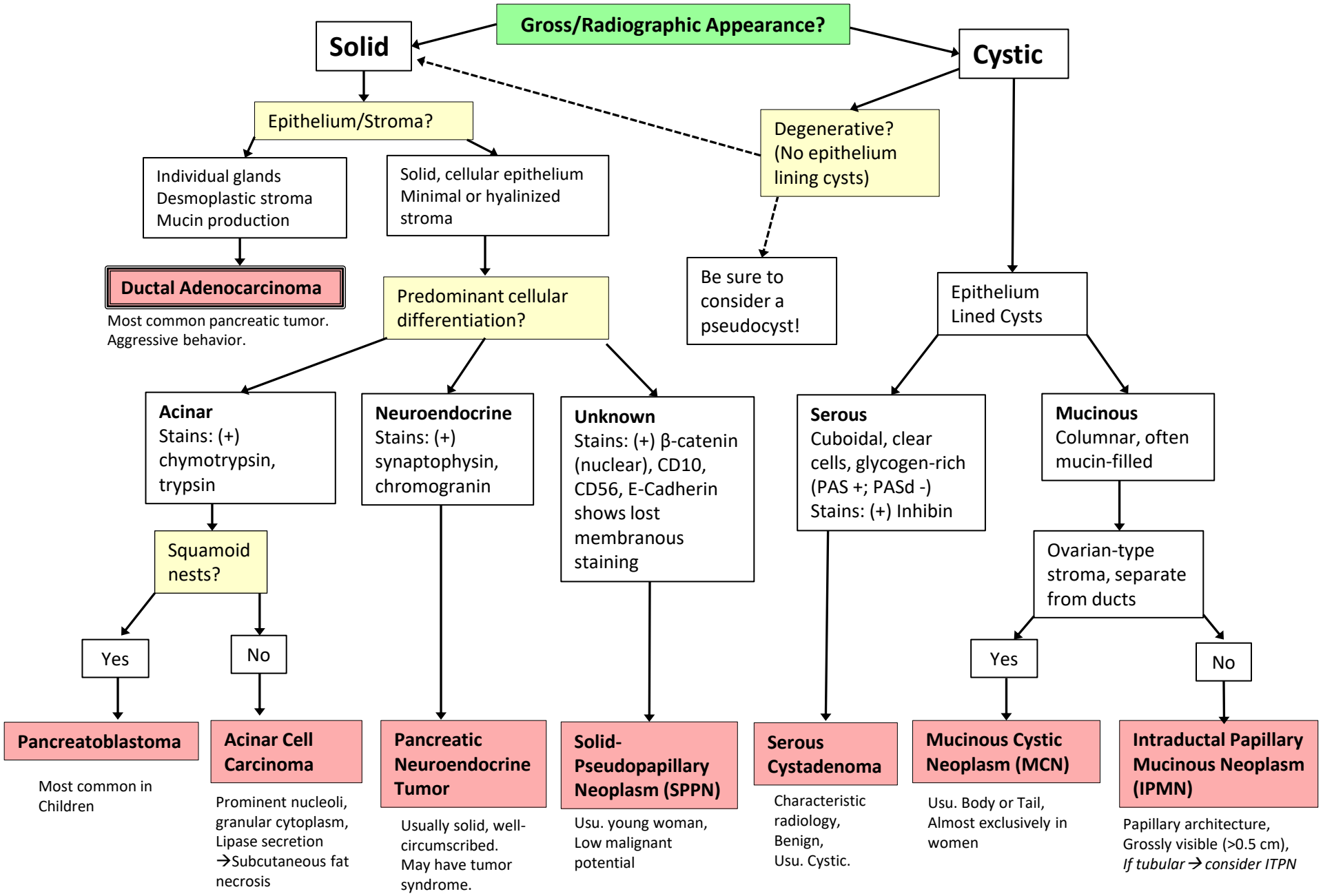
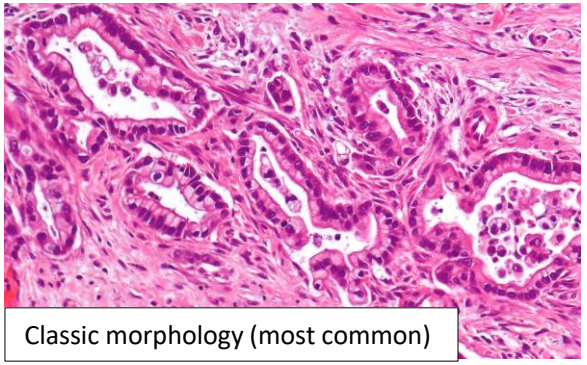
Prepared by Dr. Kurt Schaberg

Diagnostic Algorithm for **Pancreatic Tumors**



adapted from WHO Blue Book

Pancreatic Ductal Adenocarcinoma *aka **PDAC***

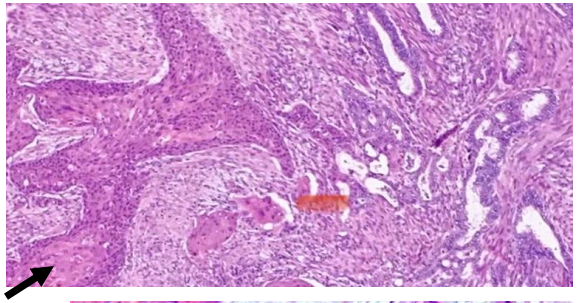


Classic morphology (most common)

Invasive carcinoma with <u>glandular/ductal differentiation</u>
90% of Pancreatic tumors *(When people say, "pancreatic cancer," they usually mean this!)*
Most common in head of pancreas→ resect with Pancreaticoduodenectomy (Whipple procedure)
<u>Often unresectable at time of diagnosis</u> → **<u>Poor Prognosis</u>** (often < 1 year)
Precursor lesions: IPMN, MCN, PanIN

Most are well to moderately-differentiated and show **duct-like glandular structures** with luminal and/or cytoplasmic mucin that <u>haphazardly infiltrate</u> and elicit a desmoplastic response (disrupting normal lobular architecture). Virtual slide 1 2
Cells can have eosinophilic, mucinous, clear, or foamy cytoplasm. Variable cytologic atypia.

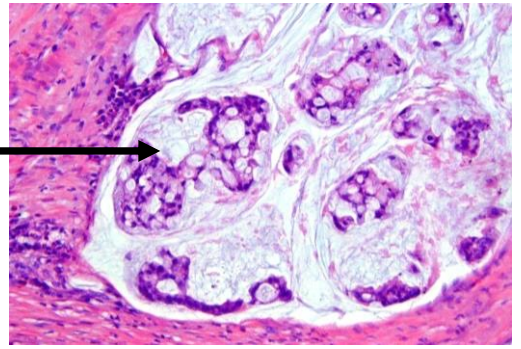
<u>Genetics:</u>
>90% show KRAS activation point mutations (also in PanIN)
Also often present are inactivating mutations in the tumor suppressors: TP53, P16, and/or SMAD4
Loss of SMAD4 (DPC4) is relatively specific to pancreatic adenocarcinomas and can be evaluated by IHC



<u>Histological Subtypes:</u>
Adenosquamous carcinoma: ductal adenocarcinoma and ≥30% of the tumor shows squamous differentiation.

Squamous cell carcinoma: exclusively squamous differentiation, with no glandular differentiation. Must exclude a metastasis. (any squamous component→ worse prognosis)

Colloid carcinoma: ≥80% of the neoplastic epithelium is suspended in abundant extracellular mucin (often large and arise in an intestinal-type IPMN). CDX2+. (much better prognosis)

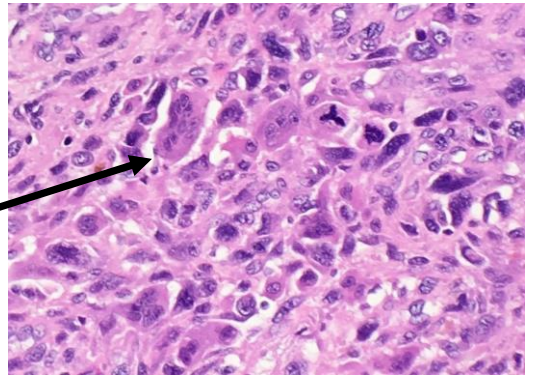


Hepatoid carcinoma: ≥50% displays histologic and IHC evidence of hepatocellular differentiation. Large, polygonal cells with abundant eosinophilic cytoplasm.

Medullary carcinoma: Limited gland formation, pushing border, and syncytial growth, frequently with abundant tumor-infiltrating lymphocytes. Often MMR-deficient.

Signet-ring (poorly cohesive cell) carcinoma: ≥80% consists of individually arrayed, poorly-cohesive cells, cords, or sheets, often with intracellular mucin vacuoles. Variable extracellular mucin.

Invasive micropapillary carcinoma: ≥50% consists of small solid nests of cells suspended within stromal lacunae (like in breast and bladder). Worse prognosis.

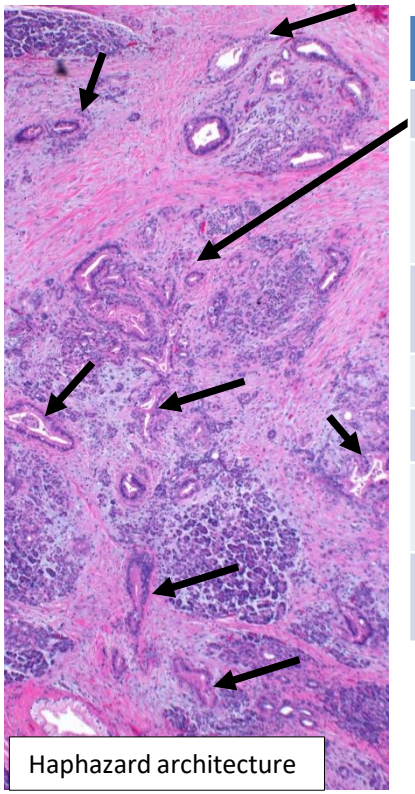


Undifferentiated carcinoma with osteoclast-like giant cells: Non-neoplastic osteoclast-like multinucleated giant cells and histiocytes mixed in with neoplastic mononuclear cells. Sometimes better prognosis. Virtual slide

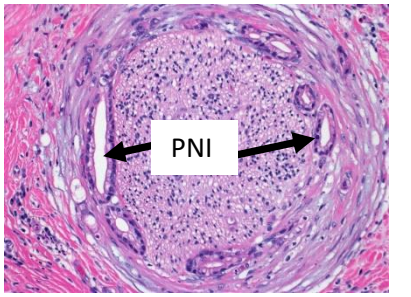
Undifferentiated carcinoma: tumor doesn't show direction of differentiation. Often sheet-like growth without glands. Very cellular. Variable IHC. Poorer prognosis. Subtypes: Anaplastic, Sarcomatoid, Carcinosarcoma.

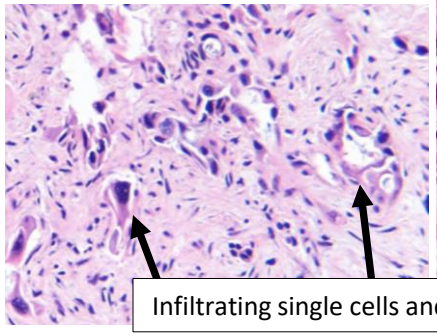
Ductal Adenocarcinoma	Chronic Pancreatitis
Haphazard, irregular architecture	Lobular, organized architecture
Incomplete luminal spaces with gland rupture. Often angulated. Interanastamosing.	Complete luminal spaces. Usually rounded glands.
Cellular pleomorphism (>4:1 variation in size)	Less pleomorphic
Perineural invasion	Absent
Vascular/perivascular invasion	Absent
Mitoses and nucleoli often prominent	Often absent
Can extend outside of the pancreas into fat, etc…	Confined to pancreas

Note: *<u>Both</u> can show edematous stroma*

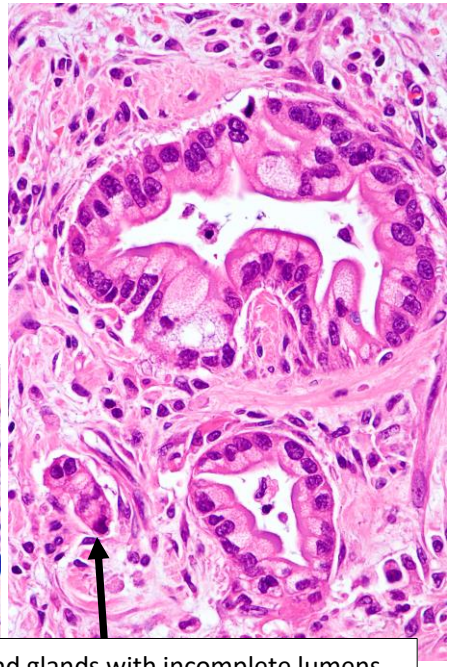


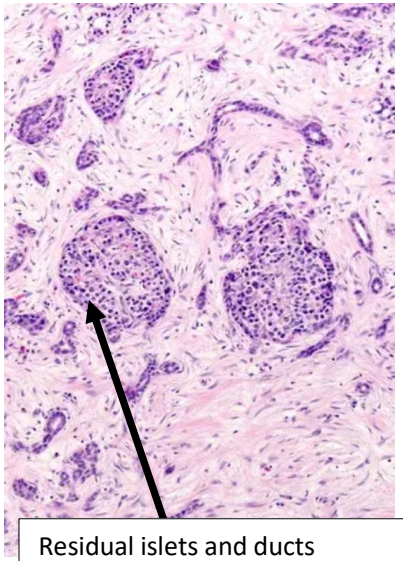
Haphazard architecture



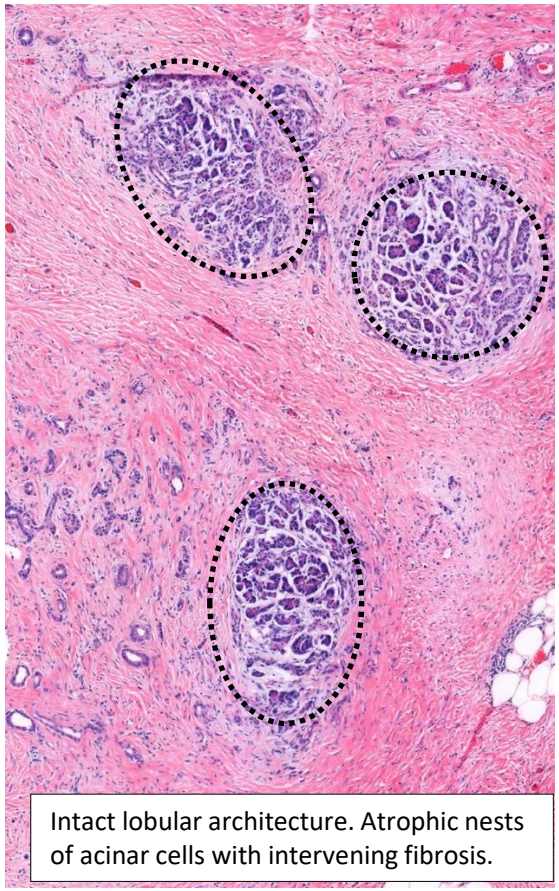


Infiltrating single cells and glands with incomplete lumens

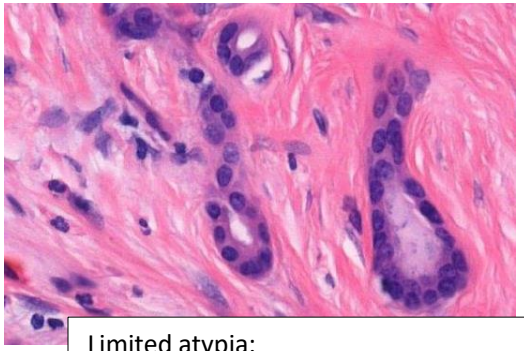




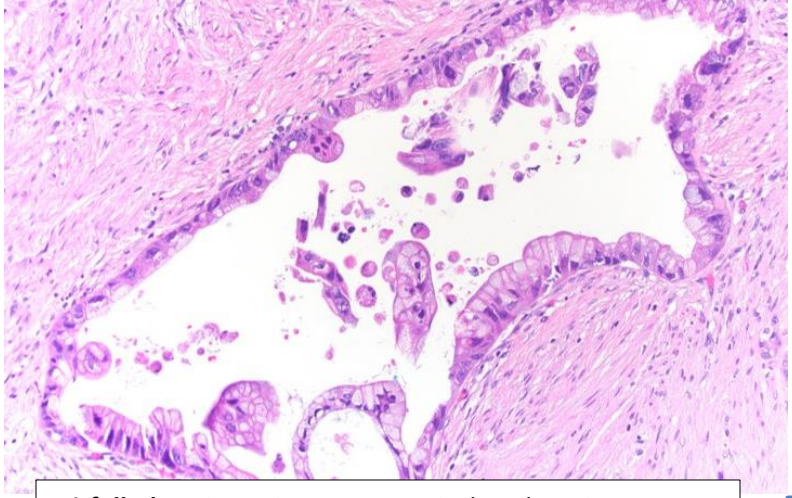
Residual islets and ducts overgrown by fibrosis.

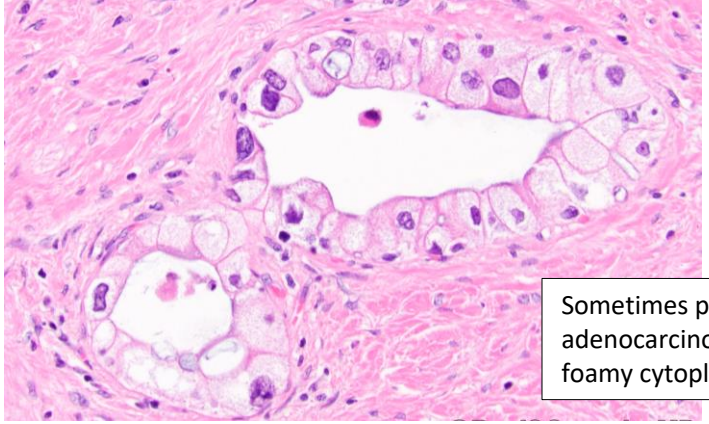


Intact lobular architecture. Atrophic nests of acinar cells with intervening fibrosis.



Limited atypia:
Most nuclei are small with “twins.”
Rounded, open lumina.





Sometimes pancreatic ductal adenocarcinoma can have striking foamy cytoplasm.

Pitfall Alert: Sometimes pancreatic ductal carcinoma can show a "large duct" pattern of growth, mimicking in situ disease (PanIN or IPMN). The haphazard pattern of growth helps to identify that it is really invasive.

Classic Age/Gender association for **cystic pancreatic tumors in women** (from radiology):
Daughter→ SPPN, Mother→ MCN, Grandma→ Serous cystadenoma

Tumor	Growth	CK7	EMA (MUC1)	Trypsin	Synaptophysin	Chromogranin	CEA	β-catenin Nuclear	Other IHC
Ductal Adenocarcinoma	Infiltrative	+	+	-	-	-	+	-	No unique IHC to exclude metastases.
IPMN	Intraductal	+	+	-	-	-	+	-	
MCN	Extraductal, Ovarian stroma	+	+	-	-	-	+	-	
Serous Cystic Neoplasm	Microcystic	+	-	-	-	-	-	-	(+) CAIX, Inhibin, GLUT1
Acinar cell carcinoma	Solid	+/-	-	**++**	-/+ *(focal/faint)*	-/+ *(focal/faint)*	-	-/+ *(rarely)*	Chymotrypsin, BCL10
Pancreatoblastoma	Solid	+	-	++	+/-	-/+	-	-/+ *(rarely)*	nuclear ß-catenin in squamoid nests
SPPN	Loosely cohesive, pseudocystic	-	-	-	-/+ *(focal/faint)*	-	-	**++**	(+)PR, CD10, CD56, Cyclin D1 (-) E-cadherin, Chromogranin
NET/NEC	Solid	+/-	-	-	**++**	**++**	-	-	

adapted from WHO Blue Book

Non-Invasive Glandular Lesions

All of these pre-invasive lesions are benign, but can *progress* to invasive adenocarcinoma, so thorough/complete histologic evaluation is often necessary to exclude malignancy.

Intraductal Papillary Mucinous Neoplasm *(IPMN)*

Grossly visible (often >5mm) proliferation of mucinous cells within the main pancreatic duct (main-duct IPMN) or its branches (branch-duct IPMN).
Most often in head. Fairly common, particularly in elderly.
Decision to resect depends on size, location, symptoms, age, etc…
A solid nodule radiographically is suspicious for invasion.

Grade based on worst area.
Low-grade: mild to moderate atypia
High-grade: severe atypia, irregular branching and budding, loss of polarity.

3 Subtypes:
Gastric: resembles foveolar cells (tall mucinous cells with basal nuclei). Most common, least aggressive. Usually in branch duct.

Intestinal: Intestinal epithelium (tall columnar cells with cigar-nuclei, basophilic cytoplasm, variable apical mucin). Usually in head.
Unique facts: IHC: CDX2+. Progresses to colloid carcinoma.

Pancreatobiliary: Resembles biliary epithelium, low cuboidal with amphophilic cytoplasm and complex papillae. Enlarged nuclei with nucleoli.

Molecular: KRAS mutations the most common (and seen in many GI cancers). GNAS mutations are also common and seem to be relatively unique to IPMNs

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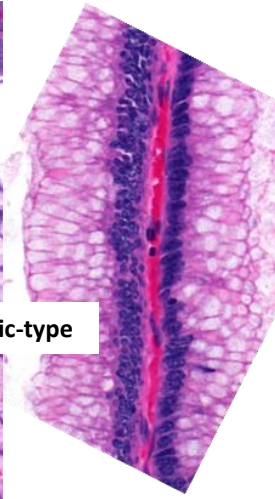
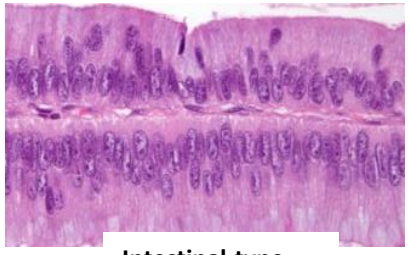
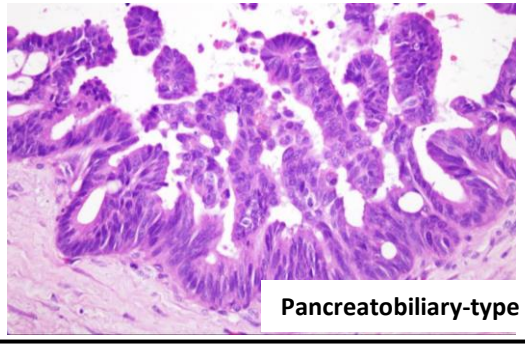


Gastric-type



Intestinal-type



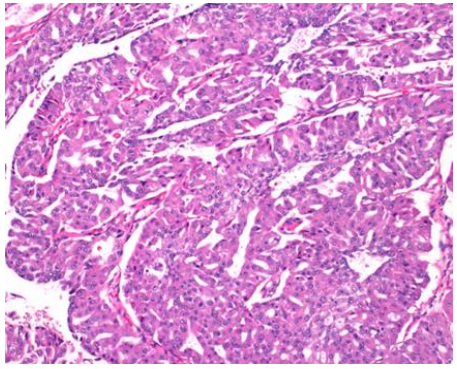
Pancreatobiliary-type

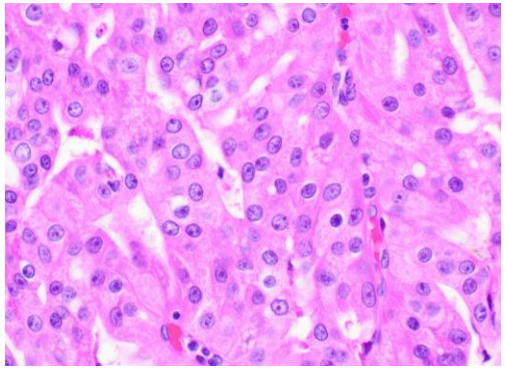
Intraductal Oncocytic Papillary Neoplasm *(IOPN)*

Essentially, an IPMN, but with abundant eosinophilic granular cytoplasm, often forming cribriform lumens.
Almost all high-grade.

Stain with Hepar-1.

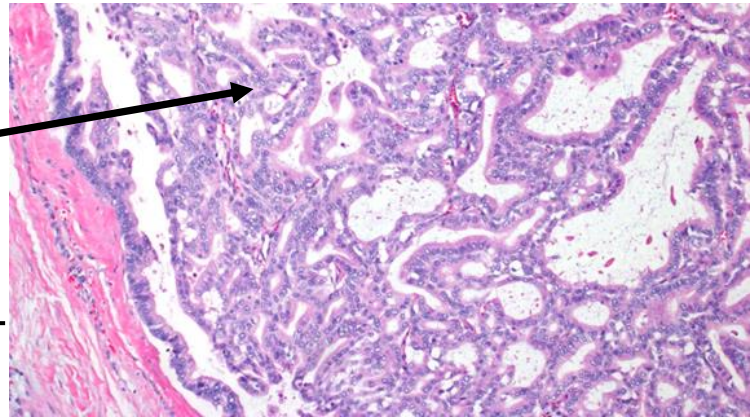
Genetically distinct with Recurrent Rearrangements in PRKACA and PRKACB (includes same fusion as fibrolamellar HCC)





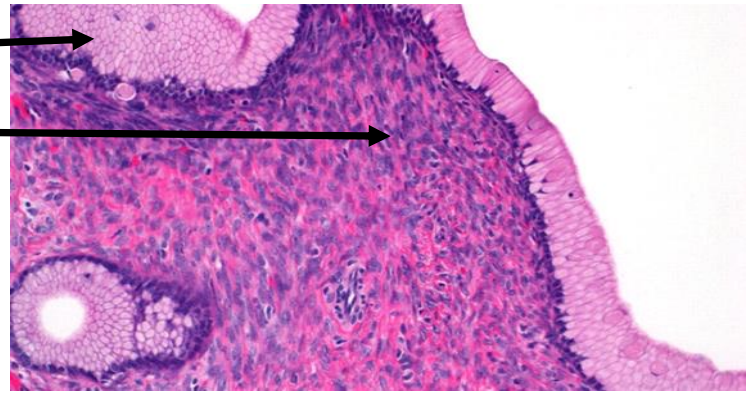
Intraductal Tubulopapillary Neoplasm *(ITPN)*

Intraductal epithelial neoplasm that forms predominantly back-to-back **tubules**.
Often have high-grade dysplasia, ductal differentiation, and no overt mucin production.
Can have focal papillary growth.
Often fill and distort ducts making hard to evaluate for invasion.
IHC: (-) Synaptophysin, Chromogranin, Chymotrypsin, Trypsin.
Genetically distinct (No KRAS mutations).
Rare.



Mucinous Cystic Neoplasm *(MCN)*

Cyst-forming, mucin-producing neoplasm with a wall of distinct ovarian-type subepithelial stroma.
Epithelium is predominantly columnar, **mucinous epithelium**
Does *not* connect to the ductal system (unlike IPMNs)
Ovarian stroma: densely packed spindled cells (+)PR/ER, SMA, inhibin, and calretinin.
Almost exclusively in women. Almost always in Body or tail.
Virtual slide 1 2



Simple Mucinous Cyst *(Not in WHO)*

Cysts >1 cm lined by nonpapillary mucinous epithelium without ovarian-type stroma
Usually gastric-type lining; Frequent KRAS mutations;
Essentially a flat IPMN or dilated PanIN for lesions that don't fit into IPMN or MCN well

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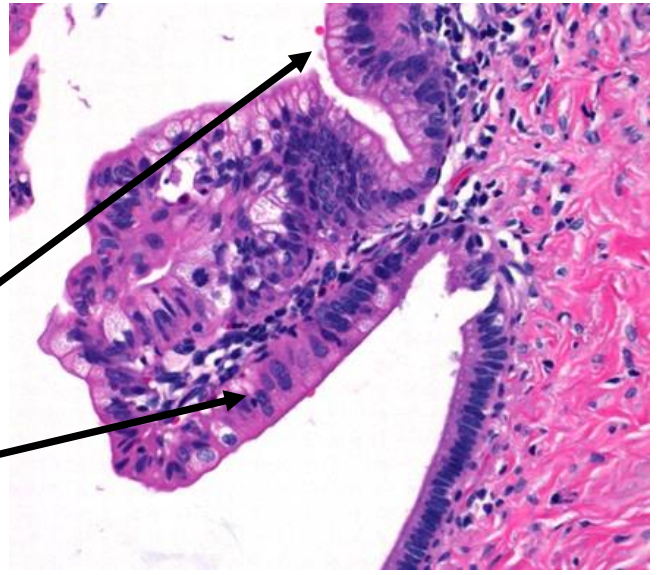
Pancreatic Intraepithelial Neoplasia *(PanIN)*:

Microscopic, Non-invasive, non-mass forming neoplasia confined to the pancreatic ducts (In situ). Can be flat or micropapillary. Variable intracellular mucin.

Main precursor to ductal adenocarcinoma. Harbors same genetic mutations (e.g., KRAS), with increasing frequency with higher grades.

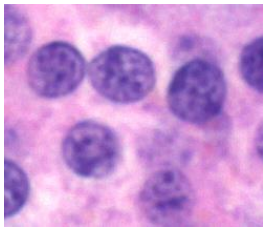
Low-grade PanIN: Basally located or pseudostratified with mild to moderate cytologic atypia. Flat or papillary. Common incidental finding. Low risk, so no need to report at margins.

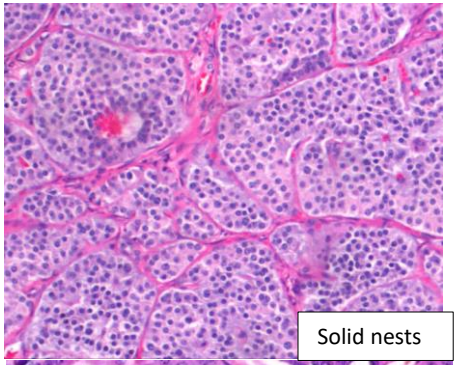
High-grade PanIN (Carcinoma in situ/CIS): Severe cytologic atypia with loss of polarity and often abnormal architecture (papillary, micropapillary, or cribriform). Higher risk, so report at margins.

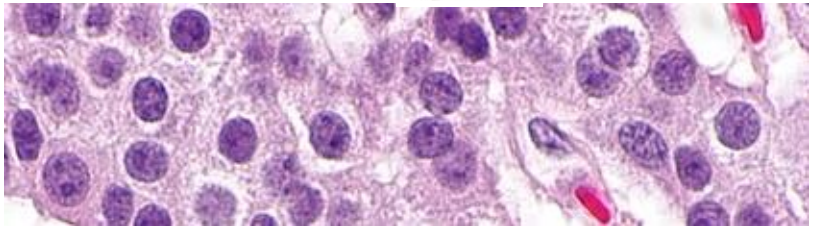


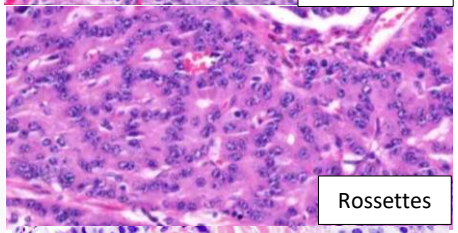
Well-differentiated Neuroendocrine Tumors *(PanNET)*

Uniform, **round nuclei** with **"Salt and Pepper"** speckled (coarsely clumped) chromatin.
Organoid architecture (i.e., nested, cords, glands-like rosettes, or ribbons)
Cuboidal cells with eosinophilic to amphophilic finely granular cytoplasm.
Minimal to moderate atypia. Usually no necrosis.
Can see amyloid or calcifications.
Can get anywhere in the pancreas.
Associated with MEN and VHL.



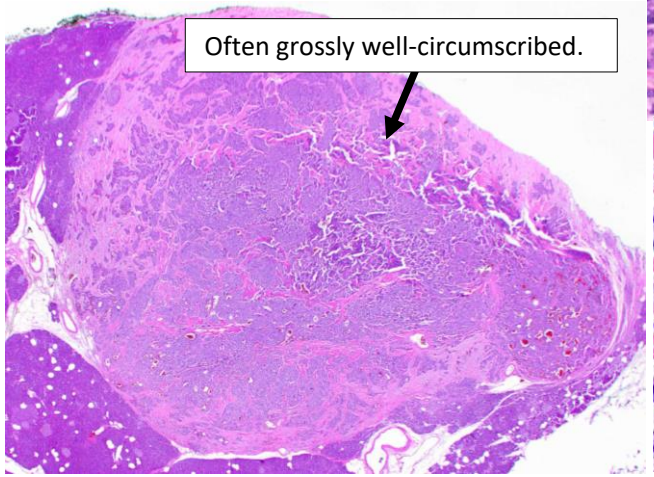


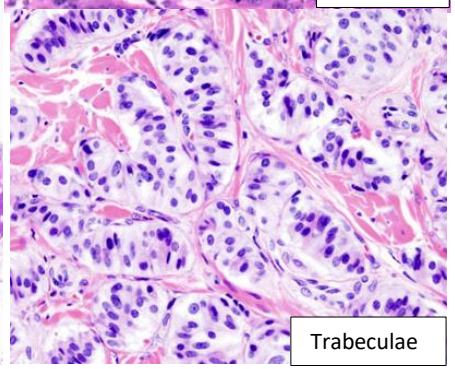




Molecular: MEN1, DAXX, ATRX mutations common
IHC: (+) Synaptophysin, Chromogranin, INSM1, CK.
If functional, may express specific hormones by IHC.

Malignant, **but slow-growing, indolent** progression
(10 year survival ~50%)
Early NETs have a low risk of metastasis
Usually middle-aged.





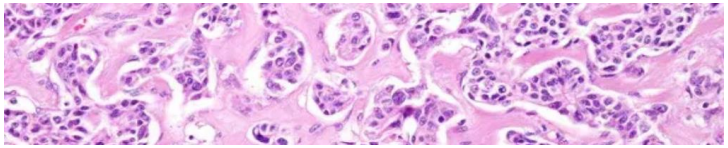
Can be "functional" (secrete hormone→ symptomatic)
If functional, can be any size.
If non-functional, must be ≥0.5 cm to call NET
If <0.5 cm & non-functional with no mitoses→
NE "**microtumor**" (very low risk)

Virtual slide 1 2 3 4

(See GI Neuroendocrine Tumor Notes for more info)

Grade	Ki67 Proliferation Index	Mitotic index
Grade 1	<3%	<2
Grade 2	3-20%	2-20
Grade 3	>20%	>20

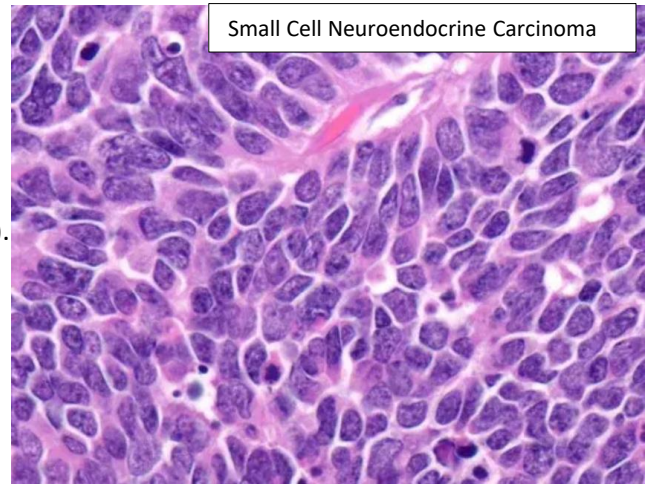
Ki67 Proliferation index based on evaluation of ≥ 500 cells in a "hot spot."
Mitotic count based on evaluating 50 Hpfs, but reported per 10 Hpfs.



"Functioning"→ hormone secreting → characteristic syndrome
Functioning tumors are often **pancreatic** and **discovered sooner** due to symptoms.
Non-functioning tumors are often discovered later (with metastases) or incidentally.

Insulinoma→ Usu. Small, present early with hypoglycemia
Gastrinoma→ Zollinger-Ellison Syndrome → acid hypersecretion → extensive peptic ulcers
VIPoma→ Watery diarrhea with hypokalemia and achlorhydria
Glucagonoma→ Necrolytic migratory erythema, diabetes, stomatitis
Somatostatin → diabetes, cholelithiasis, diarrhea → can have glandular growth and psammoma bodies
"Carcinoid syndrome"→ Serotonin and Kallikrein secretion → Flushing, diarrhea, bronchoconstriction. Usu. Only if liver metastases.

Poorly-differentiated Neuroendocrine Carcinomas *(PanNEC)*


Small Cell Neuroendocrine Carcinoma

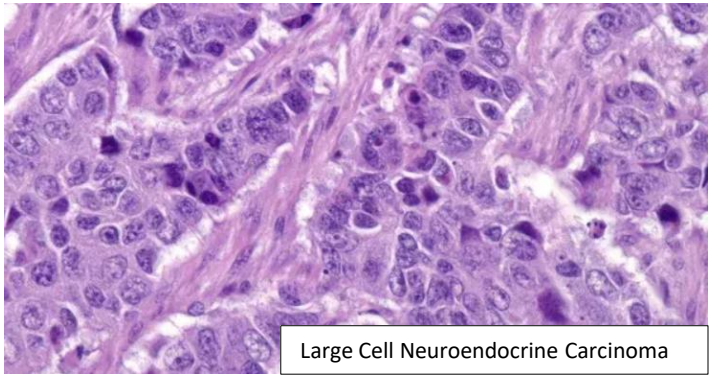
Relatively uncommon. Usually older patients.
Poorly-differentiated, High-grade neuroendocrine neoplasms.
Highly atypical cells, with frequent necrosis and mitotic activity
By definition: >20 mitoses/mm2 or Ki67 proliferation index >20%
Often arise from *non*-neuroendocrine tumors (and subsequently *develop* neuroendocrine differentiation).
Malignant! Very metabolically active/**rapidly growing**
→ see on normal FDG-PET scan

IHC: (+) Synaptophysin, chromogranin, INSM1, CD56, Keratins (staining may be variable/limited)
(-) Trypsin, Chymotrypsin, BCL10

Molecular: p53 mutations, RB1 loss (and other carcinoma-associated mutations, like KRAS)
Treatment: Platinum-containing chemotherapy

Small Cell Neuroendocrine Carcinoma
Morphology: Fusiform nuclei, **finely granular chromatin**, **scant cytoplasm** (high N:C ratio), nuclear molding, and frequent crush artifact. Extensive necrosis.
Tons of mitoses. Ki67 almost 100%.

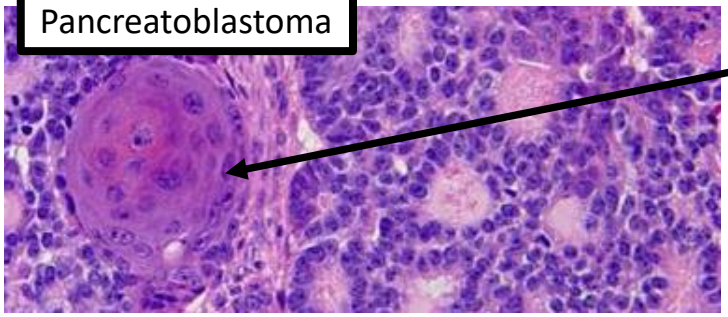
Large Cell Neuroendocrine Carcinoma
Morphology: Large, round vesicular nuclei, with **prominent nucleoli**,
and moderate amounts of polygonal, amphophilic cytoplasm. Sheet-like to nested growth.
Ki67 often 60-80% range


Large Cell Neuroendocrine Carcinoma

"Mixed" Neoplasms

Mixed Ductal adenocarcinoma—neuroendocrine neoplasm Mixed Acinar—neuroendocrine carcinoma
Mixed tumors composed of two morphologically recognizable components; ≥30% of the neoplasm composed of each type. Each component should look and stain as they would individually.
In both cases, the NE component is usually NEC, but can be NET..

Pancreatoblastoma



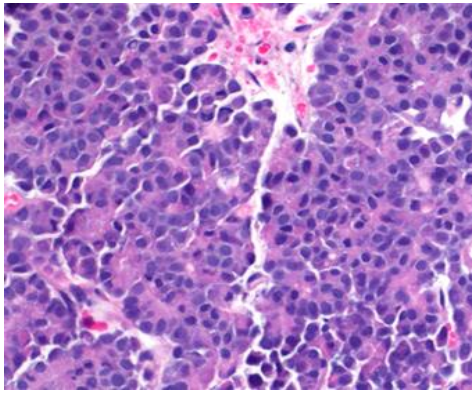
Carcinoma showing ***Multiple*** lines of differentiation including Acinar cell differentiation and **squamoid nests**. Also, often endocrine and sometimes ductal growth.
Much of the tumor looks like Acinar Cell Carcinoma, BUT **defining findings is Squamoid nests.**

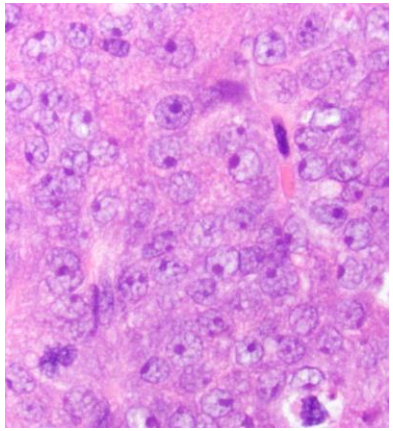
Rare. Most common in children (but can see in adults)
Associated with Beckwith-Wiedemann syndrome and FAP.

IHC: Acinar component stains with Trypsin/Chymotrypsin. Squamoid nests stain with EMA, Synaptophysin may show positivity. Often nuclear ß-catenin in squamoid nests.

Often indolent, curable tumors.

Acinar Cell Carcinoma





Carcinoma showing Acinar cell differentiation.
Most commonly older men.

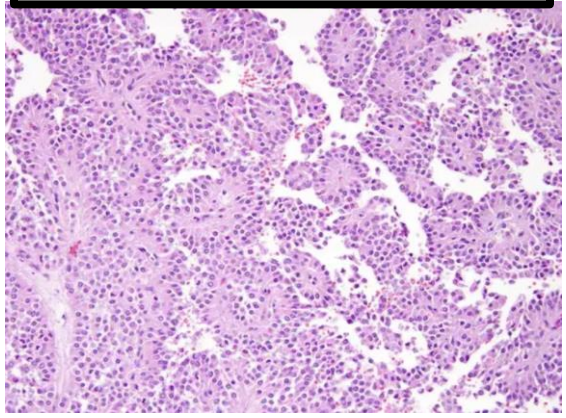
Lobular to trabecular pattern of growth, very cellular. Scant stroma.
Cells have moderate amounts of **granular cytoplasm** (***full of zymogen*** granules) with uniform nuclei and a **single prominent nucleolus**. Frequent necrosis.

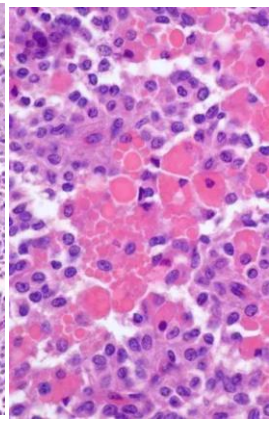
Can be *mixed* with neuroendocrine or ductal carcinomas

Immunohistochemical evidence of acinar differentiation: trypsin, chymotrypsin, lipase, or amylase; BCL10 is also good. No genetic hallmark
Can cause subcutaneous fat necrosis due to lipase hypersecretion
Poor prognosis (better than PDAC, but worse than PNET; Median 19 months)

Virtual slide 1 2 3

Solid Pseudopapillary Neoplasm *SPPN*





Most common in **adolescent girls** and young women

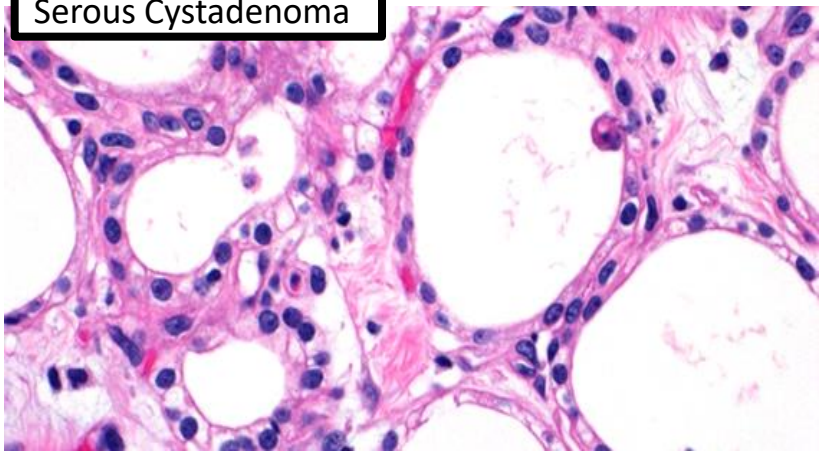
No specific line of differentiation.
Solid and pseudopapillary/cystic growth. Hemorrhage and pseudocyst formation.
Pseudopapillae are formed when cells detach from fibrovascular cores
Solid tumor resembles neuroendocrine tumor (monomorphic round cells)
Commonly see **hyaline globules** (PAS+) and cholesterol clusters/foamy histiocytes.
Cells have eosinophilic to vacuolated cytoplasm. Nuclei oval, often grooved.

IHC: **Nuclear ß-catenin.** Loss of E-cadherin. (+)Cyclin D1, CD56, CD10, PR, LEF1
Sometimes express CK or CD117. Negative for Neuroendocrine and Acinar markers.

Low-grade malignant, with often good prognoses and surgical cure.

Virtual slide 1 2 3

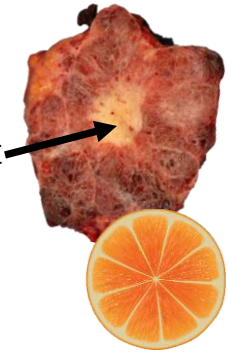
Serous Cystadenoma



Benign. Often identified incidentally. Often older women in the body.

Composed of **bland, uniform, cuboidal cells with clear, glycogen-rich cytoplasm.**
Cysts lined by a single layer of cells, with well-defined cell borders.
Small, round, dense nuclei. Can be solid.
Glycogen→ stains with PAS (and digested by diastase)
IHC: Stains with inhibin, CAIX, GLUT1

Characteristic multilocular, sponge-like appearance with a central scar (think of a cut orange!)



Associated with von Hippel-Lindau syndrome (VHL) (can get multiple).

Very Rare: If metastasizes→ Serous cystadenocarcinoma

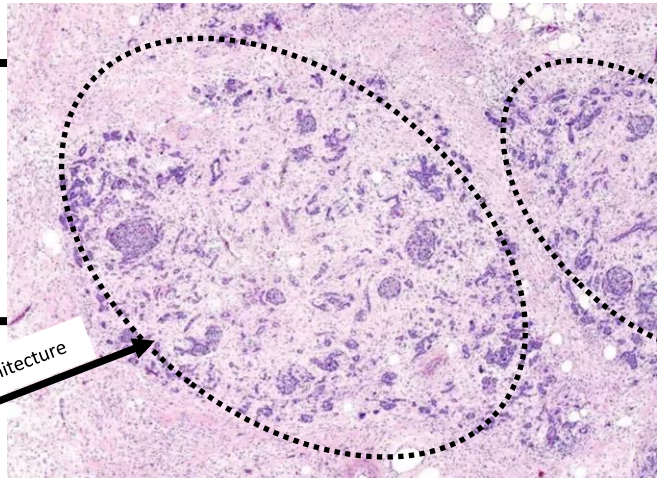
Virtual slide 1 2 3

Non-neoplastic Processes

Acute Pancreatitis

Usually a **clinical diagnosis**. Often due to Alcohol or gallstones.
Severe abdominal pain. **Elevated serum lipase** and amylase.
Treat with supportive care.

Fat necrosis, saponification, hemorrhage, thrombosis.



Chronic Pancreatitis

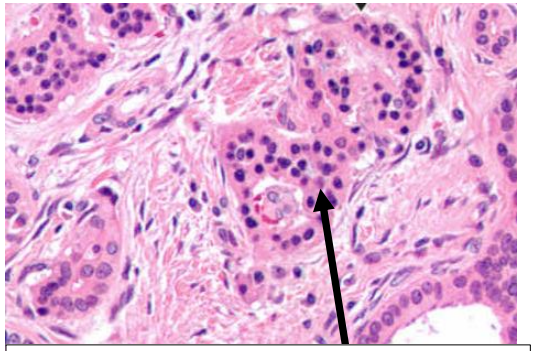
Progressive inflammation → **scarring and gland destruction** → gland dysfunction
Destruction of acini → Exocrine insufficiency → fat malabsorption → steatorrhea
Destruction of Islets → Endocrine insufficiency (comes late) → diabetes mellitus

Most often caused by excess alcohol consumption.
Several hereditary forms. Common in cystic fibrosis.

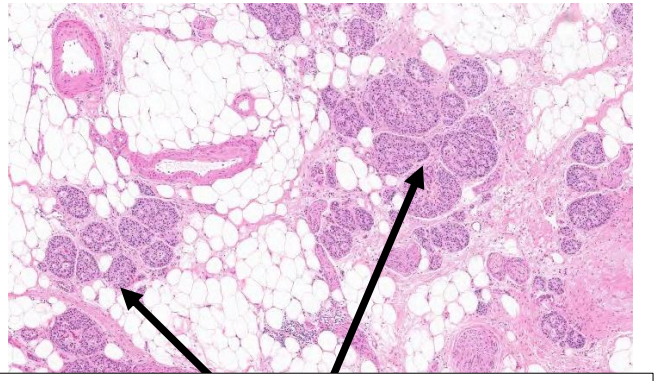
Fibrosis and glandular **atrophy** with **retained lobular architecture**.
Islets of Langerhans preserved until *late* → may show "pseudo-hyperplasia"
Ducts can show reactive changes, including metaplasia (squamous, mucinous)
Hypocellular aspirates with stromal fragments and islet cells.

Pitfall alerts: Reactive ducts can resemble invasive ductal adenocarcinoma (see prior comparison page).

Virtual slide 1 2 3



Pitfall Alert: Residual islets can resemble infiltrative ductal adenocarcinoma—the key is to recognize their bland, round "neuroendocrine" nuclei!

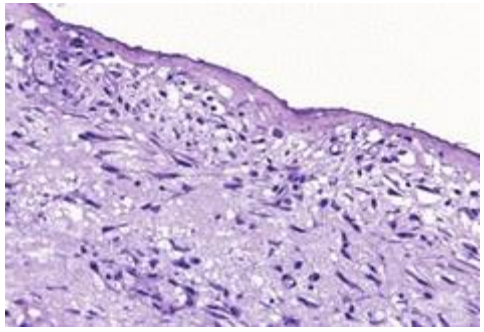


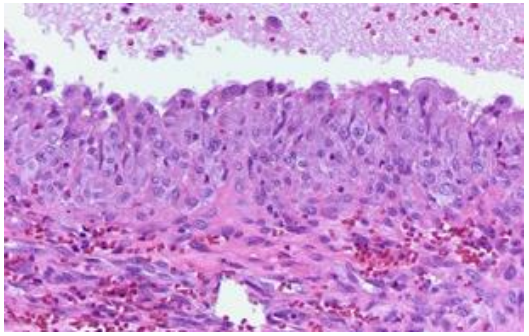
Pitfall Alert: When the acini go away with atrophy, the remaining islets can coalesce, resulting in "pseudo-hyperplasia," which can mimic a NET. A helpful clue is the intervening other tissues (fat, ducts, etc..)

Pseudocyst

Pancreatic or peripancreatic collection of **enzyme-rich fluid**
No **epithelial lining** (wall composed of **fibrosis and granulation tissue**)
Lumen contains hemosiderin, blood, histiocytes, and debris.
Often secondary to pancreatitis, and spontaneously resolves

FNA fluid analysis: High amylase (>250 IU/mL) and low CEA (<100 ng/mL)
Fluid often contains amorphous debris, bile, and inflammatory cells.



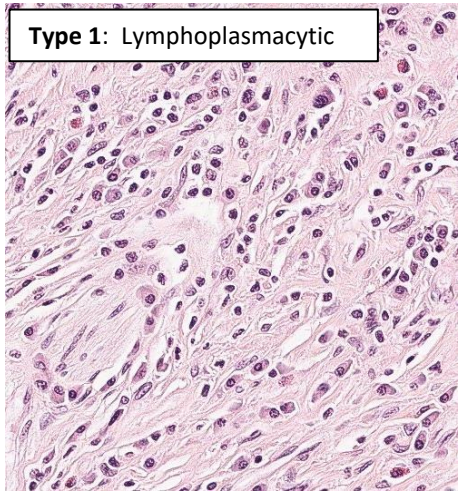


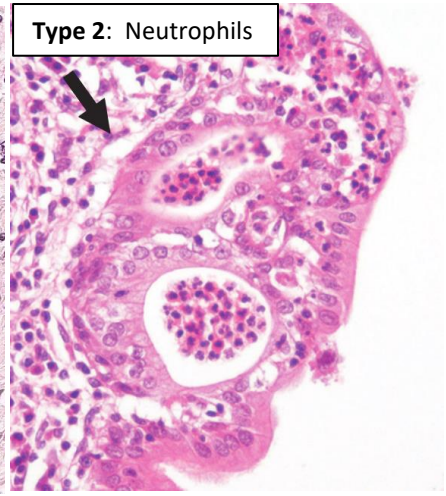
Autoimmune pancreatitis

<u>Type 1</u>: IgG4-related lobular and intralobular fibroinflammatory destruction
Key features:
1)Dense lymphoplasmacytic infiltrate,
2)Storiform fibrosis,
3)Obliterative phlebitis (can highlight with Elastin stain)
Diffuse increase in IgG4+ plasma cells
(>50/HPF on excision or >10/HPF on biopsy).

Clinically can mimic carcinoma with hard mass. Often elevated serum IgG4.
Warning: Can see some increased IgG4 focally with cancer!

<u>Type 2</u>: Duct-centric granulocytic destruction with epithelial damage with abscesses.
PD-L1 stains epithelium.

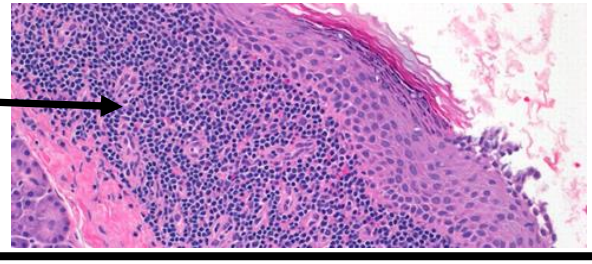




Lymphoepithelial Cyst

Cystic lesion lined by squamous mucosa with surrounding lymphoid tissue.
Rare. Virtual slide

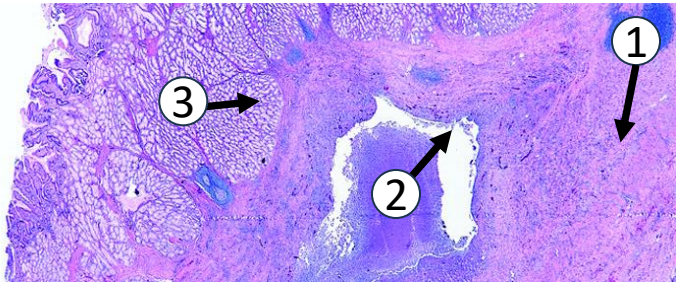
If sebaceous glands→ Dermoid cyst



Paraduodenal Pancreatitis ("Groove Pancreatitis")

Often heavy drinkers & smokers presenting with acute pancreatitis→ can mimic cancer
Solid/cystic mass identified at interface of duodenum and bile duct/pancreas near ampulla.
(in the "groove" between the pancreas and duodenum)

1) Duodenal wall near minor ampulla is thickened with fibrosis.
2) Cysts lined by granulation tissue. 3) Frequent Brunner gland hyperplasia.



Acinar Cystic Transformation of the Pancreas

Non-neoplastic transformation of pancreas, likely because of **obstruction**.
Unilocular or **multilocular cystic lesion**. Can diffusely involve gland.
Lined by benign acinar *<u>and</u>* ductal epithelium.
Surrounding atrophic pancreas.
Cysts may contain amorphous acidophilic concretions of precipitated enzymes.