An Algorithmic approach to solid neoplasms of the pancreas

JOHNS HOPKINS
MEDICAL INSTITUTIONS

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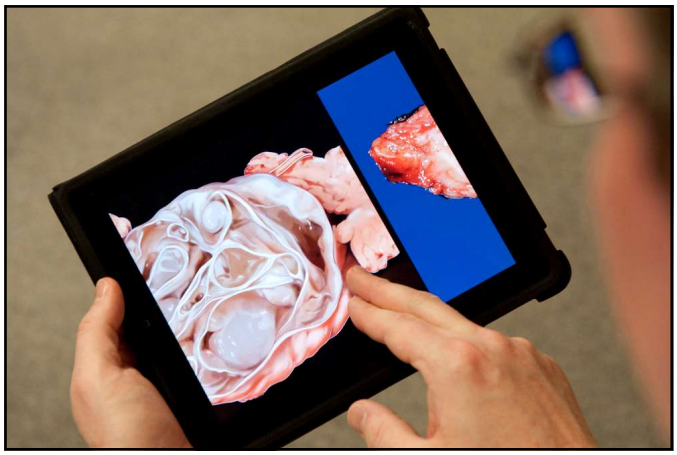
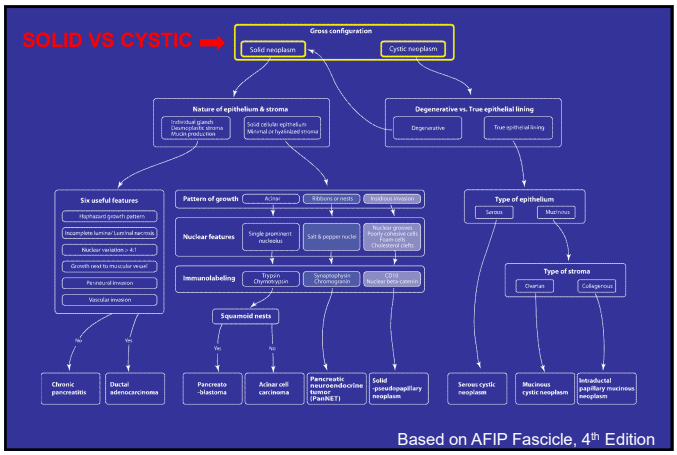
The Johns Hopkins Medical Institutions

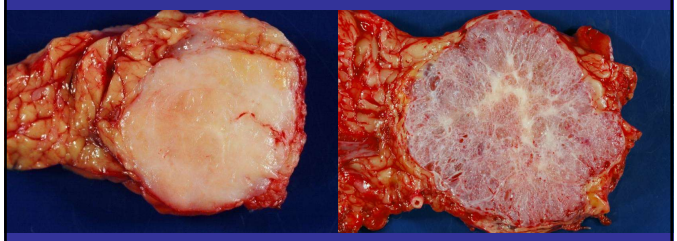
Disclosure

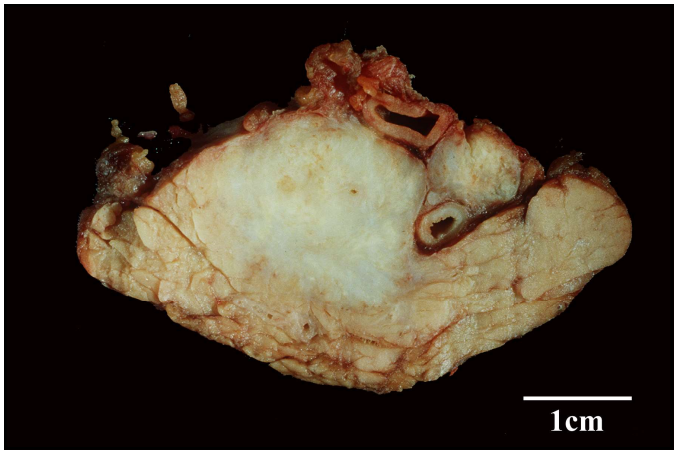
- I receive royalty payments from Myriad Genetics for the PALB2 invention.
- Selected images from the AFIP Fascicle with permission
- The pancreas pathology iPAD APPs are free through the iTunes Store

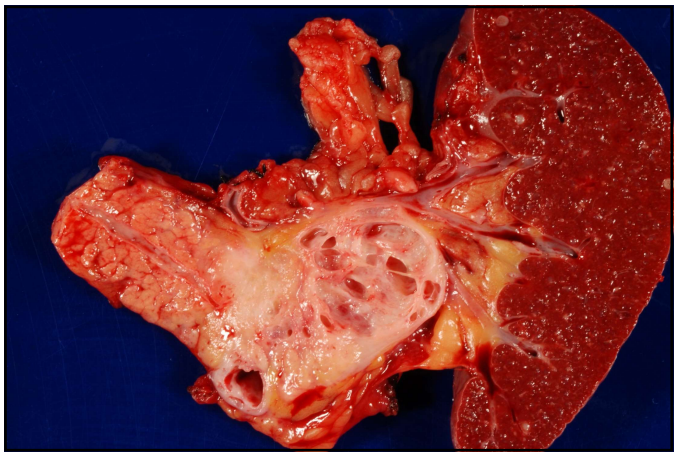


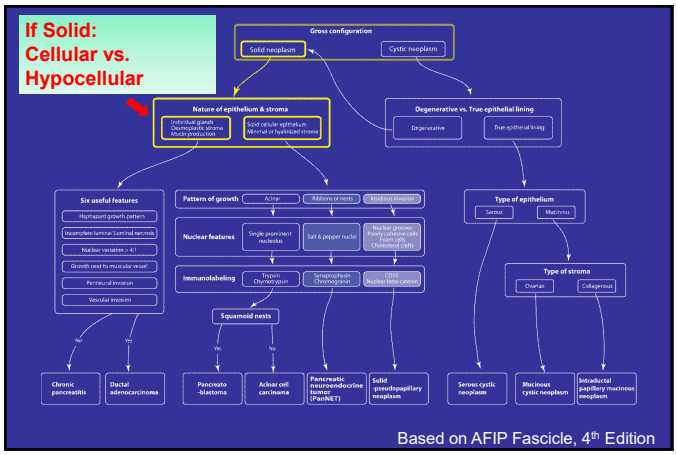


1. Is it Solid or Cystic?





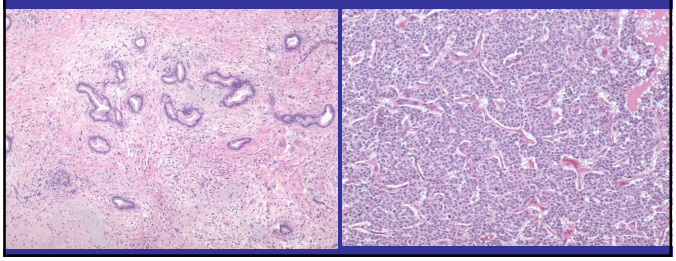



If Solid:
Cellular vs.
Hypocellular
Gross configuration
Solid neoplasm
Cystic neoplasm
Nature of epithelium & stroma
Individual glands; Desmoplastic stroma; Mucin production
Solid cellular epithelium; Minimal or hyalinized stroma
Degenerative vs. True epithelial lining
Degenerative
True epithelial lining
Six useful features
Haphazard growth pattern
Incomplete luminal / luminal necrosis
Nuclear variation > 4:1
Growth next to muscular vessel
Perineural invasion
Vascular invasion
No
Yes
Pattern of growth
Acinar
Ribbons or nests
Infiltrative invasion
Nuclear features
Single prominent nucleolus
Salt & pepper nuclei
Nuclear grooves; Poorly cohesive cells; Intracytoplasmic Cholesterol clefts
Immunolabeling
Trypsin; Chymotrypsin
Synaptophysin; Chromogranin
CD10; Nuclear beta-catenin
Squamoid nests
Yes
No
Chronic pancreatitis
Ductal adenocarcinoma
Pancreato-blastoma
Acinar cell carcinoma
Pancreatic neuroendocrine tumor (PanNET)
Solid pseudopapillary neoplasm
Type of epithelium
Serous
Mucinous
Type of stroma
Ovarian
Collagenous
Serous cystic neoplasm
Mucinous cystic neoplasm
Intraductal papillary mucinous neoplasm
Based on AFIP Fascicle, 4th Edition

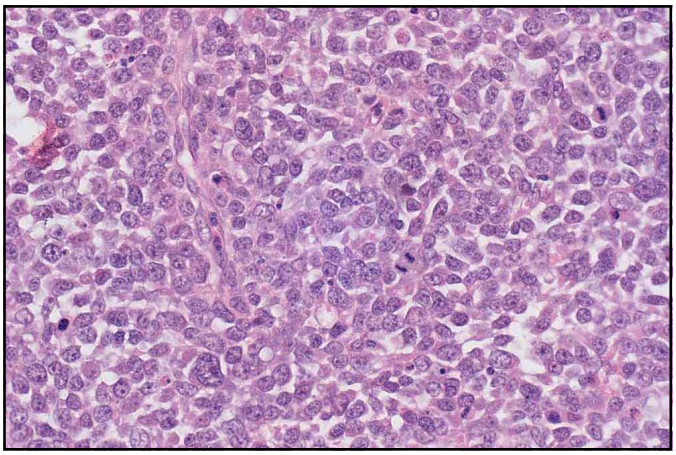
Nature of Epithelium and Stroma

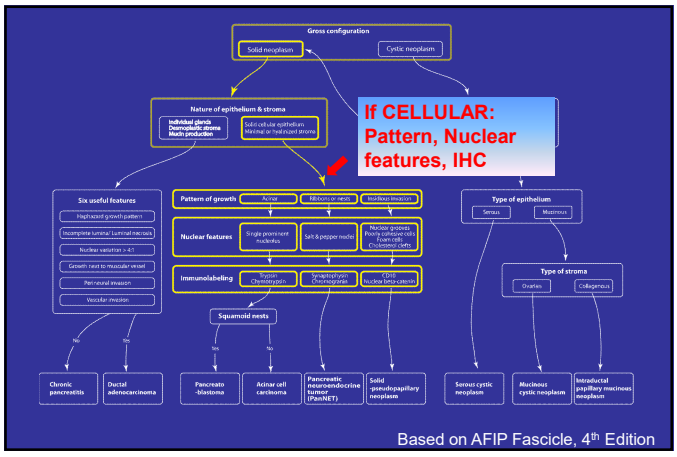
Individual glands; desmoplastic stroma; mucin production

Solid, cellular epithelium; minimal or hyalinized stroma



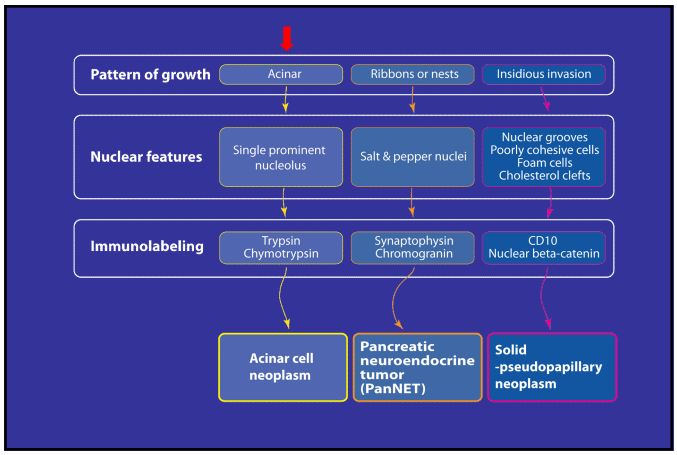
Solid Cellular Neoplasms with Minimal Stroma



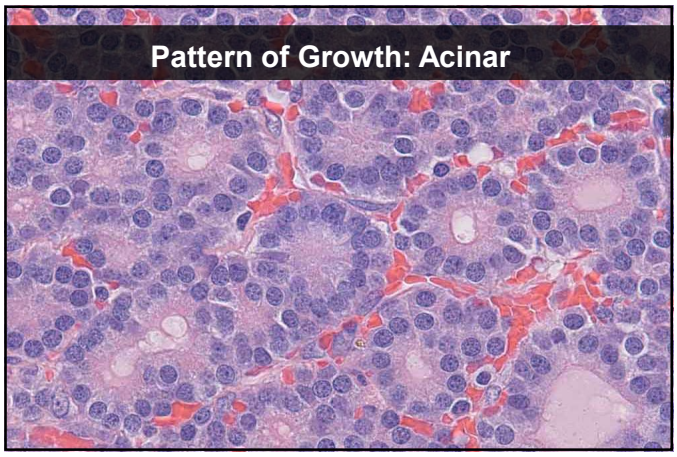


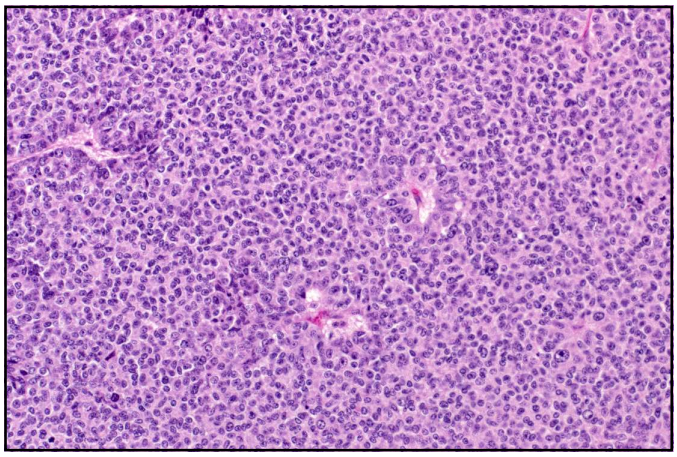
Solid, cellular epithelium; minimal or hyalinized stroma

1. Pattern of Growth
2. Nuclear Features
3. Immunolabeling

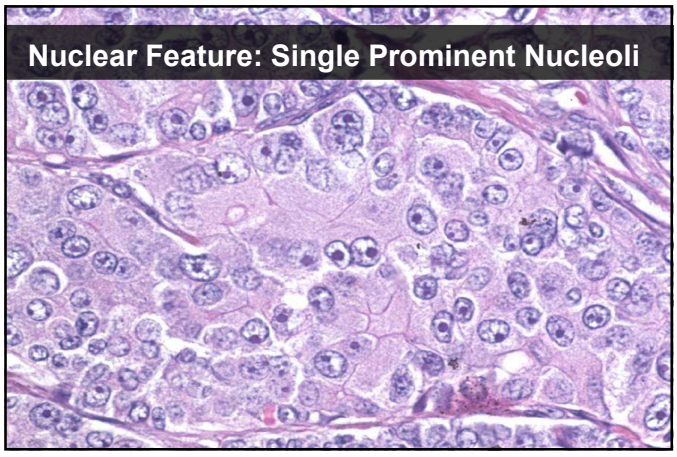


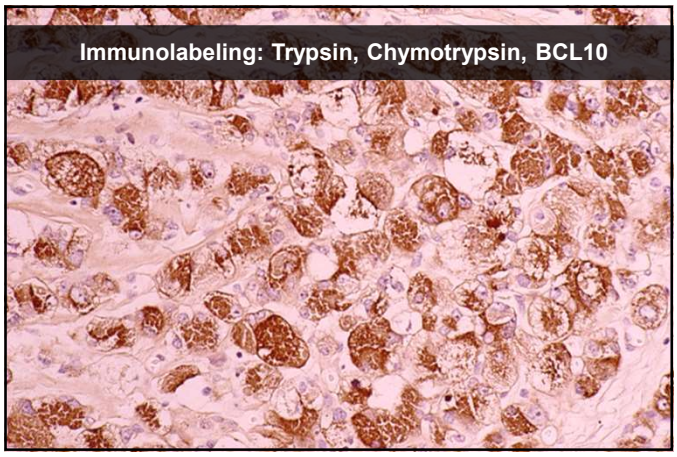
Pattern of Growth: Acinar

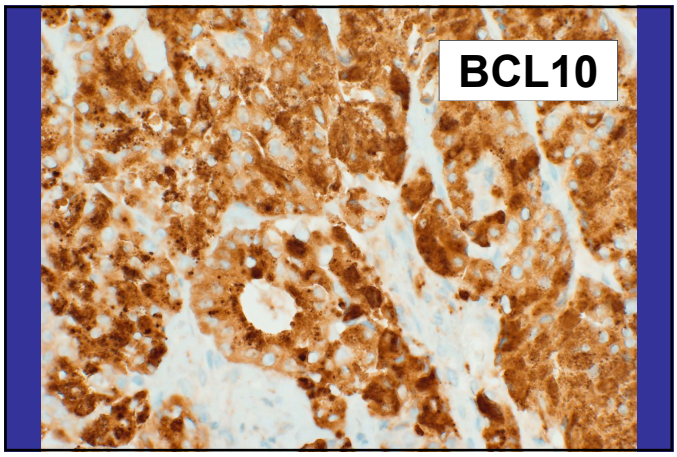


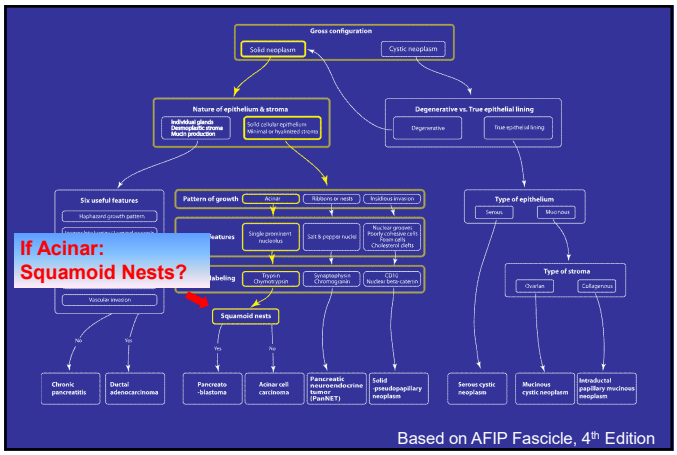


Nuclear Feature: Single Prominent Nucleoli




Immunolabeling: Trypsin, Chymotrypsin, BCL10


BCL10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Squamoid nests
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Ductal adenocarcinoma
Pancreato-blastoma
Acinar cell carcinoma
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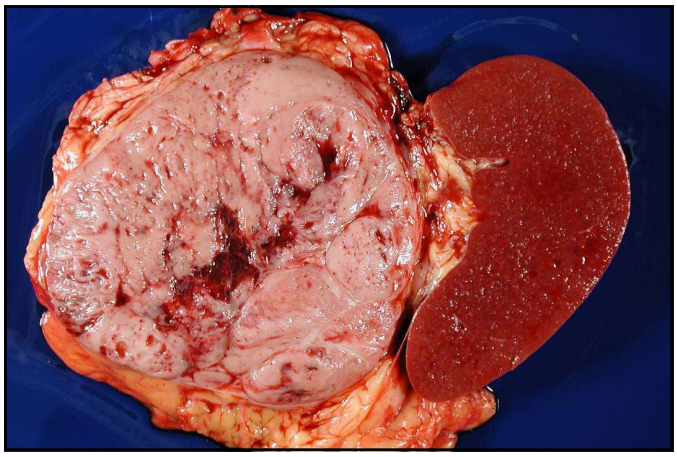
Serous cystic neoplasm
Mucinous cystic neoplasm
Intraductal papillary mucinous neoplasm
Based on AFIP Fascicle, 4th Edition

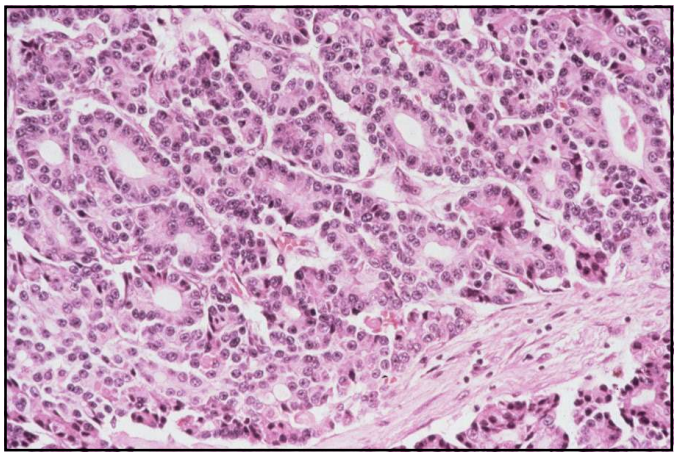
Acinar Cell Carcinoma

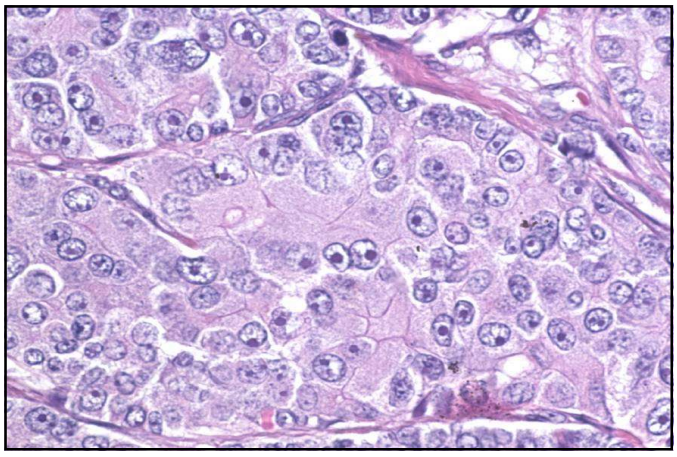
Squamoid Nests Absent

Acinar Cell Carcinomas Clinical

- Age – mostly adults (mean 62 years)
- Gender – male > female
- Symptoms – usually non-specific with weight-loss, abdominal pain, and nausea and vomiting
- Lipase – about 15% develop the syndrome of arthralgias, eosinophilia and subcutaneous fat necrosis



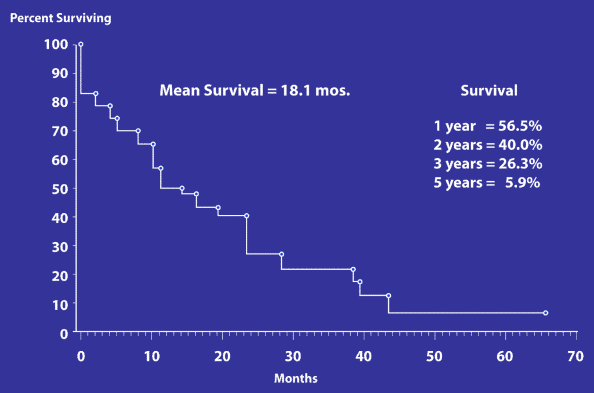




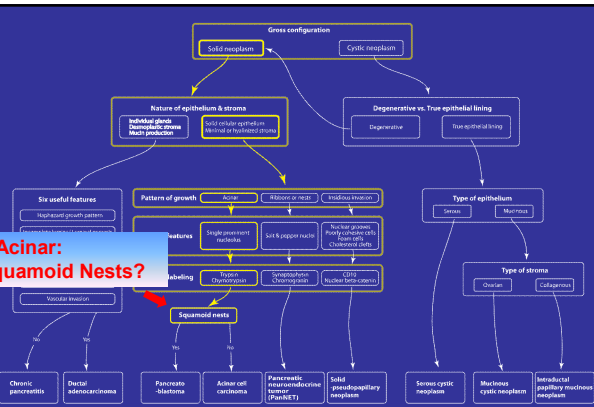
Acinar Cell Carcinoma Staining

- PASD – highlights apical granules
- Mucicarmine – negative
- Immunohistochemistry –
  - 90-100% Bcl10
  - 90-100% trypsin
  - 75% lipase
  - 40% chymotrypsin
  - 30% amylase
  - 42% minor neuroendocrine

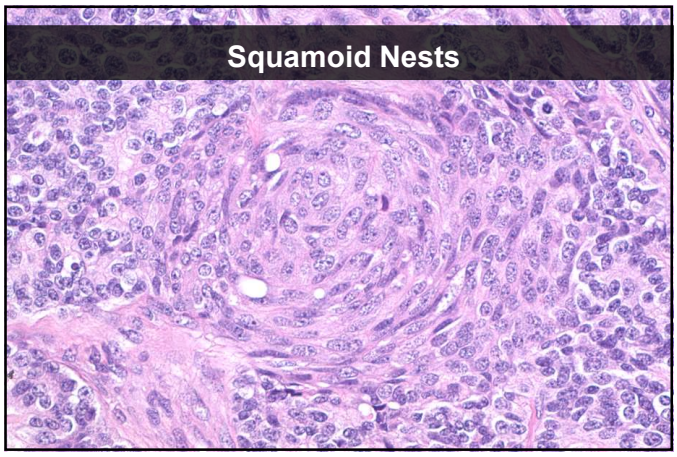
Klimstra, Am J Surg Pathol, 1992



Klimstra et al, Am J Surg Pathol

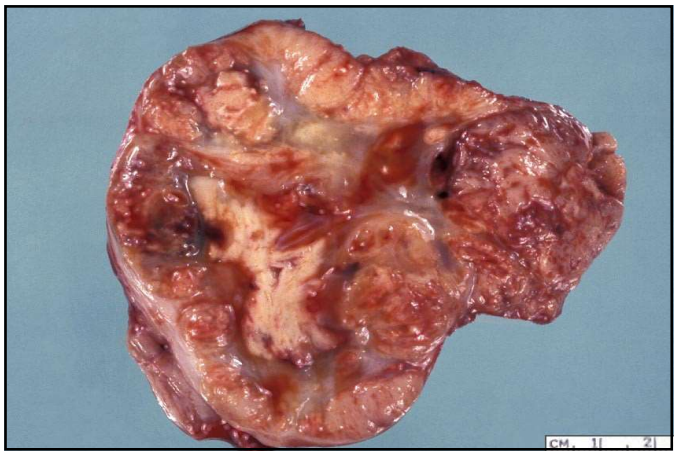


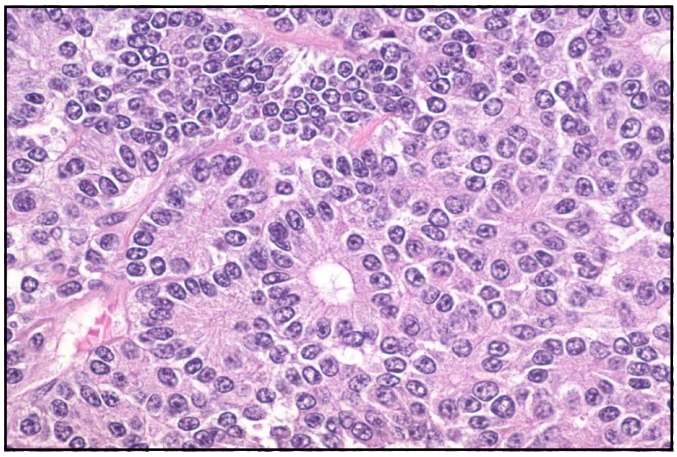
Based on AFIP Fascicle, 4th Edition

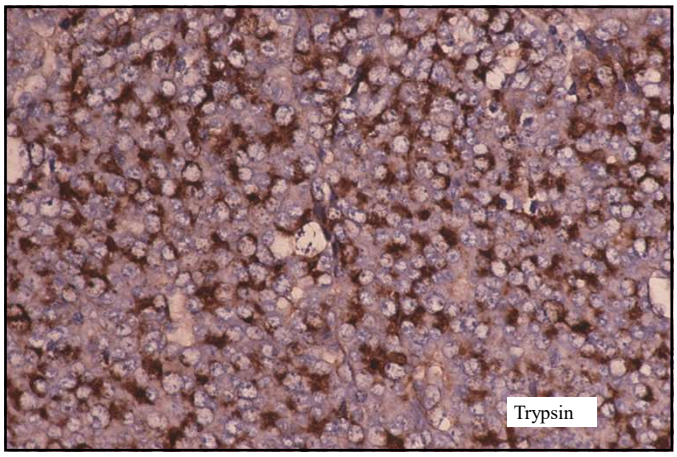


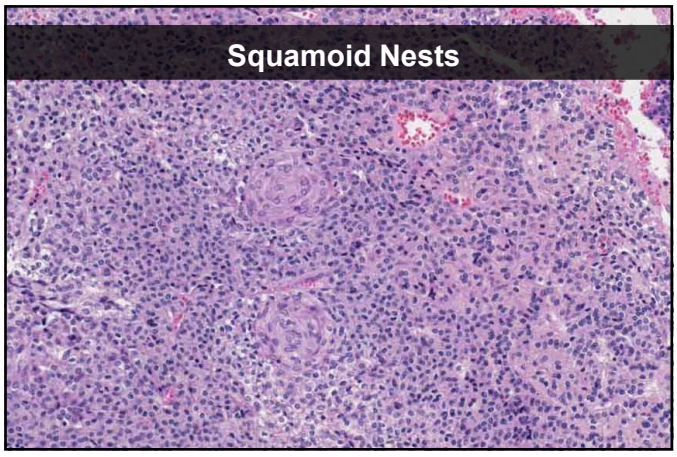
Pancreatoblastoma

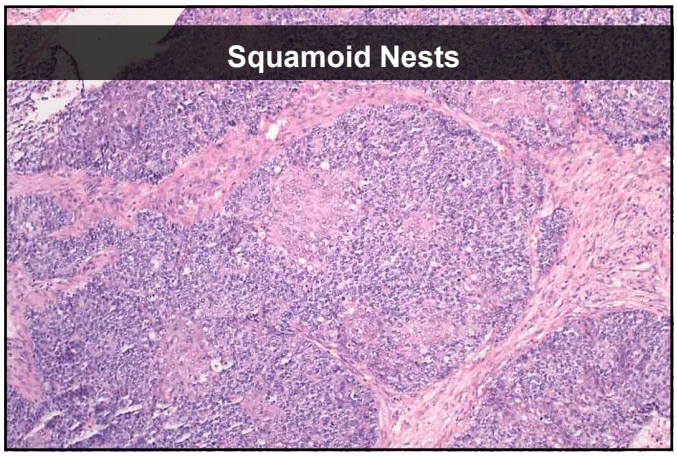
- Occurs primarily in children (1-15 years)
- Undifferentiated component – back to back small cells with a syncytial pattern
- Differentiated component – squamous, acinar, neuroendocrine
- Survival better than for ductal adenocarcinoma






Trypsin


Squamoid Nests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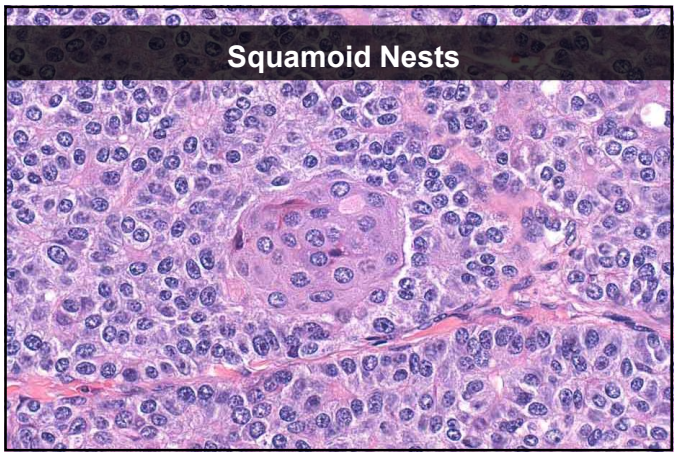
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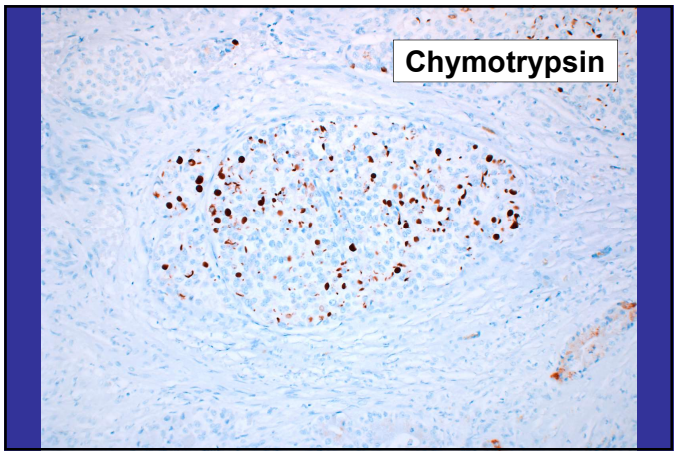
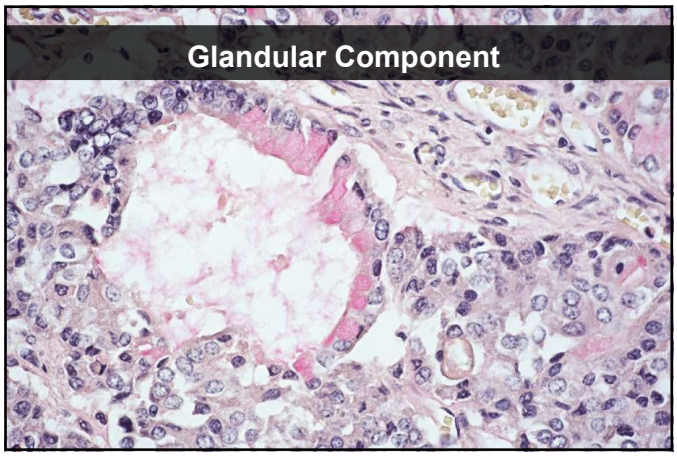
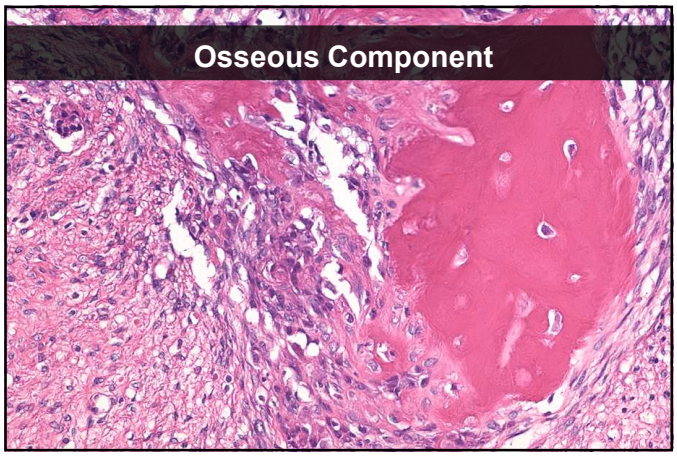

Chymotrypsin

Glandular Component



Osseous Component



Genetic Alteration in Pancreatoblastomas

- Associated with Beckwith-Wiedemann Syndrome
- 86% LOH on 11p*
- 56% β-catenin mutations
- 22% loss of *DPC4*
- 11% *APC* (Germline)
- 0% K-*ras*, *p53*

* Similar to other infantile embryonal tumors such as hepatoblastomas

Am J Pathol 159:1619

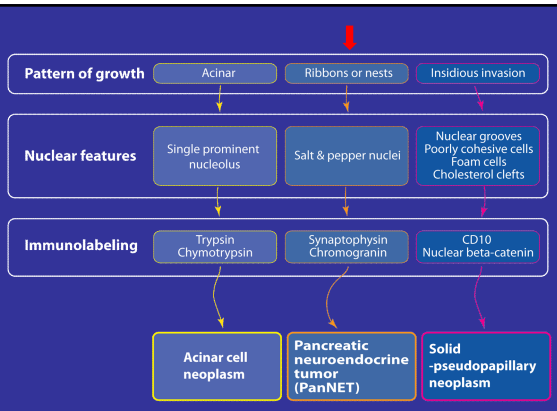
Pancreatoblastoma

- Fully malignant neoplasms
- 40% present with metastases
- Mean survival of 17 months
- Poorer survival in adults

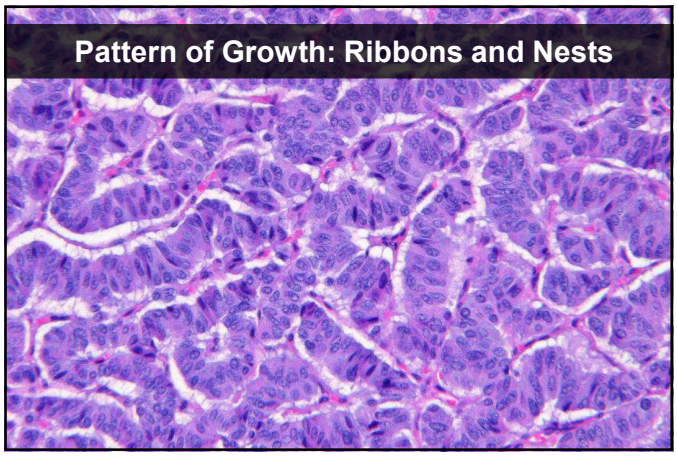
Am J Surg Pathol 19:1371

Pancreatoblastoma vs. Acinar Cell Carcinoma

Squamoid Nests



Pattern of Growth: Ribbons and Nests



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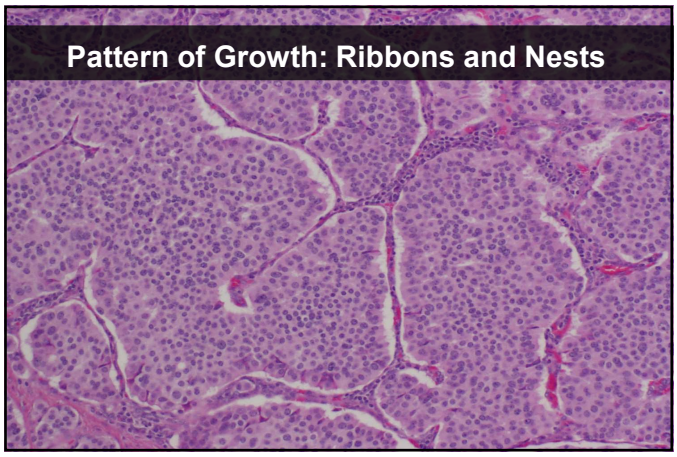
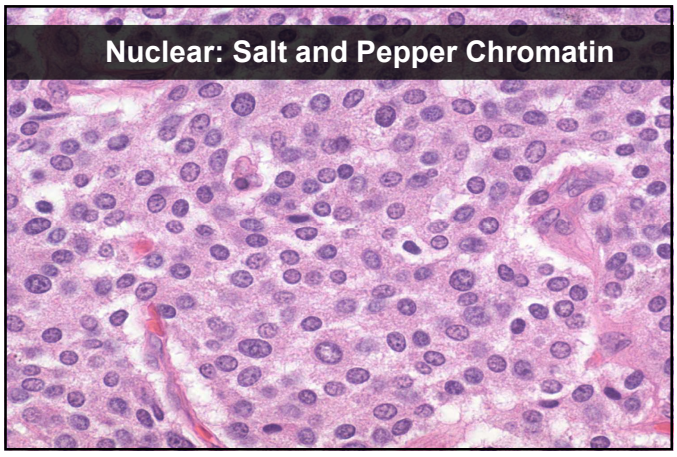
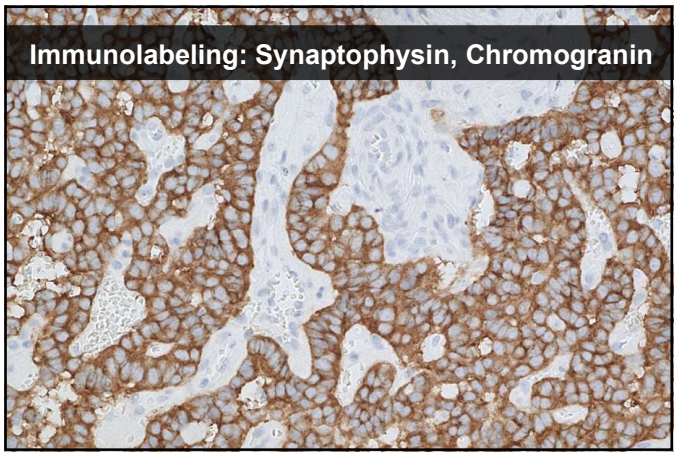


Nuclear: Salt and Pepper Chromatin





Pancreatic Neuroendocrine Tumor

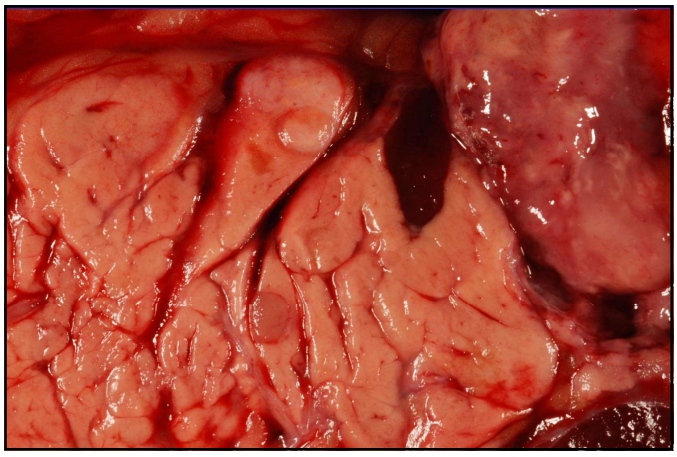
Genetic Syndromes

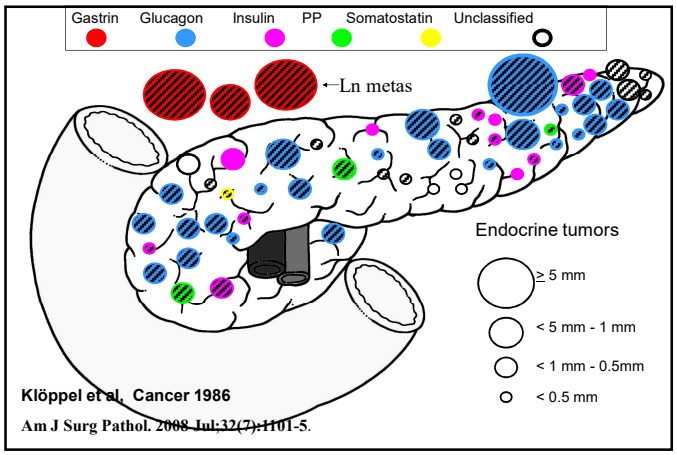
Genetic Syndromes

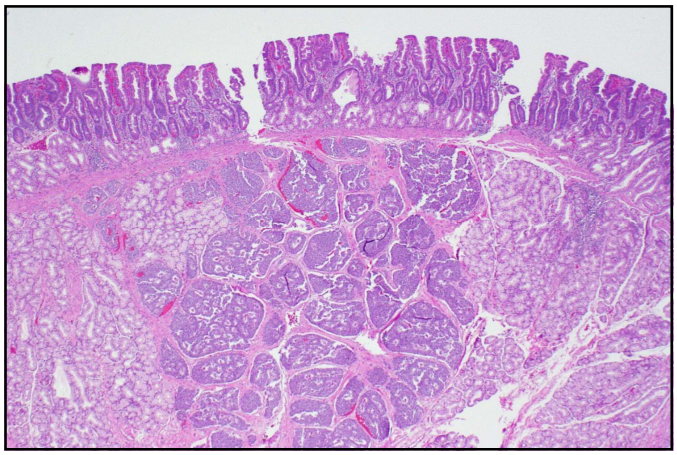
- Multiple Endocrine Neoplasia 1
- von Hippel-Lindau
- Tuberous Sclerosis
- Pheochromocytoma
- Cushing's Syndrome

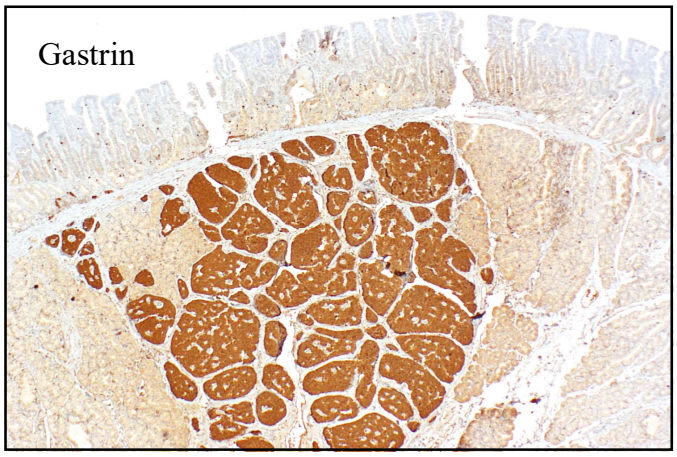
MEN-1

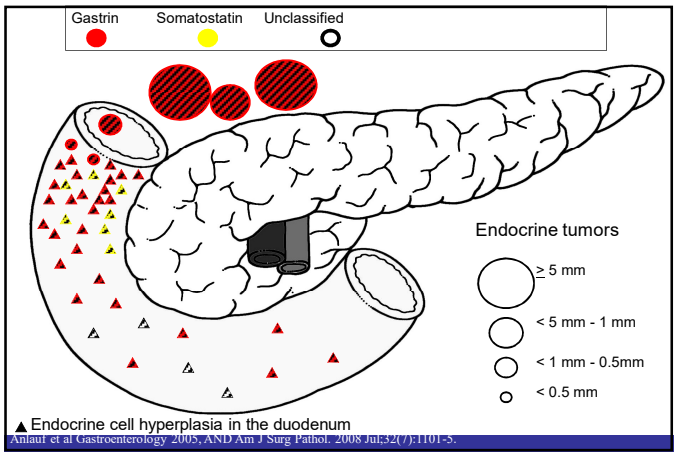
- Gene: Tumor suppressor gene on chromosome 11 (11q13)
- Pituitary: Prolactinomas, mass effect
- Parathyroid: Hyperparathyroidism, nephrolithiasis
- Pancreas-duodenum: Multicentric, Gastrinomas, ulcers




Gastrin
Glucagon
Insulin
PP
Somatostatin
Unclassified
←Ln metas
Endocrine tumors
≥ 5 mm
< 5 mm - 1 mm
< 1 mm - 0.5mm
< 0.5 mm
Klöppel et al, Cancer 1986
Am J Surg Pathol. 2008 Jul;32(7):1101-5.




Gastrin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Endocrine tumors
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< 5 mm - 1 mm
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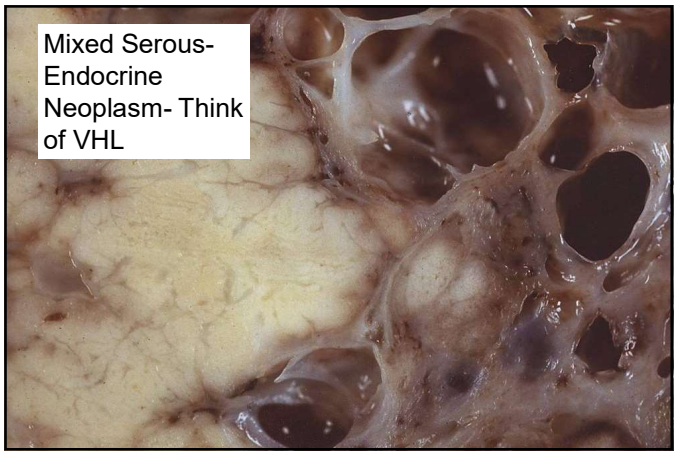
< 0.5 mm
▲Endocrine cell hyperplasia in the duodenum
Anlauf et al Gastroenterology 2005, AND Am J Surg Pathol. 2008 Jul;32(7):1101-3.

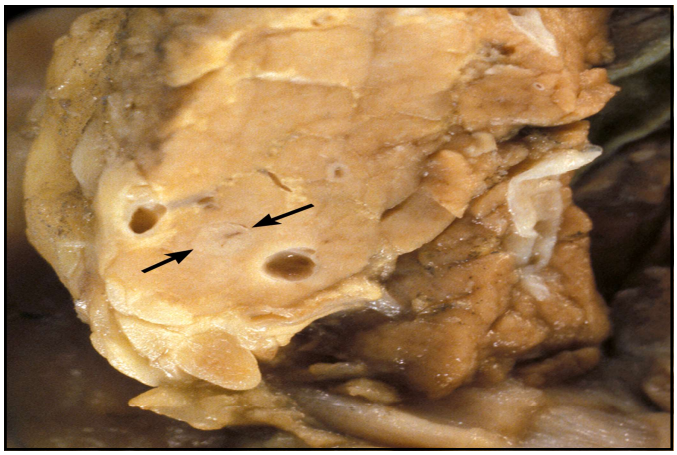

Mixed Serous-Endocrine Neoplasm- Think of VHL

Classification

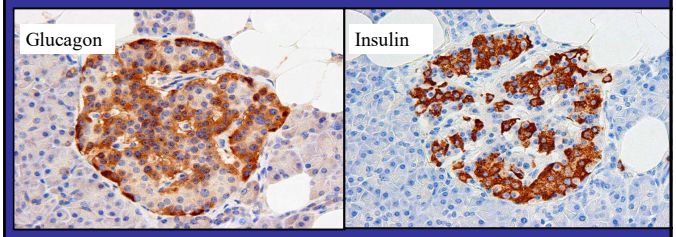
- Neurondocrine microadenoma (<0.5 cm)
- Well-differentiated pancreatic neuroendocrine tumor
  - **Nonfunctional** (≥0.5 cm)
  - **Functional**
    - Insulinoma
    - Glucagonoma
    - Somatostatinoma
    - Gastrinoma
    - VIPoma
- Poorly-differentiated neuroendocrine carcinoma (classification is changing in the new WHO)
  - Small cell carcinoma
  - Large cell endocrine carcinoma

Microadenoma

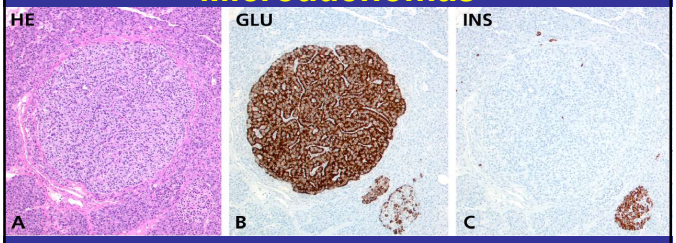
- Well differentiated, <5 mm
- Usually incidental
- Prevalent in MEN1 syndrome
- Sporadic in 1-10% of population
- Nonfunctional
- Benign



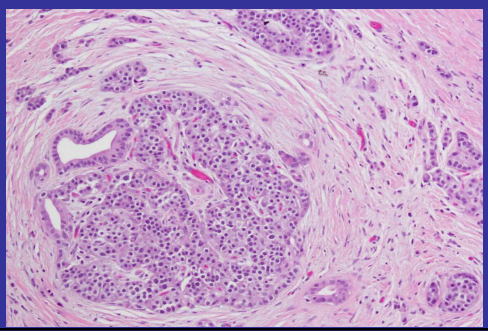
Normal peptide cell pattern



Peptide Expression in Microadenomas



Islet Cell Aggregation in Chronic Pancreatitis



Well-differentiated Pancreatic Neuroendocrine Tumors

(≥0.5cm, and Ki67<20%)

Well-differentiated Pancreatic Neuroendocrine Tumors

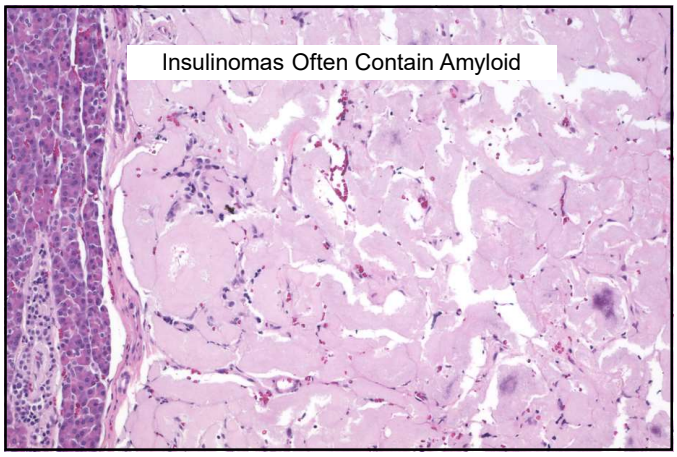
- Nonfunctional (≥0.5 cm, 50-60%)
- Functional (40-50%)
  - Insulinoma (40%), gastrinoma (25%), glucagonoma (15%), VIPoma (10%), somatostatinoma (5%), others (5%)
- 1-4% of pancreatic neoplasms
- Prevalence has been estimated to be 0.2–2 per million persons per year
- Wide age range, most 30-60 yrs (mean = 50 yrs)
- Male = female

Insulinoma

- Whipple's triad:

1. Symptoms and signs of hypoglycemia,
2. Concomitant plasma glucose level of 45 mg/dL (2.5 mmol/L) or less, and
3. Reversibility of symptoms with the administration of glucose

- ~ 9% behave in a malignant manner



Glucagonoma

- Hyperglycemia
- Anemia, diarrhea and weight loss
- Hypoaminoacidemia
- Necrolytic migratory erythema

VIPoma

- **Verner Morrison syndrome**
- Chronic watery diarrhea with resultant dehydration, hypokalemia, achlorhydria (WDHA-syndrome, or pancreatic cholera syndrome)

Syndromic PanNETs

- Pancreatic neuroendocrine tumors should only be designated “syndromic” or “functional” when they are associated with a clinical syndrome
- The expression of a hormone does NOT make a pancreatic neuroendocrine tumor “syndromic” or “functional”

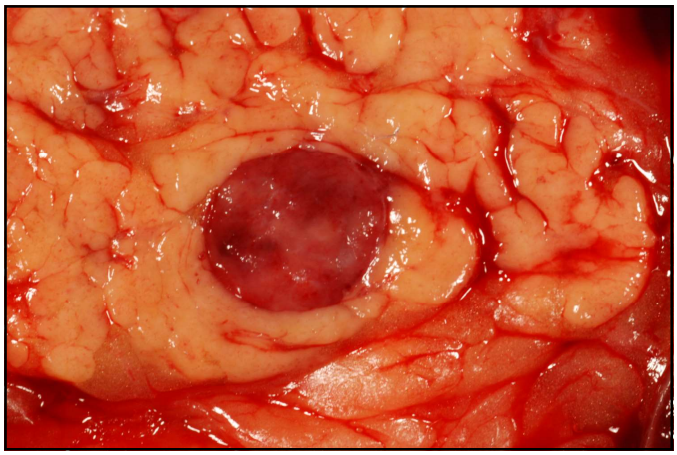
Gross

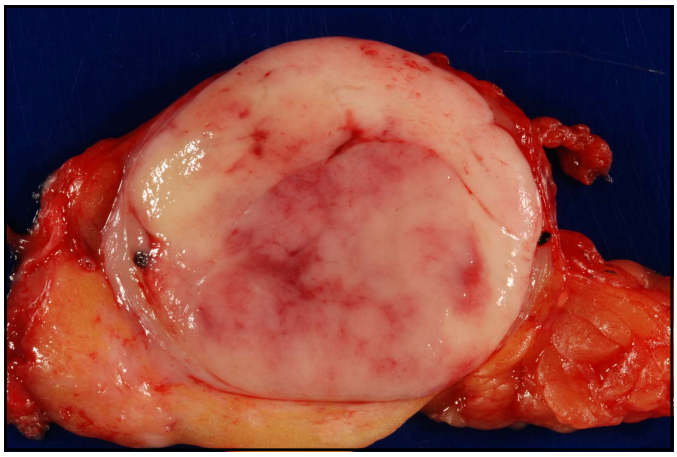
Most well-differentiated pancreatic neuroendocrine tumors are well-demarcated, solitary, and white-yellow or pink-brown

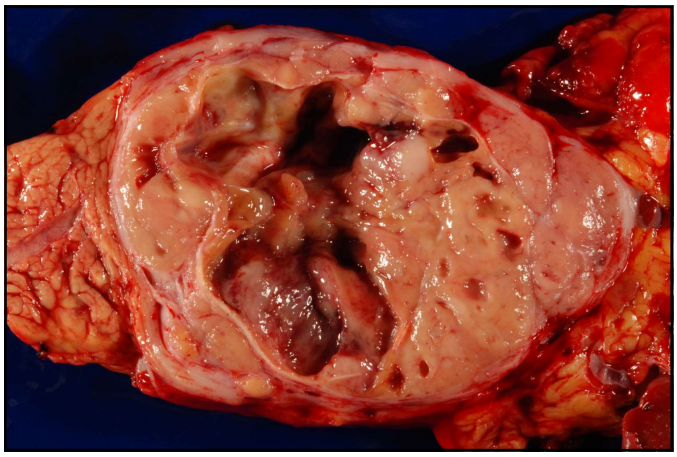
They can be soft and fleshy or densely fibrotic

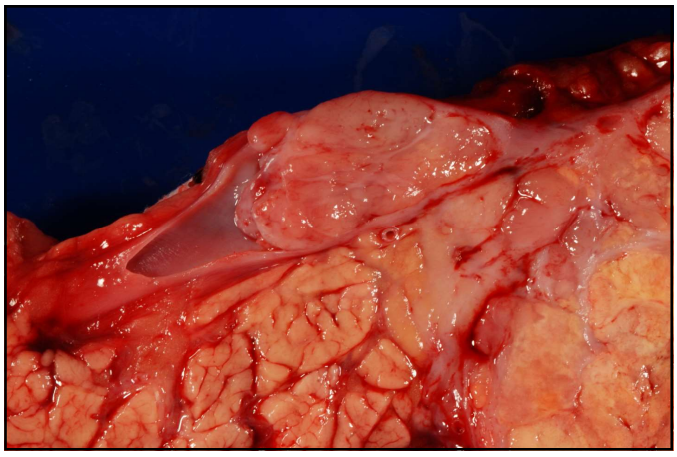
Areas of hemorrhage or necrosis can occur, usually in larger neoplasms

Rarely, pancreatic NETs are cystic









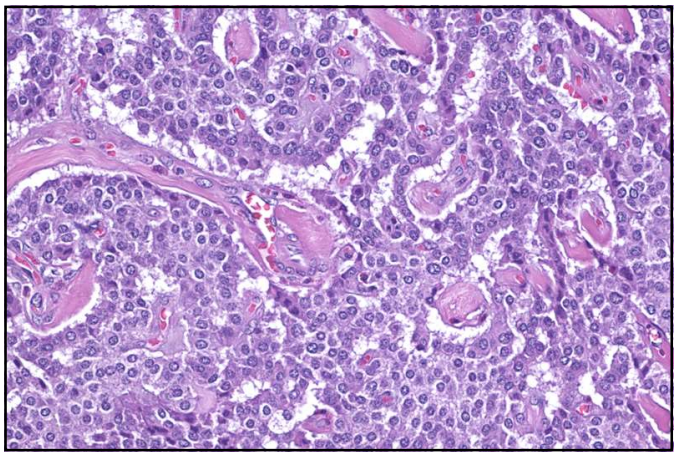
Microscopy

Various “organoid” histological patterns, characterized by a nesting, trabecular, glandular, gyriform, tubuloacinar or pseudorosette arrangements

Uniform, finely granular amphophilic to eosinophilic cytoplasm and a centrally located round to oval nucleus that may display a distinct nucleolus

Characteristically coarsely clumped chromatin pattern (“salt and pepper”)

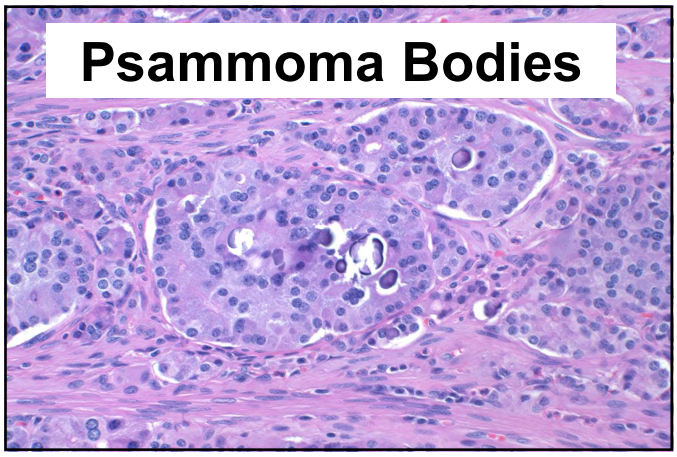
By definition, they have <20 mitoses per 10hpf



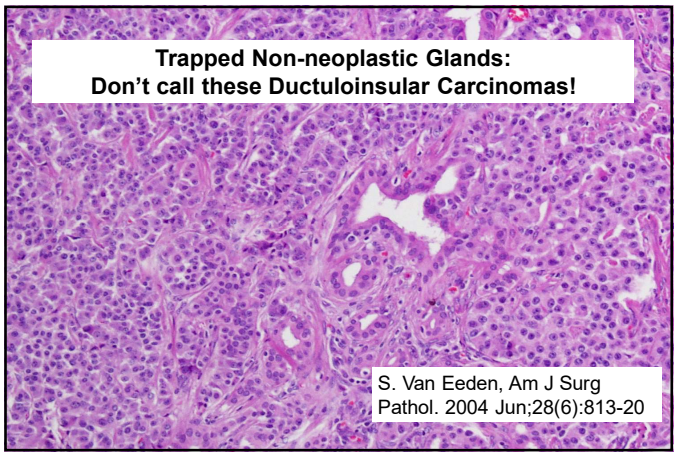
Microscopy

- Amyloid more common in insulinomas
- Psammoma bodies are more common in somatostatinomas
- Trapped non-neoplastic glands

Psammoma Bodies



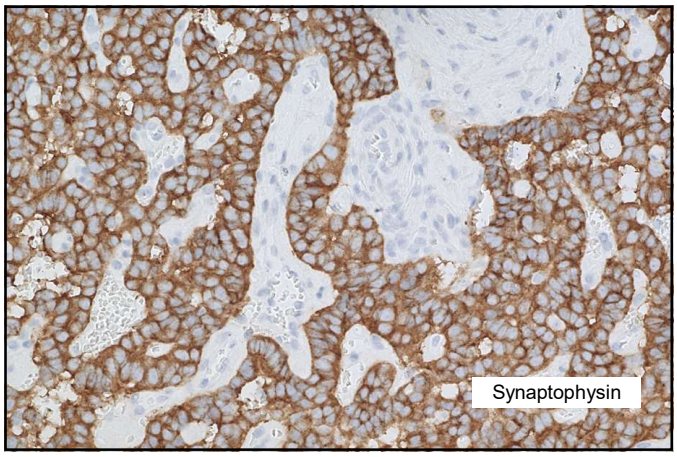
Trapped Non-neoplastic Glands: Don't call these Ductuloinsular Carcinomas!



S. Van Eeden, Am J Surg Pathol. 2004 Jun;28(6):813-20

Immunohistochemitry

- Synaptophysin and chromogranin expressed strongly and diffusely
- Keratins 8 and 18, and keratin 19 (keratin 19 is a prognostic marker)
- Lineage markers including PDX1 and Isl1 and Pax8 suggest pancreatic origin for endocrine neoplasms of unknown primary

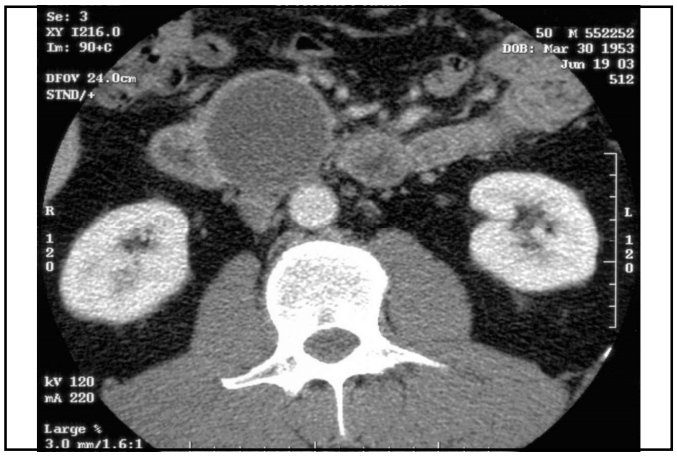


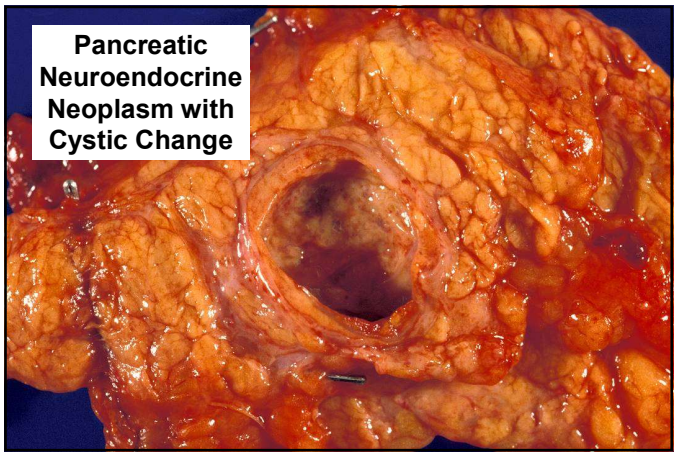
Immunohistochemitry

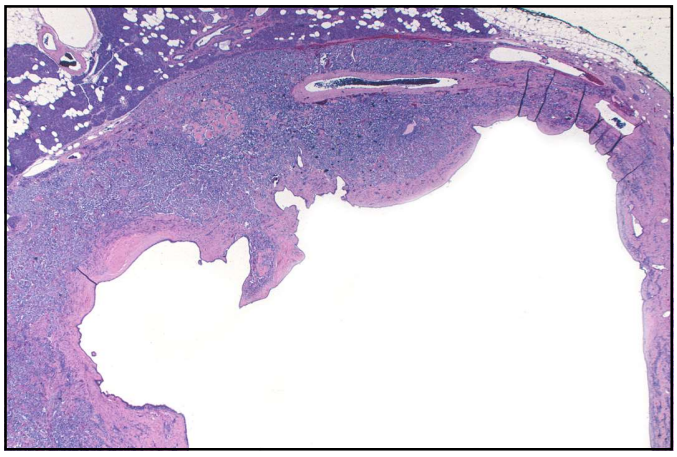
- Expression of a peptide does not equal “functioning” or “syndromic”

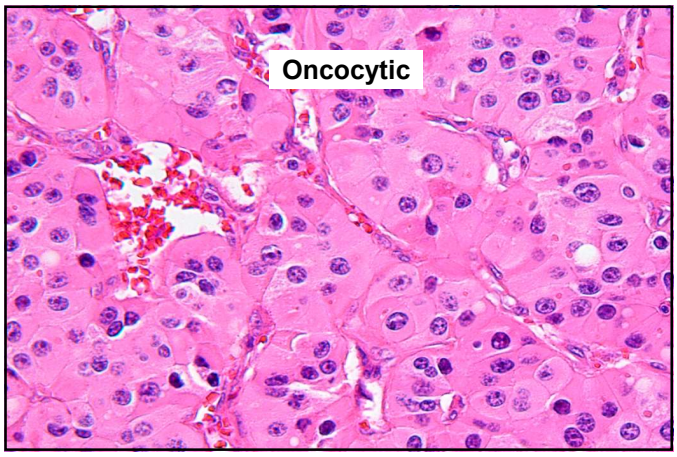
Morphologic Variants

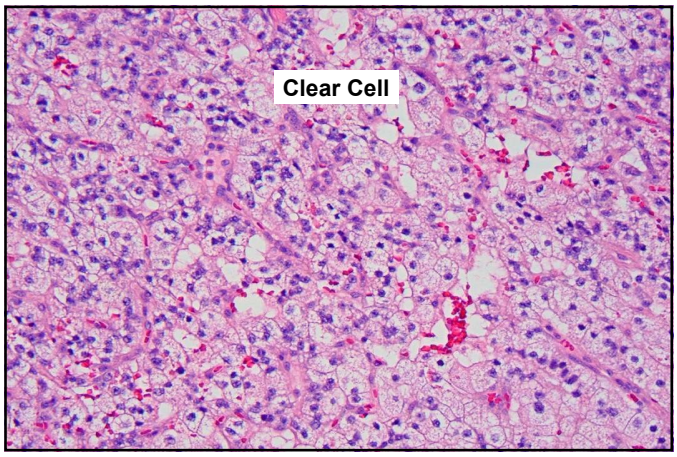
- Cystic
- Oncocytic
- Clear cell
- Pleomorphic
- Serotonin expressing fibrotic

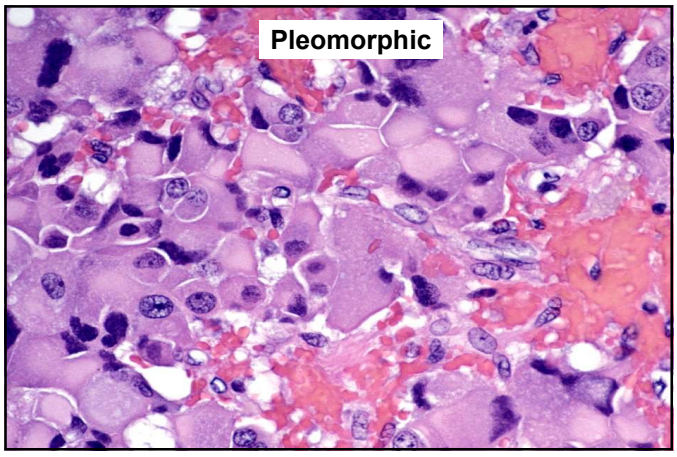

Se: 3
XY I216.0
Im: 90+C
DFOV 24.0cm
SIND/+
50 M 552252
DOB: Mar 30 1953
Jun 19 03
512
R
L
1
2
0
kV 120
mA 220
Large %
3.0 mm/1.6:1


Pancreatic Neuroendocrine Neoplasm with Cystic Change

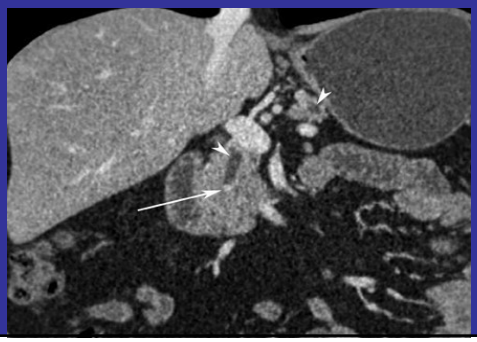


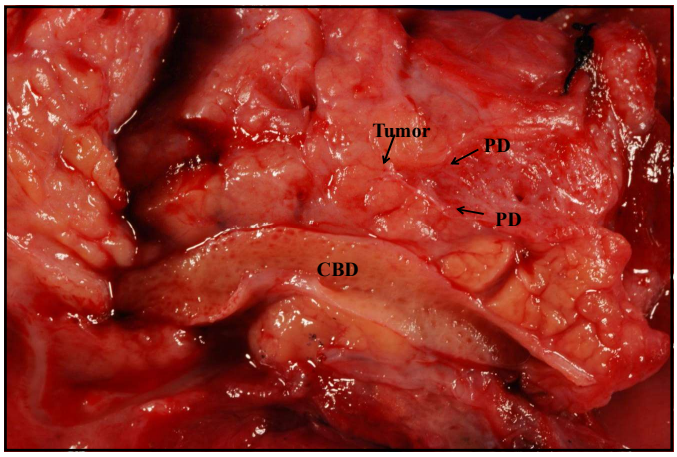

Oncocytic

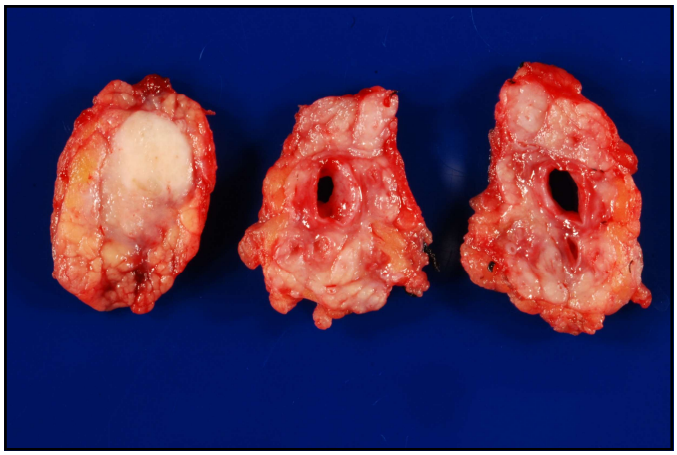

Clear Cell

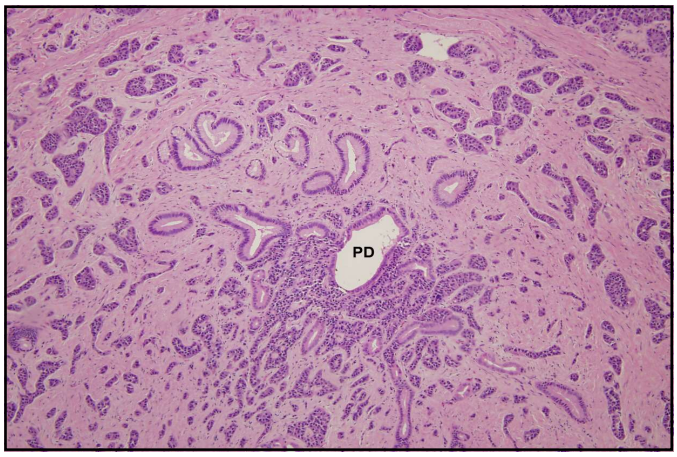

Pleomorphic

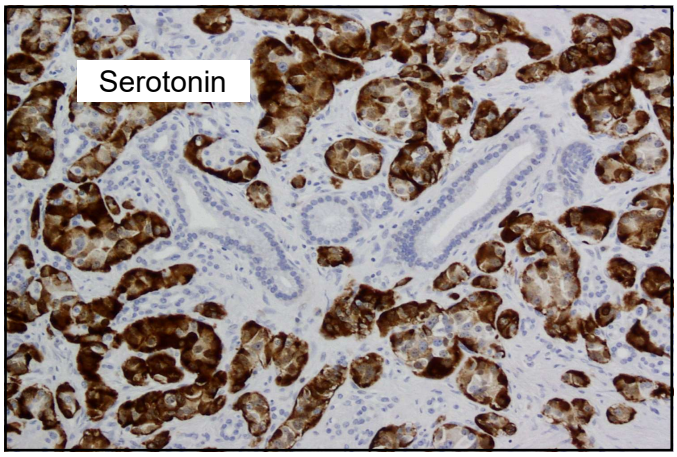
Small Serotonin-producing Duct-obstructing PanNET









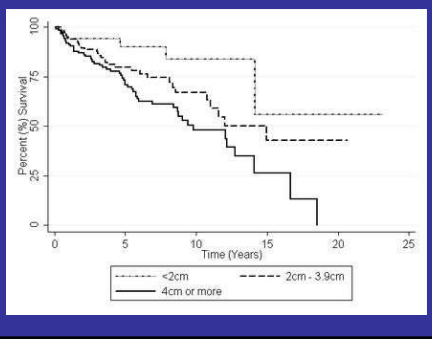


Prognostic Factors

- Natural history unpredictable
- Functional *vs.* nonfunctional
  - Insulinomas usually cured by excision (90% cured)
  - ALL others: 40-70% recur or metastasize
- Survival of PanNETs other than insulinomas after resection
  - 5 yr = 65%; 10 yr = 45%
- Adverse prognostic factors
  - Metastases
  - Size of primary
  - Mitotic rate

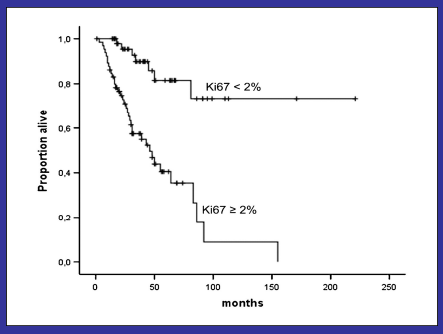
Survival with Size

Data From the Johns Hopkins Database: Size of the tumor(p=0.0018)



Barish Edil

Ki-67 and Overall Survival



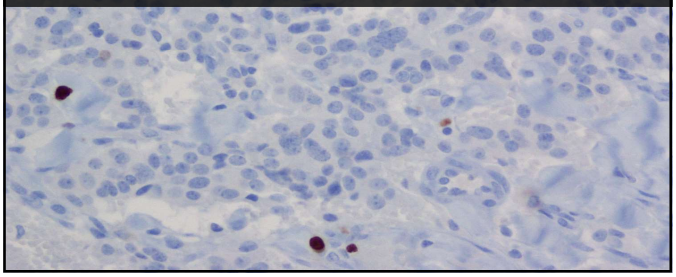
Ekeblad S et al. Clin Cancer Res 2008;14:7798-7803

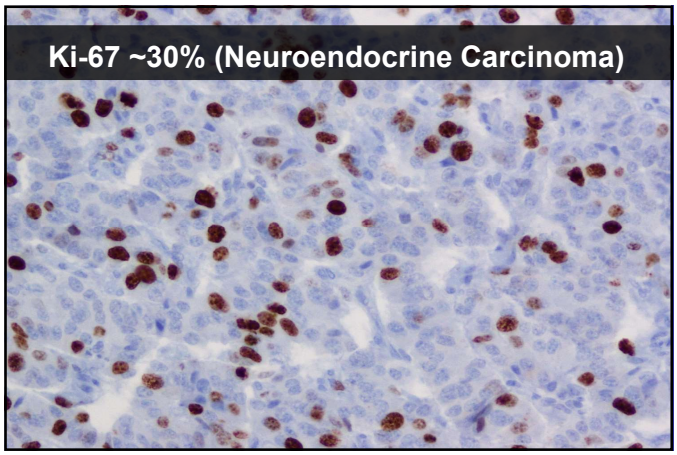
Clinical Cancer Research

Ki-67 < 2%= Grade 1

2-20%= Grade 2

>20%= Grade 3



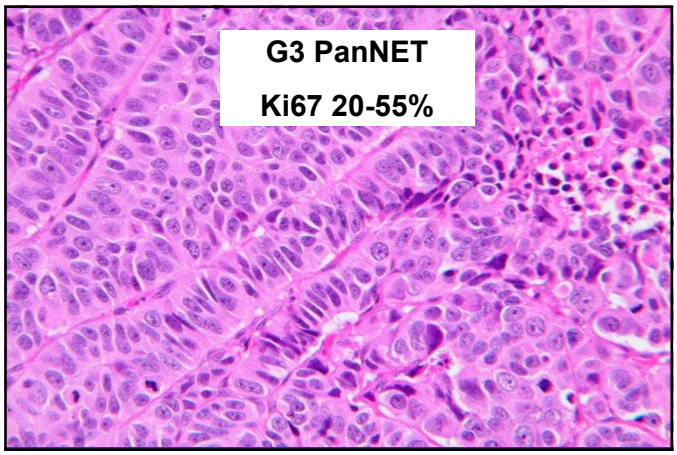


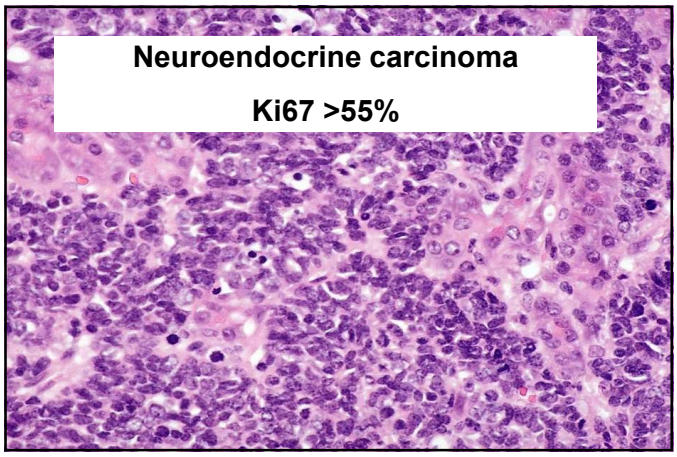
Neuroendocrine Carcinomas

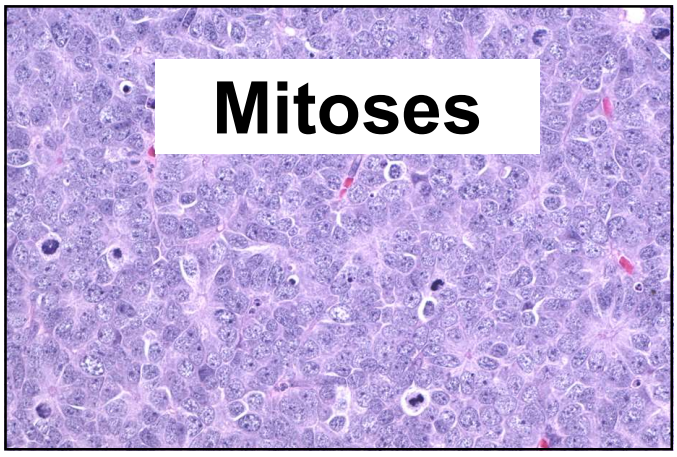
- Defined by the presence of > 20 mitoses per 10 high power fields or Ki67>20%
- New WHO will separate out those that look like well-differentiated PanNETs but have a high mitotic rate (G3 PanNETs), from those with a high-grade morphology (NECs)

Neuroendocrine Carcinomas

- Rare; 2-3% of endocrine neoplasms
- Adults; male predominance
- Highly aggressive
- Small cell and large cell types
- By definition, >20 mitoses per 10 hpf
- Must exclude a metastasis / direct invasion

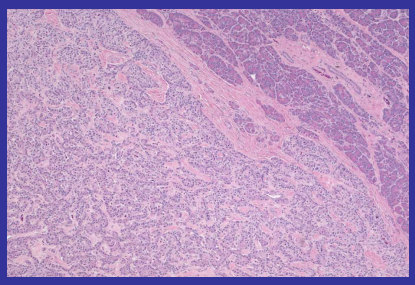

G3 PanNET
Ki67 20-55%


Neuroendocrine carcinoma
Ki67 >55%


Mitoses

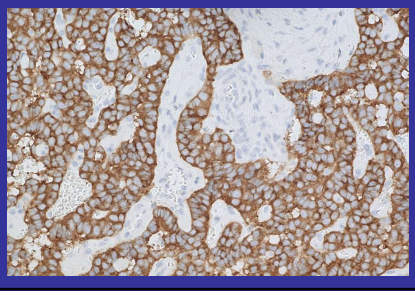
Take Home Message #1

Solid Cellular Neoplasm=Think of PanNET



Take Home Message #2

Hormone expression does NOT make a neoplasm syndromic

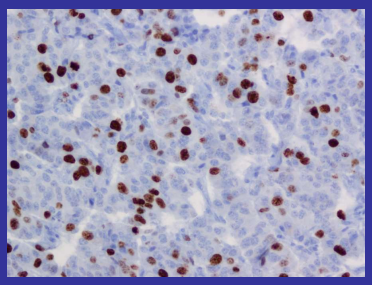


Take Home Message #3

Look at the duodenum in MEN-1

Take Home Message #4

Report the mitotic rate (count or Ki-67)



Thank You!

@Hopkins_GI_Path