# Pancreatic Non-Ductal Neoplasms

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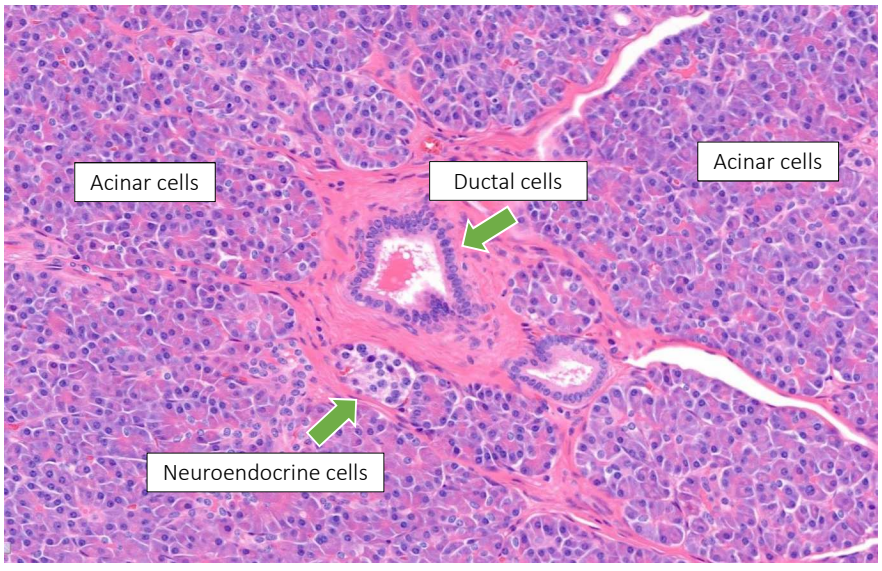
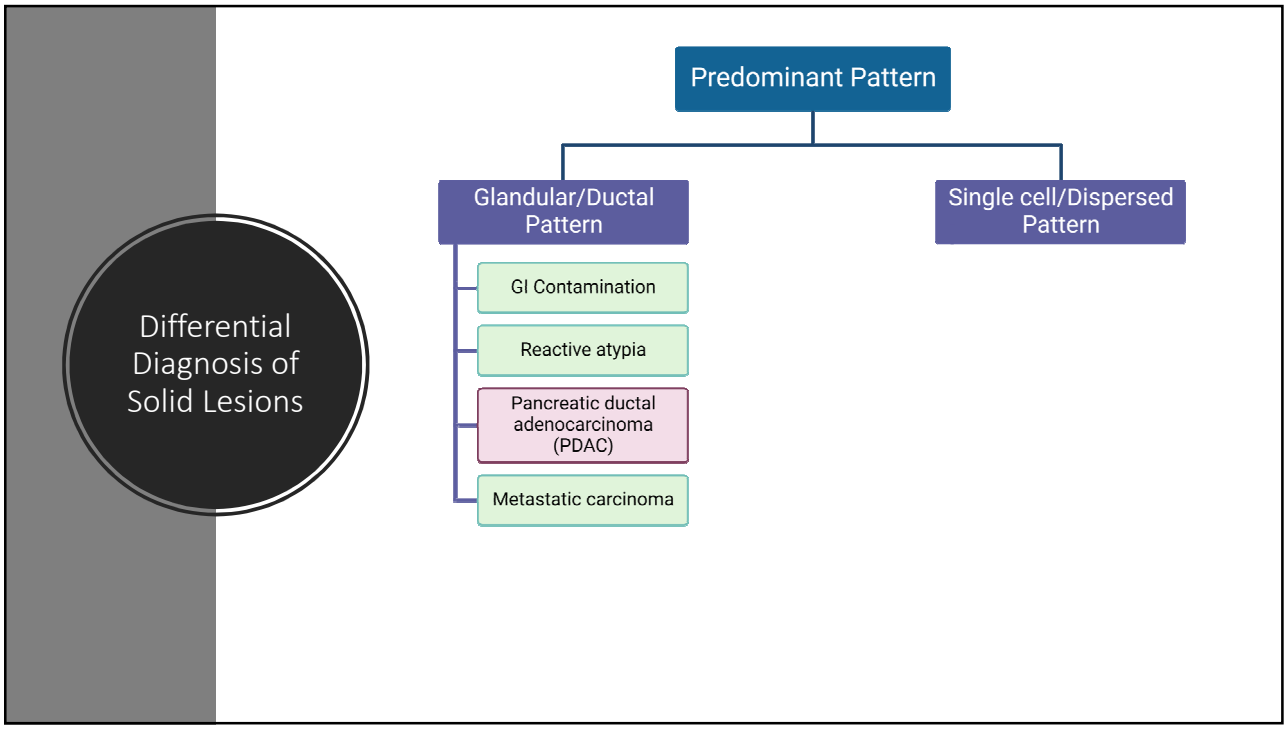
## Normal pancreas



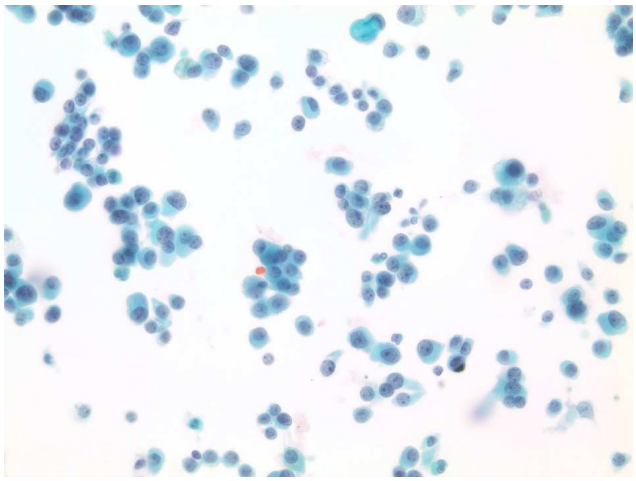



## Pancreatic neuroendocrine tumor (PanNET)

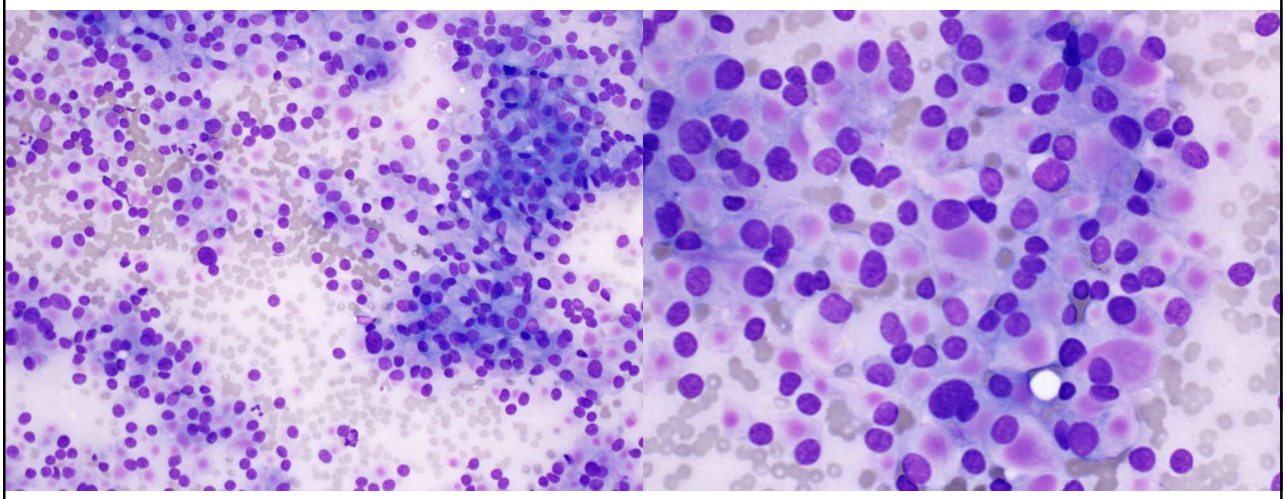
- 2-5% of all pancreatic neoplasms
- Presents at any age (highest incidence in ages 30-60), M=F
- 60% occur in pancreatic tail, but can arise anywhere within pancreas
- Non-functioning (>60%) and functioning types
- Generally slow-growing
- Surgery is the primary treatment
  - Conservative management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

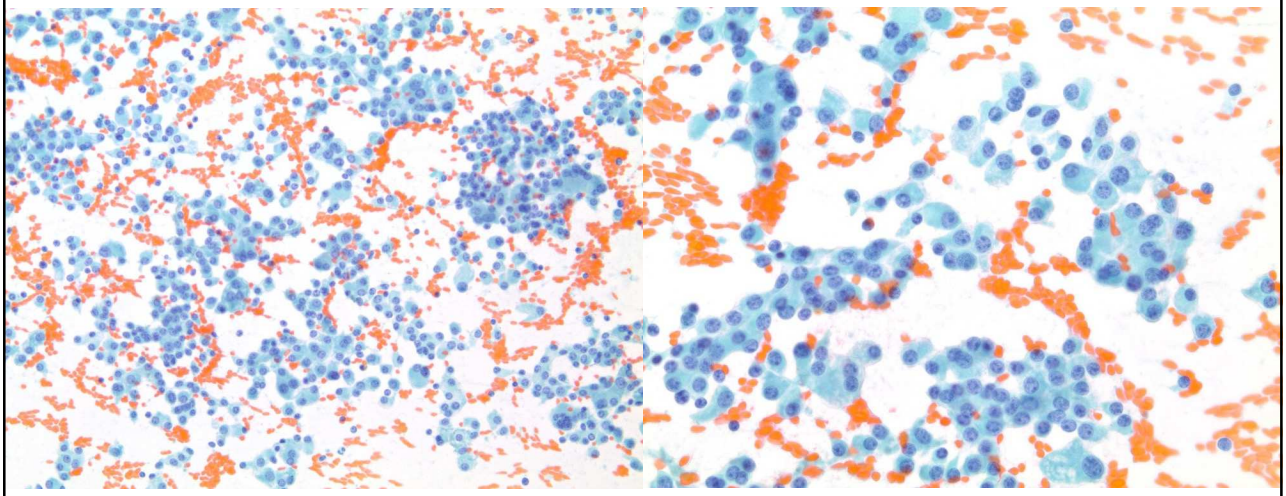


## PanNET, grade 1



Diff-Quik stain

# PanNET, grade 1



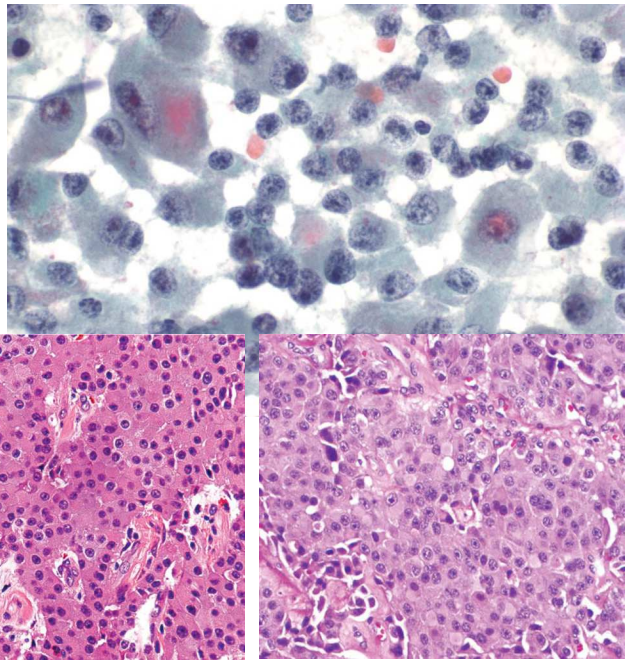
Pap stain

# Variants of PanNET

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

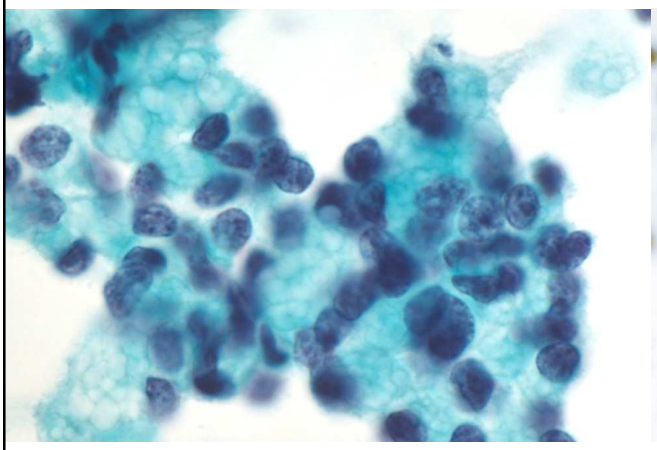
Less aggressive group
- Pleomorphic (9)
- Paraganglioma-like (10)
- Ductulo-insular (7)
- Overall

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

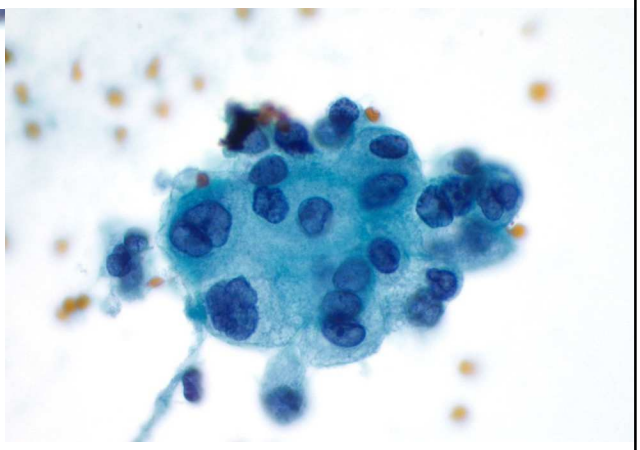


Xue Y, Reid MD, Pehlivanoglu B, et al. Endocr Pathol 2020;31(3):239–53.

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.

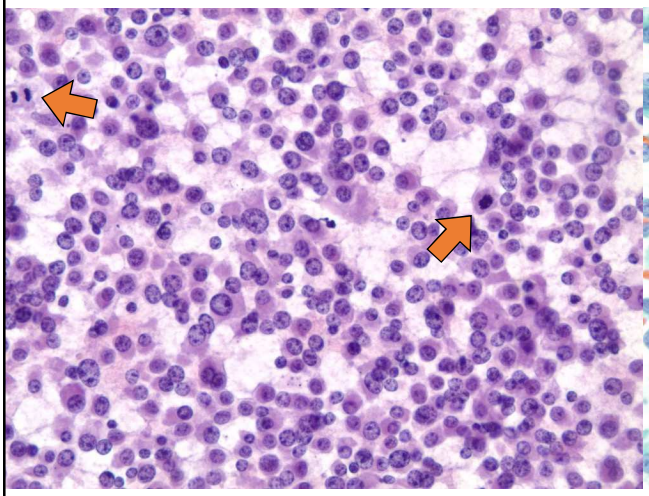
# Grading PanNENs (WHO 5th Edition)

| | | Mitotic Count/2 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 | | |

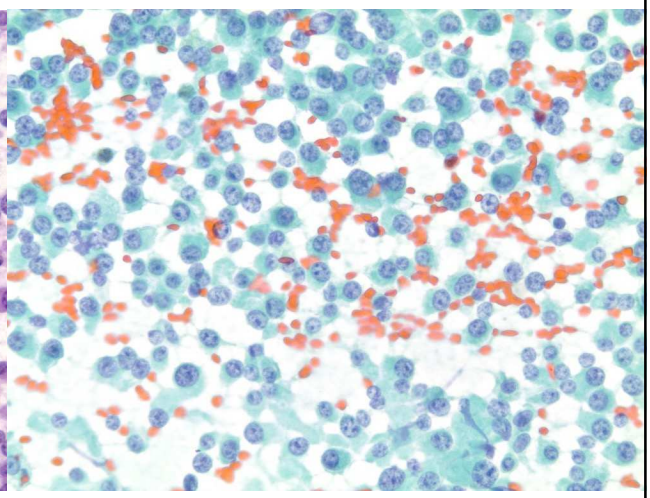
# Grading PanNENs on resections

- 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 ($mm^2$) = $\pi r^2$ = 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**

# PanNET, grade 2



Rapid H&E stain



Pap stain

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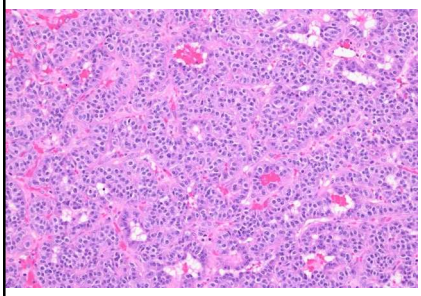

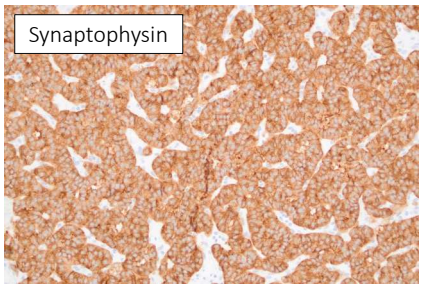


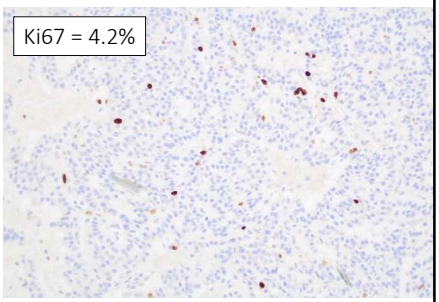


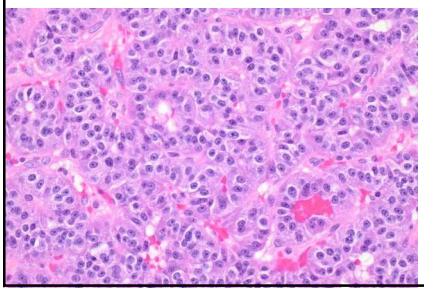

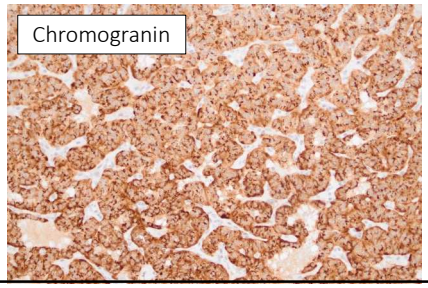

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| High-grade | Grade 3 | >20 | >20 |
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| | Large cell type | | |

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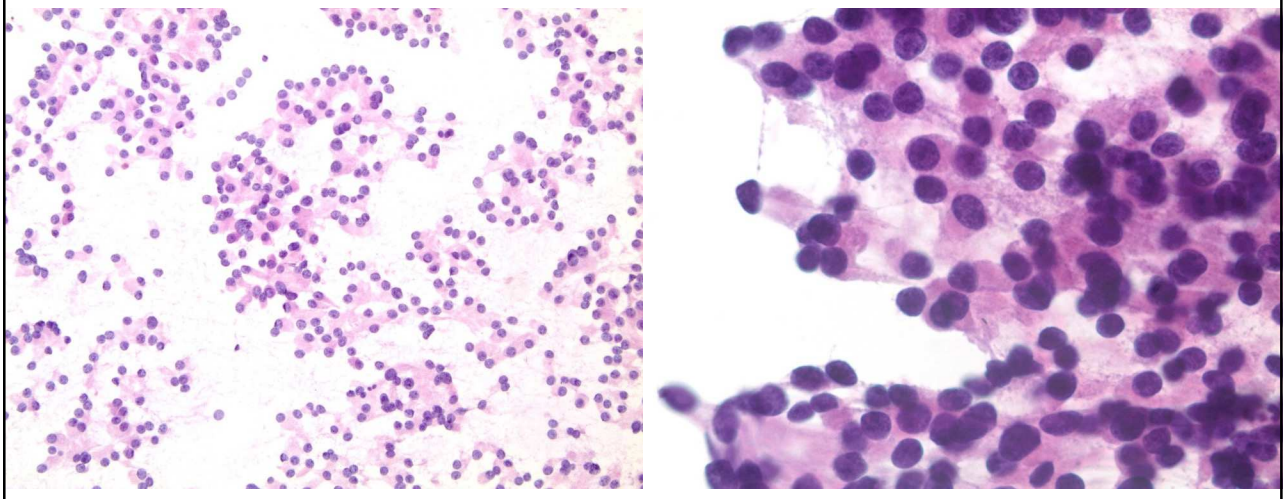
    - Recommended evaluation of 10 $mm^2$/0.238 $mm^2$ = **42 HPF**
    - Minimum evaluation of 2 $mm^2$/0.238 $mm^2$ = **8 HPF**
  - Ki67 index: minimum of 500 tumor cells be counted to determine the Ki67 index (some have recommended counting at least 2000 cells)

What about on cell blocks & small biopsies?

# Grading PanNETs on Cell Blocks

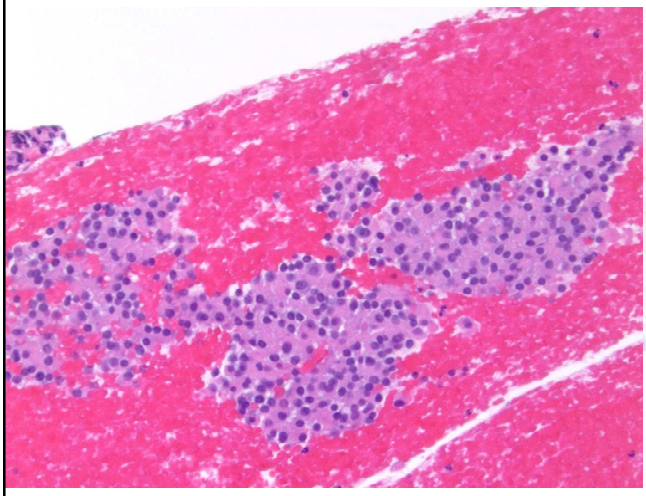
- Jin et al. 2016 (58 cases), Abi-Raad et al. 2020 (49 cases):
  - EUS-FNA cell block (CB) and corresponding surgical pathology (SP)
    - All cell blocks had >100 tumor cells
    - Analysis only included grade 1 and 2 tumors
  - Compared with SP, CB manual count correctly graded 69% (k = 0.44) and 73% (hot spot method) in each study, respectively
  - Grade 1 tumors had much higher concordance than grade 2 tumors
    - Jin et al.: ~40% of grade 2 tumors under-graded on CB
    - Abi-Raad et al.: CB <1000 tumor cells → all grade 2 under-graded, CB ≥1000 tumor cells → grade 2 concordance rate increased to 64%
- Grading concordance improved as tumor cellularity increased
- A significant proportion of grade 2 PanNETs can be under-graded based on Ki67 index evaluated on a CB

# PanNET, grade ?

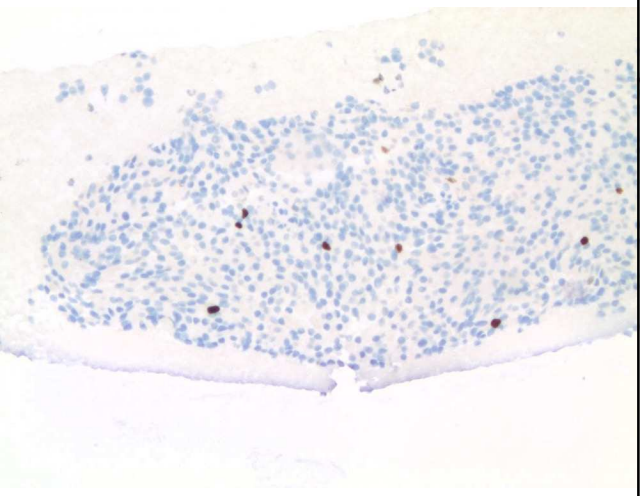


Rapid H&E stain

## PanNET, grade ?



Core biopsy, H&E



Ki67 = 2.0%

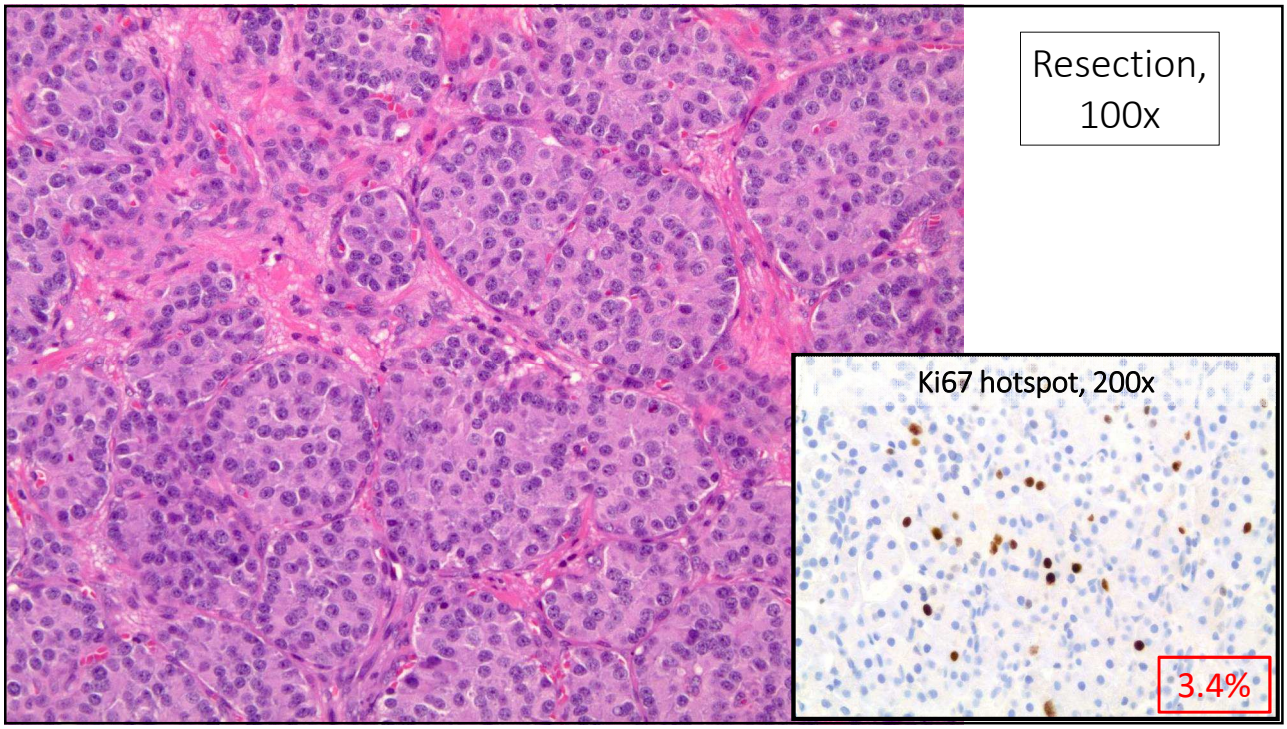
## Example report

- 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 mm² | Ki-67 (%) |
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| Grade 3 | >20 | >20 |
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| Large cell type | | |

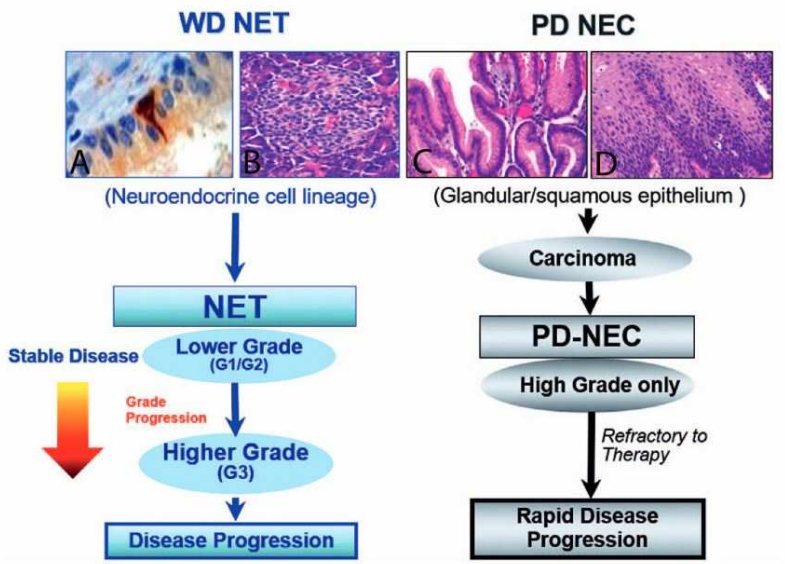
High-grade

**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



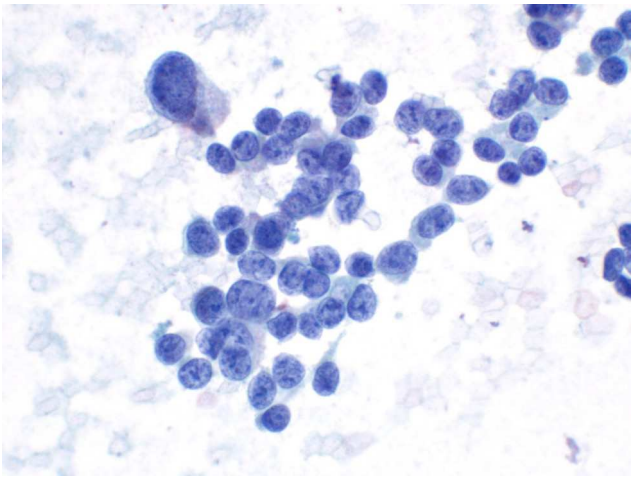

Resection (depending on size and other factors)

Platinum-based chemotherapy

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)

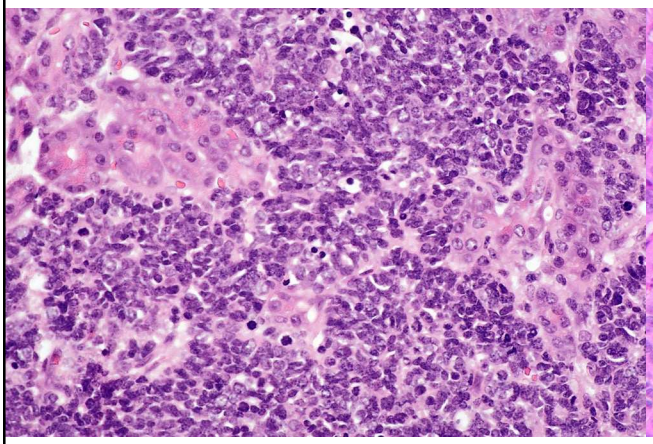


## Pancreatic neuroendocrine carcinoma (PanNEC)

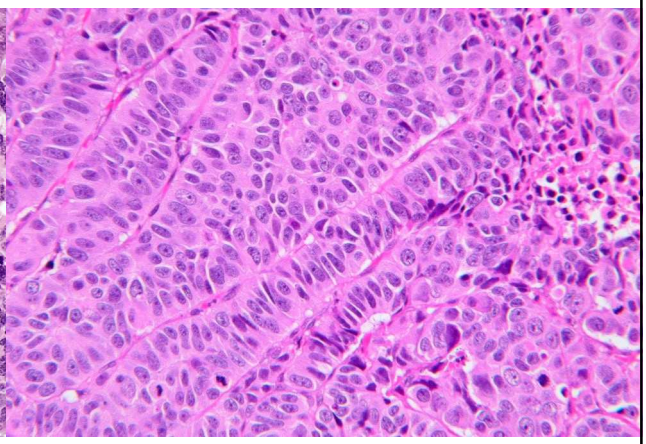
- Poorly differentiated
- Architecture
  - Clusters, loosely cohesive and single cells
- Cytomorphology
  - High-grade, overtly malignant
  - Small cell type: high N/C ratio (scant cytoplasm), molding, necrosis
  - Large cell type: lower N/C ratio
  - *"Intermediate/NOS type"*: somewhere in between

## Pancreatic neuroendocrine carcinoma (PanNEC)

Small cell type

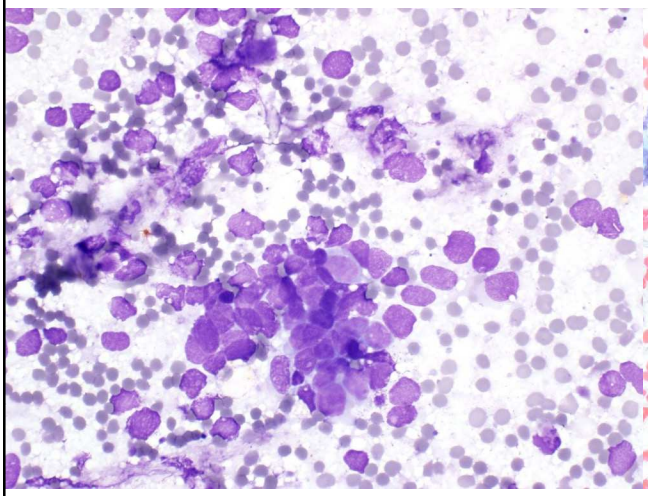


Large cell type

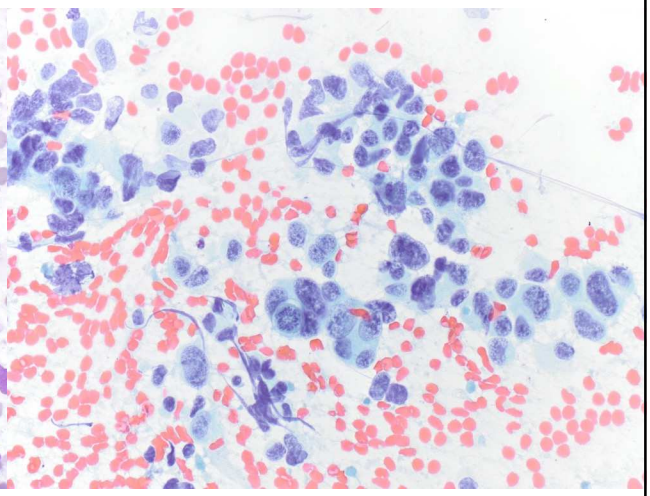


*Courtesy of Dr. Martha Pitman*

# PanNEC, small cell type

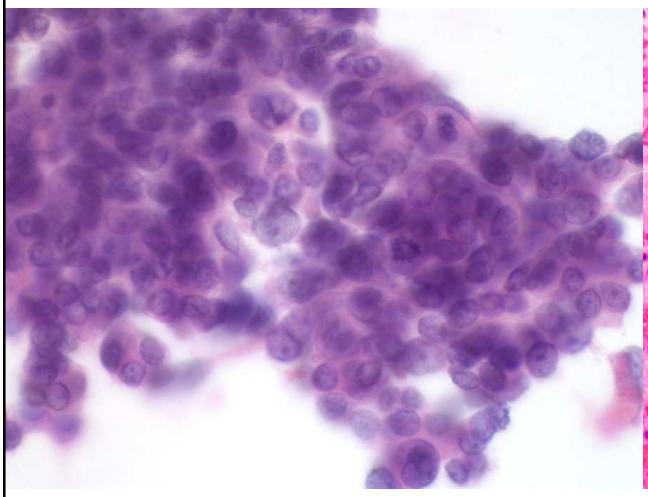


Diff-Quik stain

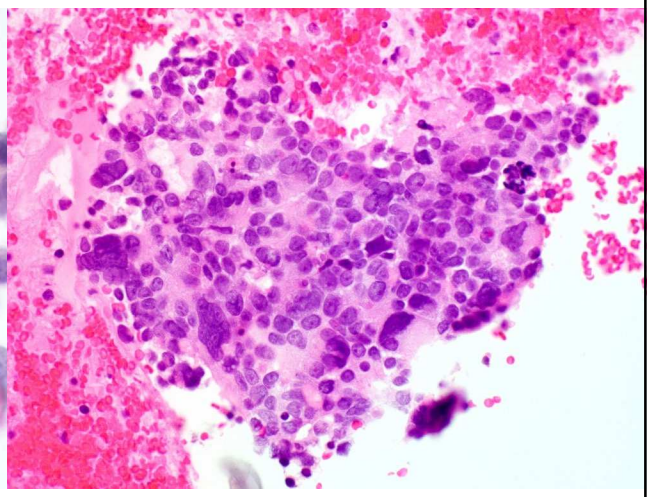


Pap stain

# PanNEC, large cell type

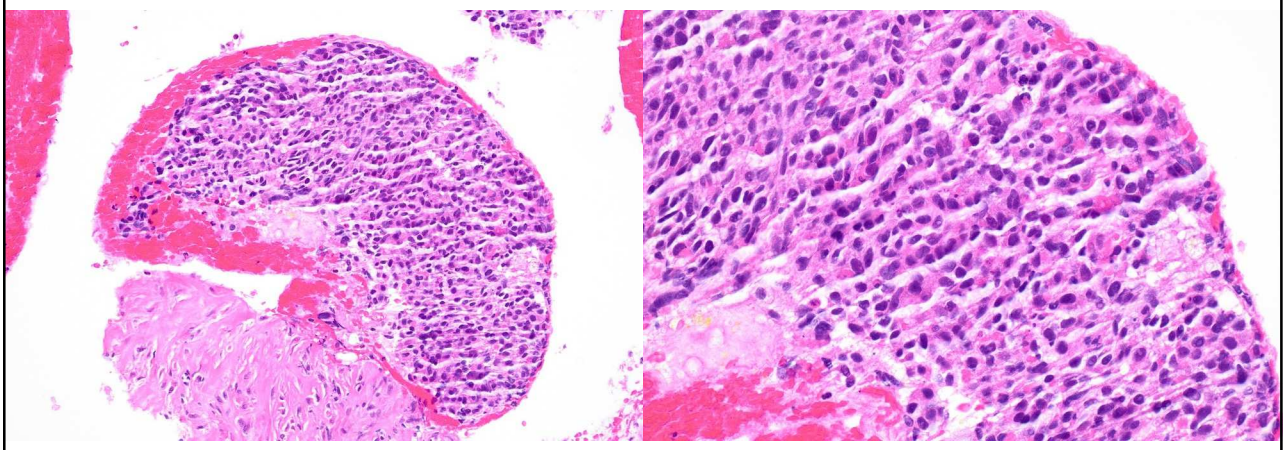


*Courtesy of Dr. Martha Pitman*

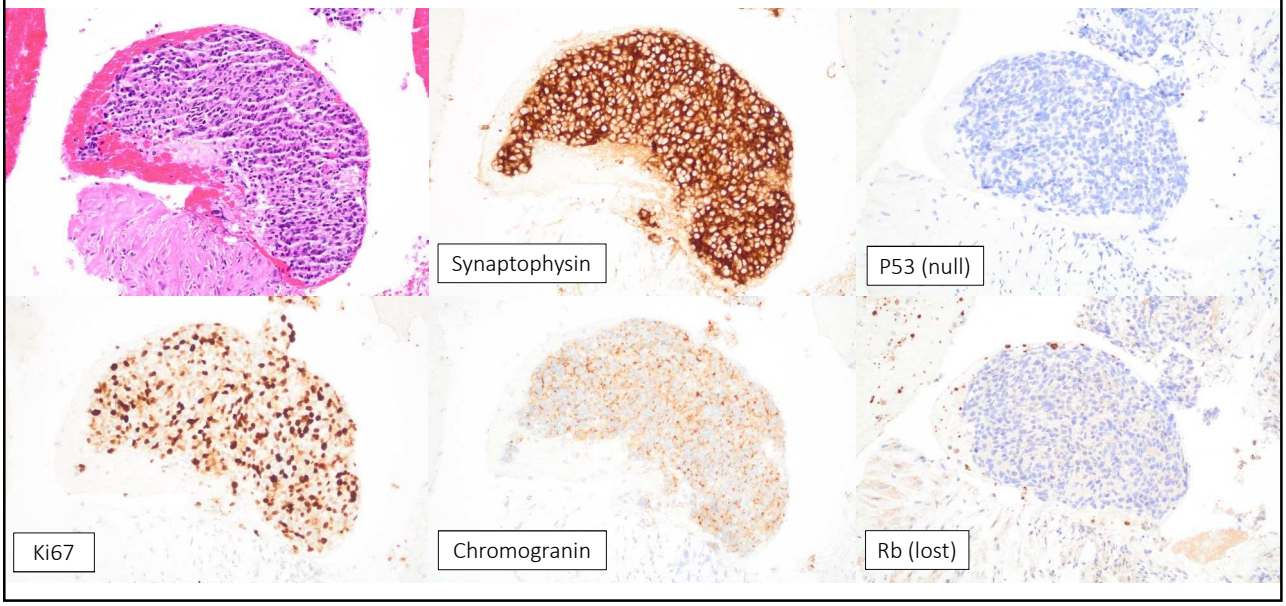


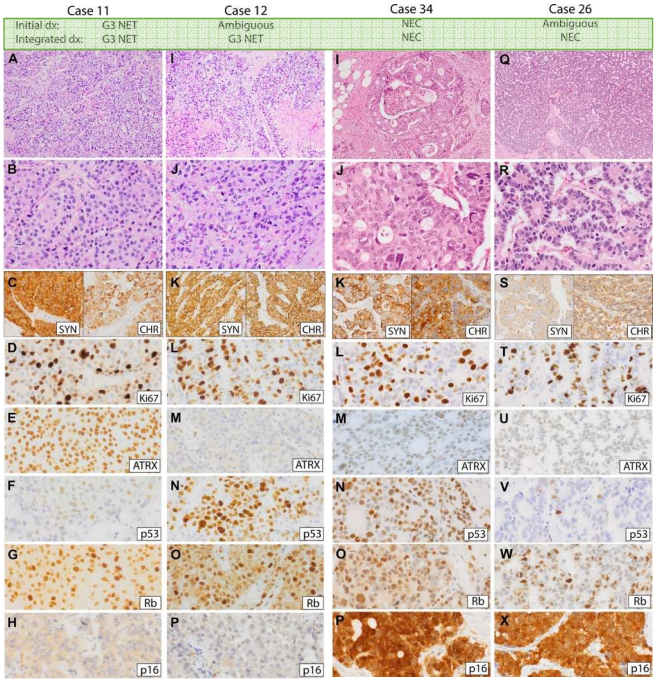
*WHO Reporting System for Pancreaticobiliary Cytopathology*

# PanNET grade 3 vs. PanNEC?



# PanNEC, large cell/NOS





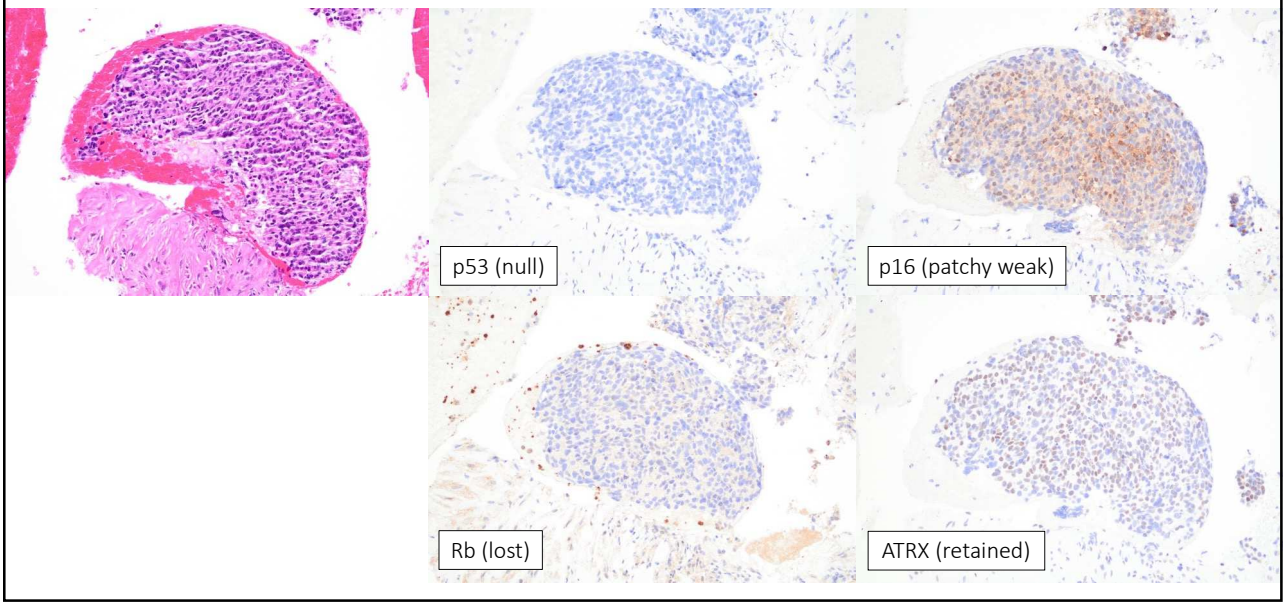

# "Integrated diagnosis"

| 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% |

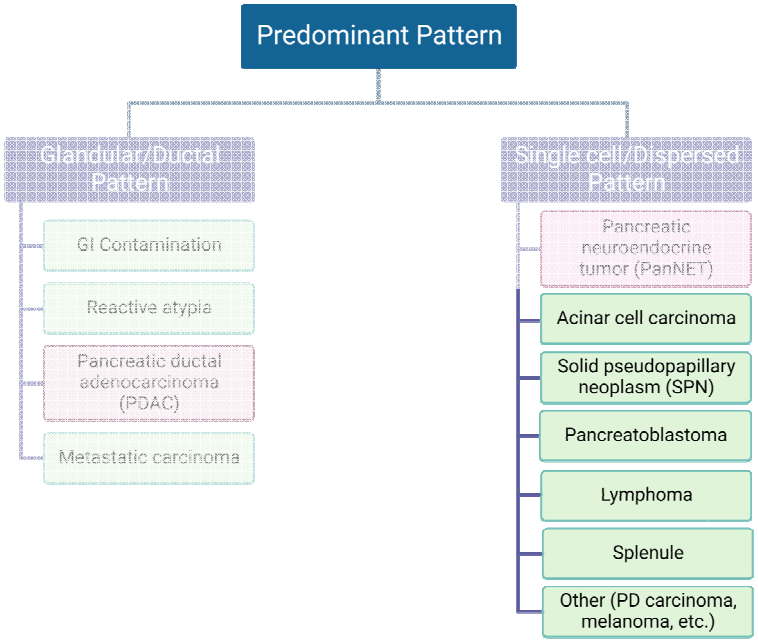
*Mutually exclusive in G3 PanNET vs. co-altered in PanNEC (30%)

Umetsu SE et al. Mod Pathol. 2023.

# PanNEC, large cell/NOS



Differential Diagnosis of Solid Lesions



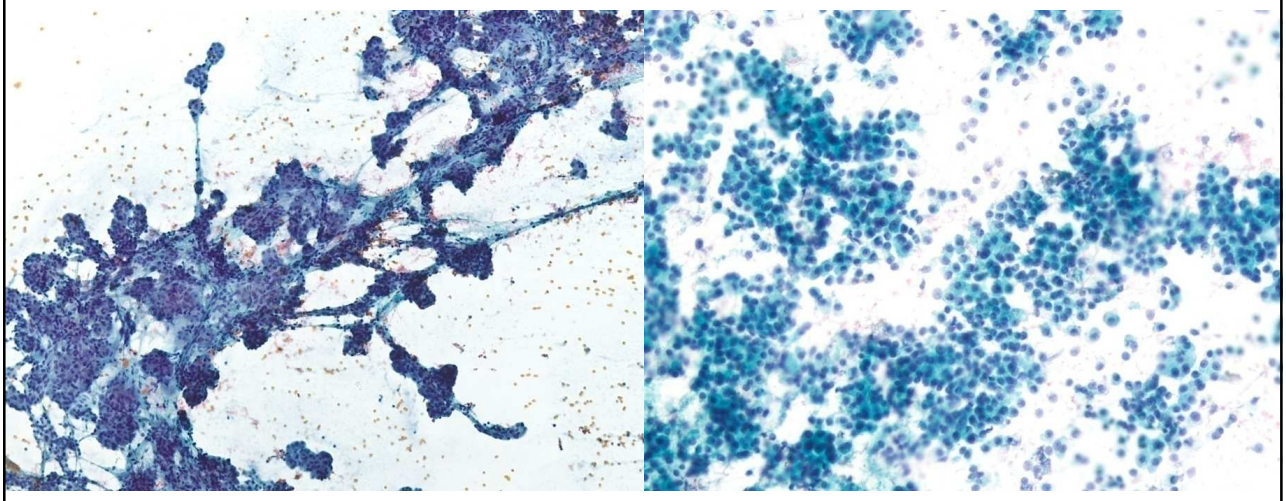

## Acinar cell carcinoma (ACC)

- 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 ~6%

## ACC Cytomorphology

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

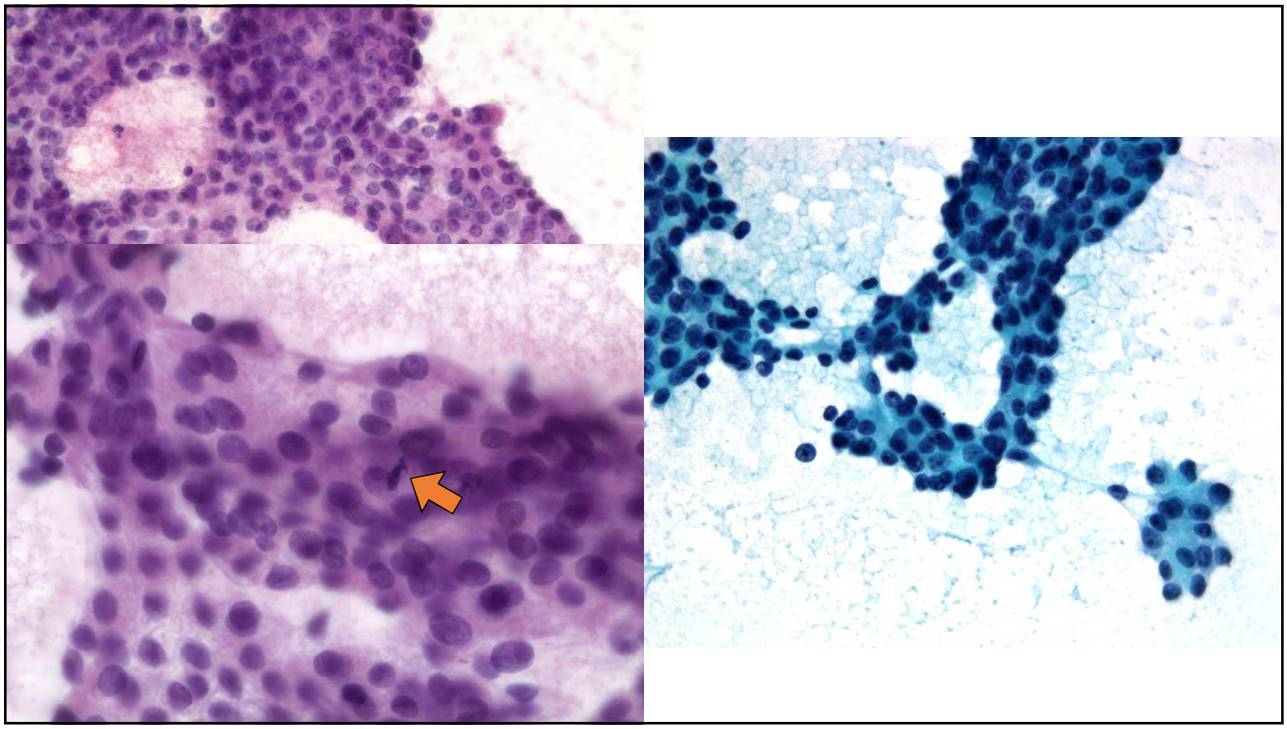
## Benign vs. malignant acinar cells

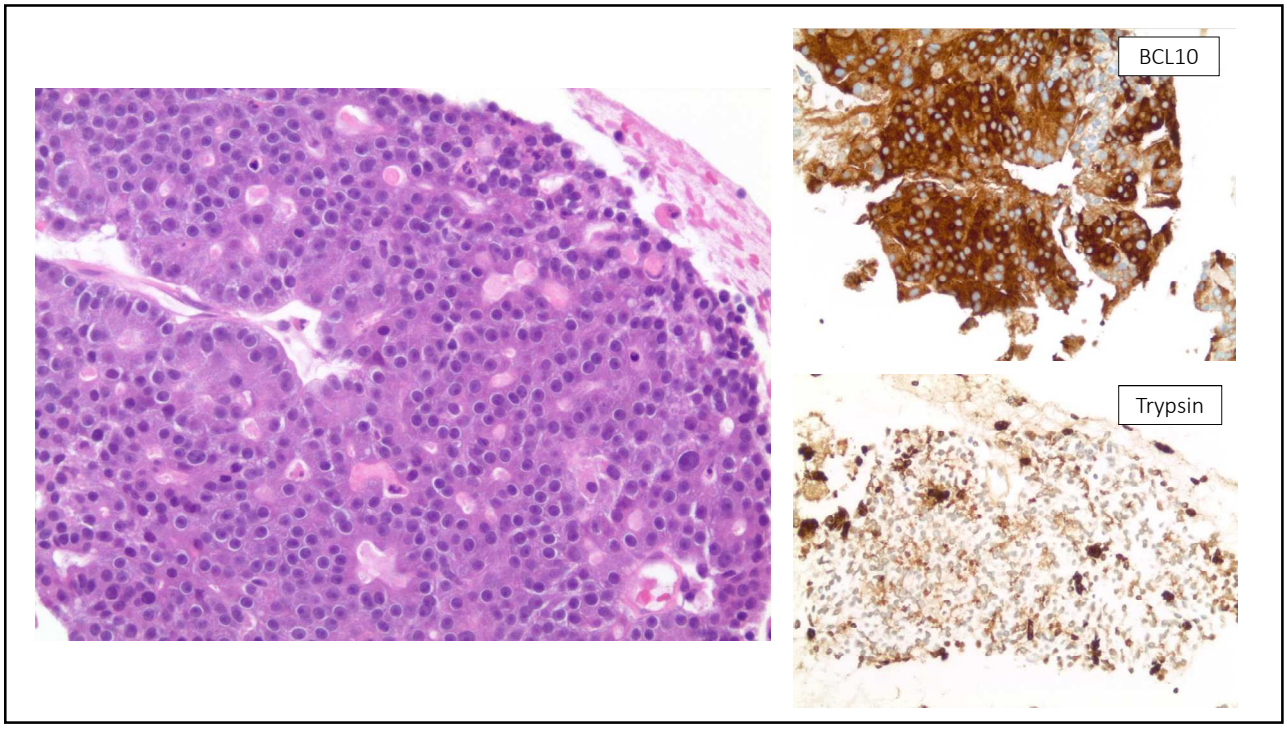


Benign

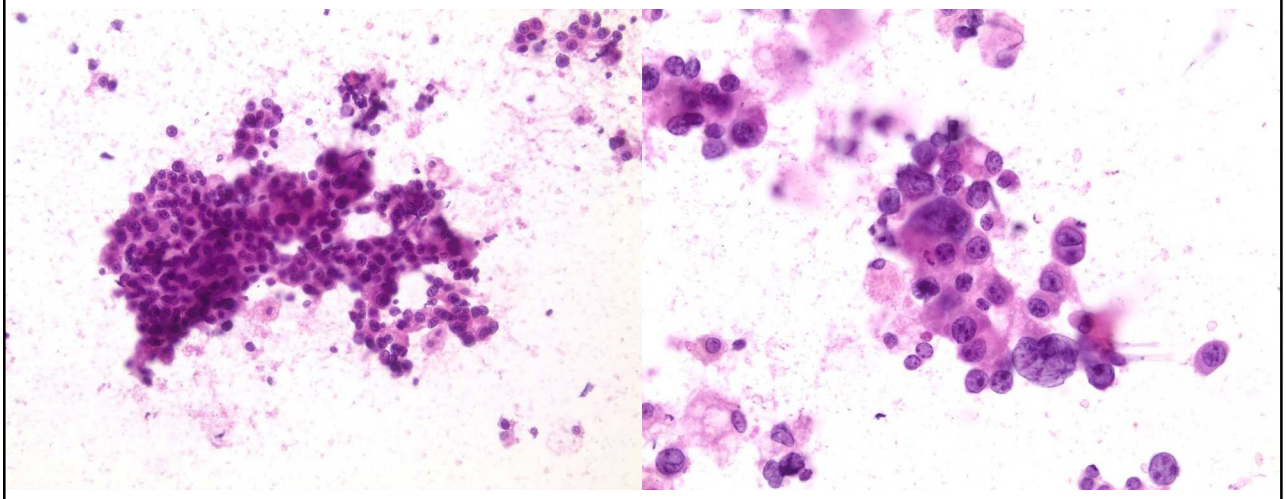
Malignant

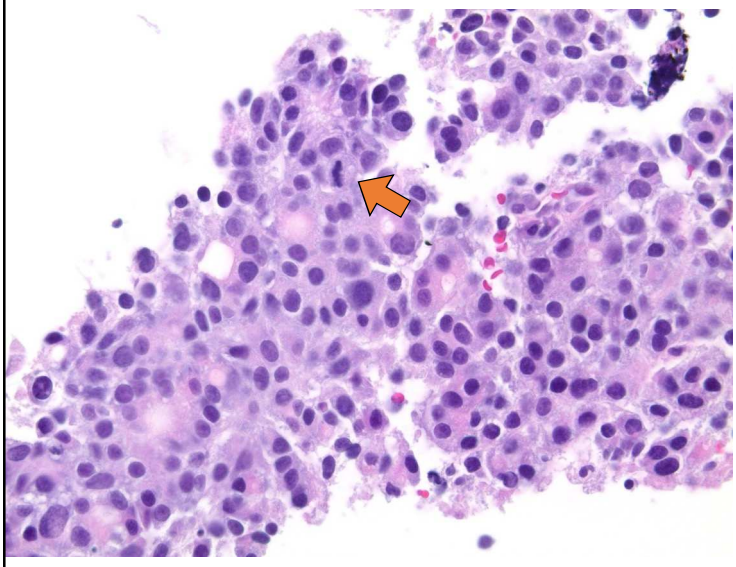
*Courtesy of Dr. Martha Pitman*

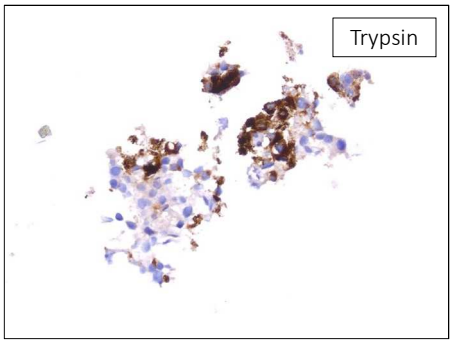


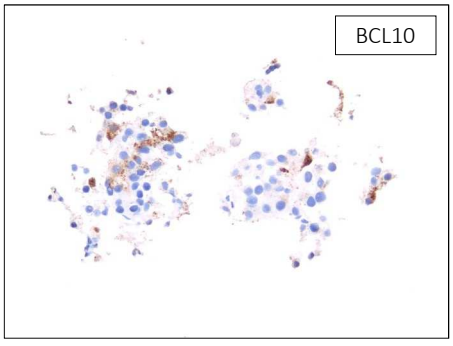

BCL10
Trypsin

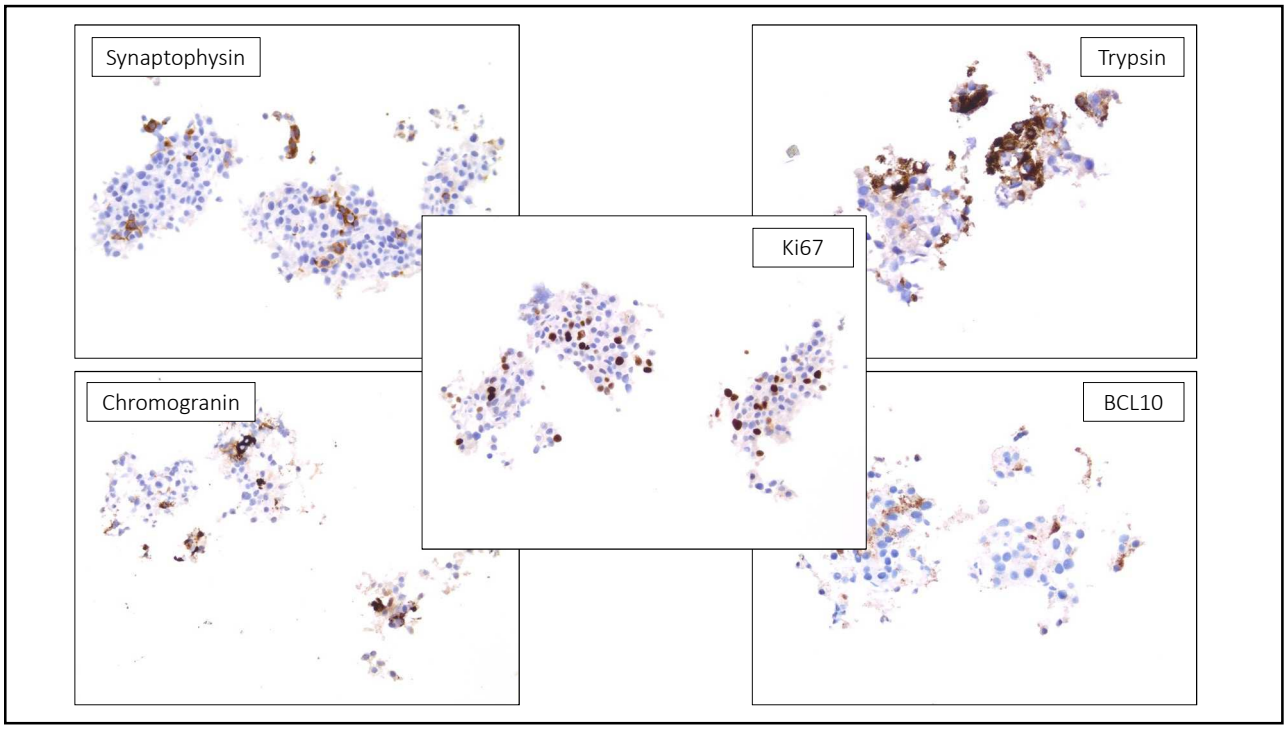
## Non-ductal neoplasm, ACC vs. PanNET grade 2-3







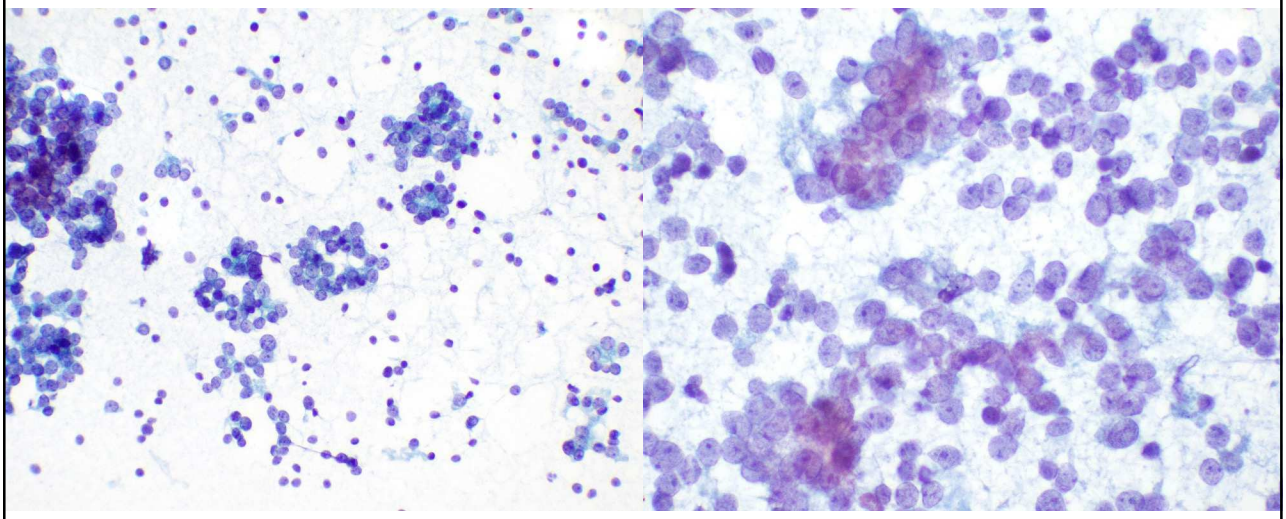



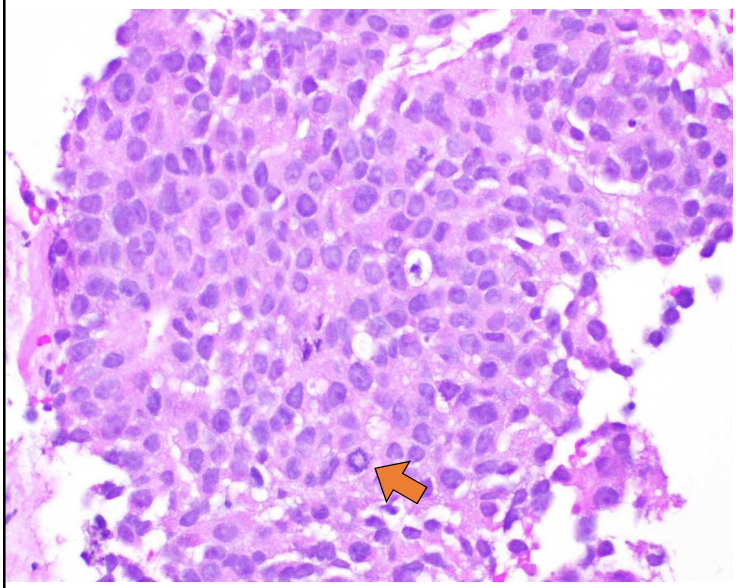


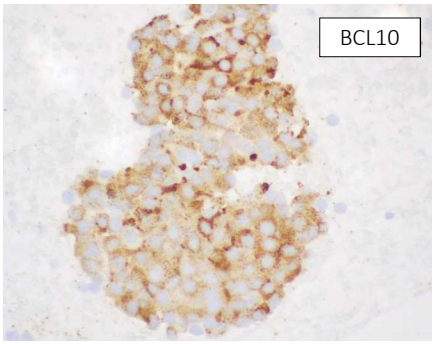

# Final diagnosis

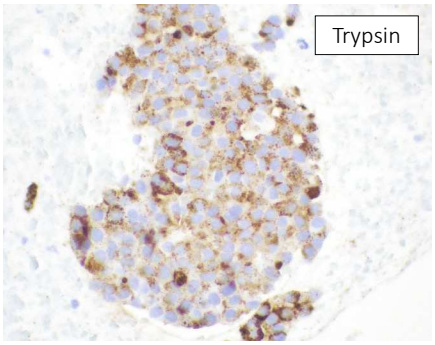
- "Non-ductal neoplasm, favor acinar cell carcinoma."

- Morphology compatible/suggestive of ACC
- Mitoses and 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






BCL10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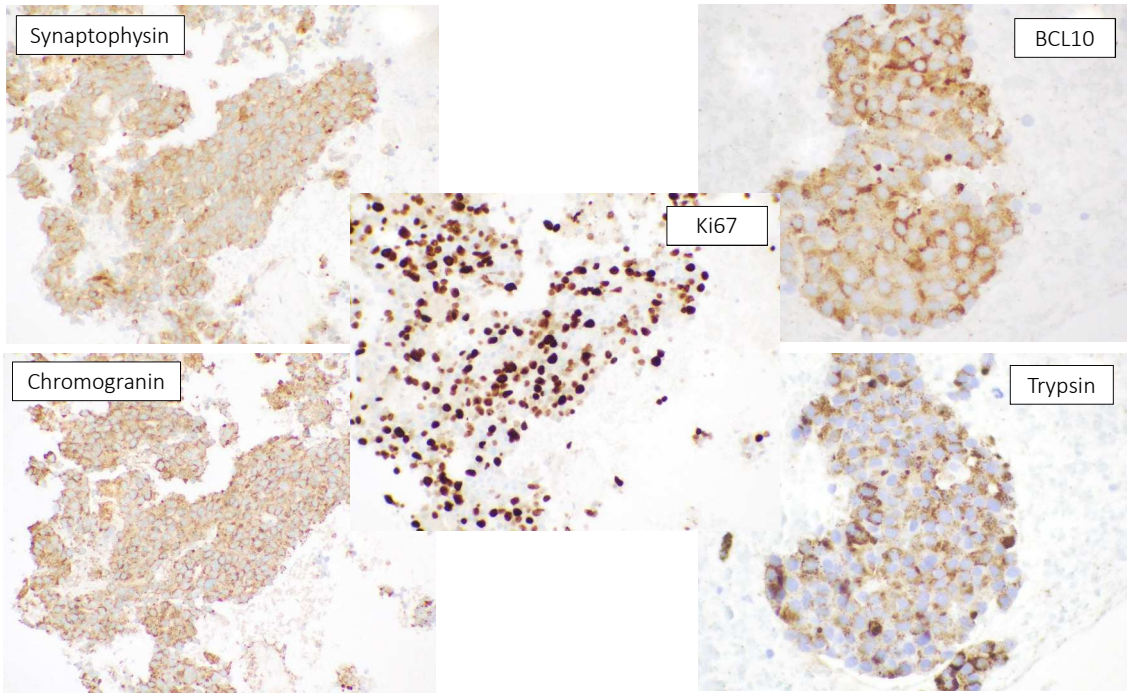



# Final diagnosis

- "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 carcinomas 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 subtype of acinar cell carcinoma due to similar clinical behavior and genetics
- Other types of mixed tumors (mixed acinar-ductal carcinomas, mixed neuroendocrine-ductal 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 |
|---|---|---|
| Synaptophysin (>30% of cells) | 0/49 (0%) | 12/12 (100%) |
| Chromogranin (>30% of cells) | 0/49 (0%) | 12/12 (100%) |
| Trypsin | 46/48 (96%) | 11/12 (92%) |
| BCL10 | 40/47 (85%) | 11/12 (92%) |

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 | | | | | | FNAB | | |
|---|---|---|---|---|---|---|---|---|
| Tumor types, case ID | BCL10 score (%) | Trypsin score (%) | Synaptophysin score (%) | Chromogranin score (%) | β-Catenin nuclear score (%) | BCL10 score (%) | Trypsin score (%) | Synaptophysin score (%) |
| ACC | | | | | | | | |
| 1 | 3+ (100) | 1+ (50) | 0 (-) | 0 (-) | 1+ (5) | 3+ (100) | 2+ (70) | 0 (-) |
| 2 | 3+ (100) | 2+ (70) | 1+ (5) | 0 (-) | 0 (-) | 3+ (100) | 3+ (80) | 0 (-) |
| 3 | 3+ (100) | 3+ (100) | 0 (-) | 0 (-) | n.a. | 3+ (100)[a] | 3+ (100)[a] | 0 (-)[a] |
| 4 | 3+ (100) | 2+ (80) | 1+ (10) | n.a. | n.a. | 3+ (100) | 3+ (80) | 0 (-) |
| 5 | 3+ (100) | 2+ (60) | 1+ (10) | 0 (-) | n.a. | 3+ (100) | n.a. | 1+ (5) |
| 6 | 3+ (100) | 1+ (30) | 1+ (20) | 0 (-) | 1+ (5) | 3+ (100) | 2+ (50) | 1+ (10) |
| 7 | 3+ (100) | 1+ (<5) | 1+ (5) | 0 (-) | 0 (-) | 3+ (100) | 1+ (10) | 0 (-) |
| 8 | 3+ (100) | 2+ (60) | 0 (-) | n.a. | 0 (-) | 3+ (100) | 2+ (80) | 0 (-) |
| 9 | 3+ (100) | 3+ (80) | 0 (-) | 0 (-) | n.a. | 3+ (100) | 3+ (100) | 1+ (10) |
| 10 | 3+ (100) | 2+ (100) | 0 (-) | 0 (-) | 1+ (5) | 3+ (100) | 2+ (80) | 0 (-) |
| 11 | 3+ (100) | 2+ (100) | 1+ (50) | 0 (-) | 0 (-) | 3+ (100) | 3+ (100) | 0 (-) |
| 12 | 3+ (100) | 3+ (70) | 0 (-) | 0 (-) | n.a. | 3+ (100) | n.a. | 0 (-) |
| MANEC | | | | | | | | |
| 1 | 3+ (100) | 3+ (80) | 2+ (70) | 1+ (30) | n.a. | 3+ (100) | 3+ (100) | 3+ (50) |
| 2 | 3+ (100) | 3+ (100) | 2+ (50) | 3+ (60) | 0 (-) | 3+ (100) | 3+ (100) | 2+ (50) |
| 3 | 3+ (100) | 3+ (80) | 1+ (40) | 1+ (10) | 0 (-) | 3+ (100) | 2+ (70) | 1+ (50) |
| 4 | 3+ (100) | 1+ (<5) | 3+ (80) | 2+ (60) | n.a. | 3+ (50) | n.a. | 3+ (70) |
| 5 | 3+ (100) | 2+ (60) | 2+ (70) | 2+ (60) | 0 (-) | 3+ (100) | 1+ (20) | 3+ (70) |
| 6 | 3+ (100) | 2+ (70) | 1+ (40) | 0 (-) | 0 (-) | 3+ (70) | 1+ (50) | 3+ (40) |
| 7 | 3+ (100) | 3+ (60) | 1+ (40) | 1+ (30) | 0 (-) | 3+ (80) | 2+ (80) | 1+ (50) |
| 8 | 3+ (100) | 1+ (40) | 2+ (60) | 0 (-) | 0 (-) | 3+ (100) | 3+ (90) | 2+ (60) |
| 9 | 3+ (100) | 3+ (80) | 1+ (40) | 3+ (60) | 0 (-) | 3+ (80) | 3+ (90) | 1+ (50) |

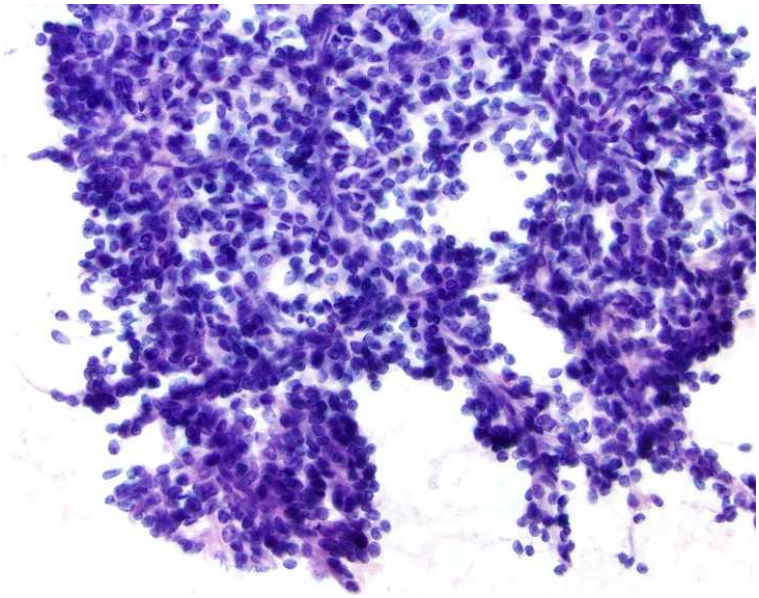
Manfrin E et al. Pathol Res Pract. 2021

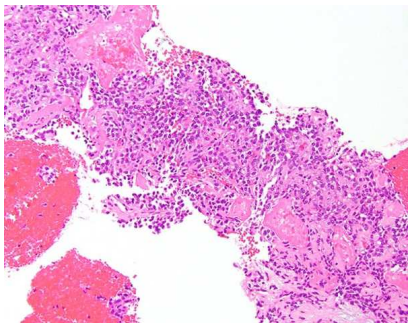
# Solid pseudopapillary neoplasm (SPN)

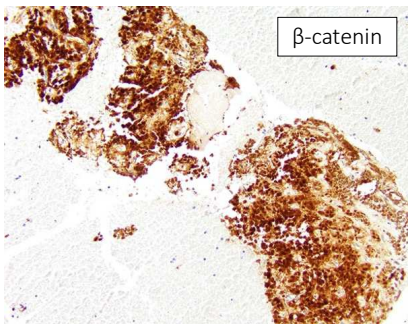
- 2-5% of all pancreatic neoplasms
- ~90% female, mean age 28 years
- Can arise anywhere in pancreas, mean 10cm
- Large solid and cystic neoplasm, often radiologically diagnosed
- Low grade malignancy, usually indolent and completely cured with resection
  - 10-15% patients have metastatic disease at 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
- Eosinophilic or vacuolated cells, PASD+ hyaline globules, stromal hyalinization



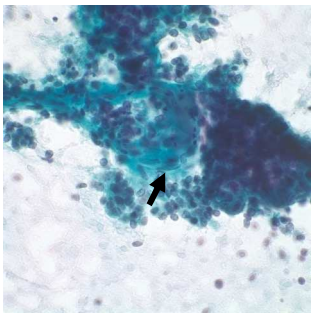




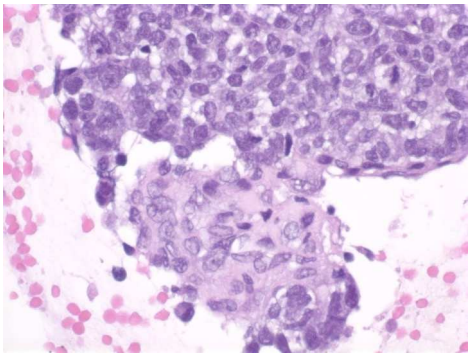
## Pancreatoblastoma

- 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*
- Stromal component
  - Primitive spindle-shaped cells
  - Occasionally heterologous elements
- Trilineage but acinar component usually predominates
  - Looks like ACC on FNA



*Courtesy of Dr. Martha Pitman*

## Immunohistochemical Profiles of the Solid-Cellular Pancreatic Tumors

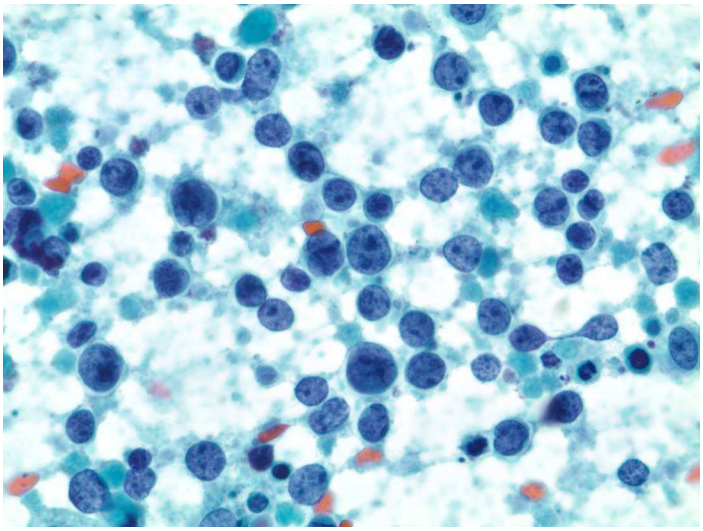
| Marker | Pancreatic neuroendocrine tumor | Acinar cell carcinoma | Solid pseudopapillary neoplasm | Pancreatoblastoma |
|---|---|---|---|---|
| Pankeratin | + | + | -/focal | + |
| Trypsin | - | + | - | + |
| Chromogranin | + | /focal | | +/- |
| Synaptophysin | + | -/focal | -/+ | +/- |
| INSM1$^{nuclear}$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

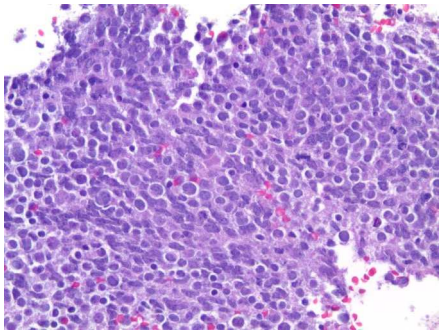
Cibas ES Ducatman BS. *Cytology: Diagnostic Principles and Clinical Correlates.* 5th ed. Maryland Heights: Elsevier; 2020.

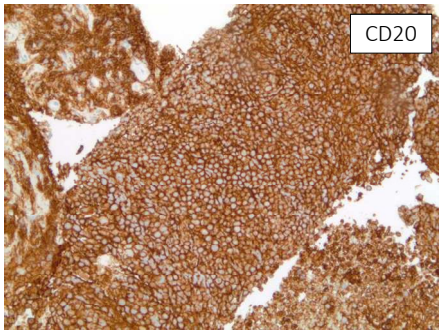
## Lymphomas in the pancreas

- 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



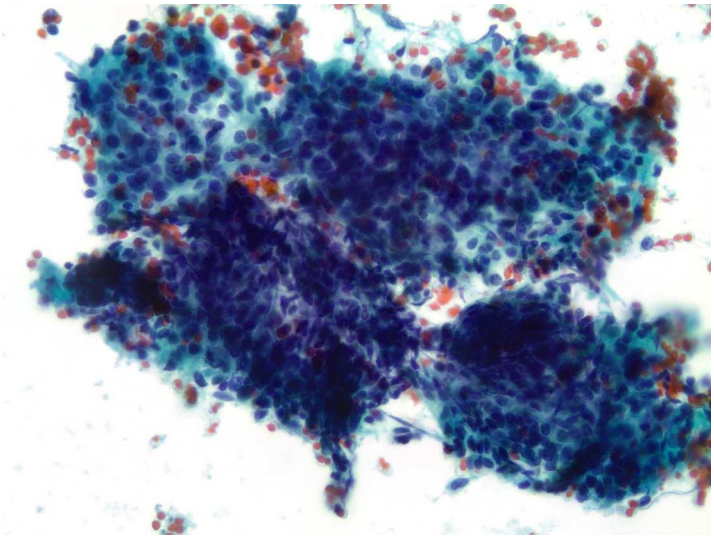


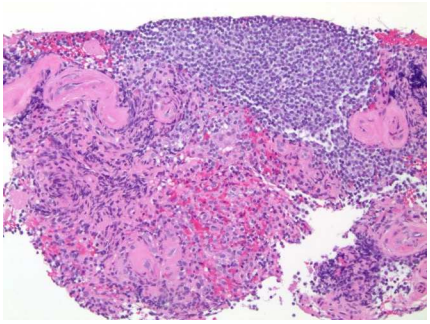


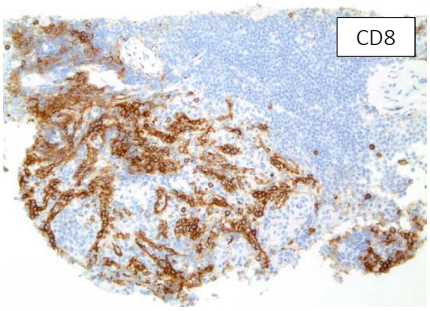

## Splenule/Ectopic spleen

- 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

- Predominant Pattern
  - Glandular/Ductal Pattern
    - GI Contamination
    - Reactive atypia
    - Pancreatic ductal adenocarcinoma (PDAC)
    - Metastatic carcinoma
  - Single cell/Dispersed Pattern
    - Pancreatic neuroendocrine tumor (PanNET)
    - Acinar cell carcinoma
    - Solid pseudopapillary neoplasm (SPN)
    - Pancreatoblastoma
    - Lymphoma
    - Splenule
    - Other (PD carcinoma, melanoma, etc.)

## 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!