Diagnostic Algorithm for Pancreatic Tumors

**Gross/Radiographic Appearance?**
- **Solid**
  - Epithelium/Stroma?
    - Individual glands
      - Desmoplastic stroma
      - Mucin production
      - **Ductal Adenocarcinoma**
        - Stains: (+) chymotrypsin, trypsin
        - Squamoid nests?
          - Yes: Pancreatoblastoma
          - No: Acinar Cell Carcinoma
        - Most common in Children
    - Predominant cellular differentiation?
      - Acinar
        - Stains: (+) chymotrypsin, trypsin
      - Neuroendocrine
        - Stains: (+) synaptophysin, chromogranin
      - Unknown
        - Stains: (+) β-catenin (nuclear), CD10, CD56, E-Cadherin shows lost membranous staining
      - Serous
        - Cuboidal, clear cells, glycogen-rich (PAS +; PASd -)
        - Stains: (+) Inhibin
      - Mucinous
        - Columnar, often mucin-filled
        - Ovarian-type stroma, separate from ducts
      - Be sure to consider a pseudocyst!

- **Cystic**
  - Degenerative? (No epithelium lining cysts)
  - Epithelium Lined Cysts
    - **Serous Cystadenoma**
    - **Mucinous Cystic Neoplasm (MCN)**
    - **Intraductal Papillary Mucinous Neoplasm (IPMN)**
      - Papillary architecture, Grossly visible (>0.5 cm), If tubular consider ITPN
Pancreatic Ductal Adenocarcinoma

Invasive carcinoma with glandular/ductal differentiation

85% of Pancreatic tumors,

Most common in head of pancreas → resect with Pancreaticoduodenectomy (Whipple procedure)

Often unresectable at time of diagnosis, Poor Prognosis (often < 1 year)

Precursor lesions: IPMN, MCN, PanIN

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

Genetics:

>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

Subtypes:

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

Ancillary testing on cytology specimens:

1) Next-gen sequencing → looking for KRAS mutations, etc..
2) FISH (e.g., Urovysion) looking for aneuploidy
Non-Invasive Glandular Lesions

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).

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)

Most often in head.

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

If pre-invasive → Benign, but have to submit entire capsule/lesion to prove no invasion.

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

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

<table>
<thead>
<tr>
<th>Classification/ Grade</th>
<th>Ki67 Proliferation Index</th>
<th>Mitotic index</th>
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<tbody>
<tr>
<td>Well-differentiated PanNET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>&lt;3%</td>
<td>&lt;2</td>
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<tr>
<td>Grade 2</td>
<td>3-20%</td>
<td>2-20</td>
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<tr>
<td>Grade 3</td>
<td>&gt;20%</td>
<td>&gt;20</td>
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<tr>
<td>Poorly-differentiated PanNET</td>
<td></td>
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<tr>
<td>Small cell type</td>
<td>&gt;20%</td>
<td>&gt;20</td>
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<tr>
<td>Large Cell type</td>
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Ki67 Proliferation index based on evaluation of ≥ 500 cells in a “hot spot.”
Mitotic count based on evaluating 50 Hpf, but reported per 10 Hpf.

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

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

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

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/Chymotrypsin. Squamoid nests stain with EMA, Synaptophysin may show positivity. Often nuclear β-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.
- **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
- 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.”

**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 and bile.

**Autoimmune pancreatitis**
Type 1: IgG4-related lobular inflammation/destruction
  - Key features: 1) Dense lymphoplasmacytic infiltrate, 2) Storiform fibrosis,
  - 3) Obliterative phlebitis; Increased IgG4+ plasma cells (>50/HPF on excision or >10/HPF on biopsy). Clinically can mimic carcinoma. Often elevated serum IgG4.

Type 2: Duct-centric granulocytic destruction with epithelial damage

**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 (not mucinous!).

**Lymphoepithelial Cyst**
Cystic lesion lined by squamous mucosa with surrounding lymphoid tissue.