PANCREAS

Kenneth Alonso, MD, FACP

Development of pancreas and gallbladder from mid-gut

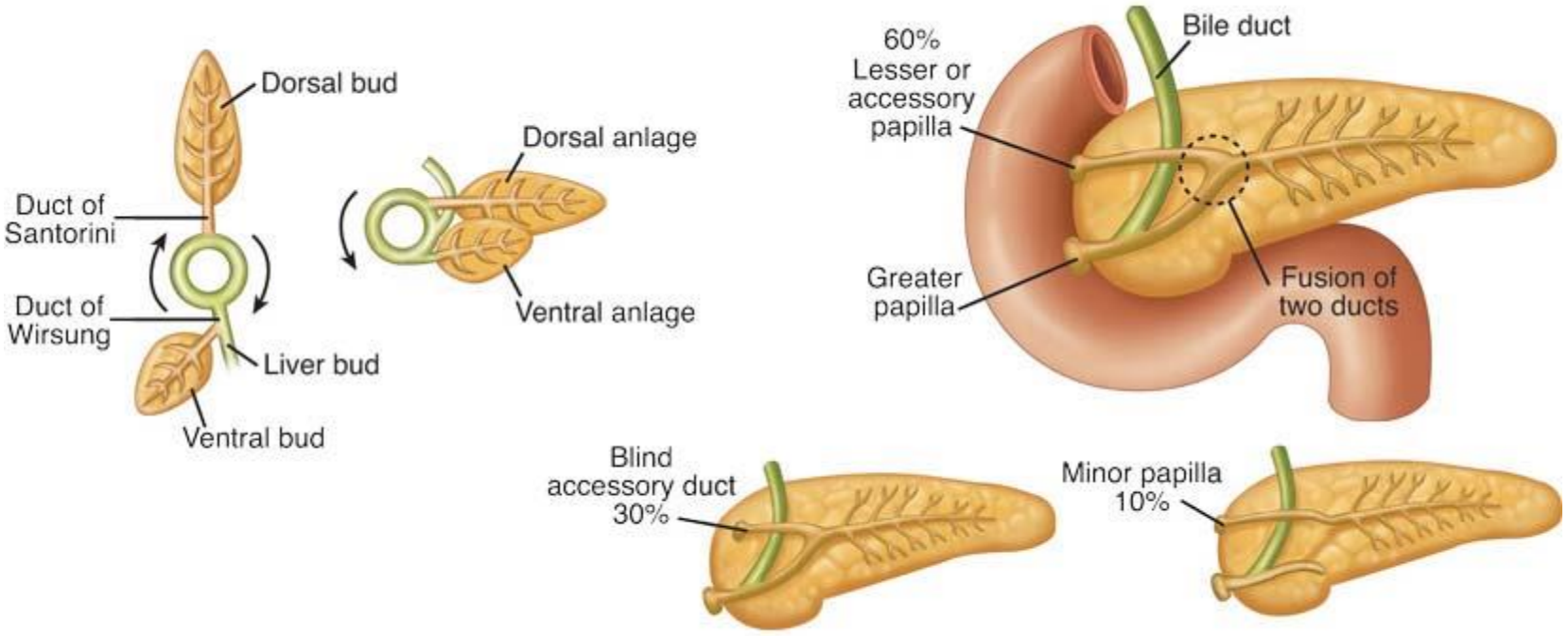


Fig. 33-3 Accessed 02/01/2010

Chapman's reflex points

- Smooth, firm, discretely palpable nodules 2-3mm in diameter located within deep fascia or on the periosteum of a bone.
- May represent viscerosomatic reflexes (empirical evidence only)
- T6 adjacent to and at base and to the right of the transverse process, associated with somatic dysfunction of the pancreas

Congenital anomalies

- Pancreatic divisum is a failure of fusion of the fetal duct systems.
- The bulk of the pancreas (dorsal bud) drains through the dorsal pancreatic duct and the small caliber minor papilla.
- Most common congenital abnormality of pancreas.
- Predisposes to pancreatitis.
- An annular pancreas develops when impaired rotation of the pancreatic buds prevents normal fusion.
- May lead to duodenal obstruction in utero.

Pancreas

- The pancreas is retroperitoneal
- Anterior to vertebral column.
- Susceptible to damage following blunt trauma.
- The head of the pancreas lies adjacent to the second segment of the duodenum while the tail abuts the spleen.

Pancreas

- The body and tail are supplied by branches from the splenic artery;
- The head is supplied by
- The superior pancreaticoduodenal from the gastroduodenal artery;
- And by the inferior, from the superior mesenteric artery.
- Veins drain into the portal system.

Pancreas

- Endocrine signaling begins at 10-15 weeks of development;
- Exocrine function begins shortly before birth.

Pancreas

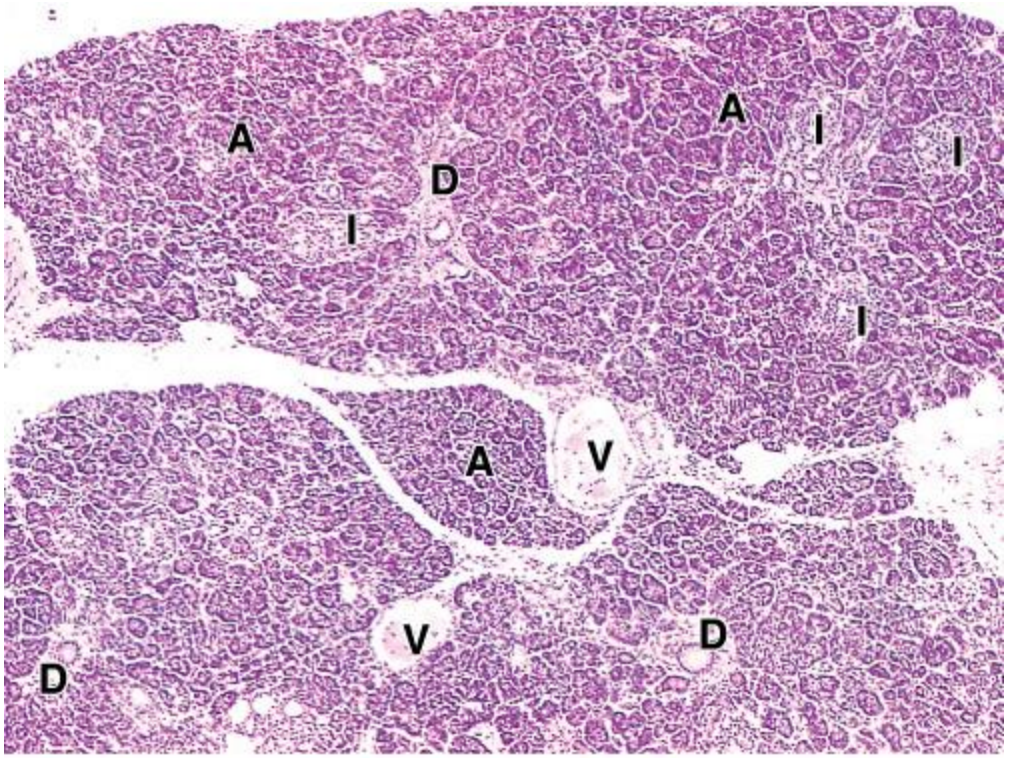


Fig. 16-8 Accessed 02/01/2010

Islets of Langerhans (I) are separated from the acini of the exocrine cells (A) and their ducts (D) by connective tissue. The connective tissue capsule sends septa into the organ to divide it into lobules.

Exocrine pancreas

- 2.5L HCO_3^- produced daily
- Secretes inert protoenzymes apart from amylase and lipase
- Trypsinogen may be self-activating
- Enzymes held in membrane-bound zymogen granules in acinar cells.
- Acinar cells resistant to action of trypsins and phospholipase A_2.
- Vagus stimulates enzyme release as well as vasoactive intestinal peptide

Exocrine pancreas

- Falling pH leads to secretin release into the blood.
- This evokes HCO_3^- release from pancreatic acini, biliary ducts, and duodenal mucosa to reverse the fall in pH.
- Duodenal luminal pH approaches 8.0.
- Cause of release of cholecystokinin and stimulation of acinar release of contents into the duodenal lumen:
- Rise in long-chain fatty acids
- Protein content of luminal fluids
- (principally tryptophan, phenylalanine, valine, methionine)
- Gastric acid itself

Exocrine pancreas

- Insulin is needed for both secretin and cholecystokinin to promote exocrine secretion.
- Serine proteases in the duodenal lumen inhibit pancreatic secretion (inactivate cholecystokinin releasing peptide).
- Acinar and ductal cells secrete trypsin inhibitors, including serine protease inhibitor Kazal type I (SPINK1), which further limit intra-pancreatic trypsin activity.
- Duodenal enteropeptidase activates trypsin in the small bowel
- Trypsin then activates other pro-enzymes

Acute pancreatitis

- Epigastric pain, with radiation to the flank, the back, or both.
- Pain characterized as constant, dull and boring, and worse when supine.
- The discomfort may lessen when the patient assumes a sitting or fetal position.
- No rebound tenderness on presentation; guarding is common.
- Nausea and vomiting generally present.

Table 19-1 Etiologic Factors in Acute Pancreatitis

Metabolic
Alcoholism
Hyperlipoproteinemia
Hypercalcemia
Drugs (e.g., azathioprine)
Genetic
Mutations in genes encoding trypsin, trypsin regulators, or proteins that regulate calcium metabolism
Mechanical
Gallstones
Trauma
Iatrogenic injury
Operative injury
Endoscopic procedures with dye injection
Vascular
Shock
Atheroembolism
Vasculitis
Infectious
Mumps

Acute pancreatitis

- Cholelithiasis and Alcohol Abuse account for 80% of cases in adults in the US.
- Pancreatitis is a rare disease in countries where alcohol is not consumed.
- Ethanol alters intestinal zymogen activation.
- Pancreatitis can occur in persons consuming only 50 g ethyl alcohol per day
- Equivalent to four 12-oz servings of beer
- The usual patient consumes 150 g ethyl alcohol per day for 4-7 years

Acute pancreatitis

- Valproic acid
- Trauma accounts for up to 33% of cases in children.
- Germline mutation in cationic trypsinogen gene, PRSS1, makes trypsin resistant to cleavage, leading to inappropriate activation
- 40% lifetime risk of pancreatitis
- Complications may be seen in 20% of cases.
- Mortality rates may be as high as 9% .

Table 19-2 Inherited Predisposition to Pancreatitis

Gene (Chromosome Location)	Protein Product	Function
CFTR (7q31)	Cystic fibrosis transmembrane conductance regulator	Epithelial anion channel. Loss-of-function mutations alter fluid pressure and limit bicarbonate secretion, leading to inspissation of secreted fluids and duct obstruction
PRSS1 (7q34)	Serine protease 1 (trypsinogen 1)	Cationic trypsin. Gain-of-function mutations prevent self-inactivation of trypsin
SPINK1 (5q32)	Serine peptidase inhibitor, Kazal type 1	Inhibitor of trypsin. Mutations cause loss-of-function, increasing trypsin activity
CASR (3q13)	Calcium-sensing receptor	Membrane-bound receptor that senses extracellular calcium levels and controls luminal calcium levels. Mutations may alter calcium concentrations and activate trypsin.
CTRC (1p36)	Chymotrypsin C (caldecrin)	Degrades trypsin, protects the pancreas from trypsin-related injury
CPA1 (7q32)	Carboxypeptidase A1	Exopeptidase involved in regulating zymogen activation

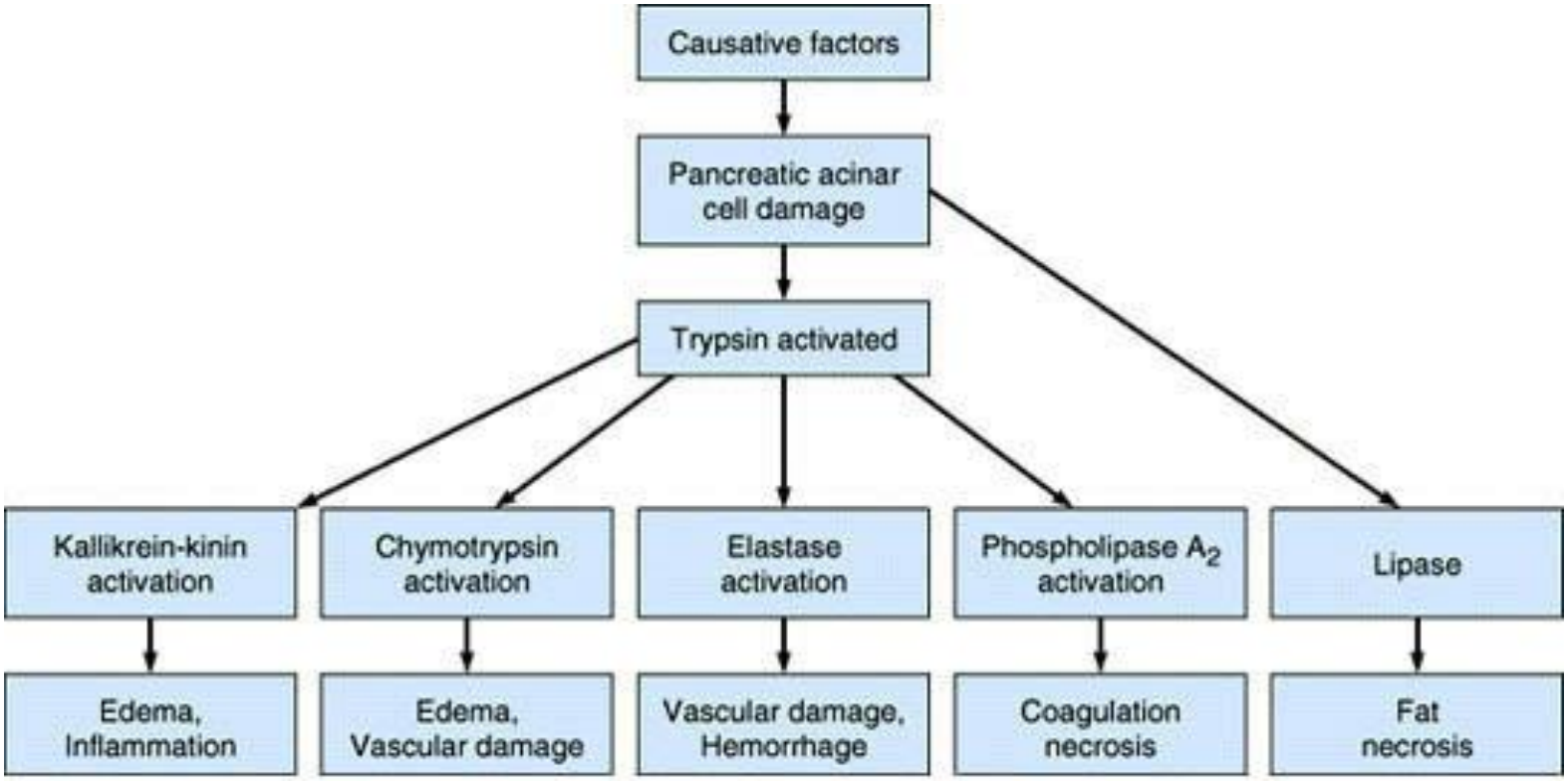
Other causes

- Hypercalcemia
- Parathyroid hyperplasia or adenoma
- Hyperlipidemia
- Triglycerides >500 mg/dl fasting
- This is an acute reactant and should not be used for diagnosis of hyperlipidemia if measured during acute episode
- Diabetes mellitus
- Metabolic syndrome
- Dialysis
- Tropical (nutritional origin, geographic clustering)

Other causes

- Drugs
- ddI
- Azathioprine
- Estrogens,
- Furosemide
- Thiazide diuretics
- Metronidazole
- Opiates
- Autoimmune
- Elevated IgG_4

Pathogenesis of pancreatitis



(Reproduced, with permission, from Marshall JB: Acute pancreatitis: a review with an emphasis on new developments. Arch Intern Med 1993;153:1185.)

Fig. 15-3 Accessed 02/01/2010

Laboratory tests

- An elevated trypsin level is diagnostic of pancreatitis.
- Serum amylase
- Starts increasing from two to 12 hours after the onset of symptoms
- Peaks at 12 to 72 hours
- Usually returns to normal within one week.

Laboratory tests

- Serum lipase
- Levels increase within four to eight hours of the onset of clinical symptoms
- Peak at about 24 hours
- Levels decrease within eight to 14 days.
- If lipase markedly elevated and AST or ALT are elevated, consider pancreatitis as secondary to gallstones.
- Lipase is not secreted as a pro-enzyme

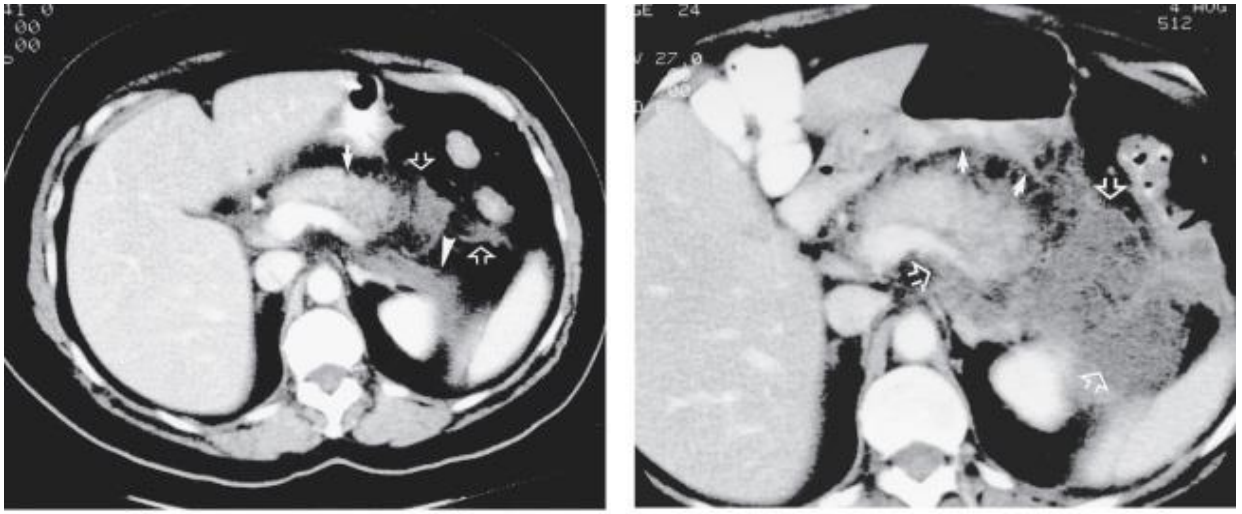
Imaging studies

- A gas-filled duodenum (sentinel loop) secondary to obstruction on a plain x-ray of the abdomen suggests pancreatitis.
- Calcification of the pancreas may be seen.
- Ultrasonography is an acceptable study for initial evaluation when biliary causes are suspected.
- Biliary obstruction or stones may be identified.

CT scan

- The contrast-enhanced CT scan provides the best imaging of the pancreas and surrounding structures.
- Order in patients with fever or leukocytosis or when other studies are inconclusive.
- The CT findings in pancreatitis may show:
- Interstitial pancreatitis
- Inflammation characterized by diffuse or segmental enlargement of the pancreas,
- With irregular contour and obliteration of peripancreatic fat
- Necrotic pancreatitis (may have peripancreatic necrosis)
- Non-enhancing at 72 hours on CT

Acute pancreatitis



(Courtesy of Dr. PR Ros, University of Florida College of Medicine; with permission.)

Fig. 307-1 Accessed 02/01/2010

A. At admission there is mildly decreased density of the body of the pancreas to the left of the midline (arrow). There are a few linear strands in the peripancreatic fat (open arrows). A small amount of fluid is seen in the anterior pararenal space (arrowhead).
B. B. Nine days after admission, there is anterior displacement of the posterior gastric wall by the pancreas (arrows), increased inflammation of the peripancreatic fat, and increased pancreatic effusion in the anterior perirenal space and around the splenic vein (open arrows).

Histopathology

- (1) microvascular leak and edema
- (2) fat necrosis
- (3) acute inflammation,
- (4) destruction of pancreatic parenchyma
- Striking in necrotizing pancreatitis
- (5) destruction of blood vessels and interstitial hemorrhage
- Striking in acute hemorrhagic pancreatitis

Acute pancreatitis

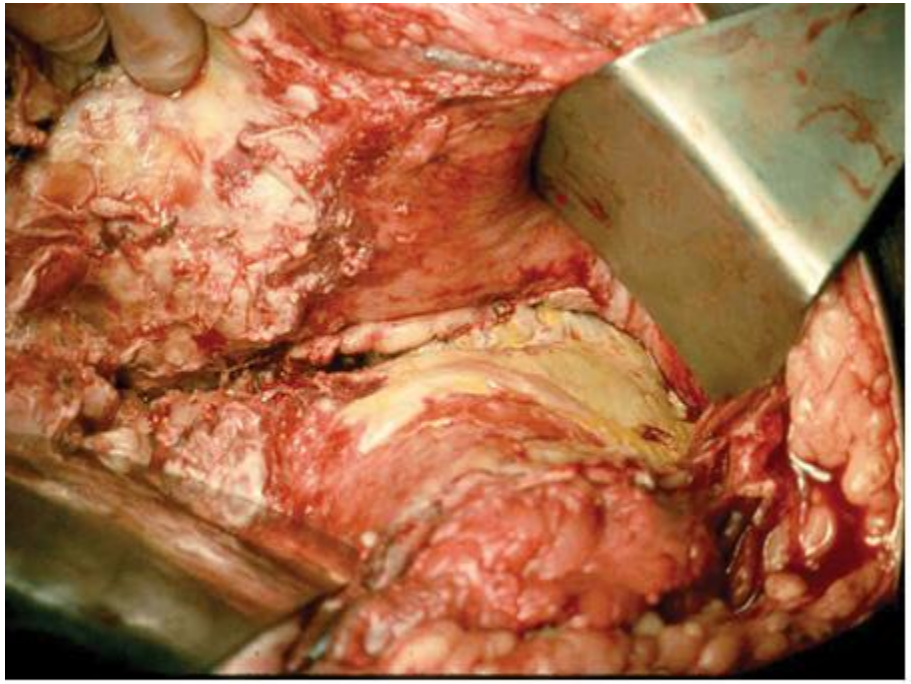


Fig. 33-15 Accessed 02/01/2010

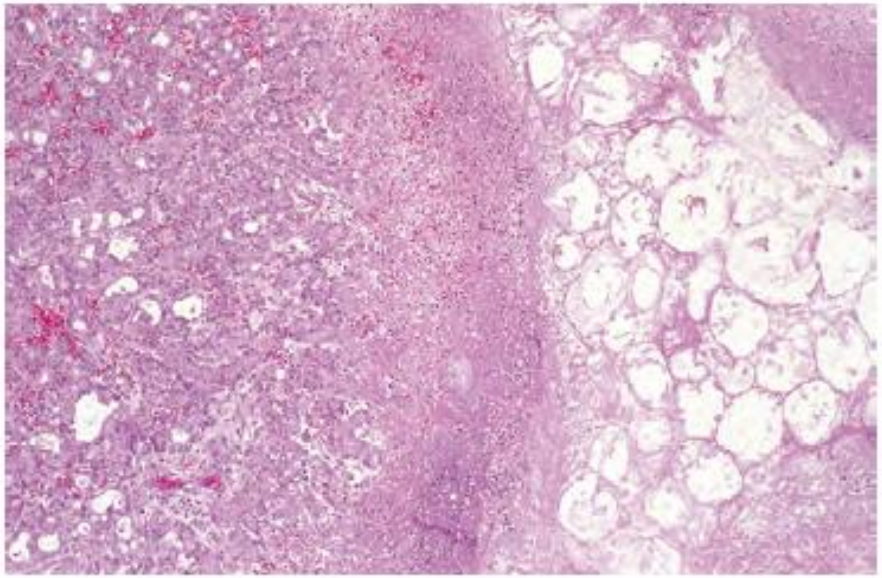


Figure 19-3 The microscopic field shows a region of fat necrosis on the right and focal pancreatic parenchymal necrosis *(center)*.

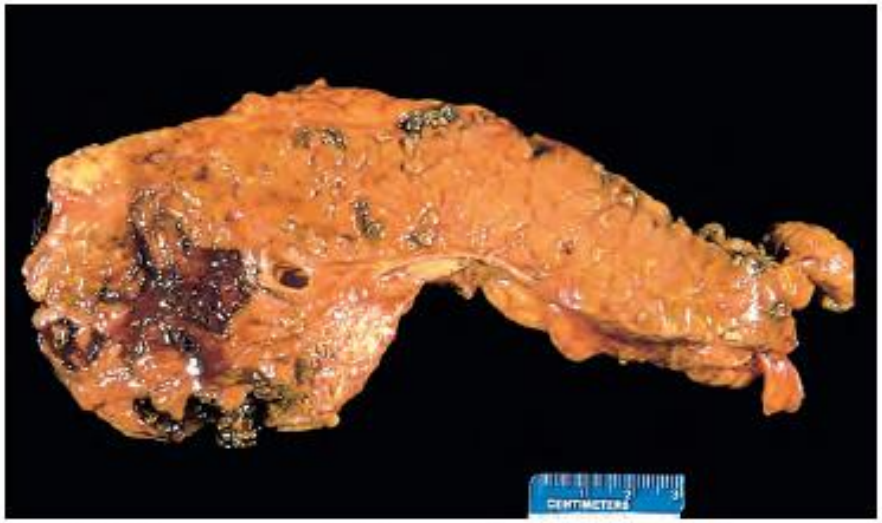


Figure 19-4 The pancreas has been sectioned longitudinally to reveal dark areas of hemorrhage in the head of the pancreas and a focal area of pale fat necrosis in the peripancreatic fat *(upper left)*.

Prognosis

- Clinical monitoring inadequate.
- APACHE II screen can be performed within hours after admission.
- A five point increase in APACHE II scores shows a direct relation with mortality.
- Scores above 30 are associated with a 73% mortality rate
- Scores above 35, 84% mortality rate

- Radiologic criteria from CT scan showing multifocal involvement and >33% necrosis is associated with high risk disease.

Prognosis

- Clinical monitoring inadequate.
- Bedside index for severity in acute pancreatitis (BISAP)
- Bedside monitoring (5 minutes)
- Equal to APACHE II
- BUN >25; disorientation, somnolence, lethargy, coma, or stupor; SIRS criteria; age >60; pleural effusion each contribute 1 point to score
- Score of <2 associated with 2% mortality
- Score of 3 is cutoff for decision making
- Score of 5 associated with 22% mortality

Acute complications

- Occur within 2 weeks of pain onset.
- Hypocalcemia.
- Secondary infection associated with 70-80% of deaths.
- Multiple organ failure
  - retroperitoneal bleeding
  - atelectasis to ARDS
  - acute tubular necrosis

Late complications

- Pseudocyst
- Acute inflammatory fluid collection where areas of intrapancreatic or peripancreatic hemorrhagic fat necrosis are collected; <4 weeks old; walled off after 4 weeks
- MRI best imaging modality at 4 weeks
- 1-8% of cases
- Usually solitary
- Situated in the lesser omental sac or in the retroperitoneum between the stomach and transverse colon or between the stomach and liver.
- Can be within the pancreas and even be subdiaphragmatic

Late complications

- Abscess
- 1-4% of cases
- CT scan best imaging modality
- Suggestive of complication requiring intervention:
- Pain
- Fever
- Leukocytosis
- Rising amylase
- Elevated CRP levels

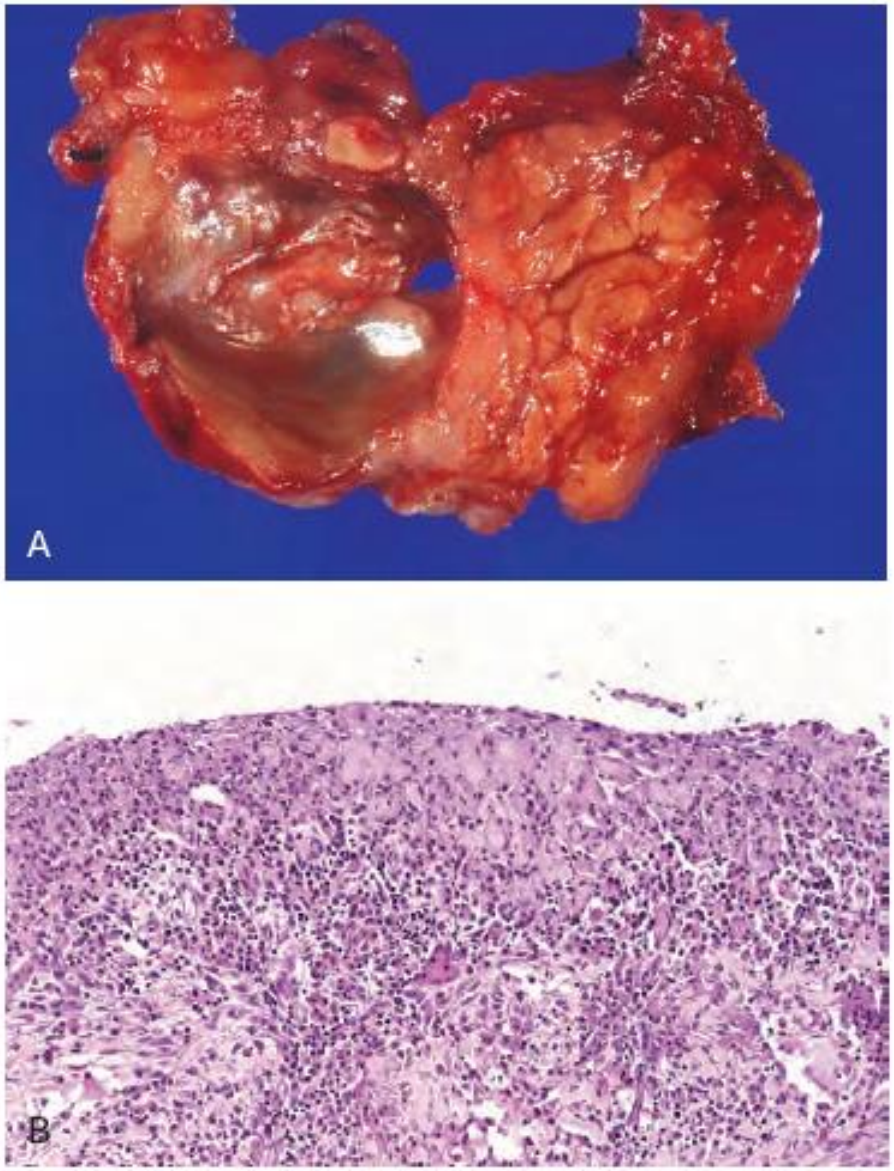
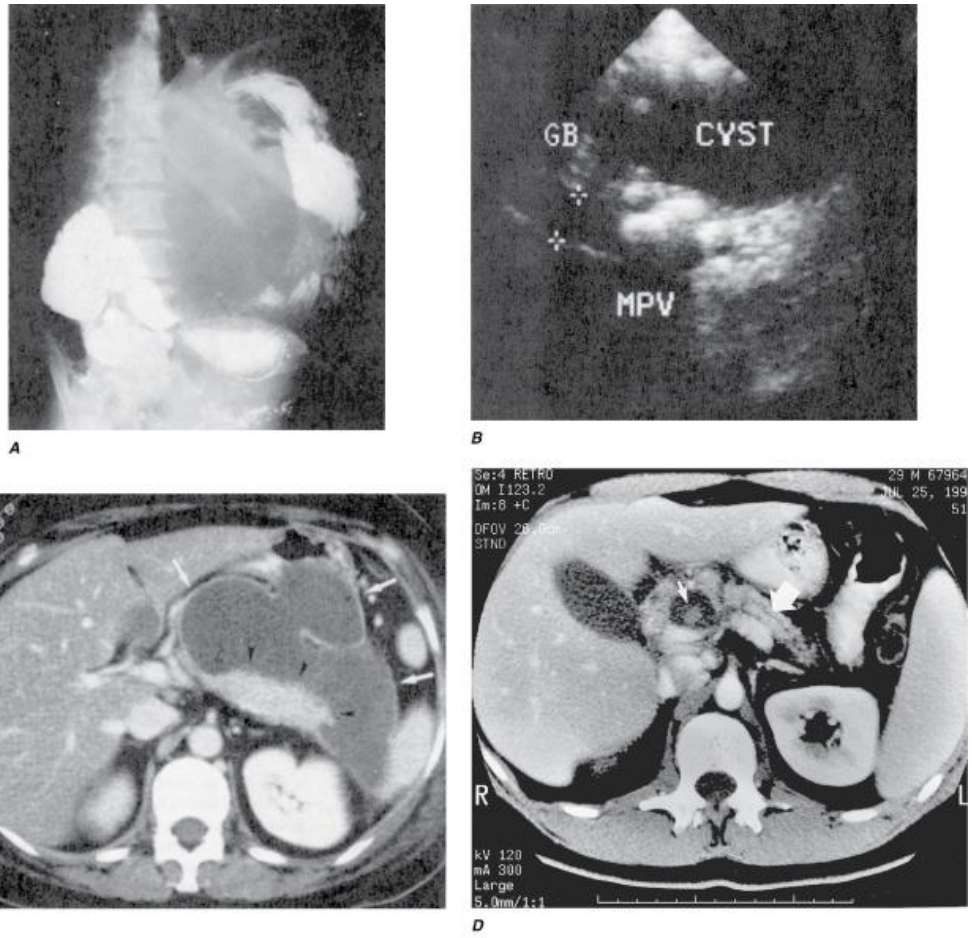


Figure 19-7 Pancreatic pseudocyst. **A,** Cross-section revealing a poorly defined cyst with a necrotic brown-black wall. **B,** The cyst lacks a true epithelial lining and instead is lined by fibrin and granulation tissue.

Acute necrotizing pancreatitis

- 90% in children
- CT directed percutaneous fine needle aspiration of necrotic tissue and peripancreatic fluid indicated if necrosis identified on scan or if patient shows signs of infection.
- Surgical debridement if fluid contains bacteria.
- 12% mortality if sterile necrosis
- 30% mortality in infected necrosis
- 47% in multisystem organ failure
- In contrast, 3-5% mortality in acute pancreatitis or interstitial edematous pancreatitis without necrosis

Pancreatic pseudocyst



(A, B, courtesy of Dr. CE Forsmark, University of Florida College of Medicine; C, D, courtesy of Dr. PR Ros, University of Florida College of Medicine; with permission.)

Fig. 307-2 Accessed 02/01/2010

A. Displacement of stomach by pseudocyst.
B. Behind the large pseudocyst is seen the calcified head of the pancreas. A dilated common bile duct (*asterisk*) is noted.
C. Note the large, lobulated fluid collection (*arrows*) surrounding the tail of the pancreas (*arrowheads*). Note also the dense, thin rim in the periphery representing the fibrous capsule of the pseudocyst.
D. pseudocyst (*small arrow*) with a pseudo-aneurysm (light area in pseudocyst).

Treatment

- Pain control
- Meperidine use is risky if patient on SSRI
- May precipitate hyperthermia
- No nasogastric suction
- NPO (rest the pancreas)
- Enteral feeding beyond the ligament of Treitz within 48 hours of onset of acute pancreatitis is associated with fewer complications
- No probiotics

Treatment

- ERCP if complicated by cholangitis or if signs of obstruction
- If stone as cause, proceed to cholecystectomy
- If moderate to severe pancreatitis, delay cholecystectomy 6 weeks
- Imipenem if infected
- Trend of amylase/lipase values more important than extent of elevation
- Feed when near normal

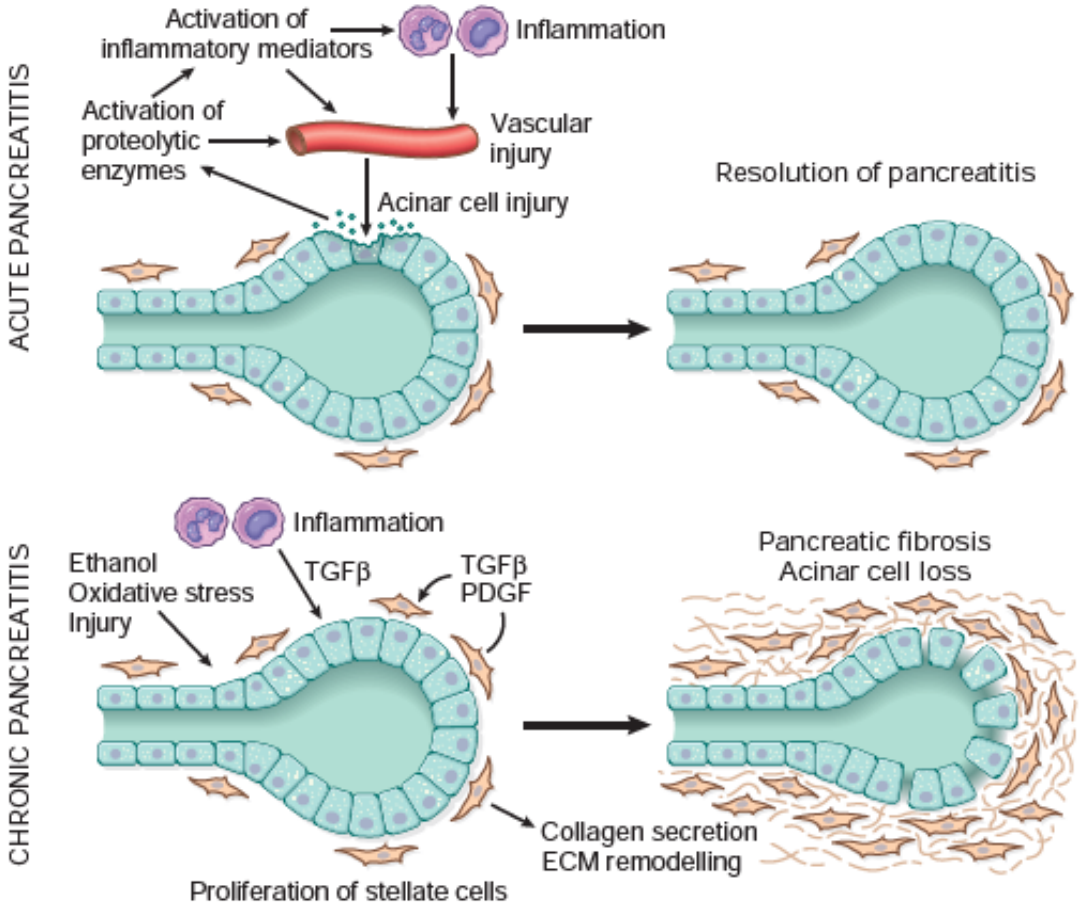


Figure 19-5 Comparison of the mediators in acute and chronic pancreatitis. In acute pancreatitis acinar injury results in release of proteolytic enzymes, leading to a cascade of events including activation of the clotting cascade, acute and chronic inflammation, vascular injury, and edema. In most patients, complete resolution of the acute injury occurs with restoration of acinar cell mass. In chronic pancreatitis, repeated episodes of acinar cell injury lead to the production of profibrogenic cytokines such as transforming growth factor β (TGF-β) and platelet-derived growth factor (PDGF), resulting in the proliferation of myofibroblasts, the secretion of collagen, and remodeling of the extracellular matrix (ECM). Repeated injury produces irreversible loss of acinar cell mass, fibrosis, and pancreatic insufficiency.

Chronic pancreatitis

- Alcohol abuse the most common cause in adults.
- Cystic fibrosis the most common cause in children.
- Up to 25% of cases have a genetic basis
- Autoimmune disease is IgG_4 related
- Smoking leads to dysregulation of duct cell CFTR function (cAMP regulated chloride channel).
- 4% will develop carcinoma.

Chronic pancreatitis

- Matrix metalloproteinase destruction of normal collagen in pancreas promotes organ remodeling.
- Pancreatic stellate cells promote fibrosis if stimulated by pro-inflammatory cytokines.
- They also secrete transforming growth factor (TGF-β) which promotes fibrosis.

Chronic pancreatitis

- Abdominal pain may not be prominent as acinar cells destroyed.
- Secretin stimulation of bicarbonate production abnormal when <40% pancreatic function present.
- Steatorrhea when lipase and protease levels <10% of normal.

Histopathology

- Characterized by fibrosis, atrophy and dropout of acini, and variable dilation of pancreatic ducts
- Chronic pancreatitis caused by alcohol abuse is characterized by ductal dilatation and intraluminal protein plugs and calcifications.
- Autoimmune pancreatitis is characterized by a duct-centric mixed inflammatory cell infiltrate, venulitis, and increased numbers of IgG4-secreting plasma cells.

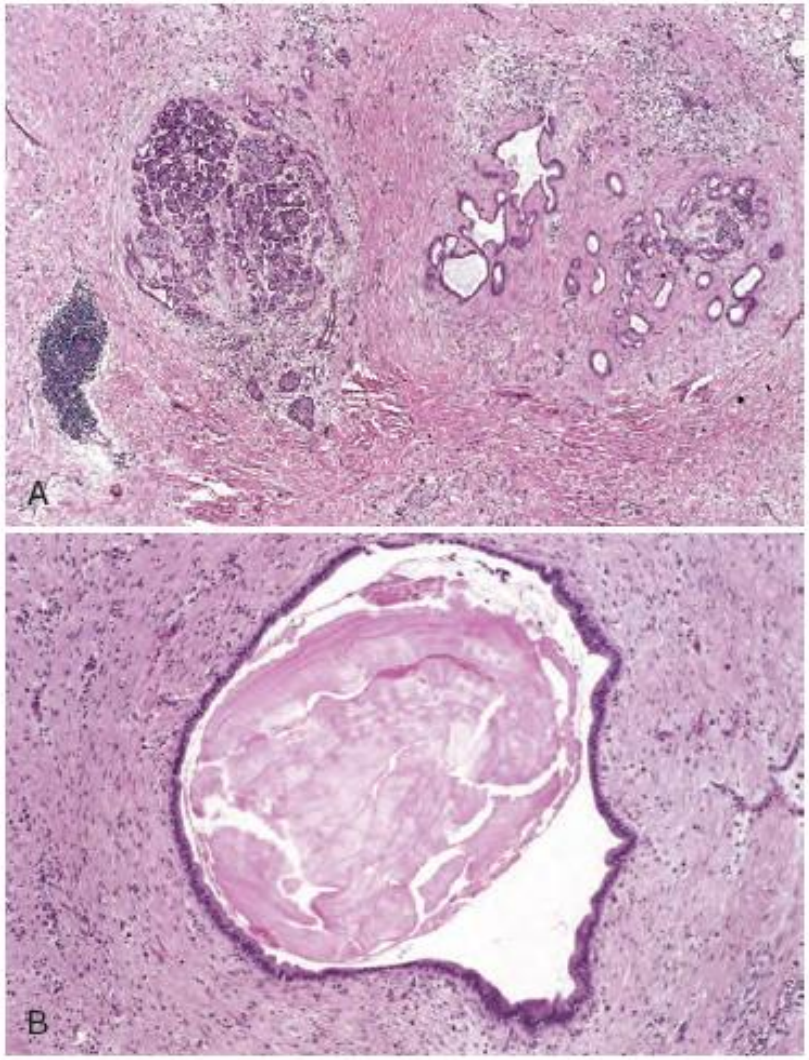


Figure 19-6 Chronic pancreatitis. **A,** Extensive fibrosis and atrophy has left only residual islets *(left)* and ducts *(right)*, with a sprinkling of chronic inflammatory cells and a few islands of acinar tissue. **B,** A higher power view demonstrating dilated ducts with inspissated eosinophilic ductal concretions in a person with alcoholic chronic pancreatitis.

Pancreatic enzyme deficiency

- Pancreatic lipase deficiency [<5%] manifests as greasy stools with undigested dietary fat.
- Non-hydrolyzed triglycerides present as oil drops separated from the stool mass and become white and firm after cooling.
- 33% lipase digestion occurs in the stomach; optimal pH 4-5.
- Pancreatic lipase is inactivated as intestinal luminal pH drops below 7.

Signs of malabsorption

- Weight loss
- Glossitis,
- Carpopedal spasms
- Absent tendon reflexes
- Cutaneous bruising
- Flatulence
- Abdominal distention, bloating, or discomfort resulting from increased intestinal bulk and gas production.
- Steatorrhea is prominent.

Steatorrhea

- Steatorrhea may occur with even relatively normal appearing stools.
- Usually they are pale, soft, bulky, malodorous stools that stick to the side of the toilet bowl or float and are difficult to flush away.
- Insulin deficiency as islet cells destroyed.
- Insulin also necessary for secretin release

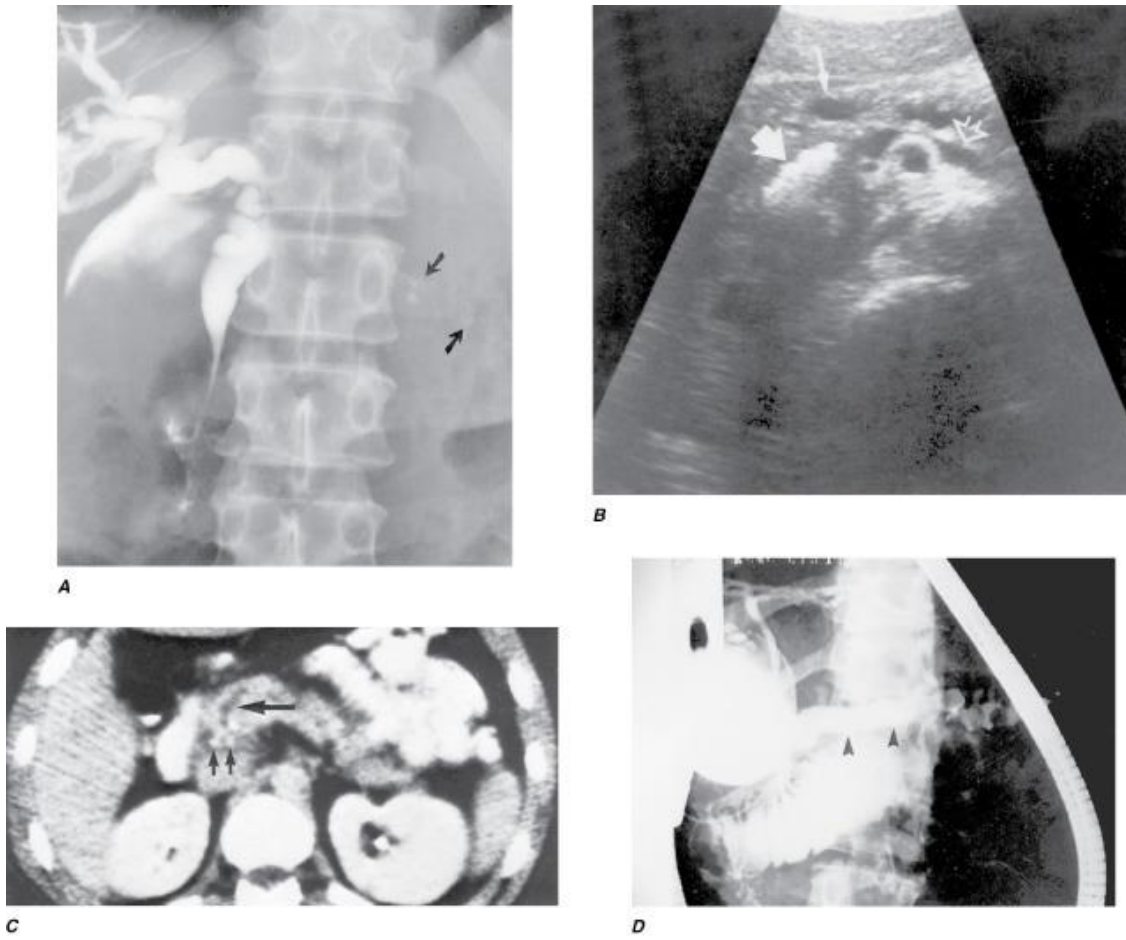
Signs of malabsorption

- The malnutrition screening tool detects those at risk for nutritional disturbances with a positive likelihood ratio (LR+) of 13; LR-, 0.3.
- Have you lost weight without trying?
- How much?
- Decreased appetite?

Laboratory diagnosis

- Direct measurement of fecal fat is the most reliable test for establishing malabsorption.
- Steatorrhea is absolute evidence of malabsorption.
- Fecal fat > 6 g/day is abnormal on a Western diet of 50-150 g/day of fat.

Chronic Pancreatitis

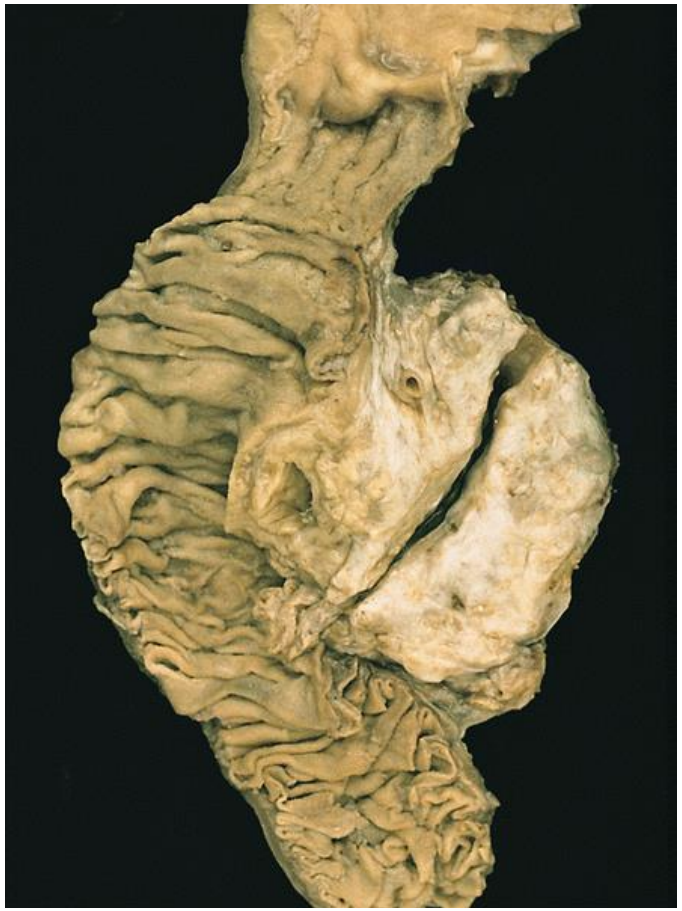


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

Fig. 307-3 Accessed 02/01/2010

A. Pancreatic calcification (*arrows*) and stenosis (tapering) of the intrahepatic portion of the common bile duct.
B. Pancreatic calcification (*large white arrow*). Dilated pancreatic duct (*thin white arrow*) and splenic vein (*open arrow*).
C. Pancreatic calcification (*vertical arrows*) and dilated pancreatic duct (*horizontal arrow*).
D. Grossly dilated pancreatic ducts (*arrows*).

Chronic pancreatitis



Whipple resection specimen from a patient with chronic pancreatitis. The cut surface shows tubular stenosis of the common bile duct. Differentiation from a ductal adenocarcinoma difficult based on the gross appearance of this inflammatory lesion.

Fig. 4-63

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Chronic pancreatitis

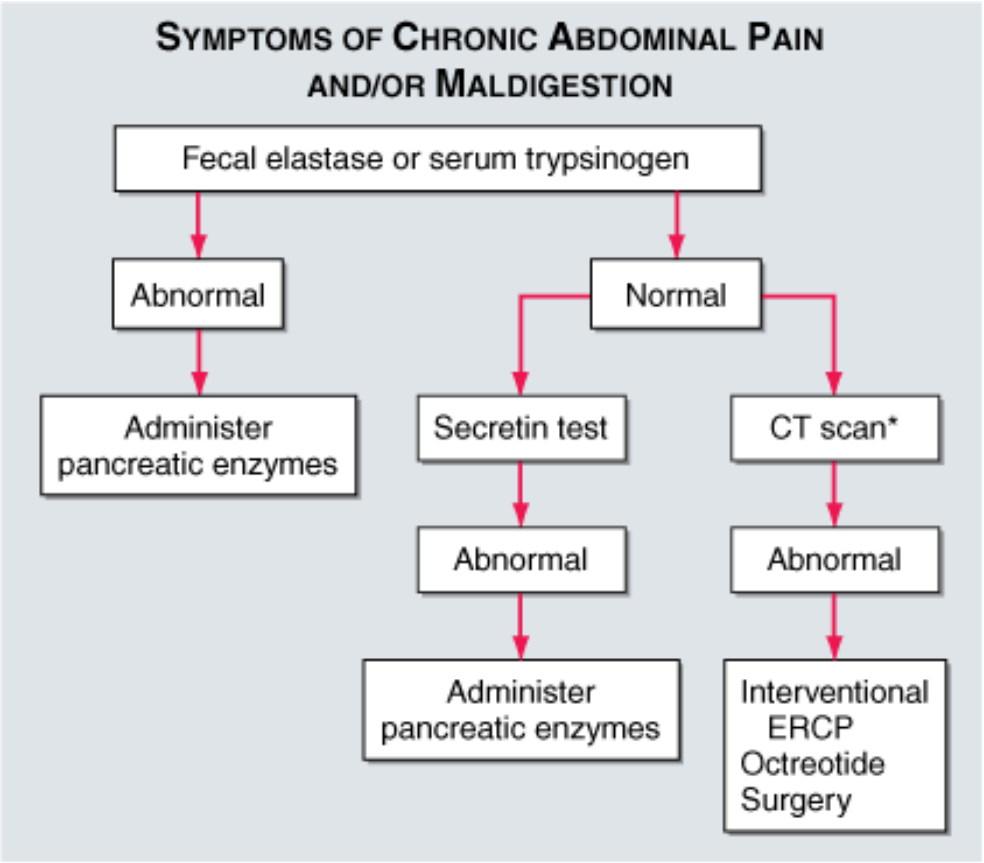


Fig. 306-1
Accessed
02/01/2010

Treatment

- Stop alcohol use.
- Stop cigarette use.
- Small feedings.
- Medium chain triglycerides supplementation.
- Limit cholecystokinin release
- Collection of duodenal contents after IV secretin administration best test for exocrine dysfunction.
- Oral enzymes (30,000 units lipase) inhibit cholecystokinin and may aid pain relief.
- Steatorrhea may resolve.
- The use of antioxidants may prevent recurrence.

Treatment

- Oral hypoglycemics, not insulin.
- May require pancreaticojejunostomy as well as cholecystectomy.

Cystic fibrosis

- In US, screened for in neonates
- Some patients may not have symptoms until adolescence
- Signs and symptoms:
- Parents may taste salt when kissing the child
- Slow growth rate.
- Often listless and irritable, tire easily.
- Difficult to clear airways.
- Repeated bouts of bronchitis.
- Lung infections due to thick mucous secretions.
- Generally, Pseudomonas.

Table 10-5 Clinical Features and Diagnostic Criteria for Cystic Fibrosis

Clinical Features of Cystic Fibrosis

1. *Chronic sinopulmonary disease manifested by*
   a. Persistent colonization/infection with typical cystic fibrosis pathogens, including *Staphylococcus aureus*, nontypeable *Haemophilus influenzae*, mucoid and nonmucoid *Pseudomonas aeruginosa, Burkholderia cepacia*
   b. Chronic cough and sputum production
   c. Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation)
   d. Airway obstruction manifested by wheezing and air trapping
   e. Nasal polyps; radiographic or computed tomographic abnormalities of paranasal sinuses
   f. Digital clubbing
2. *Gastrointestinal and nutritional abnormalities, including*
   a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
   b. Pancreatic: pancreatic insufficiency, recurrent acute pancreatitis, chronic pancreatitis
   c. Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis, or multilobular cirrhosis, prolonged neonatal jaundice
   d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia, edema, complications secondary to fat-soluble vitamin deficiency
3. *Salt-loss syndromes: acute salt depletion, chronic metabolic alkalosis*
4. *Male urogenital abnormalities resulting in obstructive azoospermia (congenital bilateral absence of vas deferens)*

Criteria for Diagnosis of Cystic Fibrosis

One or more characteristic phenotypic features,
   OR a history of cystic fibrosis in a sibling,
   OR a positive newborn screening test result
AND
An increased sweat chloride concentration on two or more occasions
   OR identification of two cystic fibrosis mutations,
   OR demonstration of abnormal epithelial nasal ion transport

Adapted with permission from Rosenstein BJ, Cutting GR: The diagnosis of cystic fibrosis: a consensus statement. J Pediatr 132:589, 1998.

Cystic fibrosis

- Thick pancreatic secretions lead to
- Clogged pancreatic ducts
- Decreased digestion of dietary proteins and lipids.
- Foul-smelling, glistening, bulky stools.
- 85% of patients have pancreatic insufficiency
- Low albumin levels compatible with protein deficiency

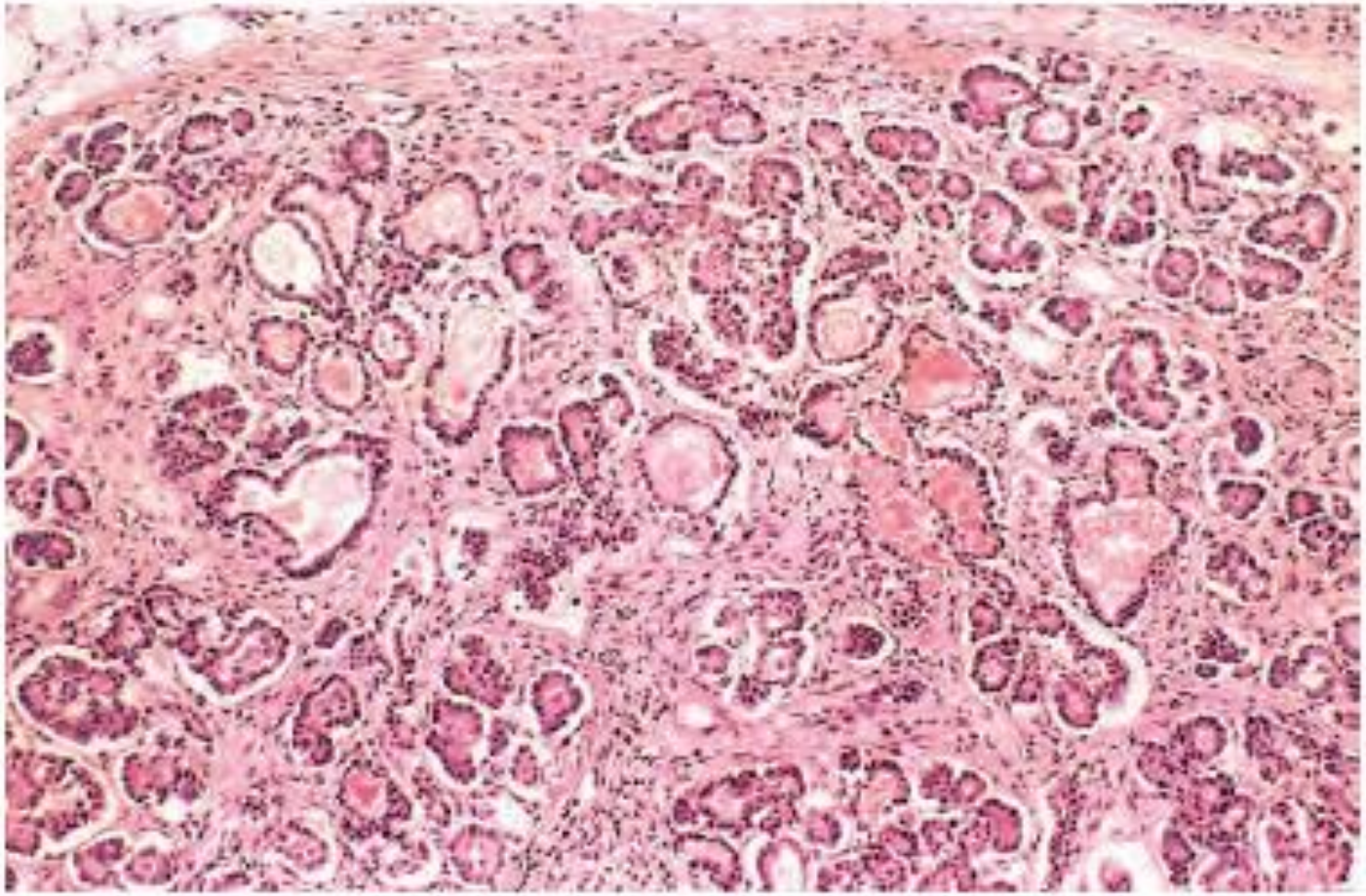


Figure 10-20 Pancreas in cystic fibrosis. The ducts are dilated and plugged with eosinophilic mucin, and the parenchymal glands are atrophic and replaced by fibrous tissue.

Cystic fibrosis

- Early presentations:
- Meconium ileus (neonatal)
- Rectal prolapse in a child
- Late complication:
- Infertility

Cystic fibrosis

- <u>The cause of thickened, viscous secretions</u>
- Abnormal transport of Cl^- and Na^+ across the epithelium of the:
- Pancreatic ducts
- Biliary ducts
- Airways
- Mutation that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein on chromosome 7.
- The CFTR protein belongs to the ABC (ATP-Binding Cassette) family of proteins.

Cystic fibrosis

- CFTR malfunction leads to
- Defective cAMP-dependent Cl^- secretion
- In addition, Na^+ absorption is increased,
- Possibly due to a failure of CFTR-mediated regulation of Na^+-channel activity.
- Bacterial killing by neutrophils and β-defensins requires a normal chloride concentration.
- The chloride content of epithelial secretions is high in cystic fibrosis.
- Disease largely found in those of Northern European ancestry.

Cystic fibrosis

- Associated abnormalities in cystic fibrosis:
- Transforming growth factor-beta is a potent suppressor of T cell activation.
- Deficiency in mannose-binding lectin
- Important component of complement system
- Poor phagocytosis
- Increases the risk for pyogenic infections.

Pancreatic cysts

- Often incidental findings
- Result from anomalous development of ducts
- 77% of patients with Von Lindau-Hippel disease
- 10% of patients with polycystic disease
- BUT, 5-10% of pancreatic cysts are neoplastic

Serous cystadenoma

- Predominant pancreatic cyst
- 90% women
- mean age at presentation of 70 years
- Not connected to pancreatic ductal system
- Predominantly in the tail of the pancreas
- Gross pathology:
- Encapsulated
- Central scar and calcification
- Histopathology:
- Glycogen rich cuboidal cells line cyst
- Surgical resection curative

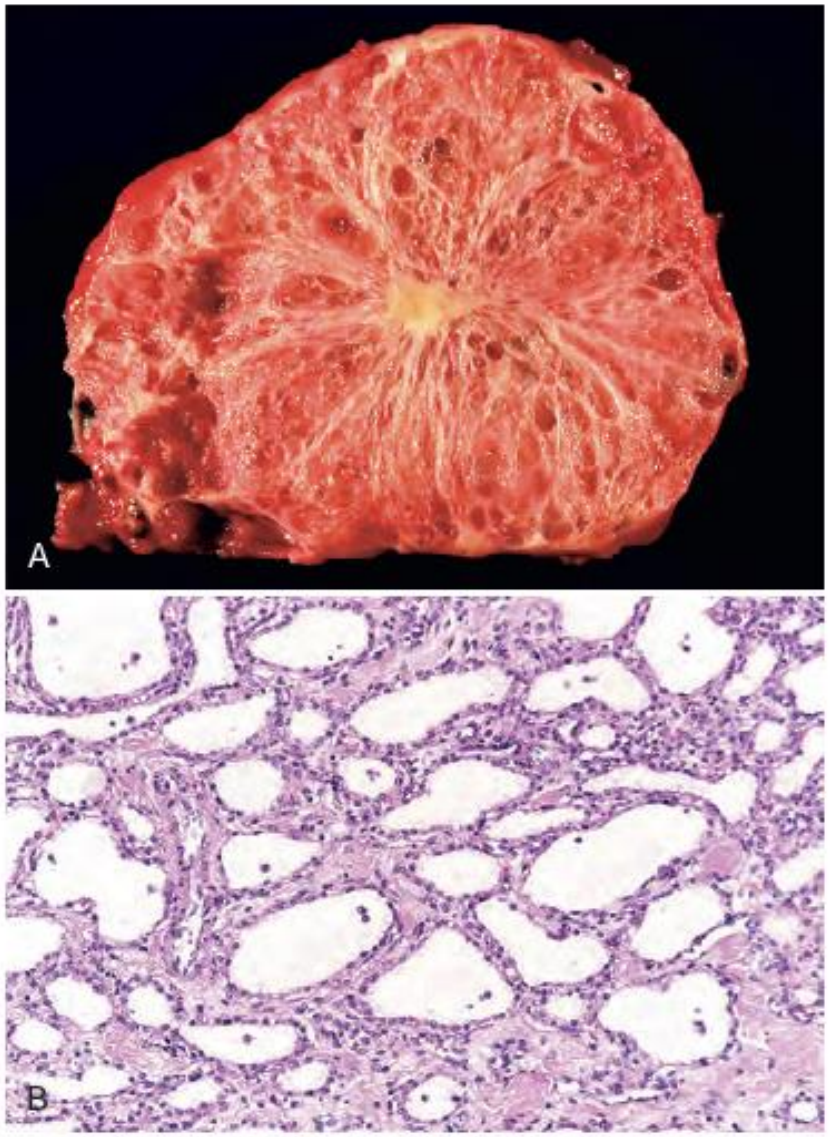


Figure 19-8 Serous cystic neoplasm (serous cystadenoma). **A,** Cross-section through a serous cystic neoplasm. Only a thin rim of normal pancreatic parenchyma remains. The cysts are relatively small and contain clear, straw-colored fluid. **B,** The cysts are lined by cuboidal epithelium without atypia.

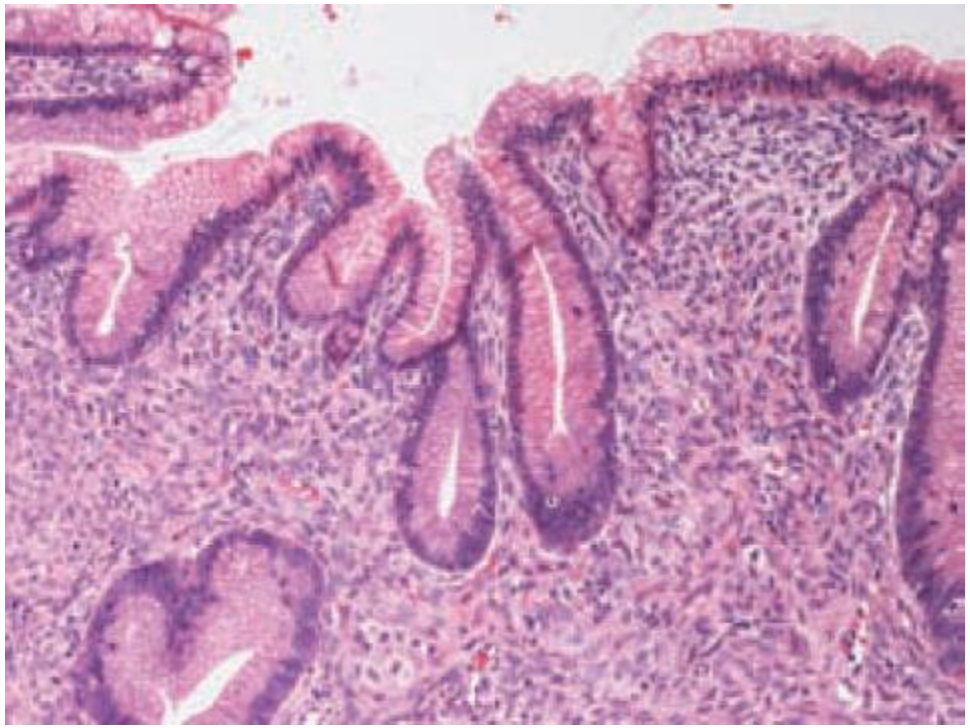
Mucinous cystic neoplasm

- 95% women
- Mean age of presentation 45 years old
- Not connected to pancreatic ductal system
- Predominantly in body and tail
- KRAS, TP53, RNF43 mutations
- Gross pathology:
- Encapsulated
- Calcification rare

Mucinous cystic neoplasm

- Histopathology:
- Lined by mucin producing columnar cells in an ovarian type stroma
- Stain for estrogen, progesterone, HCG
- High levels of CEA in cyst
- Do not recur after resection
- One-third of resected specimens contain invasive adenocarcinoma

Mucinous cystic neoplasm



There is an inner epithelial layer and an outer densely cellular “ovarian-like” stromal layer .The mucin-producing epithelium exhibits a spectrum of differentiation, ranging from histologically benign appearing columnar epithelium to severely atypical epithelium.

https://basicmedicalkey.com/mucinous-cystic-neoplasms-2/#Sec4 Accessed 01/20/2020

Solid pseudo-papillary neoplasm

- 90% women
- Mean age at presentation 30 years
- Gross pathology:
- Not encapsulated
- No calcification
- Connected to pancreatic ductal system
- Found in the head of pancreas
- β-catenin /APC pathway altered
- Locally aggressive
- Resection curative

Pancreatic ductal adenocarcinoma

- Four subtypes
- Stable
- 20%
- ≤ 50 structural variation events
- Widespread aneuploidy

Pancreatic ductal adenocarcinoma

- Locally rearranged
- 30%
- Focal event on one or two chromosomes
- Two subtypes
- Focal regions of gain/amplification
- ERBB2, MET, FGFR1, CDK6, PIK3R3 and PIK3CA
- Complex genomic rearrangements
- Broken-fusion-bridge
- Chromothripsis
- TP53 mutations common

Pancreatic ductal adenocarcinoma

- Scattered
- 36%
- Non-random chromosomal damage and <200 structural variation events
- Unstable
- 14%
- >200 structural variation events
- 50% have BRCA or PALB mutations

Intraductal papillary mucinous neoplasms

- Main duct lesion presents as acute pancreatitis
- 2/3 occur in head of pancreas
- More common in men
- 65-70 years of age
- Diffuse or segmental enlargement of pancreatic duct noted on imaging studies
- A branch duct lesion is asymptomatic
- Identified incidentally on CT
- Multilocular, grape-like appearance
- Mixed main duct and branch lesions (multifocal) behave as main duct lesions

Intraductal papillary mucinous neoplasm

- Gross pathology:
- Not encapsulated
- Histopathology:
- Lack ovarian-type stroma
- High levels of CEA and amylase in cyst
- Gastric, intestinal, pancreatobiliary types
- GNAS, KRAS, TP53, SMAD4, RNF43 mutations

Intraductal papillary mucinous neoplasm

- Gastric type
- Most common type
- Usually found in uncinate process.
- Arise in a branched duct
- Papillae lined by epithelial cells resembling gastric foveolar cells
- Pyloric gland-like structures found at base of papillae.
- 30% malignant

Intraductal papillary mucinous neoplasm

- MUC5 and MUC6 consistently expressed.
- Invasive pattern is that of a tubular carcinoma.
- Prognosis comparable to that of intestinal type.
- CDKN2a gene hypermethylation correlates with clinical stage

Intraductal papillary mucinous neoplasm

- Intestinal type
- Arise in a main duct
- Show a villous growth
- Expresses MUC2, MUC5, but not MUC1
- Invasive pattern is that of a colloid carcinoma

Intraductal papillary mucinous neoplasm

- Pancreatobiliary type shows arborizing papillae.
- Arise in main duct
- Only expresses MUC1 and MUC5.
- 70% malignant
- Invasive pattern is that of a tubular carcinoma
- Poorer prognosis than intestinal type.

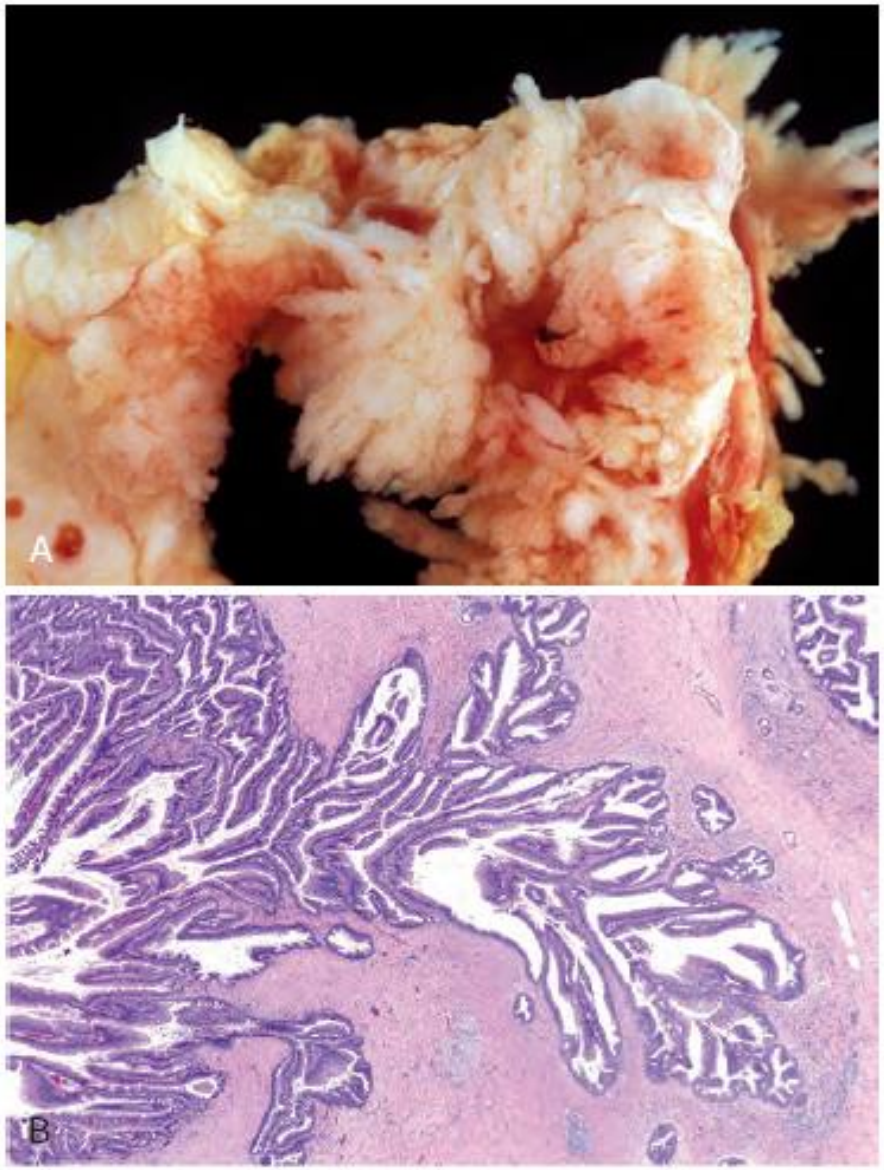
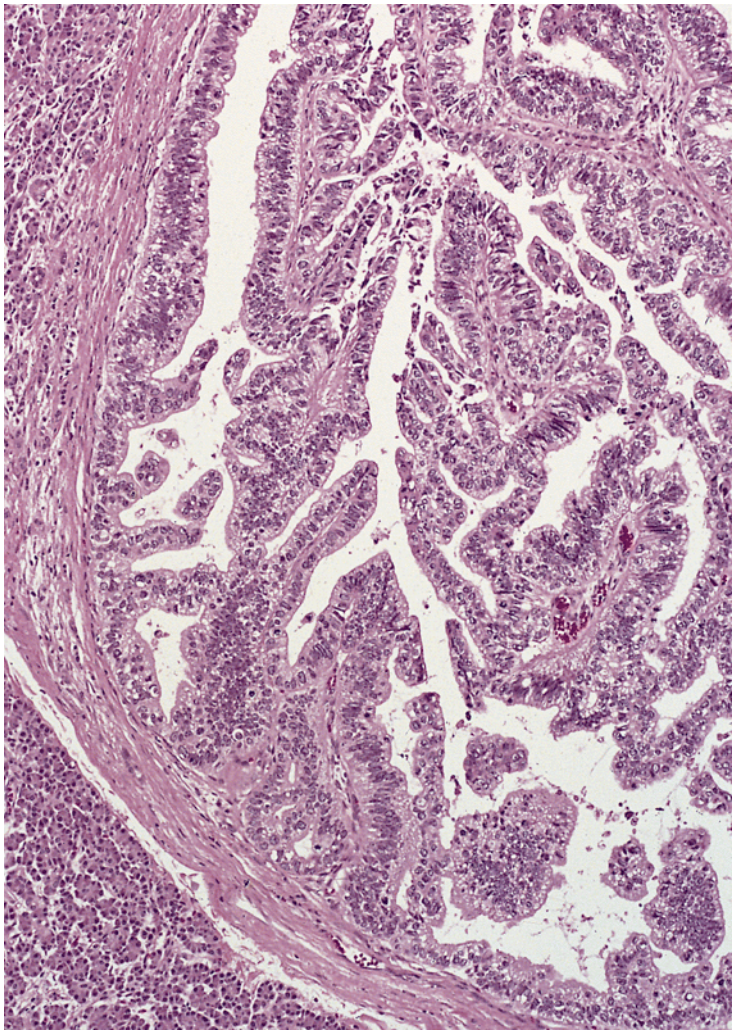


Figure 19-10 Intraductal papillary mucinous neoplasm. **A,** Cross-section through the head of the pancreas showing a prominent papillary neoplasm distending the main pancreatic duct. **B,** The neoplasm involves the main pancreatic duct *(left)* and extends down into the smaller ducts and ductules *(right)*.

Intraductal papillary tumor



Cross section through the main pancreatic duct which is filled with epithelial papillary proliferations.

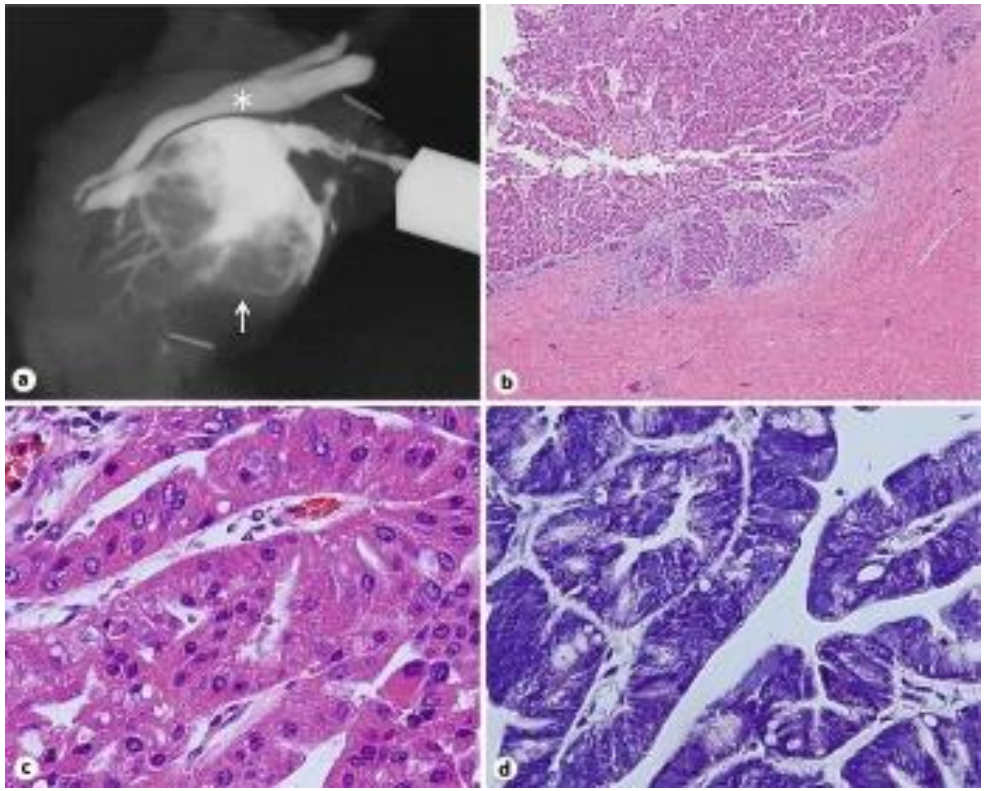
Fig. 4-33

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Intraductal oncocytic papillary neoplasm

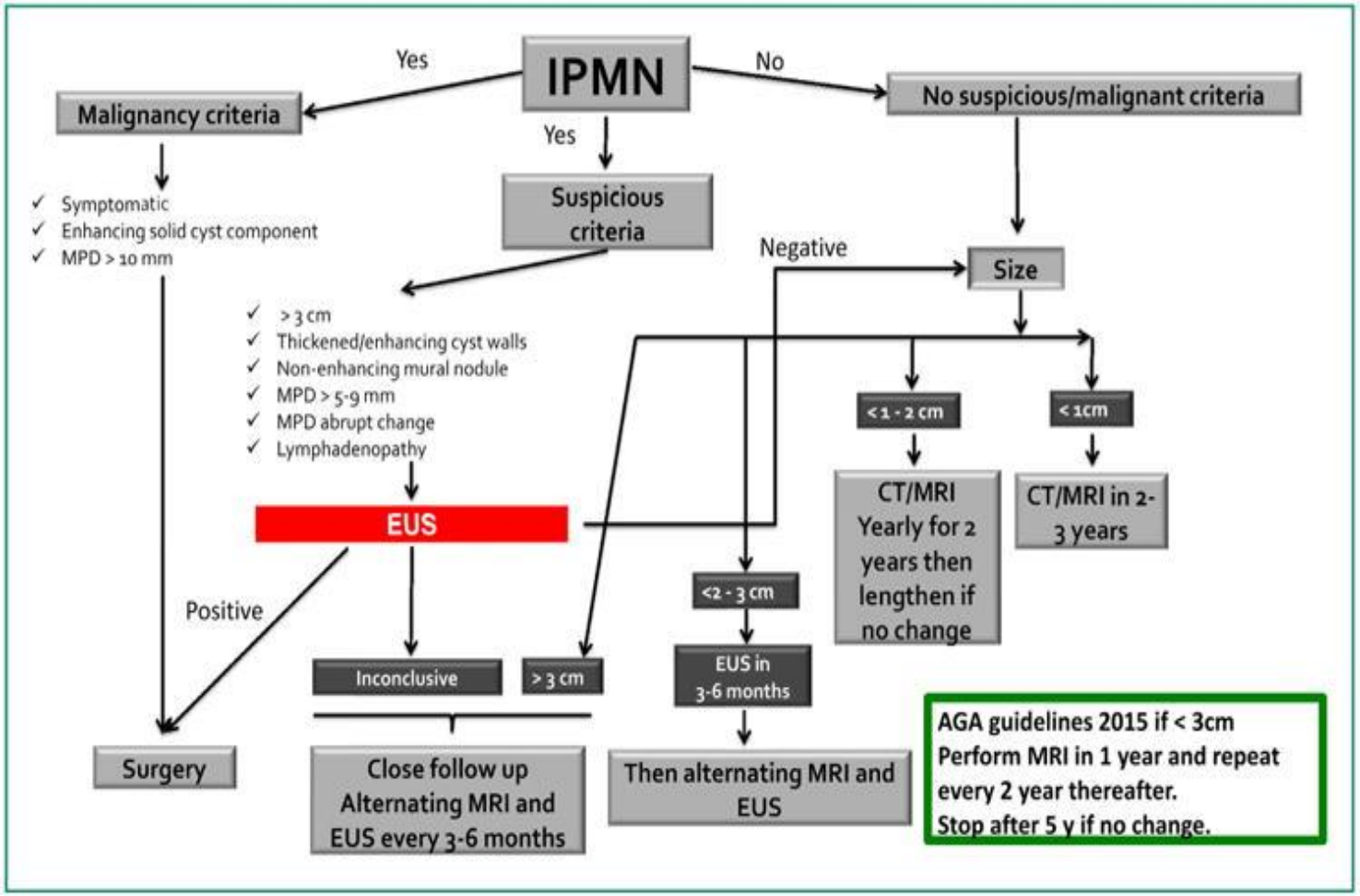
- Oncocytic type often forms large nodules in the main pancreatic duct.
- Arise in main duct
- Mean age 62 years
- Histology:
- Mucin filled cysts with nodular papillary projections
- Complex papillae with oncocytic lining
- Main cyst contains goblet cells.
- MUC1, MUC2, and MUC5AC expressed focally
- No Kras mutation

IOPN



There is a localized cystic dilatation of the main pancreatic duct with luminal filling defects (arrow). The common bile duct is observed above the cystic lesion (asterisk). **b** A papillary mural nodule is recognized in the cyst with minimally invasive growth (HE stain, ×40). **c** The tumor cells have an abundant cytoplasm with eosinophilic granules. Nuclei are oval with increased chromatin and a large nucleolus by high-power magnification (HE stain, ×400). **d** PTAH stain demonstrates dense blue cytoplasmic granularity (×200).

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398090/figure/F4/
Accessed 01/20/2020



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5546617/figure/F5/
Accessed 01/20/2020

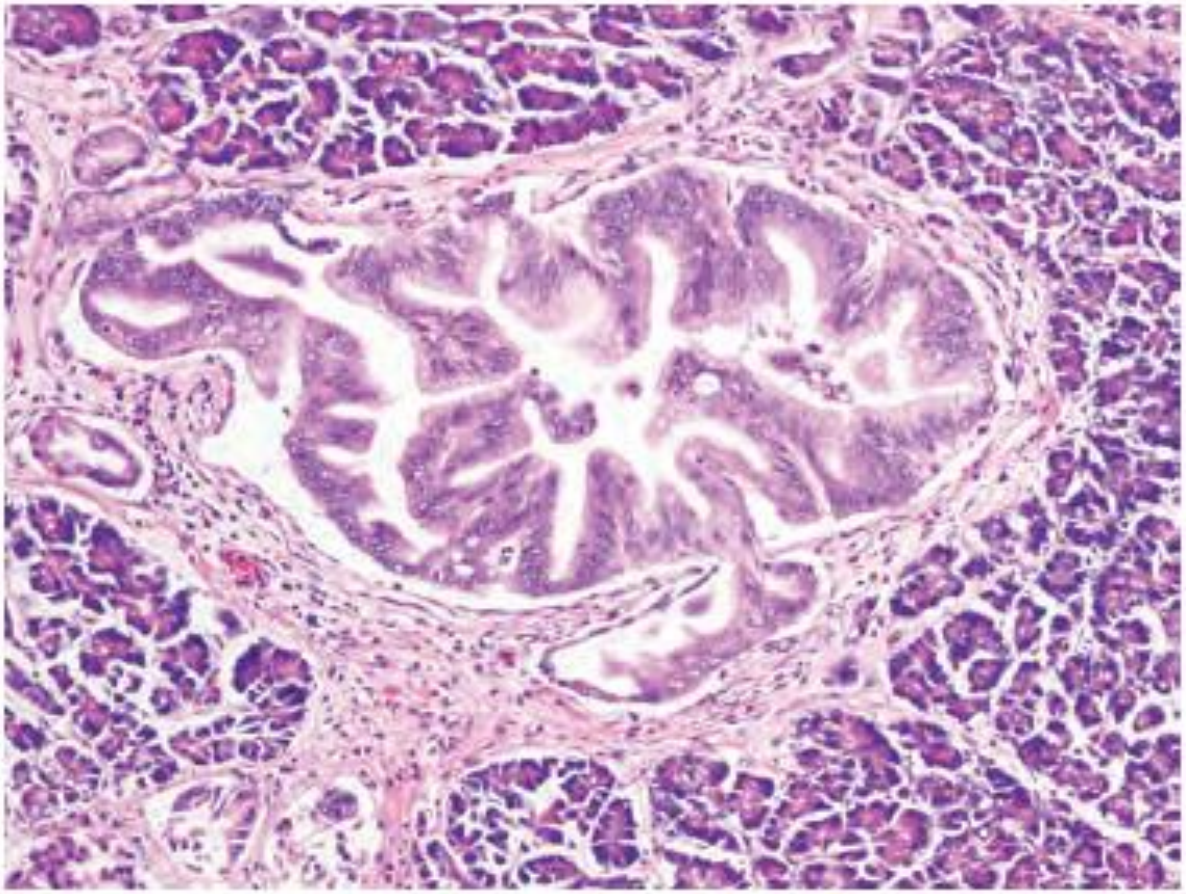


Figure 19-11 Pancreatic intraepithelial neoplasia grade 3 (PanIN-3) involving a small pancreatic duct.

Environmental, genetic and lifestyle factors associated with pancreatic cancer risk

FACTORS	INCREASES RISK	DECREASES RISK
Tobacco smoking	Risk increased with intensity (cigarettes/day) and duration	
Body fatness	Body mass index, waist circumference, adult weight gain	
Dietary factors		
limited–suggestive evidence:	Red meat, processed meat, alcoholic drinks (heavier drinking), foods and beverages containing fructose, foods containing saturated fatty acids	
unlikely effect on risk:		Coffee
limited–no conclusion:		Fruits, folate, physical activity
Other diseases	Diabetes, chronic inflammatory pancreatitis	
Occupational exposures (probable risk associated with heavy exposure at work of some chemicals)	Chlorinated hydrocarbons, solvents, pesticides, polycyclic aromatic hydrocarbons, nitrosamines	
Other	Blood type A, B or AB (as compared with O type)	
Genes with susceptibility loci	ABO, KLF, LINC, TERT, CLPTM1L, NR5A2, BCAR1, PDX1, ETAA1, ZNRF3, SUGCT, TP63, HNF1A	

Pancreatic carcinoma

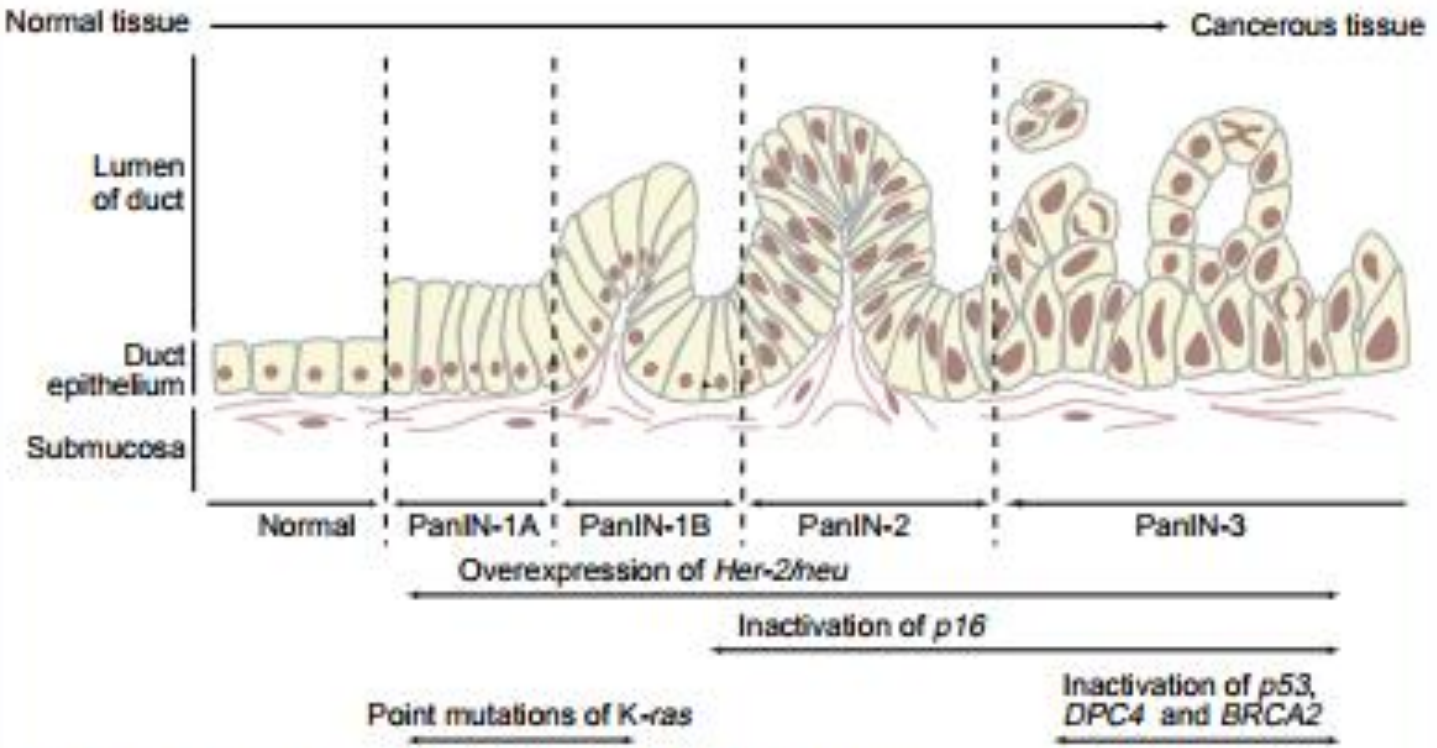
- Arise in Ductular epithelium
- 80% K-ras activated
- 95% p16 deactivated (CDKN2A).
- Mutation generally occurs in individuals from melanoma-prone families.
- 55% inactivated SMAD4 (18q21.2).
- Affects signal transduction from TGF-β family of cell surface receptors.
- A late occurrence is inactivation of p53.
- 75% of tumors

Pancreatic carcinoma

- BRCA2 mutation is a late occurrence and found in 10% of pancreatic cancers from Ashkenazi.
- Accumulation of multiple mutations more important than temporal sequence

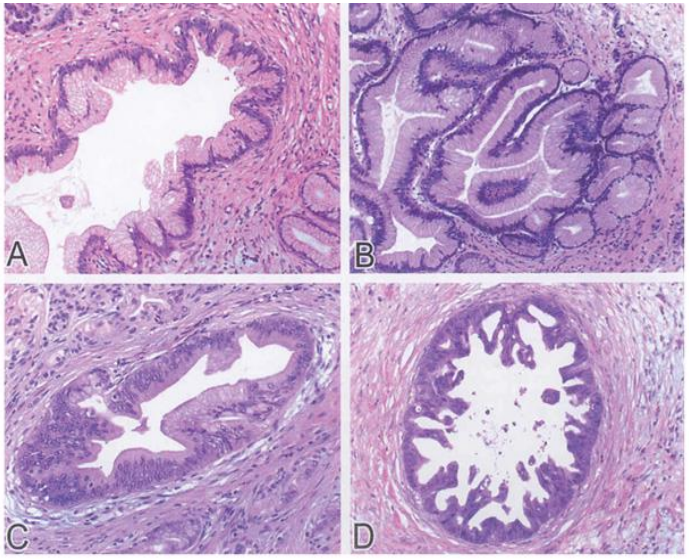
Pancreatic carcinoma

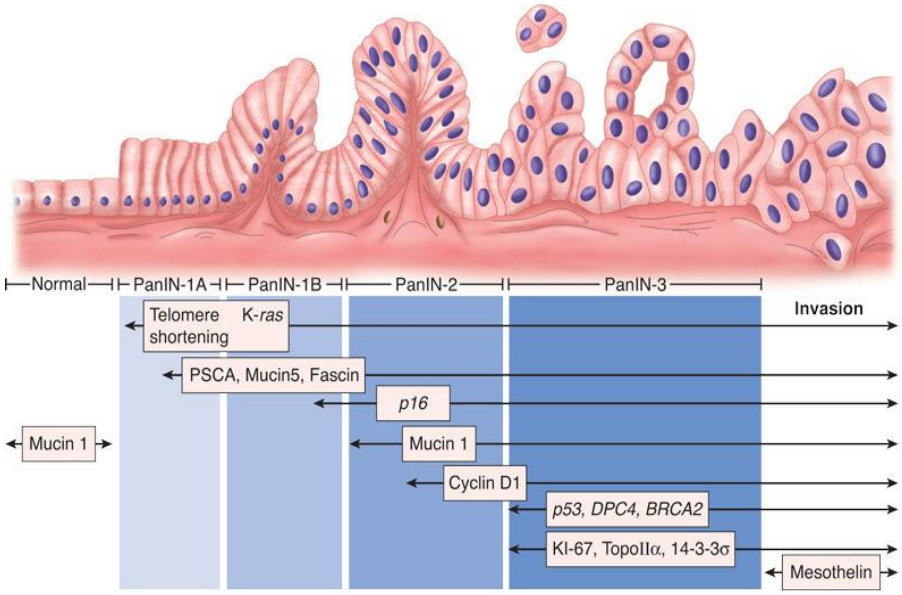
- 40%–80% have activating mutations in GNAS
- More than 50% have inactivation of RNF43 (an antagonist of WNT signaling).
- The pancreatic adenocarcinoma genome is also characterized by diverse, large-scale chromosomal changes with frequent amplifications, deletions and rearrangements.
- Accumulation of multiple mutations more important than temporal sequence



The genetic progression of pancreatic carcinoma

Oncogenesis





(From Hruban RH, Takaori K, Klimstra DS, et al: An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 28:977, 2004.)

Fig. 33-67 Accessed 02/01/2010

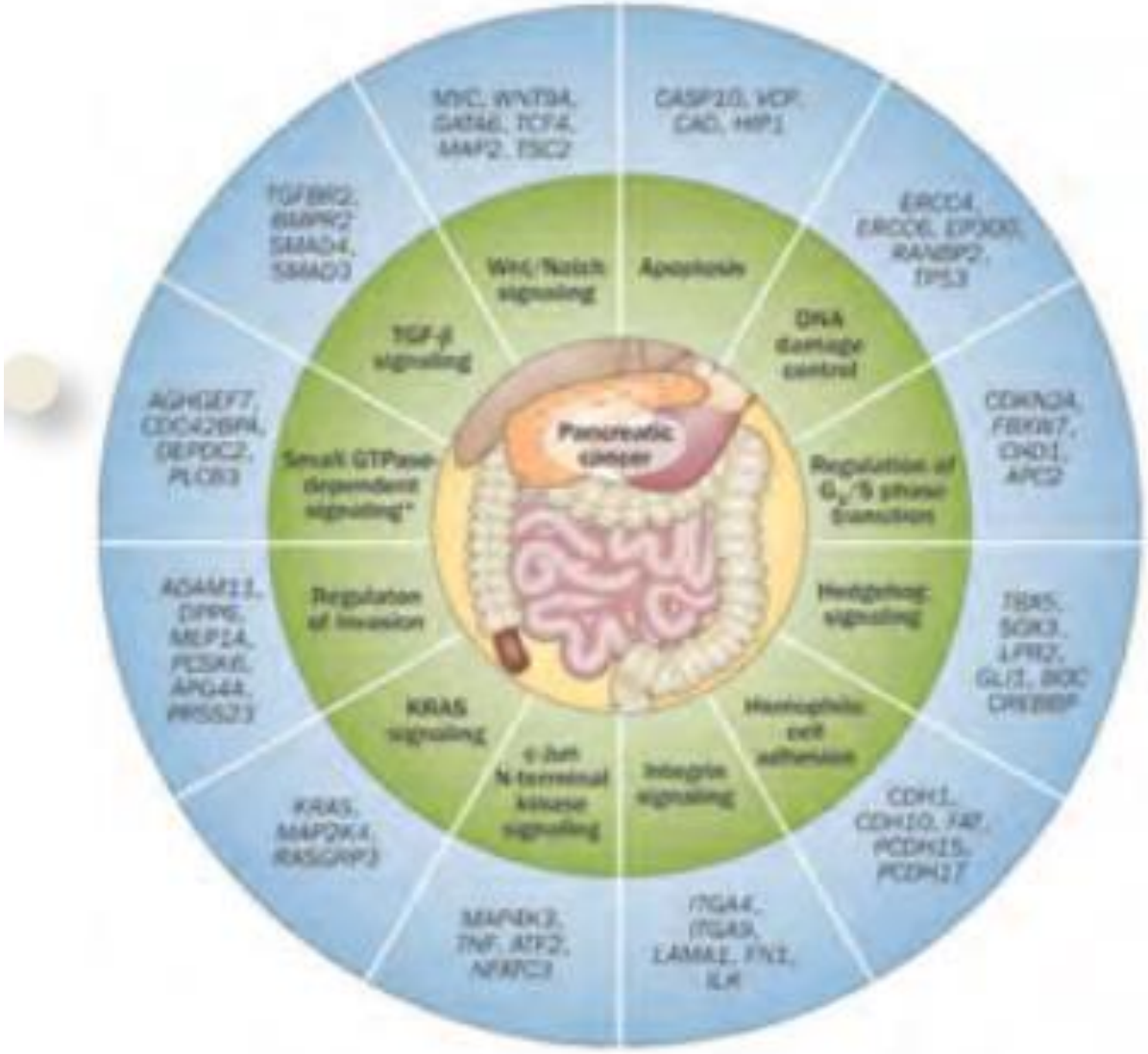

Pancreatic cancer
Wnt/Notch signaling
Apoptosis
DNA damage control
Regulation of G1/S phase transition
Hedgehog signaling
Homophilic cell adhesion
Integrin signaling
c-Jun N-terminal kinase signaling
KRAS signaling
Regulation of invasion
Smad4 GTPase-dependent signaling*
TGF-β signaling
MYC, WNT5A, GATA6, TCF4, MAP2, TSC2
CASP10, VCP, CAD, HIP1
ERCC4, ERCC6, EP300, RANBP2, TP53
CDKN2A, FBXW7, CHD1, APC2
TBX5, SOX3, LFR2, GLI3, BOC CREBBP
CDH1, CDH10, FAT, PCDH15, PCDH17
ITGA4, ITGA9, LAMA1, FN1, ILK
MAPKK3, TNF, ATF2, NFATC3
KRAS, MAP2K4, RASGRP3
ADAM12, DPP6, MEP1A, PCSK6, APG4A, PRSS23
AGHGEF7, CDC42BPA, DEPDC2, PLCB3
TGFBR2, BMPR2, SMAD4, SMAD3

Table 19-3 Somatic Molecular Alterations in Invasive Pancreatic Adenocarcinoma

Gene	Chromosomal Region	Percentage of Carcinoma with Genetic Alteration	Gene Function
Oncogenes			
KRAS	12p	90	Growth factor signal transducer
AKT2	19q	10-20	Growth factor signal transducer
MYB	6q	10	Transcription factor
NCOA3/AIB1	20q	10	Chromatin regulator
MAP2K4/MKK4	17p	5	Growth factor signal transducer
Tumor Suppressor and DNA Repair Genes			
p16/CDKN2A	9p	95	Negative cell-cycle regulator
TP53	17p	50-70	Response to DNA damage
SMAD4	18q	55	TGFβ pathway
GATA-6	18q	10	Transcription factor
RB	13q	5	Negative cell-cycle regulator
STK11	19p	5	Regulation of cellular metabolism
ATM	11q	5	DNA damage response
ARID1A	1p	4	Chromatin regulator
TGFBR1	9q	2	TGFβ pathway
TGFBR2	3p	2	TGFβ pathway

Pancreatic carcinoma

- Tobacco use and chronic pancreatitis predispose
- More frequent in Blacks.
- 60-80 years of age
- 60%, head; 15%, body; 5%, tail
- 5%, squamous carcinoma
- Often grow along nerves and invade retroperitoneum
- Very elevated CA 19-9 specific for pancreatic carcinoma.
- 10% have migratory thrombophlebitis
- Most common metastasis to pancreas is from renal cancer

Table 19-4 Inherited Predisposition to Pancreatic Cancer

Disorder	Gene	Increased Risk of Pancreatic Cancer (Fold)	Risk of Pancreatic Cancer by Age 70 (%)
Peutz-Jeghers syndrome	*STK11*	130	30-60
Hereditary pancreatitis	*PRSS1, SPINK1*	50-80	25-40
Familial atypical multiple-mole melanoma syndrome	*CDKN2A*	20-35	10-17
Strong family history (3 or more relatives with pancreatic cancer)	Unknown	14-32	8-16
Hereditary breast and ovarian cancer	Multiple, including *BRCA1, BRCA2, PALP2, BRCA2*	4-10	5
Hereditary non-polyposis colorectal cancer (HNPCC)	Multiple, including *MLH1, MSH2* (2p21)	8-10	4

Histopathology

- Hard, stellate, gray-white, poorly defined masses
- The vast majority are ductal adenocarcinomas that recapitulate to some degree normal ductal epithelium by forming glands and secreting mucin.
- Less differentiated tumors have abortive tubular structures and cell clusters
- Two features are characteristic of pancreatic cancer:
- Highly invasive
- Elicits an intense host reaction in the form of dense fibrosis (“desmoplastic response”)
- Perineural invasion is common

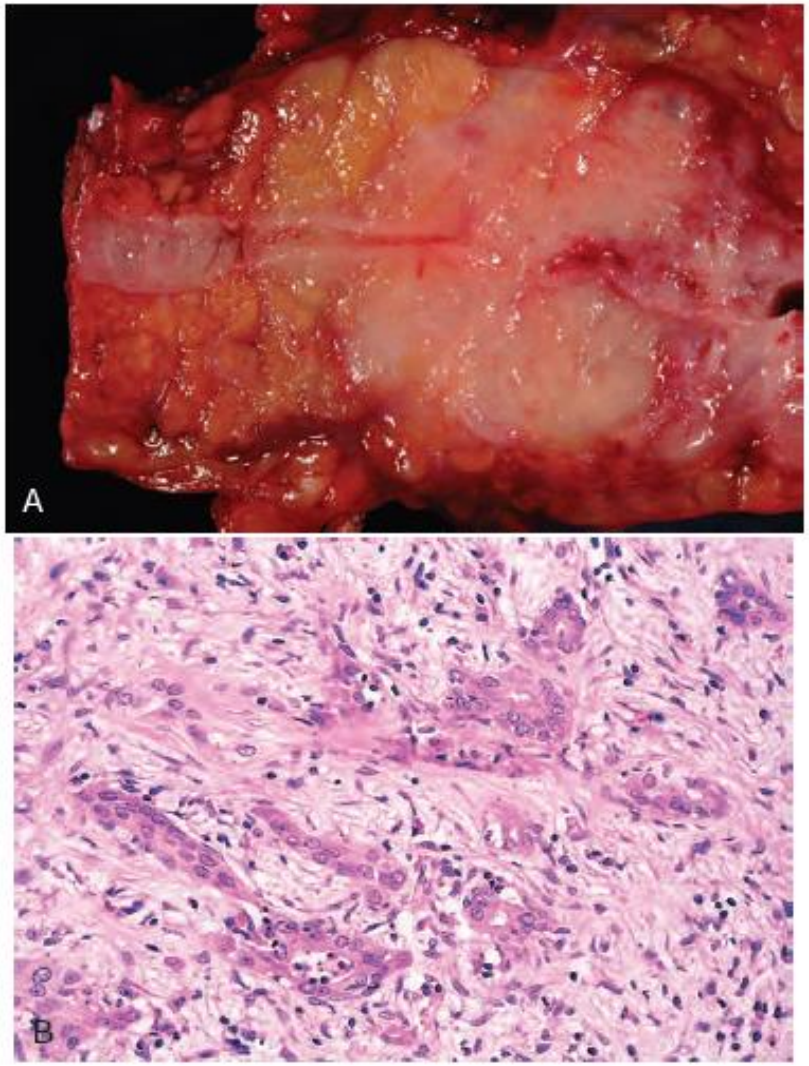
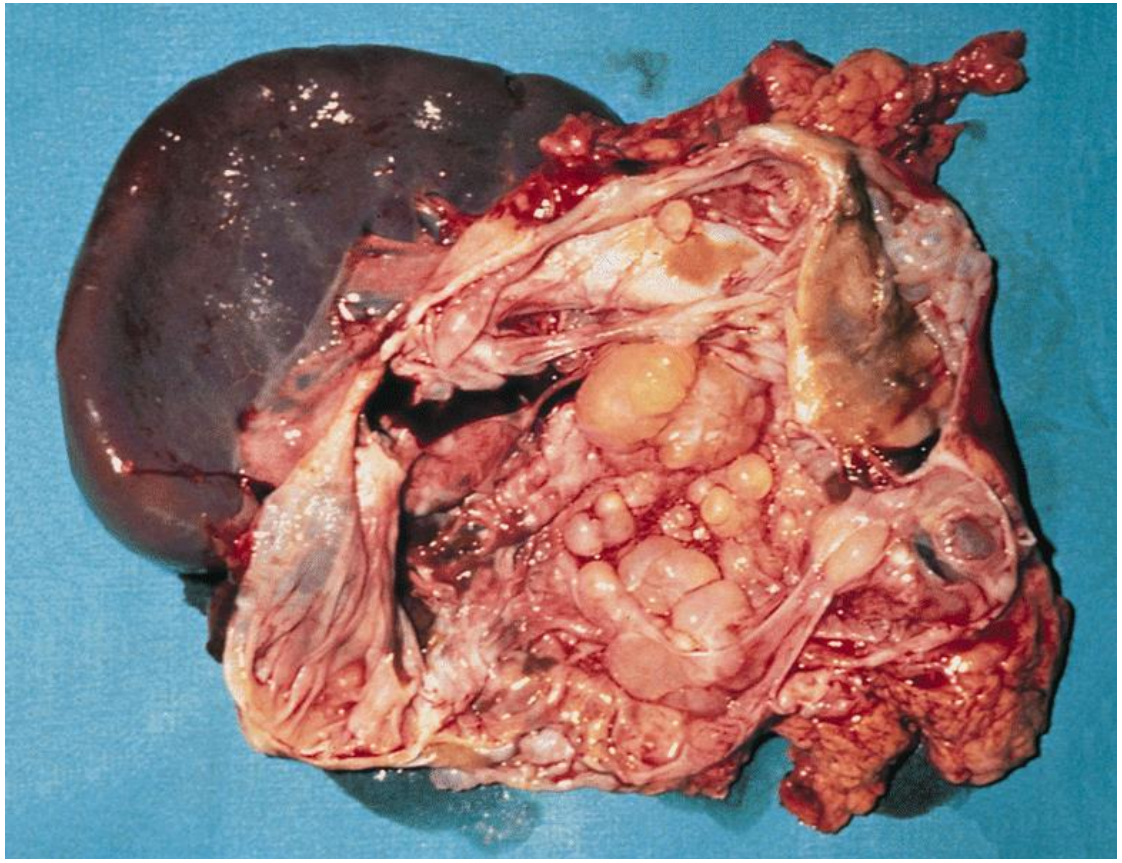


Figure 19-13 Carcinoma of the pancreas. **A,** A cross-section through the tail of the pancreas showing normal pancreatic parenchyma and a normal pancreatic duct *(left)*, an ill-defined mass in the pancreatic substance *(center)* with narrowing of the pancreatic duct, and dilatation of the pancreatic duct upstream *(right)* from the mass. **B,** Poorly formed glands are present in densely fibrotic stroma within the pancreatic substance; some inflammatory cells are also present.

Mucinous cyst adenocarcinoma

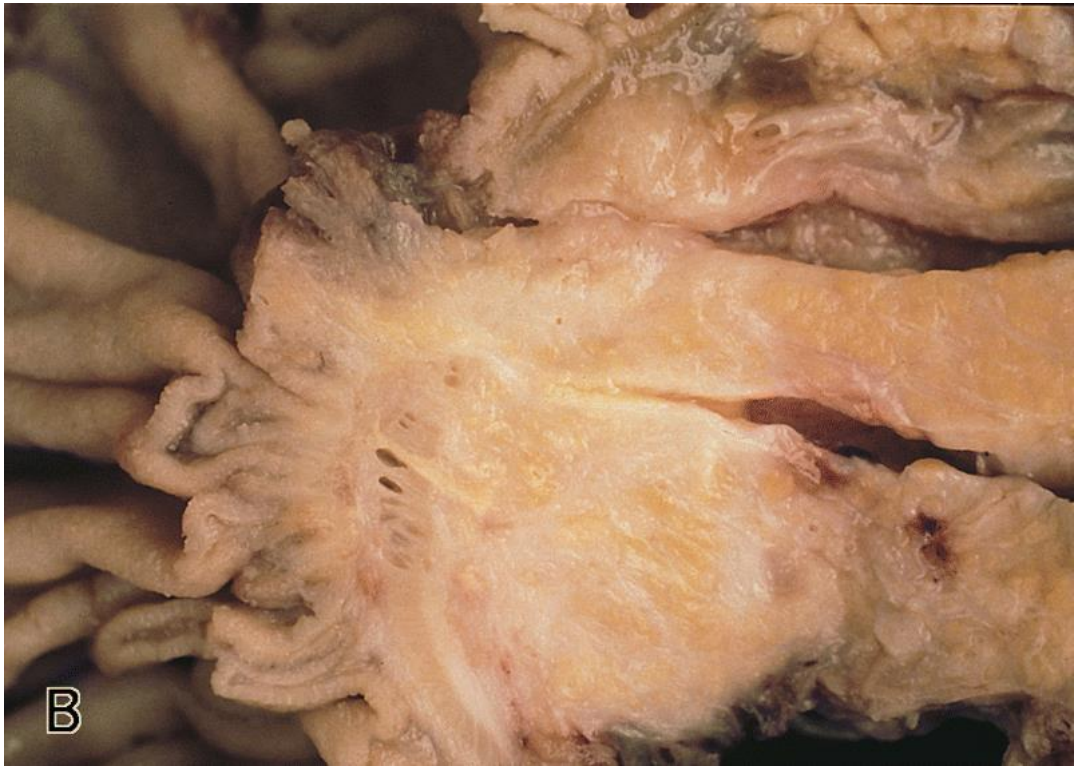


Tumor from the tail of the pancreas with adjacent spleen. The cut surface shows conspicuous, irregular, solid protuberances projecting into cystic cavities.

Fig. 4-14

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Ductal adenocarcinoma

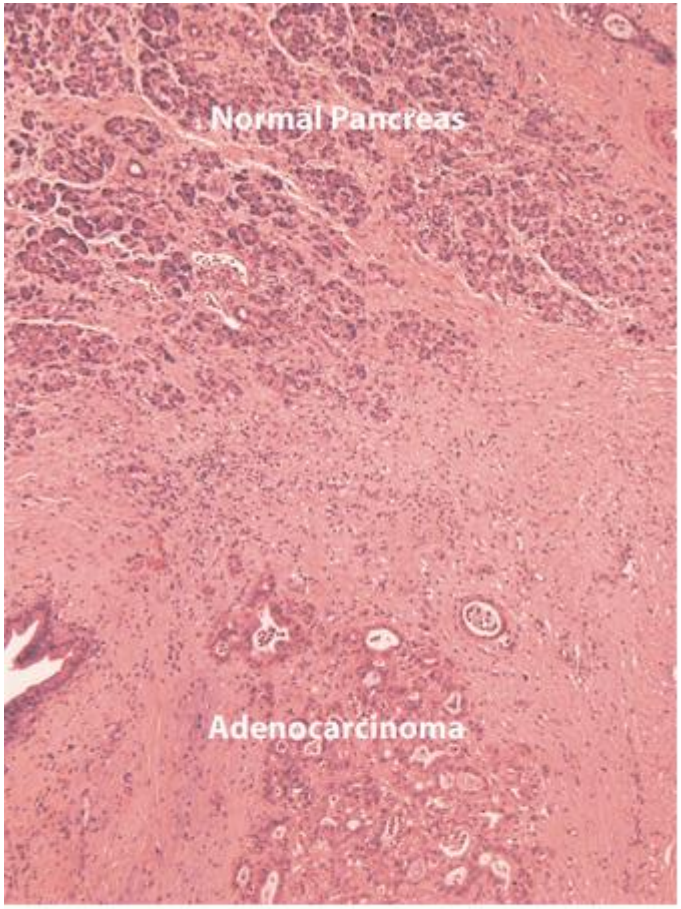


Whipple resection specimen showing a ductal adenocarcinoma with invasion of the ampulla and the duodenal wall, obstructing the common bile duct as well as the pancreatic duct. Note the ill-defined tumor demarcation.

Fig. 4-43B

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

Ductular pancreatic adenocarcinoma

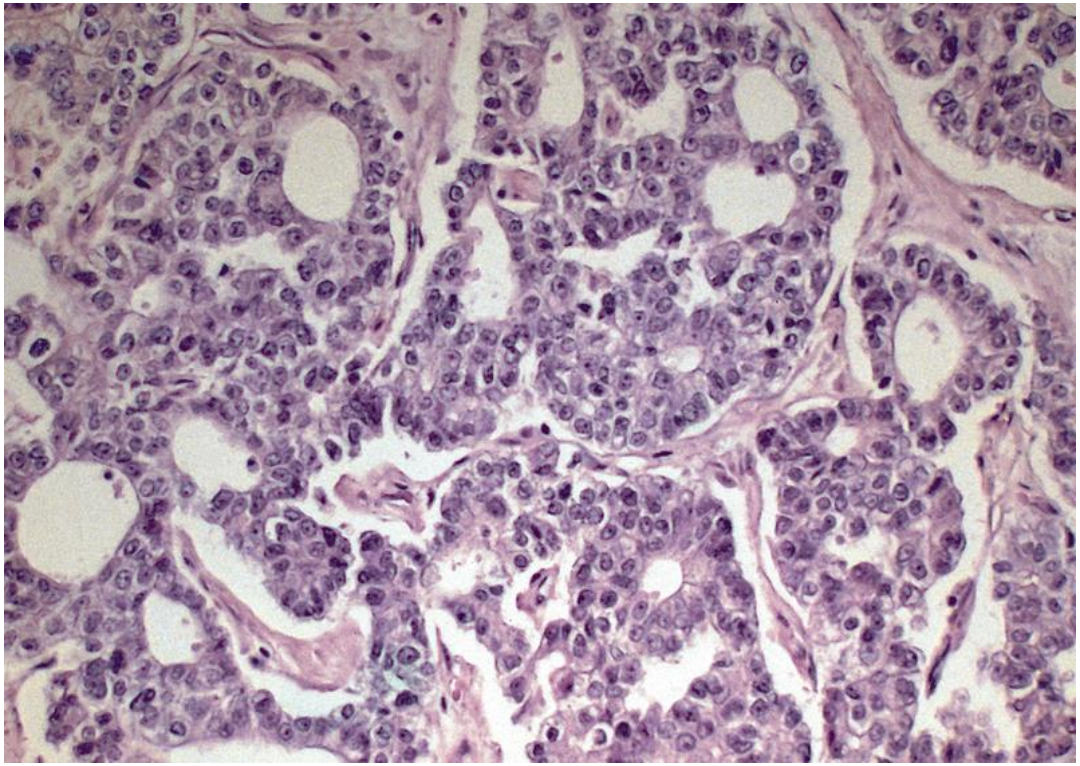


Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Photomicrograph of ductal adenocarcinoma of the pancreas with well-preserved islet cells and pancreatic architecture above and infiltrating tumor with poorly formed glandular structures below.

Fig. 15-1 Accessed 04/10/10

Acinar cell carcinoma

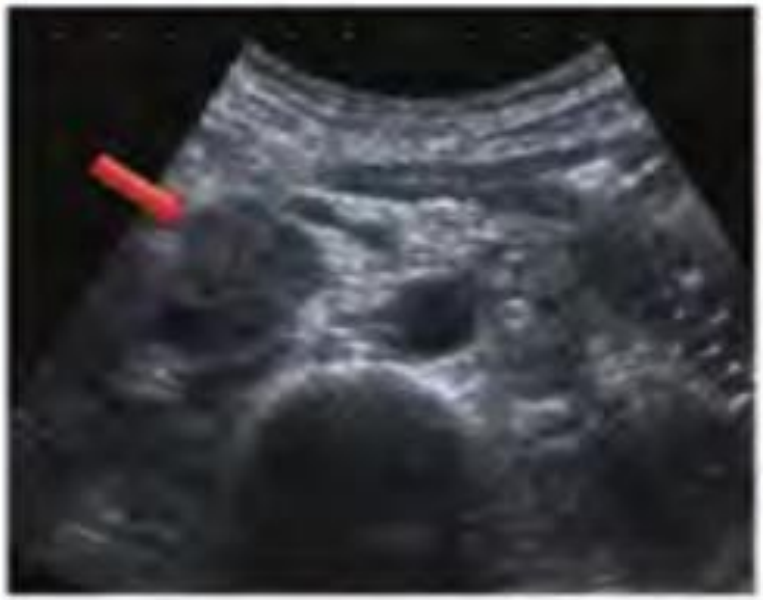


This tumor shows a pure acinar pattern, reminiscent of normal pancreatic acinar tissue.

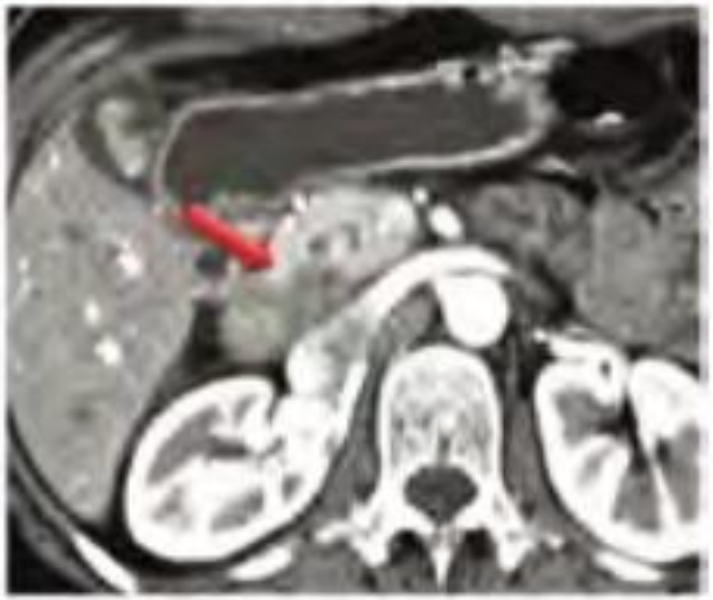
15%, metastatic fat necrosis as a result of release of lipase into the circulation.

Fig. 4-94B

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.



Hypoechoic mass, deforming gland contour with common bile duct (CBD) and dilatation



Hypoattenuation solid mass due to desmoplastic fibrotic component

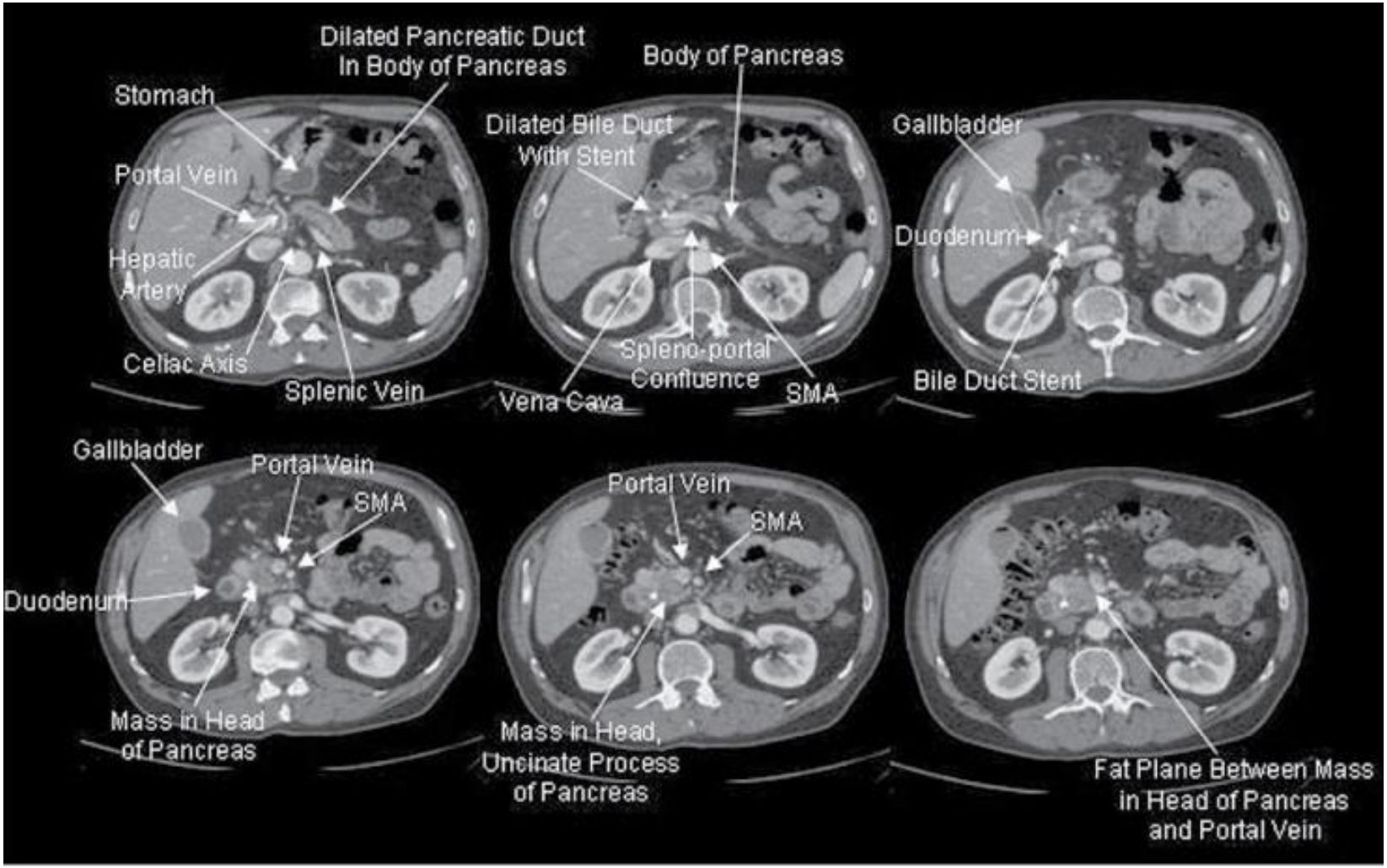
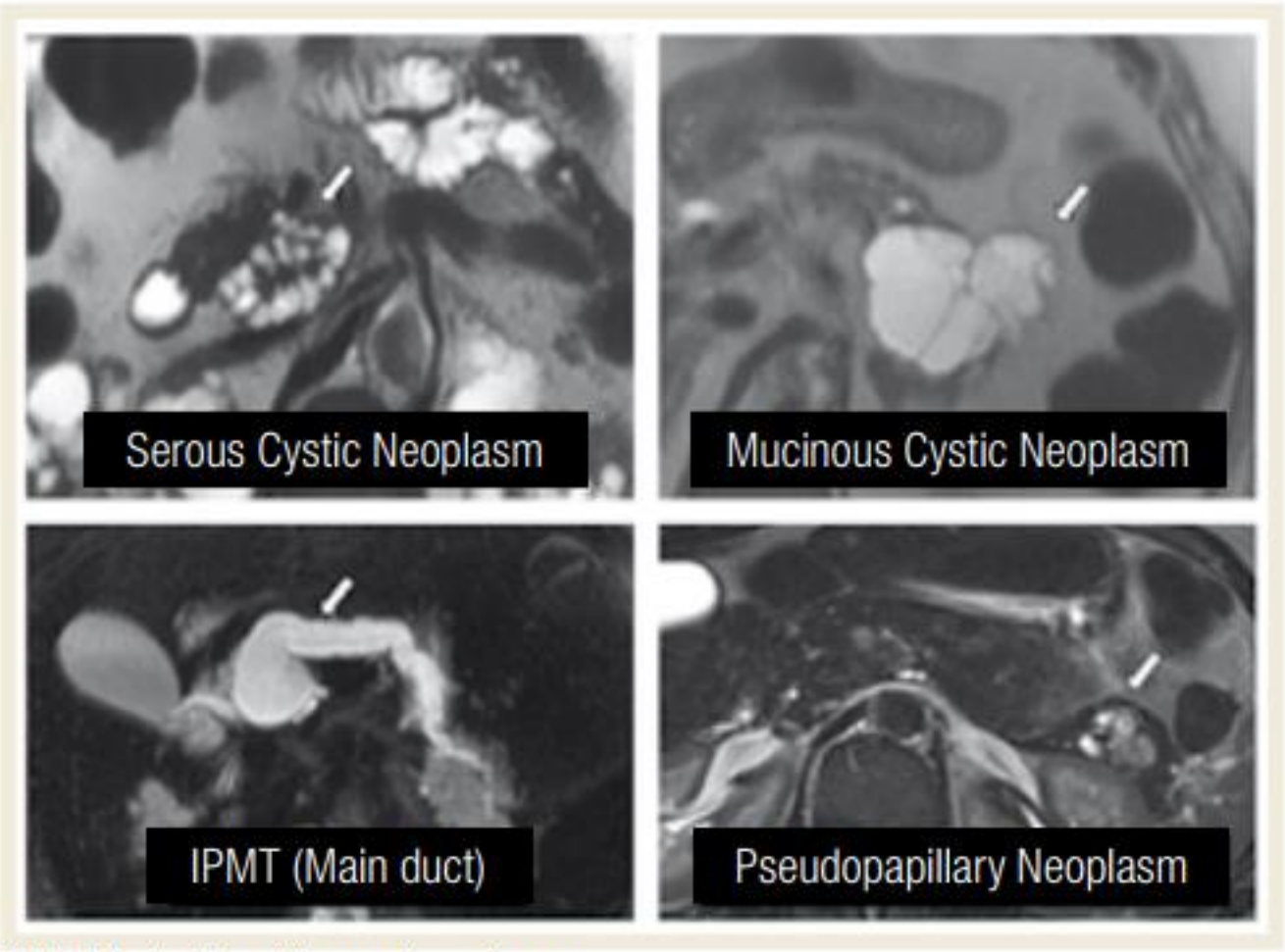


Fig. 33-68 Accessed 02/01/2010



IPMT, Intraductal papillary mucinous tumour.

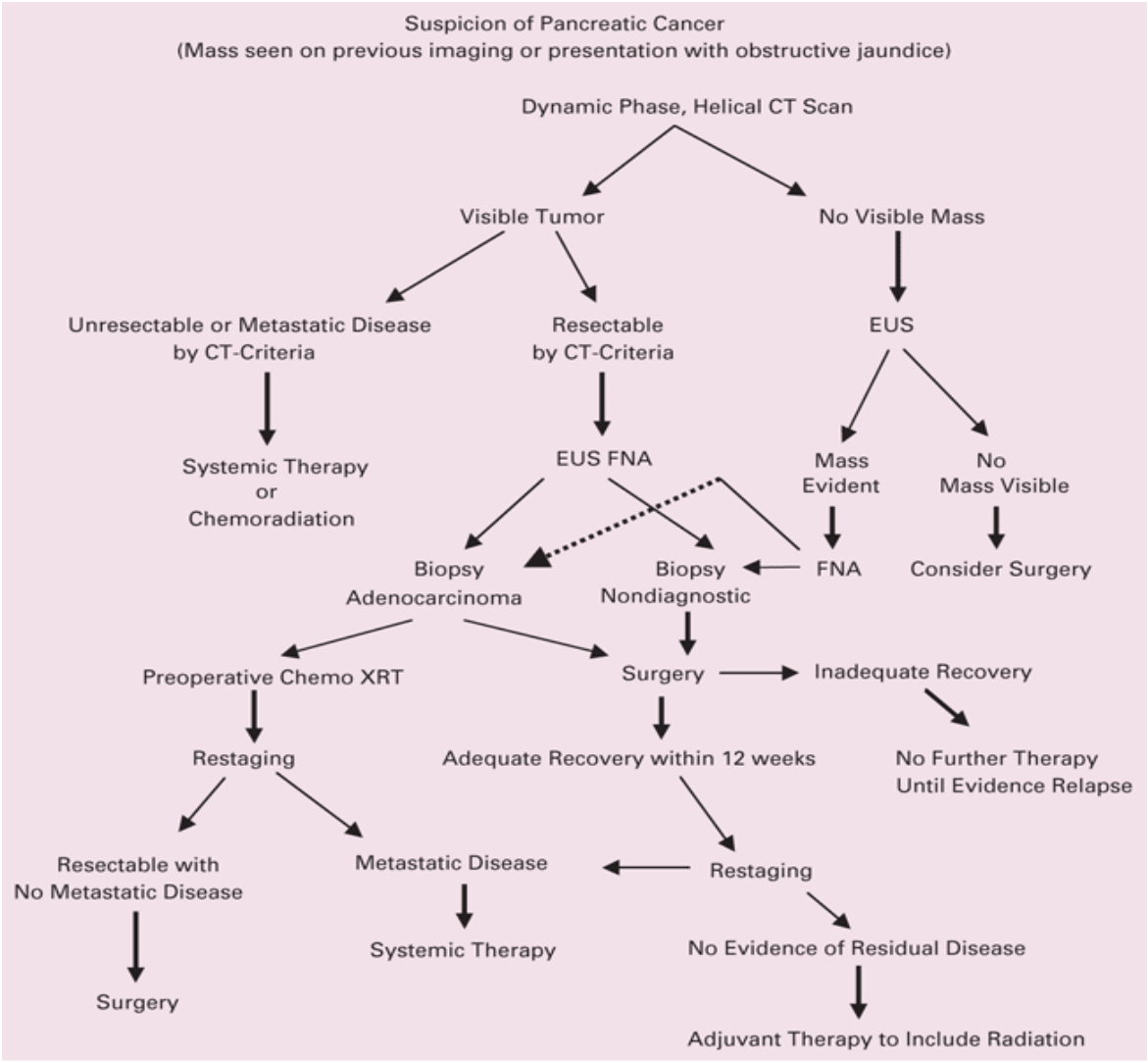
Pancreatic carcinoma

- Dual contrast, helical CT (3D reconstruction).
- 67% sensitive for lesions <1.5cm; nearly 100% sensitive for tumors >1.5cm.
- 95% positive predictive value in defining resectibility if major vessel tumor encasement is present.
- Endoscopic ultrasound.
- Tumor and nodal staging.
- Detection of portal vein invasion.
- Evaluate periampullary lesions.

Pancreatic carcinoma

- MRI represents the imaging modality of choice in the characterization of cystic pancreatic neoplasms.
- CT or MRI with magnetic resonance cholangiopancreatography (MRCP) is recommended to check for “high-risk stigmata” (enhanced solid component and main pancreatic duct [MPD] >10 mm), or “worrisome features” (cyst >3 cm, thickened enhanced walls, non-enhanced mural nodules, MPD size of 5–9 mm, abrupt change in the MPD caliber with distal pancreatic atrophy, and lymphadenopathy
- Fine needle aspiration for diagnosing tumor with minimal risk.

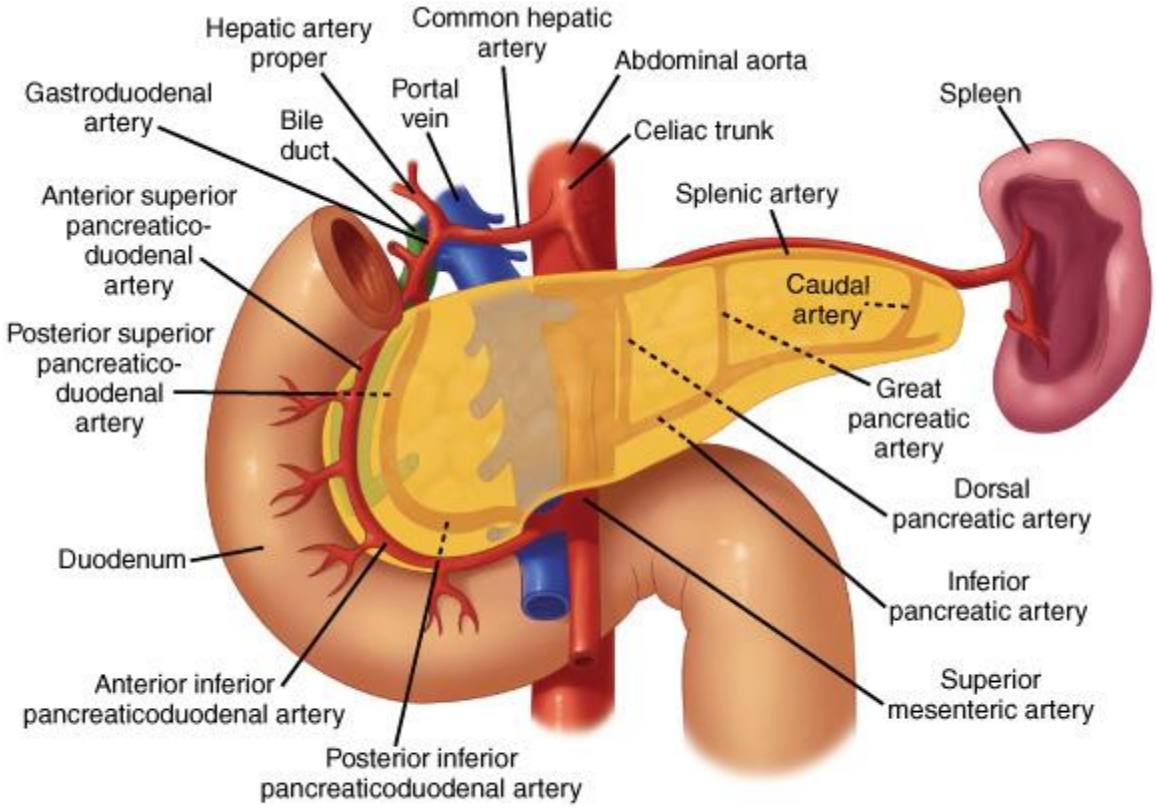
Strategy



Source: Kantarjian HM, Wolff RA, Koller CA: *MD Anderson Manual of Medical Oncology*: http://www.accessmedicine.com

Fig. 15-4 Accessed 04.10/10

Arterial supply to pancreas



Source: Brunicardi FC, Andersen DK, Billiar TR, Dunn DL, Hunter JG, Matthews JB, Pollock RE: *Schwartz's Principles of Surgery, 9th Edition:* http://www.accessmedicine.com

Fig. 33-4 Accessed 02/01/2010

Pancreatic carcinoma

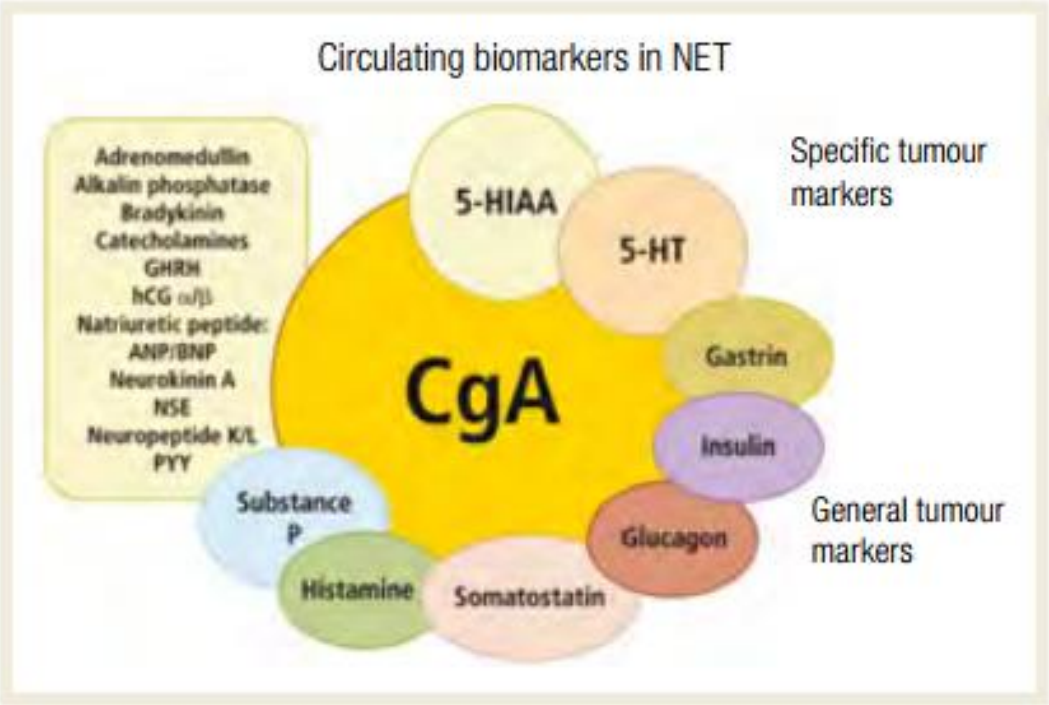
- Fewer than 10% have resectible disease at diagnosis.
- Confined to pancreas without encasement of celiac plexus or superior mesenteric artery and with patent portal vein.
- Borderline lesions abut but are not encased nor involve the short segment of the celiac artery.
- Reconstruction possible if hepatic artery involved but celiac artery is free of tumor.
- 70% will have local-regional recurrence following complete resection.

Pancreatic carcinoma

- 5 year survival following pylorus sparing Whipple procedure and chemoradiation is 17.5%.
- Locally advanced disease, 5 year survival is 6.0%; metastatic disease, 1.2%.
- 5-FU, irinotecan, oxaliplatin regimen leads to responses in 30% of patients with a median survival of 11 months.
- Gemcitabine for palliation (20% respond; median survival, 6 months).
- May have to block celiac plexus for pain control.
- Metal stent placement via endoscopy to relieve jaundice.

WHO Classifications of Neuroendocrine Neoplasms of the GEP System	
WHO 2000	**WHO 2010**
Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC)	Neuroendocrine tumours Grade 1 Grade 2
Poorly-differentiated endocrine carcinoma/small-cell carcinoma (PDEC)	Neuroendocrine carcinoma Grade 3
Mixed exocrine–endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

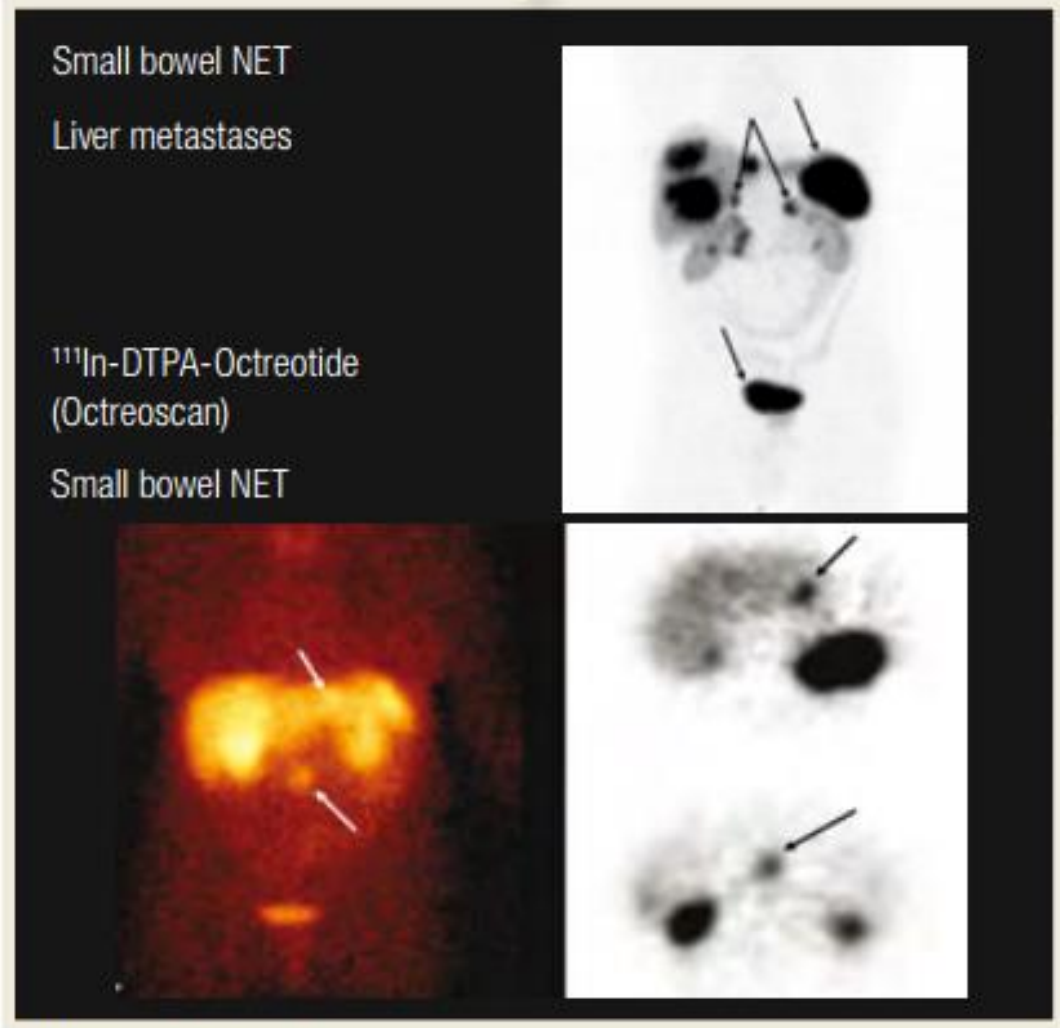
GEP, Gastroenteropancreatic; WHO, World Health Organisation.



5-HIAA, 5-Hydroxy-3-indoleacetic acid; 5-HT, serotonin; ANP/BNP, atrial natriuretic peptide and brain/ventricular natriuretic peptide; GHRH, gonadotropin hormone releasing hormone; hCG, human chorionic gonadotropin; NSE, neurone-specific enolase; PYY, peptide YY.

Imaging of Neuroendocrine Tumours: Techniques	
Morphological	**Functional**
Ultrasound Computed tomography (CT) Magnetic resonance imaging Endoscopic ultrasound	Diffusion-weighted magnetic resonance Somatostatin receptor scintigraphy ^{68}Ga-DOTA-TATE/TOC/CT ^{11}C-5-HTP, ^{18}F-DOPA/CT ^{18}F-FDG/CT
At diagnosis, CT abdomen and thorax, including a dynamic contrast enhancement of pancreas and liver + somatostatin receptor imaging	

DOPA, Dihydroxyphenylalanine; FDG, fluorodeoxyglucose; HTP, hydroxytryptophan.



NET, Neuroendocrine tumour.

Imaging of Neuroendocrine Tumours

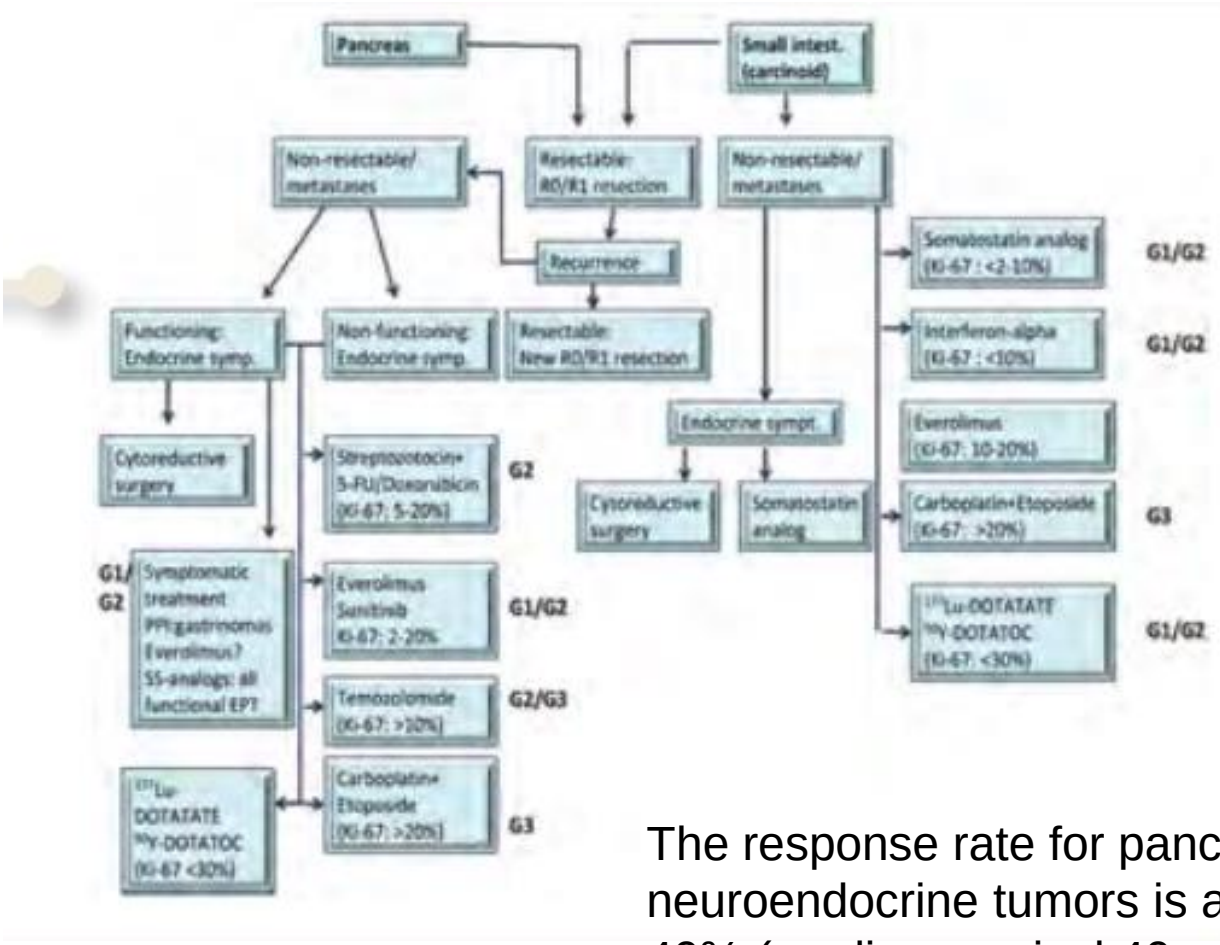
^{68}Ga-DOTATATE PET scan vs SRS

- Increased sensitivity and specificity
- Tomographic
- Exact CT co-registration
- Faster imaging 60–90 min vs 24–72 h
- Quantitative
- Lower radiation
- Onsite production

CT, Computed tomography; SRS, somatostatin receptor scintigraphy; PET, positron emission tomography.

Treatment

- In patients with intestinal neuroendocrine tumors, chemotherapy has no significant benefit (10%–15% objective responses and less than 2 years' median survival).
- Somatostatin analogues are considered to be first-line treatment for low-proliferating tumors with a Ki-67 proliferation index of up to 10%.
- ^{177}Lu-DOTATATE for patients with advanced/metastatic gastrointestinal NETs that are somatostatin receptor–positive on imaging



The response rate for pancreatic neuroendocrine tumors is about 40% (median survival 40 months).

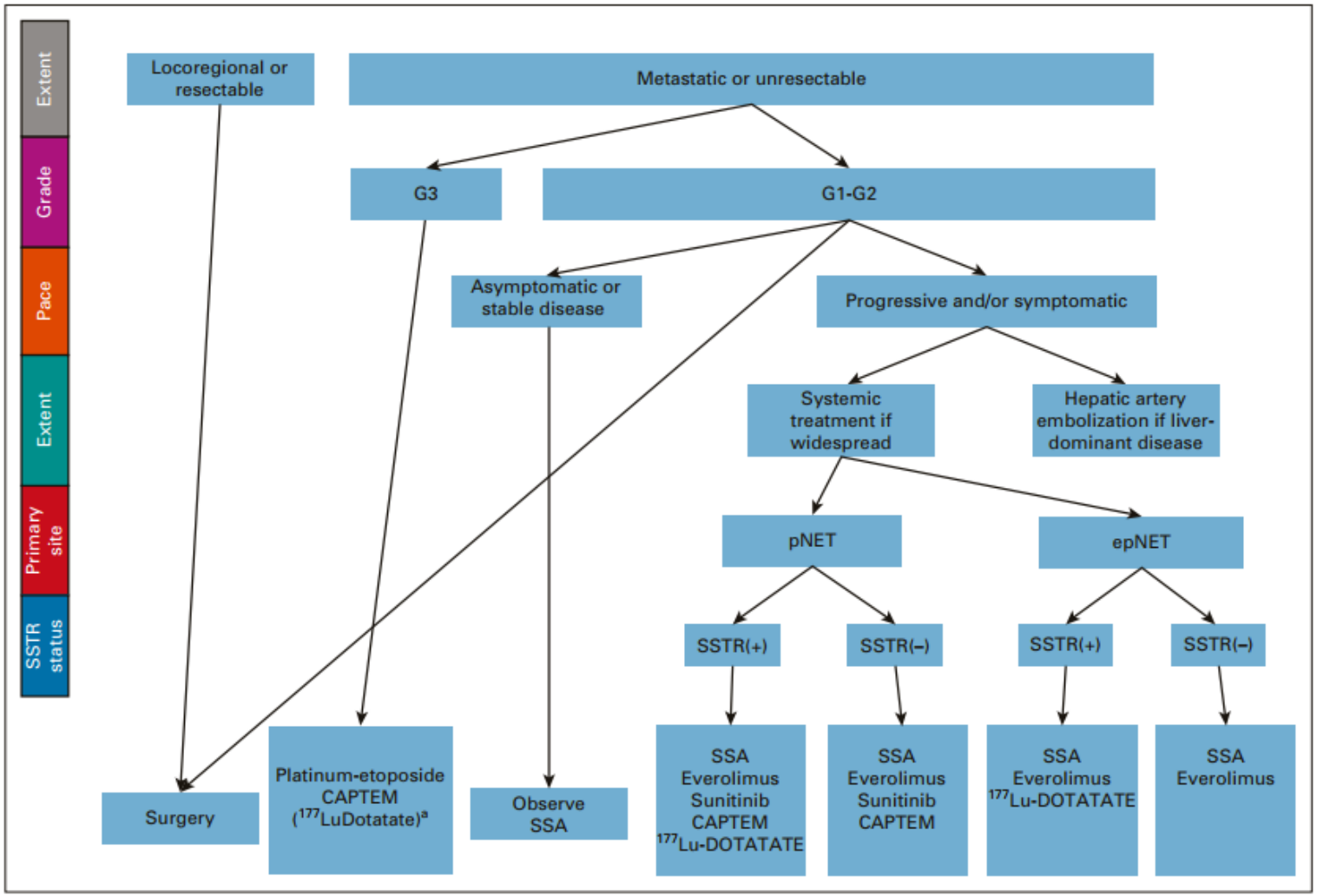


FIG 1. [a]For select cases. Schema for management of well-differentiated neuroendocrine tumors according to patient and tumor characteristics. CAPTEM, temozolomide plus capecitabine; epNET, extrapancreatic neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; SSA, somatostatin analog; SSTR, somatostatin receptor.

Pancreatoblastoma

- Mean presentation is age 5
- APC gene mutated
- AFP elevated
- Histology
- Multiple lines of differentiation and the presence of squamous nests
- Associated with Beckwith-Wiedemann syndrome
- Associated with familial adenomatous polyposis

Endocrine tumors

- Resemble giant islets.
- Regular cords of monotonous cells oriented to vasculature.
- May not be encapsulated.
- β-cell tumors most common (insulinoma).
- Blood glucose <50 mg/dL, precipitated by fasting or exercise
- Presents with confusion (neuroglycopenia).
- Amyloid deposition common in β-cell tumors.

Endocrine tumors

- Gastrinomas may arise in duodenum, pancreas, or peripancreatic tissues.
- Over half are locally invasive.
- Give rise to extreme gastric acid hypersecretion.
- 25% associated with MEN-1, are multiple.

Endocrine tumors

- Two-thirds of gastrinomas are found in the Zollinger-Ellison triangle bounded by the confluence of the cystic and common bile ducts and the second and third portions of the duodenum.
- Generally have metastasized at presentation.
- Resectible if metastases in duodenum and liver; not if in lung or other organ.
- Follow with yearly gastrin levels if completely resected.
- Carcinomas rare and diagnosed only if metastasize.

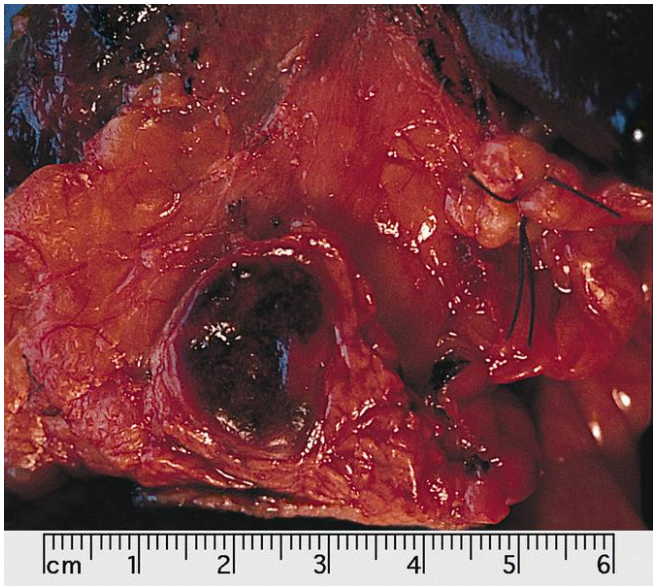
Endocrine tumors

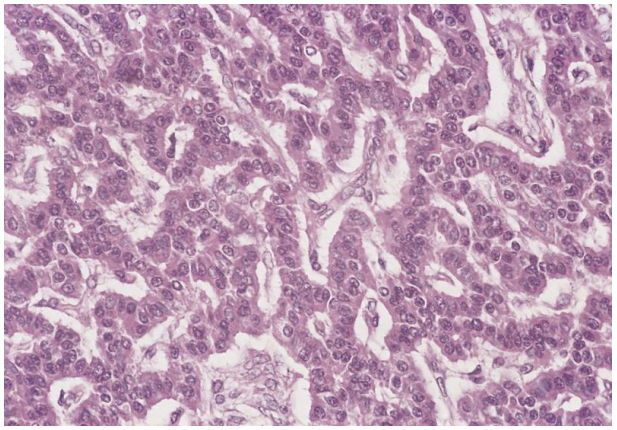
- α-cell tumors (glucagonoma) present with mild diabetes mellitus, anemia, and necrolytic migratory erythema (rash).
- Occur most frequently in perimenopausal or post-menopausal women.
- δ-tumors (somatostatinoma) are associated with diabetes mellitus, steatorrhea, hypochlorhydria, and cholelithiasis.

Endocrine tumors

- VIPoma may be invasive.
- Presents with severe watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome).
- May be associated with neural crest tumors.
- Evorlimus (mTOR inhibitor), sunitinib (tyrosine kinase inhibitor) may be effective.

Endocrine tumor



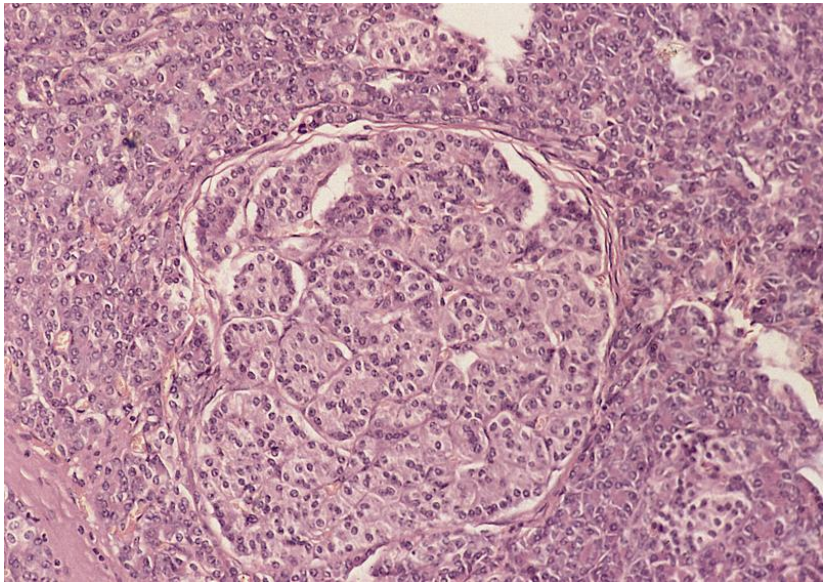


Small (2 cm in diameter) intrapancreatic tumor with expansile margins showing a relatively homogeneous, deep red, hemorrhagic appearance. (Top) Gyriform festoons separated by highly vascular stroma in a clinically nonfunctioning adenoma which was immunohistochemically glucagon- positive. (Bottom)

Figs. 5-3 and 5-8

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.

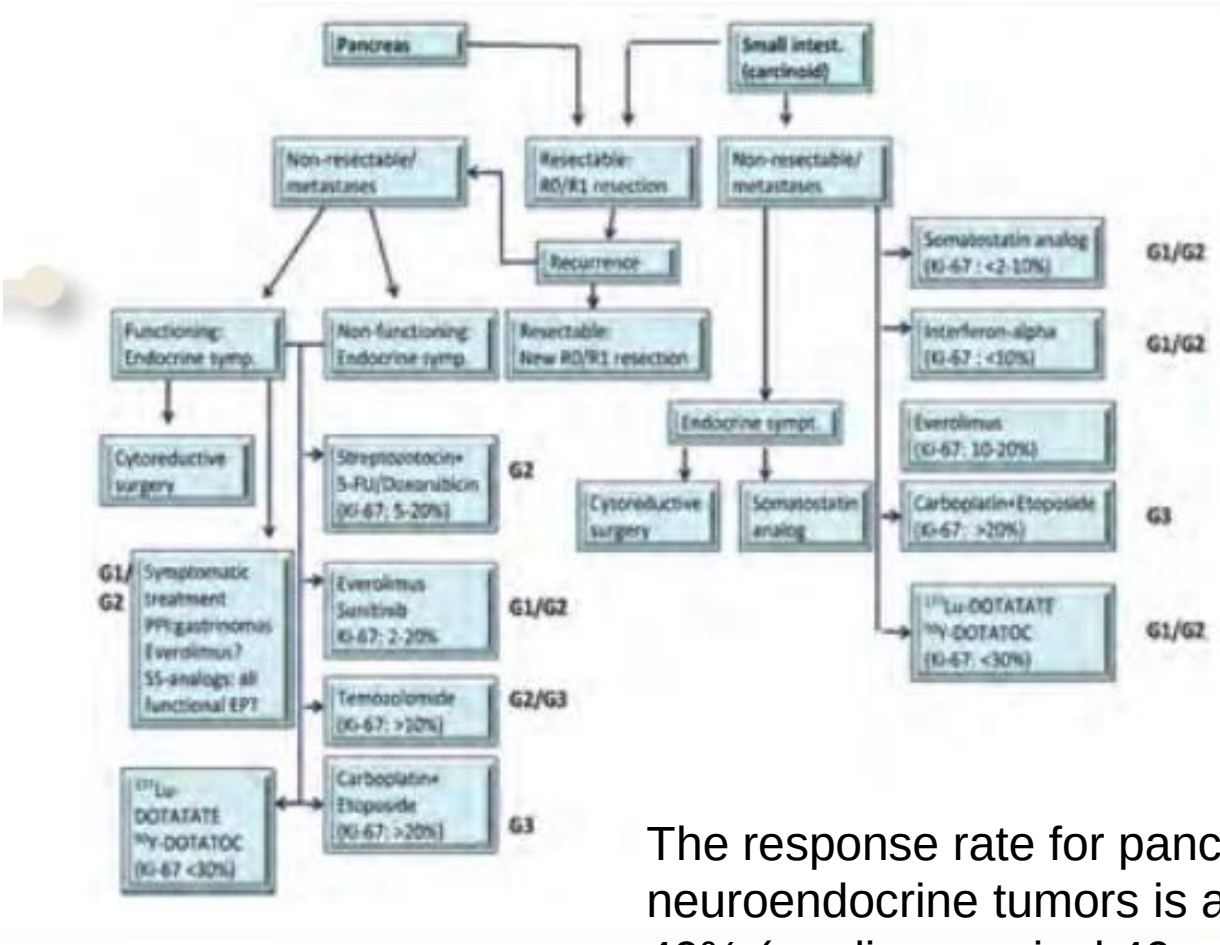
Islet cell adenoma



Well-demarcated, partly encapsulated growth of uniform cells forming regular microlobules. Compare with islet in the lower right corner.

Fig. 5-14

Solcia, E, Capella, C, Kloppel, G., “Tumors of the Pancreas. Atlas of Tumor Pathology Third Series, Fascicle 20. Armed Forces Institute of Pathology. Washington, D.C. 1997.



The response rate for pancreatic neuroendocrine tumors is about 40% (median survival 40 months).

Cancer syndromes

- Hereditary nonpolyposis colorectal cancer (Lynch II)
- Hereditary breast and ovarian cancer
- Familial atypical multiple mole melanoma syndrome
- Peutz-Jeghers syndrome
- Hereditary Pancreatitis