Non-Ductal Neoplasms of the Pancreas

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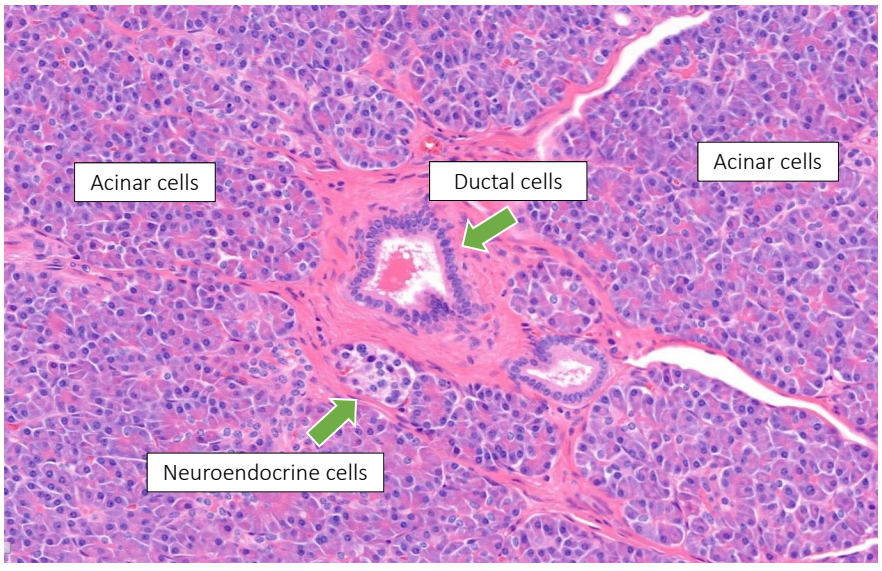
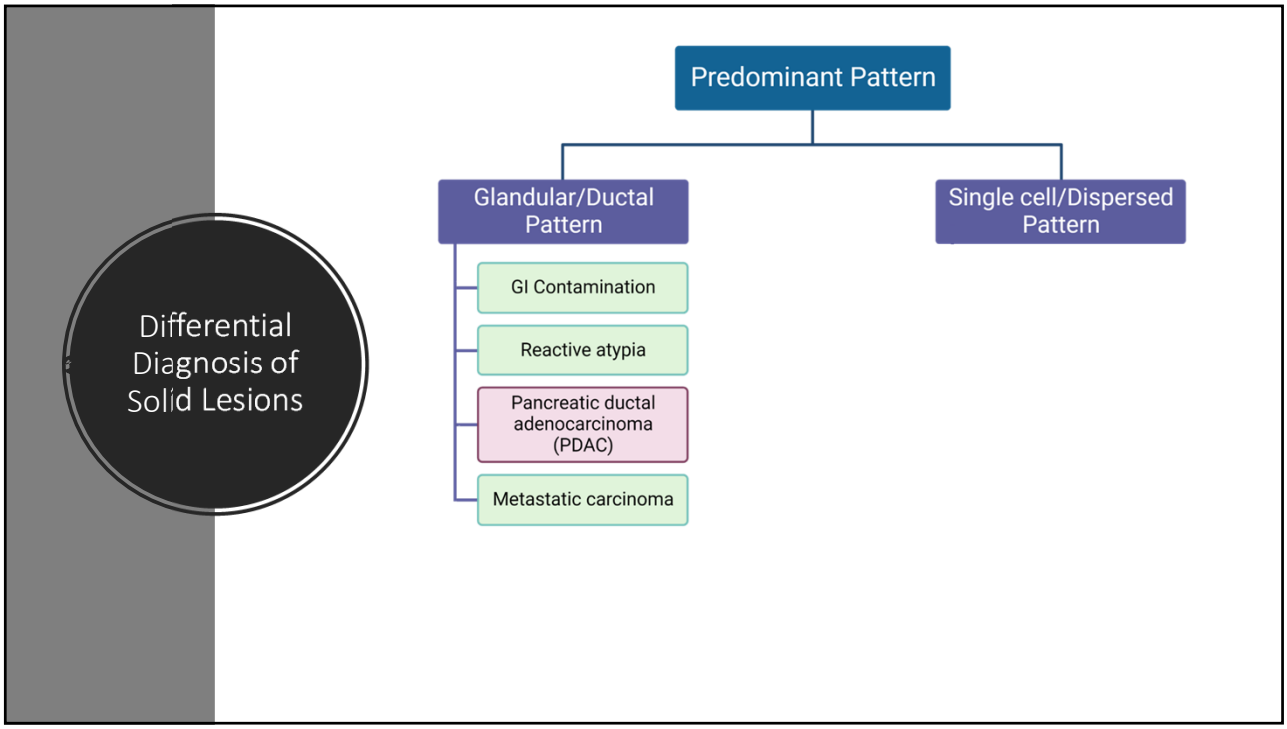
Normal pancreas



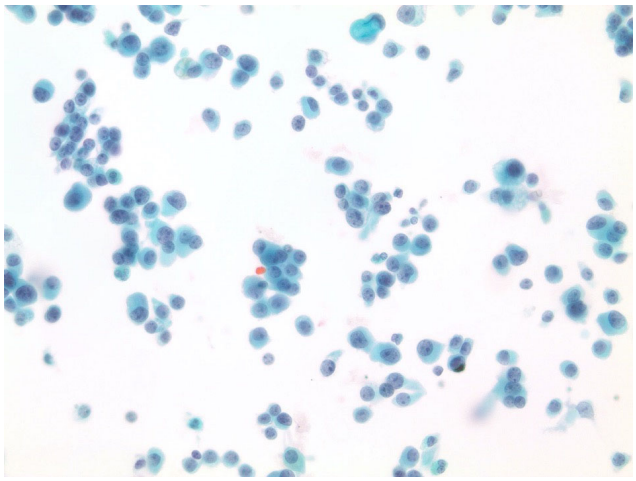


Pancreatic neuroendocrine tumor (PanNET)

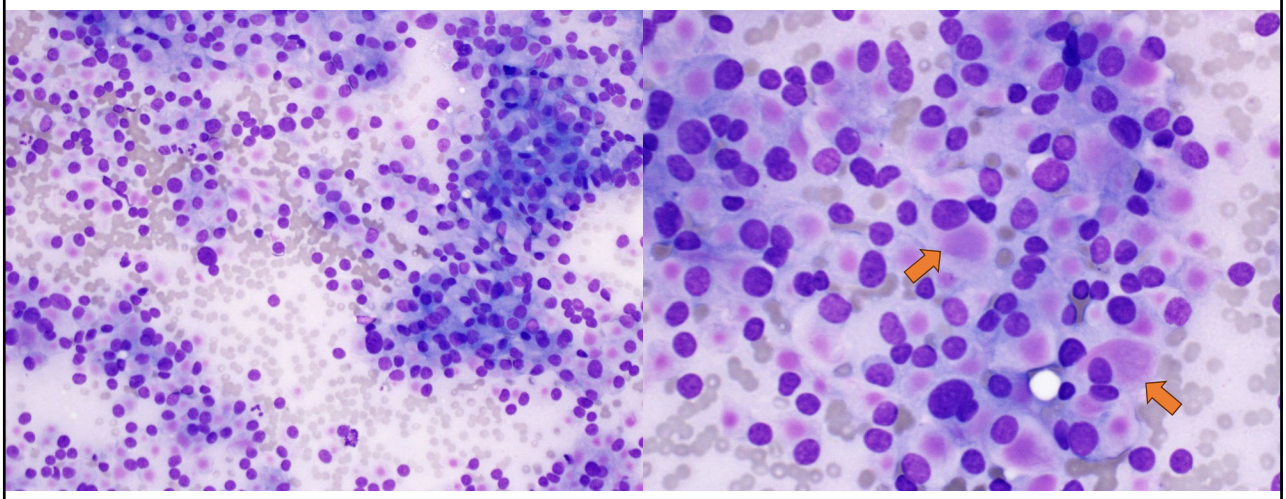
- 2-5% of all pancreatic neoplasms
- Presents at any age (highest incidence in ages 30-60), M=F
- 60% occur in pancreatic tail, but can arise anywhere within pancreas
- Non-functioning (>60%) and functioning types
- Generally slow-growing
- Surgery is the primary treatment
  - Conservative management in some cases (e.g. small tumors)

Pancreatic neuroendocrine tumor (PanNET)

- Well-differentiated
- Architecture
  - Dispersed, loosely cohesive and single cells
- Cytomorphology
  - Monomorphic
  - Plasmacytoid
  - Round nuclei
  - “Salt-and-pepper” chromatin

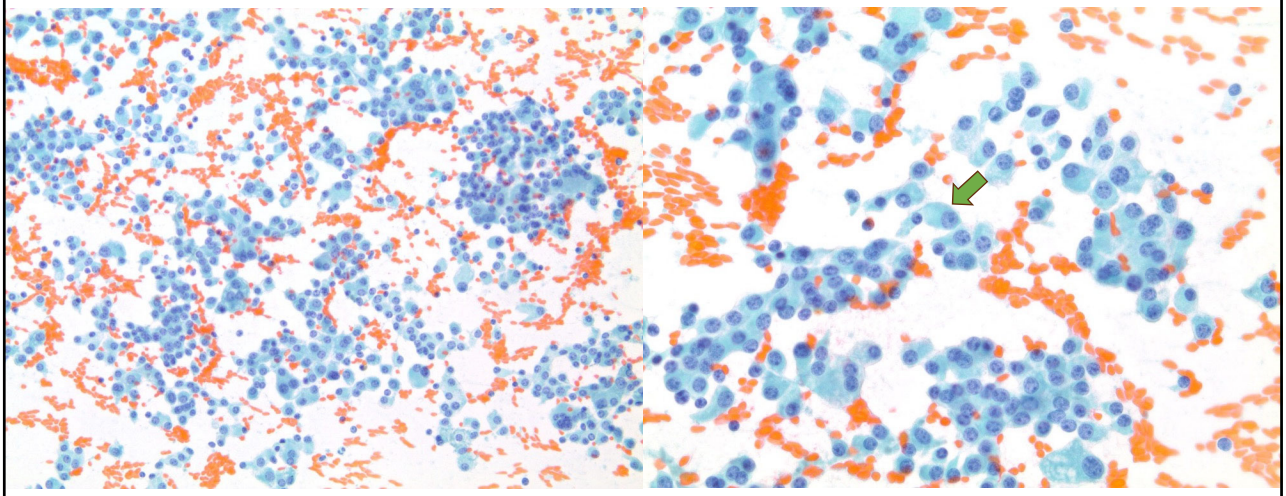


PanNET, grade 1



Diff-Quik stain

PanNET, grade 1



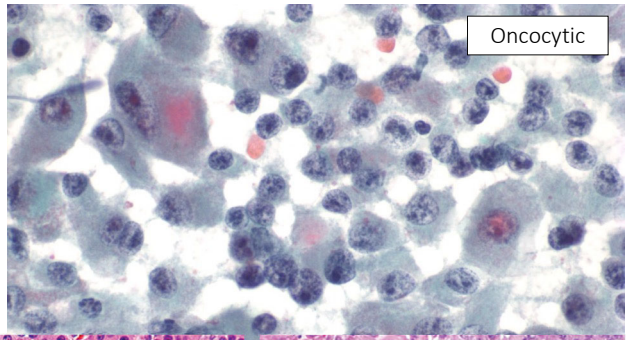
Pap stain

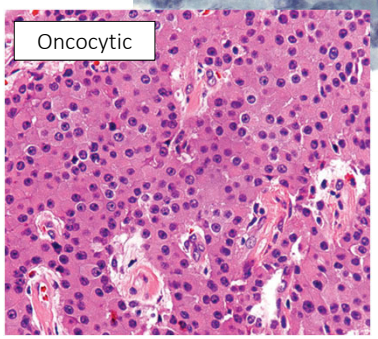
Variants of PanNET

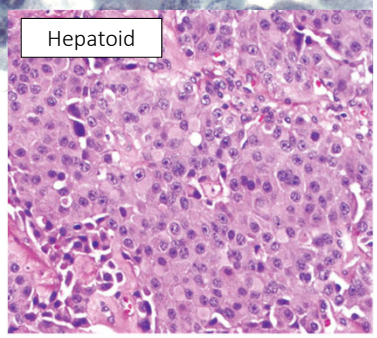
More aggressive group
- Oncocytic (8)
- Hepatoid (9)
- Lipid-rich (5)
- Discohesive, sheet-like pattern with plasmacytoid cells (14)
- Overall

Less aggressive group
- Pleomorphic (9)
- Paraganglioma-like (10)
- Ductulo-insular (7)
- Overall

Indeterminate group
- Mammary tubulo-lobular carcinoma-like (10)
- Pseudoglandular (6)
- Peliotic/angiomatous (11)
- Sclerosing (4)
- Overall

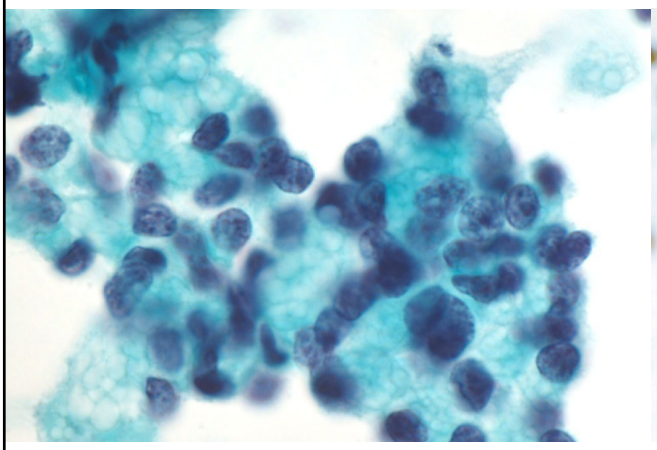




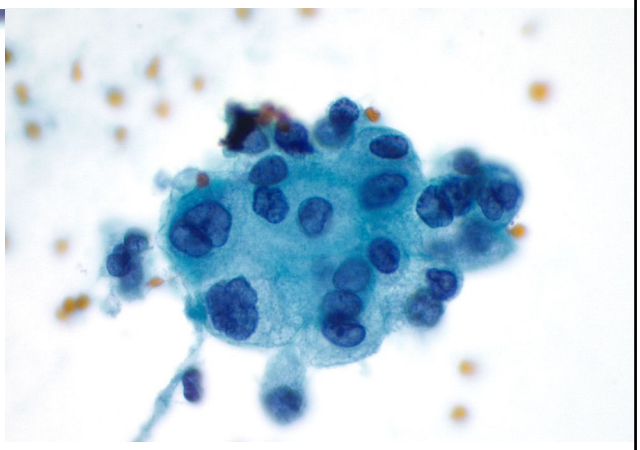


Xue Y, Reid MD, Pehlivanoglu B, et al. Endocr Pathol 2020;31(3):239–53.

PanNET, lipid-rich variant



Metastatic renal cell carcinoma



Courtesy of Dr. Martha Pitman

Table 2 Comparison between more aggressive group and the cohort

	More aggressive group	Overall cohort	*p* value
Median size (cm)	5.0	2.5	< 0.0001
Median Ki67 (%)	5.3	3.0	0.12
LN and distant metastatic rate at the surgery and during the follow-up (%)	96%	45%	< 0.0001

Table 4 Comparison between more and less aggressive groups

	More aggressive	Less aggressive	*p* value
Median size (cm)	5.0	1.6	< 0.0001
Median Ki67 (%)	5.3	2.3	0.001
LN and distant metastatic rate at the surgery and during the follow-up (%)	96%	27%	< 0.0001

Xue Y, Reid MD, Pehlivanoglu B, et al. Endocr Pathol 2020;31(3):239–53.

Grading PanNENs (WHO 5th Edition)

		Mitotic Count/2 mm^2	Ki-67 (%)
Low-grade	**Well-differentiated neuroendocrine tumors (NET)**		
	Grade 1	<2	<3
	Grade 2	2-20	3-20
	Grade 3	>20	>20
High-grade	**Poorly differentiated neuroendocrine carcinomas (NEC)**		
	Small cell type	>20	>20
	Large cell type		

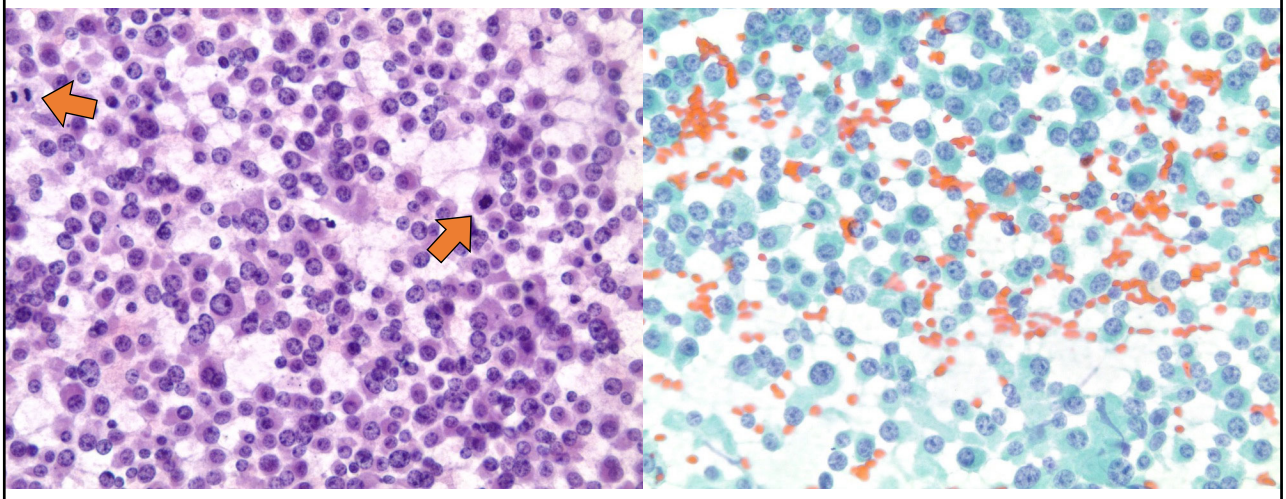
Grading PanNENs on resections

- CAP recommendations for *resection specimens*:
  - Mitotic rate: number of mitoses (at 40X magnification) per 2 mm^2, at least 10 mm^2 evaluated in the most mitotically active part of the tumor.
    - For microscope with field number (FN) = 22
    - Field diameter (mm) = FN/magnification = 22/40 = 0.55 mm
    - Field area (mm^2) = πr^2 = 3.14*(0.55/2)^2 = 0.238 mm^2
    - Recommended evaluation of 10 mm^2/0.238 mm^2 = **42 HPF**
    - Minimum evaluation of 2 mm^2/0.238 mm^2 = **8 HPF**

Grading PanNENs (WHO 5th Edition)

		Mitotic Count/2 mm²	Ki-67 (%)
Low-grade	**Well-differentiated neuroendocrine tumors (NET)**		
	Grade 1	<2	<3
	Grade 2	2-20	3-20
High-grade	Grade 3	>20	>20
	Poorly differentiated neuroendocrine carcinomas (NEC)		
	Small cell type	>20	>20
	Large cell type		

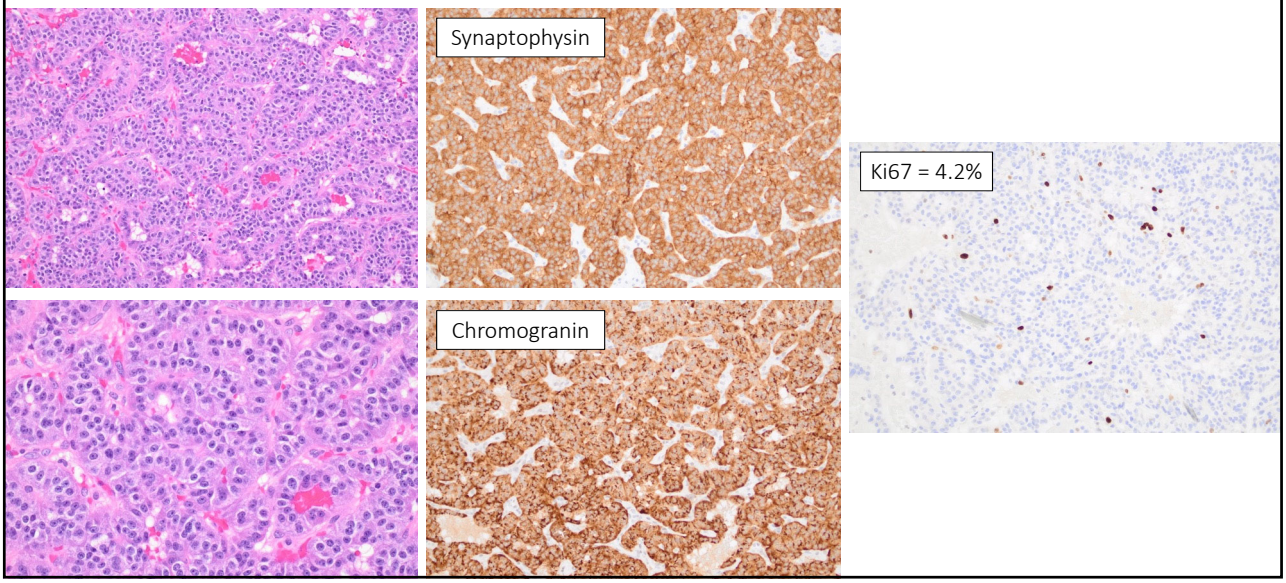
PanNET, occasional mitoses on smear



Rapid H&E stain

Pap stain

PanNET, grade 2 on resection



Grading PanNENs on resections

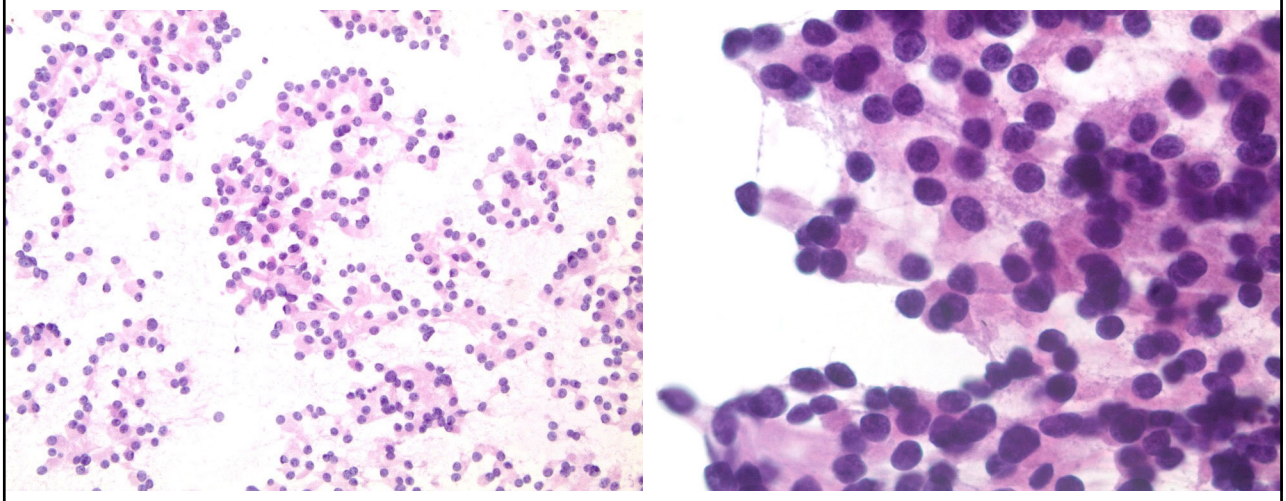
- CAP recommendations for *resection specimens*:
  - Mitotic rate: number of mitoses (at 40X magnification) per 2 mm^2, at least 10 mm^2 evaluated in the most mitotically active part of the tumor.
    - For microscope with field number (FN) = 22
    - Field diameter (mm) = FN/magnification = 22/40 = 0.55 mm
    - Field area (mm^2) = πr^2 = 3.14*$(0.55/2)^2$ = 0.238 mm^2
    - Recommended evaluation of 10 mm^2/0.238 mm^2 = **42 HPF**
    - Minimum evaluation of 2 mm^2/0.238 mm^2 = **8 HPF**
  - Ki67 index: minimum of 500 tumor cells be counted to determine the Ki67 index (some have recommended counting at least 2000 cells)

What about on cell blocks & small biopsies?

Grading PanNETs on Cell Blocks

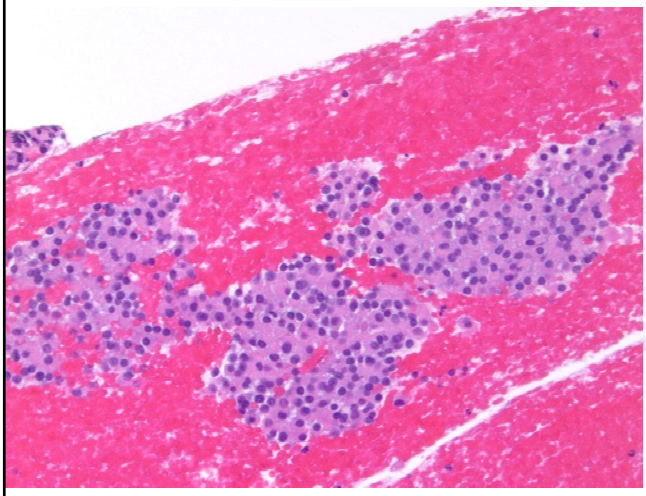
- Jin et al. 2016 (58 cases), Abi-Raad et al. 2020 (49 cases):
  - EUS-FNA cell block (CB) and corresponding surgical pathology (SP)
    - All cell blocks had >100 tumor cells
    - Analysis only included grade 1 and 2 tumors
  - Compared with SP, CB manual count correctly graded 69% (k = 0.44) and 73% (hot spot method) in each study, respectively
  - Grade 1 tumors had much higher concordance than grade 2 tumors
- Grading concordance improved as tumor cellularity increased
- 40+% of grade 2 PanNETs can be under-graded based on Ki67 index evaluated on a CB

PanNET, low-grade

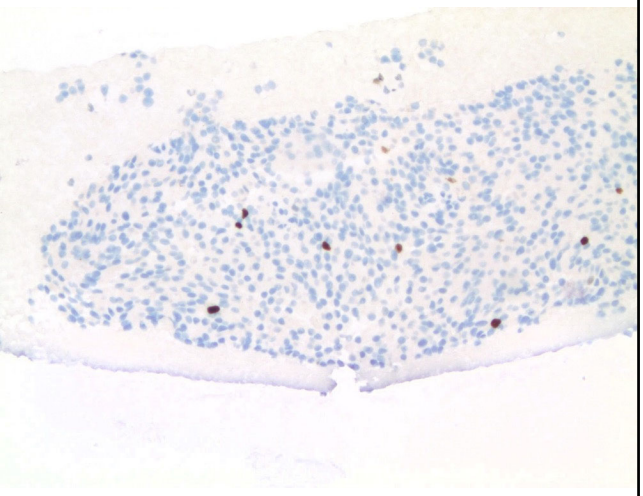


Rapid H&E stain

PanNET, grade 1



Core biopsy, H&E



Ki67 = 2.0%

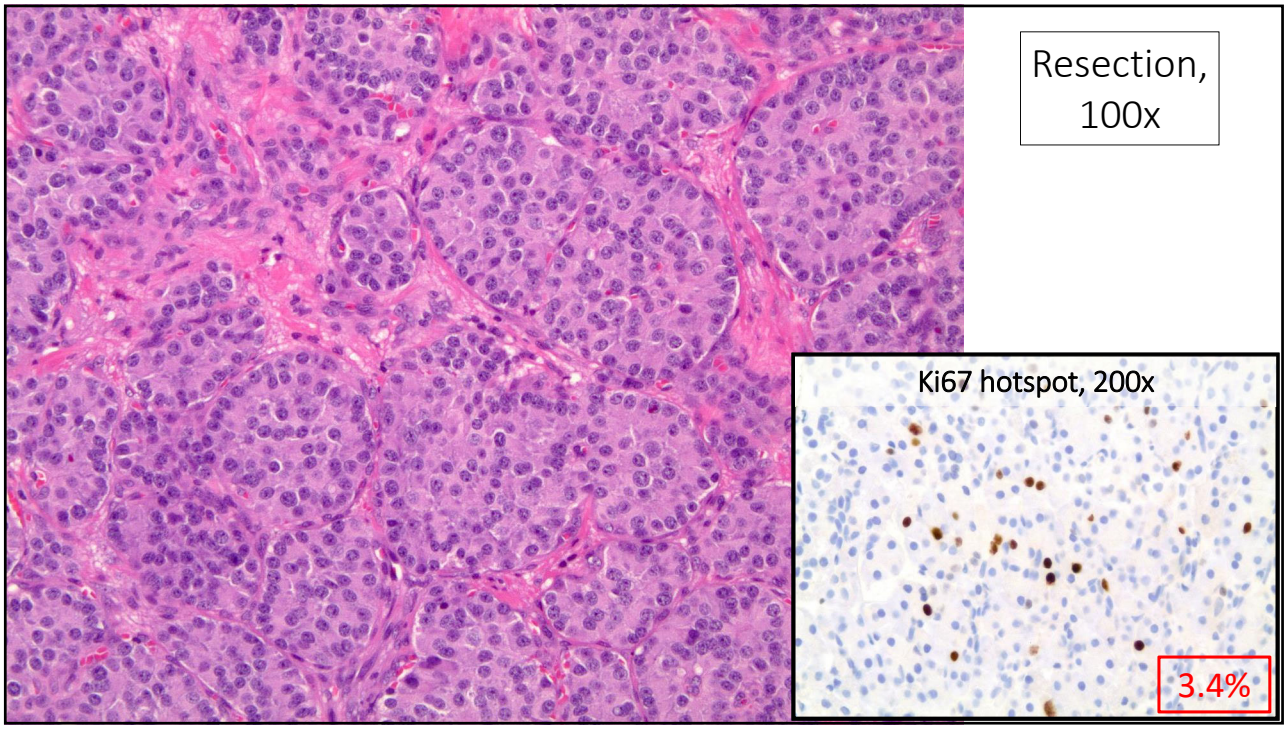
Example report

- Well-differentiated neuroendocrine tumor, provisional grade 1 (see note).

OR

- Well-differentiated neuroendocrine tumor, low-grade (see note).

- Note: No mitoses are identified. A Ki67 proliferation index is 2.0%, though there are fewer than 500 tumor cells in the specimen (8 positive out of 398 tumor cells counted). Definitive grading is deferred to histologic assessment.



Grading PanNENs (WHO 5th Edition)

	Mitotic Count/2 mm^2	Ki-67 (%)
Well-differentiated neuroendocrine tumors (NET)		
Grade 1	<2 1	<3
Grade 2	2-20	3-20 3.4%
Grade 3	>20	>20
Poorly differentiated neuroendocrine carcinomas (NEC)		
Small cell type	>20	>20
Large cell type		

Grading PanNENs (WHO 5th Edition)

	Mitotic Count/2 mm^2	Ki-67 (%)
Well-differentiated neuroendocrine tumors (NET)		
Grade 1	<2	<3
Grade 2	2-20	3-20
Grade 3	>20	>20
Poorly differentiated neuroendocrine carcinomas (NEC)		
Small cell type	>20	>20
Large cell type		

High-grade

Neuroendocrine Neoplasms

Resection (depending on size and other factors)

Platinum-based chemotherapy

Tang LH. *Arch Pathol Lab Med*. 2020

Table 1. Distinction Between Well-Differentiated Pancreatic Neuroendocrine Tumor (WD-PanNET) (G3) and Poorly Differentiated Pancreatic Neuroendocrine Carcinoma (PD-PanNEC) by Clinicopathologic and Molecular Characteristics

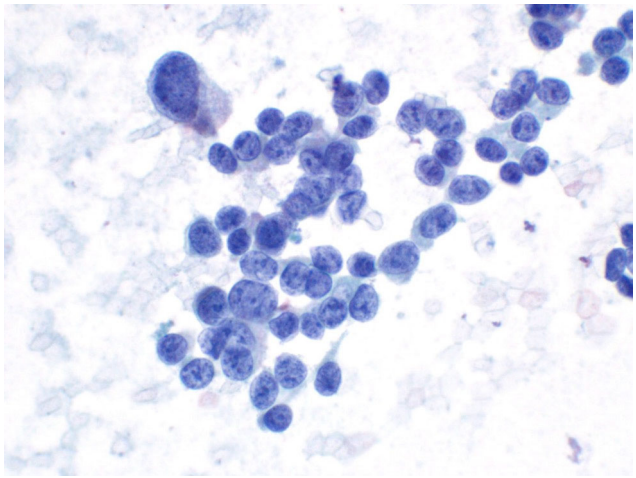
	WD-PanNET (G3)	PD-PanNEC
Clinical assessment		
Presentation	Either incidental findings or mildly symptomatic	High-grade malignancy–associated symptoms with rapid disease progression
Radiology	Diffuse avidity on SSRS	Negative or weak/focal activity on SSRS
	PET finding may be positive but heterogenous	PET finding positive with high SUV
Biomarkers	Elevated neuroendocrine markers (chromogranin-A)	Elevated carcinoma markers (CA 19.9)
Pathologic assessment	A spectrum of tumor grades: a component lower-grade tumor; or prior lower-grade tumor in another specimen	Homogenously high grade: no low-grade component; a component of ductal adenocarcinoma
Ancillary tests		
Immunohistochemistry	Loss of Daxx or Atrx expression	Loss to Rb, SMAD4, and/or abnormal p53 expression
	Expression of SSR_2	Uncommon SSR_2 expression
Gene mutations	*DAXX/ATRX* and/or *MEN1*, *PI3K/mTOR (TSC1/2, PTEN)* >40%	*TP53*, *SMAD4*, *KRAS*, *RB1* in most

Abbreviations: PET, positron emission tomography; SSRS, somatostatin receptor scintigraphy; SUV, standardized uptake value; SSR_2, type 2 somatostatin receptor.

Tang LH. *Arch Pathol Lab Med*. 2020

PanNET, grade 3

- Well-differentiated
  - Still looks neuroendocrine
- Cytomorphology
  - Increased pleomorphism
  - Increased N/C ratio
  - "Salt-and-pepper" chromatin
- Definitive grading should only be performed on adequate tissue (+/- ancillary studies)

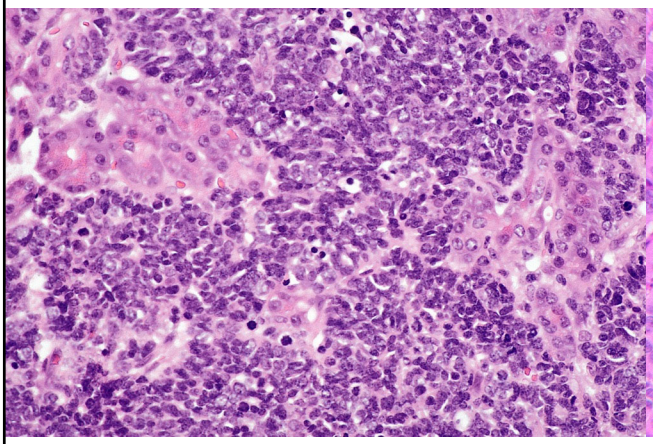


Pancreatic neuroendocrine carcinoma (PanNEC)

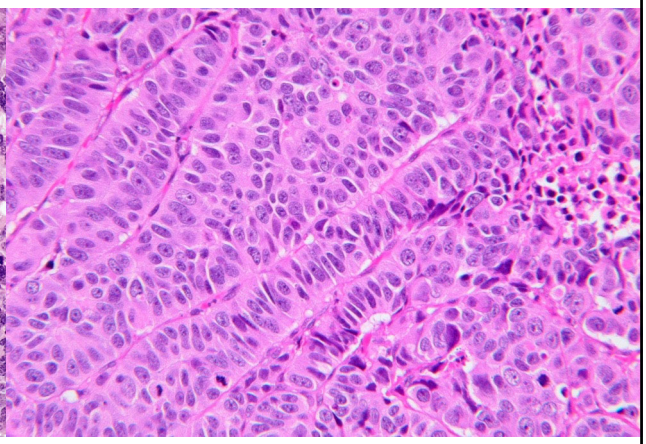
- Poorly differentiated
- Architecture
  - Clusters, loosely cohesive and single cells
- Cytomorphology
  - High-grade, overtly malignant
  - Small cell type: high N/C ratio (scant cytoplasm), molding, necrosis
  - Large cell type: lower N/C ratio
  - *"Intermediate/NOS type"*: somewhere in between

Pancreatic neuroendocrine carcinoma (PanNEC)

Small cell type

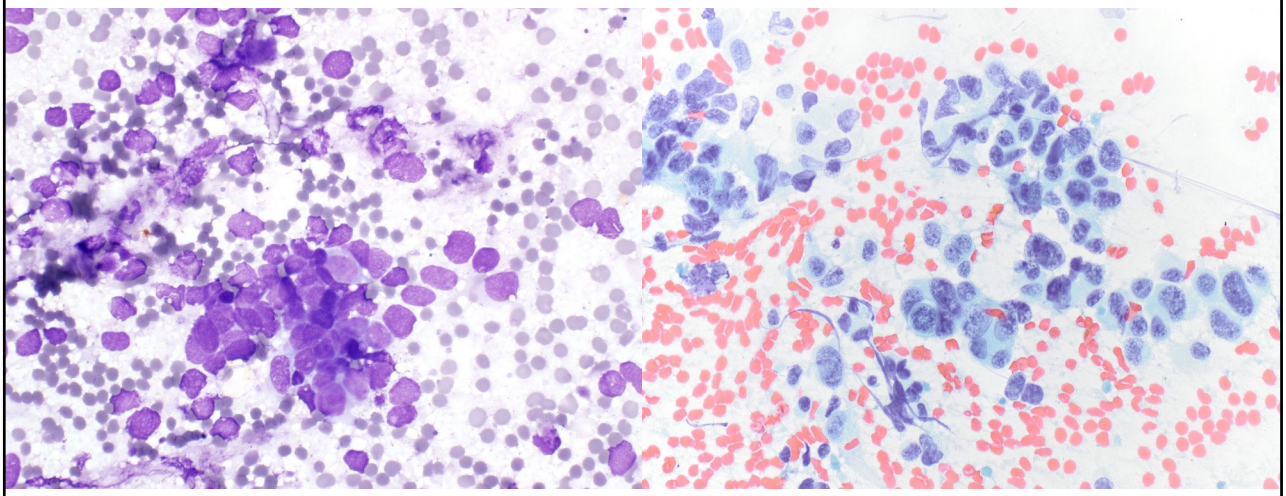


Large cell type



Courtesy of Dr. Martha Pitman

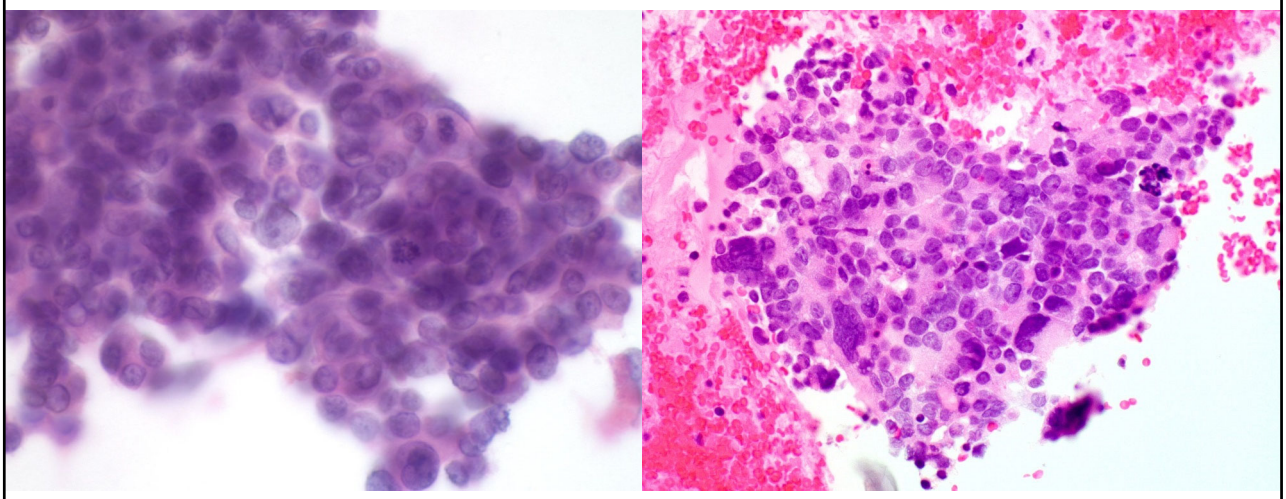
PanNEC, small cell type



Diff-Quik stain

Pap stain

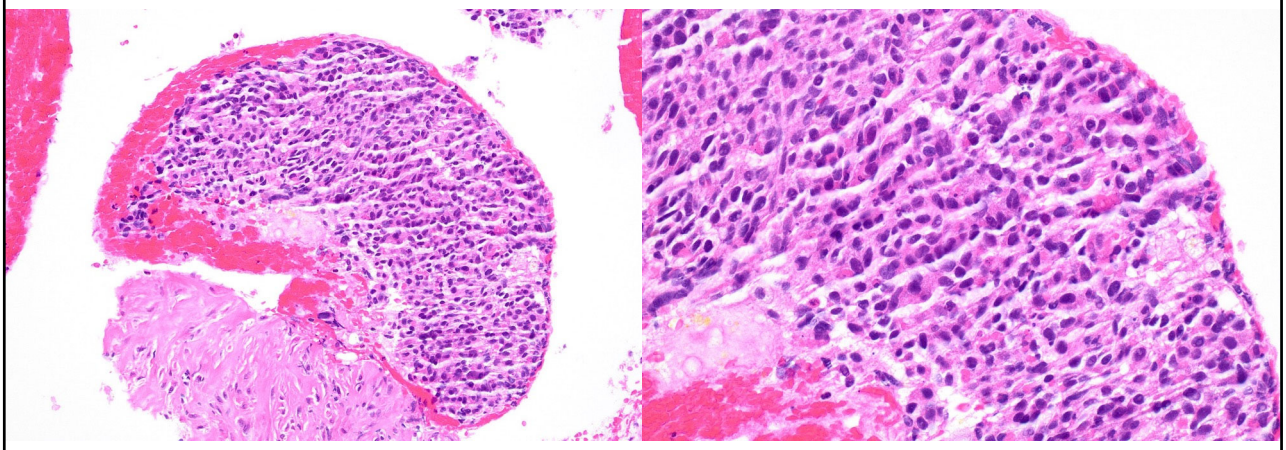
PanNEC, large cell type



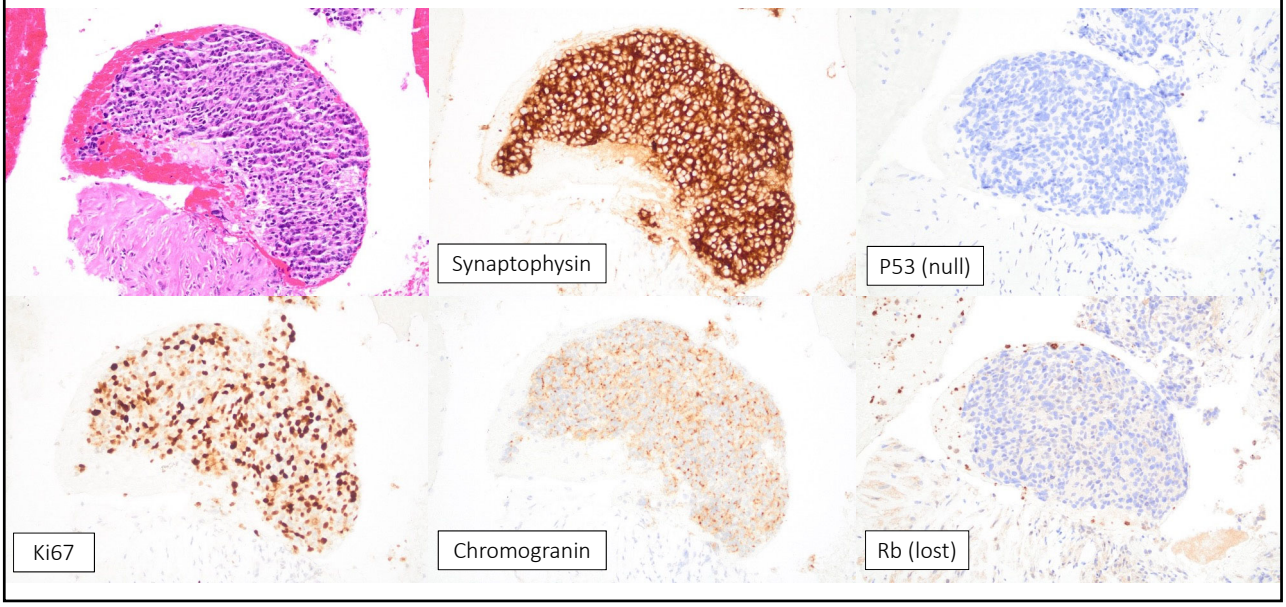
Courtesy of Dr. Martha Pitman

WHO Reporting System for Pancreaticobiliary Cytopathology

PanNET grade 3 vs. PanNEC?



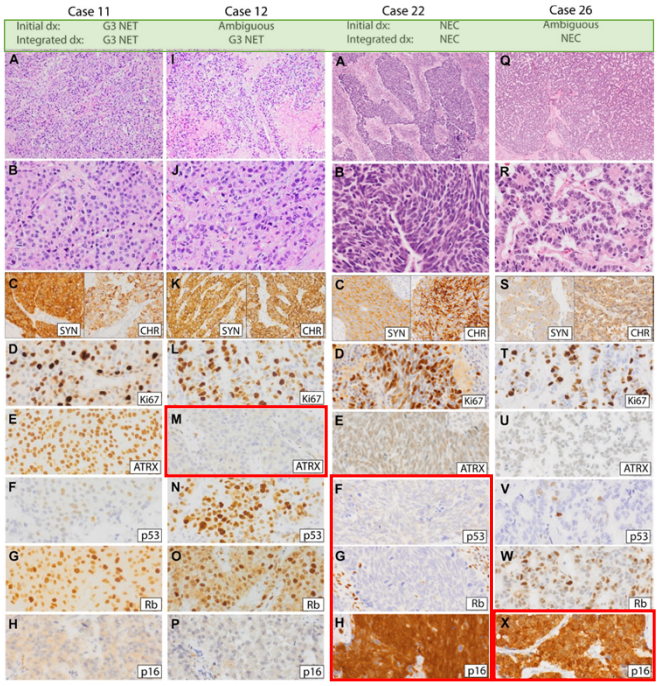
PanNEC, large cell/NOS



“Integrated diagnosis”

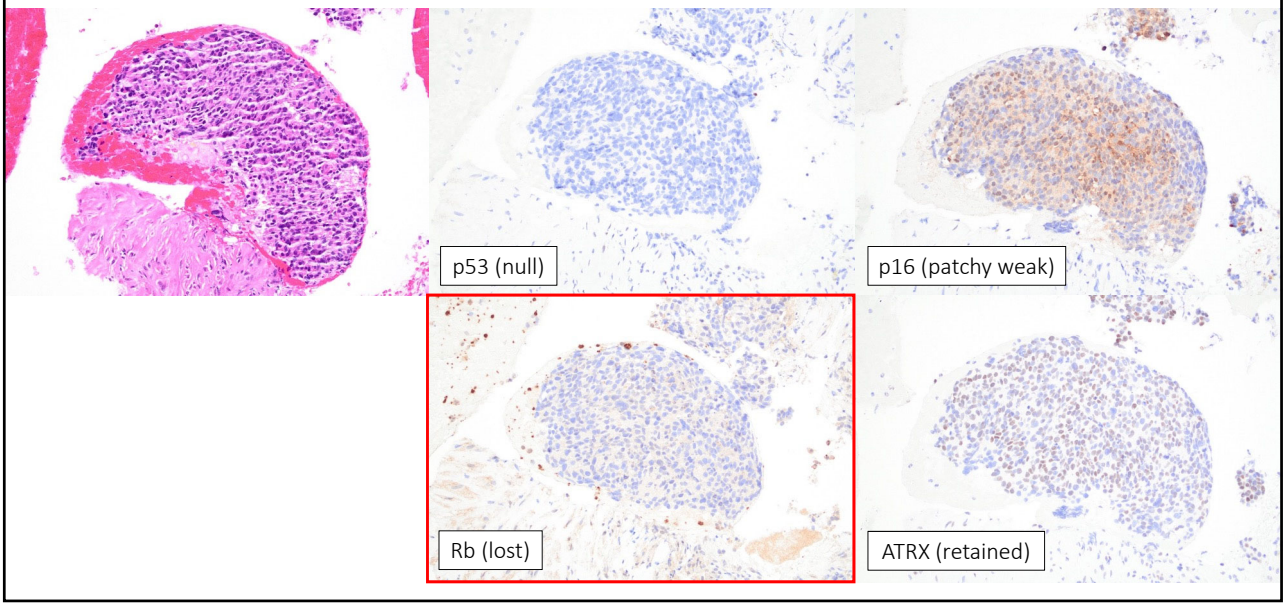
Molecular Alterations	G3 PanNET	PanNEC
*TP53**	35%	88%
p53 IHC (mutant)	24%	71%
Rb	0%	47%
Rb IHC (loss)	0%	41%
*CDKN2A (p16)**	41%	29%
p16 IHC (diffuse)	0%	65%
ATRX	24%	0%
ATRX IHC (loss)	18%	0%
DAXX	47%	0%
MEN1	71%	0%
SMAD4	6% (1 case)	41%

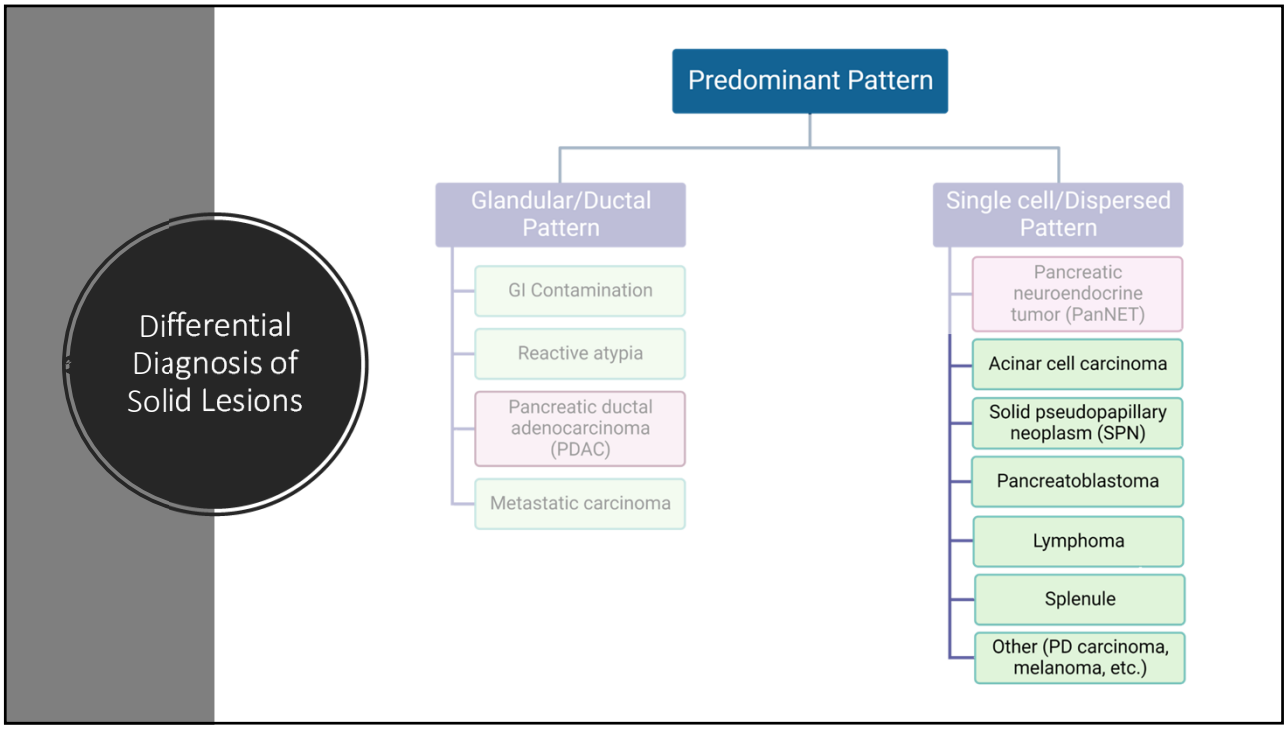
*Mutually exclusive in G3 PanNET vs. co-altered in PanNEC (30%)



Umetsu SE et al. Mod Pathol. 2023.

PanNEC, large cell/NOS



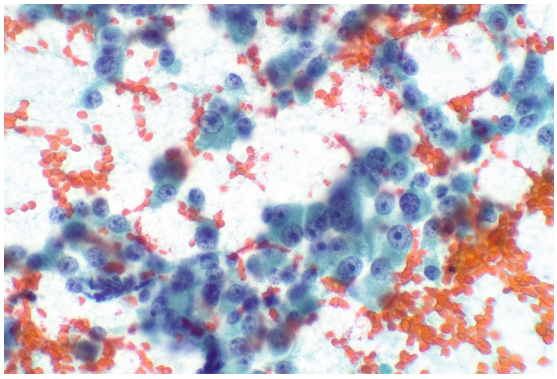


Acinar cell carcinoma (ACC)

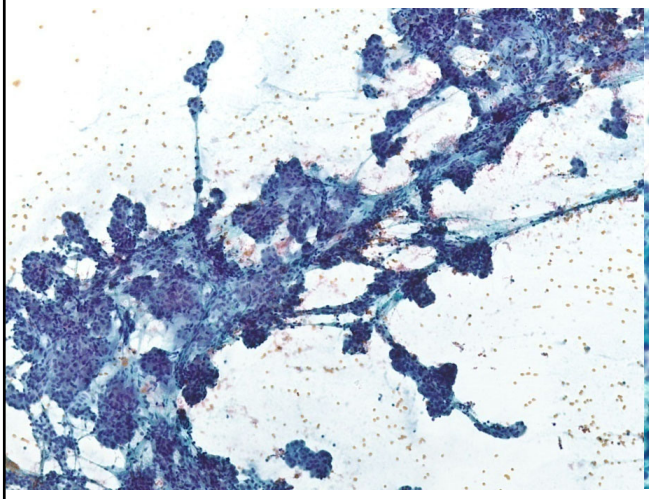
- 1-2% of adult pancreatic neoplasms, 15% of pediatric
- Mean age ~60 years, M>F 2:1
- Can occur anywhere within pancreas
- Usually large (mean 10cm)
- Highly aggressive neoplasm
  - 50% of patients have metastatic disease at presentation
  - 5-year survival 5-30%, depends on resectability

ACC Cytomorphology

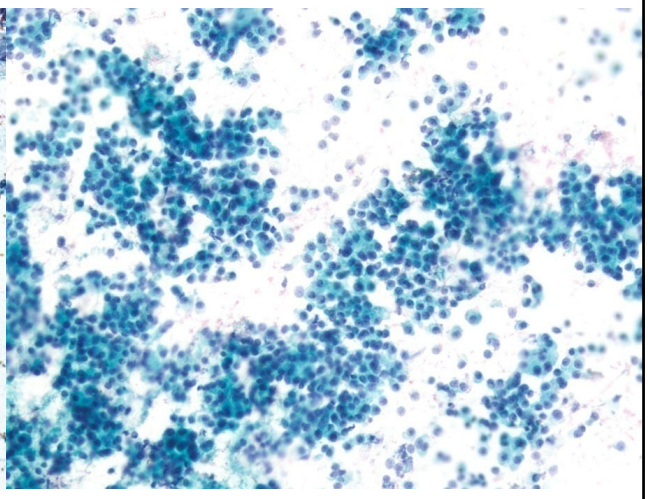
- Dispersed single cells, clusters, trabeculae
- Background stripped naked nuclei
- Granular background
- Prominent central nucleoli
- Readily identifiable mitoses



Benign vs. malignant acinar cells

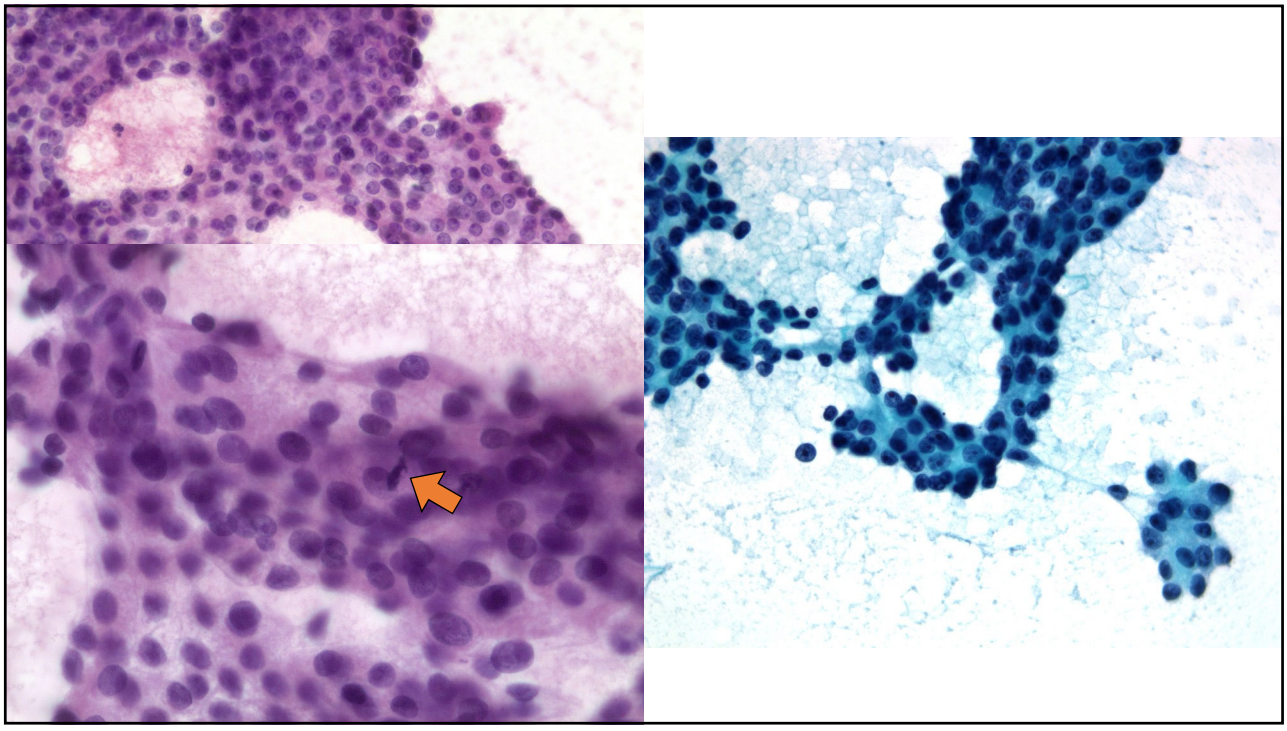


Benign

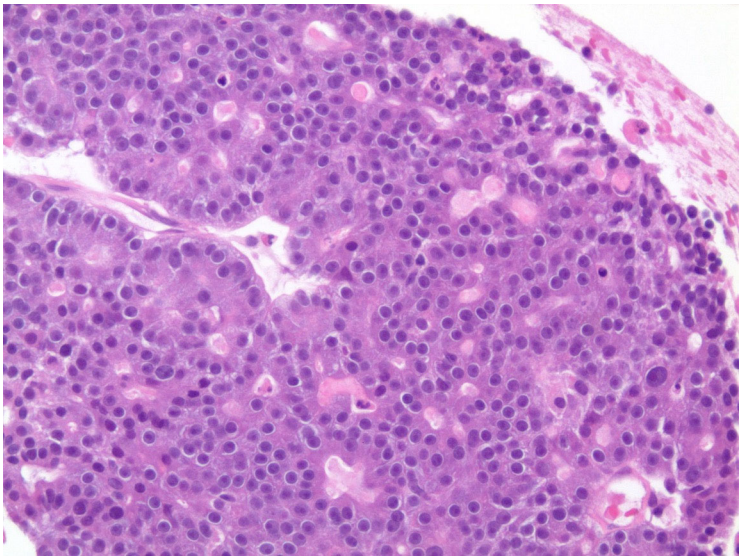


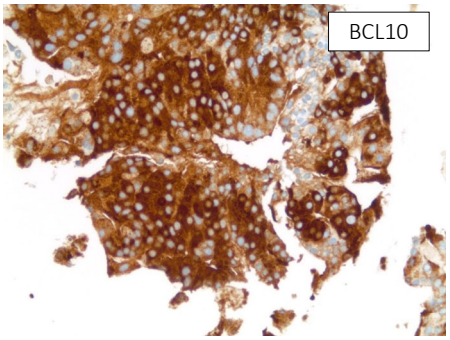
Malignant

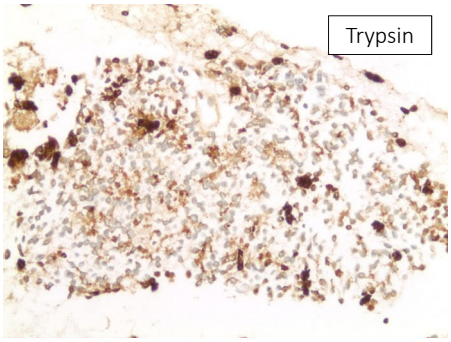
Courtesy of Dr. Martha Pitman



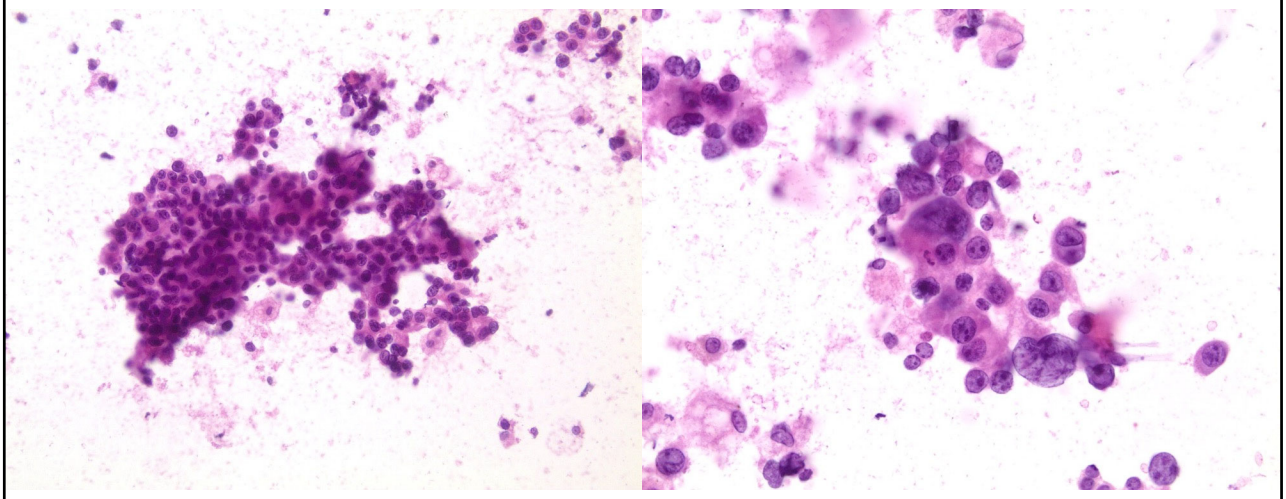
Acinar cell carcinoma

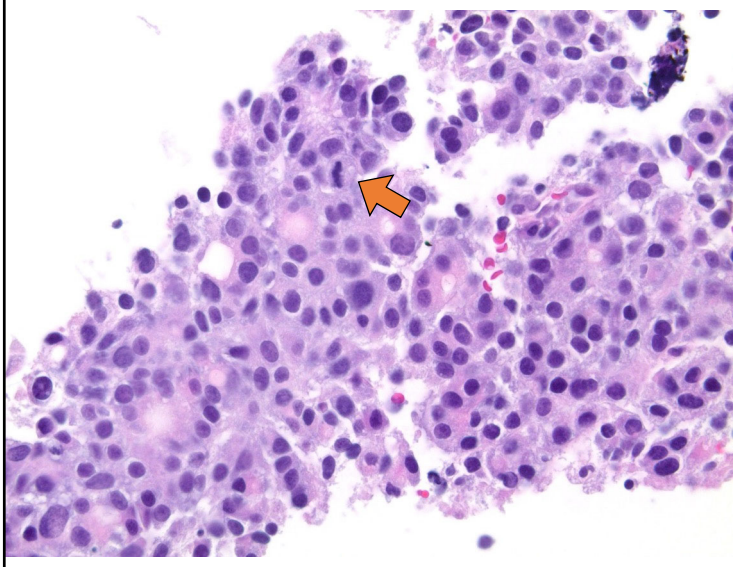


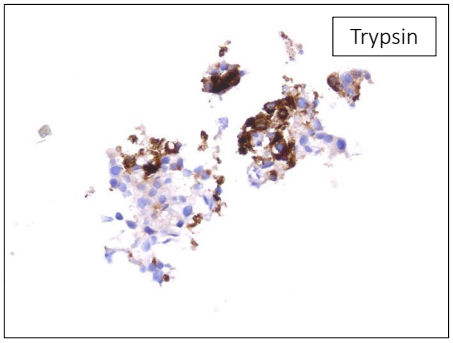


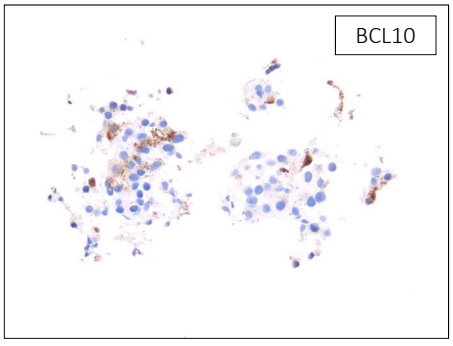


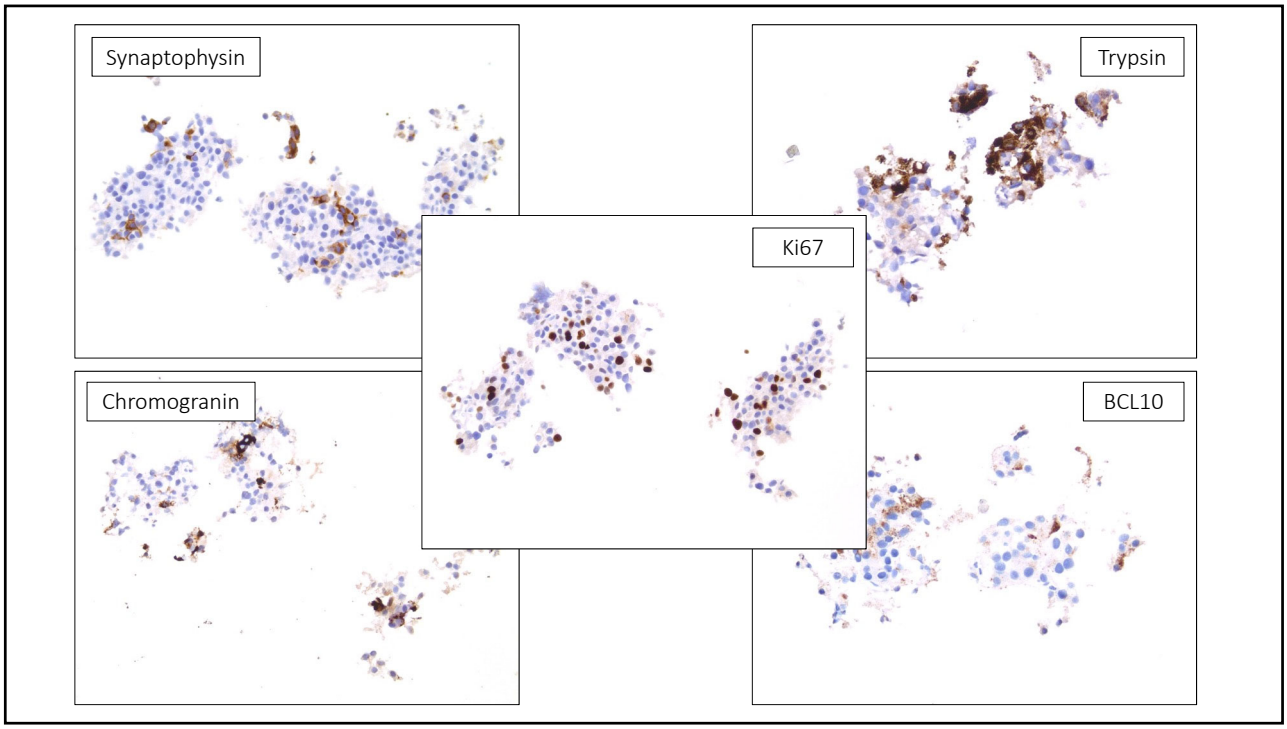
Non-ductal neoplasm, ACC vs. PanNET (grade 2-3?)









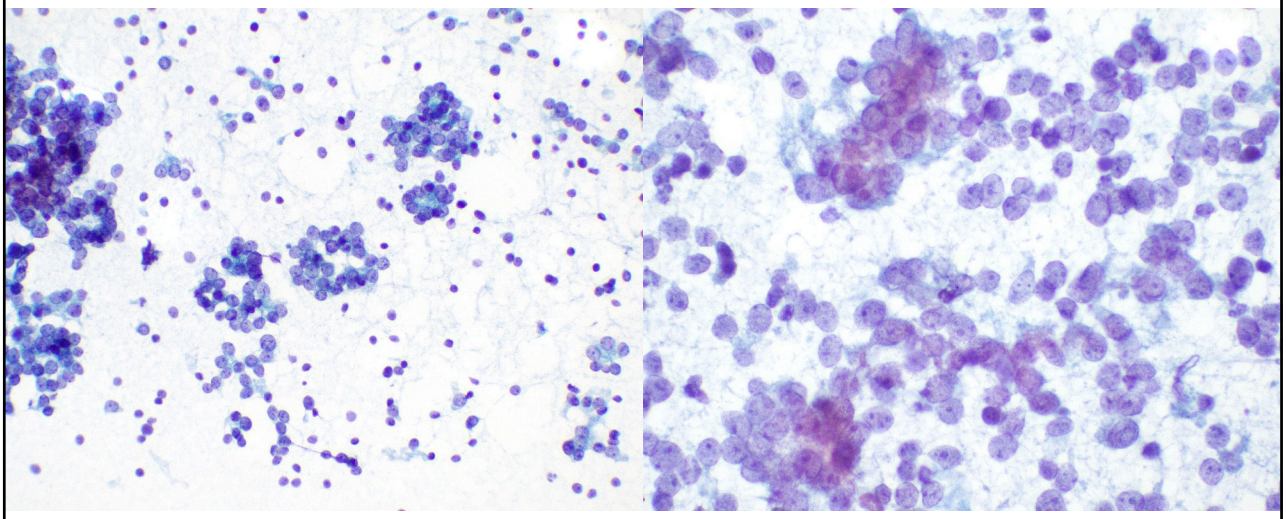


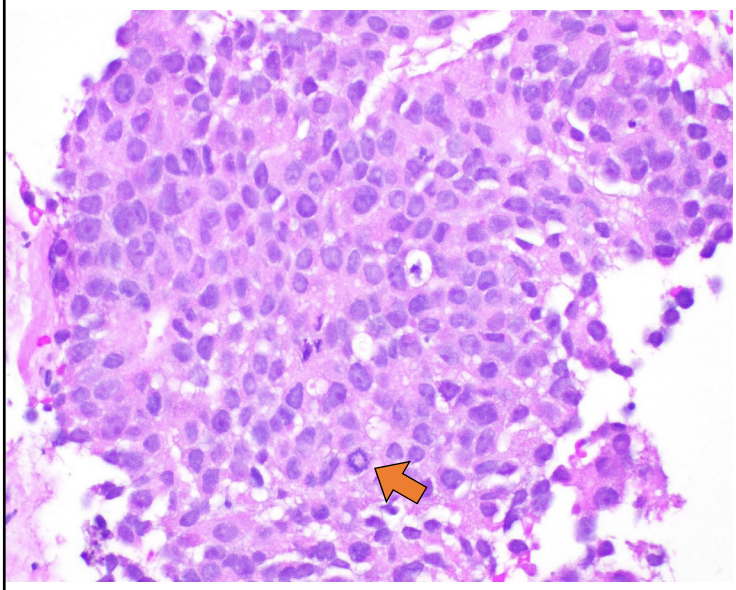
Final diagnosis

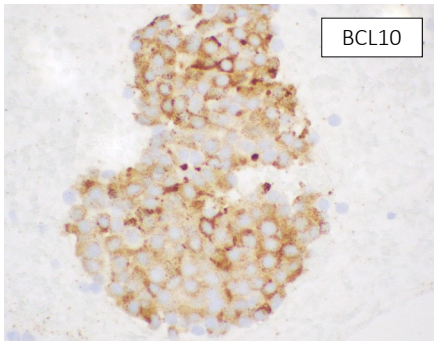
- "Non-ductal neoplasm, favor acinar cell carcinoma."

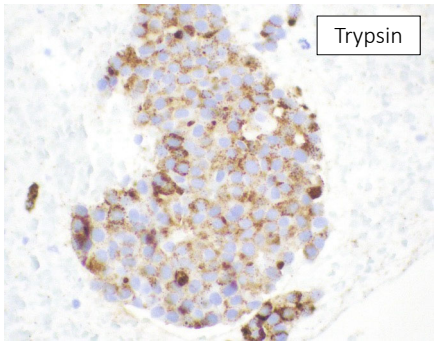
- Morphology compatible/suggestive of ACC
- Mitoses and moderately high Ki67 > 30% (based on very limited tissue)
  - ACC more common than grade 3 PanNET
- Patchy positivity for trypsin, BCL10, synaptophysin, and chromogranin
- Scant biopsy cellularity and equivocal IHC pattern precludes definitive diagnosis

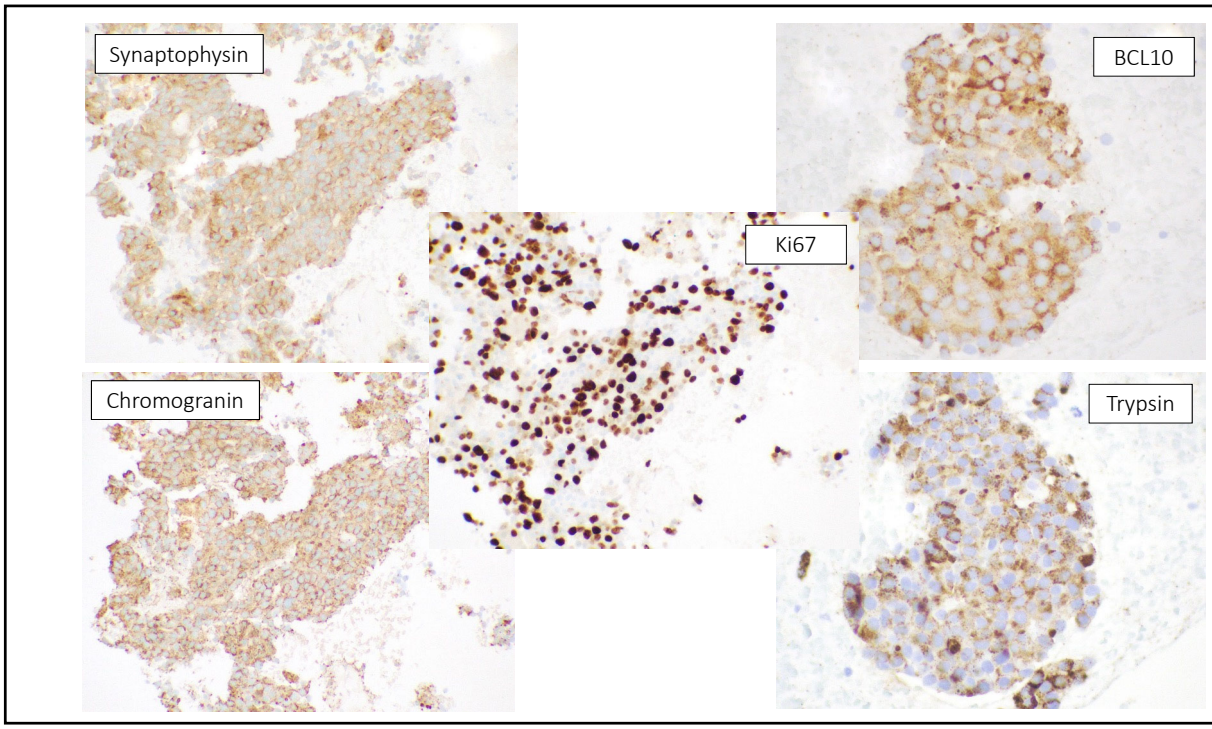
Acinar cell carcinoma?











Final diagnosis

- "Carcinoma with acinar and neuroendocrine differentiation."

- High-grade morphology
- Mitoses and very high Ki67 > 50%
- Diffuse positivity for trypsin, BCL10, synaptophysin, and chromogranin
- Can suggest diagnosis of "mixed acinar-neuroendocrine carcinoma" but definitive diagnosis requires examination of resection specimen

Mixed neoplasms of the pancreas

- Defined as having >30% of each line of differentiation
- Most common is mixed acinar-neuroendocrine carcinoma
  - 15-20% of all acinar cell carcinomas
  - Morphologically resemble pure acinar cell carcinomas
  - Co-expression of acinar and neuroendocrine markers (individual components usually NOT separate/morphologically distinguishable)
  - Treated as acinar cell carcinoma due to similar clinical behavior and genetics
- Other types of mixed tumors (mixed acinar-ductal carcinomas, mixed ductal-neuroendocrine carcinomas) more rare

Washington MK et al. "Pancreatic acinar cell carcinoma" In: Digestive System Tumours. 5th ed. IARC; 2019. WHO Classification of Tumours.

Acinar and neuroendocrine markers

- Acinar markers: BCL10, trypsin, (chymotrypsin)
- Neuroendocrine markers: synaptophysin, chromogranin, INSM1, (CD56)
- 30-55% of ACCs have scattered synaptophysin/chromogranin+ neuroendocrine cells (<<30% of tumor cells)
- PanNETs commonly express acinar markers in <<30% of tumor cells

La Rosa et al. 2012	Acinar cell carcinoma	Mixed acinar-neuroendocrine carcinoma
Trypsin	46/48 (96%)	11/12 (92%)
BCL10	40/47 (85%)	11/12 (92%)
Synaptophysin (>30% of cells)	0/49 (0%)	12/12 (100%)
Chromogranin (>30% of cells)	0/49 (0%)	12/12 (100%)

Ohike N et al. Virchows Arch. 2004
La Rosa S et al. Am J Surg Pathol. 2012

Immunophenotyping results on both fine-needle aspiration cytology samples and paired histological specimens.

FNAC FNAB					
Tumor types, case ID	BCL10 score (%)	Trypsin score (%)	Synaptophysin score (%)	Chromogranin score (%)	β-Catenin nuclear score (%)
ACC					
1	3+ (100)	1+ (50)	0 (-)	0 (-)	1+ (5)
2	3+ (100)	2+ (70)	1+ (5)	0 (-)	0 (-)
3	3+ (100)	3+ (100)	0 (-)	0 (-)	n.a.
4	3+ (100)	2+ (80)	1+ (10)	n.a.	n.a.
5	3+ (100)	2+ (60)	1+ (10)	0 (-)	n.a.
6	3+ (100)	1+ (30)	1+ (20)	0 (-)	1+ (5)
7	3+ (100)	1+ (<5)	1+ (5)	0 (-)	0 (-)
8	3+ (100)	2+ (60)	0 (-)	n.a.	0 (-)
9	3+ (100)	3+ (80)	0 (-)	0 (-)	n.a.
10	3+ (100)	2+ (100)	0 (-)	0 (-)	1+ (5)
11	3+ (100)	2+ (100)	1+ (50)	0 (-)	0 (-)
12	3+ (100)	3+ (70)	0 (-)	0 (-)	n.a.
MANEC					
1	3+ (100)	3+ (80)	2+ (70)	1+ (30)	n.a.
2	3+ (100)	3+ (100)	2+ (50)	3+ (60)	0 (-)
3	3+ (100)	3+ (80)	1+ (40)	1+ (10)	0 (-)
4	3+ (100)	1+ (<5)	3+ (80)	2+ (60)	n.a.
5	3+ (100)	2+ (60)	2+ (70)	2+ (60)	0 (-)
6	3+ (100)	2+ (70)	1+ (40)	0 (-)	0 (-)
7	3+ (100)	3+ (60)	1+ (40)	1+ (30)	0 (-)
8	3+ (100)	1+ (40)	2+ (60)	0 (-)	0 (-)
9	3+ (100)	3+ (80)	1+ (40)	3+ (60)	0 (-)

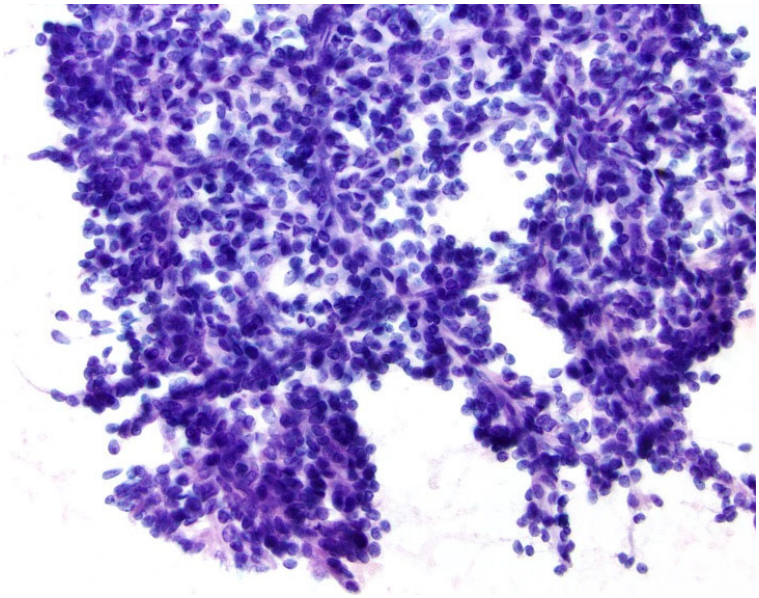
Manfrin E et al. Pathol Res Pract. 2021

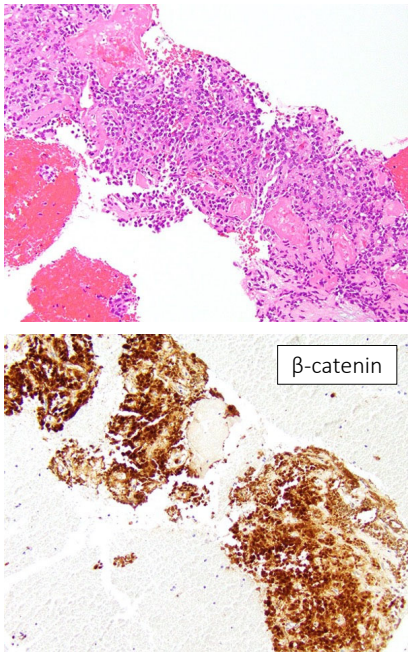
Solid pseudopapillary neoplasm (SPN)

- 2-5% of all pancreatic neoplasms
- ~90% female, mean age 28 years
- Can arise anywhere in pancreas, mean 10cm
- Large solid and cystic neoplasm, often radiologically diagnosed
- Low grade malignancy, usually indolent and completely cured with resection
  - 10-15% patients have metastatic disease at diagnosis limited to liver and peritoneum (still relatively good prognosis and die of other causes)

SPN Cytomorphology

- Dispersed cells
- Can have prominent, branching vessels
- Monomorphic nuclei, sometimes grooves
  - Falling off edge of vessels



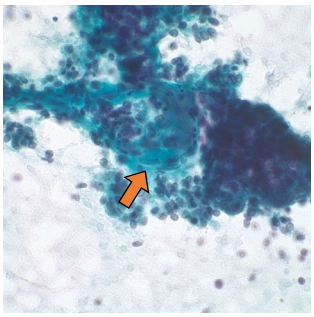


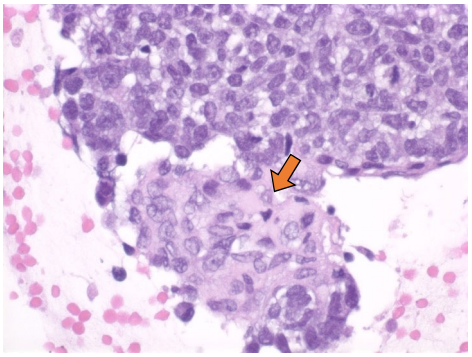
Pancreatoblastoma

- Two-thirds of cases present in children <10 years old (mean 4 years), but one-third presents in adults
- 25% of pediatric pancreatic neoplasms
- Arise equally in head/tail (large neoplasm, mean 10cm)
- Most sporadic; genetic syndromes (Beckwith-Wiedemann syndrome and familial adenomatous polyposis)
- Variable prognosis
  - Children: resectable tumors good prognosis, metastases bad prognosis
  - Adults: rapidly fatal like ACCs

Pancreatoblastoma Cytomorphology

- Epithelial component
  - Syncytial groups and dispersed cells
  - Primitive monomorphic cells with a moderate to high N/C ratio
  - Squamoid corpuscles
- Trilineage but acinar component usually predominates
  - Looks like ACC on FNA
- Stromal component
  - Primitive spindle-shaped cells
  - Occasionally heterologous elements





Courtesy of Dr. Martha Pitman

Immunohistochemical Profiles of the Solid-Cellular Pancreatic Tumors

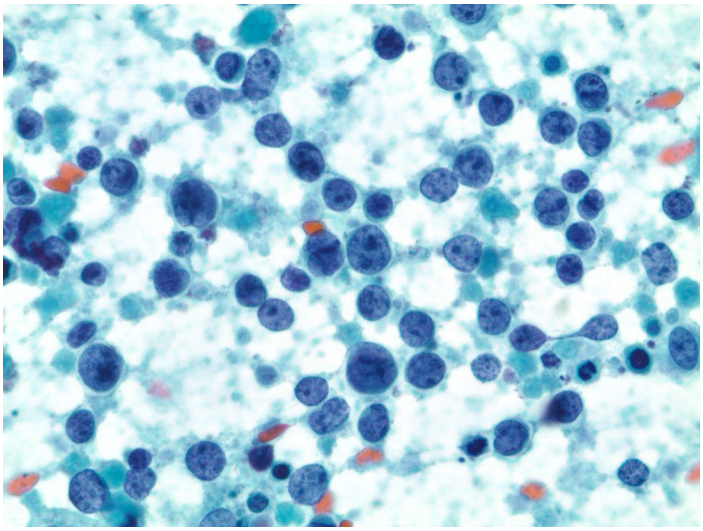
Marker	Pancreatic neuroendocrine tumor	Acinar cell carcinoma	Solid pseudopapillary neoplasm	Pancreatoblastoma
Pankeratin	+	+	-/focal	+
Trypsin	-	+	-	+
Chromogranin	+	-/focal		+/-
Synaptophysin	+	-/focal	-/+	+/-
INSM1^{nuclear}	+	-	-	+/-
CD56	+	-/focal	+	+/-
β-Catenin^{nuclear}	-	weak/focal	+	weak/focal
BCL10	-	+	-	+

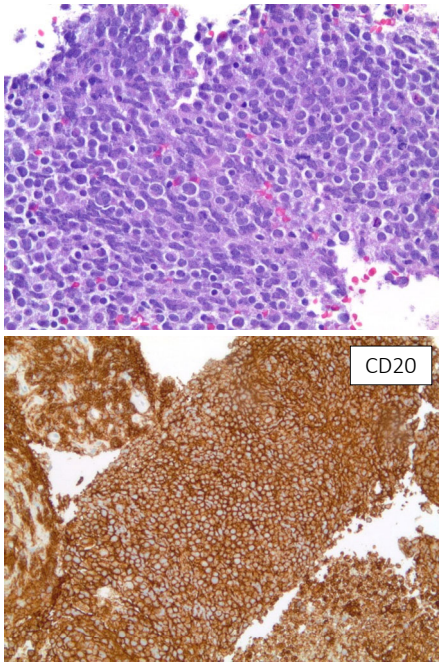
Cibas ES Ducatman BS. *Cytology: Diagnostic Principles and Clinical Correlates*. 5th ed. Maryland Heights: Elsevier; 2020.

Lymphomas in the pancreas

- Mean age 55-65, M>F
- Primary pancreatic lymphoma accounts for <1% of pancreatic neoplasms
  - Primary clinical presentation within pancreas + bulk of disease located within pancreas
- Most are secondary non-Hodgkin B cell lymphomas → >2/3 are diffuse large B cell lymphoma (DLBCL)
- Most common in the pancreatic head, can be located throughout the pancreas and multiple in number

DLBCL

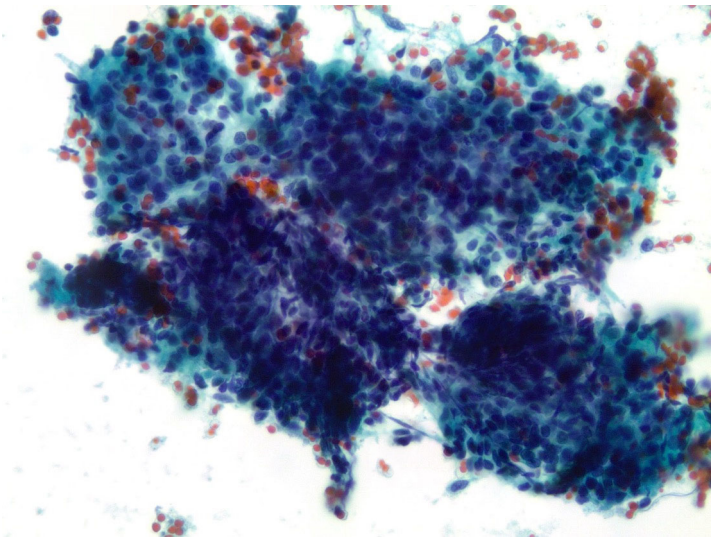


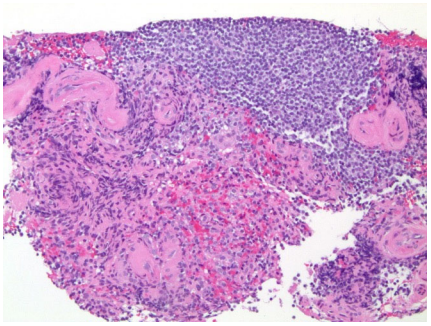


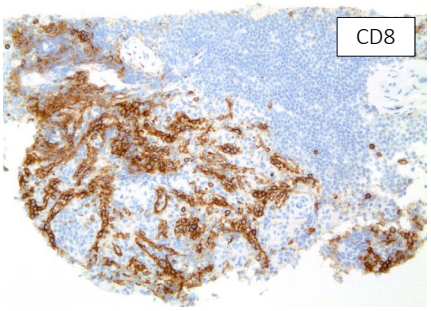
Splenule/Ectopic spleen

- Occurs in ~15% of general population
  - 80% splenic hilum, 20% pancreatic tail
- Includes *accessory spleen* (congenital) and *splenosis* (acquired auto-implants after abdominal trauma or splenectomy)
- Well-circumscribed vascular nodule in the pancreatic tail, mimics panNET by imaging
- Cytology:
  - Polymorphous lymphoid tissue, often in aggregates/clusters
  - Blood vessels
  - CD8+ highlights the splenic littoral cells lining the vascular spaces

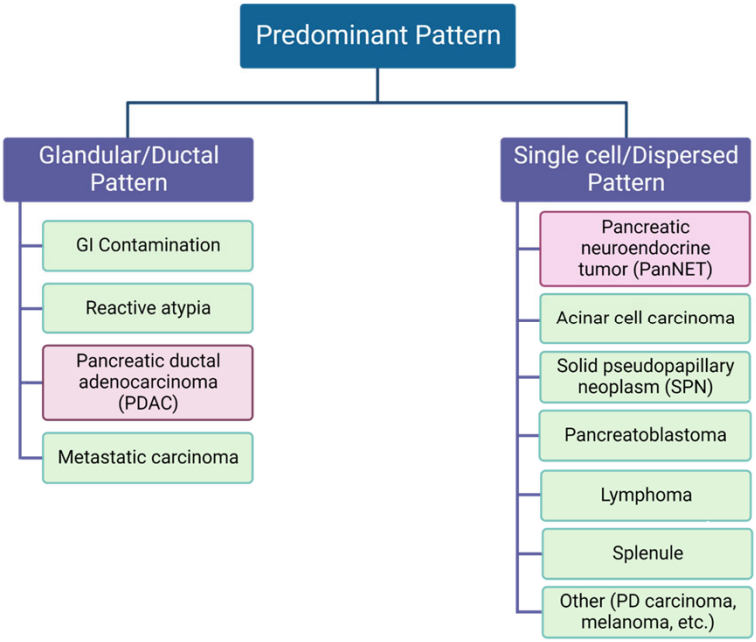
Splenule/Ectopic spleen







Differential Diagnosis of Solid Lesions



Summary

- Remember that pancreatic ductal carcinoma is still by far the most common pancreatic neoplasm (>90%)
- Of the non-ductal neoplasms, pancreatic neuroendocrine tumor (PanNET) is most likely to be encountered
  - Be aware of morphologic variants
  - Be careful with tumor grading on small tissue samples
- Definitive diagnosis of non-ductal neoplasms can be difficult without cell block/core biopsy, which is often needed for ancillary studies
  - Be familiar with the IHC patterns that can be encountered

Thank you!