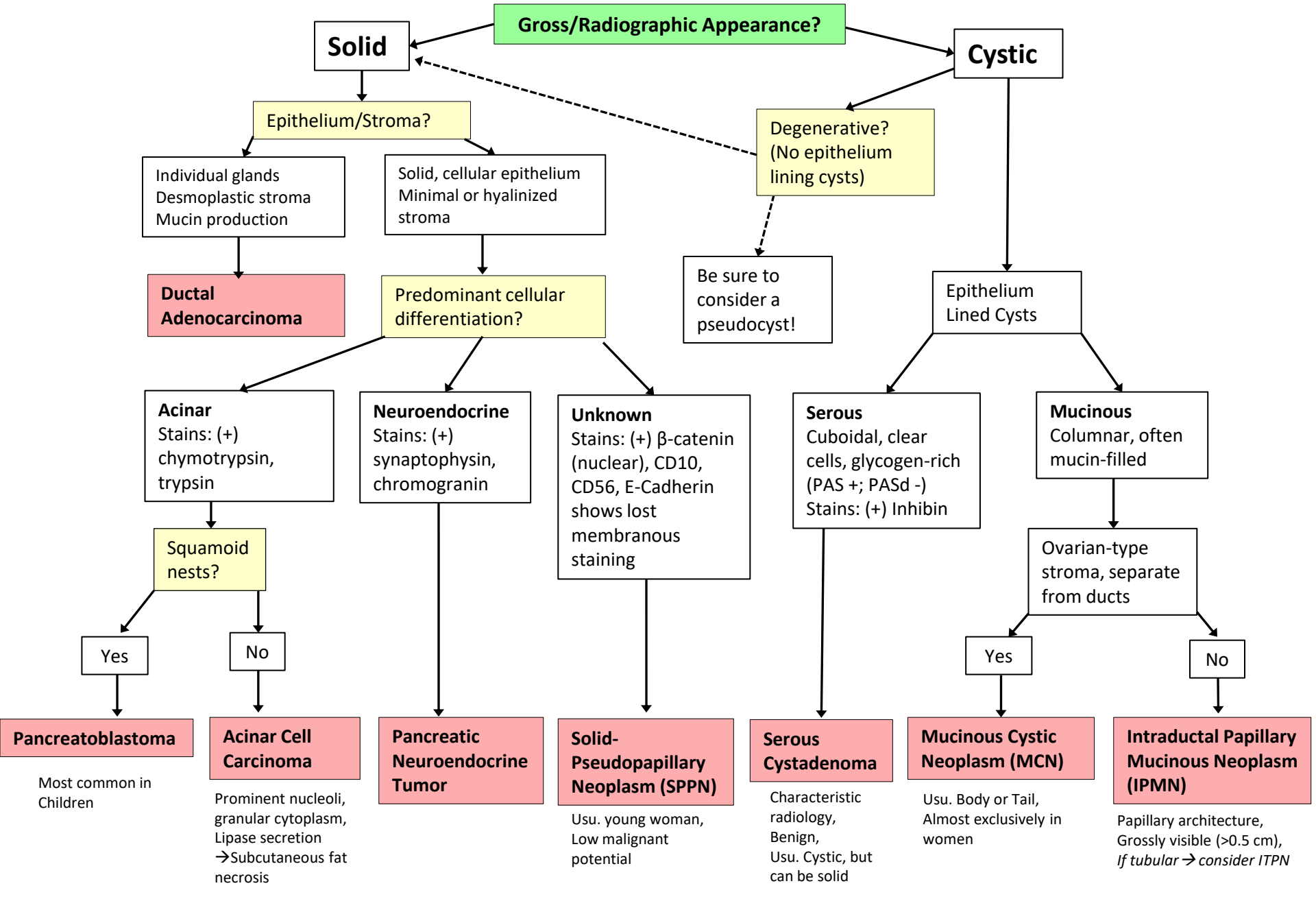
Last updated: 9/15/2024

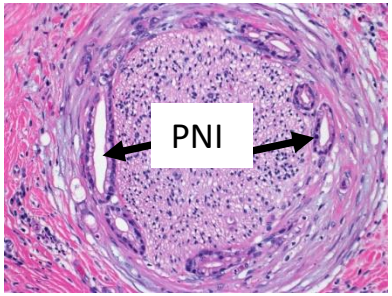
Prepared by Kurt Schaberg

Figure adapted from WHO

Diagnostic Algorithm for **Pancreatic Tumors**



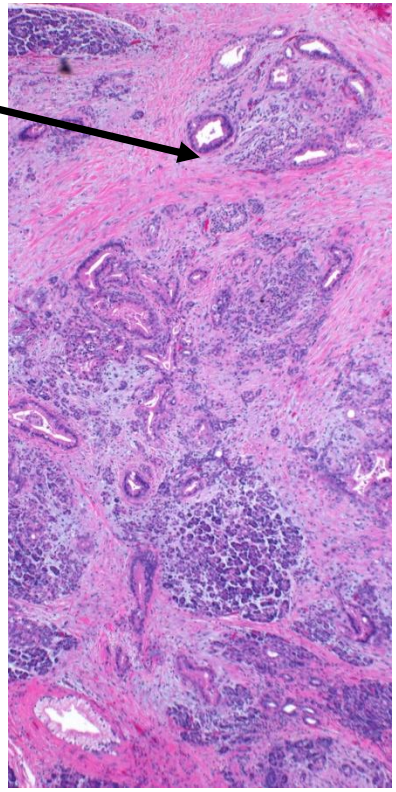
Pancreatic Ductal Adenocarcinoma



Invasive carcinoma with <u>glandular/ductal differentiation</u>
85% of Pancreatic tumors,
Most common in head of pancreas→ resect with Pancreaticoduodenectomy (Whipple procedure)
<u>Often unresectable at time of diagnosis, Poor Prognosis</u> (often < 1 year)
Precursor lesions: IPMN, MCN, PanIN

Most are well to moderately-differentiated and show **duct-like glandular structures** that <u>haphazardly infiltrate</u> and elicit a desmoplastic response (disrupting normal lobular architecture)

Haphazard architecture



<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>Subtypes:</u>
If squamous differentiation→ adenosquamous carcinoma (poorer prognosis)

If >80% of tumor has abundant extracellular mucin (often large and arise in an intestinal-type IPMN)→ Colloid Carcinoma (better prognosis)

If pleomorphic, no gland formation, +/- osteoclast-like giant cells→ Undifferentiated (anaplastic) carcinoma (with osteoclast-like giant cells)

Other Rare subtypes: Hepatoid carcinoma, Medullary carcinoma, Invasive micropapillary carcinoma, Signet-ring (poorly cohesive cell) carcinoma, Sarcomatoid carcinoma

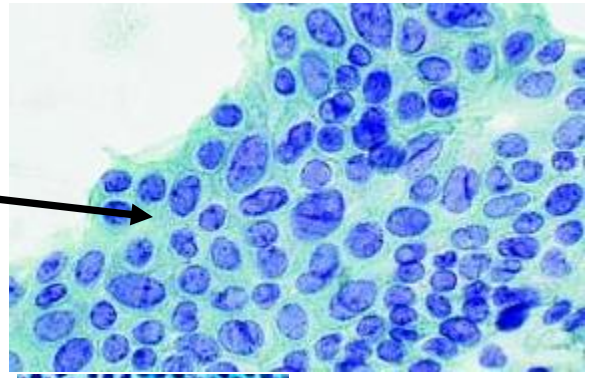
Cytology requirements:

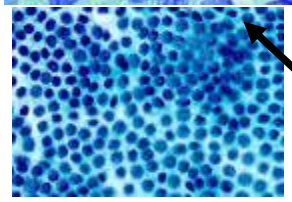
(best seen on Pap-stained slides)

1) Nuclear pleomorphism (>4:1)
2) Architectural disarray ("drunken honey comb")
3) Irregular nuclear contours
4) Single malignant cells

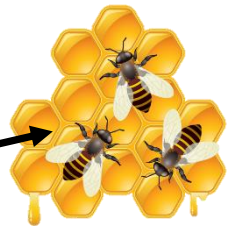
Often form 3-D clusters (vs Benign 2-D sheets) with 2 cell populations (Benign & Malignant).
If a stent is present, need to have higher threshold.

Ancillary testing on cytology specimens:
1) Next-gen sequencing→ looking for KRAS mutations, etc..
2) FISH (e.g., Urovysion) looking for aneuploidy





<u>Normal</u> "honeycomb" pancreatic ductal epithelium



Non-Invasive Glandular Lesions

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

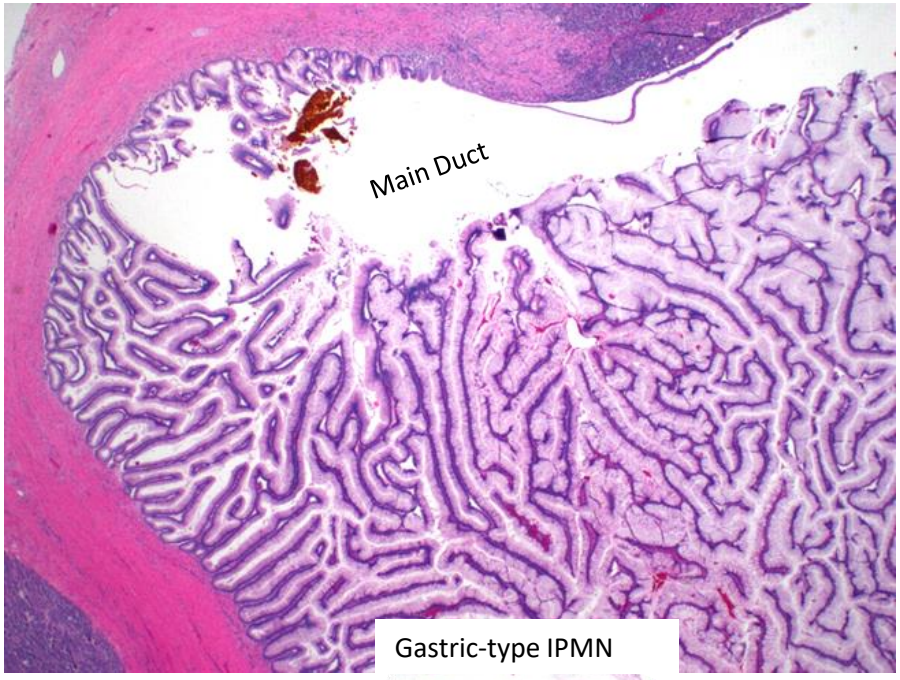
Intraductal Papillary Mucinous Neoplasm (IPMN)

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.

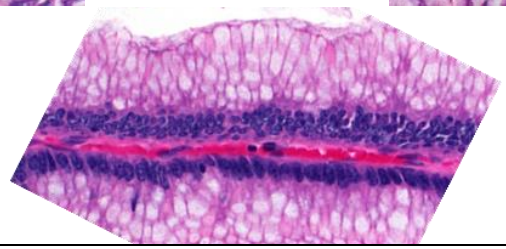
Grade based on worst area.
3 Subtypes: **Gastric** (most common, least aggressive, resembles foveolar cells), **Intestinal** (tall, cuboidal cells), and **pancreatobiliary** (resembles biliary epithelium, low cuboidal with amphophilic cytoplasm and complex papillae)

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

Decision to resect depends on size, location, symptoms, age, etc…
A solid nodule radiographically is suspicious for invasion.



Gastric-type IPMN

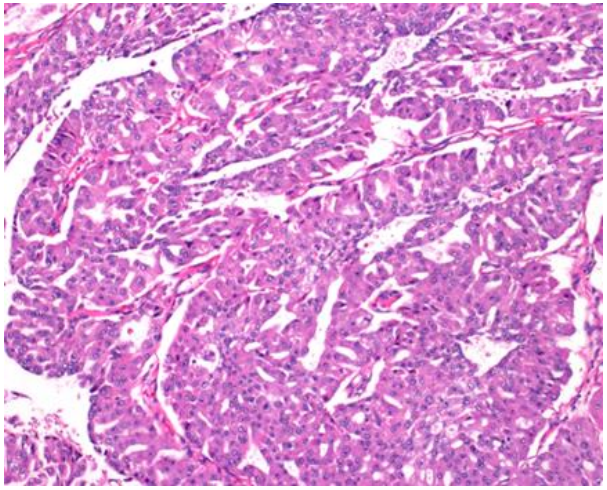


Intraductal Oncocytic Papillary Neoplasm

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)



Mucinous Neoplasms Cytology findings:

Often a background of abundant, thick, neoplastic mucin.

Abundant cohesive groups of mucinous columnar cells (must exclude GI luminal sampling!)

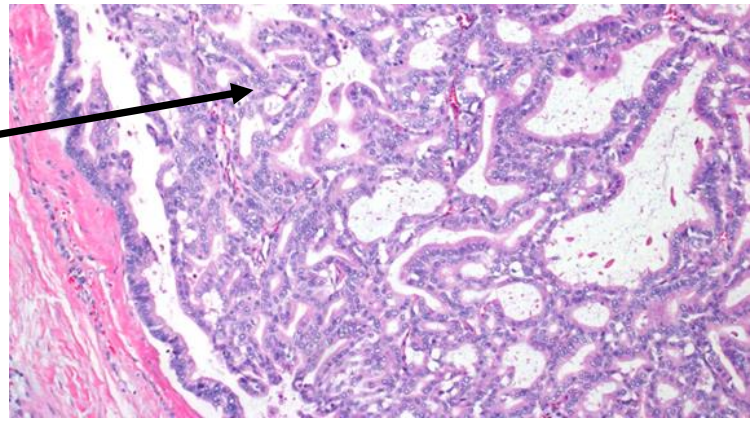
High-grade dysplasia (CIS) within a mucinous cyst looks identical on smears to invasive adenocarcinoma

Cyst fluid CEA elevated (greater than 200 ng/mL is highly suggestive of a mucinous cyst)

Non-Invasive Glandular Lesions

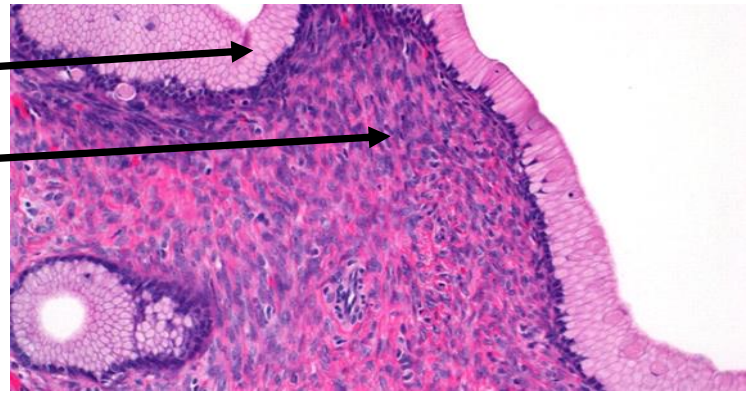
Intraductal Tubulopapillary Neoplasm

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 glands making hard to evaluate for invasion.
Genetically distinct (No KRAS mutations).
Rare. Benign if non-invasive.



Mucinous Cystic Neoplasm

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 and stains with ER, inhibin, and calretinin.
Almost exclusively in women. Almost always in Body or tail.
Must be thoroughly sampled to exclude invasive component.



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

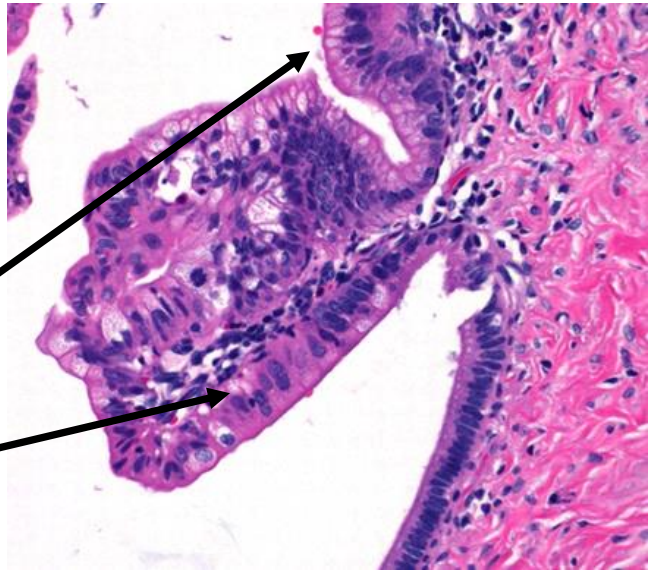
Pancreatic Intraepithelial Neoplasia (PanIN):

Non-invasive, non-mass forming neoplasia confined to the pancreatic ducts (In situ).

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. 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.



Pancreatic Neuroendocrine Tumors

Well-differentiated Neuroendocrine tumors

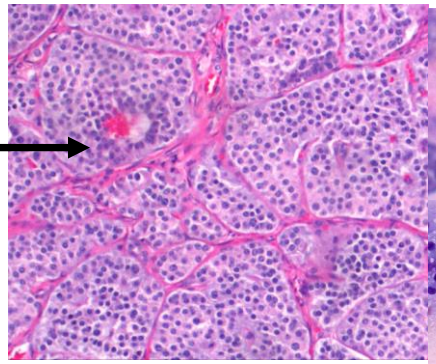
Morphology: Uniform, **round nuclei** with **"Salt and Pepper"** fine, speckled chromatin
Organoid architecture (i.e., nested, cords, glands-like rosettes, or ribbons)
Molecular: MEN1, DAXX, ATRX mutations common
IHC: express Synaptophysin, Chromogranin, INSM1

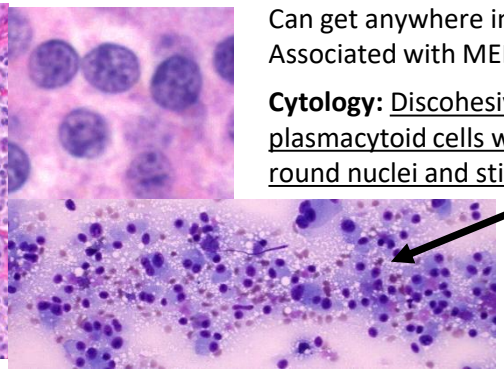
Malignant, **but slow-growing, indolent** progression.
Early NETs have a low risk of metastasis

If <0.5 cm & non-functional with no mitoses→ "**microadenoma**" (benign and often incidental)

Classification/ Grade	Ki67 Proliferation Index	Mitotic index
Well-differentiated PanNET		
Grade 1	<3%	<2
Grade 2	3-20%	2-20
Grade 3	>20%	>20
Poorly-differentiated PanNET		
Small cell type	>20%	>20
Large Cell type		

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.



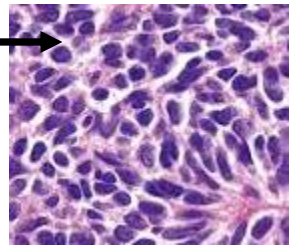


Can get anywhere in the pancreas. Associated with MEN and VHL.

Cytology: Discohesive, often plasmacytoid cells with monomorphic round nuclei and stippled chromatin

Poorly-differentiated Neuroendocrine Carcinomas

Often arise from non-neuroendocrine tumors (and subsequently *develop* neuroendocrine differentiation.
Sheet-like growth
Malignant! Very metabolically active/**rapidly growing**
→ see on normal FDG-PET scan

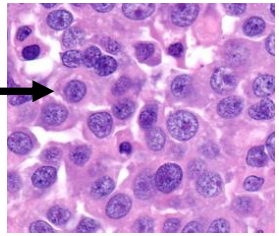


Molecular: p53, RB1 (and other carcinoma-associated mutations)
Treatment: Platinum-containing chemotherapy

Small Cell Neuroendocrine Carcinoma

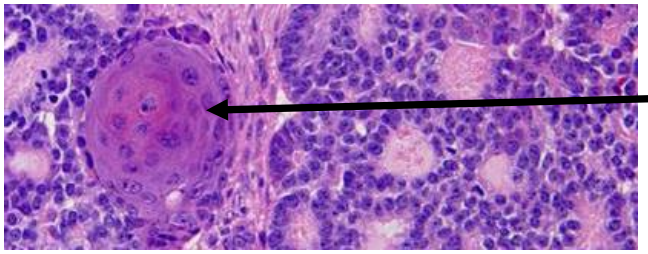
Morphology: Fusiform nuclei, **finely granular chromatin**, **scant cytoplasm**, and nuclear molding. Extensive necrosis.
Tons of mitoses. Ki67 almost 100%.

Large Cell Neuroendocrine Carcinoma



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

Pancreatoblastoma



Carcinoma showing Acinar cell differentiation with **squamoid nests**
Most common in children (but can see in adults)

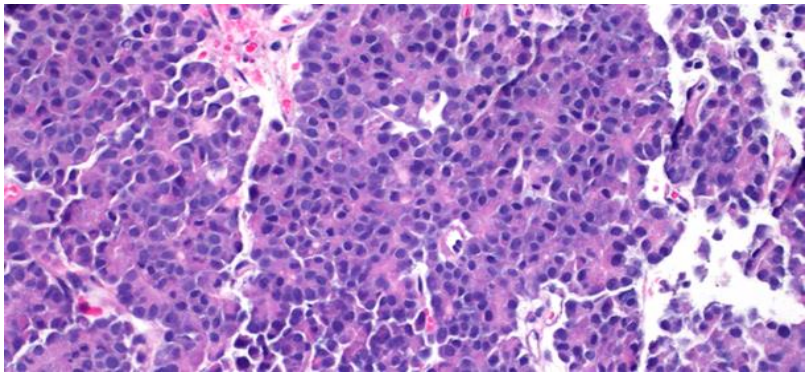
Associated with Beckwith-Wiedemann syndrome and FAP.

Much of the tumor looks like Acinar Cell Carcinoma, BUT **defining findings is Squamoid nests.**

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

Often indolent, curable tumors.

Acinar Cell Carcinoma



Carcinoma showing Acinar cell differentiation
Most commonly older men

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

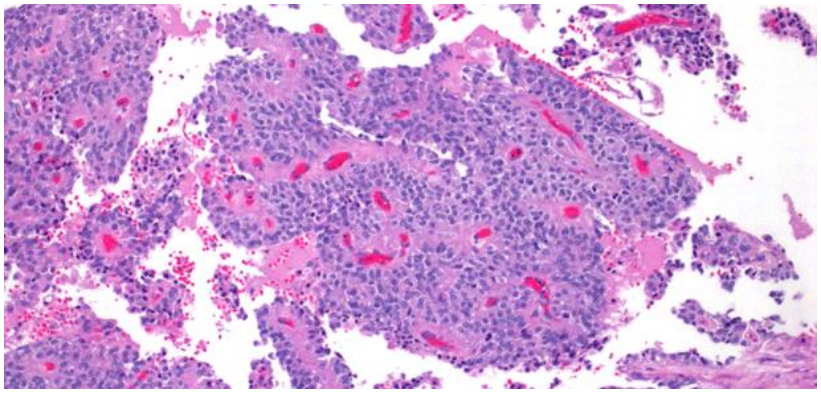
Can be mixed with neuroendocrine or ductal carcinomas

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 less than PNET; Median 19 months)

Solid Pseudopapillary Neoplasm



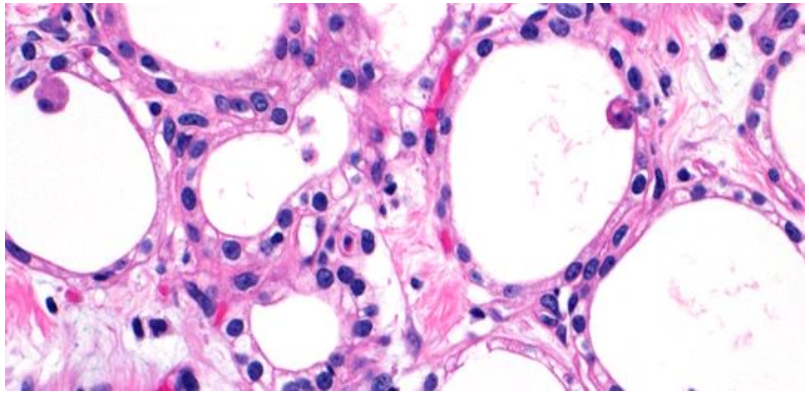
Most common in adolescent girls and young women

Solid and pseudopapillary/cystic growth
Solid tumor resembles neuroendocrine tumor (monomorphic round cells)
Pseudopapillae are formed when cells detach from fibrovascular cores
Commonly see hyaline globules and cholesterol clusters/foamy histiocytes.

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.

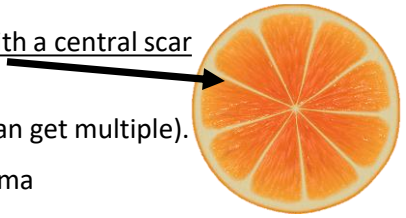
Serous Cystadenoma



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 nuclei.
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

Non-neoplastic Processes

Chronic Pancreatitis

Inflammation/destruction of gland with scarring and dysfunction
- Often associated abdominal pain, elevated serum lipase and amylase
- Causes: EtOH (most common by far), obstruction, genetic

Exocrine insufficiency → fat malabsorption → steatorrhea
Endocrine insufficiency (comes late) → diabetes mellitus

Can resemble invasive ductal adenocarcinoma (see table→)
Microscopically: Fibrosis and glandular atrophy with retained lobular architecture. Islets of Langerhans preserved until late→ may show "pseudo-hyperplasia."
Hypocellular aspirates with stromal fragments and islet cells.

Pseudocyst

Pancreatic or peripancreatic collection of enzyme-rich fluid without an epithelial lining (wall composed of fibrosis and granulation tissue)
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

Type 1: IgG4-related lobular inflammation/destruction
Key features: 1)Dense lymphoplasmacytic infiltrate, 2)Storiform fibrosis, 3)Obliterative phlebitis; 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!

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

Acinar Cystic Transformation of the Pancreas

Multilocular cystic change of acini throughout the pancreas. Lined by cells with pale or granular apical cytoplasm and acinar or ductal differentiation (<u>not</u> mucinous!).

Lymphoepithelial Cyst

Cystic lesion lined by squamous mucosa with surrounding lymphoid tissue.

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
Micro: Fibrosis, granulation tissue, necrosis, calcifications, and inflammation

Ductal Adenocarcinoma	Chronic Pancreatitis
Haphazard, irregular architecture	Lobular, organized architecture
Incomplete luminal spaces with gland rupture	Complete luminal spaces
Cellular pleomorphism (4:1 variation in size)	Less pleomorphic
Perineural invasion	Absent
Vascular/perivascular invasion	Absent
Extrapancreatic invasion	Absent
Mitoses and prominent 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*