Pancreas

Kim C. Honselmann and Tobias Keck

Contents

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9.1 Anatomy and Physiology

9.1.1 Definition, Location and Structure

- Endocrine (increment) and exocrine (excretion) gland
- Retroperitoneal position at the level of lumbar vertebrae I–II
- Structure in four parts:
  - Pancreatic head (= Caput pancreatis)
  - Pancreatic isthmus (= Collum pancreatis)
  - Pancreatic body (= Corpus pancreatis)
  - Pancreatic tail (= Cauda pancreatis)

9.1.2 Anatomy and Embryology

Embryology (◘ Fig. 9.1)

- Development from endoderm (= into 2 opposite epithelial buds at caudal end of foregut; at end of fourth week of development):
  - Ventral pancreas: In the angle of the intestine and bile duct, with connection to the choledochal duct
  - Dorsal pancreas: larger, in connection with the foregut (= later duodenum)
- Formation of the pancreatic head (caput pancreatis; ◘ Fig. 9.1):
  - Due to right rotation of the intestine + growth of the duodenum
  - Ventral pancreas origin is located caudal to the dorsal pancreas + fusion of the bile ducts (Ductus Wirsungianus) + excrete together in Papilla duodeni major (Papilla Vateri)-in case of fusion disorder Pancreas divisum
- Formation of the pancreatic corpus + tail
  - Dorsal pancreas alone forms the corpus and cauda pancreatis,
  - Ductus Santorini: Original excretory duct of this origin, opens further proximally in the duodenum at the papilla duodeni minor; frequent obliteration (Cano et al. 2007)

Anatomy

- Localization and size
  - Approx. 16 cm × 3 cm × 2 cm (L × W × D), 60–80 g weight
  - Retroperitoneal at the level of lumbar vertebrae 1–3
  - Pancreatic head in duodenal C; pancreatic tail to splenic hilum
  - Pancreatic body = dorsal border of the bursa omentalis (ventral to the abdominal aorta, inferior vena cava and left adrenal gland)
- Arterial blood supply (◘ Fig. 9.2):
  - Celiac trunc: Superior posterior and anterior pancreaticoduodenal artery and from superior mesenteric artery: anastomosis to gastroduodenal artery (Arcade described by Rio-Branco) + dorsal pancreatic artery from the splenic artery
  - Superior mesenteric artery: inferior pancreaticduodenal artery (forms arcade with superior pancreaticoduodenal artery and connection to gastroduodenal artery, see above)
- Venous outflow via:
  - Pancreaticoduodenal veins (via pancreatic head) into superior mesenteric vein and portal vein
  - Pancreatic veins (multiple veins) flow into the splenic vein (pancreatic tail area)

9.1.3 Physiology

- Two functions: Exocrine and endocrine

Exocrine Function

- External secretion (i.e., in this case, into the intestinal lumen)
- 1.5–3 L secretion daily
- Secretion stimulants: secretin and cholecystokinin
- Pancreatic exocrine tissue (98% of pancreatic tissue) =
  - Acinar cells + ductal epithelial cells
  - Arrangement in acini (=cell groups) around excretory ducts

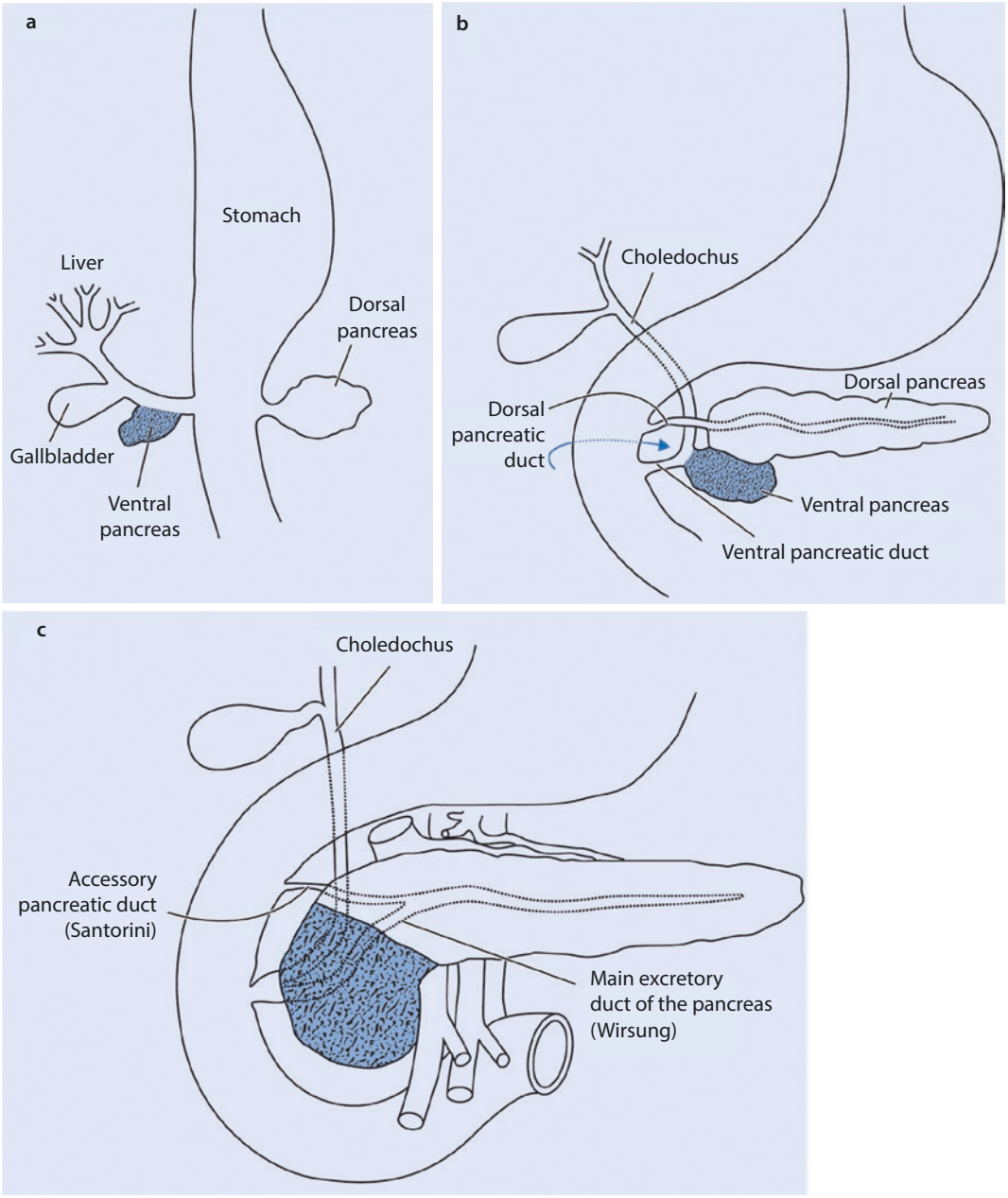


Fig. 9.1 **a**–**c** Development of the pancreatic origin (embryology). (Mod. according to Schumpelick 2011)

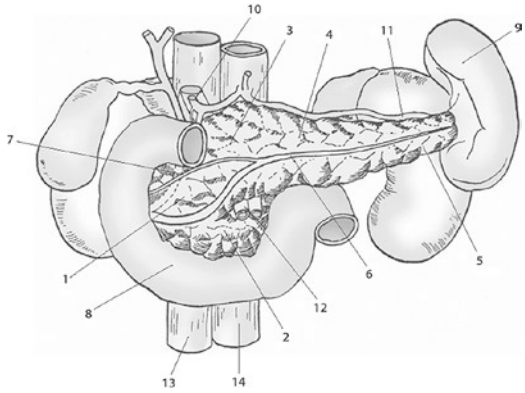


Fig. 9.2 Anatomical location of the pancreas. *1* Head, *2* Uncinate process, *3* Neck, *4* Body, *5* Tail, *6* Duct of Wirsung, *7* Duct of Santorini, *8* Duodenum, *9* Spleen, *10 Proper hepatic artery*, *11 Splenic artery*, *12* A. and Superior mesenteric vein, *13* Vena cava, *14* abdominal aorta. (From Schumpelick 2011)

- Secretion composition:
  - Ductal epithelial cells: Bicarbonate formation (creation of an alkaline environment) + chloride resorption (production of an isotonic fluid)
  - Acinar cells: Production of digestive enzymes (e.g. lipase, amylase, proteinases)

Endocrine Function

- Internal secretion (= hormone; i.e. in this case into the plasmatic compartment)
- Endocrine pancreatic tissue = about 2% of the cells (= islets of Langerhans)
  - A(α)-cells: 10% of the endocrine cells, hormone = glucagon (leads to glucose production from glycogen in the liver as well as from triglycerides from the adipocytes)
  - B(β)-cells: 80% of endocrine cells, hormone = insulin (stimulates glucose absorption in liver, fat cells and muscle cells)
  - D(δ)-cells: 10%, hormone = somatostatin (inhibits the secretion of pancreatic enzymes, gastrin and pepsin)

Control of the Functions

- Exocrine secretion:
  - Cephalic phase (olfactory, gustatory, visual stimuli)
  - Gastric phase (stretching stimuli of the stomach wall + release of gastrointestinal hormones)
- Intestinal phase (via release of gastrointestinal hormones)
- Endocrine secretion: hormonal control loop

9.2 Benign Diseases

9.2.1 Acute Pancreatitis

Key Points

- Mild edematous and severe necrotizing types
- Potentially lethal clinical course in severe form of progression
- Incidence = 18/100,000 adults in Germany
- Mortality of severe form: 10–15%
- Most frequent etiology: alcohol (m > f) or gallstones/sludge (f > m)
- Laboratory diagnosis: threefold elevation of pancreatic serum amylase above normal levels (definition), lipase, liver function tests, electrolyte imbalance, coagulation imbalance
- Diagnostic imaging: ultrasound of the abdomen within 24 h to assess the bile ducts, if CT, then wait until 72 h after admission
- Therapy:
  - Conservative: endoscopic retrograde cholangiopancreatography (ERCP), fluid intake + enteral nutrition (jejunal feeding tube if necessary), antibiotics only therapeutically (if microbiology cultures are positive), not prophylactically
  - Operative/Interventional: As late as possible (>4 weeks), only in case of complications such as necrosis or abscess, infection, pseudocyst (step-up approach: drainage → minimally invasive necrosectomy → open necrosectomy)

Definition

- Upper abdominal pain and serum amylase three times above normal
- Temporal inflammatory process
- Autodigestion of the pancreas gland (usually only partial)

Forms

Acute Edematous Pancreatitis

- Self-limiting
- Mild progressive form (80%)

Acute Necrotizing Pancreatitis

- Formation of necrosis (20%)
- Risk = secondary infection of necroses

Epidemiology

Incidence

- 40 new cases per 100,000 population (USA)
- 73 per 100,000 (Finland)
- 18 per 100,000 (Germany)
- Women:Men = 1:1 (different aetiology see above)
- Age = 38–70 years

Etiology

- Biliary (about 40%): Originating from stones in the common bile duct and secondary obstruction of the duct of Wirsung
- Alcohol-induced (approx. 40%)
- Hypertriglyceridemia (approx. 10%)
- After abdominal trauma
- Side effects from medication: Azathioprine, sulfonamides, tetracyclines, valproate, methyldopa, estrogens, 6-mercaptopurine, 5-aminosalicylic acid (5-ASA), corticosteroids, octreotide, furosemide.
- Hereditary
- Viral (children: mumps)
- Hypercalcemia
- Mechanical obstruction (tumor, pancreas divisum, papillary stenosis)
- Tropical pancreatitis

Symptoms

- Severe epigastric pain with belt-like radiation into the back
- Abdomen is taut and elastic: "rubber belly"
- Meteorism
- Fever
- Paralytic (sub)ileus
- Vomiting
- Hypocalcemia
- Skin signs (rare) as a sign of coagulation disorder and as a result of fat tissue necrosis (severe course):
  - Cullen's sign (periumbilical)
  - Grey Turner sign (flank)
  - Fox sign (inguinal)
- Sepsis
- Septic shock

Diagnosis

Laboratory Diagnosis

- In the serum:
  - Amylase (threefold above normal)
  - More specific (at more than 48 h after symptom onset) = lipase and pancreatic amylase (as distinct from salivary amylase)
  - Coagulation: Onset of *systemic inflammatory response syndrome* (SIRS)
  - Urea (elevation indicative of severe course)
  - Cholestasis parameters: Bilirubin, γ-GT, alkaline phosphatase (AP): Biliary etiology
  - C-reactive protein (for differentiation between edematous and necrotizing pancreatitis) (>120 mg/L); highly sensitive, correlation with progression/development of necrosis, also procalcitonin (PCT)
  - Blood sugar (low is indicative of a severe course)
  - Hematocrit (increase indicative of a severe course)
- In urine: amylase (rare)

Caution

No correlation between level of pancreatic enzymes and severity of pancreatitis, but correlation present for CRP, urea and hematocrit.

Diagnostic Imaging

- Chest and abdominal X-rays:
  - To exclude free abdominal air
  - Detection of pleural effusion, calcifications due to pancreatic secretion, air-fluid level formation
- Contrast-enhanced CT
  - In the presence of necrosis (necroses do not absorb contrast media)
  - Significance for disease course only after 72 h

Risk Assessment (■ Table 9.1)

- Ranson criteria:
  - For mortality estimation
  - For risk assessment of necrotizing pancreatitis: (1 point per item)

■ **Table 9.1** Ranson criteria for acute pancreatitis

Time	Criterion
On admission (1 point each)	– Age >55 years – WBC >16 G/L – AST >250 U/L – LDH >350 U/L – Glucose >200 mg/dL
After 48 h (1 point each)	– Volume deficit >6 L – BUN increase by >5 mg/dL – Base deficit >4 mmol/L – Drop in P_aO_2 to 60 mmHg – Drop in serum calcium <2 mmol/L
Point total after 48 h	*Mortality*
0–2 points	<1%
3–4 points	15%
5–6 points	40%
>6 points	100%

WBC White blood cell count, *AST* Aspartate Aminotransferase, *LDH* lactate dehydrogenase, *BUN* Blood urea nitrogen, P_aO_2 arterial oxygen partial pressure

Differential Diagnosis

- Acute cholecystitis/cholecystolithiasis
- Mesenteric ischemia/venous thrombosis
- Abdominal aortic aneurysm (AAA)
- Mechanical bowel obstruction
- Perforated gastric ulcer
- Colonic diverticulitis

Therapy

Etiology-Oriented Therapy

- Goal = Elimination of cause, if possible
- Biliary pancreatitis:
  - ERCP + papillotomy (within 24 h)
  - Laparoscopic cholecystectomy: after approx. 5–7 days (during the same inpatient stay for mild pancreatitis); Rationale: Biliary pancreatitis = high recurrence rate at 30%, early (<48 h) laparoscopic cholecystectomy possible for mild pancreatitis (Ranson score <3)
- Alcohol-induced pancreatitis: secondary alcohol withdrawal therapy in the interval
- Hypertriglyceridemia-induced pancreatitis: lower blood lipids
- Medication pancreatitis: discontinue medication

Conservative Therapy

- In edematous pancreatitis:
  - Inpatient admission and monitoring of vital parameters
  - Analgesia: paracetamol, metamizol, tramadol or buprenorphine (use opiates with restraint due to papillary spasm, but not as strictly as in the past)
  - Fluid intake (target = urine output >0.5 mL/kg bw/h)
  - Aim for early enteral feeding (but often gastric emptying disorder)
  - Propulsive medication
  - Gastric tube to prevent vomiting
  - Ulcer prophylaxis
  - Compensation for electrolyte deficiency, calcium only from corr. Calcium level of 0.9 mmol/L [corr. Ca^{2+} = measured Ca^{2+} (mmol/L) × (0.025 × albumin (g/L)) + 1]
- In acute necrotizing pancreatitis:
  - Edema to edematous pancreatitis

- Volume-controlled therapy (PICCO, CVC, pulmonary catheter)
- Intensive care unit with invasive monitoring
- No prophylactic antibiotic administration
- Antibiotics for positive microbiology cultures after diagnostic puncture of fluid accumulation or FNA
- Early enteral nutrition, if necessary via jejunal tube

Step-Up Approach

- In necrotizing pancreatitis with infected necrosis
- First CT-guided drain insertion percutaneously/endoscopically
- In the absence of improvement after 72 h (= improved function of at least 2 organ systems or at least 10% improvement of 2 out of 3 parameters, white blood cell count/CRP and temperature):
  - Retroperitoneoscopic necrosectomy or
  - Transgastric necrosectomy or
  - Open procedure

Operative Therapy Principles

- (Laparoscopic)/Open transabdominal retroperitoneal necrosectomy (disadvantage = elimination of compartmentation)
  - Indication: in the event of ineffective or unsuccessful drainage
  - Wait until the findings are consolidated (if at all possible wait more than 4 weeks until the operation)
  - Imaging of the pancreas
  - Relief from fluid retention
  - Removal of the clay-like necrosis areas in digital preparation—Beware of venous bleeding!

Surgical Procedure

Retroperitoneoscopic Necrosectomy

- CT-guided drainage of the retentive cavity with target drain
- General anesthesia
- Supine position with elevation of the punctured side
- Indwelling urinary catheter
- Access: Five circular incision around the inserted retroperitoneal drainage
- Digital exploration: drainage of the fluid accumulation
- Digital opening of the fluid collection, then insertion of a retroperitoneoscope, necrosectomy above (with grasping forceps/laparoscopic suction/via retroperitoneoscope as optical channel)
- Alternatively, insertion of a long 10-mm trocar + long 10-mm 0° optic via incision into the retroperitoneum
- Inspection of the retroperitoneal cavity + removal of the remaining loose areas with forceps (**caution**: venous bleeding from the splenic vein, if necessary tamponade with tamponade strips and revision after 24 h)
- Final placement of 2 large luminal drains
- Extensive rinsing, if necessary continuous rinsing via drains (disadvantage: rinsing lanes)

Surgical Procedure

Open Retroperitoneal Necrosectomy

- General anesthesia
- Supine position, indwelling urinary catheter
- Approach: Large bilateral subcostal incision
- Opening of the omental bursa
- Mobilization of both colonic flexures
- Removal of necrotic areas by blunt dissection with fingers: paracolic, around the mesenteric root and in the lesser sac (omental bursa) (**caution**: high risk of bleeding). Carefully remove necrotic tissue
- Extensive rinsing
- Insertion of several drains with relaparotomy on demand or
- Insertion of e.g. an ABthera vacuum dressing (3M, St. Paul, MN 55144-1000, USA) (= continuous irrigation of the necrosis area and permanent suction) (**caution**: intestinal fistulas) with

repeated relaparotomies (**caution**: irrigation lanes)
- Postoperative treatment
  - Intensive monitoring
  - SIRS/sepsis therapy

Prognosis

- Lethality (acute edematous pancreatitis) = 1%
- Lethality (acute necrotizing pancreatitis with infected necrosis) >20%

9.2.2 Chronic Pancreatitis

Key Points

- Recurrent episodes of pain
- Alcohol = most common cause
- Pain + complications = surgically treatable
- Alcohol abstinence + nicotine abstinence (progression effect) should be recommended
- Imaging diagnosis: In case of chronic recurrent course = detection of complications + localization before planned pseudocyst removal

Definition

- German Society for Gastroenterology, Digestive and Metabolic Diseases (guideline):
  - Pancreatic disease
  - Recurrent inflammatory episodes and pain
  - Gradual fibrotic remodeling of the gland
  - Progressive loss of exocrine + endocrine pancreatic function

Forms

- Chronic pancreatitis with focal fibrosis
- Chronic pancreatitis with segmental/diffuse fibrosis
- Chronic pancreatitis with or without calcifications (inflammatory pancreatic head pseudotumor)
- Special form:
  - Obstructive chronic pancreatitis (duodenal diverticulum, pancreas divisum, tumors, papillary stenosis)
  - Hereditary chronic pancreatitis
  - Idiopathic chronic pancreatitis: when no cause is found

Complications

- Pseudocysts: cyst-like pancreatic structure without epithelial lining
- Pancreatic duct stenosis: inflammation-induced narrowing of the pancreatic duct (pearl cord-like duct)
- Duodenal stenosis: inflammation-related narrowing of the duodenum
- Vascular complications: Arterial hemorrhage, aneurysm rupture, portal vein stenosis and thrombosis
- Compression or scarring stenosis of the bile ducts, with obstructive jaundice
- Duct rupture with pancreatogenic ascites or pancreato-pleural fistula

Epidemiology

- Prevalence: 25–30 cases/1 million inhabitants
- Incidence: 23 new cases/100,000 inhabitants (increases with age)
- m > f
- Average age: 3rd–4th decade of life (social problems, disability)
- 10-year survival rate: 70%
- Overall lethality: 30–35%
- Risk increase for pancreatic cancer (tenfold)

Etiology

- Mostly unclear

Alcohol Abuse (75–90%)

- Most important factor
- For women, >40 g alcohol/day for 6–12 years is considered as threshold.
- For men, >80 g alcohol/day is considered as threshold

- Time between onset of alcohol abuse and onset of chronic pancreatitis: on average 18 ± 11 years

Nicotine Abuse

- Leads to progression of the disease

Hyperparathyroidism (with Ca^{2+} Elevation)

Hereditary

- Prevalence 1/300,000
- Mutation in the cationic trypsinogen gene (PRSS1): approx. 67% of patients with hereditary pancreatitis
- Other responsible genes: SPINK1 gene, CFTR gene

Autoimmunological (IgG-4 and Lymphoplasmocytic Infiltrates)

- Plasma cellular infiltrates in the pancreas
- IgG-4 elevation in serum
- CT morphologically bulky pancreas often without visible ductal changes

Symptoms

Abdominal Pain

- Main symptom
- Mechanism = infiltration of the parenchyma, nerve myelin sheaths + pressure increase in the pancreatic duct (obstruction)
- Neuropathic pain

Symptoms Associated with Loss of Function

- Malnutrition
- Steatorrhea (lipase secretion reduced by more than 90%): Greasy stools
- Weight loss
- Vitamin deficiencies (fat-soluble vitamins A, D, E, K)
- Pancreatogenic (type III) diabetes mellitus
- Chronic pain syndrome

Diagnosis

Genetic Examination

- Indications for mutation analysis of the PRSS1 gene:
  - Positive family history (one or two first-degree relatives with idiopathic chronic pancreatitis)
  - Two or more episodes of acute pancreatitis without identifiable cause before the age of 25 years
  - Idiopathic chronic pancreatitis with first symptoms before the age of 25

Laboratory Diagnosis (◘ Table 9.2)

Diagnostic Imaging

- Only to be used in case of insufficient correlation of clinical, morphological and functional parameters or for the assessment of complications

Sonography

- Inhomogeneous organ with normal pancreatic duct, possibly calcifications = uncertain sign

Endosonography

- Highest sensitivity
- Endosonographically assisted fine needle aspiration (not percutaneous!):
  - To confirm the histological diagnosis (often false negative in cancer and chronic pancreatitis)
  - To confirm autoimmune pancreatitis (plasma cells, IgG-4)

CT/MRI/Magnetic Resonance Cholangiopancreaticography (MRCP)

- Supplementary for unclear pancreatic changes
- MRCP helpful for pancreatic duct assessment

ERCP

- Disadvantages of ERCP (vs MRCP):

Table 9.2 Non-invasive pancreatic function tests[a]

Test	Mild exocrine insufficiency sensitivity (%)	Moderate exocrine insufficiency sensitivity (%)	Severe exocrine insufficiency sensitivity (%)	Specificity (%)
Stool Elastase	54%	75%	95%	85%
Qualitative stool fat determination	0%	0%	78%[b]	70%[b]
Chymotrypsin activity	<50%	Approx. 60%	80–90%	80–90%
^{13}C-breath test (mixed triglycerides)	62–100%		90–100%	80–90%

[a] The direct invasive pancreatic function tests (secretin or secretin-pancreazymin test) were used as reference procedures
[b] Related to the quantitative stool fat determination

- Increased morbidity (5–10% overall; 3.47% post-ERCP pancreatitis)
  - Increased mortality (3.3‰)
  - Therefore, diagnostic endoscopic retrograde cholangiopancreaticography (ERCP) should be omitted in favor of MRCP for purely diagnostic indications
- Evaluation criteria of ERCP (according to Cambridge classification)
- Cambridge classification (for different examination procedures; ◘ Table 9.3)

Differential Diagnosis

- Cystic Fibrosis
- Cystic pancreatic neoplasms (especially main duct IPMN)
- Schwachmann-Diamond syndrome (autosomal recessive bone marrow disease)
- Johansen-Blizzard-Syndrome (disturbed development pancreas, nose and galea)
- Congenital enzyme defects (trypsinogen, α_1-antitrypsin deficiency)
- Divisive pancreas

Therapy

Treatment Strategy

Indications for Conservative Therapy

- For nicotine abuse: nicotine abstinence
- Pain medication according to WHO guidelines (◘ Table 9.4)
- Enzyme substitution
  - Indication: steatorrhea, pathological pancreatic function tests, weight loss
  - Start with 20,000–40,000 units per meal, 10,000–20,000 units for small snacks, doubling or tripling of dose possible if insufficient effect

Indications for Interventional or Surgical Therapy

- Sustained pain requiring analgesics (new guideline: over 3 months: consider surgical therapy)
- Complications:
  - Strictures of the common bile duct, cholestasis, jaundice, cholangitis
  - Inflammatory or unclear malignant suspicious masses
  - Pancreatic pseudocysts
  - Pancreatic duct stones

30–60% of patients with chronic pancreatitis develop pain or a complication.

- Strategy:
  - Endoscopic procedures: Possibility of short-term pain reduction (66% of cases/few years)
  - Mid-term/long-term pain control: significant superiority of surgery vs. endoscopic therapy
  - Symptomatic pancreatic duct stones, stenoses in the pancreatic head and

Table 9.3 Evaluation criteria according to the Cambridge Classification

Endoscopic retrograde cholangiopancreaticography (ERCP)	
Cambridge 0	No pathological changes on complete visualization of the pancreatic duct
Cambridge 1	<3 pathological side branches, main duct regular
Cambridge 2	>3 pathological side branches, main duct regular
Cambridge 3	Pathological side branches plus pathological main duct
Cambridge 4	Like 3 plus cyst, duct stones, strictures, involvement, adjacent orifices
Transabdominal ultrasound	
Cambridge 0	Normal organ, duct <2 mm, smooth contour
Cambridge 1	Echo dense organ contour, organ enlarged, duct <3 mm, lobulated texture with echo dense segments
Cambridge 2	Irregular contour, irregular echo-enhanced main duct >3 mm, lobulated texture with echo-dense septa
Cambridge 3	Like 2 and cysts, focal calcifications
Cambridge 4	Like 3 and ductal stones, ductal obstruction, tumorous distention of the organ >2-fold, splenic vein thrombosis
Endosonography (EUS)	
Cambridge 0	None
Cambridge 1	Honeycomb texture, honeycomb-like, aisle <3 mm
Cambridge 2	Hyperechogenic duct, hyperechogenic foci, echo-dense contour, duct <3 mm
Cambridge 3	Lobulated, septate, hyperechogenic foci, duct >3 mm, irregular duct, no duct stones
Cambridge 4	Like 3 and calcifications, duct stones, cysts
Computed tomography (CT)/Magnetic resonance cholangiopancreaticography (MRCP)	
Cambridge 0	None
Cambridge 1	Not delineable with current methods in CT/MRCP
Cambridge 2	Two or more of the following changes: – Pancreatic duct >2 and <4 mm in the corpus pancreatis – Mild pancreatic duct enlargement – Heterogeneous parenchyma structure – Small cystic changes (<10 mm) – Duct irregularities – >3 pathological secondary ducts
Cambridge 3	All changes mentioned in 2 plus pathological main duct (>4 mm)
Cambridge 4	One of the changes listed at 2 and 3 plus one or more of the following: – Cystic structures >10 mm – Parenchymal calcifications – Intraductal filling defects (limestones) – Duct obstructions (strictures) – Severe duct irregularities

Cambridge 0: No chronic pancreatitis (CP), Cambridge 1: Possible CP, Cambridge 2: Low CP, Cambridge 3: Moderate CP, Cambridge 4: Heavy CP

Table 9.4 WHO guidelines for pain medication in chronic pancreatitis

Active substance	Dosage	Analgesics effect
Paracetamol	2–3 times 500–1000 mg	Peripheral
Metamizole	1–4 times 500–1000 mg	Peripheral
Tramadol	4 times 100 mg, 2–3 times 200 mg retard	Low potent central
Tilidine	3 times 50–200 mg	Low potent central
Buprenorphine	3–4 times 0.2–0.4 mg	Highly potent central
Morphine	Individual according to effect	Highly potent central
Levopromazine	3–5 times 10 mg	tricyclic antidepressant
Clompramine	1 time 50–100 mg	tricyclic antidepressant

pseudocysts: according to the guideline, endoscopic or surgical therapy (► Sect. 9.2.3)

- In the case of suspected pancreatic cancer (unclear mass): Surgical therapy (oncological pancreatic head resection)
- For symptomatic pseudocysts + complication (e.g. gastric outlet stenosis, bleeding, cholestasis, vascular stenosis): Higher success rate for surgical procedures (vs. endoscopic pseudocyst drainage into duodenum or stomach), use according to expertise
- Asymptomatic pancreatic pseudocysts >5 cm in diameter without regression after 6 weeks: Individual treatment possible (41% of cases lead to complications)

Operative Therapy: Principles

Division: Resecting/Draining Procedures

- Resecting procedures:
  - Surgery according to Kausch-Whipple
  - Pylorus-preserving pancreatic head resection according to Longmire and Traverso (PPPD)
  - Surgery according to Beger, Frey or Bern Modification: Duodenum-preserving pancreatic head resection (DPPHR)
  - Rarely distal pancreatic resection (inflammatory pancreatic head tumor remains)
- Draining procedures
  - Partington-Rochelle or Puestow procedure
  - V-shape excision (Hamburg modification of the Frey procedure for so-called small duct disease)
- Total pancreatectomy and autologous islet cell transplantation (TPIAT)—so far not relevantly used in Europe

Surgical Strategy

- Inflammatory pseudotumor of the pancreatic head:
  - Standard = pancreatic head resection (classic Whipple operation/pylorus-preserving pancreatoduodenectomy/duodenum-preserving pancreatic head resection)
  - Duodenum-preserving therapy: better perioperative quality of life/results in some studies, long-term results equal to PPPD
- Indication for draining procedures:
  - Congested pancreatic duct >7 mm without inflammatory pseudotumor in the pancreatic head
  - Obstruction of the pancreatic duct system in risk constellations (portal hypertension with occlusion of the mesentericoportal axis)
  - Long-term inferiority of draining procedures compared to resecting procedures with regard to freedom from pain

Poor long-term results of draining procedures compared to resecting procedures with regard to freedom from pain.

- Surgery according to Kausch-Whipple or PPPD (► Sect. 9.3.1)
- Surgery according to Beger
  - Indications:
    - Segmental chronic pancreatitis with pain syndrome
    - Expression of an inflammatory pancreatic head tumor
  - Summary: Duodenum-preserving pancreatic head resection with subtotal resection of the pancreatic head (a very small margin of pancreatic tissue remains for blood supply to the duodenum) followed by anastomoses to the duodenal C, bile duct, and pancreatic remnant (corpus).

Surgical Procedure

Operation According to Beger

- General anesthesia
- Approach: Transverse laparotomy of the upper abdomen or median laparotomy
- Opening of the omental bursa
- Limited Cooker Maneuver
- Identification of the superior mesenteric vein at the lower edge of the pancreas and careful undermining of the pancreas (difficult step)
- At the upper edge of the pancreas identification of the portal vein + detachment from their adhesions
- Looping of the common bile duct and the common hepatic artery
- Transection of the pancreas after undermining, if necessary gradual transection without undermining (risky step)
- Subtle hemostasis of the pancreas after transection with single sutures (5-0 PDS)
- Free preparation at the upper edge of the pancreatic head up to the common bile duct
- For visualization of the intrapancreatic bile duct, insertion of a probe via the cystic duct
- Subtotal pancreatic head resection and uncinate process along the wall of the intrapancreatic bile duct segment (◘ Fig. 9.3)
- Extensive hemostasis on remaining pancreatic head margin (5–8 mm) at the duodenum with single sutures (preservation of gastroduodenal artery branches)
- For reconstruction: pull up a retrocolic jejunum;
- Two anastomoses as an interposition with the distal pancreas (end-to-side or end-to-end pancreato-pancreaticojejunostomy) and the head of the pancreas (side-to-side) connected with a biliodigestive anastomosis to the intrapancreatic bile duct (◘ Fig. 9.3)
- Connection of the inflow and outflow jejunum loop via a Y-Roux reconstruction
- Drainage of the anastomoses
- **Surgery according to Partington-Rochelle (pancreaticojejunostomy)**
  - Indication: only in case of massive ductal dilatation (≥7 mm) without pancreatic head pseudotumor
  - Modification of the Puestow operation, in which only a distal pancreaticojejunostomy is performed via the mesentericoportal axis to the head of the pancreas
    - Summary: Longitudinal opening of the pancreatic duct from the tail of the pancreas to the prepapillary segment; the duct of the Santorini towards the papilla should also be opened longitudinally; drainage of the opened duct via a deactivated jejunum loop side-to-side anastomosis according to Roux-Y.
  - Results:
    - Primary pain resolution 61–90%
    - Long-term success = only in 50% of cases (with complete freedom from pain)
- Surgery according to Frey (latero-lateral pancreaticojejunostomy with

duodenum-preserving pancreatic head resection (extensive excavation of the pancreatic head))
  - Indication:
    - As in Partington-Rochelle, but with inflammatory pancreatic head tumor.
    - Proximal or long pancreatic duct stricture + inflammatory pancreatic head tumor
  - Synopsis:
    - Hybrid procedure = combination of a longitudinal pancreaticojejunostomy (ductal drainage) according to Partington-Rochelle + an extensive but careful local pancreatic head excision (in the case of inflammatory pancreatic head tumor, the extent of the removed pancreatic head tissue is decisive)
- Hamburg modification (Izbicki procedure or V-shape excision): in advanced disease with large inflammatory pancreatic head tumor and small duct disease (without obstructed pancreatic duct) = V-shaped excision in pancreatic corpus and tail

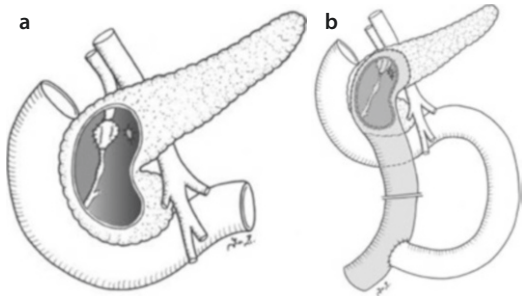


Fig. 9.3 **a**, **b** Operation according to Beger. (Mod. after Strobel et al. 2009)

Surgical Procedure

Operation According to Partington-Rochelle

- General anesthesia
- Supine
- Approach: Transverse laparotomy of the upper abdomen or median laparotomy
- In case of uncertain localisation of the duct (not palpable) = small incision with removal of an elliptical shaped tissue part in the pancreatic body or tail (if necessary palpation and prepuncture with a thin needle or intraoperative ultrasound)
- Longitudinal opening of the pancreatic duct over an overholt (curved clamp) in a small segment and then in full length
- Dissection of a V-shaped tissue block over the pancreatic duct
- If necessary, removal of pancreatic duct stones
- Pulling up an aboral jejunal loop retrocolically
- Creation of a side-to-side anastomosis
- Drainage of the pancreatic anastomosis

Surgical Procedure

OP According to Frey (Fig. 9.4)

- General anesthesia
- Supine
- Transverse laparotomy of the upper abdomen or median laparotomy
- Access to the omental bursa through dissection of the gastrocolic ligament
- Identification of the superior mesenteric vein at the lower edge of the pancreatic neck

- Identification of the portal vein at the upper edge of the pancreatic neck + release from their adhesions
- Undertunneling of the pancreatic body on the mesentericoportal axis not necessary (advantage in portal hypertension or severe adhesions)
- Identification of the pancreatic duct with 20G needle + aspiration of pancreatic juice
- Wide opening of the pancreatic duct from the pancreatic tail to the neck and further to the pancreatic head
- Probing of the duct of Wirsung with Overholt (curved clamp)
- Placement of prophylactic haemostatic sutures at the pancreatic head to the duodenum (4-0 or 3-0 Prolene)
- Generous sharp peeling of the pancreatic head up to the pancreatic duct with scalpel (sufficient extent is important for the surgical result). Some pancreatic tissue must remain caudally
- Hemostasis and manual compression
- If bile duct stricture due to compression (inflammatory, fibrotic tissue in the pancreatic head) excision pancreatic head up to the common bile duct with subsequent door-wing-like anastomosis of the common bile duct in the pancreatic head (Bern modification)
- Pulling up the aboral jejunum loop retrocolic and creation of a side-to-side pancreaticojejunostomy, Roux-Y reconstruction
- Postoperative treatment
  - Blood glucose daily profile
  - Drainage analysis: amylase and bilirubin
  - Bleeding control (caution bleeding into the anastomosed jejunal small bowel)
  - Enteral nutrition: from the first postoperative day (water + tea), from the third postoperative day: liquid diet

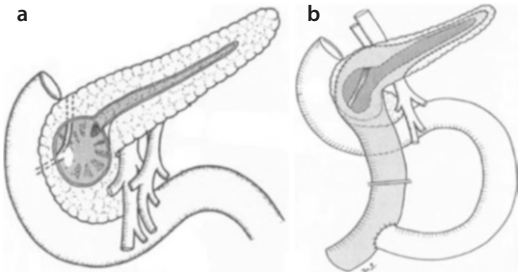


Fig. 9.4 Operation according to Frey. (**a**) Situs after resection of pancreatic head and tail. (**b**) Situs after reconstruction by latero-lateral pancreatico-jejunostomy. (Mod. after Strobel et al. 2009)

Monitoring and Follow-Up

- Rationale: mortality 20 years after initial diagnosis (ED) increased by 38% = need for follow-up, exocrine and endocrine dysfunction.
- Possible recurrence of pain after limited surgical procedures (drainage)
- Annual inspection:
  - Clinical examination
  - Transabdominal ultrasound
  - Laboratory with HbA_{1C}

9.2.3 Guidelines

German S3 guideline for chronic pancreatitis. Definition, etiology, diagnosis, conservative, interventional, endoscopic and surgical therapy of chronic pancreatitis. DGVS guideline 2012 Renewed version 2021.

9.3 Malignant Diseases

9.3.1 Pancreatic Carcinoma

Key Points

- Fourth leading cause of cancer death (incidence = mortality)
- Ductal adenocarcinoma: Histologically leading (>95%)
- 5-year survival = 10%
- Mostly asymptomatic for a long time

- So far the only curative treatment = radical removal of the tumour + regional lymph node removal

Definition

- Pancreatic carcinoma = malignant tumour of the pancreas

Epidemiology

- Incidence: 14.4 new cases/100,000 in men; 10.9/100,000 in women (Robert Koch Institute)
- Women:Men = 1:1.5
- Age peak: 65–75 years of age
- Localization: approx. 65% of all pancreatic tumors = in the pancreatic head, uncinate process or pancreatic neck
- Risk factors:
  - Age (>80-year-olds: 40-fold increase in risk compared to 40-year-olds)
  - Nicotine abuse (relative risk = 1.5-fold increased)
  - Diabetes mellitus type 2
  - Obesity
  - Hereditary syndromes

Etiology

- Malignant degeneration of the exocrine part of the pancreas
- Precursor stages = pancreatic intraepithelial neoplasia (PanIn; ◘ Fig. 9.5) or cystic neoplasia

Underlying Genetic Defects

- KRAS mutation (most common mutation)
- Inactivation of the tumor suppressor genes p16, p53 and Smad/DPC4

Hereditary Syndromes

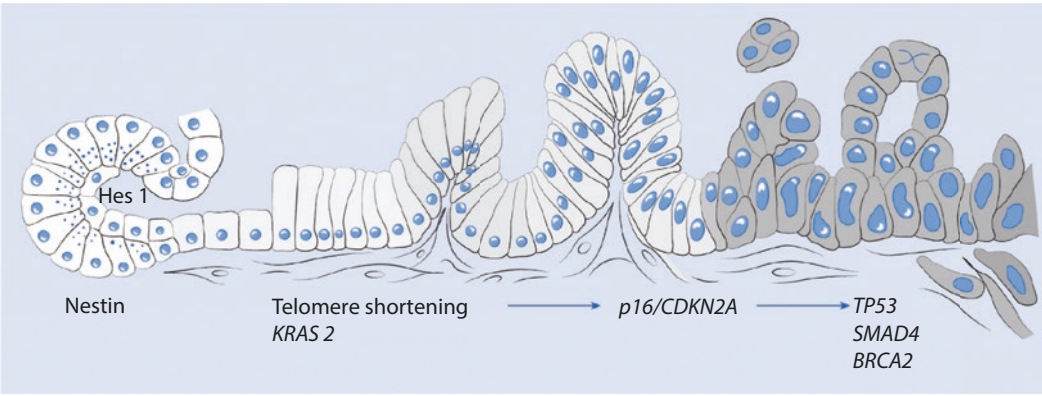
- Increased risk of pancreatic cancer: Oncology guideline programme (German Cancer Society 2013, ► Sect. 9.3.2)
- Familial atypical multiple mole melanoma syndrome (FAMMM syndrome)
- Hereditary pancreatitis
- HNPCC ("hereditary non-polyposis colorectal cancer")
- Familial breast cancer (BRCA 1 and BRCA 2)
- Peutz-Jeghers Syndrome
- Familial adenomatous polyposis
- Li-Fraumeni Syndrome
- Fanconi anemia
- Von Hippel-Lindau Syndrome

Forms

- Ductal adenocarcinoma (very common)
- Serous cystadenocarcinoma (very rare)
- Mucinous cystadenocarcinoma
- Intraductal papillary mucinous carcinoma
- Pancreatoblastoma
- Solid-pseudopapillary carcinoma
- Acinar cell carcinoma
- Adenosquamous carcinoma

Symptoms

- Initially asymptomatic



◘ **Fig. 9.5** Adenoma-carcinoma sequence in pancreatic cancer

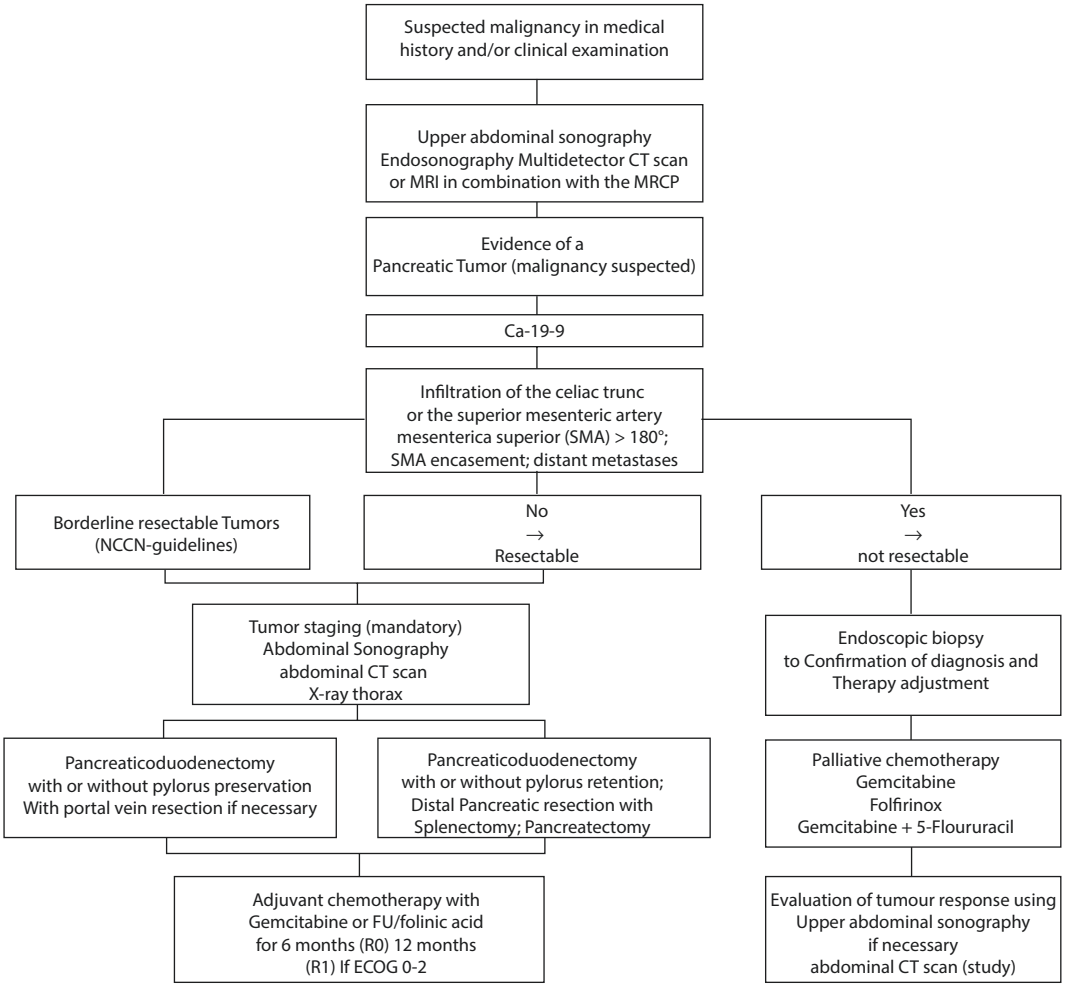
- Often unspecific
- Symptoms
  - Weight loss
  - Painless jaundice in bile duct obstruction (leading symptom)
  - New-onset diabetes mellitus over the age of 50 (**caution**!)
  - Upper abdominal or back pain

Diagnosis (◘ Fig. 9.6)

Patient History + Clinical Examination

Imaging Techniques

- Preoperative assessment of resectability
- Preferred modalities:
  - Multidetector computed tomography (thin-slice angio-CT) or MRCP
  - Endosonography
- Criteria studied (of resectability):
  - Resectable (R) and borderline resectable (BR) tumors:
    - No distant metastases
    - No infiltration of the superior mesenteric vein or portal vein (R)
    - No complete encasement of the superior mesenteric vein or portal vein (R)
    - No long-distance venous occlusion not allowing reconstruction (BR)
    - No encasement of the gastroduodenal artery up to the hepatic artery (BR)
    - No walled superior mesenteric artery or cealiac trunc >180° of circumference (BR)



◘ **Fig. 9.6** Treatment tree according to German S3 guideline of exocrine pancreatic cancer 2013

Therapy

Curative Therapy

Preoperative Therapy

- Preoperative biliary drainage using a stent: indications:
  - Cholangitis
  - If surgery cannot be performed promptly. Avoid if possible, as significant increase in infectious complications
- Neoadjuvant chemotherapy: Already used in trials for borderline resectable and locally advanced tumours, aim for inclusion in trials

Operation

- If surgery is possible: increase of 5-year survival rate to over 20% (with adjuvant FOLFIRINOX up to 55%)
- Partial duodenopancreatectomy with or without pylorus preservation
- Depending on the location, distal pancreatic resection or pancreatectomy (RAMPS, Strasberg)
- In case of infiltration of the neighbouring organs = corresponding extension of the resection (adrenal gland, portal vein, mesocolon, colon)
- Removal of at least 10 locoregional lymph nodes

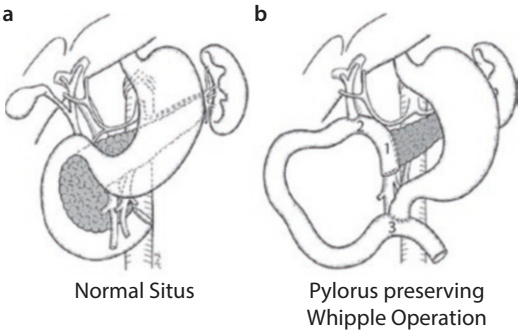
Surgical Procedure

Pylorus-Preserving/Classical Pancreatoduodenectomy (PPPD/Kausch-Whipple Operation; ◘ Fig. 9.7)

- Supine position (left arm resting, right arm extended)
- Right transverse laparotomy/longitudinal laparotomy
- Exploration of the abdominal cavity, exclusion of metastases
- Opening of the omental sac while sparing the gastroepiploic vessels with transection of the gastrocolic ligament
- Mobilization of the right colonic flexure
- Triggering of duodenal C from its retroperitoneal connections: Kocher maneuver
- Mobilization of the pancreatic head up to the mesentericoportal axis
- Open cholecystectomy
- Opening of the lesser omentum and exposure of the common hepatic artery at the upper edge of the pancreas
- Lymphadenectomy in the area of the hepatoduodenal ligament, visualization of all structures
- Ligation of the gastric and gastroduodenal arteries
- Slinging of the common bile duct and dissection proximal to the cystic duct
- Exposure of the portal vein at the upper edge of the pancreas
- Presentation of the superior mesenteric vein at the lower edge of the pancreas and ligation of the outlet of the right gastroepiploic vein
- Tunelling of the pancreas and placement of hemostatic stay sutures at the upper and lower parenchymal border
- Transsection of the duodenum post pylorus, with the GIA stapler or distal 2/3 gastric resection (classic Whipple operation)
- Transection of the pancreas at the level of the mesentericoportal axis
- Transection of the jejunum approx. 30 cm from Treitz
- Raising the proximal jejunum retrocolically
- Detachment of the uncinate process along the superior mesenteric artery
- Completion of the dissection of the mesopancreas along the superior mesenteric artery and removal of the specimen
- Marking of the incision margins with ink or sutures, intraoperative quick incision
- Start of the reconstruction phase
- Reconstruction by means of hepaticojejunostomy and either pancreaticojejunostomy and end-to-side gastrojejunostomy or pylorojejunostomy or pancreatogastrostomy with

Y-Roux reconstruction or omega loop with or without Braun anastomosis (◘ Fig. 9.7)

- Warren-Catell pancreaticojejunostomy: End-to-side anastomosis with duct-to-mucosa anastomosis (◘ Fig. 9.8)
  - Posterior wall suture: pancreatic parenchyma to jejunal serosa made in single button technique (4-0 PDS). The sutures are presented
  - After tie knotting, the anterior wall of the pancreatic duct is presented with double-armored sutures (5-0 or 6-0 PDS)
  - Punctual opening of the jejunum opposite of the pancreatic duct and single sutures of the posterior wall (duct-to-mucosa, 5-0 PDS); if necessary splinting of the pancreatic duct and completion of the anterior wall (duct-to-mucosa)
  - The external anterior wall suture is performed using a single suture technique (4-0 PDS) so that the jejunum covers the anastomosis
- **Pancreatogastrostomy** (◘ Fig. 9.9): between pancreatic parenchyma and stomach
  - A larger (7 cm) anterior gastrotomy and a small (depending on the cross-sectional size of the organ) (2 cm) dorsal gastrotomy are performed as the approach.
  - The mobilized pancreatic tail is invaginated into the stomach via the dorsal gastrotomy (posterior wall of the stomach) and fixed by means of a circular tabac pouch suture in the stomach wall and several parenchyma to serosa sutures
- Bilioenteric anastomosis: Hepaticojejunostomy
  - Length of the small intestine loop approx. 60 cm (Y-Roux)
  - Rear and front wall: single layer, interrupted, PDS 5-0/6-0
  - In case of narrow duct, if necessary, extension plastic according to Gütgemann
  - In case of high hilar anastomosis hepaticojejunostomy according to Hepp-Couinaud may be necessary
  - Enterotomy in the size of the hepatic duct
- Roux-Y reconstruction (2 loops), Omega reconstruction (1 loop) or 3-loop reconstruction (one isolated Roux-Y loop each to the pancreas and the bile duct as well as to the postpyloric duodenal remnant (PPPD)/stomach (Whipple))
- At the end of the reconstruction: rinsing and insertion of 4 easy-flow drains ventrally and dorsally of the pancreatic and biliodigestive anastomosis respectively (according to pancreatic fistula score possibly omitting drains all together)



◘ **Fig. 9.7** Pylorus-preserving or classic pancreaticoduodenectomy according to Whipple, (**a**) normal situs, (**b**) after Whipple operation. *1* pancreatic anastomosis, *2* bile duct anastomosis, *3* gastroenterostomy. (Mod. according to Künzli et al. 2004)

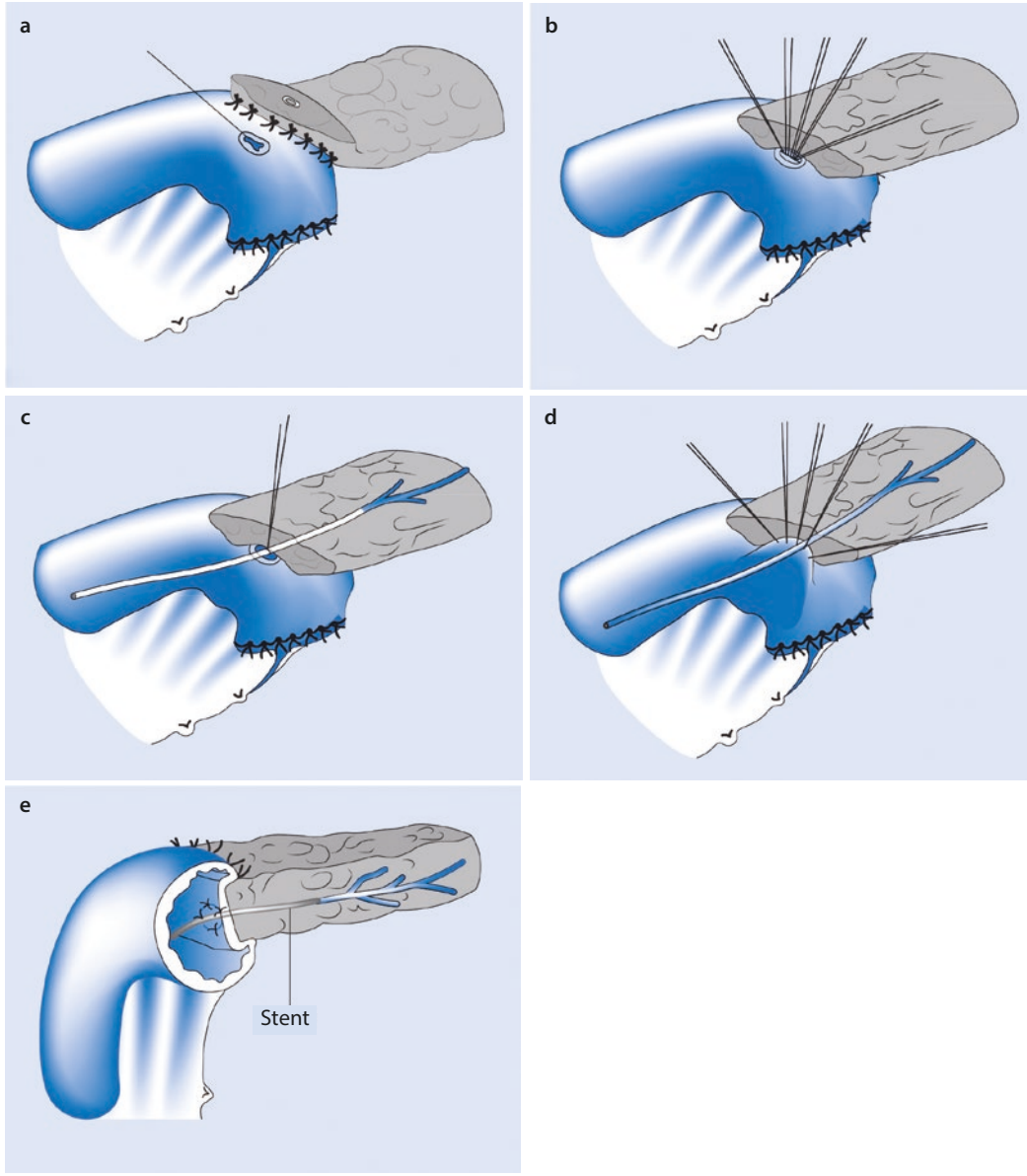


Fig. 9.8 **a**–**e** Pancreaticojejunostomy

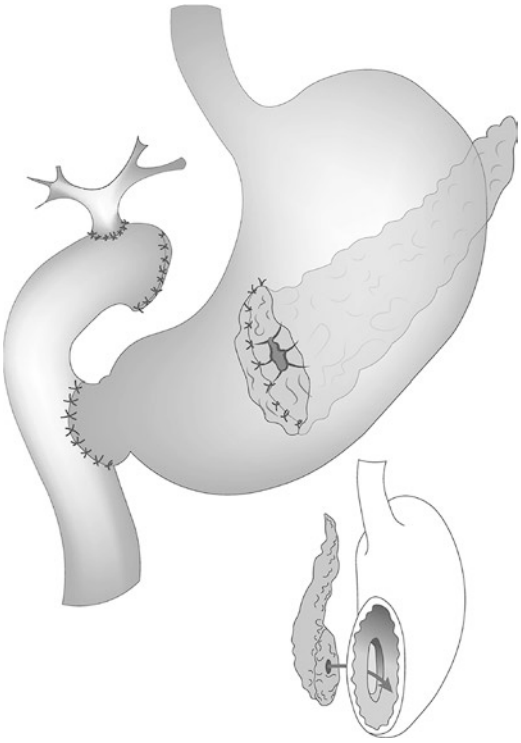


Fig. 9.9 Pancreatogastrostomy

Pathology

- R0-narrow, if circumferential resection margin (CRM) ≤1 mm
- R0-wide or CRM negative if CRM >1 mm
- With stringent pathological workup (Leeds protocol) high R1 resection rate (up to 60%)
- N0 (0 pos. LK), N1 (1–3 pos. LK), N2 (>3 pos. LK) (8th version of AJCC)

Postoperative Complications

- Post-pancreatectomy hemorrhage (gastroduodenal artery arterial hemorrhage and pancreatic sedimentation marginal hemorrhage), late post-pancreatectomy hemorrhage (late PPH)

Caution
Mortality of the arrosion hemorrhage up to 50%.

- Pancreatic fistula (type A-C) = 20%
- Gastric emptying disorders (higher with pancreatogastrostomy) = 20%.
- Bile leakage/bilioma
- Anastomosis insufficiency
- Residual pancreatitis (postoperative pancreatitis)
- Diabetes mellitus requiring insulin
- Endocrine and exocrine pancreatic insufficiency
- Wound infection = 10% (for open surgery)

Postoperative Treatment: Adjuvant Chemotherapy

- Adjuvant chemotherapy in UICC stages I-III
- Contraindications to adjuvant chemotherapy:
  - Eastern Cooperative Oncology Group (ECOG): Performance Status >2
  - Uncontrolled infection
  - Liver cirrhosis Child B and C
  - Severe coronary artery disease; heart failure (NYHA III and IV)
  - Preterminal and terminal renal failure
  - Impaired bone marrow function
  - Inability to attend regular check-ups
- Adjuvant therapy = improvement of 5-year survival after curative resection from 10% to 20% (with mFOLFIRINOX to 55%)
- 5-Fluorouracil plus gemcitabine for 6 months
- mFOLFIRINOX for 6 months (PRODIGE-Group)

Palliative Therapy

Indications

- For locally advanced or metastatic pancreatic cancer
- ECOG 0–2 (Table 9.5)

Therapy Regime

- First-line therapy: Gemcitabine (1000 mg/m^2) (to be discussed)
- 5-FU with or without folinic acid: not as sole first-line therapy
- Alternative to monotherapy with gemcitabine: combination with the EGF (epidermal growth factor) receptor tyrosine kinase inhibitor erlotinib depending on the development of skin exanthema

Table 9.5 Eastern Cooperative Oncology Group (ECOG)[a] (according to Oken et al. 1982)

Points	ECOG performance status
0	Normal, unrestricted activity, as before the disease
1	Restricted during physical exertion, able to walk, light physical work possible
2	Able to walk, self-care possible but not able to work, can stand up more than 50% of waking time
3	Limited self-care possible; confined to bed or chair for 50% or more of waking hours
4	Completely dependent, self-care not possible, completely confined to bed or chair
5	Death

[a] Performance status describes the physical condition of cancer patients and is used to quantify general well-being and limitations in activities of daily living

- In healthier patients (ECOG 0–1, age ≤75 years and a bilirubin level below 1.5 times the normal level): Combination of 5-FU/folinic acid, irinotecan and oxaliplatin (FOLFIRINOX protocol)
- Nab-paclitaxel plus gemcitabine

9.3.2 Guidelines

Oncology guideline program (German Cancer Society, German Cancer Aid, AWMF): S3 guideline Exocrine pancreatic cancer, long version 1.0, 2013, AWMF register number: 032-010OL, ► http://leitlinienprogramm--onkologie.de/Leitlinien.7.0.html, Renewed 2022.

9.4 Cystic Neoplasms

Key Points

- Increasing incidence and detection of cystic neoplasms in the last two decades
- About 90% of pancreatic cystic neoplasms are classified into four entities:
  - Intraductal papillary mucinous neoplasia (IPMN)
  - Serous cystic neoplasia (SCN)
  - Mucinous cystic neoplasia (MCN)
  - Solid pseudopapillary neoplasia (SPN)
  - Frequently incidental findings
- Malignant progression of mucinous cystic lesions in 10–50% of cases

9.4.1 Intraductal Papillary Mucinous Neoplasia (IPMN)

Definition

- Macroscopically visible, mucin-producing epithelial tumors arising from pancreatic duct epithelium (papillary)
- Precursor lesion of IPMN carcinoma
- WHO classification: inclusion of IPMN in this classification in 1996
- Breakdown:
  - Main-duct-IPMN
  - Branch-duct-IPMN
  - Mixed-type IPMN
  - IPMN with low, intermediate or high grade dysplasia or with invasive cancer
- Histologically prognostically relevant subclassification:
  - Gastric
  - Intestinal

- Pancreatobiliary
- Oncocytic

Epidemiology (■ Table 9.6)

- Estimated incidence = 1/280,000 patients
- Women:Men = 1:1
- Frequency peak: 60–70 years of age
- Often incidental findings
- 5-year survival from MD ("main-duct")-IPMN = 31–54%
  - Intestinal IPMN (20%): Roughly correspond to villous neoplasms of the colon; if invasive, 5-year survival rate = 50%
  - Pancreatobiliary IPMN (8–10%): "High-grade tumors"; in >50% presence of an invasive component; a 5-year survival = like ductal adenocarcinoma of the pancreas
  - Oncocytic IPMN: Extremely rare; frequently "high-grade carcinomas"

Etiology

- Unclear
- Association with extrapancreatic primary tumors (colorectal, breast, and prostate cancer)

Symptoms

- Most frequently due to pancreatic duct obstruction
- Nausea
- Vomiting
- Abdominal discomfort (59%)

■ **Table 9.6** Clinical and imaging features of cystic neoplasms of the pancreas. (According to Grützmann et al. 2011; Tanaka et al. 2012)

	IPMN	MCN	SCN	SPN
Age (average)	64 years	47 years	70 years	30 years
Male (%)	60%	5%	30%	13%
Symptoms	Frequently	50%	Rarely	Rarely
Localization	Mainly pancreatic head	Almost always pancreas tail	Variable	Mainly pancreatic head
Main course	Dilated ("main duct type") Non-dilated ("branch duct type")	Normal	Normal	Normal
Calcifications	No	Rarely	Central scar (30–40%)	
Main aisle connection	Always	Sometimes	No	No
Muzin	Yes	Yes	No	No
Appearance	"Grape-like"	"Orange-like"	"Honeycomb-like"	
Malignancy	Frequently (Sendai Criteria)	Very often >70%	Very rarely <5%	Up to 10%
Special features	Main and side aisle Type	Ovarian stroma	Microcystic and oligocystic	Young women
Therapy	MD: Operation always, BD: ■ Fig. 9.10	Operation	Watch	Operation

IPMN intraductal papillary-mucinous neoplasia, *MCN* mucinous-cystic neoplasia, *SCN* serous-cystic neoplasia, *SPN* solid pseudopapillary neoplasia, *MD* main duct, *BD* branch duct

- Back pain
- Weight loss (29%)
- Jaundice (biliary obstruction) (16%)
- Previous episodes of pancreatitis (14%)
- Diabetes mellitus (IDDM)

Diagnosis

CT or MRI

- MRI (MRCP) = better method in centers with experience (duct association and main duct connection)

Imaging Signs

- Endosonography (ductal association and worrying nodules)
- Dilated pancreatic duct
- BD-IPMN = "Grape-like configuration"

Therapy (◘ Fig. 9.10)

Surgical Therapy of MD-IPMN

Indication for Surgery

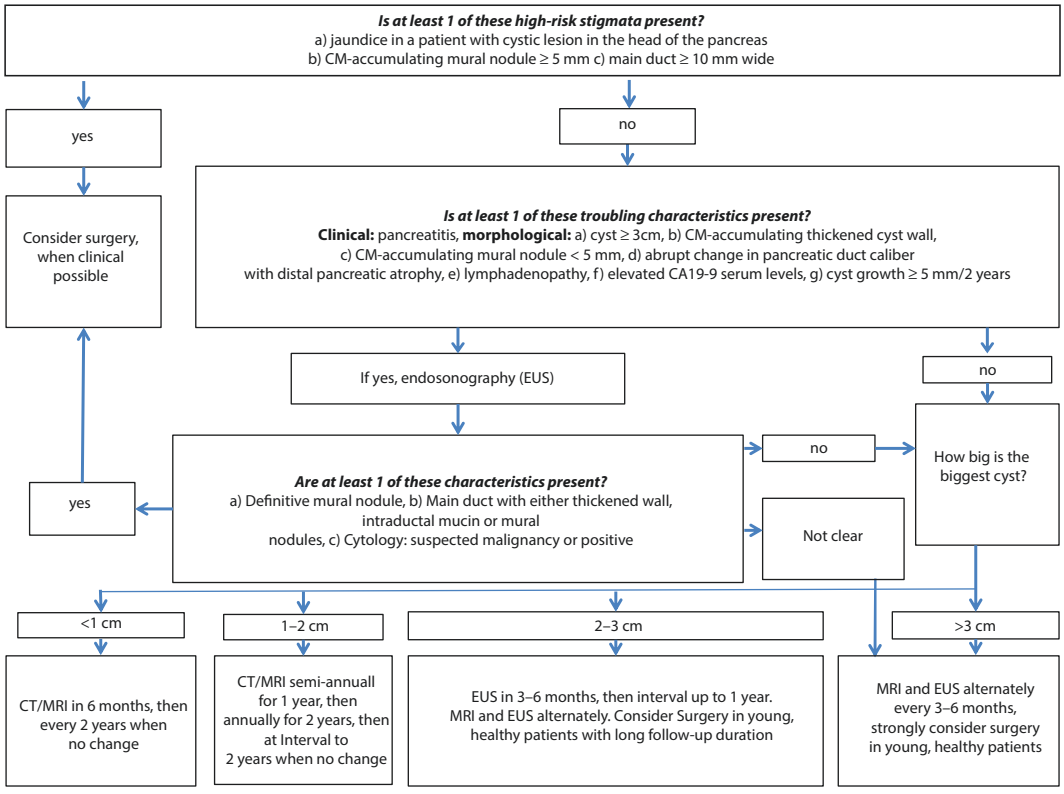
- All MD-IPMN with main duct diameter >1 cm
- Since 62% of all MD-IPMN = malignant and 43% of all MD-IPMN = invasive

Aim of the Operation

- Removal of the lesion ideally before malignant transition

Principle

- Resection according to localization: R0 resection to be aimed at (oncologic radical operation)



◘ **Fig. 9.10** Flowchart for the treatment of cystic neoplasms. (After Tanaka et al. 2017)

- Frequent PPPD vs. classical pancreatic head resection vs. pancreatectomy for multifocal type
- If necessary, total pancreatectomy in multifocal IPMN, decision according to histology of leading lesion
- Operate main finding, if frozen section shows high-grade dysplasia at the sedimentation margin, resect further until total pancreatectomy. If low-grade dysplasia, no further resection and organ-preserving procedure

Further Indications for Total Pancreatectomy

- Positive margins at the pancreatic incision margin in pancreatic head carcinoma as isolated positive margin
- Multifocal metastases of renal cell cancer (urological consultation)
- Multifocal advanced neuroendocrine tumors
- Refractory pain syndrome in chronic pancreatitis (TPIAT (see above)—very controversial!)
- Resection margin:
  - In case of high-grade dysplasia = extension of the resection
  - In moderate and low-grade dysplasia = no further additional resection necessary
  - If the main duct diameter is <1 cm = further evaluation (◘ Fig. 9.10)

Preoperative for planned splenectomy: vaccination against Pneumococcus, Haemophilus influenzae group B and Meningococcus group C 2 weeks before planned surgery.

Surgical Procedure

Total Pancreatectomy with Splenectomy

- Supine position (left arm supported, right arm extended)
- Transverse upper abdominal laparotomy, right and left extended
- exploration of the abdominal cavity
- Opening of the omental sac while sparing the gastroepiploic vessels with transection of the gastrocolic ligament
- Mobilization of the right colonic flexure
- Release of duodenal C from its retroperitoneal connections (Kocher maneuver)
- Lifting of the duodenum and pancreas from the inferior vena cava up to the left renal vein
- Extension of the Kocher maneuver by mobilization of the pars horizontalis duodeni up to the superior mesenteric vein, presentation of the same from caudal right in the region of the mesenteric root
- Elevation of the pancreatic neck = view of the avascular plane dorsal to the pancreas, here preparation up to the sinus confluens venosum, exposure of the superior mesenteric artery just to the left of the vein in this area (mesenteric artery first approach)
- Open antegrade cholecystectomy, opening of the hepatoduodenal ligament with exposure of the choledochal duct and the common hepatic artery. **Caution**: Expose the right hepatic artery with intersection of the bile duct (often variable course)
- Dissection and ligation of the gastroduodenal artery and the right gastric artery
- Dissection and ligation of the splenic artery and confluent placement and suturing of the splenic vein
- In spleen-preserving pancreatectomy, visualization of the pancreatic tail from caudal and cranial and stepwise visualization of the individual branches from the splenic artery and into the splenicvein
- Separation of the splenorenal ligament and medial elevation of the spleen together with the pancreatic tail, so that the retroperitoneal layer is exposed
- Mobilization of the distal stomach and the duodenojejunal flexure

- Approx. 10–15 cm aboral of the ligament of Treitz = deposition of the jejunum
- Removal of the specimen en bloc after stepwise separation of the pancreatic head from the mesentericoportal axis (pancreas, distal stomach, duodenum, spleen)
- Reconstruction with end-to-side hepaticojejunostomy and end-to-side duodenojejunostomy if pylorus-preserving, otherwise gastrojejunostomy (◘ Fig. 9.10)

Postoperative Management After Pancreatectomy

- Screening/prophylaxis/therapy of weight loss (80% of patients loose >10% of their weight)
- Enzyme substitution (median 8 capsules/day, taken regularly with each meal)
- Insulin administration in pancreatogenic (type III) diabetes (median 25 IU/day)
- In total pancreatectomy, sugar control is more difficult with reduced hypoglycemia sensitivity

Surgical Therapy of BD ("Branch-Duct")-IPMN

- Indication:
  - Consider surgical therapy, ideally before transition to carcinoma; in selected series, up to 26% of all BD-IPMN are malignant and up to 18% are invasive carcinomas
  - Patients <65 years and cyst size >2 cm = resection (due to cumulative malignancy rate)
- Patients with "worrisome features" (nodules, wall thickening) or symptoms (pain, new-onset diabetes mellitus, etc.)

Conservative therapy for BD-IPMN (see below)

- Only in Sendai (Fukuoka)-negative tumors: i.e. <2 cm without symptoms or "worrisome features"
- Annual malignancy rate of only 2–3%
- Patients with BD-IPMN = significantly older
- Conservative therapy + check-ups

Postoperative Follow-Up

- Recurrence rate after 5 years = 0–20% (disease of the entire pancreas!)
- 5-year survival in resected non-invasive IPMN = 80–100%
- 5-year survival in resected invasive IPMN = 40–60%
- 5-year survival rate for IPMN carcinoma = 20% (like adenocarcinoma—thus avoid transition to carcinoma by prophylactic surgery in high-risk constellations)
- Control examinations after 2 and 5 years due to general risk of development of IPMN at further sites in the pancreas (R0-situation)

Conservative Therapy of MD-IPMN (5–9 mm Main Duct) and BD-IPMN

(**Caution!**) 5 mm might still be dangerous as far as development of IPMN cancer

- ◘ Figure 9.10

9.4.2 Serous Cystic Neoplasms (SCN)

Definition

- Benign tumors consisting of numerous cysts
- 10–20% of cystic pancreatic lesions
- Honeycomb structure
- Star-shaped scar in 20% of patients
- Virtually never degenerate malignant
- Localization: Pancreatic corpus and tail (70%)

Epidemiology (◘ Table 9.6)

- Women > Men = 5:1
- Frequency peak: >60 years of age
- 18–39% of all cystic neoplasms

Symptoms

- Mostly asymptomatic
- Nausea
- Vomiting
- Abdominal discomfort
- Back pain
- Weight loss

Diagnosis
- Multi-slice CT
- MRI
- Endosonography

Therapy

Surgical Therapy
- From a size of >4 cm, due to increased growth and all with symptoms

Conservative Therapy + Monitoring
- In all other cases

9.4.3 Mucinous Cystic Neoplasia (MCN)

Definition
- Solitary, round tumors with uni- or multilocular cysts
- Cysts lined by mucin-forming cells
- Ovarian stroma (probably scattered ovarian cells)
- Approx. 10% of cystic tumors of the pancreas
- Mostly in the body-tail area
- Potential precursor for pancreatic cancer

Epidemiology (◘ Table 9.6)
- 95% women
- Frequency peak: 40–60 years of age
- Malignancy rate = 30–50%
- Prevalence of invasive cancer = up to 15%
- 5-year survival rate of invasive MCN = 57%
- 5-year survival rate of MCN adenocarcinoma = 20%

Symptoms
- 20% = asymptomatic
- Non-specific abdominal complaints

Diagnosis
- Multi-slice CT
- MRI

Therapy
- Always surgical therapy
- Principles:
  - MCN <4 cm without mural nodules = parenchyma-sparing or laparoscopic (central or distal) pancreatectomy
  - Otherwise, classic pancreatic resection with lymphadenectomy (LAD) and (often) splenectomy, if necessary
  - ◘ Figure 9.10

9.4.4 Solid Pseudopapillary Neoplasia (SPN)

Definition
- Solid, only secondary pseudocystic-degenerative tumors
- <5% of cystic pancreatic tumors
- Typically solid tissue at the edge and hemorrhagically disintegrating centrally

Epidemiology (◘ Table 9.6)
- Young women (20–30 years)
- Low malignancy potential, often very large tumors
- Metastases (liver and peritoneum): In 10–15% of cases with a long time interval to resection of the primary site, then resection again
- 5-year survival = 97%

Symptoms
- Asymptomatic
- Mostly incidental finding

Diagnosis
- Multi-slice CT
- MRI
- Endosonography

Therapy

Always Operative
- Even in metastatic stage

Principles

- Distal pancreatic resection with/without splenectomy
- Pancreaticoduodenectomy (PPPD/Whipple)

Surgical Procedure

Laparoscopic Spleen-Preserving Pancreatic Left Resection

- Y-positioning (= suppine position with spread leg; = French position)
- Access by means of a total of 4 trocars in a semilunar line around the main findings
- Pneumoperitoneum
- Exploration of the abdominal cavity for pathologies not previously described (liver/peritoneum)
- Intracorporeal sonography of the liver and the peripancreatic region as well as the pancreas
- Positioning in anti-Trendelenburg position, beach-chair positioning
- Visualization of the pancreas by mobilization of the left colonic flexure as well as the transverse colon up to the right flexure
- Opening of the omental sac
- Visualization of the gastroepiploic artery and the confluens venosum of portal vein to avoid complications
- Dissection of adhesions between upper pancreatic margin and stomach and lymphadenectomy
- Pancreas mobilization starting at the lower edge, from here visualization of the splenic vein and the venous confluence
- Visualization of the celiac trunc and the splenic artery
- Completion of the oncological lymphadenectomy at the upper pancreatic margin
- Dissection + transection of the small vessels of the pancreatic body and tail in an alternating manner centrally (confluens venosum) and peripherally (splenic hilus) = e.g. Ligasure device or PDS/metal clips
- Separation of the pancreas tail with a linear stapler (GIA with coating if necessary) and salvage using a salvage bag
- Insertion of two drains dorsal and ventral to the pancreas
- Further operative possibility = method according to Warshaw:
  - Spleen supply only via left gastroepiploic artery and short gastric arteries
  - Splenic artery and vein are severed (short gastric vessels)
  - **Caution**: Higher rate of secondary splenectomies for ischemia.

9.4.5 Guidelines

Tanaka M, Chari S, Adsay V, Fernandez-del Castillo C, Falconi M, Shimizu M, Yamaguchi K, Yamao K, Matsuno S, and International Association of Pancreatology (2006) International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 6:17–32.

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9.5 Endocrine Neoplasms

Key Points

- Rare, approx. 3% of all pancreatic neoplasms
- 5-year survival of malignant neuroendocrine tumors of the pancreas approx. 30–40%
- Grouping into functional and nonfunctional neuroendocrine tumors

9.5.1 Definition

- Neuroendocrine tumors (NET) of the pancreas = rare tumors
- Initiation from endocrine cells
- Classification of NET of the pancreas:
  - Functional (hormone-active) NET (gastrinoma, insulinoma, VIPoma, somatostatinoma, PPoma): Production and release of hormones
  - Non-functional (hormone-inactive) NET

9.5.2 Epidemiology

- Incidence: 0.4–1.5 new cases per year/100,000 population
- Increasing prevalence
- Insulinoma and gastrinoma (Zollinger-Ellison syndrome) = 1:500,000 per year
- Glucagonoma (diabetes dermatitis syndrome) = very rare
- Vipoma = Verner-Morrison Syndrome
- Nonfunctional NET of the pancreas (exclude MEN-1 syndrome in case of familial clustering)

9.5.3 Symptoms

Insulinoma

- Whipple triad:
  - Hypoglycaemia (glucose <45 mg/dL) + associated neurological symptoms (= feeling of weakness, confusion, dizziness, visual disturbances, headache, loss of consciousness)
  - Autonomic symptoms (palpitations, tachycardia, sweating and sometimes aggressiveness)
  - Rapid improvement in symptoms with glucose infusion
- Weight gain (20% of patients)
- Mechanical complications possible, but rarely due to the rather small tumors
- Mostly very small tumors
- Malignant insulinomas (10%): Production of various hormones: calcitonin, melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), etc. = variable symptomatic picture

Gastrinoma (Zollinger-Ellison Syndrome)

- Gastrin overproduction leads to:
  - Excess stomach acid = multiple ulcerations
  - Upper abdominal pain (multiple refractory gastric ulcers)
  - Reflux Disease
  - Complications of ulcers: Upper GI (gastrointestinal) bleeding + gastric or duodenal perforation

VIPom

- Massive diarrhea
- Mechanism = release of vasoactive intestinal peptide
- Resulting in:
  - Dehydration
  - Hypochloridemia
  - Hypokalemia
  - Hypomagnesemia

Glucagonom

- Severe migratory necrotizing exanthema
- Moderately elevated blood glucose levels
- Weight loss
- Anemia
- Stomatitis

Somatostatinoma

- Often clinically inapparent
- Increased fat storage: due to partial inhibition of thyroid function
- gastric distention
- Inhibition of hormones in the gastrointestinal tract results in
  - Malabsorption signs with fatty stools
  - Gallstones due to gallbladder motility disorders

Pancreatic Carcinoid Syndrome

- Paroxysmal flush
- Intestinal complaints
- Diarrhea
- Signs of right heart failure

Non-Functional NET (95%)

- Generally late diagnosis, often incidental findings
- Abdominal discomfort
- Weight loss
- Prognosis and grading according to grading (G1-G3) and proliferation rate (Ki-67 index <2%, 2–20%, >20%)

9.5.4 Diagnosis

Laboratory Diagnosis

- Determination in serum
- Detection of all hormones in serum with associated NET

Chromogranin A

- General marker for NET
- Also good follow-up parameter for diagnosis of recurrence

Caution
False-positive chromogranin A levels with proton pump inhibitor (PPI) therapy (discontinue at least 1 week before testing).

Gastrin

- In Zollinger-Ellison syndrome:
  - Fasting gastrin level >1000 pg/mL and gastric pH of <2
  - Secretion test >200 pg/mL above basal level
  - Also discontinue PPI inhibition (false positive levels of gastrin)

Fast Test

- For insulinoma: until hypoglycemia is reached

Insulin, Plasma Glucose

- Insulin (μU/mL)/plasma glucose (mg/dL) ratio >0.33
- C-peptide >0.7 mg/L (differential diagnosis hypoglycaemia facitata due to insulin injection)

5-Hydroxyindoleacetic Acid

- Degradation product of serotonin
- In the acidified 24-h collected urine
- Increased in carcinoid syndrome and small bowel NET

Imaging Techniques

Contrast Enhanced Ultrasound

- Echo-negative structure, more often hypervascular perfusion
- Not sufficient to confirm the diagnosis

Endosonography

- Very good representation of the positional relationship to surrounding organs
- Superior to other methods in localization diagnosis
- Good method for long-term follow-up of MEN-1 syndrome

Multidetector CT

- Hyperintense visualization of the NET in the early contrast phase (hypervascularized)

9.5.5 Therapy

Benign Solitary NET with Local Resection Option (>2 cm)

- Enucleation

Caution
High pancreatic fistula rate after enucleation up to 80%!

NET Without Local Resection Option

- Operation by location:
  - Pancreatic head resection
  - Central pancreatic resection
  - (Spleen-preserving) pancreatic left resection
  - Systematic lymphadenectomy in case of Ki-67 index >2%, CT suspicious LN metastases or tumor size >4 cm

Local Recurrences or Metastases of NET

- Surgical therapy

Diffuse Metastasized NET

- Treatment with somatostatin alone
- Treatment with somatostatin + α-interferon

Surgical Procedure

Central Pancreatectomy with Pancreatogastrostomy

- Supine positioning
- Transverse laparotomy of the upper abdomen or median laparotomy
- Exploration of the abdominal cavity for pathologies not previously described
- Opening of the omental sac
- Mobilization of the lower edge of the pancreatic neck and body
- Visualization of the superior mesenteric vein, at the inferior border of the pancreas
- Mobilization of the upper edge of the pancreas (lymphadenectomy in the area of the hepatica artery)
- Dissection of the pancreas from the portal vein
- Ventral luxation of the pancreas with loops around the pancreatic body/neck
- Identification of the splenic vein and transsection of the pancreas
- The splenic artery is usually located separately from the neck and proximal pancreatic body
- After complete exposure of the pancreatic body = transection with stapler (endo-GIA) on the mesentericoportal axis
- Stapling of the proximal pancreatic remnant or two-row suturing (PDS 4-0 MH, V-shape closure)
- Pancreatogastrostomy (or pancreatopancreaticojejunostomy) between the distal pancreatic remnant and the posterior wall of the stomach or intestine (jejunum), after removal of the row of staples in the area of the pancreatic duct (creation as described above)
- Insertion of 2 drains at the distal and proximal pancreatic remnant

9.5.6 Guidelines

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