. In such cases, the succeeding blood tests are carried out.
4) The following blood examinations are conducted at the end of the fasting test:
   - β-Hydroxybutyrate and free fatty acids are measured. Glucagon 1.0 mg is injected intravenously and PG measurements are taken at 10, 20, and 30 minutes. ΔPG = PG(max.) − PG (baseline) is calculated to determine the response to glucagon.
   - When insulin autoantibody syndrome is suspected, anti-insulin antibody and anti-insulin receptor antibody levels are measured.
5) Blood glucose level is promptly corrected after the test.

### Mixed-Meal Tolerance Test

There are some patients with insulinoma who present with hypoglycemic symptoms only in the postprandial state and not during fasting [12]. Furthermore, it is important to differentiate noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) from insulinoma. As hypoglycemia often occurs after meal intake in NIPHS, it is important to carry out a mixed meal tolerance test [17,25]. In this test, fasting starts the night before the test, and the mixed-meal tolerance test begins at breakfast. The meal consists of the items that are likely to induce hypoglycemia, or the commercially available mixed meal is used. Since reactive hypoglycemia often occurs over 5 hours after meal intake, observation is continued until 5 hours after the start of the test [17,26].

## Localization of Insulinomas

In typical cases of insulinoma, the tumor is well vascularized and has a well-defined border. Its image is most enhanced in the arterial phase in dynamic computed

tomography (CT) imaging (Fig. 133.1) [1,3,27,28]. On magnetic resonance imaging (MRI), insulinomas generally show low signal intensity on fat-suppressed T1-weighted images and high signal intensity on T2-weighted images [27,28]. As the size of the insulinoma is small (<2.0 cm) in 80% of cases, and MEN1-associated insulinoma often occurs at multiple sites, it is difficult to identify all tumors with conventional imaging [1,2,7–9]. owing to the recent advances in imaging technology, the sensitivity of various conventional imaging methods has improved. Comparing the periods 1983–1993 and 1994–2007, applications of transabdominal ultrasound increased from 0 to 33%, CT from 24 to 80%, and MRI from 43 to 70%, according to Nikfarjam et al. [11].

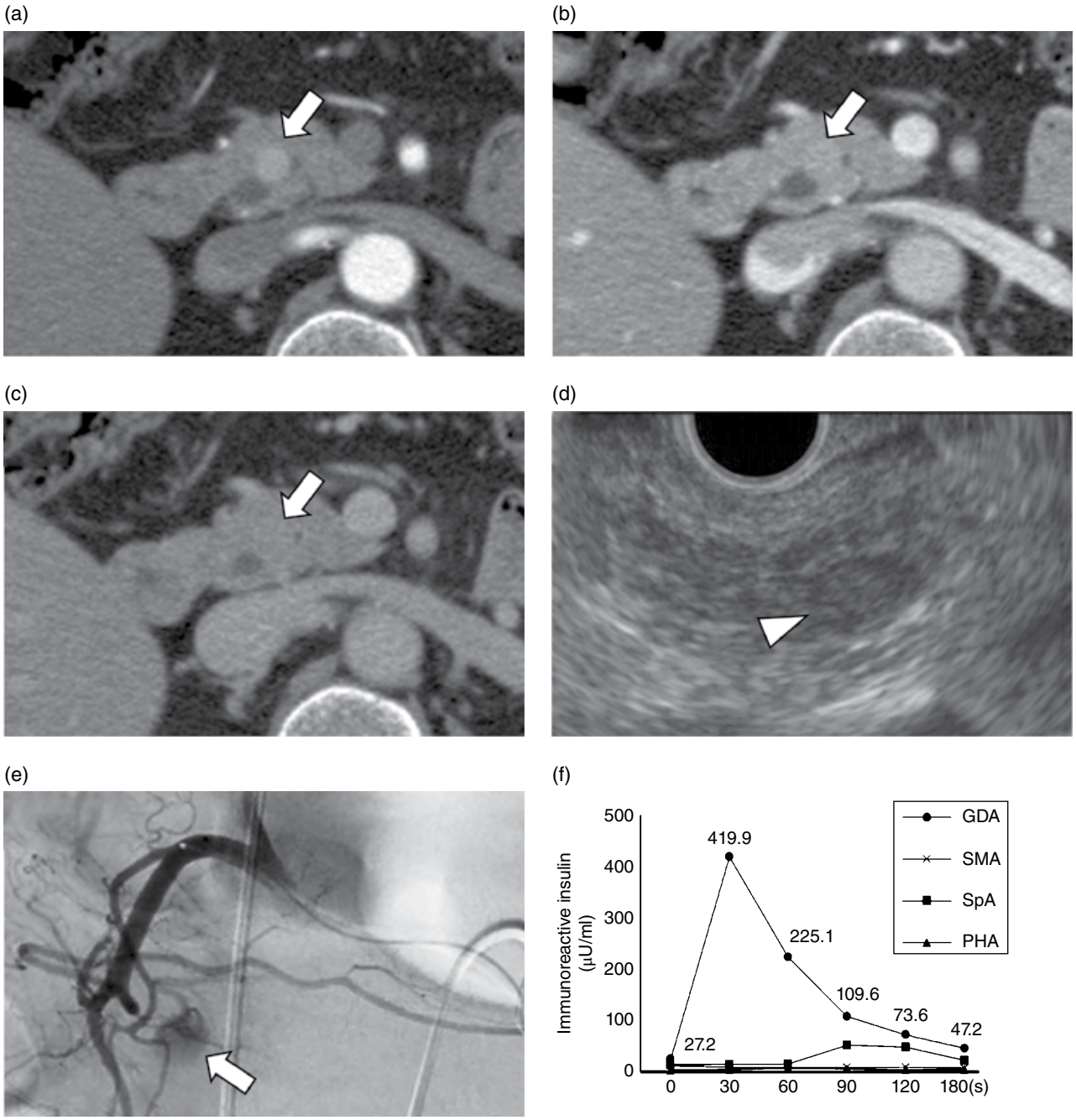


**Figure 133.1** A 68-year-old woman with insulinoma at the pancreatic head. Abdominal CT imaging (a–c) shows an oval lesion with regular margins and well-defined borders, which is most enhanced in the early phase. The lesion cannot be identified in the portal phase/late phase (arrow). EUS (d) shows an oval hypoechoic mass with regular margins and well-defined borders (arrow head). In the SACI test (e, f), a tumor is shown by gastroduodenal artery imaging, and the insulin level is markedly stepped up by glucose disposal agents. The tumor localization by the SACI test coincided with imaging findings.

Nevertheless, the diagnostic ability of these tests is not sufficient, hence these modalities are combined with endoscopic ultrasonography (EUS), the selective arterial calcium injection test (SACI test), and nuclear imaging [1–4,13].

### Endoscopic Ultrasonography

On EUS, insulinoma is revealed as an oval hypoechoic mass with a well-defined border, and a hypervascular pattern on color/power Doppler imaging (Fig. 133.1) [2,3,29,30]. Owing to its high sensitivity (80–93.8%), EUS is more useful for localization of the tumors compared with CT or MRI [2,29,30]. EUS is especially effective for the detection of small insulinomas, and when the size of the insulinoma is 12 mm or smaller, EUS is significantly superior to CT imaging [29]. It has been reported that the combination of CT and EUS permits localization of insulinoma with 100% sensitivity [30].

### Selective Arterial Calcium Injection (SACI) Test

The SACI test is useful when a tumor cannot be confirmed by other modalities (occult insulinoma). It is also useful in identifying insulinomas from among multiple pancreatic tumor masses in MEN1-associated cases [1–4,7,31–33]. For abdominal arterial angiography, calcium gluconate (0.025 mEq/kg) is injected from the feeding artery for each pancreatic region (gastroduodenal artery, superior mesenteric artery, splenic artery, etc.), and then IRI in hepatic venous blood is measured. Based on the increase in IRI, the location of insulinoma is determined (Fig. 133.1) [31–33]. IRI is measured at baseline and 30, 60, 90 and 120 seconds, and a twofold or higher increase in IRI over the baseline is considered to be positive. The sensitivity of the SACI test for insulinoma is 82.2–100%, and the method produces excellent results [2,31–33].

### Nuclear Imaging (Scintigraphy, SPECT, PET/CT)

As the proliferative ability of insulinoma is low, [$^{18}$F] fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT imaging of insulinomas is disappointing [1,3,34,35]. While [$^{68}$Ga]DOTA-TOC-PET/CT, [$^{111}$In]pentetreotide scintigraphy, and single-photon emission computed tomography (SPECT) are carried out for somatostatin receptor imaging, the expression rate of somatostatin receptor 2a is low in benign insulinomas, with a low positivity rate and sensitivity below 50% [13,34–36]. Meanwhile, the glucose-like peptide 1 (GLP-1) receptor is known to be highly expressed in more than 90% of insulinoma cases, therefore GLP-1 receptor imaging is considered useful [34–36]. GLP-1 receptor scintigraphy using [$^{111}$In]DOTA-exendin-4 has 100% sensitivity, according to a report with a small sample size [35].

## Treatment of Insulinomas

Treatment of insulinomas can be divided into two aspects: treatment of symptomatic hypoglycemia caused by excessive insulin secretion and treatment of the tumor itself. Therefore, in treating insulinomas, hormone symptoms should be well controlled, while the tumor is simultaneously treated.

### Treatment of Symptomatic Hypoglycemia

First, small, frequent meals or oral/intravenous glucose supplementation are given [1,3,37]. As for medical therapy, diazoxide (50–300 mg/day; can be increased up to 600 mg/day) is most useful [1,3–5,9]. Diazoxide acts directly on pancreatic β cells, suppressing insulin secretion, thus improving hypoglycemic symptoms. Several days are required for stabilizing blood glucose, and edema, weight increase, deterioration of renal function, and hirsutism may occur as adverse reactions [1,3,4,13]. Other drugs such as glucocorticoids, verapamil, and diphenylhydantoin are effective, according to some reports [1,3–5,13]. Somatostatin analogs, such as octreotide and lanreotide, were found to be effective for improving hypoglycemic symptoms in 35–50% of cases of insulinoma. The effects of somatostatin analogs depend on the expression of somatostatin receptor subtypes 2, 3, and 5. Therefore, in cases of no or low expression of somatostatin receptor, hypoglycemia may exacerbate by inhibiting the secretion of competitive hormones, such as glucagon [1,5,37,38]. In malignant insulinoma, the mammalian target of rapamycin (mTOR) inhibitor everolimus is effective for control of excessive insulin secretion and hypoglycemic symptoms [37,39,40].

### Treatment of Resectable Insulinoma (Surgical Treatment)

Surgical resection is a radical treatment for insulinoma. Surgical procedures are different depending upon the size and number of tumors, the tumor location, and whether MEN1 is present or not [1–5]. During surgery, palpation and intraoperative ultrasonography are conducted to examine the pancreas. Blind resection is not recommended for the occult insulinoma that cannot be localized preoperatively [2,41–44]. In general, enucleation is possible if the insulinoma is 2 cm or smaller and its distance from the main pancreatic duct is about 2–3 mm. In the case of damage to the main pancreatic

duct, pancreatic partial excision, segmental resection, pancreaticoduodenectomy, or distal pancreatectomy is carried out [1–5,41–43]. When enucleation or distal pancreatectomy is chosen for the insulinoma localized in the body or tail of the pancreas, laparoscopic surgery can be selected [1,2,42–44].

### Treatment of Unresectable Insulinoma

The therapeutic objectives in unresectable insulinoma cases are hormone symptom control and prolongation of prognosis [3–5,9,13,37]. Systemic chemotherapy for well-differentiated NEN (neuroendocrine tumor [NET] grade 1/2) generally consists of a combination of streptozotocin and doxorubicin or fluorouracil. In recent years, dacarbazine- or temozolomide-based chemotherapy has also been used as the standard chemotherapy for insulinoma [1,3,13,37,45]. In 6–70% of patients with well-differentiated NEN (insulinoma included), improvement of hormone symptoms or objective tumor response was demonstrated [37]. Among molecular target drugs, the already mentioned everolimus is considered effective against hormone oversecretion, and its antitumor effect has also been demonstrated. Therefore, everolimus is recommended [39,40,46]. Sunitinib is not thought to be capable of controlling symptomatic hypoglycemia [37]. Although cisplatin plus irinotecan or cisplatin plus etoposide is generally used to treat poorly differentiated NEN (neuroendocrine carcinoma [NEC]), the incidence of NEC is low in insulinoma, and therefore, sufficient investigations have not been conducted in this field [3,6,9,45]. If medical therapy cannot control hormone symptoms sufficiently, tumor debulking surgery is sometimes conducted even in unresectable cases, targeting the removal of at least 90% of the tumor volume, with the objective of alleviating the symptoms [2,3,5,45,47]. Other therapies for unresectable NEN including insulinoma are liver-directed therapies (embolization, chemoembolization, radiofrequency ablation), laser-induced thermotherapy (LITT), selective internal radiotherapy (SIRT) using yttrium-90 microspheres, peptide receptor radionuclide therapy (PRRT) using [$^{177}$Lu]DOTA$^{0}$-Tyr$^{3}$octreotate, and also liver transplant; alleviation of hormonal symptoms and improvement of prognosis have been reported [1,3–5,45,47–52].

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# 134

# Evidence of Medical and Surgical Treatment of Gastrinoma

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## Treatment Strategy

The goals of gastrinoma treatment are to manage gastric acid hypersecretion and to remove the risk of distant metastasis and ultimately death of the patient by resecting tumors that are usually malignant.

Treatment for gastrinoma has changed significantly since the syndrome was originally described in 1955 [1]. Initially, most patients developed severe symptoms and underwent emergency surgery for complications such as massive hemorrhage or perforation. Partial gastrectomy with or without vagotomy was insufficient treatment, hence total gastrectomy became the standard operation for patients with gastrinoma [2].

The development of effective antisecretory drugs has drastically changed the management of gastrinoma [3]. In most patients, gastric acid hypersecretion can be controlled with antisecretory agents such as $H_2$-receptor antagonists and proton-pump inhibitors. Because those agents are so effective, surgery for the control of gastric acid hypersecretion such as total gastrectomy is no longer required. About 60% of gastrinomas are malignant and those are the major cause of death during long-term follow-up, although they are relatively slow growing. Now, the roles of surgery are to remove the responsible tumor or tumors and to prevent tumor progression and ultimately death.

Along with the increasing recognition of the duodenum as the most common site for gastrinomas, and with improved localization methods, at least 50% of patients with sporadic gastrinoma can be cured by tumor resection [1,4]. Therefore, an aggressive approach to tumor localization is strongly recommended in selecting patients for operative treatment.

## Tumor Localization

Before surgical treatment, tumor localization studies are required in all patients with gastrinomas. Imaging techniques such as computed tomography (CT), ultrasonography (US), endoscopic ultrasonography (EUS), and intraoperative ultrasonography (IOU) have been useful for the localization of most neuroendocrine tumors greater than 2 cm in diameter [5]. However, imaging techniques have difficulty in visualizing neuroendocrine tumors smaller than 5 mm [5]. As gastrinoma shows characteristic symptoms even when smaller than 5 mm, the selective arterial secretagogue injection (SASI) test is useful for preoperative localization of gastrinoma leading to curative resection surgery [6–8]. Somatostatin receptor scintigraphy (SRS) is indispensable for localization of ectopic gastrinoma and the metastatic lesions of gastrinoma throughout the body [9].

### Selective Arterial Secretagogue Injection (SASI) Test with Secretin or Calcium

The SASI test was first described for localization of gastrinoma, and has gradually proved useful for the localization of other symptomatic pancreatic neuroendocrine tumors (PanNET) [6–8,10]. At the time of abdominal arteriography, secretagogue is injected into the splenic artery, the gastroduodenal artery, and the superior mesenteric artery (Fig. 134.1). Then 2 mL blood samples are drawn from the hepatic vein through a catheter inserted via the femoral vein before and 20, 40, and 60 seconds after the injection of secretagogue to detect the change in gastrin levels in hepatic venous blood. When the rise in gastrin levels at 40 seconds after injection is

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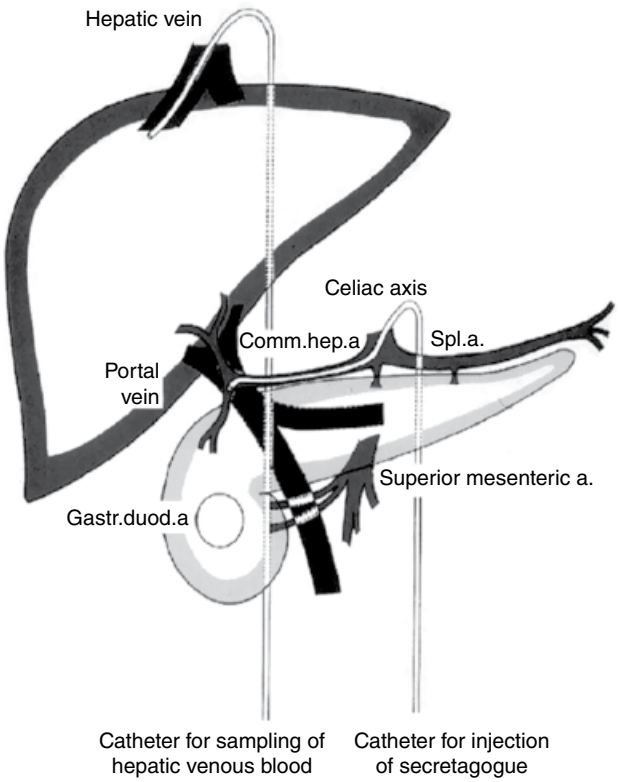


**Figure 134.1** Scheme of the selective arterial secretagogue injection test. Results of the selective arterial secretagogue injection (SASI) test in a patient with Zollinger–Ellison syndrome. In this patient, serum immunoreactive gastrin at 40 s after the injection of 30 units of secretin rose only after injection into the gastroduodenal artery. Hence it was diagnosed that the gastrinoma(s) was located in the upper part of the pancreas and/or the duodenum. Gastr.duod.a, gastroduodenal artery; Spl.a., splenic artery; Superior mesenteric a., superior mesenteric artery.

significantly higher than the measurement errors, the artery is diagnosed as a feeding artery of gastrinoma. Functioning gastrinoma is then located in the feeding area of the identified feeding artery.

More precise localization is possible by injecting secretagogue into a branch of the identified artery. Both the sensitivity and specificity of the SASI test for gastrinoma have been shown to be more than 90% [7].

### Somatostatin Receptor Scintigraphy (SRS)

SRS is clearly able to visualize PanNET larger than 2 cm in diameter in the body, and has contributed to the staging of PanNET [11–13]. SRS can visualize 100% of gastrinomas larger than 3 cm in diameter, but only 20% of gastrinomas are smaller than 5 mm and 30% are smaller than 1 cm [12]. SRS visualized 73% of gastrinomas, depending both on the extent of the presence and the differences in subtypes of somatostatin receptors and on the size of the tumor [13]. For the localization of ectopic gastrinoma, SRS is indispensable [14].

### Intraoperative Ultrasonography (IOU)

IOU is useful in estimating the character of a tumor and in measuring the distance between gastrinoma and the main pancreatic duct. In addition, the form and size of the gastrinoma can be measured more correctly with IOU than any other preoperative imaging technique [15].

## Surgery

Surgery for gastrinoma needs a thorough exploration and careful technique. The omentum is widely opened, and the entire pancreas from head to tail is mobilized. This allows careful bimanual palpation of the gland.

IOU should be performed in any patient undergoing exploration for gastrinoma to identify tumors that are difficult to palpate. It may also detect signs suggestive of malignancy in addition to the relationship of the tumor to the main pancreatic duct and major blood vessels. IOU is not particularly useful in identifying duodenal wall gastrinomas; however, intraoperative endoscopy with transillumination of the duodenum is capable of locating duodenal wall gastrinomas.

The most accurate method of detecting duodenal wall gastrinomas is duodenotomy with careful palpation, a technique employed by experienced surgeons during surgical exploration for gastrinoma. Duodenotomy has been shown to increase the gastrinoma detection rate to 98% compared with 76% without duodenotomy, and also the short-term cure rate (65 versus 44%) and long-term cure rate (52 versus 26%) [16].

Because primary duodenal gastrinomas are associated with lymph node metastases in 60% of patients, a more aggressive lymph node dissection has been recommended. Major vascular involvement is not a contraindication to attempt a resection. A study of 273 patients showed that 46 (17%) had evidence of major vascular involvement on preoperative imaging, and 42 of these 46 patients underwent successful resection [17].

The use of endoscopic and/or laparoscopic approaches for the management of neuroendocrine tumors, including gastrinomas, has been reported in small numbers of patients. However, the role for such an approach in patients with gastrinomas appears to be limited owing to a variety of technical issues, including the multiplicity of lesions, the small size of duodenal tumors, the frequent presence of lymph node metastases, and the presence of critical structures in the usual gastrinoma location in the pancreatic head region. These difficulties tend to favor an open surgical approach.

## Treatment of Hepatic Metastases

A very aggressive management approach has been advocated for advanced and metastatic gastrinomas because of the poor outcome of patients and the overall disappointing results with systemic therapy. It was reported that aggressive resectional procedures were associated with no operative deaths and a 5-year actuarial survival of 80% in 20 patients with locally advanced and metastatic neuroendocrine tumors including 10 gastrinomas [18]. Another study in 85 patients with liver metastases suggested that chemoembolization may be preferred unless a curative resection is possible or 90% of the tumor volume can be removed [19]. Bilobar disease and patients with more than 75% liver involvement were least likely to benefit from surgery.

The role of liver transplantation in patients with liver metastasis remains controversial. The UNOS database showed that 150 liver transplantations were carried out for patients with liver metastasis from neuroendocrine tumors out of 87,280 performed. Among them, 11 cases of gastrinoma (7.3%) were included. Overall survival rates were similar to those for patients who underwent transplantation for hepatocellular carcinoma [20].

Other liver-directed therapies include chemoembolization, radioembolization, and percutaneous radiofrequency ablation. These therapies continue to play a role in the management of neuroendrocrine tumors metastatic to the liver, including gastrinomas. In general, transarterial chemoembolization (TACE) has been shown to be a relatively safe procedure with improvements in symptom control, time to progression, and survival.

## Systemic Chemotherapy

Streptozotocin appears to be the most active single agent in patients with metastatic gastrinoma with objective response rates reported in up to 50% of patients [21]. There is no evidence that the addition of 5-fluorouracil (5FU) with or without doxorubicin improves the outcome compared with streptozotocin alone [21].

A study using a combination of 5FU, cisplatin, and streptozocin for metastatic or locally advanced neuroendocrine tumors of a variety of sites in 79 patients showed that the overall results are not superior to those with streptozocin alone [22].

Octreotide, either alone or combined with interferon, appears to have a role in the management of patients. The development of a long-acting somatostatin analog has greatly facilitated management, and is effective in reducing symptoms.

A randomized multi-institutional double-blind placebo-controlled trial studying the vascular endothelial growth factor (VEGF) inhibitor sunitinib was reported in 171 advanced well-differentiated neuroendocrine tumors, including 19 patients with gastrinoma. Progression-free survival (PFS) was 11.4 months in the sunitinib group compared with 5.5 months in the placebo group. The objective response rate was 9.3% in the sunitinib group versus 0% in the placebo group. Nine deaths were reported in the sunitinib group (10%) versus 21 in the placebo group (25%).

The use of mTOR inhibitors, either alone or combined with octreotide therapy, has recently been studied in patients with pancreatic neuroendocrine tumors. The RADIANT 1 trial, a multinational Phase II study, studied the efficacy of everolimus alone and in combination with octreotide in patients with metastatic PanNET who had progressed on chemotherapy [23]. Treatment with everolimus alone resulted in stable disease in 67.8% of patients and partial response in 9.6%. Combination therapy with everolimus and octreotide LAR resulted in stable disease in 80% of patients and partial response in 4.4%.

In the RADIANT III trial, 410 patients with radiologic progression of disease were randomized to everolimus 10 mg daily or usual therapy, which could include somatostatin [24]. The median PFS was 11 months with everolimus compared with 4.6 months with usual therapy. The proportion of patients alive and progression free at 18 months was 34% with everolimus compared with 9% with placebo.

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# 135

# Rare Neuroendocrine Tumors of the Pancreas: Management and Evidence of Surgical Treatment

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## Introduction

As pancreatic neuroendocrine tumors (PanNET) are rarely encountered in hospitals, standardization of diagnosis and/or the treatment strategy have not progressed until recently. However, recent advances in localization techniques such as the selective arterial secretagogue injection (SASI) test and somatostatin receptor scintigraphy (SRS) have promoted curative resection surgery of PanNET [1,2]. As the number of resections has rapidly increased, a few important characteristic pathologic features of PanNET have been revealed year by year.

PanNET include both PanNET associated with a functional syndrome (functional PanNET) or those associated with no distinct clinical syndrome (nonfunctional PanNET) [3–6]. Nonfunctional PanNET are the most common but they do not usually produce specific symptoms and are therefore considered clinically to be nonfunctional tumors, but they produce and frequently even secrete small amounts of pancreatic polypeptide, chromogranin A, neuron-specific enolase, calcitonin, neurotensin, and other peptides [4,5,7–9]. Gastrinoma and insulinoma are the two most common functional PanNET, but there are also various kinds of rare functional PanNET (rare PanNET) [3–6], including glucagonomas, vasoactive intestinal peptide-releasing tumors (VIPomas) (Verner–Morrison syndrome, pancreatic cholera, watery diarrhea, hypokalemia, and achlorhydria [WDHA] syndrome) and somatostatinomas (Table 135.1) [3–7,9]. Each of the established rare PanNET syndromes is associated with a distinct clinical syndrome reflecting the actions of the secreted excess hormone.

## Clinical Features

Gastrinoma, insulinoma, and nonfunctional PanNET represent over 90% and other rare PanNET less than 10% of all PanNET [4,7]. Rare but well-known PanNET include glucagonomas, VIPomas, and somatostatinomas whose syndromes are established. Rare and lesser-known tumors include PanNET that secrete calcitonin, renin, luteinizing hormone, erythropoietin, and insulin-like growth factor II whose status is unclear as to whether they represent a specific syndrome because of the small numbers of cases (Table 135.1) [3–5,7,9–11].

The majority of patients with rare PanNET have liver metastases at initial diagnosis (40–90%). Somatostatinomas can occur in the pancreas or upper small intestine; however, the duodenal somatostatinomas are rarely associated with a functional clinical syndrome [4,10,12]. In addition to somatostatinomas, a number of the other rare PanNET also occur in extrapancreatic locations (Table 135.1).

The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with rare PanNET is multiple endocrine neoplasia type 1 (MEN1). Glucagonomas occur in 3% of MEN1 patients, VIPomas in 3%, and GRHomas (secreting growth hormone-releasing hormone) and somatostatinomas in less than 1% [13,14]. Somatostatinomas are seen in up to 10% of patients with von Recklinghausen disease (neurofibromatosis type 1) but in almost all cases they are not associated with a functional syndrome [7,12,13].

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**Table 135.1** Rare pancreatic neuroendocrine tumors.

| Name | Biologically active peptide(s) secreted | Estimated incidence (new cases/$10^6$ population/year) | Tumor location | Malignant (%) | Associated with MEN1 (%) | Main symptoms/signs |
|---|---|---|---|---|---|---|
| Glucagonoma | Glucagon | 0.01–0.1 | Pancreas (100%) | 50–80 | 1–20 | Rash (67–90%); glucose intolerance (38–87%); weight loss (66–96%) |
| VIPoma | Vasoactive intestinal peptide | 0.05–0.2 | Pancreas (90%, adult); other (10%, neural, adrenal, periganglionic) | 40–70 | 6 | Diarrhea (90–100%); hypokalemia (80–100%); dehydration (83%) |
| Somatostatinoma | Somatostatin | Rare | Pancreas (55%); duodenum/jejunum (44%) | >70 | 45 | Diabetes mellitus (63–90%); cholelithiases (65–90%); diarrhea (35–90%) |
| GRHoma | Growth hormone-releasing hormone | Unknown | Pancreas (30%); lung (54%); jejunum (7%); other (13%) | >60 | 16 | Acromegaly (100%) |
| ACTHoma | ACTH | Rare | Pancreas (4–16% all ectopic Cushing) | >95 | Rare | Cushing syndrome (100%) |
| PanNET causing carcinoid syndrome | (Serotonin; tachykinin) | Rare | Pancreas (<1% all carcinoids) | 60–88 | Rare | Carcinoid syndrome |
| PanNET causing hypercalcemia (PTHrpoma) | PTHrp; others unknown | Rare | Pancreas (rare cause of hypercalcemia) | 84 | Rare | Abdominal pain due to hepatic metastases, symptoms due to hypercalcemia |
| PanNET secreting calcitonin | Calcitonin | Rare | Pancreas (rare cause of hypercalcitonemia) | >80 | 16 | Diarrhea (50%) |
| PanNET secreting renin | Renin | Rare | Pancreas | Unknown | No | Hypertension |
| PanNET secreting luteinizing hormone | Luteinizing hormone | Rare | Pancreas | Unknown | No | Anovulation, virilization (female); reduced libido (male) |
| PanNET secreting erythropoietin | Erythropoietin | Rare | Pancreas | 100 | No | Polycythemia |
| PanNET secreting IGF-II | Insulin-like growth factor II | Rare | Pancreas | Unknown | No | Hypoglycemia |

## Prognosis and Survival

Most rare PanNET present with metastatic disease and patients' survival time is determined by the growth of the tumor rather than the hormone excess state. Five-year survival for the group with advanced disease is 29–45% [3,4,6,7]. All of the survival or prognostic data on the individual rare PanNET come from retrospective studies and in recent studies their results are often included in noninsulinoma or nongastrinoma series that include nonfunctional PanNET. These studies demonstrated tumor Ki-67 index ≥62%, presence of lymph node metastasis, presence of cytokeratin-19 staining, and various molecular features that were associated with a poor prognosis [4,15].

## Diagnosis

Rare PanNET characteristically present with the symptoms of the specific hormone excess state, and in most cases present late in the disease course when advanced disease is already present [4,6,7]. In a few of patients with a rare PanNET, a second functional syndrome may develop over time. Therefore, the diagnosis of all rare PanNET requires the demonstration of an inappropriate elevation of the specific serum hormones combined with clinical and/or laboratory evidence of oversecretion of the appropriate hormone [3–5,16,17]. The diagnosis of functional rare PanNET requires clinical evidence of hormonal overexpression and is not based solely on immunohistochemical results [3–5,16,17].

General markers such as serum chromogranin A also support the presence of a neuroendocrine tumor, and may be helpful for monitoring during the disease's course [3,5,17,18].

All biochemical tests should be performed at first visit. PanNET causing Cushing syndrome should be suspected from the clinical examination and history, and the diagnosis established by performing 24-hour urinary cortisol determinations, midnight plasma or salivary cortisol assessments, and dexamethasone suppression tests as needed [9,17].

## Tumor Localization

Tumor localization studies are important in all patients with rare PanNET. Tumor localization studies are necessary to determine whether surgical resection is indicated, to localize the primary tumor, to determine the extent of the disease and whether metastatic disease to the liver or distant sites is present, and to assess changes in tumor extent with treatments. All aspects of their management require knowledge of tumor extent. It is important to know that the majority of all pancreatic functional tumors except insulinomas are malignant. Accurate localization of the tumor can result in complete surgical resection with cure of PanNET (10–40%).

Numerous localization studies have been recommended, including conventional imaging studies (computed tomography [CT], magnetic resonance imaging [MRI], ultrasonography [US]), selective angiography, SASI test, SRS, and endoscopic ultrasonography (EUS), in addition to various intraoperative localization methods including intraoperative ultrasonography (IOU).

Most prospective studies show that the sensitivity of conventional imaging studies for localizing the primary tumor is 10–50%, angiography 20–50%, and SRS 30–70% [19]. The use of SRS changes management in 15–45% of patients with PanNET. For SRS and all conventional studies, tumor size is an important variable and tumors smaller than 1 cm are missed in 50% or more cases. The combined use of multidetector computed tomography (MDCT) scanning or MRI and SRS is always recommended. Conventional imaging studies suggesting vascular or tissue invasion may provide important information on whether surgical resection is contraindicated.

If measurement of target hormone is easy accessible, the SASI test is the most reliable approach for tumor localization. The SASI test was first described for localization of gastrinoma, and has gradually proved useful for the localization of other functional PanNET [2,20–22]. At the time of abdominal arteriography, secretagogue is injected into the splenic artery, the gastroduodenal artery, and the superior mesenteric artery. Then 2 mL blood samples are drawn from the hepatic vein through a catheter inserted via the femoral vein, before and 20, 40, and 60 seconds after the injection of secretagogue to detect the change in hormone levels in hepatic venous blood. When the rise in hormone levels at 40 seconds after injection is significantly higher than the measurement errors, the artery is diagnosed as a feeding artery of the tumor. Functioning tumor is then located in the feeding area of the identified feeding artery.

Functional localization studies are not limited by tumor size but are somewhat invasive. Prospective studies of the metastatic liver disease from a malignant PanNET showed that CT and US could detect their presence in 30–80% of patients with metastases, MRI and angiography in 50–85%, and SRS in 70–95% [23]. IOU should be routinely used to assess and identify PanNET [24].

EUS is particularly sensitive for PanNET; however, its ability to detect small duodenal tumors is controversial. Hence EUS is not universally recommended as a first-line procedure in the investigation of rare PanNET. It

may be used in circumstances where MDCT, MRI, and SRS are inconclusive, especially preoperatively. However, in patients with rare PanNET presenting with lymph node metastasis, EUS is rarely necessary. EUS may be helpful in patients with large or aggressive tumors define to more clearly the tumor involvement where surgery is considered.

Insufficient data are available to recommend positron emission tomography (PET)/CT methods on a routine basis, its use remains investigational, and its availability is limited. If results with the earlier recommended imaging are unclear or negative in a patient with rare PanNET, $^{68}$Ga-labeled somatostatin analog PET should be considered with performance by an experienced center.

A number of studies have demonstrated that PET, especially with $^{68}$Ga-labeled somatostatin analogs (DOTA-TOC [DOTA-Tyr-octreotide], DOTA-TATE [DOTA-Tyr-octreotate], DOTA-NOC [DOTA-Nal-octreotide]) when combined with CT ([$^{68}$Ga]DOTA-TOC PET/CT, for example), has high specificity and is more sensitive that SRS or other modalities [25–28]. At present it is not available in many centers and the exact place in the localization algorithm where it should be used has not been clearly defined.

Standard PET with [$^{18}$F]fluoro-2-deoxy-D-glucose (FDG-PET) is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive poorly differentiated pancreatic neuroendocrine carcinomas [7]. Other examinations that may be useful are [$^{18}$F]DOPA-PET or [$^{11}$C]-5-HTP-PET if available and costs are affordable.

## Surgical Treatment

The best treatment for rare PanNET is curative surgical resection. This needs to be performed before liver metastasis develops. Indications for surgery depend on clinical symptom control, tumor size, location, extent, malignancy, and metastatic spread [3,4,7,24,29]. Curative surgery should be indicated whenever possible, even in the presence of metastatic disease, including resectable metastatic disease to the liver and when the patient can tolerate the surgery[3,4,7,24,29]. The types of surgery include pancreaticoduodenectomy, distal pancreatectomy, tumor enucleation, and enucleation in combination with resection depending on the location of the primary tumor.

Curative surgery is always recommended following optimal symptomatic control of the clinical syndrome by medical treatment. Owing to the usually large size of the tumor and the high prevalence of lymph node metastasis in rare PanNET, curative surgery should include pancreatic resection with lymph node dissection through laparotomy. In the case of localized lymph node metastasis or more extensive disease spread, surgery should also be considered if at least 90% of the gross tumor can be resectable.

Laparoscopic resection is currently not recommended because lymphadenectomy and careful inspection for invasion and metastases are needed [7]. Surgery for lymph node metastasis may be performed during treatment of the primary tumor. Cytoreductive surgery should be considered when the metastatic disease is localized or more than 90% of the tumor load can be resected, which may help to improve hormonal control and perhaps extend survival.

## Medical Treatment

Several decades ago, the major cause of death of patients was the untreated effects of the hormone excess state; therefore, it is important to control the hormone levels [4,7], which can be achieved with the combined use of medical, surgical, and radiologic therapies.

Both somatostatin analogs and interferon have been shown to be effective in the control of symptoms in rare PanNET [30]. Somatostatin analogs are an effective treatment in the control of symptoms of rare PanNET, especially in patients with VIPomas, GRHomas, and glucagonomas [30]. Long-acting somatostatin analogs are also reported to be effective in controlling the excess hormone secretion in some cases of somatostatinomas. If somatostatin analogs are ineffective or lose efficacy in controlling the hormone excess state, treatment with interferon may be effective at controlling the symptoms, either alone or in combination with somatostatin analogs.

Somatostatin analogs also have antigrowth effects on PanNET. For the control of symptoms, somatostatin analog therapy should be initiated with the short-acting substance for 1–2 days with titration according to clinical response. The patient can then be transferred to slow-release lanreotide-SR i.m., lanreotide autogel s.c., or octreotide long-acting release i.m. every 4 weeks [31]. Likewise, interferon treatment may help control symptoms of the hormone excess state in rare PanNET, although it has been less well studied than the use of somatostatin analogs. It is reported to be effective in VIPomas not responding to somatostatin analogs and also in isolated cases when combined with somatostatin to control the symptoms of a rare PanNET, which with somatostatin treatment alone there was inadequate symptom control; however, this requires confirmation in a controlled manner [32].

Prospective studies of mammalian target of rapamycin (mTOR) inhibitors with or without octreotide and

tyrosine kinase inhibitors have shown significant prolongation of the survival time of patients with gastrinoma. New cytotoxic chemotherapy with temozolomide and capecitabine has also been reported to be effective.

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# Treatment of Neuroendocrine Tumors of the Pancreas and Biliary Tract

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## Introduction

Neuroendocrine tumors (NET) of the pancreas, duodenum, and biliary tract constitute a rare and heterogeneous group of neoplasms derived from the embryogenetically defined "foregut." Most likely, they originate from pluripotent neuroendocrine stem cells distributed throughout the human body. Traditionally, the term "carcinoids" has been used to define these tumors. Once it became evident that "carcinoids" encompass a unique cluster of tumors with an expansive range of morphologic and biologic characteristics, modern classifications of these neoplasms adopted the terms "neuroendocrine tumor," "neuroendocrine carcinoma," and "neuroendocrine neoplasia" [1].

One of the hallmarks of NET and also of neuroendocrine carcinoma (NEC) is the synthesis and secretion of numerous amines and peptides capable of inducing distinct clinical syndromes. In addition to tumor-specific hormones including insulin and gastrin, proteins such as neuron-specific enolase (NSE), chromogranin A (ChA), pancreastatin, and synaptophysin—commonly expressed in neuroendocrine cells—are produced. Not only do such proteins serve for immunohistochemical diagnosis of NET, they have also been recognized as clinically useful tumor markers in clinical practice. Additional characteristic features of NET encompass specific amine uptake mechanisms and cell surface peptide receptors, namely for somatostatin, that have utility in diagnosis and treatment [2,3].

Foregut NET can occur sporadically or as a component of the genetically determined autosomal dominant syndromes multiple endocrine neoplasia type 1 (MEN1) and MEN4, a recently described, very rare type of MEN. In MEN1-associated pancreatic tumors and in up to 40% of sporadic tumors, loss of the wild-type *MEN1* (MEN1 tumor suppressor gene, menin) allele located on 11q13 can be identified [4]. In cases of heredity, multicentric tumor manifestation should be expected.

## Neuroendocrine Tumors of the Pancreas

Of the NET originating from the pancreas, 65–80% are hormonally active. Although the majority of such tumors secrete insulin or gastrin, less commonly secretion of vasoactive intestinal polypeptide (VIP), glucagon, growth hormone-releasing factor (GRF), or somatostatin can also be observed. Particularly rare are serotonin-producing tumors, with fewer than 150 cases documented in the literature [5]. Tumor nomenclature depends upon the hormone predominantly secreted, namely: insulinoma, gastrinoma, VIPoma, glucagonoma, GRFoma, or somatostatinoma.

### Insulinomas

Insulinomas represent 60% of all pancreatic neuroendocrine tumors (PanNET). More than 90% of such tumors are benign lesions measuring 1–2 cm in size (Fig. 136.1). Approximately 10% of insulinomas are multicentric, most of them associated with MEN1, and 10% are malignant. Malignant insulinomas metastasize to the regional lymph nodes and liver. Localized or diffuse islet cell hyperplasia as a very rare cause of hyperinsulinemic hypoglycemia has been reported in adults and in children (nesidioblastosis). The clinical hallmark of the disease is neuroglycopenia, followed fairly regularly by catecholaminergic responses.

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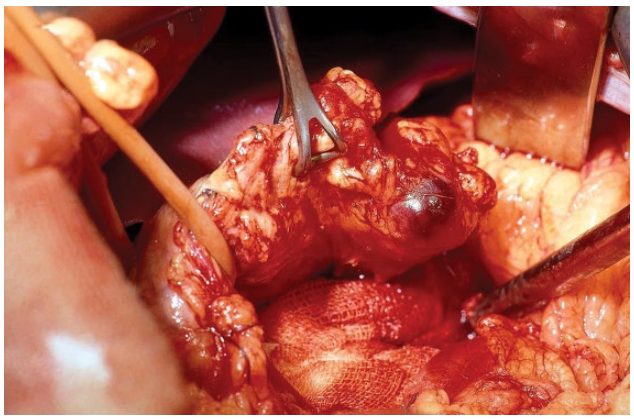

**Figure 136.1** Intraoperative finding of a 1 cm insulinoma at the tail of the pancreas.

The diagnosis of insulinoma is based on following criteria:

- the signs and symptoms of hypoglycemia during periods of fasting or exertion
- documented blood glucose levels near or below 40 mg/dL (<2.2 mmol/L)
- concomitant insulin levels of ≥6 μU/mL (43 pmol/L)
- elevated C-peptide levels (≥0.2 nmol/L)
- absence of sulfonylurea in the plasma.

As the most reliable investigative test, a 72-hour fast has been traditionally considered. In the presence of insulinoma, 80% of the patients will become symptomatic within 24 hours of fasting. The introduction of upgraded assays for insulin, proinsulin, and C-peptide might supersede the standard full 72-hour fast by a 48-hour fast [6]. Although rarely required, provocative tests (tolbutamide test, glucagon test, calcium infusion test) can be of help in cases of anomalous or equivocal standard test results. Once the biochemical diagnosis of an insulinoma has been established, search for adenopathies typical for MEN1 and meticulous evaluation of the family history must be carried out. The diagnosis of MEN1-associated insulinoma can be confirmed by DNA analysis and by proof of menin gene mutations most commonly detected in exons 2, 7, 9, and 1.

#### Localization Studies

The striking advantage of preoperative localization of PanNET has generally been recognized, although some authors suggest that skilled surgical exploration utilizing intraoperative ultrasonography (IOU) is sufficient for a successful outcome [7,8]. In the presence of newer imaging techniques and refinement of standard radiologic procedures, most lesions can be accurately identified prior to surgery.

The sensitivity of transabdominal ultrasonography (US) depends strongly on the experience of the examiner and has been reported more recently to be around 60–70%. For some authors, this is the only preoperative imaging modality. Despite improvements in computed tomography (CT) through the introduction of dynamic contrast-enhanced techniques coupled with 5 mm "cuts," the sensitivity does not exceed 40–65% [9]. In single series, encouraging results have been reported with T1-weighted fat-suppressed and dynamic gadolinium-enhanced magnetic resonance imaging (MRI) [10]. For endoscopic ultrasound (EUS) imaging of PanNET, overall sensitivity and accuracy of up to 95% have been reported [11]. Either as a single technique or in combination with fine-needle aspiration biopsy [12], EUS has emerged as one of the most valuable modalities in the imaging of PanNET. Somatostatin receptor (SR)-based imaging is not very effective in the radiologic interrogation of insulinomas since most of the lesions do not express SR subtype 2, necessary for binding of the radiolabeled octreotide. Owing to high monoamine oxidase A levels in PanNET, promising results were achieved using [$^{11}$C]harmine-labeled tracers [13]. Glucagon-like peptide-1 receptor imaging ([$^{111}$In]diethylenetriaminepentaacetic acid [DTPA]-exendin-4 single-photon emission computed tomography [SPECT]/CT) has recently been reported as an effective second-line imaging modality for patients with negative results on standard imaging.

Grant et al. [14] and Norton et al. [15] were among the first to emphasize the immense usefulness of IOU in the management of PanNET. The method not only allows the identification of the lesion, but also provides additional information concerning the relation of the tumor to the pancreatic duct, the common bile duct, the portal vein, and the superior mesenteric vessels. Particularly for tumors located within the uncinate process, exposure of the complete gland is crucial.

Assignment of insulinomas to regions of the pancreas is possible by selective transhepatic portal venous sampling for insulin. The method regionalizes the lesion to a certain part of the pancreas; however, it does not determine the specific location. Since this highly invasive technique is extremely demanding, it is reserved mainly for reoperations and MEN1-associated tumors [16]. Further improvement of tumor regionalization can be achieved by selective arterial calcium stimulation and blood sampling for insulin gradients in the hepatic veins [17], a technique originally reported by Imamura et al. for regionalization of gastrinomas [18].

#### Perioperative Management of Serum Glucose

The main goal of the preoperative preparation is to avoid severe hypoglycemia. Intravenous administration of glucose is recommended during the night before surgery. Patients suffering from severe hypoglycemia may be

treated with diazoxide or octreotide. Intraoperatively, blood glucose monitoring should continue. Increases in blood sugar levels may confirm successful insulinoma removal. More reliable confirmation concerning completeness of surgery can be gained by insulin measurement with intraoperative rapid insulin assay [19]. Shortly after insulinoma removal, transient hyperglycemia usually occurs. Since glucose levels rarely exceed 200 mg/dL, no specific treatment is necessary.

#### Surgical Management

In patients with tumors expressing malignant features or in the presence of contradictory imaging results, a standard surgical approach to the pancreas and exploration of the liver for metastases, meticulous exposure of the whole organ including the uncinate process, allowing palpation and visual assessment of anterior and posterior pancreatic surfaces, should be carried out [20]. Even if the lesion is already visible, IOU should be performed to assess the relationship of the tumor to the surrounding structures. Regardless of the specific site of the tumor, enucleation or limited parenchyma-sparing resection should be attempted as the "gold standard" for the surgical treatment of benign insulinoma. Blunt dissection close to the capsule of the tumor with the aim of avoiding injury to the main pancreatic duct is recommended in order to prevent fistula formation. The parenchymal defect can be closed or left opened. Local application of sealants can lower the incidence of postoperative fistulas, traditionally reported with an incidence of 13–40%, irrespective of the management of the enucleation cavity [21]. In addition, perioperative somatostatin administration may contribute to a reduction of pancreatic complications.

Laparoscopic resection of PanNET is feasible and safe, particularly in left-sided lesions [22,23]. The majority of patients with sporadic insulinomas localized on imaging and selected patients with MEN1-associated insulinomas nowadays undergo laparoscopic resections [24,25]. The rate of fistulas, however, remains comparable to that in open surgery. If the tumor is not identifiable, blind resections cannot be recommended. Rather than performing a blind distal pancreatectomy, the procedure should be stopped and the patient referred to a center with the possibility of advanced localization techniques and adequate surgical experience [26]. Patients with insulinomas who are not fit for surgery and not manageable conservatively may be considered for EUS-guided radiofrequency ablation using a novel needle electrode [27].

Larger lesions within the body or tail are managed by distal pancreatectomy with preservation of the spleen, if technically feasible. Very rarely seen large tumors within the head of the pancreas, or tumors located deep within the parenchyma and in close proximity to the pancreatic duct, require partial cephalectomy or even pancreaticoduodenectomy [28,29]. For tumors located within the middle portion of the gland that cannot be enucleated, central segmental pancreas resection may be the appropriate technique [30].

Insulinomas associated with the MEN1 syndrome are invariably multifocal and scattered throughout the whole pancreas. Although the number of well-documented patients is rather small, distal subtotal pancreatectomy with splenic preservation and enucleation of any tumors in the head and/or uncinate process appears to be the best procedure [31–34]. Peripancreatic lymphadenectomy is recommended in patients with concomitant gastrinoma or suspected malignancy [35].

### Gastrinoma

Zollinger–Ellison syndrome (ZES) accounts for the clinical manifestation of gastrinomas. Although virtually all gastrinomas derive from the duodenum, some patients present with additional pancreatic lesions. In 60–90% of cases, gastrinomas can be found within the "gastrinoma triangle," a region defined by the junction of the cystic and common bile duct posteriorly, the junction of the second and third portions of the duodenum inferiorly, and the junction of the pancreatic neck and body medially. Although subject to controversial debate, the existence of primary lymph node gastrinomas has been postulated [36]. The majority of the duodenal gastrinomas are multicentric and only few millimeters in size. Of them, approximately 40% are linked to the MEN1 syndrome [37]. In contrast to insulinomas, sporadic gastrinomas are frequently malignant and larger than 2 cm in diameter. Depending upon primary tumor size, liver metastases in combination with paraduodenal and peripancreatic lymph node metastases can be found at the initial diagnosis in up to 70% of patients.

#### Localization Studies

Sensitivities of standard imaging techniques (US, CT, MRI) has been reported to be between 40 and 70% for pancreatic gastrinomas 1–3 cm in size [38]. EUS provides 75% sensitivity for pancreatic gastrinomas and 50% sensitivity for duodenal wall lesions [39]. For the majority of localized gastrinomas and for metastatic disease, SR-based imaging utilizing positron emission tomography (PET)/CT technology (e.g., [$^{68}$Ga]-1,4,7,10-tetraazacyclododecane-4,7,10-tricarboxymethyl-1-yl-acetyl-D-Phe$^{1}$Try$^{3}$-octreotide ([$^{68}$Ga]DOTA-TOC) PET/CT) accounts for the single most accurate localization method [40]. In order to localize preoperatively gastrinomas that remained undetectable by standard imaging techniques, Imamura et al. developed the selective arterial secretagogue injection (SASI) test with secretin or calcium [18]. With this test, over 90% of gastrinomas can be accurately localized [41].

### Surgical Management

Surgical exploration with an attempt at tumor resection is recommended for all sporadic gastrinomas in the absence of multiple nonresectable liver metastases [42]. Compared with medical treatment, surgical tumor removal significantly reduces the risk of metachronous liver metastases. Surgical approaches can be guided by the SASI test [41]. If the test result indicates a tumor within the duodenum only, 80% of patients with sporadic gastrinomas might be successfully treated with resection of the single tumor and periduodenal lymphadenectomy. The remaining 20% typically have multiple duodenal gastrinomas or a combination of duodenal and pancreatic tumors. In patients presumed to have a sporadic gastrinoma in whom no preoperative SASI test was carried out, pancreatic and duodenal exploration are necessary. IOU, careful palpation, and endoscopic transillumination of the duodenal wall are extremely valuable aids. For larger gastrinomas in the head of the pancreas without duodenal tumor, pylorus-preserving pancreatoduodenectomy is recommended. Smaller gastrinomas may be locally resected. In the case of duodenal and pancreatic lesions, pancreatoduodenectomy represents the appropriate therapy. Distal pancreatectomy with regional lymphadenectomy is the treatment of choice for gastrinomas within the body or tail of the pancreas.

For MEN1-associated gastrinomas, recommendations for surgery are much more controversial concerning timing and extent of the procedure [43,44]. Whereas some authors are in favor of less aggressive surgery encompassing spleen-saving distal pancreatectomy, enucleation of NET within the head and uncinate process, duodenotomy and excision of NET, and regional lymph node dissection, others propose more aggressive duodenopancreatic resections in order to achieve durable eugastrinemia [45,46].

Liver metastases are the main prognostic determinant in patients with gastrinomas. No uniform guidelines for the management of tumors in advanced metastatic stage exist. Treatment options are the same as those for other NET metastasized to the liver or primary neuroendocrine tumors of the liver (see later) [47].

## Nonfunctioning Tumors

Patients with nonfunctioning (NF) (non-secreting) PanNET have no clinical symptoms related to hormonal hyperfunction and negative biochemistry for peptides secreted by the pancreatic islets. Immunohistochemically, however, expression of hormones in tumor cells can be revealed. The reported incidence of NF PanNET is 15–53% [48]. In the experience of surgical centers, the majority of such tumors are malignant. As in functioning tumors, the lesions can occur sporadically or within the MEN1 syndrome. At the time of diagnosis, most symptomatic patients are between 40 and 60 years old, presenting with abdominal pain, jaundice, and weight loss. Tumors located within the body or the tail of the pancreas may be clinically silent yet palpable as a bulky mass. In the past, the majority of tumors were diagnosed at an advanced stage. Nowadays, however, small NF NET are increasingly diagnosed incidentally on imaging for reasons unrelated to the pancreas.

Upon diagnosis, differentiation from the pancreatic adenocarcinoma must be considered. In general, patients with NF NET are in a better clinical condition. Synchronous metastases in the liver and/or lymph nodes are frequently present. In our experience, [$^{68}$Ga]DOTA-TOC PET/CT is the most valuable imaging technique for staging well-differentiated and moderately differentiated NF NET (Fig. 136.2). For higher grade tumors or poorly differentiated neuroendocrine carcinomas, [$^{18}$F] fluoro-2-deoxy-D-glucose (FDG) PET/CT is a more accurate imaging modality.

An aggressive surgical approach is the only therapy with potentially curative intent. Resection rates of 26–79% with an overall 5-year survival of 30–80% have been reported [49]. For MEN1-associated NF PanNET, no uniform suggestions exist [43]. Whereas some authors suggest resection of all tumors regardless of the size as soon as visualized, others postulate that with consideration of risk–benefit ratios, surgery may not be necessary in tumors less than 2 cm in diameter [50]. Controversy also exists regarding the management of sporadic small (<2 cm) NF NET; whereas in the opinion of some groups these tumors can be treated conservatively, others recommend surgical resection since both liver metastases and lymph node metastases have been reported in single patients with NF NET <2 cm in size [51]. Another topic under ongoing debate is the resection of primary NF PanNET in the setting of unresectable liver metastases. Although the quality of the evidence in the existing reports in favor of primary tumor resection is rather poor, the resectional approach can be justified in selected patients with tumors amendable for distal pancreatectomy and synchronous liver metastases suitable for interventional or medical treatment [52]. Most recently, peptide receptor radionuclide therapy has been introduced in the multimodal management of advanced PanNET as a potential tool for downstaging in patients with primarily nonresectable tumors [53,54].

# Neuroendocrine Tumors of the Duodenum

Histopathologically, five types of duodenal NET can be discriminated, namely duodenal gastrinomas, somatostatinomas, nonfunctioning serotonin-, gastrin-,

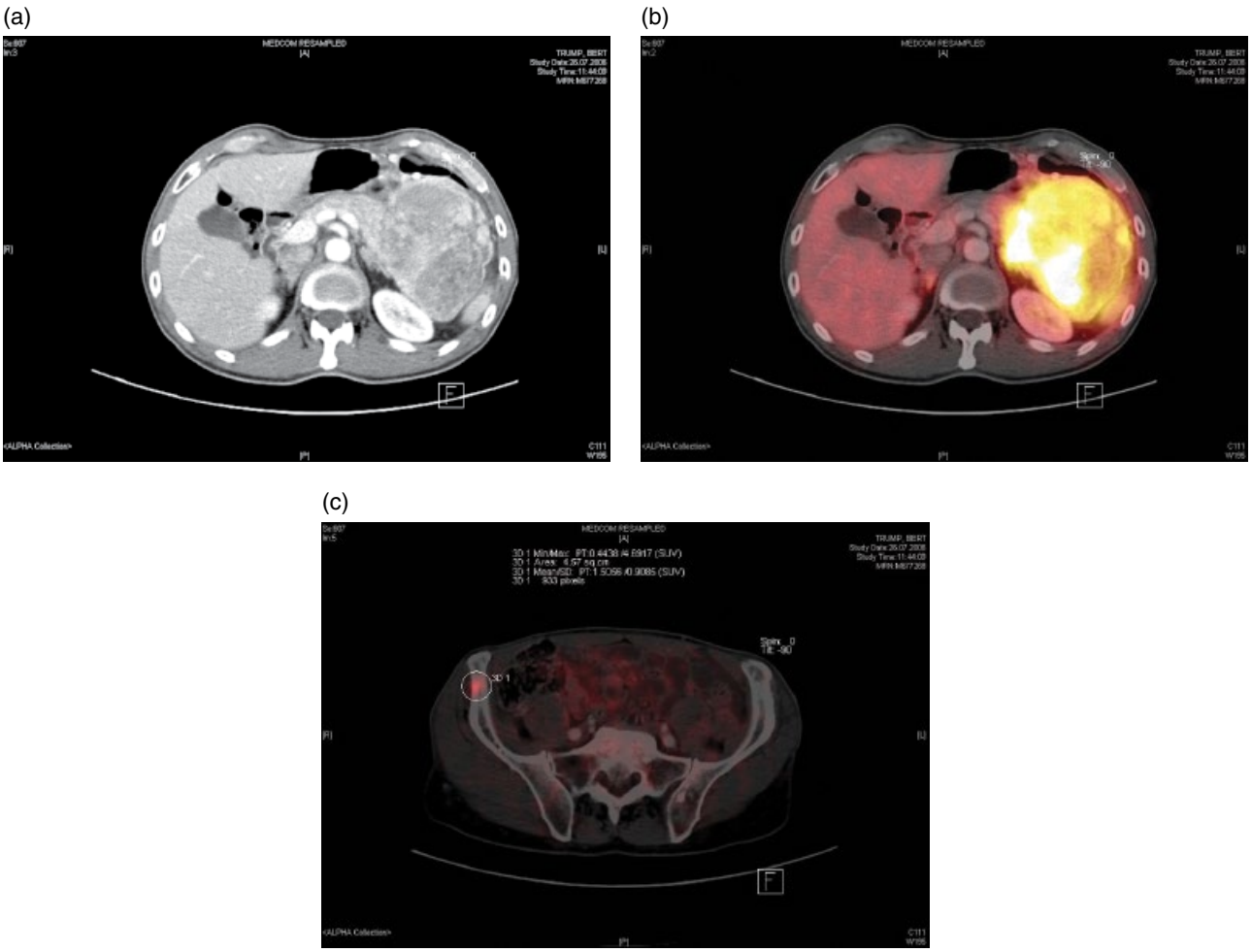


**Figure 136.2** Preoperative imaging studies in a patient with an NF NET of the pancreas. (a) On CT scan, a 20 cm diameter tumor in the left abdomen is shown. (b) [$^{68}$Ga]DOTA-TOC PET/CT demonstrates significant radionuclide uptake in the left upper abdomen. (c) Additionally, pathologic uptake, indicating a metastasis, is demonstrable within the right ilium. This finding was not seen on CT scan.

or calcitonin-producing tumors, poorly differentiated and predominantly ampullary NEC, and duodenal gangliocytic paragangliomas [5,55,56]. Approximately 30% of duodenal NET are related to von Recklinghausen disease (neurofibromatosis type 1 [NF1]), MEN1, and/or pheochromocytomas [57]. The majority of duodenal NET express ChA and NSE. In contrast to other locations, NET originating from the duodenum were found to be the only neuroendocrine lesions expressing the peptide marker xenin [58]. Based on the experience with a heterogeneous group of 99 NET of the duodenum, Burke et al. [59] determined three pathologic characteristics of the primary tumor as independent risk factors for metastatic spread: involvement of muscularis propria, size greater than 2 cm, and the presence of mitotic figures.

Gastrinomas located in the first and second portions of the duodenum account for approximately two-thirds of all duodenal NET. These tumors occur either sporadically or as a component of the MEN1 syndrome. Both sporadic and hereditary tumors are generally small (<1 cm), but multifocal in cases of familial determination. Although of small size and growth limited to the mucosa and submucosa, duodenal gastrinomas frequently present with significant lymph node metastases [3,60]. In contrast to pancreatic gastrinomas, distant metastases rarely occur in sporadic and hereditary duodenal tumors [44,55].

Duodenal somatostatinoma, located either within the ampulla of Vatar or periampullary, account for 15% of all duodenal NET. Insular growth pattern and psammoma body formation are histologic hallmarks of these tumors. In case of muscularis propria infiltration, malignancy must be assumed. Tumor size and mitotic activity have no correlation with metastatic potential [61]. Somatostatinoma syndrome, typical for PanNET expressing somatostatin, does not occur in these duodenal tumors. Association with NF1 and bilateral pheochromocytoma has been documented [62]. Owing to the

unpredictable behavior of ampullary or periampullary NET, a radical surgical approach, most frequently in the form of a Whipple procedure, is recommended [63].

NF duodenal NET encompass lesions with both favorable and less favorable prognoses. Whereas well-differentiated tumors confined to submucosa behave benignly, advanced metastases are frequently associated with poorly differentiated neoplasms. Gangliocytic paragangliomas represent a unique subgroup of duodenal NET located within the para-ampullary region, and despite a tumor size of >2 cm and infiltration of the muscularis propria, they generally have a benign clinical course.

With the exception of ampullary/periampullary NET, duodenal NET smaller than 1 cm and in the absence of signs of invasion of the muscularis propria and of metastases may be excised locally by endoscopic resection with or without submucosal saline injection [64–67]. In this regard, EUS proved to be of extremely high value. It should be stressed, however, that lymph node metastases can be found also in tumors less than 1 cm in size [68]. For tumors between 1 and 2 cm or larger, local full-thickness excision through an open transduodenal approach or segmental duodenal resection with a side-to-side duodenostomy and regional lympadenectomy is recommended in order to achieve complete and curative resection [44,69].

## Neuroendocrine Tumors of the Liver

Despite the liver being the predominant site of neuroendocrine tumor metastases, primary NET arising within the liver are rare. In a study of 13,715 carcinoid tumors accumulated by the National Cancer Institute in Bethesda, MD, over a 50-year period, only 45 primary hepatic tumors were documented [2]. Prior to the assumption that a hepatic NET presents a primary lesion, a meticulous search for extrahepatic tumor manifestation is pivotal for the effective management of such patients [70,71].

Patients with these tumors present with nonspecific hepatic clinical syndromes such as biliary obstruction or upper abdominal discomfort. In contrast to neuroendocrine liver metastases, flushing, diarrhea, bronchial construction, and carcinoid heart syndrome, which are pathognomonic for the classic carcinoid syndrome, will be found in only about 5% of cases [2]. On transabdominal US, the tumor appears as a hyperechoic lesion; nevertheless, the appearance on radiologic imaging is not characteristic [72]. The treatment strategy comprises several curative and palliative options including surgery, locally destructive techniques such as radiofrequency or laser-induced thermoablation, transarterial embolization alone or with chemotherapy, selective internal radiotherapy, somatostatin analogs, targeted medical therapy, and peptide receptor radionuclide therapy. In contrast to the poor overall 5-year survival of 18.4% reported in early studies [2], a more radical surgical approach including advanced hepatic resections or liver transplantation in selected cases and multimodal treatment concepts achieved 3-year disease-free survival rate of more than 75% [73,74].

## Neuroendocrine Tumors of the Extrahepatic Biliary Tract

These very unusual neoplasia account for 0.2–2% of all gastrointestinal NET [2]. In approximately 60% of patients, the tumor develops within the common bile duct [75–77]. Further locations are the perihilar region (28%), cystic duct (11%), and common hepatic duct (3%) [76]. Unlike adenocarcinomas of the extrahepatic biliary system, biliary NET predominantly affect female patients younger than 50 years of age. The symptom most frequently seen is painless jaundice with or without pruritus. The diagnostic spectrum includes US, CT, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, and percutaneous transhepatic cholangiography. For tumor staging purposes, SR-based imaging provides valuable information. As with other tumors originating from the biliary system, accurate preoperative diagnosis remains difficult, particularly regarding delineation from cholangiocarcinoma [78]. Upon microscopic examination, the tumors present with a trabecular or nesting pattern with occasional tubule formation, and cells expressing ChA, synaptophysin, serotonin, pancreatic polypeptide, and/or somatostatin [79]. Whereas local invasion is not common, metastatic lymph node involvement and liver metastases can be found in 30% of patients [75,77,80].

An aggressive surgical approach provides an overall favorable long-term prognosis. In early tumor stages and in the absence of metastases, 5-year survival of 60–100% has been documented [2,77,79]. The extent of resection depends mainly upon the size, the stage, and the location of the tumor. Common bile duct resection and Roux-en-Y hepaticojejunostomy represent the standard treatment of choice for lesions within the central portion of the common bile duct. For tumors affecting the hepatic duct bifurcation, resection of the bifurcation, in some cases in combination with partial hepatectomy, is necessary. Tumors of the distal part of the common bile duct require either segmental bile duct resection or partial pancreaticoduodenectomy (Whipple procedure). Extensive hilar lympadenectomy is a mandatory part of the procedure.

## Neuroendocrine Tumors of the Gallbladder

Approximately 0.2% of all NET of the gastrointestinal tract originate from the gallbladder [5]. They usually affect females, causing right upper abdominal discomfort and jaundice. As in NET of the extrahepatic biliary tree, the diagnosis is frequently made first after surgery for presumed cholecystitis or adenocarcinoma of the gallbladder. Histologically, the tumor cells are positive for Grimelius staining and ChA, and less commonly for NSE or pancreatic polypeptide [81,82]. Nishigami et al. pointed out that owing to the entirely different prognosis of the lesions, a discrimination between the carcinoid tumors and endocrine cell carcinomas of the gallbladder must be considered [81].Whereas classical carcinoids of the gallbladder virtually never metastasize or grow invasively, endocrine cell carcinoma (atypical carcinoids) exhibit a much more aggressive behavior [81–83]. Clear-cell carcinoid tumors of the gallbladder, either as a sporadic tumor [84] or in association with von Hippel–Lindau syndrome [85], have been reported as a distinctive entity. Immunohistochemical positivity for inhibin was found to be pathognomonic for the genetically determined tumor form [85].

Although laparoscopic resection might be feasible in a small classical carcinoid confined to the wall of the gallbladder [86], the majority of patients, particularly those with endocrine cell carcinoma, require a more radical surgical approach in terms of hepatic resection, removal of the extrahepatic bile duct, and extended hilar lymphadenectomy [83,87]. An overall 5-year survival of approximately 60% has been reported [2].

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# Long-Term Outcome After Treatment of Neuroendocrine Tumors of the Pancreas

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## Long-Term Outcome After Treatment of Endocrine Tumors

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## Introduction

Pancreatic endocrine tumors (PanNET), representing 1–2% of pancreatic neoplasms, comprise an array of heterogeneous, mostly slow-growing tumors. This wide spectrum ranges from indolent, hormone-secreting, localized, and easily accessible tumors to nonfunctioning, widely metastatic, and surgically less amenable tumors, at various time points on the tumor growth trajectory. These tumors may differ in tumor entity, clinical presentation (symptomatic versus asymptomatic), hormone secretion (functioning versus nonfunctioning), genetic background (sporadic versus hereditary), anatomic location (pancreatic head versus body and tail; anterior versus posterior pancreas), staging (primary tumor size, number and size of lymph node and distant metastases), and grading (differentiated versus poorly differentiated).

Clinical interventions, sometimes due to disparate surgical skills and the patient's physical condition, have varied because of the need to be attuned to the individual situation: enucleation versus limited resection versus extended resection; primary surgery versus reoperation; clear versus involved surgical margins; tumor resectability versus irresectability. Nor have neoadjuvant and adjuvant therapies, employing different agents and regimens, been standardized. Given the longevity of many patients with PanNET, many observation periods were short, differing in duration and the intensity of clinical monitoring. Because treatment must be commensurate with the extent of disease, surgical and nonsurgical patients form selected groups of patients defying standardization of therapy.

Because many series lumped together disparate endocrine tumors, no high-quality outcome studies have been forthcoming for any of these scenarios, leaving univariate risk factors unvalidated. Although some general principles have emerged from institutional series and tumor registries, the role and extent of surgery remain to be delineated for a number of clinical settings.

## Risk Stratification of Pancreatic Endocrine Tumors

### Tumor Staging

Measuring extent of cancer is also relevant to PanNET. In 2006, the European Neuroendocrine Tumor Society (ENETS) developed the first staging system for neuroendocrine tumors (henceforth referred to as the ENETS TNM) from the combined published experience of single centers at the level of the neuroendocrine tumor patient. A competing staging system, derived from a cancer registry database by the International Union Against Cancer, now the Union for International Cancer Control (UICC), in 2010 and now endorsed by both the American Joint Committee on Cancer (AJCC) and the World Health Organization (WHO), followed suit (henceforth referred to as the UICC/AJCC/WHO TNM).

It is noteworthy that the UICC/AJCC/WHO TNM, unlike the ENETS TNM, is the same as for exocrine pancreatic tumors and not meant for high-grade PanNET [1]. As a consequence, tumor definition and stages differ greatly between the ENETS TNM and the UICC/AJCC/WHO TNM staging systems. Of note, the UICC/AJCC/WHO TNM requires information on peripancreatic soft tissue invasion regardless of tumor size, a feature difficult to assess, to distinguish between UICC/AJCC/WHO categories pT2 and pT3.

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#### Recurrence-Free Survival

Five-year recurrence-free survival rates in 123 patients with nonmetastatic, surgically resected PanNET [2] were 78, 53, and 33% for AJCC stages I, II, and III ($P < 0.01$) and 100, 70, and 53% for ENETS stages I, II, and III ($P = 0.18$). On excluding patients referred with metastatic recurrence, the 5-year recurrence-free survival rates were 90, 73, and 66% for AJCC stages I, II, and III and 100, 84, and 75% for ENETS stages I, II, and III, with recurrence rates peaking at 2 years after surgery [2].

#### Cancer-Specific Mortality

For a large series of 1072 patients with neoplasms of the endocrine pancreas and at least 2 years of follow-up from eight European centers, cancer-specific mortality was compared between the two TNM staging systems [1]. On Cox regression, the ENETS TNM system allocated patients to four significantly different ($P < 0.001$) and equally populated risk groups, with odds ratios (OR) for death of 16.2 for stage II, 51.8 for stage III, and 161.0 for stage IV compared with stage I. In contrast, the UICC/AJCC/WHO TNM compressed the disease into three differently populated classes, with OR for death of 9.6 for stage II, 9.3 for stage III, and 30.8 for stage IV compared with stage I ($P < 0.001$). Multivariable modeling revealed that curative surgery, TNM staging, and grading effectively indicated cancer-specific death. Although the ENETS and UICC/AJCC/WHO TNM staging systems independently predicted cancer-specific survival, the latter resulted in much larger 95% confidence intervals for each stage. Wider confidence intervals may reflect more limited discriminatory power of the UICC/AJCC/WHO TNM system in patients with PanNET [1].

In a series of 326 patients with sporadic, nonfunctional, surgically resected PanNET, 5-year overall survival rates were 93, 74, and 56% for AJCC stages I, II, and IV and 97, 87, 73, and 56% for ENETS stages I, II, III, and IV [3].

### Tumor Grading

Because the percentage of tumor cells staining positive on Ki-67 immunohistochemistry can be heterogeneous, more substantial tumor samples are needed to facilitate the distinction of low-grade from intermediate-grade tumors. The 2010 WHO grading, based on the mitotic count (<2, 2–20, and >20 mitoses per 10 high-power fields) and the Ki-67 index (<3, 3–20, and >20%), holds important prognostic information, especially in the absence of staging information.

In the largest cohort of patients with PanNET published to date, grading became the second most powerful independent predictor of survival after curative surgery when TNM staging, the previously second most important predictor of death, had been omitted from multivariable modeling [1].

These results were confirmed in a study of 483 patients with PanNET, in which Ki-67 (>20 versus ≤2%; $P = 0.01$) and surgical resection (yes versus no) (hazard ratio [HR] 0.92, $P = 0.001$) were the only independent predictors of survival [4]. Among patients who underwent surgery, high Ki-67 index (HR 10.4, $P = 0.02$) and poor differentiation (HR 8.2, $P = 0.03$) were the only independent predictors of clinical outcome [4].

## Surgical Considerations for Pancreatic Endocrine Tumors

Unlike functional PanNET presenting with signs and symptoms of hormone excess, nonfunctioning PanNET do not produce identifiable symptoms. This is why nonfunctioning PanNET frequently manifest with complaints caused by tumor expansion, invasion, and/or metastatic disease and generally have a graver prognosis. Some clinically "nonfunctioning" tumors synthesize hormones in quantities too low to elicit complaints (e.g., glucagonoma) or hormones unable to produce symptoms in humans (e.g., pancreatic polypeptide).

Because curative surgery determines survival more than tumor stage, the patient's clinical outcome hinges on the feasibility of complete tumor resection.

### Nonfunctioning Tumors

#### Localized Tumors

Although no high-quality data comparing expectant observation with surgical intervention have been forthcoming, pursuing a "wait and see," "first, do not harm" policy for small, nongrowing, benign-appearing tumors may be a viable alternative option in certain patients [5]. This concept is epitomized by a series of 46 patients with asymptomatic sporadic nonfunctioning PanNET <2 cm over a median follow-up of 34 months [6]. In six (13%) patients, a ≥20% increase in tumor size was observed. Median tumor growth was estimated at 0.12 mm per year. No lymph node or distant metastases were seen on serial imaging. Eight (17%) patients underwent surgery for grade 1, node-negative PanNET T1 (seven patients) or T2 (one patient) after a median of 41 months [6].

***Unifocal Tumors*** Localized tumors are easier to cure surgically when they are small, benign, stay clear of large vessels and the bile duct, and involve only the anterior aspects of the pancreas, preferably the body or tail. To develop an effective surgical treatment plan, a thorough clinical workup is essential to settle these important points before the operation and ensure that no additional tumors are missed.

There are basically three surgical techniques, each of which may be adequate depending on the circumstances of the case: tumor enucleation (leaving peritumoral tissue behind); excision (clearing peritumoral tissue together with the tumor); and pancreatic resection, which is bound to vary greatly in extent and scope depending on tumor location and type.

From an oncologic perspective, all three surgical interventions are equally effective as to clinical outcome provided that they clear the pancreatic tumor in its entirety [1,7]. Pancreatic surgery that leaves gross tumor behind is unlikely to benefit the patient. In patients without distant disease, every effort should be made to clear the mesenteric vessels of malignancy.

***Multifocal Tumors*** When additional endocrine tumors are present or the family history is suggestive of hereditary disease, specifically multiple endocrine neoplasia type 1 (MEN1) or von Hippel–Lindau syndrome (VHL), the surgical plan needs to be adjusted accordingly. All endocrine tumors identified need to be considered both individually and in conjunction with one another. Intraoperatively, the pancreas should be mobilized to allow for careful examination of the posterior aspect of the organ.

Owing to the variety of constellations conceivable, multiple tumors are notoriously difficult to standardize, hampering predictions about clinical outcome. A recent series of 60 MEN1 patients from four institutions, who harbored one or more nonfunctioning PanNET ≤2 cm, yielded progression-free survival rates of 63% at 5 years, 39% at 10 years, and 10% at 15 years, with no difference between the surgical and nonsurgical groups [8]. However, missed, unresected, and metachronous endocrine tumors, especially when malignant, can have a detrimental impact on the patient's clinical outcome.

### Metastatic Tumors

***Lymph Node Metastases*** The frequency of lymph node metastasis is higher for tumors of the pancreas larger than 1.5 cm (OR 4.7) and for tumors of the head as compared with the body and tail of the pancreas (OR 2.8) [9]. Furthermore, the time to development of liver metastases is significantly reduced for patients with lymph node metastases alone compared with those with none [10].

Disease-related survival decreases as the number of lymph nodes involved increases [10]. Overall, node-positive tumors have worse 5-year disease-specific survival rates than node-negative tumors (69–70 versus 81–90%) [11,12]. In nonfunctional PanNET ≤2 cm, the 10-year survival rate was better, reaching 87% in node-negative patients and 34% in node-positive patients [13].

These data hint at an interrelation between primary tumor size, lymph node metastasis, and liver metastasis, which signify increasing cancer-specific mortality for these three risk factors.

***Distant Liver Metastases as the Sole Systemic Manifestation*** Several retrospective studies focused on liver metastases, the predominant manifestation of systemic disease, as the sole clinical appearance of PanNET. These series included a mixture of hormone-secreting and nonfunctional, benign and malignant, sporadic and hereditary tumor entities arising from the head, body, and tail of the pancreas. This heterogeneity, compounded by different surgical interventions for disparate tumor types, grades, and stages, compromised the quality of these studies, hindering the generation of high-quality data for any tumor entity. Furthermore, liver metastases may be limited or diffuse, occurring synchronously or metachronously from first diagnosis of the primary tumor, or originating from within the residual liver tissue after hepatic resection. The prognostic ramifications of synchronous versus metachronous liver metastases are ill-defined, although the former seem to portend a bleaker prognosis than the latter. Despite these limitations, 5- and 10-year survival rates in most of these series have been in the order of 60–80 and 40–60%, respectively.

In 291 patients with poorly differentiated PanNET, the presence of distant metastasis (HR 2.41; $P < 0.001$) and lymph node metastasis (HR 2.10; $P = 0.004$), and poor differentiation (HR 6.96; $P = 0.032$) were independent predictors of worse survival, with distant metastasis having a significant impact (0 versus 43%; $P = 0.036$) on 5-year overall survival [14].

Enucleation of hepatic metastases, leaving surrounding parenchyma behind, is associated with greater short-term morbidity than hepatic resection, which entails the excision of metastases together with the surrounding liver parenchyma. In light of these data, it is challenging to conduct head-to-head comparisons between enucleation of and hepatic resection for liver metastases from PanNET. To facilitate surgical decisions, information about the biological behavior of the PanNET at hand (low versus high risk) is needed. According to current thinking, debulking needs to reduce the liver tumor burden by as much as 90% to improve outcome [15]. In some patients, total hepatectomy with subsequent liver transplantation has been used. Liver resection has been shown to improve symptom relief and survival compared with nonsurgical therapy [16].

***Widespread Systemic Disease*** In 8% of patients, malignant PanNET have spread to other distant organs, usually the lung [17]. Peritoneal carcinomatosis is uncommon in patients with foregut-derived neuroendocrine tumors but, if present, is frequently associated with liver metastases [18]. When the disease is widespread and

affects distant sites other than the liver, extended surgery may not change the clinical course. In this scenario, adjuvant treatments, including targeted therapies, come into play.

## Functioning Tumors

Whereas nonfunctioning tumors often become clinically apparent through complaints caused by tumor expansion, invasion, or metastatic disease, functional tumors, such as insulinoma, gastrinoma, and vasoactive intestinal peptide-releasing tumor (VIPoma) tend to be diagnosed at earlier stages when they present with signs and symptoms of hormone excess. The nature and intensity of these clinical signs and symptoms depend on both hormone type(s) and the quantities of the secreted hormone(s). In hereditary disease, regionalization of PanNET by selective arterial stimulation tests should be performed to avoid overlooking secondary functioning tumors [19].

Hormone excess typically produces clinical complaints that are more debilitating and diminish health-related quality of life more than those produced by tumor expansion, invasion, or metastatic disease. Hormonal symptoms cannot resolve if secondary hormone-secreting tumors are missed on enucleation or pancreatic resection, usually in hereditary conditions, or may occur again if the resection is inadequate, failing to remove the tumor in its entirety.

### Insulinoma

Because it almost always is benign, insulinoma forms an ideal surgical target for enucleation. Surgical cure rates for insulinoma are excellent, approaching 99% in experienced hands. Rare instances of failure were due to missed secondary insulinomas in the context of MEN1, malignant insulinomas that (i) were misdiagnosed as benign, (ii) were too large to be removed completely, or (iii) at first diagnosis had spread beyond the confines of the pancreas to involve regional nodes and distant organs, including the liver.

Malignant insulinoma takes a more varied clinical course. Some present with isolated lymph node metastases from the outset, whereas others, developing clinically apparent solitary or multiple liver metastases in the course of the disease, recur later on. Owing to the rarity and variable presentation of malignant insulinoma, comparative effectiveness research investigating surgical resection techniques for benign or malignant insulinoma has not been performed.

In patients with insulinoma, the clinical–histopathologic risk profile is heavily stacked in favor of surgical cure: small tumors, benign in nature; young patients with little, if any, comorbidities; enucleation or very limited pancreatic resection required only. As a natural consequence, patients with insulinoma, as a group, enjoy one of the best clinical outcomes among all patients with PanNET [1].

### Gastrinoma

Contrary to previous assumptions, sporadic gastrinomas are solitary tumors that rarely originate from within the pancreas (16%). Patients with gastrinoma also are younger than patients with nonfunctioning PanNET [1]. Most gastrinomas arise from outside the pancreas [20]: the duodenum (57%), lymph nodes (19%), or ectopic sites (9%). Because most duodenal gastrinomas (83%) do not exceed 10 mm in greatest dimension, transduodenal exploration is necessary to localize and eliminate the tumoral source of gastrin excess [20]. Multiple duodenal gastrinoma is such an exceptional condition that duodenectomy or pancreaticoduodenectomy is unwarranted in the absence of a definite surgical target identified on imaging and/or intraoperative digital palpation.

Metastatic liver disease is the principal cause of death in patients with gastrinoma. Although prospective clinical trials randomizing surgical, medical, and supportive care treatment are unfeasible on ethical grounds, retrospective data support the use of extended surgery in an effort to decrease metachronous liver metastasis. A study of a large series of 124 patients with nonmetastatic Zollinger–Ellison syndrome (ZES) compared 98 patients with abdominal surgery for gastrinoma with 26 patients similar in extent of disease and follow-up who were managed conservatively [21]. In the surgical group, the incidence of hepatic metastases was 3%, as opposed to 23 % in the medical group. Within the limitations of this observational study, these data pointed toward the usefulness of early transduodenal exploration and tumor resection coupled with resection of liver metastases and supported by adjuvant therapy.

### Glucagonoma, Somatostatinoma, and VIPoma

Most glucagonomas and somatostatinomas are considered "nonfunctional" even when they present with characteristic signs and symptoms, as with necrolytic migratory erythema, which is pathognomonic of glucagonoma. Somatostatinomas, lacking characteristic stigmata, are often so large at the time of diagnosis that they can no longer be enucleated.

VIPoma typically causes Verner–Morrison syndrome, which is characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA). These tumors, being the subject matter of single reports or small case series, are extremely rare, precluding the generation of comprehensive evidence-based data.

## Conclusion

Although great strides have been made in terms of staging and grading of PanNET, it has proved challenging to assemble large enough series of patients with PanNET and sufficiently long follow-up periods that would permit the adjustment of postoperative outcome for a large number of confounding variables: tumor entity, clinical presentation, hormone secretion, genetic background, location within the pancreas, tumor stage and grade, type and extent of surgery, surgical margins, and neoadjuvant and adjuvant therapies.

Because adjuvant chemotherapy and targeted therapies are palliative rather than curative, adoption of extended surgery has been advocated for the majority of patients with PanNET who are reasonably fit to tolerate the procedure. Although the need for surgical removal of larger tumors is undisputed in the absence of systemic disease, this need is much less evident for smaller tumors, many of which warrant expectant observation. There is a dire need for predictive molecular markers that afford better risk stratification of PanNET than currently provided for by Ki-67 grading and current imaging modalities.

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# Section 9

# Periampullary Cancers and Tumors Other Than Pancreatic Cancer

# 138

# Periampullary Cancer: Clinical Presentation and Diagnostic Strategies

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## Introduction

Periampullary tumors include both benign and malignant neoplasms arising at or near the ampulla of Vater. The hallmark symptom of these tumors is painless obstructive jaundice, arising from their common location. The vast majority of periampullary tumors are malignant, with pancreatic adenocarcinoma being the most prevalent, followed by cancers of the ampulla of Vater, distal common bile duct, and duodenum, respectively. Surgical resection is the mainstay of therapy for periampullary tumors. Almost all resectable malignant and most benign tumors in this area are ultimately managed with pancreaticoduodenectomy. In patients with unresectable disease, relief of biliary obstruction, through either biliary stenting or surgical biliary bypass, is essential for palliation. Determining the exact etiology of a periampullary malignancy can be challenging for both the surgeon and the pathologist. The clinical presentation, preoperative imaging studies, and intraoperative findings may not allow differentiation of the specific site of origin. The most common location for periampullary malignancy is the head of the pancreas, which accounts for 55–65% of tumors identified in resected specimens (Table 138.1). The incidence of ampullary, distal common bile duct, and duodenal carcinomas presented in the table is somewhat higher than their overall incidence, because they have higher rates of resectability than tumors arising in the head of the pancreas. With this in mind, analysis of patients with both resectable and unresectable disease would suggest adenocarcinoma of the pancreas accounts for up to 90% of cases.

Although indolent neoplasms such as neuroendocrine tumors or benign tumors (e.g., adenomas) occasionally occur in the periampullary region, they are much less frequent. The benign tumors occasionally present with unrelenting jaundice secondary to bile duct obstruction, as seen with periampullary carcinoma. Therefore, benign disease is sometimes mistaken for carcinoma in a persistently jaundiced patient. The more common clinical scenario involves distinguishing malignant biliary obstruction from fibrosing chronic pancreatitis or the benign condition, autoimmune pancreatitis (also known as IgG4-associated pancreatitis or lymphoplasmacytic sclerosing pancreatitis) [1,2].

The management of pancreatic cancer is discussed in depth in Section 5. Therefore, this chapter reviews the clinical presentation and diagnostic strategy for periampullary neoplasms.

## Clinical Presentation

Many of the difficulties in the treatment of periampullary carcinomas result from the difficulty in diagnosing the disease in its early stages. Early symptoms of periampullary cancer tend to be nonspecific and are often minimized by both the patient and the physician. This frequently leads to a delay of weeks to several months in making the diagnosis. It is often not until the patient develops jaundice that the diagnosis is made. Jaundice is usually progressive, relentless, and often associated with significant pruritis. For tumors of the ampulla of Vater, distal common bile duct, and periampullary duodenum, clinical jaundice tends to present early, contributing to a higher resectability rate with these lesions compared with tumors of the pancreas. The development of jaundice in any patient over age 40 should arouse suspicion of a periampullary neoplasm and warrants an aggressive pursuit of the diagnosis. Ampullary carcinoma can

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

**Table 138.1** Relative frequencies of resected periampullary cancers.

| Location | Percentage |
|---|---|
| Head of pancreas | 60 |
| Ampulla of Vater | 20 |
| Distal common bile duct | 10 |
| Duodenum | 10 |

present with intermittent jaundice either due to a polypoid tumor that only intermittently obstructs the bile duct orifice or as a result of growth and necrosis leading to transient biliary obstruction during the growth phase. In this case, it requires a high level of suspicion on the part of the primary physician to pursue the appropriate evaluation.

Other symptoms of periampullary neoplasms include abdominal pain, anorexia, nausea, and weight loss. Moderate intensity pain may be present as a result of obstruction of the biliary or pancreatic duct. This pain in the epigastrium or right upper quadrant is often described as dull, may be accompanied by back pain, and is often aggravated by eating. Duodenal obstruction causing vomiting is usually a late manifestation of periampullary cancers, although duodenal cancers may circumferentially narrow the lumen at an earlier stage. Melena or hematemesis may occur as a result of significant bleeding from ampullary or duodenal tumors, although commonly blood loss is chronic and intermittent. Finally, an unexplained attack of pancreatitis in an older patient must be thoroughly investigated once the acute attack has subsided, as this may be the first manifestation of a periampullary neoplasm. In a report by Rattner et al. [3] acute pancreatitis was the initial symptom in 25% of patients with ampullary neoplasms. Similarly, intraductal papillary mucinous neoplasms can also present with abdominal pain and hyperamylasemia due to ductal obstruction by mucin [4,5].

In addition to the presenting symptoms, the patient's past medical and family history may also be highly relevant. Patients with the hereditary disorders of Gardner's syndrome and familial adenomatous polyposis of the colon have more than a 200-fold increased risk of ampullary and duodenal carcinomas compared with the general population [6]. In most of these patients, the polyps will be multiple and involve much of the duodenal mucosa.

In many patients, physical findings are absent, especially early in the course. The most common findings in patients with periampullary cancers are jaundice and hepatomegaly. Hepatomegaly usually reflects congestion associated with biliary obstruction, and does not imply the presence of metastatic disease. The gallbladder may also be palpable in approximately 25% of patients. Occult fecal blood is found in those patients with periampullary cancers that bleed into the intestinal lumen.

## Diagnostic Evaluation

### Laboratory Data

There are no specific diagnostic laboratory tests for periampullary carcinoma. Virtually all patients present with abnormal liver functions tests, characteristic of extrahepatic obstruction, including increased plasma concentrations of bilirubin and alkaline phosphatase. A patient's transaminases may also be elevated, but usually not to the same extent as the alkaline phosphatase. In cases of malignant obstruction, marked elevations of bilirubin greater than 10–15 mg/dL may be seen. If extrahepatic obstruction has been longstanding, the prothrombin time may also be prolonged. Anemia may also be present with periampullary cancers arising from the duodenum or ampulla, as these patients are more likely to experience clinically significant bleeding.

Elevation of the tumor-associated carbohydrate antigen (CA) 19-9 above 37 kU/L has been reported to have a sensitivity of 81% and a specificity of 90% for pancreatic adenocarcinoma [7]. The sensitivity of CA 19-9 for the diagnosis of cholangiocarcinoma is approximately 70% [8,9]. Unfortunately, CA 19-9 concentrations are frequently normal in early stages of pancreatic and periampullary neoplasms and elevated CA 19-9 levels are seen in many benign hepatobiliary processes, such as pancreatitis and cholestasis. In addition, approximately 6% Caucasian and up to 22% of non-Caucasian patients have Lewis A-B genotype and do not make CA 19-9 [10]. Although a number of genetic markers or alterations have been associated with pancreatic cancer (K*ras*, p53, SMAD4, CDKN2A), little such information is available for nonpancreatic periampullary neoplasms [10,11].

### Imaging and Radiologic Evaluation

Early diagnosis of periampullary cancer requires an appropriate level of clinical suspicion and aggressiveness in pursuing the diagnosis. Prompt evaluation of a patient with jaundice offers the opportunity for early diagnosis. Any patient presenting with jaundice should undergo focused diagnostic imaging in order to evaluate the level of biliary obstruction, the most likely etiology of the abnormality, and the resectability of the lesion if a tumor is identified.

#### Ultrasonography

Transabdominal ultrasound may be the initial imaging modality for patients presenting with abdominal pain or obstructive jaundice as it documents the presence of

gallstones or other biliary or hepatic abnormalities that may mimic malignancy (e.g., Mirizzi syndrome). Ultrasound can also accurately define the level of biliary obstruction, thereby narrowing the differential diagnosis. Other important findings that can be visualized with ultrasound include ascites, liver metastases, and regional lymphadenopathy. A major limitation of ultrasound in the periampullary region is a 15–20% rate of technically inadequate studies, which can be due to patient habitus, intervening bowel gas, or technical limitations of the operator. Conversely, advantages of ultrasound include a lack of radiation exposure and relative low cost.

#### Computed Tomography

Despite the advantages of ultrasound, the high accuracy and reproducibility of computed tomography (CT) and its widespread availability make it the most useful and often most cost-effective test for the evaluation of a patient with a suspected periampullary malignancy [12]. CT can detect pancreatic masses as small as 1 cm and provides important information about the level of biliary obstruction with respect to the pancreatic parenchyma if no mass is seen (Fig. 138.1). The optimal technique for evaluation of the periampullary region involves administration of both intravenous and oral contrast and acquisition of 1–2 mm cuts within a single breath-hold during both arterial and venous phases of intravenous contrast enhancement. Scans obtained during the rapid intravenous injection of an iodinated contrast agent result in an increase in parenchymal evaluation as well as excellent contrast enhancement of the peripancreatic blood vessels. This technique not only results in clear delineation of the tumor, but may also demonstrate involvement of adjacent major visceral vessels, such as the portal vein or superior mesenteric complex, suggesting borderline resectability. CT has nearly 100% sensitivity for the detection of liver metastases at least 1 cm in size [13]. It can also demonstrate ascites and often evidence of peritoneal metastases.

The value of CT lies in the virtual absence of technically unsatisfactory examinations and its high accuracy for the detection and staging of periampullary carcinoma. The positive predictive value associated with CT determination of unresectability is greater than 90% [14]. Magnetic resonance imaging (MRI) is equivalent, but not superior, to CT for either detection of or staging of periampullary tumors, but has a higher cost [15]. It does offer the advantage of avoiding exposure to radiation or ionic contrast, so is the preferred test for patients with contrast allergies or renal insufficiency.

#### Magnetic Resonance Cholangiopancreatography

Magnetic resonance cholangiopancreatography (MRCP) is a noninvasive method for determining the most likely etiology of a pancreaticobiliary abnormality. It is most helpful in evaluating abnormalities of the proximal bile ducts and liver. In periampullary lesions, the thick-slab magnetic resonance images will delineate the biliary and pancreatic ductal anatomy [14] with detail that is similar to the more invasive techniques of endoscopic or percutaneous cholangiography. The other magnetic resonance sequences will define the presence or absence of a mass, the level of obstruction, and the location of any abnormality relative to the regional vessels.

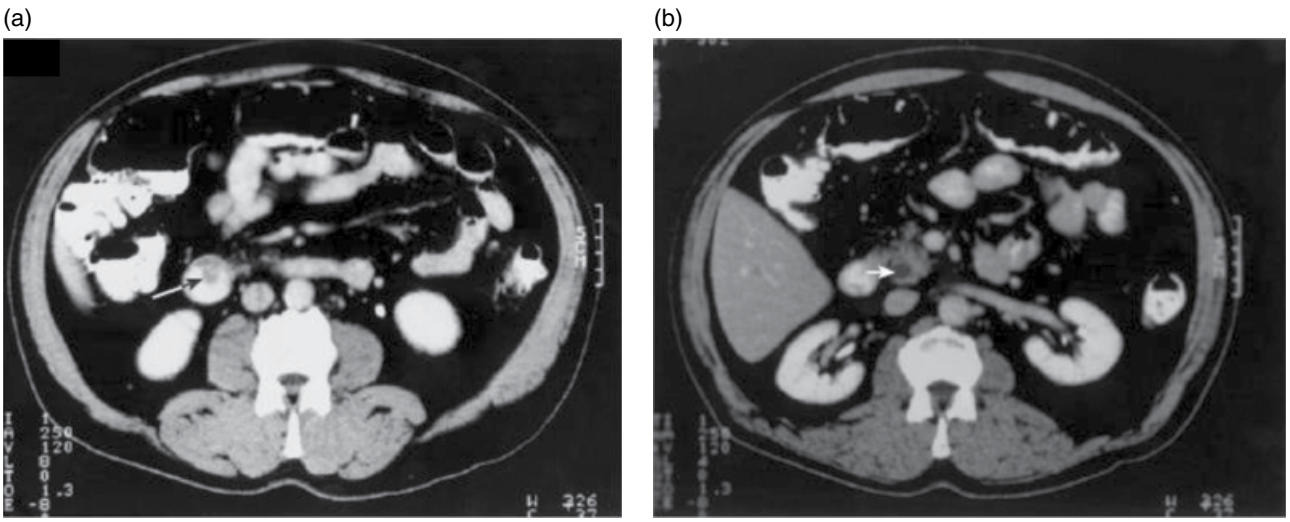


**Figure 138.1** CT scans of a patient with obstructive jaundice due to ampullary carcinoma. (a) Scan demonstrates a 30 cm ampullary mass (arrow). (b) Scan at a higher level demonstrating bile duct dilatation within pancreatic parenchyma, indicating distal duct obstruction (arrow).

### Endoscopic Ultrasound

Endoscopic ultrasound (EUS) is a diagnostic modality that combines and modifies the techniques of gastrointestinal endoscopy and ultrasound. This combination decreases the distance between the ultrasonic source and the organ of interest, thereby markedly improving the resolution and imaging of the surrounding structures. Real-time EUS enables the clinician to evaluate and integrate, during the same examination, mucosal, vascular, ductal, and parenchymal abnormalities (Fig. 138.2). It allows detection of periampullary tumors, evaluation of their size and depth of invasion, as well as assessment of regional lymph nodes. EUS appears to be superior to CT and MRI for the detection of small pancreatic tumors (<2 cm) [16,17]. However, the sensitivity of EUS decreases in the setting of chronic pancreatitis [14]. EUS assessment of depth of invasion (T stage) has an overall accuracy of about 73% with accuracy increasing with higher T stages [18,19]. In the case of mucosally based tumors, such as ampullary and duodenal neoplasms, EUS is particularly valuable for assessment of depth (T stage) and invasion of surrounding structures. Although results are not conclusive, several reports have also indicated that EUS is more sensitive and accurate for detection of vascular invasion than CT [16,20]. The reported accuracy of EUS assessment of lymph node status has ranged from 63% to 84%, which is at least equivalent to CT, although this may be operator dependent [14,16,21,22]. Finally, EUS can be used to guide fine-needle aspiration (FNA) of both the primary lesion and suspicious regional lymph nodes. In addition to having a reasonable diagnostic accuracy, a study by Micames et al. [23] suggests that patients undergoing EUS-guided FNA, as opposed to CT-guided percutaneous FNA, are less likely to subsequently develop peritoneal carcinomatosis.

Limitations of EUS include its need for skill in both operating and interpreting, its invasive nature, and its limited view, which does not allow evaluation for distant metastases. The combination of CT and EUS is better than either alone in determining resectability in patients with periampullary cancers, and a strategy of CT for all patients with suspected periampullary malignancies, followed by EUS in those patients in whom CT does not clearly demonstrated unresectability has been shown to be the most cost-effective strategy for preoperative staging and determination of resectability in these tumors [22,24].

### Endoscopy/Cholangiography

Upper endoscopy is useful for defining the extent, size, and gross appearance of a periampullary mucosal lesion and allows simultaneous performance of an endoscopic biopsy and cytologic brushings. However, the endoscopic appearance of an ampullary lesion is often similar for benign and malignant tumors (Fig. 138.3). Furthermore, endoscopic biopsies of periampullary malignancies may be inaccurate in 15–25% of patients, yielding false-negative results, largely due to sampling error. The demonstration

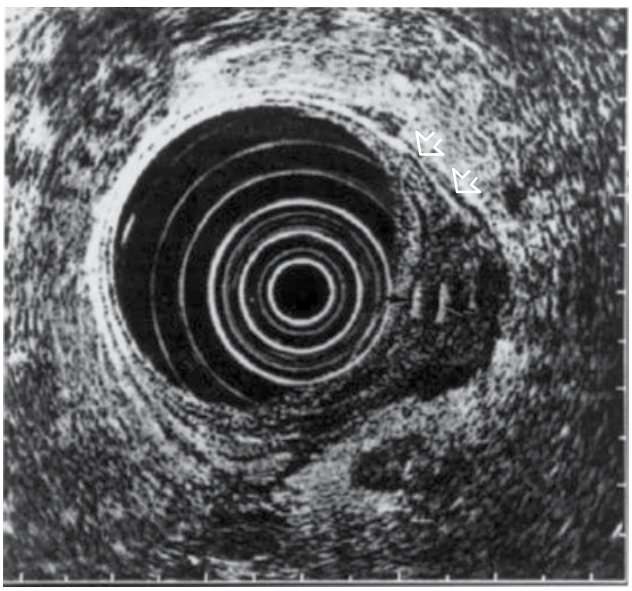

**Figure 138.2** EUS scan of ampullary tumor, represented by the hypoechoic area on the right. An endoprosthesis (small black arrows) can be seen running through the center of the tumor. The tumor infiltrates beyond the muscularis propria (open arrows) into the pancreas.

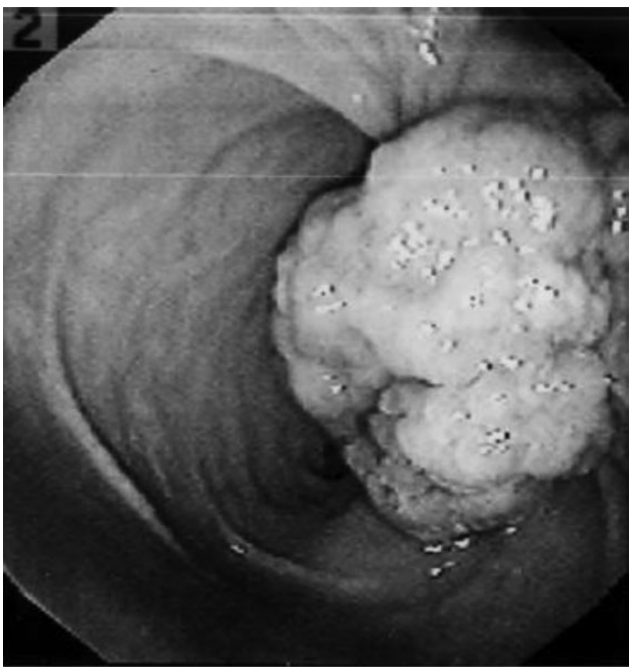

**Figure 138.3** Endoscopic appearance of benign villous adenoma.

of malignancy on biopsy specimens is definitive, but diagnosis of a benign adenoma does not rule out the presence of an adenocarcinoma elsewhere in the adenoma. Another important consideration is that ampullary adenomas are considered a premalignant condition since they tend to progress to carcinoma [25]. Therefore, regardless of whether or not the biopsy shows malignant or benign histology, complete resection (either operative or endoscopic) is warranted.

Cholangiography can be performed via either a percutaneous or an endoscopic approach. In most patients, however, percutanoues transhepatic cholangiography (PTC) offers little advantage over endoscopic retrograde cholangiopancreatography (ERCP), has a greater morbidity, and should be considered only if an endoscopic cholangiogram is technically not possible, such as after resection or bypass.

Prior to the improvements in current imaging and the advent of MRCP, ERCP was a routine part of evaluation of patients with suspected periampullary tumors. A cytologic diagnosis could often be made based on brushing of the lesion. With ERCP or MRCP, pancreatic or ampullary carcinomas are most often assumed when abnormalities of both the pancreatic and bile ducts are seen, yielding a "double-duct" sign (Fig. 138.4), whereas bile duct cancers typically show a characteristic "apple-core" appearance with an often normal pancreatic duct. ERCP offers the advantage over PTC of allowing a pancreaticogram to be performed, which may be important if pancreatitis is in the differential diagnosis [26].

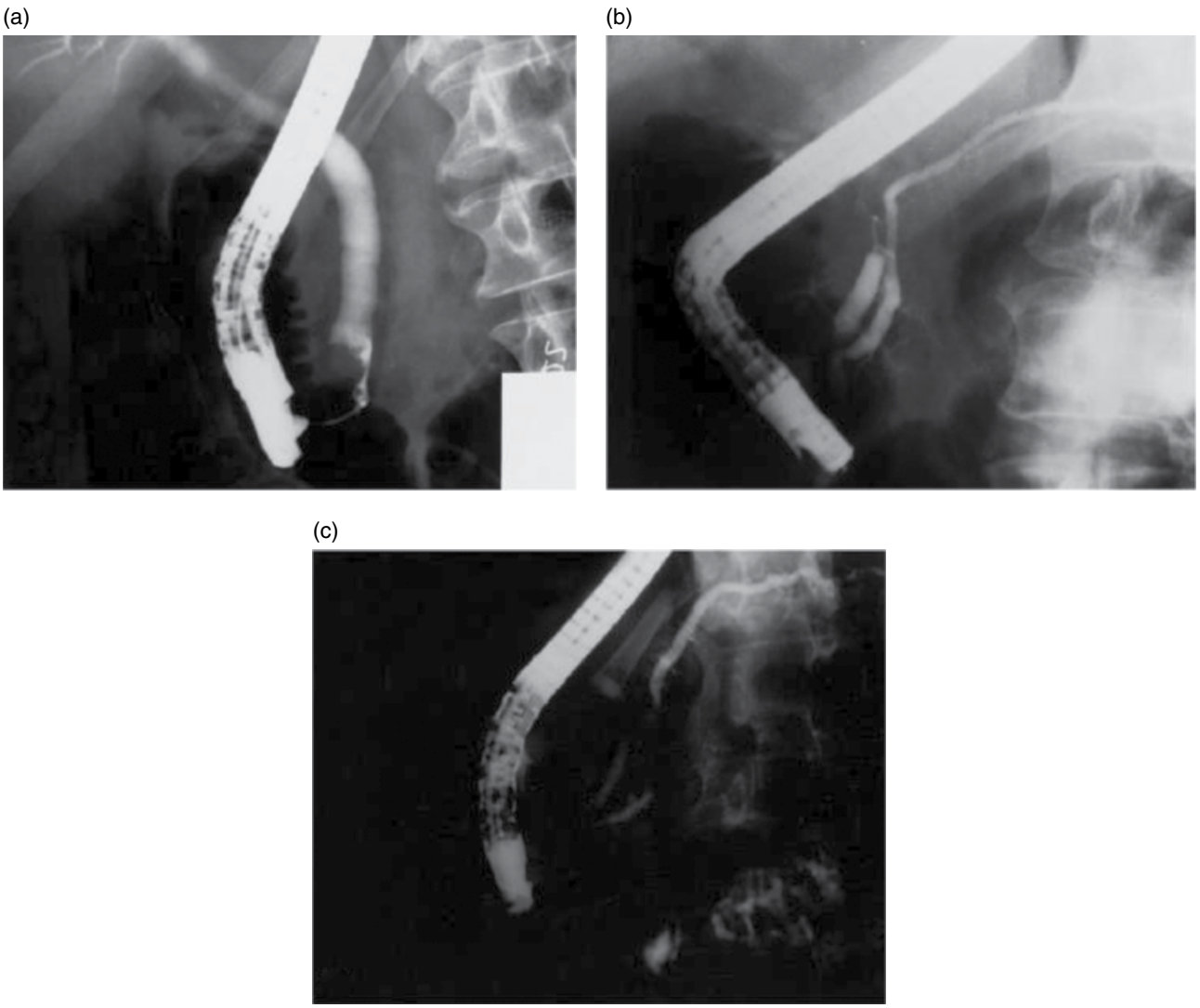


**Figure 138.4** (a) ERCP showing ampullary carcinoma obstructing the distal common bile duct. (b) ERCP with distal common bile duct carcioma. Note the normal appearance of the main pancreatic duct, indicating a bile duct origin for the tumor. (c) ERCP of a pancreatic carcinoma, with partial obstruction of both the main pancreatic duct and the common bile duct ("double- duct" sign).

The most common indication for ERCP in patients with periampullary tumors is for placement of an endoscopic stent in the common bile duct to relieve biliary obstruction preoperatively or for palliation. Although stent placement may result in colonization of the biliary tree and a higher wound infection rate in resected patients [27–29], it is indicated for medical reasons in a number of clinical circumstances: (i) in patients who present with symptoms of cholangitis requiring immediate intervention to treat the biliary infection; (ii) in patients presenting with intractable pruritus needing to be relieved during the period of preoperative evaluation; and (iii) in patients with hyperbilirubinemia associated with vitamin K deficiency, which will correct with relief of the biliary obstruction. Under these circumstances, at least 2–3 weeks should be waited prior to definitive resection to allow the metabolized bilirubin to normalize and to ensure the absence of active infection after instrumentation. A common current indication for endoscopic biliary stenting is to relieve jaundice when there is an anticipated delay in scheduling the surgical procedure to allow referral to a high-volume institution or for planned neoadjuvant therapy. In the latter situation, the use of a metallic stent is indicated to avoid recurrence of biliary obstruction with cholangitis in the midst of neoadjuvant therapy [30,31].

## Preoperative Staging

Since its introduction by Whipple et al. in 1935 [32], pancreaticoduodenectomy has been the most effective treatment for periampullary carcinomas. Perioperative morbidity and mortality rates have improved over the past decades, with mortality rates of 2% or less and morbidity rates of 30–40% expected in patients currently treated at high-volume hospitals [33–35]. The goal of preoperative staging is to determine which tumors are potentially resectable and have not already metastasized to distant sites or directly invaded the major peripancreatic vessels. Improvement in preoperative imaging and the addition of EUS to our clinical armamentarium have allowed better selection of patients for operation, with fewer patients being found to be unresectable at the time of operation, thereby minimizing unnecessary morbidity. Nonoperative techniques for the management of obstructive jaundice secondary to a periampullary tumor have also improved and can provide adequate palliation for most patients with unresectable neoplasms. Although the response is less durable than with surgical palliation, nonoperative palliation is often the most appropriate therapy for patients with a short life expectancy. These improvements in nonoperative management have made appropriate staging more important. In the past, laparotomy was required in all patients in order to establish the diagnosis and, thereafter, resection or operative palliation was performed.

The modalities currently considered most useful in staging patients with periampullary neoplasms are dual-phase CT and EUS. Dynamic spiral CT is currently the most valuable of these studies, playing a role in both diagnosis and staging of periampullary neoplasms. Its primary advantages are the lower cost and noninvasive nature of the technique. CT scans detect liver metastases (>1 cm) or large peritoneal implants. Obstruction and/or encasement of the major visceral arteries and veins in the region can be defined by loss of the perivascular fat planes and encroachment on the vessel lumen or the development of venous collaterals in the area (Fig. 138.5).

EUS is primarily used for determining local resectability with respect to visceral vessel invasion. EUS can also provide local staging by evaluating T stage. In the situation of a questionable lymph node status, it can also be used to perform FNA for cytologic evaluation of the nodes. However, EUS cannot be used as the sole modality for staging. Given its inability to adequately exclude peritoneal or hepatic metastases, it should be combined with CT for complete staging.

One of the limitations of CT is its poor sensitivity for detection lesions on the liver, omentum, or peritoneal surface that are less than 1 cm in size. For this reason, laparoscopy has been suggested as a method of further minimally invasive staging. In the past, advocates of laparoscopy have reported that more than 40% of patients previously staged by CT were found to have small metastases at laparoscopy [36]. Although reaching different conclusions about whether laparoscopy should be used, more recent reports have shown that staging laparoscopy

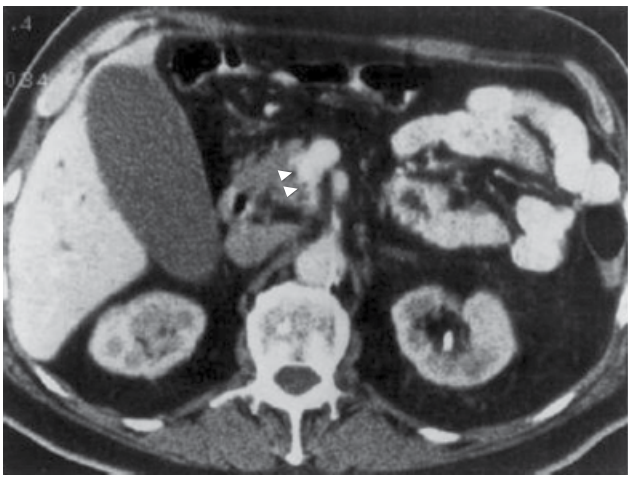

**Figure 138.5** Spiral CT demonstates superior mesenteric vein involvement by tumor–vessel contiguity. Abnormal enhancement of the medial border of the head and uncinate process of the pancreas is seen (arrowheads)

subsequent to CT staging, even when combined with laparoscopic ultrasound, identifies only an additional 10–14% of patients with unresectable disease [37,38]. This yield is even lower for patients with ampullary and duodenal tumors [38]. One cost-effectiveness analysis found that despite improving the rate of unresectability, diagnostic laparoscopy was not cost-effective in patients with periampullary malignancies [39].

## Determination of Extent of Resection

Local resection of an ampullary tumor with reimplantation of the pancreatic and common bile ducts was first described by Halsted in 1899 [40]. Recently, local resection of the ampulla of Vater has been reappraised for small (<3 cm) benign ampullary tumors or low-grade ampullary carcinomas. The most important criterion for determining malignancy is confirmation by histologic diagnosis. Although multiple endoscopic biopsies can detect malignancy in most patients with ampullary carcinoma, up to 25% of such biopsies will be negative [41–43]. This problem can even be extended to frozen-section analysis of resected specimens, which can fail to detect malignancy in 14% of patients [44,45]. The use of EUS provides another method for selecting patients for local resection. However, it is essential to acknowledge that EUS cannot replace histologic evaluation. EUS cannot differentiate a T1 carcinoma (limited to the submucosa) from an adenoma; however, T3 and T4 tumors are easily differentiated from an adenoma or early carcinoma by EUS. In a series reported by Mukai et al. [46], EUS accurately defined wall-depth penetration in 78% of ampullary carcinomas. Underestimating the depth of tumor penetration seldom occurs, while overestimation is more common and is often due to edema of the submucosa from associated pancreatitis, which occurs in up to one-third of T1 lesions [47]. Finally, as noted above, EUS cannot definitively determine the presence or absence of regional lymph node metastases;

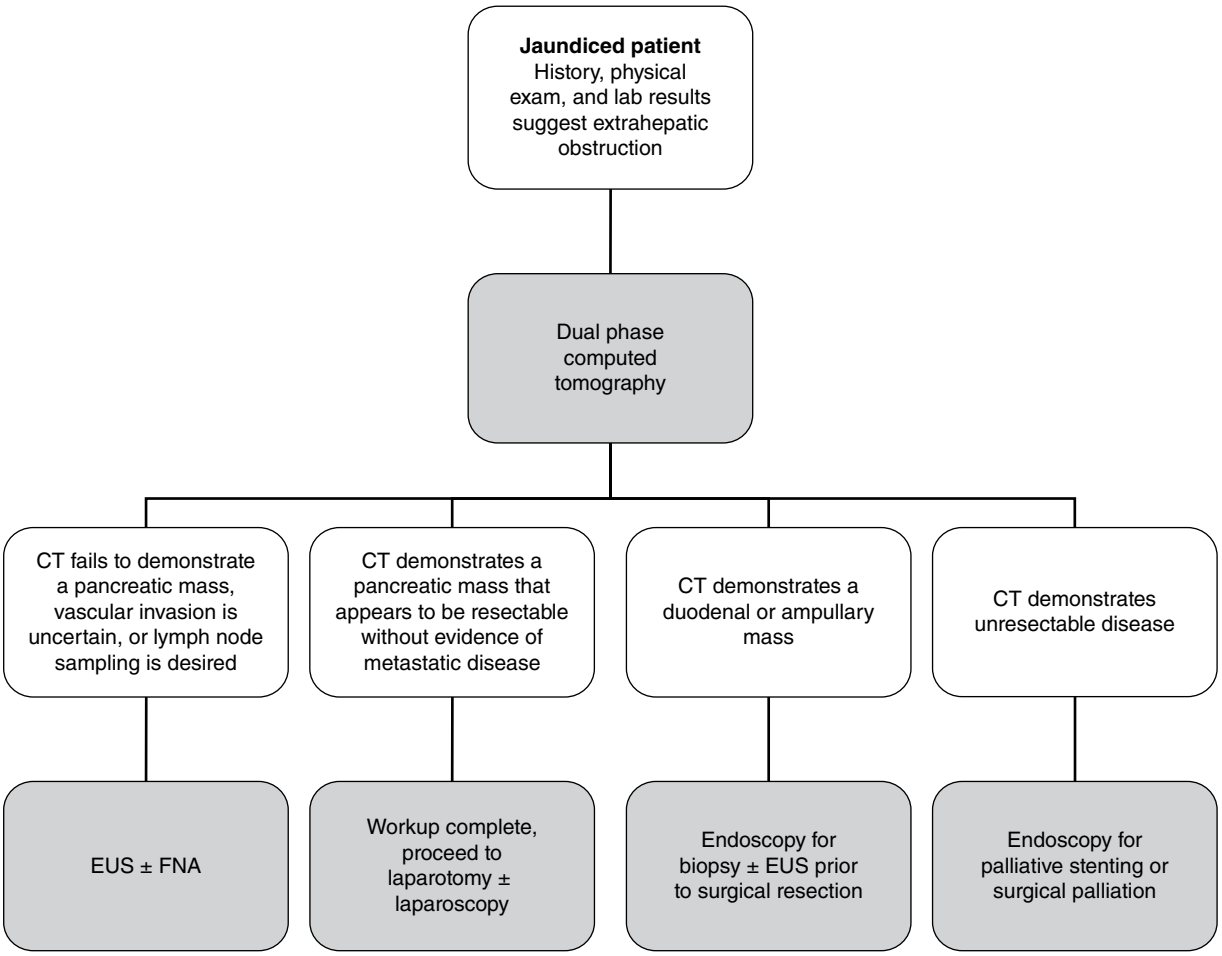


**Figure 138.6** Algorithm for the workup of a jaundiced patient. CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration.

because of these limitations, EUS, while providing extremely useful information, cannot be the only criterion used to choose between ampullectomy and pancreaticoduodenectomy.

## Summary

Patients with periampullary tumors typically present with painless jaundice and a hepatic profile consistent with obstructive jaundice (Fig. 138.6). If the history and physical examination do not point to gallstone disease or another benign etiology, the most high-yield initial imaging study is high-quality dual-phase CT. If CT demonstrates a lesion that is typical for pancreatic or distal bile duct carcinoma, and does not provide any evidence of unresectability (i.e., invasion of major vascular structures or distant metastases), the surgeon may choose to proceed directly to resection without a tissue diagnosis. If CT suggests an ampullary or duodenal tumor, endoscopic evaluation with biopsy and potentially EUS should be performed. In the situation of an uncertain diagnosis or where there is a question of involvement of major vascular structures, EUS should be performed. EUS-guided FNA is able to yield a diagnosis in up to 90% of pancreatic cancers [48]. The presence of vascular invasion and lymph node metastases can also be further evaluated with EUS, potentially sparing the patient an unnecessary operation and expediting referral for nonsurgical treatments such as aggressive neoadjuvant therapy, which has been shown in recent series to lead to tumor "downsizing" and resectability in a number of cases [49,50]. With the current level of sophistication of CT and a talented endoscopist, this combination of imaging is able to accurately stage a majority of patients and thus laparotomy will rarely identify occult metastatic disease or local unresectability. Diagnostic staging laparoscopy should be considered in patients with large periampullary pancreatic cancers. This technique will detect occult metastatic disease in an additional 10% of patients [38]. The ability of perform laparoscopic palliative procedures may expand the indications for laparoscopic staging.

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# 139

# Histology and Genetics of Cancer of the Papilla, Distal Common Bile Duct, and Duodenum

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## Carcinoma of Papilla (Ampulla of Vater)

The ampulla of Vater is a complex anatomic and histologic structure. Histologically, it consists of four compartments featuring three types of epithelia: (i) The distal common bile duct (CBD) and pancreatic duct are lined by pancreatobiliary-type ductal epithelium. (ii) The mucosa of the papilla of Vater itself shows a specialized epithelium with features that resemble gastric foveolar epithelium and scattered goblet cells. (iii) The duodenum-facing surface of the papilla is virtually identical to the duodenal mucosa elsewhere. (iv) On the wall of the ampulla is Oddi musculature, within which are pancreatobiliary-type ductules lying individually and in clusters. These different compartments not only have distinct histologic and functional properties but also bring with them their own chemical milieu, which makes this small region highly complex and challenging. Thus it is not surprising that there are vastly different impressions regarding the characteristics of the cancers of this region. Recently, careful analysis of tumors of this area processed with more standardized grossing protocols [1,2] have led to refined classification and elucidated the specific characteristics of tumors arising from the different compartments [3–5].

### Preinvasive Neoplasms

A significant proportion of the ampullary cancers (estimated more than a third) arise from adenomatous lesions (i.e., preinvasive mass-forming neoplasia), which are also called tumoral intraepithelial neoplasms [6,7]. According to their location, these can be put into two groups [3,7]: adenomas of the ampullary duodenum and intra-ampullary papillary tubular neoplasms.

#### Adenomas of the Ampullary Duodenum

Adenomas with all the characteristics of colonic adenomas also arise from the duodenal surface of the ampulla. They can be sporadic or associated with familial adenomatous polyposis (FAP) syndrome. In fact, ampulla is a common extracolonic site of FAP involvement [8–12].

Adenomas of the ampullary duodenum are more likely to harbor an invasive carcinoma than similarly sized colorectal adenomas. Invasive carcinomas that arise in adenomas are often hidden in the deep creases of the tumor at the base of the polyp and are difficult to detect in surface biopsies. Microscopically, adenomas of the ampullary duodenum are similar to those that occur in the large intestine but present some challenges in their diagnosis at the pathologic level. For example, reactive changes can mimic adenomas closely [13,14]. More importantly, when an underlying invasive carcinoma of the pancreas or bile duct involves the ampullary epithelium by colonization ("cancerization") of the mucosal basement membrane, it can closely simulate (pseudo-adenomatous change) a native in situ disease [15].

#### Intra-Ampullary Papillary Tubular Neoplasms

Intra-ampullary papillary tubular neoplasms (IAPN) are adenomatous (tumoral intraepithelial neoplasms) lesions that occur almost exclusively within the ampulla [7,16]. They represent the intra-ampullary counterpart of intraductal neoplasms of the pancreas (IPMN) and biliary tract (IPNB). Papillary or polypoid tumors can fill the ampullary channel and distal segment of the CBD or main pancreatic duct. By definition, involvement of the

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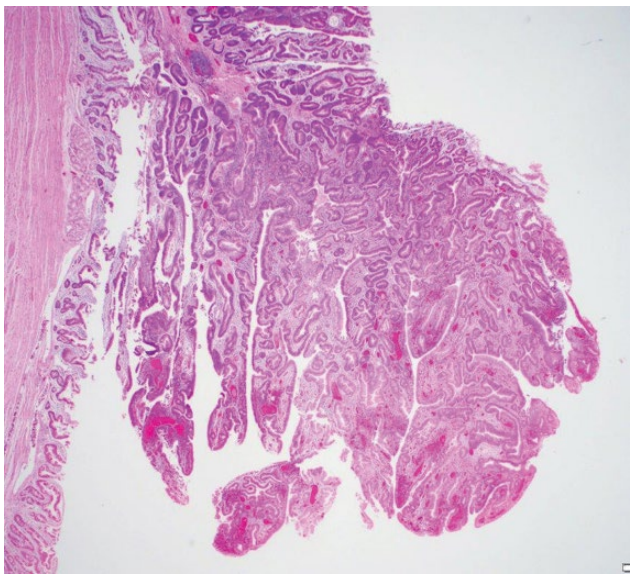

**Figure 139.1** Intra-ampullary papillary tubular neoplasm is preinvasive tumor growth within the ampulla. It shows various degrees of papillary and tubular growth.

ampullary duodenum and intramucosal extension into the proximal aspect of the CBD and main pancreatic duct is minimal (<25%) [17]. The mean age of affected patients is 64 years with male predominance [13,17].

Gross examination of the ampullary duodenum typically reveals a hemispheric elevation of intact mucosa, often with a patulous papilla orifice from which nodules of friable granular material protrude into the duodenal lumen [1]. Ulceration may be evident, but overt mucinous discharge, characteristic of pancreatic intraductal neoplasms, is seldom encountered. On sectioning the ampullary wall, the tumors are characterized by a prominent exophytic growth pattern within the ampulla, in the dilated distal bile duct and pancreatic duct. Microscopically, IAPN show various degrees of papillary or tubular growth (Fig. 139.1). Most have a mixture of these patterns. They exhibit a spectrum of dysplasia, and most cases show a mixture of low-grade dysplasia (the criteria is the same as that used for adenomas of ampullary duodenum) and high-grade dysplasia, which is defined as substantial cytologic atypia and architectural complexity. Unlike adenomas of the ampullary duodenum, approximately 50% of IAPN show mixed (intestinal, gastric, pancreatobiliary) differentiation [7]. Approximately 75% of IAPN are associated with invasive carcinoma at the time of diagnosis, but the invasive component is usually less than 1 cm in diameter [7]. Invasion is mostly tubular and often shows a mixture of intestinal and gastropancreatobiliary features. Since the invasive carcinoma is often small, proper sampling and examination becomes crucial. It should be noted that because of the complexity of this site it becomes very difficult to distinguish true invasive carcinoma from adenomatous (preinvasive) cells pagetoidly extending into complex glandular units in a pseudo-invasive pattern.

The hybrid nature of these lesions is also reflected in their immunophenotype. More than 50% of cases coexpress CK7 and CK20 [7]. Immunostaining for MUC2 and CDX2 is positive in cases with intestinal differentiation; immunostaining for MUC1, MUC5AC, and MUC6 are positive in cases with gastropancreatobiliary differentiation. However, overlaps are very common, and a significant proportion of the cases reveal mixed immunophenotype [7,18].

Noninvasive cases have an excellent prognosis. However, cases with extensive high-grade dysplasia can recur and this recurrence can be seen many years after the resection [7]. Therefore, long-term follow-up is warranted, even in noninvasive cases. Cases with invasive carcinoma are associated with better survival than conventional (invasive) ampullary carcinomas unaccompanied by an IAPN (3-year survival of 69% vs. 44%) [7]. This survival advantage is likely attributable to early detection of invasion but also reflects differences in tumor biology [3,19].

## Invasive Adenocarcinomas

Until recently, the definition of ampullary cancer lacked uniformity, with most studies analyzing them under the rubric of "periampullary cancers" along with pancreatic and CBD cancers. Furthermore, in many studies noninvasive carcinomas (adenomatous lesions with carcinoma in situ) have also been included in analysis of "ampullary cancers." These variations in definition have led to the vastly different reports regarding the characteristics and behavior of ampullary cancer. Nonstandardized and limited pathologic evaluations seem to have been a great contributor to this variation as well. In January 2016, refined definitions were provided and adopted by the College of American Pathologists (CAP); these currently serve as the main guide for the documentation of ampullary tumors in the United States. According to this scheme, four categories are recognized as "ampulla of Vater" cancers. Their clinicopathologic characteristics are described in the following sections [3].

### (Peri)ampullary Duodenal Cancers

(Peri)ampullary duodenal cancers arise from the ampullary duodenum (duodenum-facing surface of the ampulla that is lined by intestinal epithelium normally), which form bulky ulcero-vegetating lesions readily observed in the duodenal lumen, in which the ampullary orifice is often eccentrically located (Fig. 139.2a). They typically prove to have a prominent adenoma component and

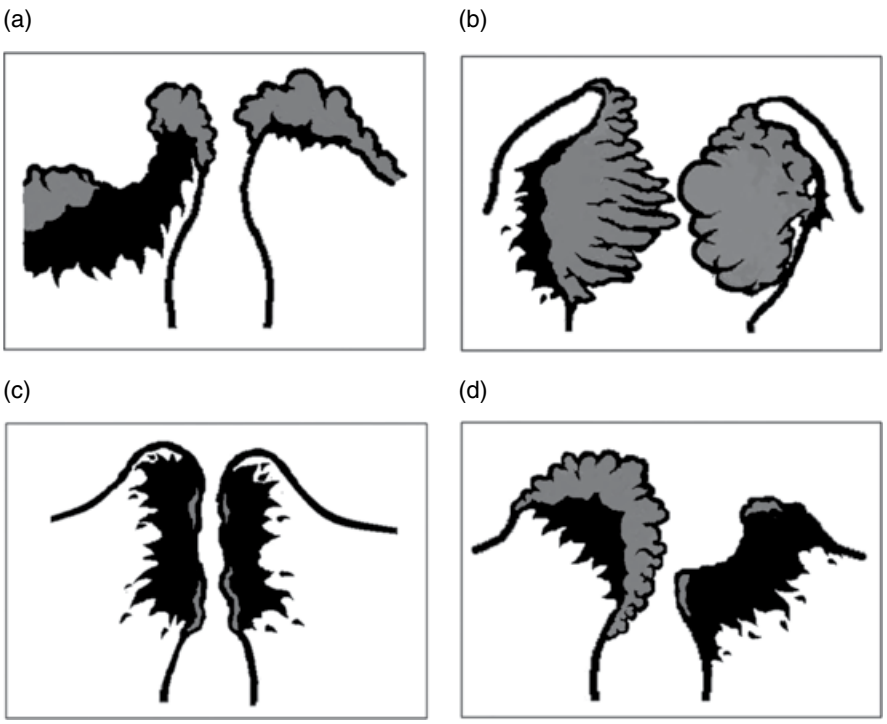


**Figure 139.2** Subtypes of ampullary carcinoma. The diagrams illustrate four subtypes of ampullary carcinoma: gray color indicates the preinvasive component and black color indicates the invasive component. (a) (Peri)ampullary duodenal carcinomas form ulcerovegative tumors that grow predominantly (>75%) on the duodenal surface of the ampulla. (b) Intra-ampullary papillary tubular neoplasm (IAPN)-associated carcinomas are characterized by a prominent preinvasive neoplasm that grows predominantly as an exophytic mass within the ampullary channel. (c) Ampullary duct carcinomas show minimal or no preinvasive lesion, and instead form a plaque-like stricture at the distal ends of the ducts. (d) Ampullary carcinomas not otherwise specified (ampullary-NOS): carcinomas arise from the papilla of Vater.

their invasive component is most commonly intestinal or mixed mucinous intestinal phenotype. Although they are usually very large (>4 cm) and produce lymph node metastases (~60%), their behavior is often significantly better than expected.

#### Intra-Ampullary Papillary Tubular Neoplasm-Associated Carcinomas

IAPN-associated carcinomas are characterized by preinvasive mucosal nodules located *within* the ampullary channel (i.e., distal portions of the CBD and main pancreatic duct). From the duodenal perspective, these tumors are less impressive, they show a dilated orifice, from which granular material may protrude into the lumen of the bowel. Upon sectioning the ampullary wall, the main bulk of the tumor is elucidated and typically reveals light tan, friable nodules (Fig. 139.2b). Probes placed in the CBD and pancreatic duct typically exit into the center of the lesion. They are by default rich in adenomatous component and microscopic examination often reveals only a small invasive carcinoma, and thus, not surprisingly, the prognosis is relatively good (median survival close to 10 years), especially if invasion is limited in amount; however, many cases experience recurrences in long-term follow-up.

#### Ampullary Duct Carcinoma

Ampullary duct carcinoma is the other category that can be technically regarded under the "intra-ampullary" tumor category but they are biologically very different from the IAPN-associated carcinomas discussed above. In essence, they are intra-ampullary counterparts of pancreatic ductal adenocarcinomas and distal CBD carcinomas (DBDC). Ampullary ductal cancers by default do not have a significant adenomatous (preinvasive neoplasm) component, and instead form circumferential scirrhous lesions that constrict the distal end of the CBD and pancreatic duct, with preservation (or minimal alteration) of the papilla of Vater and ampullary duodenal mucosa. Therefore, from the duodenal perspective, these tumors are fairly underwhelming, and typically show a button-like elevation of mucosa or a small, subtle ulcerating lesion (Fig. 139.2c). If proper dissection approaches are not employed, ampullary duct carcinomas can easily be missed because they are small and subtle. Microscopically, they often prove to be pancreatobiliary-type carcinomas. Although these tumors are usually less than 2 cm in diameter, they have a high rate of lymph node metastasis (57%) and an aggressive behavior (median 38 months), the worst among the ampullary

carcinoma subtypes, but nevertheless significantly better than pancreatic ductal adenocarcinomas.

#### Ampullary Carcinomas Not Otherwise Specified

Ampullary carcinomas not otherwise specified (ampullary-NOS) includes two subsets of tumors: (i) those that are presumed to arise from the papilla of Vater itself (i.e., the edge of mucosa where the CBD and main pancreatic duct merge into the duodenal mucosa) (Fig. 139.2d) and thus do not qualify for one of the three categories discussed earlier and (ii) those that cannot be confidently placed into one of the three categories above because of inadequate processing in the gross room. In our archival database, this group constituted >50% of the cases in the earlier years, but with the improved grossing and classification, more recently, <10% are placed in this category.

Microscopically, ampullary adenocarcinomas are highly versatile in their morphologic appearance. Most are "tubular type," characterized by glandular arrangement. Few of these "tubular" adenocarcinomas are pure intestinal-type tumors that are similar to conventional colonic adenocarcinomas (Fig. 139.3a). They are commonly associated with intestinal-type adenomas. An extensive mucinous component (>50% of the tumor volume) justifies a diagnosis of mucinous adenocarcinoma [20].

Those that resemble pancreatic or bile duct adenocarcinomas are called *pancreatobiliary-type adenocarcinomas* (Fig. 139.3b). Most ampullary cancers that are ampullary duct origin prove to be of this type.

A significant proportion of ampullary carcinomas (>40% in our experience) have a mixed phenotypic appearance and are difficult to place into one of the categories as intestinal or pancreatobiliary [7,18,21]. If noninvasive carcinomas and carcinomas of neighboring sites (pancreatic and CBD) are excluded carefully and the true ampullary carcinomas with the refined definition are analyzed separately, the survival advantage of the intestinal-type over pancreatobiliary-type adenocarcinomas proves to be much less significant [18,22] than previously reported [23–28].

Recently, immunohistochemically based classifications of ampullary carcinomas have been proposed [29,30] and are now being utilized by oncologists in management protocols. These panels are based on the observation that the intestinal phenotype tends to stain for MUC2, CK20, and CDX2 and the pancreatobiliary phenotype stains positively for MUC1 and CK7. However, in carefully selected cohorts analyzing true ampullary carcinomas with the refined definitions, these putative lineage markers and their corresponding panels fail to show direct and significant correlation with prognosis [22]. Having said that, we have found MUC5AC, the gastric marker, which has been overlooked in almost all of the ampullary studies, to be a significant prognosticator of ampullary carcinoma [22].

Since ampullary carcinomas are highly heterogeneous, one ought to be careful when making generalizations regarding its molecular alterations [31]. *KRAS* mutations are found in approximately 40% of cases [31–35] and increased expression of p53 is detected in 70% of cases [32,36–39]. Sixty-four percent of ampullary carcinomas that arise in FAP contain *APC* gene mutations, but only 17% of sporadic ampullary carcinomas carry this type of mutation [40]. Mutations of the β-catenin gene

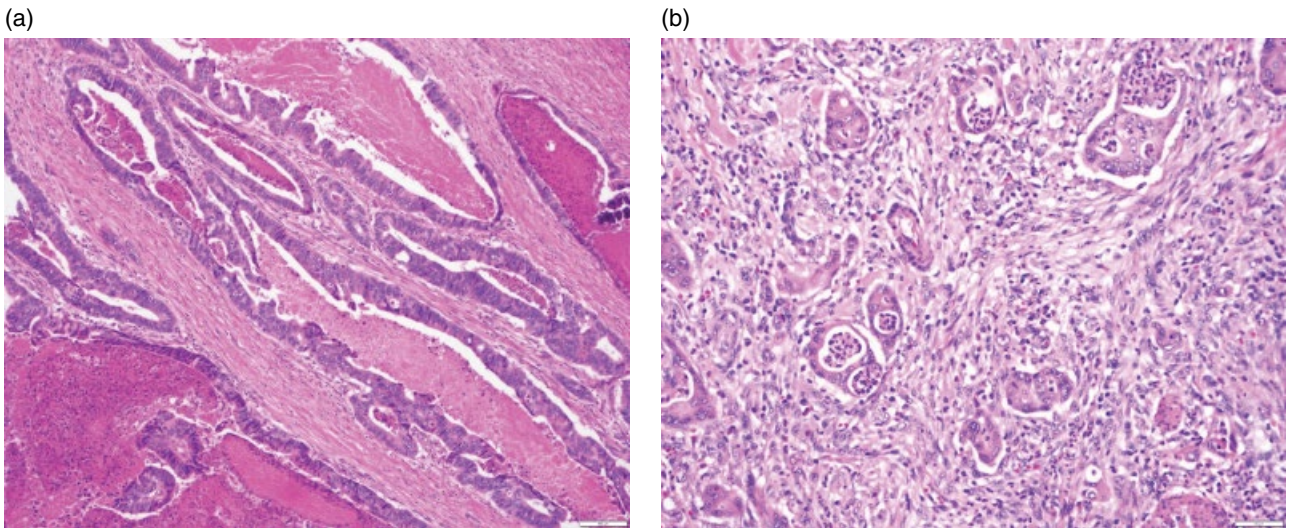


**Figure 139.3** Intestinal-type adenocarcinomas are characterized by longer branching and interconnected tubules with narrower lumina. They often have necrotic/granular debris in their lumina. The cells are more columnar shaped and pseudostratified. Pancreatobiliary-type adenocarcinomas usually form widely scattered, small, well-formed tubules lined by 1- to 2-cell layers of more cuboidal nuclei.

(*CTNNB1*) and alterations of the *SMAD4* (*DPC4*) gene are rare in ampullary carcinomas [41,42]. A small proportion of poorly differentiated ampullary carcinomas with morphologic features that resemble medullary carcinomas of the large bowel demonstrate microsatellite instability [18], and in fact, a recent study has shown that loss of DNA mismatch repair proteins may be as common as in colorectal cancers [43], although the earlier literature had conflicting results on this [44]. Genome array has been utilized to classify ampullary carcinoma into biliary-like and intestinal-like subtypes [45].

Ampullary carcinomas have an overall survival rate far better than pancreatic and DBDC. The 5-year survival rate is approximately 40% [3,19,46–48]. Even the ampullary duct carcinomas, which are mostly pancreatobiliary-type adenocarcinomas (i.e., ampullary counterparts of CBD cancers and pancreatic ductal adenocarcinomas) have a much better prognosis than ordinary pancreatic ductal adenocarcinomas. Invasion size is considered to be an important factor. Ampullary carcinomas often arise from a precursor (adenomatous) lesion, and the mean size of the invasive component is usually significantly smaller than primary pancreatic carcinomas [46]. For instance, IAPN-associated invasive carcinomas often have only a small invasive component (mean 1.5 cm) [3,7]. Not surprisingly, they have a better prognosis [3,7]. Positive margins occur in less than 5% of ampullary carcinomas, compared with at least 35% of pancreatic tumors [46]. The carcinomas arising from the four distinct compartments of the ampulla have different biologic behavior as discussed earlier. Other factors associated with prognosis include tumor budding and perineural and lymphovascular invasion [19,49–53].

### Uncommon Carcinomas in Ampulla

There are other carcinoma types that occur in the ampulla, such as poorly cohesive carcinoma (with or without signet ring cells), medullary carcinoma, and mucinous (colloid) carcinoma [13,14,54–56]. These have some specific associations. For example, poorly cohesive cell carcinomas are usually diagnosed at advanced stage and behave aggressively [55]. In contrast, medullary carcinomas are closely associated with microsatellite instability, and despite their large size and poorly differentiated appearance, their clinical behavior appears to be similar, if not better, than that of other ampullary cancers [54]. Mucinous carcinomas are often of ampullary duodenal origin, often present as advanced tumor and higher lymph node metastasis rate but their prognosis does not seem to be significantly worse. Unlike their lower gastrointestinal counterparts, they do not show association with microsatellite instability [56].

## Distal Common Bile Duct Carcinoma

DBDC is relatively uncommon and thus poorly characterized. Established risk factors for these tumors include parasites and congenital/anatomic variations such as choledochal cyst [57,58] and pancreatobiliary maljunction [59,60] and we have also seen examples associated with low (intrapancreatic) union of cystic and common hepatic ducts [47].

One of the biggest challenges regarding DBDC has been in its definition as to what really qualifies for this category. CBD involvement is extremely common in pancreatic ductal adenocarcinomas if careful sampling is performed [61], and can even show focal circumferential involvement. In addition, ampullary ductal carcinomas are often classified by pathologists as distal CBD carcinoma. Therefore, many studies have included cases from these secondary sites into the analysis of DBDC. Careful dissection of the resection specimens and correlation of the findings with the imaging and clinical findings become crucial in establishing the true primary site in many cases [47]. A recent study reported that intrapancreatic tumors symmetrically/concentrically involving the CBD are likely to be DBDC, which are frequently associated with high-grade biliary dysplasia, lack *KRAS* mutations, and have a superior prognosis with an actual 5-year overall survival of 35%; whereas asymmetric/eccentric involvement generally implies a pancreatic ductal adenocarcinoma, which are commonly associated with high-grade pancreatic intraepithelial neoplasia (PanIN), *KRAS* mutations, and a poor 5-year overall survival of 17% [47,62]. Microscopically, DBDC commonly exhibit a small tubular pattern, having a similar morphology to pancreatic ductal adenocarcinoma. In addition, intraglandular neutrophil-rich debris is often seen [47]. Median survival is better than that for pancreatic ductal adenocarcinoma, but worse than for ampullary carcinoma [47,62]. Poor prognostic indicators include node metastasis, lymphovascular invasion, size of invasion, and margin positivity [47,62]. T-staging of the tumors based on depth of invasion or size is shown to be much more applicable and prognostically relevant [5,47,63].

The vast majority of biliary tract cancers are adenocarcinomas of the pancreatobiliary type. These are very similar to ordinary pancreatic ductal adenocarcinomas and are often histologically indistinguishable from each other except for subtle differences [47].

### Incipient Cancers (Preinvasive Neoplasms)

#### Biliary Intraepithelial Neoplasms

Biliary intraepithelial neoplasia (BilIN) is the term used for nontumor-forming dysplastic lesions in the biliary tract [64]. These flat lesions cannot be detected by

preoperative image analysis or even macroscopic examination. In the current World Health Organization (WHO) guide (2010 edition), the BilIN classification scheme employed a three-tiered approach (BilIN-1, -2, and -3) based on the degree of epithelial atypia [65]. However, it is becoming clear that both biologically and for management purposes, a two-tiered system is more applicable: low grade (encompassing BilIN-1 and -2), and the term high grade for BilIN-3/carcinoma in situ. Since BilIN is most commonly detected incidentally in association with invasive carcinoma, its biological behavior and natural history have been difficult to determine. There are no reliable data regarding the risk of progression of BilIN in the absence of invasive carcinoma. Low-grade dysplasia (BilIN-1 and -2) is largely believed to be clinically inconsequential; however, high-grade dysplasia is believed to be a significant lesion that is often associated with (or progress into) invasive carcinoma with relatively high risk, and thus warrants careful clinical attention [6,66]. It should be noted here that high-grade BilIN can also be detected in resection of risk lesions, such as choledochal cyst, pancreatobiliary maljunction, or primary sclerosing lesions.

Although many biliary carcinomas arise in association with nontumoral dysplastic lesions (BilINs), an estimated 10% arise in mass-forming preinvasive neoplasms (tumoral intraepithelial neoplasms). These are, in essence, biliary counterparts of pancreatic intraductal papillary mucinous neoplasms or intraductal tubulopapillary neoplasms [4,67], or IAPN [7] or intracholecystic papillary tubular neoplasms [68], and comprise two distinct categories: intraductal papillary neoplasm of the bile duct (IPNB) [69,70] and intraductal tubulopapillary neoplasm (ITPN) [71].

#### Intraductal Papillary Neoplasms of the Bile Ducts

IPNB show a florid papillary proliferation of atypical epithelium that fills the bile duct and may lead to a fusiform or cystic dilatation of the affected duct segment [69]. It may be multifocal and extensive ("papillomatosis"). IPNB can be detected by imaging and gross examination. The degree of cytologic atypia is graded with the criteria used for BilIN. Similar to intraductal papillary mucinous neoplasm of the pancreas, IPNB is classified into gastric, intestinal, pancreatobiliary, and oncocytic types [69]. IPNB are often associated with invasive carcinomas [69,71] but invasive carcinomas arising from these tumoral intraepithelial neoplasms have a much more protracted clinical course than those arising from BilIN. Of note, as in the pancreas, those arising in oncocytic examples are currently classified as oncocytic variants of IPNB, but are increasingly being recognized as a separate entity of intraductal oncocytic papillary neoplasm (IOPN), as in the pancreas [72,73] and they are very distinctive in terms of both behavior and molecular characteristics.

#### Intraductal Tubulopapillary Neoplasm

ITPN, initially described in the pancreas, is now also a well-established entity in the biliary tract [71], characterized by prominent tubular configuration of relatively mucin-poor cells. Nodular growth pattern is characteristic and solid areas can be seen [71]. Punctate or geographic foci of necrosis can be present in a "comedocarcinomalike pattern" [71]. ITPN show a pancreatobiliary epithelial phenotype with MUC1 (80%) and MUC6 (30%) expression and negativity for MUC2 and MUC5AC [71]. Molecular pathways altered in ITPN seem to be different from both ordinary cholangiocarcinomas as well as from IPNB. Most ITPN are associated with invasive carcinomas but still have a protracted clinical course [71].

## Nonampullary Duodenal Carcinoma

Nonampullary duodenal carcinomas (NADC) are rare and, when studied, frequently have been grouped with jejuno-ileal adenocarcinoma. However recent studies have shown that they have several distinctive characteristics [74,75]. Those occurring in the distal duodenum can be associated with intestinal-type adenomas; however, many, especially the proximal examples, often form plaque/ulcero-plaque-like lesions rather than arising from large vegetating adenomatous lesions. Mismatch repair protein deficiency was found in 13% of NADC overall, and more commonly in those with the plaque-like growth and pushing-border infiltration [74]. Proximal examples may be arising from Brunner glands or metaplastic gastric-like epithelium [74] and are presumed to have different etiopathogenesis and biology than the colonic adenocarcinomas. In addition, NADC, similar to ampullary carcinomas, are seldom pure "intestinal" type, and instead often exhibit a striking degree of morphologic versatility, with the gastropancreatobiliary being the predominant type and also unusual carcinoma types not described in the remainder of gastrointestinal tract [74,75]. This is also reflected in the frequency with which the hybrid immunophenotype is seen, with less than 50% expressing "intestinal lineage markers" MUC2, CDX2, and CK20 [74]. The presence of gastric pancreatobiliary histology appears to be associated with more aggressive behavior [74,75], and thus it is important to attempt to recognize and report this lineage (no matter the quantity) in any NADC case. The prognosis for NADC is fairly similar to that for ampullary duodenal cancers and better than that for the ampullary ductal cancers discussed earlier (5-year survival 29% vs. 57%)

[74]. More importantly, the prognosis of NADC is incomparably better than that of pancreatic ductal adenocarcinoma [74]. This is important, because, for NADC that occurs close to the pancreas, pancreatic ductal adenocarcinoma with secondary invasion into duodenum becomes an important and highly challenging differential and the latter has been shown to have highly aggressive behavior [61].

## Pathologic Staging of Cancers of this Region

Because of anatomic complexity, the pathologic staging of carcinomas of this region is fraught with challenges. It appears that some of the problems of reproducibility and applicability that have been identified in recent publications [76] are being addressed in the 8th edition of the American Joint Committee on Cancer manual. However, many will continue to present problems in daily practice. Readers are referred to the pertinent publications in this matter [76].

## Neuroendocrine Neoplasms and Related Tumors

Neuroendocrine neoplasms should be regarded as being in two vastly distinct groups: well-differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas (PD-NEC). Well-differentiated neuroendocrine tumors constitute a heterogeneous group of neoplasms [20] including ordinary carcinoids (often showing serotonin production), "ampullary somatostatinomas" [77] (glandular psammomatous carcinoids with somatostatin positivity at the cellular level), gastrinomas, and other hormonal types as well as nonfunctional tumors [78,79]. Ampullary somatostatinomas are worth specific mention because they seem to be unique to the ampulla, and conversely, a significant proportion of neuroendocrine tumors in the ampulla prove to be of this type. These can be associated with neurofibromatosis and gastrointestinal stromal tumors. Although they are low-grade tumors, they are often infiltrative and show lymph node metastasis in close to half of the cases, but seem to behave in a very protracted fashion nevertheless [77,80,81]. Neuroendocrine tumors are graded based on mitotic activity and Ki-67 index. Accurate counting of Ki-67 can be challenging [82]. Eye-balling is discouraged. Currently, a manual count performed on camera-captured printed images of tumor hotspots appears to be the most practical approach [82].

A distinct but related entity is *duodenal gangliocytic paraganglioma*, a neoplasm that combines features of a well-differentiated neuroendocrine tumor with those of a nerve sheath tumor admixed with ganglion cells [83–86]. This is a very peculiar entity that is almost unique to ampulla and duodenum in the vicinity of the ampulla. The vast majority of the cases seem to be benign with only a few showing lymph node metastasis, and even those seem to have benign behavior.

PD-NEC of this region need to be distinguished from the well-differentiated neuroendocrine tumors. They often occur in association with adenocarcinomas or glandular preinvasive neoplasms (adenomatous lesions). They are typically high-grade carcinomas, recognizable as such by morphology, showing highly atypical cytology (with differential diagnosis of other poorly differentiated carcinomas, melanomas, and lymphomas) as well as brisk mitotic activity and necrosis characteristic of high-grade malignancies. Ki-67 labeling index is typically higher than 50%. Retinoblastoma gene alteration is common. Recent studies suggest that such tumors warrant *cis*-platinum treatment, as opposed to the well-differentiated neuroendocrine tumors which grow slowly and not only do not require *cis*-platinum, but also do not benefit much from it. They have a highly aggressive behavior.

## Pseudotumors that Commonly Mimic Cancer

### Paraduodenal Pancreatitis

*Paraduodenal* (*groove*) *pancreatitis* (PDP) often present with the clinical/imaging picture of "periampullary cancer"; in fact, close to two-thirds of PDP cases are preoperatively diagnosed as "cancer" [87–90]. PDP occurs predominantly in male patients who are generally younger (mean age 50 years) than the patients with cancer (mean age 64 years), and with a history of alcohol, smoking, diabetes, or prior gallstone disease [87–90]. Grossly, there is typically a pseudotumor characterized by thickening and scarring of the duodenal wall, particularly in the area corresponding to the minor papilla, but it often extends to the adjacent pancreatic head tissue, often with sieve-like cystic changes in the duodenal wall. Often, there is marked mucosal nodularity in this region as well, but ulceration is uncommon.

*Fibroinflammatory biliary stricture* (FIBS) [91] is the name proposed for idiopathic sclerosing pseudotumors that result in stricture of the bile ducts that leads to cholangiocarcinoma diagnosis. It is unrelated to autoimmune pancreatitis, primary sclerosing cholangitis, cholangiocarcinoma, prior bile duct injury or repair, and

choledocholithiasis [91]. By comparison with patients having bile duct cancer, FIBS patients present at a significantly younger age, are more likely to be female, and have a high incidence of coexisting autoimmune diseases [91]. A subset of these cases appear to represent IgG4-related sclerosing cholangitis. Because preoperative cytology is not diagnostic of FIBS, surgical resection remains the mainstay of diagnosis and treatment, while immunosuppression may reduce the risk of recurrence.

## Secondary Tumors

Almost every malignant neoplasm described in the body can also occur in this region [6,66]. These include melanomas, lymphomas, and sarcomas, all of which can mimic primary cancers and thus ought to be considered in the differential diagnosis of more common adenocarcinomas, both at clinical and pathologic evaluation.

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# 140

# Adenoma and Adenocarcinoma of the Ampulla of Vater: Diagnosis and Management

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## Introduction

Ampullary malignancies belong to the family of periampullary tumors, which arise from ampulla of Vater. The significant premalignant potential and strategic location of ampullary neoplasms makes them unique [1]. Typically ampullary tumors are classified as benign or malignant. Benign neoplasms account for less than 10% of periampullary neoplasms [1,2] and ampullary carcinomas are the second most common periampullary carcinomas (after pancreatic adenocarcinoma) [3]. Although ampullary adenomas are classified as benign, they have a tendency to undergo malignant transformation. The true ampullary cancer is usually difficult to distinguish from other periampullary malignancies and is usually diagnosed at an earlier stage, which means it has a better prognosis compared to periampullary cancers originating from the bile or pancreatic duct [2]. An aggressive diagnostic and therapeutic approach is therefore needed for these lesions.

## Epidemiology and Biologic Behavior

In autopsy series, periampullary adenoma prevalence is estimated to be 0.04–0.12 [4,5], however prevalence increases with the widespread availability of flexible endoscopy and screening programs. The incidence of ampullary carcinoma is 4–6 cases per million population and accounts for 4–8% of periampullary carcinomas [6,7]. Caucasian populations are mostly affected [6], there is a male predominance [7], and the peak incidence is in the seventh decade.

Both benign and malignant ampullary tumors arise in the setting of a genetic syndrome or spontaneously. Familial adenomatous polyposis (FAP) is the most common genetic predisposition [8] and most patients with FAP manifest some degree of dysplasia in the ampulla [9,10]. The second most common cause of death in patients with FAP is periampullary tumor [7]. Gardner syndrome, Lynch syndrome, neurofibromatosis type 1, and Muir–Torre syndrome are the other reported genetic predispositions for ampullary carcinoma [11–14].

Local factors are believed to play an important role in sporadic tumors and the earliest histopathologic changes are seen in the common pancreatobiliary channel, followed by the pancreatic duct [15]. Concentrated bile is thought to produce mutagenic effects on ductal epithelium resulting in epithelial apoptosis that is prone to malignant transformation [16]. On the other hand, chronic liver fluke infection is reported to be a risk factor for ampullary carcinoma [7].

## Pathology and Pathogenesis

Ampullary malignancies are classified macroscopically as: (i) intra-ampullary (intramural protruding), (ii) periampullary (extramural protruding), or (iii) ulcerating ampullary [7]. Ulcerating ampullary lesions have high lymph node metastasis rate and are mostly diagnosed at an advanced stage. Adenocarcinoma account for 75% of ampullary neoplasms, followed by benign adenomas (20%) and neuroendocrine tumors (5%) [3]. Villous and tubulovillous adenomas are the most common benign lesions; the others include hemangioma, lipoma, leiomyoma, lymphangioma, and leiomyofibroma [1,8–10,16,17]. Adenocarcinoma (90%) is the most common ampullary malignancy [3] (Box 140.1).

Most of the ampullary neoplasms exhibit an adenoma–carcinoma sequence, which can be seen elsewhere in

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**Box 140.1 Major types of ampullary tumors**

**Benign**

- Adenoma
- Hemangioma
- Lipoma
- Leiomyoma
- Lymphangioma
- Leiomyofibroma

**Malignant**

- Adenocarcinoma
- Neuroendocrine tumor
- Mucinous carcinoma
- Signet cell carcinoma
- Undifferentiated carcinoma
- Adenosquamous carcinoma
- Granular cell tumor
- Paraganglioma

gastrointestinal tract [18–26]. Ampullary neoplasms are classified histopathologically into pancreatobiliary and intestinal types [27,28]. The intestinal type classically arises from an adenoma, however a premalignant precursor lesion is often absent in the pancreaticobiliary type [7,9]. *KRAS* mutation is common (24–40%) in ampullary carcinogenesis, and is also observed in colon cancer [29,30]. p53 overexpression is also a common (46%) molecular finding. Immunochemically, the intestinal type expresses apomucin (MUC2) and cytokeratin 20 and the pancreatobiliary type overexpresses cytokeratin 7, but not MUC2 [31]. Although several studies suggest that the biology of ampullary neoplasms is similar to the intestinal type (ampullary neoplasms are histologically more often identical in intestinal origin, exhibiting adenoma–carcinoma sequence, and *KRAS* mutation is common) [9,29,32], rather than the pancreaticobiliary type (which is believed to have a worse prognosis), current literature reveals comparable results regarding the frequency, metastasis rates, and prognosis of these two types [27,28,31].

## Clinical Features

As with ampullary adenomas, the presenting symptoms of ampullary adenocarcinomas are nonspecific (the most common is painless obstructive jaundice, which is seen in two-thirds of patients) [33–37]. Occult gastrointestinal bleeding, diarrhea, fatigue, weight loss, and duodenal obstruction may be the symptoms associated with ampullary cancer. Due to cholestasis, 25% of ampullary adenomas develop common bile duct stones [38]. Furthermore, small distal intraductal benign adenomas simulate an ampullary malignancy and may cause significant biliary obstruction [39].

## Diagnosis and Staging of Ampullary Malignancy

Because ampullary adenomas have a premalignant potential and an occult focus of carcinoma may be present within an adenoma [18,24,40–42], the primary concern in evaluating ampullary lesions is to rule out malignancy. Diagnosis is usually established by the combination of radiology, endoscopy, and histology, which are also similar in evaluating both ampullary adenoma and carcinoma. However, without complete resection, it is usually difficult to differentiate between them. Ampullary carcinomas are frequently diagnosed with their macroscopic appearance on endoscopy and histopathologic examination of the obtained biopsy specimen. In patients with obstructive jaundice, transabdominal ultrasound (TUS) is the first choice of imaging to rule out other causes such as choledocholithiasis and pancreaticobiliary tumors, however it rarely reveals the neoplasm itself. In the setting of staging and preoperative evaluation, as well as differentiating an ampullary adenoma from carcinoma, cross-sectional techniques and endoscopic ultrasound (EUS) are usually preferred.

### Cross-Sectional Imaging

Although computed tomography (CT) is superior to TUS in evaluating ampullary lesions, it is not sensitive enough for staging and detecting small lesions. It is also highly accurate in detecting distant metastasis, which usually includes lymph nodes, peritoneum, liver, bone, and lungs. Magnetic resonance imaging (MRI) can provide more detailed images of the ampulla and periampullary tissue [43]. Ampullary cancers are usually hypodense distinct masses on MRI with magnetic resonance cholangiopancreatography (MRCP). A double-duct sign" (dilation of both pancreatic and bile duct) or only the dilated bile duct can be observed, however single dilation of pancreatic duct is rare [44]. Positron emission tomography has not been well studied in detecting ampullary malignancies, but is highly sensitive in detecting distant metastasis [45].

### Endoscopy

Most ampullary lesions are apparent endoscopically. Ulcerated masses, lesions >3 cm, ampullary rigidity, and nonlifting of the periampullary component with submucosal injection are highly suspicious for malignancy.

The ampulla is best examined and biopsied with a side-viewing duodenoscope. Endoscopic retrograde cholangiopancreatography (ERCP) does not only help obtain biopsies, it also excludes an associated stricture or stone and permits an evaluation of the adenoma's extension into the pancreatic or biliary duct (Fig. 140.1). However, endoscopic forceps biopsies have high false-negative rates (16–70%) and comparable diagnostic accuracy rates (45–80%) [46–50]. In addition, sphincterotomy may interfere with the performance of biopsy in detecting a malignancy [51,52]. Obtaining multiple biopsies can increase its performance [42]. As a general rule, negative endoscopic biopsy for malignancy does not completely exclude a malignant focus in an adenoma. Therefore, diagnostic accuracy of biopsies can be increased by obtaining at least six biopsies, preferably at least 48 hours following sphincterotomy [40,41], and by complete resection of ampullary adenomas (endoscopic ampullectomy). Moreover, narrow band imaging with magnification endoscopy has been suggested to have a possible role in differential diagnosis of ampullary masses, since, in contrast with carcinomas, abnormal vessels are not present in ampullary adenomas [53].

## Endoscopic Ultrasound

With its ability to place an ultrasound transducer in close proximity to the ampulla, EUS is superior to CT, MRI, and TUS for tumor staging and is as sensitive as duodenoscopy in detecting small ampullary tumors (Fig. 140.2). EUS and intraductal ultrasonography provide detailed information about the endoscopic appearance, tumor size, localization, tumor extension, and existence of metastatic lymph nodes. These data help the preoperative staging of ampullary malignancy [54–64].

EUS-guided fine-needle aspiration (FNA) can assist in providing tissue from ampulla, lymph nodes, and surrounding deeper structures. However, as for endoscopic biopsies, EUS-FNA does not rule out a malignant focus within an adenoma. Besides, the overall accuracy of EUS-guided fine-needle biopsy (EUS-FNB) is reported to be 89%, with 82% sensitivity and 100% specificity [65].

EUS is the best modality for T-staging of ampullary carcinoma (invasion of adjacent organs), which is reported to have 70–90% accuracy in several studies [56,66,67]. EUS also has 70% sensitivity and 90% specificity for detecting vascular invasion [68,69]. On EUS, T2 is

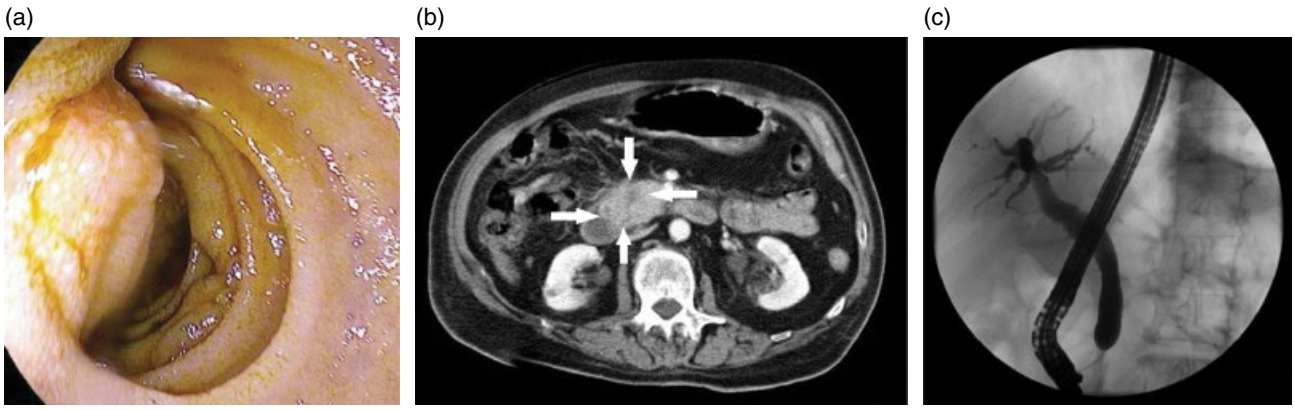


**Figure 140.1** (a) Ampullary adenoma on forward-viewing endoscopy. (b) CT image of the same lesion. (c) Endoscopic retrograde cholangiopancreatography of the same patient showing distally complete obstruction of bile duct.

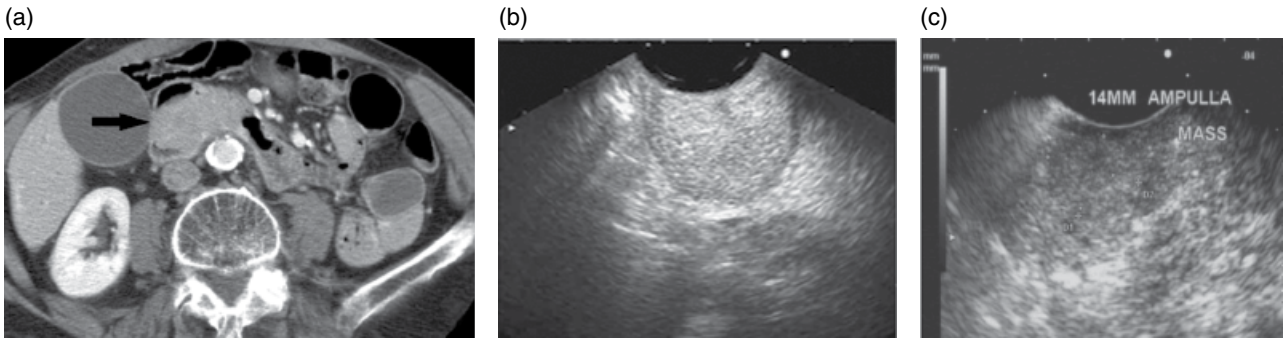


**Figure 140.2** (a) A large soft tissue mass consistent with ampullary cancer in duodenal wall on CT. (b) Ampullary adenoma on endoscopic ultrasound (EUS). (c) 14 mm ampullary cancer on EUS.

called when the tumor invades the muscularis propria of the duodenum, T3 is extension into the pancreas <2 cm, T4 is extension into the pancreas >2 cm or contiguous spread to adjacent organs. However, the accuracy of EUS for N-staging is lower, with a sensitivity of 21–71% and a specificity of 38–100% [54,67,69,70].

### Staging

Ampullary tumors are commonly classified according to the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) Staging, TNM staging system [71] (Table 140.1). For Stages 0, IA, IB, IIA, IIB, III, and IV, 5-year survival rate has been reported as 49%, 40%, 44%, 33%, 26%, 16%, and 4%, respectively [27,31]. Lymph node metastasis is a negative predictor for overall survival [72,73], however, at perioperative evaluation 42–60% of patients are reported to have metastases [74,75].

**Table 140.1** TNM and American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) Staging Systems for Ampullary Cancer.

| TNM stage | Criteria |
|---|---|
| Tx | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Tis | Carcinoma in situ |
| T1 | Tumor limited to ampulla of Vater or sphincter of Oddi |
| T2 | Tumor invades duodenal wall |
| T3 | Tumor invades pancreas |
| T4 | Tumor invades peripancreatic soft tissue or other adjacent organ or structures other than pancreas |
| Nx | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastases |
| N1 | Regional lymph node metastases |
| M0 | No distant metastases |
| M1 | Distant metastases |

| AJCC/UICC Stage | Tumor | Node | Metastasis |
|---|---|---|---|
| 0 | Tis | NO | MO |
| IA | T1 | NO | MO |
| IB | T2 | NO | MO |
| IIA | T3 | NO | MO |
| IIB | T1–T3 | N1 | M0 |
| III | T4 | Any N | M0 |
| IVB | Any T | Any N | M1 |

## Management and Treatment

It can be difficult to differentiate an ampullary adenoma including a carcinoma focus and true ampullary carcinomas from other periampullary cancers (prognosis is better in ampullary carcinomas). Furthermore, there are no consensus and guidelines regarding the optimal management of patients with ampullary adenomas. It is not clearly defined who requires excision (endoscopic or surgical) and who should be followed-up with surveillance endoscopy [76]. The initial assessment in diagnosis is looking for a sign of malignancy with ERCP, which is also useful in differential diagnosis. EUS is usually preferred for further preoperative evaluation and staging.

Removal of the adenoma is suggested in cases with sporadic adenoma, especially those that have high-grade dysplasia or are causing a symptom. Endoscopic surveillance with biopsies every 6–12 months may be recommended when a patient declines excision. In cases with FAP, excision should be suggested since prognosis seems better compared with sporadic cases [77]. On the other hand, removal of ampullary adenoma does not eradicate cancer risk, because multiple upper intestinal adenomas are usually present in patients with FAP.

There are three excision options for ampullary neoplasms: endoscopic ampullectomy (Fig. 140.3), surgical ampullectomy (surgical local excision), and Whipple's procedure (pancreaticoduodenectomy). The decision is based on the degree of surgical risk, life expectancy, the stage of malignancy, and the patient's wishes. Although there are no definite criteria on which patients require endoscopic or surgical removal, especially in centers that are not experienced in advanced endoscopy, patients with large lesions, adenomas that contain carcinoma, lymph node involvement, and adenoma ingrowth into bile duct or pancreatic duct on EUS should be referred to surgery. Patients with ampullary carcinoma without lymph node and vessel involvement and who are in early stages (Tis and T1) should be candidates for endoscopic ampullectomy [78]. There are comparable reports in the literature regarding the size or diameter above which an ampullary mass should not be removed endoscopically. Lesions ranging from 1.3 cm to 4 cm are reported to be treated endoscopically [38,74,79–81]. Generally, lesions less than 2–3 cm should be suggested for endoscopic ampullectomy in the absence of other malignant findings.

The only curative treatment for carcinoma and to eliminate histologic progression to carcinoma and eradicate a malignant focus within an adenoma is R0 (margin-negative) resection. Although pancreaticoduodenectomy has been associated with higher morbidity and mortality rates compared with surgical ampullectomy, it achieves curative excision for ampullary adenomas with almost no local recurrence risk [75,82,83], and 90% curative

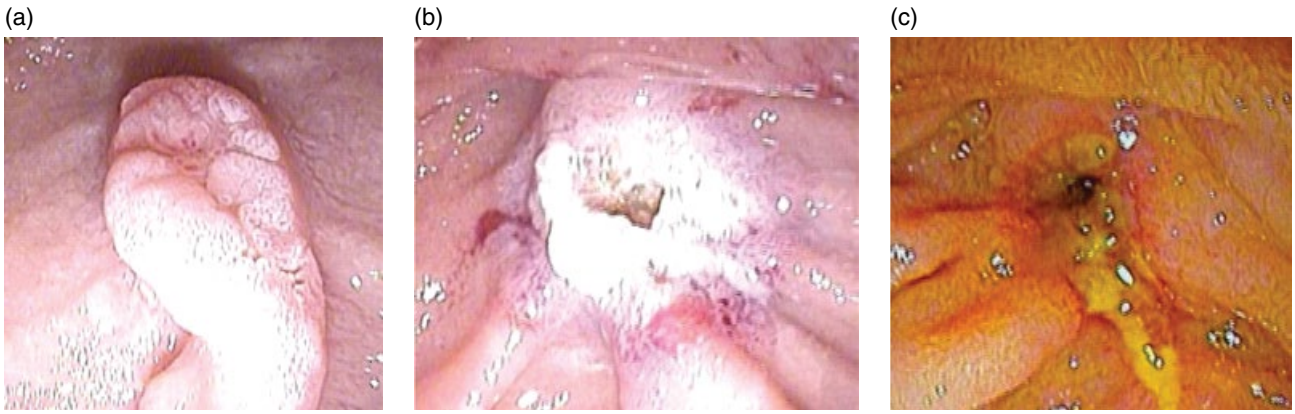


**Figure 140.3** (a) Ampullary adenoma in a patient with familial adenomatous polyposis. (b) Endoscopic appearance of the lesion 2 weeks after endoscopic ampullectomy. (c) Endoscopic appearance of the lesion 3 months after endoscopic ampullectomy.

**Table 140.2** Stage-based approach to endoscopic and surgical management of ampullary malignancy.

| Stage | Therapeutic approach High operative risk | Low operative risk |
|---|---|---|
| T0 adenoma | Endoscopic ampullectomy | Endoscopic ampullectomy |
| T1a malignancy | Endoscopic ampullectomy | Whipple |
| T2 malignancy | Endoscopic ablation | Whipple |
| T3 malignancy | Stenting | Whipple |
| T4 malignancy | Stenting | Biliary bypass |

resection rates for carcinomas [84–88]. In addition, surveillance endoscopies are not needed thereafter. On the other hand, with the advantages of lower morbidity and mortality rates, surgical ampullectomy has 0–50% recurrence rates for adenomas and lower survival in ampullary carcinoma patients compared with pancreaticoduodenectomy [48,89–94]. Patients with evident malignancy on an adenoma should be suggested for pancreaticoduodenectomy rather than either endoscopic or local surgical excision. After pancreaticoduodenectomy, 5-year survival rates for lymph node metastasis-negative patients are 59–70%, and for positive patients rates are 16–25% [95–97]. Although some studies report that endoscopic ampullectomy has lower morbidity and similar efficacy rates (46–93%) than surgical ampullectomy (0–30%), the role of endoscopic ampullectomy is still controversial [98,99]. Complete removal of the neoplasm is the aim of the procedure and en bloc excision is the preferred method, since occult carcinoma and negative margins should be ensured entirely. Monopolar or bipolar coagulation [2,42] argon plasma coagulation [80,81], photodynamic therapy [40], and Nd:YAG laser ablation [2,40,100] are thermal ablation methods when piecemeal excision is performed and the lesion cannot be excised completely. A stage-based approach to surgical and endoscopic management of ampullary malignancy is summarized in Table 140.2.

After ampullary cancer resection neither the National Comprehensive Cancer Network (NCCN) [101] nor the European Society for Medical Oncology (ESMO) [102] guidelines include management strategies. However, especially in lymph node-positive patients, two large randomized controlled studies suggested adjuvant chemotherapy and chemoradiation therapy with a median survival of 58 and 76 months [103] and an increased 5-year survival rate from 6% to 28% [97]. In addition, there is no consensus on the management of unresectable ampullary carcinomas, and the optimal chemotherapy regimen for true ampullary cancers has not been established yet.

Nonsurgical therapy methods such as endoscopic ampullectomy, photodynamic therapy, and laser ablation should be provided in the palliative treatment of patients with ampullary carcinoma who decline surgery or those are not candidates for surgery. As a cancer-related complication, duodenal and biliary obstructions are the major causes of morbidity in unresectable ampullary cancers. These patients can be treated palliatively either by surgical bypass or endoscopic stenting [104–110].

## Posttreatment Surveillance

Patients with ampullary adenoma who have been treated with either endoscopic or surgical ampullectomy are at risk of recurrence and require endoscopic surveillance. In contrast, surveillance is not needed after pancreaticoduodenectomy except for patients with FAP. The suggested surveillance is endoscopic evaluation after 1–6 months of ampullectomy and repeated evaluations in 3–12 months for 2 years. After 2 years, surveillance may continue as with the surveillance of flat colonic polyps (every 3 years if initial histology shows high-grade dysplasia, otherwise every 5 years) [76]. Since patients with FAP are at risk of development of upper intestinal polyps other than ampullary adenomas, patients with FAP require regular endoscopic surveillance according to the Spigelman classification [111]. In patients with ampullary cancer, endoscopic surveillance similar to that for locally resected ampullary adenomas may be recommended, although no guidelines are available.

## Long-Term Results of Surgical Resection

Factors affecting prognosis after surgery include the depth of invasion, lymph node involvement, and surgical clean margins [6,21,48,87,112]. For patients with node-negative cancer 5-year survival rate is 64–80% and for node positives 17–50% [29,48,84,86,96,113–115]. In a series, 5-year overall survival was 84%, 70%, 27%, and 0% for Stages I, II, III, and IV, respectively [48,112].

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# 141

# Endoscopic Treatment of Adenomas of the Ampulla of Vater: Techniques, Results, Benefits, and Limitations

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## Introduction

Tumors of the ampulla of Vater are comparatively rare and arise from the duodenal papilla. Symptoms of ampullary tumor include biliary colic, obstructive jaundice, recurrent cholangitis, and pancreatitis. These are arise due to obstruction of the bile and pancreatic ducts. Occult bleeding is relatively common. However, most ampullary tumors are asymptomatic. They are often found incidentally by screening endoscopy. There is no consensus on when ampullary adenomas should be followed up and when they should be resected.

Ampullary tumors are thought to develop either from the intestinal epithelium or the epithelium covering the pancreatobiliary ducts. Most ampullary tumors are adenomas or adenocarcinomas [1]. From the results of familial adenomatous polyposis surveillance, ampullary adenoma is thought to be associated with the progression of adenoma to carcinoma and is recognized as a premalignant lesion, as is colonic adenoma [2–5]. Though the natural history of ampullary adenoma has not been well investigated in sporadic lesions, many endoscopists advocate the resection of ampullary adenoma in this regard.

## Endoscopic Papillectomy

Classically, surgical resection (pancreaticoduodenectomy or transduodenal ampullectomy) has been recognized as the gold standard for treatment of ampullary adenoma. Surgical resection has the advantage of a low recurrence rate, but it is too invasive for cases of localized ampullary adenoma. Currently, endoscopic papillectomy has been accepted as a less invasive alternative to surgical treatment for cases of ampullary adenoma in patients for whom curative resection was possible.

Endoscopic papillectomy was first documented by Suzuki et al. in 1983 [6] and by Binmoeller et al. [7] in 1993 in English. It involves the resection of the mucosa and submucosa of the duodenal wall, in the area of the anatomical attachments of the ampulla of Vater, including the tissue around the bile duct and the pancreatic duct orifices [8].

At present, the indications for endoscopic papillectomy are still not established. The American Society for Gastrointestinal Endoscopy 2015 guideline did not show selection criteria for endoscopic papillectomy [9]. From previous reports, endoscopic papillectomy is accepted for patients with ampullary adenomas smaller than 4–5 cm [10] without ductal extension. Intraductal involvement of the lesion is considered as a noncurative lesion, or those with a high risk of recurrence [11]. Ampullary cancer is not recommended for endoscopic resection because of the risk of lymph node metastasis. In contrast, high-grade dysplasia or carcinoma which is restricted to the mucosal layer is reported to be suitable for endoscopic papillectomy; there is a rare risk of lymph node metastasis [12].

## Preprocedural Evaluation

The preprocedural diagnosis of ampullary tumor is performed through endoscopic appearance, biopsy, endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP) with intraductal ultrasonography (IDUS).

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### Endoscopic Appearance and Pathological Diagnosis

A duodenoscope is generally used to visualize ampullary tumors. The typical endoscopic finding of ampullary adenoma is a villous tumor. The characteristic feature distinguishing between adenoma and adenocarcinoma is the presence of ulceration, which has been observed in patients with malignancy but never in patients with benign disease. The fold convergence of the duodenum wall around the ampulla indicates tumor invasion into the duodenal wall. However, ampullary adenomas cannot always be distinguished from ampullary carcinomas according to endoscopic appearance alone. Observation of the ampullary tumor with narrow-band imaging (NBI) is reported to be helpful for providing endoscopic images of microvessels and the surface structure of tumors [13] or to enhance tumor margins [14].

Biopsy is very important in differentiating adenoma from carcinoma or other tumors. However, the accuracy of biopsy is reportedly not high, at around 70% [15–18]. It is thought that severe atypism is observed in the ampullopancreatobiliary common duct rather than in the ampulla–duodenum. Therefore, biopsy must be taken from the deep portion of the orifice. When adenocarcinoma is suspected, biopsy followed by endoscopic sphincterotomy [19] or EUS-guided fine-needle aspiration are considered. However, it is also reported that the sensitivity of biopsy did not change after sphincterotomy [20]. In these results, endoscopic papillectomy is sometimes performed as diagnostic treatment or a major biopsy prior to surgery.

### Endoscopic Retrograde Cholangiopancreatography, Intraductal Ultrasonography, and Endoscopic Ultrasound

ERCP with both biliary and pancreatic duct evaluation should be performed at the time of endoscopic resection to assess for evidence of extension into either ductal system. IDUS is inserted through the working channel of the jejunoscope and into the bile and pancreatic ducts after cholangiopancreatography. IDUS may be useful for imaging the detailed anatomy of the ampulla of Vater.

EUS is essential for deciding whether or not endoscopic resection is indicated. The EUS provides information on the presence of invasion to the muscularis propria, intraductal extension of the lesion, and metastasis to regional lymph nodes. EUS is reported as being superior to computed tomography (CT), magnetic resonance imaging, or transabdominal ultrasonography as a diagnostic modality [21,22]. In meta-analysis, the pooled sensitivity and specificity of EUS in the diagnosis of T1-stage tumors were 77% and 78% [23]. The combination of EUS and IDUS was reported to improve the accuracy of preprocedural diagnosis [21].

It is uncertain whether all cases of ampullary adenoma require EUS before endoscopic resection. Some experts suggest that EUS is not required when the tumor is 1 cm or less in diameter or when obvious endoscopic signs of malignancy are not present [24].

## Techniques

In general, endoscopic papillectomy is performed with a duodenoscope in the same manner as polypectomy, using a snare, followed by pancreatic duct stenting for prophylaxis of postprocedural pancreatitis (Fig. 141.1).

Achieving en bloc resection without complication is fundamental in performing endoscopic papillectomy. Complete pathologic evaluation is important for the evaluation of the resected margins or malignant foci with invasiveness, as previous pathologic diagnosis is often incomplete. In a few case reports, balloon catheter-assisted papillectomy was documented to facilitate en bloc resection [25,26]. Piecemeal resection is performed for large lesions, which aims to decrease complications and recurrence. However, histopathologic evaluation of the resected margin is then difficult. There are no data comparing safety or recurrence rates between en bloc and piecemeal resections.

### Submucosal Lifting

Submucosal injection with epinephrine diluted in saline solution and indigo carmine prior to endoscopic papillectomy has been performed in some reports [27, 28]. Submucosal lifting may reliably indicate malignancy, may prevent the effect of electrosurgical current, and therefore may prevent postprocedure pancreatitis. It may be useful for cases with predominant lateral periampullary extension [29]. However, the mucosal tissue at ampullary lesions does not lift because of tethering by the biliary and pancreatic ducts. In addition, the elevation of mucosal tissue around the papilla makes snaring difficult. Therefore mucosal injection is not routinely recommended. Recently, “underwater ampullectomy” without submucosal lifting for lateral spreading tumor has been introduced, but its effectiveness is still under investigation [30].

### Snaring and Transection

Electrosurgical snare resection is the most common technique. There is no specific type or size of snare for endoscopic ampullectomy. The snare is placed with the tip on the oral side of the lesion. The snare is closed at

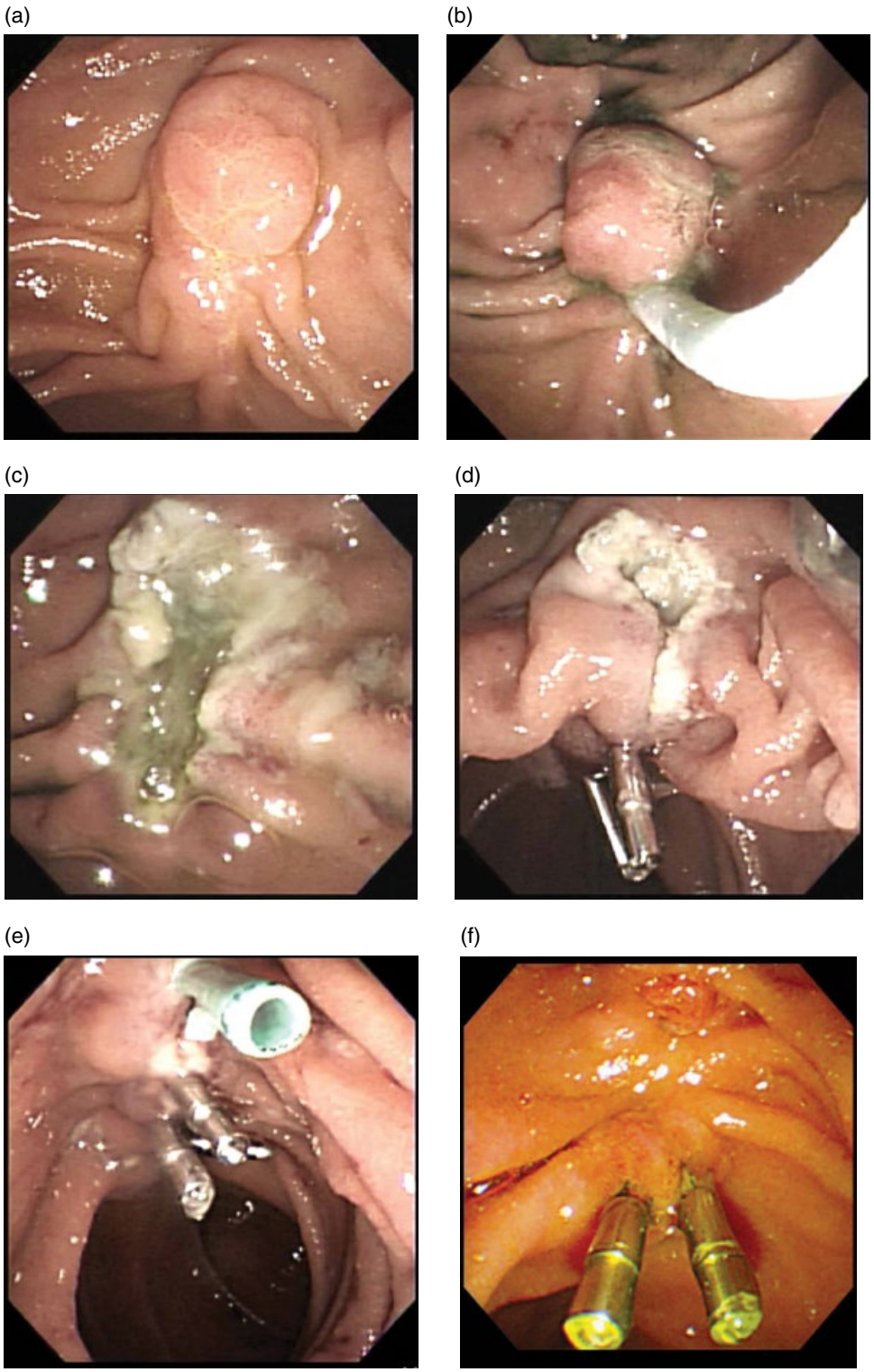


**Figure 141.1** Technique of en bloc ampullectomy by snaring. (a) Endoscopic view of ampullary adenoma. (b) The adenoma is grasped by a snare. (c) The adenoma is resected. (d) The anal side of the ulcer was closed by using clipping to prevent bleeding. (e) A 5F pancreatic stent is placed for the prevention of obstructive pancreatitis. (f) Endoscopic view at 1 year after the resection.

the base, and the lesion is resected. In some reports, an incision is made with an electrosurgical needle knife circumferentially around the lesion to facilitate snare capture [17]. Although there are no general recommendations regarding the optimal current and power output, there are reports of both pure cutting and blended cutting. Many endoscopists prefer the "blended" or "ERBE Endocut" mode, which aims to decrease bleeding by coagulation.

### Retrieval of the Resected Tumor

Retrieval of the specimen is very important for accurate evaluation and tumor staging. Immediately after the transection, the specimen is grasped by a snare and removed from the body in order to avoid intestinal migration. If the specimen is large, a basket catheter or net forceps should be used. It is important that the tissue is not collected by aspiration through the endoscope, as this will cause the specimen to fragment, making it impossible to evaluate the cut end histopathologically.

### Treatment of Remnant Tissue

Snares, biopsy forceps, and thermal ablation such as argon plasma coagulation are used for the treatment. Argon plasma coagulation is the most common, and is useful for ablating remnant tumor as well as for hemostasis or prophylaxis of postprocedural bleeding. However it must be carefully applied to the tissue around the pancreatic and bile duct orifice because it may induce bile duct obstruction or pancreatitis by the thermal effect.

### Sphincterotomy/Pancreatic and Biliary Stent Placement

Sphincterotomy is often performed during endoscopic papillectomy to facilitate pancreatic and biliary drainage after resection. Some studies suggest that bilateral sphincterotomy with pancreatic duct stent placement before resection would avoid the difficulty of locating the orifice at the base of the ampullary lesion [27].

Pancreatic stent placement is recommended to prevent postprocedural pancreatitis. In general, a pancreatic stent of 5F or 3F diameter is used after the resection of the tumor. The techniques of bilateral sphincterotomy with pancreatic duct stent placement before resection [27], pancreatic duct wire-guided endoscopic papillectomy, or retrieval of intraductally migrated pancreatic stents after endoscopic papillectomy [31] have been introduced.

The aim of pancreatic stenting is to maintain the pancreatic duct orifice and to prevent pancreatic duct obstruction. One small randomized control trial concluded that pancreatic stenting prevented postprocedural pancreatitis [32]. However, pancreatic damage by thermal ablation cannot be prevented. A recent retrospective study also suggested that routine pancreatic stent placement may not be necessary.

Apart from the risk of postprocedural pancreatitis, obstructive cholangitis does not frequently occur except when caused by obstruction by a clot due to major bleeding. Prophylactic biliary stent placement is generally unnecessary.

## Clinical Results

Curative resection by endoscopic papillectomy is reported to be achieved in 52–92% of cases [7,11,16,17,27,33–35]. Multiple procedures may be required to completely remove all adenomatous tissue. Larger lesions are more likely to be incompletely excised at the initial endoscopic procedure. The recurrence rate of ampullary adenoma after endoscopic papillectomy is reported to be 0–33%, with a median follow-up period of from 19 to 65 months [16,17,33–36].

## Complications

At present, endoscopic papillectomy is considered a less invasive option then surgery, but is a high-risk endoscopic procedure. Therefore the procedure requires specialist expertise. Careful observation after the procedure is important to detect acute complications.

Endoscopic papillectomy is associated with an increased risk of postprocedural pancreatitis, which is reported to be 3–25% [16,37]. Pancreatitis is considered to occur due to obstruction of the pancreatic duct and thermal damage to the pancreatic parenchyma. Currently, as described earlier, pancreatic stent placement is recommended though it does not prevent pancreatitis in all cases.

Postprocedural bleeding is also a serious complication. The duodenal papilla is a hypervascular area and bleeding is often observed on the anal side of the resected margin [38]. Postprocedural bleeding can be treated by adrenaline injection, argon plasma coagulation, and clipping. Hemostatic procedures may induce perforation or pancreatitis. Therefore excessive hemostasis should be avoided.

Perforation usually occurs in the retroperitoneal area. The patient may not have peritoneal irritation signs. However, pancreatitis or bleeding is often observed concurrently with perforation. When perforation is

suspected, evaluation by CT scan is informative. If perforation occurs, surgery may be considered, but selected patients can be treated conservatively with antibiotics [16,17,27].

Late adverse events include the development of pancreatic or biliary stenosis [7,16,17,27,34,35].

## Postprocedural Surveillance

Although there is no consensus, surveillance post procedure is important for detecting local recurrence. There are some reports that in sporadic cases of duodenal adenoma including ampullary adenoma there is a higher risk for the development of colorectal neoplasia [39]. At present screening colonoscopy should be performed in patients with duodenal or ampullary adenomas [9].

## Conclusions

Endoscopic papillectomy has been established as a first-line treatment for ampullary adenoma without ductal extension. There is still no consensus on preprocedural assessment, technique of endoscopic papillectomy, management of complications, or surveillance. Biopsy, EUS evaluation for large lesions, ERCP for further information, pancreatic stent placement for the prevention of pancreatitis, and endoscopic surveillance are recommended.

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# 142

# Surgical Treatment of Adenoma and Cancer of Papilla of Vater

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## Introduction

Cancer of the ampulla of Vater is a neoplastic lesion of two anatomically different structures of the duodenal wall, including the papilla and ampulla. Histologically, the ampulla of Vater is complex and consists of three different cell types lining the duodenum, common bile duct, and pancreatic main duct. Neoplastic lesions of the ampulla have histologically corresponding different cellular characteristics. From a histological point of view, determination of the origin of a periampullary tumor is often uncertain and it may be difficult to determine whether it is duodenal, ampullary, papillary, distal bile duct, or pancreatic cancer. Adenoma of the papilla is not infrequent (see Chapter 141); cancer of the ampulla seems to be the most frequent periampullary malignancy, but the ratio to pancreatic head cancer is 1:12. Carcinoma of the papilla of Vater, defined as the junction of the biliary and pancreatic ducts within the duodenum, accounts for 6–20% of all periampullary tumors. Ampullary cancers frequently contain adenomatous tissue, which is considered a precursor lesion [1–4].

An adenoma–carcinoma sequence with stepwise accumulation of genetic alterations, similar to colorectal cancer, has been proposed for tumors of the ampulla [5,6]. Because the ampulla is lined with epithelial cells derived either from biliary and pancreatic or duodenal lineages, many ampullary adenocarcinomas exhibit different histologic subtypes. Histologic, immunohistologic, and molecular biologic characteristics have established an intestinal and pancreatobiliary histologic subtype of neoplasia [7,8]. The prevailing cancer cell type is intestinal (45%) compared to the pancreatobiliary type (27%) [9]. The influence of the histologic cell type of the tumor on prognosis is not yet clearly established. Patients with a resected pancreatobiliary-type cancer have a significantly poorer prognosis than those with intestinal-type cancers [9].

Ampullary adenocarcinoma is also related to the extracolonic tumor spectrum of hereditary nonpolyposis colorectal cancer syndrome (HNPCC) [10]. The question of whether carcinomas from intestinal and pancreaticobiliary types of the ampullary region develop under different molecular pathologic conditions remains unanswered. Many ampullary carcinomas develop from preexisting adenomas. Residual tissue of papillary adenomas can be found in 30–60% of ampullary carcinomas. More than 95% of benign ampullary neoplasms are adenomas of the intestinal type [11]. These neoplasms have a tubular, villous, or mixed tubulovillous pattern and closely resemble intestinal adenomas. The favorable prognosis of periampullary carcinoma is thought to be due to early clinical presentation with upper abdominal pain, obstructive jaundice, and intestinal bleeding, leading to endoscopy and histologic diagnosis of the nature of the tumor.

## Molecular Pathology of Ampullary Cancer

Carcinomas of the ampulla display molecular alterations in the K-ras, p53, DPC4, and p16 proteins. Ampullary and ductal pancreatic carcinomas share similar molecular pathways of tumorigenesis [5]. K-ras mutations have been observed in 24–47% of ampullary carcinomas [12–14] and molecular alterations of the p53 protein in 60% [12]. Pure adenomas lack any p53 protein accumulation, whereas p53 positivity was found in 36% of carcinomas

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

with adenomatous tissue and in 56% of pure carcinomas. The cell cycle modulators p16, p21, and p27 have been found to be expressed at a lower level in ampullary carcinoma compared to pancreatic cancer [15]. Ampullary carcinomas in association with familial adenomatous polyposis frequently display a germline mutation in the adenomatous polyposis coli genes. Achill et al. found that 20% of ampullary carcinomas displayed a high level of microsatellite instability (MSI) [16]. Ampullary cancers with a high level of MSI showed a significantly better clinical outcome than microsatellite-stable tumors [9,17]. The MSI-phenotype is an early event, developing in the adenoma stage and is detectable in precursor lesions.

In addition to their histology, the two ampullary cancer subtypes display distinct molecular and immunohistologic characteristics that allow their discrimination. The intestinal subtype cancer expresses cytokeratin 20 and the transcription factor CDX2 and stains for MUC2, whereas the pancreatobiliary subtype cancer stains for MUC1, MUC5a, and CK7, and is negative for CDX2 [5].

## Endoscopic and Surgical Treatment of Large Adenomas and Carcinoma of the Ampulla of Vater

In 1899, Halstad performed the first local extirpation of a carcinoma of the papilla of Vater in a patient with a T1 cancer by applying an ampullectomy. In 1909, Kausch was the first to successfully operate an advanced cancer of the ampulla of Vater by applying a two-staged pancreatoduodenectomy. Local surgical resection of a papillary/ampullary neoplasm is recommended for all villous and tubulovillous adenomas with a diameter >3 cm. Endoscopic resection using piecemeal or snare excision technics (see Chapter 141) are the first-choice treatment for benign adenomas of the intraduodenal segment of the papilla. Endoscopic papillectomy is currently accepted as the first-choice treatment in sporadic papillary and ampullary adenomas up to a size of 3–5 cm. The accepted criteria to apply endoscopic treatment are adenoma size, no evidence of intraductal growth, and an absence of signs of malignancy on endoscopic findings, respectively ulceration, frayability, and spontaneous bleeding [18]. The application of endoscopic treatment for a papillary adenoma should be weighed against the procedure-related complications. To achieve complete excision, normally two to four separate endoscopic resection procedures are required. The recurrence rate after a mean follow-up time of 3 years was reported to be up to 15% and the endoscopic procedure-related mortality was 0.3%. Up to 15% of the patients eventually required a surgical resection following endoscopic resection because of incomplete cancer cell clearance [3].

**Box 142.1 Indications for surgical ampullectomy for neoplasm of the ampulla of Vater**

- Villous/tubulovillous adenoma >3–5 cm maximum diameter
- Adenoma with intraampullary/intraductal extension [4]
- Adenoma + severe dysplasia/carcinoma in situ
- T1a, N0, M0, G1/2 carcinoma restricted to mucosa/submucosa
- Carcinoid tumor of papilla of Vater, T1

**Table 142.1** Correlation between frequency of lymph node metastasis to invasion depth and size of tumor in ampullary cancer.

| | Yoon 2005 [18] 201 pts % pN pos. (*n*/*N* pts) | Winter 2010 [19] 345 pts % pN pos. (*n*/*N* pts) |
|---|---|---|
| **Tumor size** | | |
| <1.0 cm | 11.6% (5/43) | – |
| Up to 1.5 cm | 25.8% (8/31) | – |
| Up to 2.0 cm | 43.2% (19/44) | – |
| Up to 3.0 cm | 38.8% (19/49) | – |
| >3.0 cm | 47.1% 16/34) | – |
| **pT stage/tumor invasion** | | |
| pTis / pT1 | 9.0% (6/67) | 28% (7 pT1/222) |
| pT2 | 50.8% (32/63) | 50.9% (57/222) |
| pT3 | 38.1% (24/63) | 71.1% (81/345) |
| pT4 | 62.5% (5/8) | 77.3% (77/345) |

pN pos., lymph node cancer cell positive; *n*/*N*, index patients/determinator patients.
*Source:* Modified from Yoon et al. 2005 [18]. Reproduced with permission of Wolters Kluwer Health.

Because of a high level of recurrence (up to 37%) after endoscopic resection of adenomas with intra-ampullary and intraductal extensions, an oncologic ampullectomy should be the first-choice treatment (Box 142.1). Because up to 30% of benign villous and tubulovillous adenomas of the papilla are associated with severe dysplasia or carcinoma in situ, a curative ampullectomy is recommended [20]. For low-risk Tis and T1aN0M0G1/2 ampullary cancer restricted to mucosal and submucosal layers, application of a local resection using a surgical ampullectomy is the most effective treatment modality (Table 142.1).

The ampulla of Vater has a distinct pattern of lymphatic drainage and, in contrast to pancreatic head tumor with a diffuse lymphatic spread, tumors of the

papilla and ampulla tend to involve a local group of lymph nodes near the papillary segment of the duodenum, even in advanced cancers. These morphological features make ampullary neoplastic lesions a distinct clinical entity, yielding a substantial benefit in survival when infiltration does not include pancreatic tissue. However, patients who have a high-risk lesion belonging histologically to the cancer type pT1N0G3/4 grading class should have a radical oncologic Kausch–Whipple type resection.

## Ampullectomy for Large Adenomas and Low-Risk Ampullary Cancer

Ampullectomy for low-risk ampullary cancer is a local surgical technique, which intends to resect en bloc the adenomatous cancer tissue, including resection of the papillary entrance of the common bile duct and the pancreatic main duct (Fig. 142.1). The observed overall surgery-related frequency of complications is approximately 32%. The most frequent local complications are fistulas of the pancreatic and biliary systems, which occur in approximately 9% of cases. Reinterventions or reoperations of 7.5%, are caused by severe grade of pancreatic fistula (International Study Group on Pancreatic Fistula [ISGPF] grades B and C), or duodenal fistula or periduodenal abscess. However, the hospital mortality of 0.6% after ampullectomy is low (Table 142.2).

For patients with a low-risk ampullary cancer, an ampullectomy should be combined with lymph node dissection of the anterior and posterior pancreatic head lymph nodes to ensure oncologic curative resection. A close correlation exists between the invasion depth, tumor size, and lymph- ode metastases [18–20] (Table 142.1). Lymph node involvement of the anterior or/and posterior pancreatic head lymph nodes was found in ampullary pT1a cancer of a size up to 1 cm and lymph node metastases in 12% of cases [20]. Conversion to a Kausch–Whipple resection is recommended when intraoperative or final histology reveals an advanced cancer.

## Pancreatoduodenectomy for Advanced Ampullary Cancer

Ampullary cancer of stages pT1b and T2–T3 should be treated by a Kausch–Whipple pancreatic head resection. The partial pancreatoduodenectomy includes resection of the duodenum/antrum of the stomach, distal common bile duct, gallbladder, and head of the pancreas in combination with lymph node dissection around the head of the pancreas, including all N1 and, in advanced cases, N2 lymph nodes. In high-volume centers, hospital mortality after pylorus-preserving pancreatic head resection is <5% (Table 142.2). Patients with UICC Stages I and II cancer have a significantly better prognosis after Kausch-Whipple resection than patients with advanced Stage III

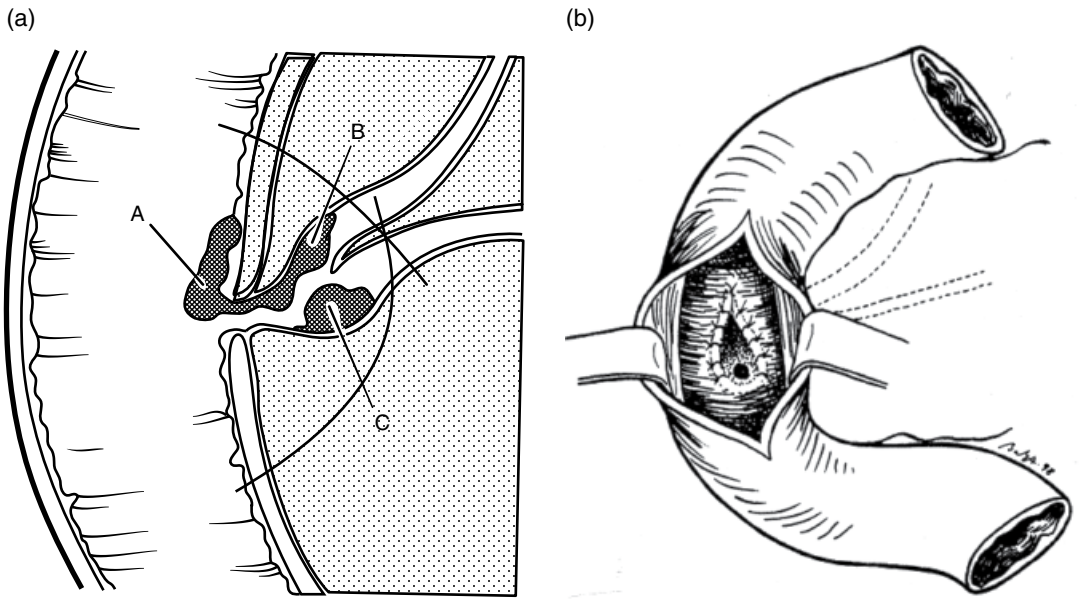


**Figure 142.1** (a) Adenomatous lesion of the ampulla of Vater. A, Adenoma of the papilla (roof of the papilla); B, adenoma of the ampulla; C, intraductal ampullary adenoma. Resection line for ampullectomy. (b) Single stitch suturing of the papillary cut edge to the duodenal wall. Final situs after resection of the papilla.

**Table 142.2** Postoperative outcome after resection of neoplasm/cancer of the ampulla of Vater.

| Reported period | Surgical ampullectomy[a] 1996–2016[c] | Pancreatoduodenectomy 2000–2015[b] |
|---|---|---|
| Total no. of patients analyzed | 308 pts | 1666 pts |
| Overall surgery-related complications (%/*n*/*N*) | 31.6% (91/288 pts) | 38.1% (239/626 pts)[d] |
| Fistula[e] (%/*n*/*N* pts) | 8.4% (15/178) | 16.1% (77/478) |
| Reoperation/reintervention | 7.6% (18/236) | 5.2% (22/425) |
| Hospital mortality (%/*n*/*N* pts) | 0.6% (2/308) | 3.9% (43/1115) |
| Recurrence (%/*n*/*N* pts) | 9.1% (28/307) | – |
| Follow-up postop (mean) | 38 months | – |

[a] Ampullectomy: Final histology: 58.9% adenoma; 9.2% carcinoma in situ; 9.2% advanced cancer; 23.8% others.
[b] Rattner [21], Cahen [22], Witzigmann [23], Dixon [24], Moneghetti [25], Kahayashi [26], Grobmyer [27], Winter [19], Ceppa [28] Schneider [29], Beger [30], Schoenberg [31], Heidecke [32].
[c] Takashima [33], de Castro [34], Duffy [35], Beger [36], Yoon [18], Qiao [37], Kim [38], Miyakawa [39], Berbarat [40], Winter [19], Bourgouin [41], Golussi [42].
[d] Index pts/total cohort pts.
[e] Fistula: postoperative pancreatic fistula, biliary, duodenal.

and IV cancers. Standardization of the surgical technique has led to a decrease in surgical morbidity with regard to the frequency of pancreatic fistula, postoperative hemorrhage, local abscess, biliary leakage, and delayed gastric emptying. The overall rate of surgery-related complications is up to 40% of patients. The most frequent complication is the development of local fistulas in approximately 16% of cases. The application of fast-track principles to surgical resections of ampullary cancer has resulted in a significant decrease in severe postoperative morbidity. Systemic postoperative morbidity remains at a level of up to 20–25% regarding pulmonary, cardiovascular, and renal dysfunctions. The indication for reoperation or reintervention includes local septic complications, for example, abscess and intra-abdominal and intraintestinal bleeding. The surgeons' contribution to curing patients with periampullary cancer is to perform an R0 resection, including systematic lymph node dissection and the application of highly skilled surgical techniques for pancreaticointestinal anastomosis. An important point to ensure a cure of the patient, whether applying local ampullectomy or a Kausch–Whipple pancreatic head resection for advanced ampullary cancer, is the intraoperative control of the resection margin by frozen-section investigations.

## Survival After Ampullectomy and Pancreatoduodenectomy

The chance of survival after Kausch–Whipple resection of an advanced ampullary cancer ranges within a median of 45–65 months. A published series of 1666 patients who underwent a Kausch–Whipple resection revealed a survival probability after 2 years of 62–88% and a 5-year overall survival of 35–67% (Table 142.3). The 10-year survival probability was 35–50%. The difference in survival rates after surgery is related to prognostic factors. After ampullectomy for carcinoma in situ or low-risk T1aN0G1/2 ampullary cancer, the 5-year survival probability was observed as 70–90%. After a mean follow-up time of 3.1 years for 308 ampullectomies, a recurrence occurred in 9.1% of cases (Table 142.2). The most frequent cause of recurrence was the reappearance of an intraduodenal adenoma. Independent prognostic factors for long-term survival after radical local or multiorgan resection were lymph node involvement, degree of cancer infiltration into the pancreatic tissue, and the degree of cancer cell dissemination along the nerves [43]. An incidence rate of 16% of lymph node metastases around the superior mesenteric artery was found in advanced carcinoma of the ampulla. The authors were able to identify lymphatic pathways from posterior pancreatoduodenal lymph nodes to para-aortic lymph nodes via lymph connection around the superior mesenteric artery [44]. The application of an R0 resection is the most important step to achieve long-term survival. Based on multivariate regression analysis, negative lymph nodes, an absence of infiltration into pancreatic head tissue, and an absence of perineural invasion are significant and independent oncologic factors for long-term survival after surgery for advanced ampullary cancer.

## Conclusion

Local ampullectomy is recommended for large adenomas of >3–5 cm, intra-ampullary and intraductal neoplasms, and tumors with low-risk cancer T1aN0G1/2. Surgical treatment of advanced papillary/ampullary

**Table 142.3** Long-term survival of cancer of ampulla of Vater after Kausch–Whipple type pancreatoduodenectomy.

| | | Survival probability | | | | |
|---|---|---|---|---|---|---|
| | | | 5 years | | | |
| Author/year | Pts | 2/3 years | Lymph node negative | Lymph node positive | Overall | 10 years |
| Takashima 2000 [33] | 198 | | 53.4% | 30.1% | 42% | |
| Duffy 2003 [35] | 55 | | 76.5% | 53.4% | 67.7% | |
| De Castro 2004 [34] | 178 | | | | 41% | |
| Beger 2004 [46] | 126 | | 45.6% | | 64% | |
| Yoon 2005 [18] | 201 | 72.1% | 69.2% | 24.6% | 59.8% | 49.2% |
| Qiao 2007 [37] | 124 | 46.8% | | | 43.3% | 35.7% |
| Kim 2006 [38] | 43 | | | | 67.4% | |
| Miyakawa 2009 [39] | 785 | –/78.6% | 68.7% | 34.5% | 52.8% | |
| Berbarat 2009 [40] | 78 | | | | 53.4% | |
| Winter 2010[a] [19] | 347 | | 56.4% | | 35% | |
| Bourgouin 2015 [41] | 55 | 69% | 73% | 29% | 51% | |
| Colussi 2015 [42] | 152 | 88.7% | – | 20.1% | 67.9% | – |

[a] Total of 450 ampullary tumors.

cancer is the Kausch–Whipple type resection. Independent prognostic factors are lymph node involvement and an absence of infiltration into pancreatic tissue. The 5-year survival after ampullectomy is 70–90% whereas after pancreatoduodenectomy of advanced cancer it is 35–55%.

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# 143

# Surgical Treatment of Duodenal Cancer

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Duodenal cancer is rare disease. Primary duodenal adenocarcinoma accounts for about 0.5% of all gastrointestinal cancers. The incidence of duodenal cancer is 5.4 per 1,000,000 [1]. It forms 60–100% of all duodenal malignancies and 30–45% of all small intestinal malignancies. Besides sporadic duodenal adenocarcinoma, other sources of adenocarcinoma include the gastrointestinal polyposis syndrome with a genetic background, such as familial adenomatous polyposis, Peutz–Jeghers syndrome, and duodenal polyposis.

Long-term survival is obtained only by complete surgical resection. The standard surgical procedure for the disease is pancreatoduodenectomy with regional lymph node dissection (lymphadenectomy). Regional lymph nodes include nodes along the inferior pancreatoduodenal artery and first jejunal artery, infra- and suprapyloric nodes, nodes along the common hepatic artery, and nodes on the posterior and superior surface of the pancreas head. En-bloc regional node dissection requires total mesoduodenum excision. Segmental partial resection of the duodenum can be applied in some cases [2], depending on the location and extent of the tumor. Partial segmental resection of the tumors in the proximal (1st part) or distal part (distal 3rd or 4th part) can achieve negative margins.

The most significant prognostic factor for duodenal cancer is resectability. Curative resection (R0 resection) determines the outcome for patients with duodenal cancer. After R0 resection, 5-year survival has been reported to be 17–74% (Table 143.1). The results obtained are 40–50% reproducible as reported by recent large series [13–15]. Deep extension of the primary tumor (T), presence of nodal metastases (N), margin-positive resection (R), large tumor size, poor histologic grade, and higher age are associated with poor prognosis after resection. In the largest series by database analysis [17] for Stage I–IV cancers, 5-year survival rates are 65.9, 50.4, 31.4, and 11.9%, respectively. Common recurrence sites are locoregional, intra-abdominal distant organ including the liver and peritoneum and extra-abdominal distant organ including lung.

Systemic chemotherapy or chemoradiotherapy has been applied after resection of advanced disease in the setting of good postoperative performance status. However, the role of adjuvant therapy for patients with duodenal cancer after resection is not well established [15]. Survival outcome after resection of duodenal cancer has not changed significantly over the past several decades [14]. Further work is needed to improve the outcome of surgical treatment for duodenal cancer.

**Table 143.1** Survival of duodenal cancer.

| First author | Year | No. of patients | 5-year survival (%) |
|---|---|---|---|
| Jones [2] | 1985 | 12 | 17 |
| Herter [3] | 1982 | 13 | 27 |
| Sarma [4] | 1987 | 9 | 33 |
| Michelassi [5] | 1989 | 29 | 21 |
| Sohn [6] | 1988 | 55 | 53 |
| Ryder [7] | 2000 | 49 | 43 |
| Kaklamanos [8] | 2000 | 63 | 40 |
| Bakaen [9] | 2000 | 101 | 54 |
| Sarela [10] | 2003 | 72 | 74 |
| Gold [11] | 2007 | 106 | 68 |
| Lee [12] | 2008 | 28 | 44 |
| Cecchini [13] | 2012 | 103 | 42 |
| He [14] | 2014 | 158 | 49 |
| Solaini [15] | 2015 | 150 | 43 |
| Buchbjerg [1] | 2015 | 28 | 27 |
| Oyasiji [16] | 2015 | 21 | 17 |

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# 144

# Surgical Treatment of Distal Cholangiocarcinoma

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## Introduction

Extrahepatic bile duct tumors have been conventionally classified into proximal, middle, and distal tumors. However, the American Joint Committee of Cancer (AJCC) recently published new staging criteria for extrahepatic bile duct tumors in its 7th edition [1]. In this staging system, the middle tumors have been removed, and extrahepatic bile duct tumors were newly classified as perihilar and distal bile duct tumors. TNM staging system was separated for these two subgroups because their pathologic features, surgical approach, and prognosis are different.

Distal cholangiocarcinoma is a relatively uncommon disease, comprising approximately 30% of all cholangiocarcinomas [2]. Although pancreatoduodenectomy is commonly selected as a surgical procedure for both pancreatic head cancer and distal cholangiocarcinoma, a minor arrangement in the procedure for each type of tumor is necessary as biological behavior is different. Because the incidence rate of distal cholangiocarcinoma is lower than that for pancreatic head carcinoma, there are limited publications that focus solely on the clinicopathologic features of distal cholangiocarcinoma. The hospital mortality after resection in high-volume centers for distal cholangiocarcinoma is 0–7%. The most common surgery-related complications are pancreatic fistula (7–42%) because patients have a normal soft pancreas in most cases of distal cholangiocarcinoma. Lymph node metastasis is commonly observed (38–68%) and this is a major factor that determines prognosis after surgery.

The mode of lymph node involvement is slightly different between the middle and lower cholangiocarcinoma. The 5-year overall survival after resection of distal cholangiocarcinoma is 30–73% in patients without nodal involvement, whereas it is 4–36% in patients with nodal involvement. Other important factors that determine prognosis are depth of invasion, pancreatic invasion, perineural invasion, tumor histology, and resection margin status. The surgical approach for distal cholangiocarcinoma should be carefully arranged depending on the tumor location, longitudinal or extramural tumor extension, and mode of lymph node and perineural involvement.

## Pyloric Ring Preservation

When selecting the operative procedure for distal cholangiocarcinoma, the question of whether pylorus-preserving pancreatoduodenectomy or pancreatoduodenectomy with pyloric resection (either by conventional Whipple or subtotal stomach-preserving pancreatoduodenectomy) should be selected arises. One of the merits in removing the pyloric ring is removal of lymph nodes in the perigastric region. Mode of lymph node involvement in the perigastric region is different in pancreatic head carcinoma and in distal cholangiocarcinoma. Nakao et al. previously reported that perigastric lymph node involvement was observed in 14% in patients with pancreatic head carcinoma, whereas no patient with distal cholangiocarcinoma had a lymph node metastasis in this region [3]. Based on these observations, pylorus-preserving pancreatoduodenectomy is indicated in almost all patients with distal cholangiocarcinoma, but not for the pancreatic head carcinoma. In fact, randomized controlled trials comparing the clinical outcome between pylorus-preserving pancreatoduodenectomy and conventional pancreatoduodenectomy (thus removal of perigastric lymph nodes) for patients with periampullary carcinoma showed no significant difference in long-term survival between the two

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procedures [4,5]. However, in the case of a tumor in the middle region of the extrahepatic bile duct, this concept is not applicable because the location of the tumor is close to the duodenal bulb. Therefore, removal of the duodenal bulb together with the pyloric ring is recommended to obtain a safe surgical margin, especially in a case with severe extramural tumor extension.

## Lymph Node Dissection

There are several reports on the prognostic factors relating to distal cholangiocarcinoma. The significant prognostic factors identified include the presence of lymph node metastasis [6–12], depth of invasion [13], pancreatic invasion [8,14,15], perineural invasion [15,16], resection margin status [7,12,15], and tumor histology [14] (Table 144.1). Among these factors, presence of lymph node metastasis has been reported to be the most important factor that determines the survival of patients with distal cholangiocarcinoma. The survival is clearly different between patients with and without lymph node involvement (Table 144.2).

As with other type of cancers, such as breast, gastric, or colorectal cancer, the number of involved nodes is critical in determining the severity of cancer progression in distal cholangiocarcinoma [9–12,16–19]. The proposed cut-off value of the number of involved lymph node was 2–5. In a report by Kiriyama et al. analyzing the largest number of patients of distal cholangiocarcinoma to date ($n = 370$) [15], median survival rate worsened with increasing number of involved lymph nodes. Survival was significantly better in patients with fewer than four than in those with four or more involved nodes (Fig. 144.1).

The total lymph node count (TLNC) examined is another important factor that has an impact on survival because inadequate assessment of lymph nodes, due to either an insufficient extent of resection or pathologic examination, results in understaging of cancer [20,21]. It should be noted that the numbers of dissected lymph nodes substantially differ depending on the extent of lymph adenectomy and additional organ resection. In particular, the TLNC can vary depending on the extent of lymphadenectomy for the perigastric and mesenteric lymph nodes. The AJCC recommend a "12-node minimum" for distal cholangiocarcinoma to prevent inadequate staging [1], but the theoretical background for this number is obscure. An optimal number of TLNC requirement for distal cholangiocarcinoma should be determined in a future study.

TLNC also changes the results of lymph node ratio (LNR), which is calculated as a ratio between the number of lymph node metastases and the total number of lymph node examined, because the greater the TLNC, the lower the LNR. According to the report by Kiriyama et al. [15], the median (range) TLNC was 19 (3–59). Nodal metastasis occurred in 157 patients (42.4%); the median (range) number of involved nodes was 2 (1–19) and LNR was 0.11 (0.02–0.80). An LNR of at least 0.17 was associated with a significantly shorter median survival (1.3 vs. 2.2 years). Another report by Kawai et al. indicated that the LNR >0.2 is an important factor to predict survival after resected middle and distal cholangiocarcinoma [16].

For distal cholangiocarcinomas, mode of nodal involvement is different depending on the location of the tumor,

**Table 144.1** Clinical factors that have an impact on survival.

| | | Clinical factors | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Author/year** | **Pts** | **Age** | **N (+)** | **Depth** | **Panc** | **Duo** | **Pn** | **R status** | **Histology** | **Ad Tx** |
| Kayahara 1999 [7] | 50 | NS | ● | ○ | | | NS | ● | | |
| Sasaki 2001 [9] | 59 | | | | | | | | | |
| Yoshida 2002 [12] | 27 | NS | ● | | NS | | NS | ● | NS | NS |
| Sakamoto 2005 [13] | 55 | | NS | ● | ○ | | NS | ○ | NS | |
| Cheng 2006 [8] | 112 | NS | ● | | ● | | | ○ | ○ | NS |
| Murakami 2007 [11] | 36 | NS | ● | | ○ | ○ | ○ | ○ | NS | NS |
| Ebata 2007 [14] | 100 | | ○ | ○ | ● | ○ | ○ | NS | ● | |
| Kawai 2010 [16] | 62 | NS | ○ | | ○ | NS | ● | ○ | NS | ○ |
| Kiriyama 2015 [15] | 370 | NS | ● | ○ | ● | | ● | ● | ○ | |

Pts, number of analyzed patients; N (+), lymph node metastasis; Panc, pancreatic invasion; Duo, duodenal invasion; Depth, depth of tumor invasion; Pn, perineural invasion; R status, resection margin status; Histology, tumor histology; Ad Tx, adjuvant therapy; NS, not significant; ○, significant by univariate analysis; ●, significant by multivariate analysis.

**Table 144.2** Long-term survival after resection of distal cholangiocarcinoma.

| | | Total | LN negative | LN positive |
|---|---|---|---|---|
| **Author/year** | **Pts** | **Overall 1/3/5-year survival (%)** | **Overall 1/3/5-year survival (%)** | **Overall 1/3/5-year survival (%)** |
| Kayahara 1999 [7] | 50 | –/47/35 | –/86/65 | –/30/21 |
| Sasaki 2001 [9] | 59 | –/43/34 | 94/57/53 | 81/14/0 (pN1) |
| Yoshida 2002 [12] | 27 | 65/37/37 | 91/61/61 | 47/20/20 |
| Sakamoto 2005 [13] | 55 | 78/52/24 | –/–/42 | –/–/16 |
| Cheng 2006 [8] | 112 | 86/51/25 | 94/62/30 | 56/12/4 |
| Murakami 2007 [11] | 36 | 75/54/50 | –/–/73 | –/–/17 |
| Ebata 2007 [14] | 100 | 75/47/35 | 86/60/46 | 57/25/19 |
| Kawai 2010 [16] | 62 | –/–/– | 95/72/60 | 78/48/36 |
| Kiriyama 2015 [15] | 370 | –/–/– | –/66/53 | –/36/24 |

Pts, number of analyzed patients; LN negative, lymph node negative for cancer cells; LN positive, lymph node positive for cancer cells; pN1, nodal involvement of a primary lymph node group close to the tumor.

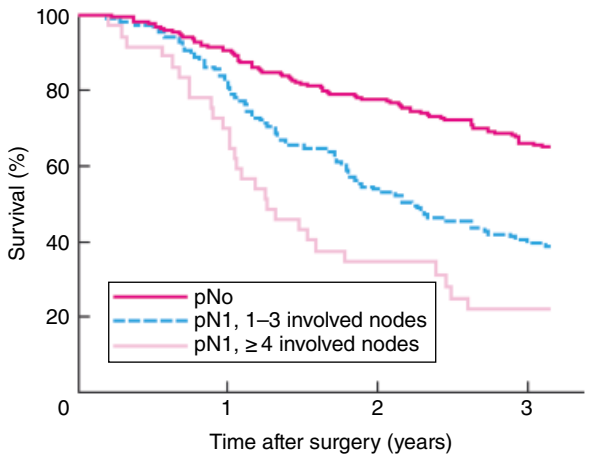



**Figure 144.1** Survival according to the number of involved nodes in 370 patients with distal cholangiocarcinoma. $P < 0.001$ (pN0 vs. pN1, 1–3 involved nodes; pN0 versus pN1, 4 or more involved nodes) (log rank test). Source: Kiriyama et al. 2015 [15]. Reproduced with permission of John Wiley & Sons Ltd.

according to the report by Kayahara et al., which meticulously examined the lymph nodes in different regions removed after resection of middle (Bm) and lower (Bi) cholangiocarcinomas [7]. The frequency of nodal involvement for patients with Bm was observed in the nodes along the common hepatic artery, in the hepatoduodenal ligament, and in the posterior pancreatoduodenal region. Among them, frequency was the highest in nodes in the hepatoduodenal ligament (50%). However, there was no lymph node metastasis in nodes around the superior mesenteric artery. In contrast, in patients with Bi cholangiocarcinoma, there was less nodal involvement in nodes along the common hepatic artery and more involvement in posterior pancreatoduodenal nodes. Notably, in 28% of patients with Bi cholangiocarcinoma, there was a lymph node metastasis in nodes around the superior mesenteric artery, with the highest frequency in nodes at the origin of the inferior pancreatoduodenal artery. These differences in the mode of cancer spreading through lymphatic vessels and lymph nodes should be carefully considered preoperatively when planning a surgical approach for distal cholangiocarcinoma. Radical lymph node dissection along the superior mesenteric artery is especially recommended in the case of lower cholangiocarcinoma. To accomplish a thorough lymph node dissection along the superior mesenteric artery, combined resection of the mesentery along the 1st jejunal artery and vein is recommended (Fig. 144.2).

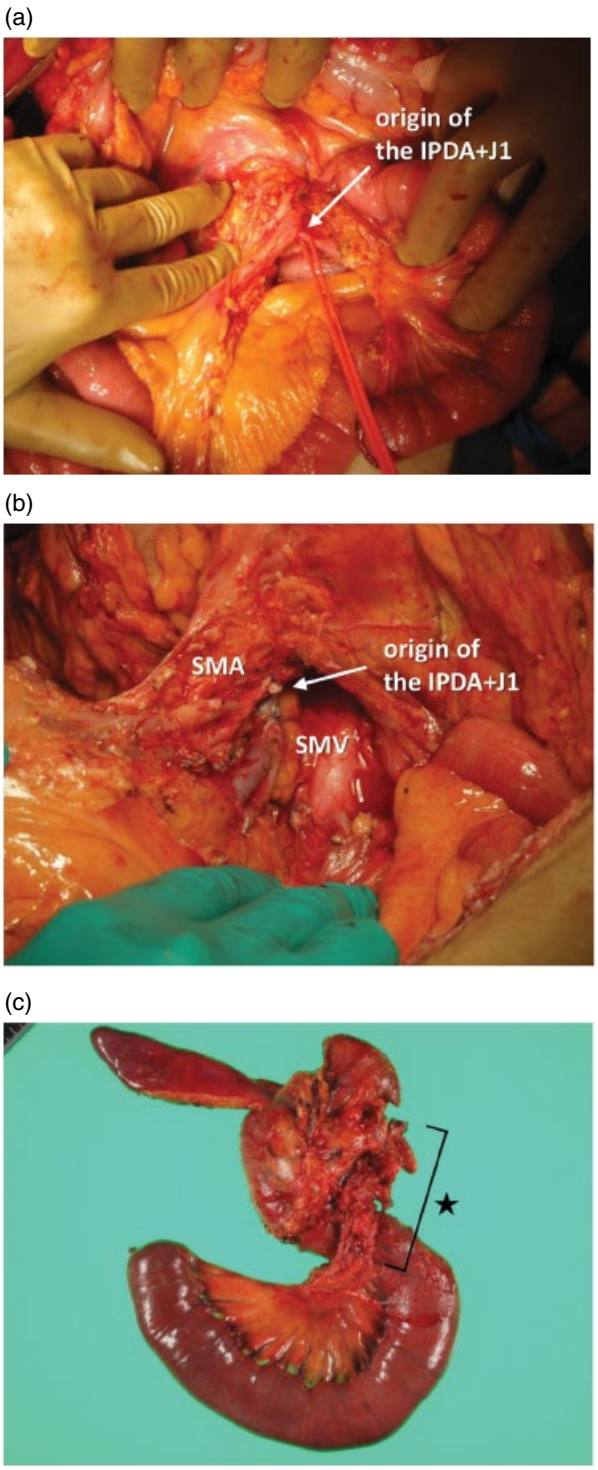



**Figure 144.2** Lymph node dissection along the superior mesenteric artery. (a) The jejunal mesentery is dissected with the common trunk of the inferior pancreatoduodenal artery (IPDA) and the 1st jejunal artery (J1). (b) After resection, the superior mesenteric artery (SMA) was exposed and the common trunk of the IPDA and the J1 was dissected at its origin. In this case, the lymph nodes along the SMA were thoroughly dissected (without nerve plexus dissection). SMV, superior mesenteric vein. (c) Macroscopic photo of the resected specimen. Star indicates lymph nodes along the SMA.

## Skeletonization of the Hepatoduodenal Ligament and Dissection of Pancreatic Head Neural Plexus

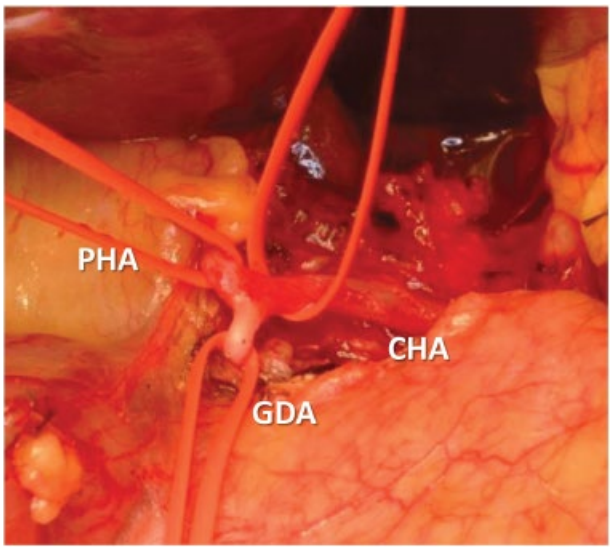
Neural plexus invasion is another important prognostic factor of cholangiocarcinoma, although its impact is not greater than that of lymph node involvement [15,16]. In the study by Bhuiya et al., the overall incidence of perineural invasion in the resected specimen of bile duct carcinoma (including perihilar cholangiocarcinoma and distal cholangiocarcinoma) was 81.4% [22]. The 5-year survival rate for patients with perineural invasion was significantly lower than that for those without perineural invasion (67% vs. 32%) [22].

In an analysis of 50 patients with distal cholangiocarcinoma, neural plexus invasion occurred in 20% of patients, particularly in the hepatoduodenal ligament and pancreatic head [7]. Neural invasion was observed more frequently when the tumors invade the subserosa. Therefore, skeletonization of the hepatoduodenal ligament including the removal of neural plexus around the hepatic artery and portal vein is recommended for the treatment of advanced distal cholangiocarcinoma (Fig. 144.3a). In contrast, dissection of the neural plexus around the hepatic artery in the hepatoduodenal ligament is not routinely recommended (unless there is an invasion of the tumor) in the pancreatoduodenectomy for the pancreatic head carcinoma (Fig. 144.3b). As with the mode of lymphatic spreading, neural invasion is mainly observed within the hepatoduodenal ligament in the middle cholangiocarcinoma, whereas that is more frequently observed in the pancreatic head plexus in the lower cholangiocarcinoma. These differences should be carefully considered in planning a surgical approach to distal cholangiocarcinoma.

## Bile Duct Cut Margin

It is now widely recognized that margin status is one of the most critical predictors of long-term survival in cholangiocarcinoma [23]. After surgical resection for extrahepatic cholangiocarcinoma, invasive carcinoma at ductal resection margins appears to have a strong adverse effect on patient survival. Superficial spreading is sometimes observed in cholangiocarcinoma (approximately 15% of all tumors according to the report by Igami et al.) [24]. Histologically, superficial spreading is more commonly observed in papillary and well-differentiated adenocarcinomas than in other types of carcinoma [24]. When considering the site of proximal bile duct cut margin in the pancreatoduodenectomy for distal cholangiocarcinoma, the extent of superficial spreading from the main tumor should be carefully examined either by

(a)




(b)

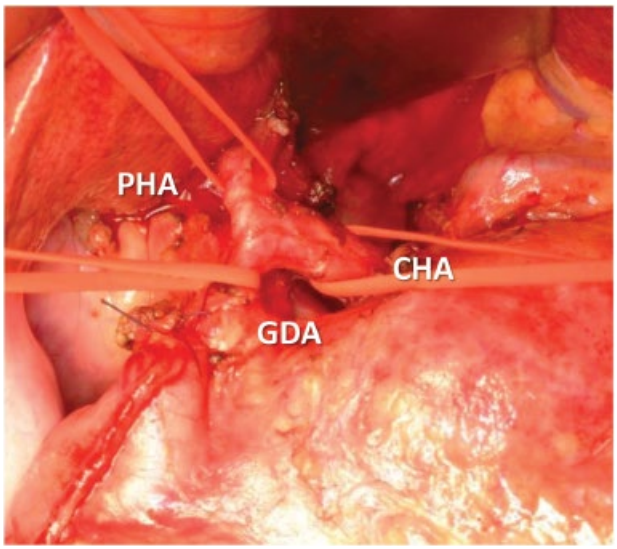



**Figure 144.3** Skeletonization of the hepatoduodenal ligament. (a) The neural plexus around the common hepatic artery (CHA) and the proper hepatic artery (PHA) were dissected with the lymph nodes and surrounding tissues (a case of the distal cholangiocarcinoma). GDA, gastroduodenal artery. (b) The lymph nodes around the CHA and the PHA were dissected by preserving neural plexus (a case of the pancreatic head carcinoma).

cholangiography, intraductal ultrasonography, and/or mucosal biopsy. It is also important to examine the proximal bile duct cut margin by intraoperative frozen sectioning to avoid a residual carcinoma at the bile duct cut margin. It should be noted, however, that the clinical significance of the residual carcinoma in situ at the bile duct cut margin is controversial. Several reports indicated that the residual carcinoma "in situ" in the proximal cut margin of the bile duct does not have an impact on survival [24–26], although a positive margin with "invasive" carcinoma is the independent risk factors of survival after surgery for distal cholangiocarcinoma [7,12,15]. Nevertheless, some patients have poor prognosis after surgery with residual carcinoma in situ. There may be a difference in the biological malignant potential between patients who do survive long term with residual carcinoma in situ and those who do not [27]. This should be clarified in a further biological approach.

## Surgery-Related Complications

Pancreatoduodenectomy is commonly selected as a surgical procedure for distal cholangiocarcinoma. Extrahepatic bile duct resection is selected only for cases of middle cholangiocarcinoma with limited tumor extension. The morbidity and mortality rates after resection of distal cholangiocarcinoma are 19–54% and 0–7%, respectively [7,8,11–14]. In general, the main pancreatic duct is not affected by the tumor in the distal bile duct and patients have a normal soft pancreas with small main pancreatic duct. Therefore, the rate of pancreatic fistula is more commonly observed in patients with distal cholangiocarcinoma (7–42%) than in patients with pancreatic head cancer [7,8,14]. Other commonly observed complications include biliary fistula (0.1–3%), delayed gastric emptying (0.1–10%), bleeding (2–7%), and intra-abdominal abscess (2–7%) [8,12,14,23].

## Summary

When a surgeon performs a pancreatoduodenectomy for distal cholangiocarcinoma, dissection of the pyloric ring (pylorus-preserving, subtotal stomach-preserving, or conventional pancreatoduodenectomy), extent of lymph node dissection (dissect lymph nodes along the superior mesenteric artery or not), skeletonization of hepatoduodenal ligament, and the proximal cut line of the bile should be carefully arranged depending on the tumor location as well as the intramural and extramural tumor extension.

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# Adjuvant and Palliative Chemotherapy of Periampullary Cancers

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## Introduction

The term periampullary cancer encompasses three pathologically distinct tumor subtypes which are in close anatomic proximity to the pancreatico-ampullary apparatus, including tumors arising from the distal common bile duct, ampulla of Vater, and the duodenum. The incidence of these tumors remains low, with European figures ranging between 0.3 to 0.84 per 100,000 population, placing them within the European Union definition of rare cancers [1,2]. These tumors possess different biological and molecular characteristics, but they are often grouped together as their curative surgical approach would usually mandate a pancreaticoduodenectomy [3,4]. Occasionally, the true pathologic origin of the malignant process is difficult to be established until full histologic assessment of the specimen is performed [5]. The heterogeneity of the histologic and biological profiles has profound implications for their long-term survival rates and response to various available chemotherapy regimens [5,6].

Periampullary tumors demonstrate a higher resectability rate, in contrast to pancreatic tumors. The ideal treatment strategy is achieved by surgical resection, which offers a chance of cure and prolonged survival in 60–80% of patients with resectable disease on presentation [7]. The remainder usually present with manifestations consistent with locally advanced disease or evidence of distant widespread metastasis. The mainstay of therapy in this setting is achieved by palliation of symptoms, with relief of jaundice, alleviation of pain, and providing nutritional support [8]. The focus on prolonging survival by the use of adjuvant and palliative treatments should not overlook the psychologic and emotional aspects for patients affected with this debilitating disease.

At present the overall prognosis remains bleak despite adequate tumor clearance by surgical resection as the locoregional and distant relapse incidence rates are known to be high in these tumors [9]. Surgical resection alone is associated with 5-year survival rates of 20–30%. The worst prognosis is associated with positive local lymph nodes and involved surgical margins [5,10,11]. Given the above, attempts to improve long-term survival by the addition of adjuvant chemotherapy have been tested in various clinical studies.

Most of the evidence in published literature on the use of adjuvant and palliative chemotherapy is limited to institutional retrospective case series and often contains a mixture of periampullary and pancreatic tumors with limited randomized controlled trials. The heterogeneity and quality of the evidence can lead to conflicting results about the genuine value of chemotherapy in periampullary cancers. The inherent rarity of these tumors has governed the paucity of published useful data that could be translated into effective clinical and oncological management paradigms.

## Distal Cholangiocarcinoma

### Adjuvant Therapy

Patients with distal cholangiocarcinoma have the worst prognosis among periampullary cancer patients. The long-term survival figures resemble those achieved in pancreatic adenocarcinoma. Tumors arising within the intrapancreatic portion of the distal bile duct account for approximately 27–40% of all cholangiocarcinomas [12,13]. These are closely linked to tumors arising in the proximal pancreatic duct as they share the same

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embryological origins with common phenotypic and functional characteristics. This supports the hypothesis that they should be considered as a congruent disease entity [14].

Takada et al. [15] conducted one of the first Phase III randomized controlled trials in Japan with adjuvant 5-fluorouracil (5-FU) and mitomycin C in 508 patients with resected pancreaticobiliary tumors (containing 139 patients with cholangiocarcinomas) compared to surgery alone and concluded that adjuvant chemotherapy compared to surgery alone did not have an impact on the 5-year survival rate (26.7% vs. 24%).

Following this the European Study Group for Pancreatic Cancer 3 (ESPAC-3) periampullary trial was designed to explore the benefit of adjuvant chemotherapy on overall survival in patients with resected periampullary cancer [16]. In this study 428 patients were randomized (of whom 96 had cholangiocarcinomas) to either fluorouracil- or gemcitabine-based chemotherapy versus surgery alone. The use of adjuvant treatment was associated with a potential survival advantage that did not reach statistical significance (median 43 months vs. 35 months, hazard ratio HR = 0.86, 95% CI: 0.66–1.11) but on multivariable analysis and after adjusting for prognostic variables a statistically significant survival benefit was demonstrated with adjuvant chemotherapy with HR = 0.75 (95% CI: 0.57–0.98; $P = 0.03$). The median survival of patients with cholangiocarcinoma assigned to either observation, fluorouracil plus folinic acid, or gemcitabine arms was 27.2, 18.3, 19.5 months, respectively.

These studies have demonstrated some evidence for the use of adjuvant therapy (Table 145.1). Horgan et al. [11] conducted a large meta-analysis of 20 studies, which included a randomized trial of chemotherapy, two registry, and 17 institutional series. The treatment protocol contained chemotherapy alone in three studies, radiotherapy only in nine, while eight studies contained radiation and chemotherapy combinations. There was a total of 6712 patients of whom 1797 received some form of adjuvant treatment during the course of their disease and 4915 in the surgery-only group. In this meta-analysis, the improvement in 5-year survival with any adjuvant therapy was not statistically significant (pooled odds ratio OR = 0.74, 95% CI: 0.55–1.01), however, the survival benefit from adjuvant therapy was statistically significant when the data from the two large registry series ($n = 1233$ patients) were excluded (OR = 0.53, 95% CI: 0.39–0.72). Pooled data extracted from the studies confirmed a statistical significant overall survival advantage for any adjuvant therapy in node-positive disease (OR = 0.49, 95% CI: 0.30–0.80) and patients with margin-positive disease (OR = 0.36, 95% CI: 0.19–0.68).

These studies have demonstrated survival benefit for the use of adjuvant treatment in patients with cholangiocarcinoma especially in those with poor prognostic indicators [20,21]. Currently there are two randomized controlled trials under way of adjuvant therapy in patients with resected cholangiocarcainoma: the BILCAP trial using adjuvant capecitabine and the French PRODIGE-12 trial studying combination gemcitabine and oxaliplatin. Both studies have completed accrual and their results will provide further prospectively validated evidence on the use of adjuvant treatment in patients with resected bile duct cancer.

## Palliative Therapy

The benefits of systemic chemotherapy in addition to best supportive care in patients with metastatic and recurrent distal cholangiocarcinoma are well established. Patients treated with chemotherapy were noted to have a significantly better median overall survival of more than 6 months with a better quality of life. The reported high incidence of local relapse and distant recurrence would advocate early referral for palliation treatment in patients with satisfactory performance status [20,22].

Eckel and Schmid [23] performed a pooled analysis of 104 trials examining the role of chemotherapy in advanced biliary tract cancer which showed combination treatment to have a better treatment effect compared to monoagent therapies. The gemcitabine- and platinum-based combinations demonstrated the greatest benefit in the pooled analysis.

The randomized Phase III study ABC-02 [24] of up to 6 months of gemcitabine versus gemcitabine and cisplatin recruited 410 patients (73 distal cholangiocarcinomas) with unresectable, recurrent, or metastatic biliary tract carcinoma (Table 145.2). This trial demonstrated a significant overall survival advantage with the combination arm versus the gemcitabine arm (11.7 months vs. 8.1 months; HR = 0.64, 95% CI: 0.52–0.80) and a median progression-free survival of 8.0 months versus 5.0 months (HR = 0.63, 95% CI: 0.51–0.77), respectively. Patients who received the combination therapy were 36% less likely to die at any time compared to those who received gemcitabine alone (HR = 0.64, 95% CI: 0.52–0.80). Grade 3 and 4 toxicities occurred with similar frequency in both study arms without any substantial difference. The combination of gemcitabine and cisplatin is the first-line treatment of choice recommended by the European Society of Medical Oncology (ESMO) [25] in patients with favorable performance status (PS 0–1). Patients with PS 2 should be considered for gemcitabine monotherapy while oxaliplatin could be substituted for cisplatin in patients with impaired renal function. A second trial by the same group looking at oxaliplatin and

**Table 145.1** Studies of adjuvant treatments in resected periampullary cancers.

| Study, year | Total no. of patients (*n*) | Subdivision of tumor types | | | Treatment | Median survival (months) | 5-year survival (%) |
|---|---|---|---|---|---|---|---|
| | | Distal cholangiocarcinoma | Duodenal adenocarcinoma | Ampullary carcinoma | | | |
| Bakkevold et al., 1993 [17][a] | 61 | – | – | 14 | 5-FU/Dox/MMC | 23 | 4 |
| | | | | | Surgery | 11 | 8 |
| Takada et al. [15][a] | 436/508 evaluated | 118 | – | 48 | 5-FU/MMC | – | 26.7 vs. 24.1 months (distal cholangio)* |
| | | | | | Surgery | | 28.1 vs. 34.3 months (ampullary)* |
| ESPAC-3, 2012 [16][a] | 428 | 96 | 10 | 297 | Gemcitabine | 45.7 | 44 |
| | | | | | 5-FU/FA | 38.9 | 40 |
| | | | | | Observation | 35.2 | 36 |
| Poultsides et al. [18][b] | 122 | – | 122 | – | 5-FU + Rx | – | 47 |
| | | | | | Observation | | 48 |
| Bhatia et al., 2006 [19][b] | 125 | – | – | 125 | 5-FU + Rx 50.4 > Gy | – | 48 |
| | | | | | Observation | | 11 |

[a] Randomized controlled trial.
[b] Case series.
DOX, doxorubicin; MMC, mitomycin C; 5-FU, 5-fluorouracil; FA, folinic acid; NS, nonsignificant.
* Log rank test = NS.

**Table 145.2** Studies of palliative treatments in locally advanced and metastatic periampullary cancers.

| Study, year | Type of tumor | No. of patients | Treatment | Median survival (months) | Median progression-free survival (months) |
|---|---|---|---|---|---|
| ECOG, 2005 [26][a] | Small bowel/ampullary | 31 | 5-FU/DOX/MMC | 8 | – |
| ABC-02, 2010 [24][b] | Biliary (some ampullary) | 204 | Gem + cisplatin | 11.7 | 8 |
| | | 206 | Gem + cisplatin | 8.1 | 5 |
| Zaanan et al. [27][a] | Small bowel | 10 | LV/5-FU | 13.5 | 7.7 |
| | | 48 | FOLFOX | 17.8 | 6.9 |
| | | 19 | FOLFIRI | 10.6 | 6 |
| | | 16 | LV/5-FU/cisplatin | 9.3 | 4.8 |
| Overman et al., 2009 [28][c] | Small bowel/ampullary | 30 | CAPOX | 20.4 | 11.3 |

[a] Case series.
[b] Randomized controlled trial.
[c] Phase II trial.
DOX, Doxorubicin; MMC, mitomycin C; Gem, gemcitabine; 5-FU, 5-fluoruracil; CAPOX, capecitabine and oxaliplatin; LV, leucovorin; FOLFOX, folinic acid and fluorouracil and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan.

5-FU versus supportive care as second-line treatment for advanced biliary tract cancers (ABC-06) is currently open and recruiting.

## Duodenal Adenocarcinoma

### Adjuvant Therapy

Complete surgical resection with regional lymphadenectomy confers prolonged survival for patients with duodenal cancer. Important prognostic factors include the degree of tumor differentiation and local lymph nodes involvement. Several studies have shown no survival benefit for the routine use of adjuvant chemotherapy in completely resected, nodal disease-free duodenal adenocarcinoma [29,30]. Increased number of involved lymph nodes is associated with decreased overall survival with 5-year survival ranging from 68% for node negative patients to 17% when four or more lymph nodes were involved [18] with high incidences of local and distant recurrence [31–33].

The global low incidence of duodenal adenocarcinoma and challenges in conducting adequately powered future studies was reflected in the ESPAC-3 trial which contained only 10 patients with duodenal adenocarcinoma in addition to 25 nondescriptive periampullary tumors out of the original study cohort (see Table 145.1). The eight patients who were assigned to observation in this group survived a median of 28.7 months (95% CI: 4.7–∞ months); 12 patients in the fluorouracil plus folinic acid group survived 22.4 months (95% CI: 9.6–54.6 months); and 15 had high but not estimable survival with gemcitabine therapy [16].

There is currently no agreed regimen as a first-line therapy but many centers would advocate the use of adjuvant oxaliplatin-based chemotherapy in patients with high-risk features (e.g., nodal metastasis) similar to the recommendations for resected colonic adenocarcinoma. Other regimens which demonstrated disease-related activity are capecitabine and oxaliplatin (CAPOX), 5-FU and leucovorin with oxaliplatin (FOLFOX), 5-FU and leucovorin with irinotecan (FOLFIRI) [27,28,34]. To date there are no randomized controlled trials testing the superiority of any of these combinations.

Chemoradiation has been tested in the adjuvant setting and showed improvement in locoregional control but this did not translate into any survival benefit [35]. In a retrospective series published by Poultsides et al. [18] from a single institution, 122 patients with local lymph node involvement showed no difference in overall survival with adjuvant chemoradiotherapy compared to patients who underwent surgery alone (5-year survival 47% vs. 48%, $P = 0.82$) [36].

An international collaboration for the study of rare tumors has launched an open-label, randomized controlled multicenter trial (BALLARD trial) to assess the efficacy of 6 months of adjuvant chemotherapy compared to observation only in Stage I–III resected small bowel adenocarcinoma. The study will also compare fluoropyrimidine monotherapy versus fluoropyrimidine plus oxaliplatin. Recruitment into the study is currently ongoing and is expected to finish by 2020.

### Palliative Therapy

A number of studies support the use of palliative chemotherapy in patients with recurrent and metastatic duodenal adenocarcinoma (see Table 145.2) as it adds a clear

survival benefit over best supportive care [29,37,38]. The Eastern Cooperative Oncology Group (ECOG) published one of the early studies on 31 patients with locally advanced and metastatic small bowel tumors who received combination treatment 5-FU, doxorubicin, and mitomycin C with a median survival of 8 months [26].

Zaanan et al. [27] published results of a retrospective study of 99 patients with advanced and metastatic small bowel adenocarcinoma (55 duodenal) comparing first-line treatments with FOLFOX, leucovorin–FU, FOLFIRI, and leucovorin–FU–cisplatin. In the report, 48 patients with advanced cancer who received FOLFOX as front-line therapy had a median progression-free survival of 7.4 months and median overall survival of 17.8 months. A study by Overman et al. [28] conducted at M.D. Anderson Cancer Center evaluated the combination of capecitabine and oxaliplatin (CAPOX) in 30 patients with either metastatic or locally advanced small bowel or ampullary adenocarcinoma. In the 18 patients who had small bowel adenocarcinoma, the response rate was 61%, with a median time to progression of 9.8 months and median overall survival of 20.4 months. Of note, 10% of treated patients had a complete radiographic response to CAPOX therapy. The treatment combination of fluoropyrimidine and oxaliplatin was also reported to have a better disease activity in Phase II randomized controlled trials. Three studies, including that by Overman et al., combining a fluoropyrimidine with oxaliplatin have shown similar activity with response rates of 42–50%, and a median time to progression ranging from 7.8 to 9.8 months [28,39,40].

Other studies have tested different agents, including irinotecan- and gemcitabine-based treatments which were found to have some disease activity in a small number of patients [27]. Targeted therapies such as antivascular endothelial growth factor receptor (VEGFR) or antiepidermal growth factor receptor (EGFR) therapies have not been evaluated in any formal study as yet and therefore there is currently no evidence to support their use outside the context of experimentation in a clinical trial.

## Ampullary Carcinoma

### Adjuvant Therapy

Ampullary carcinomas constitute 0.2% of the tumors arising in the gastrointestinal tract. These tumors show different immunohistochemical differentiation and molecular characteristics including alterations of *KRAS*, *SMAD4*, and *APC* genes. The intestinal subtype mimics behavioral and oncogenic responses similar to duodenal adenocarcinoma, while the pancreaticobiliary subtype tends to be more aggressive, resembling pancreatic ductal adenocarcinoma with poor prognosis and unfavorable outcomes [41–44]. One of the earliest randomized controlled trials was published by Bakkevold et al. in 1993 [17]. This study demonstrated a median survival of 23 months versus 11 months ($P = 0.02$) using adjuvant combination chemotherapy agents 5-FU, doxorubicin, and mitomycin C in 61 patients (14 ampullary, 47 pancreatic tumors) who underwent a radical resection versus observation but with limited 5-year survival (4 vs. 8 years, respectively) and increased treatment-related toxicity.

ESPAC-3 [16] remains the landmark study in evaluating the role of adjuvant chemotherapy in periampullary carcinomas (see Table 145.1). There were 297 patients with ampullary adenocarcinoma who were randomized to either observation, 5-FU/leucovorin, or gemcitabine. The use of adjuvant chemotherapy demonstrated a trend toward improved overall survival favoring the chemotherapy group versus observation (median overall survival of 43 vs. 35 months, $P = 0.25$). Moreover, when the analysis was limited to patients with ampullary cancer, those treated with gemcitabine had a remarkable survival that was almost double that in the observation group (median 71 vs. 41 months). Subsequent analysis did not show different treatment responsiveness between intestinal and pancreaticobiliary subtypes.

The ESPAC-4 trial [45] randomized 730 patients with resected pancreatic cancer between gemcitabine and combination therapy gemcitabine and capecitabine (GemCap). The median survival was 25.5 months (95% CI: 22.7–27.9) for gemcitabine and 28.6 months (95% CI: 23.5–31.5) for GemCap. The hazard ratio was 0.82 (95% CI: 0.68–0.98, $P = 0.032$) with a substantial difference in 5-year survival of 28.8 versus 16.3% in the combination group. The ampullary arm of ESPAC-4 (comparing adjuvant gemcitabine vs. gemcitabine plus capecitabine) is currently recruiting and has a target of 346 patients and is anticipated to complete follow-up and report by 2022.

A number of retrospective series examined the benefit for chemoradiotherapy as an adjuvant treatment [46,47]. In a study coordinated by the European Organisation for Research and Treatment of Cancer (EORTC), 218 patients with resected pancreatic and periampullary cancers were randomized to postoperative radiotherapy plus concurrent 5-FU (25 > mg/kg per day by continuous infusion) or observation. There were 104 patients with periampullary cancers (which included cancers of the ampulla, distal common bile duct or duodenum), and there was no difference in the 2-year survival rate (67% radiotherapy vs. 63% observation) or in the incidence of locoregional recurrence in the postoperative radiotherapy group compared to controls. This was contrary to the findings from another series at the Mayo Clinic of

29 out of 125 patients with ampullary cancer who underwent curative surgical resection in addition to 5-FU and concurrent radiotherapy with a median total radiation dose of 50.4 > Gy (range 45.0–54.0 > Gy) while the remainder underwent surgery alone. The 5-year survival figures of 48% versus 11% were in favor of the adjuvant chemoradiation group [19].

Results from the ESPAC-4 ampullary trial will help inform future adjuvant therapy options for this patient group.

### Palliative Therapy

Systemic chemotherapy remains the mainstay to halt disease progression and prolong survival in unresectable and metastatic ampullary carcinoma. Survival figures beyond 3–6 months are dismal without additive palliative therapy. Most of the existing evidence is extrapolated from large studies that contained a mixture of periampullary tumors with ampullary tumors forming a subset. Agents that have been examined in this disease include antimetabolites (fluoropyrimidine and/or gemcitabine) with or without a platinum compound (cisplatin or oxaliplatin) with variability in response rates ranging from 10% to 40% [48,49]. A Phase II study evaluating CAPOX in patients with advanced adenocarcinoma of the small bowel or the ampulla reported a response rate of 33% with improved overall survival (20.4 vs. 15.5 months in patients with metastasis). The primary site of disease was the ampulla of Vater in 12 out of 30 patients [28].

In the ABC-02 trial (see Table 145.2) which randomly assigned 410 patients with locally advanced or metastatic biliary tract cancer to receive combination cisplatin and gemcitabine versus gemcitabine alone [24], there were 206 patients in the gemcitabine group (ampullary: 11 cases) and 204 patients in the cisplatin plus gemcitabine group (ampullary: 9 cases). The median progression-free survival was 8 months in the cisplatin plus gemcitabine versus 5 months in the gemcitabine-only cohort. The overall median survival was 11.7 months versus 8.1 months, respectively.

## Conclusion

Periampullary tumors constitute a diverse group of tumor subtypes. Despite the advances in diagnostics and clinical cancer care their treatment remains challenging for clinicians and oncologists worldwide. The rarity of these tumors, in addition to disparity of the published data, has slowed the advancements made in the field. There is a high unmet need for these patients. Future randomized trials should be of high quality and use efficient novel study designs to ensure that the best clinical evidence is available for these patients.

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# Long-Term Survival After Tumor Resection

## 146

## Long-Term Survival After Resection of Periampullary Cancer

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### Introduction

Periampullary cancers are grouped as a heterogeneous malignant lesions arising from anatomic sites around the pancreatico-biliary-digestive junction. They consist of pancreatic cancer in the head of the pancreas, ampullary region cancer, distal bile duct cancer, and duodenal cancer. Because of their anatomical proximity, periampullary cancers share similar clinical presentations and treatment strategies. Surgical resection is the most effective treatment option regardless of the site of the origin of these cancers. Pancreaticoduodenectomy represents the surgical procedure of choice for periampullary cancers, although limited resections are indicated for some patients.

The incidences and the long-term survival rates after surgical resection are very different according to the type of cancer. Pancreatic cancer is the most common, and accounts for 80% of all periampullary cancers, and has the poorest prognosis with 5-year survival rate of around 20%. Other cancers are less common than pancreatic cancer. Patients with ampullary region cancer and duodenal cancer are known to have relatively favorable prognosis after surgical resection.

This chapter focuses on the long-term survival after surgical resection in patients with periampullary cancers other than pancreatic cancer.

### Distal Bile Duct Cancer

#### Overall Survival

There are few reports describing the clinicopathologic data of patients with distal bile duct cancer (Table 146.1). According to the Biliary Tract Cancer Registry in Japan [1], 4091 patients with distal bile duct cancer were registered from 2008 to 2013. Of these patients, 3800 (92.9%) underwent surgical resection. On the basis of the Japanese classification of the biliary tract cancers [2], T3a disease was the most frequently seen (53.4%), followed by T2 disease (28.6%). In this patient population, the 5-year survival rate was reported to be 39.1%.

In a multi-institutional study, the Nagoya Surgical Oncology Group [3] reported 370 patients undergoing pancreaticoduodenectomy, including 38 cases (10.3%) of T1 disease, 96 (25.9%) of T2 disease, and 236 (63.8%) of T3 disease, classified by the American Joint Committee on Cancer (AJCC) TNM classification system [4]. They reported that the 3-year, 5-year, and 10-year survival rates were 53.3%, 40.8%, and 28.4%, respectively, with a median survival of 42 months. Another multi-institutional study from France [5] included 55 patients with 4 (7.3%) T1, 15 (27.3%) T2, 28 (50.9%) T3, and 8 (14.5%) T4 diseases. The 5-year survival rate of all patients was 34% with a median survival of 24 months.

In high-volume single-center studies, a Johns Hopkins Medical Institution series in the United States [6] found that the 3-year and 5-year survival rates were 33% and 18%, respectively, with a median survival of 20.3 months in 147 patients. In their series, 88.5% of all cases were classified as T3 or higher. In a Samsung Medical Center series in Korea [7], the 3-year, 5-year, and 10-year survival rates were 55.3%, 48.3%, and 33.7%, respectively, with a median survival of 73.0 months, after pancreaticoduodenectomy in 237 patients. Among these patients, 173 (73.0%) had T3 or T4 diseases. Similarly, in our series consisting of 75 patients including 21 (28%) patients with T2 disease, 46 (61%) with T3a, and 8 (11%) with T3b according to the Japanese classification [2], the 1-year, 3-year, and 5-year survival rates were 85.2%, 63.3%, and 38.2%, respectively, with a median survival of 46.0 months.

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Companion website: www.wiley.com/go/beger/thepancreas

**Table 146.1** Published series of survivals after surgical resection of distal bile duct cancer.

| Reference | Country/institution | Study period | No. of patients | 5-year survival | MST (months) | Stage I[a] | Lymph node metastasis | R0[a] |
|---|---|---|---|---|---|---|---|---|
| **Nationwide study** | | | | | | | | |
| Ishihara et al. [1] | Japan | 2008–2013 | 3800 | 39.1% | ND | 32.5% | 28.1% | ND |
| **Multi-institutional study** | | | | | | | | |
| Kiriyama et al. [3] | Japan | 2001–2010 | 370 | 40.8% | 42 | 29.2% | 42.4% | 93.5%[b] |
| Bourgouin et al. [5] | France | 2001–2011 | 55 | 34% | 24 | 24% | 46% | 82% |
| **Single-center study** | | | | | | | | |
| Hong et al. [6] | USA/Johns Hopkins Medical Institution | 1984–2004 | 147 | 18% | 20.3 | ND | 63.3% | 90.5% |
| Chung et al. [7] | Korea/Samusung Medical Center | 1995–2011 | 237 | 48.3% | 73.0 | 22.3% | 30.4% | 95.8% |
| Our data | Japan/Chiba University | 2000–2015 | 75 | 38.2% | 46.0 | 18.7% | 52.0% | 81.3% |

[a] According to AJCC TNM classification system [4].
[b] Including patients with positive duct margins with carcinoma in situ.
MST, median survival time; ND, not determined.

### Prognostic Factors

Several reports indicated prognostic factors for patients with distal bile duct cancer (Table 146.2). According to the meta-analysis of 25 studies [8], R1 resection, lymph node metastasis, perineural invasion, lymphatic invasion, vascular invasion, pancreatic invasion, and pathological tumor stage ≥ T3 were significantly associated with shorter overall survival, while sex, age, and blood transfusion have no impact on survival. Of these, R1 resection is one of the strongest prognostic factors, which was also indicated in other studies as a factor influencing survival after pancreaticoduodenectomy in patients with distal bile duct cancer [3,5,7]. Since distal bile duct cancer often spreads along the bile duct, a cancer-positive margin at the stump of the bile duct is sometimes encountered, resulting in a R0 resectability rate of 46–96% [8], which is lower than the frequency for other periampullary cancers.

Another important factor is lymph node metastasis, which was reported at appreciably different frequencies ranging from 22% to 68% [8]. According to the Japanese classification [2], the most frequently involved lymph nodes were nodes on the surface of the head of the pancreas (station nos. 13 and 17), followed by nodes in the hepatoduodenal ligament (station no. 12), nodes along the common hepatic artery (station no. 8) and nodes at the root of the superior mesenteric artery (station no. 14). Among these nodal stations, metastases to station no. 12 [9] or no. 8 [3] were reported to be associated with unfavorable outcome after pancreaticoduodenectomy. The lymph node ratio—the number of lymph nodes with metastases/the total number of removed lymph nodes—may be a possible predictor for survival, but variable results have been reported [10,11].

When the analysis was limited to patients with lymph node metastasis, the number of involved nodes ≥4 was shown to be a strong predictor of survival [3]. However, because of the limited data, further validation is required.

### Recurrence

A few studies have reported on cancer recurrence after pancreaticoduodenectomy. Recurrence occurred in 39–67% of patients [7,12,13] with a mean follow-up of 29–32 months. Mean delay was reported to be 13 months after surgical resection [12]. The frequent form of recurrence was intrahepatic and local recurrence, followed by peritoneal and systemic recurrence [7,12]. Intrahepatic recurrence occurs with higher frequency in patients with distal bile duct cancer than with ampullary region cancer [13].

## Ampullary Region Cancer

### Overall Survival

The survival in patients with ampullary region cancer is favorable (Table 146.3) compared with that in patients with distal bile duct cancer. According to the Biliary

**Table 146.2** Published series of prognostic factors after surgical resection of distal bile duct cancer.

| | | | Negative prognostic factors | | |
|---|---|---|---|---|---|
| **Reference** | **Study period** | **No. of patients** | **Not significant** | **Significant (univariate)** | **Significant (multivariate)** |
| Kiriyama et al. [3] | 2001–2010 | 370 | Age, sex, tumor length ≥2 cm | Vascular resection, nonpapillary type, lymphovascular invasion, perineural invasion, pancreatic invasion, histologic grade 2–3, pT3, nodal metastasis, positive margin | Perineural invasion, pancreatic invasion, nodal metastasis, positive margin |
| Bourgouin et al. [5] | 2001–2011 | 55 | Nodal metastasis, vascular invasion | Biliary dilatation, biliary drainage, T3/4, UICC stage, positive margin, neural invasion | T3/4, positive margin |
| Chung et al. [7] | 1995–2011 | 237 | Age, sex, bilirubin at operation, operation time, transfusion, reoperation | Biliary drainage, CA 19-9 > 35 U/L, tumor size >2 cm, positive margin, adjuvant therapy, T category, nodal metastasis, AJCC stage | CA 19-9 > 35 U/L, positive margin, ≥T3, nodal metastasis |
| Andrianello et al. [9] | 2000–2013 | 46 | Age, sex, T category, positive margin, lymphatic invasion, perineural invasion, vascular invasion, morbidity, adjuvant therapy | Nodal metastasis, histologic grade, metastatic nodes in station 12 | – |

UICC, International Union Against Cancer; AJCC, American Joint Committee on Cancer.

**Table 146.3** Published series of survivals after surgical resection of ampullary region cancer.

| Reference | Country/institution | Study period | No. of patients | 5-year survival | MST (months) | Stage I[a] | Lymph node metastasis | R0[a] |
|---|---|---|---|---|---|---|---|---|
| **Nationwide study** | | | | | | | | |
| Ishihara et al. [1] | Japan | 2008–2013 | 2053 | 61.3% | ND | 56.3% | 23.6% | ND |
| O'Connell et al. [14] | USA | 1998–2003 | 1301 | 36.8% | ND | 37.5% | 57.6% | ND |
| **Multi-institutional study** | | | | | | | | |
| Balci et al. [15] | USA, Japan, Turkey | ND | 313 | 49% | ND | 36.1% | 45% | 96% |
| **Single-center study** | | | | | | | | |
| Winter et al. [16] | USA/Johns Hopkins Medical Institution | 1970–2007 | 347 | 45.0% | ND | 21.2% | 54.5% | 96.1% |
| Klein et al. [17] | Germany/Charité Campus Virchow Universitätsmedizin | 1992–2007 | 143 | 40% | 37 | 34% | 48% | 92% |
| Chen et al. [18] | Taiwan/National Yang Ming University | 1999–2014 | 194 | 42.7% | 45.1 | 33% | 37.1% | 100% |

[a] According to AJCC TNM classification system [4].
MST, median survival time; ND, not determined.

Tract Cancer Registry in Japan [1], 2161 patients were registered from 2008 to 2013. Of these patients, 2053 (95.0%) underwent surgical resection. On the basis of the Japanese classification of biliary tract cancers [2], T2 disease was the most frequently seen (38.5%), followed by T1a disease (17.5%), and tumor stage was most frequently classified as Stage IA (29.1%), followed by Stage IB (27.2%). The overall 5-year survival rate was reported to be 61.3%. This survival rate decreased significantly with increasing degree of pathologic T category and tumor stage: the 5-year survival rates were 92.8% and 85.8% in patients with T1a and T1b diseases, respectively, and 92.2% and 74.7% in patients with Stage IA and Stage IB, respectively. In the database of the Surveillance, Epidemiology, and End Results (SEER) national cancer registry from the United States [14], 3292 patients were registered from 1998 to 2003, and 1301 of them (40%) underwent resection. The 5-year cancer-specific survival after resection was 47.3%. In this database, patients with Stage IIb were most frequently seen, and only 37.5% of patients were classified as Stage I.

In a multi-institutional study from the United States, Japan, and Turkey [15], the 1-year, 3-year, and 5-year survival rates were 85%, 63%, and 49%, respectively in 313 patients. This study included 32 patients (10.2%) with T1N0 and 81 patients (25.9%) with T2N0, according to the AJCC TNM classification system [4].

In high-volume single-center studies, the Johns Hopkins Hospital series [16] revealed that 5-year survival rate was 45.0% in 347 patients. In their series, 21.2% of all cases were classified as Stage I. In the Charité Campus Virchow Universitätsmedizin series in Germany [17], the 1-year and 5-year survival rates were 79% and 40%, respectively, with a median survival of 37 months in 143 patients undergoing pancreaticoduodenectomy. This series included 49 (34%) patients with Stage I. The National Yang Ming University series in Taiwan [18] showed that the 5-year survival rate was 42.7% with a median survival of 45.1 months in 194 patients, including 64 (33%) patients with Stage I.

## Prognostic Factors

Although diverse prognostic factors for resected ampullary region cancer have been described in the literature (Table 146.4), lymph node metastasis has been identified as the strongest prognostic factor. Lymph node metastasis could be found in 24–58% of patients [1,5,14–24]. Once tumor invades the sphincter of Oddi, lymph node metastasis can be found, and the frequency increases

**Table 146.4** Published series of prognostic factors after surgical resection of ampullary region cancer.

| | | | Negative prognostic factors | | |
|---|---|---|---|---|---|
| **Reference** | **Study period** | **No. of patients** | **Not significant** | **Significant (univariate)** | **Significant (multivariate)** |
| Bourgouin et al. [5] | 2001–2011 | 55 | Pre-illness BMI, ASA score, grade 2–3, neural invasion | Loss of BMI ≥4%, T category, nodal metastasis, UICC stage, vascular invasion | Loss of BMI ≥4%, nodal metastasis, UICC stage |
| Winter et al. [16] | 1970–2007 | 347 | Adjuvant chemoradiation | Blood transfusion, perineural invasion, nodal metastasis | Blood transfusion, perineural invasion, nodal metastasis |
| Klein et al. [17] | 1992–2007 | 143 | PPPD, tumor size >2 cm | Reduced general condition, blood transfusion, pancreatic fistula, pT4, nodal metastasis, grade 4, positive margin, vascular or lymphatic invasion, CA 19-9 > 37 U/L | Lymphatic invasion, blood transfusion, CA 19-9 > 37 U/L |
| Sakata et al. [19] | 1978–2009 | 71 | Age, sex, tumor size >2 cm, adjuvant chemotherapy, number of lymph nodes evaluated | Ulcerating type, histologic grade, pancreatic invasion, lymphatic invasion, venous invasion, perineural invasion, positive margin, number of positive nodes, lymph node ratio | Lymphatic invasion, venous invasion, number of positive nodes |
| Qiao et al. [20] | 1987–2002 | 102 | Age, jaundice, tumor size, grade, adjuvant chemotherapy | Nodal metastasis, AJCC stage IIA–III, T3/4 | Nodal metastasis, T3/4 |
| Sudo et al. [23] | 1988–2006 | 46 | Age >65, PPPD, blood transfusion, tumor size >2 cm, ulcerating type, papillary histological type | T3/4, nodal metastasis, perineural invasion | Perineural invasion |

BMI, body mass index; UICC, International Union Against Cancer; PPPD, pylorus-preserving pancreaticoduodenectomy.

with advancing depth of infiltration. The 5-year survival of patients with lymph node metastasis was reported to be 20–46% [1,5,15,16,18–21], while without lymph node metastasis it was 54–85%. Among node-associated variables, some reports indicated that the number of involved nodes was a significant independent prognostic factor, but cut-off point for the number of nodes was variable among studies [5,15,18,19]. Few reports showed the significance of the lymph node ratio [5,10].

The depth of infiltration or T category also influences long-term survival. Patients with T1/2 and Stage I disease have apparently favorable prognosis after pancreaticoduodenectomy, while limited resection such as transduodenal ampullectomy for these patients could not yield similar results [25,26]. In contrast, the survival of patients with pancreatic invasion, especially invasion ≥5 mm in depth, was reported to be significantly worse than that of patients without pancreatic invasion [27].

Ampullary region cancer represents a heterogeneous cancer group with different cell types: intestinal and pancreatobiliary types. Since it was first reported by Kimura et al. [28], several authors have revealed that ampullary region cancers with intestinal type are associated with favorable survival [29,30], although there are some controversial reports [31,32].

### Recurrence

A few studies have reported on cancer recurrence after pancreaticoduodenectomy. Recurrence occurred in 17–38% of patients with a median follow-up of 30–115 months [13,22–24]. Median time from surgical resection to recurrence was reported to be 50.2 months [22]. The most frequent form of recurrence reported was various among the literature, but intrahepatic and local recurrences were found to be relatively frequent [13,23,24]. Preoperative bilirubin, T category, pancreatobiliary cell type, lymph node metastasis [22], venous invasion, and perineural invasion [13] have been reported as factors related to recurrence.

## Duodenal Cancer

### Overall Survival

Duodenal cancer (adenocarcinoma) may be located in any part of the duodenum. In most studies, therefore, duodenal cancers arising in the periampullary duodenum, which has not been clearly defined yet, and in other parts of the duodenum (extra-ampullary duodenum) have been grouped together, although periampullary and extra-ampullary duodenal cancers were reported to have similar long-term survival after resection [33]. These cohorts generally included patients undergoing not only pancreaticoduodenectomy, but also segmental resection of the duodenum chiefly for duodenal cancer arising in the fourth portion of the duodenum.

The survival in patients with duodenal cancer is similar to that in patients with ampullary region cancer (Table 146.5). In a multi-institutional study in the United Kingdom [34], the 1-year, 3-year, and 5-year survival rates were 83.9%, 66.7%, and 51.2%, respectively, with a median survival of 84 months in 143 patients including 8 (5.6%) T1, 12 (8.5%) T2, 50 (35.2%) T3, and 72 (50.7%) T4 diseases.

Several high-volume single-center studies indicated similar survival rates. The Mayo Clinic series in the United States [33] found 5-year and 10-year survival rates of 43% and 39%, respectively, in 99 patients. In this series, the majority of patients had T3 disease and Stage II disease. In the Johns Hopkins Hospital series [35], the 5-year and 10-year survival rates were 48% and 41%, respectively, in 112 patients undergoing pancreaticoduodenectomy. The majority of patients also had T3 disease. The university of Texas M.D. Anderson Cancer Center series [36] found that the 5-year survival rate was 55.9% with a median survival of 149.8 months in 68 patients, including 31 (45.6%) patients with T3 and 32 (47.1%) with Stage III. In the Massachusetts General Hospital series [37], the 3-year and 5-year survival rates were 57% and 42%, respectively, with a median survival of 44 months in 103 patients who most frequently presented with Stage III disease (45%).

### Prognostic Factors

Recently reported prognostic factors are positive surgical margin, lymph node metastasis, AJCC Stage III/IV, poor differentiation, perineural invasion, and lymphovascular invasion (Table 146.6), while patient age, gender, and size of the tumor have not been consistently associated with the outcome. As for other periampullary cancers, lymph node metastasis is recognized as one of the most significant prognostic factors. Noteworthy is the relationship between an increased number of involved nodes and poor survival. The current AJCC TNM classification system [4] stratifies N category as N0 (no regional lymph node metastasis), N1 (metastasis in 1–3 regional lymph nodes), and N2 (metastasis in four or more regional lymph nodes). In fact, the survival rate was reported to decrease with N category [34,35]. For assignment of the N category, however, the number of lymph nodes examined is important. Sarela et al. [38] showed that examination of ≥15 regional lymph nodes improved prognostic discrimination by the N category. They found that the survival difference between pN0 and pN+ was significant in patients with ≥15 nodes, but was lost in those with <15 nodes probably because of a stage-migration effect.

The lymph node ratio might be also a possible prognostic factor. Poultsides et al. [35] demonstrated that the 5-year survival decreased as the lymph node ratio increased from 0 to >0–0.2 to >0.2–0.4 to >0.4.

**Table 146.5** Published series of survivals after surgical resection of duodenal cancer.

| Reference | Country/institution | Study period | No. of patients | 5-year survival | MST (months) | Stage I[a] | Lymph node metastasis | R0[a] |
|---|---|---|---|---|---|---|---|---|
| **Multi-institutional study** | | | | | | | | |
| Solaini et al. [34] | UK | 2000–2013 | 143 | 51.2% | 84 | 10.1% | 55.7% | 74.7% |
| **Single-center study** | | | | | | | | |
| Onkendi et al. [33] | USA/Mayo Clinic | 1994–2009 | 99 | 43% | 38.4 | ND | 42% | 98.0% |
| Poultsides et al. [35] | USA/Johns Hopkins Medical Institution | 1984–2006 | 112 | 48% | ND | 8.9% | 63% | 95.5% |
| Zenali et al. [36] | USA/The University of Texas M.D. Anderson Cancer Center | 1990–2011 | 68 | 55.9% | 149.8 | 8.8% | 48.5% | 97.1% |
| Cecchini et al. [37] | USA/Massachusetts General Hospital | 1982–2010 | 103 | 42% | 44 | 23.3% | 47.6% | 88.3% |

[a] According to AJCC TNM classification system [4].
MST, median survival time; ND, not determined.

**Table 146.6** Published series of prognostic factors after surgical resection of duodenal cancer.

| | | | Negative prognostic factors | | |
|---|---|---|---|---|---|
| **Reference** | **Study period** | **No. of patients** | **Not significant** | **Significant (univariate)** | **Significant (multivariate)** |
| Bourgouin et al. [5] | 2001–2011 | 25 | Pre-illness BMI, loss of BMI ≥4%, grade 2–3, T category, UICC stage | Nodal metastasis | – |
| Solaini et al. [34] | 2000–2013 | 143 | Age, sex, duodenal resection, morbidity, nodes harvested, tumor size, adjuvant chemotherapy | Grade, T category, N category, lymph node ratio, positive margin, lymphovascular invasion, perineural invasion | N category, lymphovascular invasion |
| Poultsides et al. [35] | 1984–2006 | 112 | Age, sex, race, preoperative weight loss, transfusion, T3/4, tumor size ≥2 cm, adjuvant chemoradiation | Nodal metastasis, grade 3, perineural invasion, vascular invasion, positive margin | Nodal metastasis |
| Cecchini et al. [37] | 1982–2010 | 103 | Age, sex, race, FPH of cancer, PMH of cancer, PMH of FAP, symptom, type of operation, morbidity, tumor location, tumor size, grade, positive margin, nodes harvested, lymphovascular invasion, origin from a villous adenoma | AJCC stage, nodal metastasis, lymph node ratio, perineural invasion | Perineural invasion |

BMI, body mass index; AJCC, American Joint Committee on Cancer; FPH, family past history; PMH, past medical history; FAP, familial adenomatous polyposis.

### Recurrence

Recurrence occurred in 14–45% of patients with a median follow-up of 26–39 months, although some reports did not clearly describe a median follow-up time [34–37,39]. A median time from surgical resection to recurrence was reported to be 14.5 months [37]. The frequent form of recurrence was distant metastases, followed by locoregional recurrence [34,35,37]. Among distant metastases, liver metastasis is the most frequent.

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# Section 10

# Transplantation of the Pancreas

# 147

# Transplantation of Pancreatic Islets

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## Introduction

Transplantation of allogeneic islets has evolved as an effective treatment for selected patients with type 1 diabetes (T1D) [1]. Transplantation of autologous islets has become an established treatment to mitigate the severity of surgical diabetes in patients with severe chronic pancreatitis (CP) undergoing total pancreatectomy [2,3]. This chapter provides an update on the status of human islet allotransplantation in T1D and islet autotransplantation in severe CP and briefly reviews research priorities in these fields. Excellent and more comprehensive reviews have recently been published by other authors [1,2,4–12] and updated results on clinical islet allotransplantation have been provided by the Collaborative Islet Transplant Registry (CITR) in their latest annual report [13].

## Manufacturing, Release Testing, and Infusion of Allogeneic Human Islets

The preeminent procedures involved in transplantation of allogeneic human islets in T1D are illustrated in Fig. 147.1 and in more detail in Fig. 147.2. The selection of deceased pancreas donors is a critical factor in determining the yield of islets available for transplant [14–16]. Based on characteristics of 1235 deceased pancreas donors and islet yields obtained from their pancreata, a scoring system has been developed to predict postpurification islet yields of >400,000 islet equivalents (IEQ). Adherence to validated principles of donor pancreas procurement [17] and utilization of optimized enzyme blends for pancreatic tissue dissociation [18] increase the yield and transplant rate of human islet products. To advance allogeneic islet products toward licensure in the United States, eight manufacturing facilities participating in the National Institutes of Health-sponsored Clinical Islet Transplantation (CIT) Consortium jointly developed and implemented a harmonized process for the manufacture of allogeneic purified human pancreatic islet product (PHPI) for evaluation in a Phase 3 trial in subjects with T1D [19]. Manufacturing was controlled by a common master production batch record (MBPR), standard operating procedures (SOP) that included acceptance criteria for deceased donor organ pancreata and critical raw materials, PHPI product specifications, certificate of analysis, and test methods. The process was compliant with Current Good Manufacturing Practices and Current Good Tissue Practices. The quality systems and regulatory and operational strategies developed by the CIT Consortium yielded product lots that met the prespecified characteristics of safety, purity, potency, and identity and were successfully transplanted into participating subjects. No adverse events attributable to the product and no cases of primary nonfunction were observed. The CIT MPBR and SOPs are publicly available (referenced in [19]). The most commonly used islet implantation site is the liver with islets being infused intraportally. The portal vein is accessed by percutaneous transhepatic catheterization [20–22] or by minilaparatomy [23,24].

## Selection of Islet Allotransplant Recipients

Transplants of allogeneic islets have been performed in patients with T1D either as islet transplant alone (ITA) in nonuremic recipients, as simultaneous islet kidney

*The Pancreas: An Integrated Textbook of Basic Science, Medicine, and Surgery*, Third Edition. Edited by Hans G. Beger, Andrew L. Warshaw, Ralph H. Hruban, Markus W. Büchler, Markus M. Lerch, John P. Neoptolemos, Tooru Shimosegawa, and David C. Whitcomb.

Companion website: www.wiley.com/go/beger/thepancreas

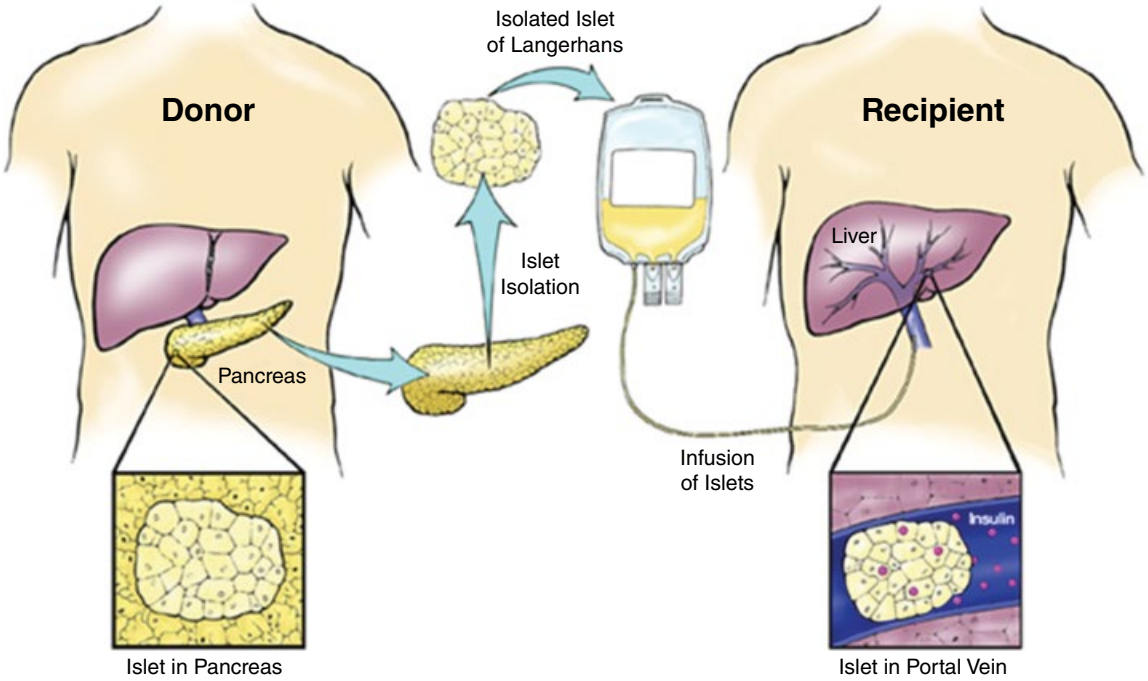


**Figure 147.1** Diagram depicting the standard approach to transplantation of human allogeneic islets. A pancreas is retrieved from a suitable deceased donor. Islets are isolated from the donor pancreas, transferred to a transfusion bag, and infused intraportally into a type 1 diabetic recipient.

(SIK) transplant in uremic recipients, or as islet after (previous) kidney (IAK) transplant in posturemic recipients [25].

As ITA recipients are exposed to chronic and generalized immunosuppression only for the purpose of protecting the islet graft, in each individual ITA candidate the morbidity of diabetes complications must be perceived to be more serious than the risks associated with immunosuppression and the expectation of benefit associated with the islet graft must be high. Most ITA have been performed in patients in whom T1D is complicated by impaired awareness of hypoglycemia (IAH) and recurrent severe hypoglycemic episodes (SHE) [25]. Because of profound neuroglycopenia, severe hypoglycemia is a greatly feared acute complication [26,27] that requires the assistance of another person for recovery [28,29]. IAH is found in up to one-third of adult patients with T1D and increases their risk of SHE sixfold [30]. Recurrent hypoglycemia can have a profound impact on people's confidence, careers, and personal relationships [31], it can disrupt many everyday activities such as driving, work performance, leisure pursuits, and sleep [27,32], and it can cause embarrassment, social ostracism, and employment discrimination [33].

Although several new educational and technological interventions have recently been developed and should always be employed as first-line therapy in patients with SHE [34], not all patients with IAH benefit from these interventions [35]. Despite accepting elevated hemoglobin $A_{1c}$ ($HbA_{1c}$) targets of 8.0% and having access to behavioral therapies and sensor-augmented insulin pumps at a specialist hypoglycemia service, only 50% of patients with T1D and recurrent SHE experienced resolution of SHE, and 30% required pancreas or islet transplantation because of persistent SHE [36]. As will be outlined in more detail later, islet transplantation is very effective in restoring near-normoglycemia, awareness of hypoglycemia, and protection from SHE in patients with T1D and IAH who accept the risks associated with immunosuppression. Accordingly, recently published evidence-informed clinical practice recommendations identify patients in whom T1D is complicated by IAH and recurrent episodes of SHE as candidates for islet or pancreas transplantation under the following condition: SHE persist after completion of a structured stepped care approach or a formalized medical optimization run-in period that provides access to hypoglycemia-specific education including behavioral therapies, insulin analogs, and diabetes technologies under the close supervision of a specialist hypoglycemia service [35]. Recent reports of multicenter trials of ITA in T1D complicated by hypoglycemia provide additional information on patient selection and eligibility [37–39].

SIK and IAK recipients [40–56] are already obligated to immunosuppression because of their concurrent or previous kidney transplant. Therefore, the risks of the

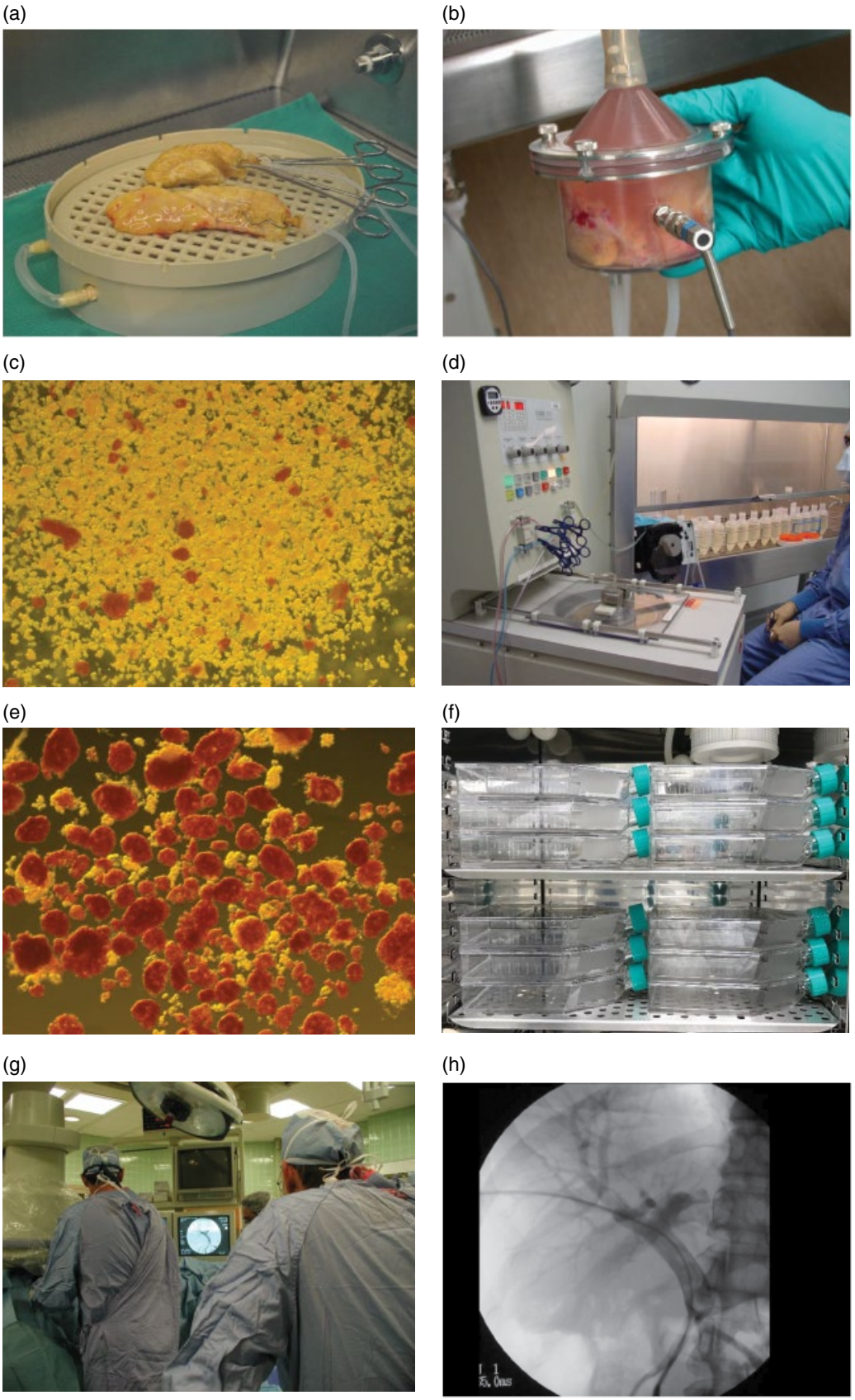


**Figure 147.2** Manufacturing and transplanting allogeneic human islets. (a) Intraductal perfusion of the donor pancreas with tissue-dissociating enzymes. (b) Automated, enzyme-mediated dissociation of the distended pancreas in the Ricordi chamber. (c) Sample of tissue suspension prior to purification showing dithizone-stained, isolated human islets and nonstained acinar tissue. (d) Continuous density gradient purification of isolated islets from acinar tissue on a Cobe 2991 cell separator. (e) Sample of purified islet preparation stained with dithizone. (f) Pretransplant culture of purified human islets in T-flasks. (g) Percutaneous transhepatic catheterization of the portal vein by interventional radiologist. (h) Portal angiogram documenting the correct location of the infusion catheter in the main branch of the portal vein prior to islet infusion. *Source:* Photographs courtesy of Dr A.N. Balamurugan, University of Louisville, and Jeffrey Ansite and Josh Wilhelm, University of Minnesota.

islet transplant procedure, as in ITA recipients, should be minimal by following well-defined precautions (as discussed later). Thus, the risk–benefit ratio of an added islet transplant could be very favorable, especially in those SIK and IAK recipients with T1D, who cannot meet clinically appropriate glycemic goals or continue to experience SHE after completion of a formalized medical optimization program under the guidance of an expert diabetes care team [35]. These recipients may also include patients who are not surgical candidates for or willing to accept the risks of a pancreas transplant [35,54,57].

## Outcomes of Islet Allotransplantation in T1D

### One- and Two-Year Metabolic Efficacy Results in ITA and IAK/SIK Recipients

The achievement of insulin independence in all of seven nonuremic ITA recipients by Shapiro et al. in Edmonton in 2000 marked a major breakthrough in the clinical development of islet transplantation [58]. All patients quickly attained insulin independence after transplantation of a mean ± SD islet mass of 11,547 ± 1604 IEQ/kg body weight. All recipients required islets from two donor pancreases and one required a third transplant from two donors to achieve sustained insulin independence. After a median posttransplant follow-up of 11.9 months (range 4.9–14.9 months), the mean glycosylated hemoglobin values were normal and episodes of hypoglycemic coma were avoided in all recipients. The complications were minor. The high success rate of the Edmonton protocol in restoring insulin independence has been attributed to the infusion of a high islet mass from more than one donor pancreas and the use of a glucocorticoid-free, low-dose tacrolimus and sirolimus maintenance immunosuppressive protocol, which is considerably less diabetogenic than previous protocols [40,41].

The insulin independence rate in the subsequent international multicenter trial of the Edmonton protocol for islet transplantation was 44% (16 of 36 patients) at 1 year posttransplant [59]. The trial confirmed that persistent islet function even without insulin independence provides both protection from severe hypoglycemia and improved levels of glycated hemoglobin [60]. The lower insulin independence rate compared with the initial and follow-up single-center reports by Edmonton [58,60] was in large part explained by the highly variable results achieved among the nine participating centers [59].

Consequently, and as already discussed, the manufacture of islet products for testing in the subsequent CIT trials was controlled by a harmonized process using a common batch record. Adherence to prespecified batch release criteria was demonstrated in qualification runs at each of the selected participating centers [19]. The purpose of the CIT-07 Phase 3 trial, conducted at eight centers in North America, was to demonstrate the safety and effectiveness of transplantation of allogeneic islets in T1D complicated by SHE. Forty-eight adults with T1D for >5 years and persistent IAH and SHE were enrolled. The treatment protocol included three key features that were adopted from a single-center trial performed at the University of Minnesota, in which insulin independence was achieved in all of eight recipients after infusion of a mean (± SD) islet mass of 7271 ± 1035 IEQ/kg body weight prepared from a single deceased donor pancreas [61]. These protocol elements were pretransplant islet culture for 48 hours, potent induction immunosuppression with antithymocyte globulin, and peritransplant administration of the tumor necrosis factor α (TNF-α) inhibitor etanercept, high-dose heparin, and intravenous insulin [39]. Maintenance immunosuppression was with low-dose tacrolimus combined with sirolimus [58]. The primary endpoint of the CIT-07 trial was achievement of $HbA_{1c}$ <7.0% at day 365 and freedom from SHE from day 28 to day 365 after the first of up to three islet transplants.

This composite endpoint, clinically considered more relevant than insulin independence in the study population of patients with T1D and SH and suggested by the Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) as the primary endpoint for licensure trials in their 2008 guidance on allogeneic pancreatic islet cell products [62], was met in the CIT-07 trial by 87.5% of participants at 1 year and by 71% at 2 years after the first transplant [39]. The Australian multicenter trial reported results on the same composite endpoint; of the 17 recipients with T1D and IAH enrolled in the Australian trial, 14 (82%) met this endpoint [38]. Comparable metabolic goals were achieved by the Integrated UK Islet Transplant Program in its multicenter trial [37]. The CIT-07 trial also demonstrated highly significant improvements in several other measures of glycemic control (e.g., glycemic lability index, mean amplitude of glycemic excursions, time within glucose target range) and also restoration of hypoglycemia awareness, as evidenced by normal posttransplant Clarke and Ryan HYPO scores [39]. The median daily insulin use decreased from 0.49 units/kg at baseline to 0.00 units/kg (range 0.00–0.43 units/kg) at day 365 posttransplant; 52.1% of participants were insulin independent at day 365.

More detailed metabolic studies demonstrated that intraportal islet transplantation can restore partial glucagon secretion, improve epinephrine secretion, restore autonomic symptom perception, and normalize endogenous glucose production in response to

insulin-induced hypoglycemia in patients with long-standing T1D and IAH enrolled in the CIT-07 protocol [63]. Trials performed in Europe showed that, by increasing endogenous glucose production, even partial islet graft function improves hypoglycemia counterregulation [64], explaining in part that minimal islet graft function is sufficient to abrogate hypoglycemia (<54 mg/dL) [65].

IAK and SIK transplantation has been studied in pilot clinical trials by single centers and the French–Swiss GRAGIL Network (Group de Recherche Rhin, Rhône-Alpes et Genève pour la Transplantation d'Ilots de Langerhans) using several immunosuppressive protocols and endpoints [40–56]. These studies suggest that insulin independence and near-normoglycemia can be restored in IAK/SIK recipients at rates comparable to those for ITA recipients. The CIT-06 trial, performed by the CIT Consortium, is the first Phase 3 trial of transplantation of human islets in T1D patients with established kidney transplants [66]. The primary endpoint of the trial is the proportion of subjects with both an $HbA_{1c}$ ≤6.5% or a reduction in $HbA_{1c}$ of ≥1% and absence of SHE at 1 year after the first islet transplant. The results of this trial are expected to be reported in 2018.

The Ninth CITR Annual Report analyzed islet transplants in 819 ITA and 192 IAK/SIK recipients, who received their first infusion between 1999 and 2013 (Scientific Summary, Exhibit D) [13]. In this report, the CITR identified a small number of favorable factors that define the subgroup of recipients with significantly higher prevalence of several clinically relevant metabolic efficacy outcomes (except absence of SHE, which showed remarkably high and sustained prevalence in islet allograft recipients). The favorable factors in ITA recipients were total IEQ ≥325,000, recipient age ≥35 years, induction immunosuppression with T-cell depletion and/or TNF-α inhibition, and maintenance immunosuppression with mammalian target of rapamycin (mTOR) and calcineurin inhibitor (CNI); the favorable factors identified in IAK/SIK recipients were total IEQ ≥325,000 over one or several infusions and insulin administration during organ donor management. When ITA and IAK/SIK recipients met all of the factors uniquely favorable for their subgroup, at 1 year after the last infusion the proportions of both ITA and IAK/SIK recipients with $HbA_{1c}$ <6.5% or drop by 2% were 78.6 and 83.9%, the proportions of recipients free of SH were 92.9 and 96.9%, and the rates of insulin independence were 74.8 and 68.1%, respectively.

## Long-Term Metabolic Efficacy Results in ITA and IAK/SIK Recipients

Although only a minority (~10%) of 63 patients transplanted under the Edmonton protocol maintained insulin independence for 5 years posttransplant, approximately 80% showed sustained partial islet allograft function associated with $HbA_{1c}$ levels of <7.0% and protection from SH for at least 4 years [60]. The French–Swiss GRAGIL Network also reported sustained benefits of islet transplants in a cohort of 44 islet allograft recipients [48]. At 5 years posttransplant, 26% of recipients had remained insulin independent and 60% met the composite endpoint of $HbA_{1c}$ levels of <7.0% and absence of SHE. In an independent study with more than 7 years of follow-up, the Zurich group showed improved glycemic measures after SIK/IAK transplantation compared with intensified insulin therapy [53]. A CITR analysis reported in 2012 showed that, regardless of sustained graft survival, >90% of all T1D islet allograft recipients in their database, of whom >90% had IAH, had remained free of SH through 5 years of follow-up [25]. Of the ITA recipients meeting the four favorable factors identified by CITR (see earlier), 95.5% were free of SHE and 72.9% had $HbA_{1c}$ <7.0% at 5 years after the last islet infusion (Fig. 147.3). Refined peritransplant management including more potent induction immunosuppression was associated with an insulin independence rate of 50% at 5 years after the final islet infusion [67], suggesting that a higher engrafted islet mass [68] could improve the longevity of the graft [69]. Of note, these improved results match long-term insulin independence rates after vascularized pancreas transplantation alone in nonuremic recipients [70]. The maintenance of insulin independence in an exceptional case for >10 years suggests that continued, long-term islet allograft function is an attainable target [71].

## Effects on Chronic Diabetes Complications, Patient Survival, and Quality of Life

Very few studies have examined the effects of islet transplantation on chronic diabetes complications. The Milan group demonstrated in a cohort of IAK recipients followed for 7 years that successful islet transplantation, when compared with controls, was associated with lower cardiovascular mortality and improved endothelial function, kidney graft function, and kidney graft survival rates [50,72]. Sustained islet graft function was also associated with improved cardiovascular function for up to 3 years [73]. In a prospective, crossover cohort study examining the effects of ITA and intensive medical therapy on the progression of microvascular diabetes complications, the rate of decline in glomerular filtration rate (GFR) was slower and the rate of progression of retinopathy was lower after ITA than on medical therapy [74]. Quality of life (QOL) studies using existing questionnaires showed that islet transplants, although having no impact on overall health-related QOL, were associated with improved diabetes-specific QOL, less fear of

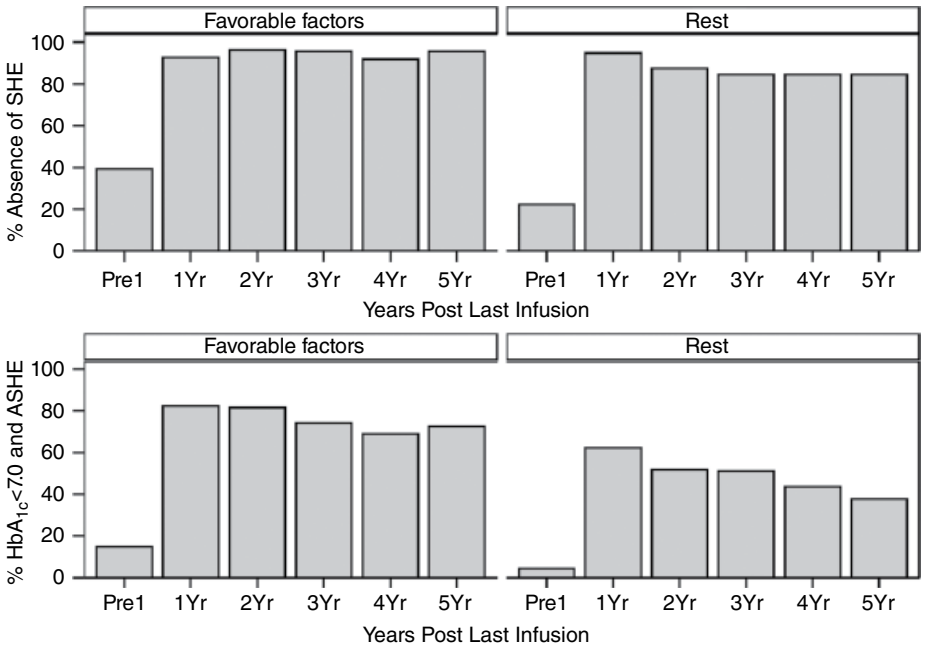


**Figure 147.3** Observed prevalence rates of primary outcomes in T1D ITA recipients reported to CITR. Rates are shown according to subgroups with all four "favorable factors," (i) induction immunosuppression with T-cell depletion and/or TNF-alpha inhibitor, (ii) maintenance immunosuppression with mTOR inhibitor and calcineurin inhibitor, (iii) number of islet equivalents transplanted ≥325,000, and (iv) recipient age ≥35 years (left panels), and less than four favorable factors ("Rest"; right panels). Top row: proportion of recipients with absence of SHE in both subgroups prior to the first islet transplant (Pre1) and at each of the first 5 years after the last islet infusion. Of the 565 recipients analyzed, $n = 148$ met all four favorable factors, whereas $n = 417$ recipients met less than four of the favorable factors ("Rest"). Of those meeting all four favorable factors ($n = 148$), 39.2% (58 of 148) were free of SHE prior to transplantation; whereas 95.5% (42 of 44) of recipients were free of SHE at 5 years post-last islet infusion. Bottom row: proportion of recipients meeting the composite endpoint of $HbA_{1c}$ <7.0% and absence of SHE prior to the first islet transplant and at intervals post-last islet infusion. Of the 619 recipients analyzed, $n = 149$ met all four favorable factors, whereas $n = 470$ recipients met less than four of the favorable factors ("Rest"). Of those meeting all four favorable factors ($n = 149$), 14.8% (22 of 149) met the composite endpoint prior to transplantation; whereas 72.9% (35 of 48) of recipients met the composite endpoint at 5 years post-last islet infusion. *Source:* Courtesy of Franca Barton and Cassandra Ballou, The Emmes Corporation and CITR.

hypoglycemia, a reduction in behaviors adopted in avoiding hypoglycemia, and attenuation in concerns about SHE [75–80]. Importantly, when balancing the outcomes against the immunosuppressant side-effects and the procedure, most recipients reported "no regrets" about undergoing islet transplantation [81].

## Adverse Effects of Islet Transplantation and Immunosuppression

Procedure-related complications of intraportal islet infusion include portal venous thrombosis, transient increase in liver enzymes, puncture of the gallbladder, and bleeding. Portal thrombosis is a preventable complication, provided that therapeutic anticoagulation is maintained and the infused packed cell volume is limited to <5.0 mL [82]. The risk of puncturing the gallbladder injury is minimized by ultrasonic guidance [83]. Postprocedural bleeding can be avoided by effective obliteration of the intraparenchymal catheter tract in the liver [22,84] or by accessing a mesenteric vein via minilaparatomy for intraportal islet infusion [23,24].

Immunosuppression- and immunity-related complications in ITA recipients include nephrotoxicity and sensitization to donor human leukocyte antigen (HLA) antigens. Although the decrease in GFR is common and significant, the GFR typically remains in the normal range. The decline in GFR is explained by an acute CNI effect [85] and is possibly, in part, also associated with correction of hyperfiltration after restoration of near-normoglycemia [86,87]. Whether the decline in GFR is progressive or stable in ITA recipients, as demonstrated in kidney transplant recipients immunosuppressed with CNI [88], remains to be determined. Of note, the rate of decline in GFR was slower in CNI-treated ITA recipients than in control patients on intensive medical therapy [74]. The risk of HLA class I sensitization is significant in ITA recipients in whom immunosuppression is discontinued after complete graft loss; it can be minimized by minimizing the number of islet donors used per recipient and by repeating HLA class I mismatches with

subsequent islet infusions [89,90]. In the CIT-07 Phase 3 trial, six of 48 participants had positive panel reactive antibodies at 2-year follow-up and donor-specific antibodies developed in two patients [39].

Neoplasms were diagnosed in 32 of 864 islet recipients who collectively represent a total of 5762 person-years of observed follow-up [91]. Neoplasms diagnosed were (No. of recipients) basal or squamous cell carcinoma (17), malignant ovarian cysts (6), breast cancer (2), lung cancer (2), thyroid cancer (2), and posttransplant lymphoproliferative disorder (PTLD) (3). The mortality risk is very low in islet transplantation; only three of the 25 deaths in 864 recipients reported to the CITR were definitely related to the transplant or immunosuppression [91].

## Outcomes of Islet Autotransplantation in Chronic Pancreatitis

Total pancreatectomy with islet autotransplantation (TPIAT) is most often utilized in patients with painful and debilitating CP who have not responded to medical, endoscopic, and/or surgical therapies and whose impairment in QOL due to pain is substantial enough to accept the risk of developing postoperative insulin-dependent diabetes and a lifelong commitment to pancreatic enzyme replacement therapy [92]. The criteria for selecting patients with CP for TPIAT have evolved over the years [3]. TPIAT has recently also been considered and performed for an increasing number of other conditions, including benign cystic lesions, pancreatic trauma, and premalignant conditions such as intraductal papillary mucinous neoplasm [2]. TPIAT for malignancy remains highly controversial [93].

Currently, more than 20 academic institutions across the world have active TPIAT programs and the number is rapidly increasing [2,92]. The University of Minnesota, the center with the largest experience (>675 cases since 1977), published a detailed analysis of their first 409 patients [3]. This series included 53 children. Etiologies of chronic pancreatitis were idiopathic, 41%; sphincter of Oddi dysfunction/biliary, 9%; genetic, 14%; divisum, 17%; alcohol, 7%; and other, 12%. The mean age was 35.3 years, 74% were female, and 21% had had earlier operations. Actuarial patient survival post-TPIAT was 96% in adults and 98% in children (at 1 year) and 89% and 98% (at 5 years). Complications requiring relaparotomy occurred in 15.9% and bleeding (9.5%) was the most common complication. IAT function was achieved in 90% (C-peptide >0.6 ng/mL). At 3 years, 30% were insulin independent (25% in adults, 55% in children) and 33% had partial function. Mean $HbA_{1c}$ was <7.0% in 82%. Earlier pancreas surgery lowered islet yield (2712 versus 4077/kg; $P = 0.003$). Islet yield (<2500, 2501–5000, and >5000/kg) correlated with degree of function with insulin-independent rates at 3 years of 12, 22, and 72% and rates of partial function of 33, 62, and 24%, respectively. All patients had pain before TPIAT and nearly all were on daily narcotics. After TPIAT, 85% had pain improvement. By 2 years, 59% had ceased narcotics. All children were on narcotics before and 39% at follow-up; pain improved in 94% and 67% became pain-free. In the SF-36 survey for QOL, there was significant improvement from baseline in all dimensions, including the Physical and Mental Component Summaries, whether on narcotics or not. In a retrospective survey, >95% of the patients stated that they would recommend TPIAT [94].

The University of Minnesota analyzed factors predicting outcomes after TPIAT in their first 581 patients [95]. The duration (mean ± SD) of CP before their TPIAT was 7.1 ± 0.3 years and of narcotic usage 3.3 ± 0.2 years. Pediatric patients had better postoperative outcomes. Among adult patients, the odds of narcotic use at 1 year were increased by previous endoscopic retrograde cholangiopancreatography and stent placement and a high number of previous stents (>3). Independent risk factors for pancreatic pain at 1 year were pancreas divisum, previous body mass index >30, and a high number of previous stents (>3). The strongest independent risk factor for islet graft failure was a low islet yield in IEQ per kilogram of body weight. There was a strong dose–response relationship between the lowest-yield category (<2000 IEQ) and the highest (≥5000 IEQ or more). Islet graft failure was 25-fold more likely in the lowest-yield category. A retrospective review of 75 children undergoing TPIAT at the University of Minnesota [96] showed that pancreatitis pain and the severity of pain statistically improved in 90% of patients after TPIAT and that 41.3% of the children achieved insulin independence. By multivariate analysis, three factors were associated with insulin independence after TP-IAT: (i) male gender, (ii) lower body surface area, and (iii) higher total IEQ per kilogram body weight. Total IEQ (100,000) was the single factor most strongly associated with insulin independence (odds ratio 2.62; $P < 0.001$).

## Research Priorities in Islet Transplantation

Optimizing donor pancreas procurement and transportation, refining islet isolation and release testing, establishing extrahepatic sites and novel islet delivery techniques for enhanced islet engraftment, developing CNI-free immunosuppressive protocols lacking islet toxicity, and incorporating islet imaging and donor-specific immune assays into monitoring will improve the outcomes and utilization of islet allotransplantation [97].

However, the two most impactful research priorities are the generation of an unlimited supply of islet cells for transplant and the development of a maintenance immunosuppression-free rejection and autoimmune recurrence prophylaxis. Although substantial progress has been made in generating functional, insulin-producing stem cell-derived pancreatic islet cells *in vitro* [98,99], important questions remain to be addressed [100]. Remarkable progress has also been made in preclinical studies of porcine islet xenotransplantation [101–103] and in defining the conditions for initiating clinical trials of porcine islet xenotransplantation [104]. Long-term functional supply of allogeneic human islets in an oxygenated immunoisolation device suggests that such technologies could permit testing and possibly drug-free survival of stem cell-derived islet products in humans in the not too distant future [105]. Donor thymus transplantation, mixed xenogeneic chimerism, and other strategies are being developed for tolerance induction to porcine xenografts [106]. The CRISPR/Cas system (clustered regularly interspaced short palindromic repeats/CRISPR-associated system) [107], a novel gene editing platform technology with unmatched precision and efficiency, will accelerate the generation of porcine donors with multiple genetic modifications [108] for the purpose of facilitating xenotransplantation with reduced immunosuppression.

Research gaps and opportunities in TPIAT include selection of the "right" patient, optimal timing of surgery, opportunities to address better pain remission, islet engraftment, and functional survival, unique features of children with CP, psychological comorbidities, standardization of care, and a comprehensive registry that addresses the complexities of CP and TPIAT [92].

## Conclusions

Islet allotransplantation has become a viable treatment option for patients with T1D and IAH in whom optimized medical therapy has been ineffective in preventing SHE [35,39]. Islet transplantation should also be considered in patients with T1D and end-stage renal failure who cannot meet clinically appropriate glycemic goals or in whom SHE persist [53]. TPIAT is now an accepted treatment modality for CP and intractable pain [2]. Although important goals remain to be met, including cost efficiency, durability of graft function, and safety of immunosuppression in allotransplant recipients, real opportunities now exist to overcome these challenges.

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# Transplantation of the Pancreas

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## Introduction

Over the past 10–15 years, pancreas transplantation has emerged as a standardized, widely accepted option for selected patients with insulin-dependent diabetes mellitus (IDDM) [1]. Several options for pancreas transplant exist: simultaneous pancreas–kidney transplantation (SPK) for patients already in renal failure, pancreas transplantation after a kidney transplant (PAK) for patients who still have problems with blood glucose control or patients who had received a live donor kidney previously, and pancreas transplantation alone (PA) for patients with very brittle diabetes.

From 2010 to 2014, 1-year patient survival for SPK in the United States was reported to be 97.4%, pancreas graft function 91.3%, and kidney survival 95.5%. The improvements were due to fewer technical and immunologic failures. Survival for PAK and PA has also improved dramatically (A.C. Gruessner, International Pancreas Transplant Registry [IPTR], personal communication, 2016).

## Epidemiology and Sequelae of Insulin-Dependent Diabetes Mellitus

According to the Centers for Disease Control Fact Sheet, over 20 million people in the United States, 7% of the population, have IDDM. Type 1 diabetes accounts for about 10% of the prevalence of diabetes, whereas type 2 diabetes accounts for 90% and is caused by impaired insulin action.

IDDM is caused by destruction of the pancreatic β cells by an autoimmune process [2–4]. Without insulin, homeostasis of energy and glucose regulation is severely disturbed, leading to hyperglycemia and ketoacidosis after oral glucose intake. It occurs mostly in young patients, constantly threatening life and impairing quality of life significantly. In the long term, numerous sequelae are linked to diabetes, including nephropathy, neuropathy, retinopathy, and vascular problems, to mention only the most common complications [5]. Overall life expectancy is shortened [6]. The cost for the healthcare system is also significant, mostly in treating advanced diabetic complications [7,8]. Treatment involves insulin injection, aiming to achieve maximum control of glucose levels. On the other hand, achieving tight control of glucose may put the patient at risk of life-threatening hypoglycemia [5]. At present, no insulin therapy, either regular daily injections or artificial insulin pumps, can control glucose levels perfectly. For selected patients, the best option is pancreas transplantation, aiming to restore a functioning feedback mechanism involving glucose measurement and insulin release. Several studies have proved that pancreas transplantation may mitigate the long-term complications of diabetes [9,10]. However, these studies are difficult to interpret as none of them were controlled.

## Historical Aspects

The discovery of insulin in 1920 in Toronto by Banting and Best, an orthopedic surgeon and his medical student, transformed diabetes mellitus from an acutely fatal disease to a chronic illness that may result in kidney failure, blindness, vascular disease, and disabling neuropathy. Transplantation of the vascular pancreas was proposed as a potential cure for this disease, as this operation normalizes blood glucose control without the need for exogenous insulin, normalizes hemoglobin $A_{1c}$ ($HbA_{1c}$) levels, dramatically improves quality of life, and

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potentially prevents or mitigates secondary complications. The first pancreas transplant was performed on December 16, 1966, by Kelly and Lillehei's group [11]. This was followed by a series of transplants utilizing modified surgical techniques. For more than a decade, the lack of powerful immunosuppressants, antibiotics, and antivirals in a population of severely ill patients yielded very poor results. In 1980, the few centers performing pancreas transplants reported a graft survival at 1 year posttransplant of 20% and patient mortality as high as 40% (D.E.R. Sutherland, IPTR, personal communication, 1982). It was not surprising, therefore, that pancreas transplantation acquired a bad reputation among diabetologists and nephrologists and referrals for this operation were sparse. In 1978, Dubernard and the Lyon group suggested avoiding anastomosis of the pancreatic duct or duodenum altogether and obliterating the pancreatic duct with neoprene, a liquid synthetic rubber that hardened after injection [12]. The technique lost its appeal when it became obvious that pancreaticocutaneous fistulas and infections complicated the postoperative course. The Lyon experience demonstrated that the pancreas must be drained and, in an attempt to avoid contamination by opening bowel, Sollinger and the Wisconsin group first suggested using the urinary bladder as a drainage conduit [13]. This drainage technique proved to be safer and temporarily boosted the enthusiasm for pancreas transplantation. However, in a review of 500 SPKs, we concluded that urologic complications were too significant to continue with bladder drainage [14], and in 1995 we converted to enteric drainage. This technique is now standard in the majority of transplant centers performing pancreas transplantation. About 50% of our patients who had undergone bladder drainage required enteric conversion [15]. For practical purposes, it should be mentioned that enteric conversion is highly successful if performed within 1 year after transplantation. At a later time, the chronically distended duodenal segment is much more prone to anastomotic leakage and we recommend Roux-en-Y diversion.

From December 1966 to December 2014, 48,000 pancreas transplants were reported to the International Pancreas Transplant Registry (A.C. Gruessner, IPTR, personal communication, March 2016). More than 29,000 were reported from the United States. Since 2004, pancreas transplantation has decreased in the United States, whereas other countries have shown a steady increase.

## Indications for Pancreas Transplantation

Our general rule for any type of pancreas transplantation is that the potential beneficial effects of the transplantation must outweigh the possible complications of surgery and the side-effects of immunosuppressive therapy. Patients should be in good general health, since the operation is challenging and has its morbidities. No strict age limit exists, but most transplanted patients are less than 50 years old as complication rates increase with age [16,17]. We recommend 55 years as the upper age limit. Our youngest patient was 11 years old; indeed, younger patients in particular might obtain increased benefit from a transplant, since diabetic comorbidities may reverse better in the young. Obese patients should be encouraged to lose weight before transplantation, since complication rates increase with a body mass index (BMI) >30 [18–20].

SPK is indicated in patients with IDDM and end-stage renal disease (ESRD). Transplantation of the pancreas as a part of an SPK is easily justifiable, as the patient has to undergo immunosuppressive therapy for the kidney transplant in any case. Also, the fact that both organs are transplanted during the same operation makes SPK attractive. Although SPK remains the most frequently performed form of pancreas transplantation, the numbers performed in the United States have decreased since 2004. In the opinion of the authors, this is due to improved medical treatment that delays diabetic end-stage nephropathy (thus causing an increase in the age of potential recipients who develop ESRD), and a progressive increase in donor age making the pancreas organ less suitable for transplant.

The indications for PAK are somewhat controversial. In general, the procedure is reserved for patients who have difficulties controlling diabetes after kidney transplantation. However, in the United States, because of allocation rules in many regions, no preference is given to SPK recipients. Therefore, many patients first receive a live donor or deceased donor kidney followed by a pancreas transplant. Isolated pancreatic grafts are available in larger quantities. There has been controversy regarding the survival benefit of PAK. As a reflection, PAK has decreased by 50% over the past 10 years.

The indications for PA are difficult to standardize. Careful monitoring of long-term survival and immunosuppressive complications is required. In our view, the procedure is indicated only in extremely rare cases. Some surgeons consider the procedure when several severe diabetic complications are present and the diabetes is hyperlabile with severe episodes of hypoglycemia and ketoacidosis in addition to unawareness of hypoglycemia. There is controversy about the degree of difficulty that a patient must experience before he or she qualifies for this operation. At the University of Wisconsin (UW), it is required that the patient be evaluated by an experienced endocrinologist and that at least several types of insulin administration and glucose controls have been attempted. If the patient continues to experience frequent hypoglycemic episodes, the indications for PA are given.

Some centers have performed pancreas transplantation in patients with type 2 diabetes. Hence this indication is becoming more frequent, but the benefits in this scenario still require further study. Most recently, a BMI of 30 or below and a C-peptide level >2 are required for a patient to be listed by the United Network for Organ Sharing (UNOS).

Only a small number of living related pancreas transplants have been performed since 1994 [21]. The procedure bears significant risks for the donor and should be performed only under strict study conditions. The procedure is not performed at our center.

## Preoperative Workup and Cardiac Risk Assessment

The preoperative workup is comparable to a kidney transplant workup and aims to exclude potential risks for the recipient [16]. The workup includes past medical history and a general physical examination, laboratory studies (creatinine, $HbA_{1c}$, C-peptide, etc.), viral serology, immunologic studies, computed tomography (CT) to assess the quality of the iliac arteries, and cancer screening, which includes mammography, PAP smear, prostate-specific antigen, and colonoscopy (in those over 50 years old).

Additionally, patients with diabetes are more prone to have coronary artery disease. Therefore, a thorough evaluation of the status of the coronary arteries is mandatory. Cardiovascular complications are a major cause of both short- and long-term death [22]. Complex algorithms have been published regarding the preoperative cardiac workup for pancreas transplant recipients [23,24]. A review of all studies prompted us to mandate coronary angiography in all patients over 35 years of age and in younger patients with a cardiac history and/or abnormal stress testing.

## Donor Selection and Donor Pancreatectomy

Selection of the pancreas donor is difficult unless the donor is young and slim. The age of the donor is one of the principal factors impacting postoperative pancreas graft survival [25]. The lower age limit at our center is 3 years. In fact, we have shown that pancreatic grafts from younger donors have over 90% success for 10-year patient and graft survival rates [26]. Older donors and obese donors are only accepted if visual inspection of the graft demonstrates a satisfactory graft. Careful evaluation of the graft, considering consistency, fibrosis, steatosis, and status of the arterial vessels, is crucial. In the absence of objective criteria, the donor surgeon's experience is of paramount importance. Grafts from obese donors have a higher rate of thrombosis, fluid collections, abscesses, and anastomotic leaks. The upper age limit at our center is 60 years.

A history of donor pancreatitis or any pancreatic surgery is a contraindication for use. Abdominal trauma may or may not affect the pancreas, hence surgical exploration is justified in an attempt to procure the organ. Elevated glucose levels can be caused by steroid treatment for brain edema or can be stress related, and therefore should not be considered as a contraindication. In questionable cases, one might consider obtaining $HbA_{1c}$ from the donor to rule out latent diabetes. Donors with type 2 diabetes and high C-peptide levels are acceptable unless they are obese. Hyperamylasemia is often encountered in brain-dead donors and therefore is not a contraindication if no other reason is evident. Finally, a pancreas donor risk index (pDRI) has been developed to inform organ acceptance decision making, which considers 10 common donor variables and one transplant factor (ischemia time) as factors associated with an increased risk of allograft failure [27].

## Donor Operation

The medical management of the donor by the anesthetist aims at hemodynamic stability until cross-clamping. Before and during procurement, the urine output is a good measure of sufficient abdominal organ perfusion. Hemodynamic instability enhances the danger of graft pancreatitis and thrombosis and therefore graft loss.

The donor operation is usually a part of multiorgan retrieval. It is preferable that the same team retrieves both liver and pancreas en bloc (Fig. 148.1). This approach is fast and is associated with the least amount of injuries to vascular structures. If divided on the back table or *in situ*, the superior mesenteric artery and splenic artery are handled with care in order to avoid intimal dissection. In the case of an aberrant right hepatic artery, the mesenteric artery is divided distally and the mesenteric origin stays with the liver graft. The splenic artery might retract into the tissue; a marking suture avoids time-consuming back-table exploration. The common bile duct is ligated in order to avoid posttransplant leakage. Dividing the mesentery at the base of the pancreas is crucial. Some surgeons use GIA staplers; however, we prefer double ligation with 2-0 silk. The mesenteric vessels, if not properly ligated, may retract into the pancreatic tissue. Bleeding can occur after reperfusion and the subsequent swelling can lead to venous outflow obstruction, venous thrombosis, and graft loss [28].

If the liver and pancreas teams are separate, then it is the liver team that has priority in deciding where to

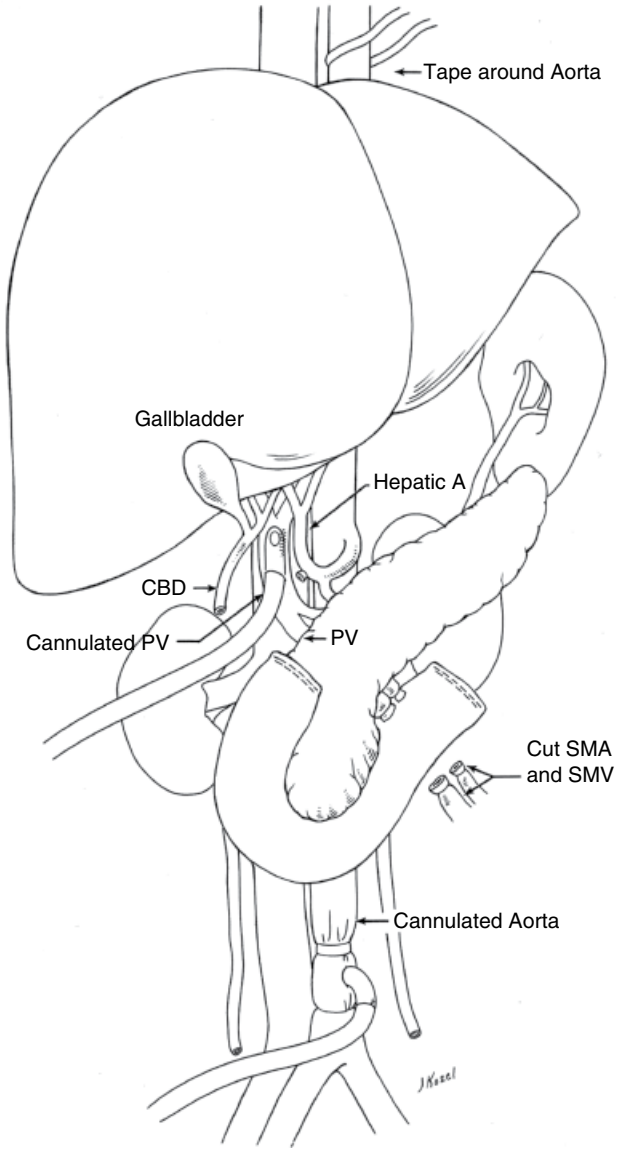


**Figure 148.1** En bloc procurement procedure for liver and pancreas. The abdominal aorta is cannulated distally and prepared for cross-clamping on top. The celiac trunk in dissected to identify the splenic and common hepatic artery. Anatomic variances of the liver arterial supply are identified. The portal vein is cannulated if required. The mesenteric root is divided and the pancreas is mobilized gently, avoiding any tissue trauma, using the spleen as a handle.

transect the portal vein. There is usually enough portal vein to perform a primary anastomosis. Some transplant groups almost routinely use a portal venous interposition graft without any evidence of a higher incidence of pancreas graft venous thrombosis. Transection of the stomach at the antrum and of the proximal jejunum is performed with staplers and leaves sufficient safety margins. Shortening of the intestinal structures is left for the back-table preparation. Instillation of antibiotic solution via the nasogastric tube is optional. Gentle mobilization of the pancreas, not injuring the parenchyma or the capsule, is essential in order to avoid postoperative leakage and pancreatitis. Keeping the pancreas cold with ice during the procurement process is important. Overflushing with preservation fluid leads to graft edema and must be avoided. An arterial graft also has to be procured for the arterial reconstruction. Usually, the bifurcation of the iliac artery is used. Alternatively, the brachiocephalic trunk can be used.

## Deceased Cardiac Death Donors (DCD)

Because of organ shortages and increasing waiting lists, strategies to enlarge the donor pool are under investigation. One option is the utilization of organs from donors after cardiac death. In a study at our center [29], the 5-year patient, pancreas graft, and kidney graft survival rates were similar to those with donation after brain death. Pancreas graft function was unaffected by the mode of procurement, whereas kidney grafts had more delayed graft function but with no sequelae for long-term function [30]. In a follow-up study be Scalea et al. [31], emphasis was placed on the fact that older DCDs carry a higher risk for postoperative dysfunction and careful individual evaluation of each donor is required as outlined in the paper.

## Preservation

The standard preservation fluid for pancreas grafts is the University of Wisconsin (UW) solution developed by Belzer and Southard in 1987. Under clinical conditions, cold ischemia preservation times of up to 40 hours have been reported [32]. Whether UW solution is the gold standard for the pancreas is still a matter of discussion, although large-scale studies by Stuart et al. [33,34] provided solid evidence for its superiority. Another solution, histidine–tryptophan–ketoglutarate (HTK), has been used for heart transplantation since 1986. At present, some large centers in the United States and Europe use HTK as their standard preservation solution for the pancreas and have reported good results.

## Technical Aspects of the Recipient Operation

As discussed in the Introduction, it took several decades to develop a technique for pancreas transplantation that provides reproducibly good results with a minimum of complications.

## Back-Table Graft Preparation

If the procurement is not done by the same team, the transplant surgeon thoroughly inspects the pancreas on the back table. If signs of fibrosis, necrosis, steatosis, or severe trauma are present, the procedure should be aborted. As a first step, the spleen is removed and the vessels are ligated separately. The duodenum is shortened on both sides using GIA staplers and the duodenal segment is inverted with sutures. Excessive tissue, especially lymphatic tissue around the superior mesenteric artery, is removed. The portal vein is lengthened by ligation of smaller branches. Arterial reconstruction is performed by an iliac arterial Y graft by connecting the external iliac artery to the superior mesenteric artery and the internal iliac artery to the splenic artery (Fig. 148.2).

## Recipient Operation

The abdomen is entered via a midline incision. In SPK, the kidney is also usually implanted through a midline incision, although either a separate incision or mobilization of the extraperitoneal space alone has been used to allow extraperitoneal positioning of the kidney graft. In our experience, this has not proven beneficial. The iliac vessels are exposed. In general, the pancreas is implanted on the right side, because venous access is easier. With the bladder draining technique, the head of the pancreas is positioned toward the pelvis (Fig. 148.3), whereas in the current technique with enteric drainage, the head is positioned upwards (Fig. 148.4).

## Vascular Anastomosis

The venous anastomosis is performed first. At the implantation site of the distal vena cava/proximal right common iliac vein, the vein is controlled with a side-biting clamp and the anastomosis is performed end-to-side with 6-0 running Prolene suture. A technical controversy existed about the preferred type of venous drainage. Several authors described drainage into the portal system to one of the mesenteric veins, claiming that the first-pass effect of insulin through the liver leads to a more physiologic insulin distribution. In our view, there is no clear-cut demonstration that there are any metabolic consequences of peripheral venous drainage, and after an initial wave of enthusiasm, more recently reported series have failed to show a benefit for the portal drainage technique [35].

The arterial anastomosis is performed second. The iliac graft extension is sutured to the common iliac artery of the recipient using 6-0 Prolene. The length should be adapted to allow for distension following graft edema. On the other hand, the graft should not be left too long in order to avoid kinking and risk of thrombosis. Thereafter, removal of the vascular clamps is sequential: first the venous clamp, followed by the distal and then proximal arterial clamps, allowing enough time for thorough hemostasis after each step.

## Management of Exocrine Pancreatic Secretion

Many surgical complications originated from the difficulty of securing the drainage of the exocrine pancreas. Bladder drainage techniques evolved from use of a duodenal button to use of a duodenal segment (Fig. 148.3). At the UW, we chose this technique in the early 1980s, as a review of technical failures after enteric anastomosis suggested rejection of the small bowel as the cause. This, of course, occurred before the introduction of cyclosporin and mycophenolate mofetil (MMF). For this reason, a drainage site was chosen in which the anastomosis could be protected for 5–10 days by urinary catheter

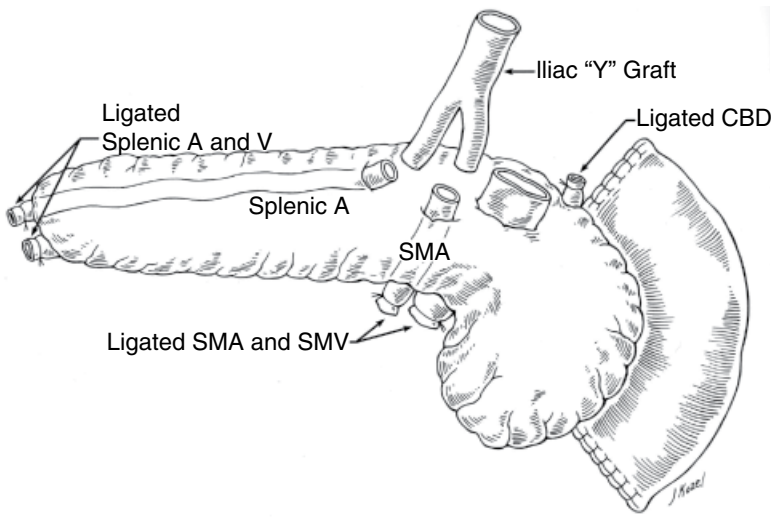


**Figure 148.2** Posterior view of the pancreas graft after back-table preparation. The iliac Y graft is anastomosed to the superior mesenteric and the splenic artery. All the vessels in the mesenteric root at the lower border of the pancreas and the distal splenic vessels are thoroughly tied. The duodenal stumps are stapled and oversewn additionally.

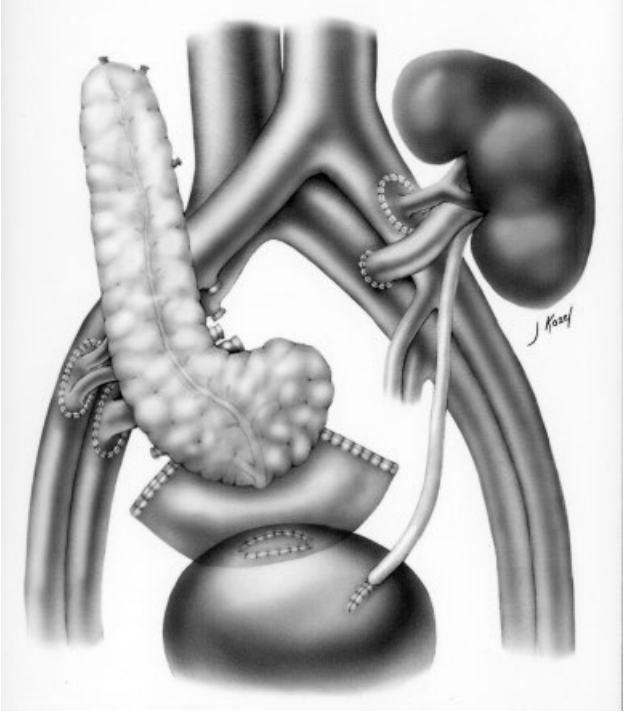

**Figure 148.3** Pancreas transplantation with bladder drainage.

decompression. In our view, duct injection was never acceptable after we visited multiple centers around the world and observed the high complication rates associated with this technique. Bladder drainage uses the bladder as the draining conduit. In the most frequently used technique, a duodenal segment is anastomosed side-by-side to the urinary bladder. This is usually done in two layers. Although this technique is relatively safe, later urinary complications such as frequent urinary tract infections, urethral erosions, and leaks and bleeding from the bladder, and also large loss of bicarbonate, made it clear that this is not an ideal technique [14]. Nevertheless, and to our surprise, this technique is still used by some large centers today. These centers claim that determination of urinary amylase is useful in the early diagnosis of rejection of the pancreas.

Enteric drainage, initially performed by Kelly and Lillehei, was later championed by the Stockholm group. After we had introduced MMF into pancreas transplantation, the incidence of acute rejection decreased by more than 50% [36]. This made us sufficiently comfortable to switch from bladder drainage to enteric drainage in 1995. Our center has now performed 400 bladder-drained and more than 800 enteric-drained transplants, and there is no question that enteric drainage carries a much lower complication rate [35]. In fact, more than 50% of our bladder-drained patients have had to undergo enteric conversion. Early enteric conversion (within 1 year of transplant) is usually well tolerated, whereas late

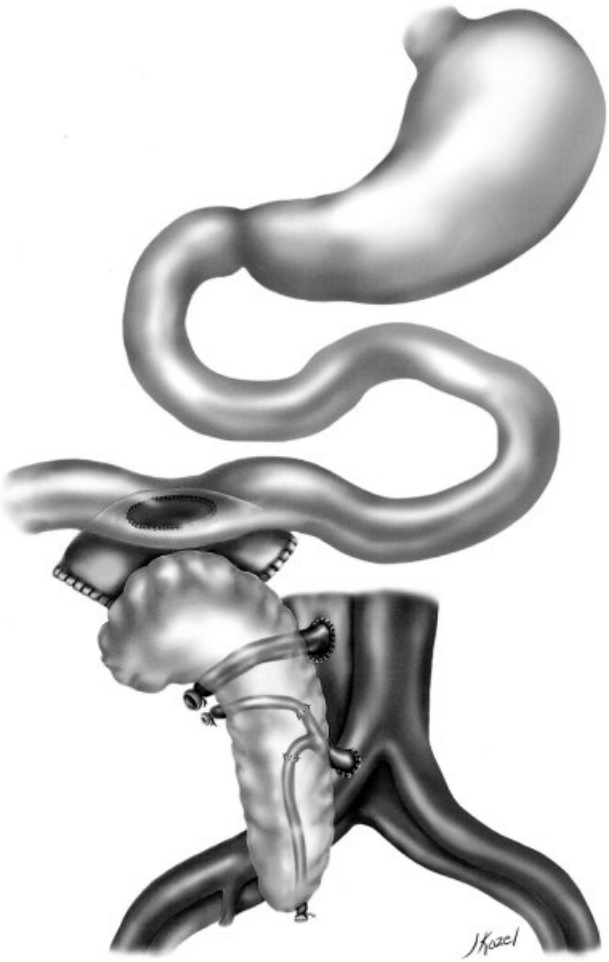

**Figure 148.4** Pancreas transplantation with enteric drainage.

conversions are technically difficult owing to a very thin duodenal segment and anastomotic leakage as high as 50%. We now recommend that every late conversion must be diverted through a Roux-en-Y loop. The indications for enteric conversion are leaks, hemorrhage from the bladder, loss of bicarbonate, and recurrent urinary tract infections.

In enteric drainage, the duodenal segment is anastomosed to the proximal jejunum side-to-side in a two-layer suture (Fig. 148.4). The postoperative complications of enteric drainage are few. Anastomotic leaks are rare; the most common site of a leak is the mesenteric side of the proximal staple line. If, during the retrieval, the length of bowel distal to the pylorus has been cut too close to the pancreas, inversion of the bowel is difficult, resulting in an ischemic corner of bowel that is prone to leak.

According to the IPTR, outside the United States more than 98% of all SPK transplants are managed with enteric drainage, whereas within the United States slightly more cases have used bladder drainage, but these nonetheless constitute only a minority of transplants.

### Postoperative Care

The patient with diabetes who undergoes SPK, PA, or PAK requires meticulous postoperative management. In the postoperative period, the patient is monitored in the recovery unit. The majority of patients do not require admission to an Intensive Care Unit. Pancreas function is monitored by measuring glucose levels, as a rise in glucose indicates graft dysfunction, most likely due to vascular thrombosis in this early stage. If there is a question in this regard, an urgent ultrasound examination is performed. Although there have been reports of successful rescue operations for arterial and venous thrombosis, these cases are rare. Urine output is the measure of kidney function. Conversely, if delayed kidney graft function is present, careful fluid management avoiding fluid overload is mandatory. Overall hemodynamic stability should be achieved in the early postoperative period and, if any signs of intra-abdominal hemorrhage are present, the patient should be brought back to the operating room immediately.

In addition to antibiotic and antiviral prophylaxis, careful immunosuppressive and anticoagulation management is required. Thrombosis of the pancreas is one of the most feared complications. We reported series [1] that demonstrated one of the lowest thrombosis rates. In fact, we believe that the use of heparin will not reduce thrombosis rates, and we have argued that systemic anticoagulation might enhance not only posttransplant bleeding, but also the incidence of thrombosis itself [28]; therefore, we do not use any anticoagulation apart from aspirin (375 mg daily). The use of a nasogastric tube, even after enteric drainage, not only seems to be unnecessary, but also prolongs posttransplant ileus. We therefore do not support the routine use of nasogastric decompression.

### Biopsy of the Pancreas

Biopsy of the pancreas is routinely performed at our center if there is suspicion of allograft rejection. Common indicators are rising amylase and lipase levels or elevated blood glucose values. The biopsies are performed under ultrasound guidance and the complication rate is low. Banff criteria are used for the degree of rejection and the determination of antirejection therapy.

## Current Status and Results of Pancreas Transplantation in the United States

Although the described technical and management innovations have contributed to pancreas transplantation becoming a standardized procedure in the United States, the numbers of both SPK and PTA have declined; the overall decline was 34% between 2005 and 2014. The addition of new patients to the waiting list has also declined. It is possible that improvements in competing therapies or higher standards for donor selection may be responsible. On the other hand, the results of pancreas transplantation have improved. From 2006 to 2014, early graft failures decreased from 12.8 to 8.2%. Kidney graft survival rates for SPK at 1, 5, and 10 years for the recent cohort (2004–2014) were 93, 74 and 47%, respectively. At 10 years, PTA mortality decreased from 46 to 26%. Mortality for all pancreas transplants improved substantially across all groups. The 1-year mortality for SPK decreased from 8% in 1995 to 2% in 2013. There are approximately 14,000 patients in the United States today with a functioning pancreas transplant.

Although this progress is encouraging, pancreas transplantation is available to only 2% of all patients with newly diagnosed type 1 diabetes. Therefore, newer therapies are under investigation. There is particular interest in the areas of stem-cell research and gene therapy.

## Conclusion

A remarkable amount of progress has been made in the field of pancreas transplantation since the first successful procedure in humans in 1966. Pancreas transplantation has evolved from an experimental procedure, with high morbidity and mortality, into an operative procedure with expected excellent outcomes akin to a kidney-alone transplantation. The rise of the field is due to great strides in surgical techniques, immunosuppressive protocols, donor evaluation, preoperative recipient assessment, and postoperative management. The techniques described have been in routine use at our center with excellent results and continue to evolve to make pancreas transplantation a safer and more effective treatment option for patients with diabetes.

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# Index

Note:
Abbreviations used in the index are listed on pages xxx–xli.
Alphabetization order: This index is in word-by-word order, whereby terms like 'duct obstruction' precede 'ductal'.
Cross-reference targets in *italics* refer to general entries, or to subentries within the same main entry.
Page numbers in **bold** refer to pages on which tables or boxes appear; page numbers in *italics*, refer to figures.
*vs* denotes differential diagnosis, or comparisons.



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