

New York Pathology Society  
Unknown Slide Conference  
Solid Pancreatic Neoplasms:  
A Cyto-Histologic Review of Challenging Cases

10/18/18

Michelle Reid, MD, MS

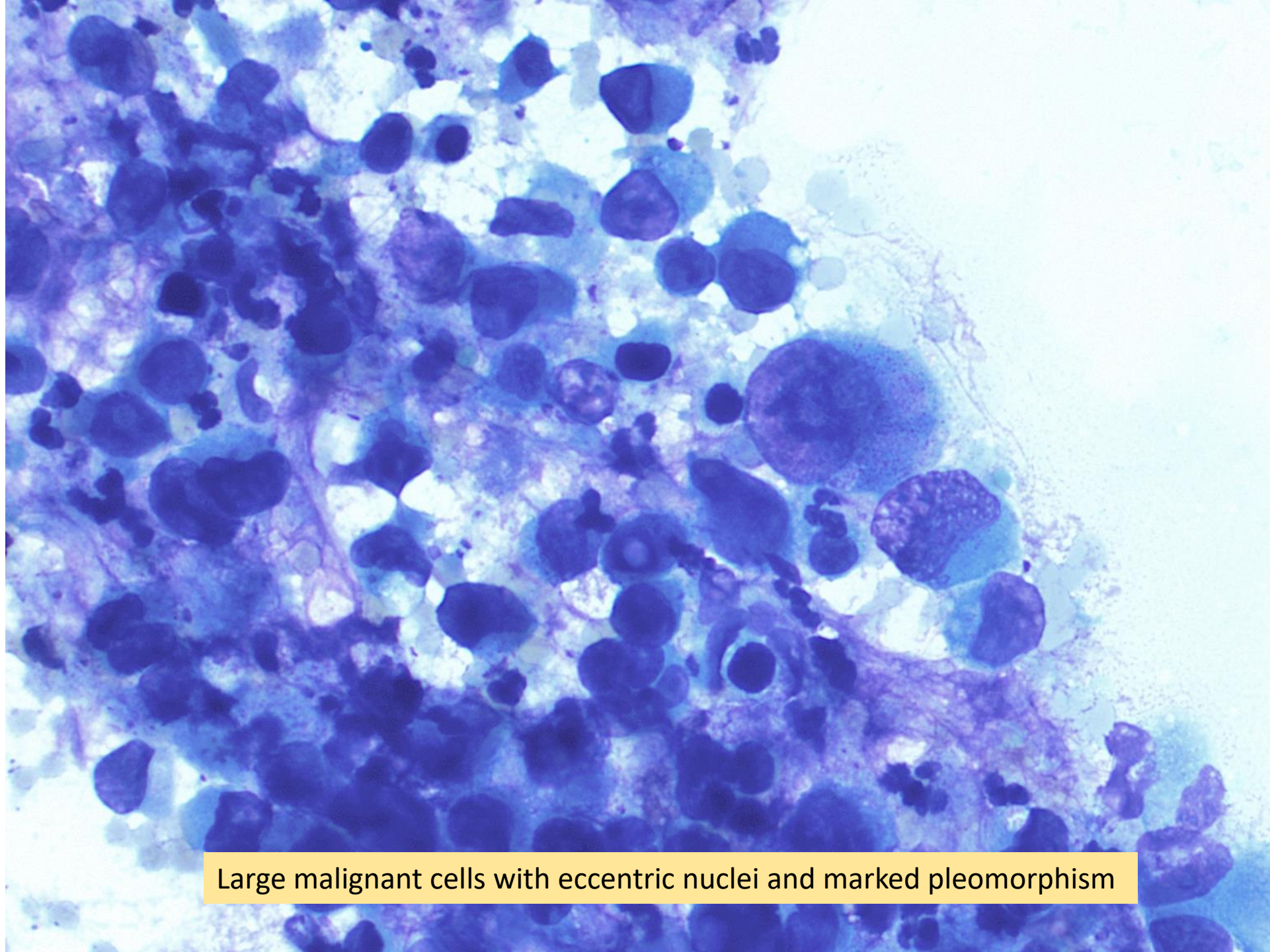
Professor

Director of Cytopathology

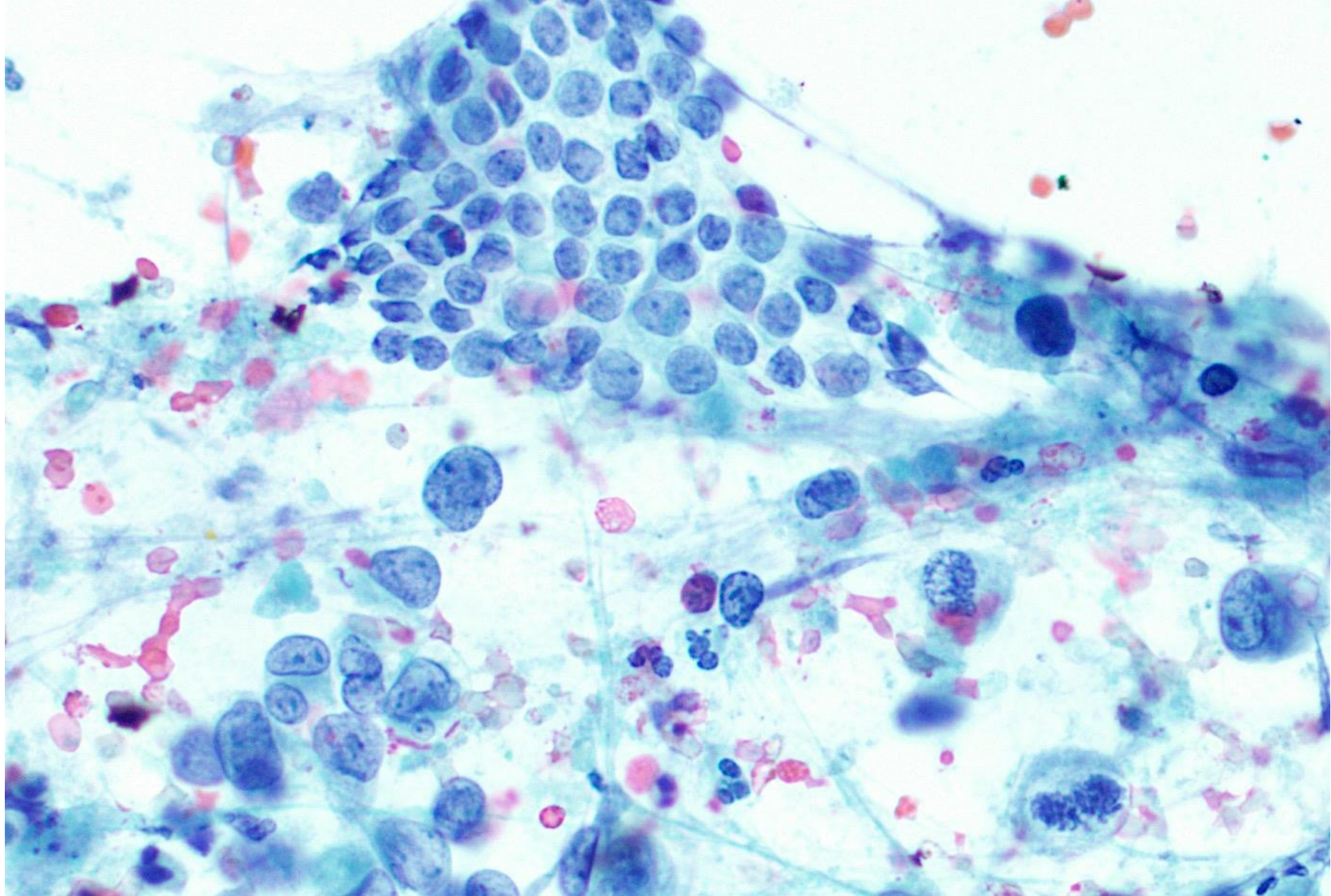
Emory University Hospital

# Case # 1

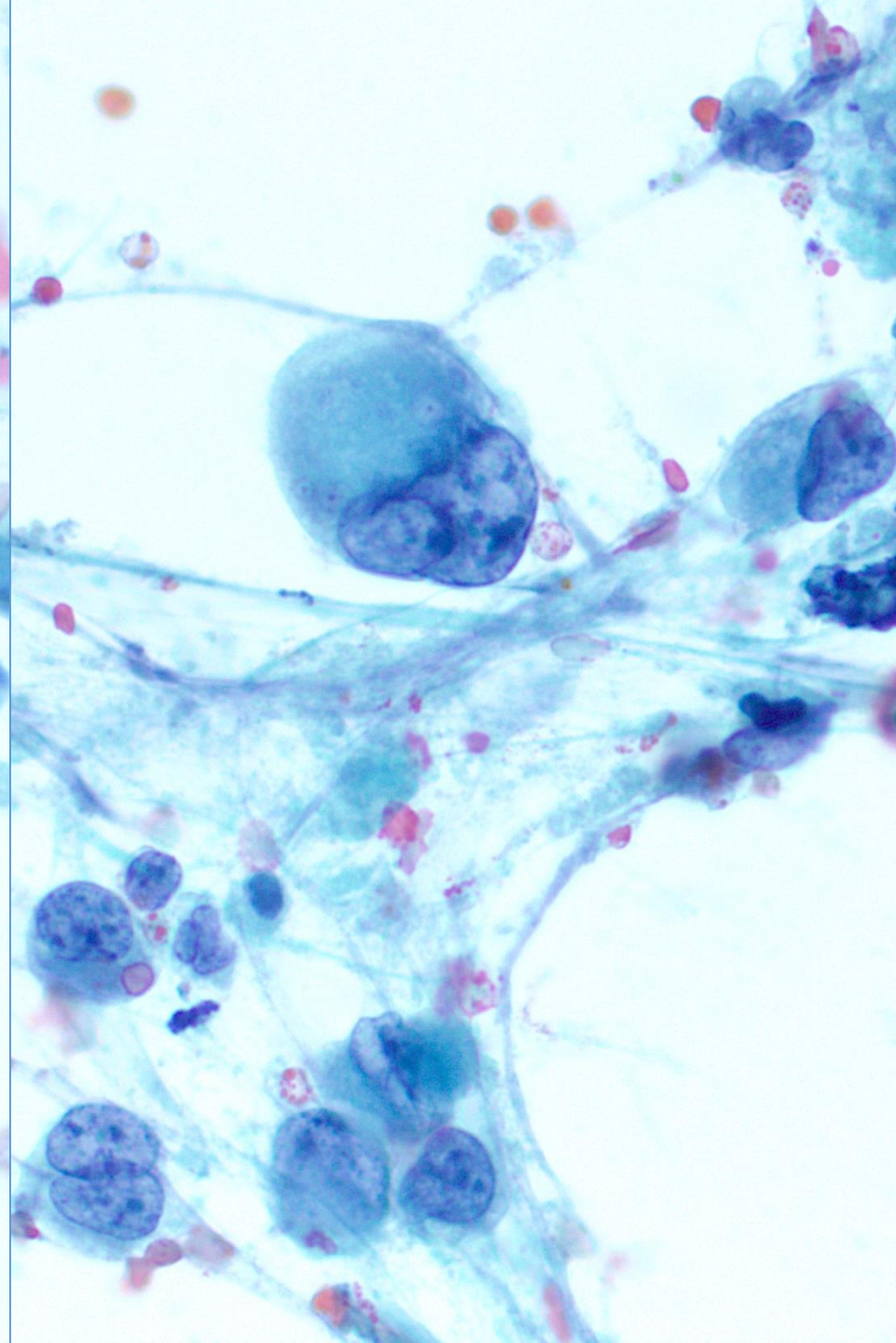
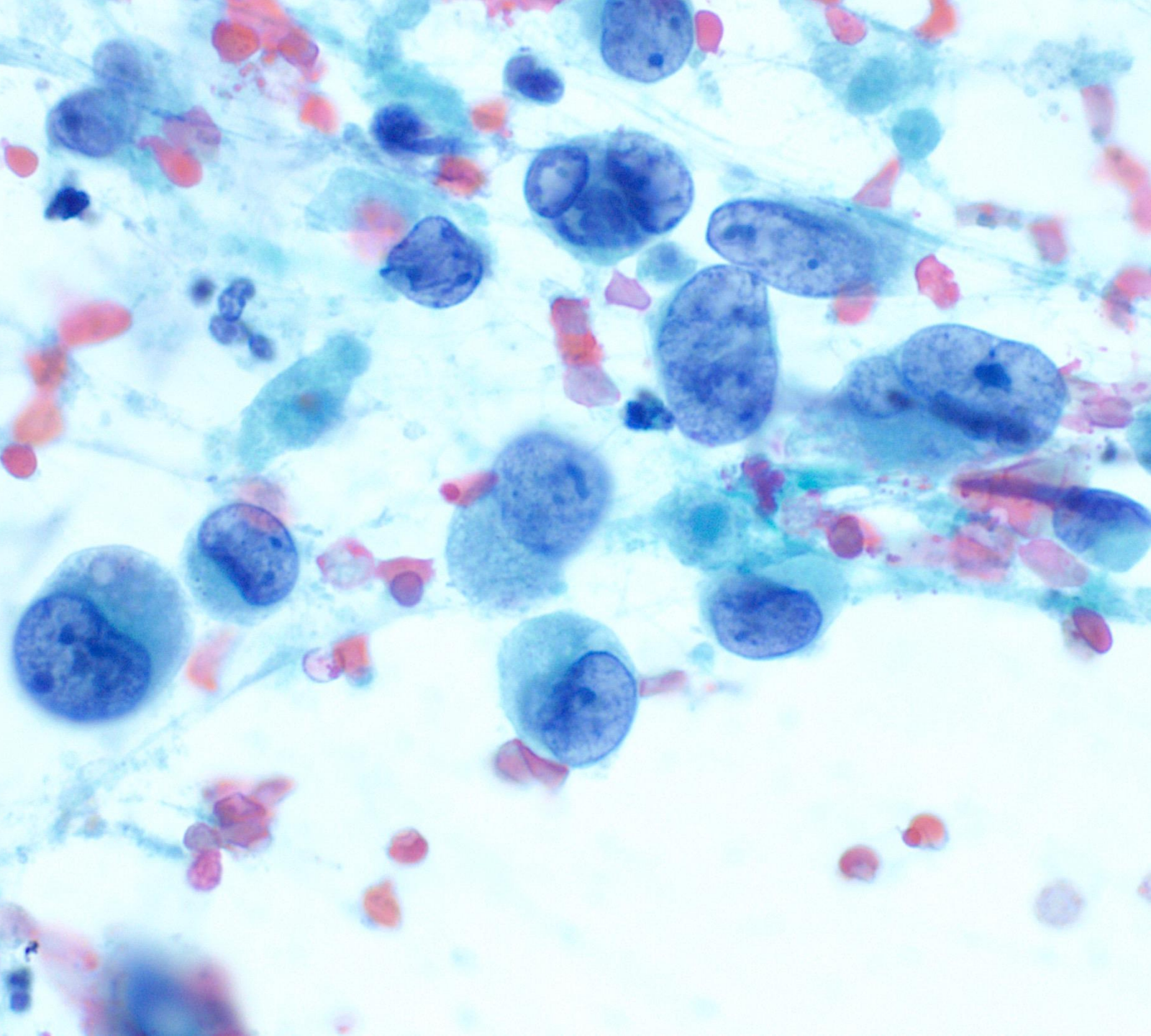
- 56 year old female with jaundice
- Imaging showed 2 pancreatic masses, one in the head (3.0 cm) and one in the body (2.0 cm)
- Both masses were aspirated and showed the same findings



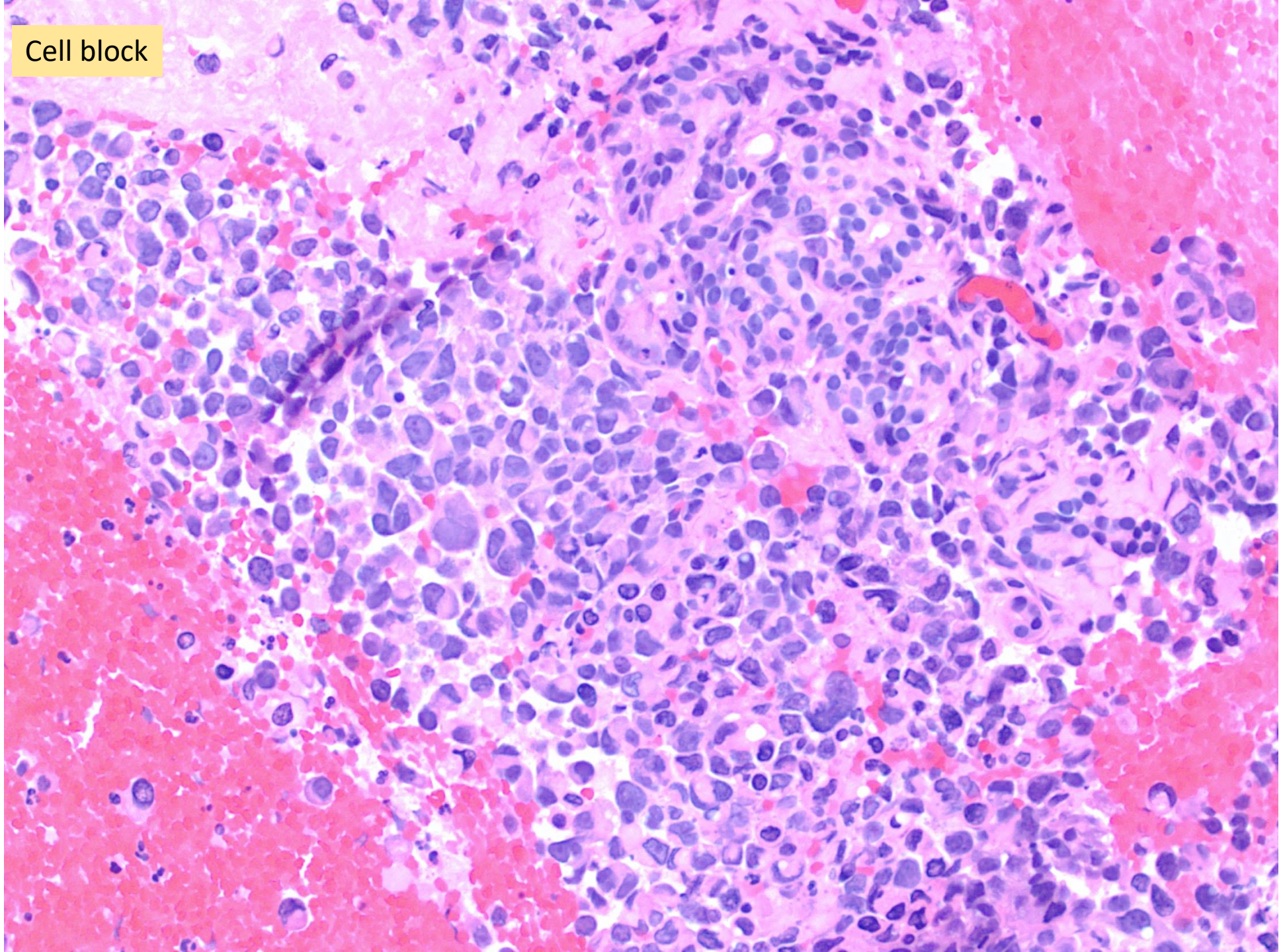
Large malignant cells with eccentric nuclei and marked pleomorphism



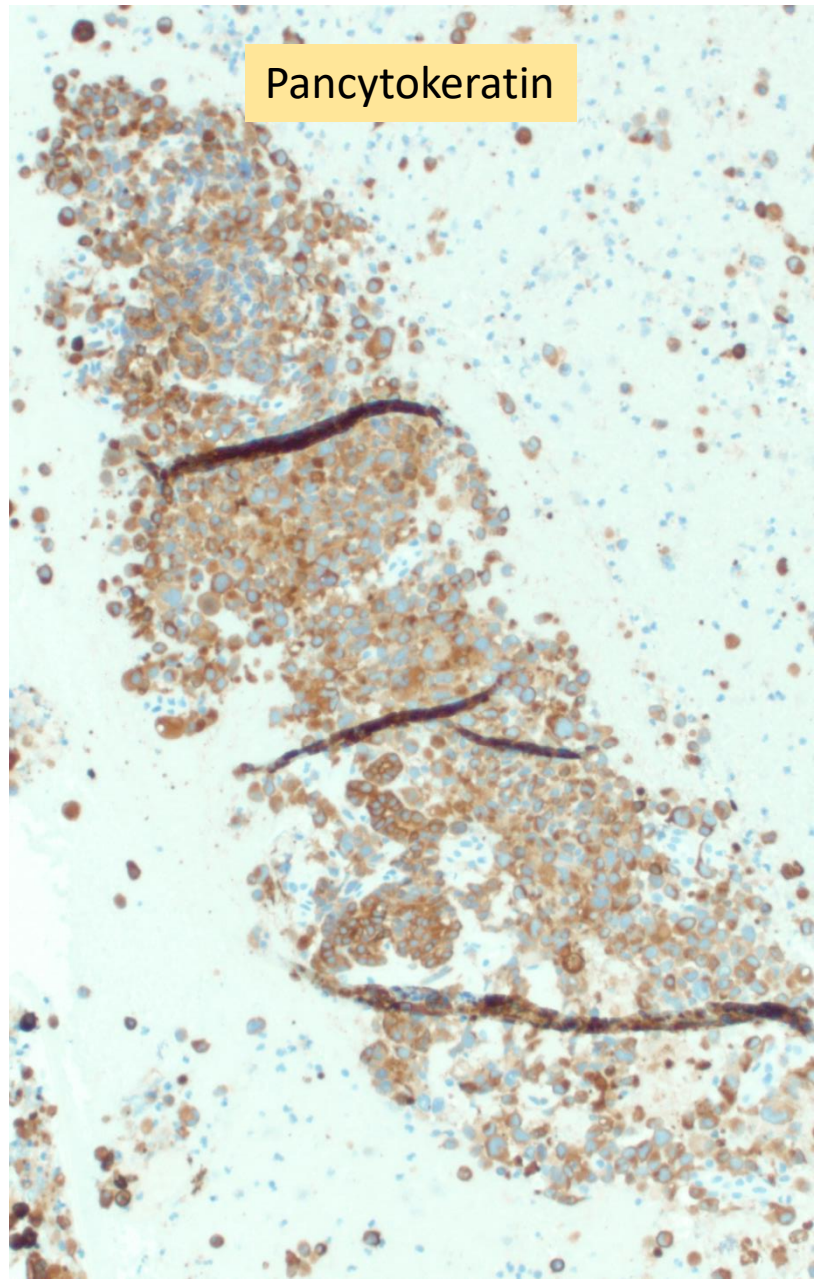
Large malignant single cells with eccentric nuclei, mitoses and marked pleomorphism; ductal cells were also present



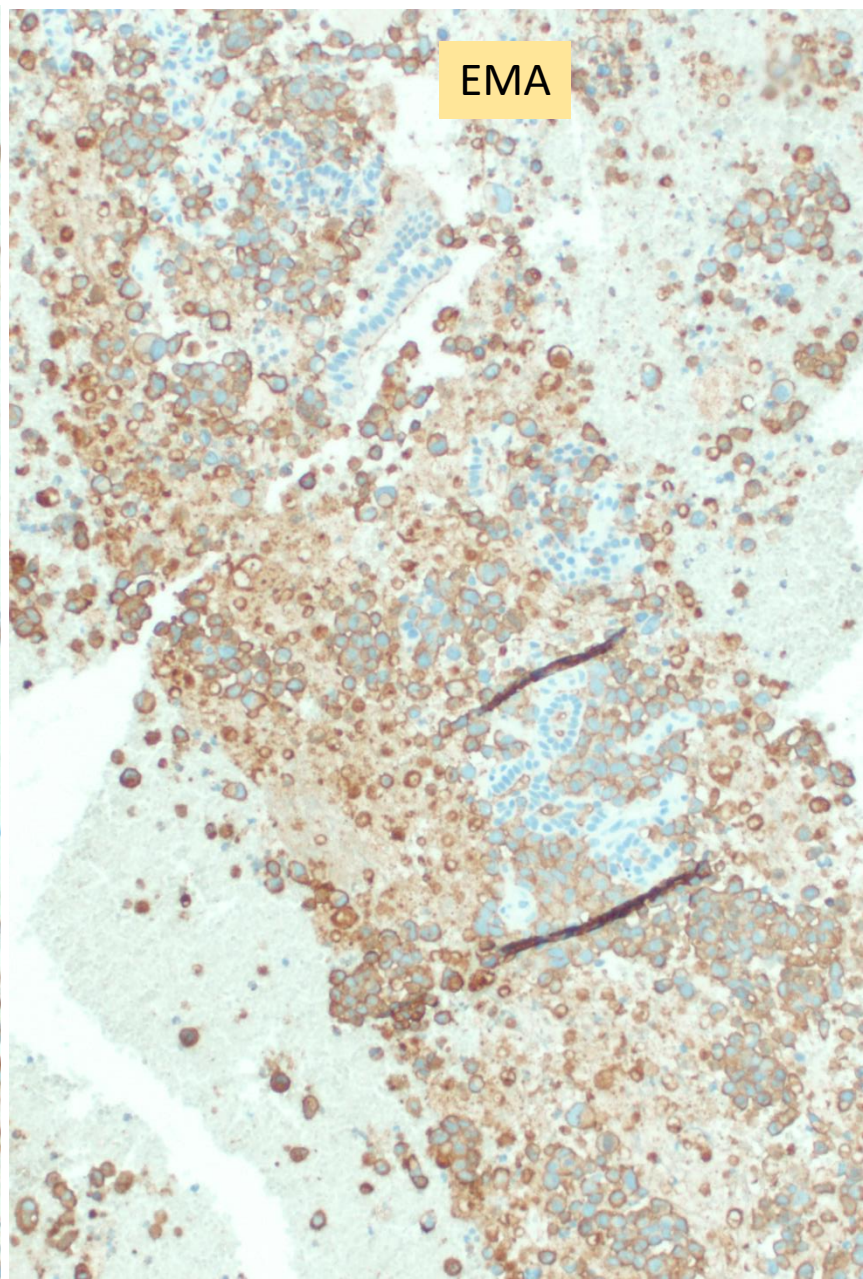
Cell block



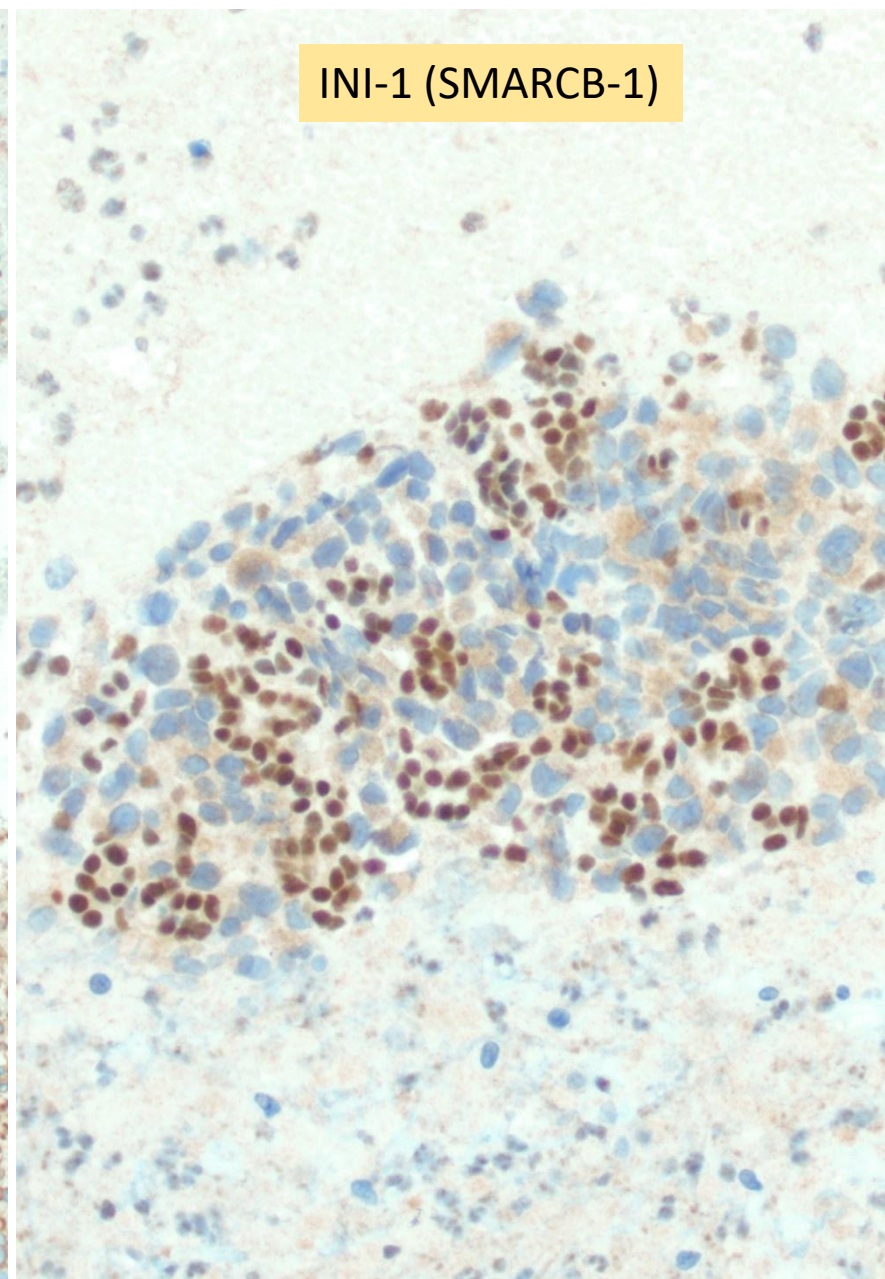
Pancytokeratin



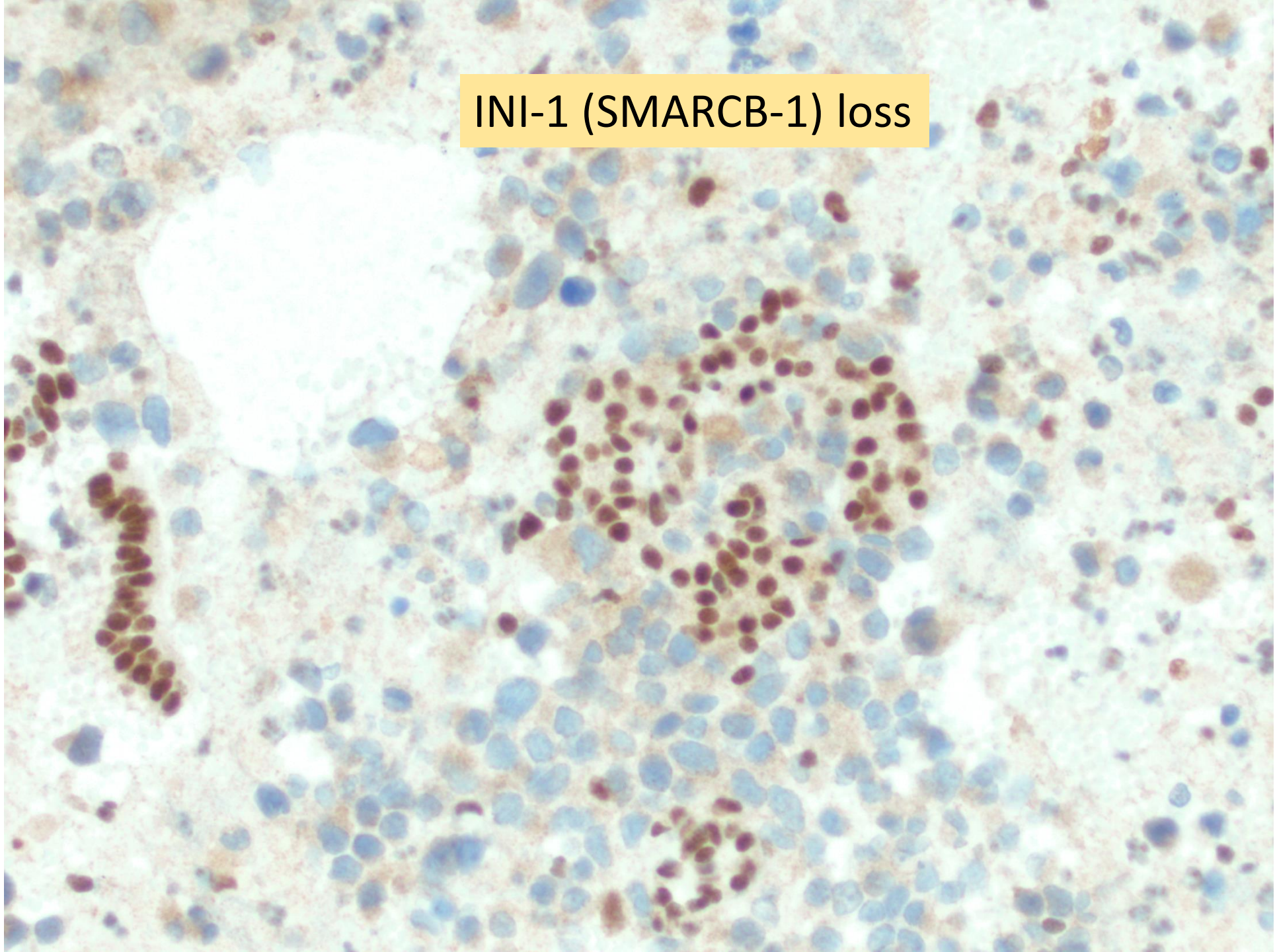
EMA



INI-1 (SMARCB-1)



INI-1 (SMARCB1) loss





# Case # 1 - Diagnosis

Undifferentiated rhabdoid carcinoma  
with SMARCB1 (INI-1) loss

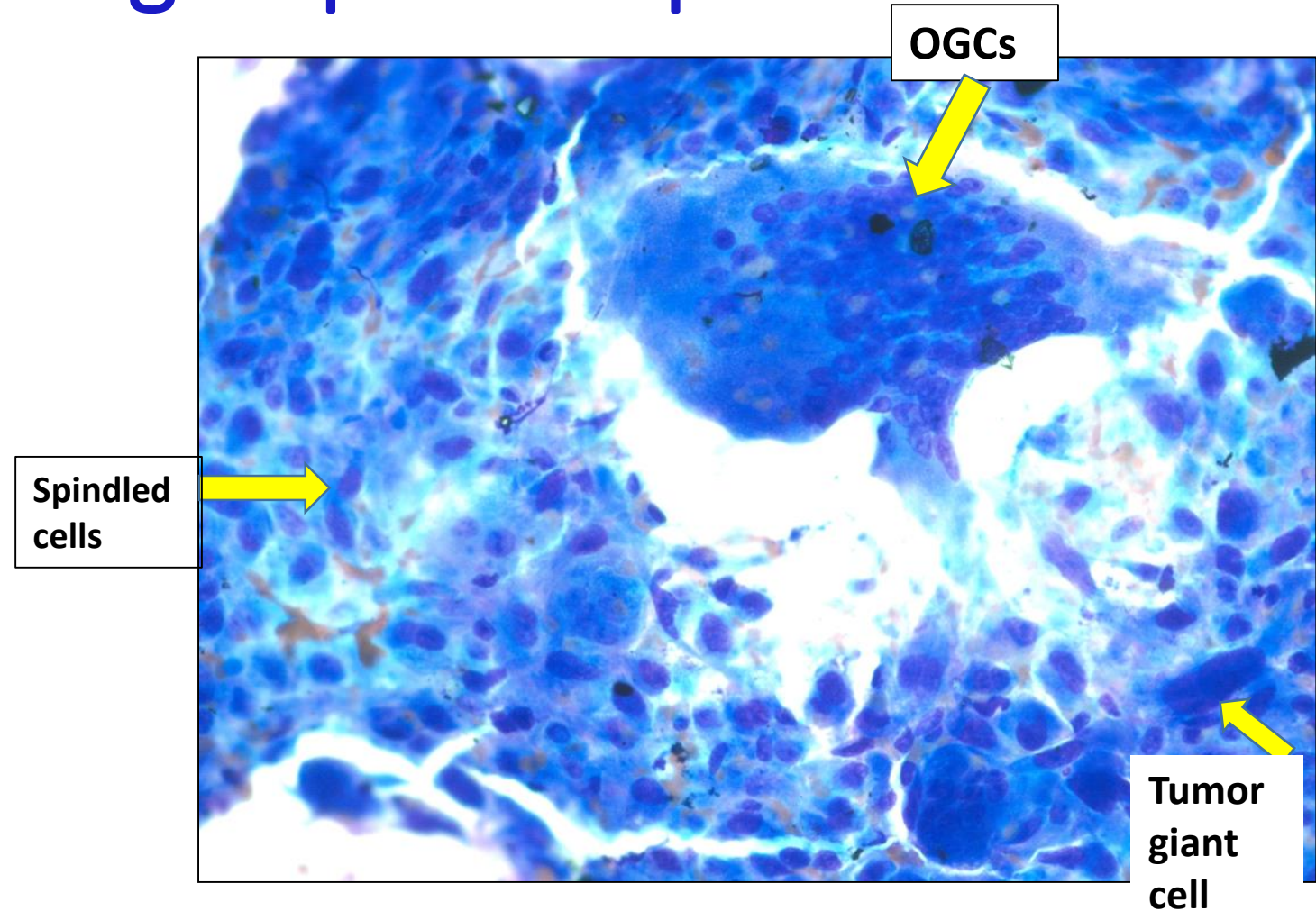
# Pancreatic undifferentiated rhabdoid carcinoma: *KRAS* alterations and SMARCB1 expression status define two subtypes

Abbas Agaimy<sup>1</sup>, Florian Haller<sup>1</sup>, Judith Frohnauer<sup>1</sup>, Inga-Marie Schaefer<sup>2,3</sup>, Philipp Ströbel<sup>3</sup>, Arndt Hartmann<sup>1</sup>, Robert Stoehr<sup>1</sup> and Günter Klöppel<sup>4</sup>

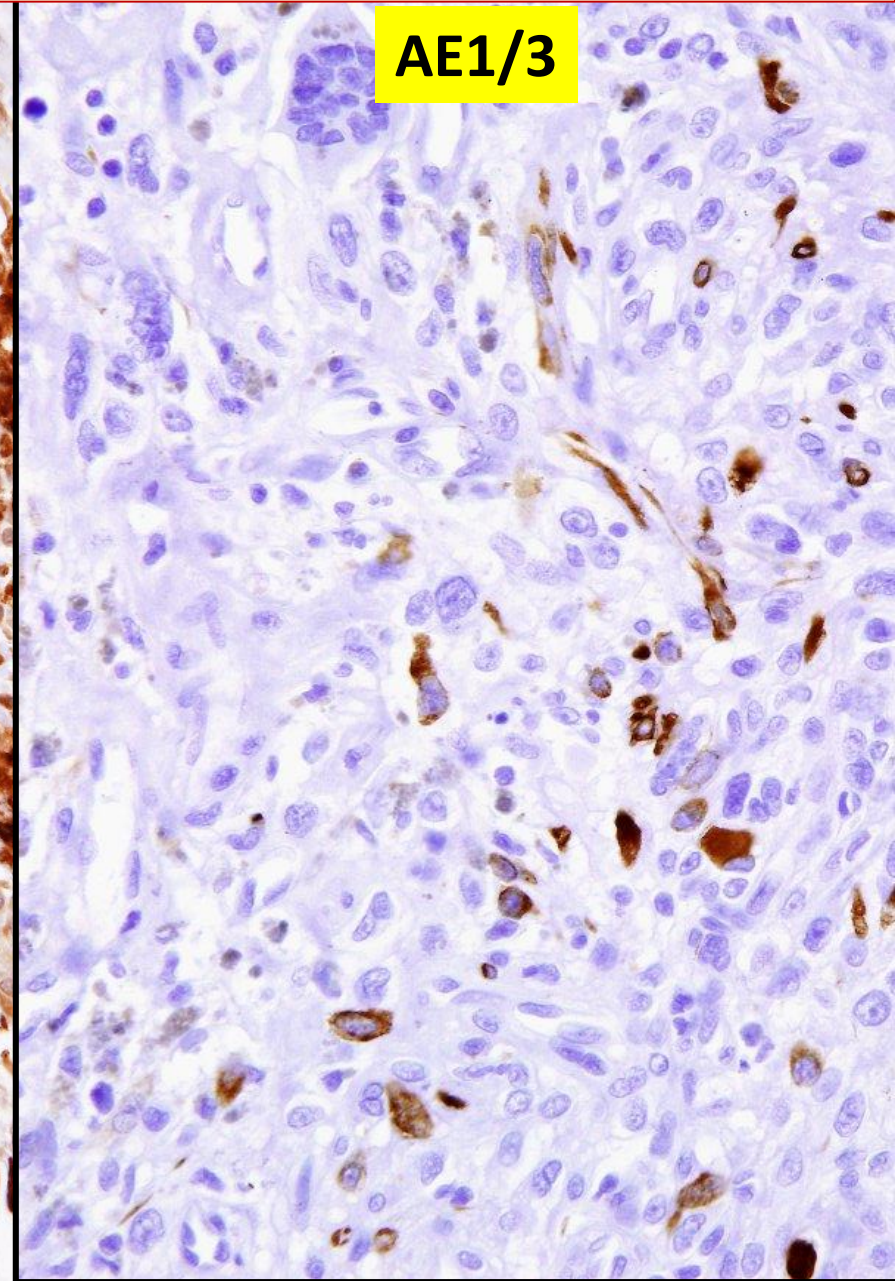
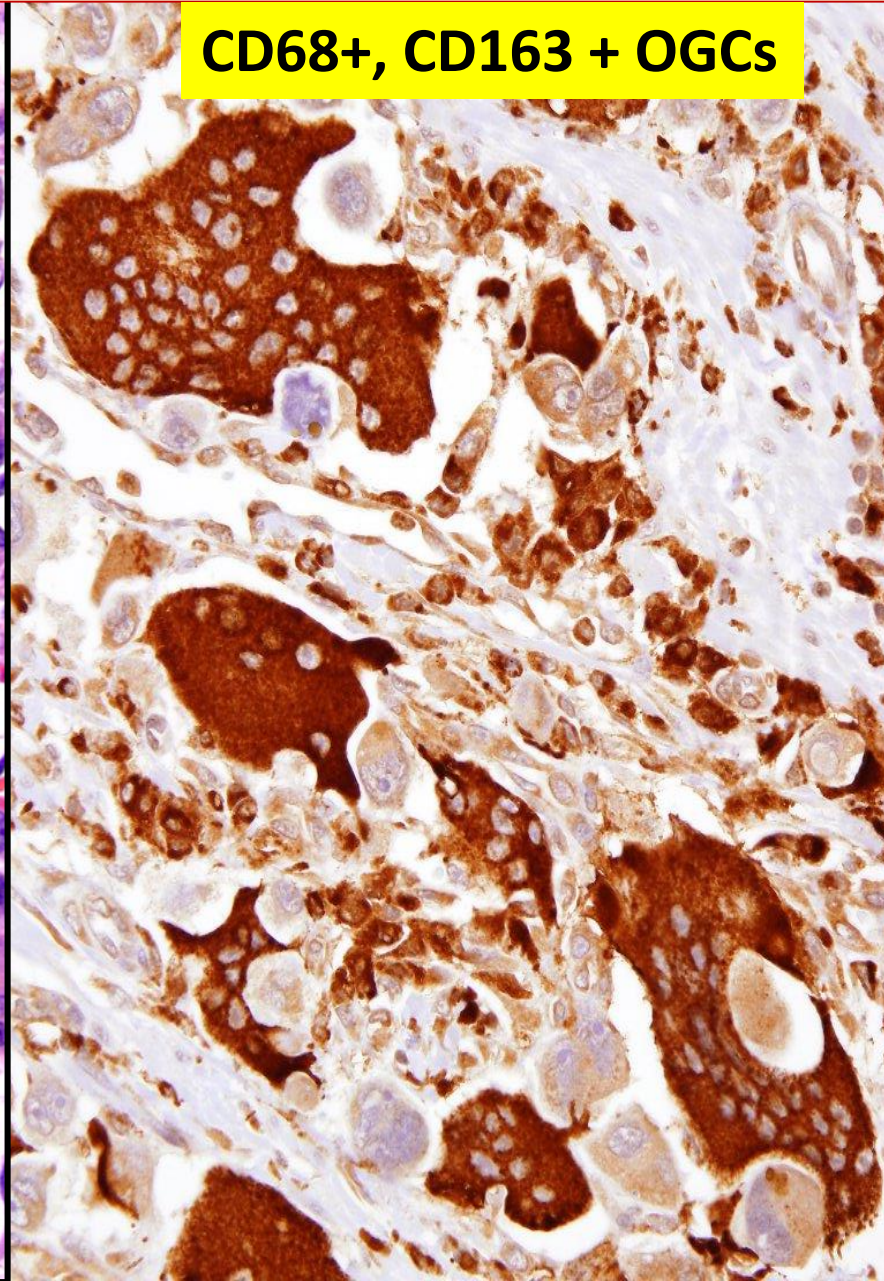
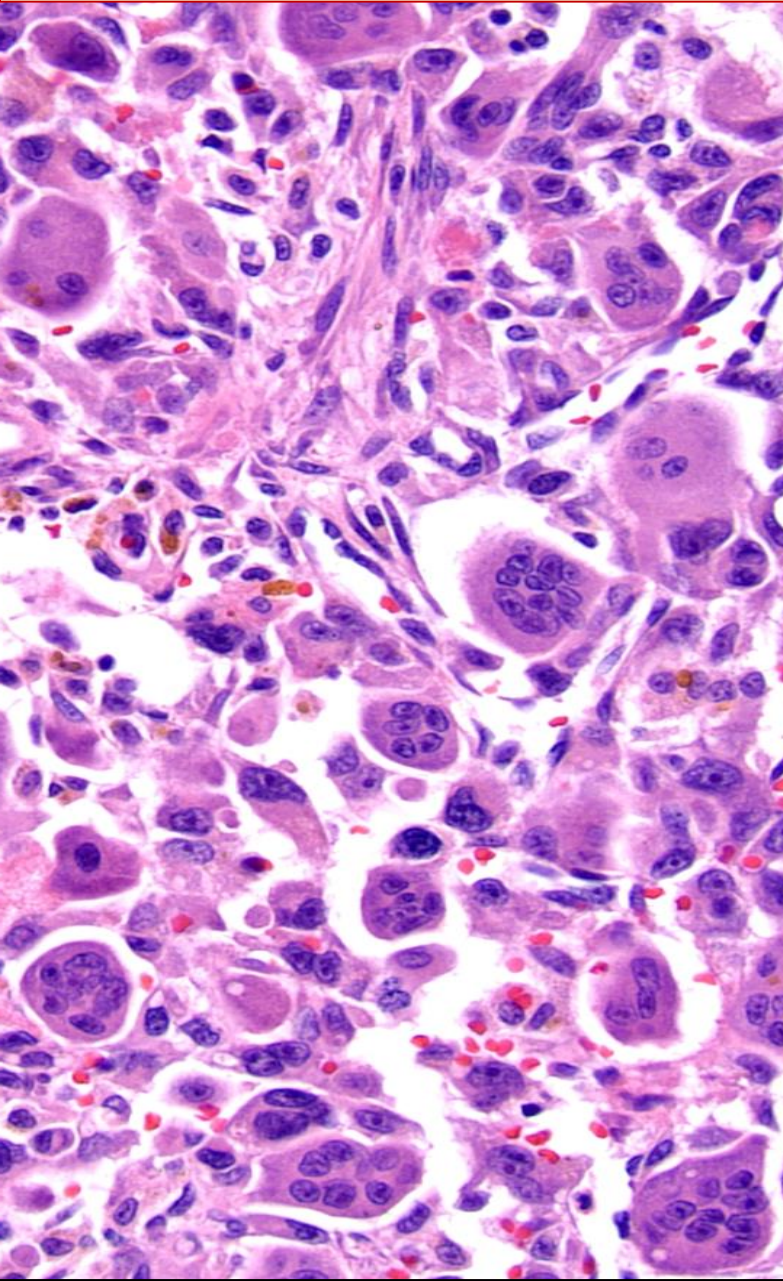
New kid on the “solid pancreatic tumor” block

# Pancreatic undifferentiated carcinoma is a heterogeneous group of neoplasms

- Pleomorphic giant cell carcinoma
- Osteoclastic giant cell carcinoma
- Sarcomatoid carcinoma
- Rhabdoid carcinomas



# Osteoclastic Giant Cell Carcinoma



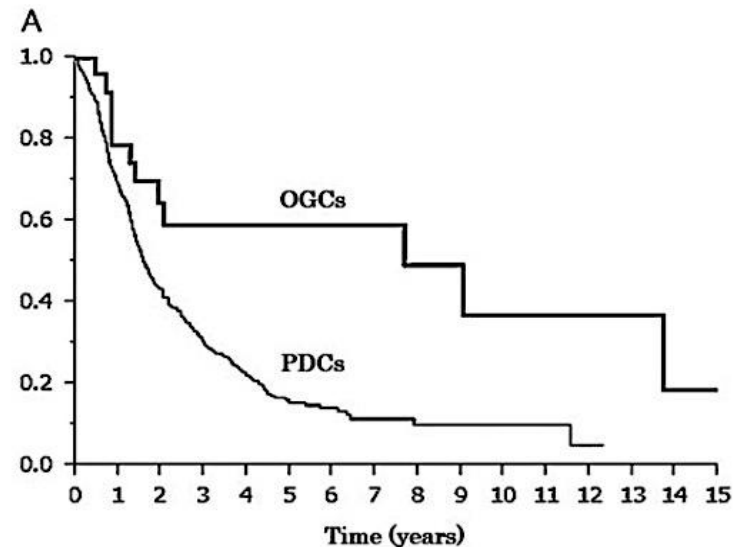
ORIGINAL ARTICLE

# Undifferentiated Carcinoma With Osteoclastic Giant Cells of the Pancreas

*Clinicopathologic Analysis of 38 Cases Highlights A More Protracted Clinical Course Than Currently Appreciated*

*Takashi Muraki, MD, PhD,\* Michelle D. Reid, MD,\* Olca Basturk, MD,† Kee-Taek Jang, MD,‡  
Gabriela Bedolla, MD,\* Pelin Bagci, MD,§ Pardeep Mittal, MD,|| Bahar Memis, MD,\*  
Nora Katabi, MD,† Sudeshna Bandyopadhyay, MD,¶|| Juan M. Sarmiento, MD,#  
Alyssa Krasinskas, MD,\* David S. Klimstra, MD,† and Volkan Adsay, MD\**

Better prognosis than  
conventional PDAC



# **Cytologic Features and Clinical Implications of Undifferentiated Carcinoma With Osteoclastic Giant Cells of the Pancreas: An Analysis of 15 Cases**

Michelle D. Reid, MD<sup>1</sup>; Takashi Muraki, MD<sup>1</sup>; Kim HooKim, MD<sup>2</sup>; Bahar Memis, MD<sup>1</sup>; Rondell P. Graham, MBBS<sup>3</sup>; Daniela Allende, MD<sup>4</sup>; Jiaqi Shi, MD, PhD<sup>5</sup>; David F. Schaeffer, MD<sup>6</sup>; Remmi Singh, MD<sup>7</sup>; Olca Basturk, MD<sup>B</sup>; and Volkan Adsay, MD<sup>1</sup>

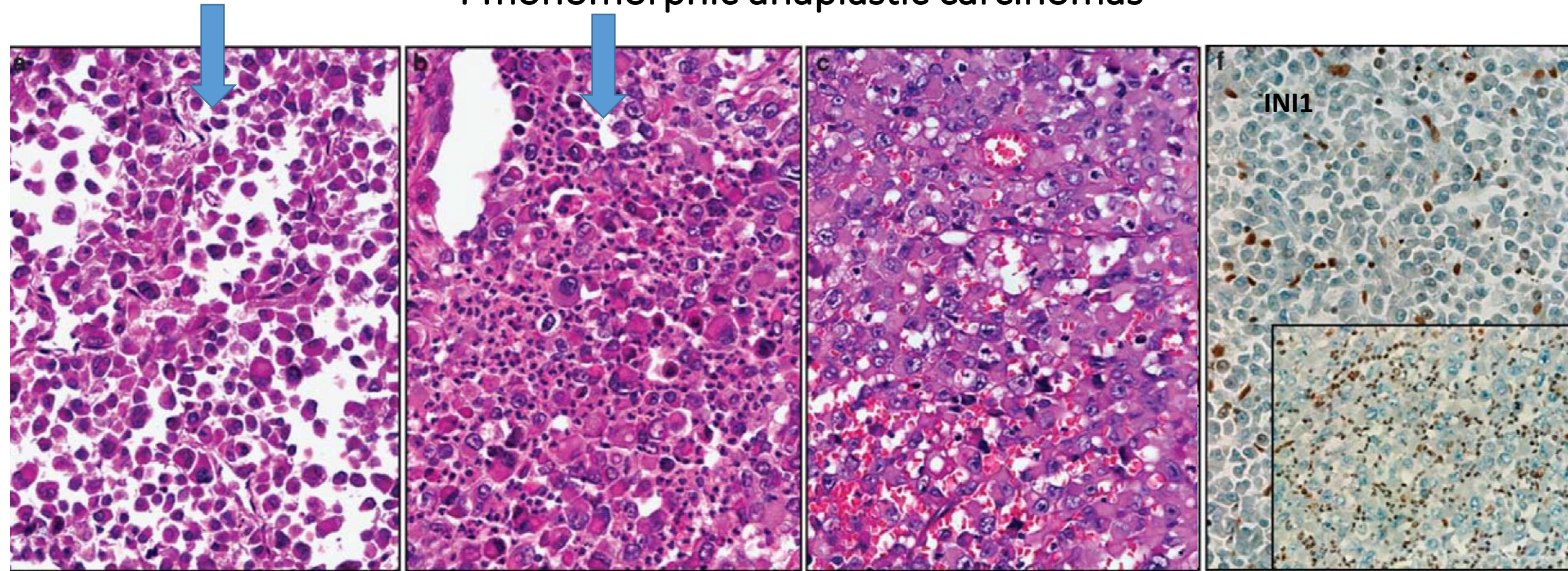
Cancer Cytopathol 2017;125:563-75.

Except if FNA is performed when they seem to do worse

# Undifferentiated rhabdoid carcinoma with SMARCB1 (INI-1) loss

- Agaimy et al examined 14 undifferentiated carcinomas with prominent rhabdoid cells
- M:F 1:1, mean age 65 (44–96 years)
- 10 tumors qualified as pleomorphic giant cell carcinoma
- 4 as monomorphic anaplastic carcinomas
- A glandular component was seen in 5 out of 14 tumors
- Osteoclast-like giant cells were absent

## 4 monomorphic anaplastic carcinomas



Co-express cytokeratin and vimentin; Loss of beta-catenin and E-cadherin

Nuclear SMARCB1 (INI1) loss in 28%

*KRAS* amplification in 38% and exon 2 mutations in 54%

***KRAS* alterations correlated with intact SMARCB1 expression (87%) (pleomorphic giant cell type)**

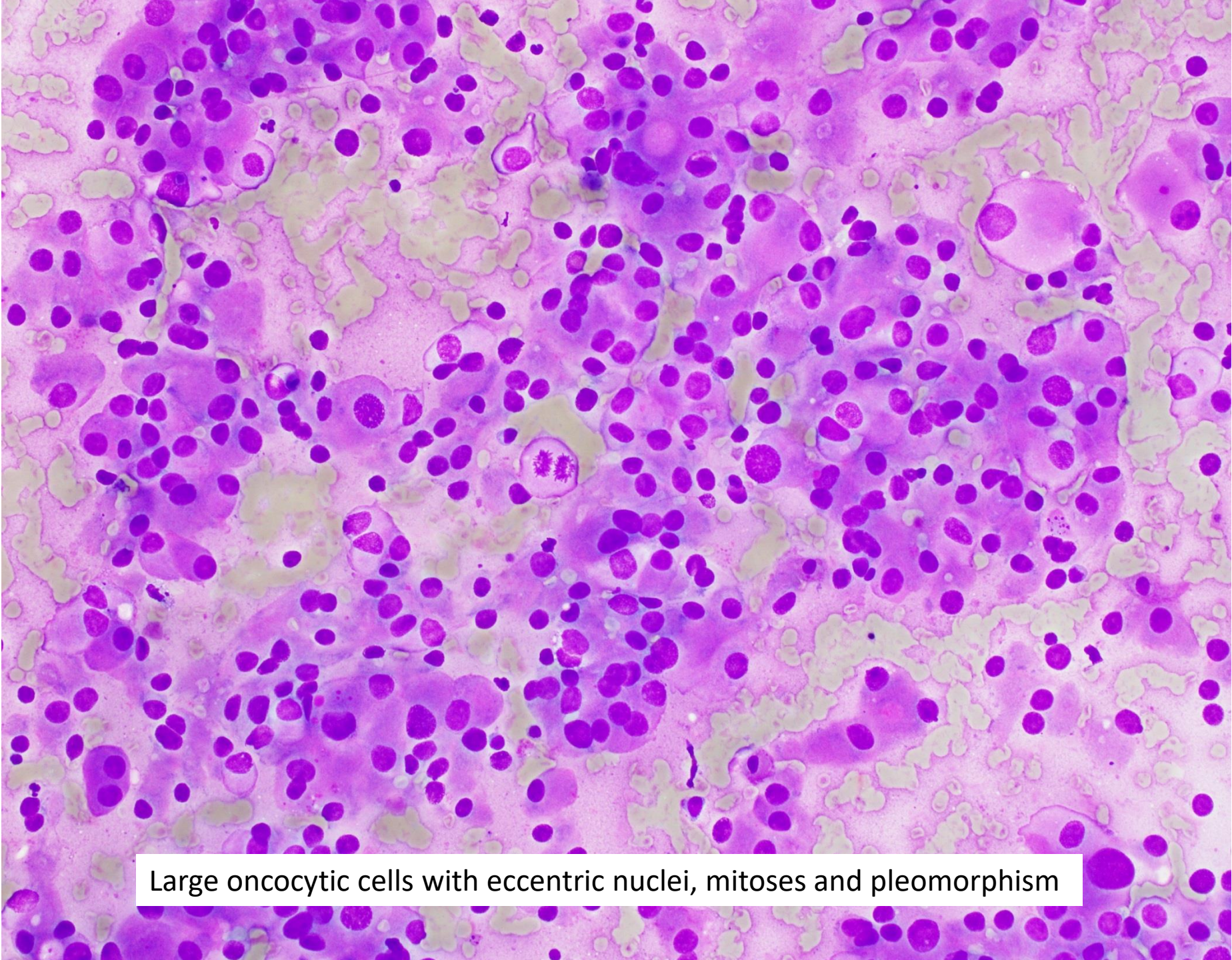
**Loss of SMARCB1 correlated with absence of *KRAS* alterations (60%)**

Agaimy A et al Mod Pathol. 2015; 28.

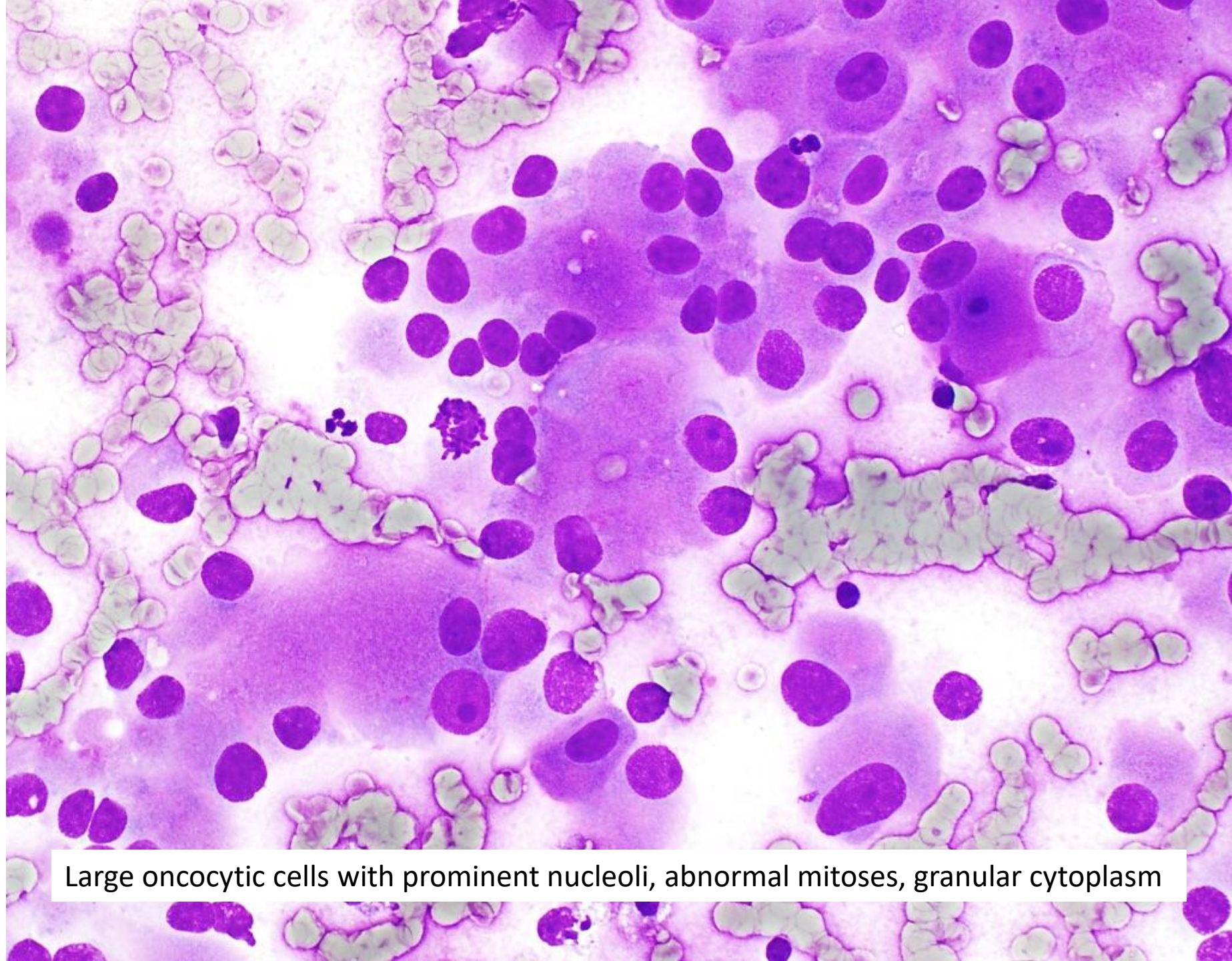


## Case # 2

- A 49 year-old male had an incidental 3.0 cm mass in the pancreatic head
- Fine needle aspiration was performed followed by a pancreatoduodenectomy

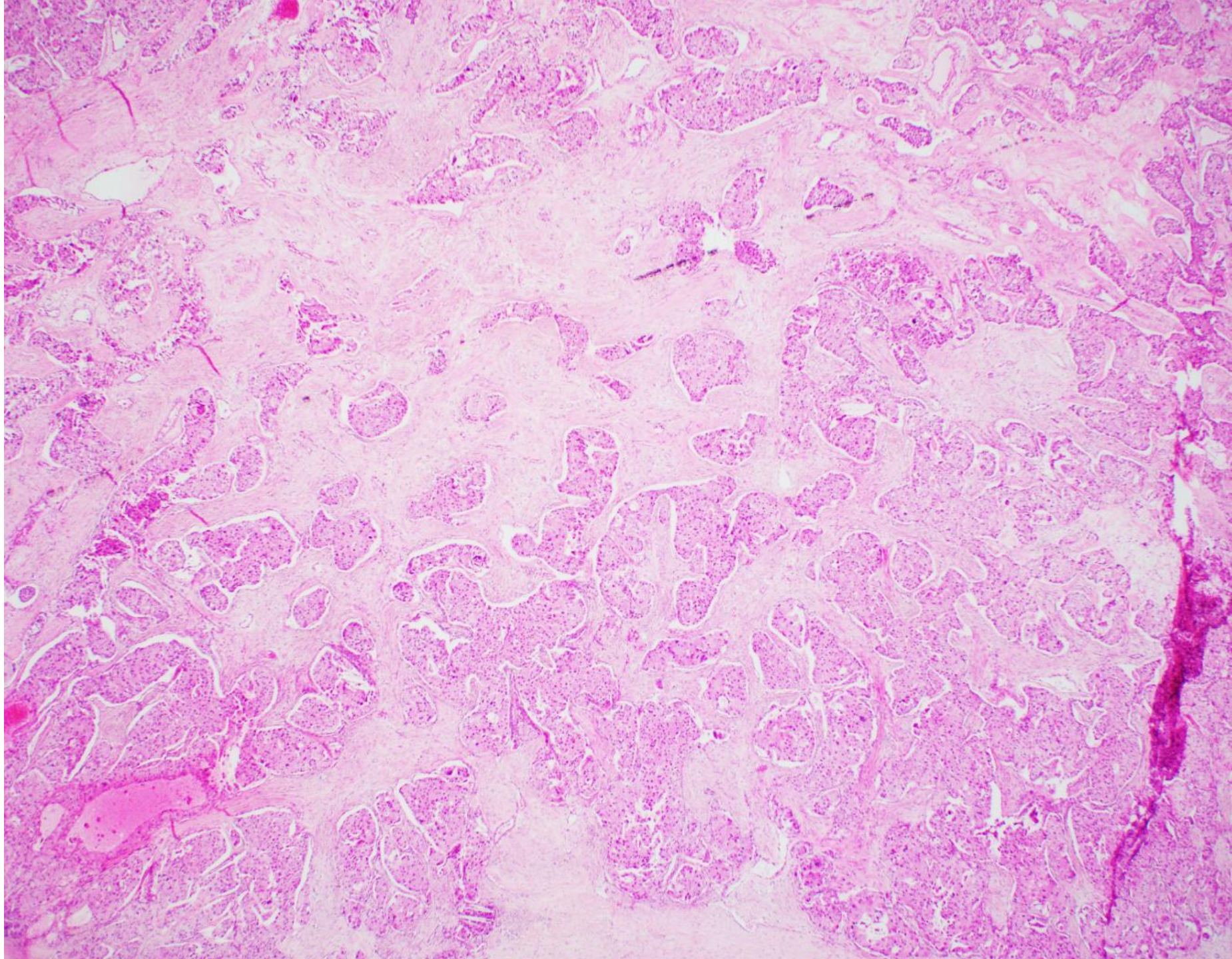


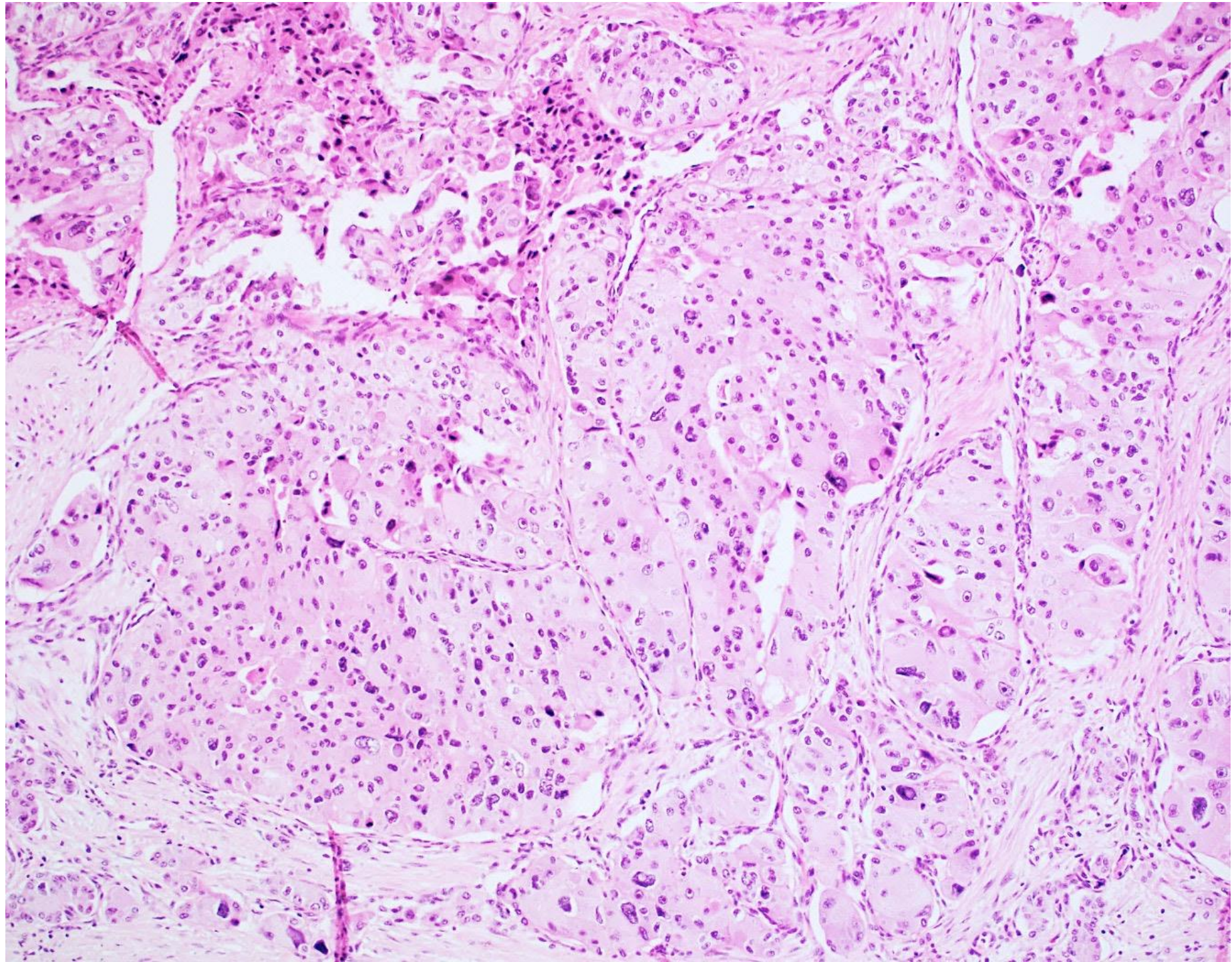
Large oncocytic cells with eccentric nuclei, mitoses and pleomorphism

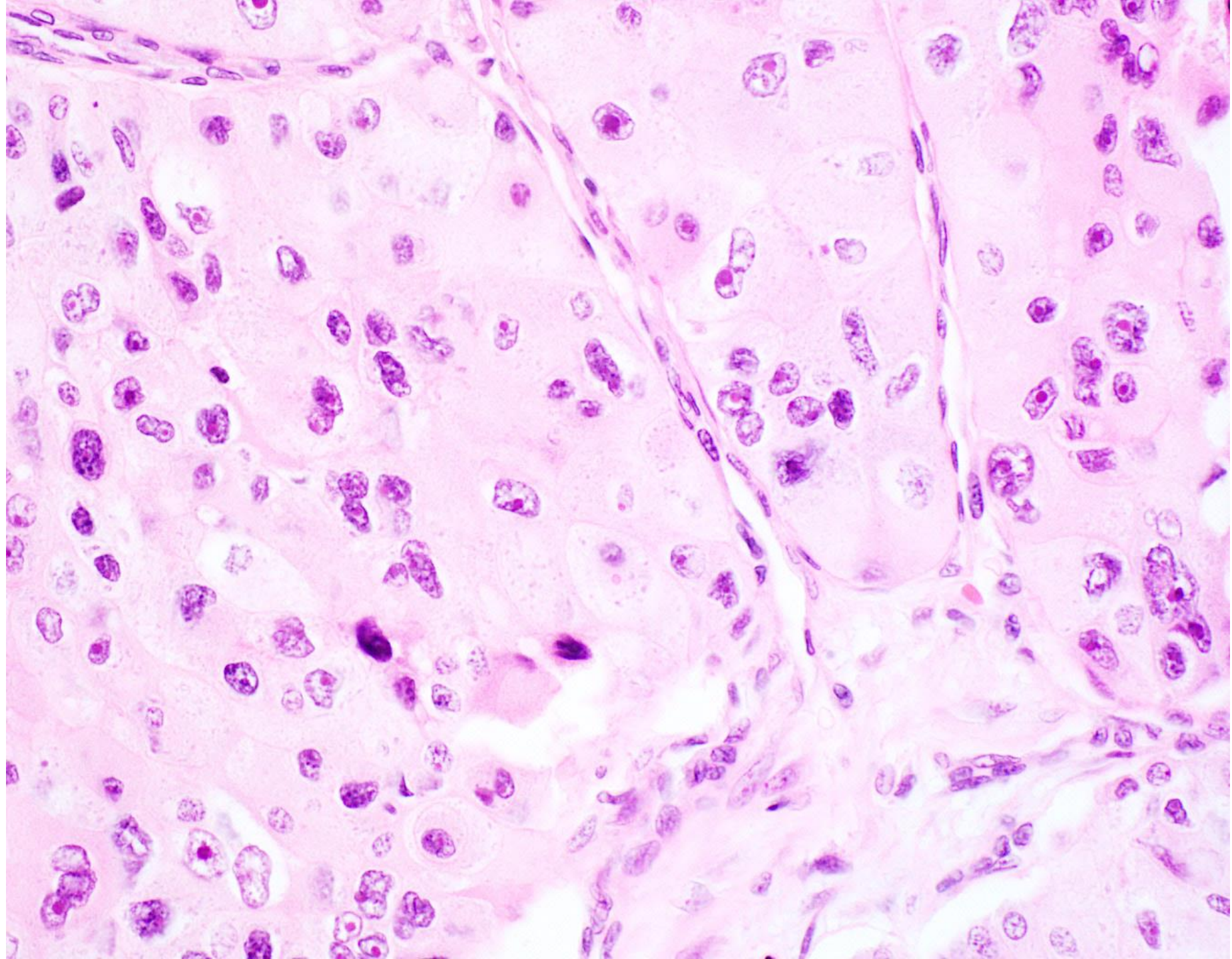


Large oncocytic cells with prominent nucleoli, abnormal mitoses, granular cytoplasm

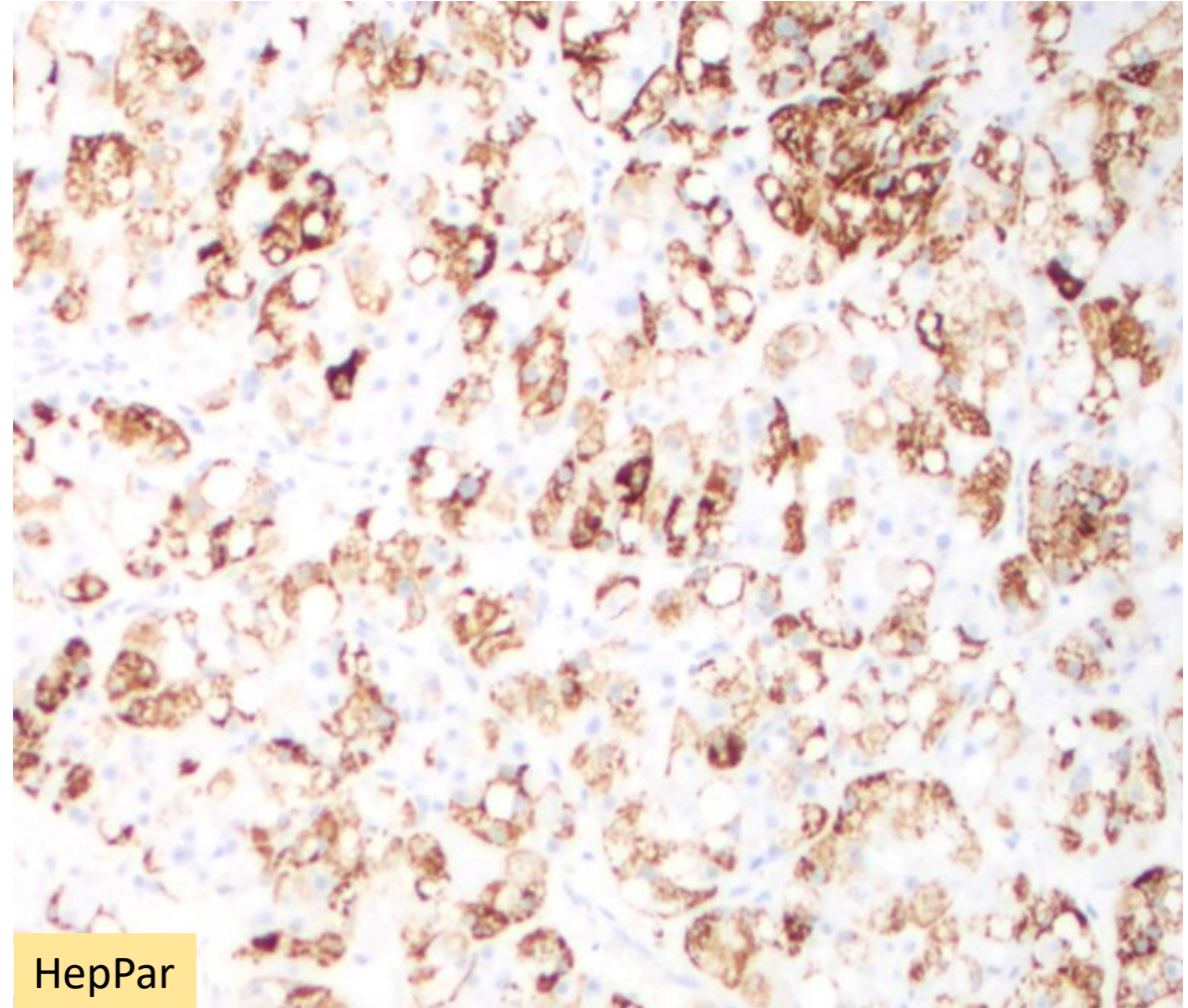
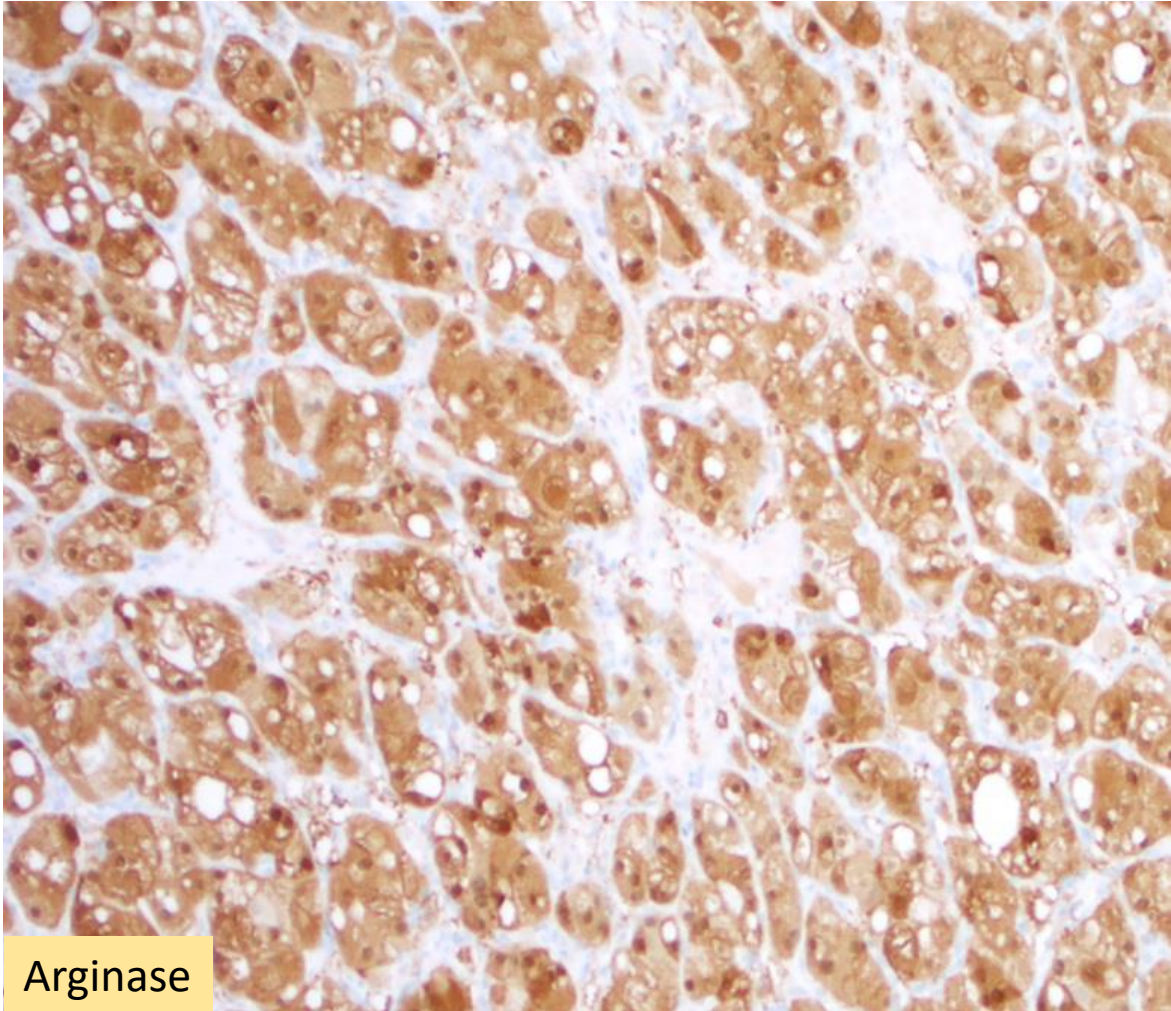




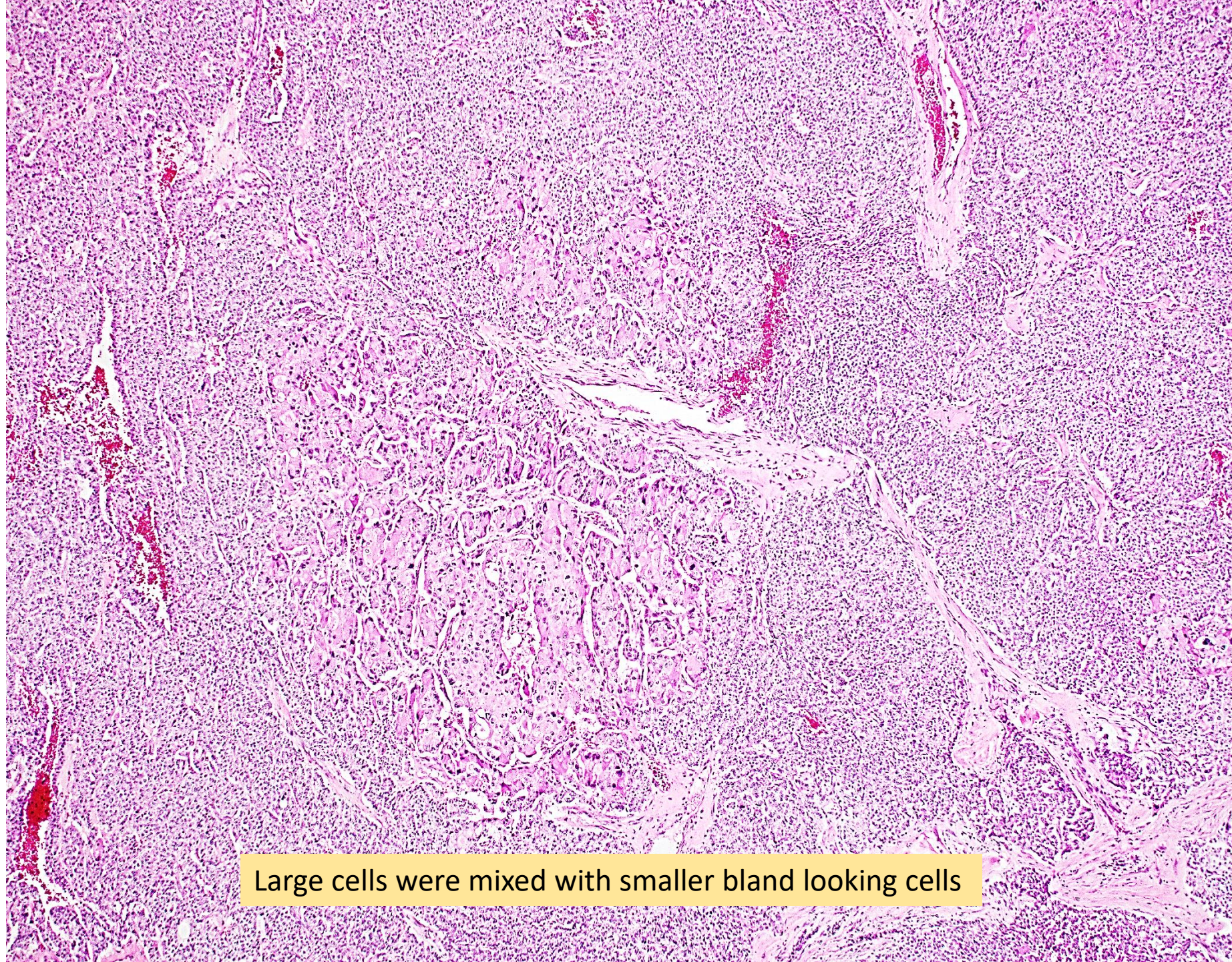




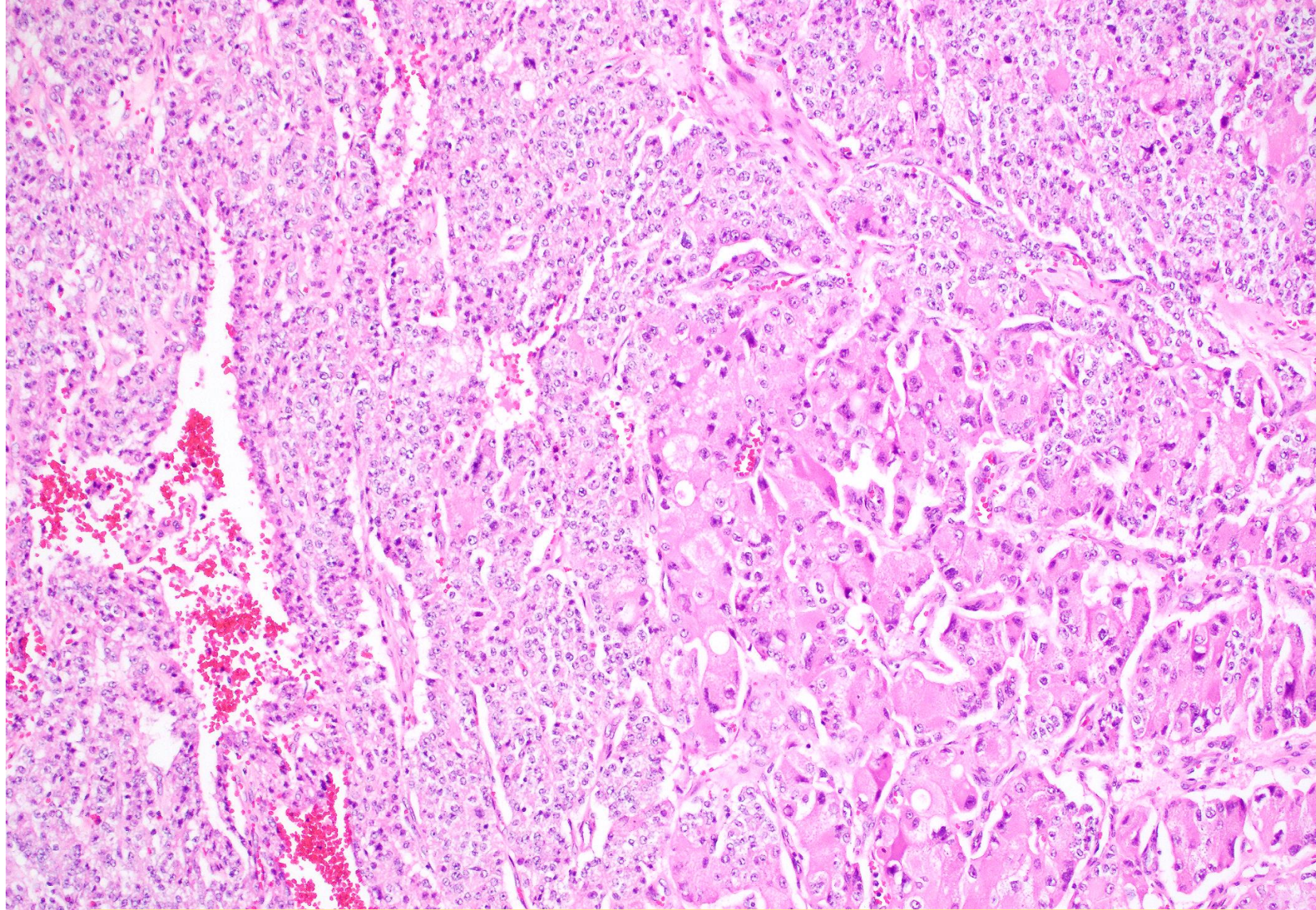
Tumor cells were positive for pancytokeratin, HepPar and arginase. Ki-67 index was 27%



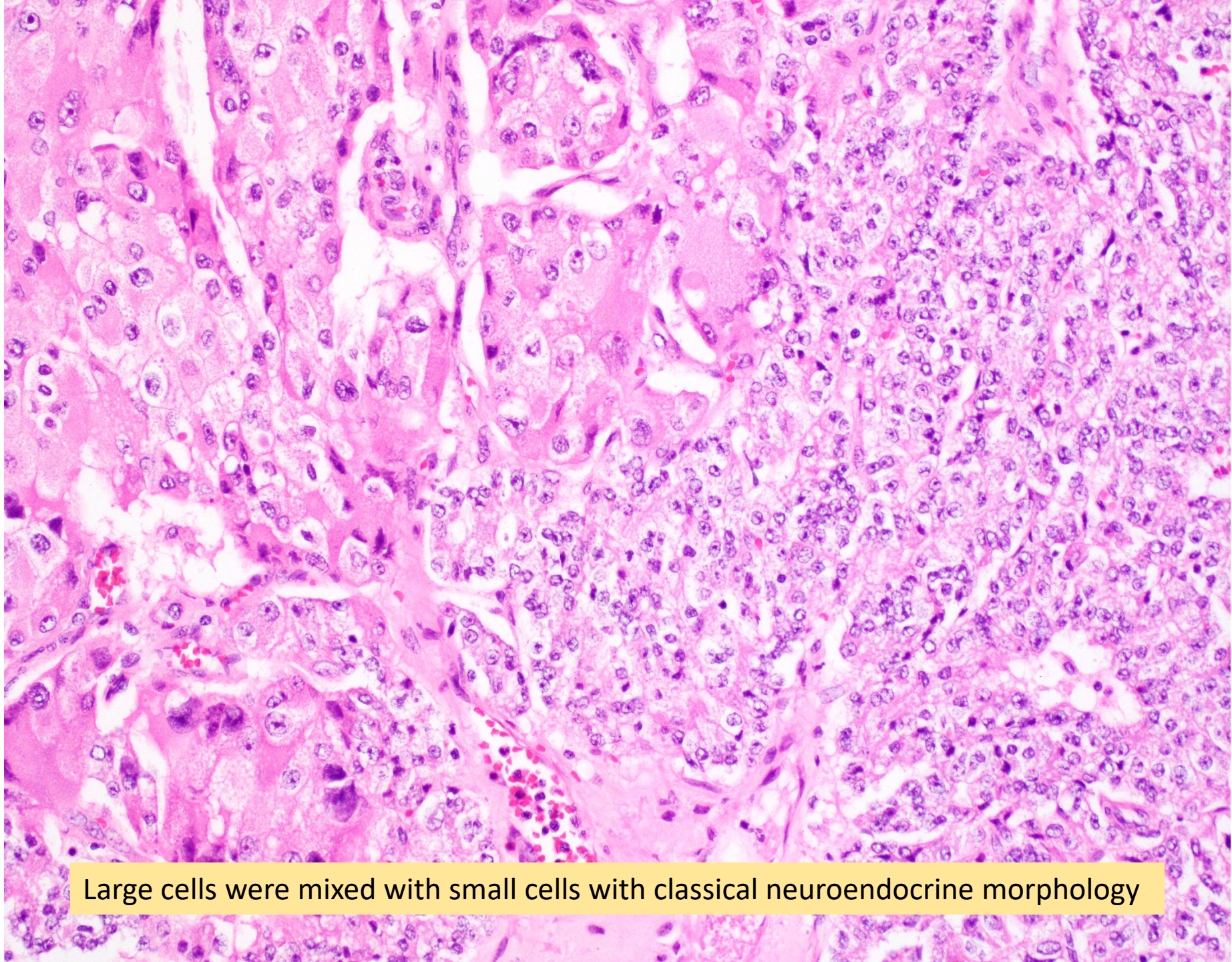




Large cells were mixed with smaller bland looking cells

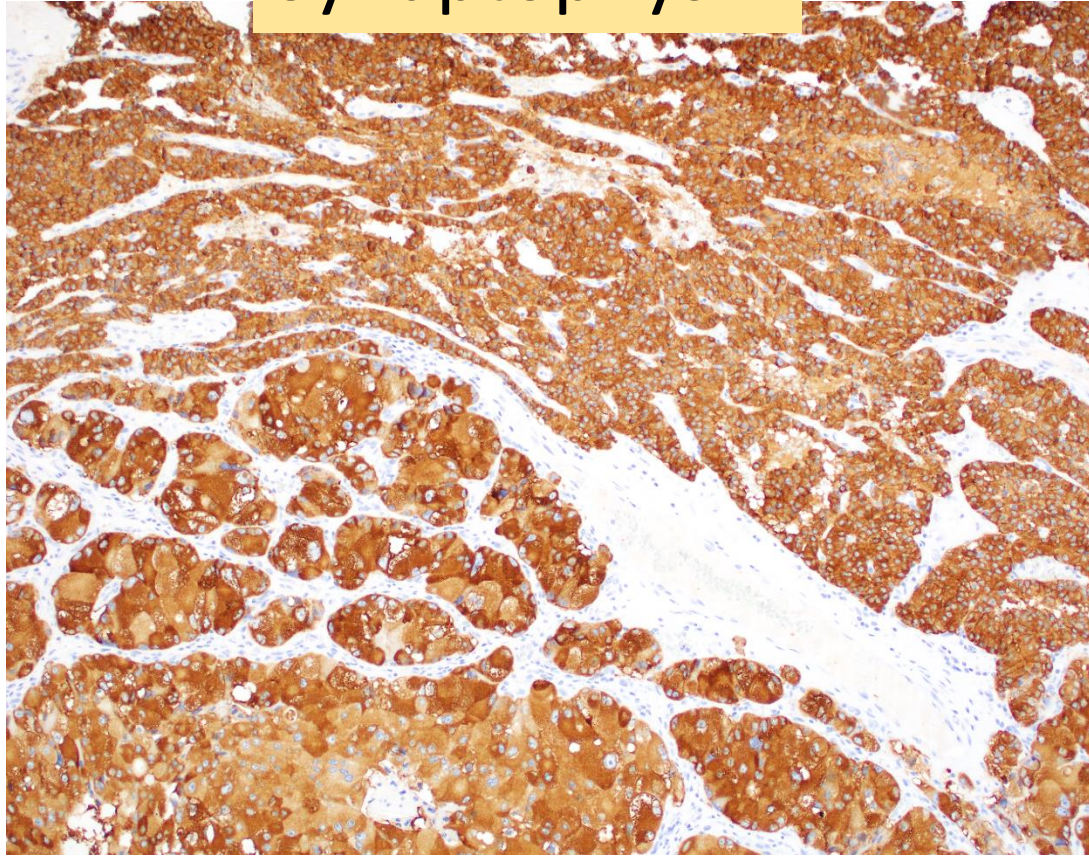


Large cells were mixed with classical small cells with neuroendocrine morphology

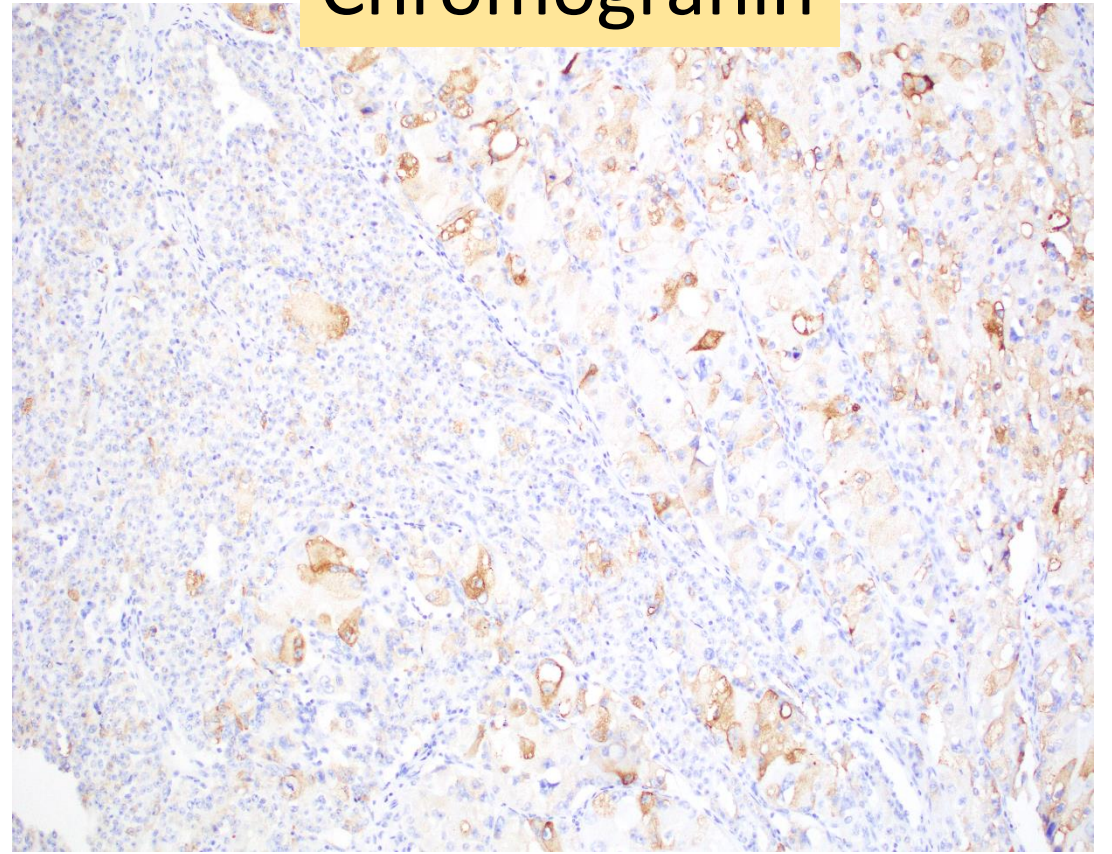


Large cells were mixed with small cells with classical neuroendocrine morphology

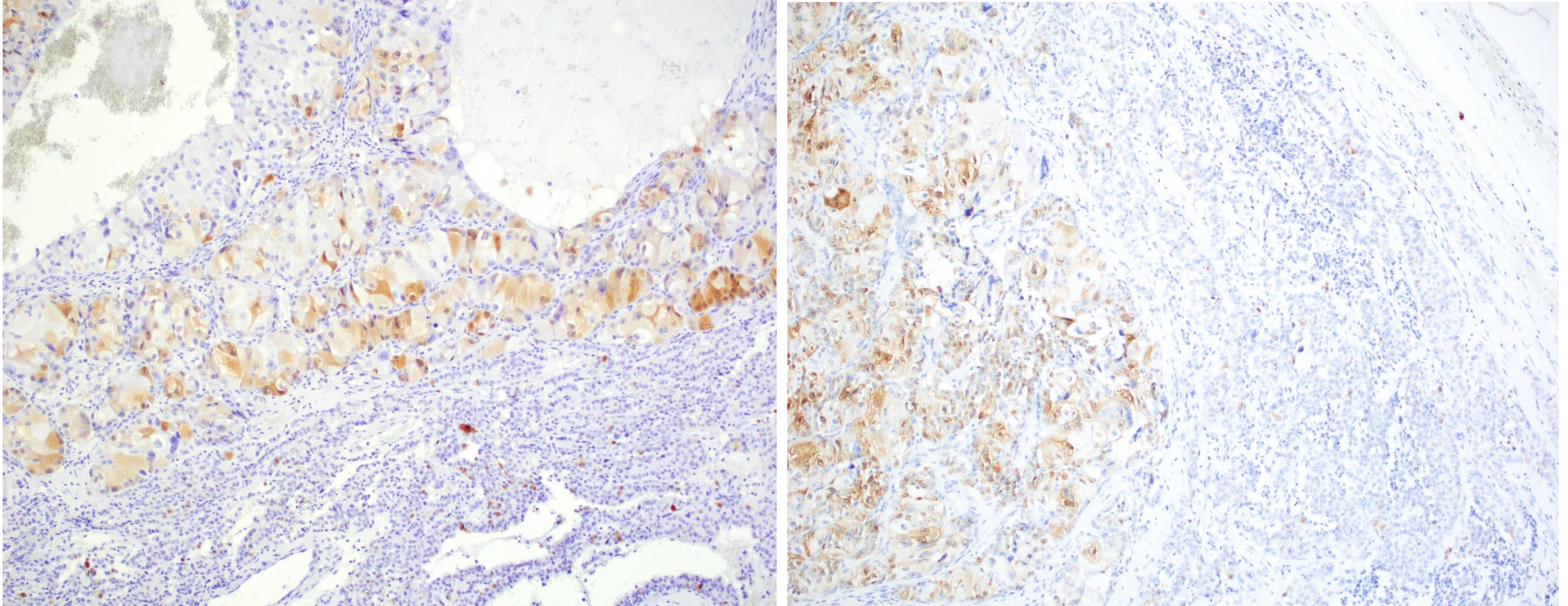
Synaptophysin



Chromogranin



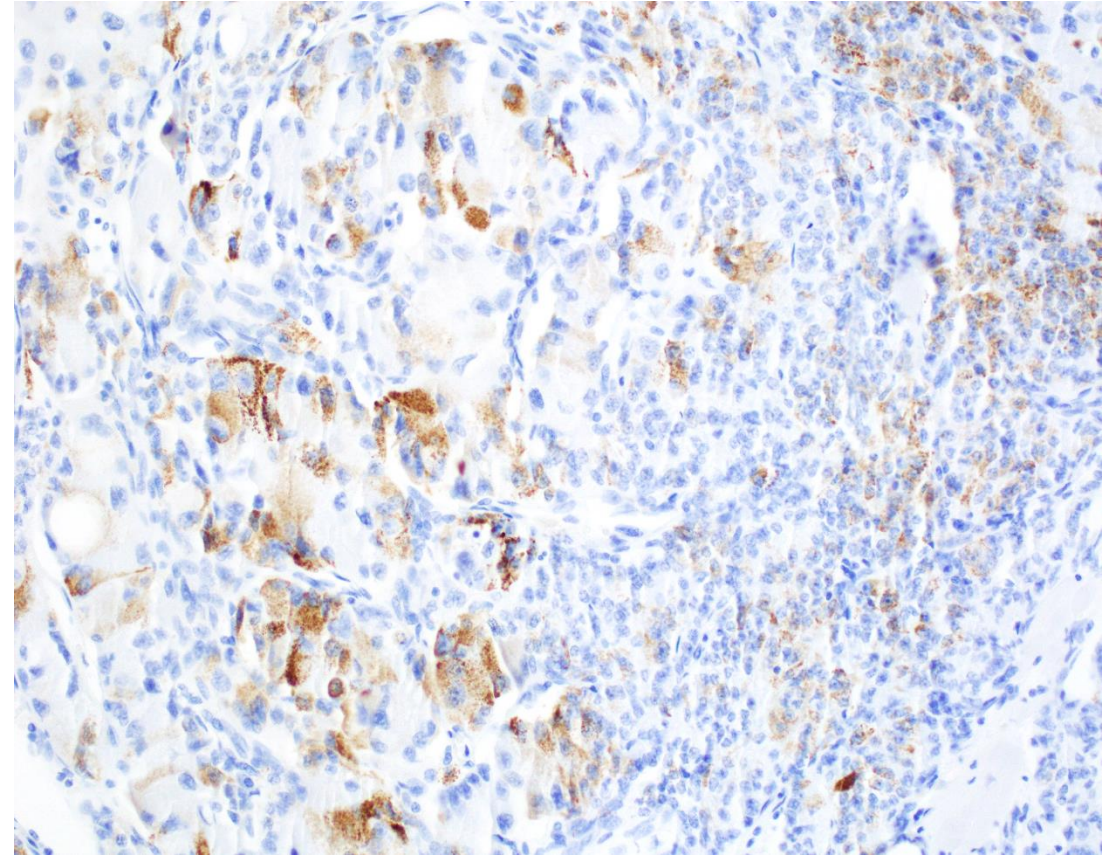
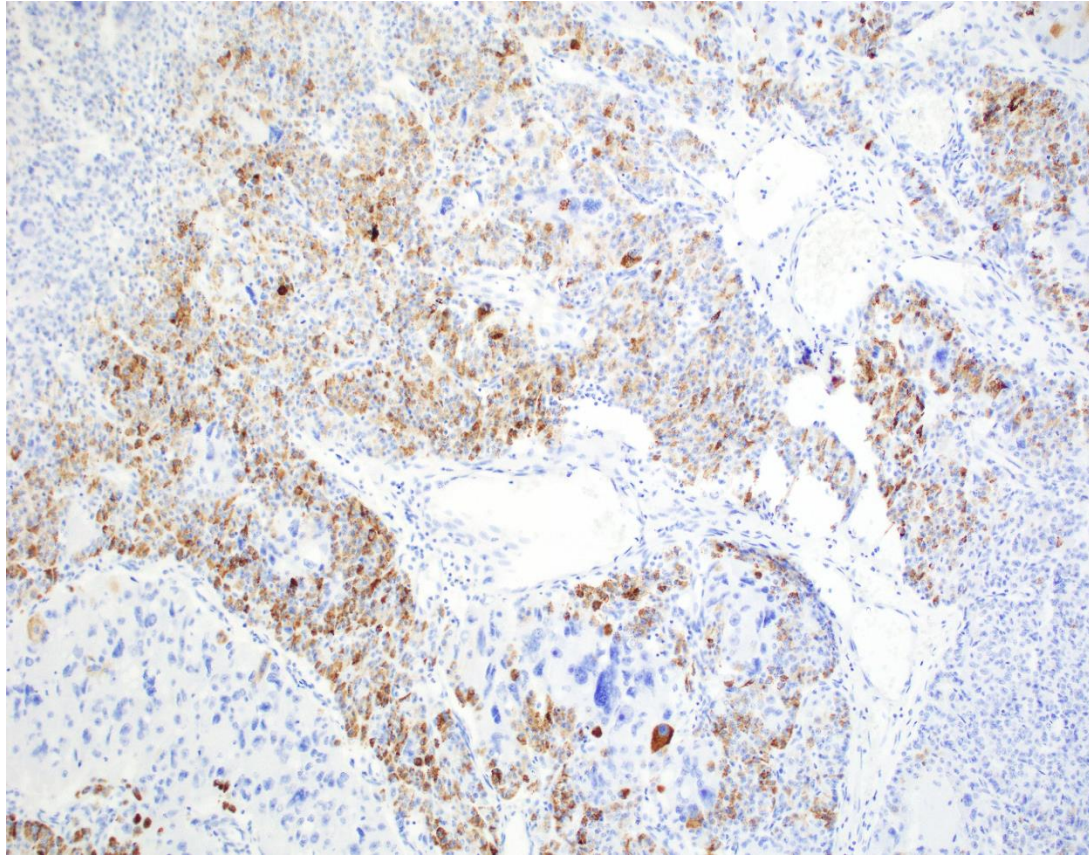
# Arginase + in larger cells, negative in smaller neuroendocrine cells



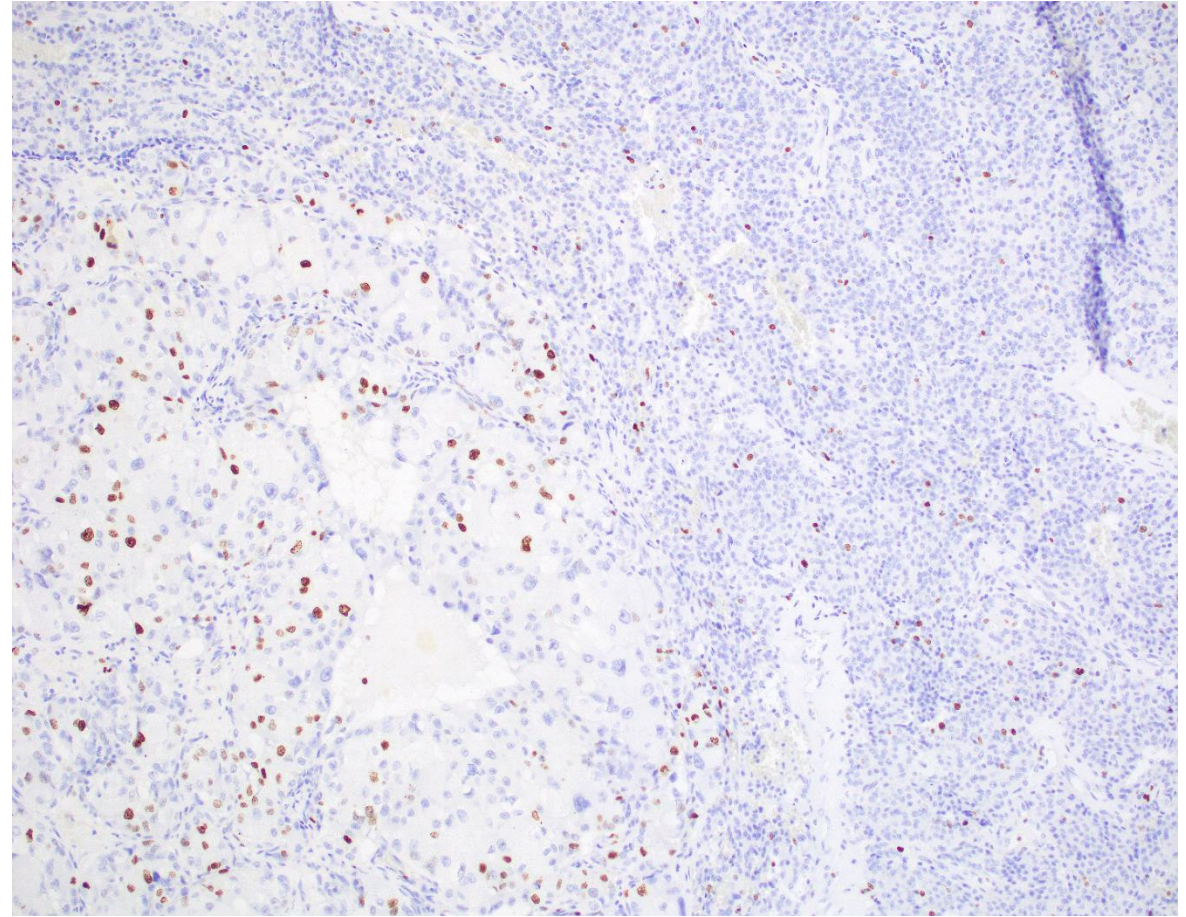
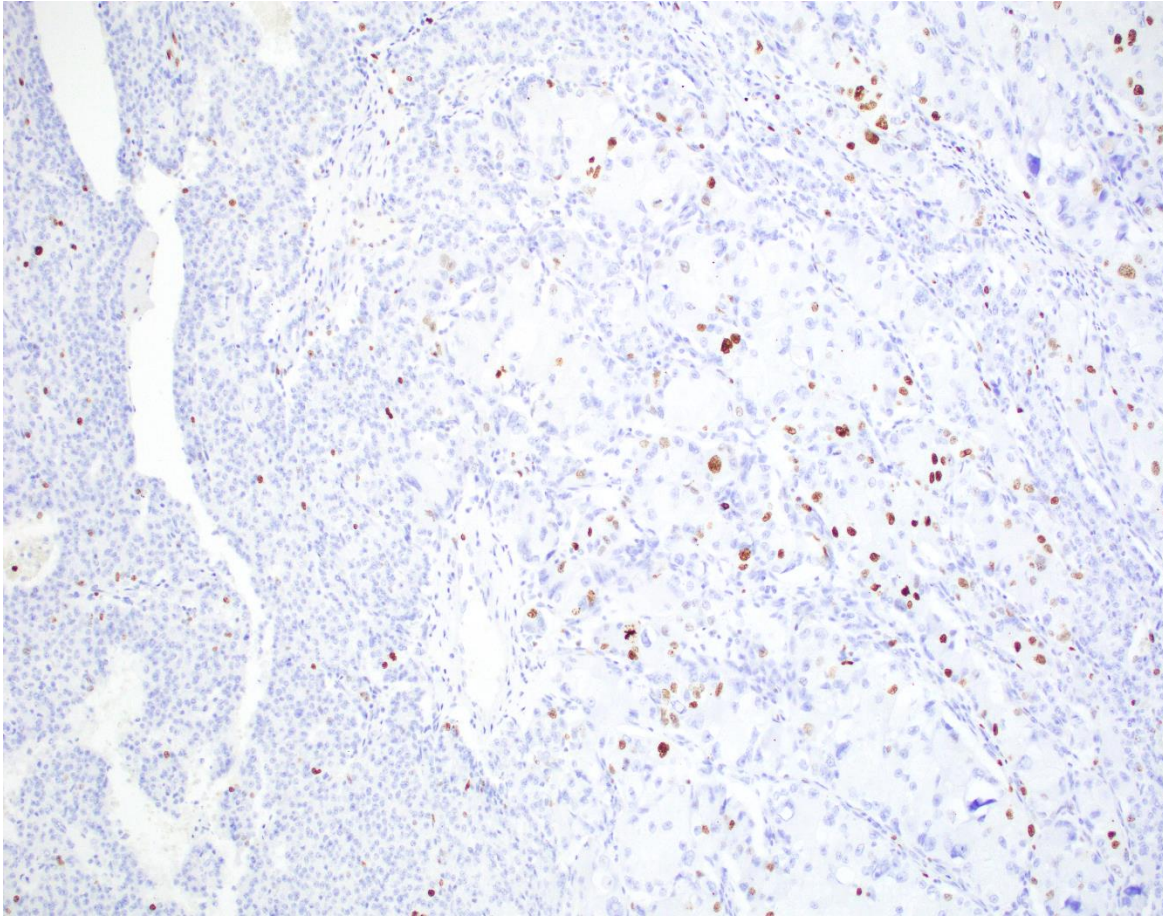
Arg-1 has high sensitivity and specificity for HCC but gastric, prostate and gallbladder cancer may stain.

Yan et al. [Am J Surg Pathol. 2010 Aug; 34\(8\): 1147–54](#)

HepPar more even distribution – non-specific stain in several non-hepatocytic tumors



Ki67 index was 27%



Ki67 index was higher in areas with large eosinophilic cells which were counted as hot spots

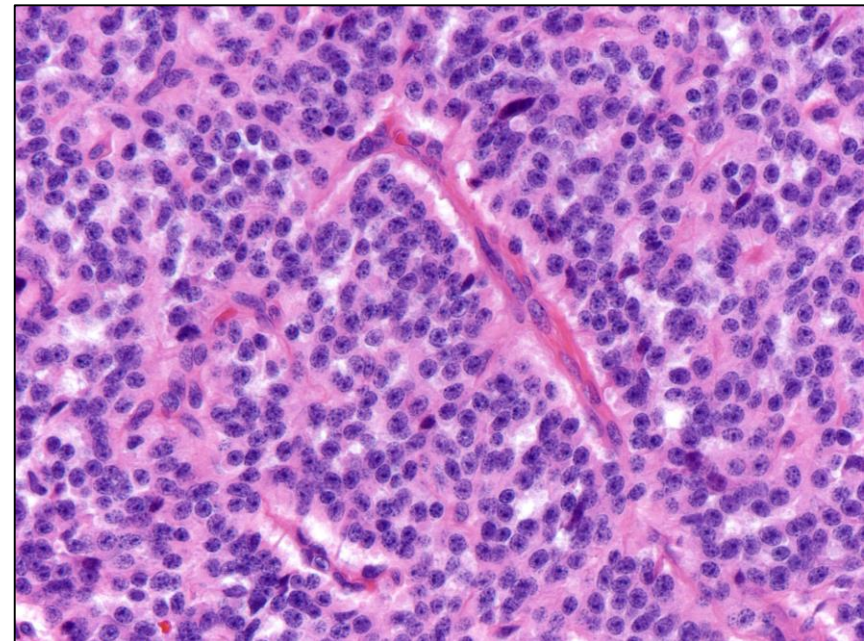
# Case # 2 - Diagnosis

Well-differentiated neuroendocrine tumor,  
grade 3 of 3 (2017 WHO guidelines)

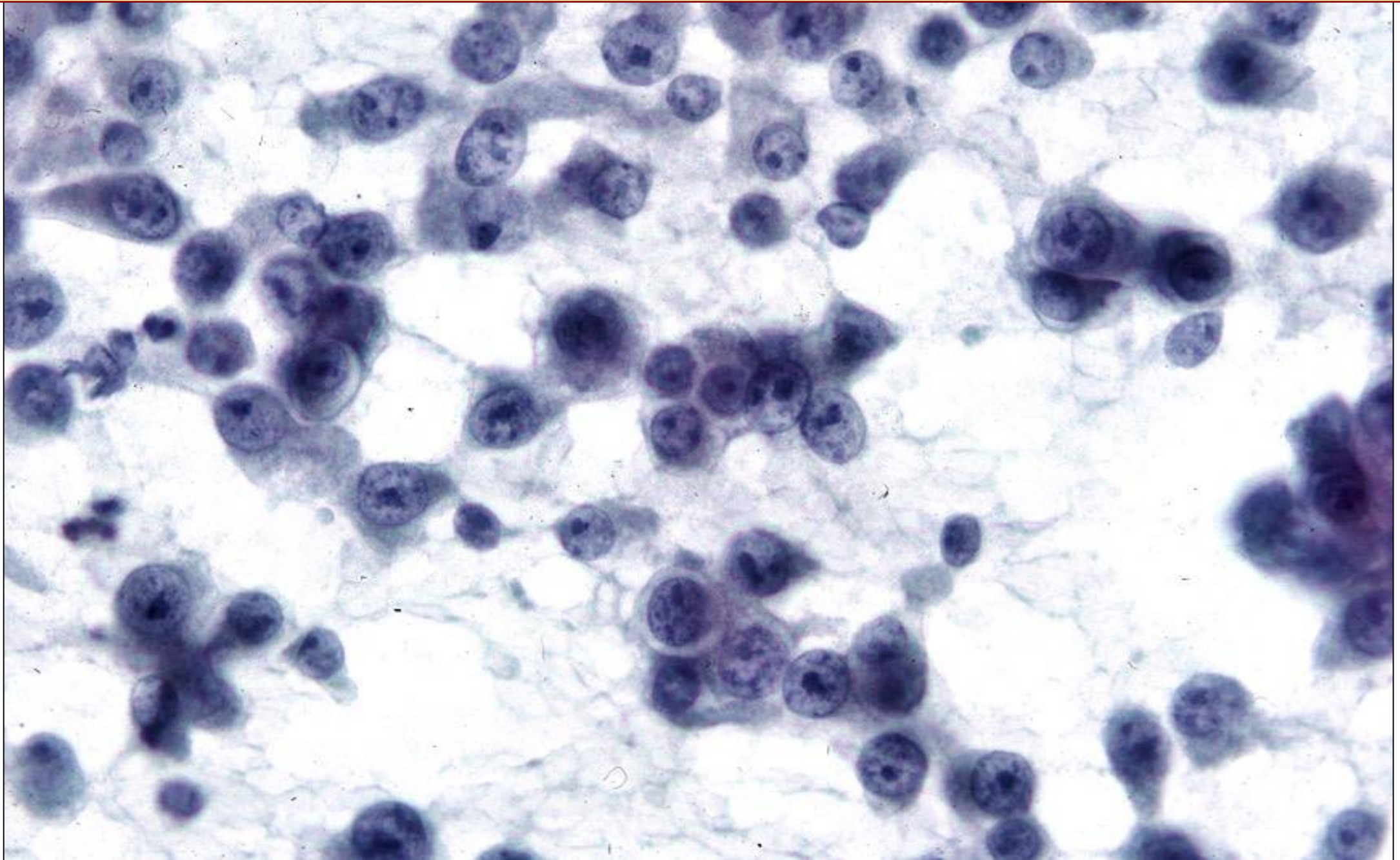
- With “hepatoid” features



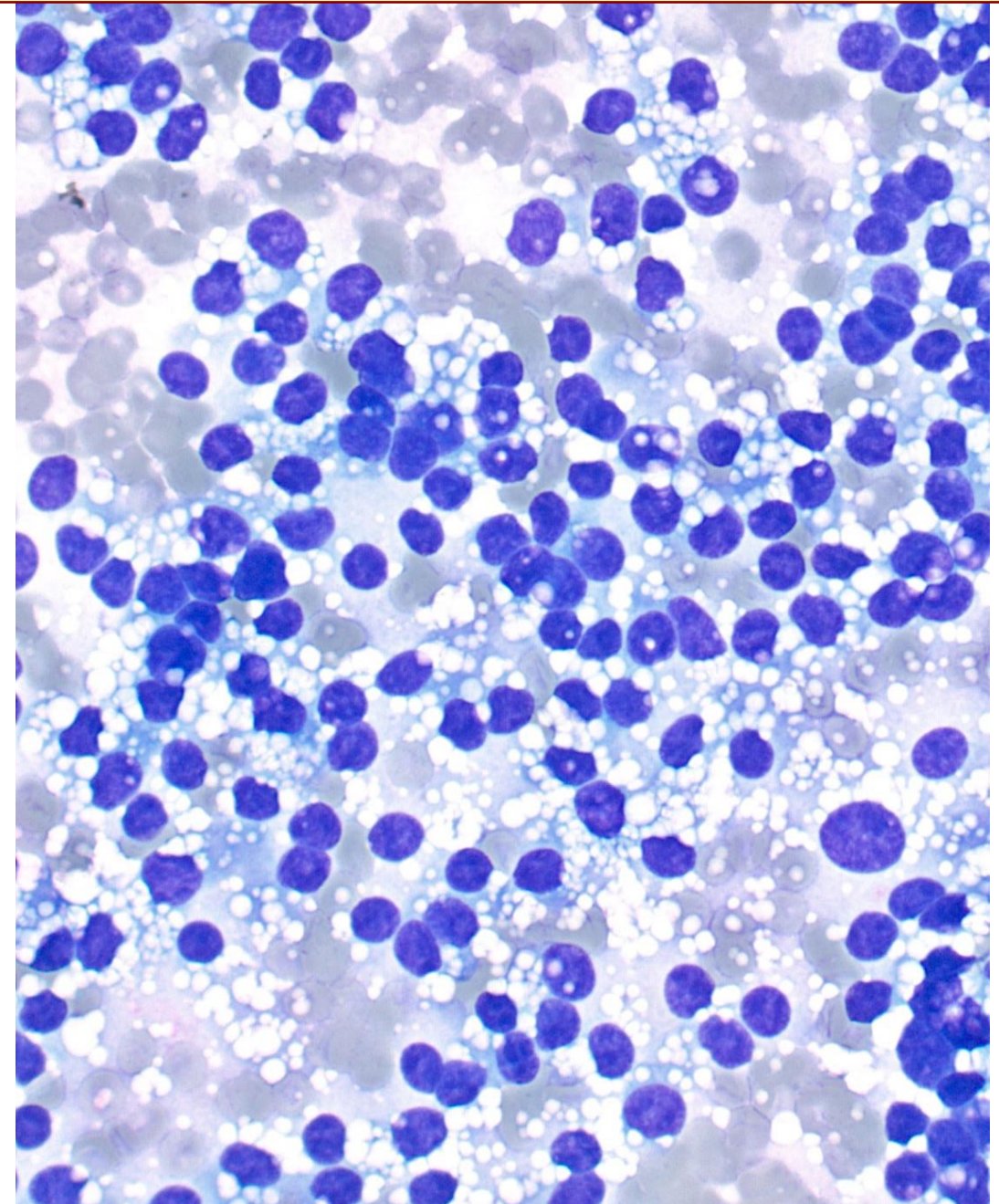
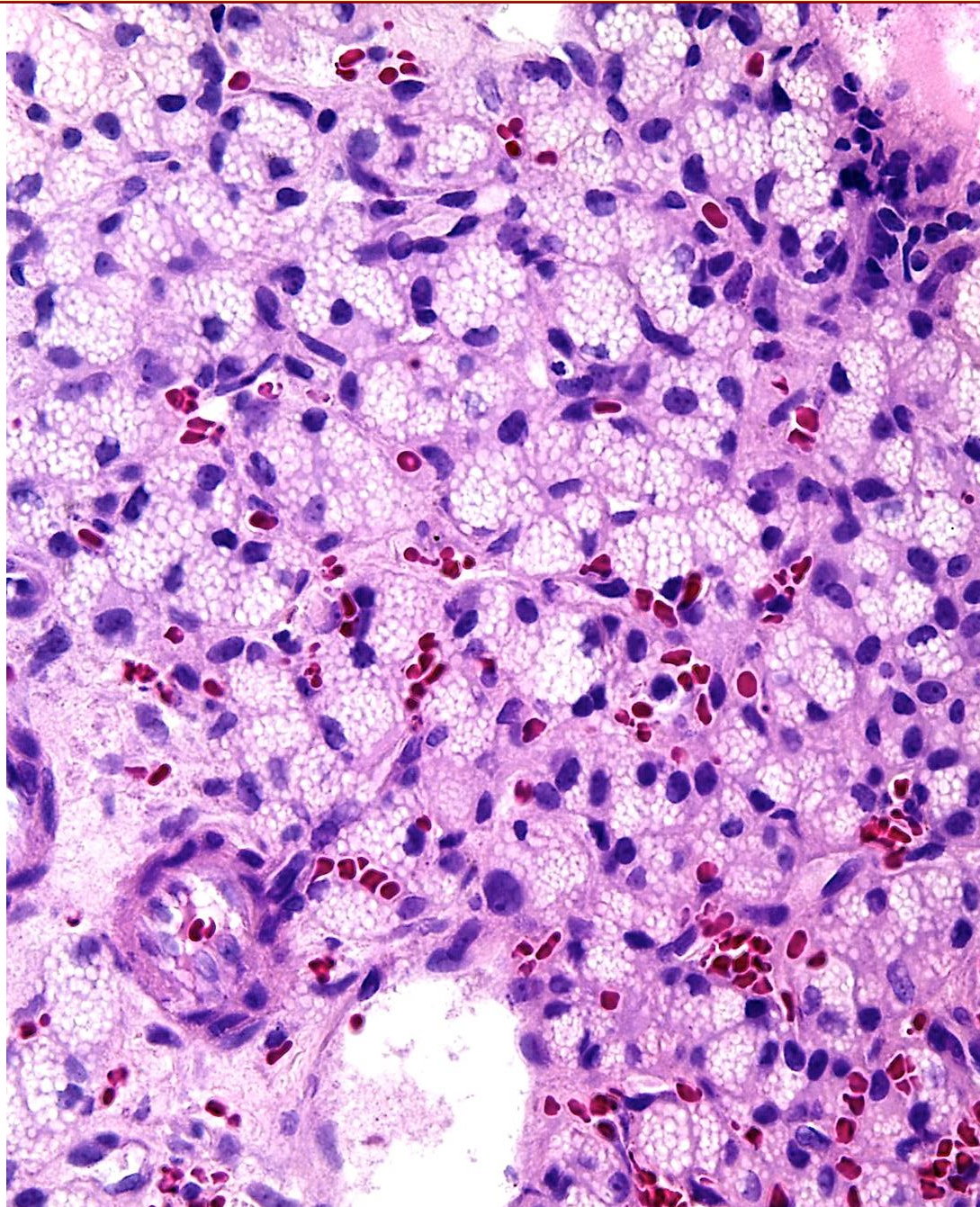
# Morphologic Repertoire of Well-Differentiated PanNETs



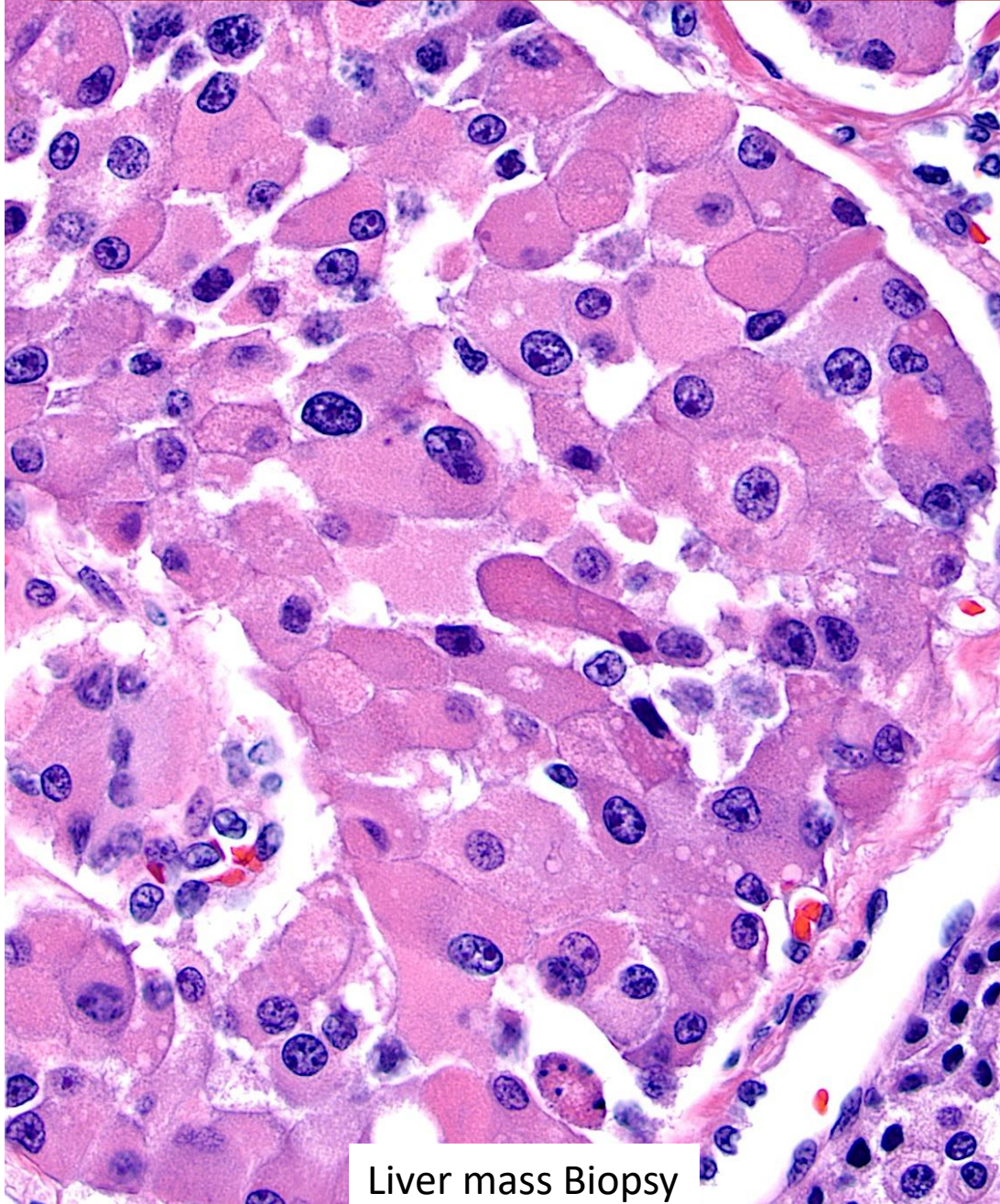
**PanNETs: Nucleoli may be prominent on cytology – misdiagnosed as carcinoma**



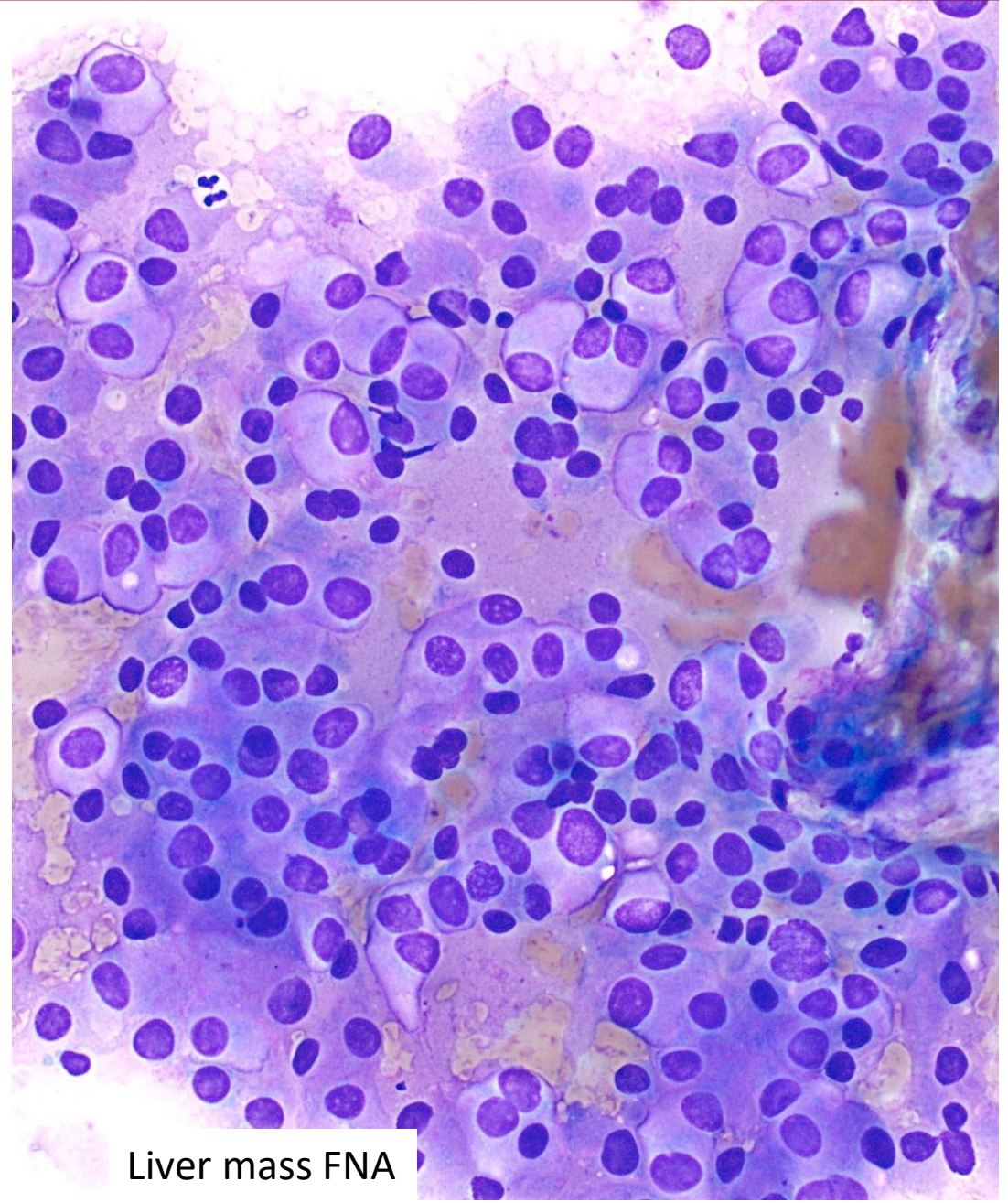
# Lipid-rich PanNETs: Cytoplasmic droplets present on both histology and cytology



# Oncocytic PanNETs: More aggressive, larger, often grade 2

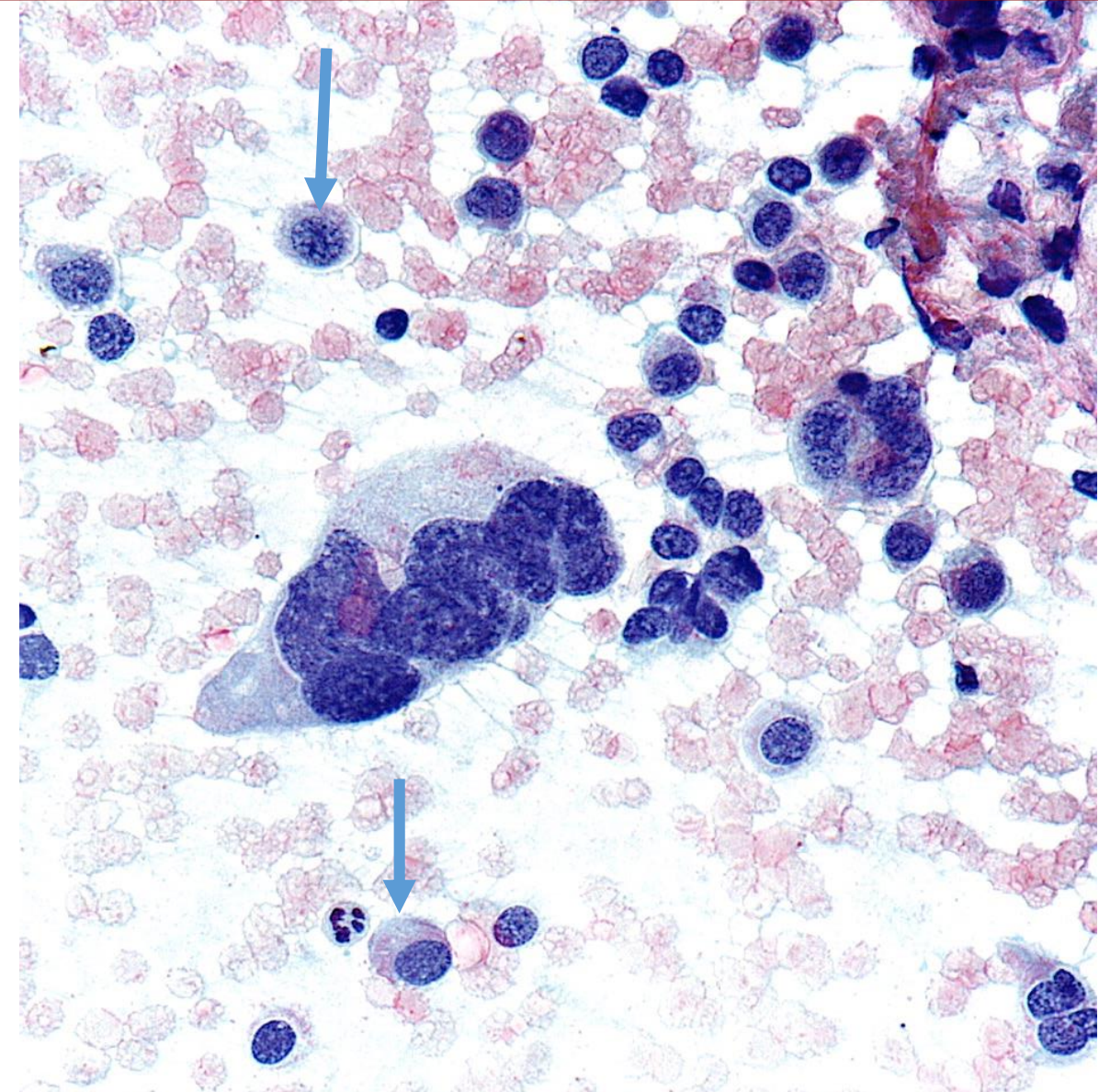
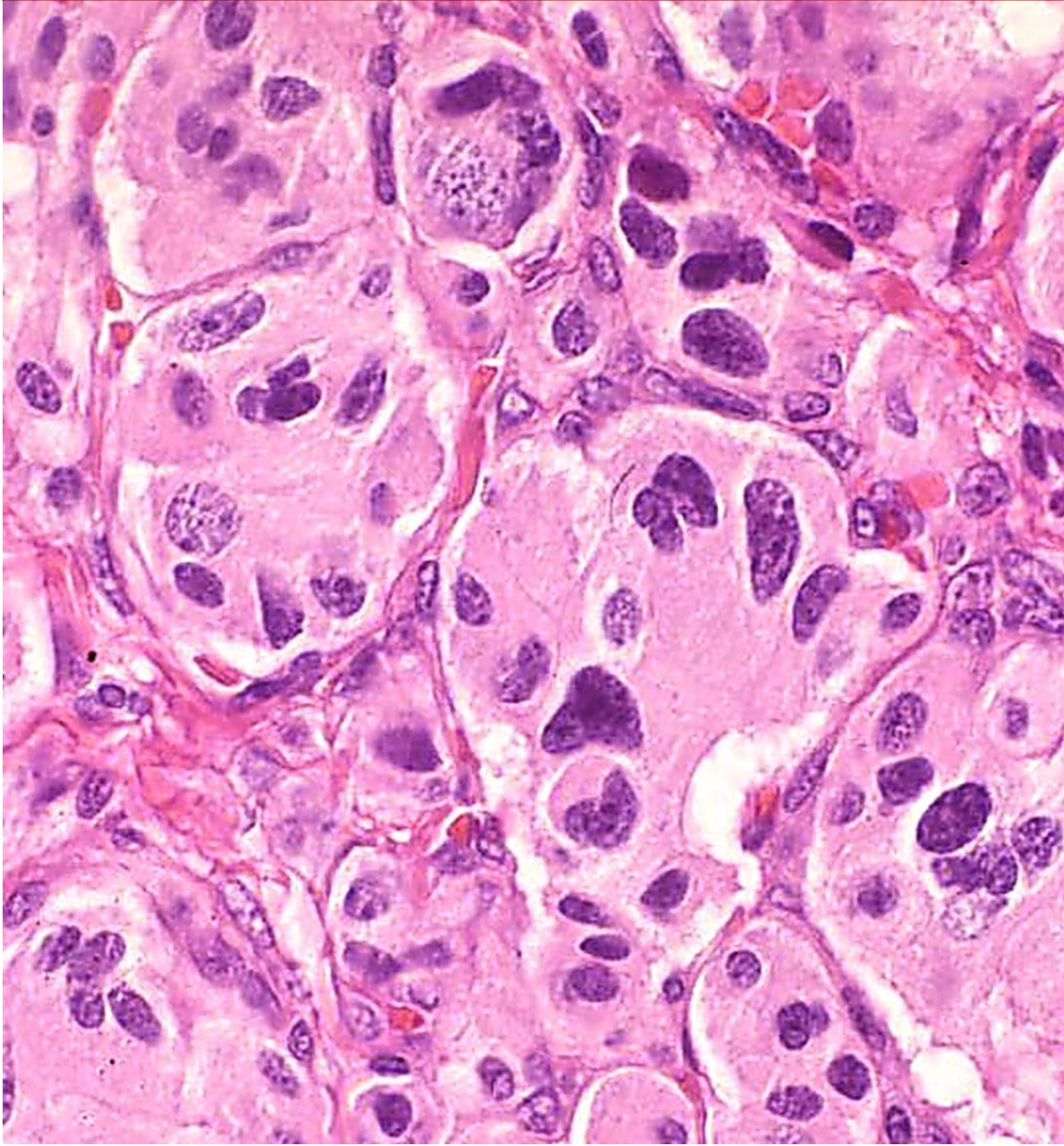


Liver mass Biopsy



Liver mass FNA

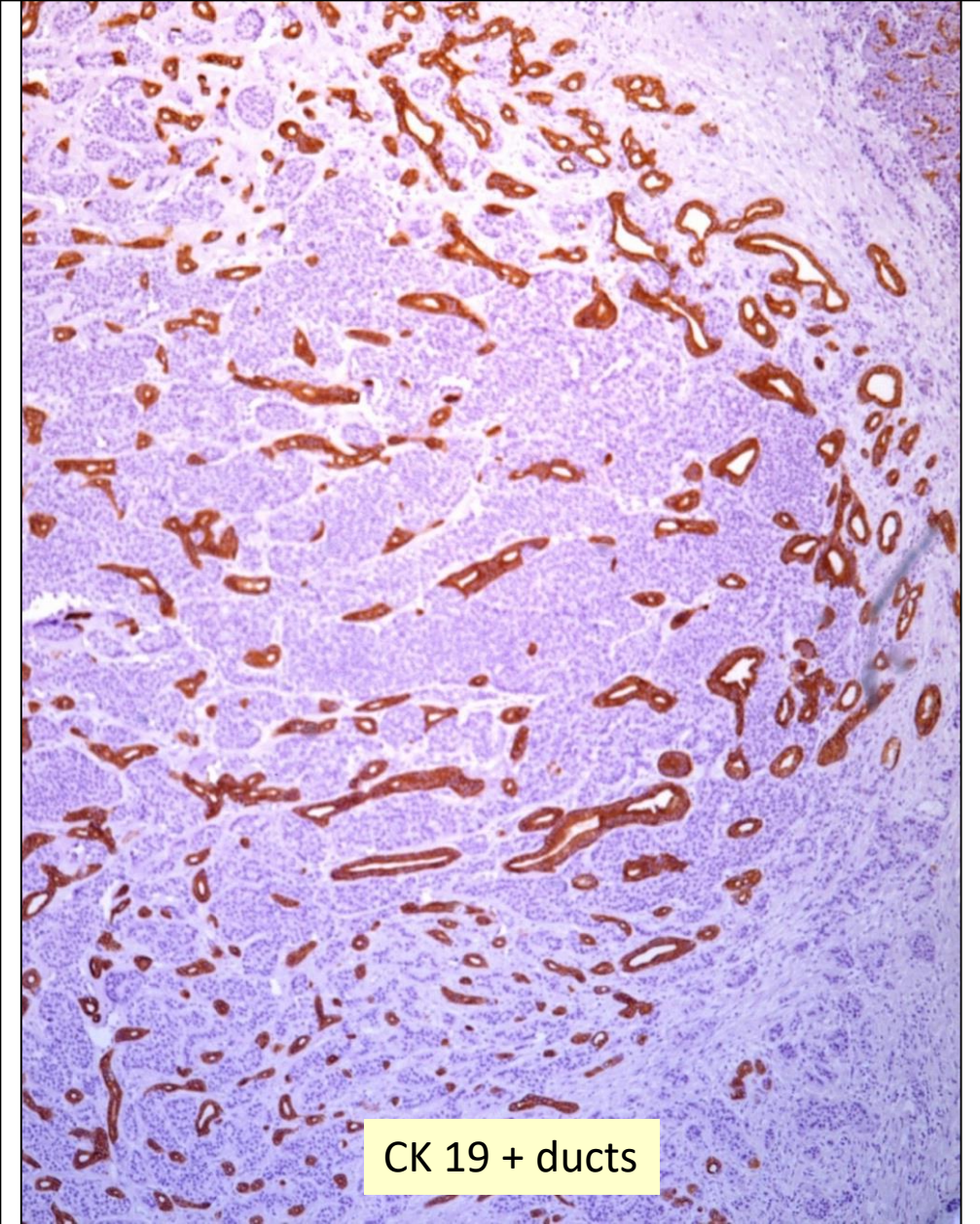
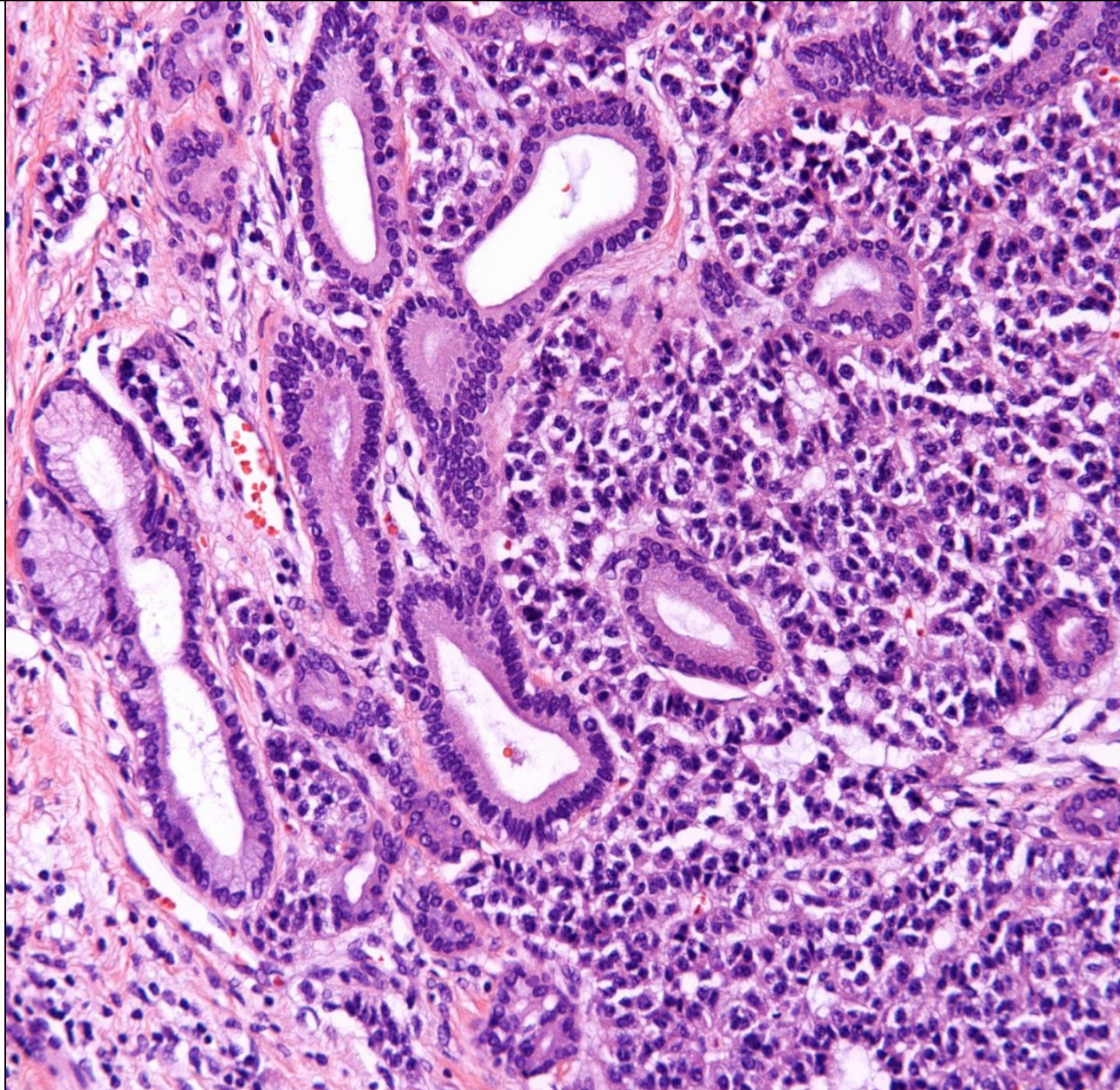
# Pleomorphic Variant of PanNET: Has no clinical significance



Note single plasmacytoid cells and cells with focal degenerative "endocrine" atypia

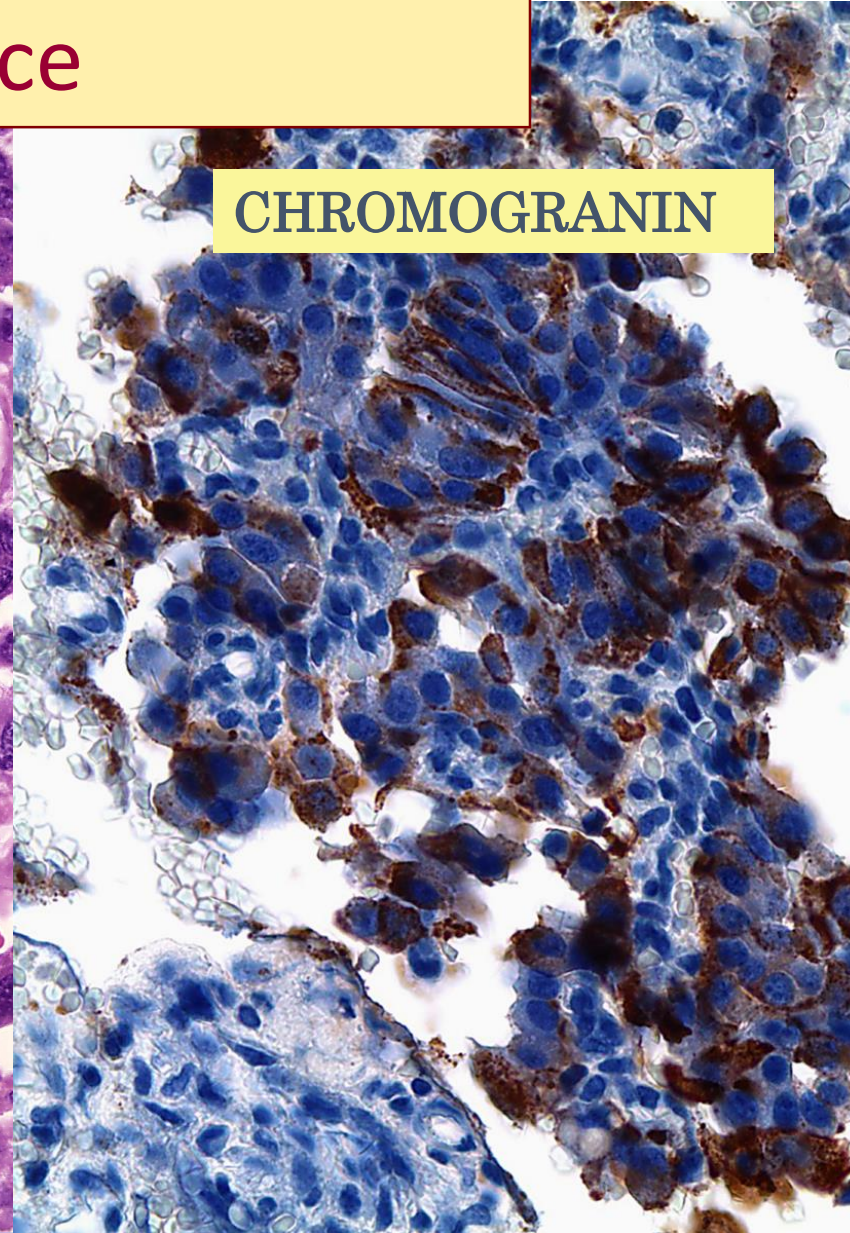
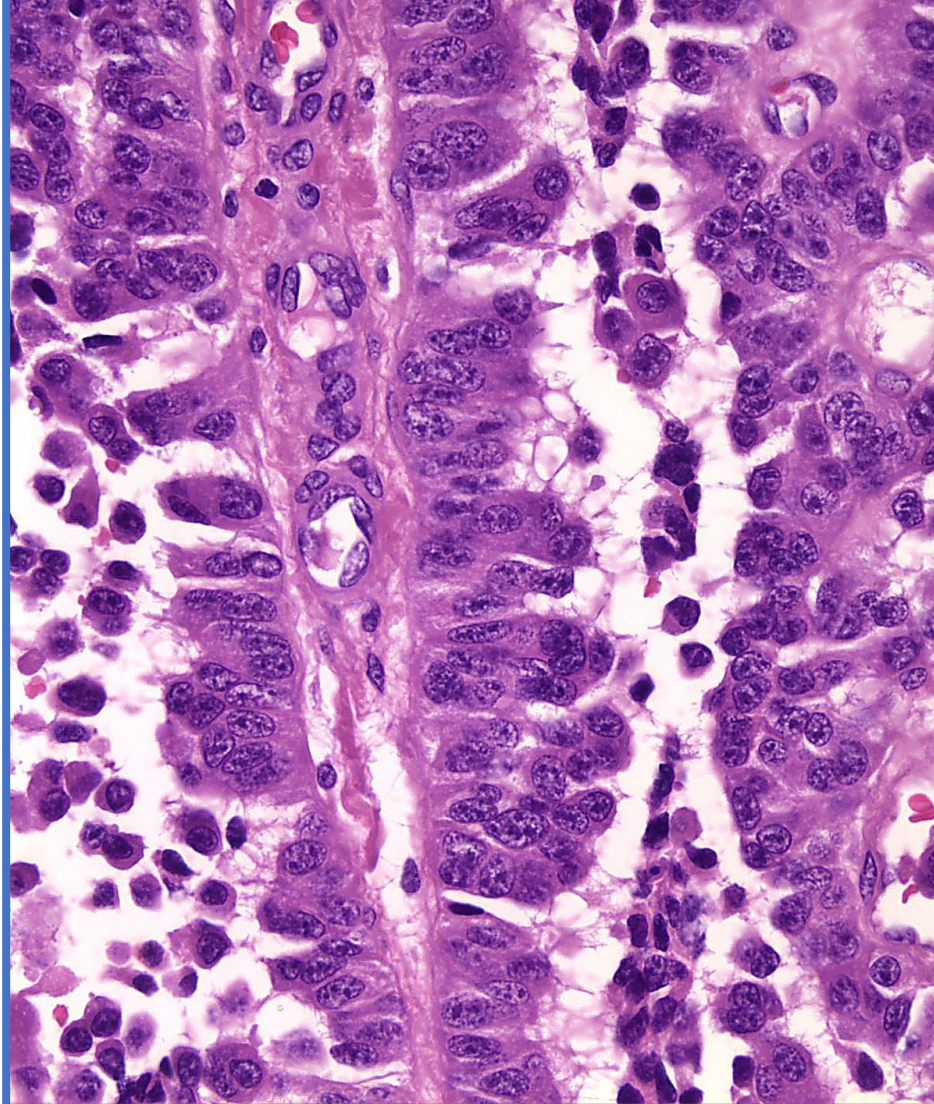
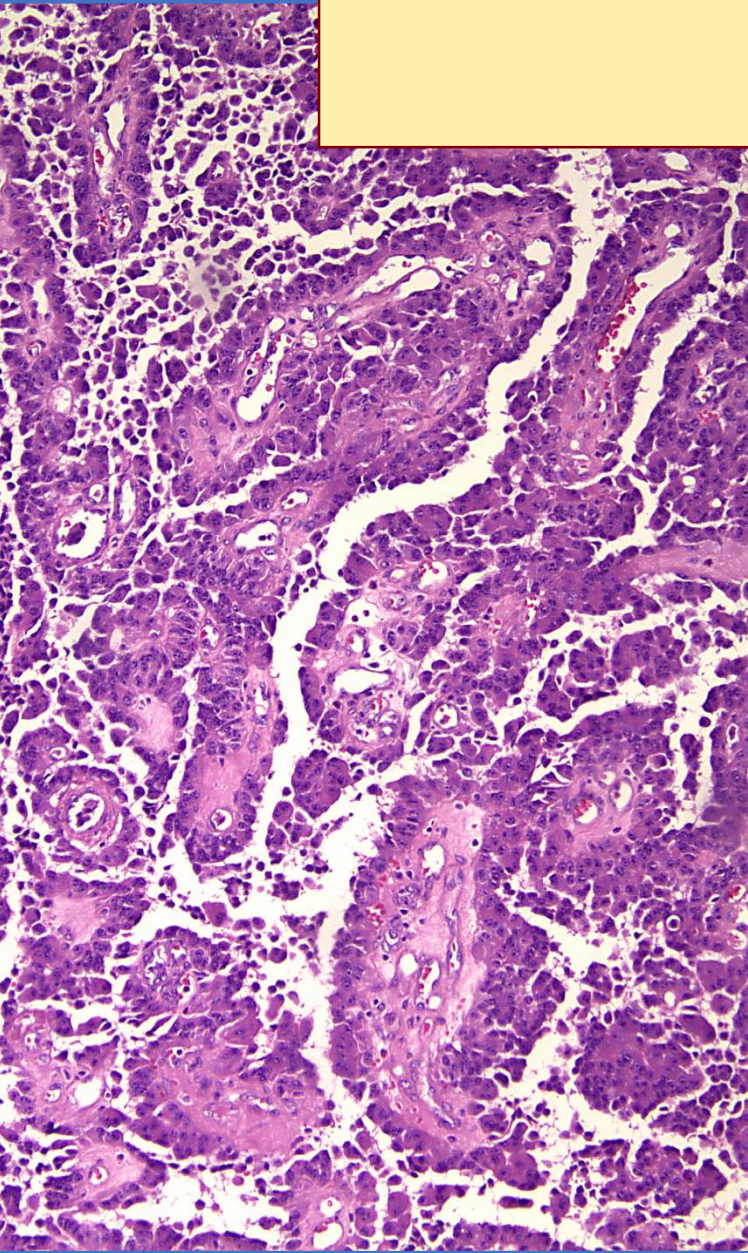
## Benign ducts can be prominent in PanNETs

“Ductulo-insular NET, no clinical significance, NOT adenocarcinoma



CK 19 + ducts

# PanNET with Prominent Papillary Growth: Has no clinical significance



**NEW (2017) WHO CLASSIFICATION OF  
NEUROENDOCRINE  
NEOPLASMS**



# Tumor vs Carcinoma further clarified (but still problematic)

## What do you call a metastatic NE neoplasm in the liver?

Table 6.01 2017 WHO classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)

Classification/grade	Ki-67 proliferation index <sup>a</sup>	Mitotic index <sup>a</sup>
<b>Well-differentiated PanNENs: pancreatic neuroendocrine tumours (PanNETs)</b>		
G1 PanNET	< 3%	< 2
G2 PanNET	3–20%	2–20
G3 PanNET	> 20%	> 20
<b>Poorly differentiated PanNENs: pancreatic neuroendocrine carcinomas (PanNECs)</b>		
PanNEC (G3)	> 20%	> 20
Small cell type		
Large cell type		
<b>Mixed neuroendocrine–non-neuroendocrine neoplasm</b>		

## Ki67 indices between 2 and 2.99 is now G1 (not G2)

**Table 6.01** 2017 WHO classification and grading of pancreatic neuroendocrine neoplasms (PanNENs)

Classification/grade	Ki-67 proliferation index <sup>a</sup>	Mitotic index <sup>a</sup>
<b>Well-differentiated PanNENs: pancreatic neuroendocrine tumours (PanNETs)</b>		
G1 PanNET	< 3%	< 2
G2 PanNET	3–20%	2–20
G3 PanNET	<b>~ 15% of PanNETs fall into this 2-3% range</b> <b>(Reid, M. et al. Modern Pathol, 2014)</b>	
<b>Poorly differentiated</b>		
PanNEC (G3)	> 20%	> 20
Small cell type		
Large cell type		
<b>Mixed neuroendocrine–non-neuroendocrine neoplasm</b>		

## NENs with a Ki67 > 20% can be “tumor” OR “carcinoma”

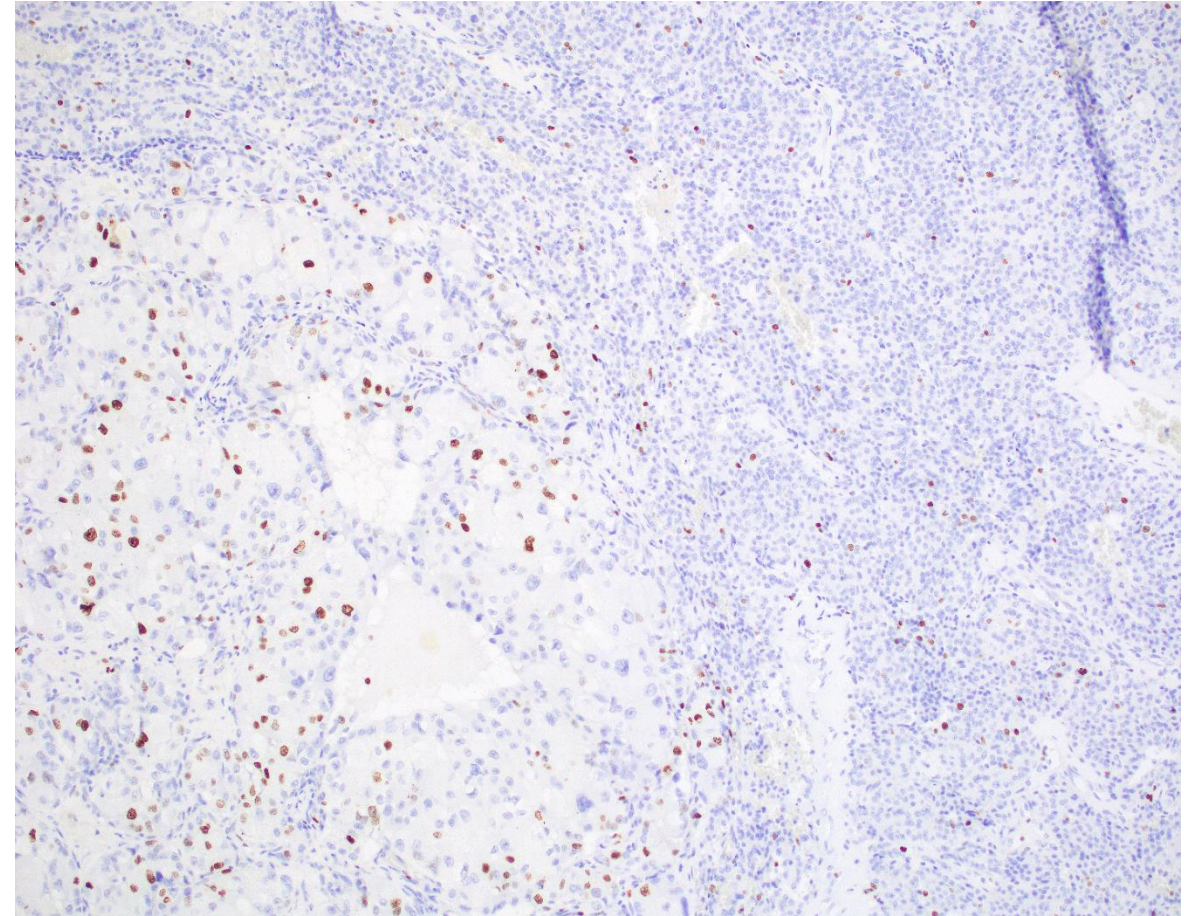
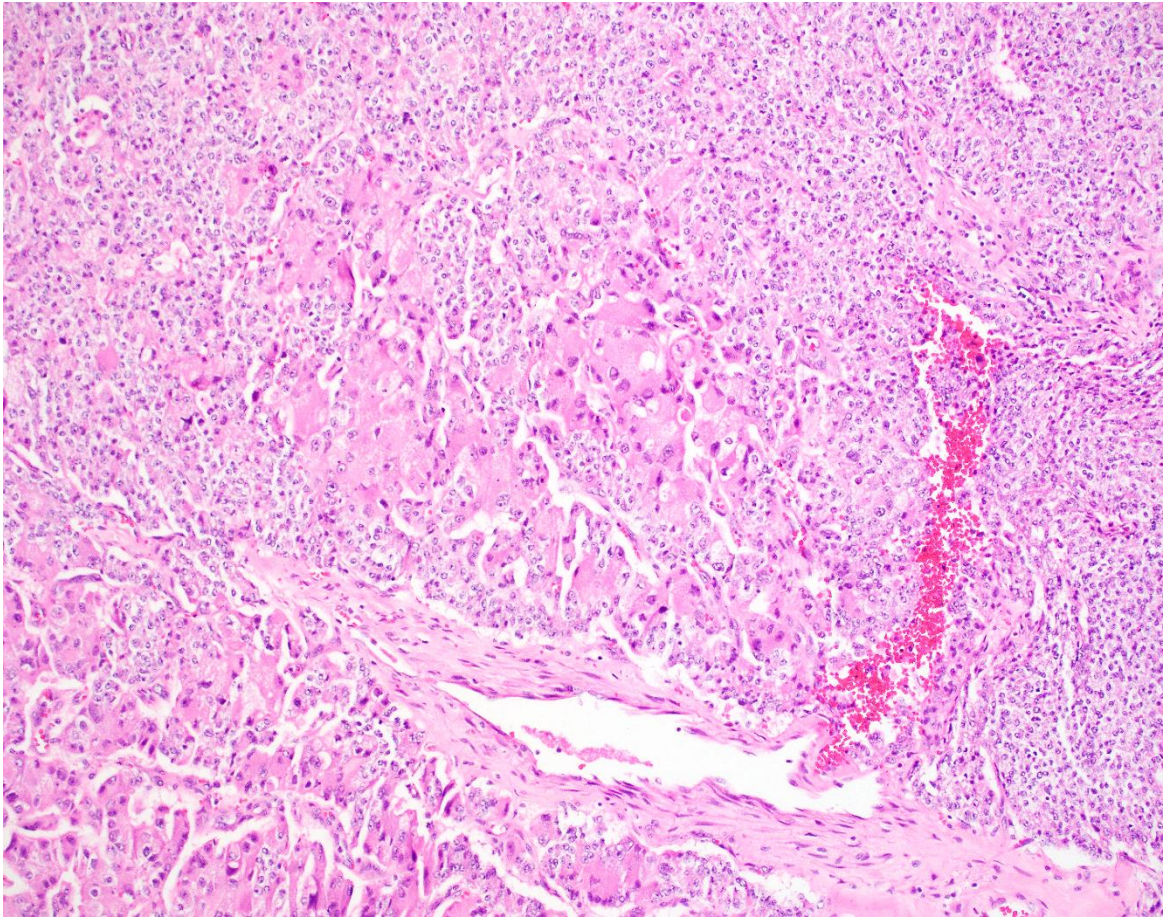
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PanNEC (G3)	> 20%	> 20
Small cell type		
Large cell type		
<b>Mixed neuroendocrine–non-neuroendocrine neoplasm</b>		

## Case # 2

Ki67 index was 27% = Grade 3, but well differentiated

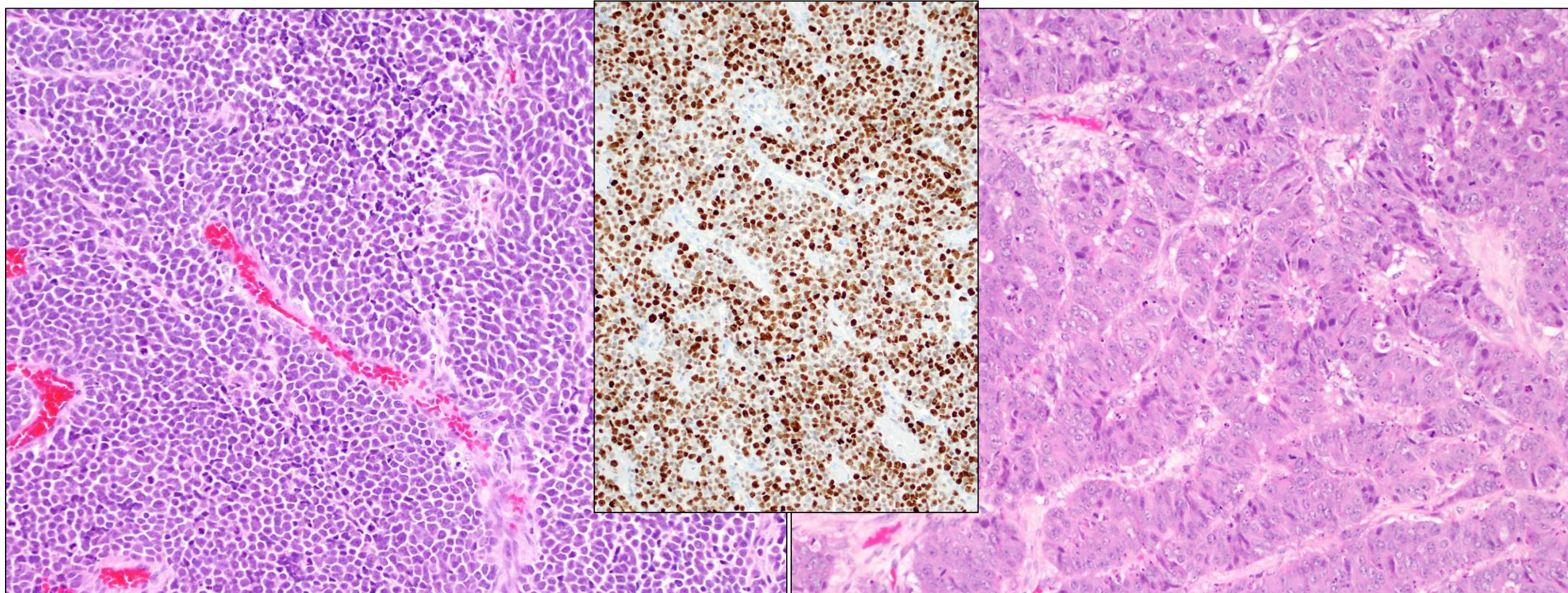
*(per 2017 WHO)*



# Poorly Differentiated Neuroendocrine carcinoma

Small Cell Type

Large Cell Type



The average Ki67 index: > 75%

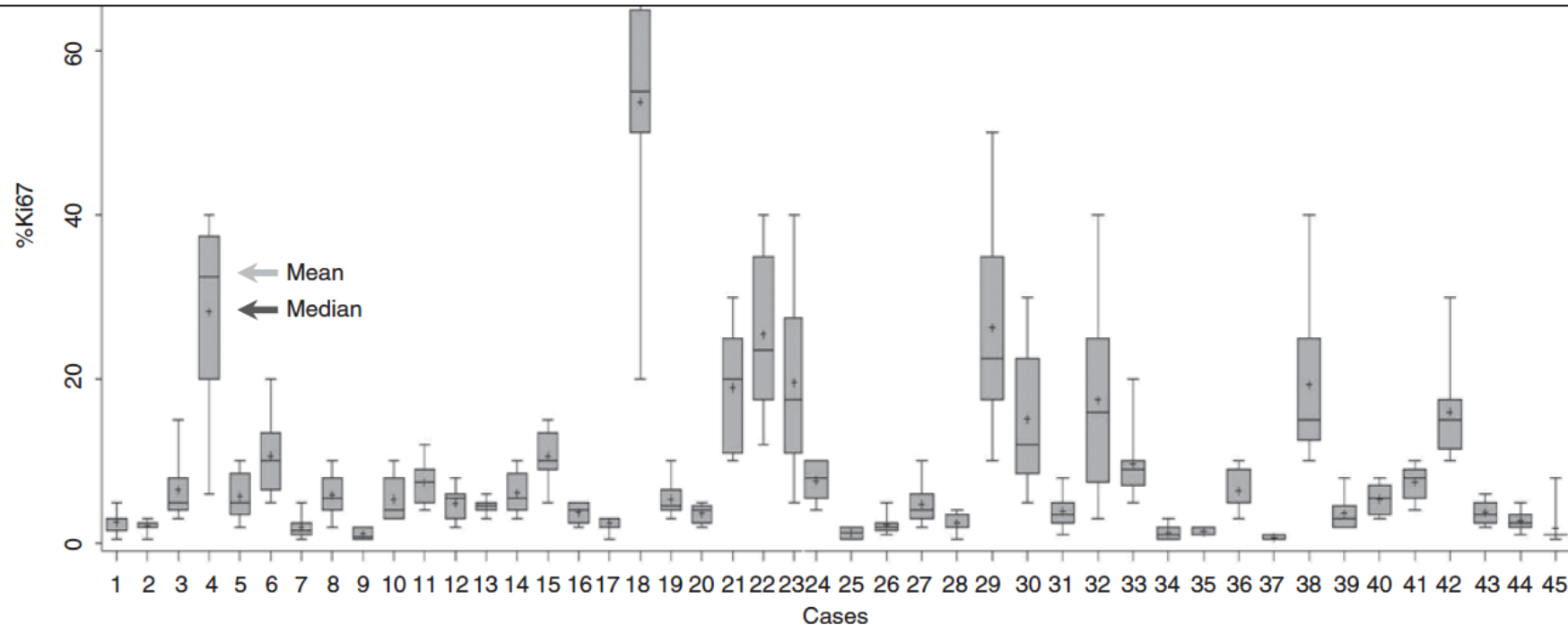
Calculation Ki67 Index is therefore  
important in NENs

How to count?

# Objective Quantification of the Ki67 Proliferative Index in Neuroendocrine Tumors of the Gastroenteropancreatic System

## *A Comparison of Digital Image Analysis With Manual Methods*

*Laura H. Tang, MD, PhD,\* Mithat Gonen, PhD,† Cyrus Hedvat, MD, PhD,\*  
Irvin M. Modlin, MD, PhD,‡ and David S. Klimstra, MD\**



**Results of “eye-balling” of Ki67 index by 18 observers in 45 cases illustrates striking inter-observer variability (as well as grade variability)**

# Problems with Ki67: How to count?

1. Counting # of cells at **microscope in real time**
2. Have the **machine** count it (automated)

**Machine also counts:**

*Hemosiderin*

*Lymphocytes*

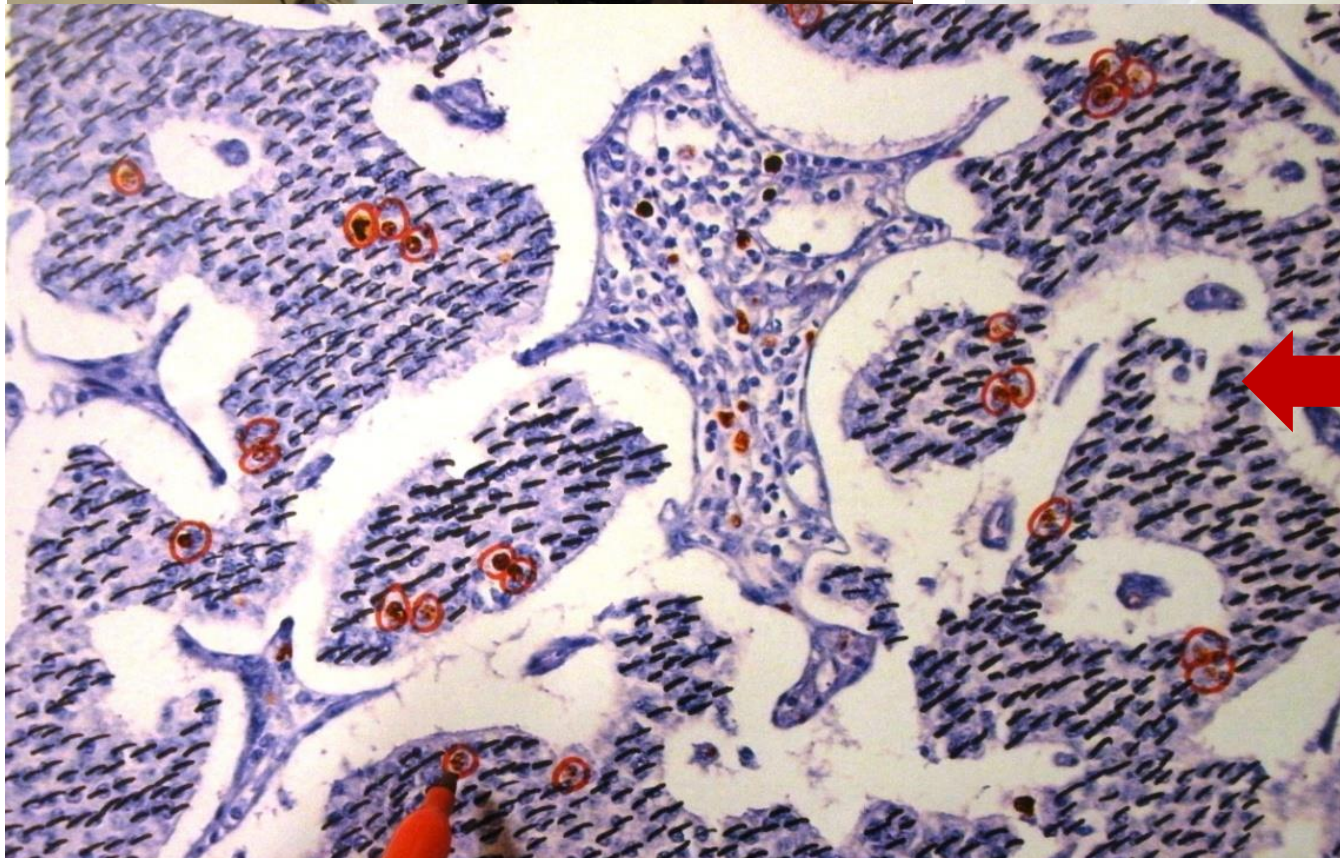
*Endothelial cells*



*Reid et al. Mod Path; 28(5): 686-694, 2015*



# Manual count on camera-captured-printed image



# Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies

Michelle D Reid<sup>1,12</sup>, Pelin Bagci<sup>2,12</sup>, Nobuyuki Ohike<sup>3</sup>, Burcu Saka<sup>4</sup>, Ipek Erbarut Seven<sup>2</sup>, Nevra Dursun<sup>5</sup>, Serdar Balci<sup>6</sup>, Hasan Gucer<sup>7</sup>, Kee-Taek Jang<sup>8</sup>, Takuma Tajiri<sup>9</sup>, Olca Basturk<sup>10</sup>, So Yeon Kong<sup>11</sup>, Michael Goodman<sup>11</sup>, Gizem Akkas<sup>1</sup> and Volkan Adsay<sup>1</sup>

**Table 1** Comparison of the Ki67 index counting methodologies

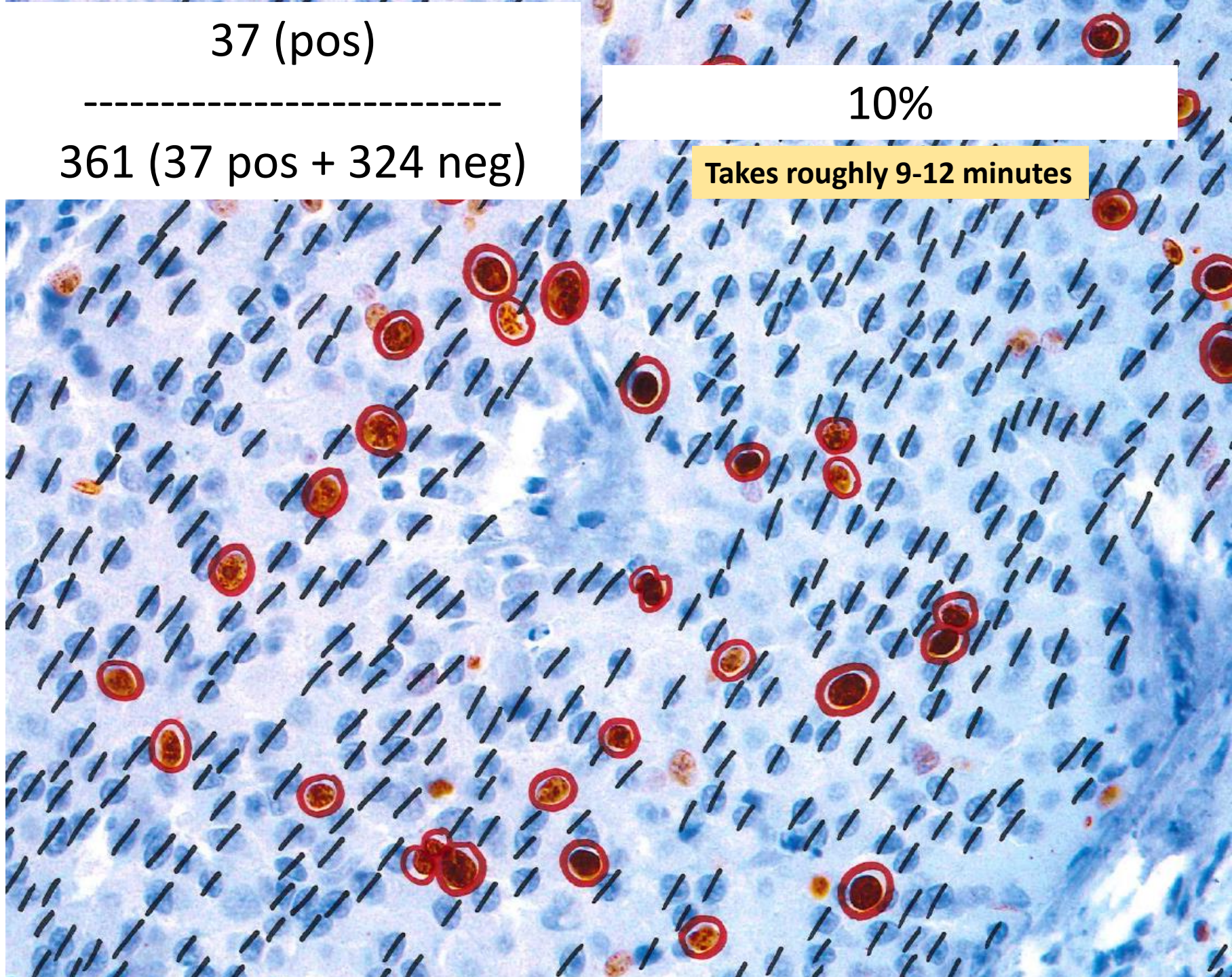
<i>Methodology</i>	<p style="text-align: center;"><b><u>Manual count on camera-captured-printed image</u> is the most applicable approach (practical and accurate) in daily life</b></p>	<i>cost</i>
Eye-balling Eye-counting Manual count on printed image Automated c		

37 (pos)

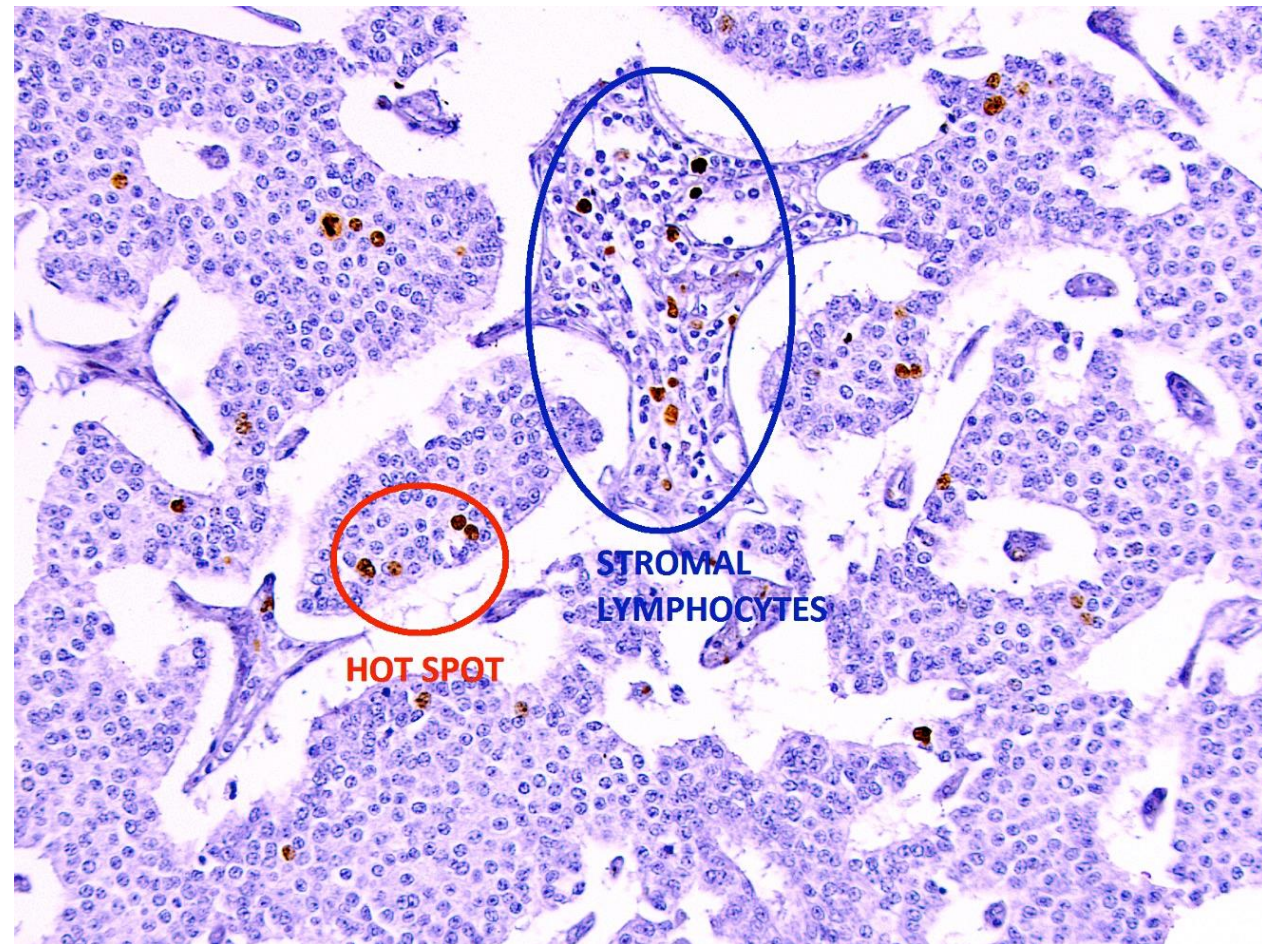
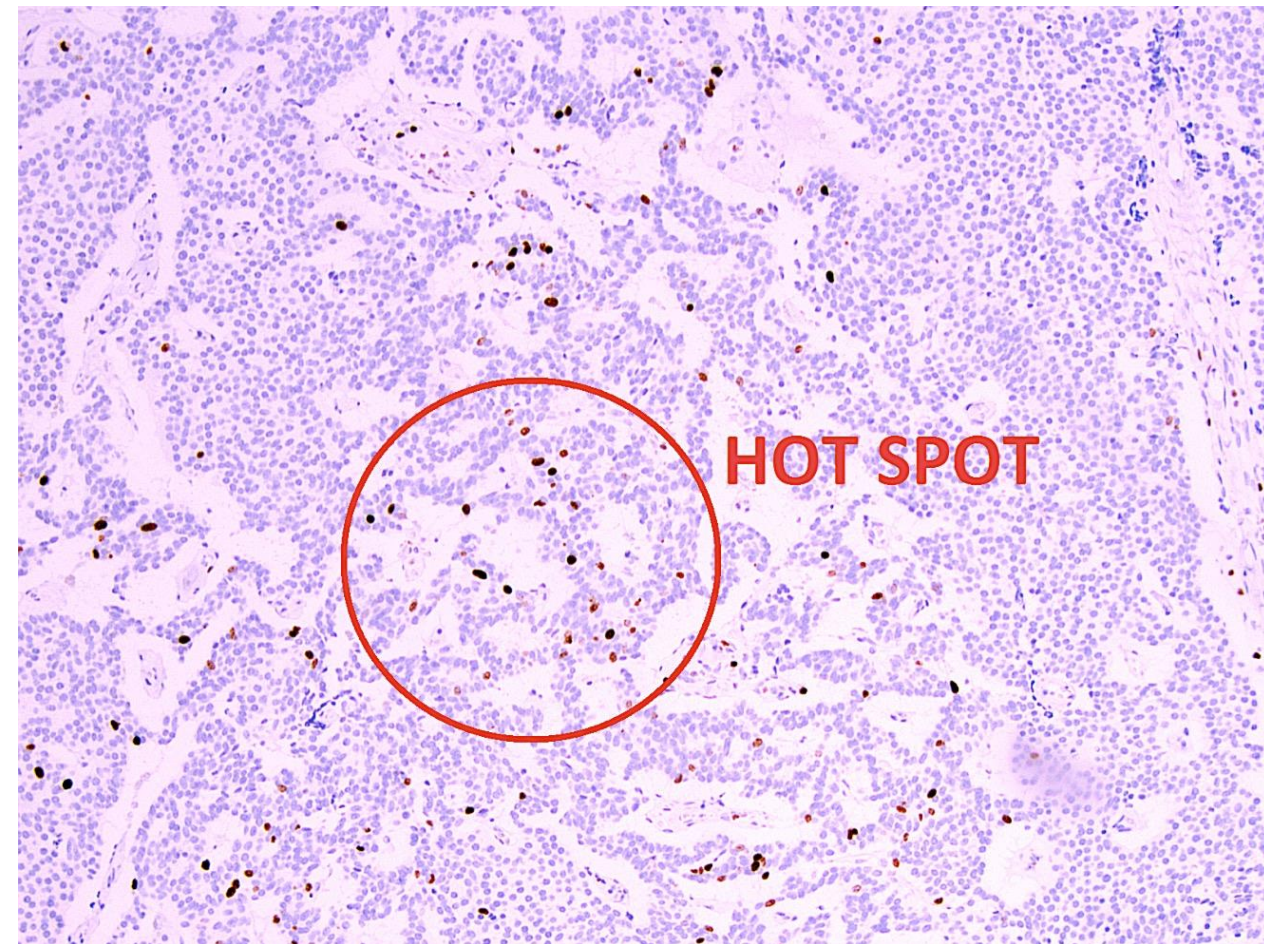
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361 (37 pos + 324 neg)

10%

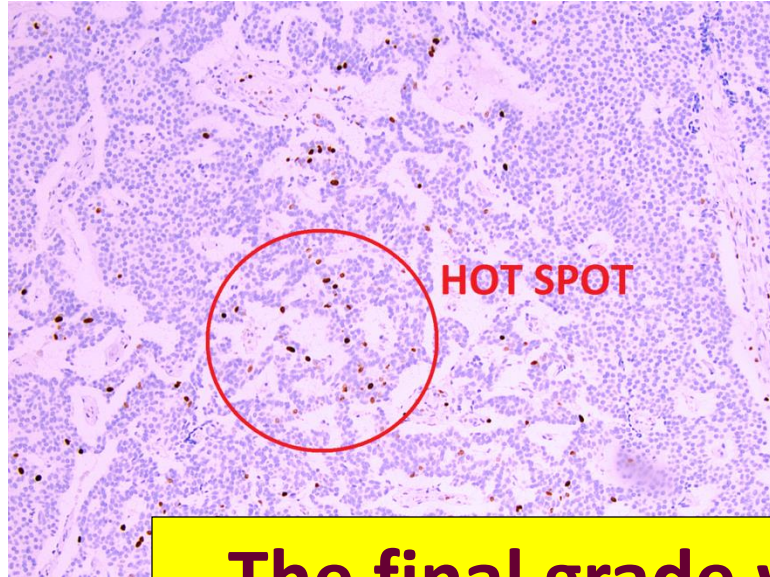
Takes roughly 9-12 minutes



# Defining the hot spot

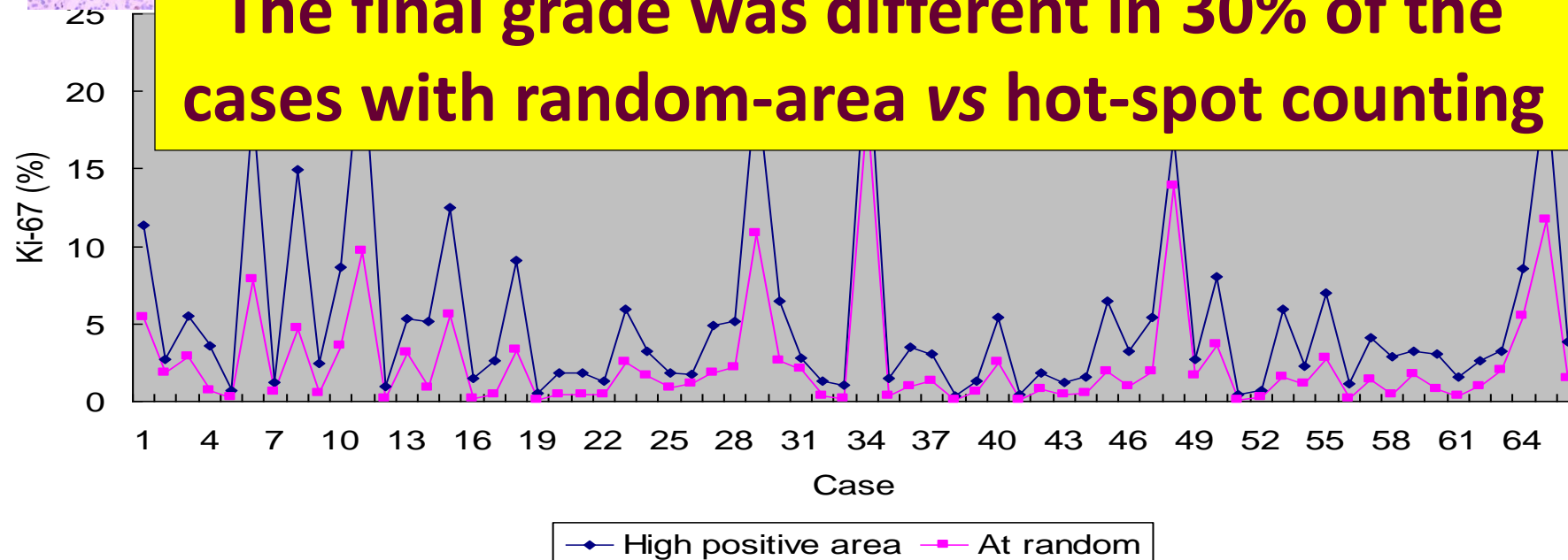


# Intratatumoral Ki-67 heterogeneity

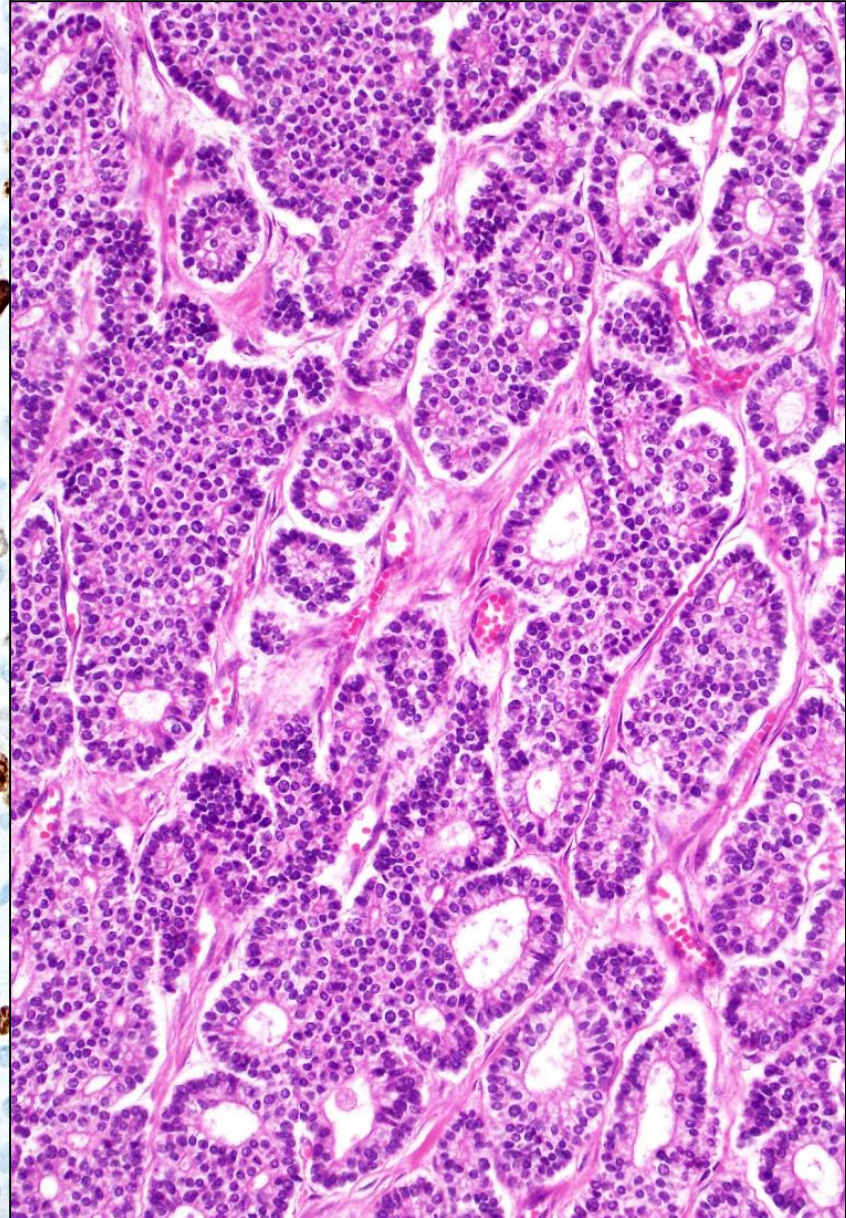
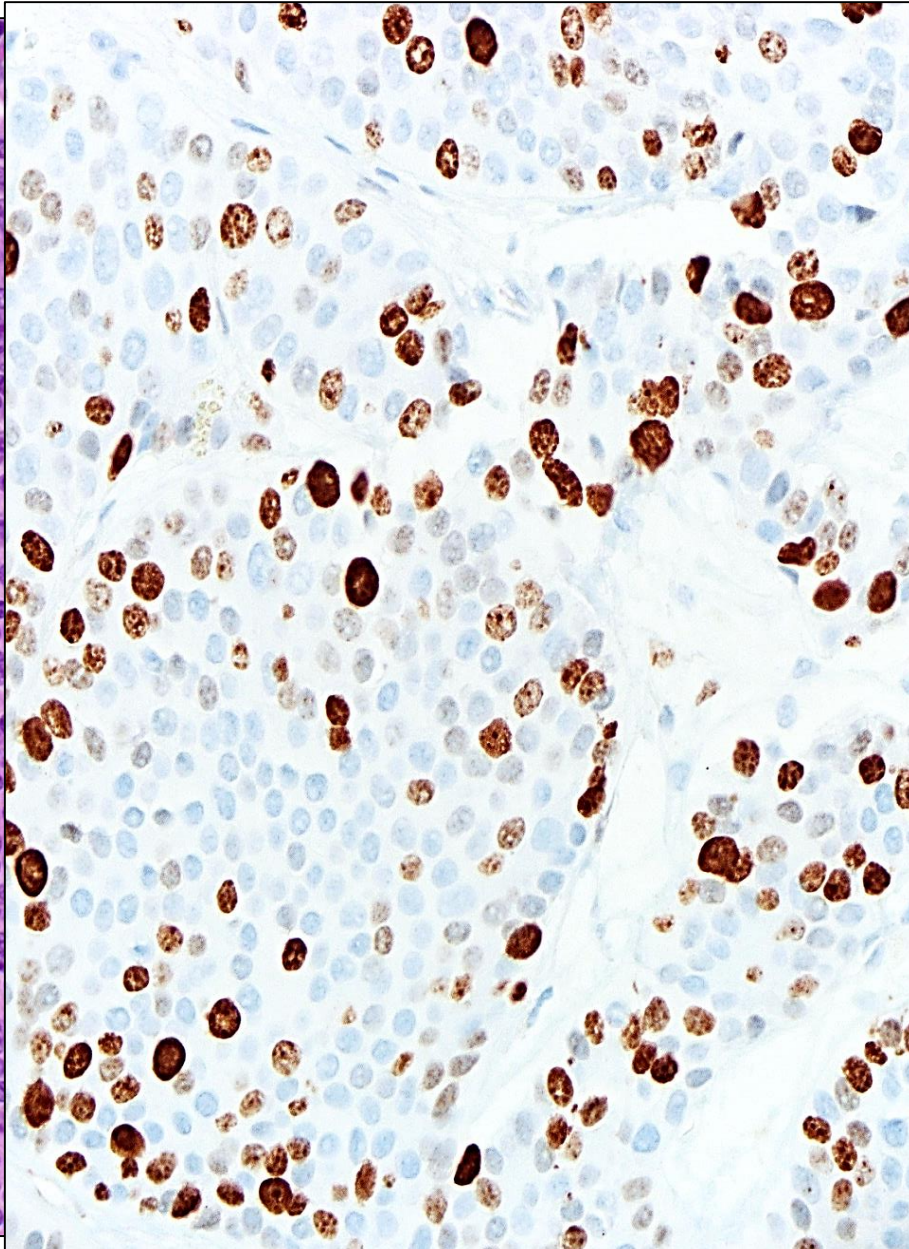
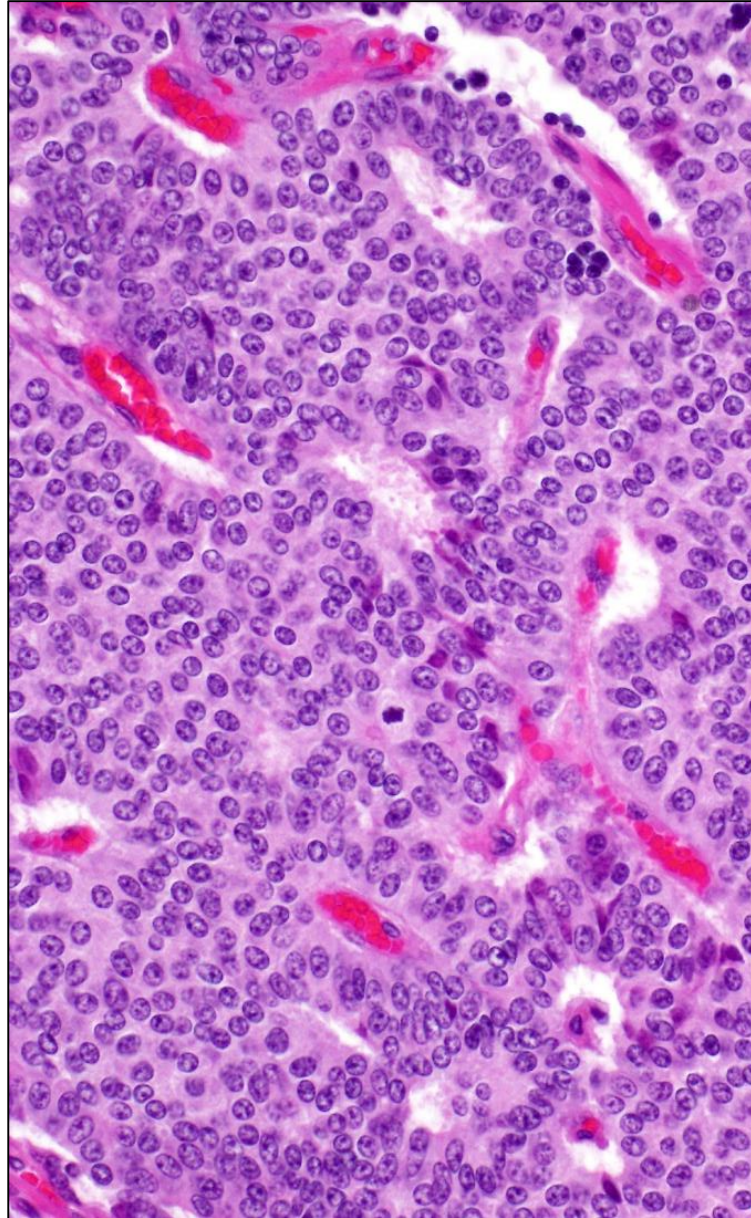


66 cases	K-67-index (%)
Areas	Mean
Highest positive area ( <b>HOT SPOT</b> )	5.3
<b>At random</b>	2.5

**The final grade was different in 30% of the cases with random-area vs hot-spot counting**



# Well differentiated PanNET with Ki67 index >20%



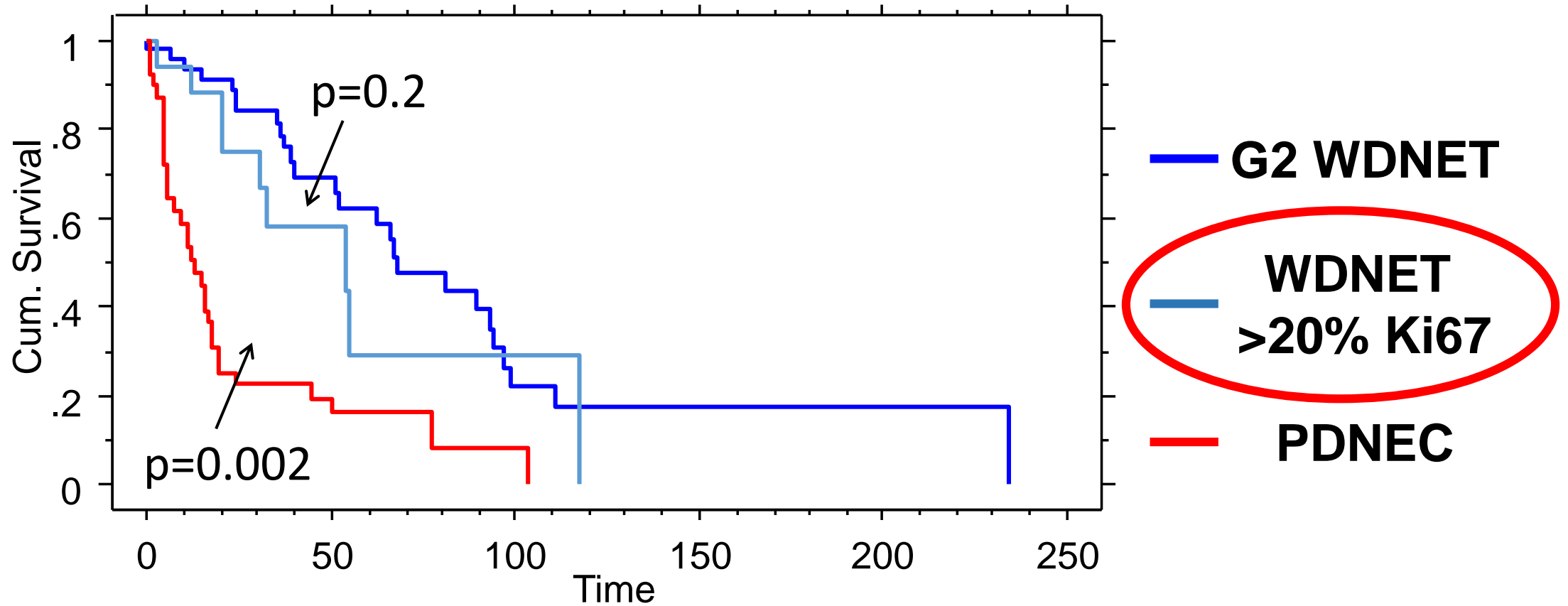
# The High-grade (WHO G3) Pancreatic Neuroendocrine Tumor Category Is Morphologically and Biologically Heterogeneous and Includes Both Well Differentiated and Poorly Differentiated Neoplasms

*Olca Basturk, MD,\* Zhaohai Yang, MD, PhD,† Laura H. Tang, MD, PhD,\*  
Ralph H. Hruban, MD,‡ Volkan Adsay, MD,§ Chad M. McCall, MD,†  
Alyssa M. Krasinskas, MD,§ Kee-Taek Jang, MD,|| Wendy L. Frerking, MD,¶  
Serdar Balci, MD,§ Carlie Sigel, MD,\* and David S. Klimstra, MD, PhD,\**

## **Are G3 ENETS neuroendocrine neoplasms heterogeneous?**

**Fritz-Line Vélayoudom-Céphise<sup>1</sup>, Pierre Duvillard<sup>2</sup>, Lydia Foucan<sup>3</sup>, Julien Hadoux<sup>1</sup>, Cecile N Chougnet<sup>1</sup>, Sophie Leboulleux<sup>1</sup>, David Malka<sup>4</sup>, Joël Guigay<sup>5,8</sup>, Diane Goere<sup>6</sup>, Thierry Debaere<sup>7</sup>, Caroline Caramella<sup>7</sup>, Martin Schlumberger<sup>1</sup>, David Planchard<sup>5,8</sup>, Dominique Elias<sup>6</sup>, Michel Ducreux<sup>4,8</sup>, Jean-Yves Scoazec<sup>2</sup> and Eric Baudin<sup>1</sup>**

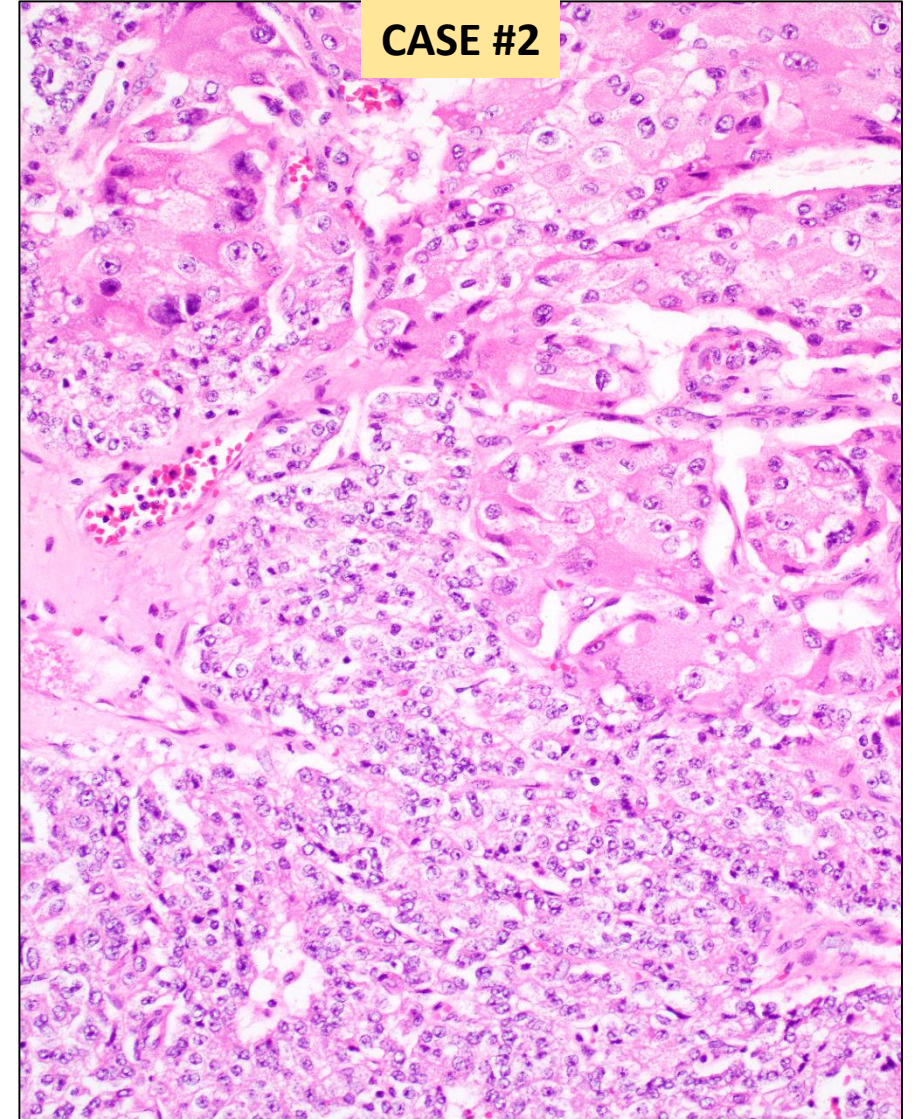
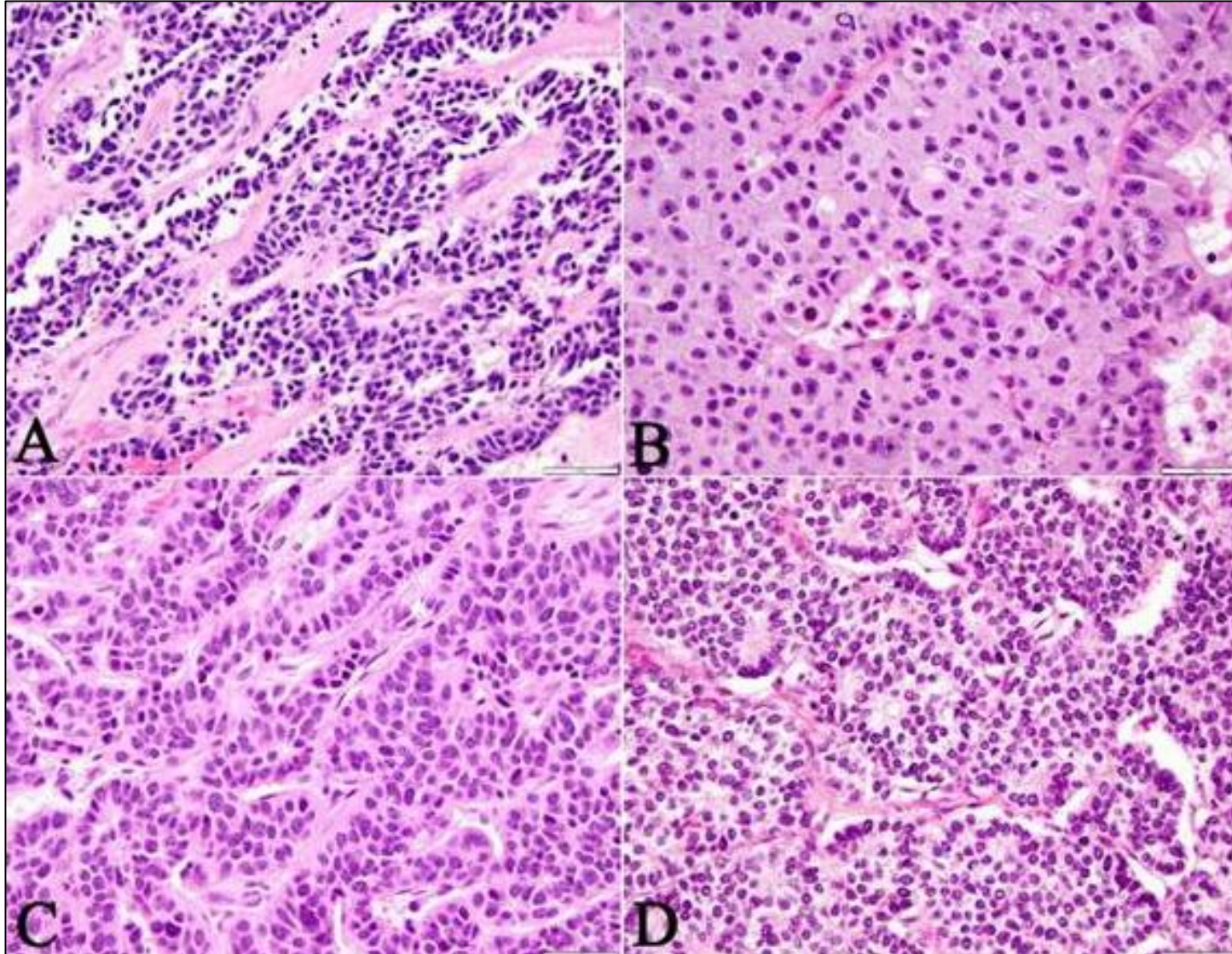
**A subset of morphologically well differentiated PanNETs have a Ki67 proliferation index >20%**



*Basturk et al. Am J Surg Pathol; 39(5):683-90, 2015*



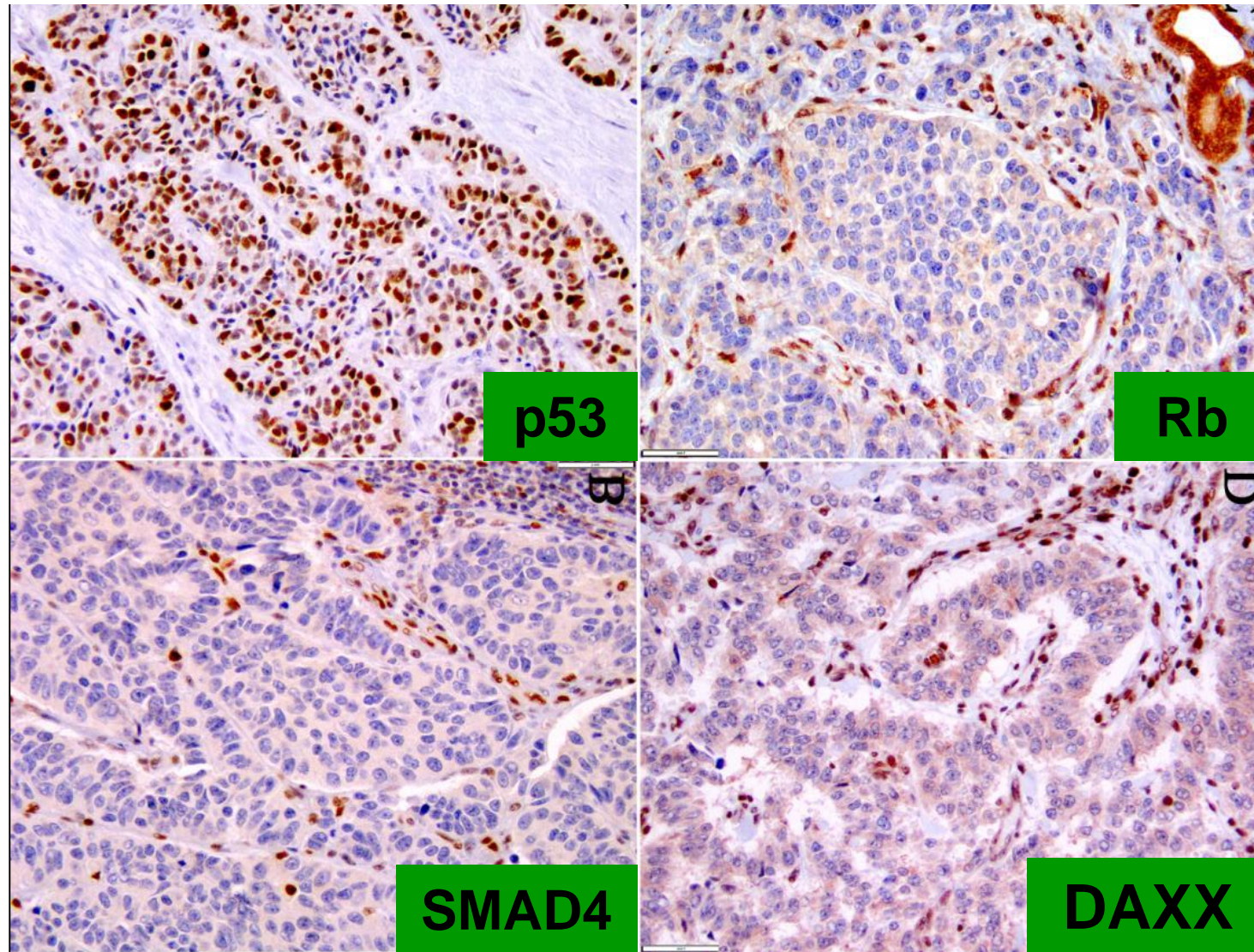
# Morphologically **Ambiguous** Pancreatic Neuroendocrine Neoplasms



# Morphologically Ambiguous Pancreatic Neuroendocrine Neoplasms

- If there is a **G1/G2 WDNET component** in the tumor, consider G3 WDNET
- If there is a **coexisting conventional carcinoma**, consider PDNEC since the combination with a non-neuroendocrine carcinoma component is very rare in WDNETs

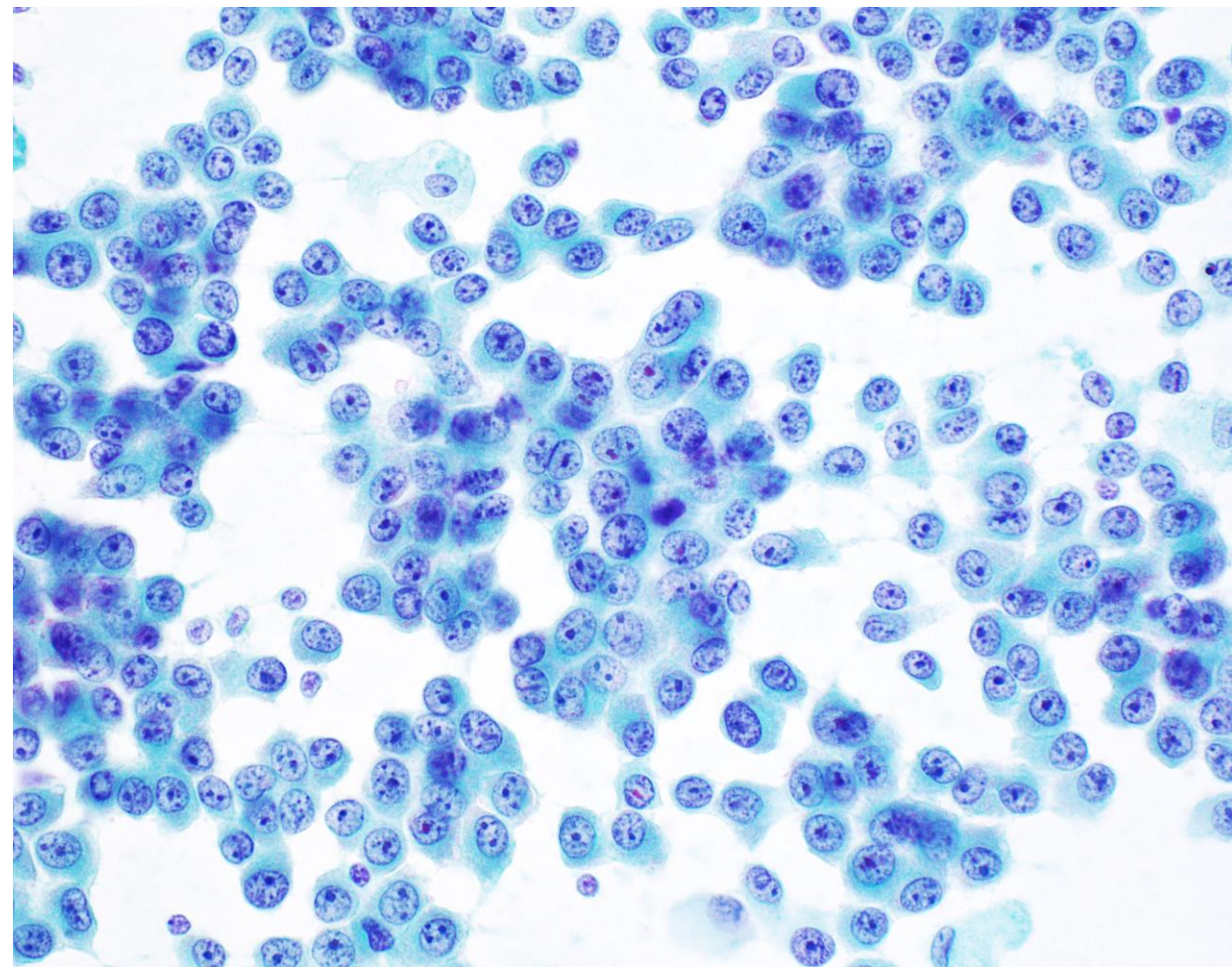
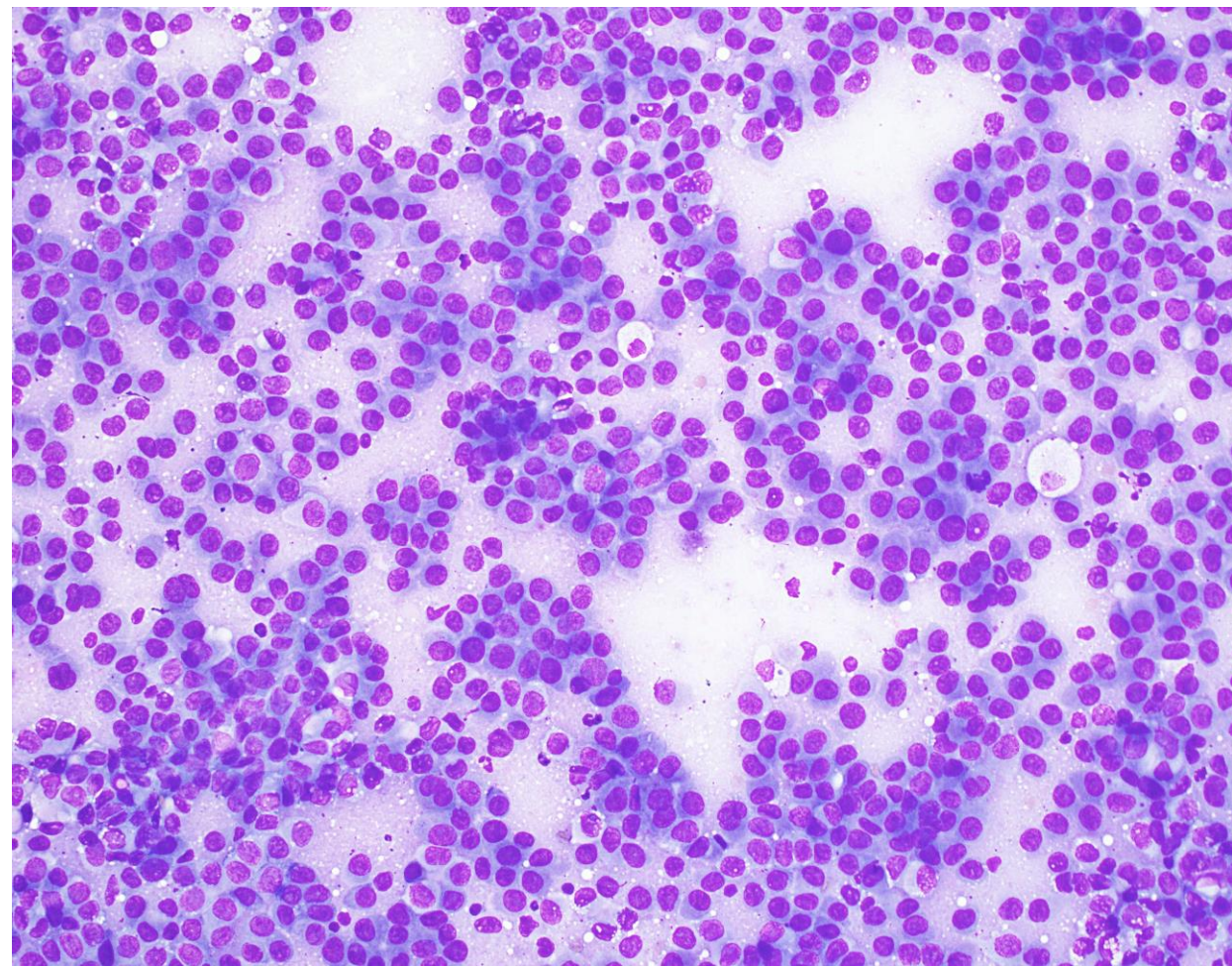
Loss of RB, SMAD4: PDNEC  
Loss of ATRX/DAXX: WDNET

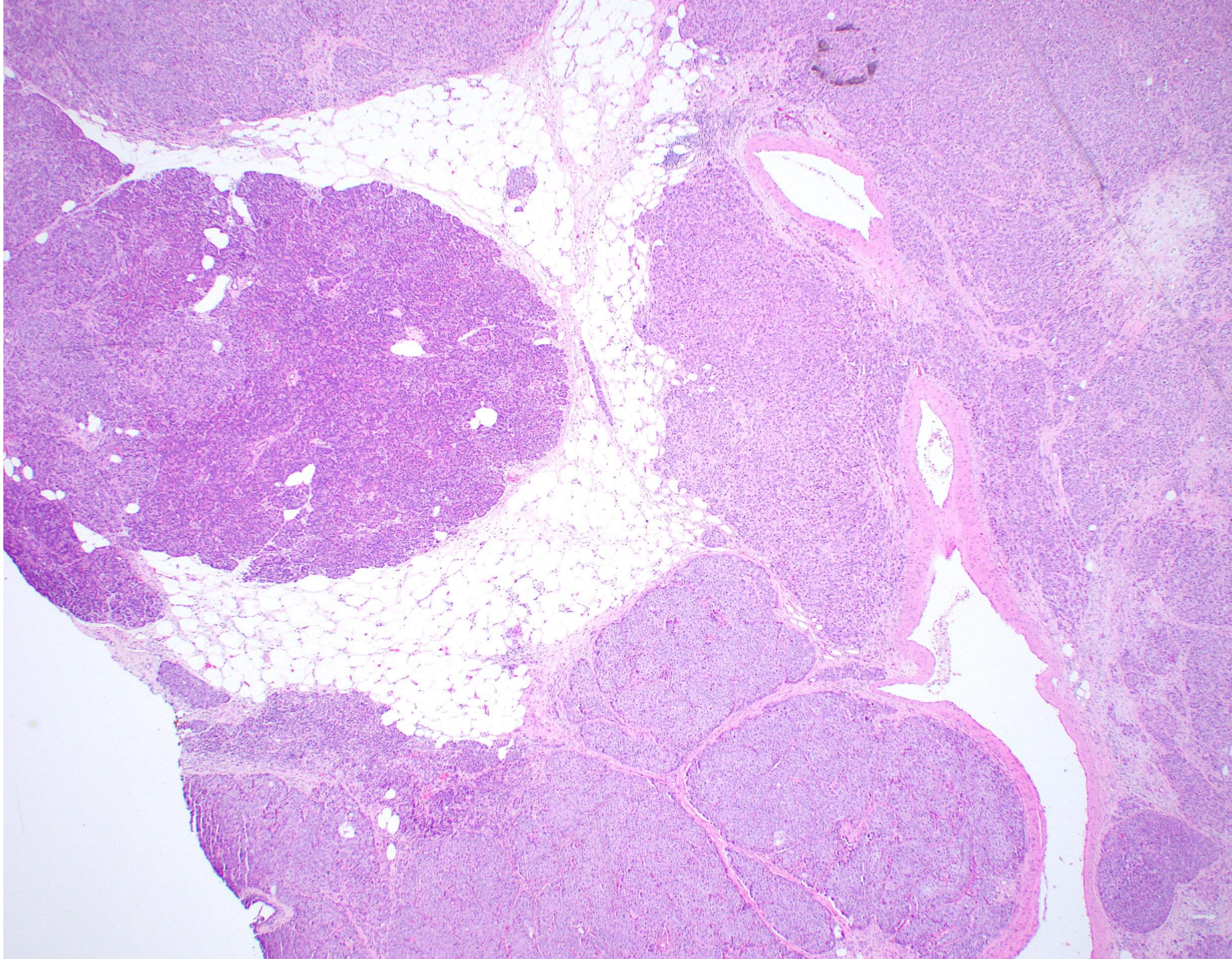


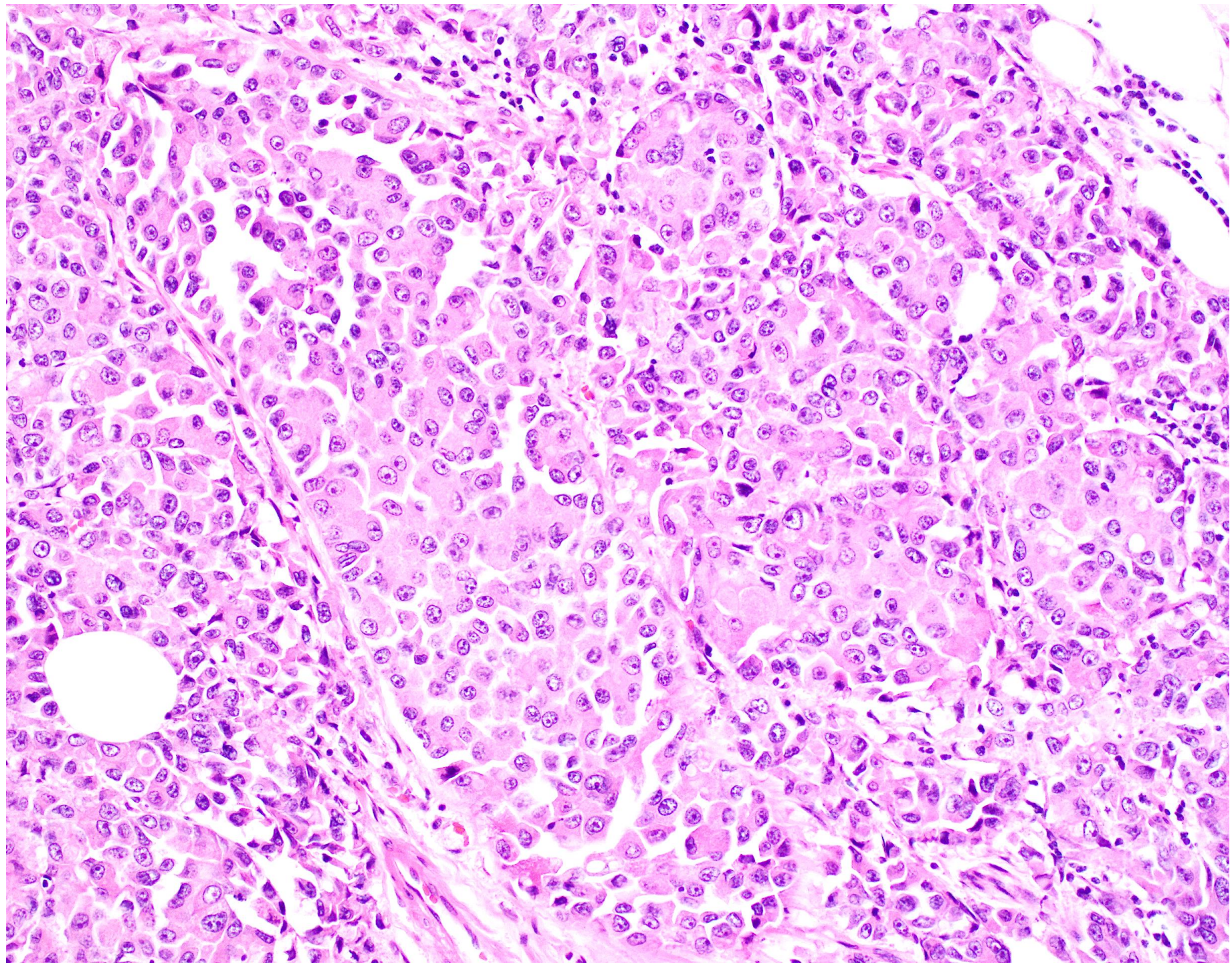
# Case # 3

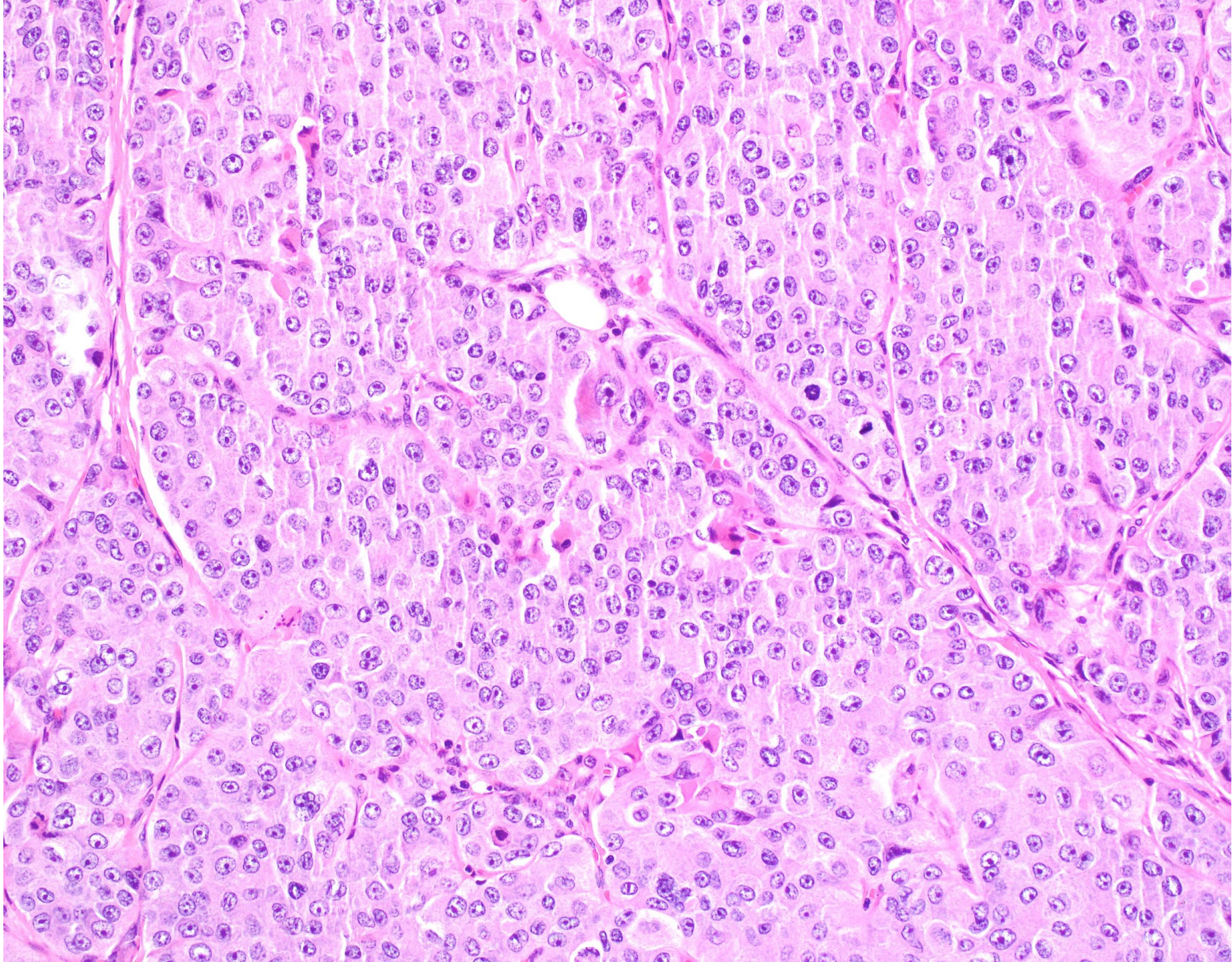
- 77 year-old male complained of abdominal pain
- Imaging revealed a 5.2 cm pancreatic head mass
- Pancreatoduodenectomy was performed and a 6.0 cm cystic and solid mass was found

# Touch Preparation

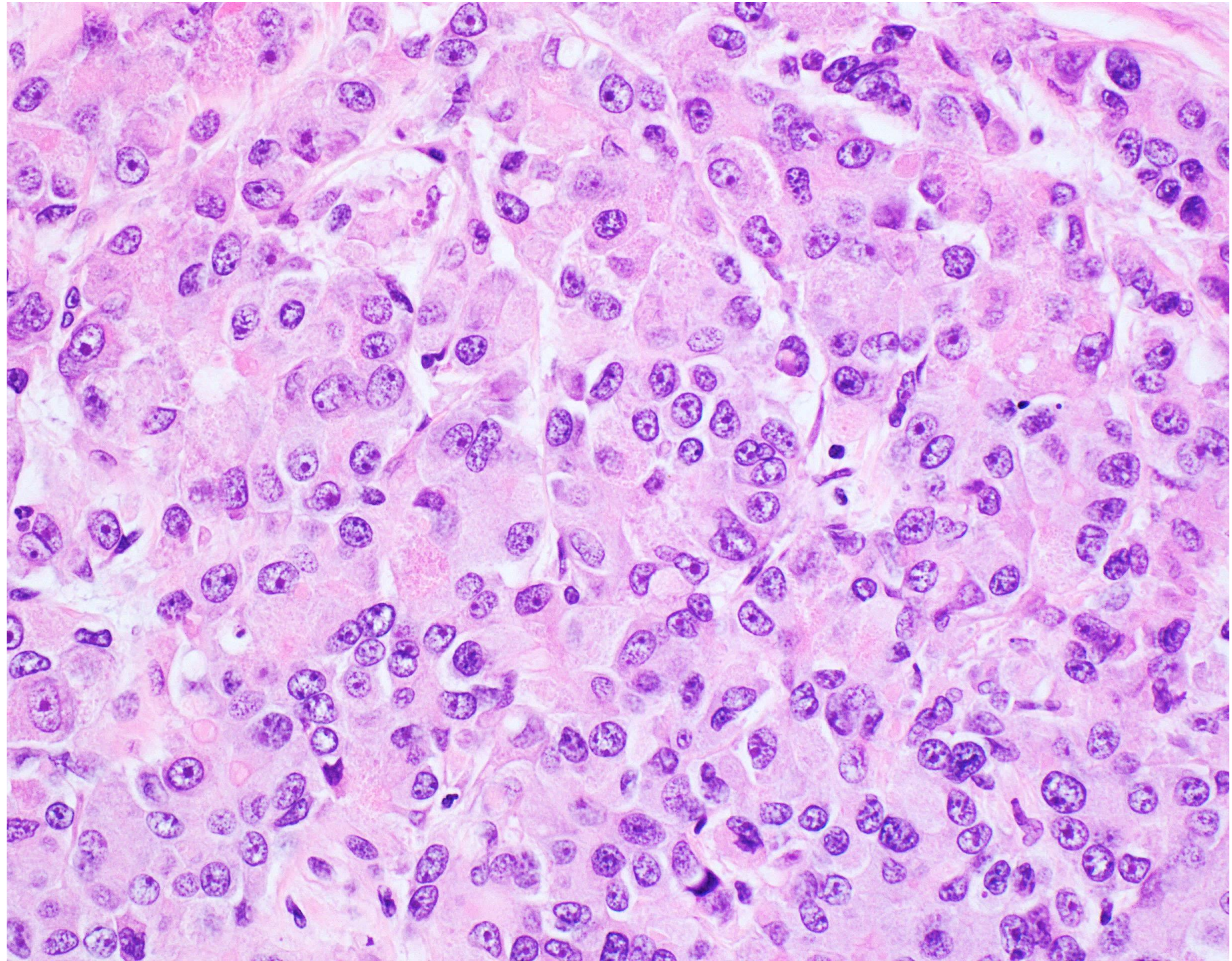




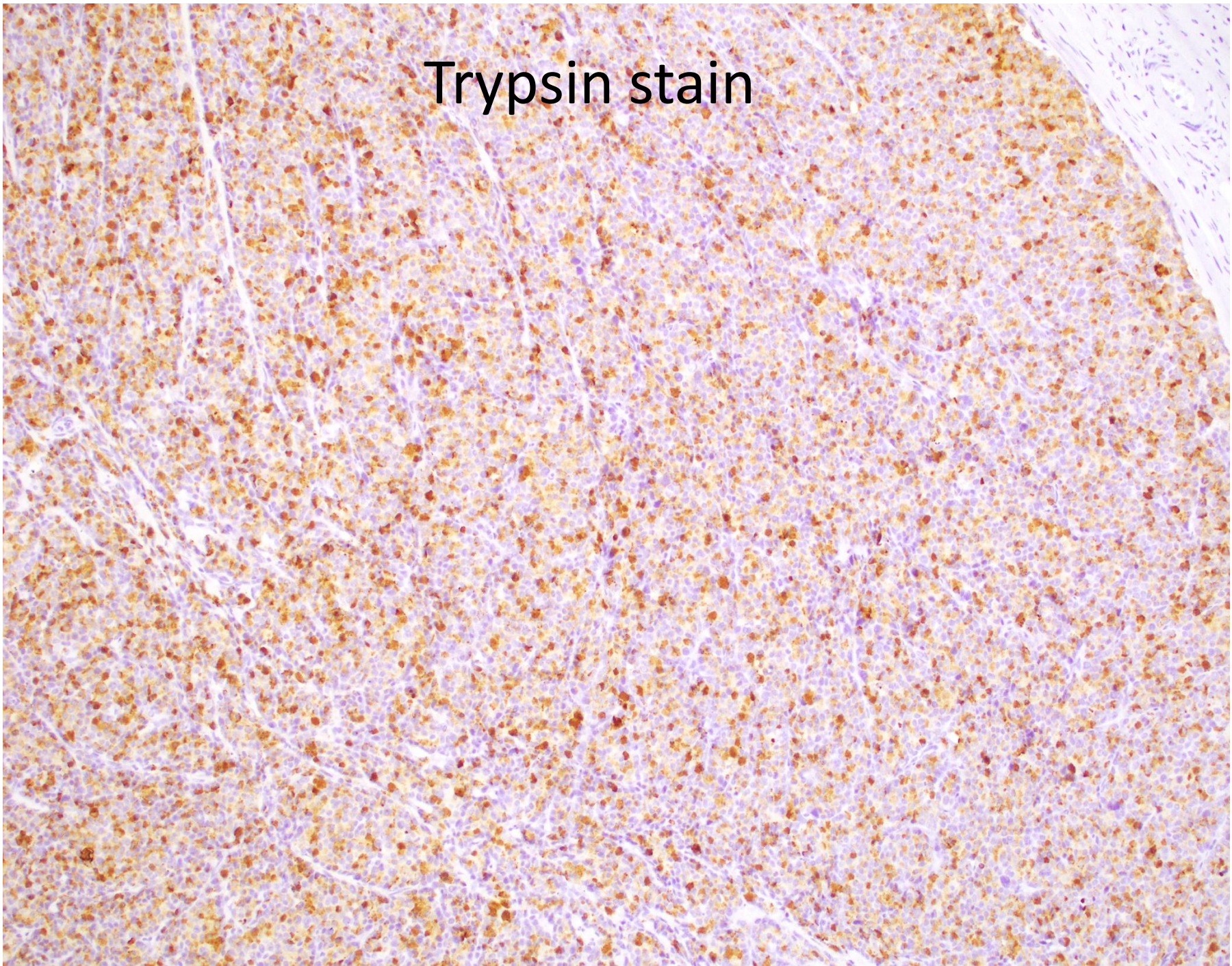








Trypsin stain

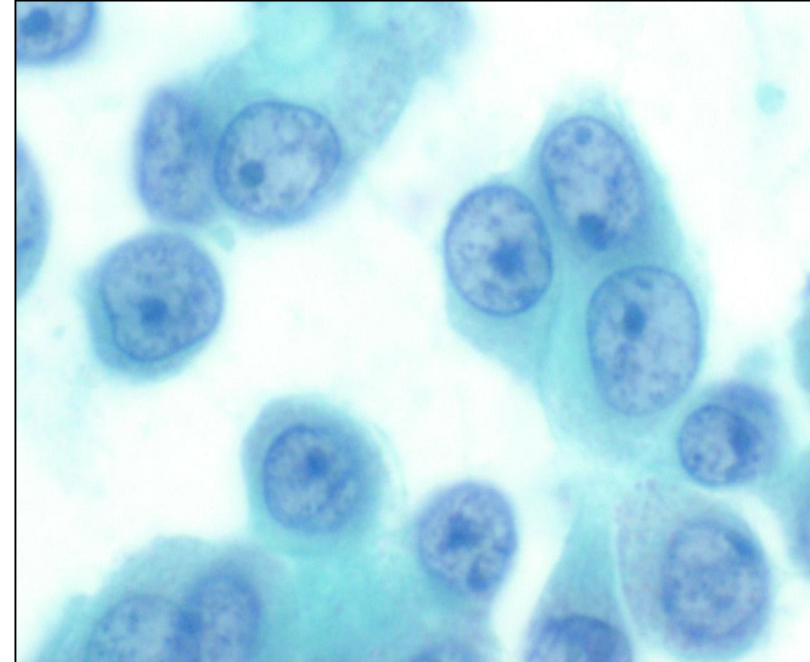
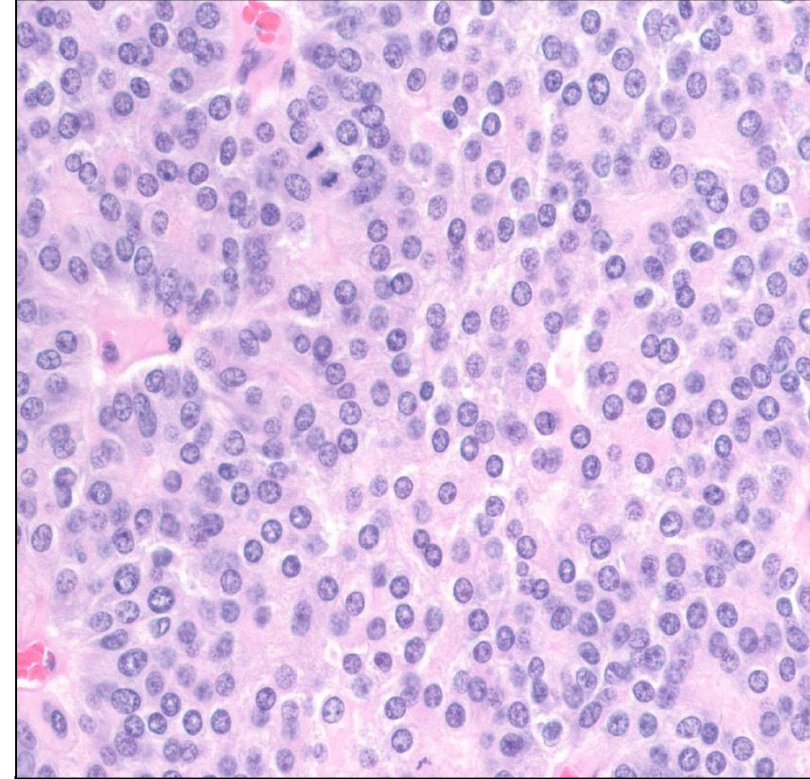


## Case #3 - Diagnosis

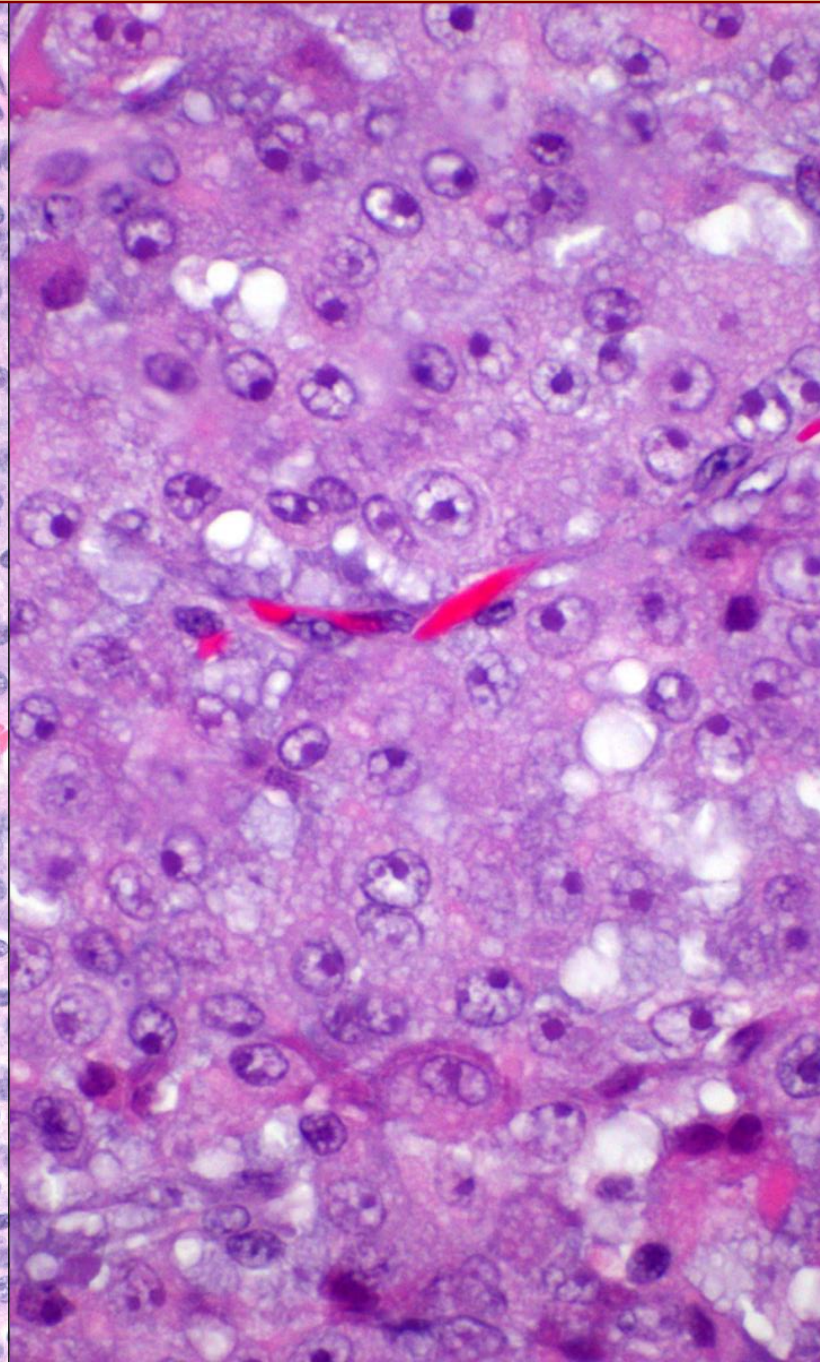
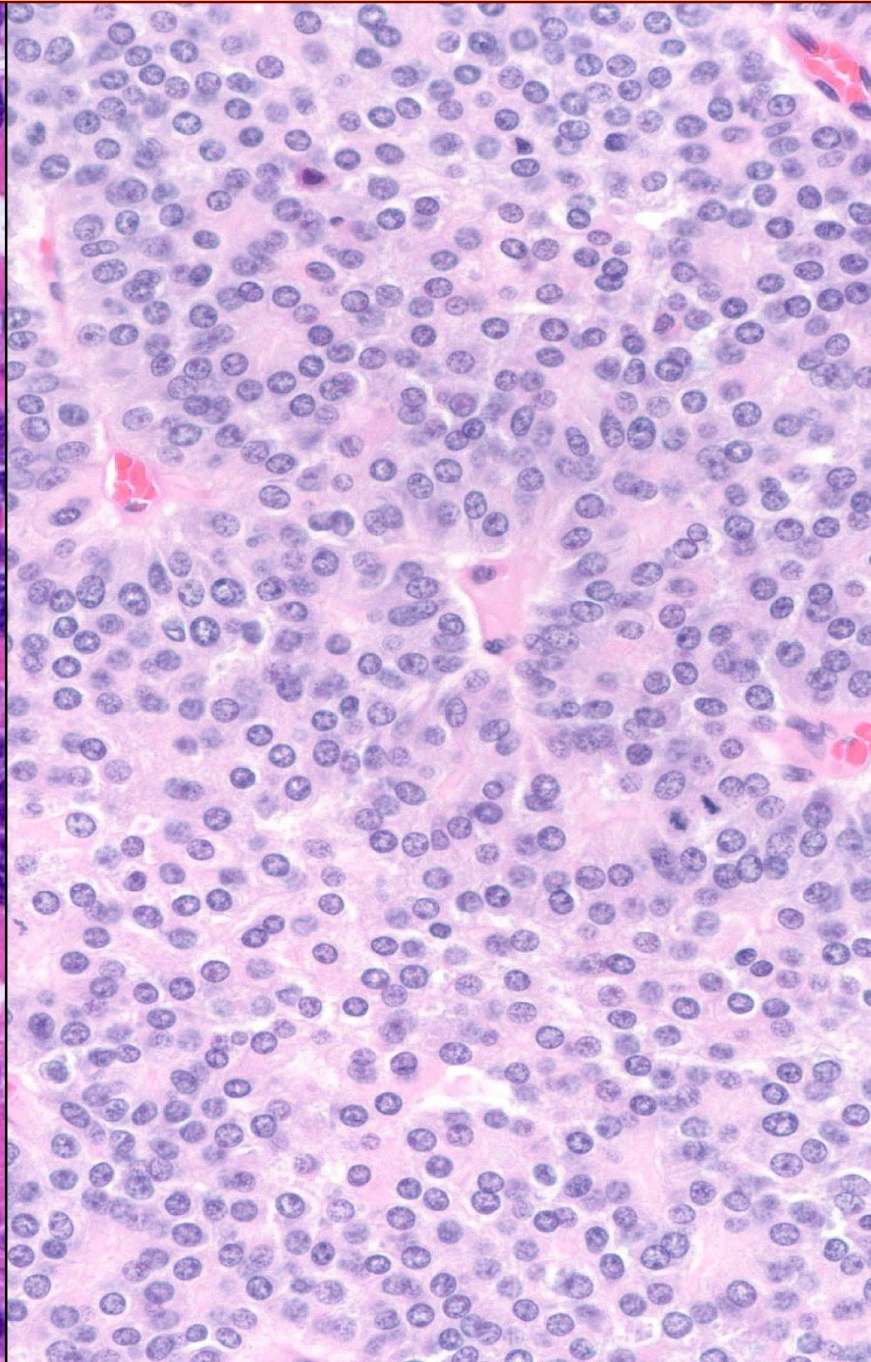
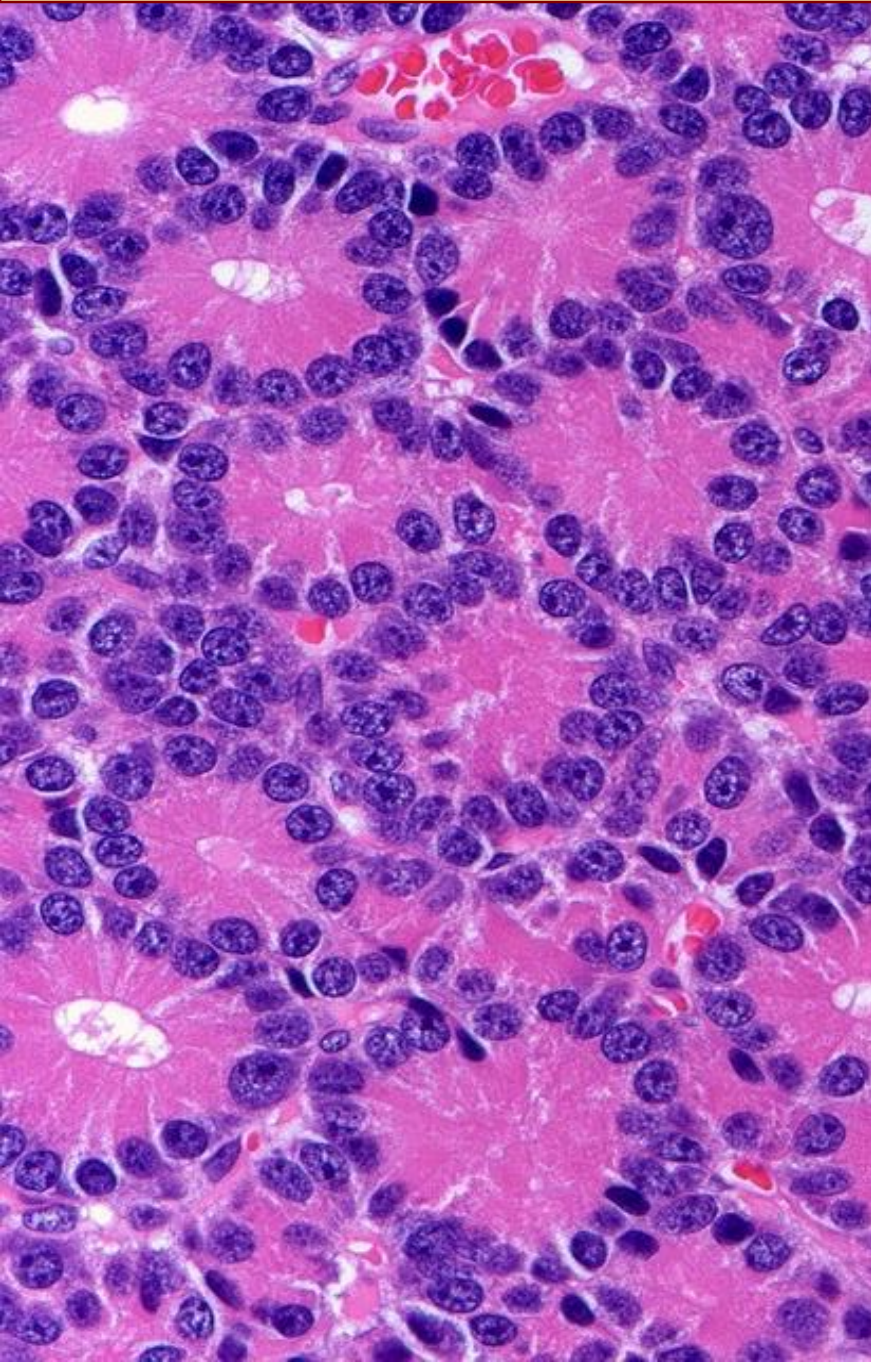
Acinar cell carcinoma

# Acinar Cell Carcinoma

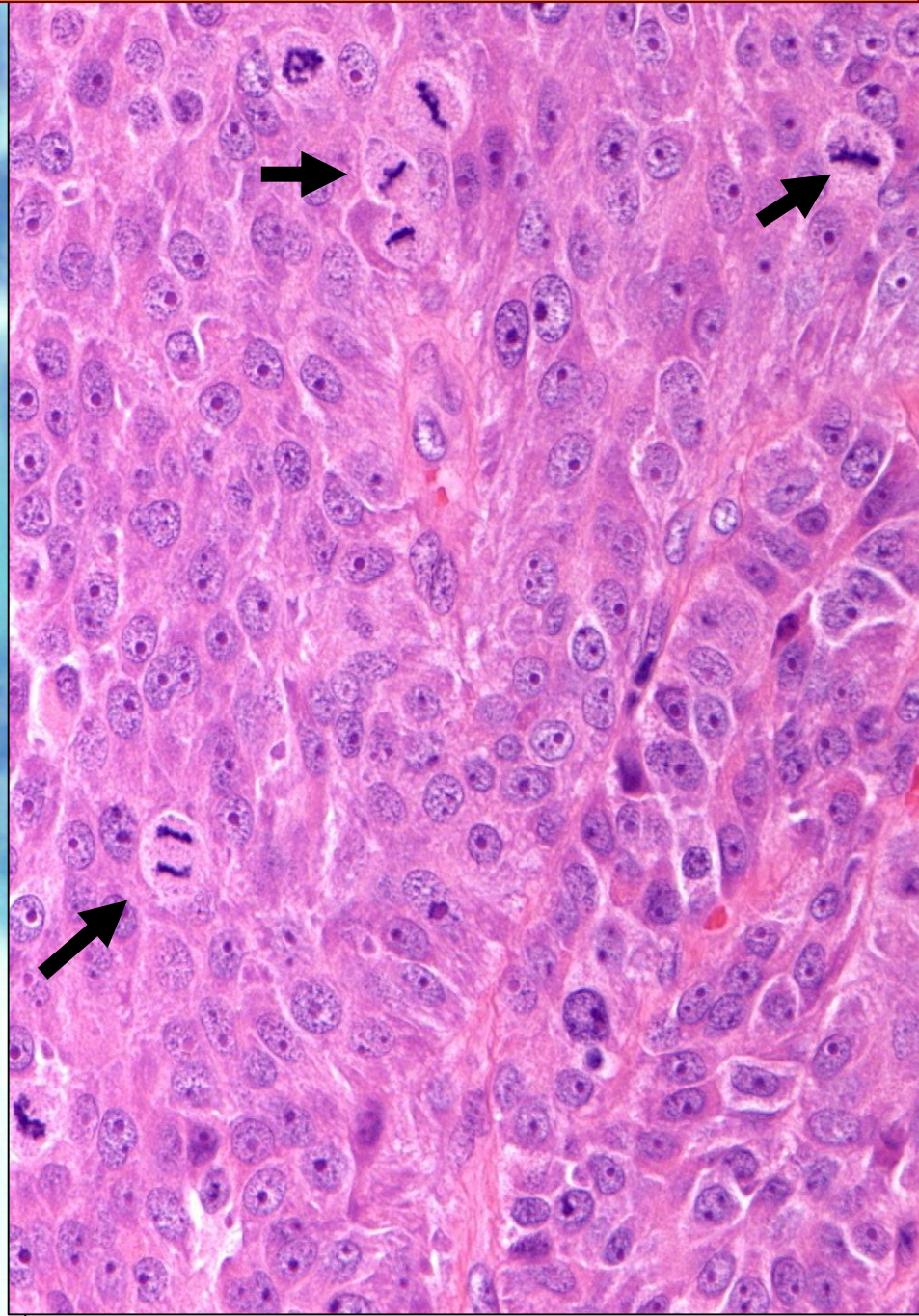
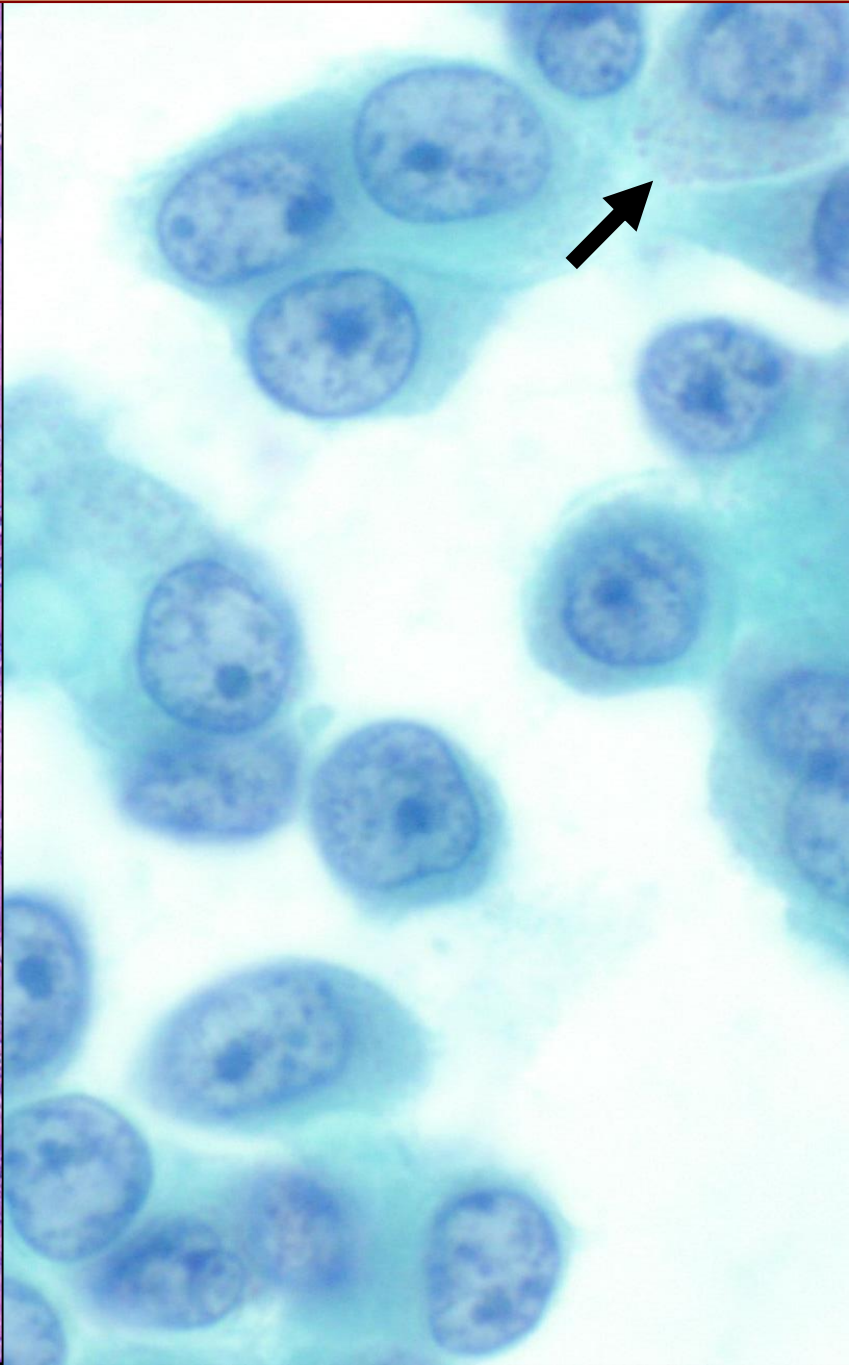
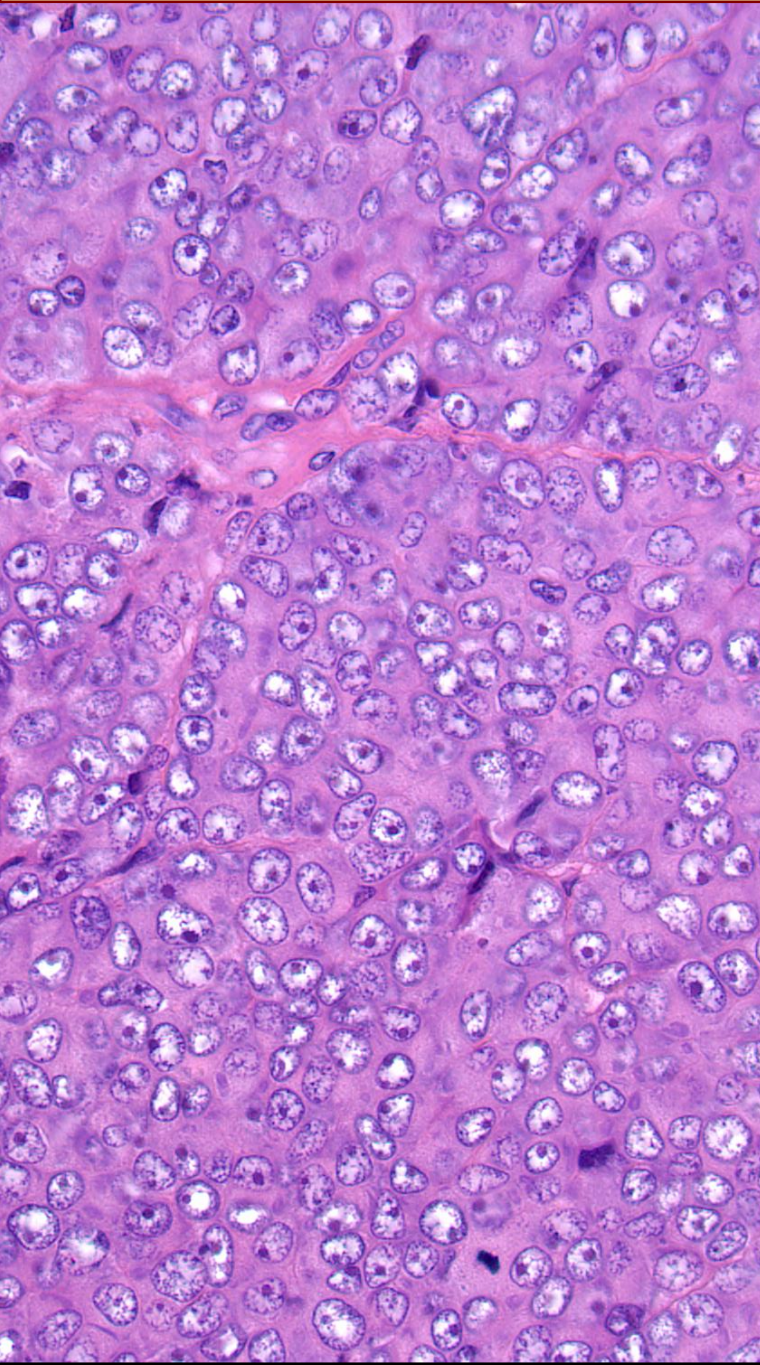
- **Stroma-poor** cellular **tumor**
- Typically large, **circumscribed** tumor (mean size 10 cm)
- Often metastatic at time of diagnosis
- Acinar cells form sheets and acinar units
- Granular cytoplasm with PAS+ zymogen granules
- Smooth nuclear contours, fine to coarse chromatin
- Single prominent (sometimes cherry red) nucleoli
- Very mitotically active



ACC: Tumor cells form acini; cells have granular, eosinophilic to basophilic PAS+ cytoplasm with zymogen granules

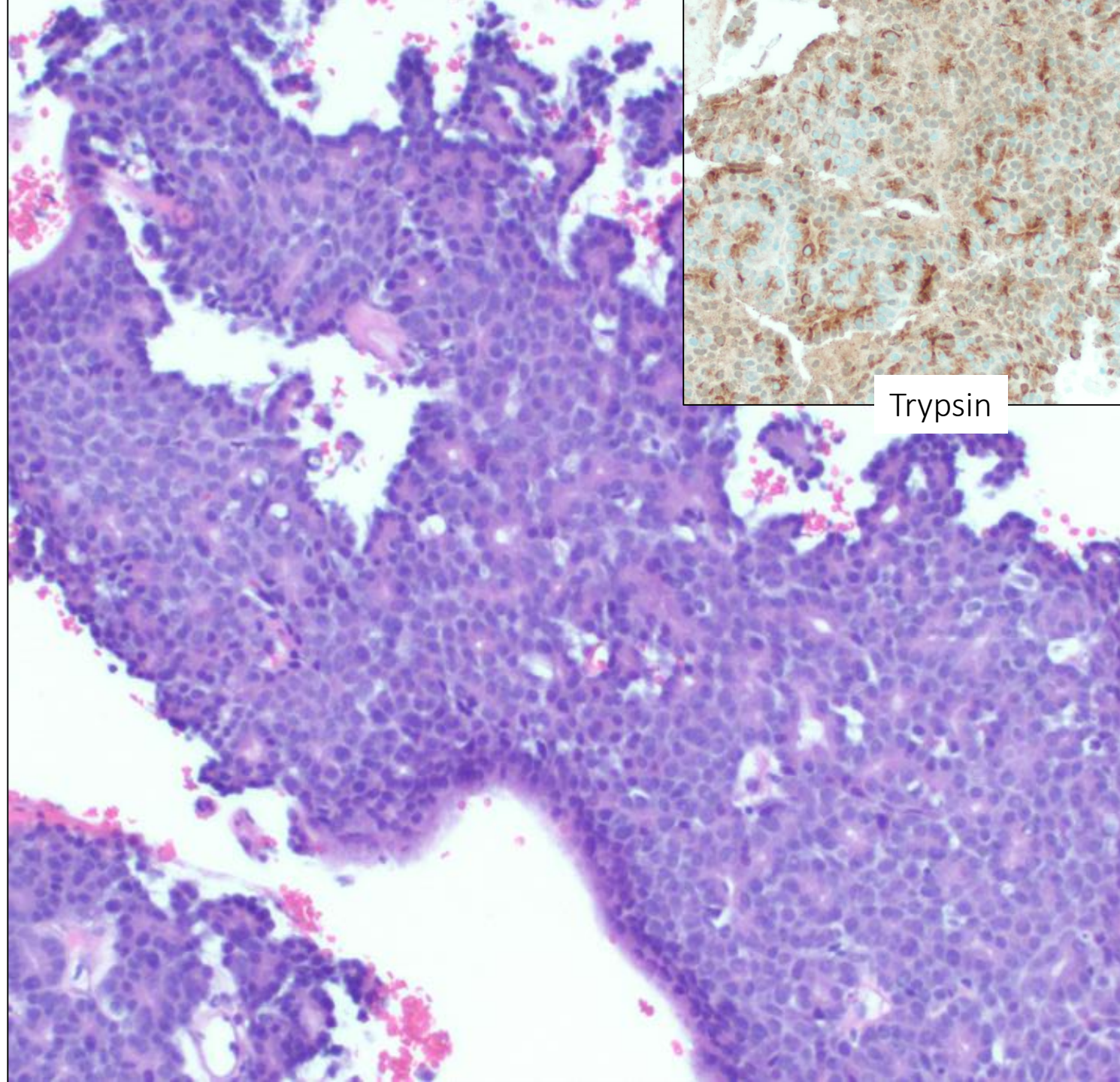


Tumor cells have round nuclei, large cherry red nucleoli, red cytoplasmic zymogen granules and increased mitoses



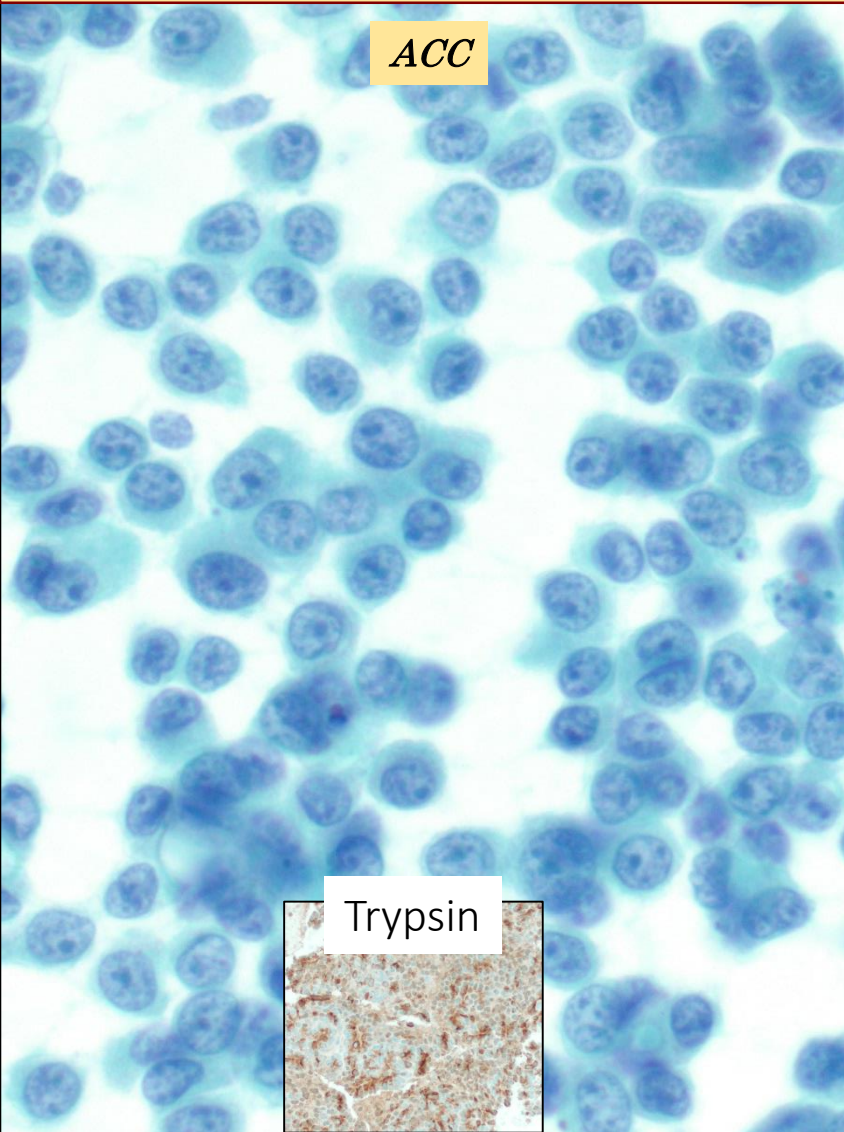
# Acinar Cell Carcinoma

- Stains positively for:
  - Pancreatic enzymes:
    - Trypsin (**almost 100%**)
    - Chymotrypsin (40%)
    - Amylase (30%)
  - BCL10 is (+) even in trypsin-negative cases
  - Mutations in APC, TP53
  - SND1- BRAF fusions or allelic loss on chromosome 11p
  - Absence of RAF fusion a/w sensitivity to platinum-based therapies and PARP inhibitors



# Cytologic distinction of ACC from common mimics

ACC

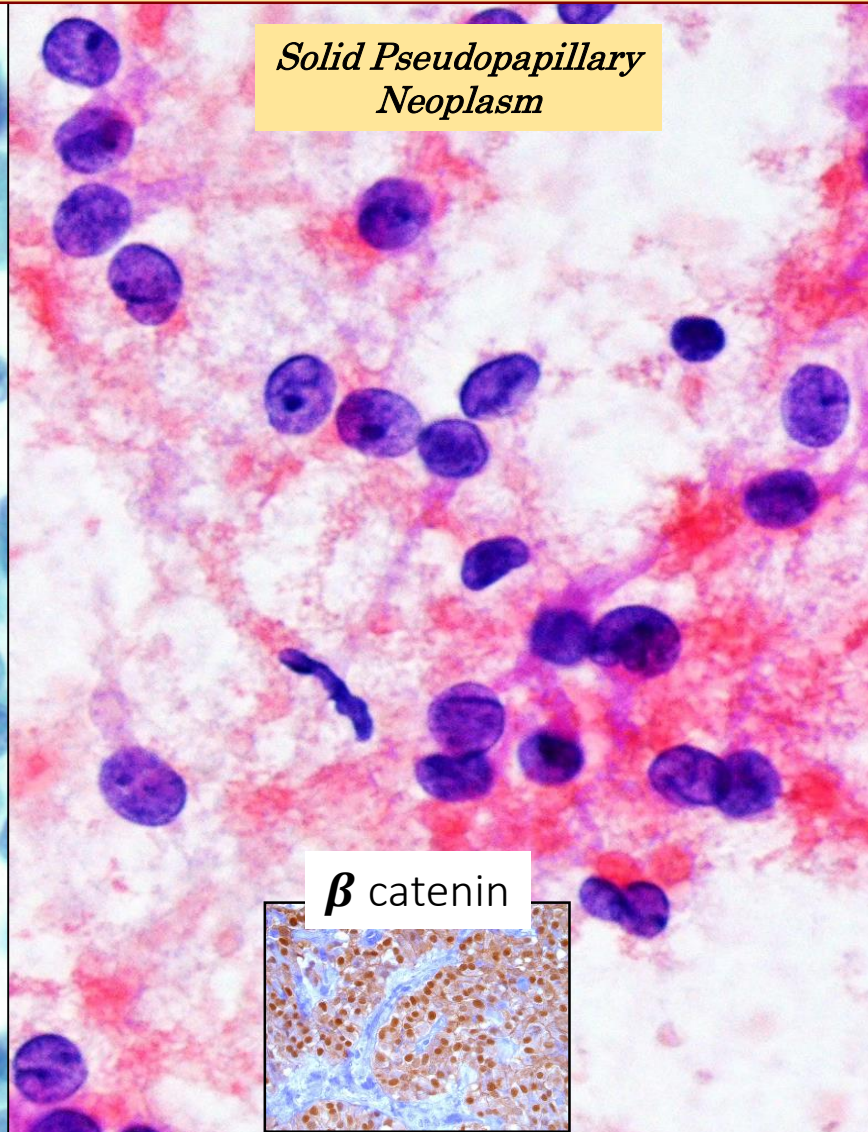


Trypsin

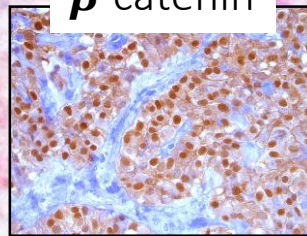


*Neoplastic cells have vesicular chromatin, pink cytoplasmic zymogen granules, prominent nucleoli*

*Solid Pseudopapillary Neoplasm*

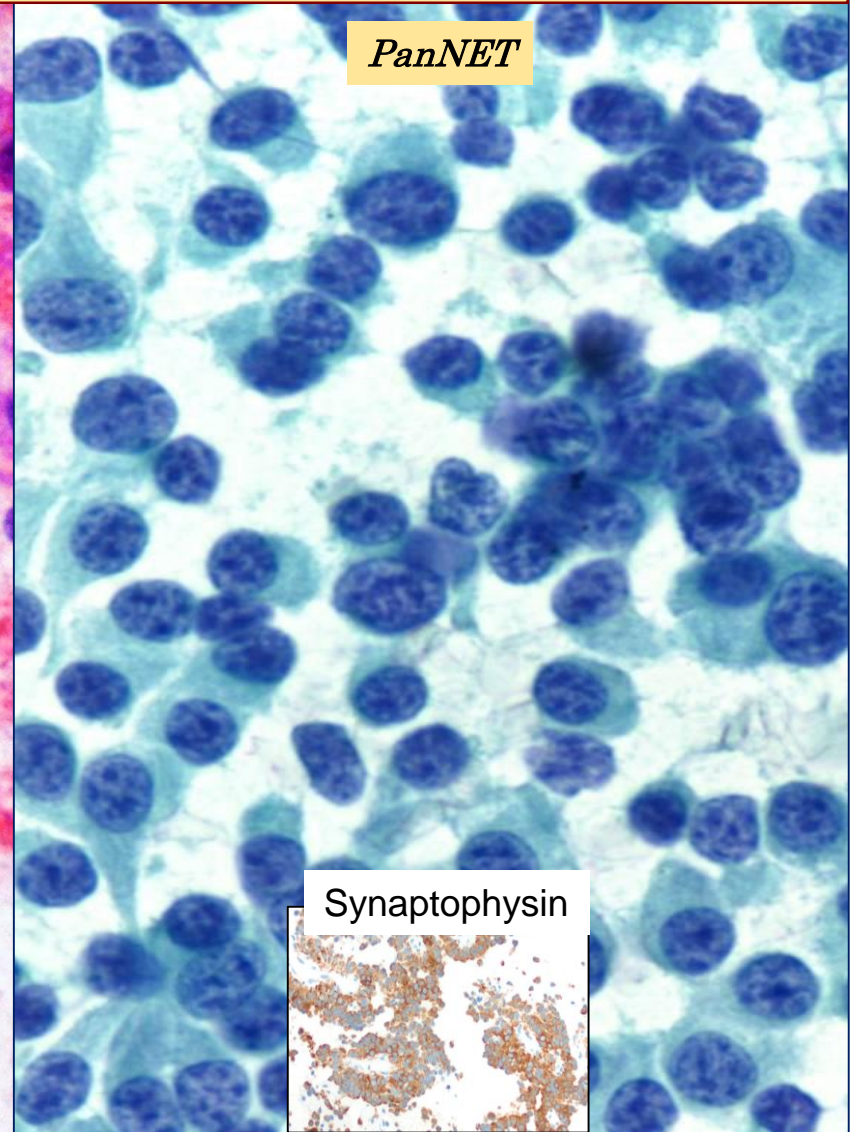


$\beta$  catenin

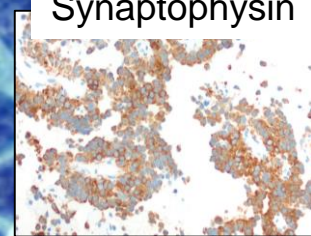


*Neoplastic cells have coffee bean nuclei, fine powdery chromatin, scant cytoplasm, prominent nuclear grooves*

PanNET



Synaptophysin



*Tumor cells are plasmacytoid with round to oval nuclei and salt and pepper chromatin*



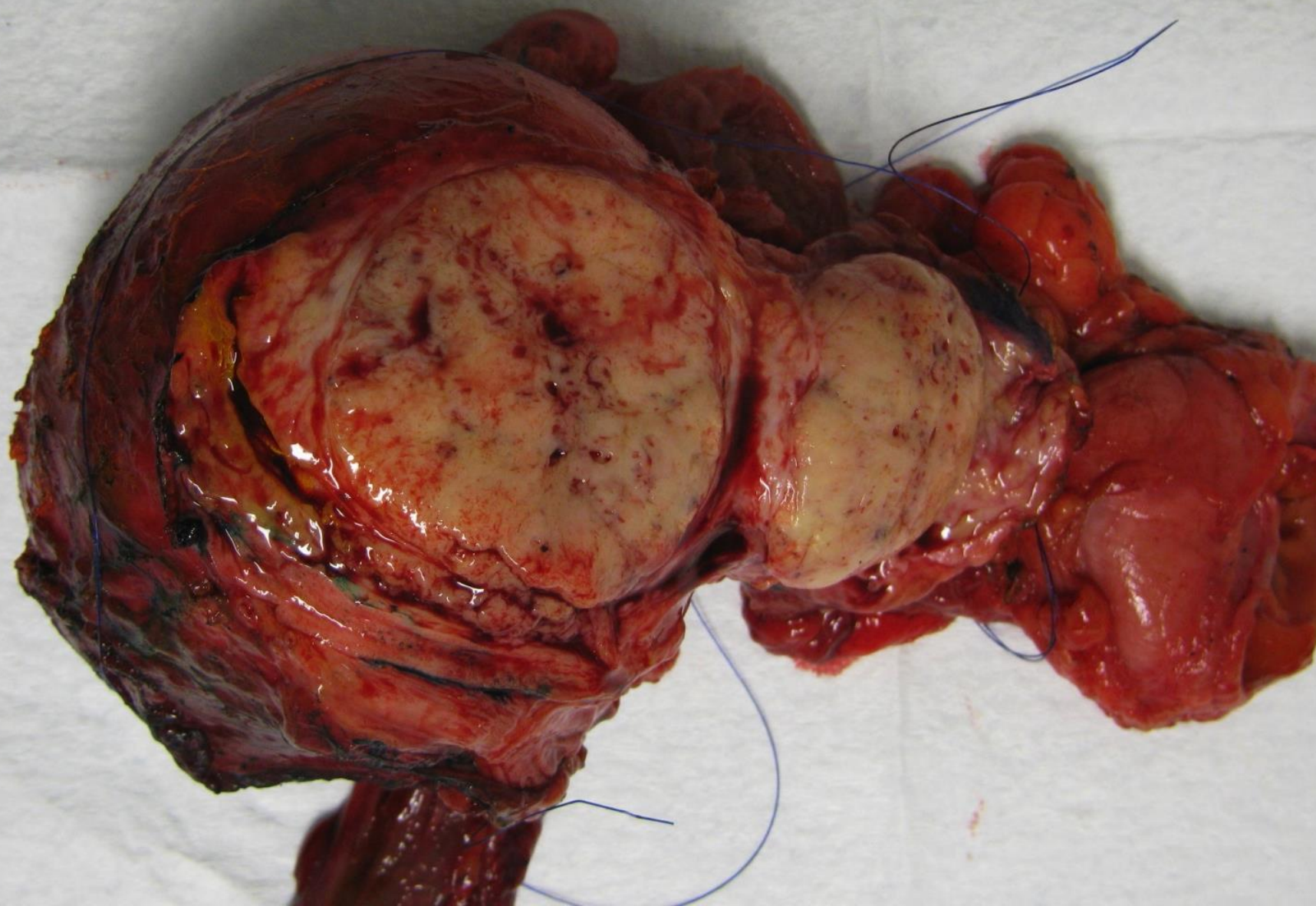
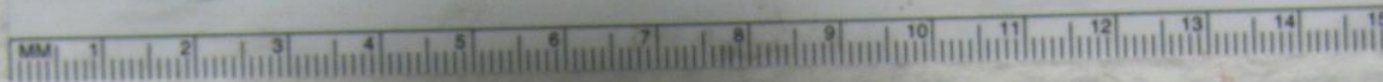
# Case # 5

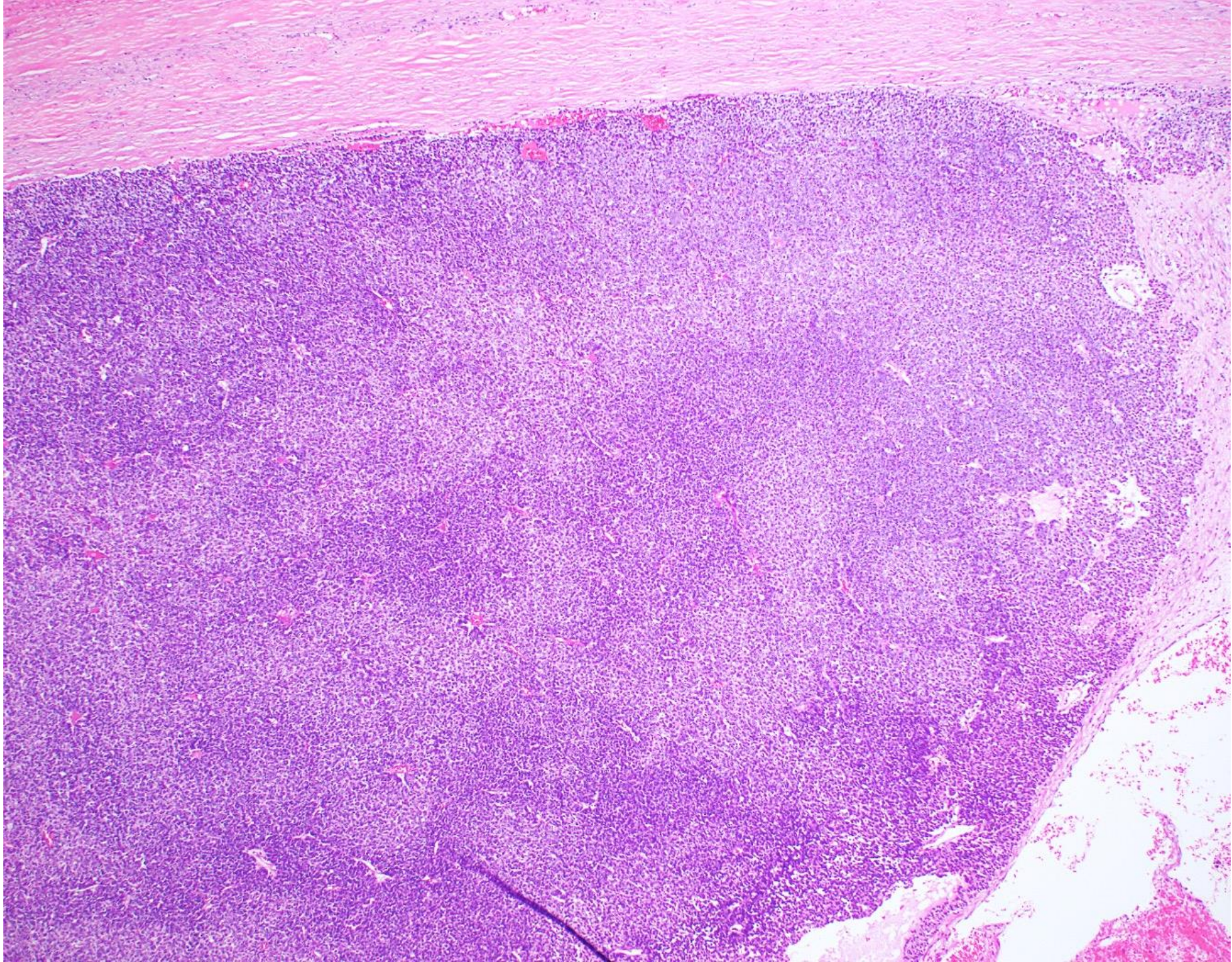
- 57 year-old female presented with abdominal pain and weight loss
- CT revealed a 10.0 cm pancreatic head mass
- Pancreatoduodenectomy was performed

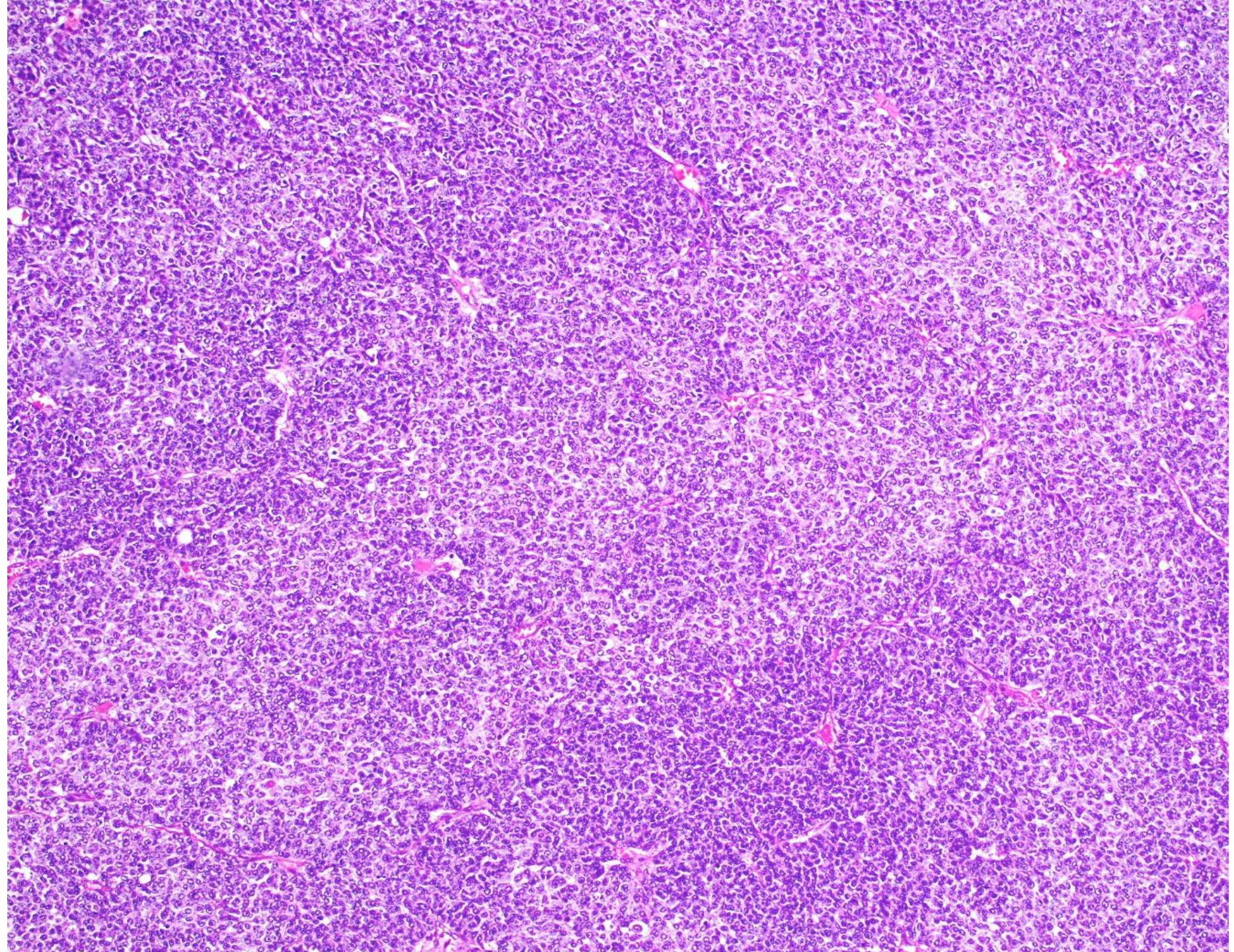


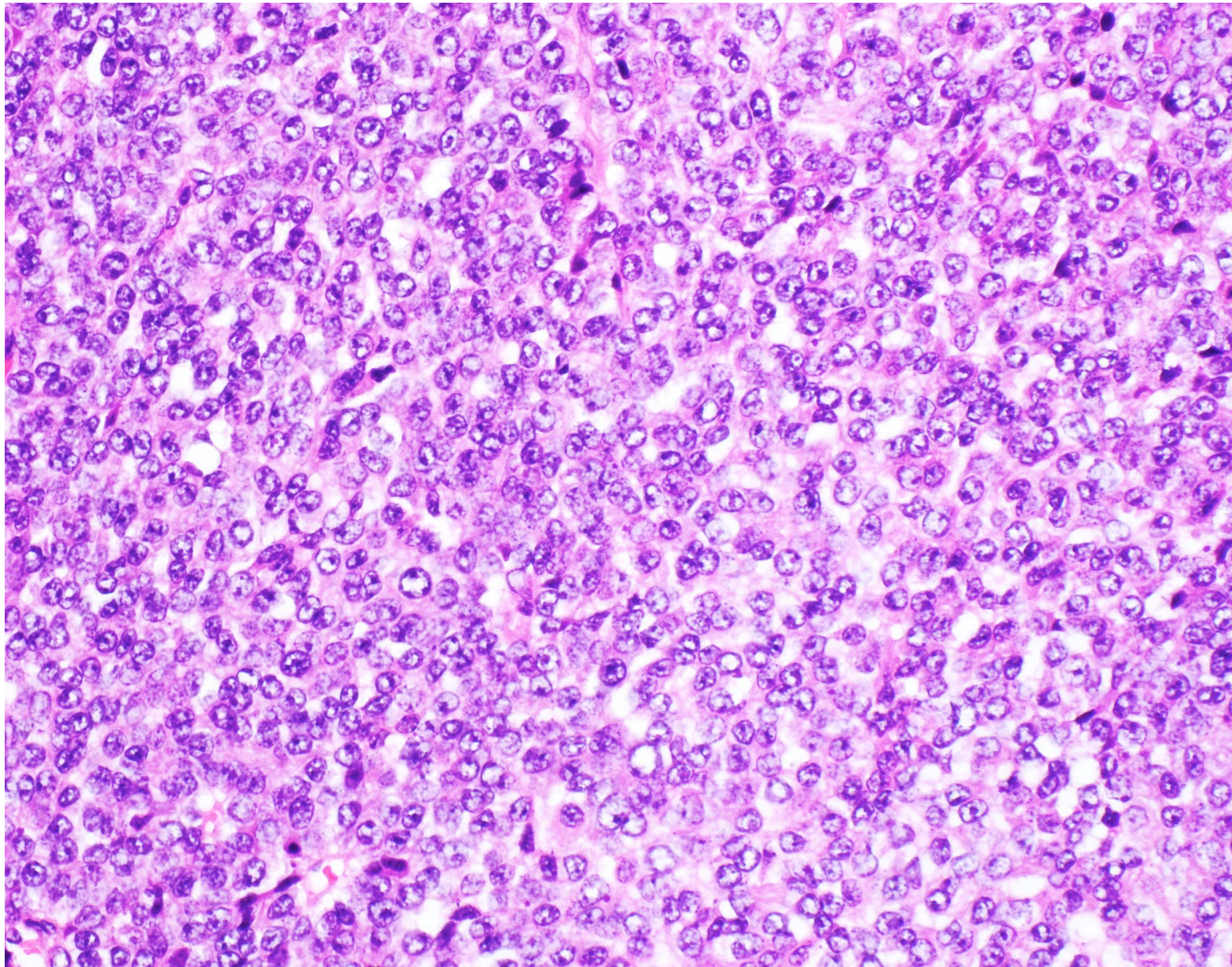
800-725-8723

Proven Reliability

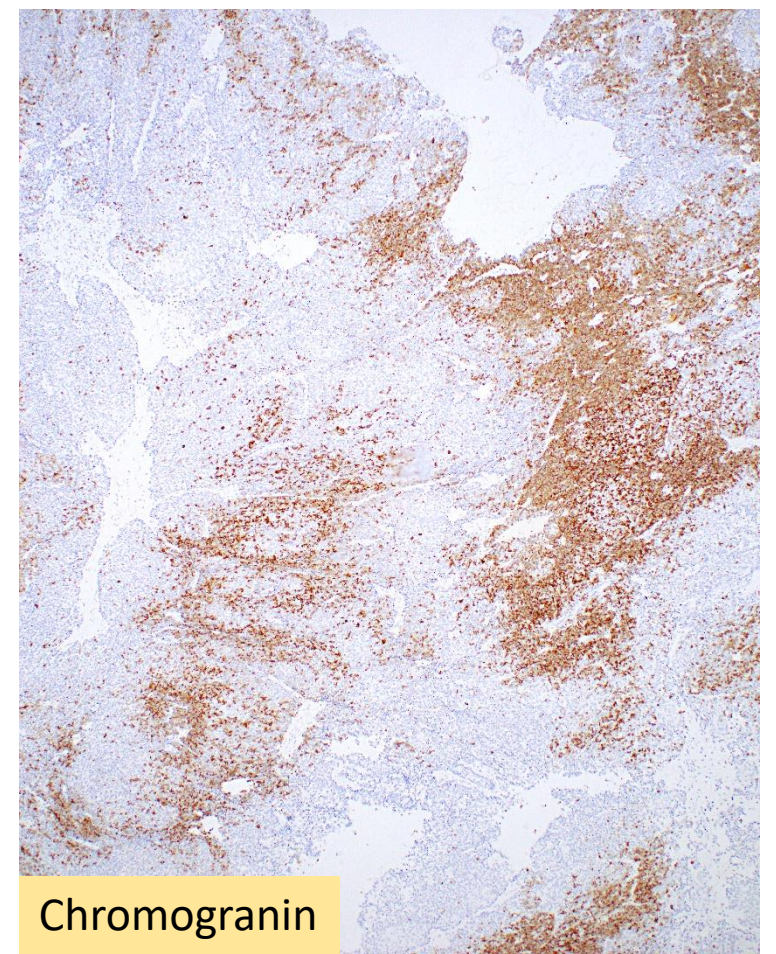
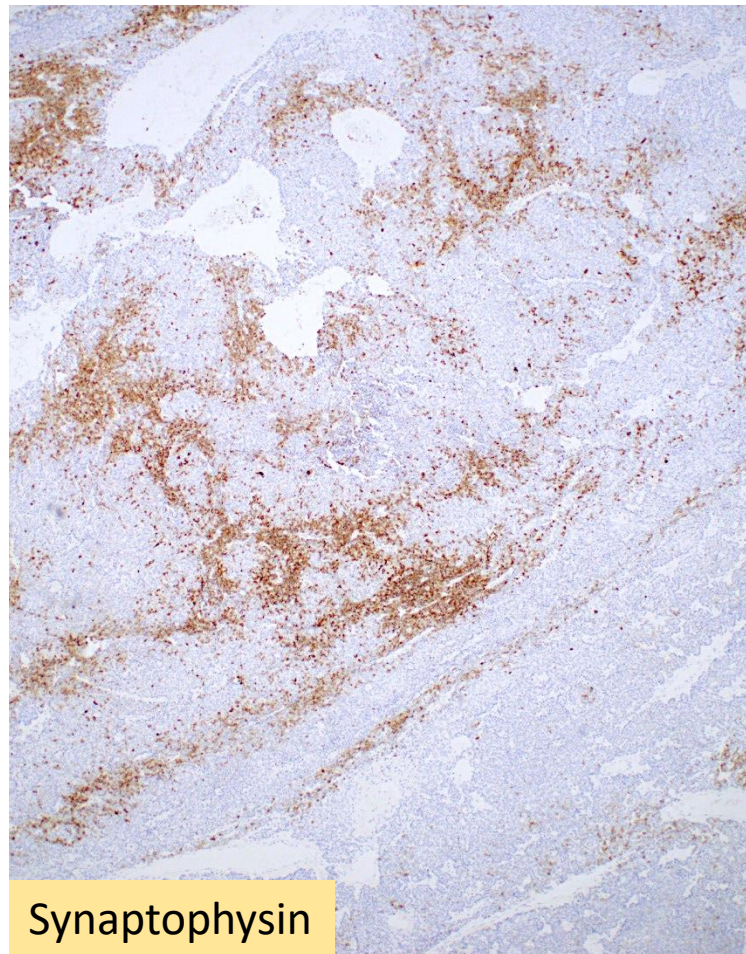
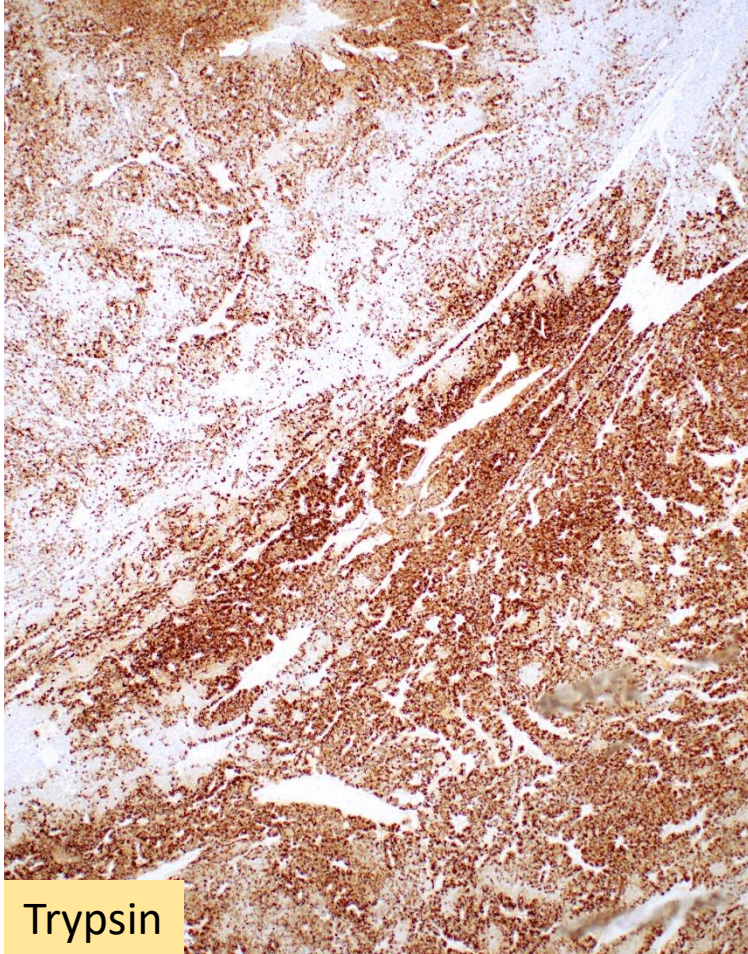






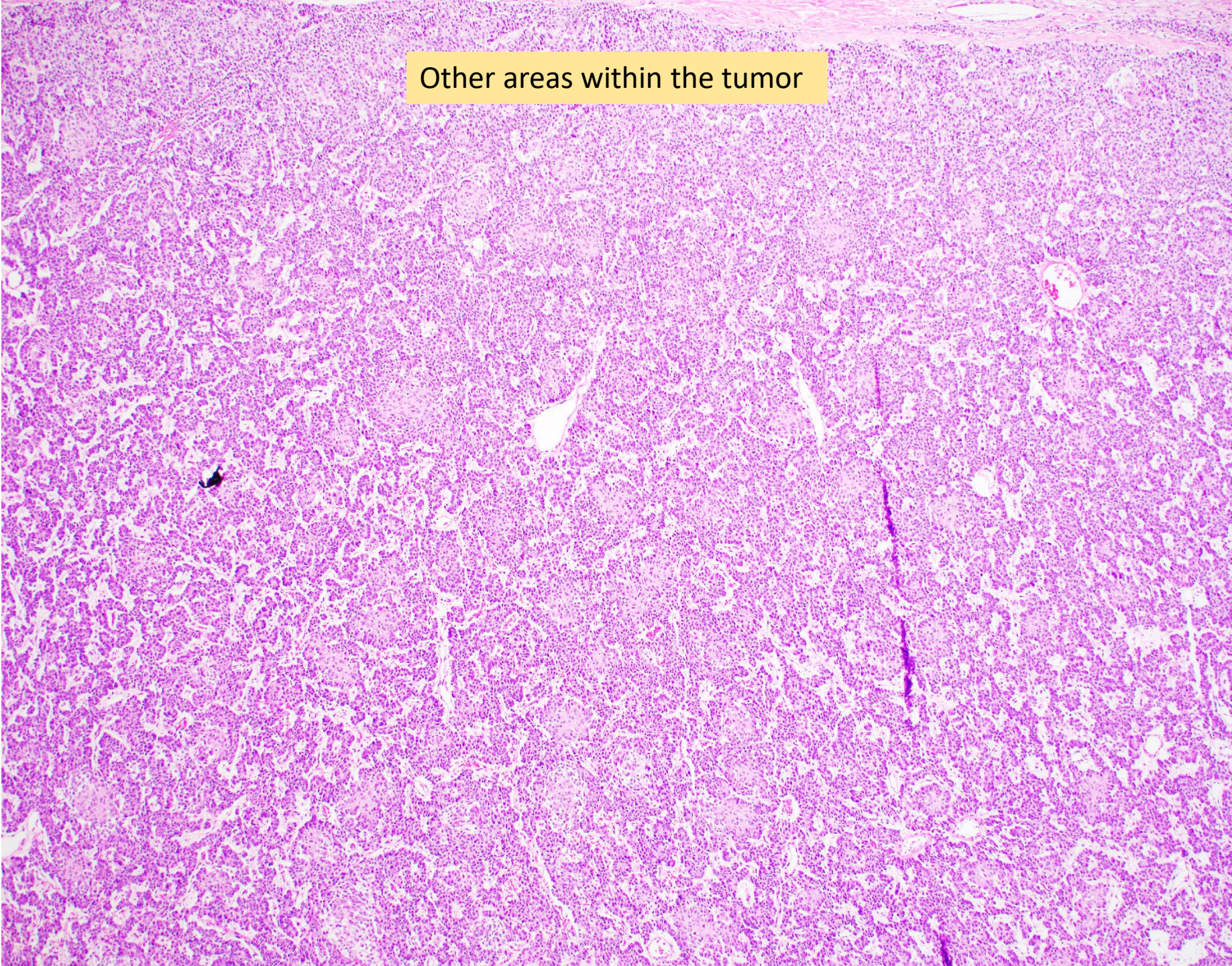


Tumor cells were positive for pancytokeratin,  
trypsin, synaptophysin and chromogranin



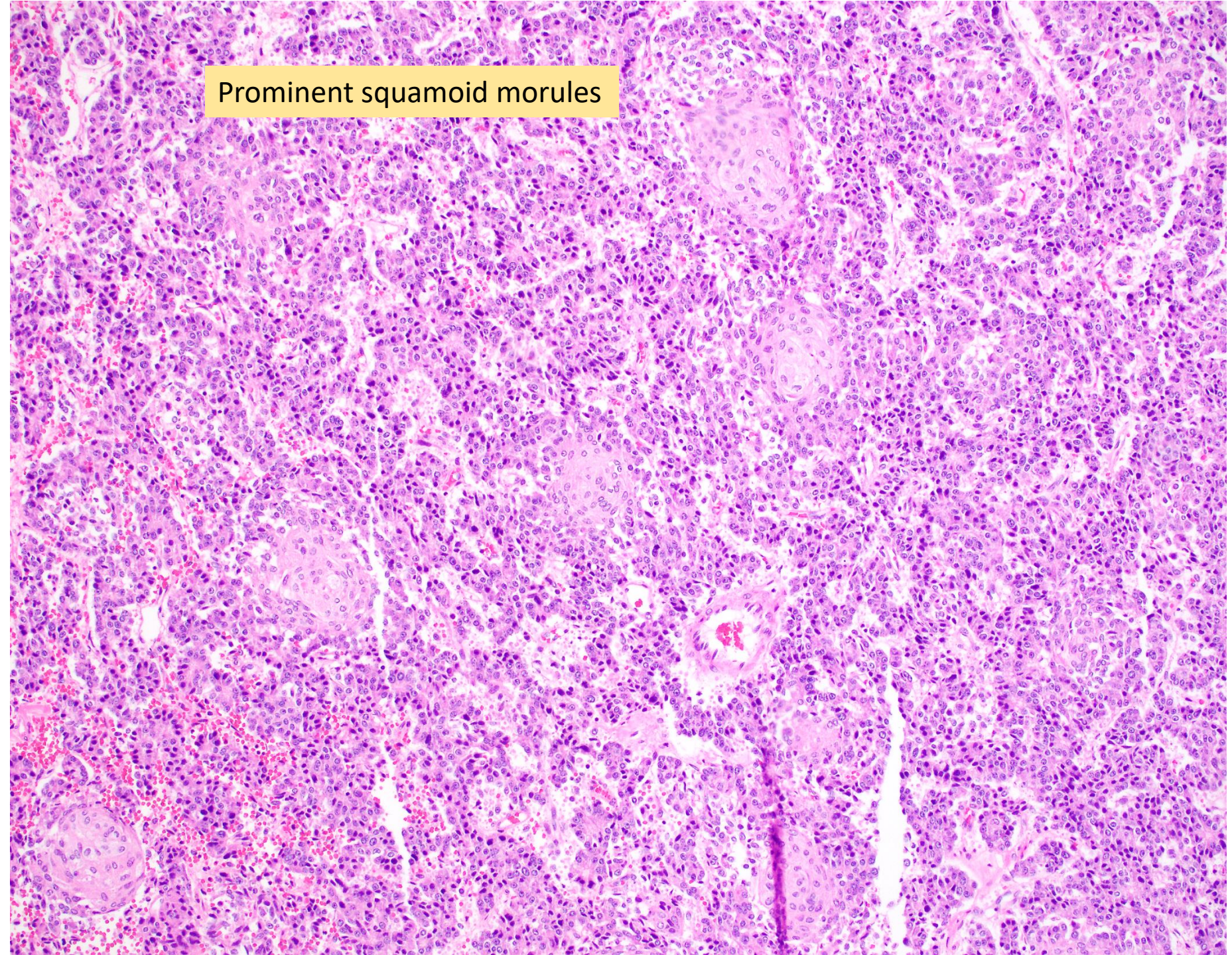
# Mixed Acinar- Neuroendocrine Neoplasm

Other areas within the tumor

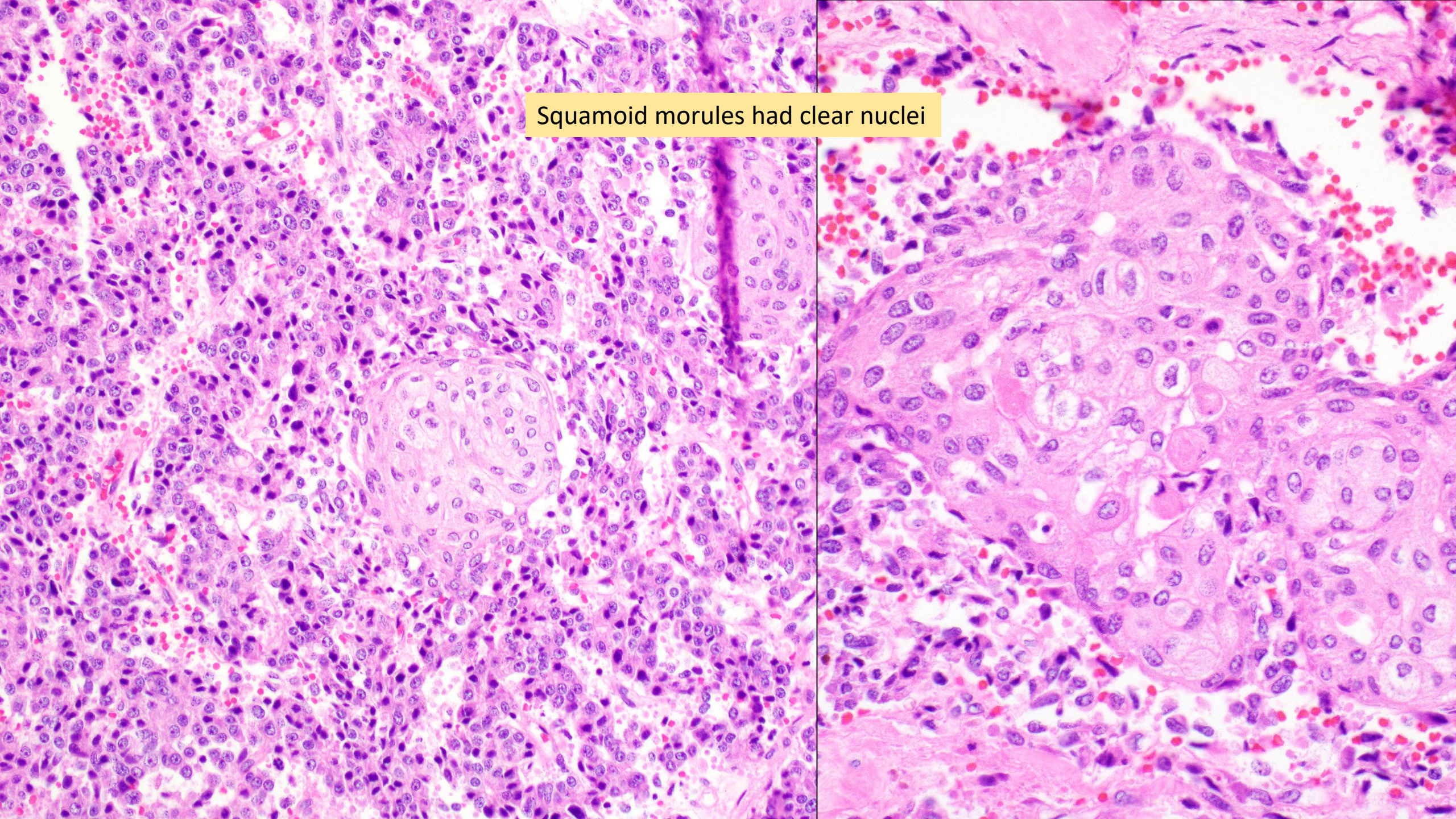




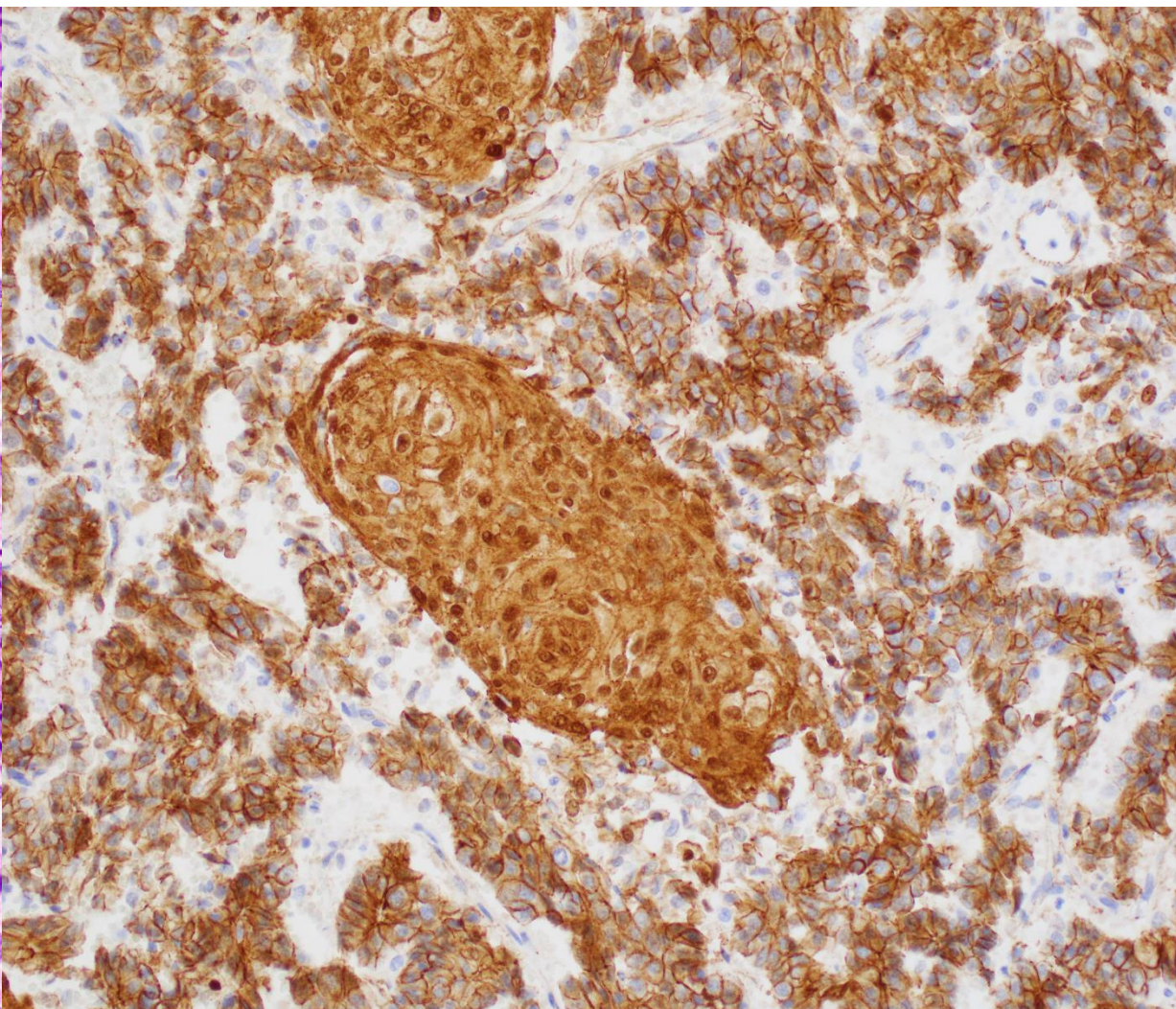
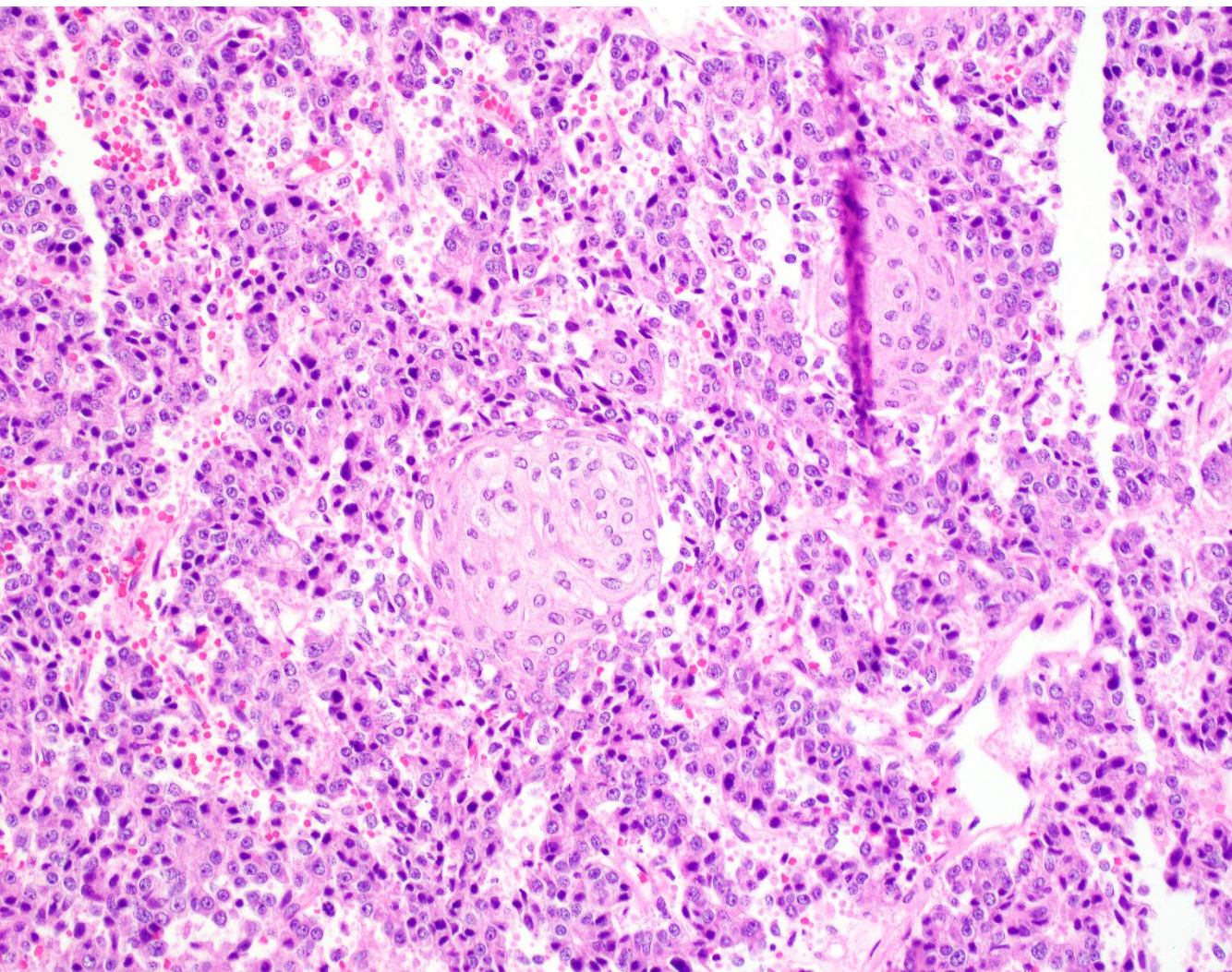
Prominent squamoid morules



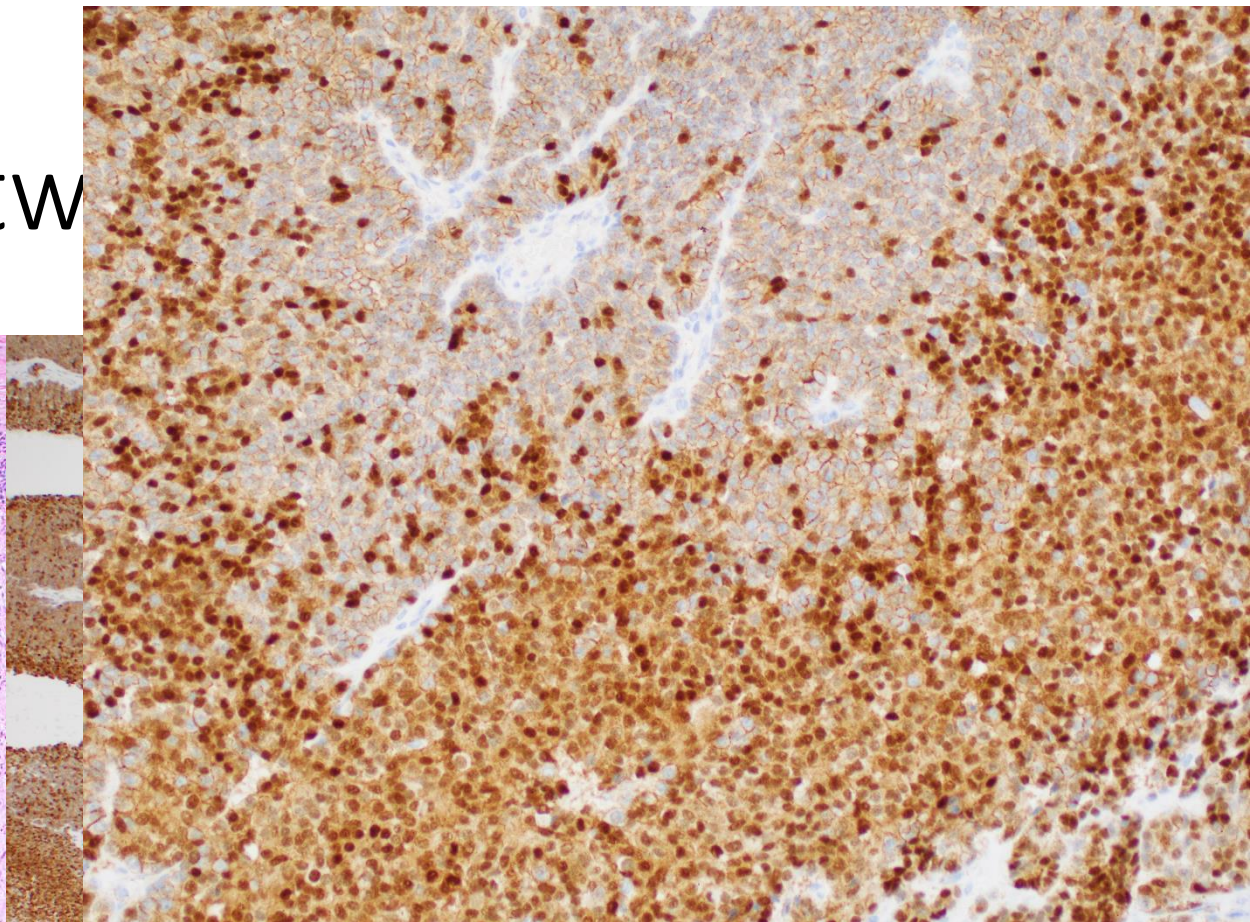
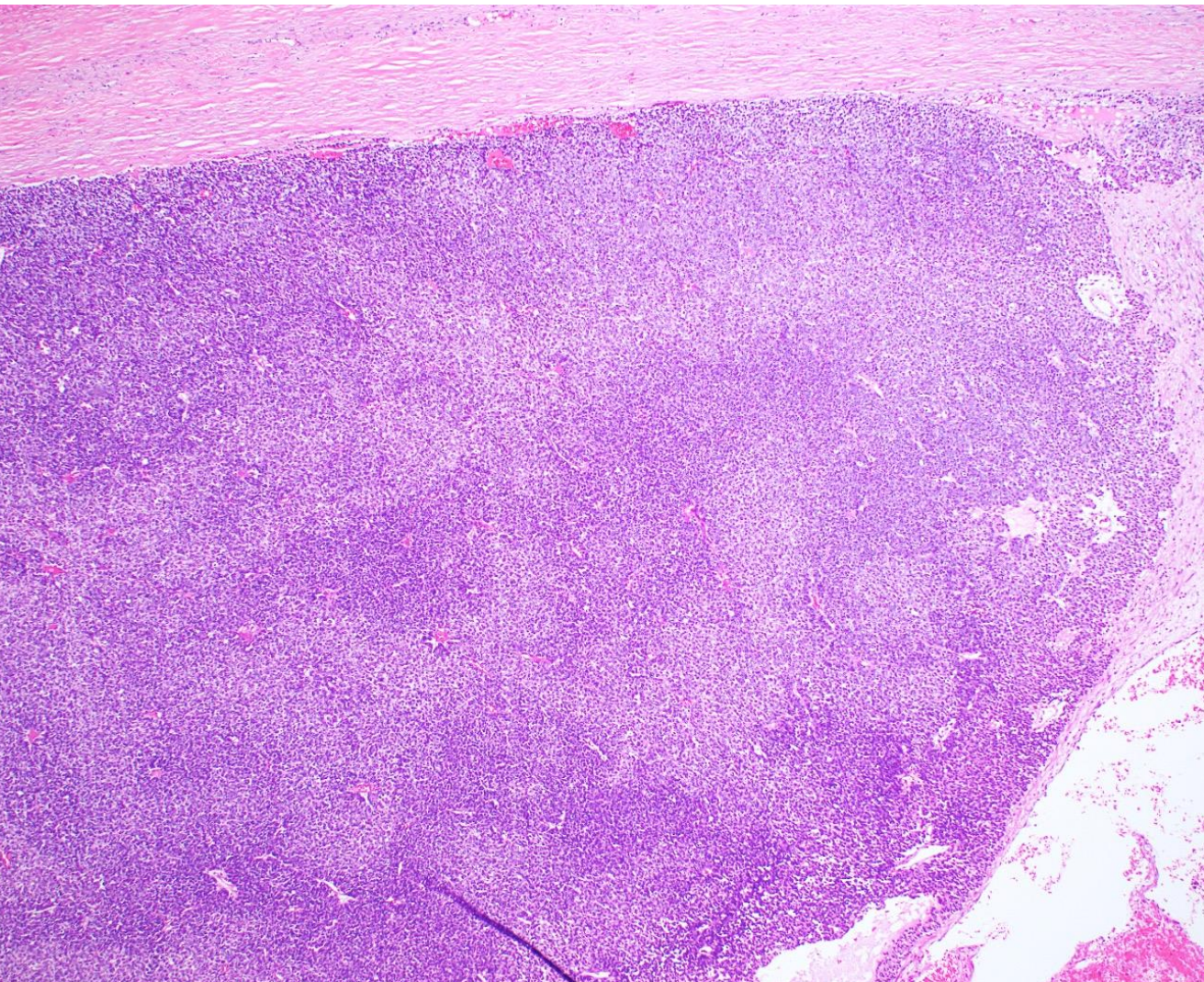
Squamoid morules had clear nuclei



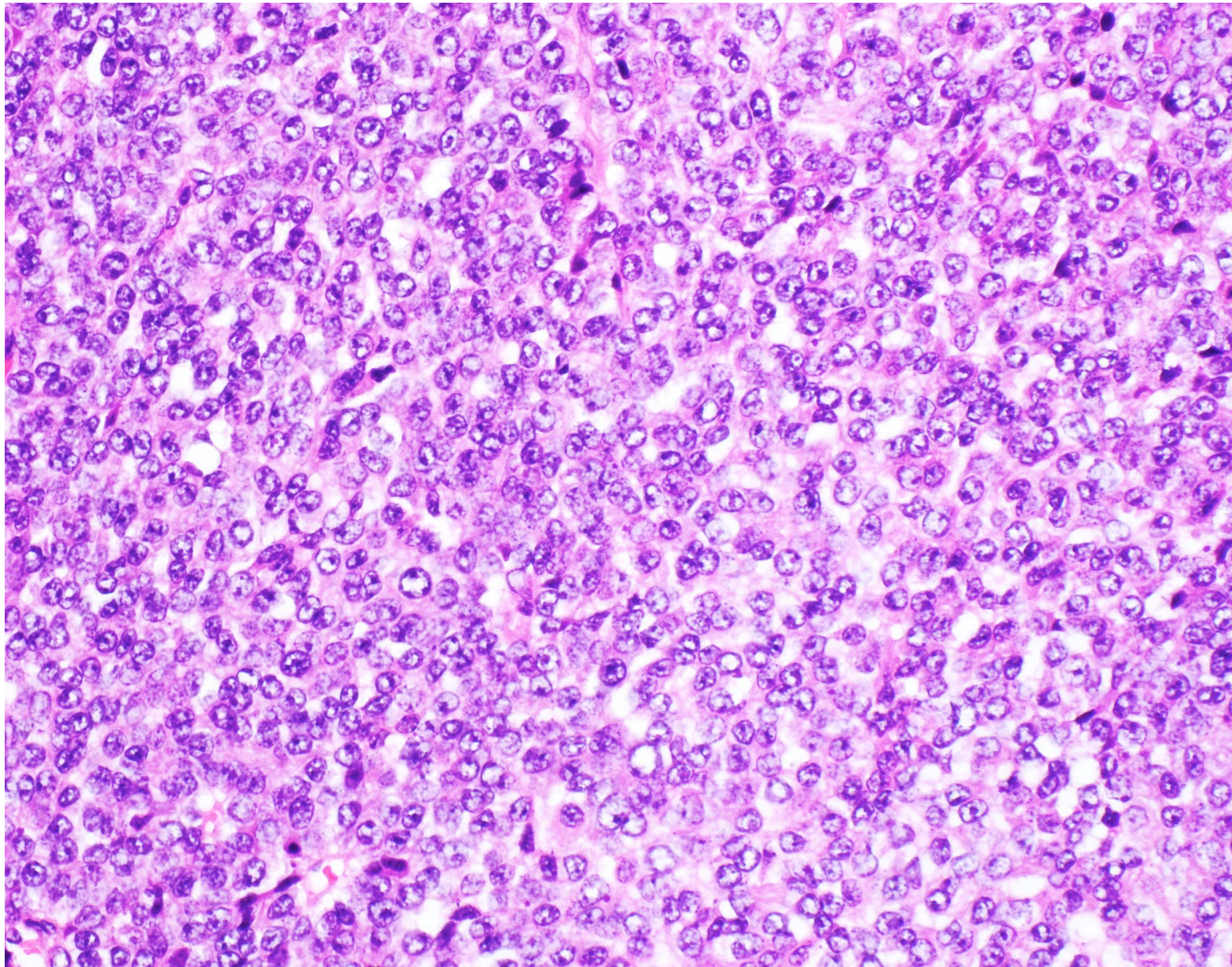
Squamoid morules were + for nuclear beta-catenin

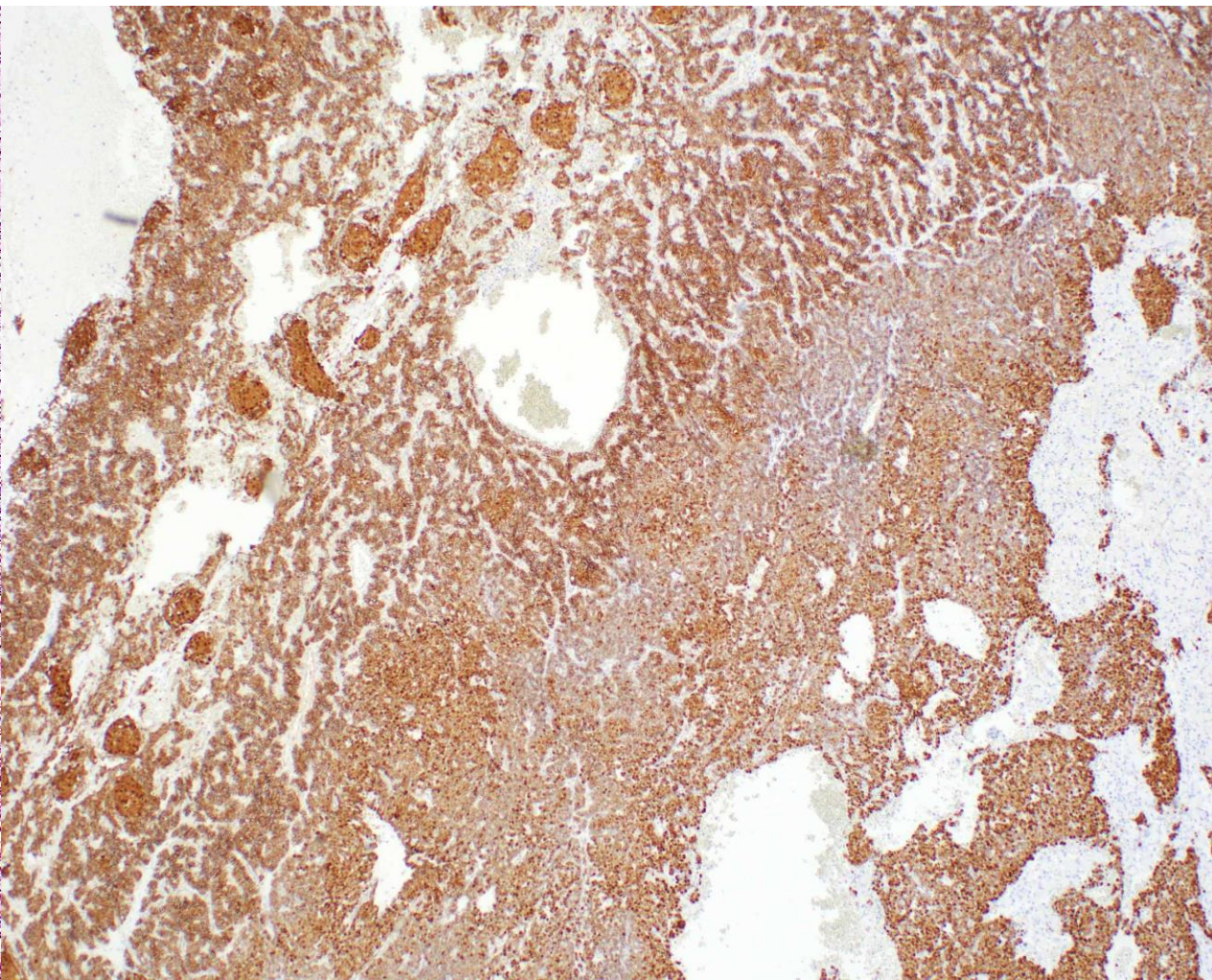
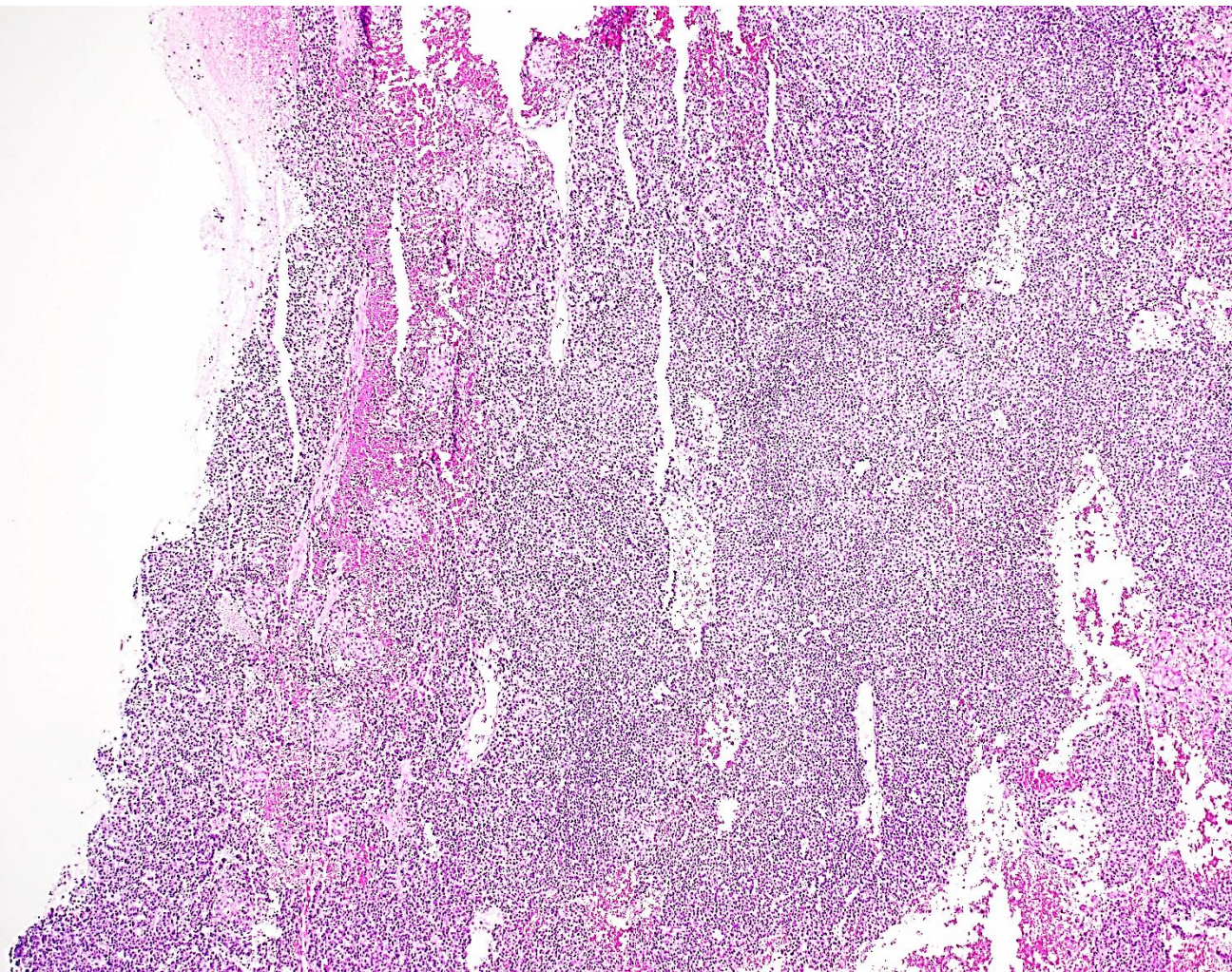


Note the pale zones betw



Beta -catenin stain





**Case # 5 –Diagnosis**

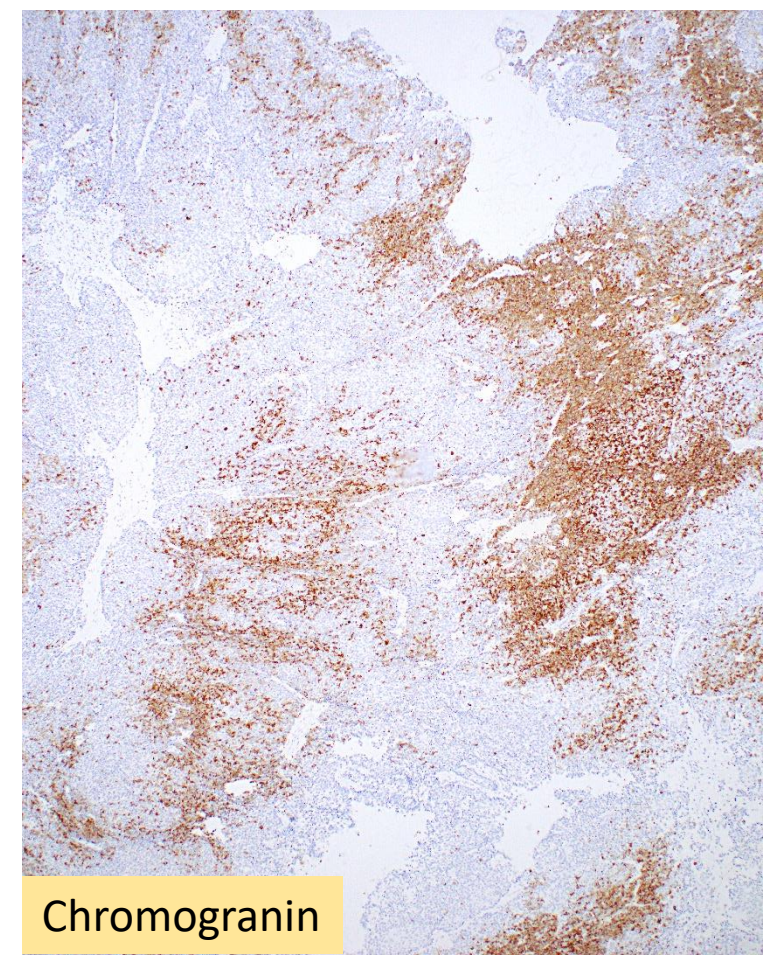
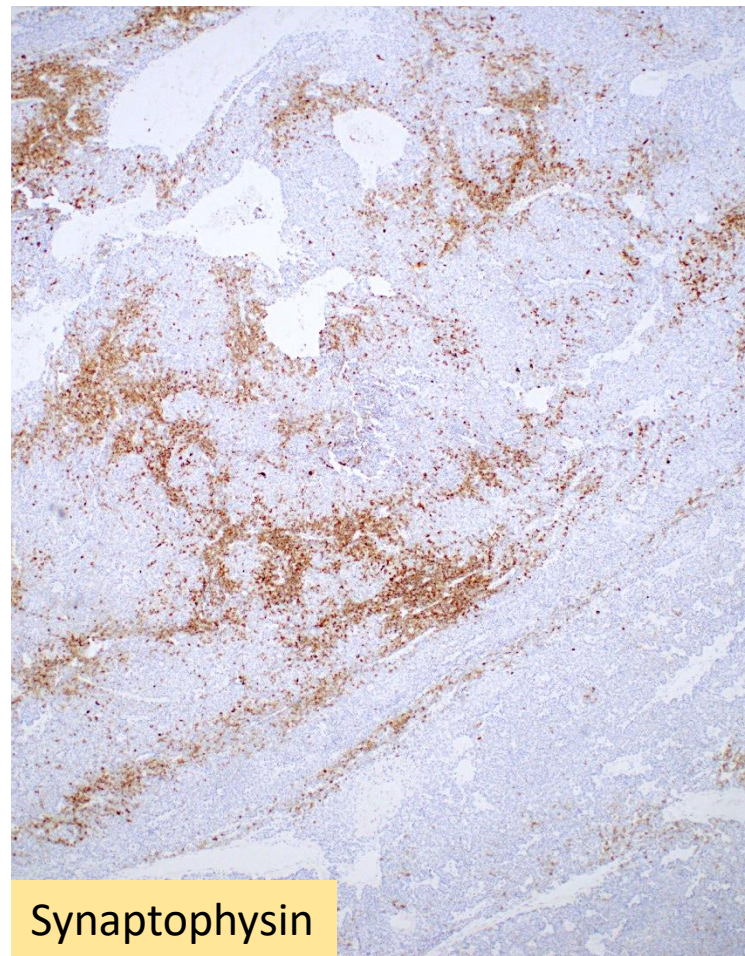
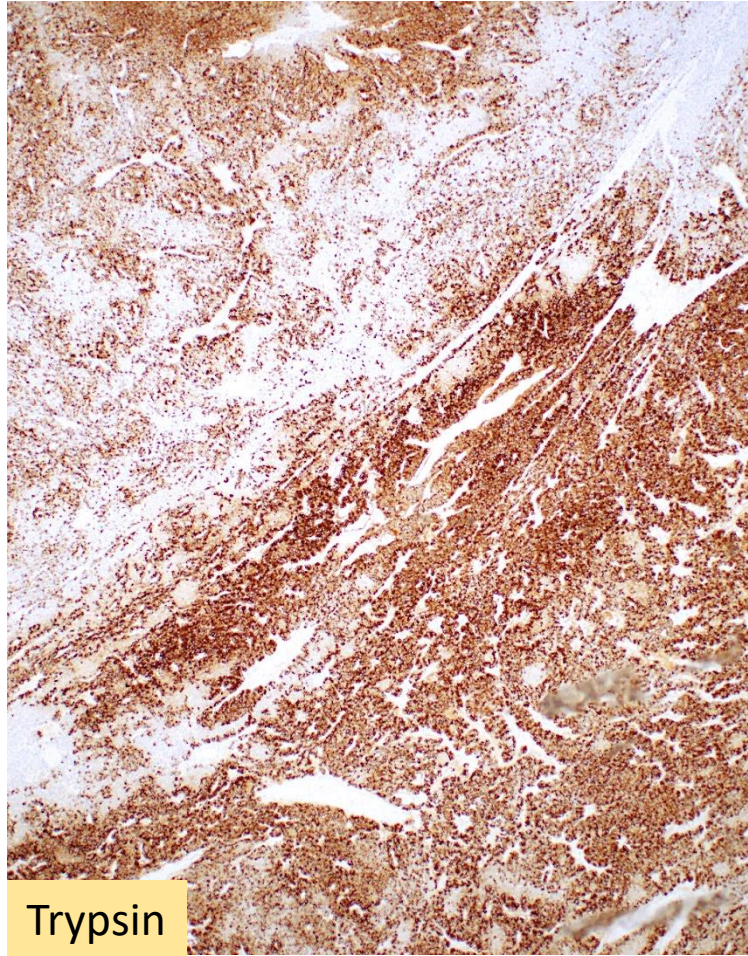
Pancreatoblastoma

# Pancreatoblastoma

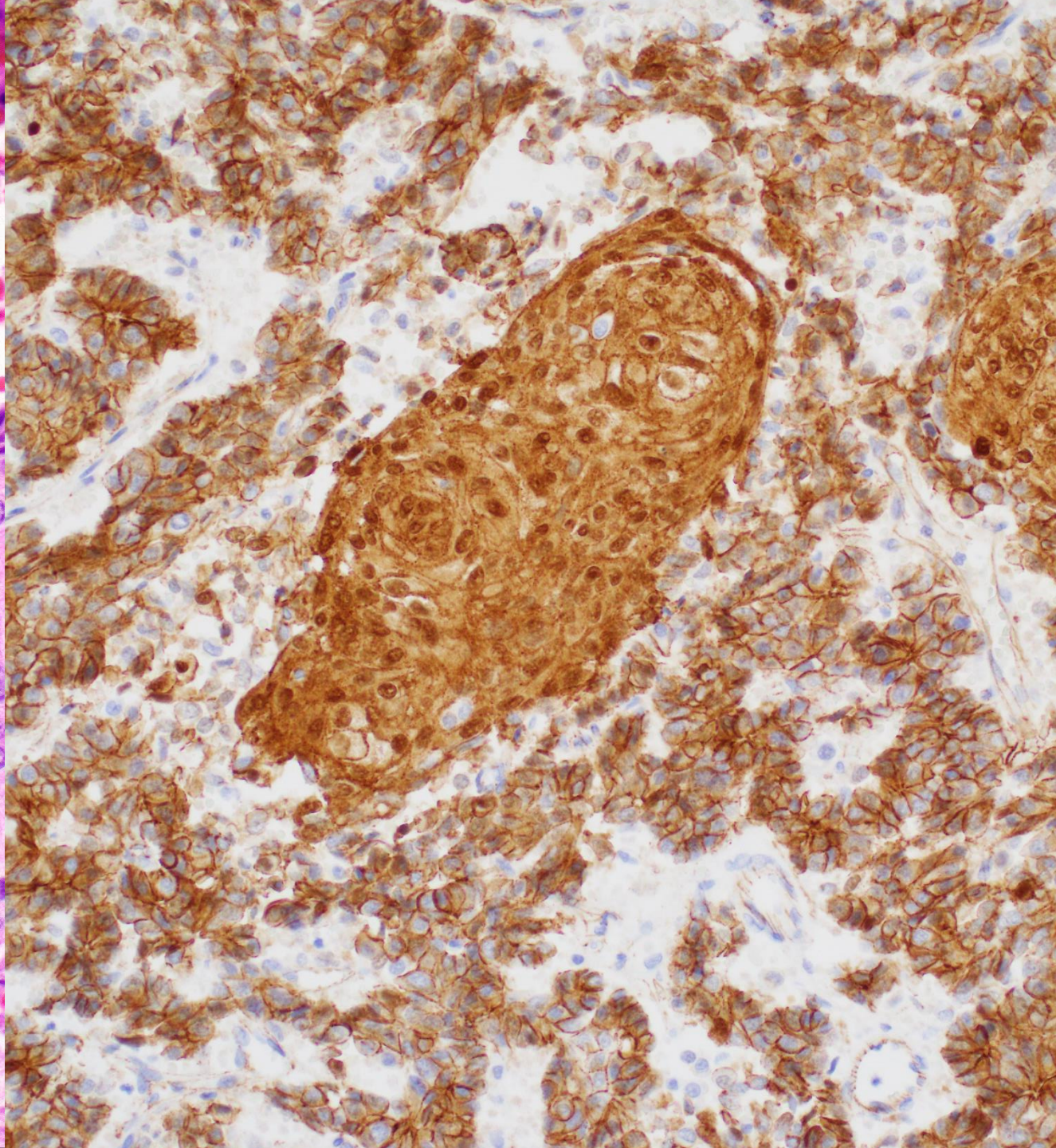
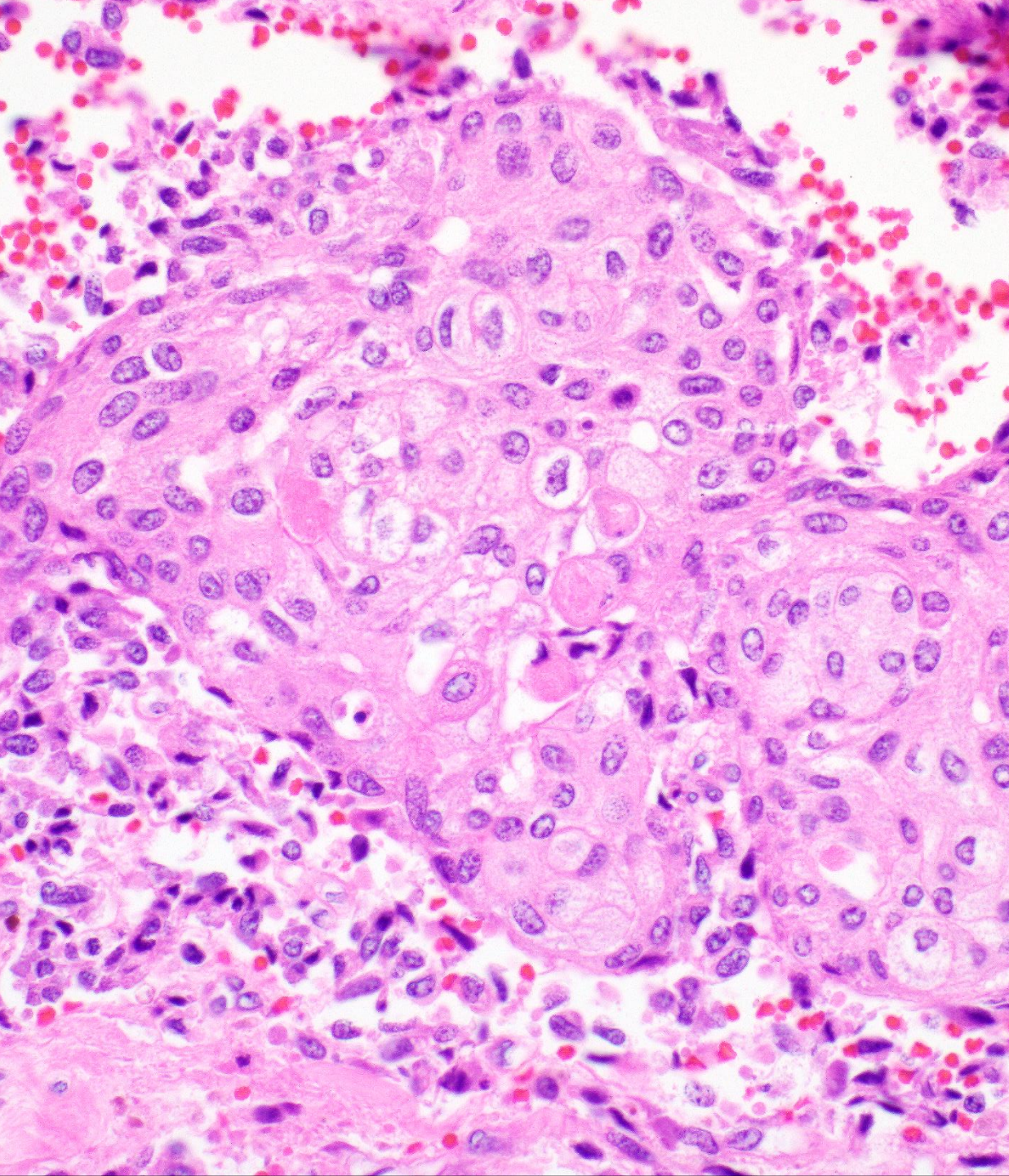
- Malignant pancreatic tumor
  - Most common in children but may also occur in adults
- Show multiple lines of differentiation (acinar, ductal, mesenchymal, primitive blastema)
- **Squamoid morules are a HALLMARK**
  - Contain biotin-rich, optically clear nuclei (BROCN)
  - Morules overexpress estrogen receptor (ER)- $\beta$  and (aberrant) nuclear/cytoplasmic  $\beta$ -catenin
  - Upregulated Wnt signaling pathway (promotes keratinization and hair folliculogenesis) in embryo
  - ER- $\beta$  and  $\beta$ -catenin highlight even subtle squamoid morules



# Mixed acinar (trypsin, chymotrypsin) and neuroendocrine differentiation by IHC



Loss of chromosome 11p; Somatic alterations in APC/beta-catenin pathway including *CTNNB1* and *APC*

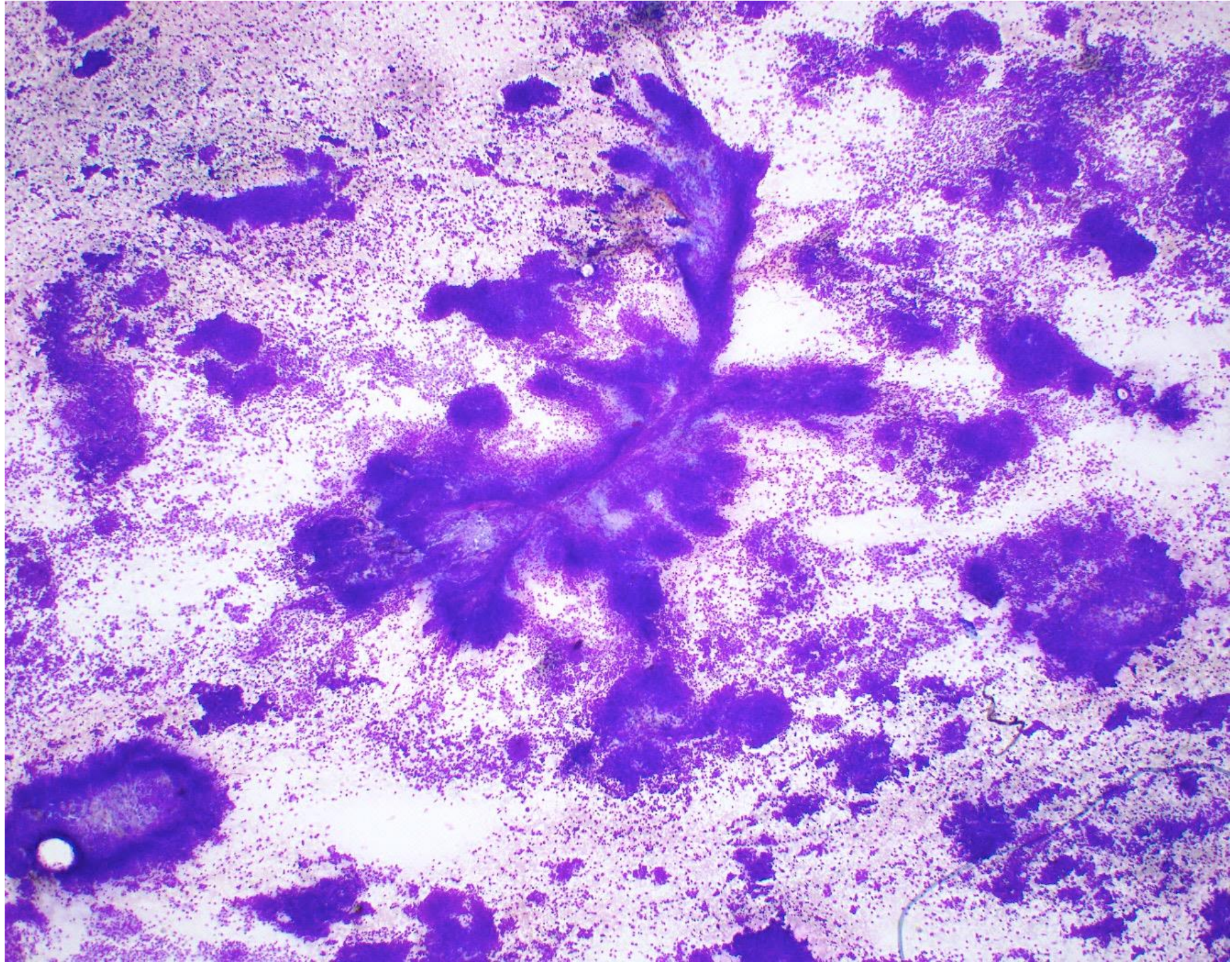


# We recently analyzed 10 pancreatoblastomas

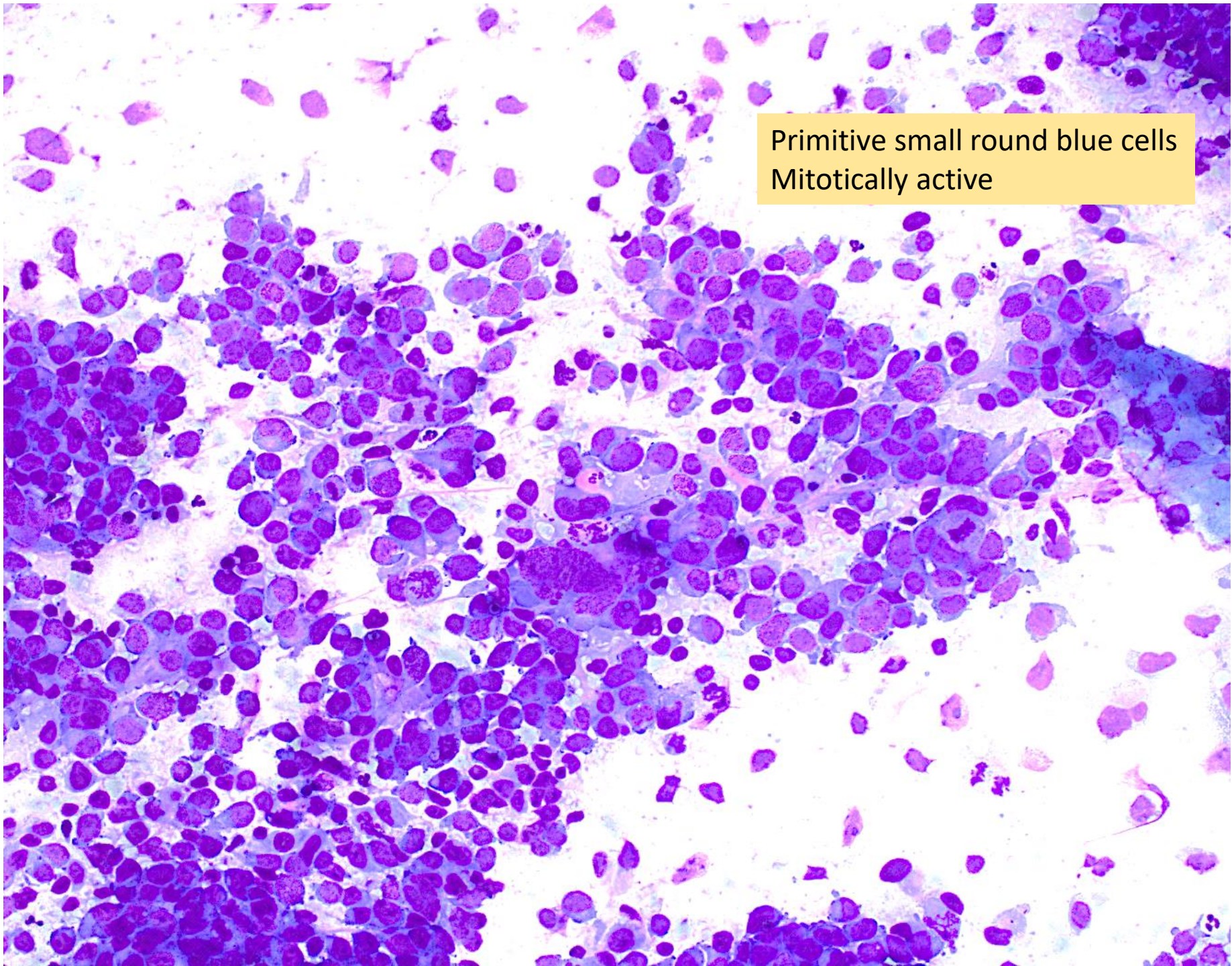
- All were adults
- 5 men and 4 women
- median age 50 yrs (range 34– 60), median size 5cm (range 2.5 – 12 cm)
- Aggressive tumors
  - 4 were metastatic at diagnosis
  - 5/9 died of disease
- Two patients had Gardner's syndrome
  - One of those patients is case # 4

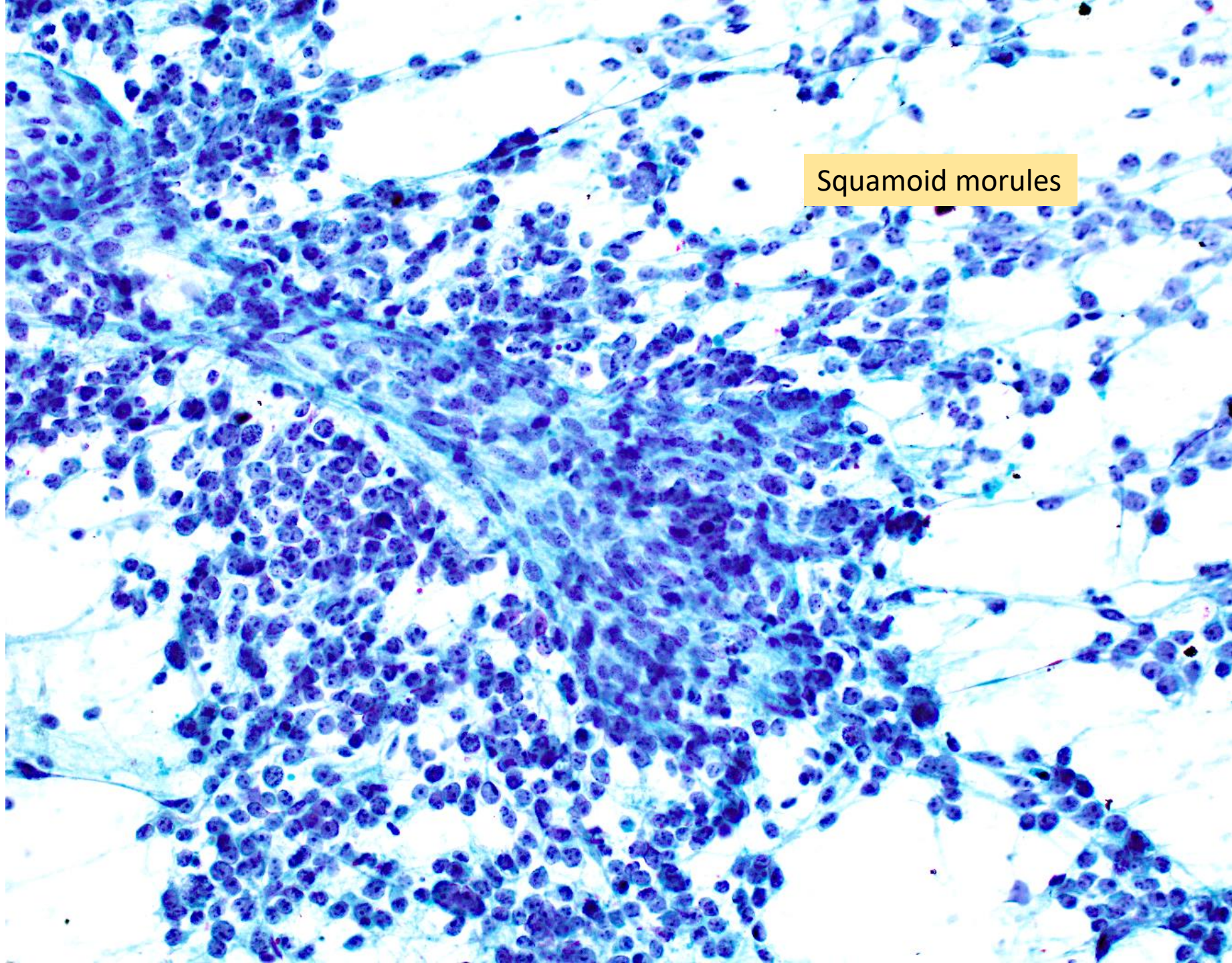
# Case #4

- 34 year old male with history of Gardner's syndrome presented with abdominal pain
- On CT there was an 8.0 cm cystic and solid pancreatic tail mass and multiple liver lesions
- FNA was performed on one of the liver lesions

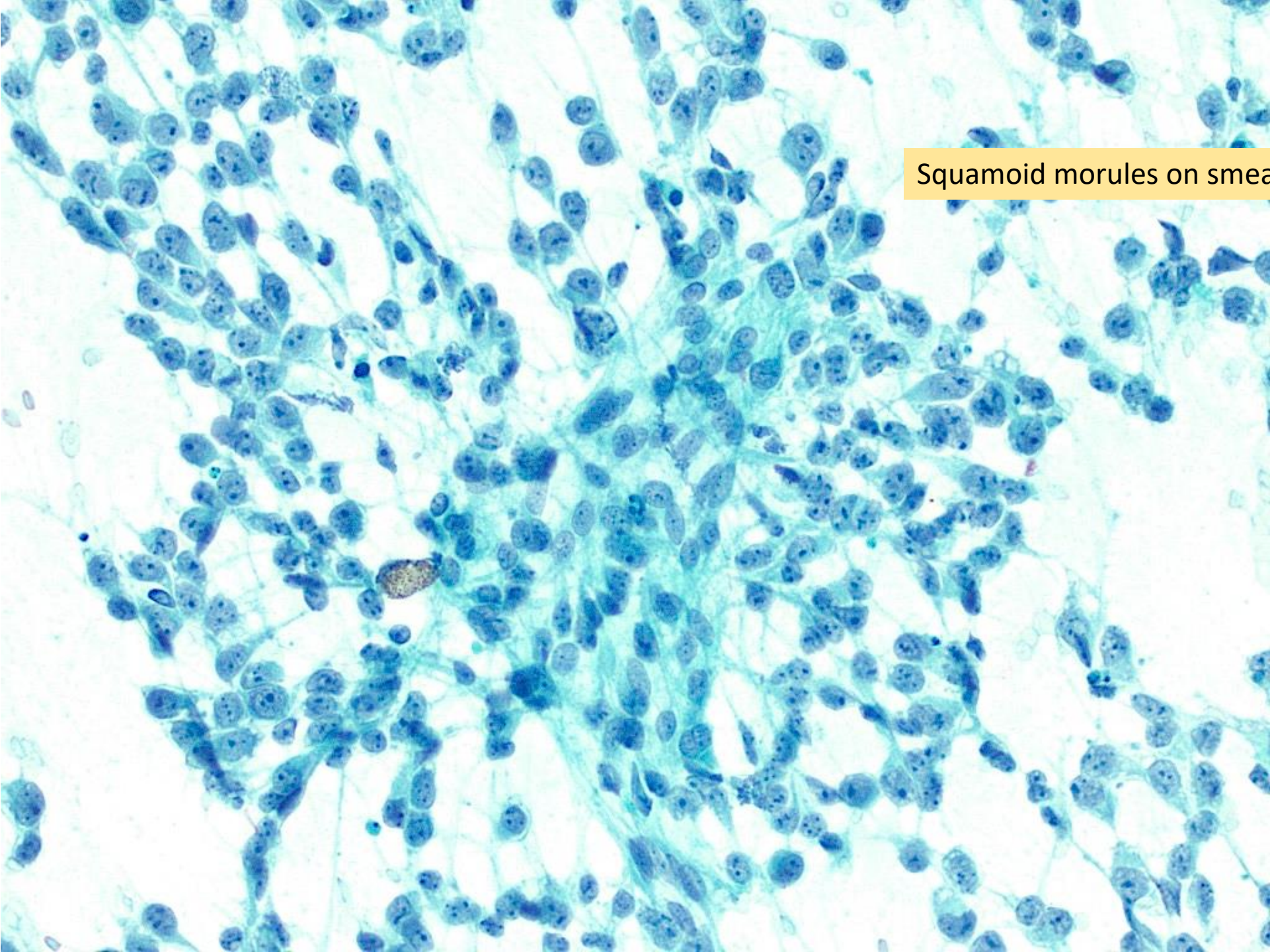


Primitive small round blue cells  
Mitotically active



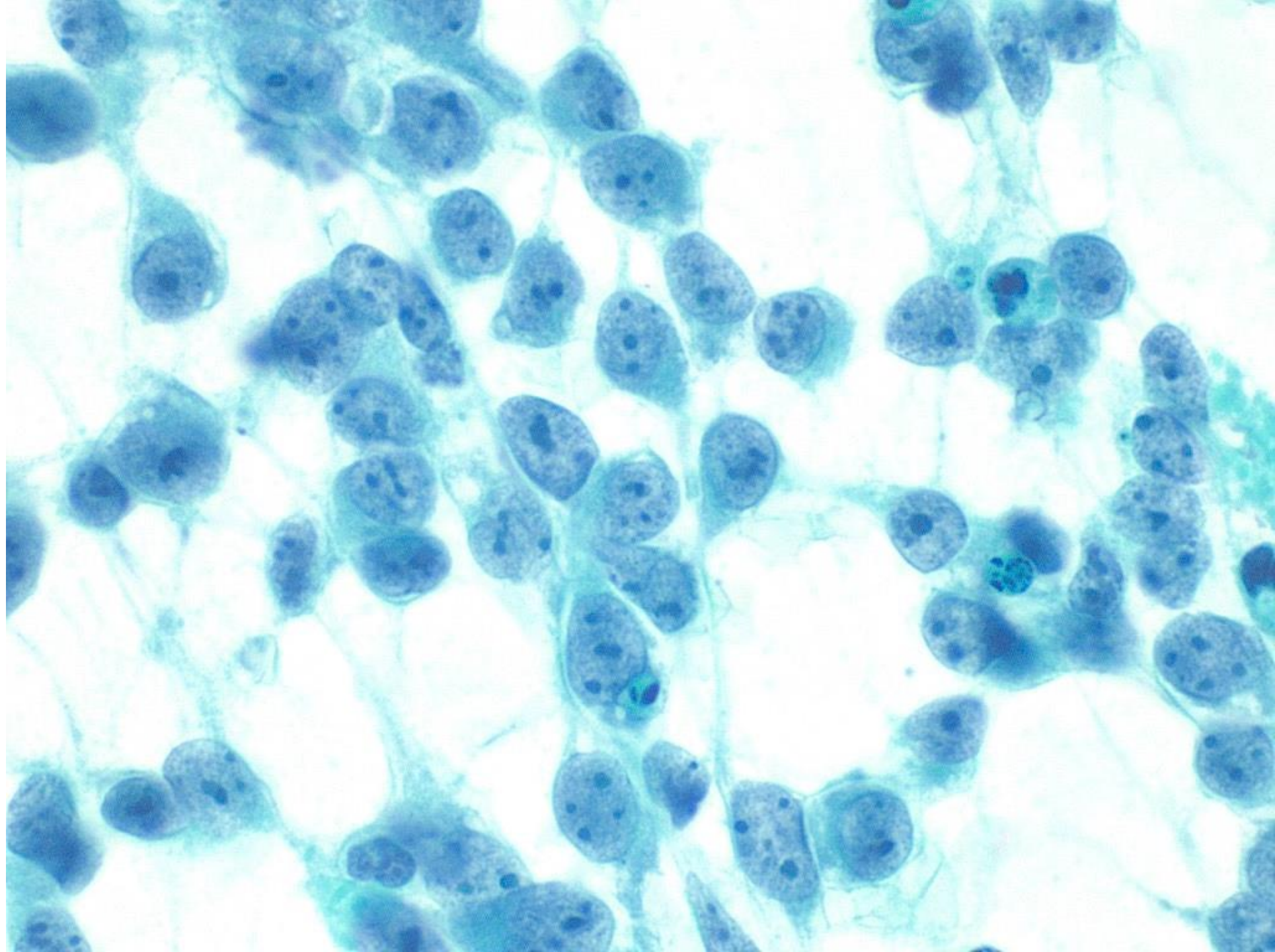


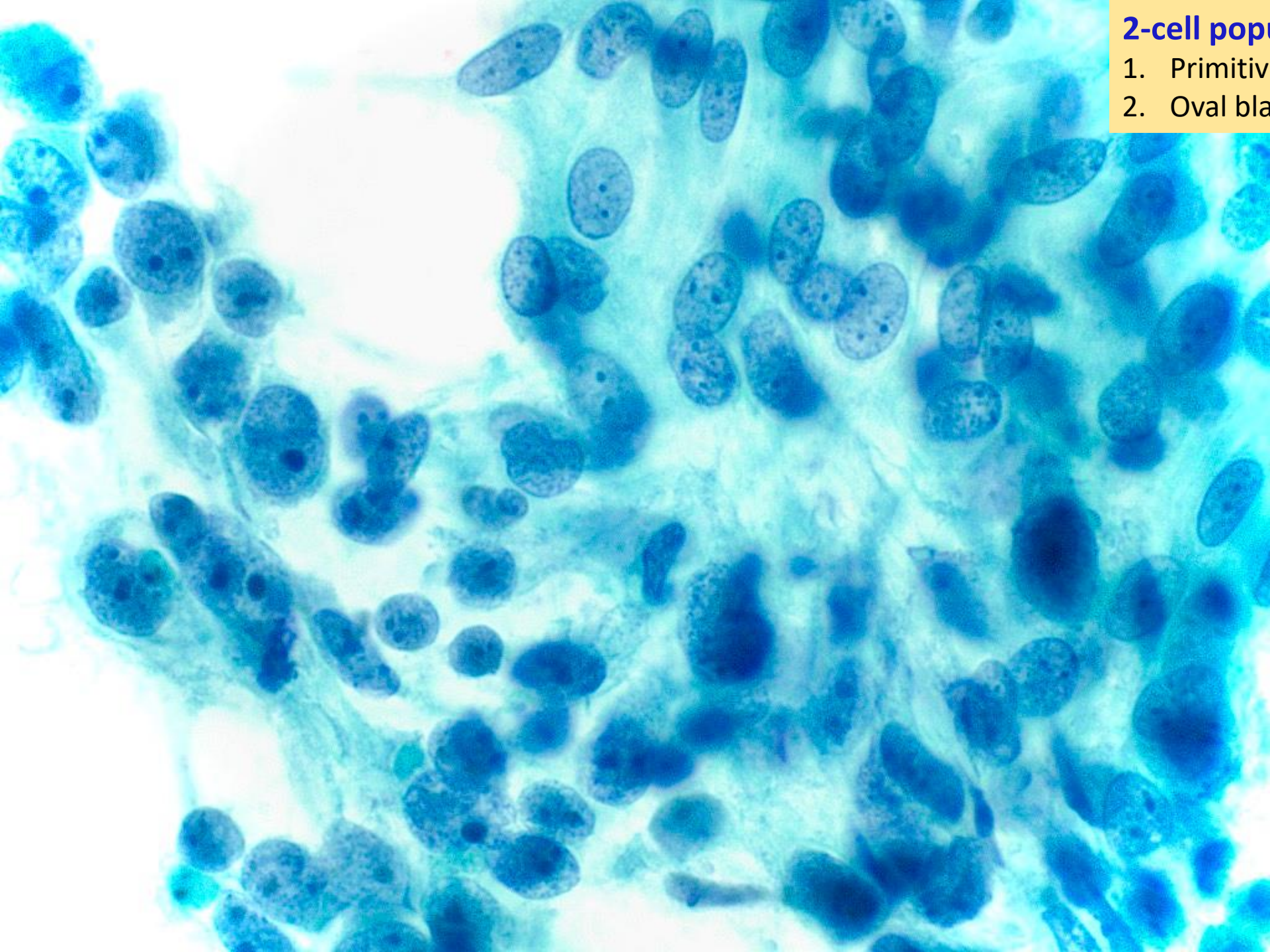
Squamoid morules



Squamoid morules on smear



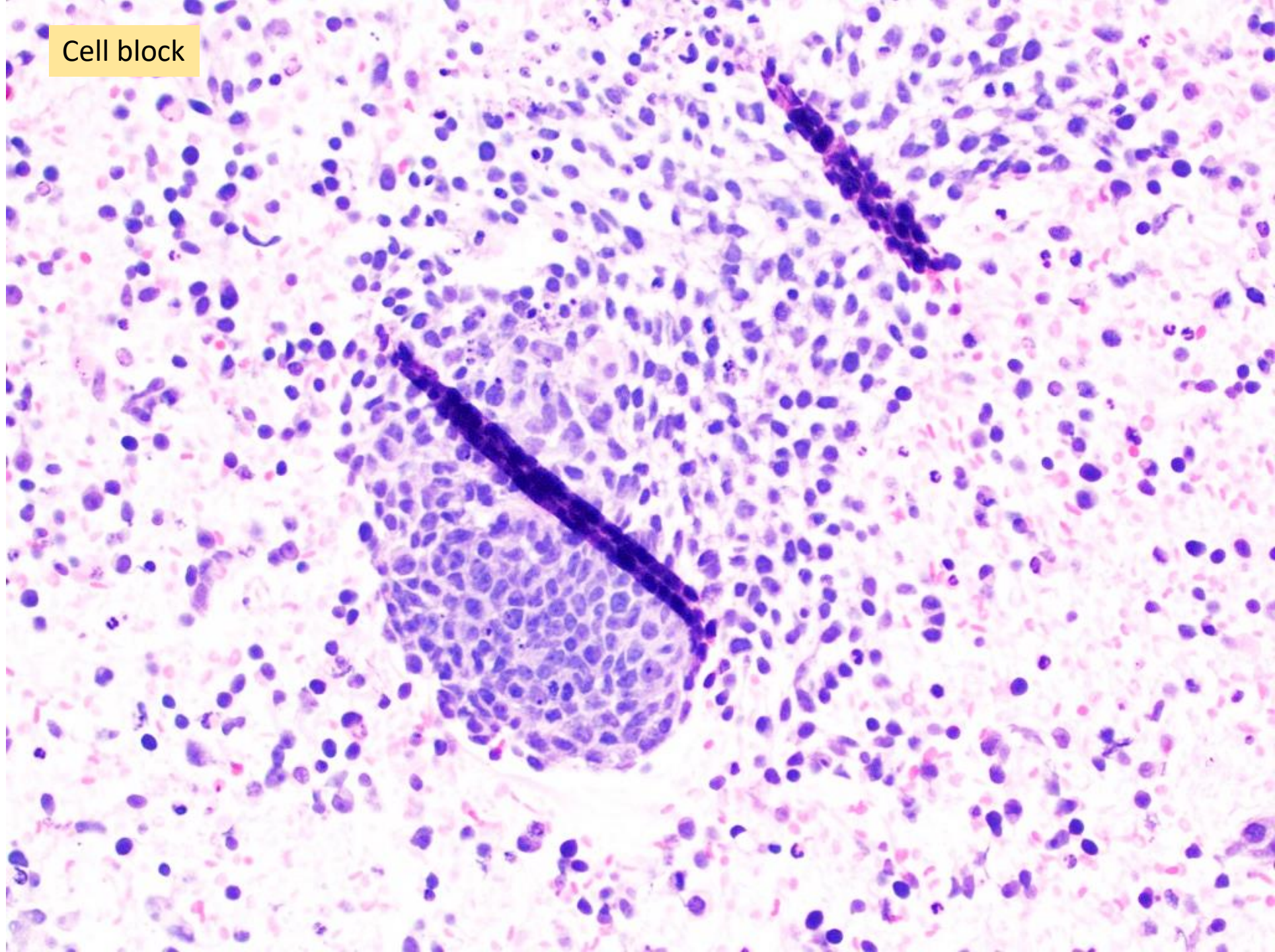




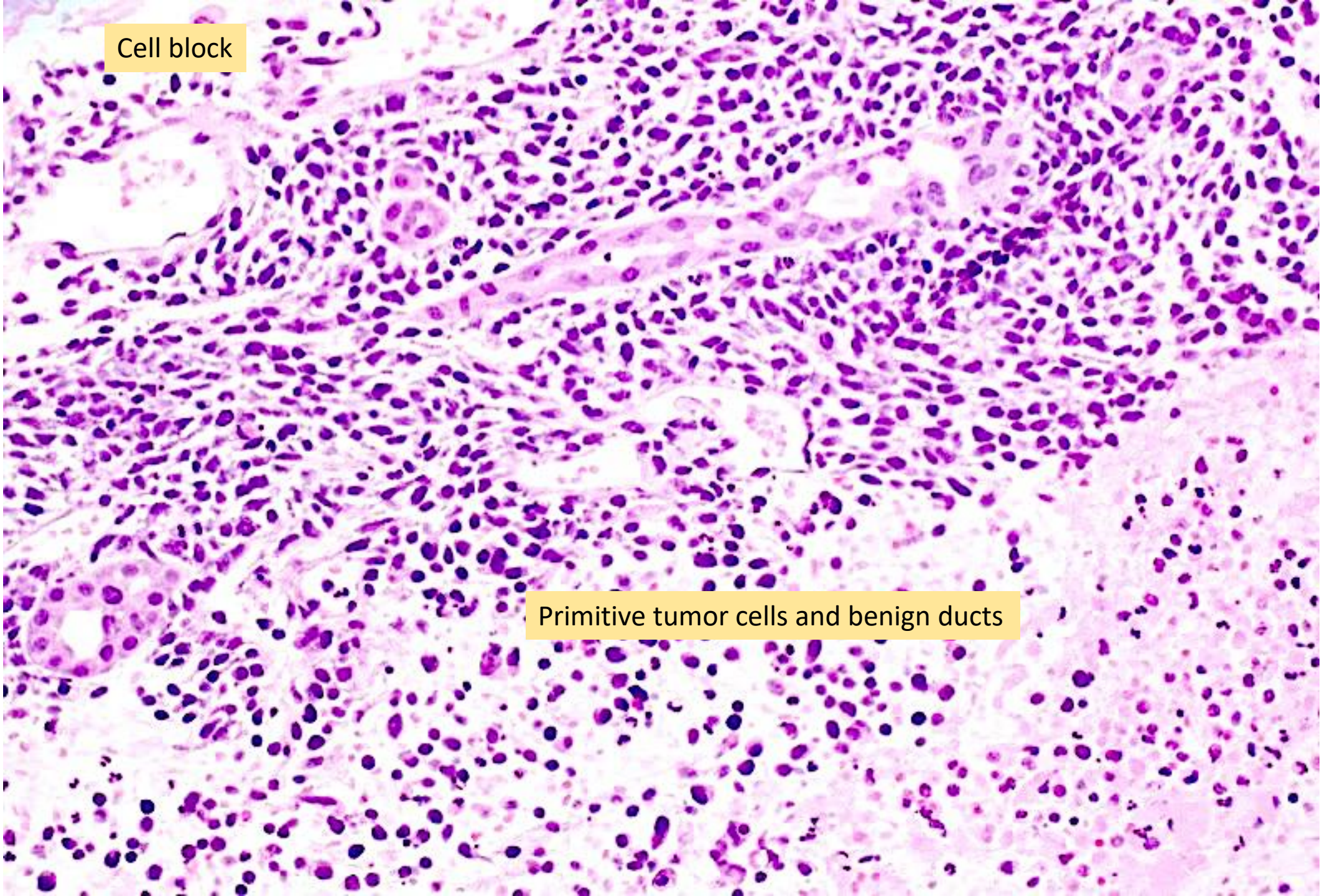
## 2-cell population

1. Primitive cells with prominent nucleoli
2. Oval bland cells from squamoid morule

Cell block



Cell block



Primitive tumor cells and benign ducts

# Case #4 – cell block

Tumor cells were positive for:

Pancytokeratin

Synaptophysin

CD56

$\beta$ -catenin

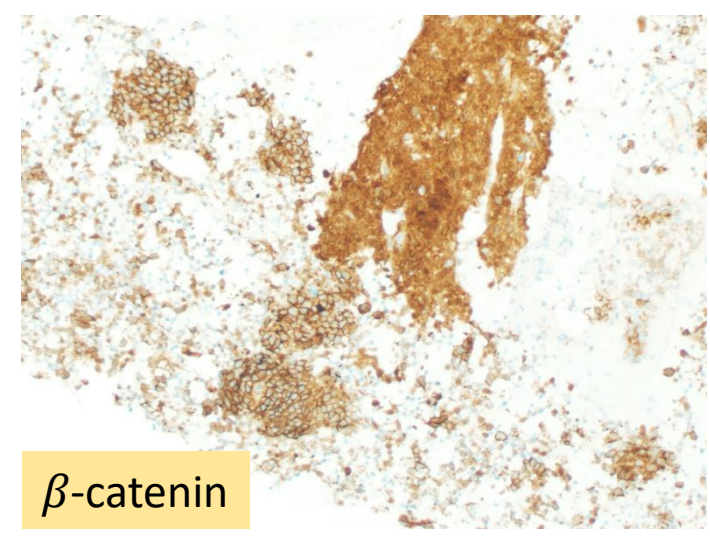
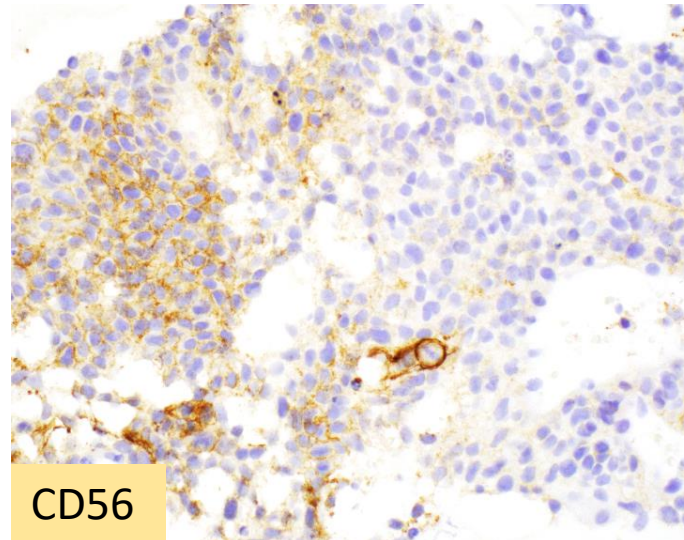
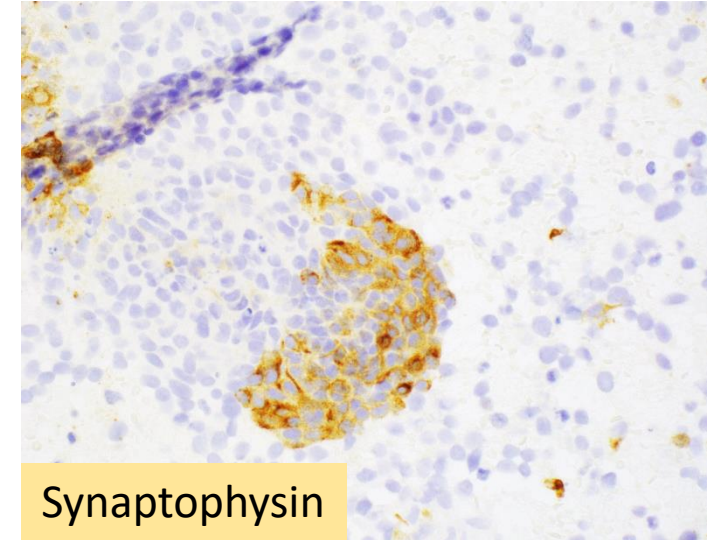
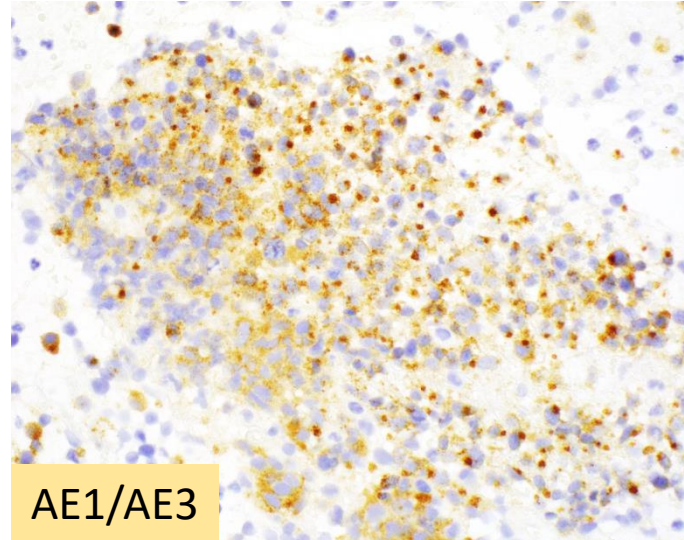
Ki67 index was 60%

Tumor cells were negative for:

OCT3/4

PLAP

CD117



Nuclear and cytoplasmic staining

Case # 4 - Diagnosis?

Pancreatoblastoma

Patient died 1 week later

## Differential Diagnosis of Solid Cellular Stroma-Poor Tumors of Pancreas

	ACC	Pancreatoblastoma	SPN	PanNET
Clinical	7 <sup>th</sup> decade	Children, rarely late adulthood (bimodal)	Young females	Syndrome (MEN)
Histology	<ul style="list-style-type: none"> <li>• Acidophilic granules</li> <li>• Cherry red nucleoli</li> <li>• Mitotically active</li> </ul>	<ul style="list-style-type: none"> <li>• Squamoid morules</li> <li>• Multiphenotypic differentiation (endocrine, acinar, ductal)</li> </ul>	<ul style="list-style-type: none"> <li>• Pseudopapillae</li> <li>• Areas of macrophages</li> <li>• Hyaline globules</li> <li>• Nuclear grooves</li> </ul>	<ul style="list-style-type: none"> <li>• Nesting</li> <li>• NE chromatin</li> <li>• Delicate vascularity</li> </ul>
IHC	Keratins+ Trypsin/chymo+ NE+/-	Keratins+ Trypsin + NE+ N/C $\beta$ -catenin	Keratins --/+ N/C $\beta$ -catenin PR+ Chromogranin -	Keratins+ NE+ Trypsin -