

*6th Annual Mid-Atlantic Pathologists' Assistants
Conference*

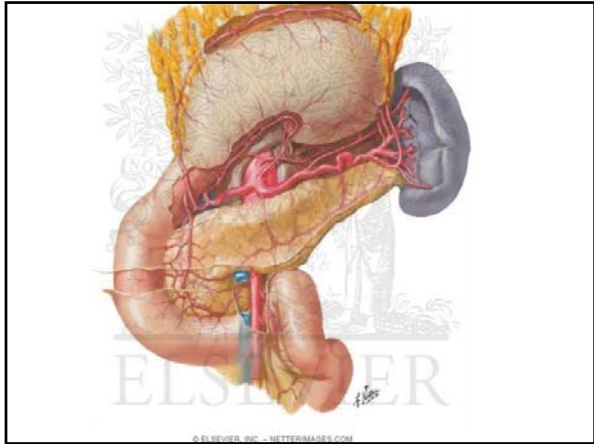
Tumors of the Pancreas

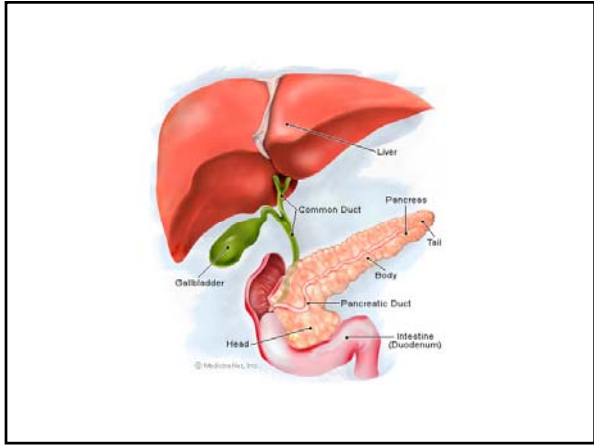
Heather Peterman, MD
Hospital of the University of Pennsylvania
June 4, 2011

Outline

- Anatomy of pancreas
- Grossing of pancreatic resection specimens
- Normal pancreas histology
- Reviewing gross and histologic features of more common pancreatic tumors

PANCREATIC ANATOMY

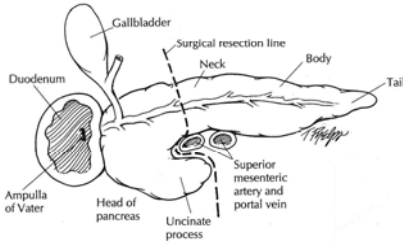




PANCREATIC RESECTION SPECIMENS

Whipple procedure

- Duodenectomy, partial pancreatectomy, partial gastrectomy (+/-), gallbladder (+/-)
- Origin of tumor (duodenum, ampullary, peri-ampullary, bile duct, pancreatic duct, head of pancreas)



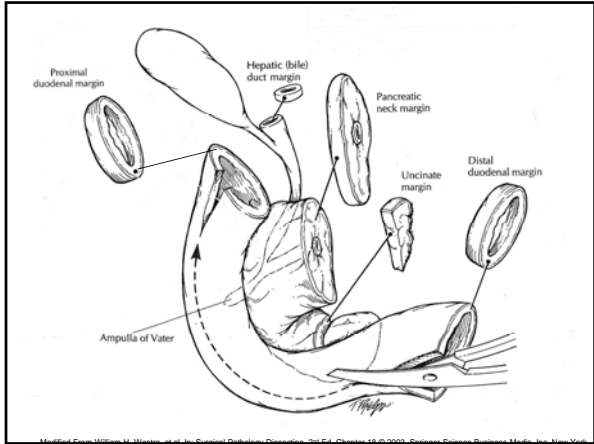
From: Whipple PL, Williams PL, eds. Surgical Pathology. Diagnosis. 2nd ed. Chichester: 1993: 200. Copyright 1993, John Wiley & Sons Ltd.

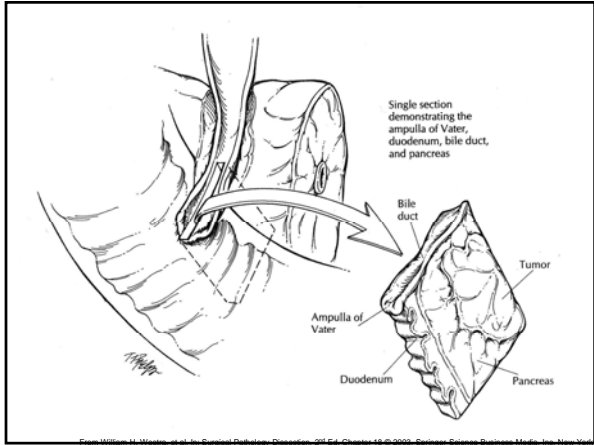
Whipple procedure

- Duodenum (length and circumference), pancreas (three dimensions), common bile duct (length and diameter), margins (stapled vs. open, diameter), tumor (three dimensions), dimensions of stomach (length and circumference), gallbladder (three dimensions including length and diameter of cystic duct)

Whipple procedure

- MARGINS
 - Pancreatic resection (either en face or perpendicular)
 - Uncinate process (either en face or perpendicular)
 - Posterior (non-peritonealized) soft tissue
 - Bile duct
 - Proximal stomach/duodenal and distal small bowel
- REPRESENTATIVE
 - Ampulla
 - Tumor (including relationship to pancreas, ducts, ampulla, duodenum, and surrounding soft tissue)
 - Normal pancreas, small bowel, gallbladder
 - All lymph nodes





Distal pancreatectomy

- Pancreas, spleen (+/-)
- Dimensions of pancreas (three dimensions), spleen (weight, three dimensions)

This diagram illustrates a distal pancreatectomy. It shows the 'Tail of the pancreas', 'Pancreatic Duct', and 'Pancreatic Resection Margin'. The 'Spleen' is also shown, indicating its relationship to the distal pancreas. The diagram shows the pancreas being resected, with the spleen remaining attached to the remaining pancreatic body.

Figure 19-7. Distal pancreatectomy.

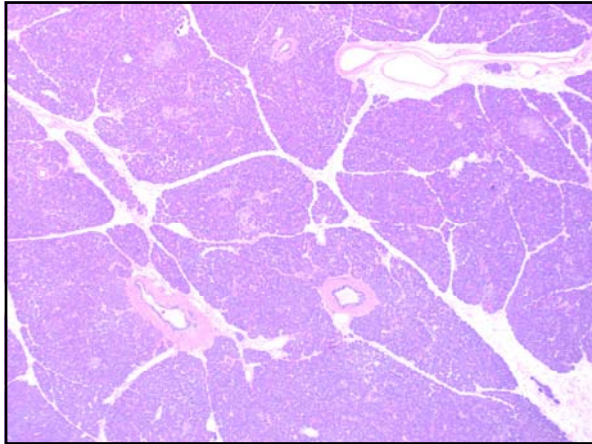
Distal pancreatectomy

- MARGINS
 - Pancreatic resection margin (either en face or perpendicular)
 - Posterior (non-peritonealized) soft tissue
- REPRESENTATIVE
 - Tumor (including relationship to pancreas, ducts, spleen, and surrounding soft tissue)
 - Normal pancreas and spleen
 - All lymph nodes

NORMAL HISTOLOGY

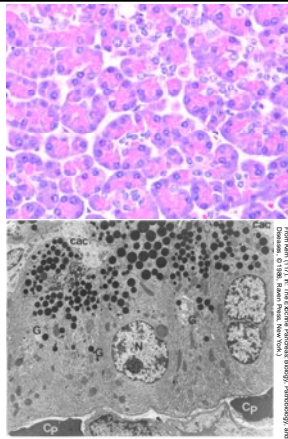
Pancreas

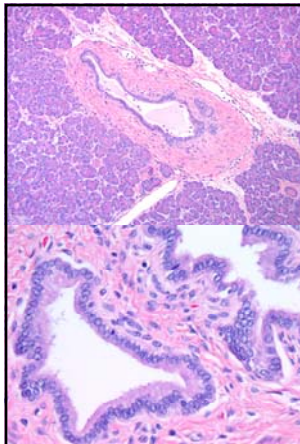
- Secretory organ with two distinct components:
 - exocrine: serous gland that synthesizes and secretes digestive enzymes
 - endocrine (1-2%): synthesizes and secretes insulin and glucagon which regulate glucose, lipid, and protein metabolism



Acinar Cells

- Make up the exocrine component (along with ducts), forming acini which empty into centroacinar cells, which merge into ductules
- Acinar cells produce and secrete digestive enzymes, appearing with a basally located round nucleus, with basal basophilic cytoplasm and apical granular eosinophilic cytoplasm
- By EM, conspicuous rough ER and electron-dense zymogen granules which contain all of the various enzymes



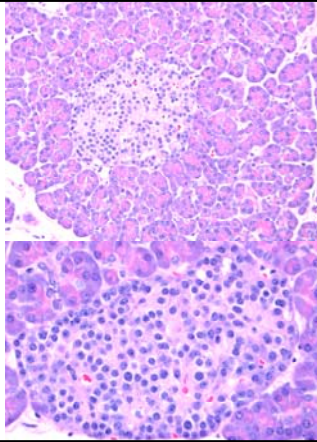


Ducts

- Digestive enzymes are carried by ductules which empty into intra- and then interlobular ducts, until reaching the main pancreatic duct and duodenum
- Secrete water, sodium and bicarbonate (about 1 L per day)
- Lined by non-mucinous cuboidal epithelial cells with central round nuclei
- May undergo mucinous, squamous, oncocytic, goblet cell and acinar metaplasia

Islets

- *Islets of Langerhans*
- Randomly distributed throughout pancreas, most numerous in tail
- Major cell types include:
 - B cells – insulin
 - A cells – glucagon
 - D cells – somatostatin
- Minor cell types secrete pancreatic polypeptide (PP), vasoactive intestinal peptide (VIP), secretin, motilin and substance P
- Differentiation of cell types can be done by staining properties and ultrastructural (EM) characteristics of granules



PANCREATIC TUMORS

Classification of pancreatic tumors

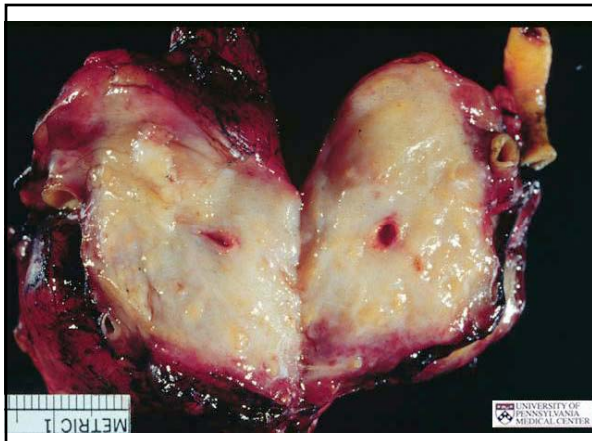
- Line of cellular differentiation: ductal (90%), endocrine, acinar
- Gross configuration: solid vs. cystic
- If potentially non-invasive: benign, borderline, carcinoma

Ductal adenocarcinoma

- Most common pancreatic tumor
- 6th to 8th decades, M:F = 2:1
- Multifactorial etiology (smoking, high dietary fat intake are risk factors)
- Worldwide
 - ~227,000 deaths yearly
 - 8th leading cause of cancer death
- In the US
 - ~37,000 deaths yearly
 - 4th leading cause of cancer death

Ductal adenocarcinoma

- Head of pancreas (>75%)
- Solid, firm, with irregular, poorly defined borders
- White, tan, gritty cut surface, obscures normal lobular architecture
- Common to see direct invasion into common bile duct and duodenum – important to recognize center of tumor in pancreas (vs. ampullary, duodenum, bile duct)
- Degeneration, necrosis, or cystic dilatation



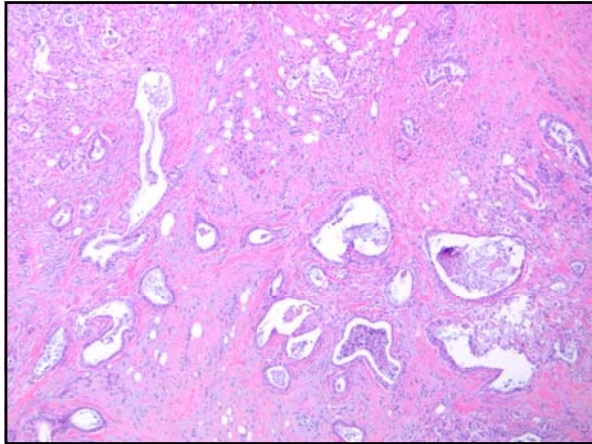


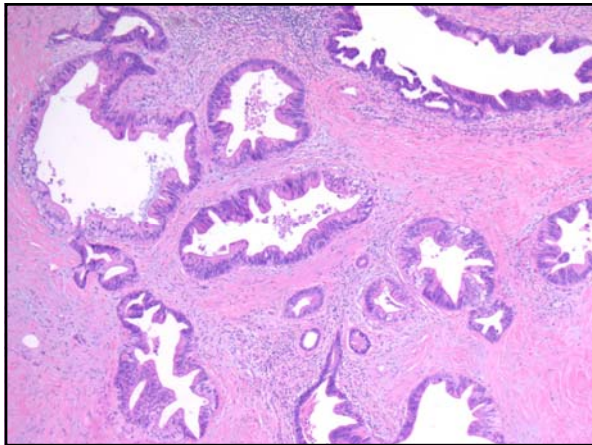


Ductal adenocarcinoma

Conventional (tubular) type – most common type

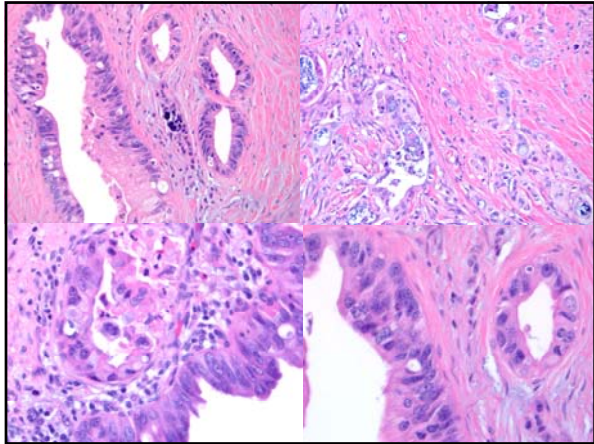
- Infiltrative gland-forming mucin-producing epithelial neoplasm with prominent desmoplastic stromal reaction
- Grows in a disorganized haphazard fashion, may extend into adjacent normal pancreatic lobules, peripancreatic adipose tissue, duodenal wall

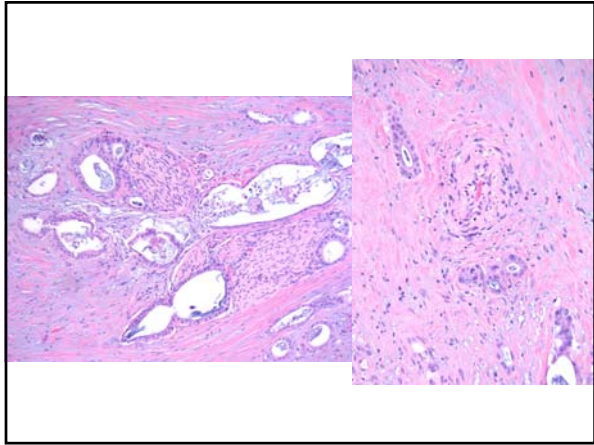




Ductal adenocarcinoma

- Well to moderate to poorly differentiated
- Cytologically, nuclei are polymorphic
- Have enlarged nuclei, but also may have abundant mucin, so N:C ratio may be preserved
- Perineural and lymphovascular invasion common
- Subtypes: foamy, large duct, vacuolated, lobular, solid





Ductal adenocarcinoma

- Treatment is surgical resection, though >80% are unresectable at time of diagnosis, predominantly due to encasement of major mesenteric vessels or metastasis (liver, peritoneum, other)
- Poor prognosis:
 - 5 yr survival <5%, median survival 9 months
 - If resected, 5 yr survival up to 20%, median survival 12 to 18 months
- Chemotherapy/radiation

PANCREAS STAGING FORM		
Clinical <small>Extent of disease before any treatment</small>	STAGE CATEGORY DEFINITIONS	Pathologic <small>Extent of disease through completion of definitive surgery</small>
<input type="checkbox"/> y clinical - staging completed after neoadjuvant therapy but before subsequent surgery	Tumors Size*	<input type="checkbox"/> y pathologic - staging completed after neoadjuvant therapy AND subsequent surgery
<input type="checkbox"/> TX <input type="checkbox"/> T0 <input type="checkbox"/> T1a <input type="checkbox"/> T1 <input type="checkbox"/> T2 <input type="checkbox"/> T3 <input type="checkbox"/> T4	PRIMARY TUMOR (T) Primary tumor cannot be assessed No evidence of primary tumor "Carcinoma in situ" Tumor limited to the pancreas, 2 cm or less in greatest dimension Tumor limited to the pancreas, more than 2 cm in greatest dimension Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor) *Note: This also includes the "Pan/III" classification REGIONAL LYMPH NODES (N) Regional lymph nodes cannot be assessed No regional lymph node metastasis Regional lymph node metastasis	<input type="checkbox"/> TX <input type="checkbox"/> T0 <input type="checkbox"/> T1a <input type="checkbox"/> T1 <input type="checkbox"/> T2 <input type="checkbox"/> T3 <input type="checkbox"/> T4 <input type="checkbox"/> NX <input type="checkbox"/> N0 <input type="checkbox"/> N1
<input type="checkbox"/> M0 <input type="checkbox"/> M1	DISTANT METASTASIS (M) No distant metastasis (no pathologic M; use clinical M to complete stage group) Distant metastasis	<input type="checkbox"/> M1

American Joint Committee on Cancer • 2010 7th edition

Acinar Cell Neoplasms

- Benign
 - 12 reported cases of acinar cell cystadenoma
 - Benign cystic lesion lined by cells with acinar differentiation
 - ? Acinar metaplasia of ducts
- Malignant
 - Acinar cell carcinoma – malignant epithelial neoplasm with evidence of exocrine enzyme production, without significant (<25%) endocrine or ductal component

Acinar Cell Carcinoma

- Uncommon, 1-2% of adult pancreatic neoplasms
- Mean age 6th decade (range 10 – 87, rare pediatric cases)
- Male >female (M:F = 4:1)
- 10-15% of patients will develop a syndrome of lipase hypersecretion syndrome (multifocal nodules of subcutaneous fat necrosis with peripheral blood eosinophilia and elevated serum lipase)

Acinar Cell Carcinoma

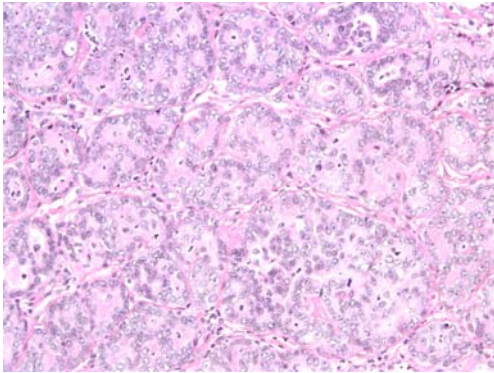
- Arise anywhere in pancreas
- Large (average size 10 cm), solid, well-circumscribed
- Tan-red, soft and fleshy, +/- lobulation
- May have necrosis and degeneration

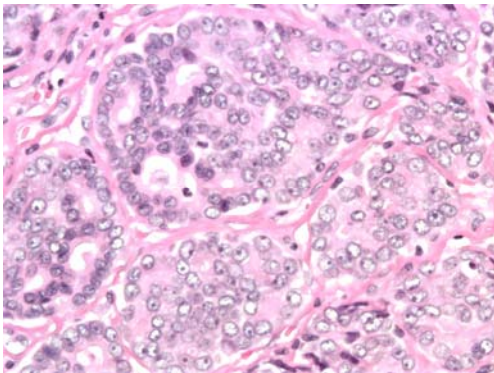


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Acinar Cell Carcinoma

- Marked cellularity with paucity of fibrous stroma
- Most exhibit acinar and solid patterns, less common glandular and trabecular patterns
- Monotonous tumor cell proliferation, usually with moderate amounts of cytoplasm with eosinophilic granularity in the apical regions, reflecting aggregates of zymogen granules
- Uniform nuclei with prominent central nucleolus





Acinar Cell Carcinoma

- Prognosis
 - 50% of patients have metastases at diagnosis; another 25% will develop them
 - Slightly better than conventional ductal type adenocarcinoma, but still poor
 - 5 year survival 6%, median survival 18 months

Pancreatic endocrine neoplasms (PEN)

- 1-2% of all pancreatic neoplasms
- 5th to 6th decades (mean age 58 yrs)
- M:F = 1:1
- Occur throughout pancreas
- Sporadic but also occur (multiple) as part of Multiple Endocrine neoplasia (MEN I), along with parathyroid and anterior pituitary endocrine lesions, and von Hippel-Lindau syndrome

Pancreatic endocrine neoplasms (PEN)

- Functional or non-functional
- Patients with functional PEN's may have elevated hormone levels without symptoms
- Of the functional PEN's:
 - insulinomas > gastrinomas > glucagonomas > VIPoma > somatostatinoma
- Serum hormone levels do not correlate with IHC

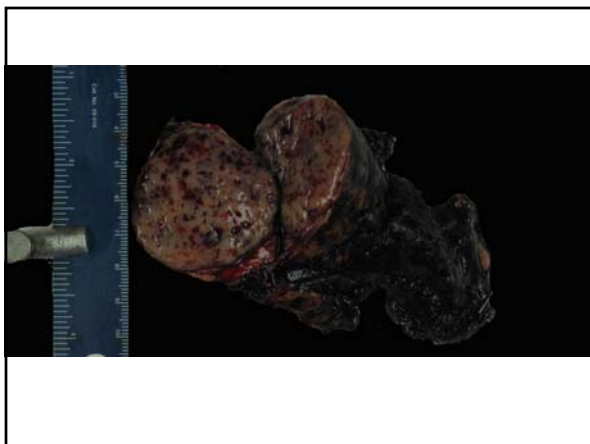
WHO Classification

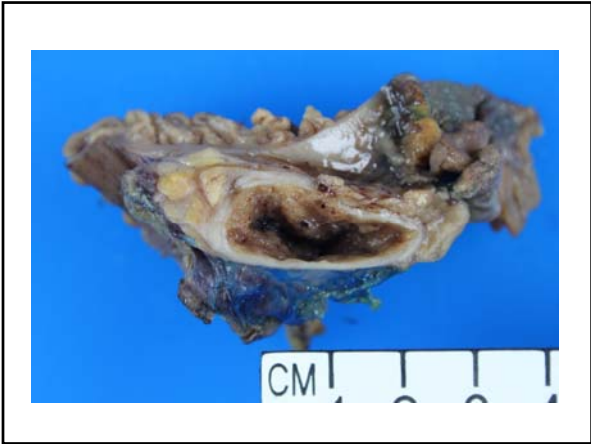
- Well differentiated pancreatic endocrine neoplasm
 - Low grade
 - No invasion, <2 cm, <2 mitoses/50 hpf, and no necrosis
 - Intermediate grade
 - Vascular or perineural invasion, ≥2 cm, 2 – 50 mitoses/50 hpf or foci of necrosis
- Well differentiated pancreatic endocrine carcinoma
 - Gross local invasion or metastases
- Poorly differentiated (small cell) pancreatic endocrine carcinoma
 - >50 mitoses/50 hpf

Well differentiated endocrine neoplasms

- Solid, circumscribed, homogenous, red-tan-yellow mass, usually soft
- May be nodular or cystic
- Larger PEN may exhibit invasiveness

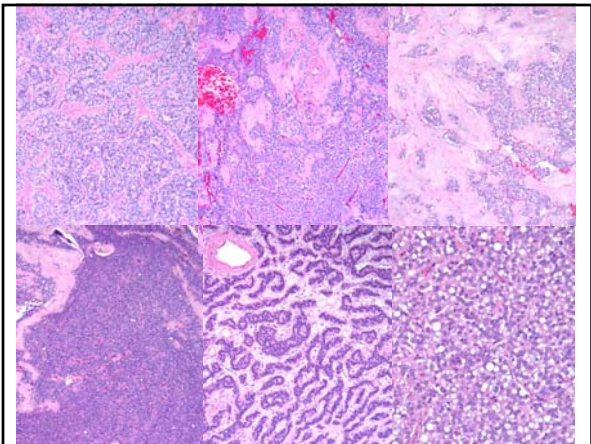


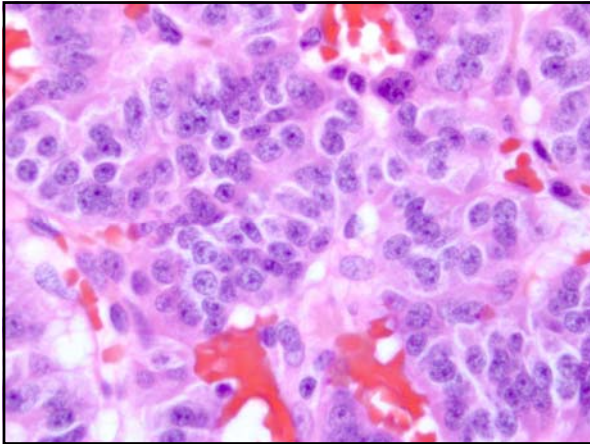




Well differentiated endocrine neoplasms

- Epithelial neoplasm with organoid growth of cells cytologically resembling normal islet cells or other hormone-producing cells, with low mitotic rate
- Pushing border with local invasion, including perineural and/or lymphovascular invasion
- Trabecular, nested, or gyriform architecture
- Hyalinized amyloid-like stroma (amyloid may be present)
- Moderate amounts of eosinophilic or amphophilic cytoplasm
- Round to oval nuclei uniform in size and shape with “salt and pepper” chromatin



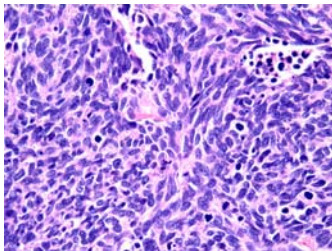


Well differentiated endocrine neoplasms

- Surgical resection
- Adjuvant therapy does not have proven benefits
- More aggressive than endocrine tumors of the luminal GI tract

Poorly differentiated endocrine carcinoma

- Clinically aggressive poorly differentiated carcinomas with morphologic or immunohistochemical features of endocrine differentiation, with high proliferative rate or extensive necrosis
- 2-3% of all PEN
- Probably more closely related to ductal adenocarcinoma rather than dedifferentiated well differentiated pancreatic endocrine carcinoma

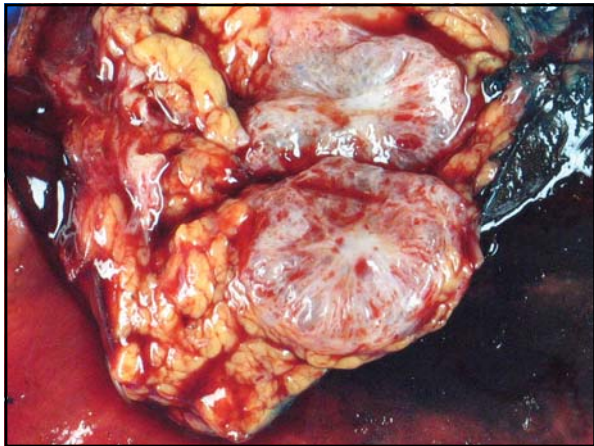


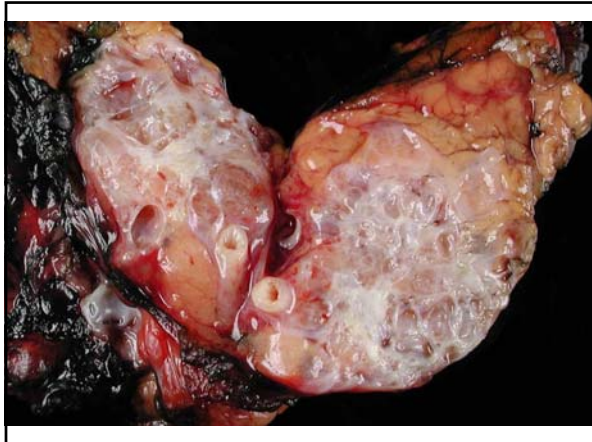
Microcystic serous cystadenoma

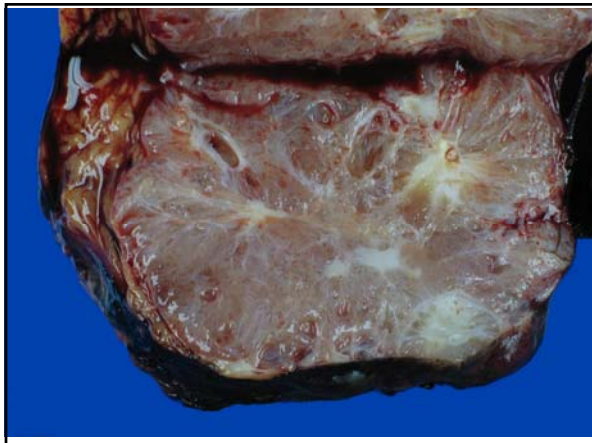
- Also called Serous cystadenoma or Microcystic adenoma
- Most common true cystic tumor of the pancreas
- Female predominance (3:1), mean age 66 yrs
- Mostly body and tail
- Solitary (except in VHL)

Microcystic Serous Cystadenoma

- Ave 6 cm, up to 30 cm, circumscribed
- Innumerable small thin-walled cysts (delicate septae) with sponge or honeycomb cut surface
- Stellate central scar
- No communication with ductal system

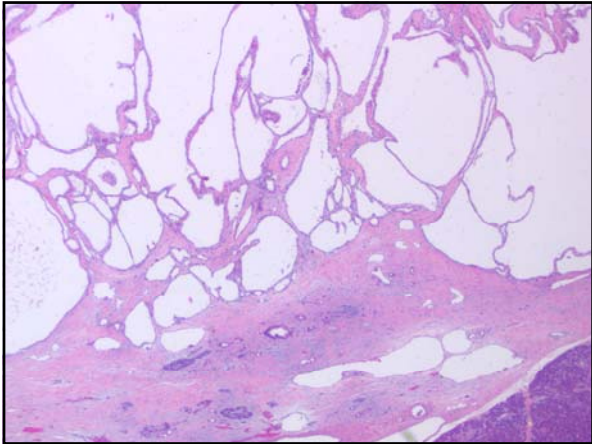


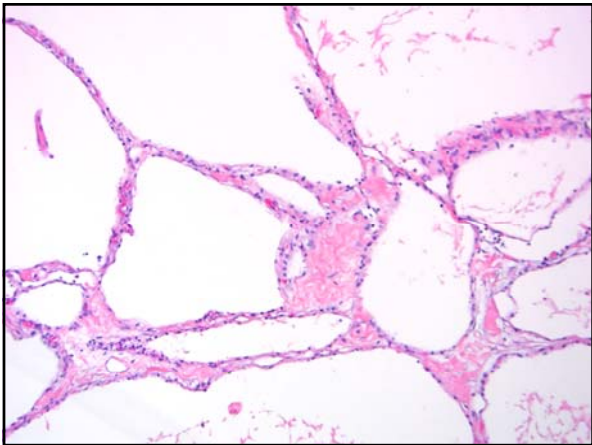


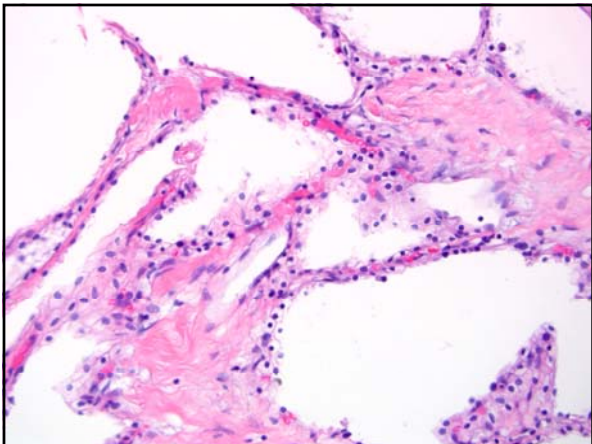


Microcystic Serous Cystadenoma

- Cysts, lined by single layer of uniform, clear (glycogen-containing) cuboidal cells
- Small round nuclei with uniform hyperchromatic chromatin and inconspicuous nucleoli
- No atypia and mitoses
- Variants: Macrocystic or solid
- Treatment based on symptoms
- Morbidity and mortality related to location and operative complications







Mucinous cystic neoplasm (MCN)

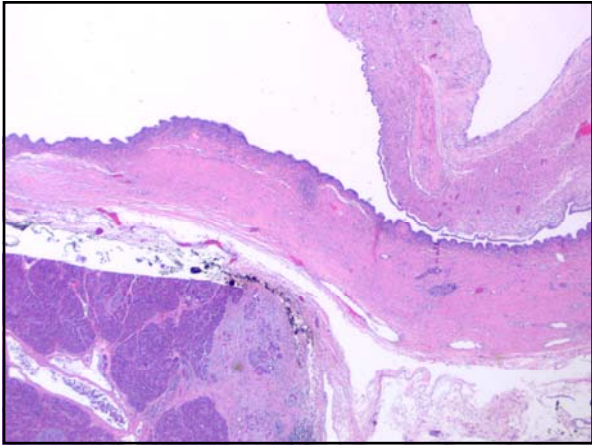
- Almost exclusively female, 5th to 6th decades
- Almost always body and tail
- Single, multiloculated cyst
- Mean 7-10 cm, range 2-36 cm
- Multilocular cystic lesion with large cysts with thin septae and thick fibrotic capsule
- Variably papillated internally
- No communication with ductal system

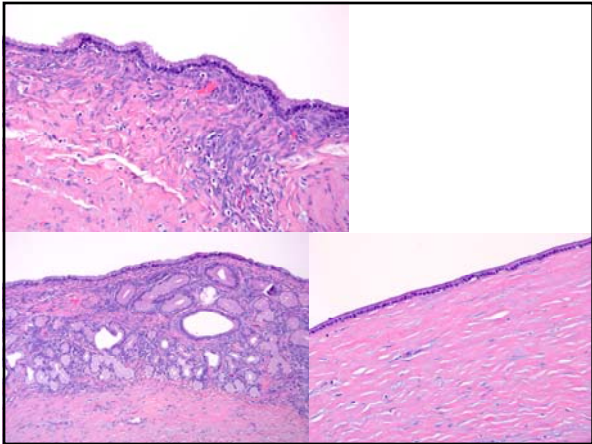


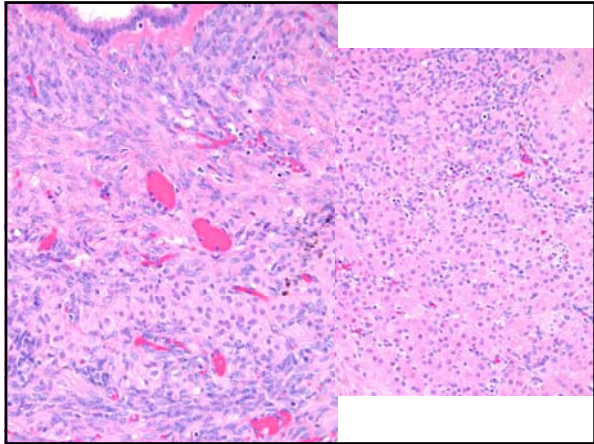


Mucinous cystic neoplasm

- Cysts lined by tall columnar mucin-producing epithelium with basal nuclei and abundant intracytoplasmic apical mucin
- Septae contain stroma composed of densely packed spindle cells with sparse cytoplasm and uniform, elongated wavy nuclei, admixed with clusters of plump, eosinophilic epithelioid cells resembling luteinized cells

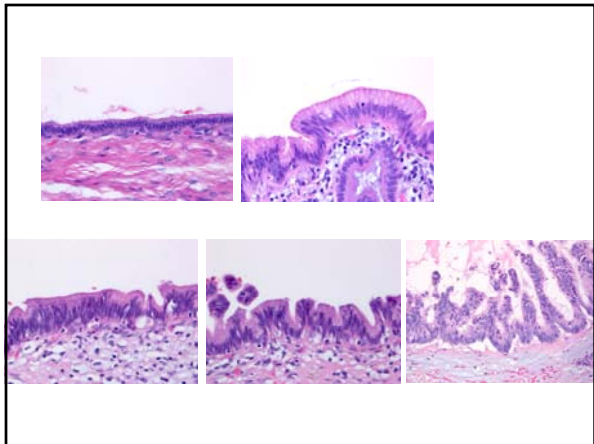






Mucinous cystic neoplasm

- Lining epithelium should be assessed for dysplasia which manifests as cellular crowding, loss of nuclear polarity, cytologic pleomorphism, increased N:C ratio, mitoses
- Dysplasia can be focal and abrupt
 - Low grade – Mucinous cystadenoma
 - Moderate – Borderline malignant potential
 - High grade – In situ mucinous cystadenocarcinoma

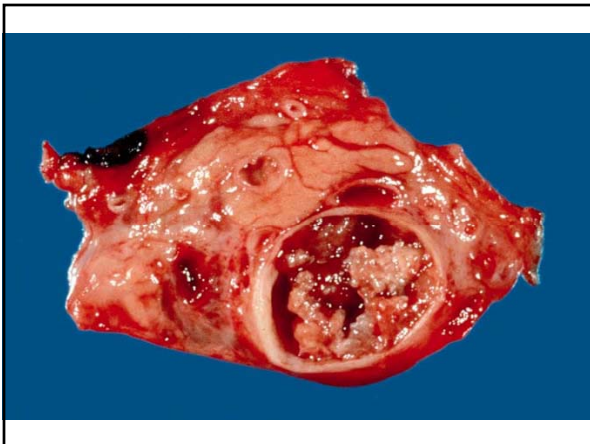


Mucinous Cystic Neoplasm

- ~20% of mucinous cystic neoplasms are associated with invasive carcinoma, usually conventional ductal type
- Invasive component can be focal → embed entire lesion (can start with grossly suspicious areas)
- Prognosis
 - If no invasion,
 - Cured with complete resection
 - If an invasive component,
 - 2 year survival 67%
 - 5 year survival 50%

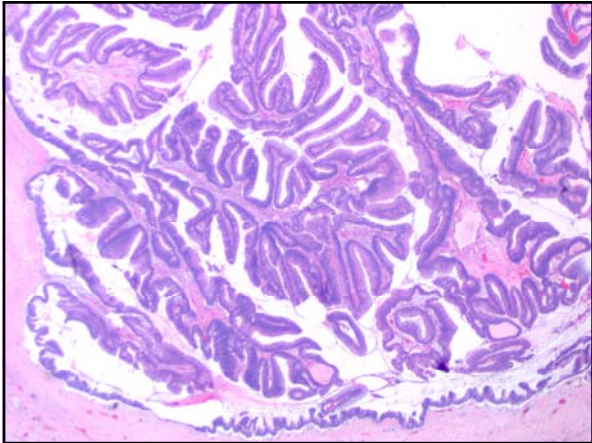
Intraductal papillary mucinous neoplasm (IPMN)

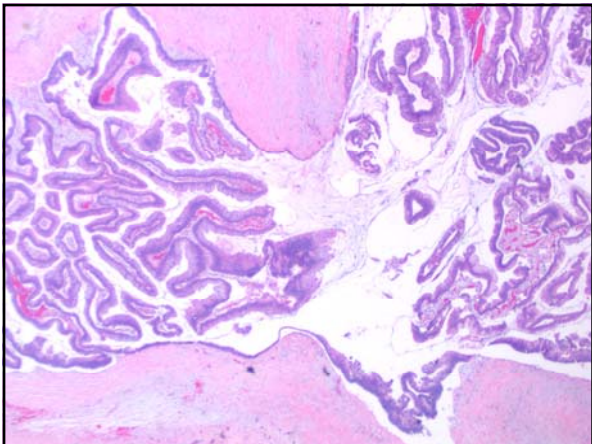
- Male > female (M:F = 3:2)
- Mean age 6th decade (range 25-94 yrs)
- No established environmental risk factors
- Head of pancreas (80%)
- Communicates with ductal system with markedly distended main pancreatic duct or numerous cysts (representing dilated secondary ducts)
- Wide variation in size

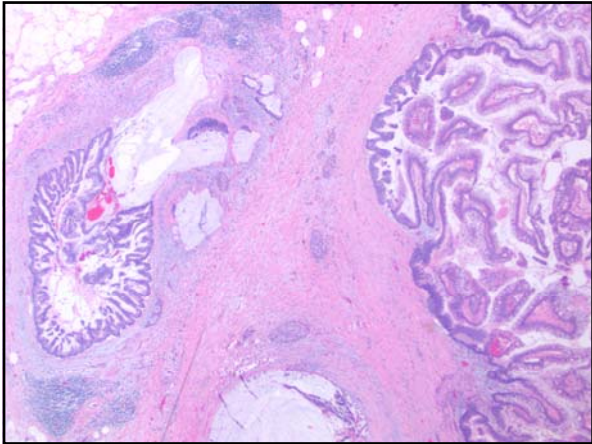


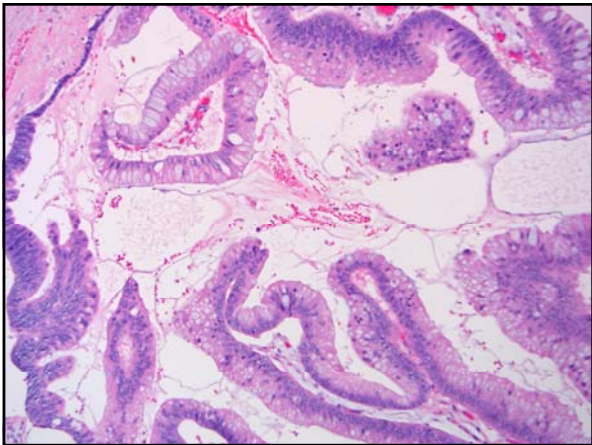
IPMN

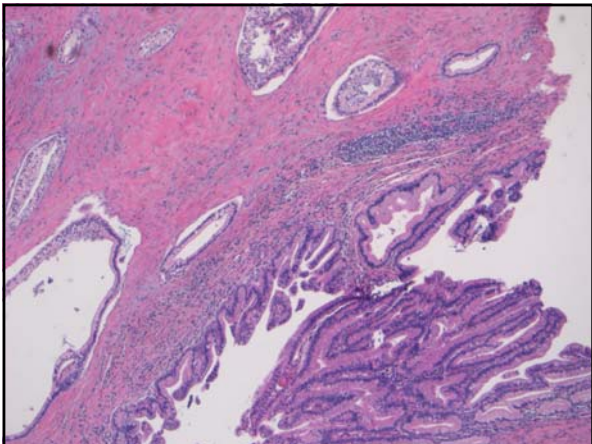
- Intraductal proliferation of mucinous epithelial neoplasm, with growth predominantly within the main pancreatic duct or one of its side branches
- Usually with papillary architecture, ranging from microscopic to grossly visibly papillations
- Mucin-secreting columnar epithelial cells with varying degrees of atypia
- May have intestinal (85%) or pancreaticobiliary differentiation
- No distinctive stroma











IPMN

- ~35% of IPMN's are associated with invasive carcinoma, usually colloid or conventional ductal type
- Invasive component can be focal or multifocal → embed entire lesion (can start with grossly suspicious areas)
- Prognosis: may recur even if noninvasive
 - 5 yr survival, 75% free of disease
 - If invasive, prognosis is better than just ductal (5 yr survival 40%), and colloid better than ductal

Mucinous tumors

Intraductal papillary mucinous neoplasm (IPMN)

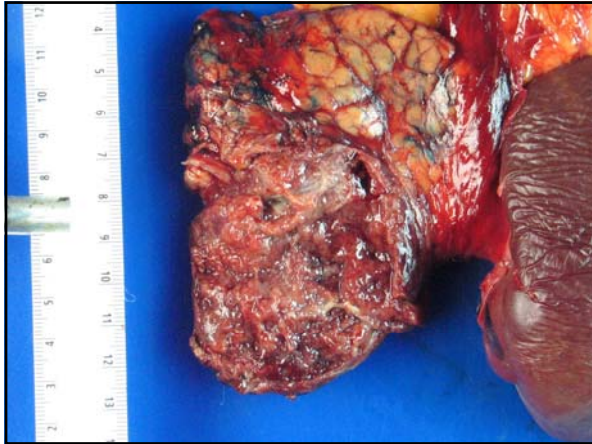
- 50-70 yrs
- Male>female
- Head>tail
- Intraductal
- Multiple cysts
- Usually extensive papilla formation
- Absent ovarian-like stroma

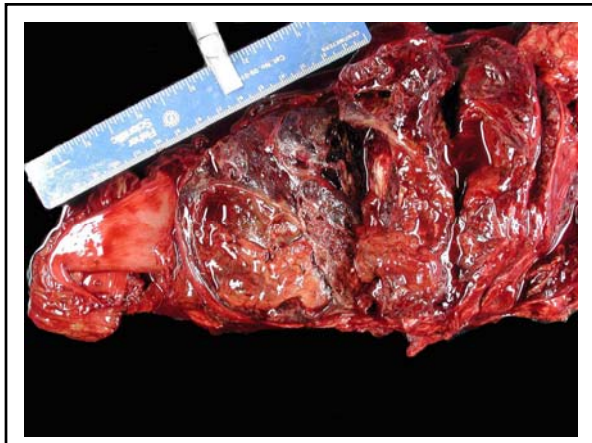
Mucinous cystic neoplasm (MCN)

- 40-50 yrs
- Female preponderance
- Tail>>>head
- Not intraductal
- Single, multilocular cyst
- Usually minimal papilla formation
- Ovarian-like stroma present

Solid-pseudopapillary tumor

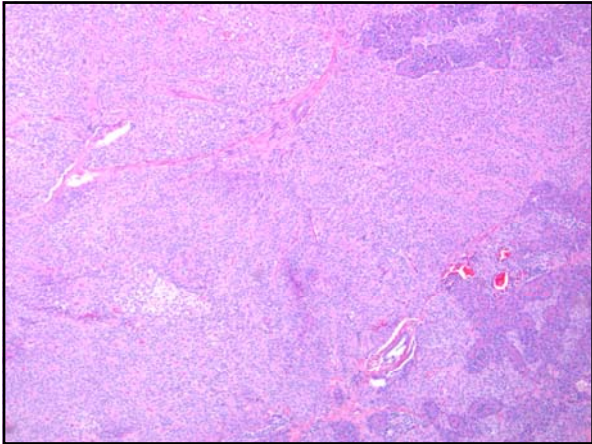
- 1 – 3% of all pancreatic tumors
- Predominantly female (M:F = 1:9), 2nd to 3rd decades
- Distributed evenly throughout pancreas
- Average size 9 – 10 cm
- Well demarcated +/- encapsulation, +/- calcifications, with soft, white-gray-yellow solid areas with irregular cavities of friable necrotic material and hemorrhage

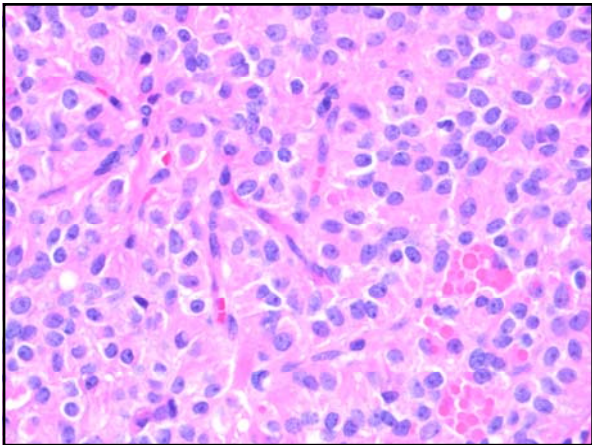


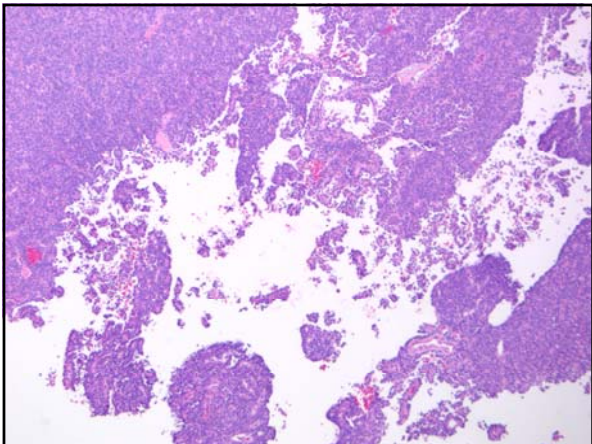


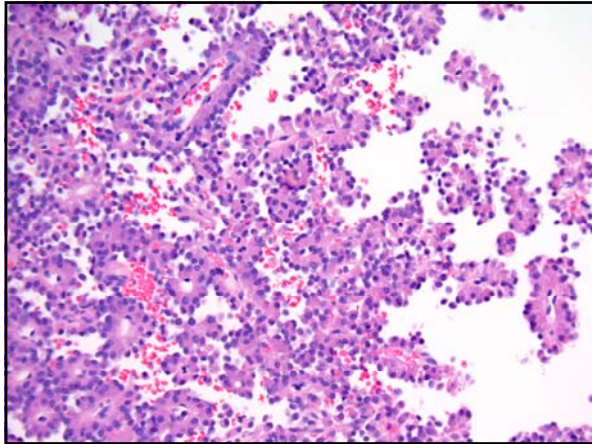
Solid-pseudopapillary tumor

- Solid areas contain sheets of uniform polygonal cells admixed with delicate capillaries
- Other areas show marked degenerative changes with formation of pseudopapillae
- Eosinophilic to clear cytoplasm and nuclei that are round to oval and uniform with finely stippled chromatin and grooves
- Mitoses and pleomorphism are unusual
- Some cells contain intracytoplasmic hyaline globules
- Though grossly circumscribed, neoplastic cells often infiltrate into adjacent pancreas
- Vascular invasion, pleomorphism, and necrosis are associated with the presence of metastases









Solid-pseudopapillary tumor

- Uncertain malignant potential
- Metastases occur in 10-15% of case, usually to liver or peritoneum (rare to have LN mets)
- Even with mets, survival for many years is still seen with few symptoms

Pancreatoblastoma

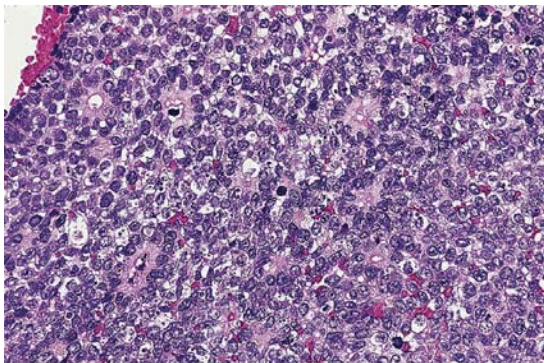
- Overall rare; most common malignant pancreatic neoplasm of childhood; do occur in adults
- Bimodal distribution
 - Peaks at 2.4 and 40 yr
 - Overall mean age 9 yr (range: neonatal to 68 yr)
- M:F=1:1
- Beckwith-Wiedemann syndrome
- May have elevated AFP

Pancreatoblastoma

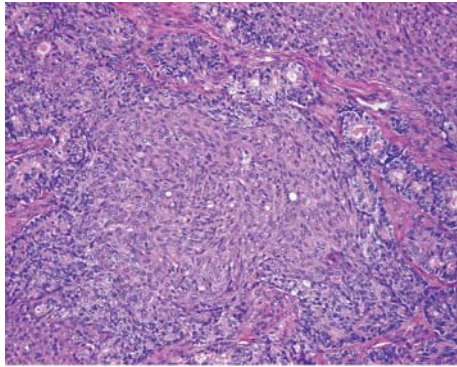
- Solitary, all throughout pancreas
- Average 11 cm
- Well-circumscribed, partially encapsulated
- Soft, fleshy, gray-tan-yellow lobulated (cystic in BWS)

Pancreatoblastoma

- Malignant epithelial neoplasm of the pancreas showing multiple lines of differentiation including acinar and squamoid; endocrine, ductal and mesenchymal components may also be present
- Nested, with lobules separated by fibrous bands
- Lobules have several components
 - Sheets of uniform polygonal cells with distinct borders, pale basophilic cytoplasm, central nuclei with prominent nucleoli
 - Squamoid nests, usually in the center, present by definition
 - Acinar, endocrine, ductal and fibrous components
 - Primitive component, immature, small monotonous cells



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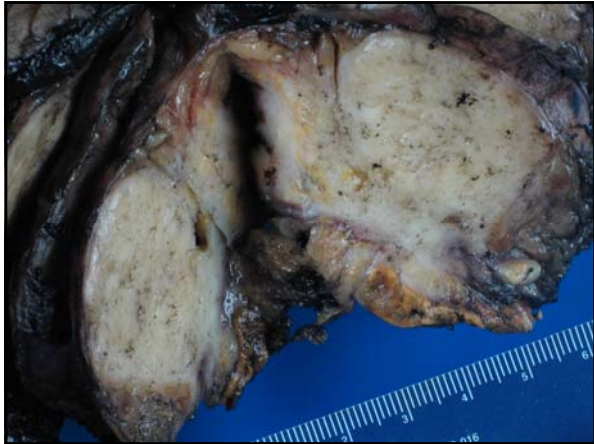
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Pancreatoblastoma

- Prognosis differs for infants versus adults
- In childhood:
 - if detected before metastases, most curable by complete surgical resection
 - if detected after metastases, prognosis is poor, with though some response has been seen with newer chemotherapy
- In adults: Almost all cases are fatal

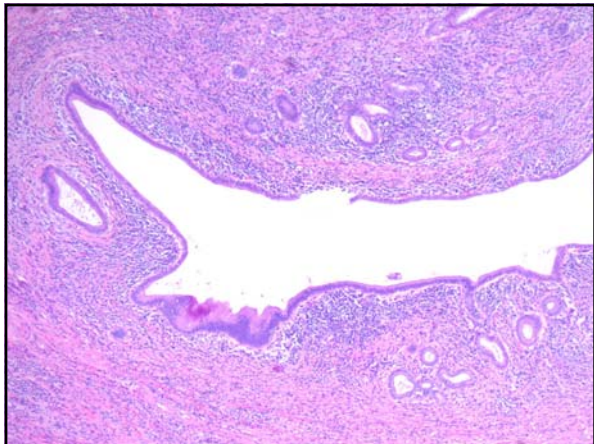
Lymphoplasmacytic sclerosing pancreatitis

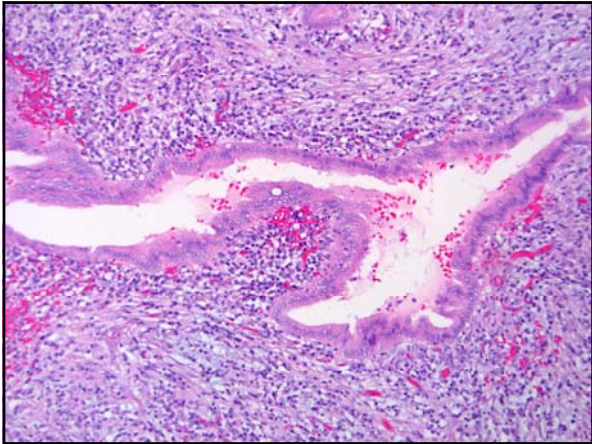
- "Tumor-like" lesion
- Also called autoimmune pancreatitis
- Usually male, wide age range (mean 57 yr)
- Predominantly head of pancreas, though seen throughout
- May be associated with other autoimmune diseases
- May have elevated serum levels of IgG4
- White tan irregular ill-defined mass lesion, may focally constrict bile duct (grossly similar to pancreatic adenocarcinoma), also can present as diffuse firm enlargement of the pancreas without a distinct mass

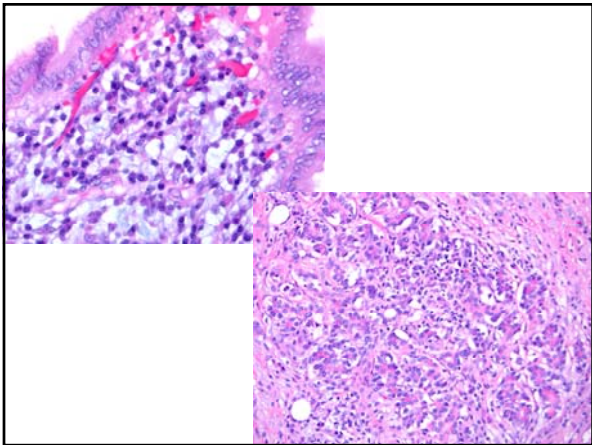


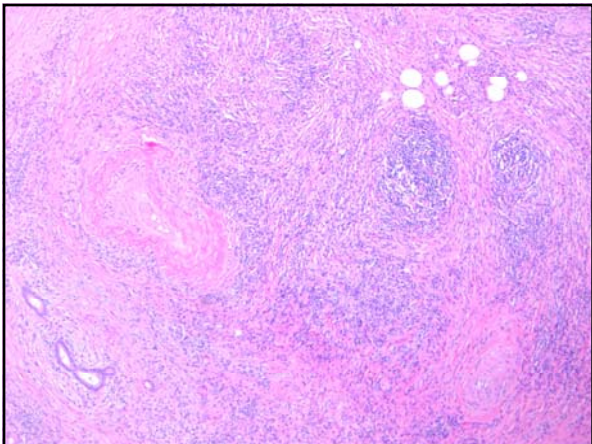
Lymphoplasmacytic sclerosing pancreatitis

- Prominent periductal and acinar lymphoplasmacytic infiltrate (IgG4+ plasma cells), with or without lymphoid follicles
- “Storiform” perilobular fibrosis which may extend into peripancreatic soft tissue
- Phlebitis of small to medium sized veins
- No calcifications, fat necrosis or cyst formation (findings seen with typical chronic pancreatitis)









Lymphoplasmacytic sclerosing pancreatitis

- Favorable response to steroids
- Often leads to surgical resection

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