



# Intraoperative Consultation: Tips and Tricks for Successful Outcomes

Alessandra Ceolin Schmitt, MD  
Surgical Pathologist and Cytopathologist  
Mayo Clinic Scottsdale, Arizona  
08/11/2020

# It is not all about the FS slides...

- Look up:
  - Clinical impression
  - Path diagnosis
- Imaging:
  - Mass location, size,
  - Behavior:
    - ?growth rate ?infiltrative
- Prior treatment
- History of malignancy
- Pull prior slides





# Clinical History = Compass





*“Without clinical history you will be more lost than a stray dog in a hail of gunfire”*

# Outlines

- Top 3 reasons for a frozen section (FS)
- 10 common FS challenges
- Advices for better FS outcomes

# The Most Common Intraoperative Consultations

1. Margins
2. Lymph nodes
3. Diagnosis

# The Most Common Intraoperative Consultations

1. Margins
2. Lymph nodes
3. Diagnosis
- 4. All of the above**



# The Most Common for Intraoperative Consultations

1. Margins (MG)
2. Lymph nodes (LN)
3. Diagnosis (Dx)

# 1. Margins (MG)

- Good communication with surgeons:
  - Specimen's orientation
  - Agreement
  - Keep designation provided
- Document: specimen size, tumor location, size, and distance from margins
- Shave vs perpendicular:
  - Shave: embed true MG facing up, tumor on slide = positive margin



## Case 1

- 58 yo female with multiple prior oral cavity invasive SCC,
- Multifocal high grade dysplasia,
- Now with hard palate lesion

# Best Practice: Specimen- Driven Margin Assessment

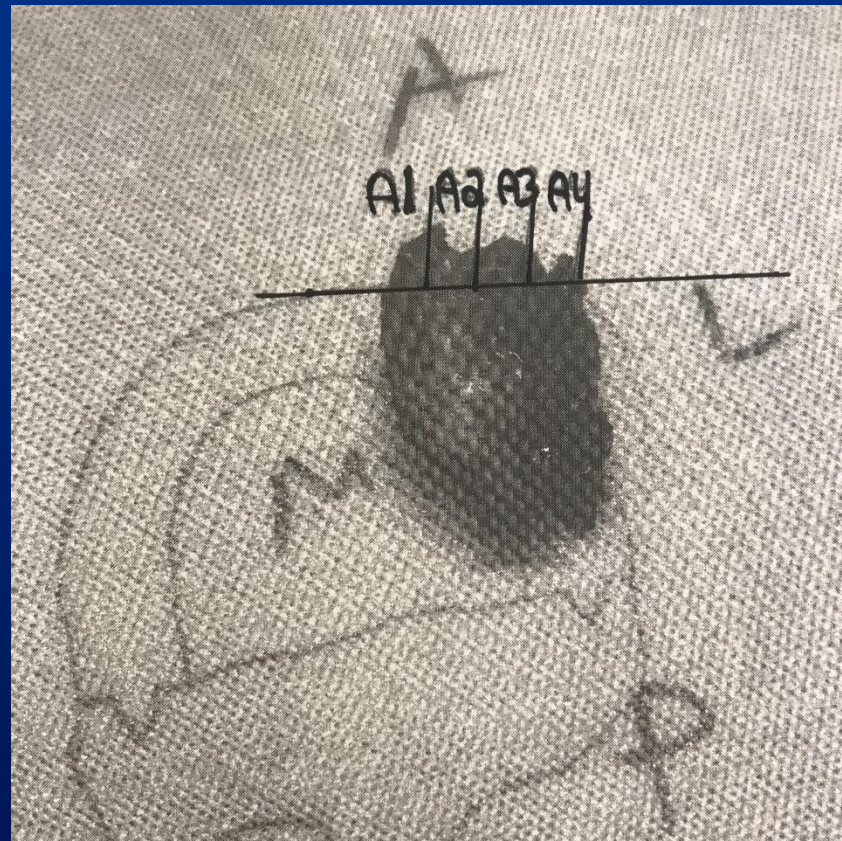


Kubik MW. Intraoperative Margin Assessment in head and Neck Cancer: A Case of Misuse and Abuse? *Head and Neck Pathology* 2020 (14): 291-302



# FS Worksheet

- Patient name
- Specimen overall dimension
- Tumor size
- Distance to MG
- Ink designation



Block	Shave	Perp.	Designation	Interpretation
1FS	X		Anterior medial	Positive for invasive carcinoma
2FS		X	Anterior	Negative for invasive carcinoma
3FS		x	Anterior	Negative for invasive carcinoma
4FS	x		Anterior lateral	Negative for invasive carcinoma

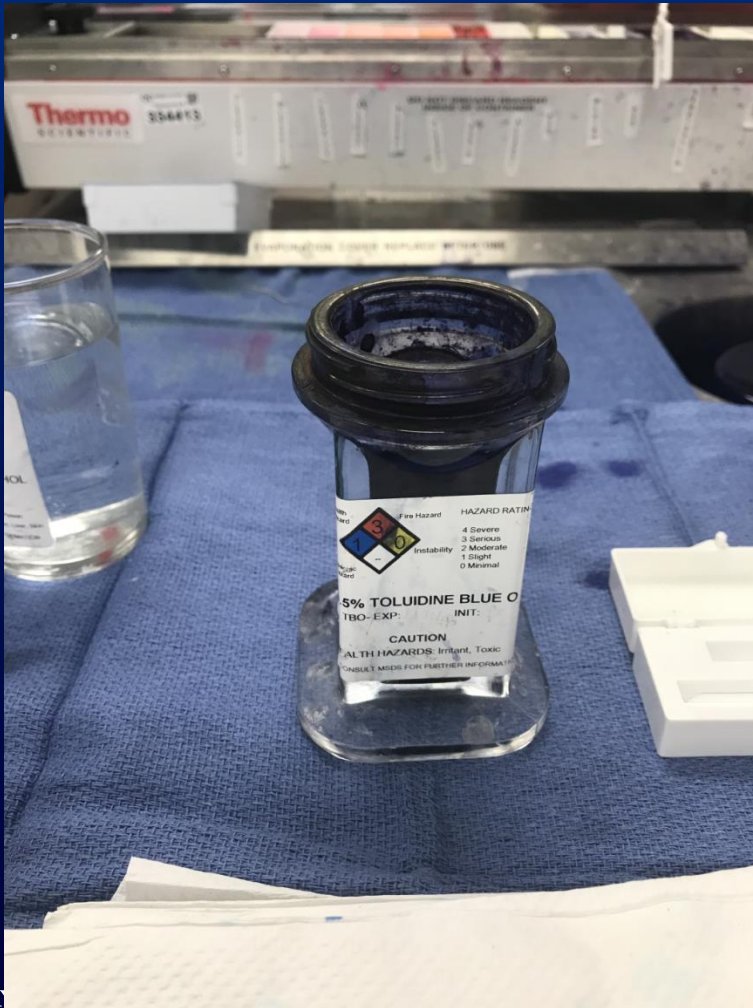
Grossed by:

Reviewed by:



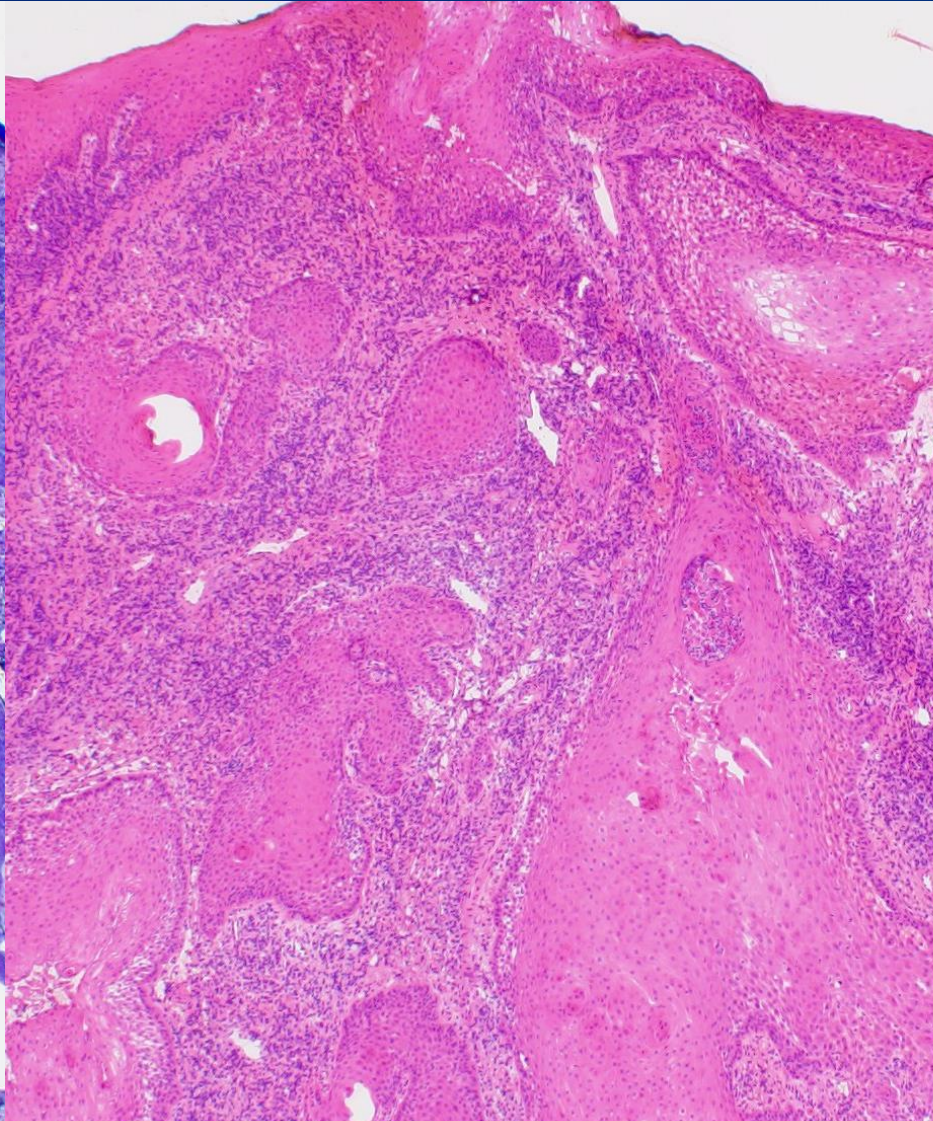
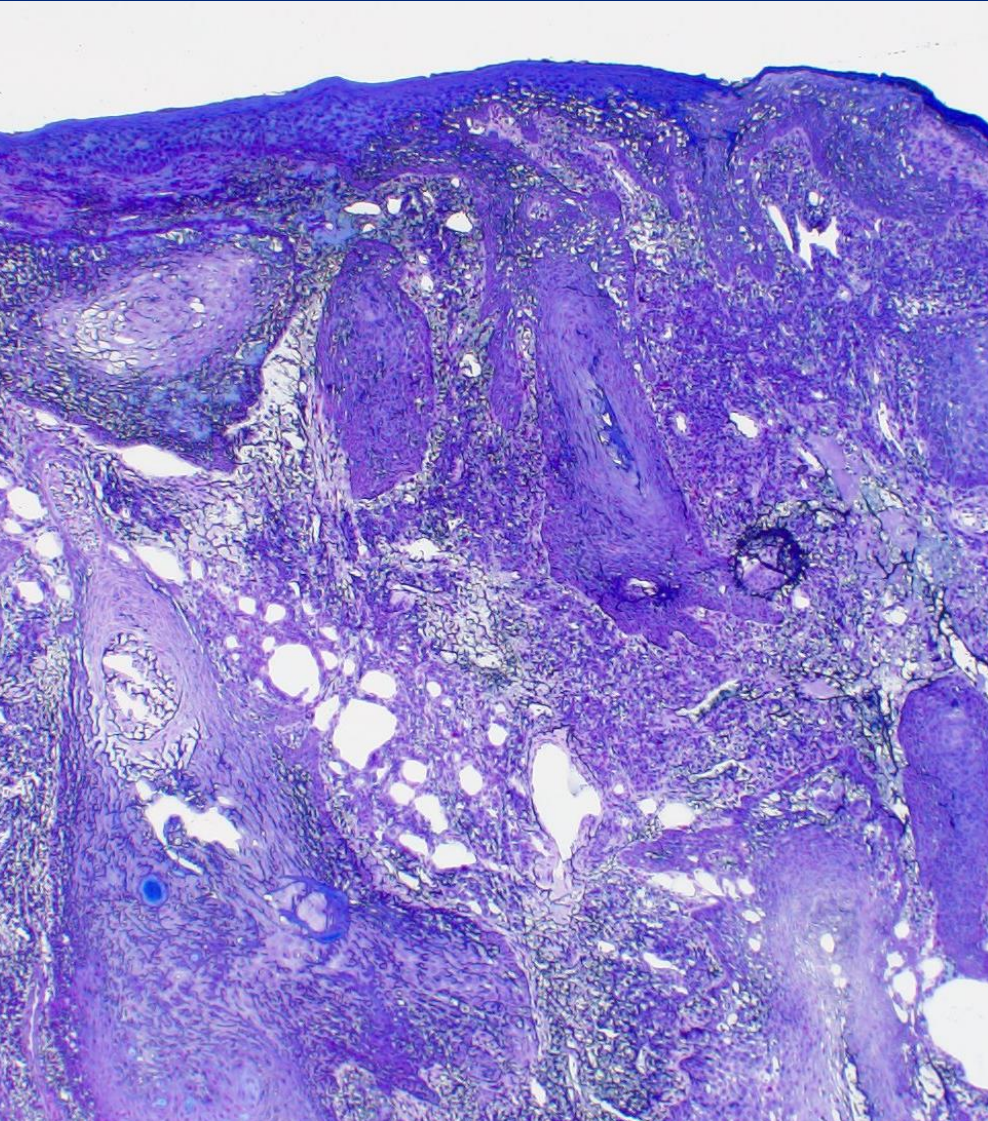
# Toluidine- Blue

- Additional section after section for HE cut
- Ready in less than 1 min



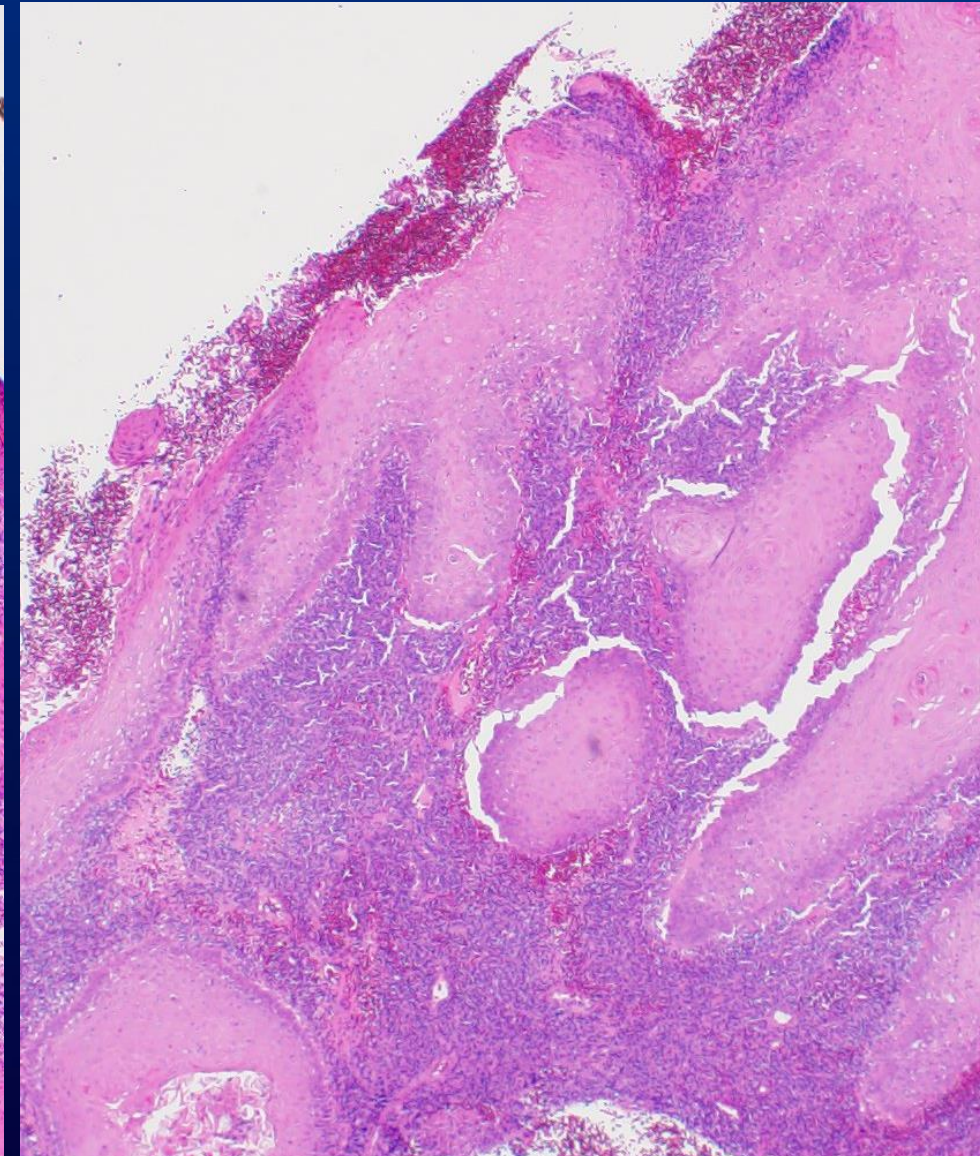
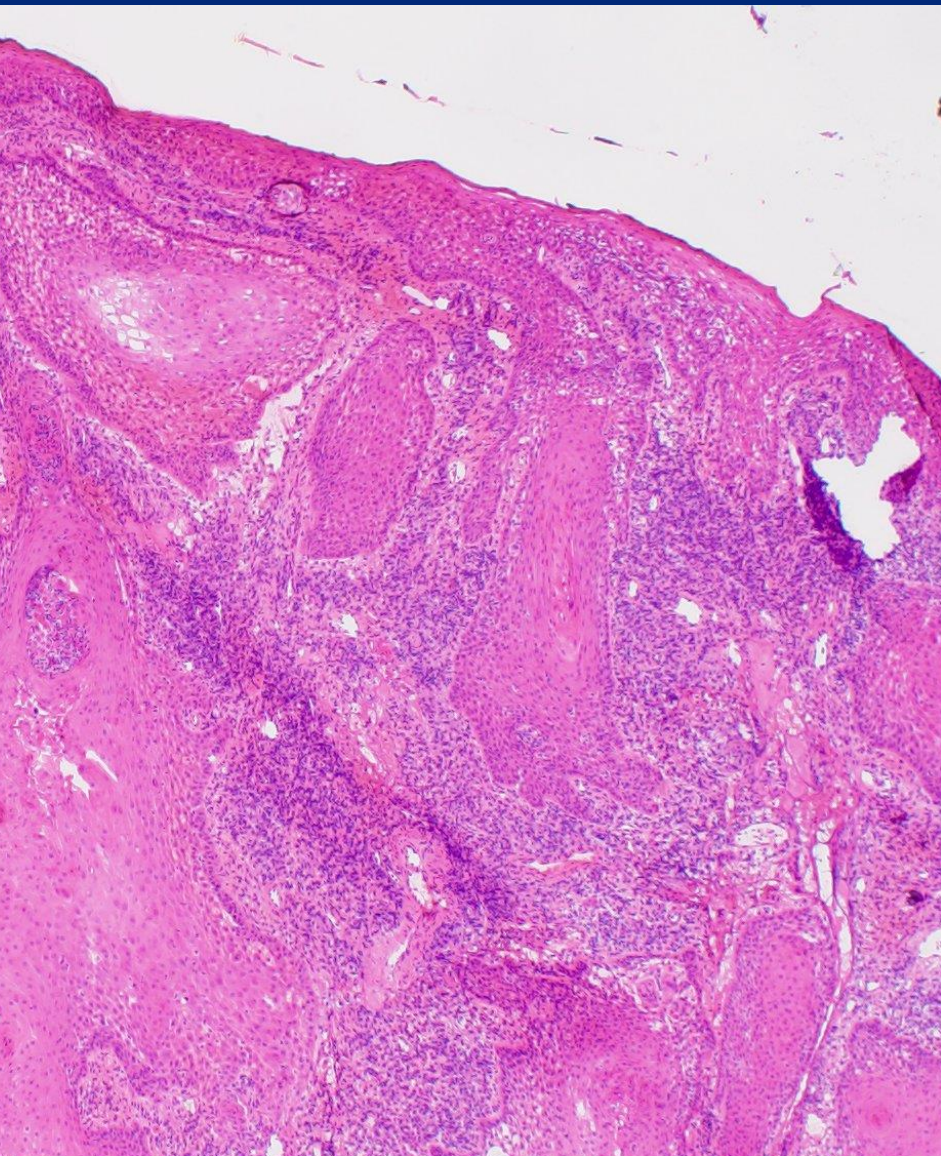


# Toluidine Blue vs HE MG FS



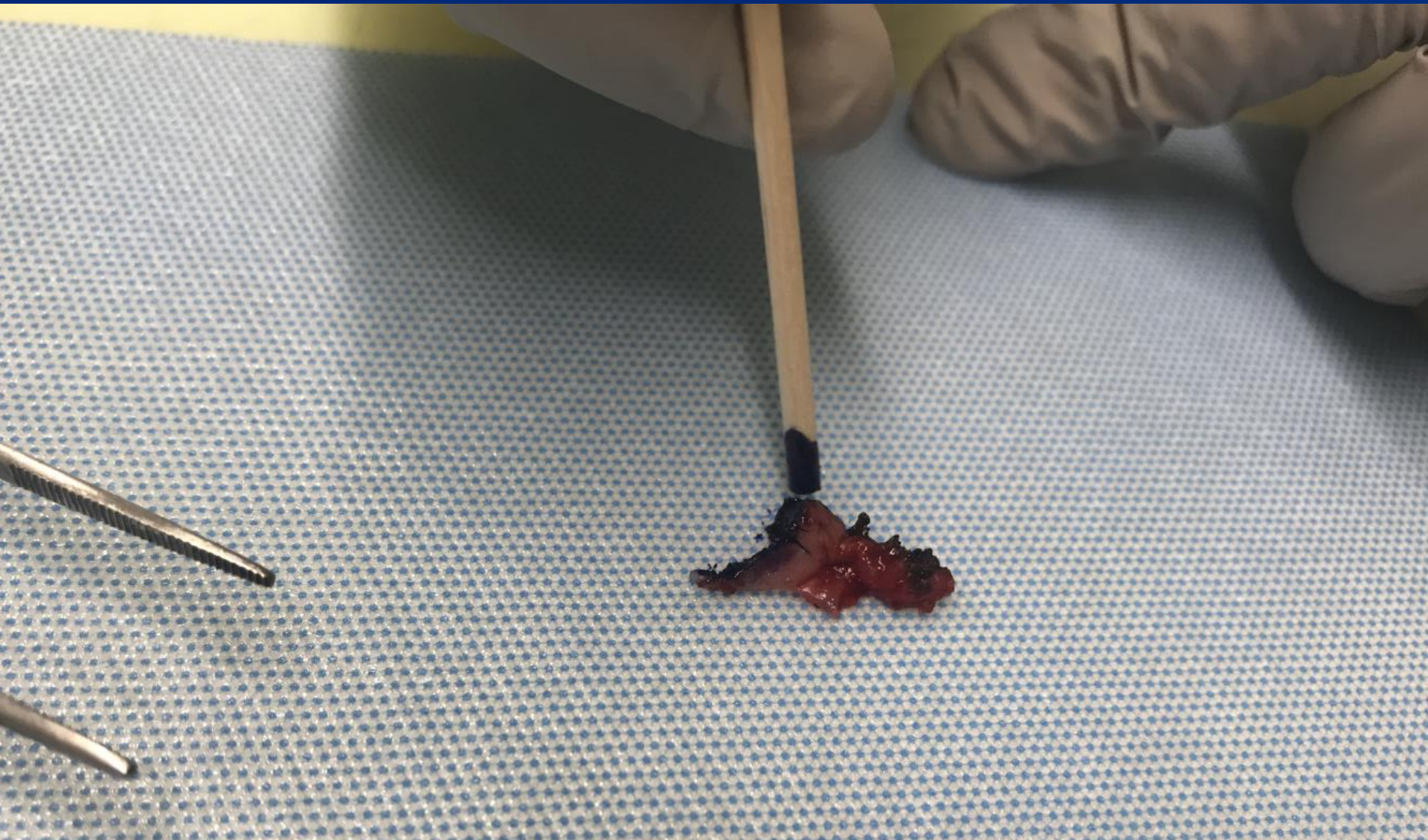


# +MG FS vs Prior Biopsy





# Revised Margin



# FS MG= True MG



- Tissue size and number of fragments on FS slide must match chuck
- If tumor on permanents but not on FS:
  - FS MG close, not +

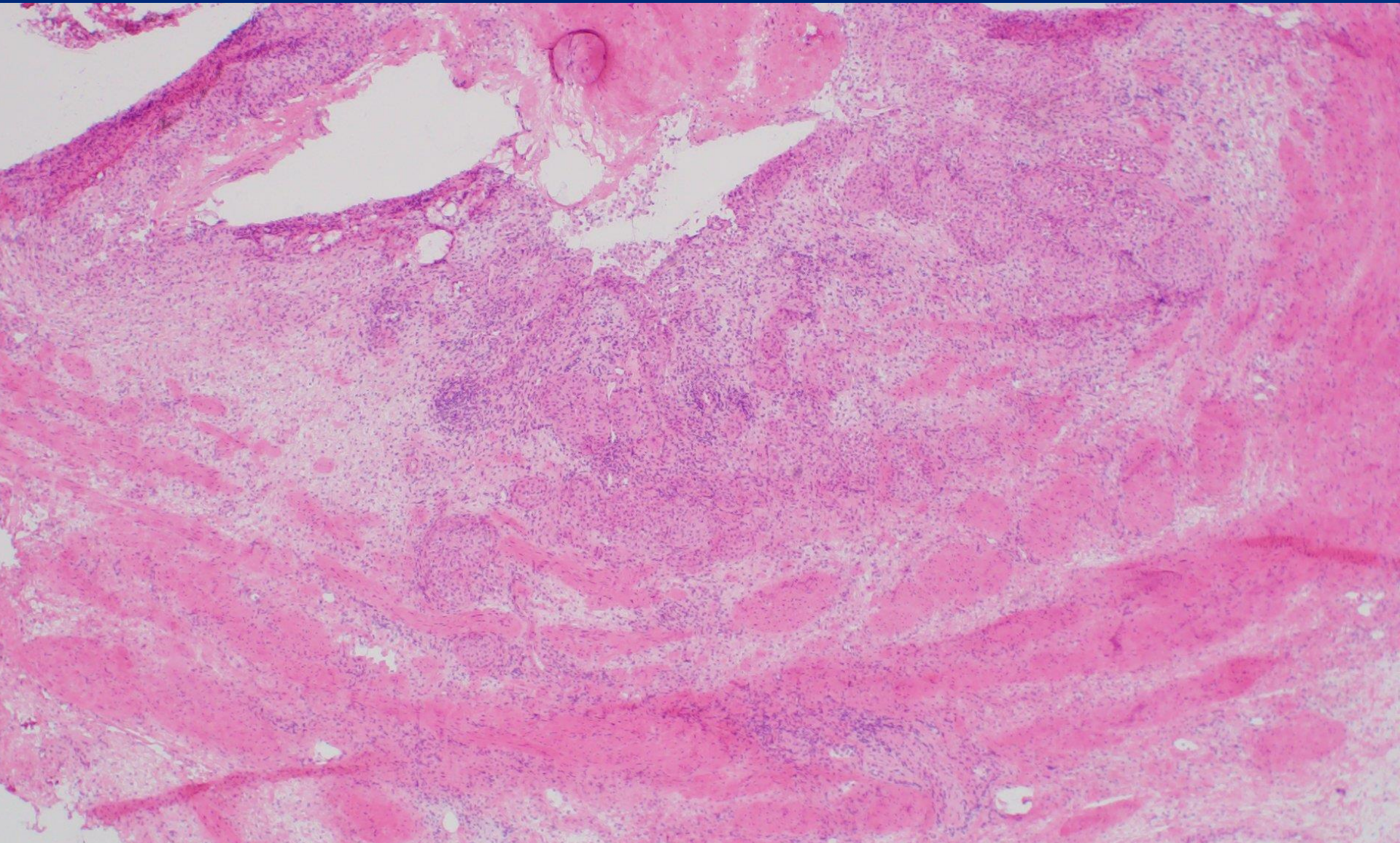




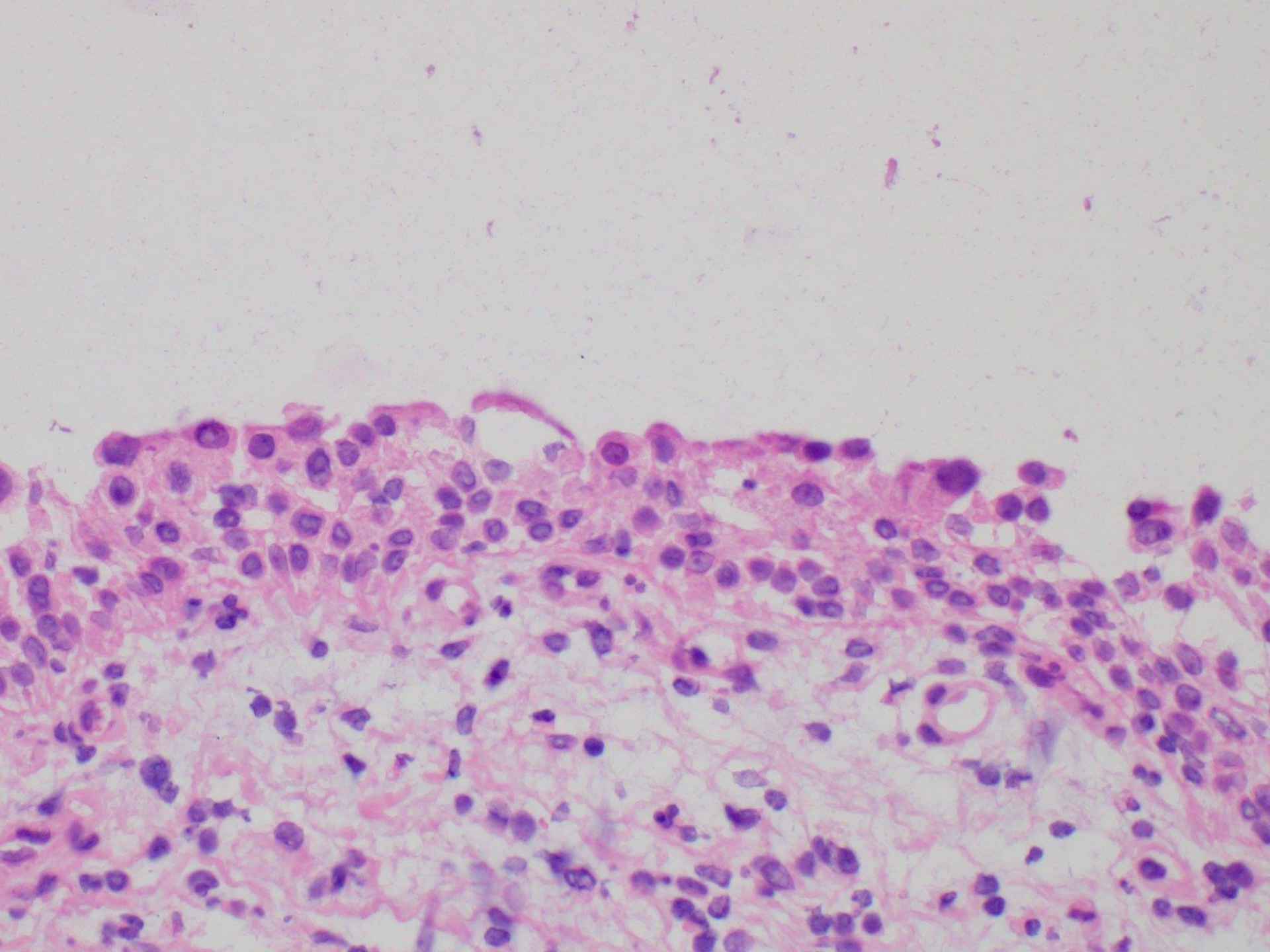
## Case 2

- 68 yo male with invasive high grade urothelial carcinoma (UC) of the bladder

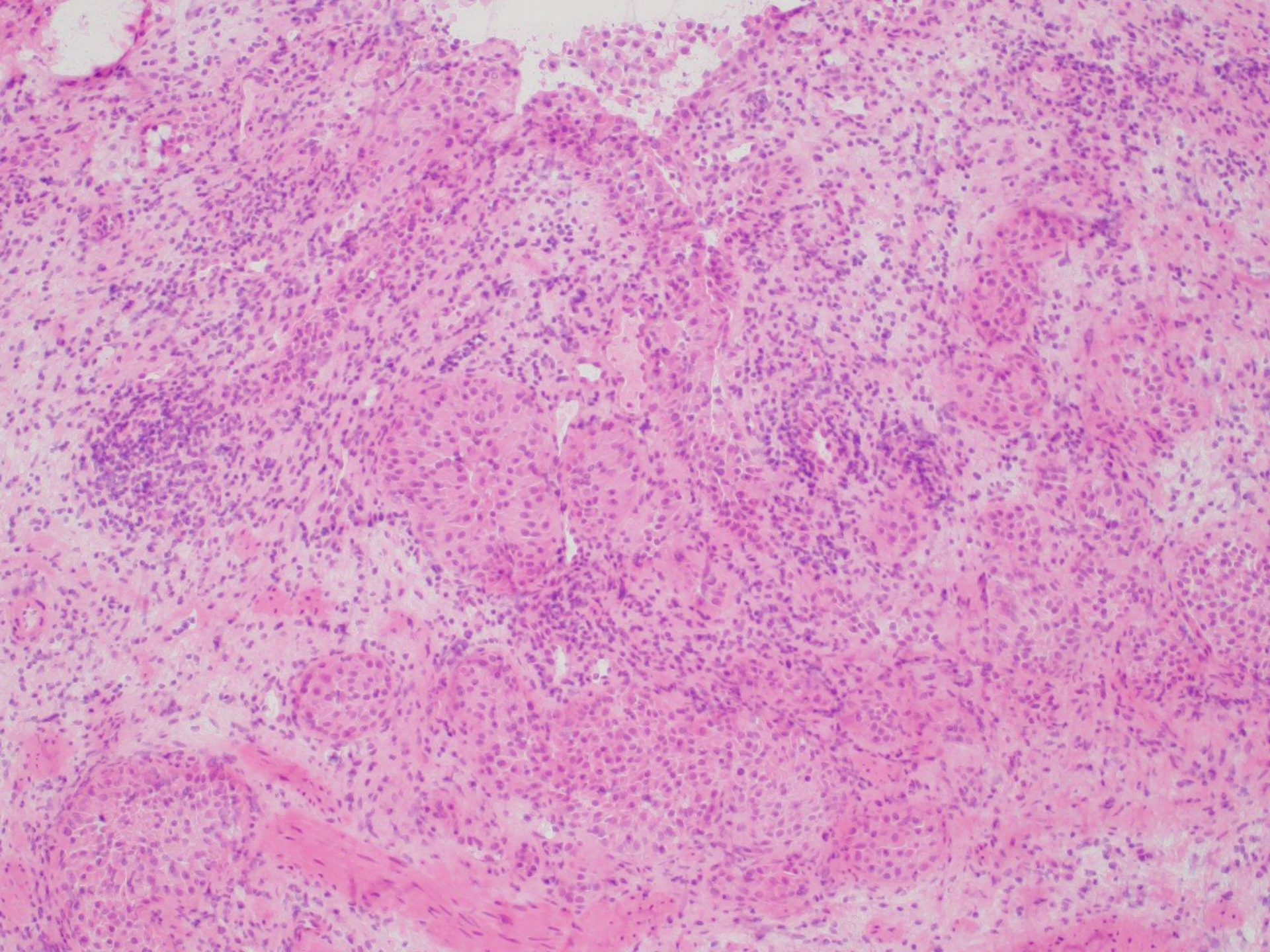
# Ureter MG FS



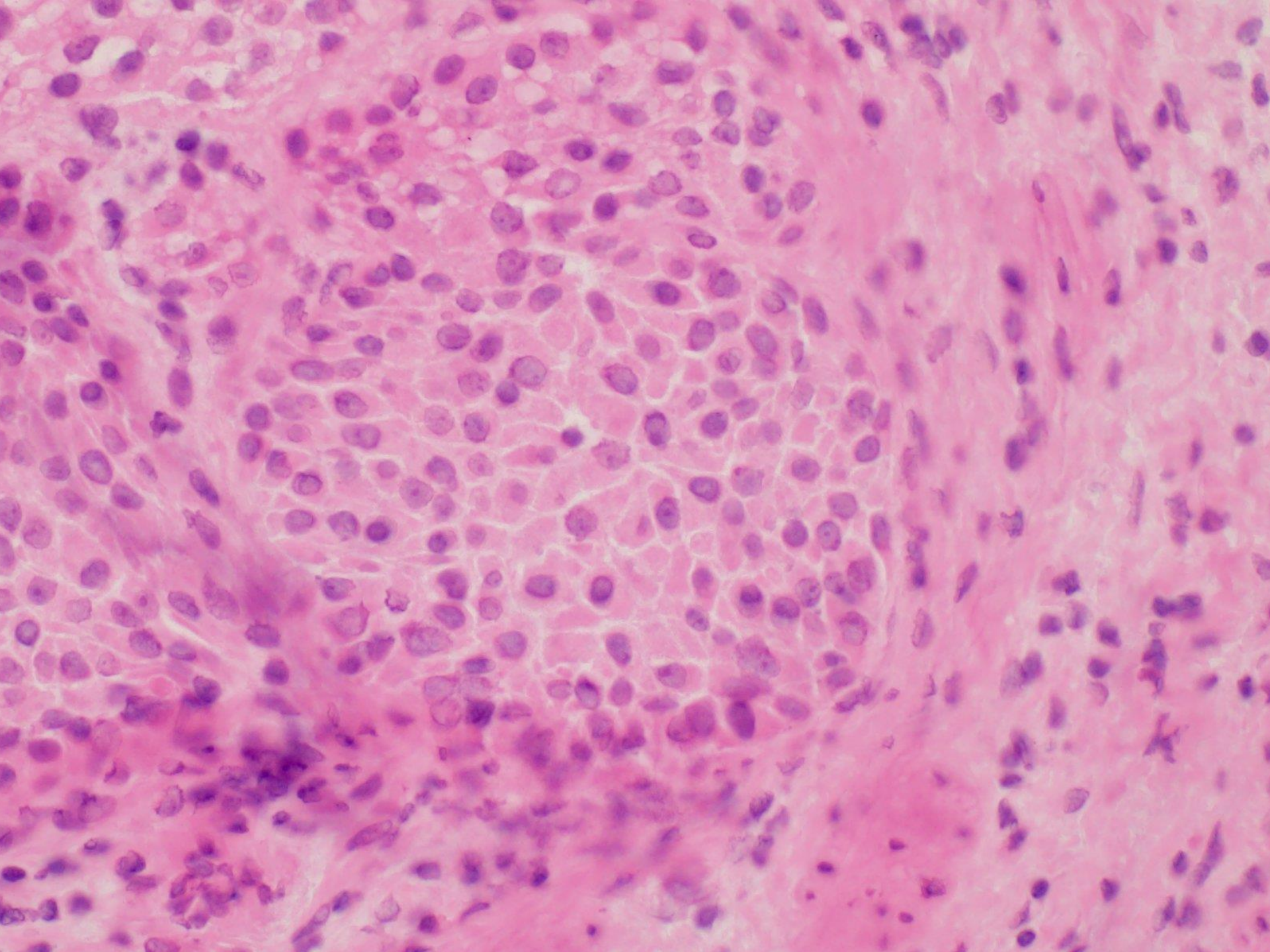








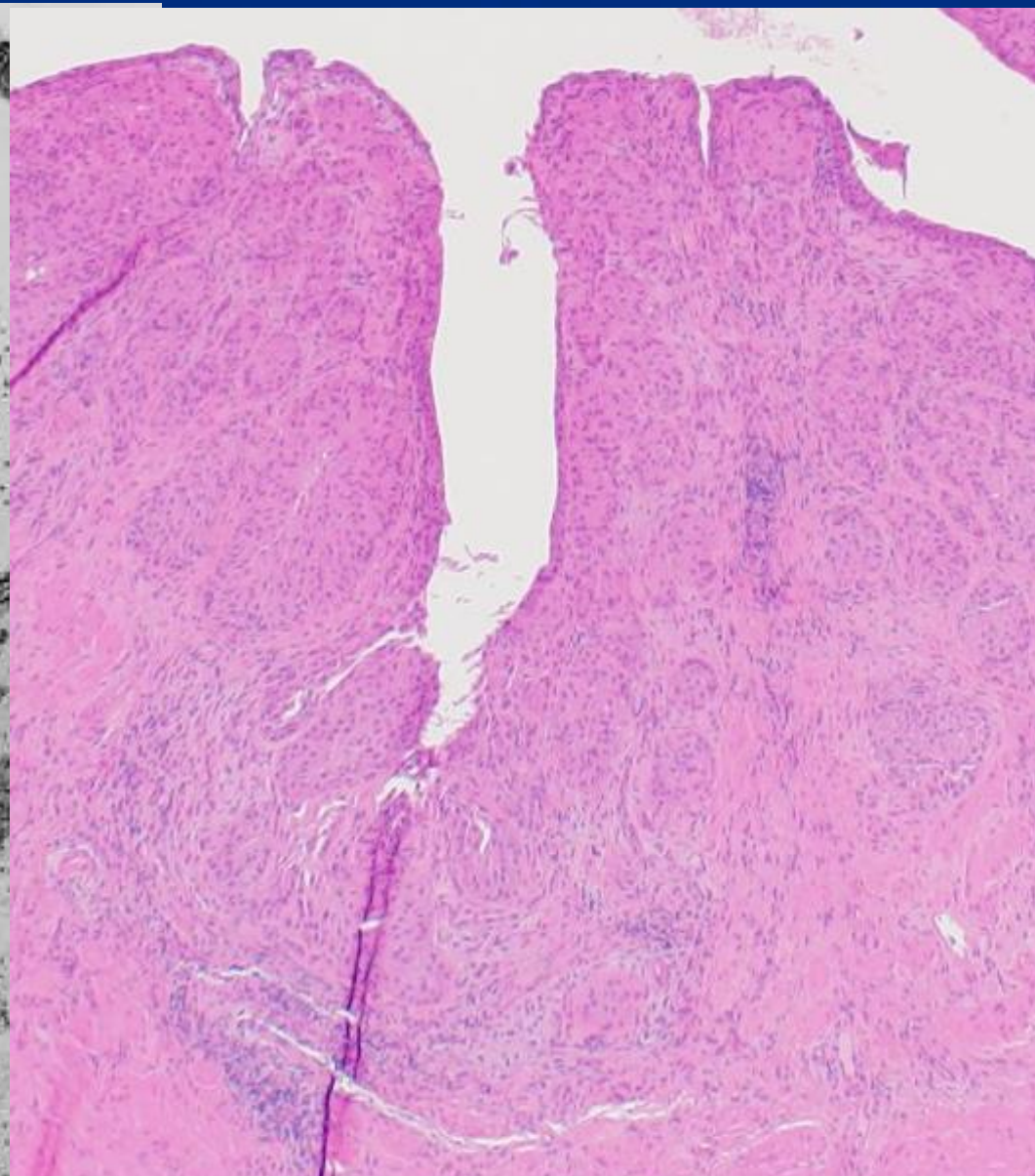
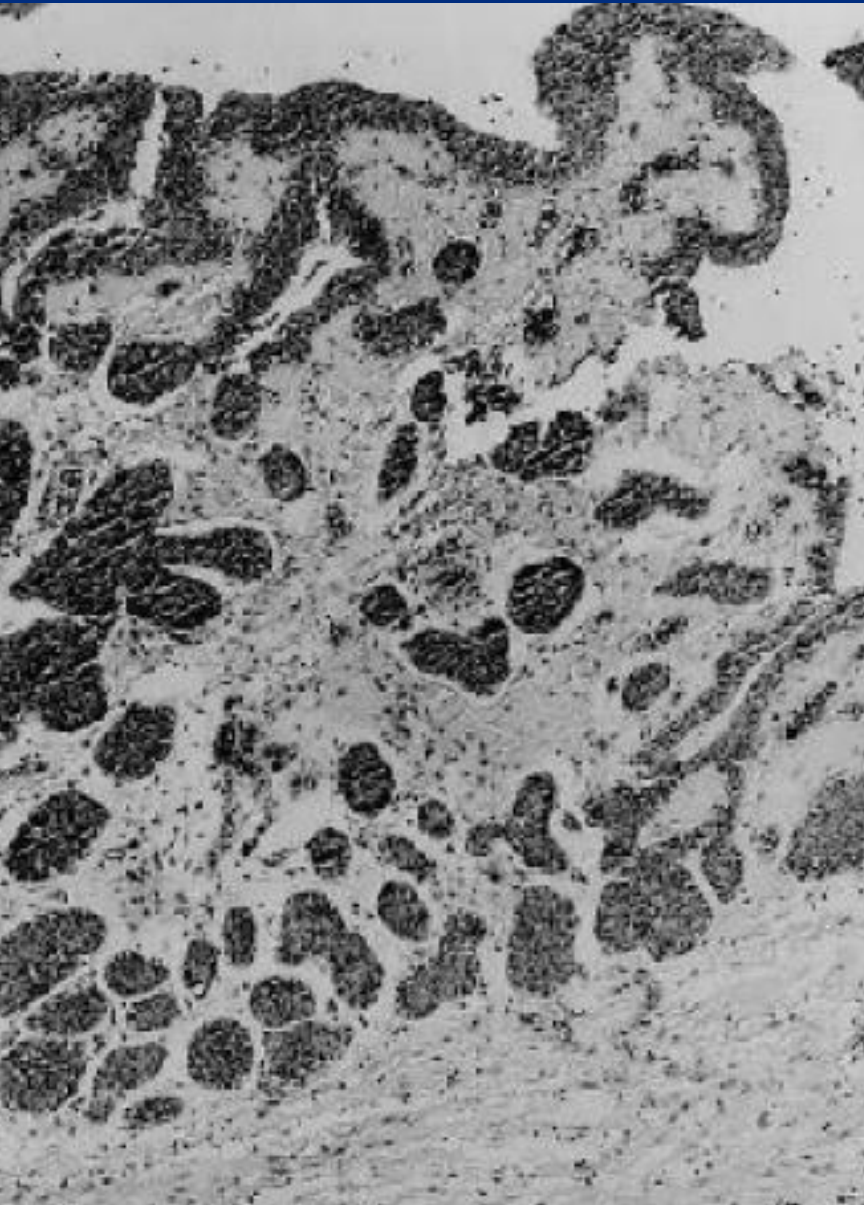






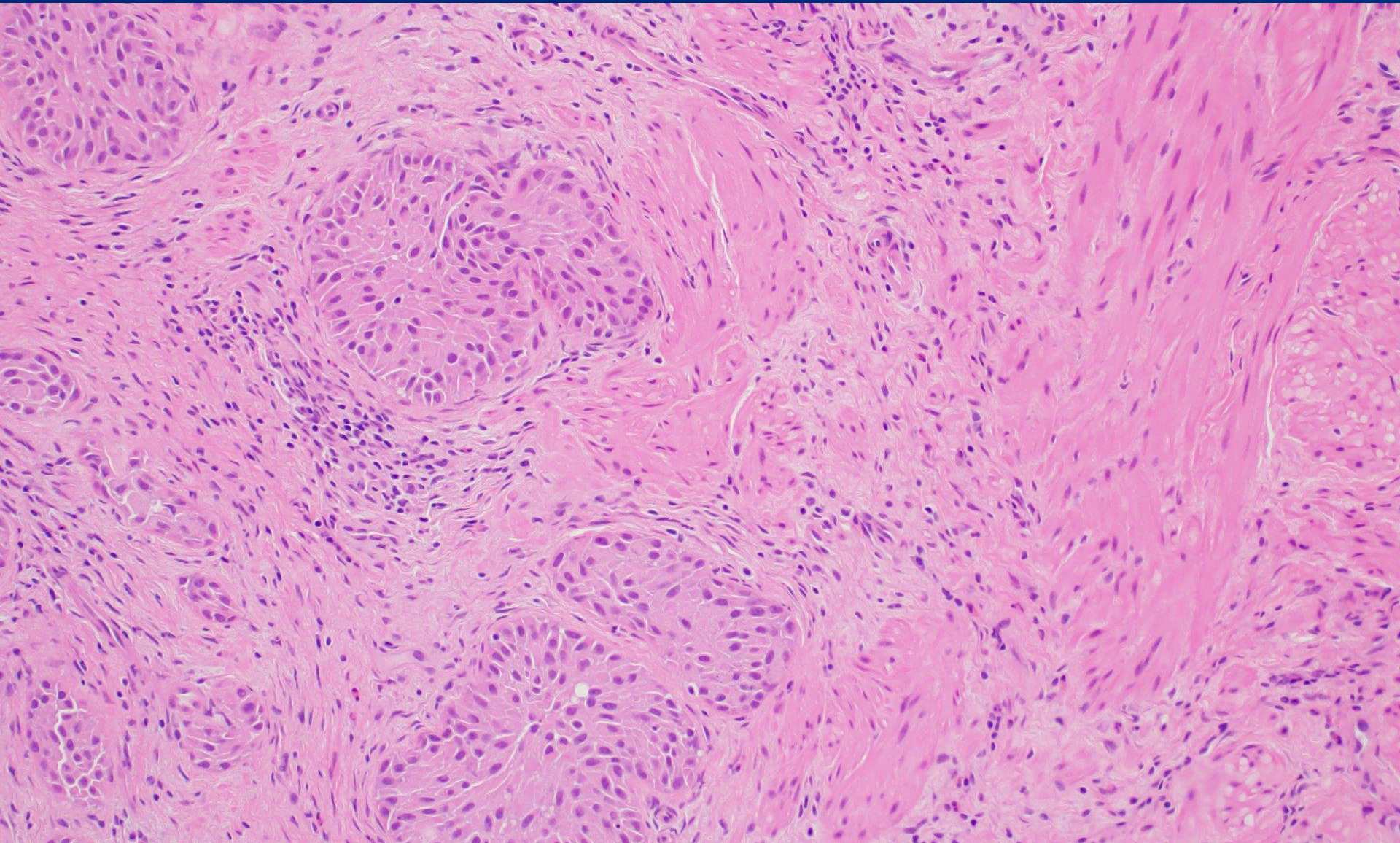
**What is your FS diagnosis?**

# Florid Von Brunn Nests vs Our MG





# Ureter MG HE



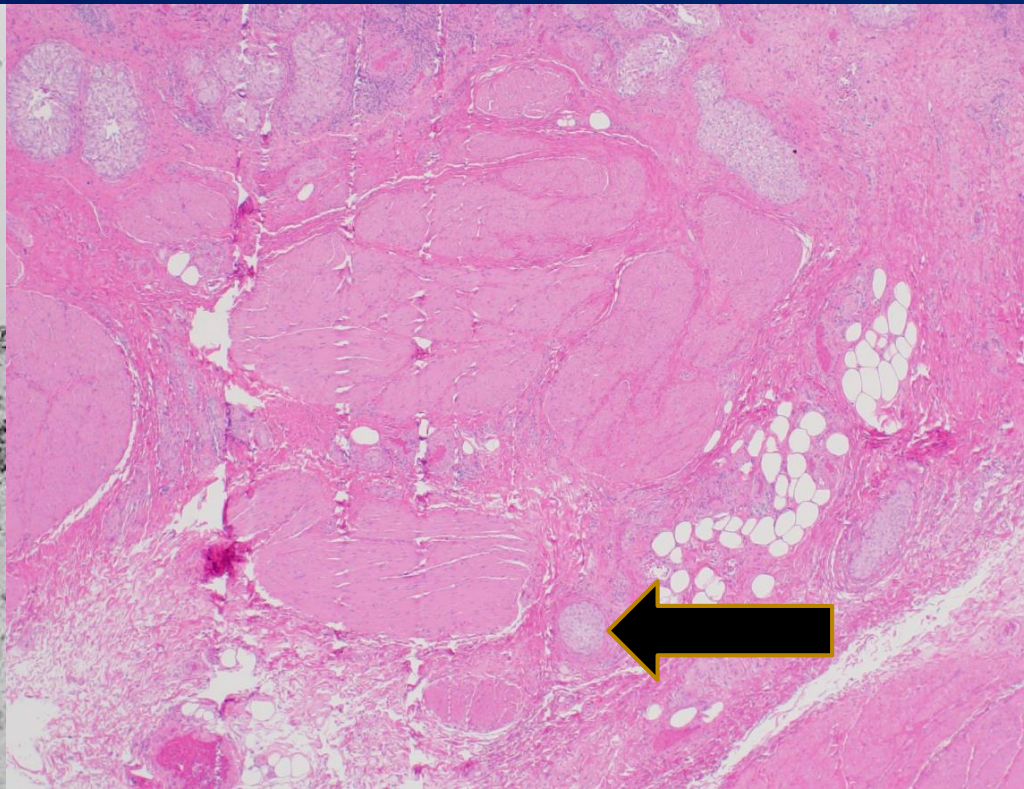
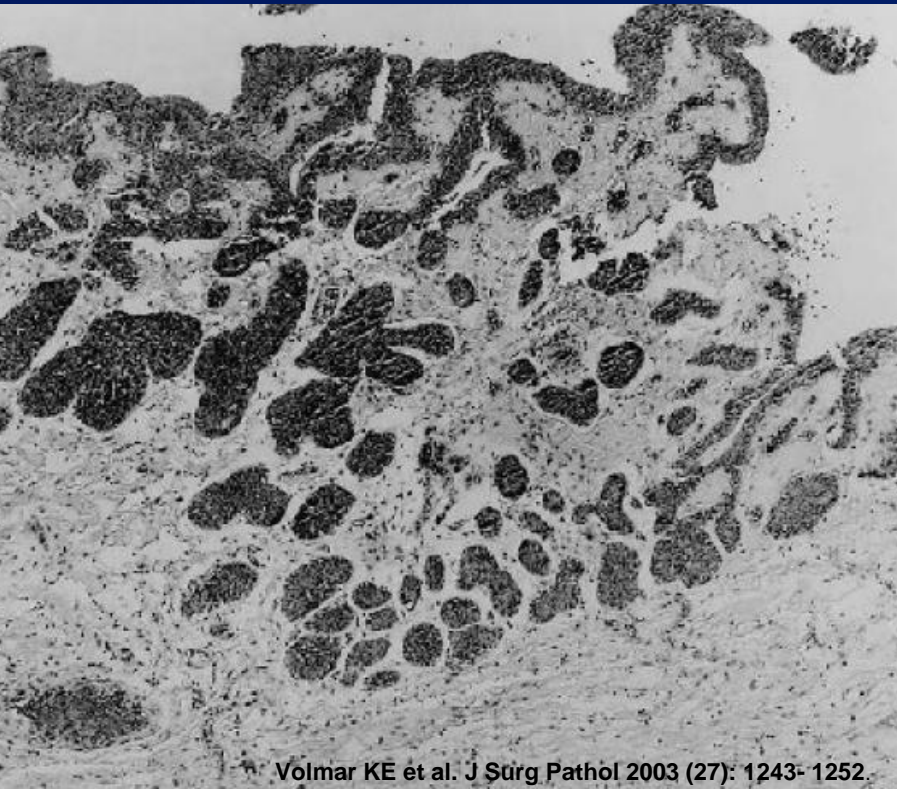
**Need to know ...prior biopsy:**

*“Muscle invasive high grade urothelial carcinoma, multiple patterns, including micropapillary, and **nested variant**”*



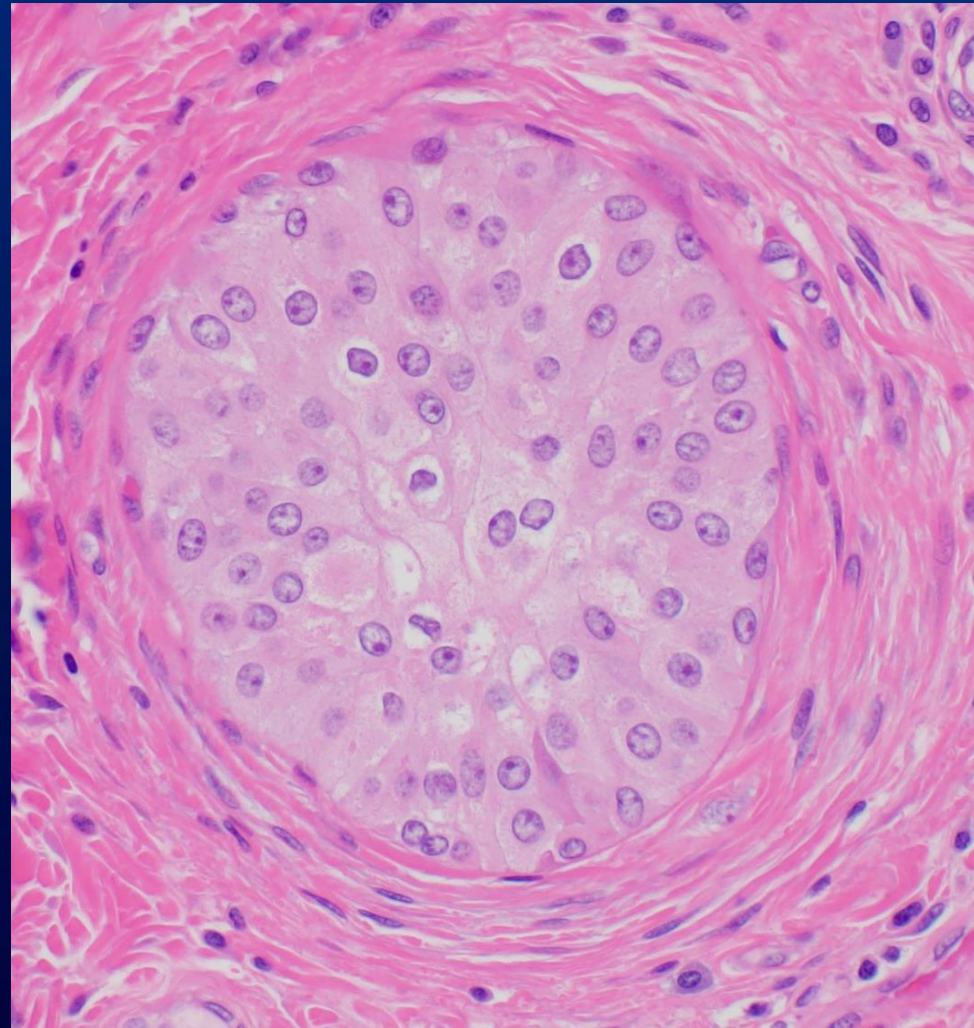
# Florid von Brunn Nests vs Nested Variant UC

- Ureter/ pelvis: smaller, variable nests, irregular spacing
- Non- infiltrative base
- Small crowded nests with variable spacing
- Infiltrative base



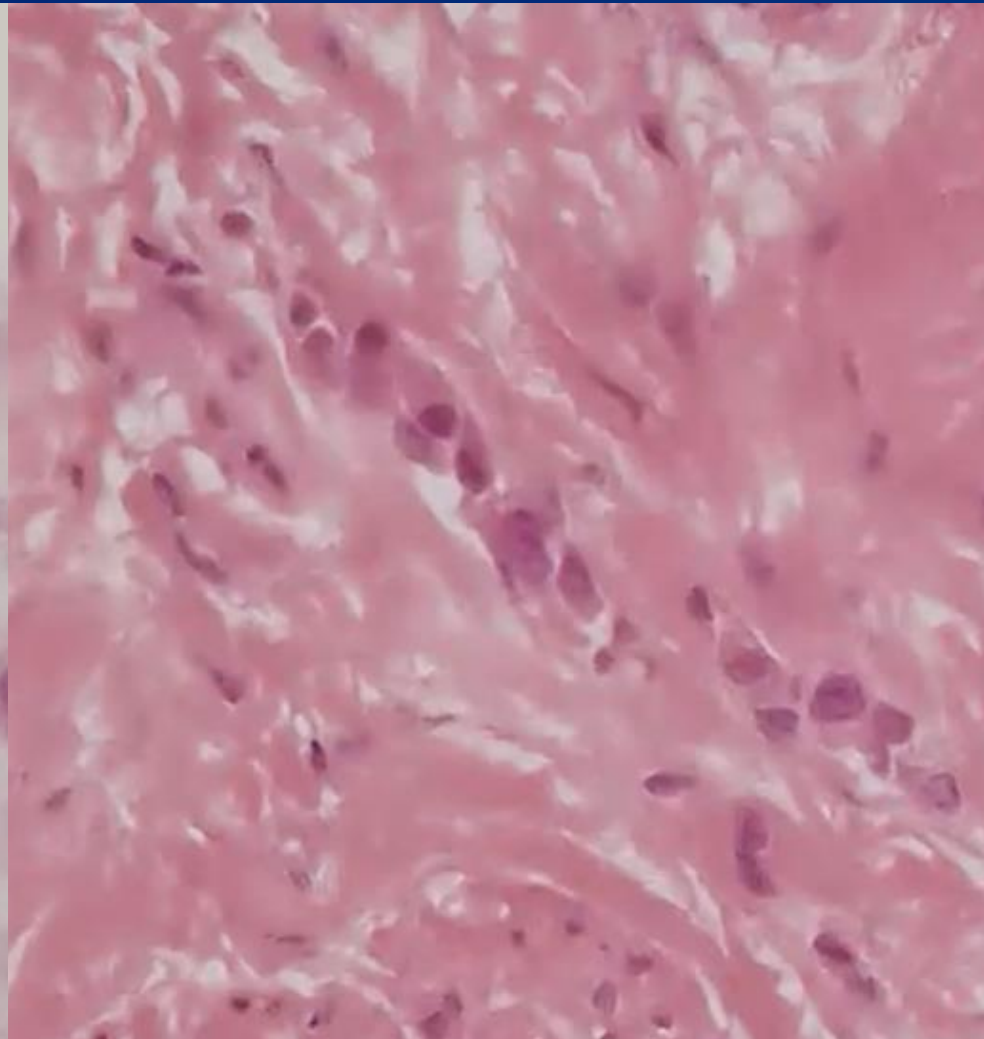
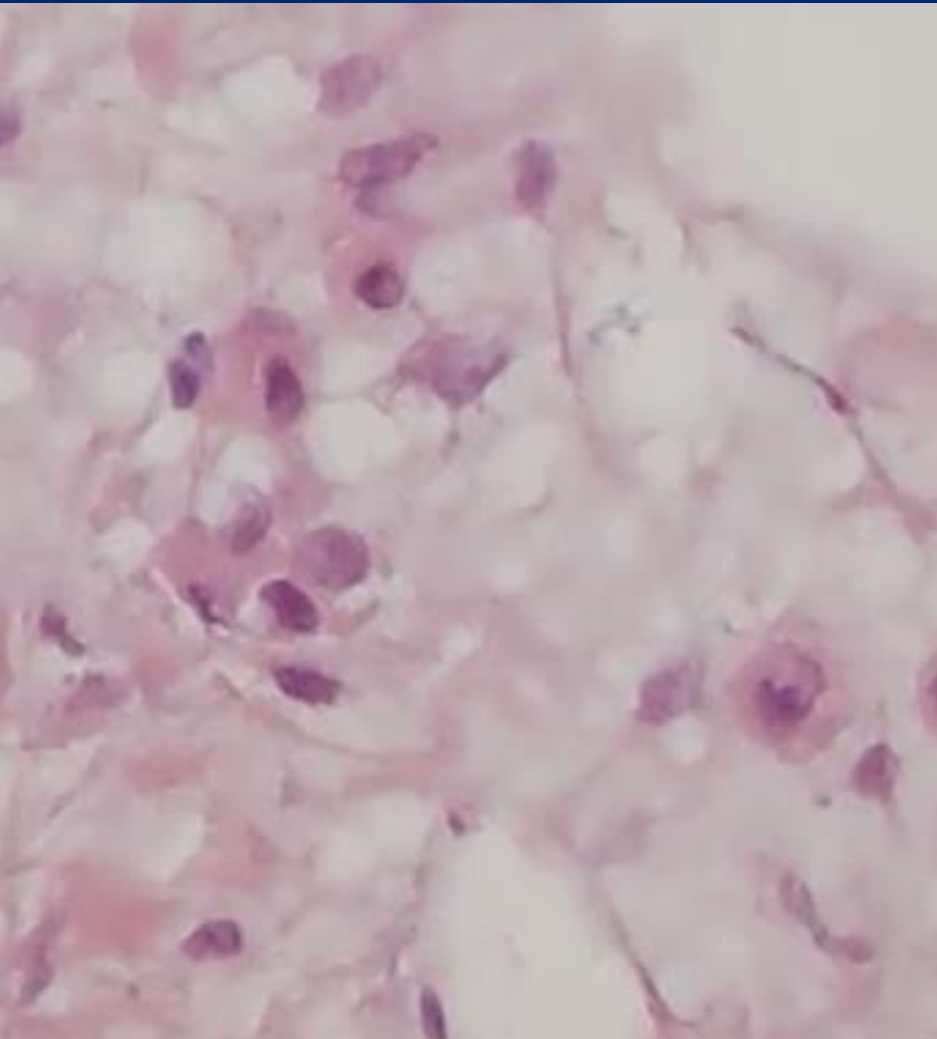
# FS MG+: Invasive UC, Nested Variant

- Challenging diagnosis on small superficial biopsies and FS
- Attention:
  - Rare variants of malignancies mimicking B9
- Carefully read all prior diagnosis and comments



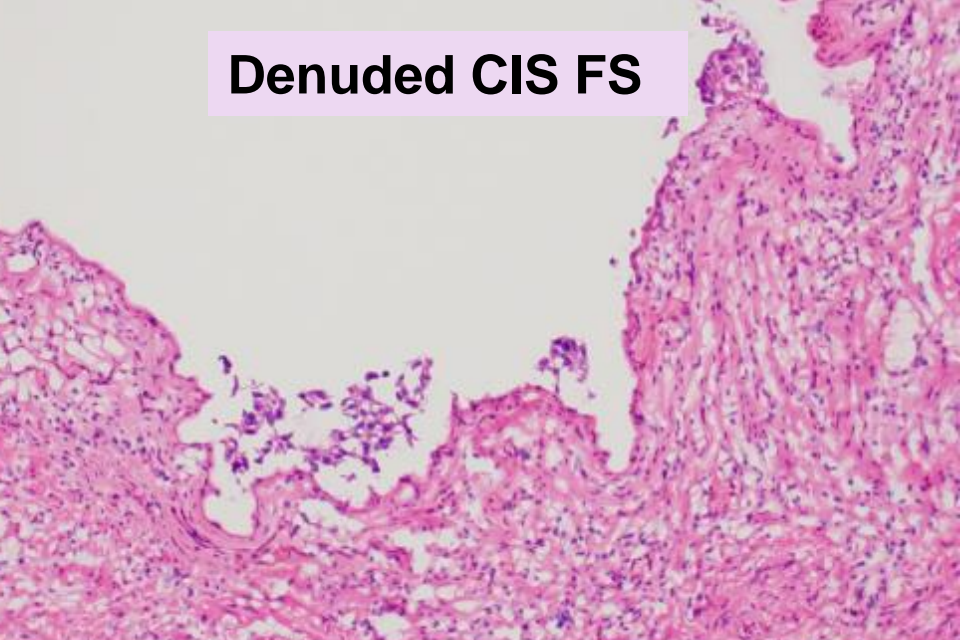


# Other Challenges in Ureteral MG Interpretation

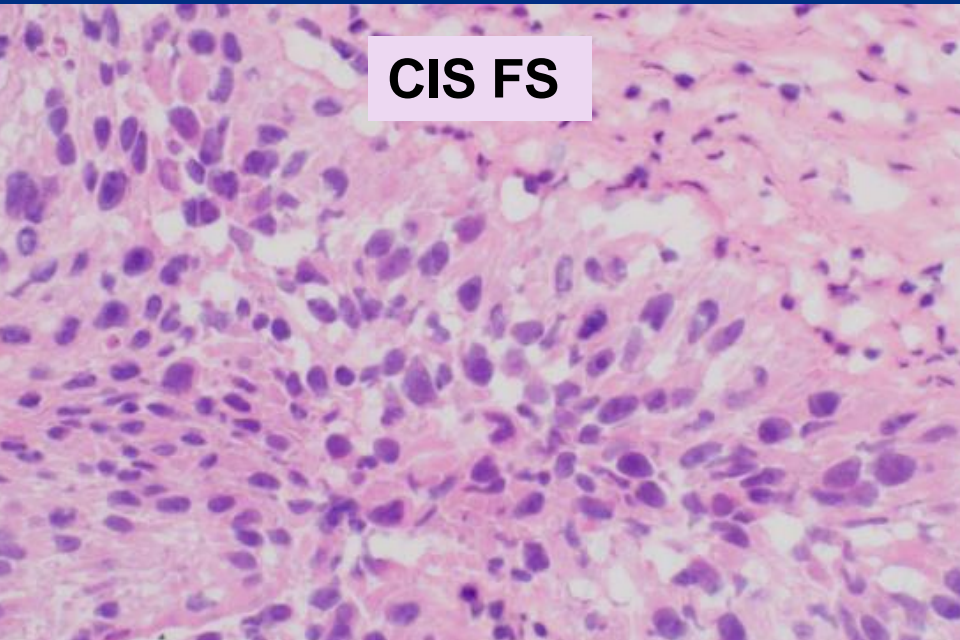


# Common Challenges in Ureteral MG Interpretation

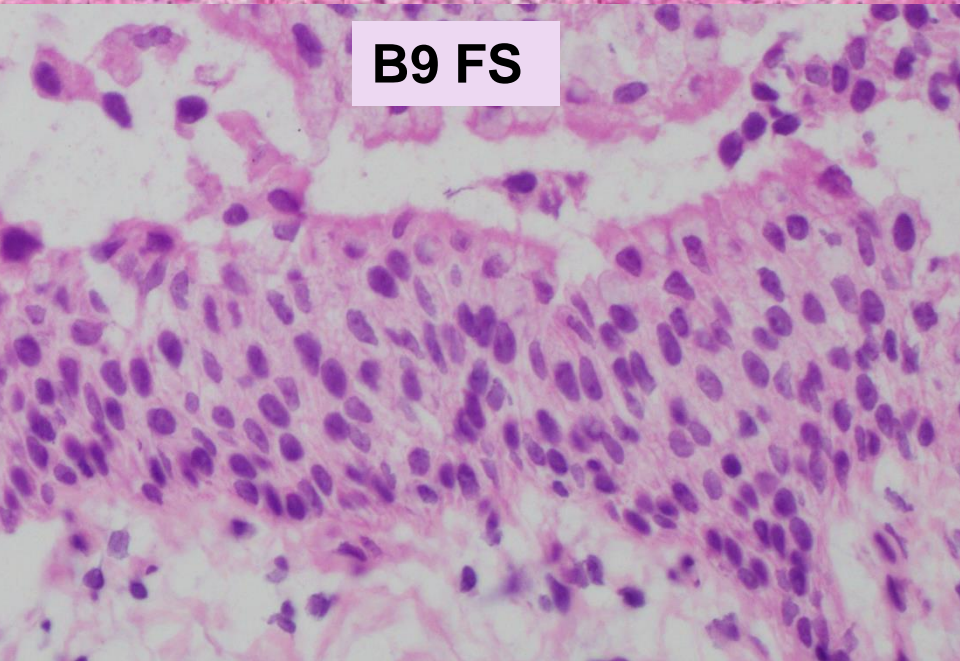
Denuded CIS FS



CIS FS



B9 FS

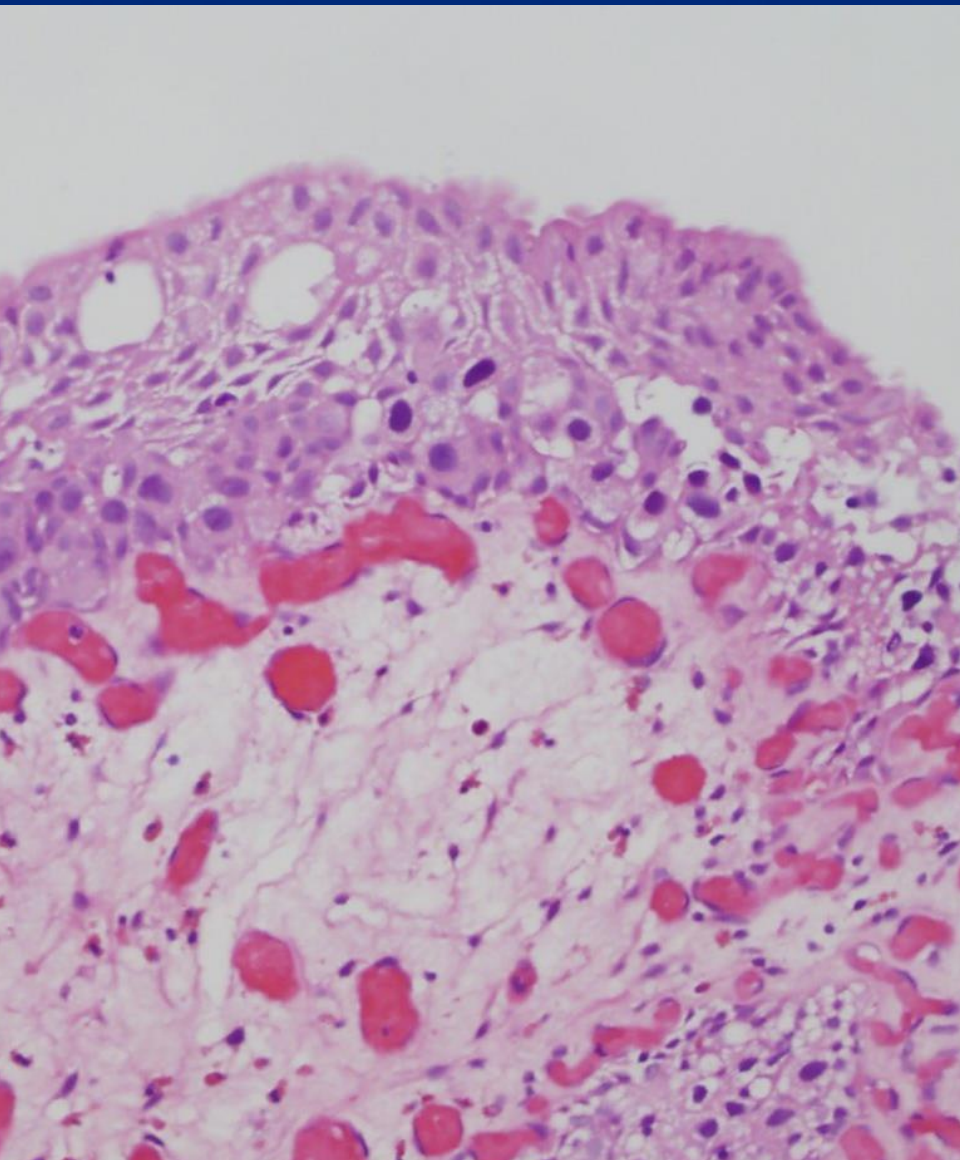


CIS HE

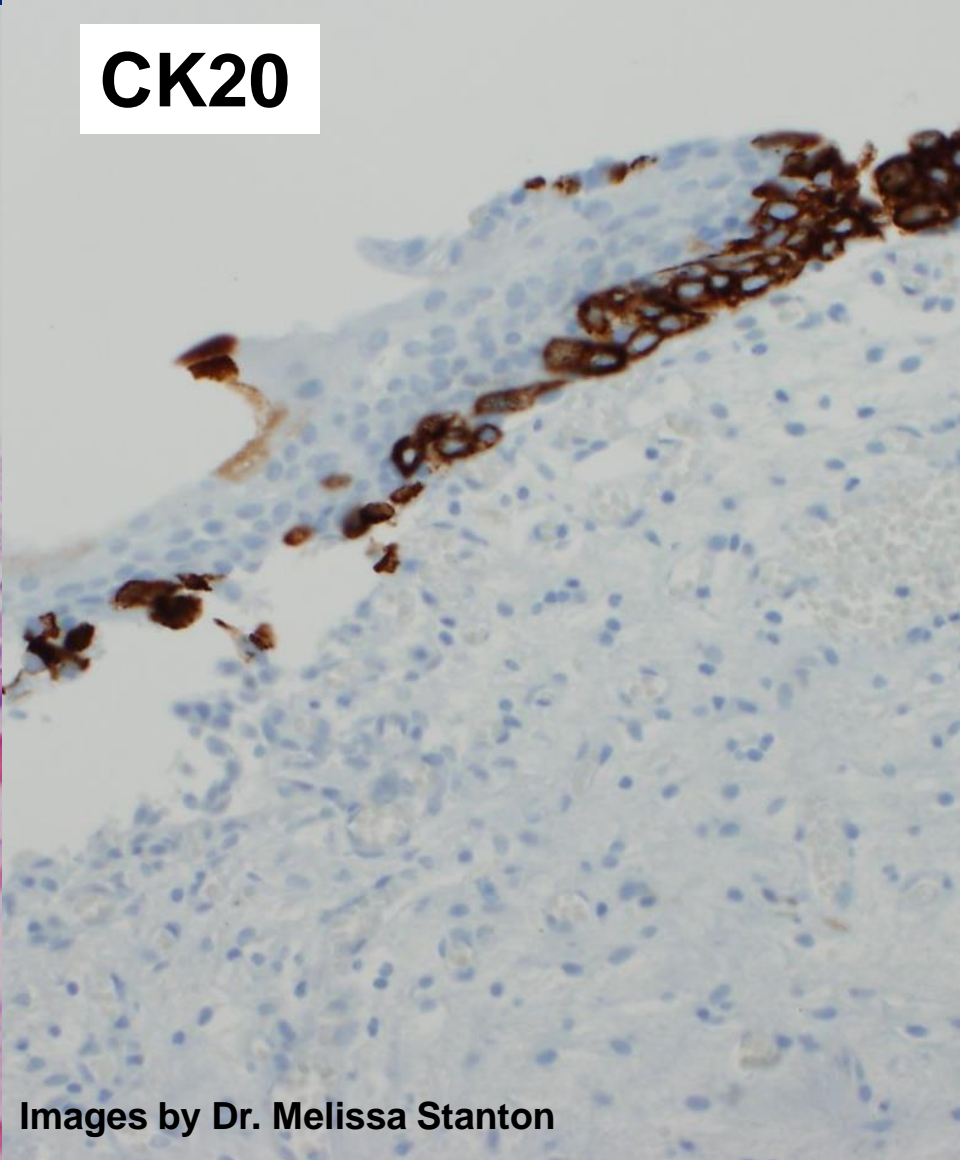




# Pagetoid CIS



**CK20**



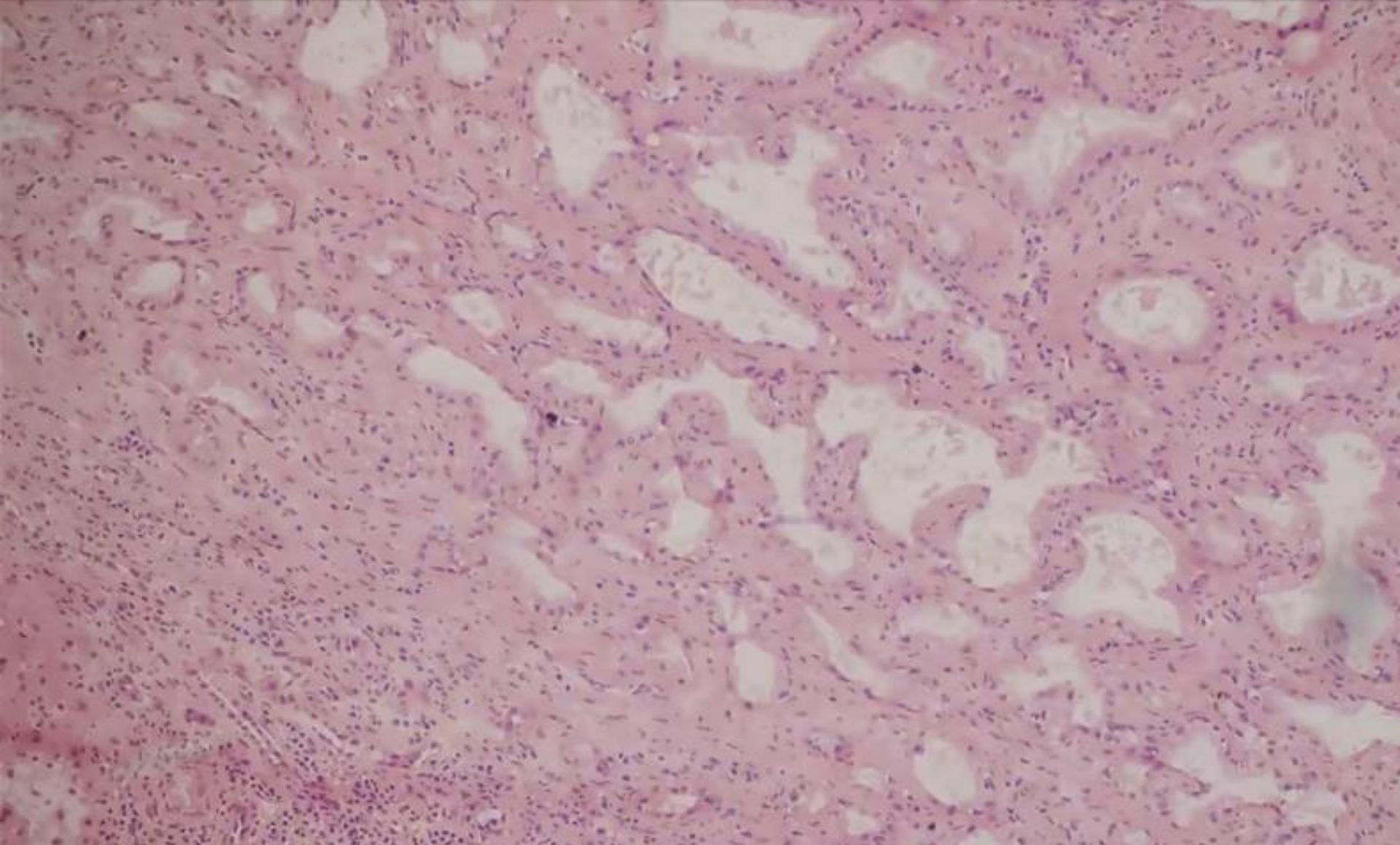


## Case 3

- 58 yo male diagnosed months ago with
- borderline resectable pancreatic head adenocarcinoma,
- S/P chemotherapy and radiotherapy
- Whipple scheduled



# FS: “Suspicious Hepatic Nodule”

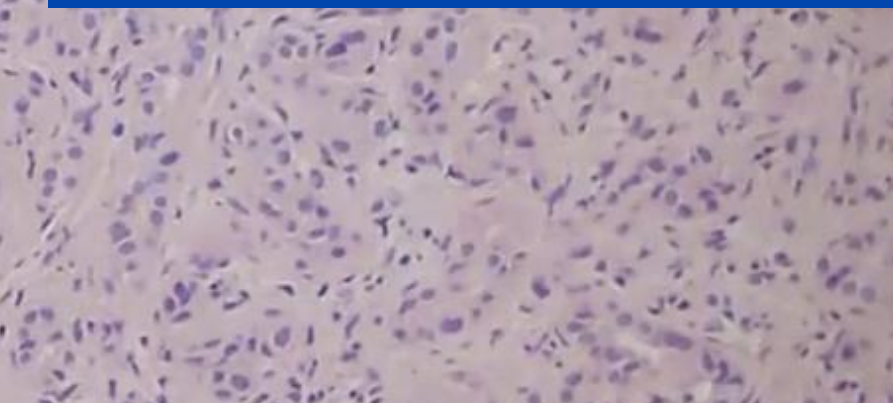




## Bile Duct (BD) Adenoma

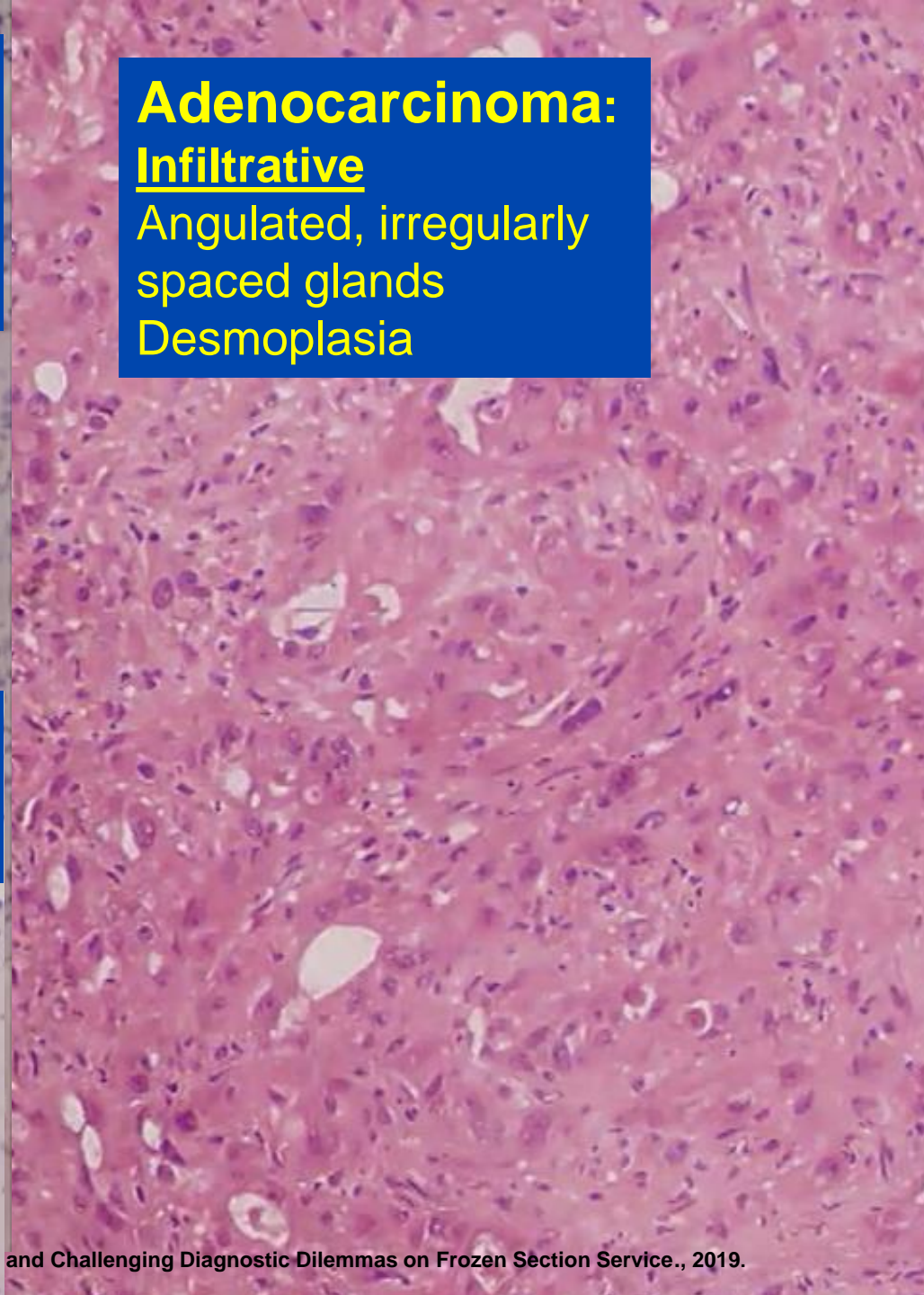
Small, circumscribed

Bland, tightly packed small tubules,  
single layer, scant fibrous stroma



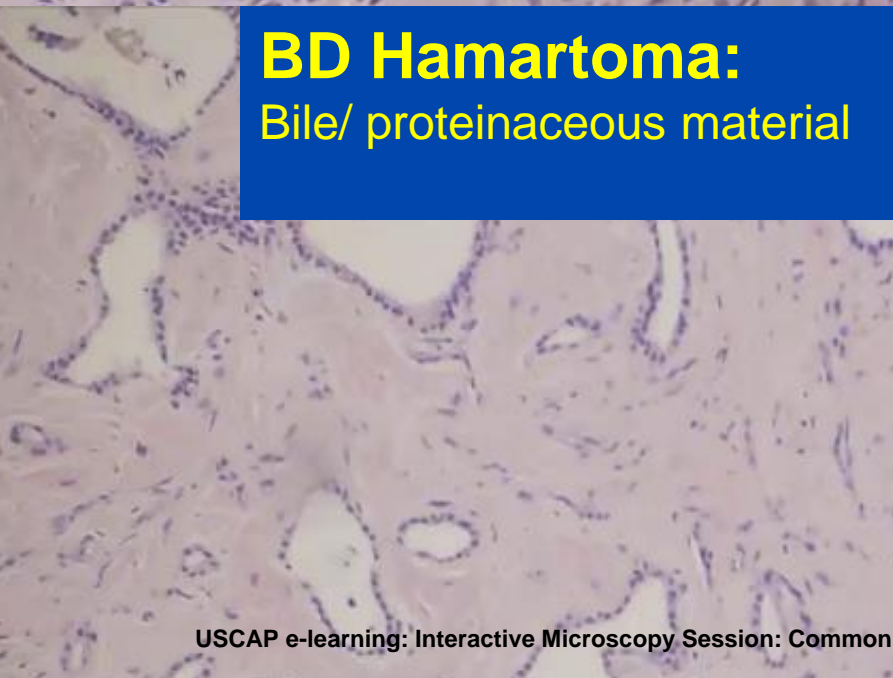
## Adenocarcinoma: Infiltrative

Angulated, irregularly  
spaced glands  
Desmoplasia



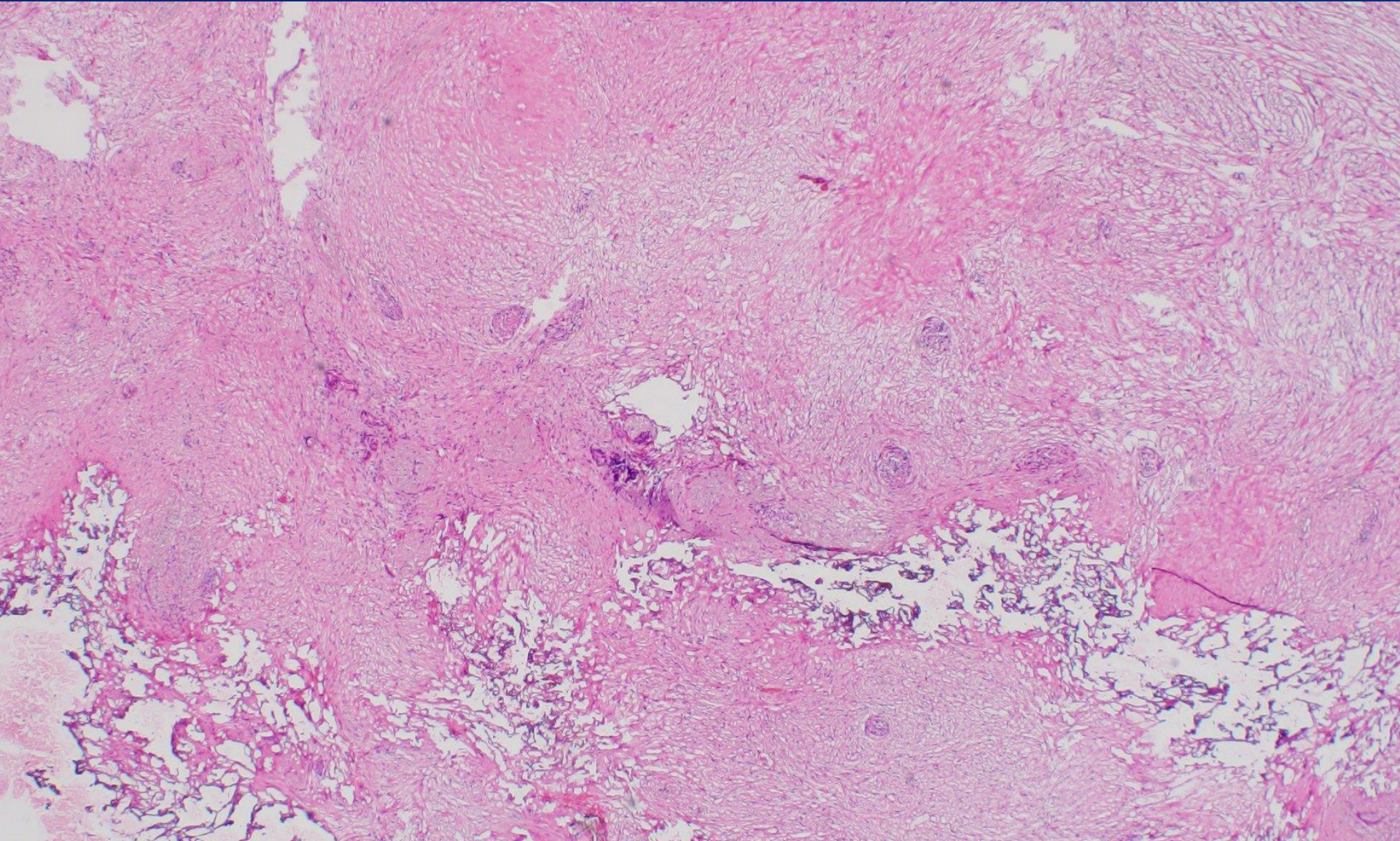
## BD Hamartoma:

Bile/ proteinaceous material

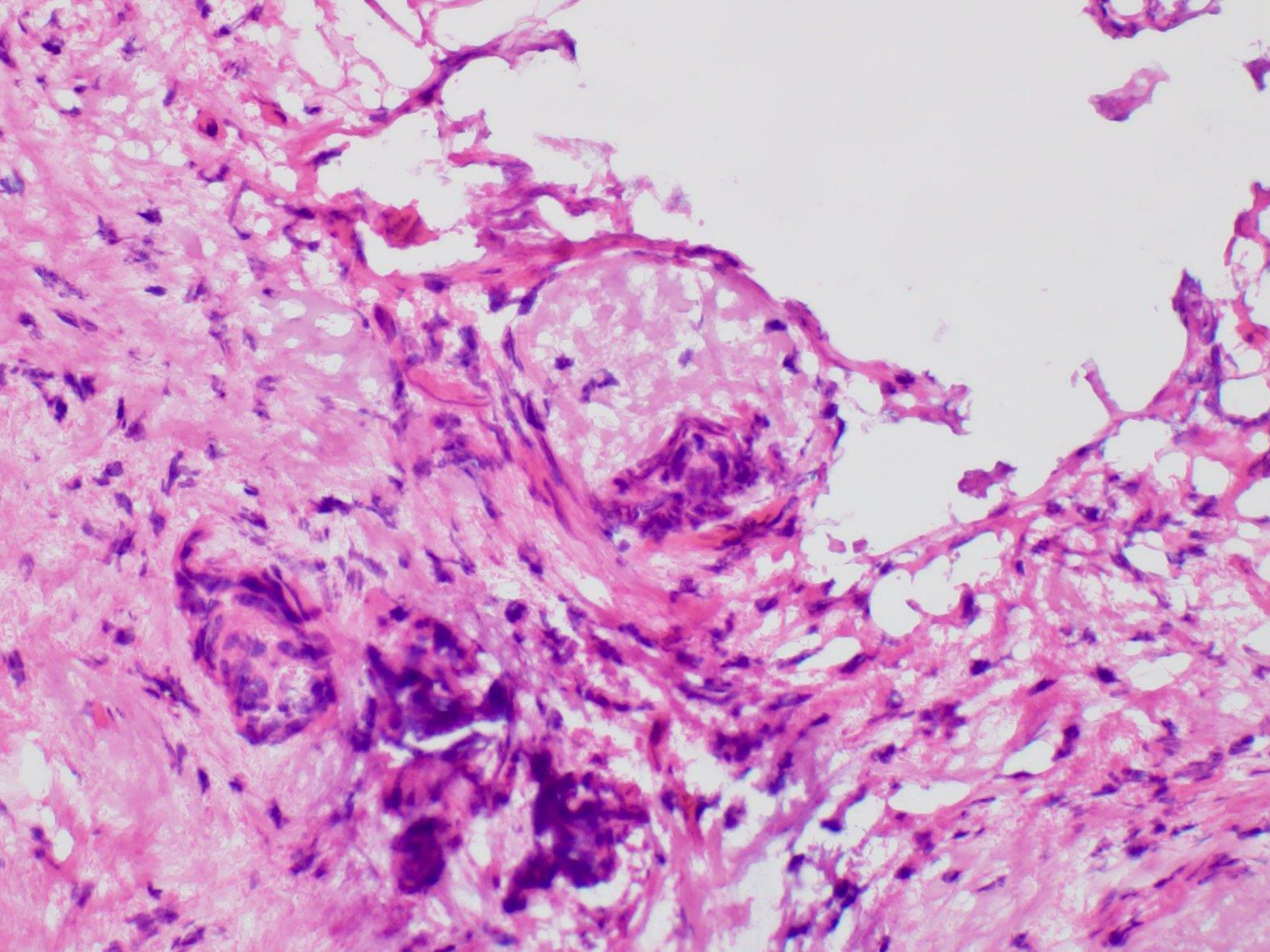




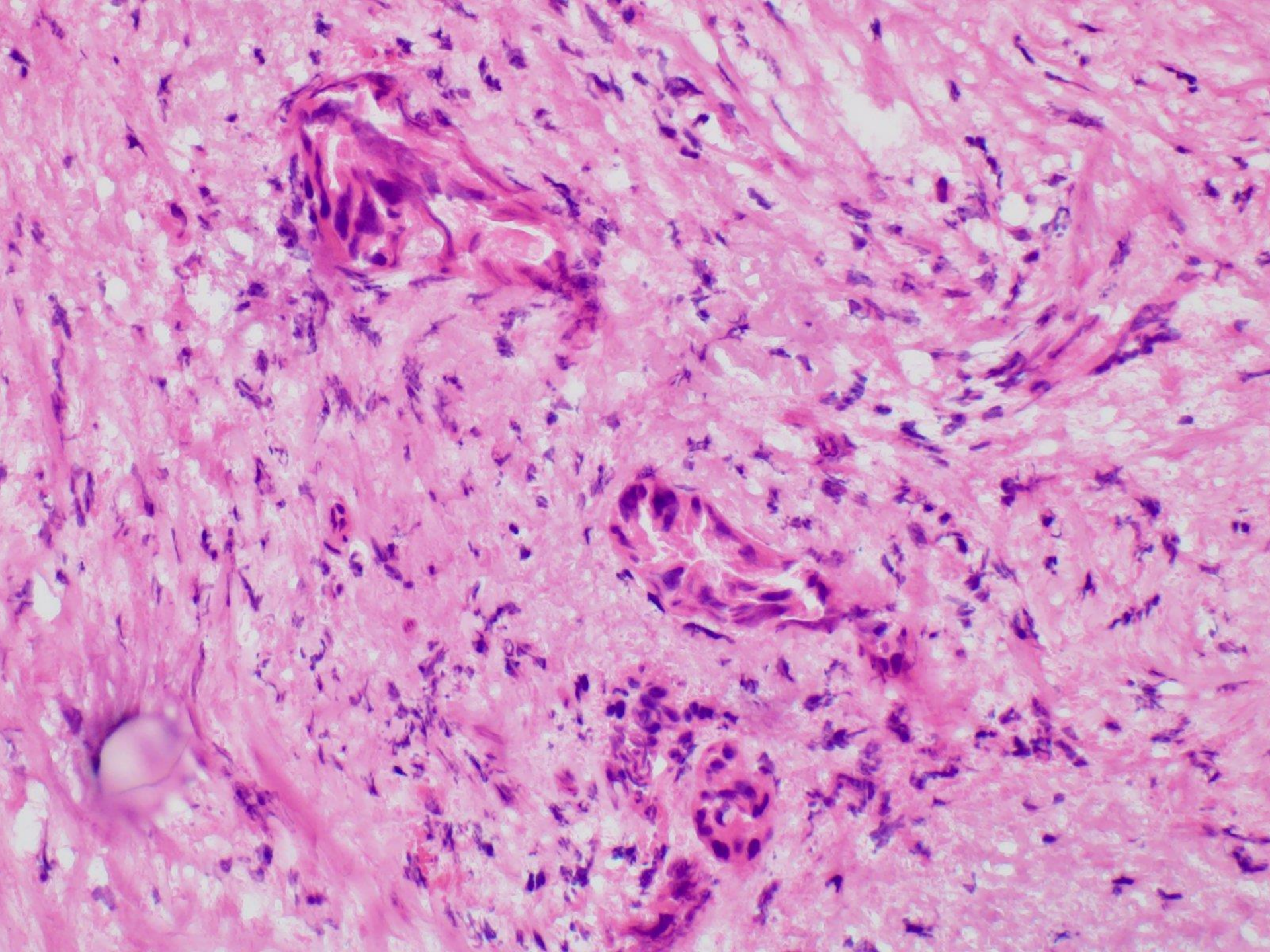
# Pancreatic Neck Margin FS







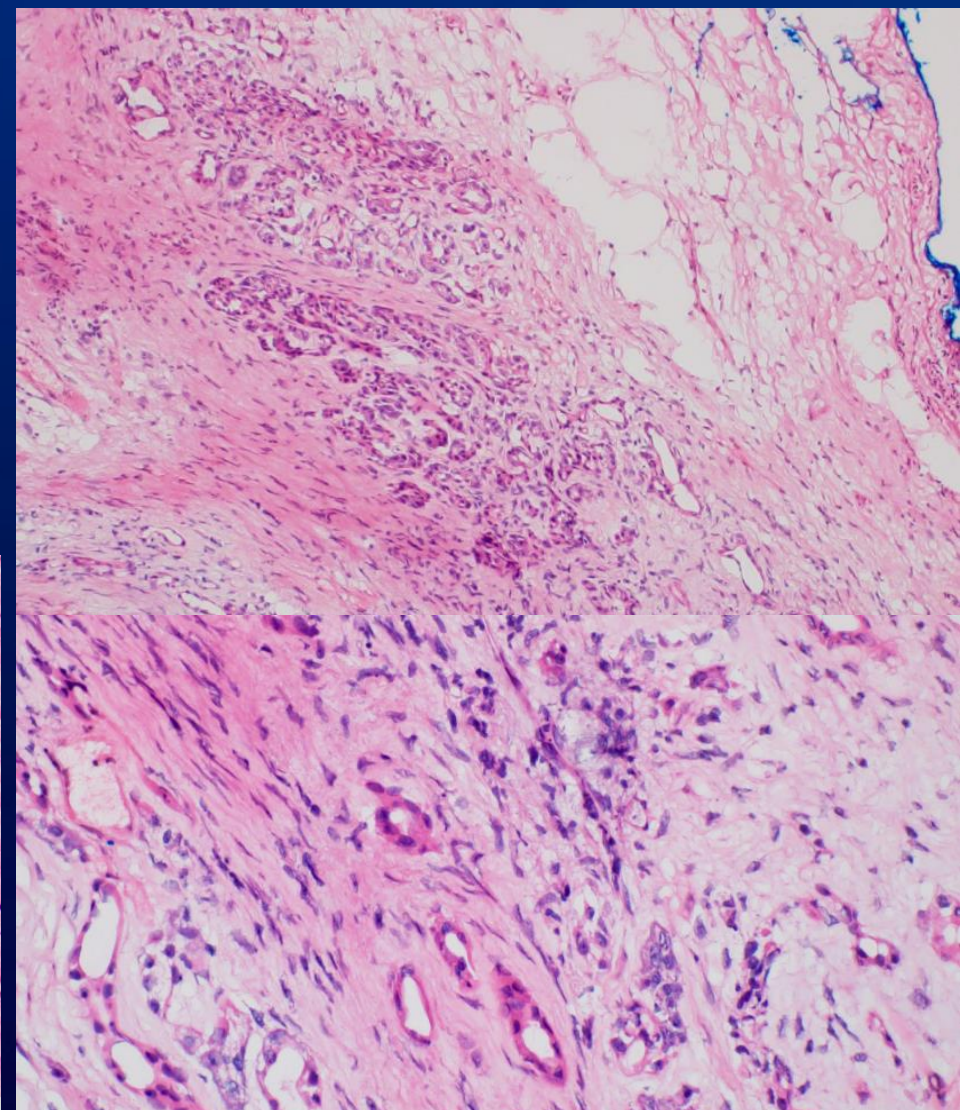
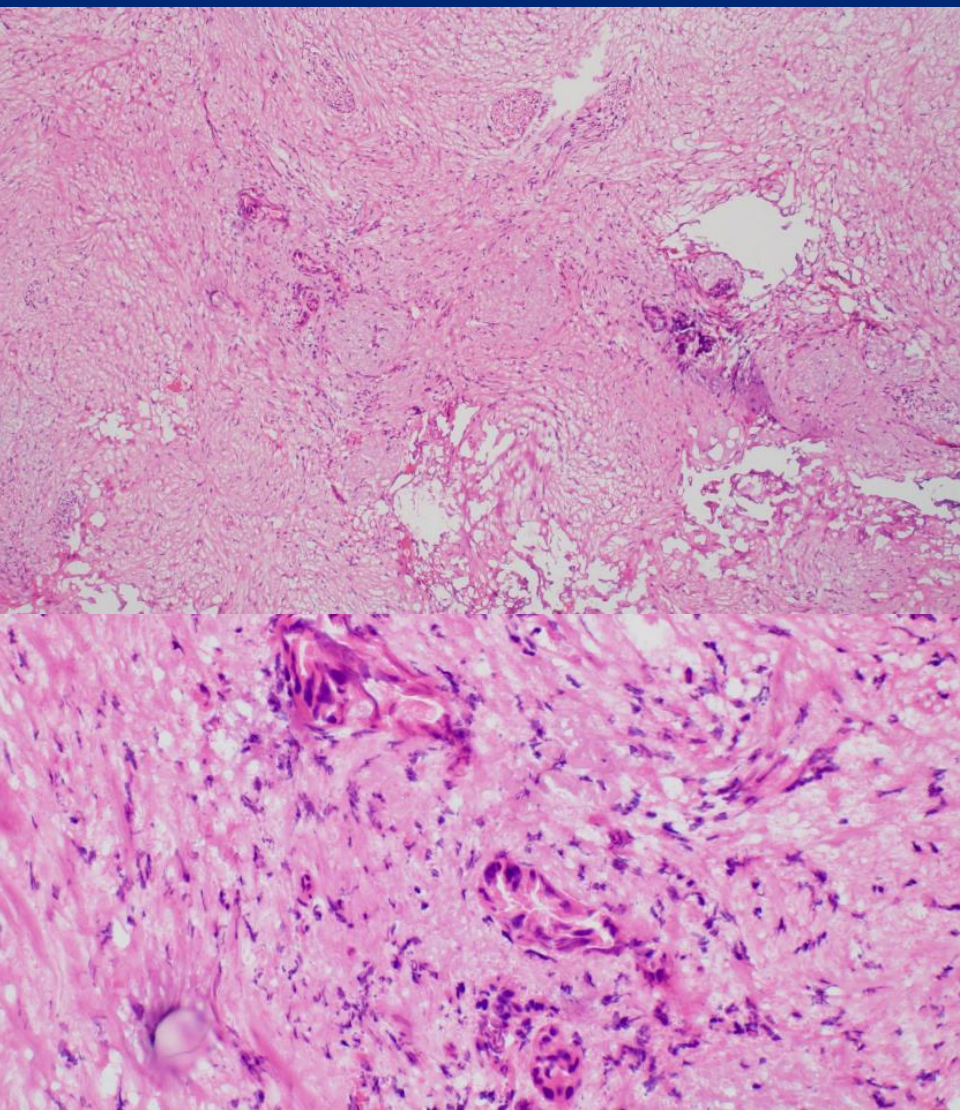






# +Margin vs Chronic Pancreatitis

Preserved Lobular Architecture





# Favor +Margin:

- **Haphazard** ducts with:
  - Different size/ shapes
  - Incomplete lumens, luminal necrosis
  - Nuclear hyperchromasia, atypical mitosis, size variation  $\geq 4:1$ , large irregular nucleoli
  - Abnormal location:
    - adjacent to muscular vessel
    - in muscle without stroma
- **PNI, LVI**

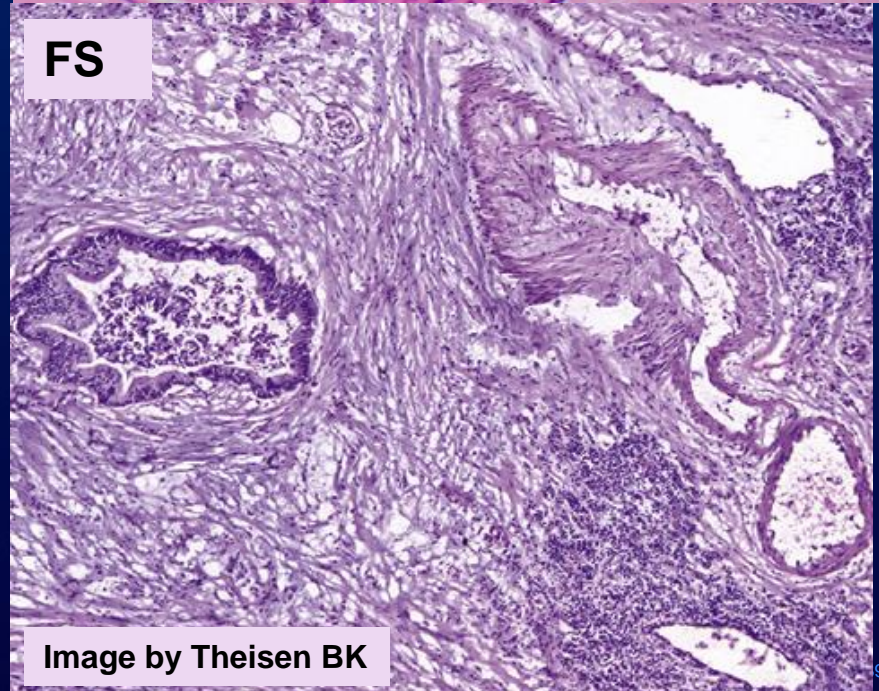
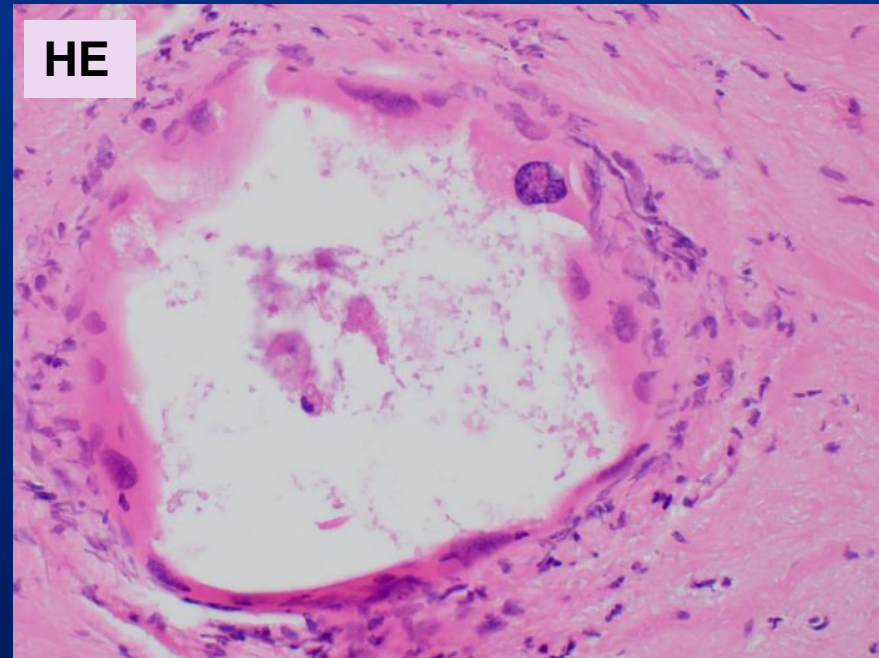
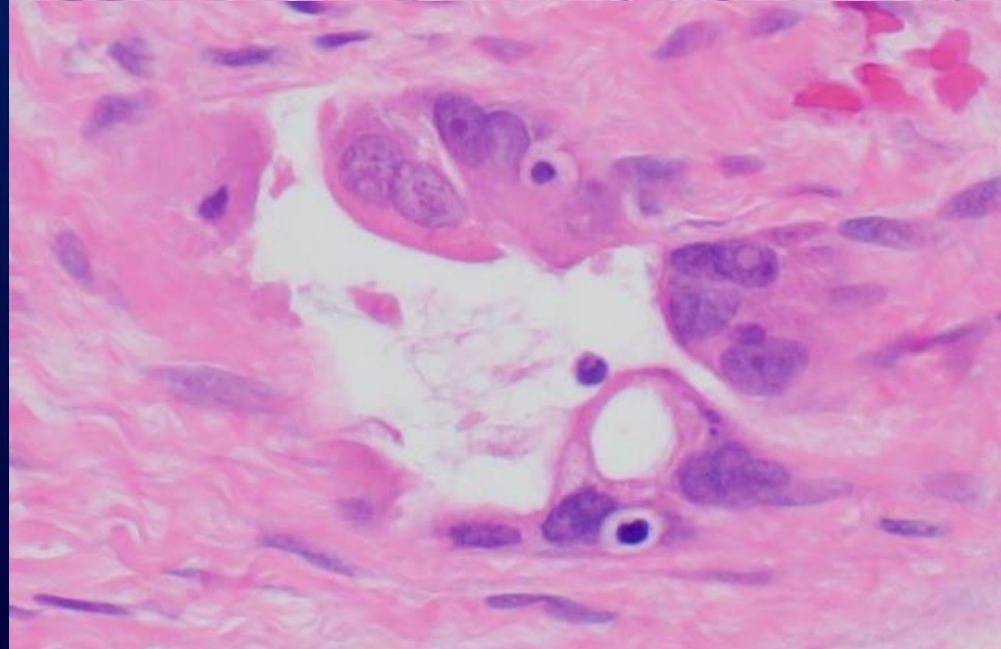
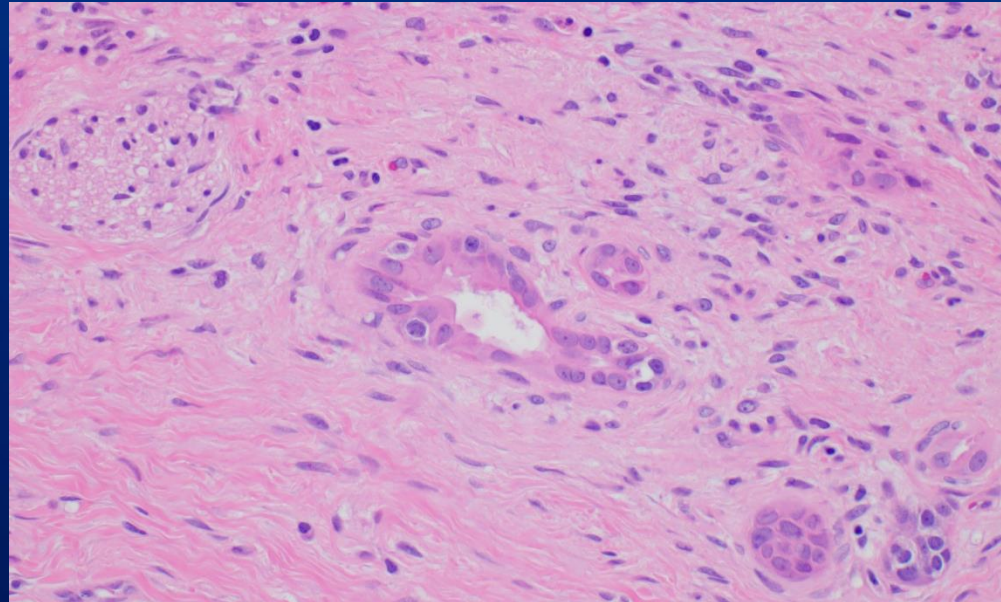


Image by Theisen BK

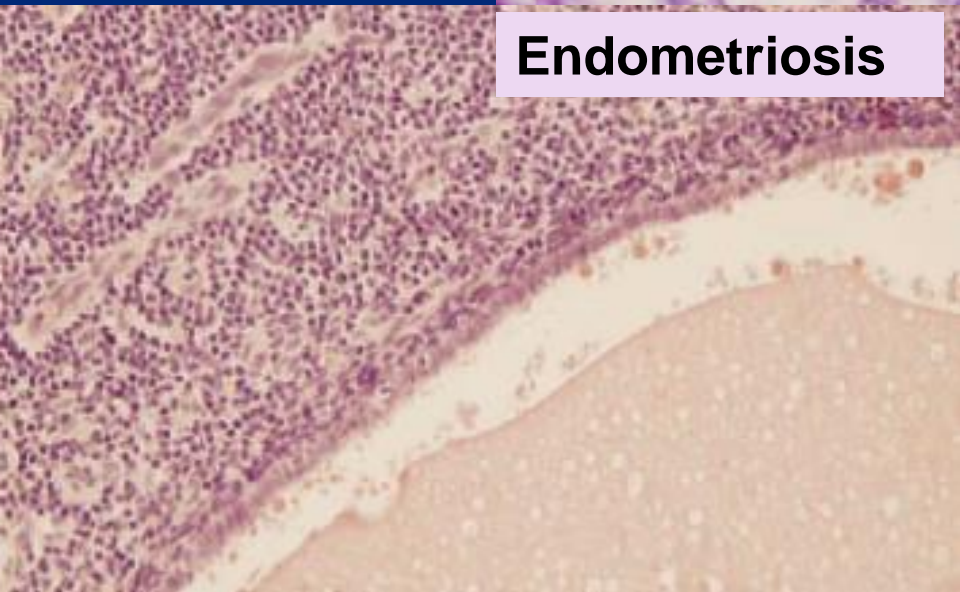
# Tip If Suspicious Cells at Mg

- Cut deeper
- Obtain a benchmark FS from the tumor for comparison
- Limitation:
  - Post-treatment (hypo cellularity)

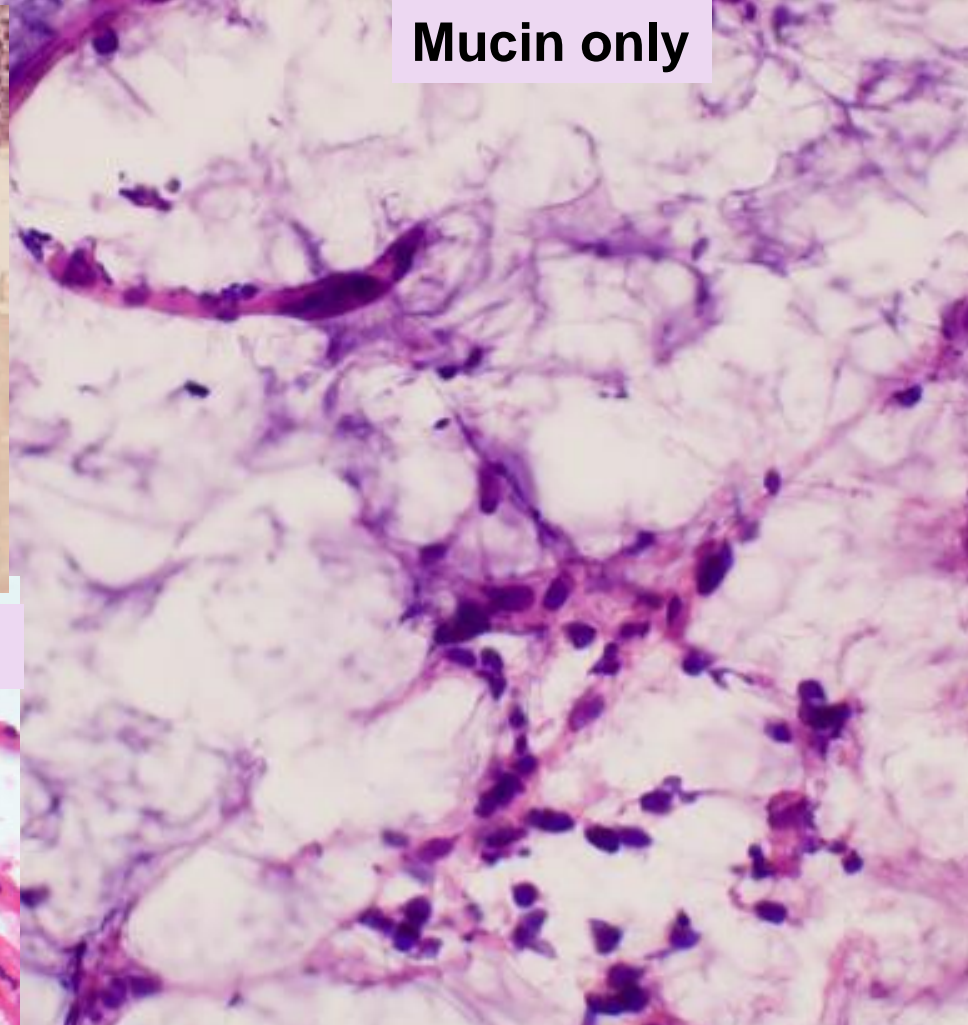




# Other FS Pitfalls in Below the Diaphragm LN



Endometriosis



Mucin only



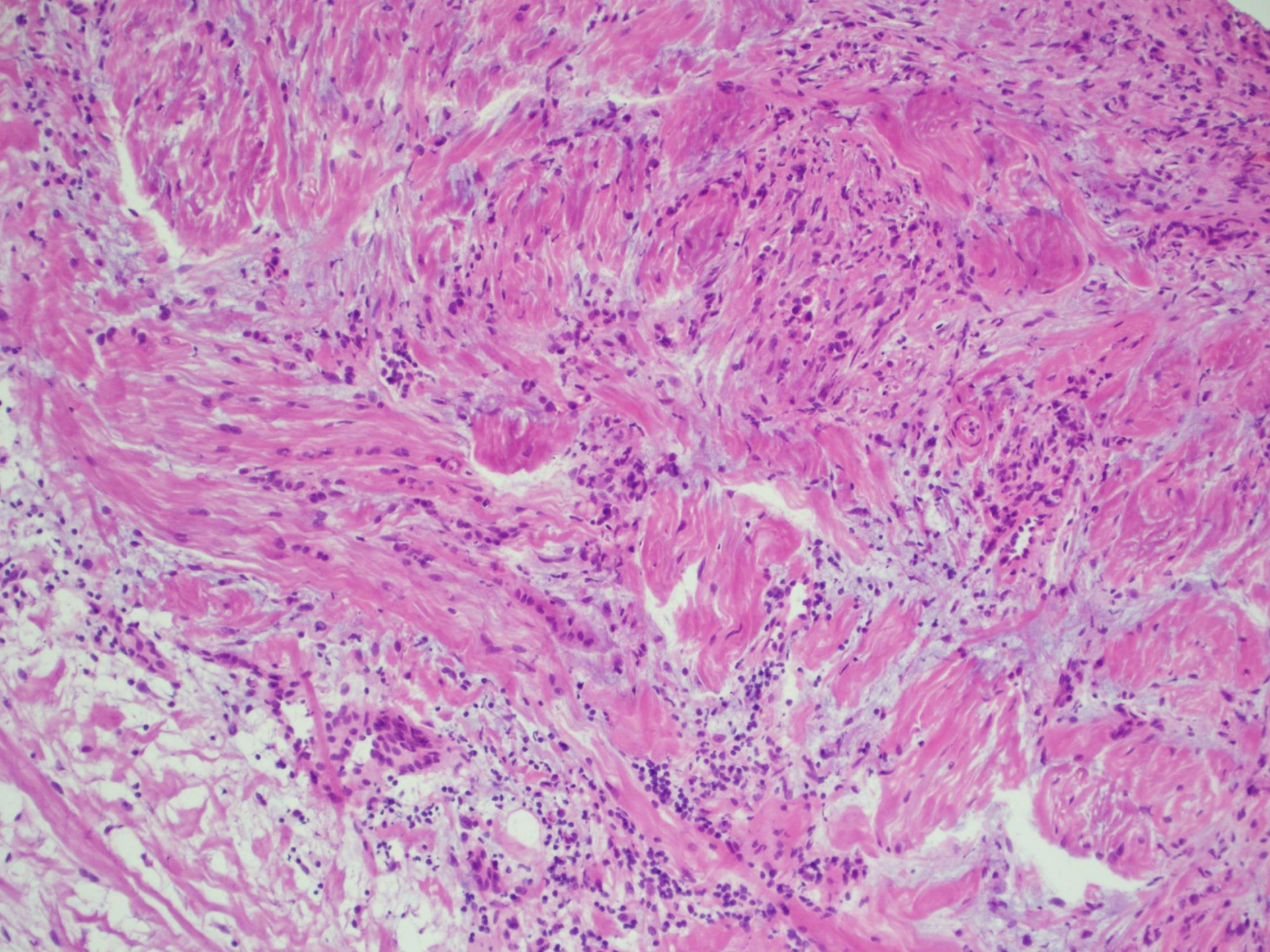
Endosalpingiosis



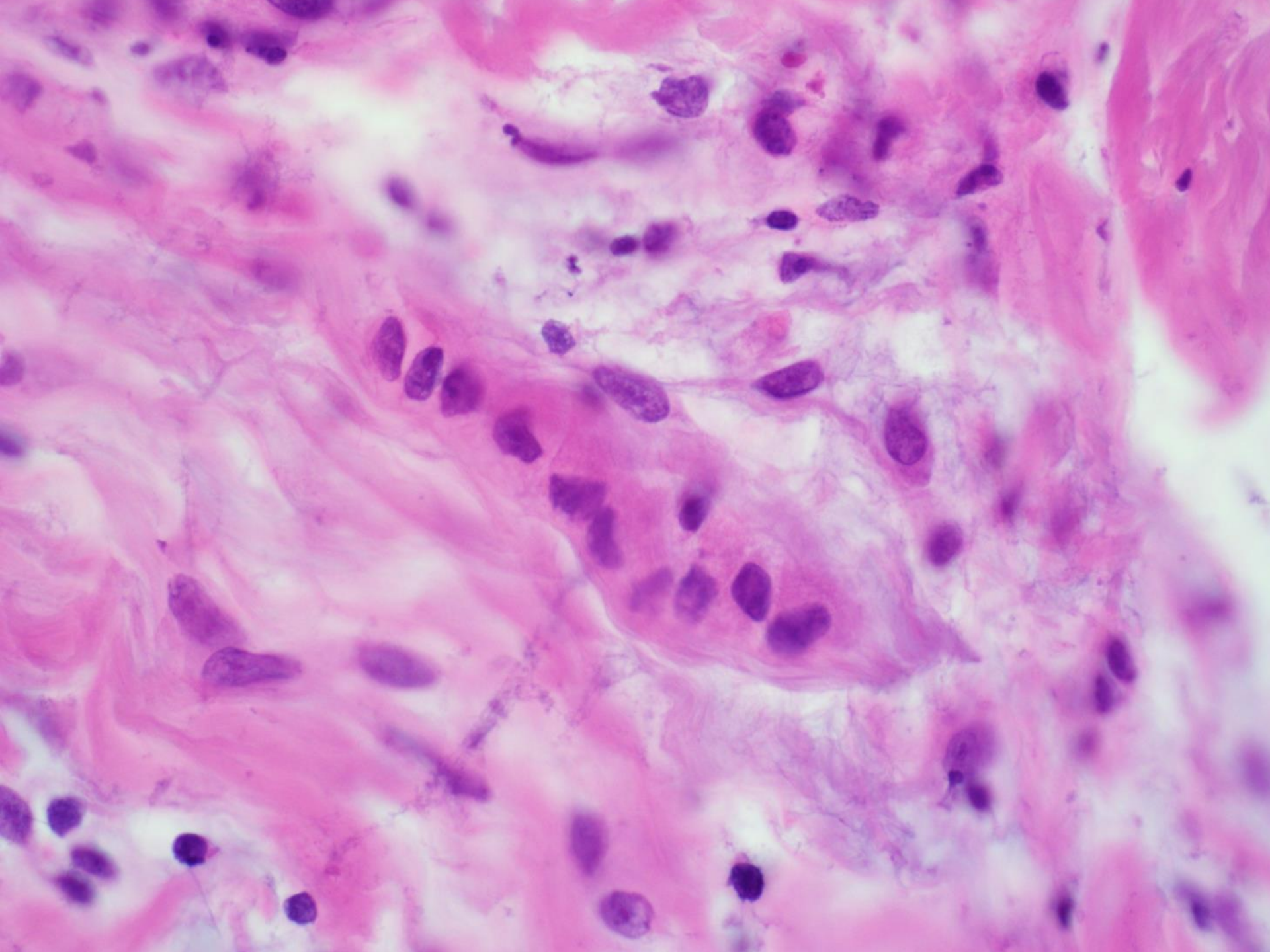
## Case 4

- 65 yo male with poorly differentiated gastric adenocarcinoma
- History of prior abdominal surgery
- Scheduled for Gastrectomy
- FS: Abdominal wall biopsies

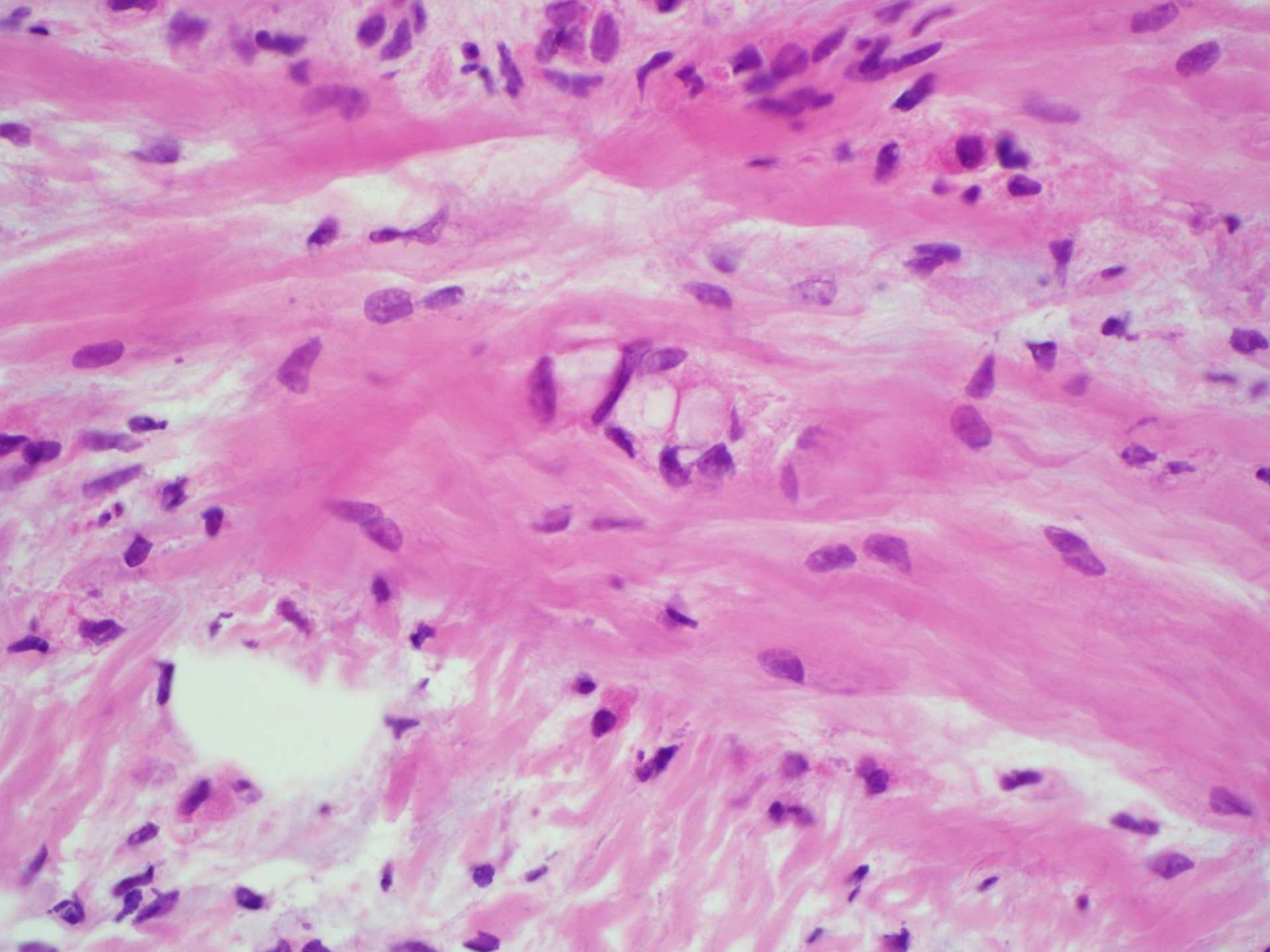






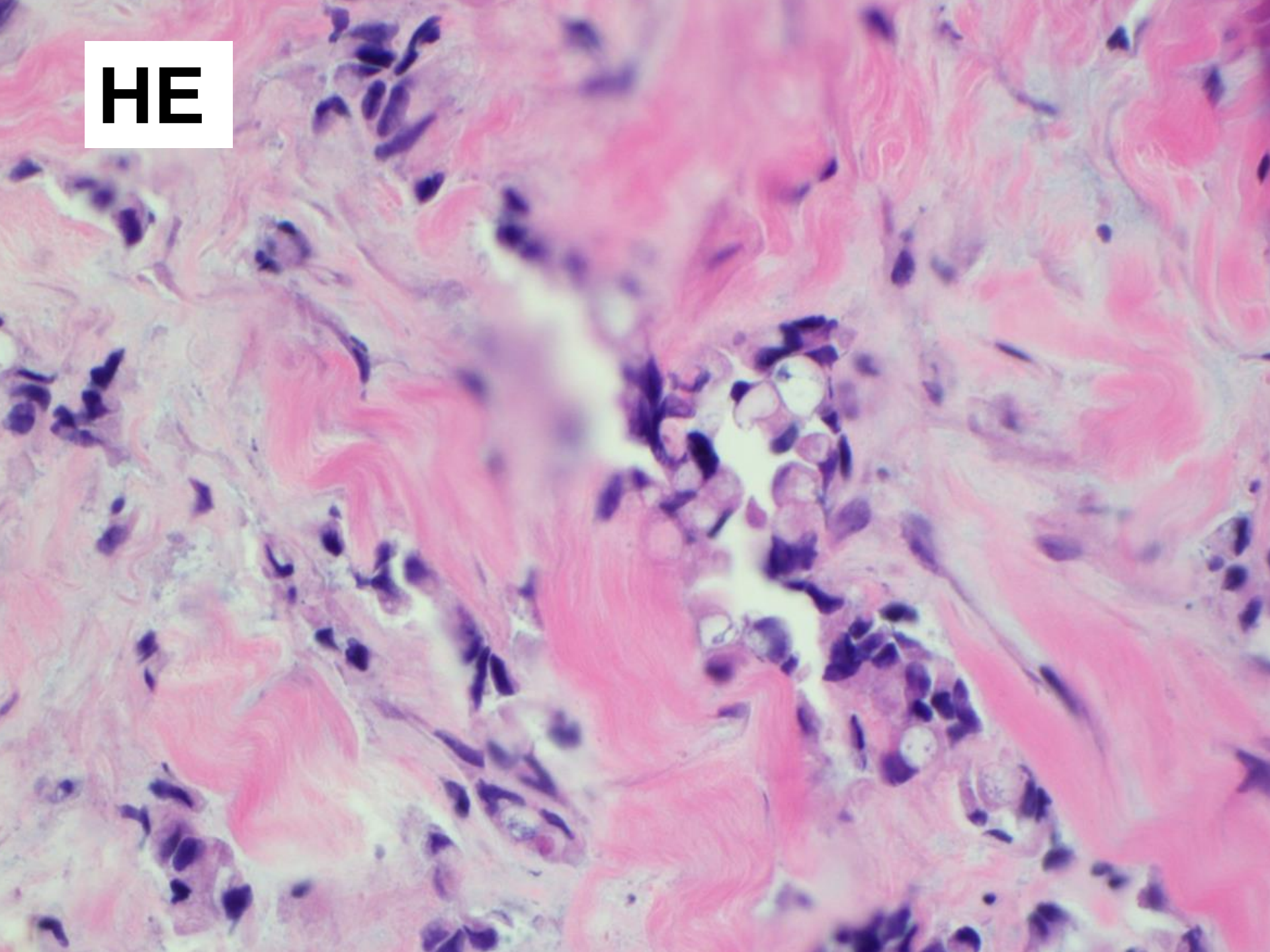






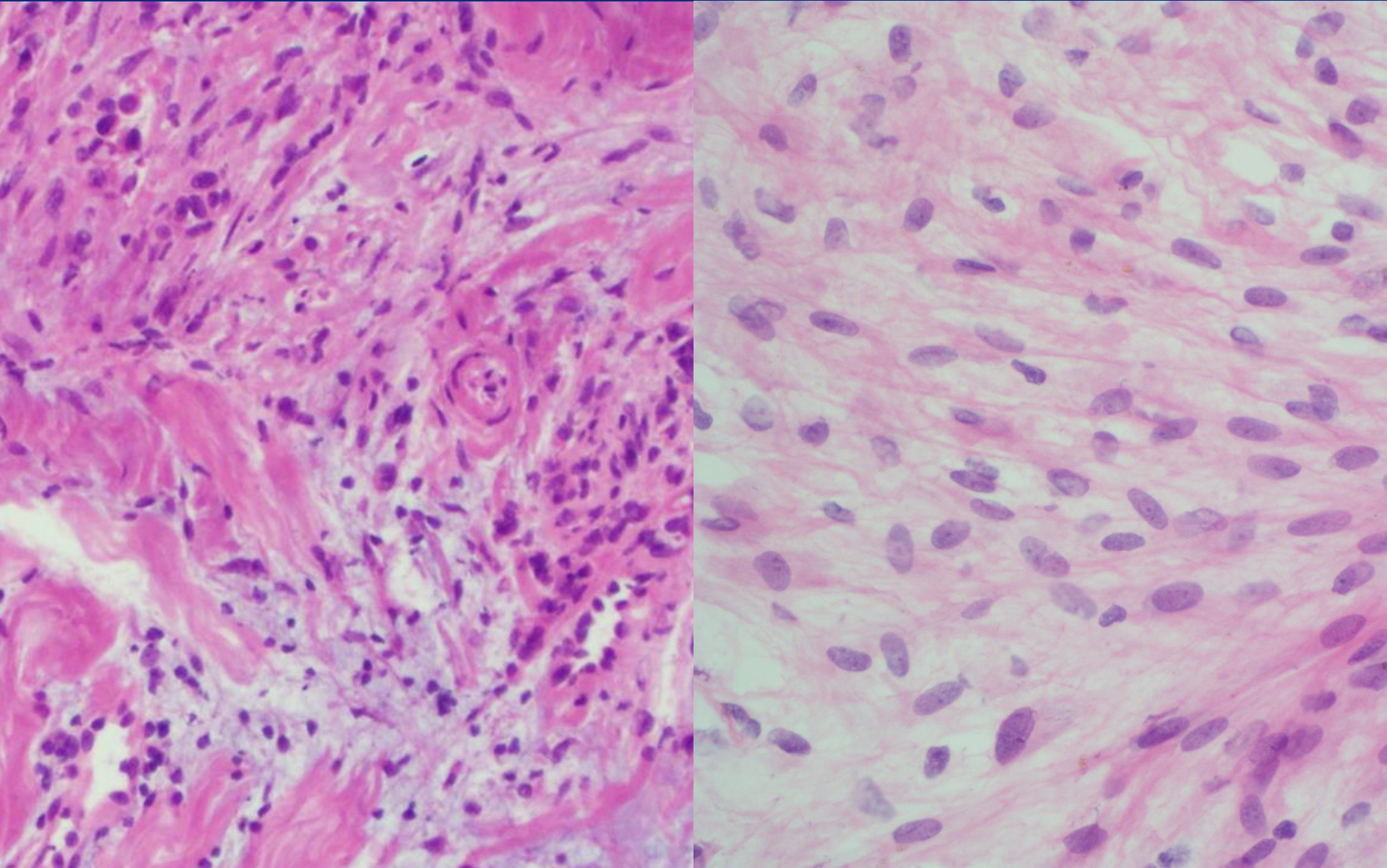


**HE**

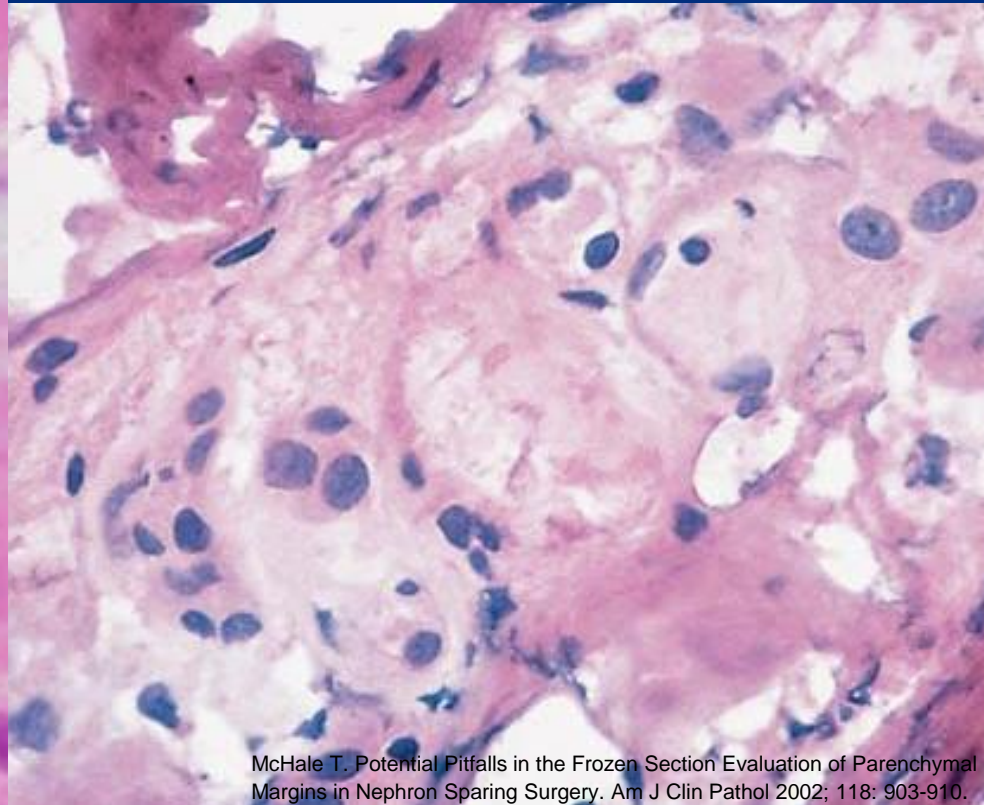
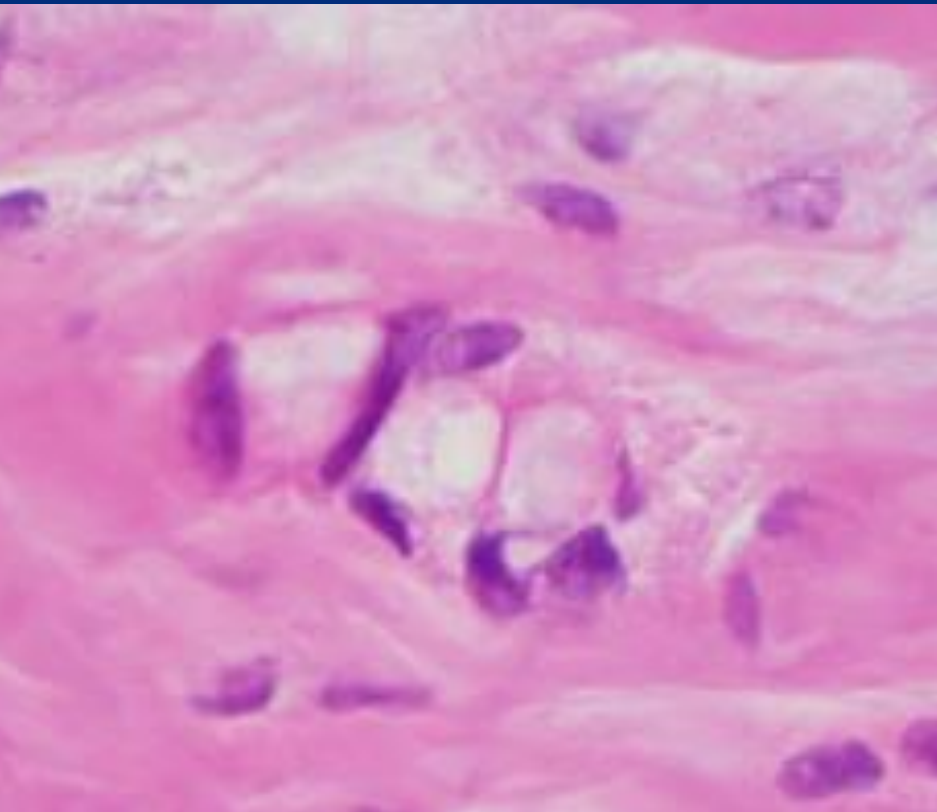




# PD CA vs Histiocytes on FS



# PD CA vs Histiocytes on FS



McHale T. Potential Pitfalls in the Frozen Section Evaluation of Parenchymal Margins in Nephron Sparing Surgery. *Am J Clin Pathol* 2002; 118: 903-910.

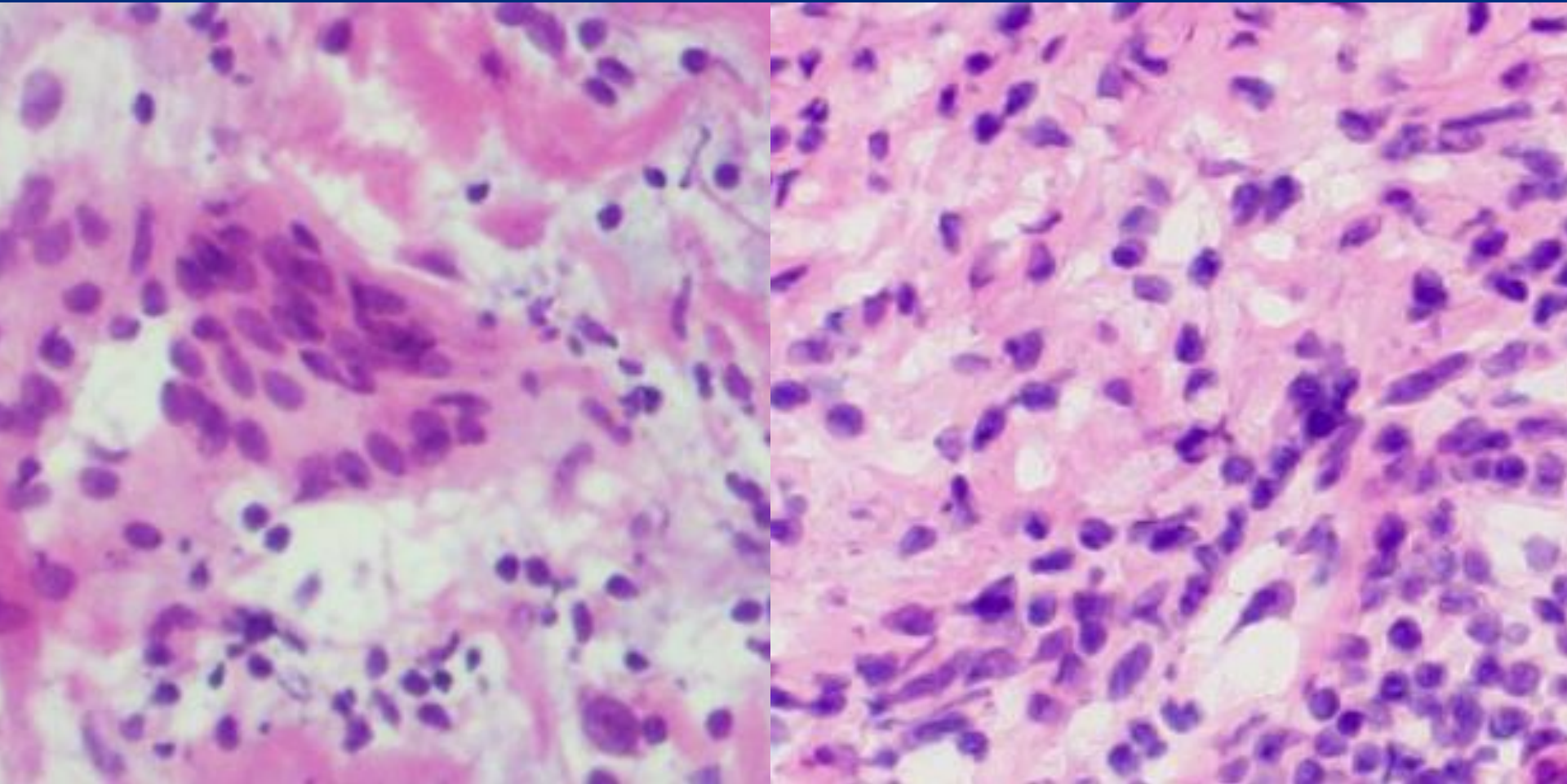
- Anisonucleosis
- Irregular N contours
- Prominent nucleoli

- Bland nuclei (N)

Zhu X. Frozen section diagnosis of gastrointestinal poorly cohesive and signet-ring cell adenocarcinoma: useful morphologic features to avoid misdiagnosis *Virchows Arch.* 2020



# PD CA vs Histiocytes on FS



- Nucleus  $>4x$  larger than lymphocyte

- Nucleus slightly larger than lymphocyte

# Frozen section diagnosis of gastrointestinal poorly cohesive and signet-ring cell adenocarcinoma: useful morphologic features to avoid misdiagnosis

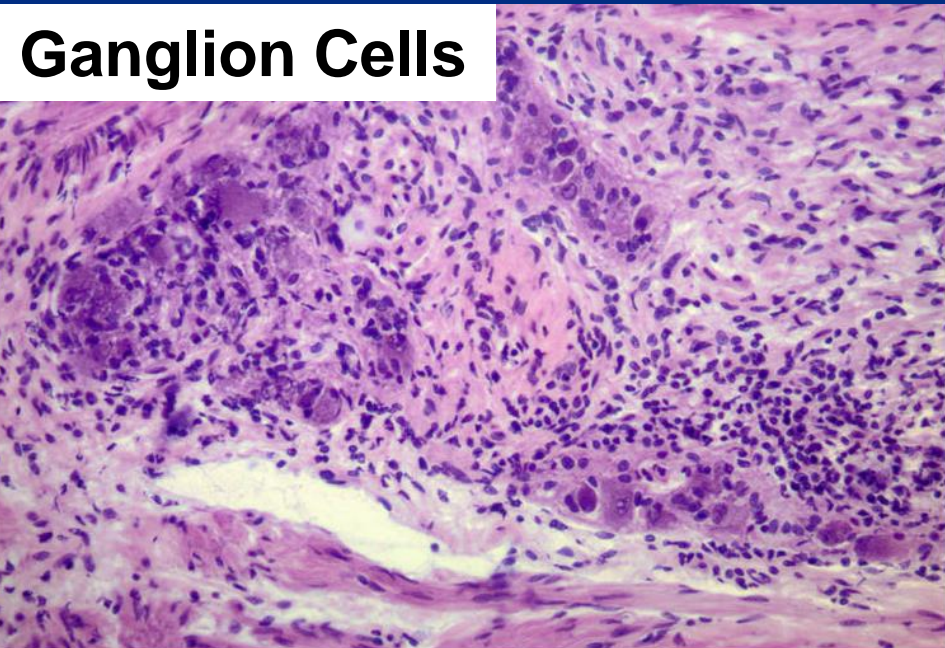
Xiaoqin Zhu<sup>1</sup> · Jacob R. Bledsoe<sup>1</sup>

Feature	Inflammatory/stromal cells	Poorly cohesive carcinoma
Perineural invasion	No	Yes
Focal gland formation	No	Yes
Intracytoplasmic mucin vacuole with peripheral nucleus	Uncommon	Yes
Irregular nuclear contours	Uncommon	Yes
Prominent nucleoli	Uncommon	Yes
Multinucleation	Uncommon	Yes
Anisonucleosis (> 4:1)	Uncommon	Yes
Nuclear size > 4× the size of a small lymphocyte	Uncommon	Yes
Mitotic figures	Uncommon	Yes
Atypical cells associated with disrupted/obliterated normal structures	Uncommon	Yes

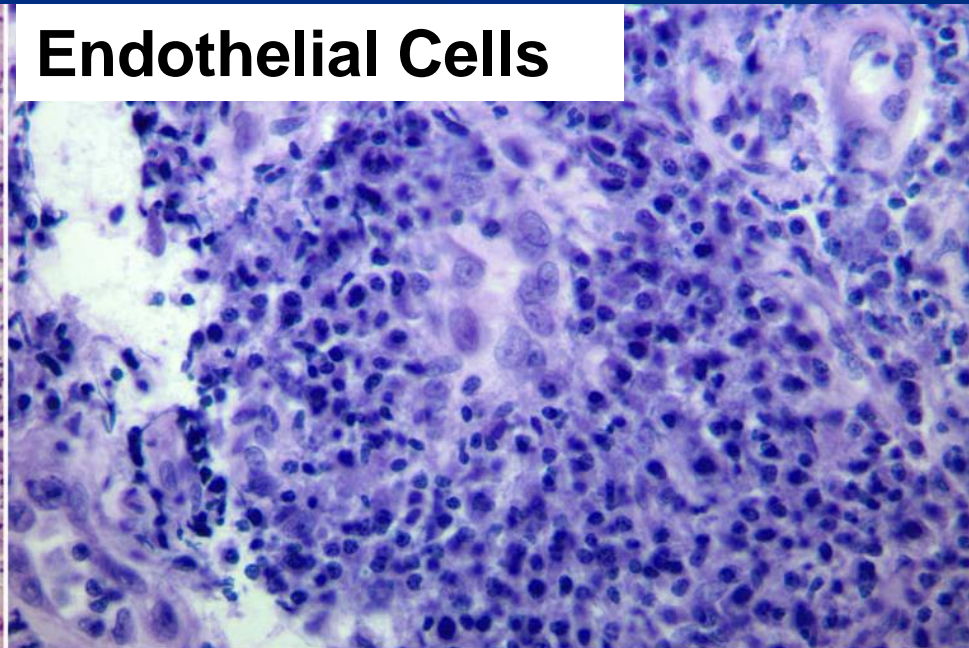


# B9 mimickers of PD CA on FS MG

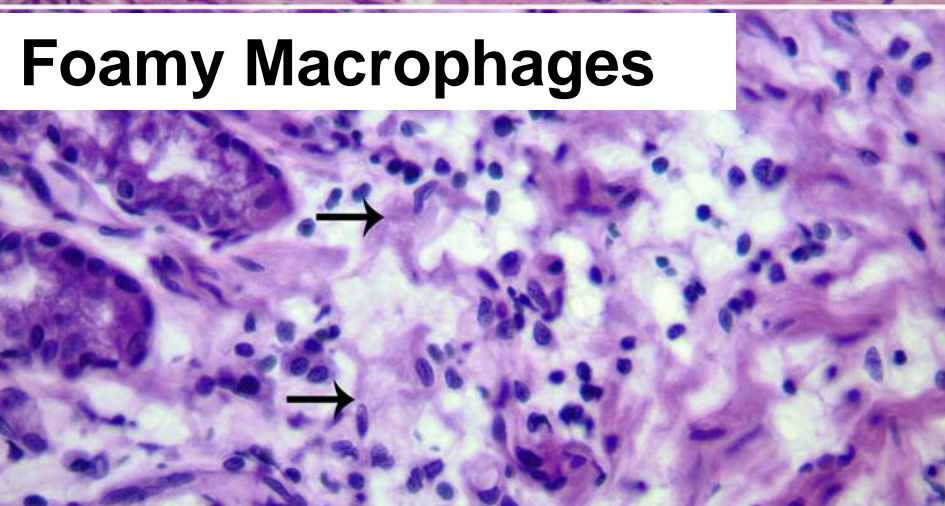
**Ganglion Cells**



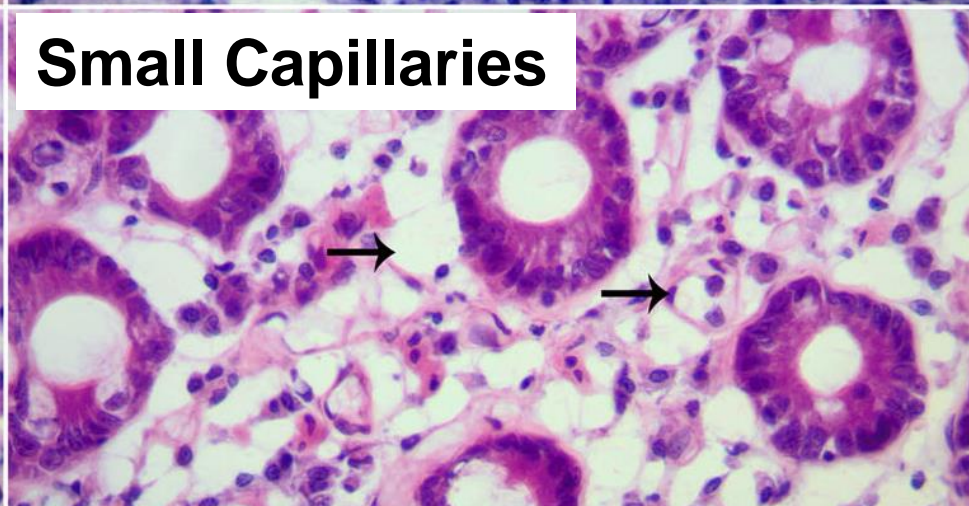
**Endothelial Cells**



**Foamy Macrophages**



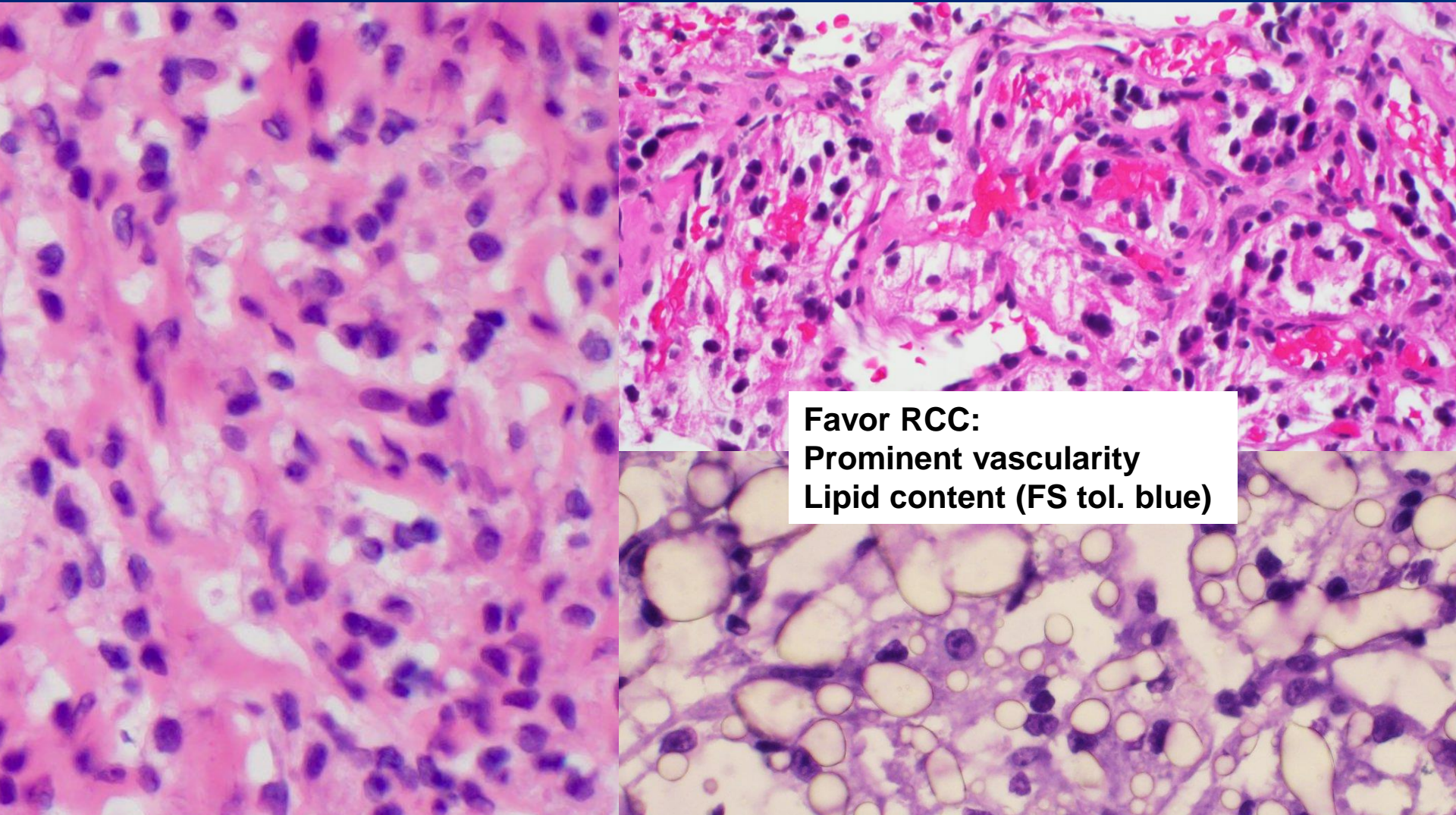
**Small Capillaries**



Zhu X et al. Frozen section diagnosis of gastrointestinal poorly cohesive and signet-ring cell adenocarcinoma: useful morphologic features to avoid misdiagnosis *Virchows Arch.* 2020



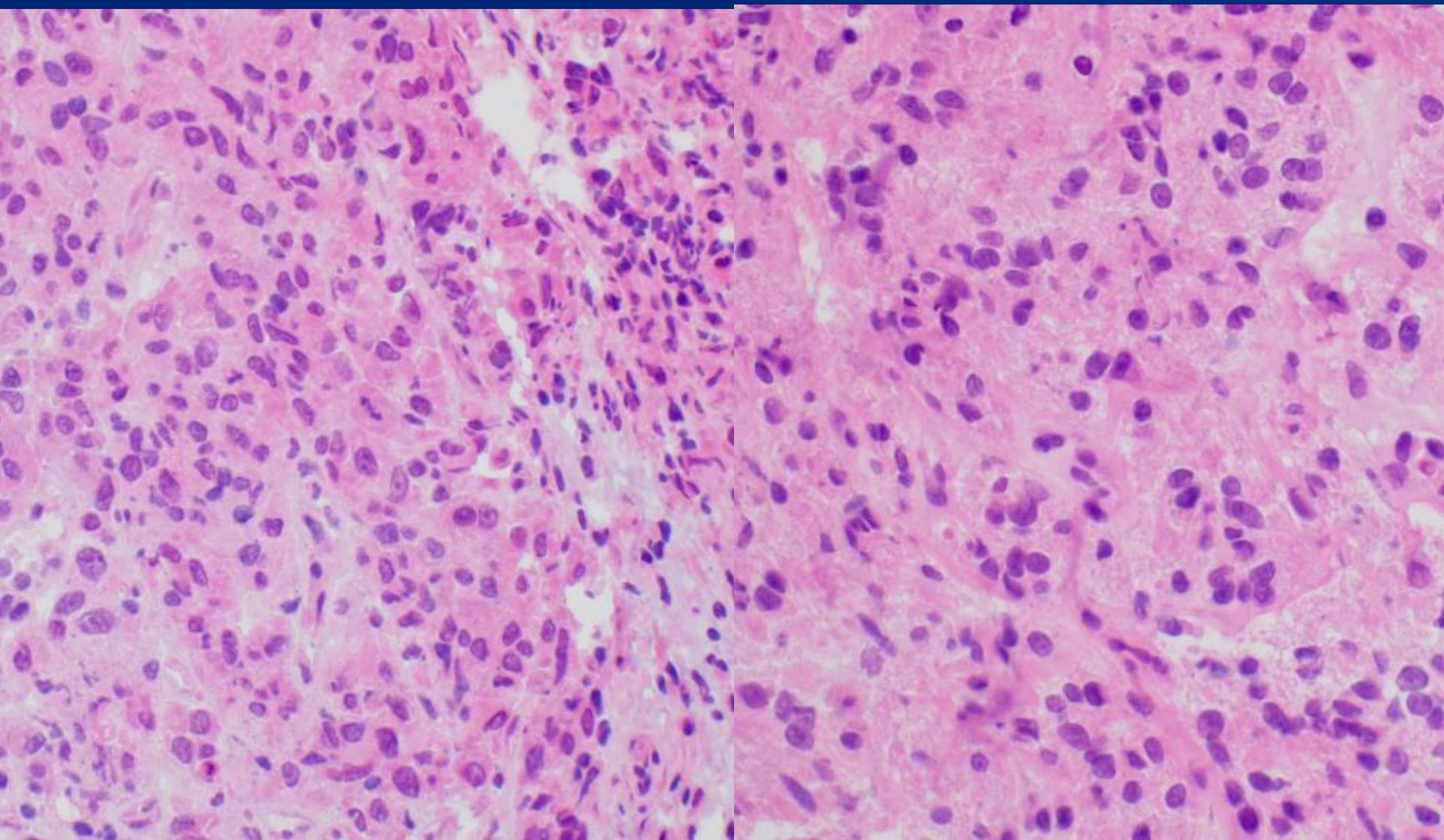
# Other challenges: Histiocytes (Xantogranulomatous Pyelonephritis) vs Renal Cell CA (RCC)



**Favor RCC:**  
**Prominent vascularity**  
**Lipid content (FS tol. blue)**

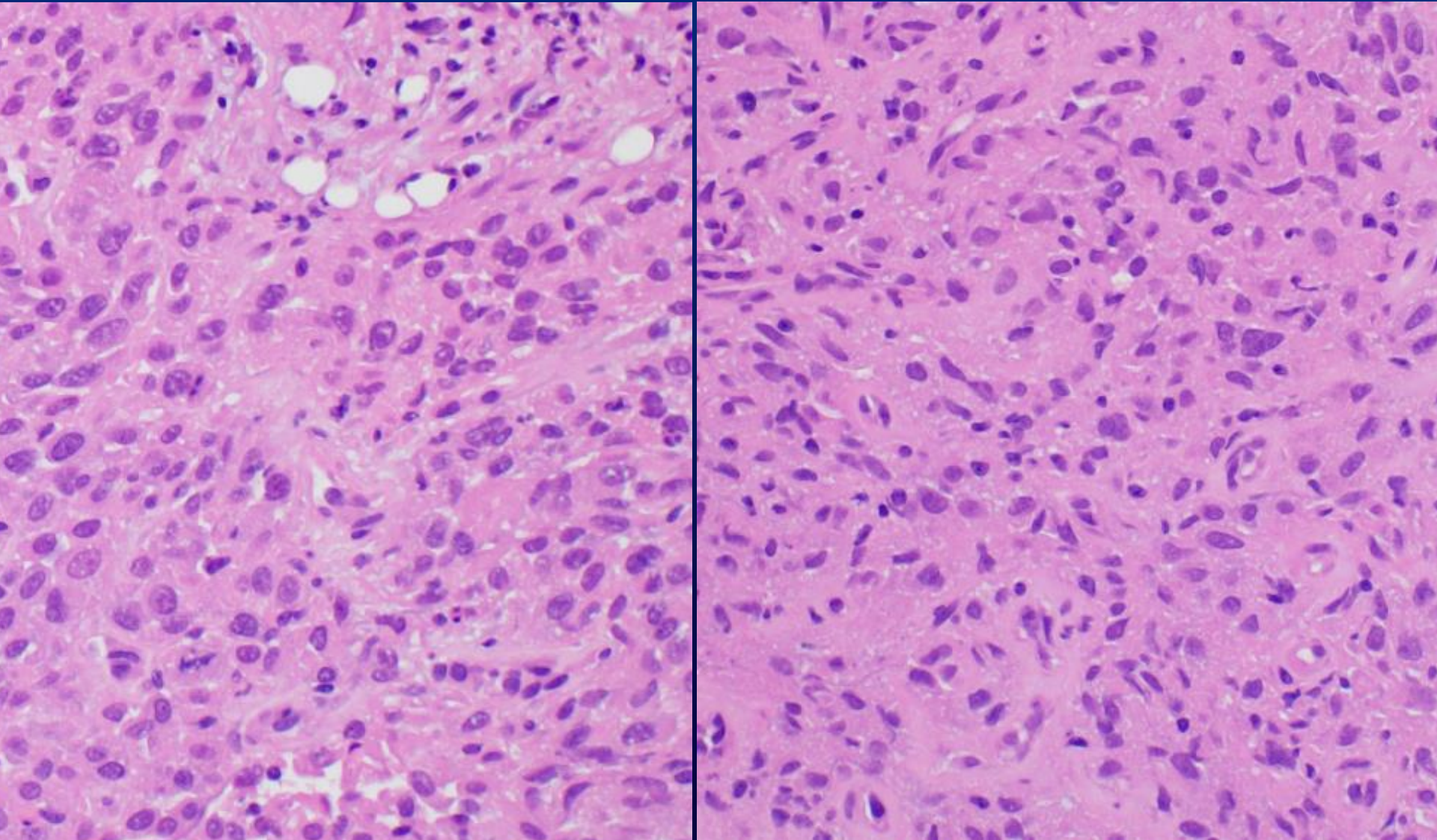


# SCC post Radiotherapy FS (Mimicking Histiocytes)



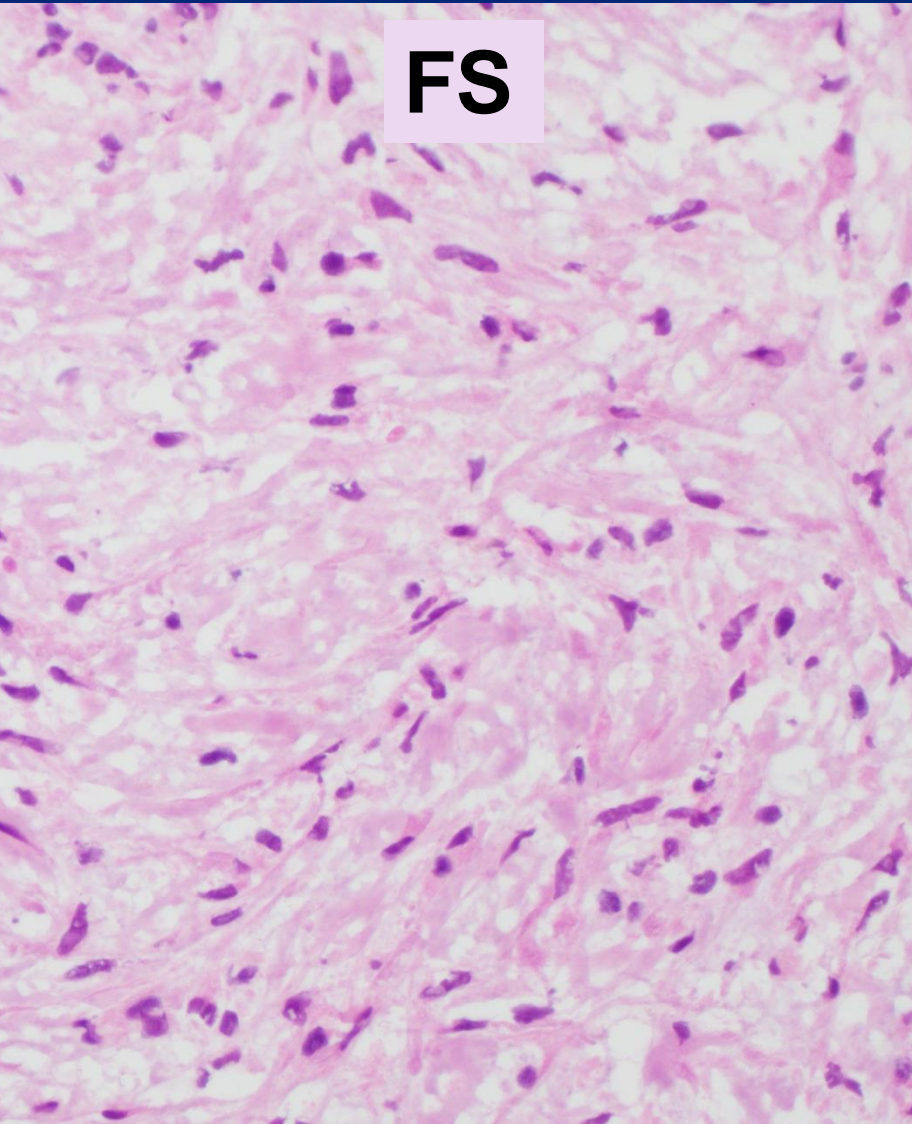


# SCC post Radiotherapy HE (Mimicking Histiocytes)

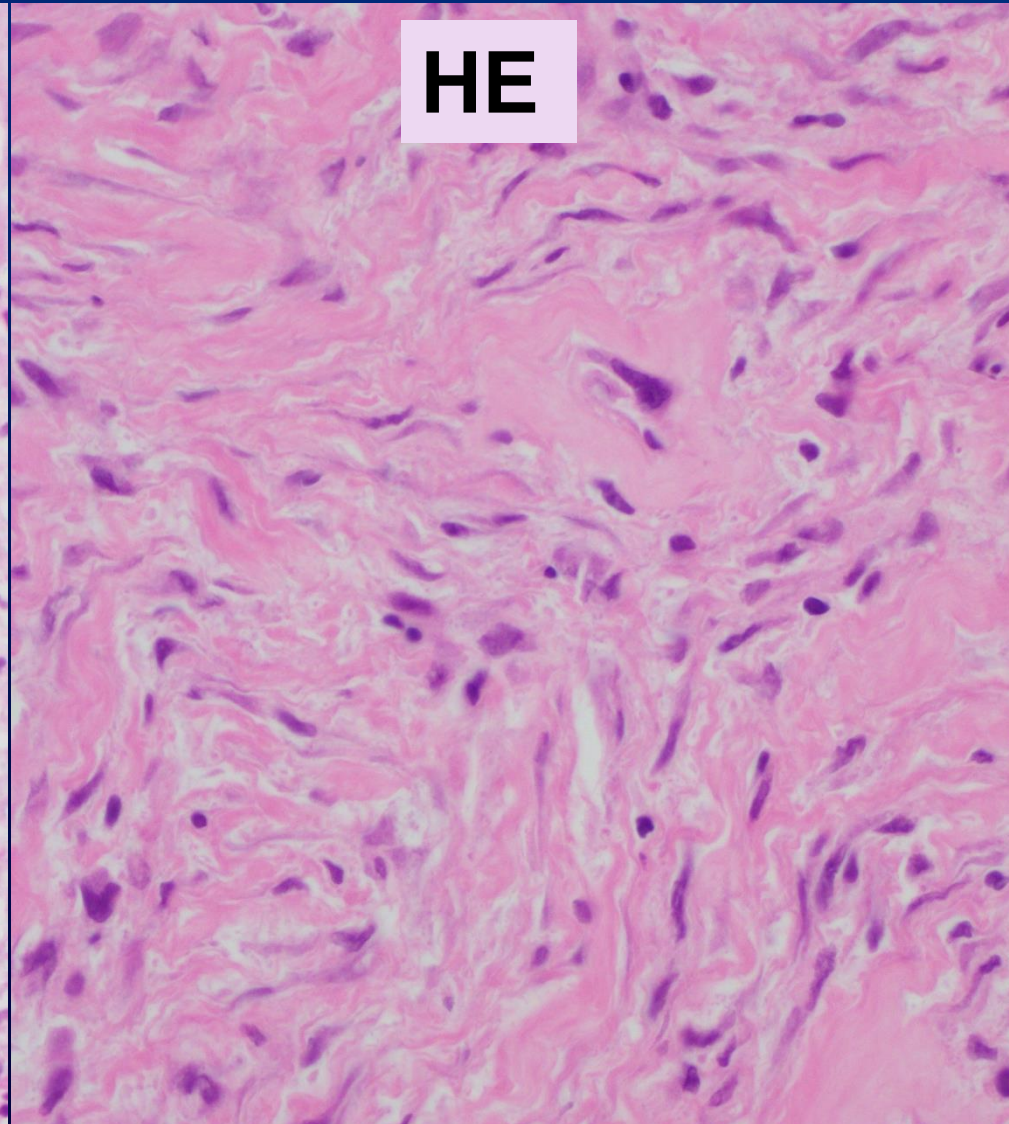




# MT Lung Adeno S/P Chemo



**FS**

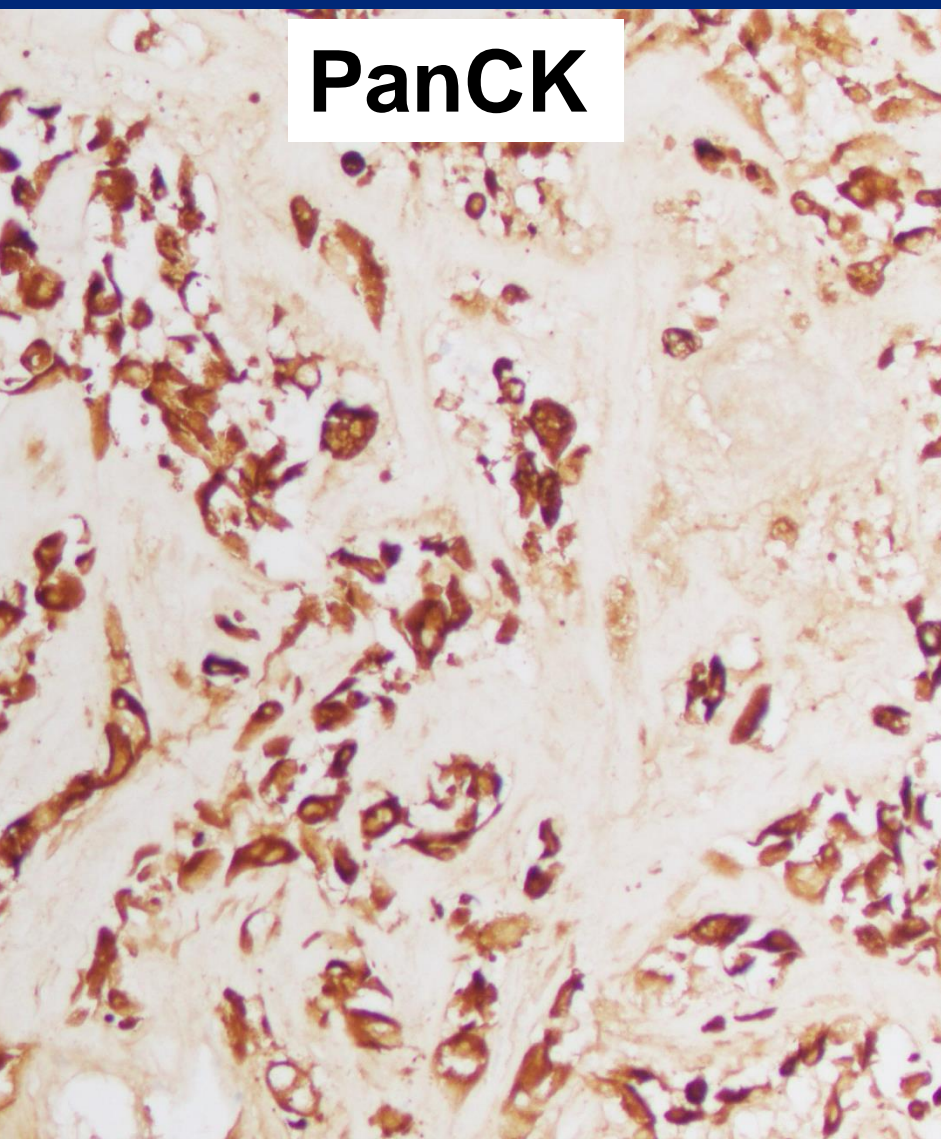


**HE**

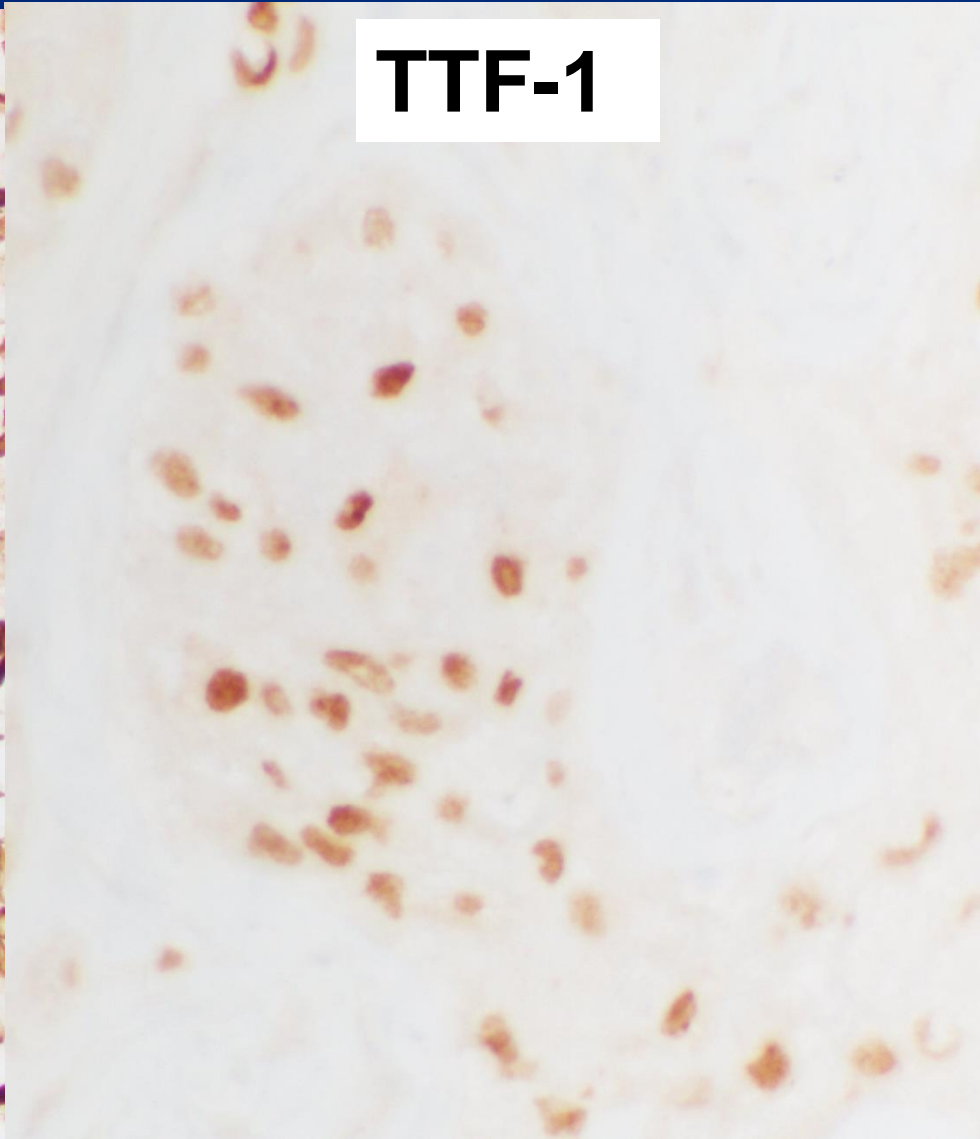


# MT Lung Adeno S/P Chemo

**PanCK**



**TTF-1**





# The Most Common Intraoperative Consultations

1. Margins
2. Lymph nodes
3. Diagnosis

## 2. Evaluation of LN

- FS for:
- CA staging:
  - Freeze entire node
- Lymphadenopathy of unknown etiology:
  - Freeze 1 section (+/- Smear):
  - If **normal** : freeze the rest (communicate with surgeon= specimen may be **non-lesional**)
  - If **abnormal**: save unfrozen tissue for permanent slides +/- additional studies
  - =**Lesional** tissue obtained/ “Suspicious for... lymphoproliferative disorder”

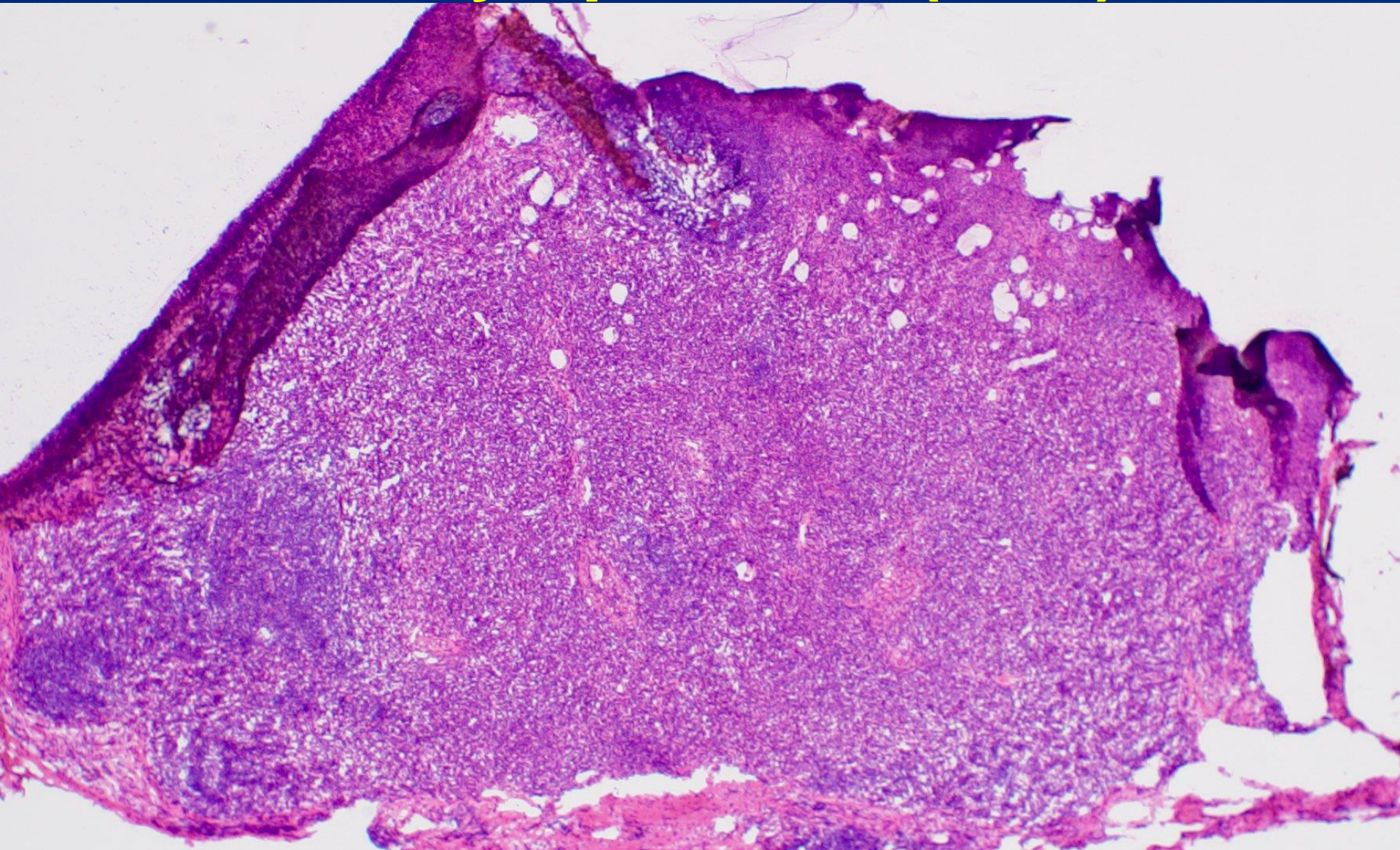




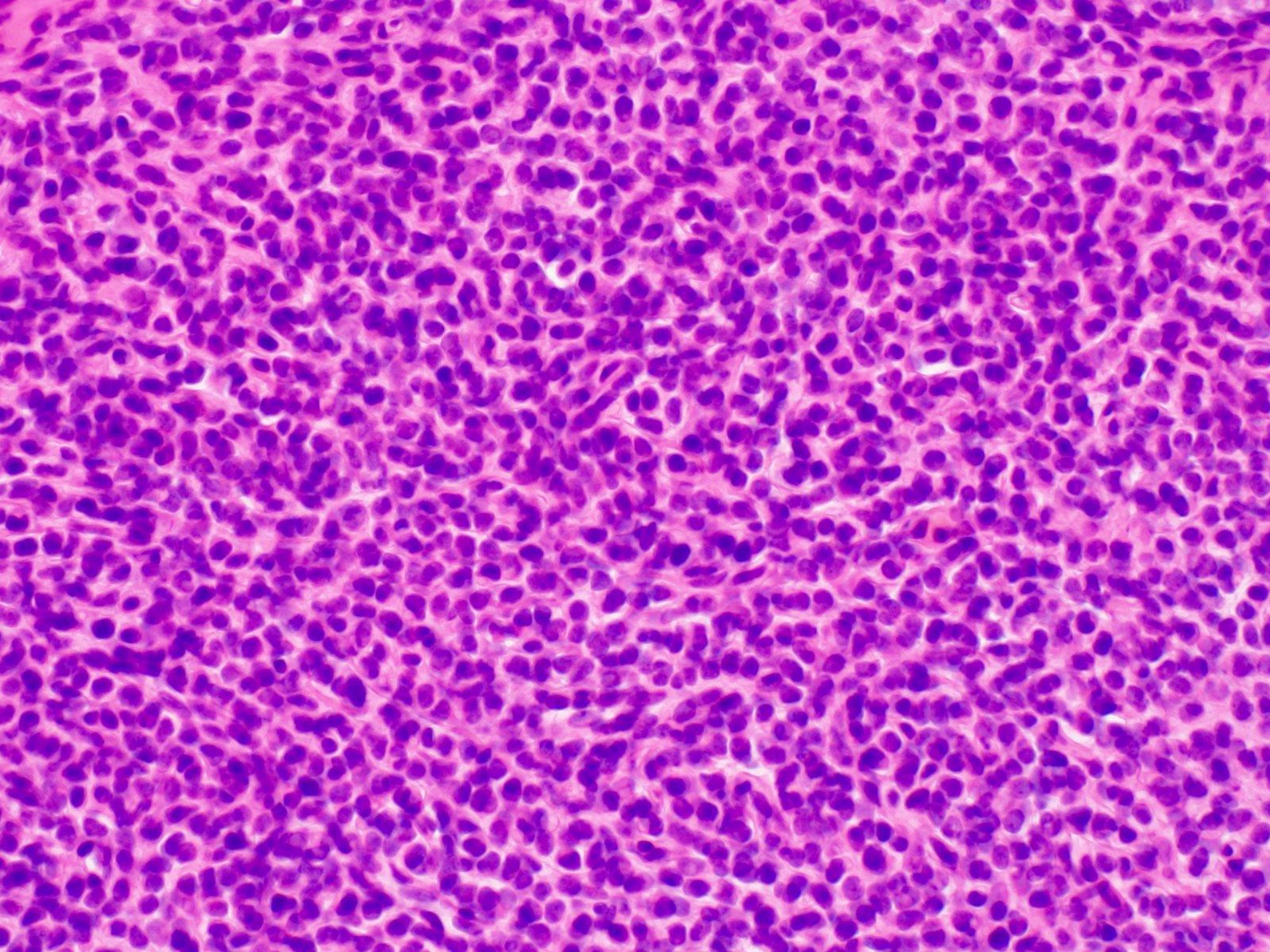
## Case 5

- 55 yo woman with breast cancer

# Sentinel Lymph Node (SLN) FS











## Need to know more...

- What kind of breast cancer
- LN size, imaging



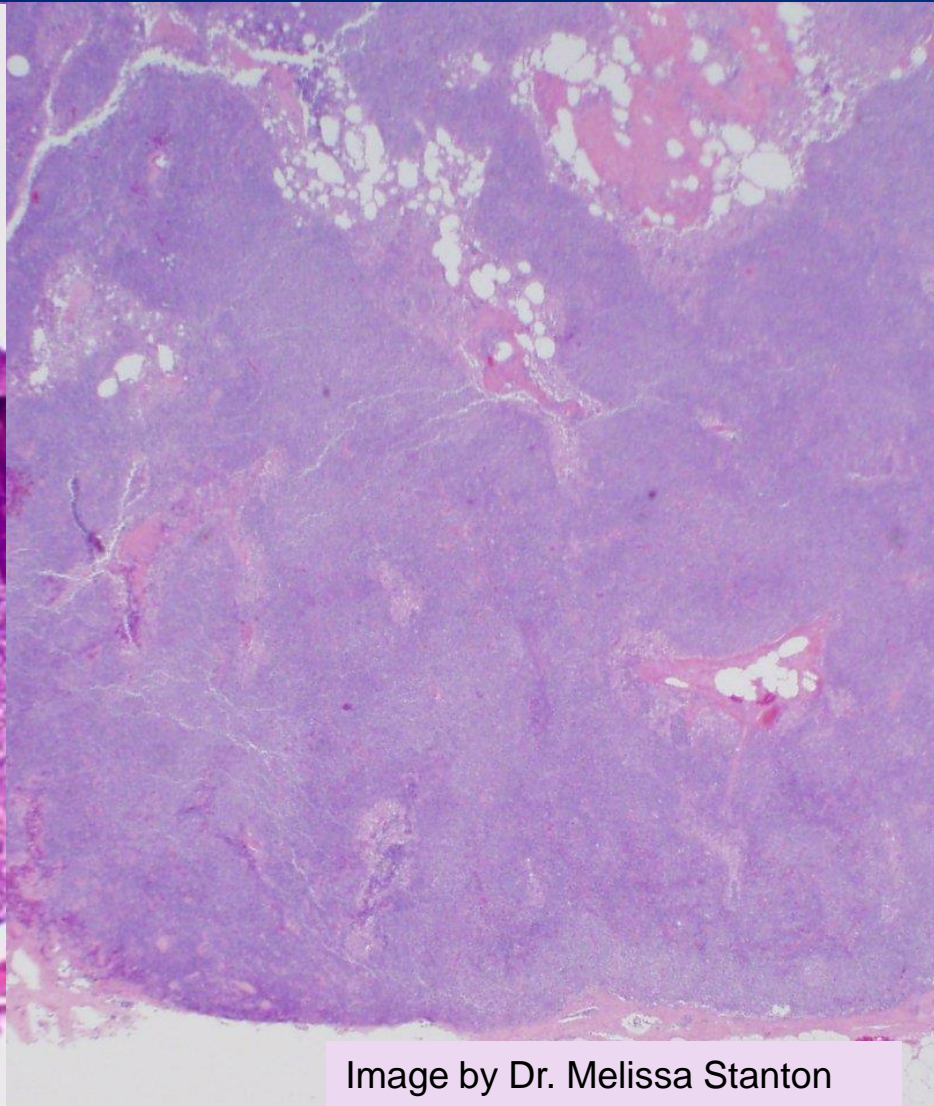
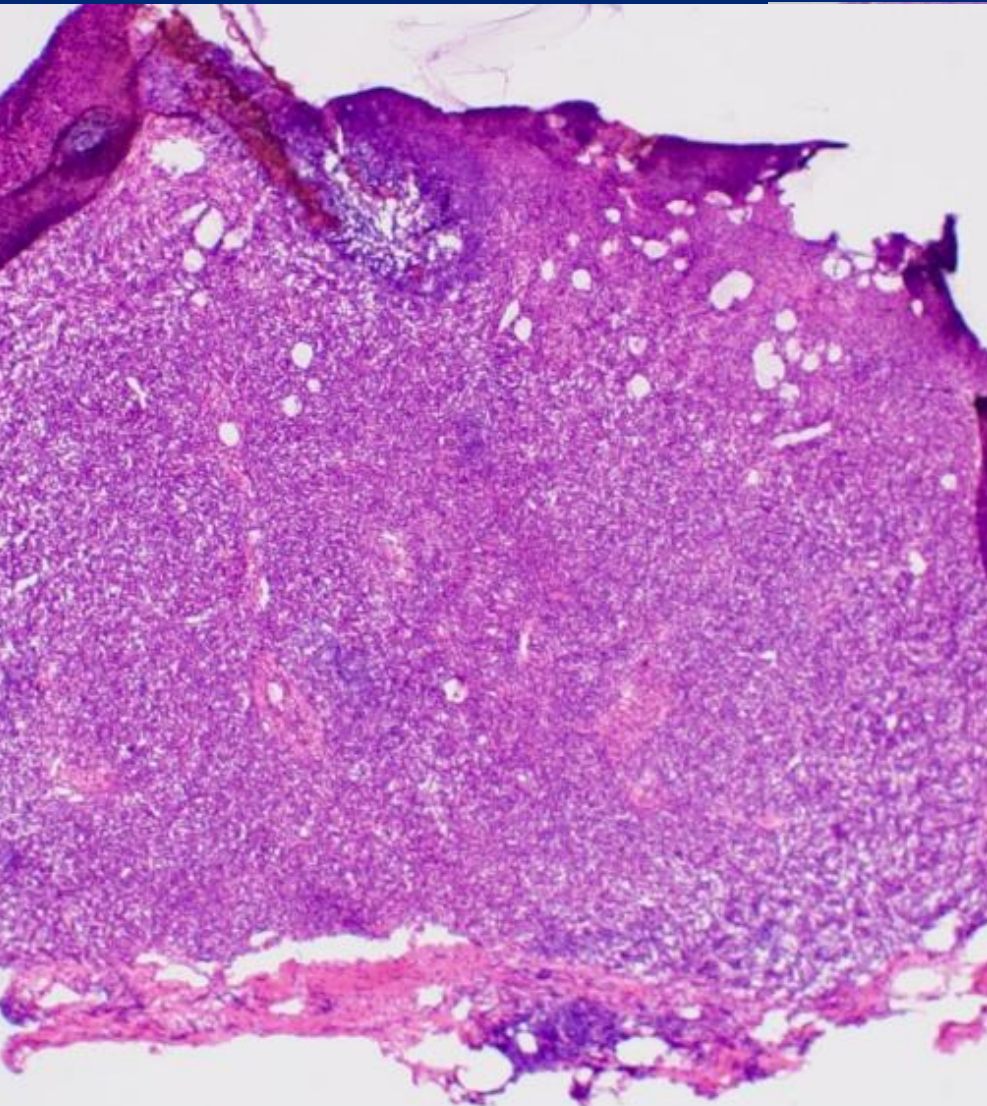
# Invasive Lobular Carcinoma...



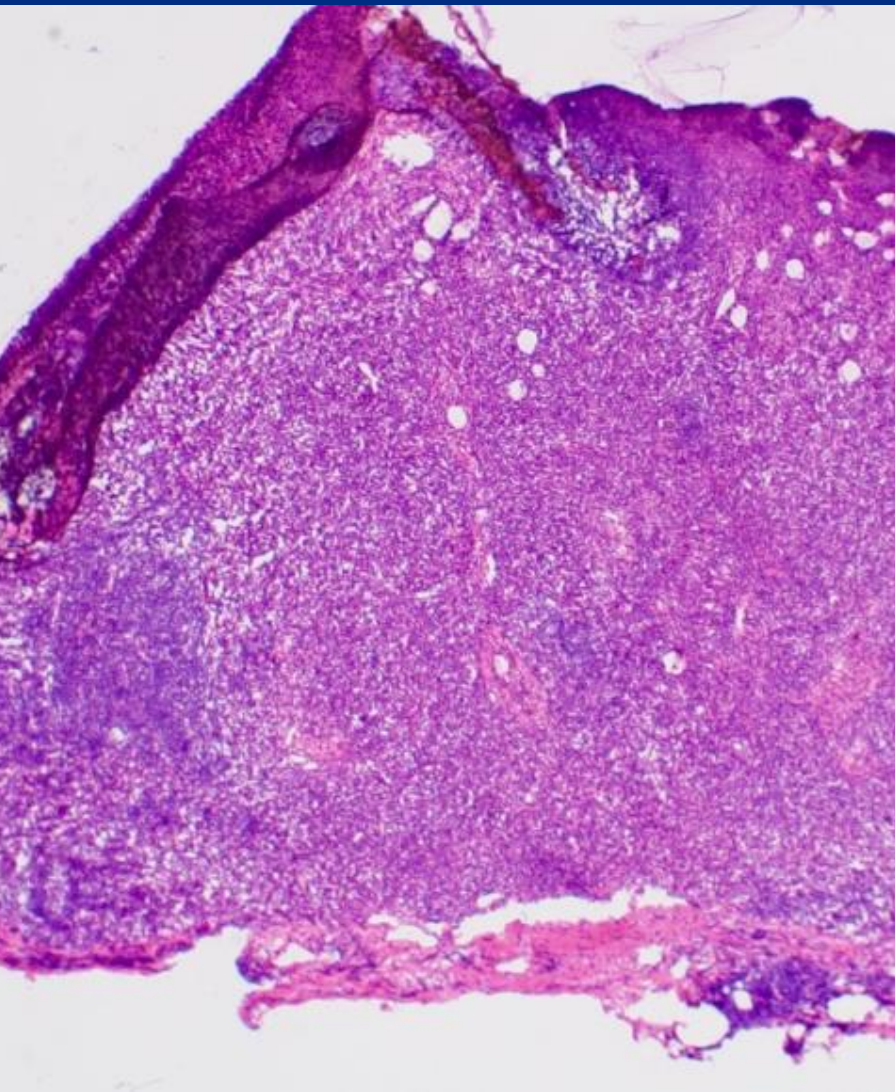
**FS Diagnosis:  
“3 lymph nodes, all negative for  
carcinoma”**



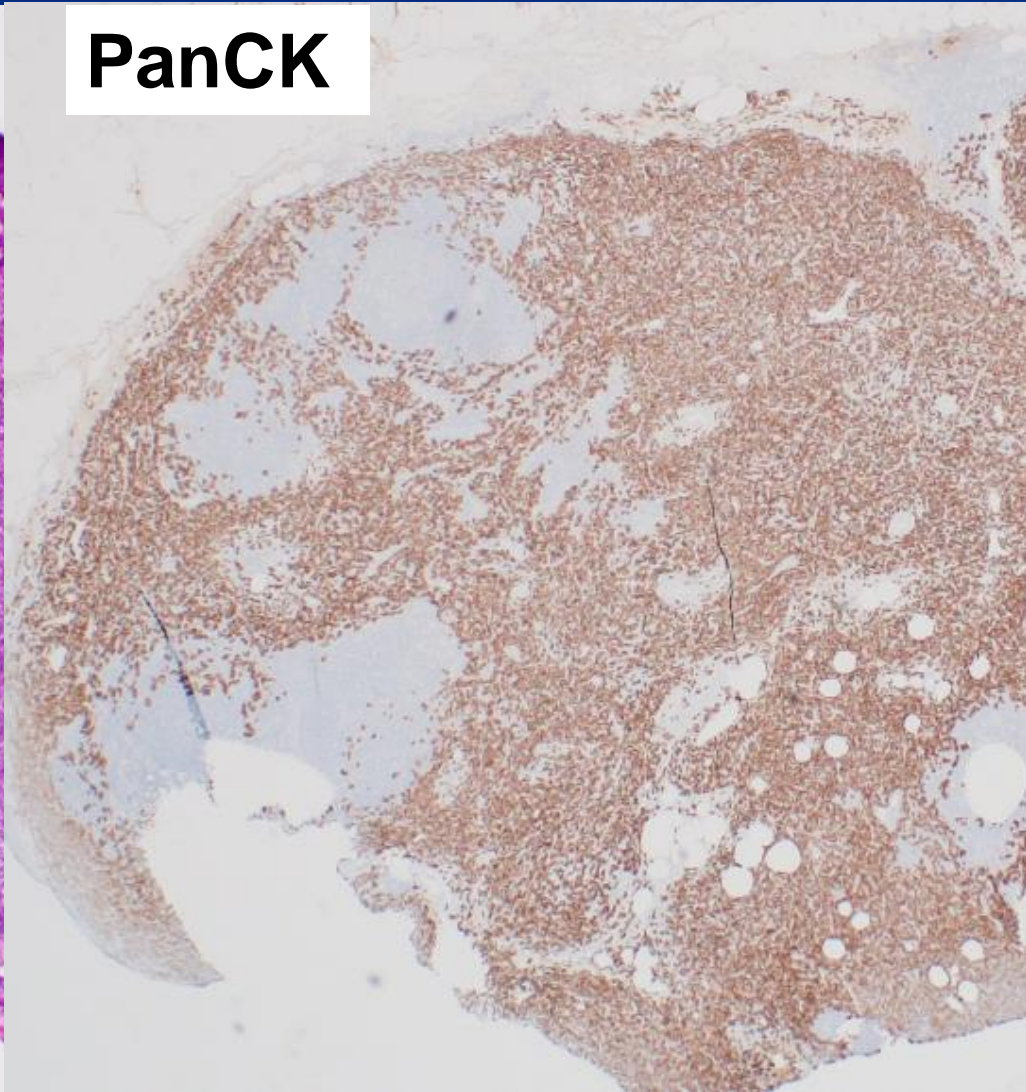
# Our Case vs Lymphoma (CLL)



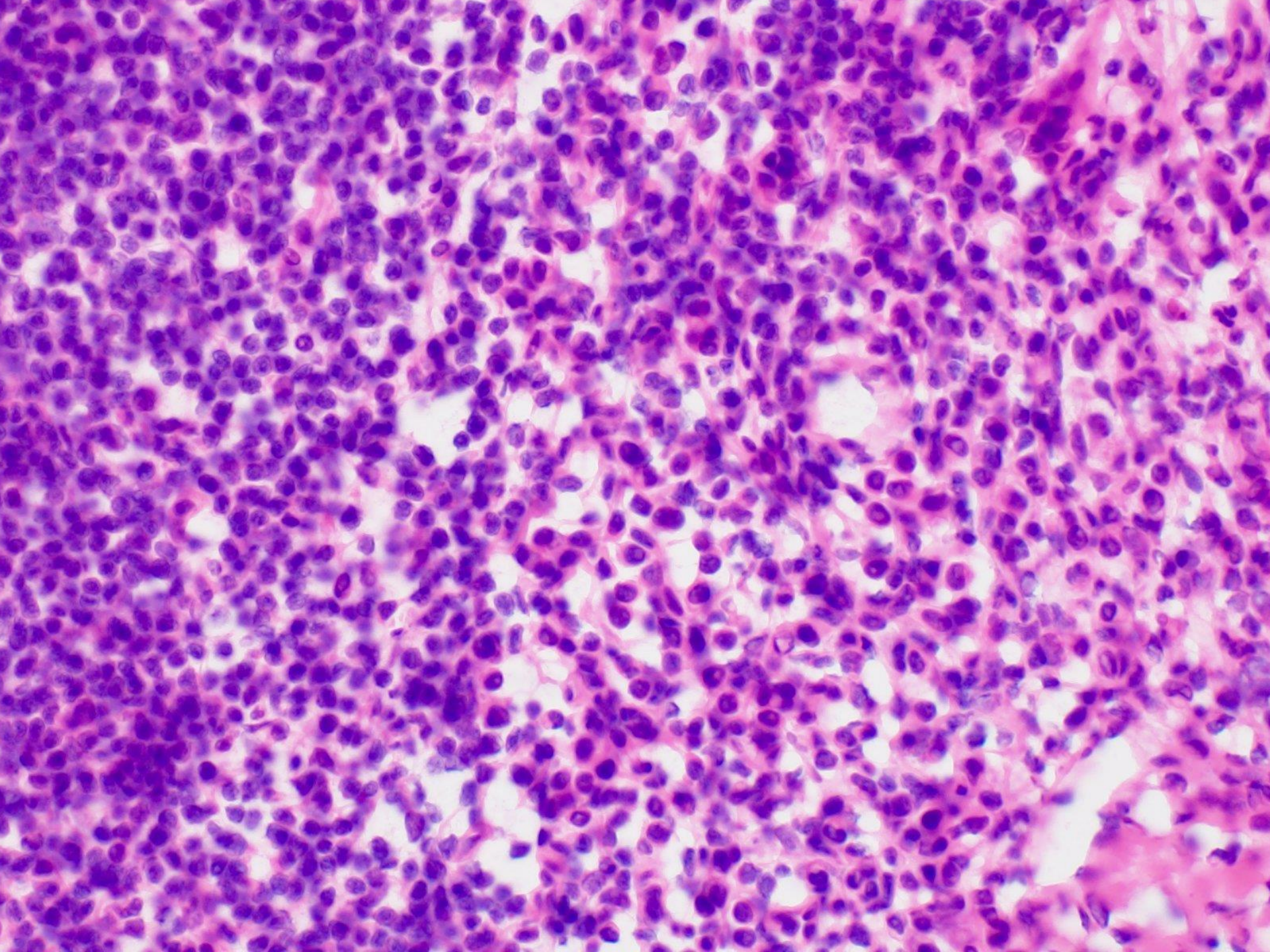




**PanCK**



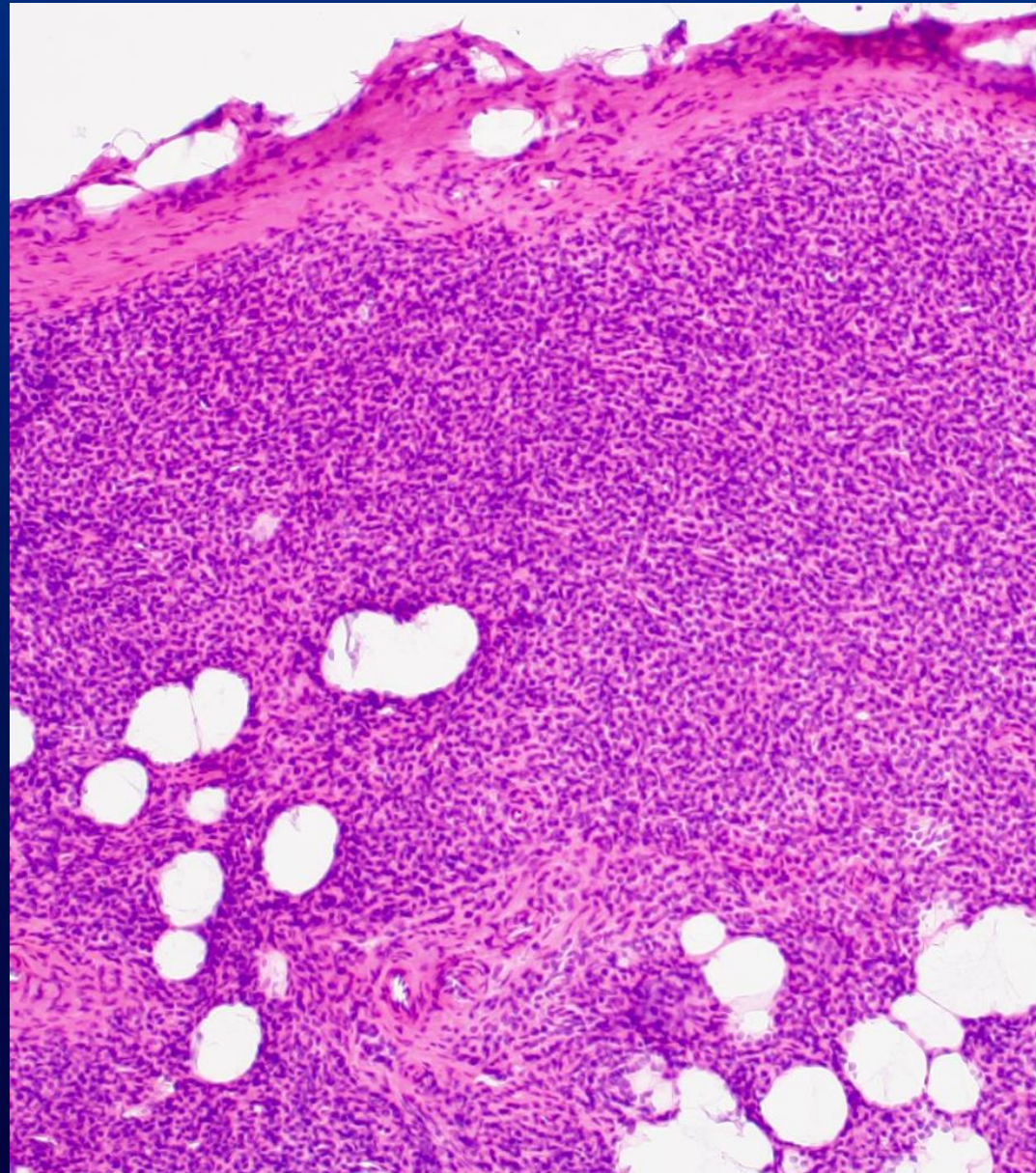






# MT Pitfalls

- Single cells:
  - Melanoma, stomach (signet ring ca), breast (ILC)
- MT to unusual LN location:
  - Center or entirely replaced LN

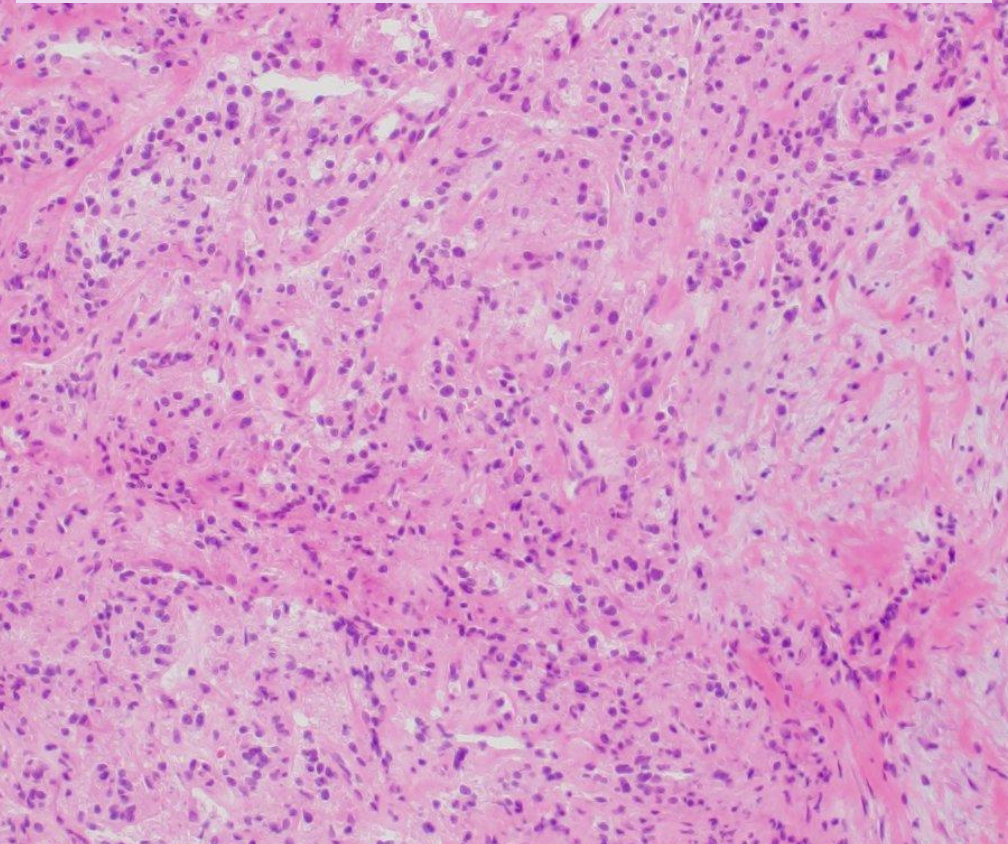




# MT Pitfalls

## CA with prior treatment:

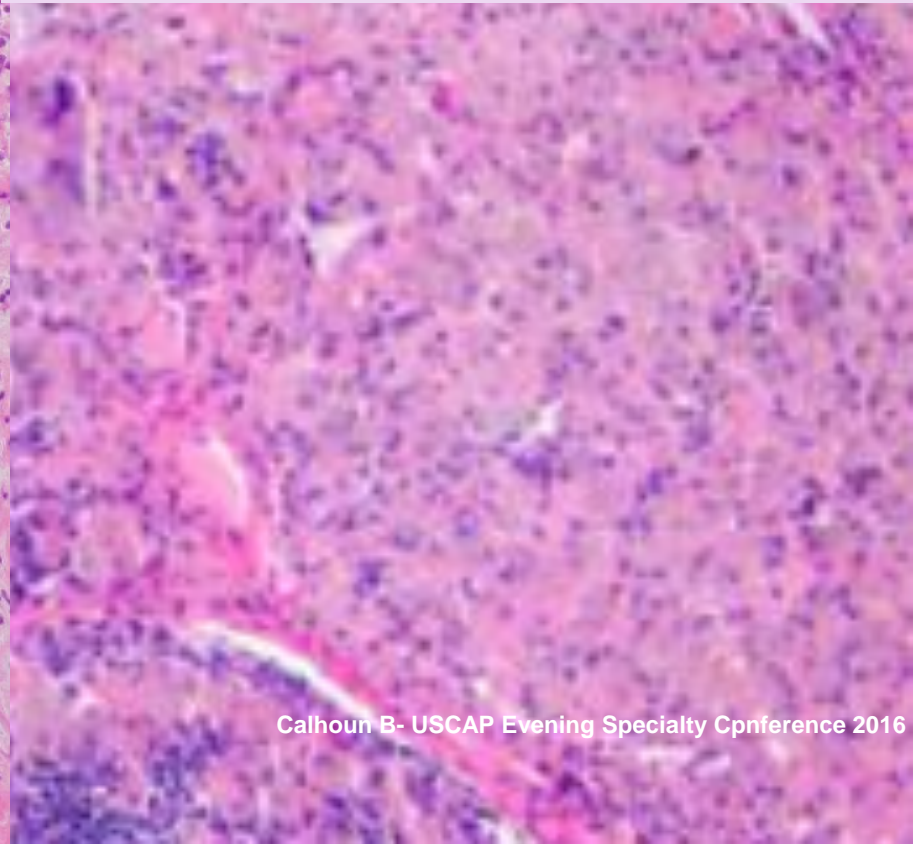
May resemble histiocytes, be sparsely distributed



# Clues

## Histiocytes:

Abundant cytoplasm, bland nuclei, small nucleoli, pigment



# The Most Common Intraoperative Consultations

1. Margins
2. Lymph nodes
3. Diagnosis:
  1. Obtain diagnostic tissue
  2. Guide extent surgical resection



# 3. Diagnosis

- Why is the frozen section being performed?
- How much does the surgeon need to know at the time of FS?
- What will he/she do with the info?
  - Stage the patient?
  - Perform a more radical excision?

# How to communicate results when a specific diagnosis cannot be determined?

## Lesional tissue present

- Negative for neoplasm:
  - granuloma, abscess, other
- +Neoplasm:
  - low vs high grade
  - ?MT
- “Suspicious for a lymphoproliferative process”:
  - Defer for permanents (additional studies)

## Lesional tissue absent

- LEVELS
- “Tissue may not represent lesion”
- “Additional tissue needed”

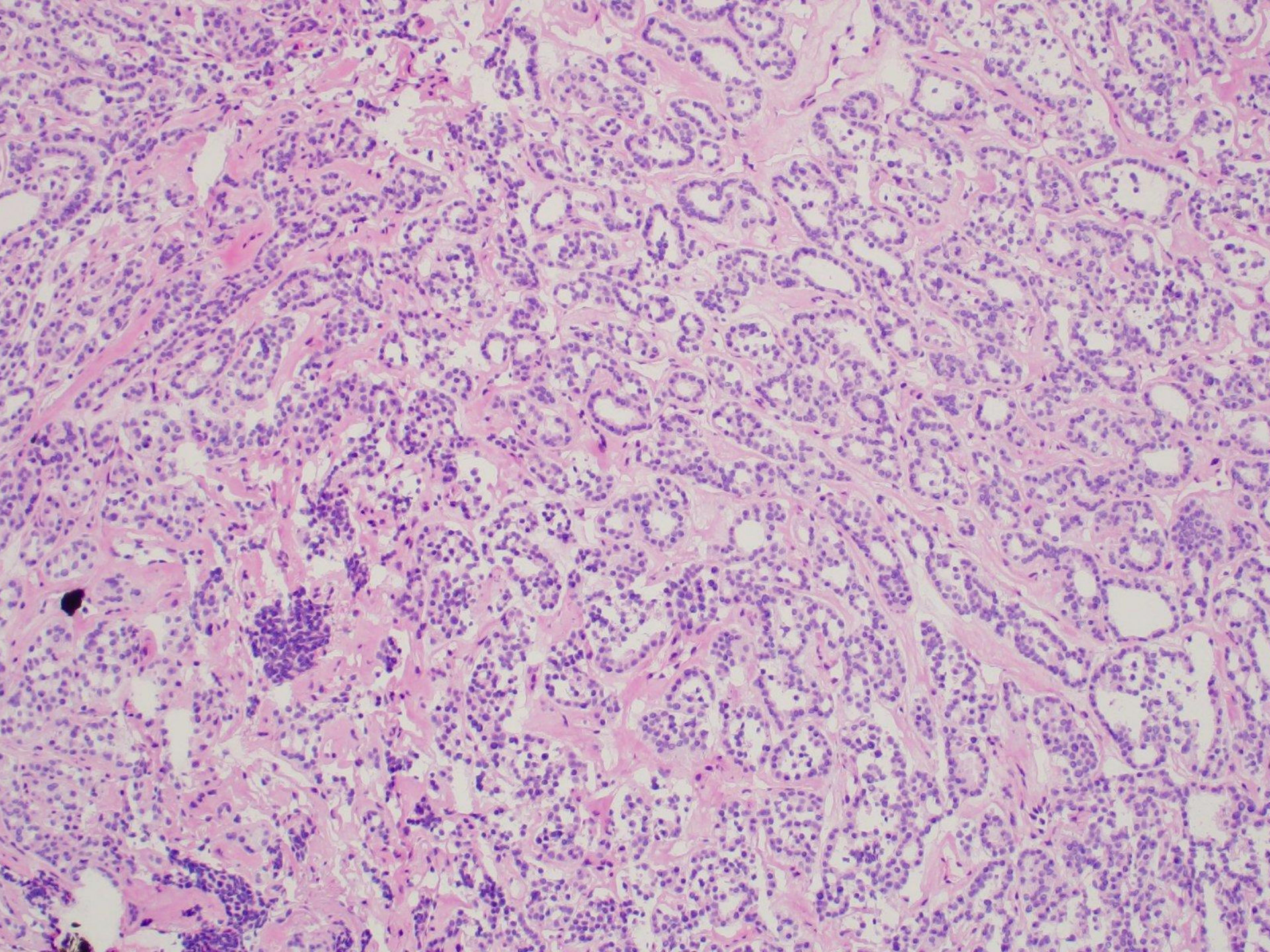




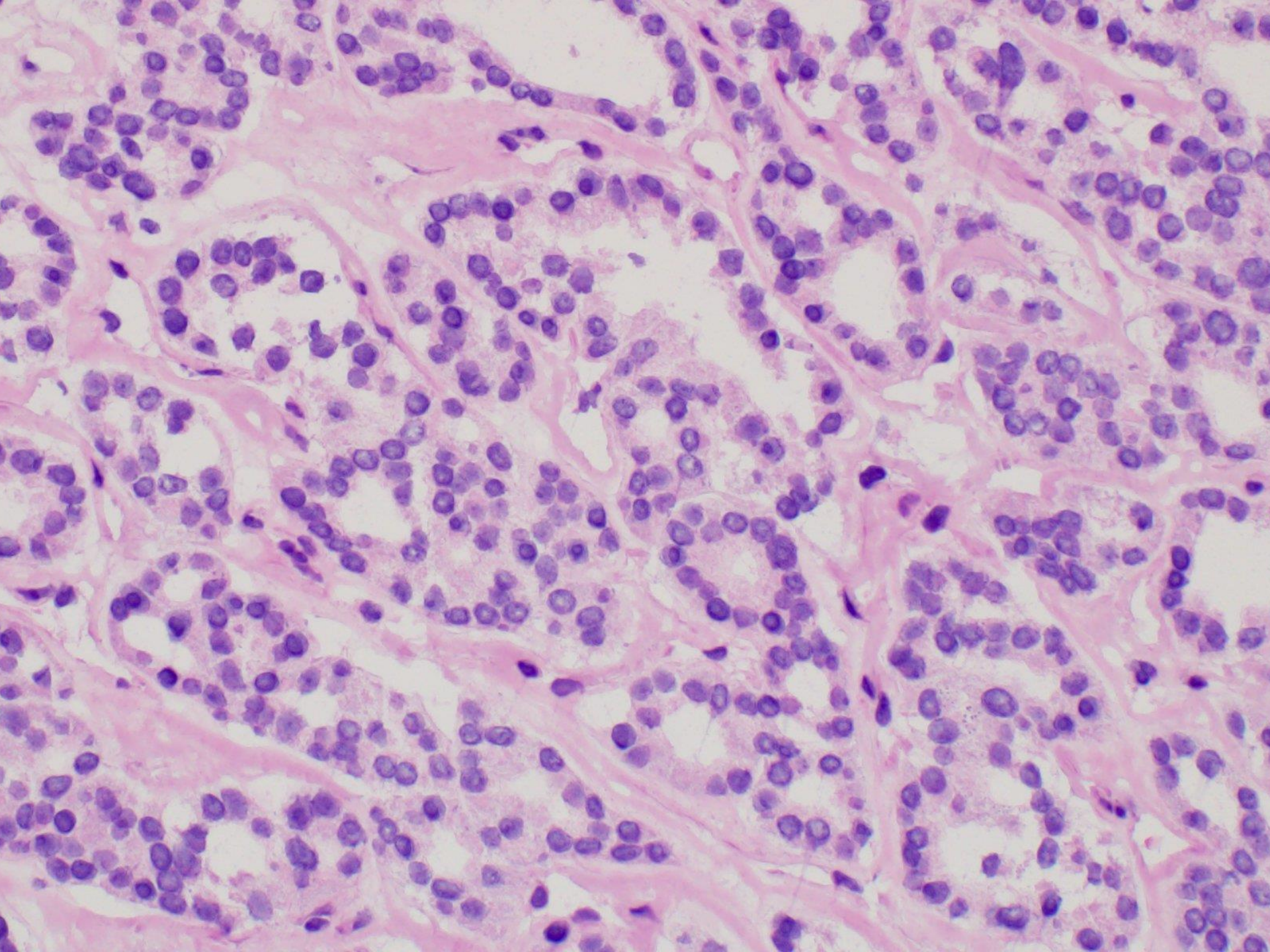
## Case 6

- 45 yo female with hyperparathyroidism
- Clinically suspicious for parathyroid adenoma









# FS Diagnosis:

*“Hypercellular parathyroid”,*  
however...

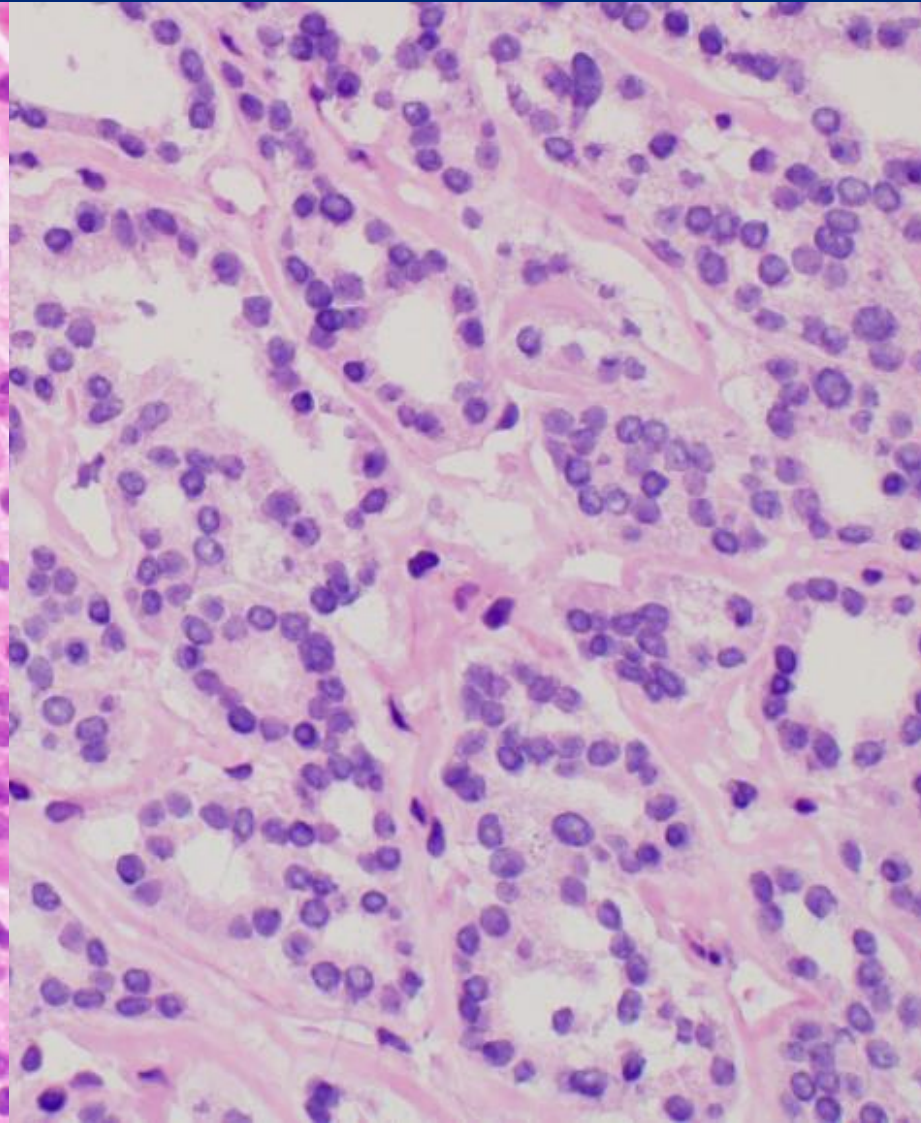
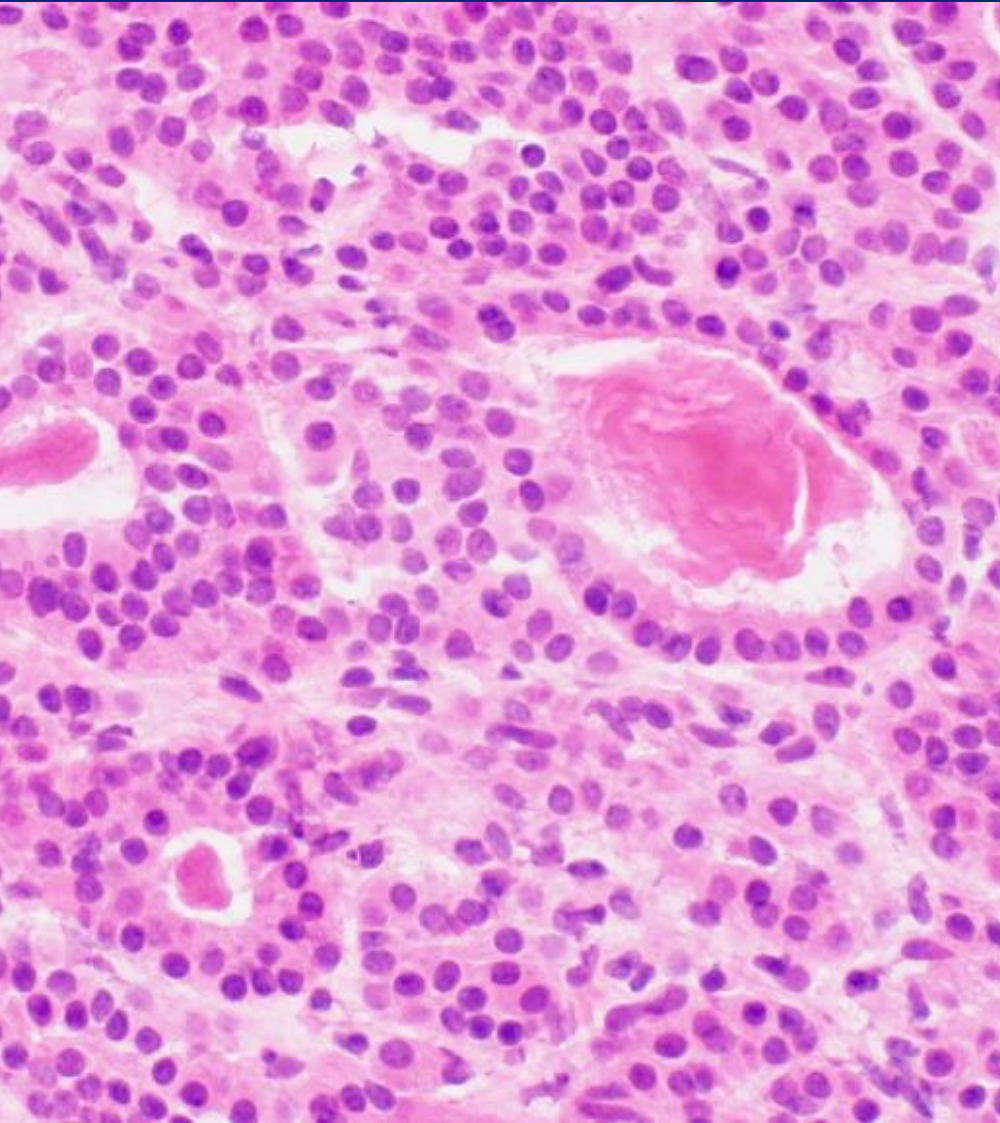


## FS Diagnosis:

*“Hypercellular parathyroid”,*

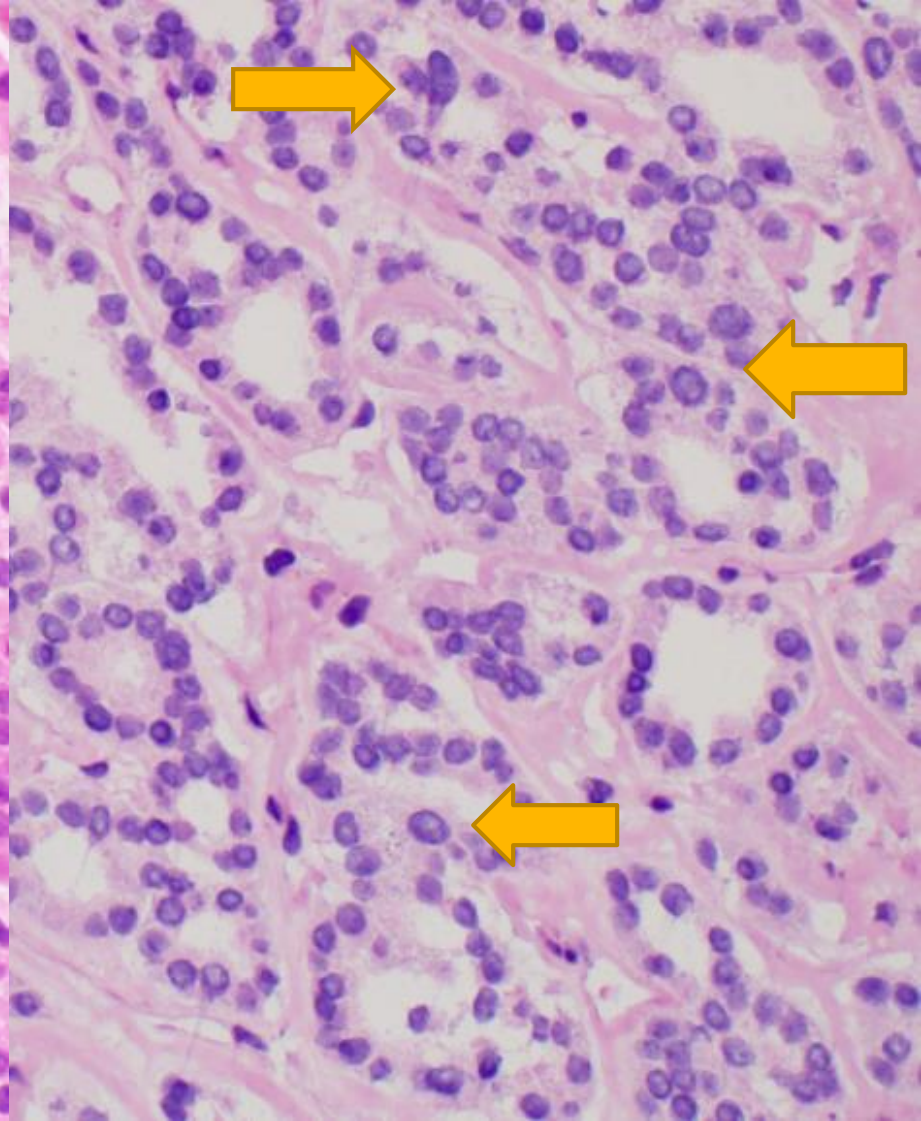
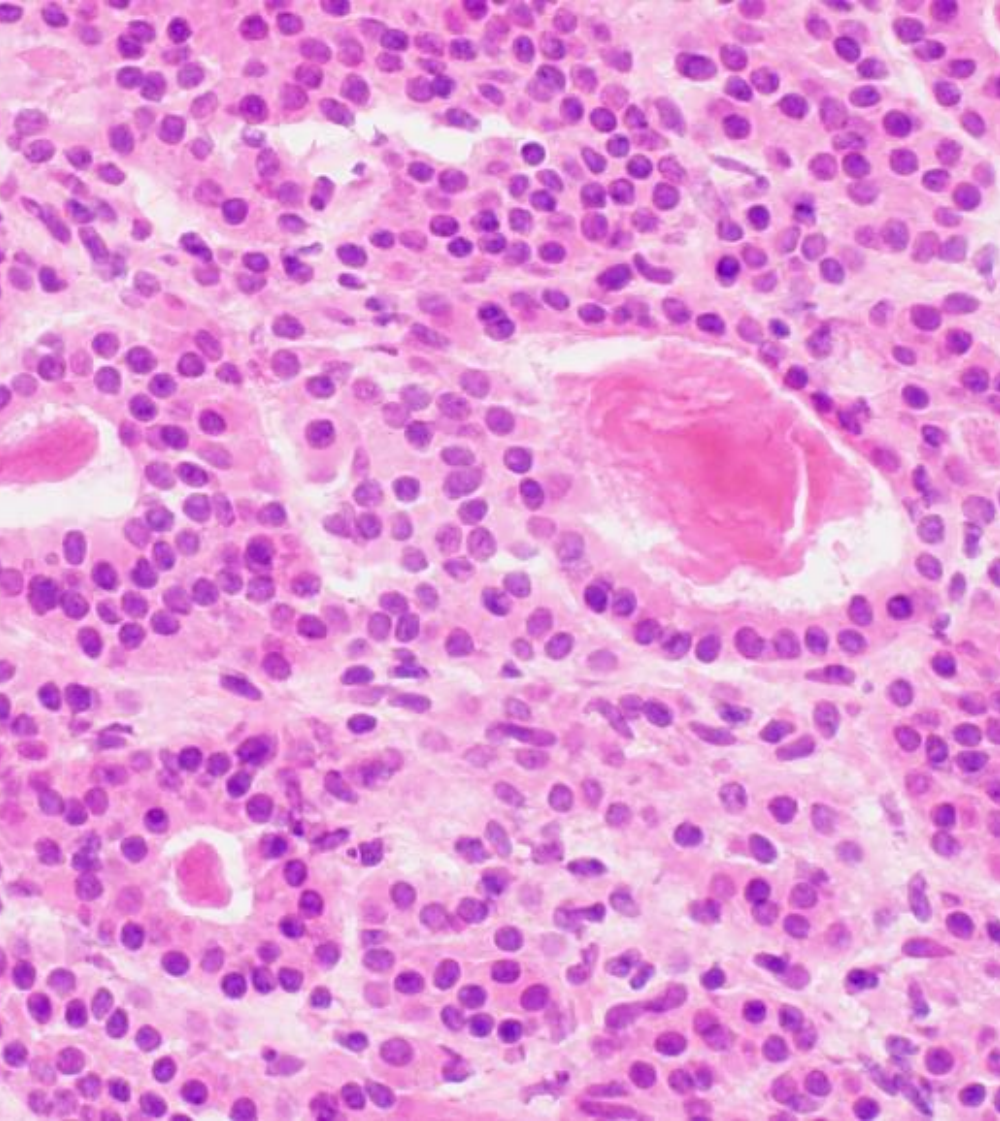
however...PTH levels did not drop 😞

# Parathyroid vs Thyroid on FS



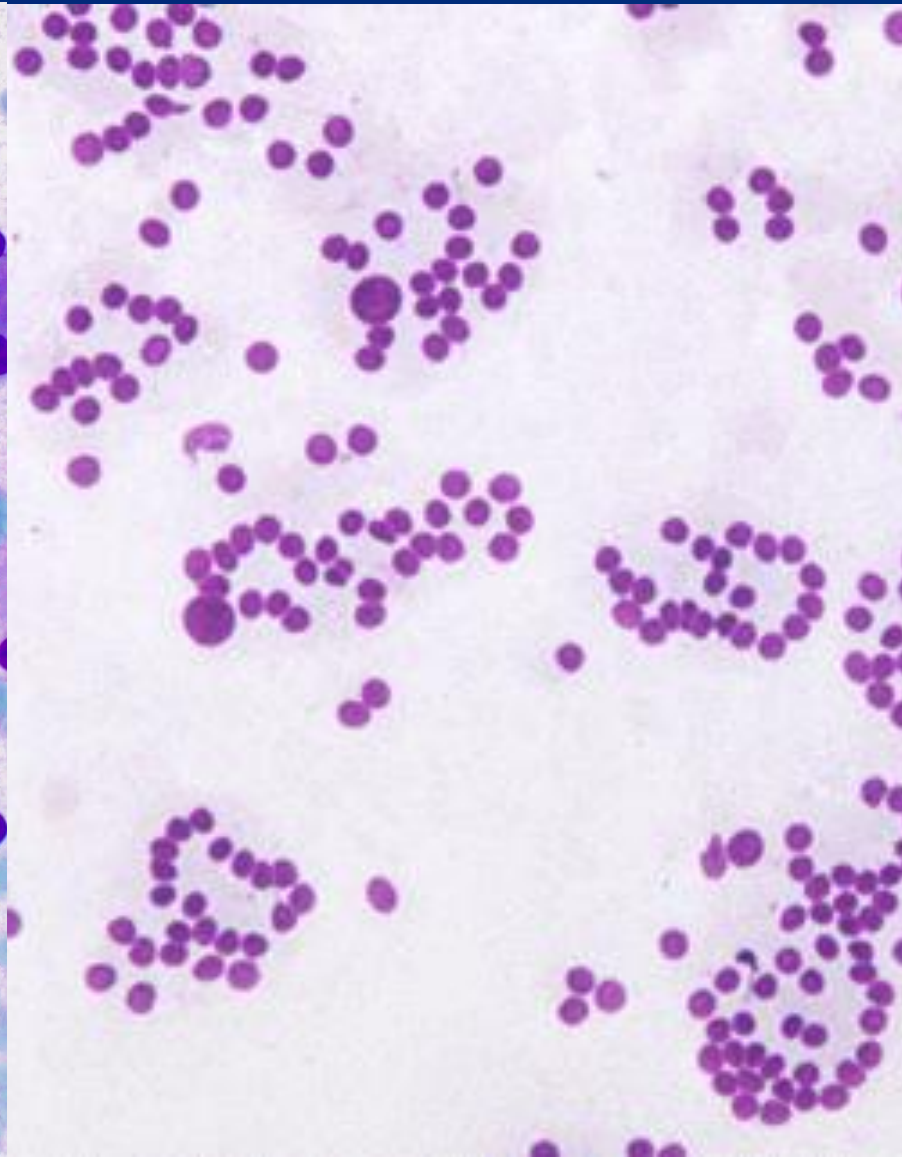
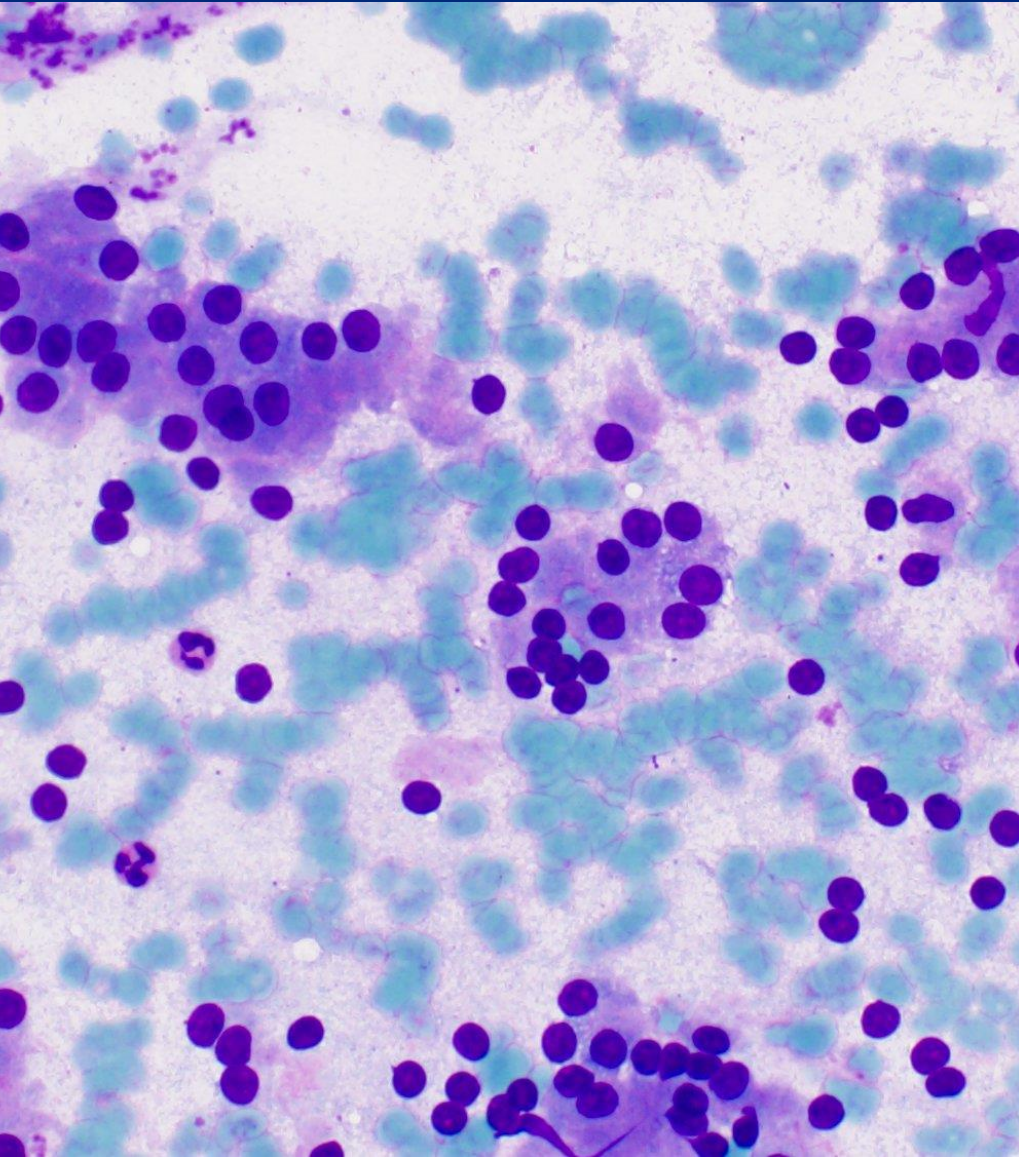


# Parathyroid vs Thyroid on FS





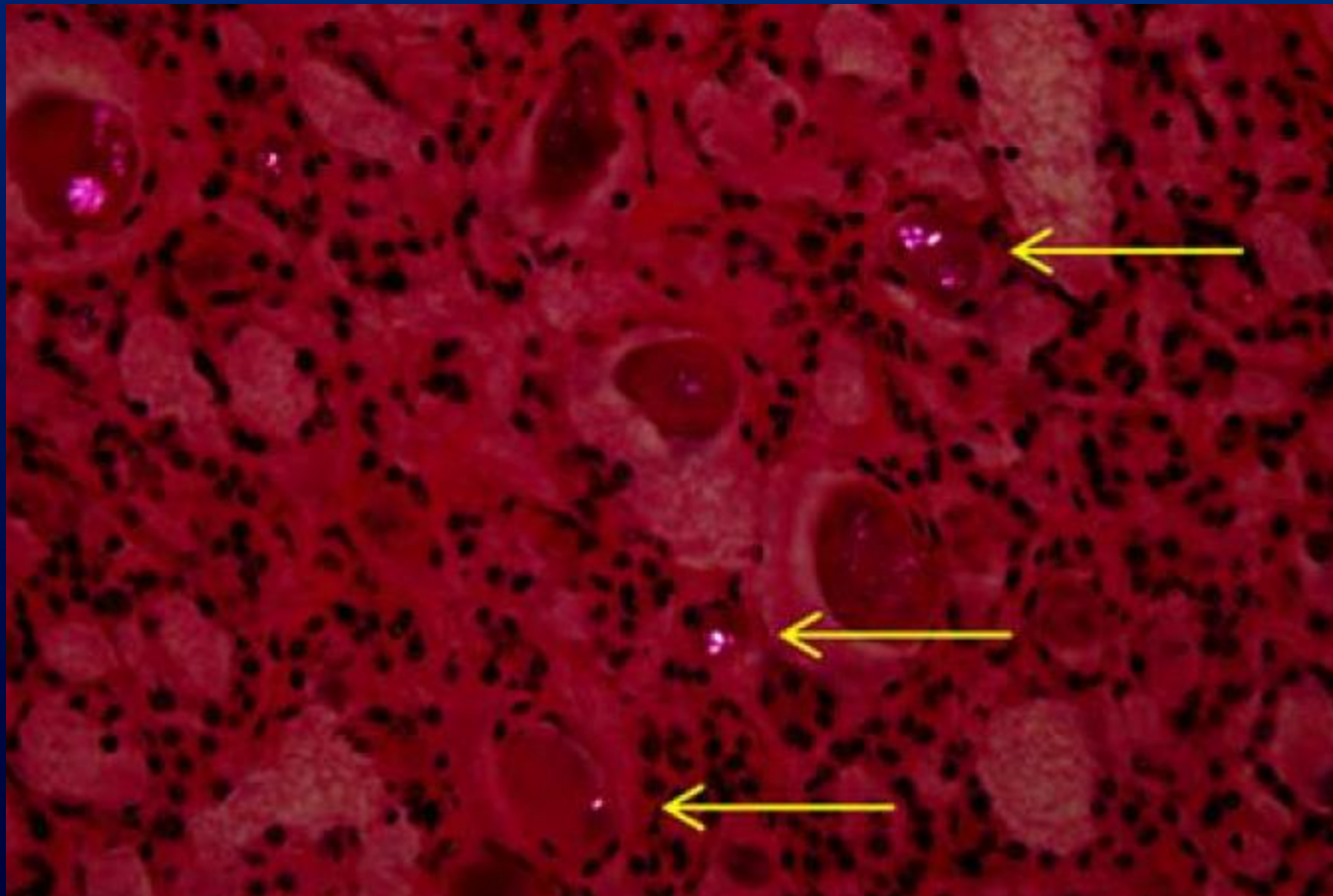
# Smear: Parathyroid vs Thyroid



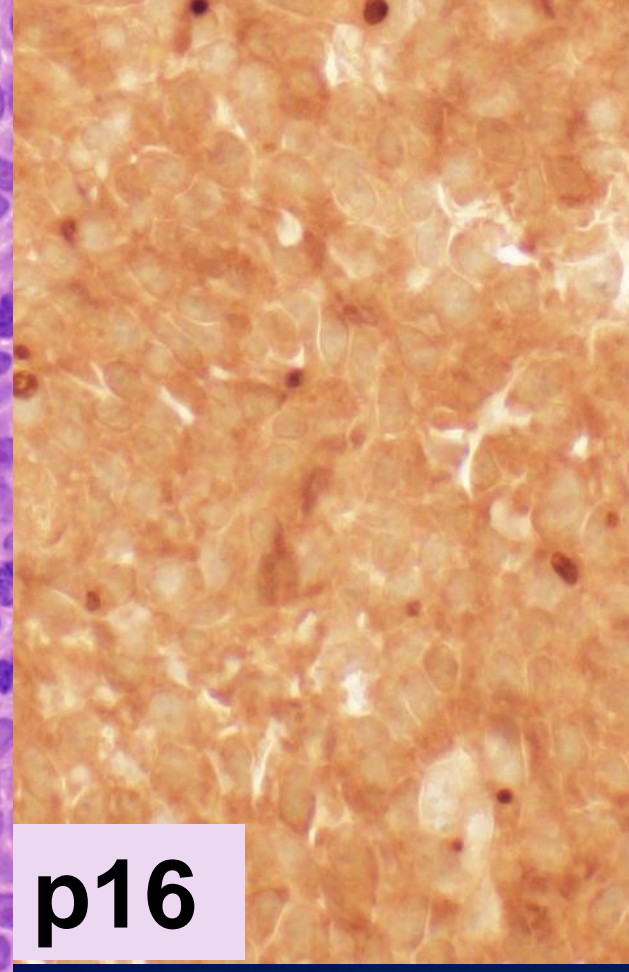
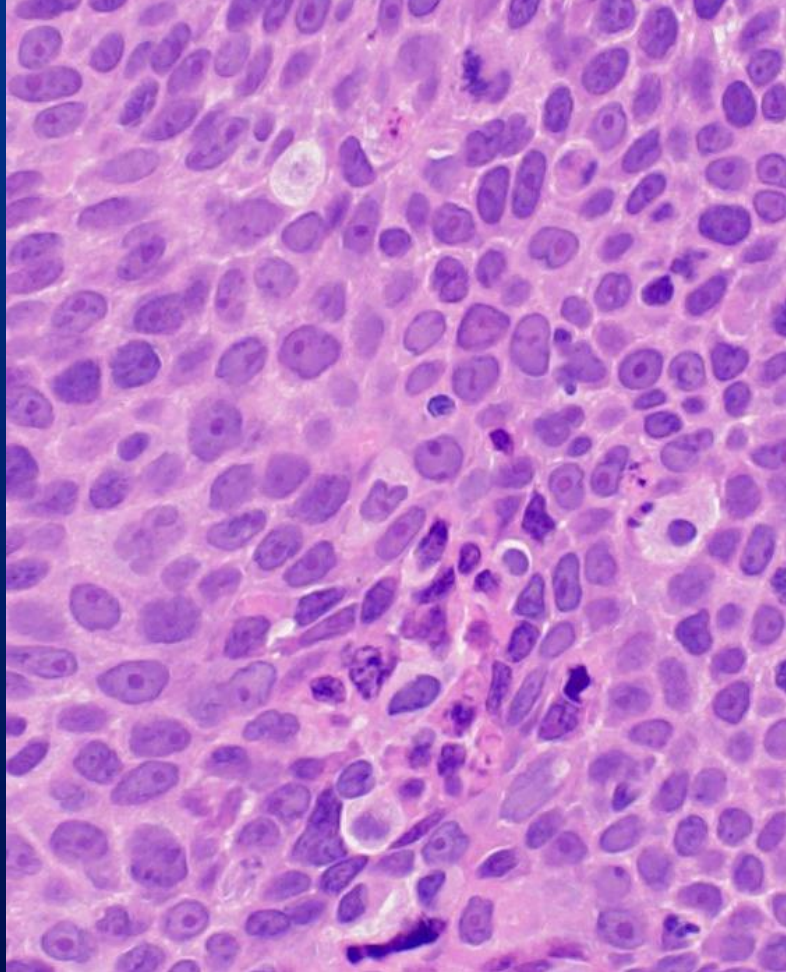


# Utility of Birefringent Crystal Identification by Polarized Light Microscopy in Distinguishing Thyroid From Parathyroid Tissue on Intraoperative Frozen Sections

*Kristine S. Wong, MS,\* James S. Lewis, Jr, MD,†‡ Srinivas Gottipati, MD,§  
and Rebecca D. Chernock, MD†‡*



## Case 7

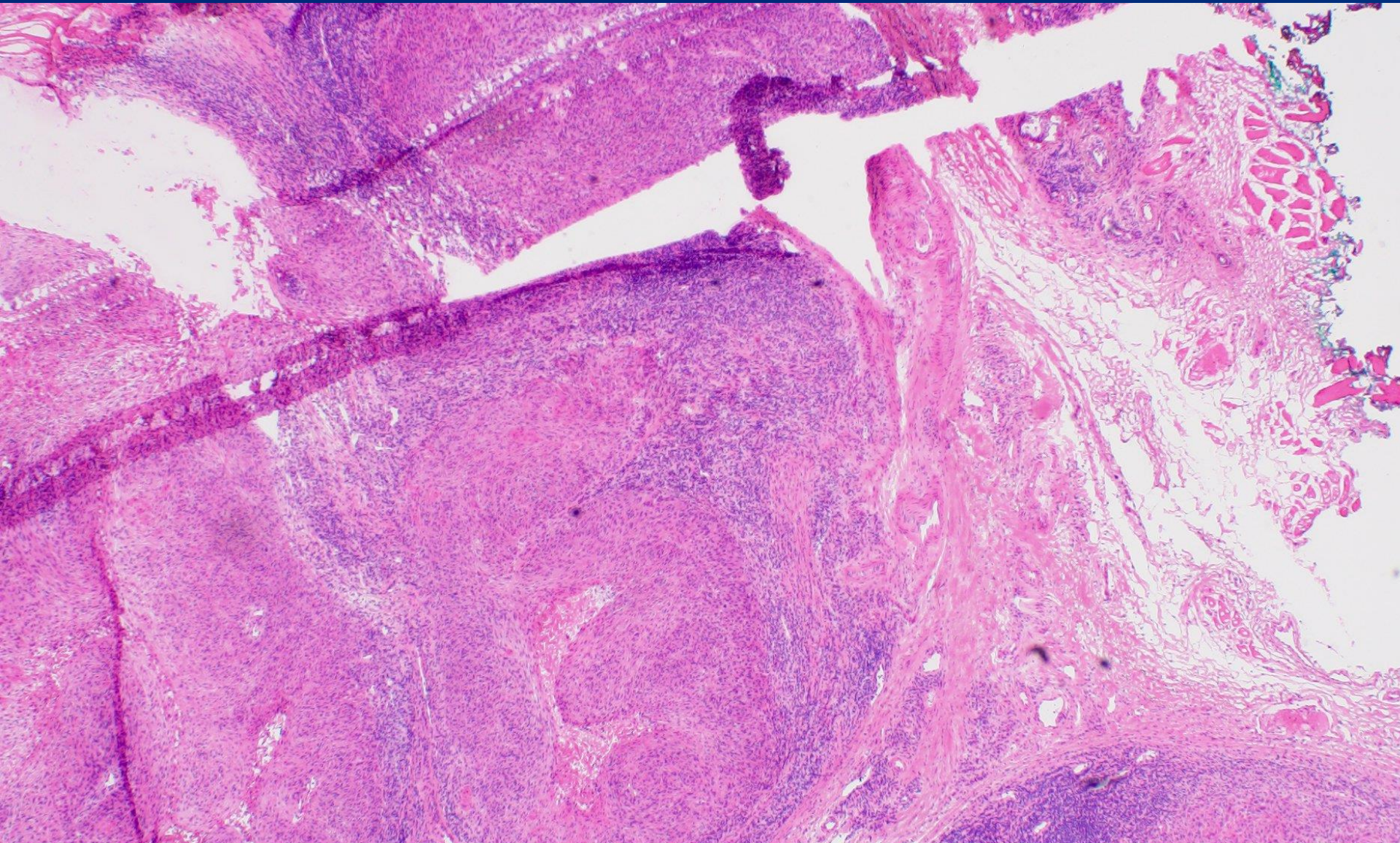


p16

- 50 yo male with
- MT p16 + SCC to neck (level 2 LN)
- Occult primary site

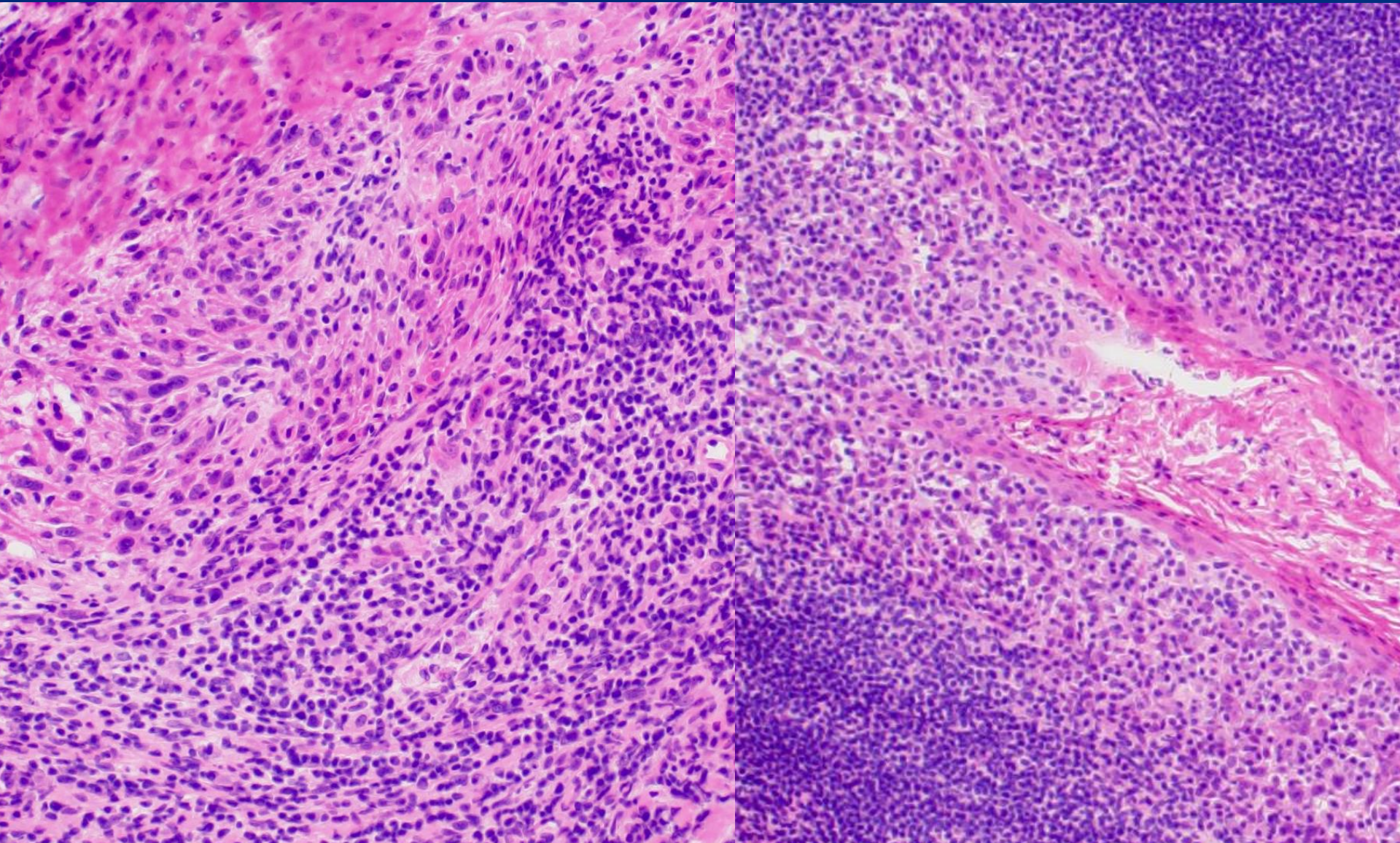


# Tonsillectomy FS



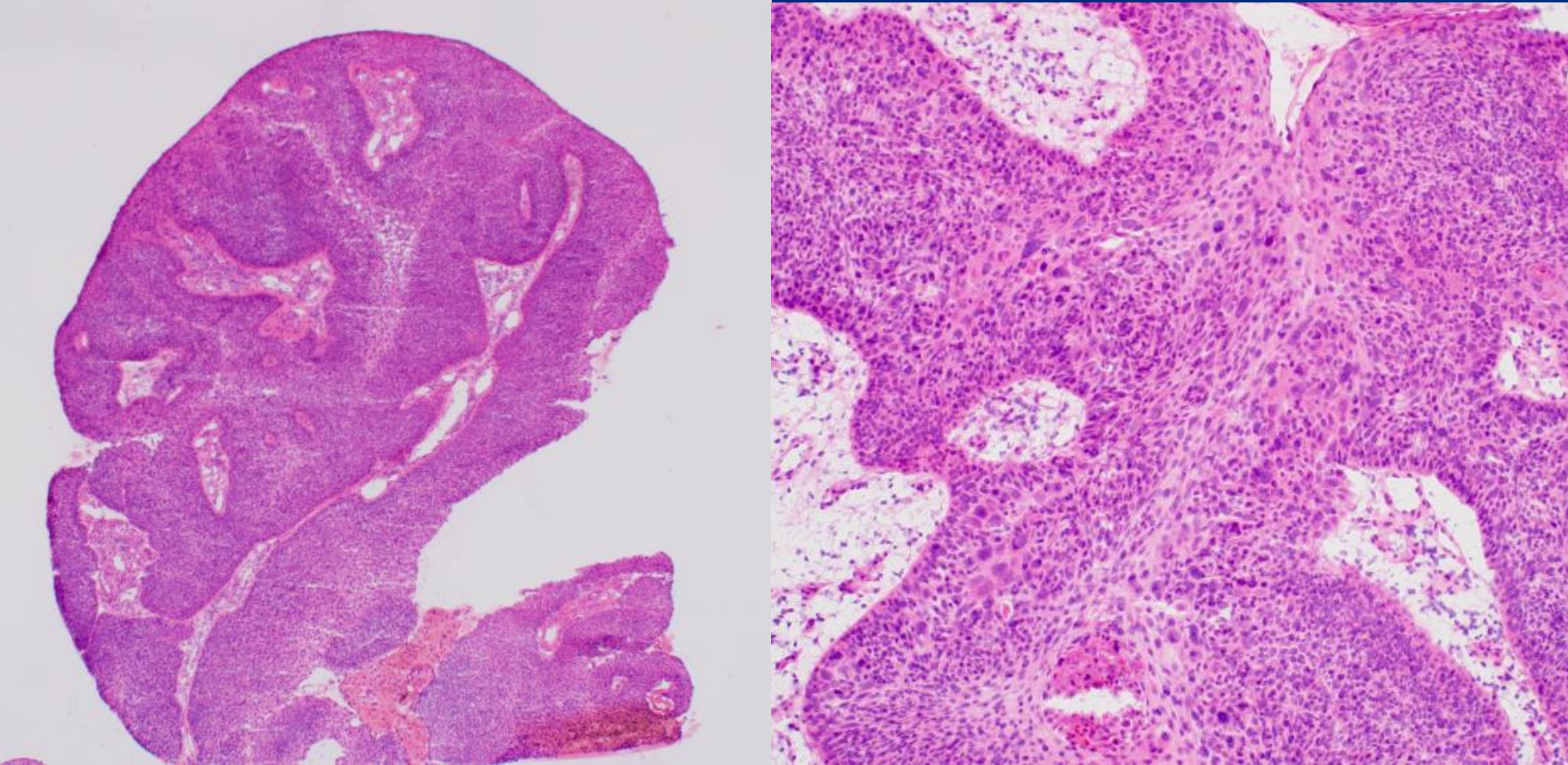


# Our case: p16+ SCC vs Normal Tonsil





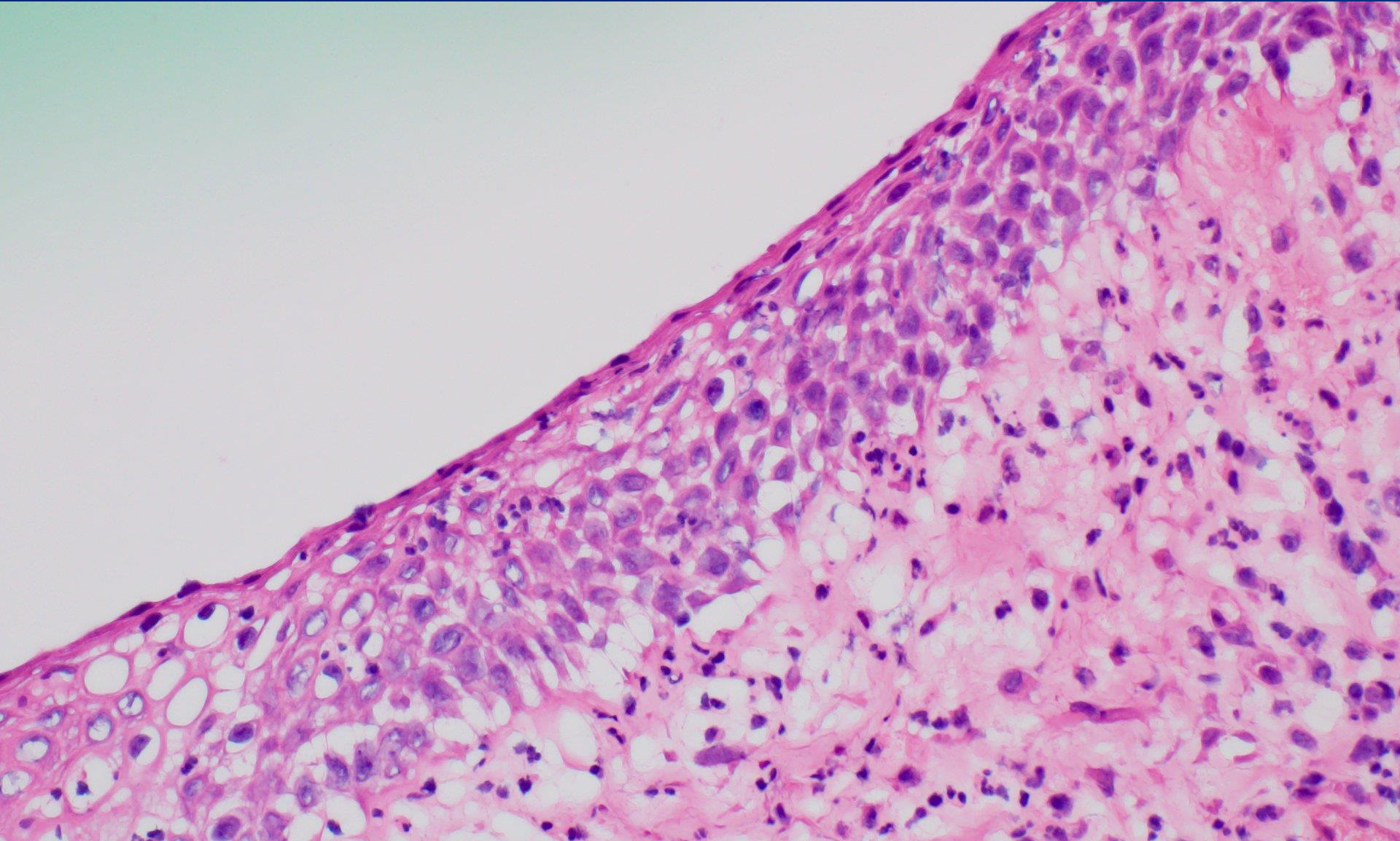
# Different case, tonsil Bx



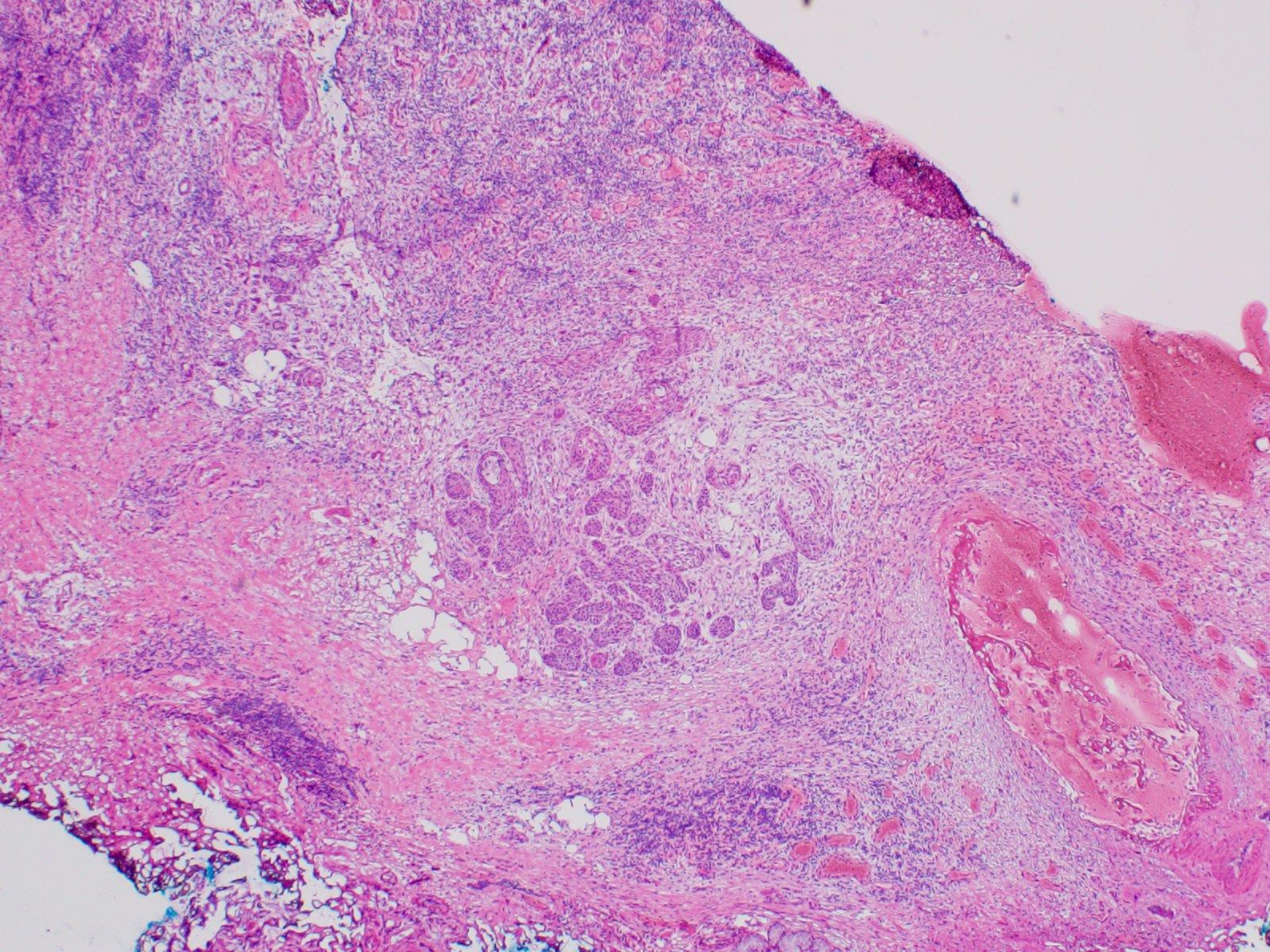
**In the oropharynx: do not diagnose p16+ SCC as “in situ”**



# Re-excision for p16+ SCC, previously incompletely excised

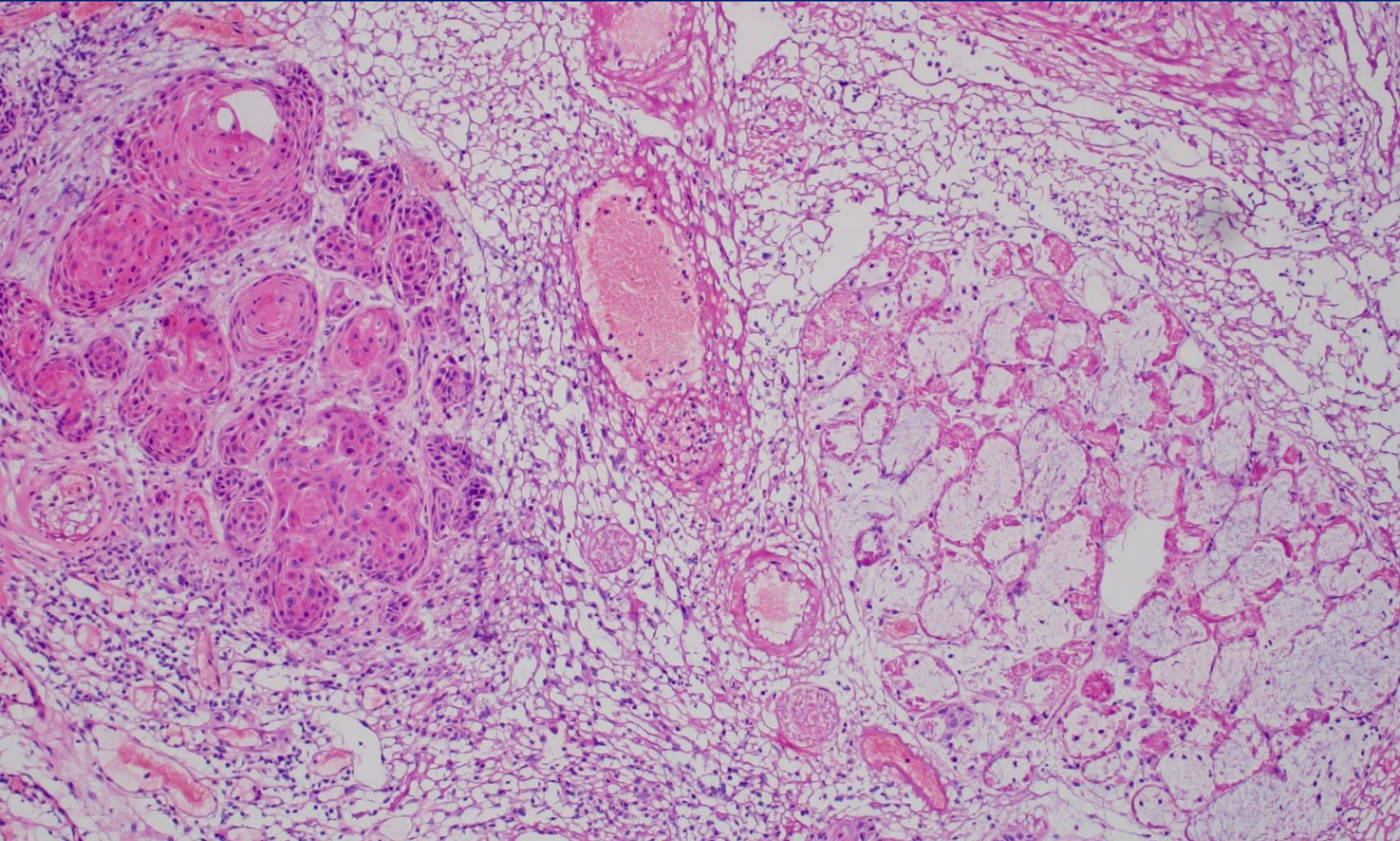




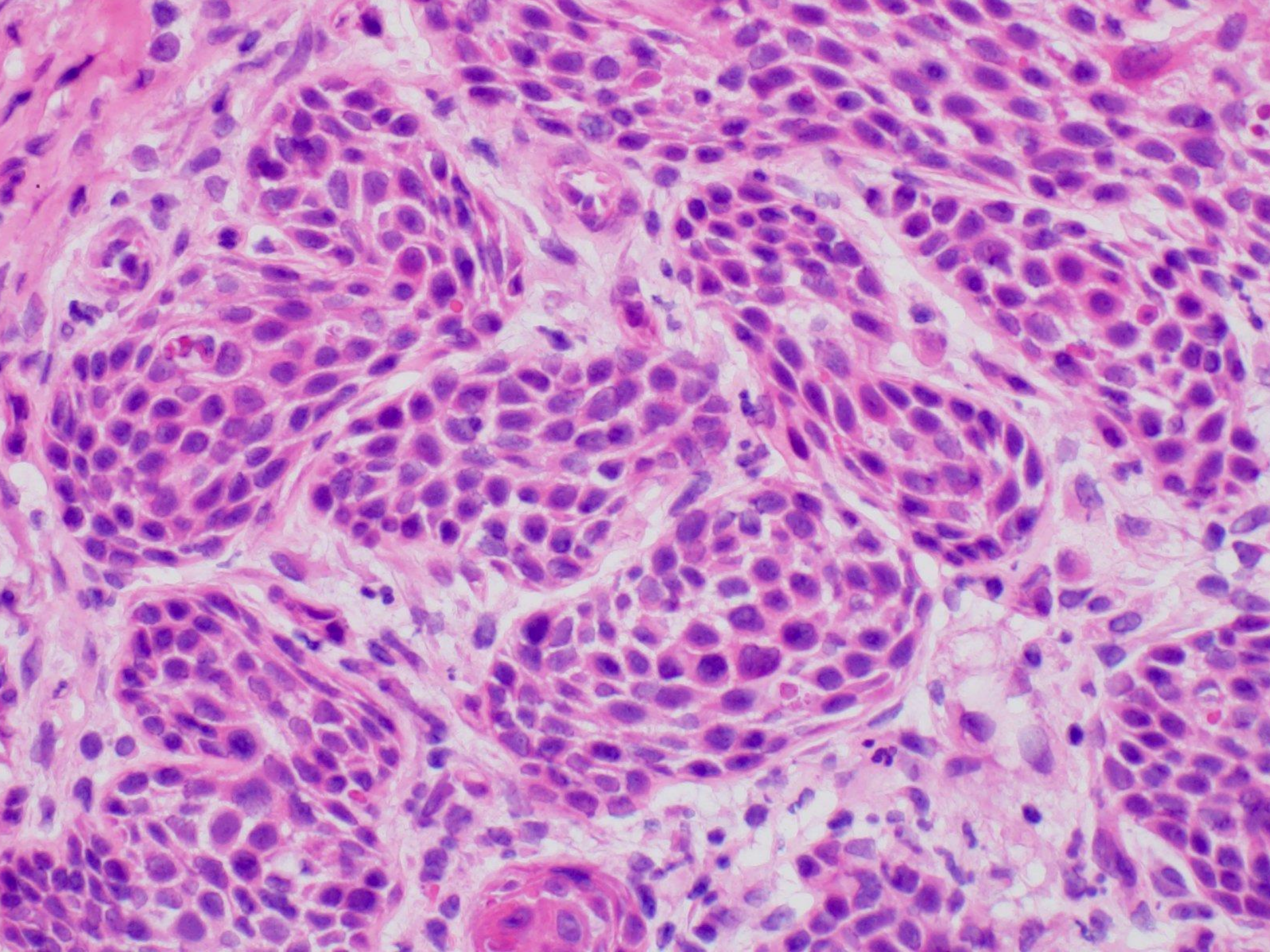




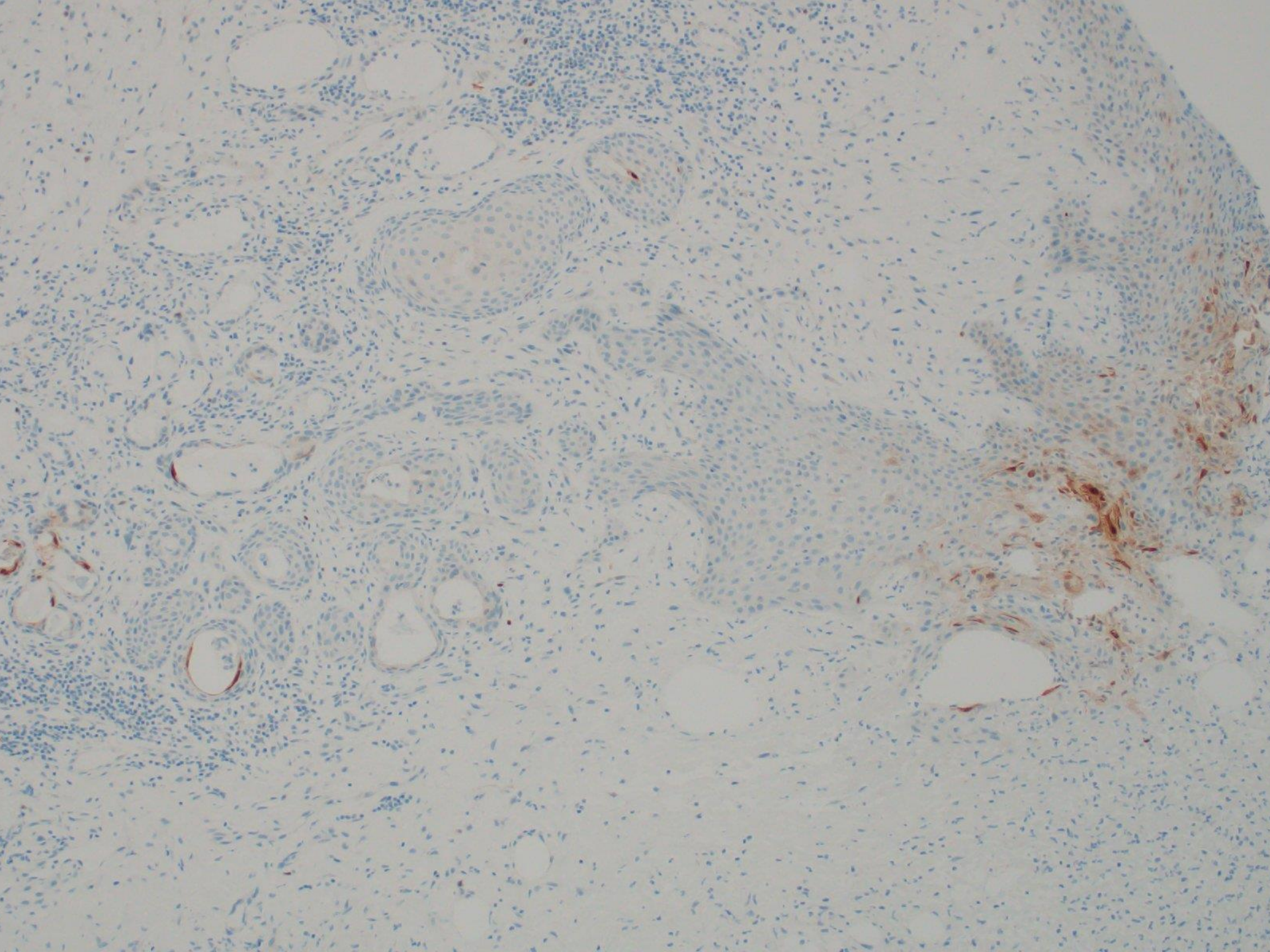
**Comparison with adjacent tissue:  
Retained architecture, well circumscribed**





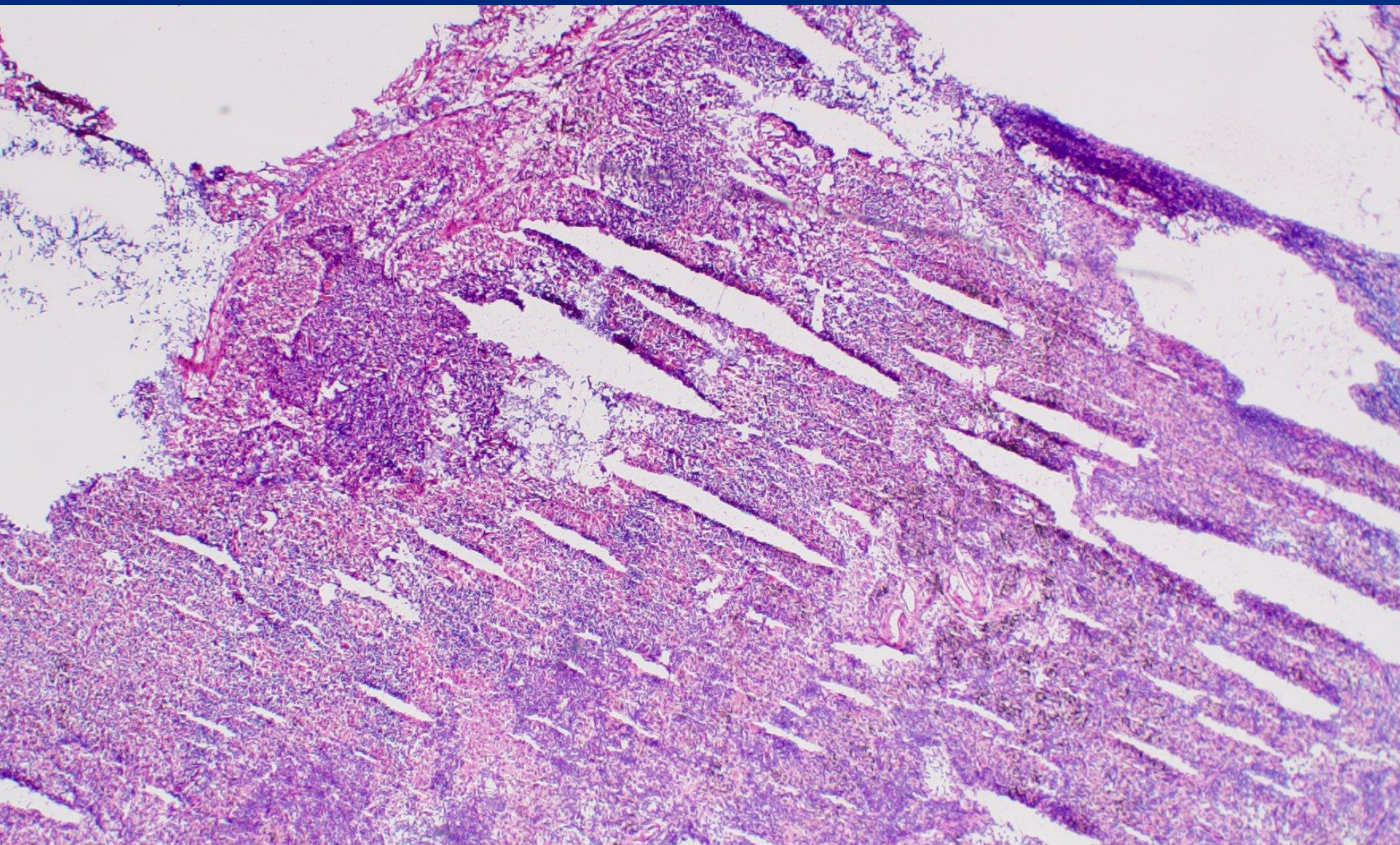






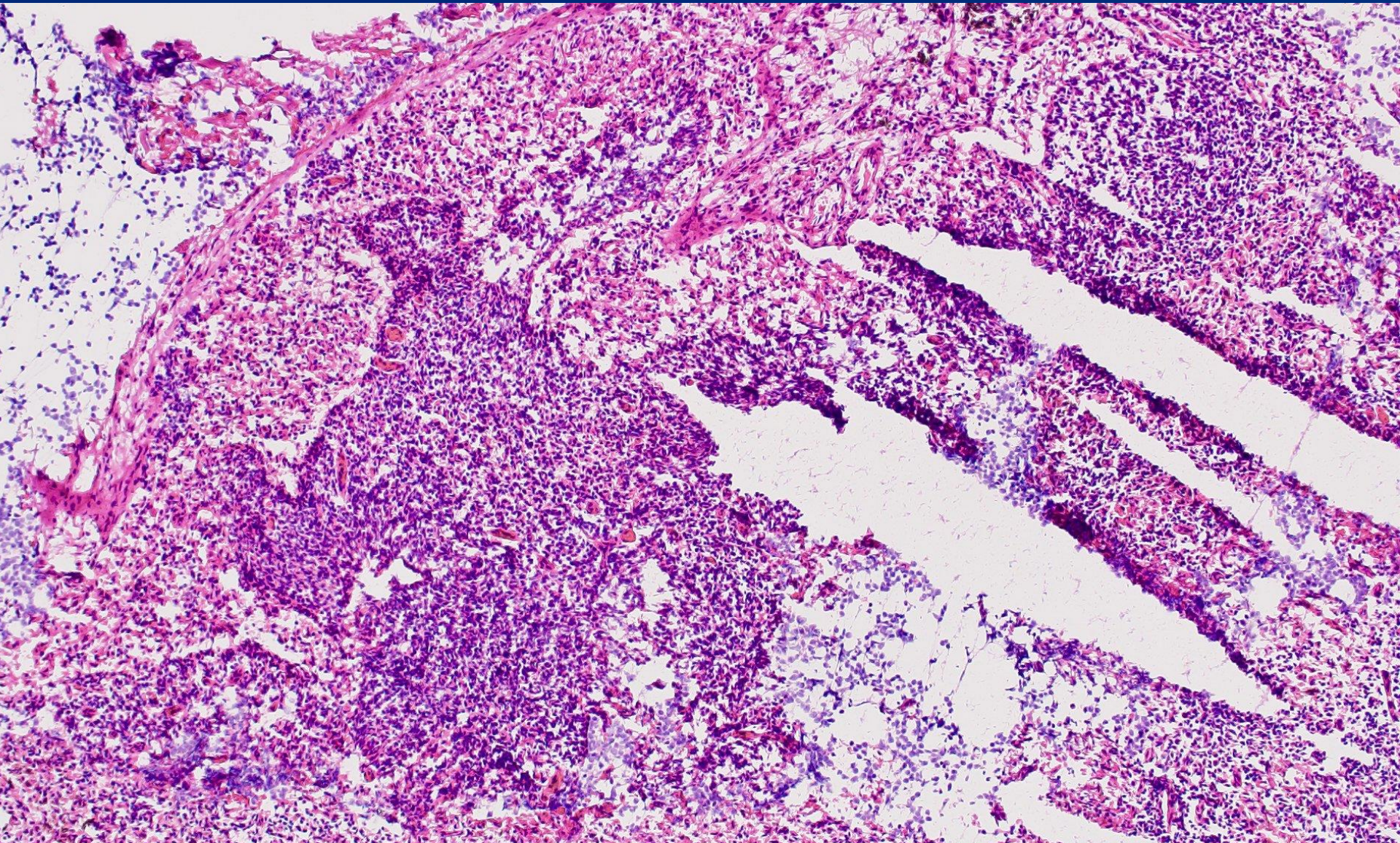


# FS NECK LN



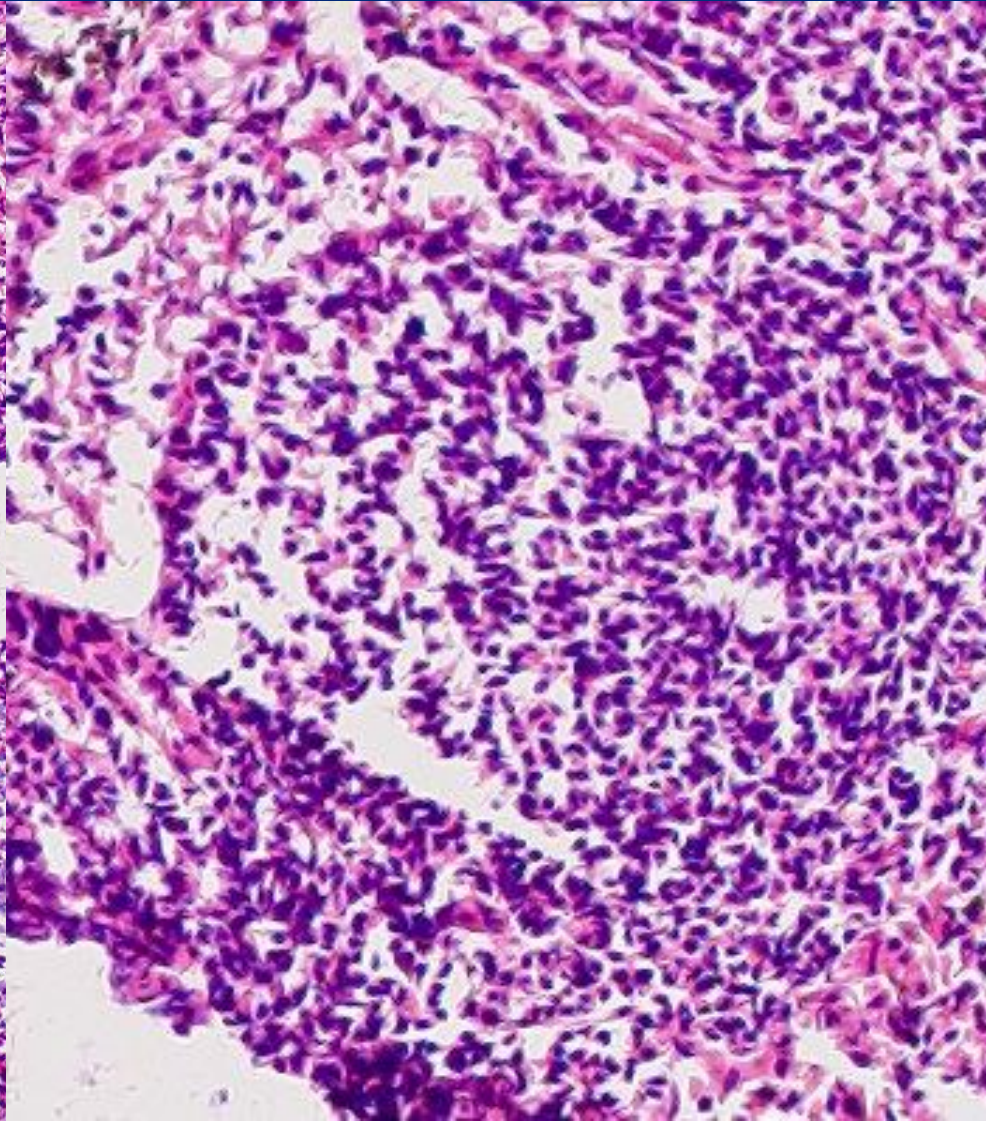
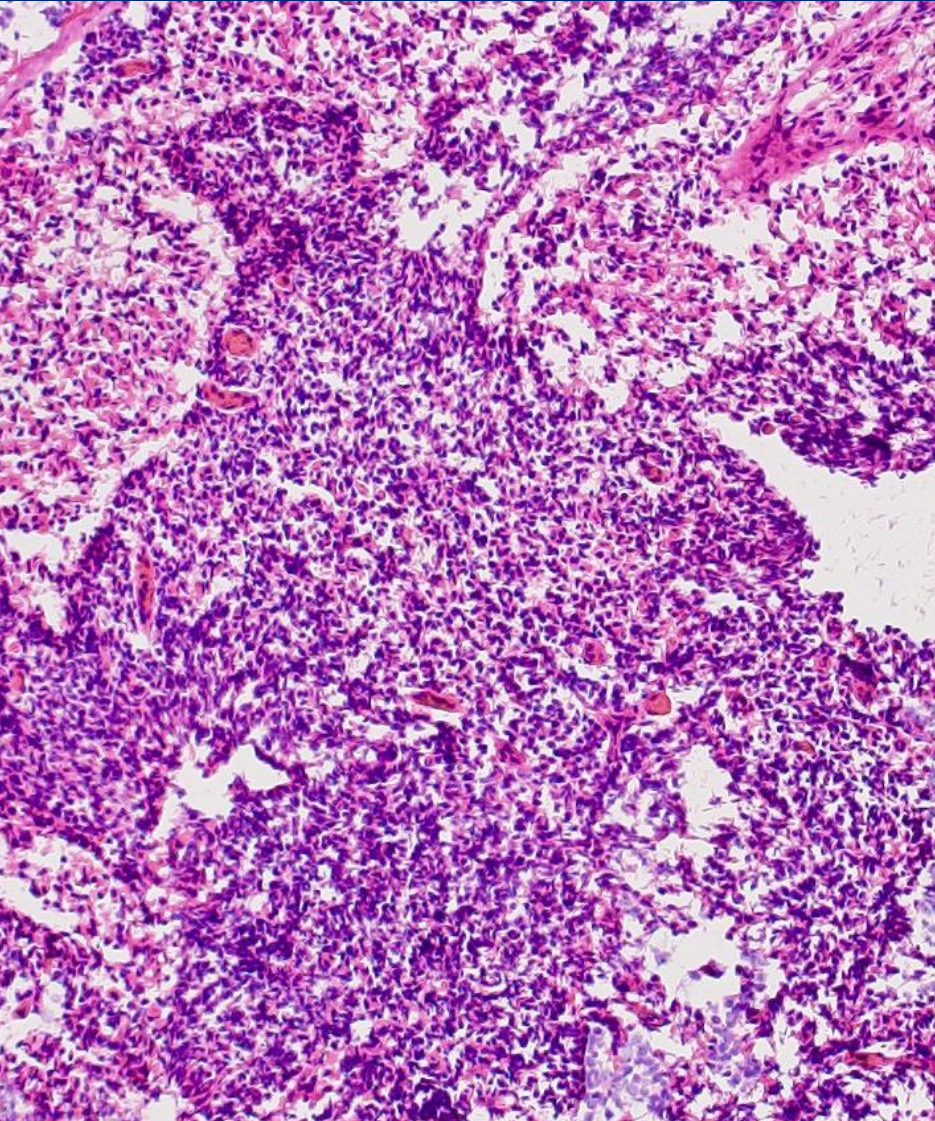


# Positive vs Reactive LN???



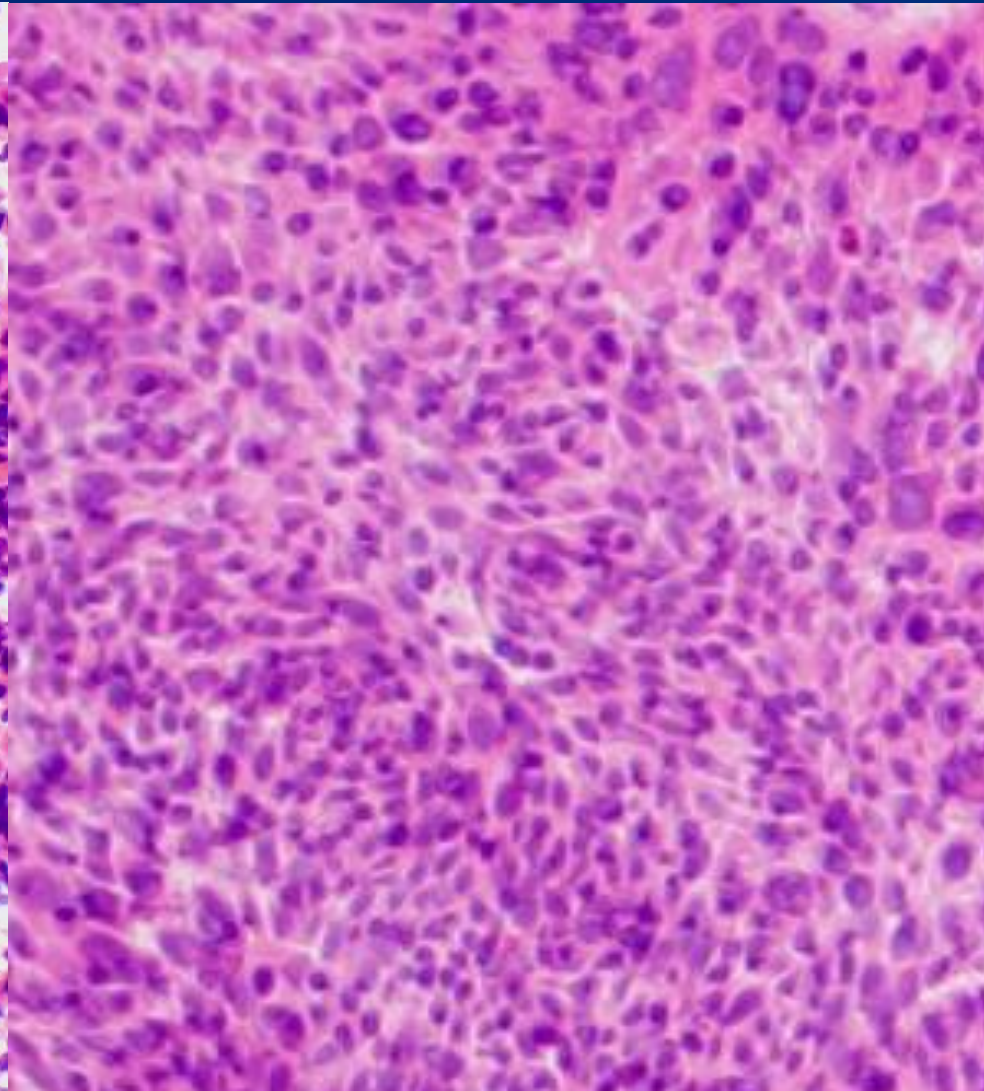
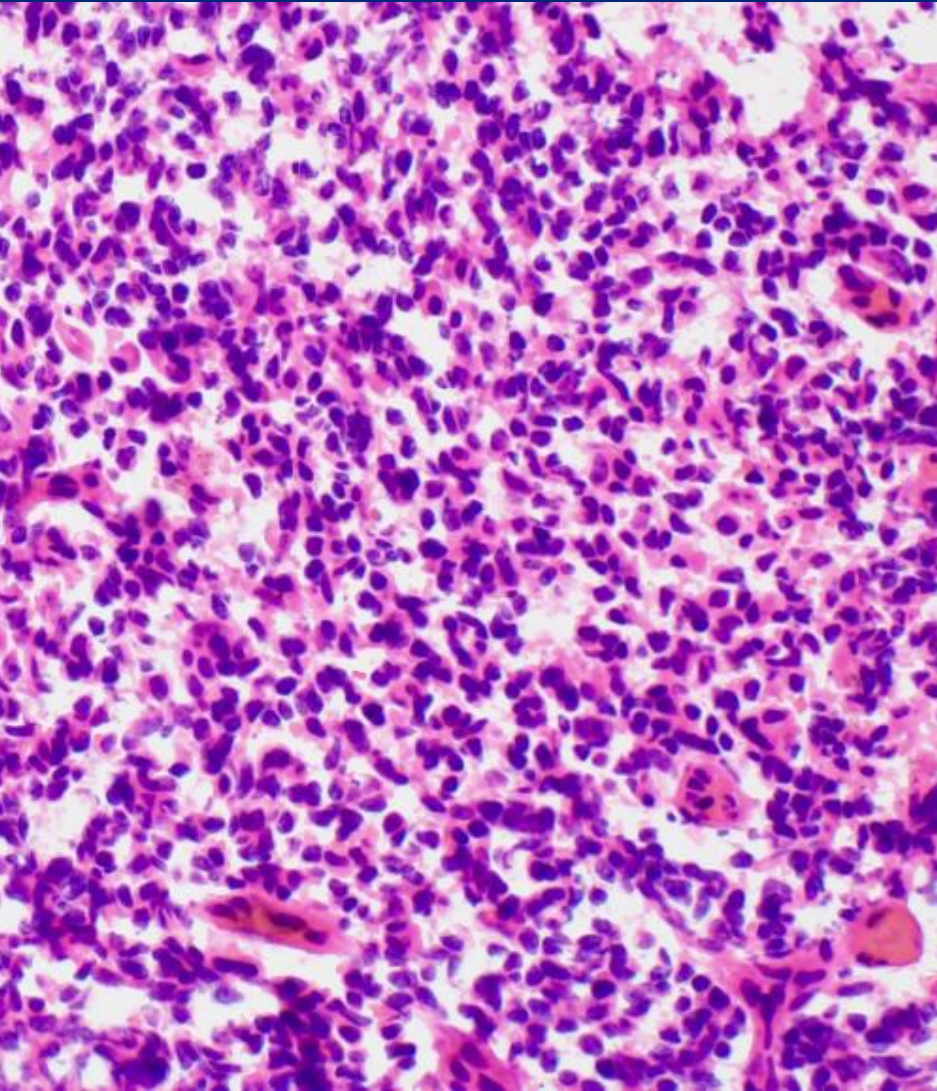


# Compare suspicious area with clear cut germinal centers





# RCC LN vs MT p16+ SCC (FS)



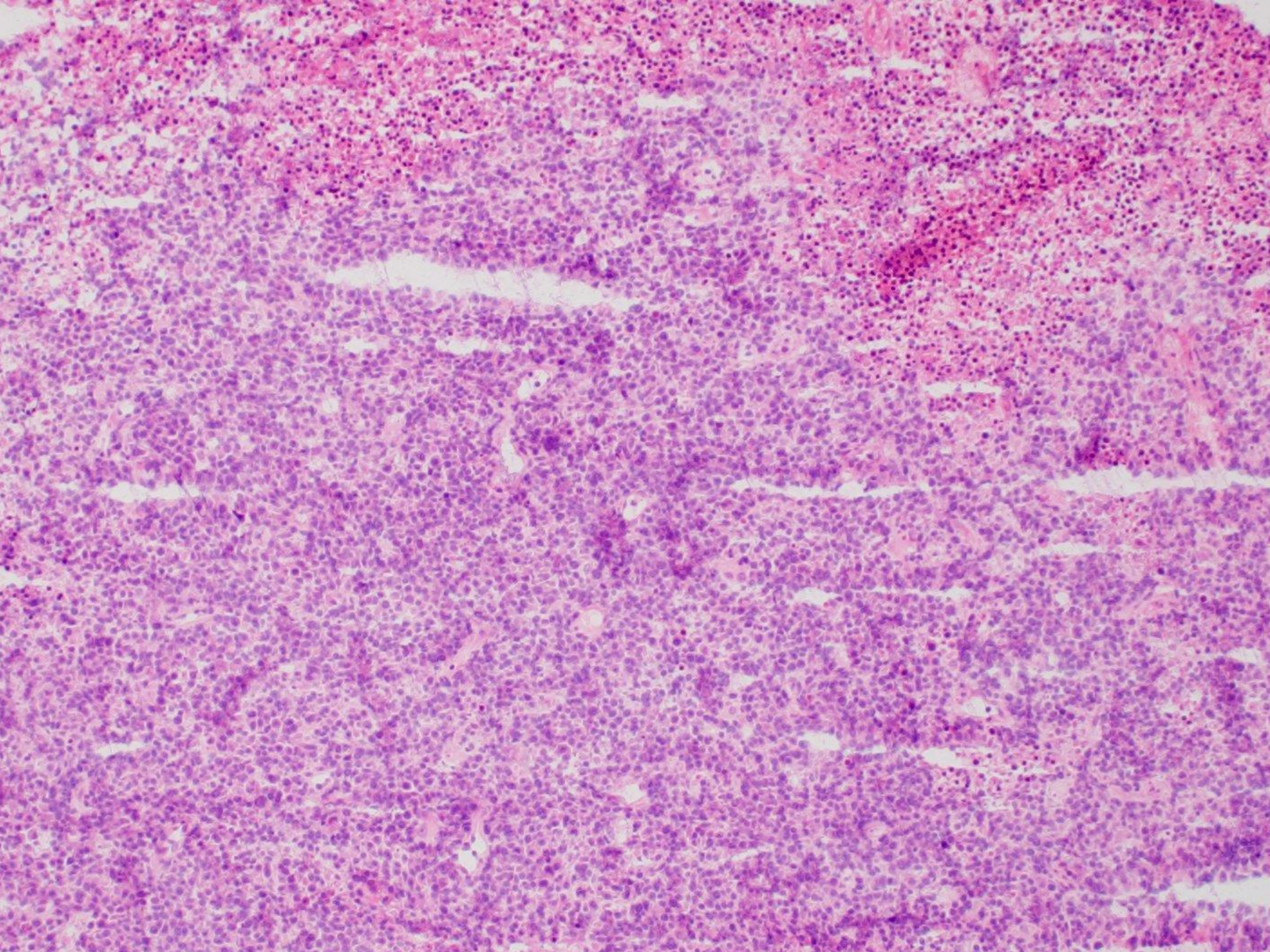




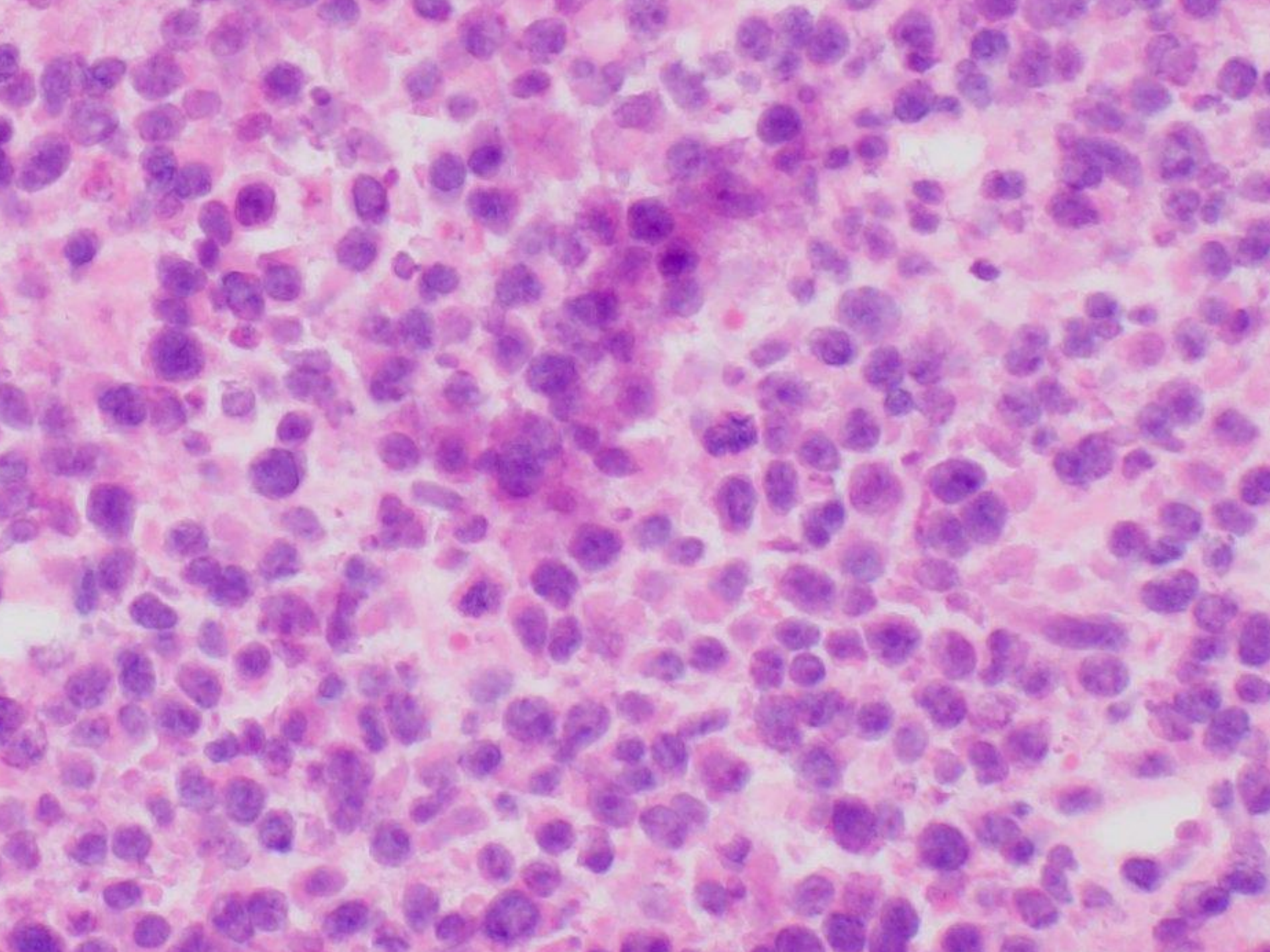
## Case 8

- 61 yo male with bilateral nasal obstruction for 12 weeks
- CT: L. maxillary sinus mass,
- Suspicious for primary malignancy













## ???

# Frozen section diagnosis

Surgeon would like to proceed with an extensive resection and clear the margins



## ???

# Frozen section diagnosis

Surgeon would like to proceed with an extensive resection and clear the margins if possible





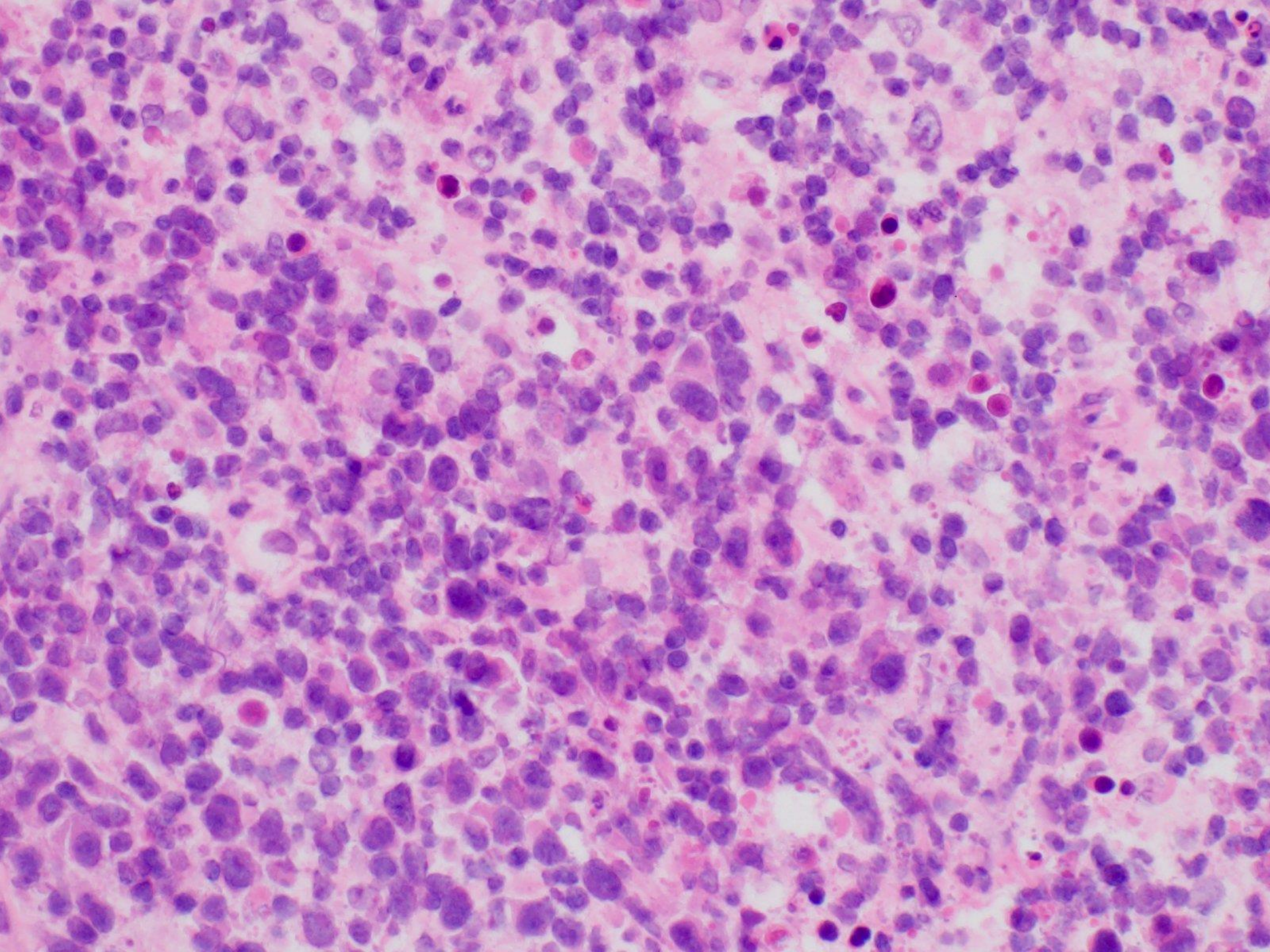
# Diagnostic Considerations

- Non-keratinizing SCC
- INI-1 deficient carcinoma
- NUT carcinoma
- Small cell carcinoma
- Melanoma
- Olfactory Neuroblastoma
- Rhabdomyosarcoma
- Ewing Sarcoma
- Mesenchymal chondrosarcoma
- Lymphoma

# Diagnostic Considerations

- Non-keratinizing SCC
- INI-1 deficient carcinoma
- NUT carcinoma
- Small cell carcinoma
- Melanoma
- Olfactory Neuroblastoma
- Rhabdomyosarcoma
- Ewing Sarcoma
- Mesenchymal chondrosarcoma
- **Lymphoma**





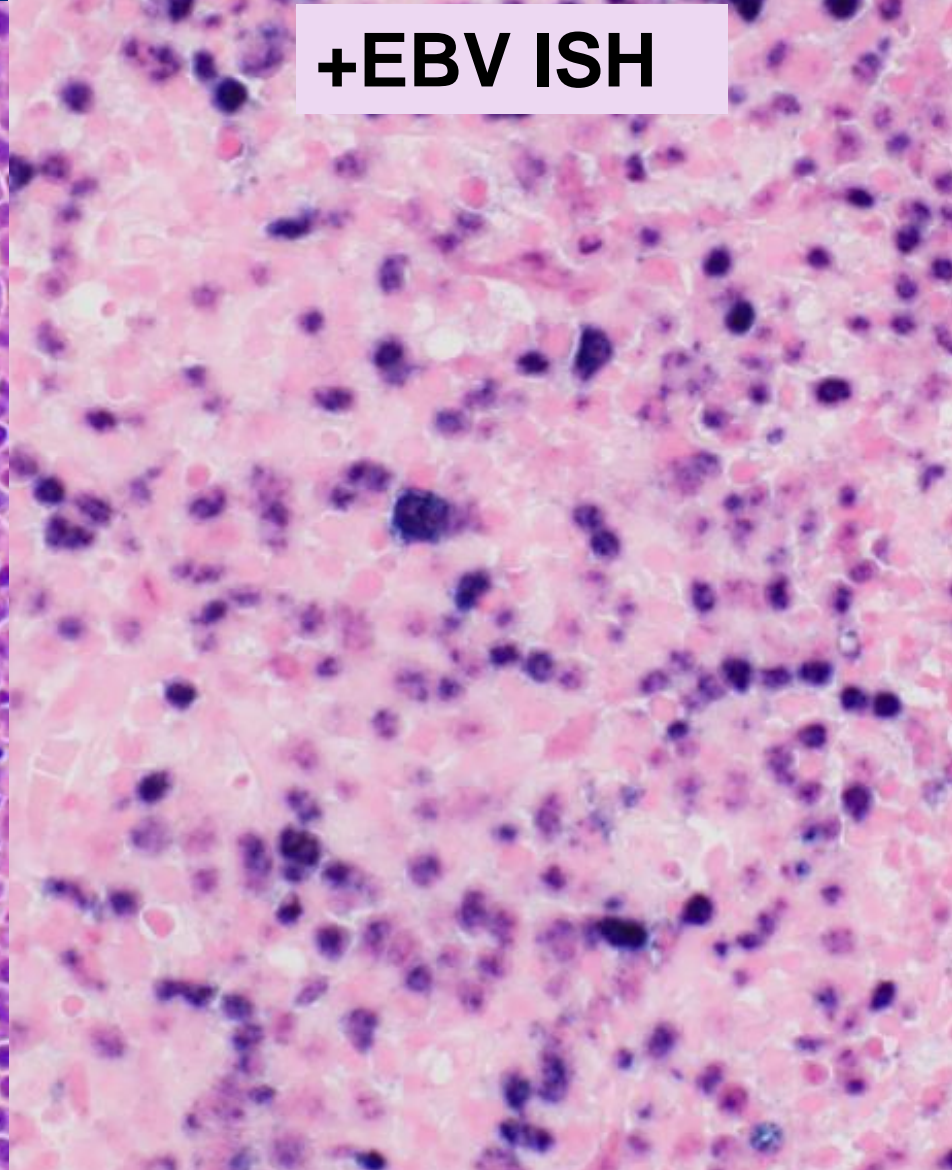
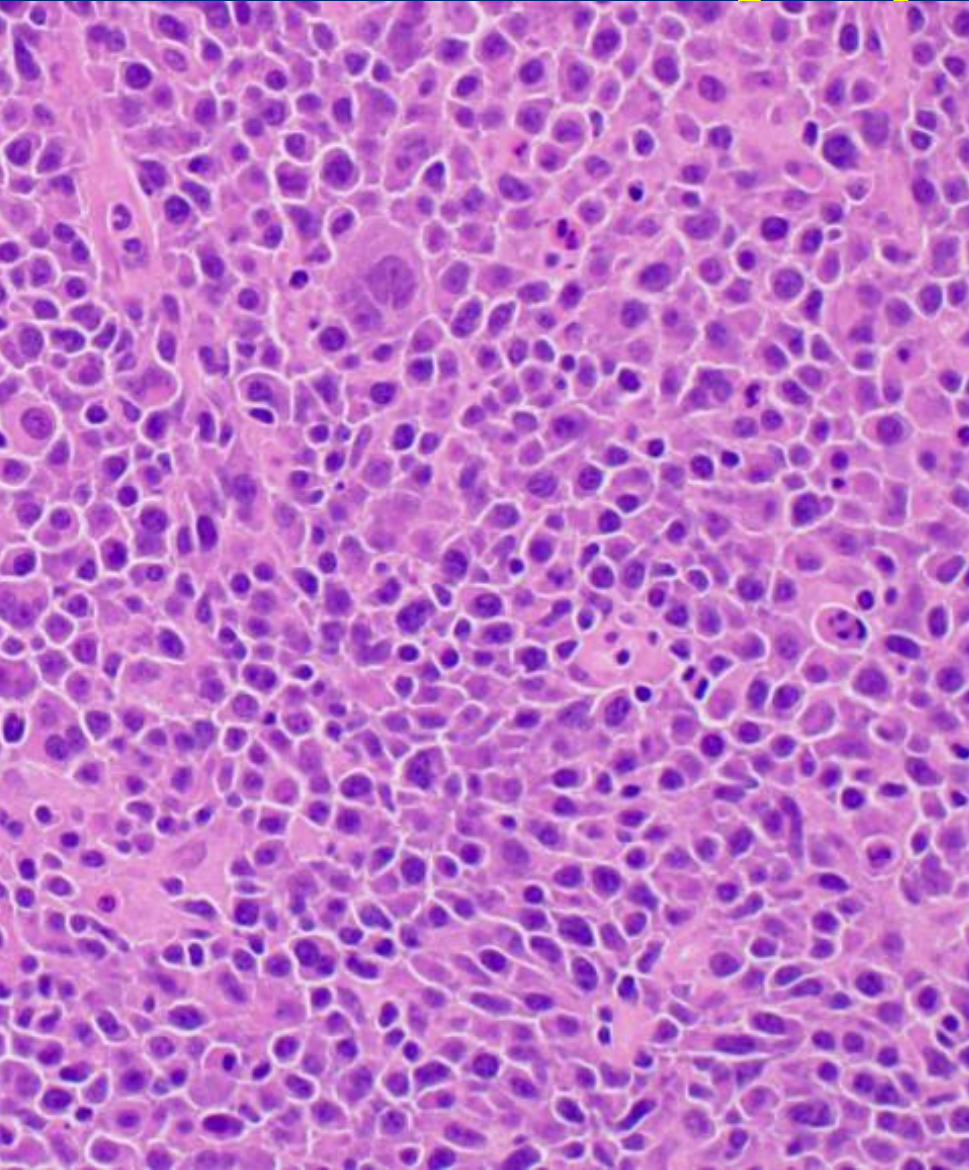
# Frozen Section Diagnosis:

*Poorly differentiated neoplasm, possible lymphoma, defer for permanents”*

(unfrozen tissue for flow cytometry and permanent slides)



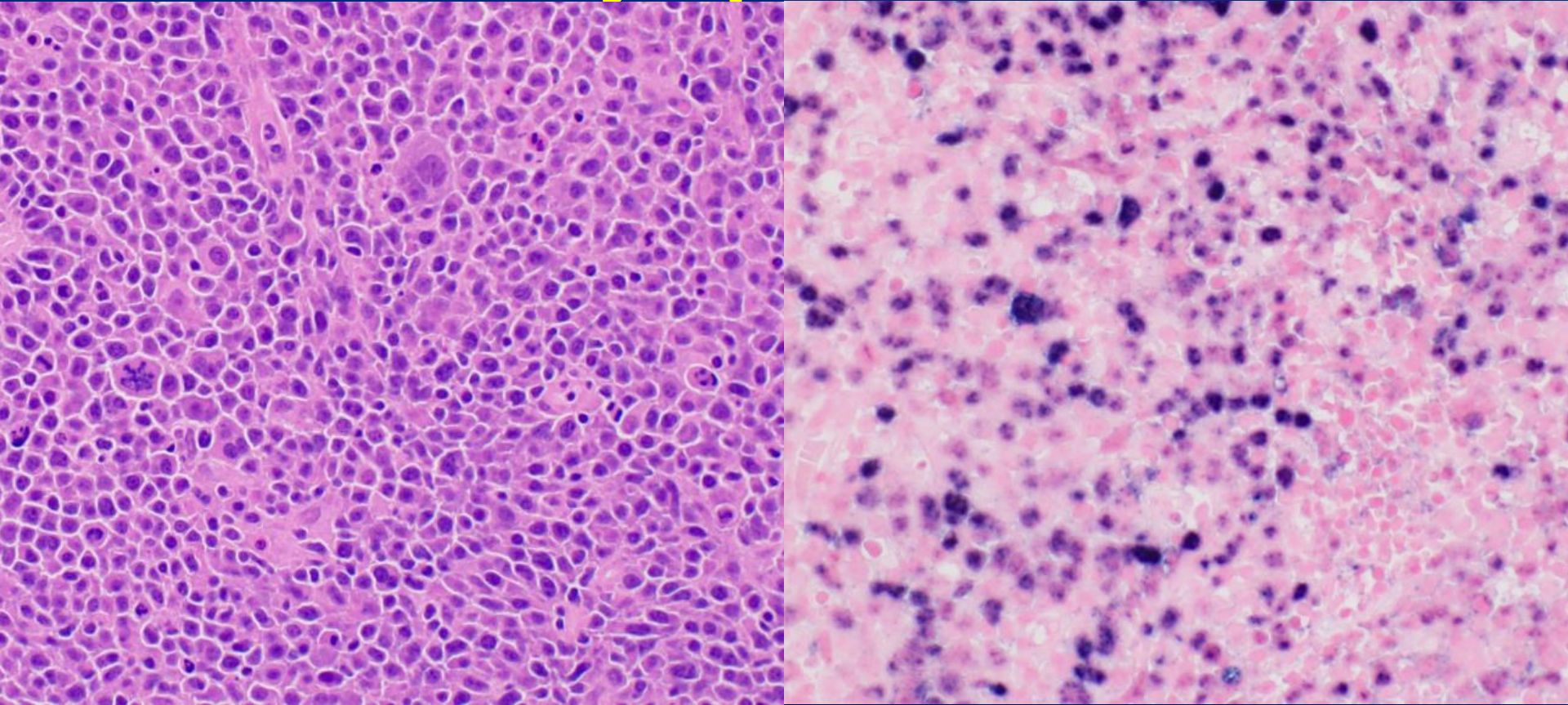
# NK T- Cell Lymphoma



**+EBV ISH**



# NK T- Cell Lymphoma



**Extranodal Lymphoma on FS:  
may mimic CA!!!!**

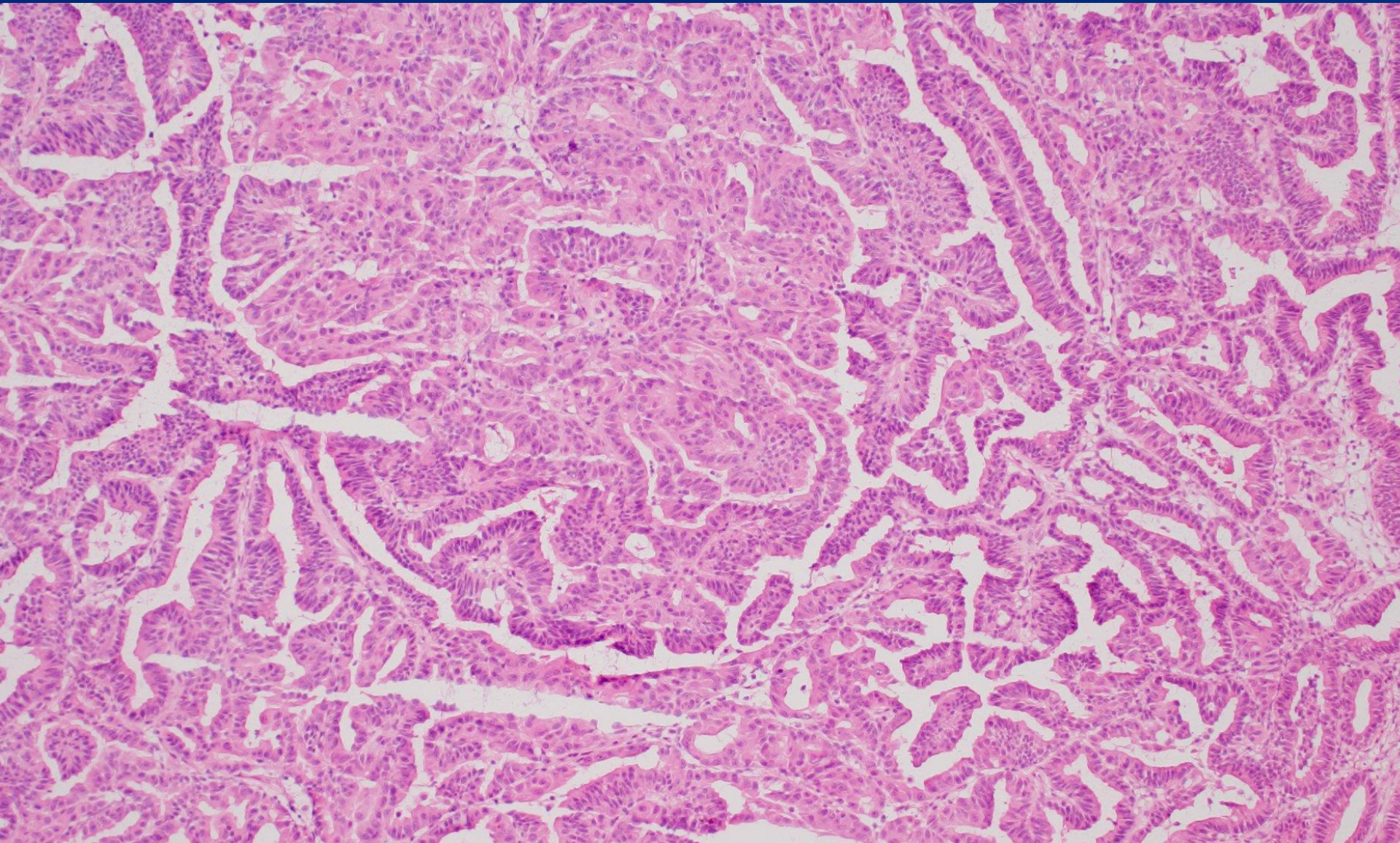




## Case 9

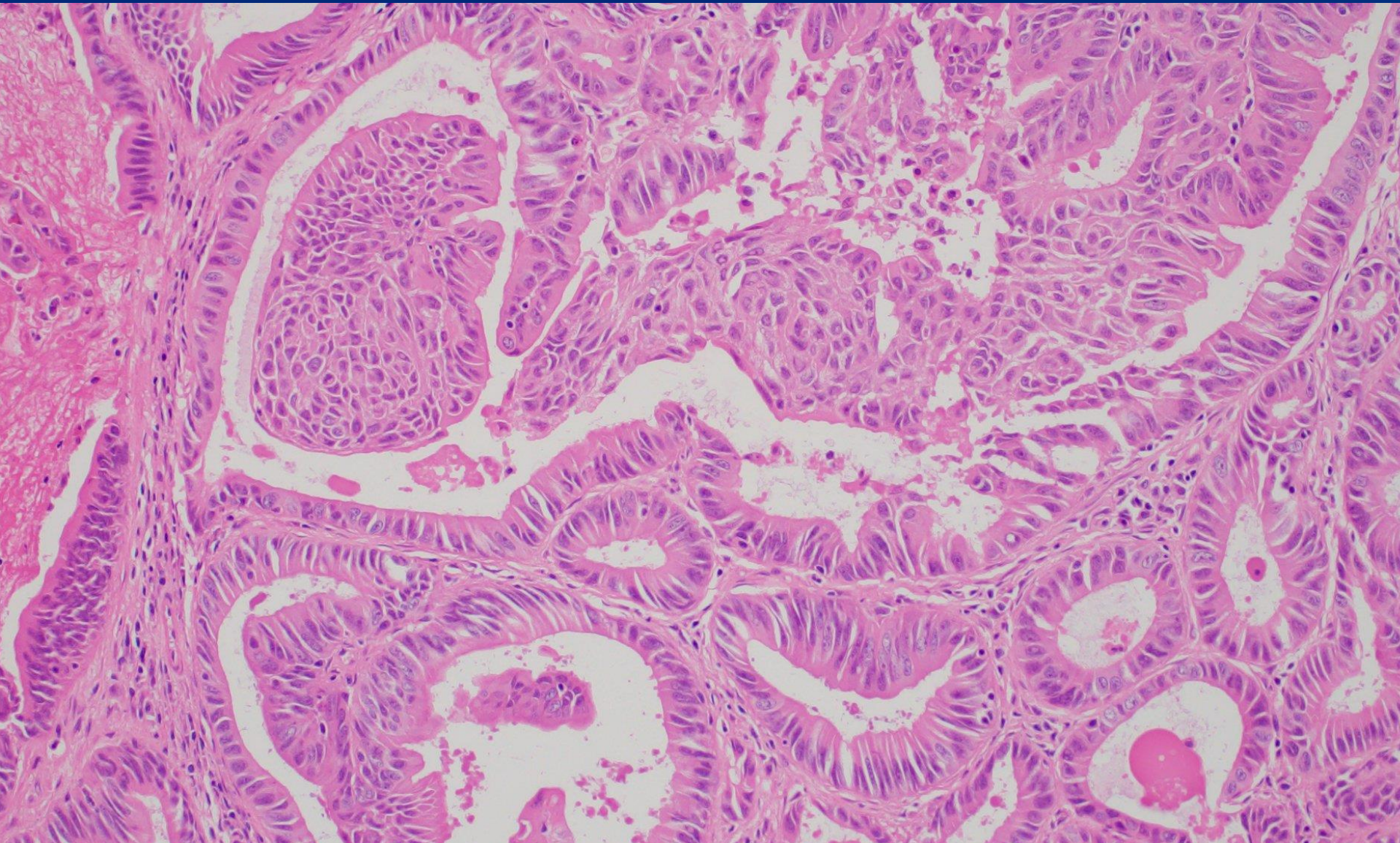
- 60 yo with uterine mass,
- Prior biopsy “atypical glands,”
- Scheduled for hysterectomy

# Uterine Mass FS Biopsy



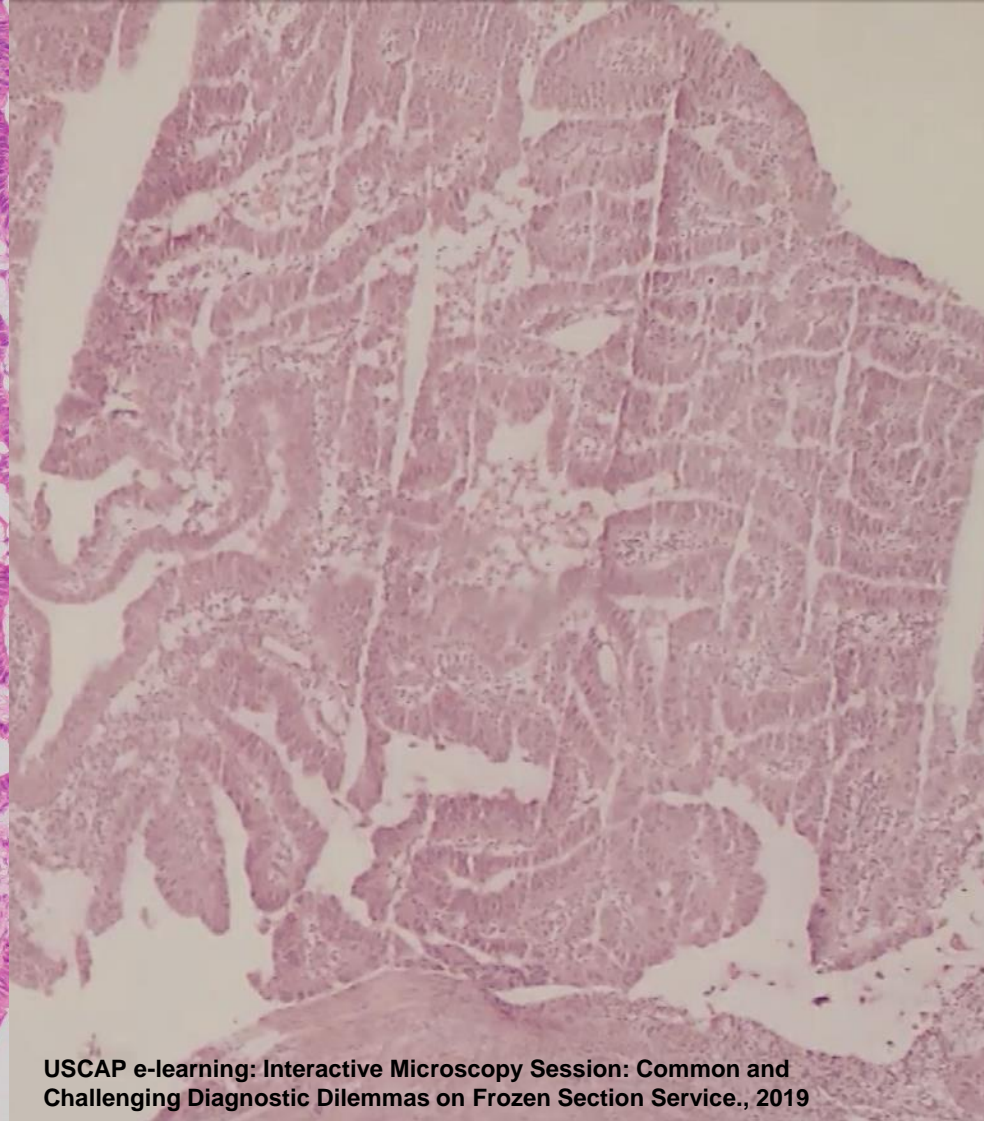
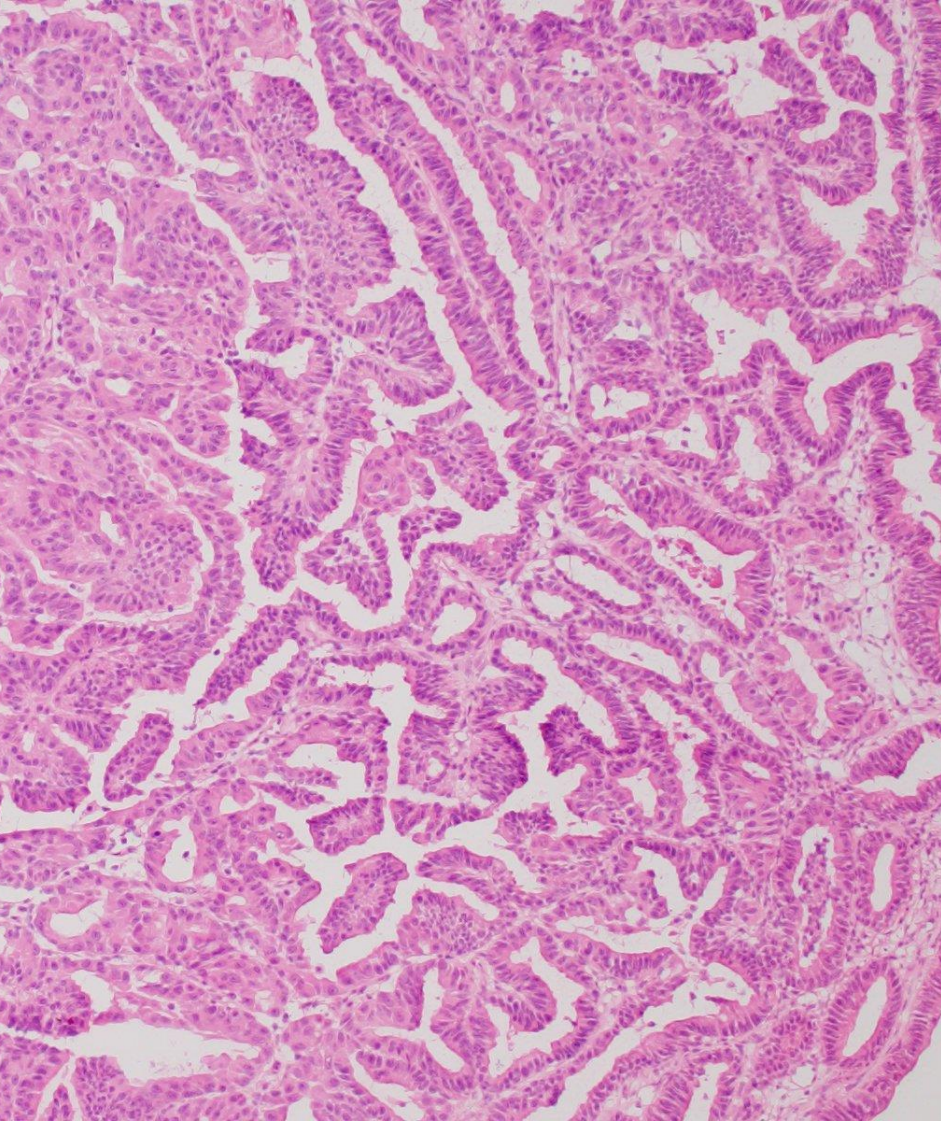


# Uterine Mass FS Biopsy



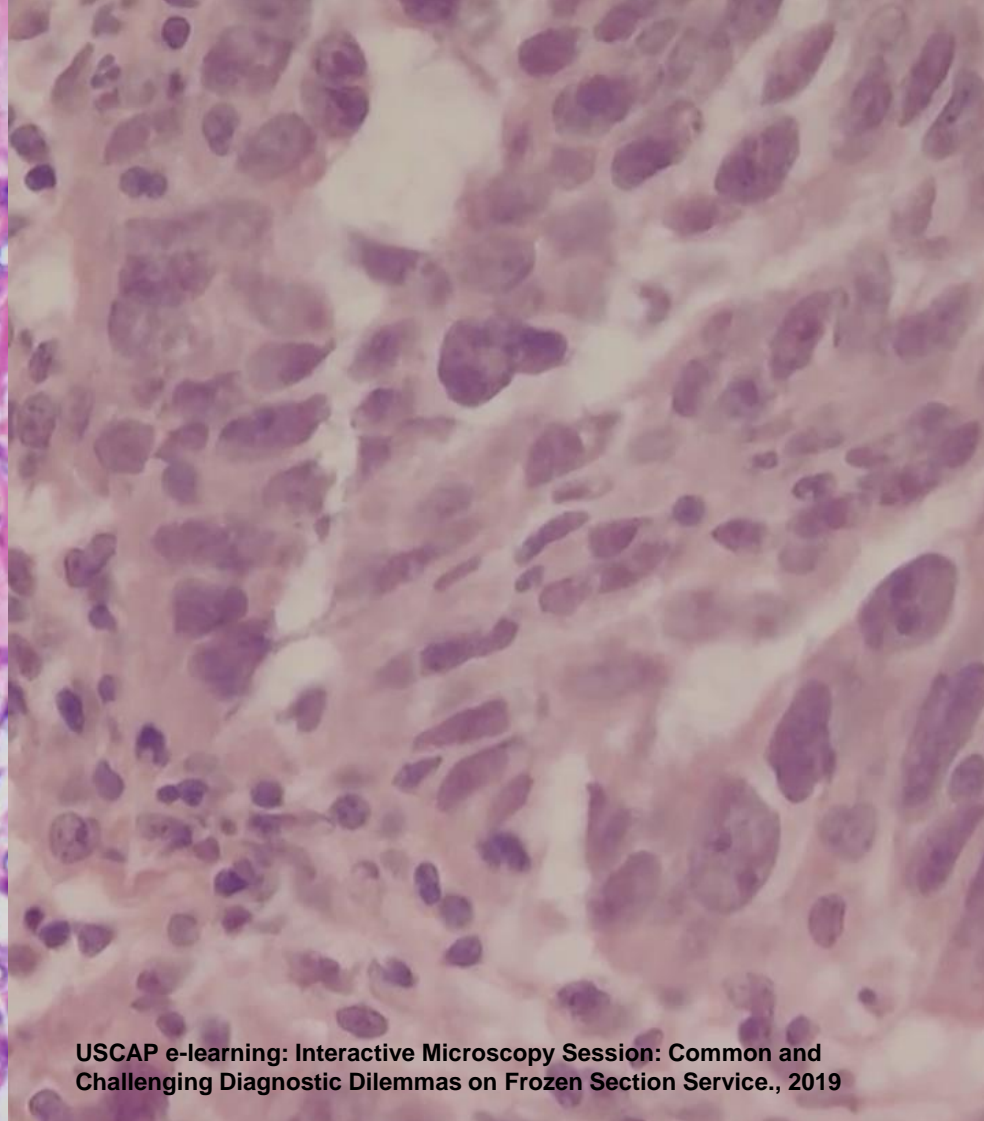
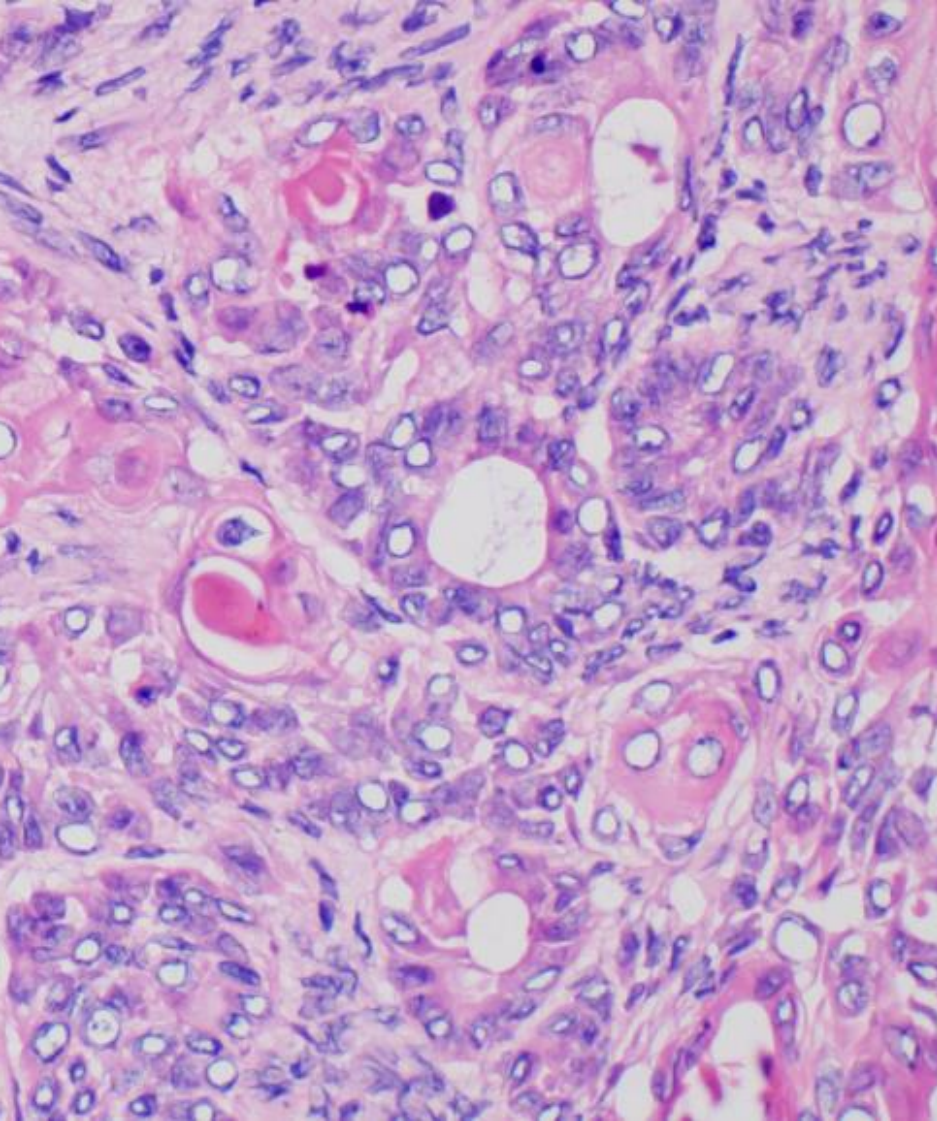


# Endometrioid vs Serous CA



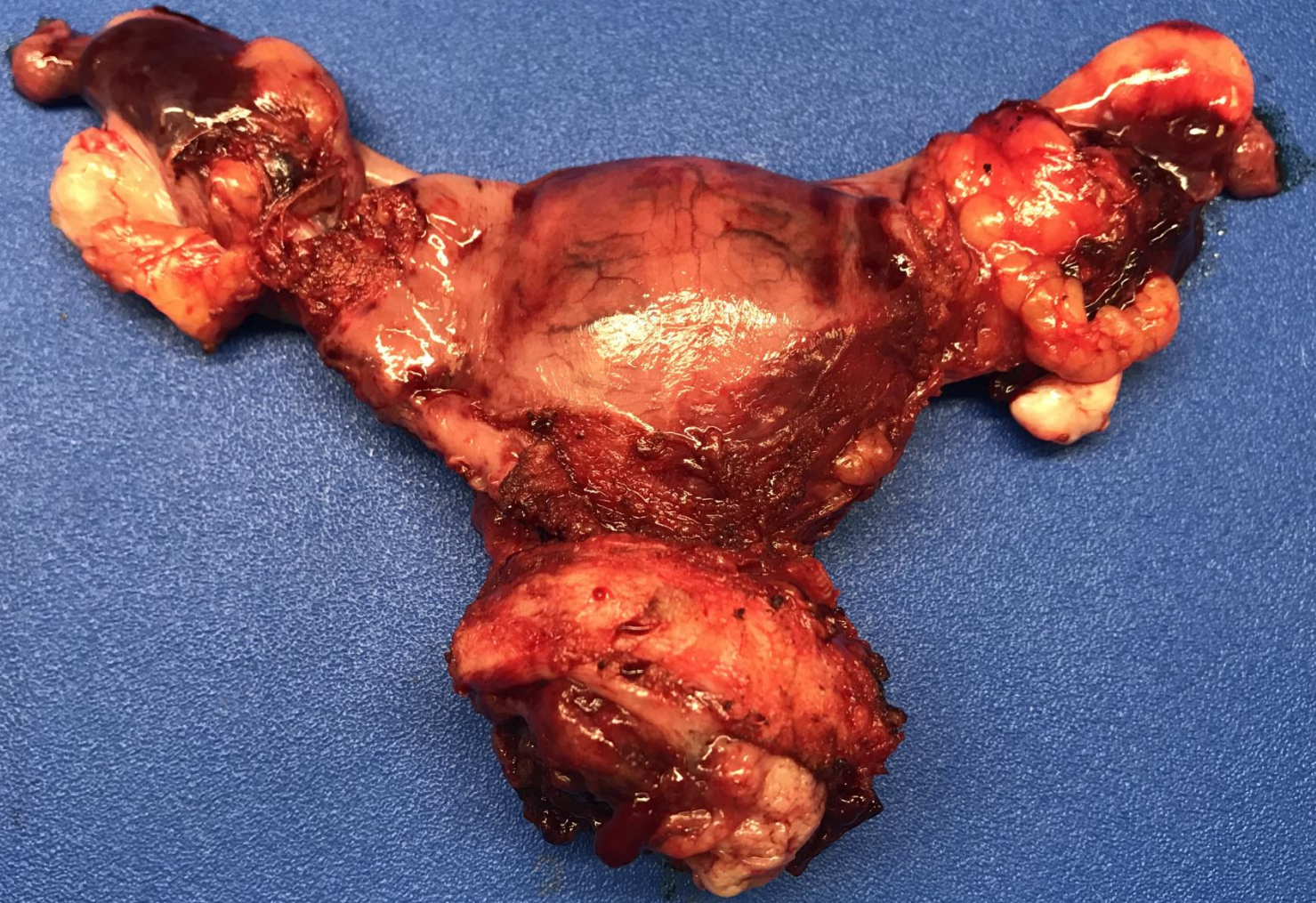


# Endometrioid vs Serous CA



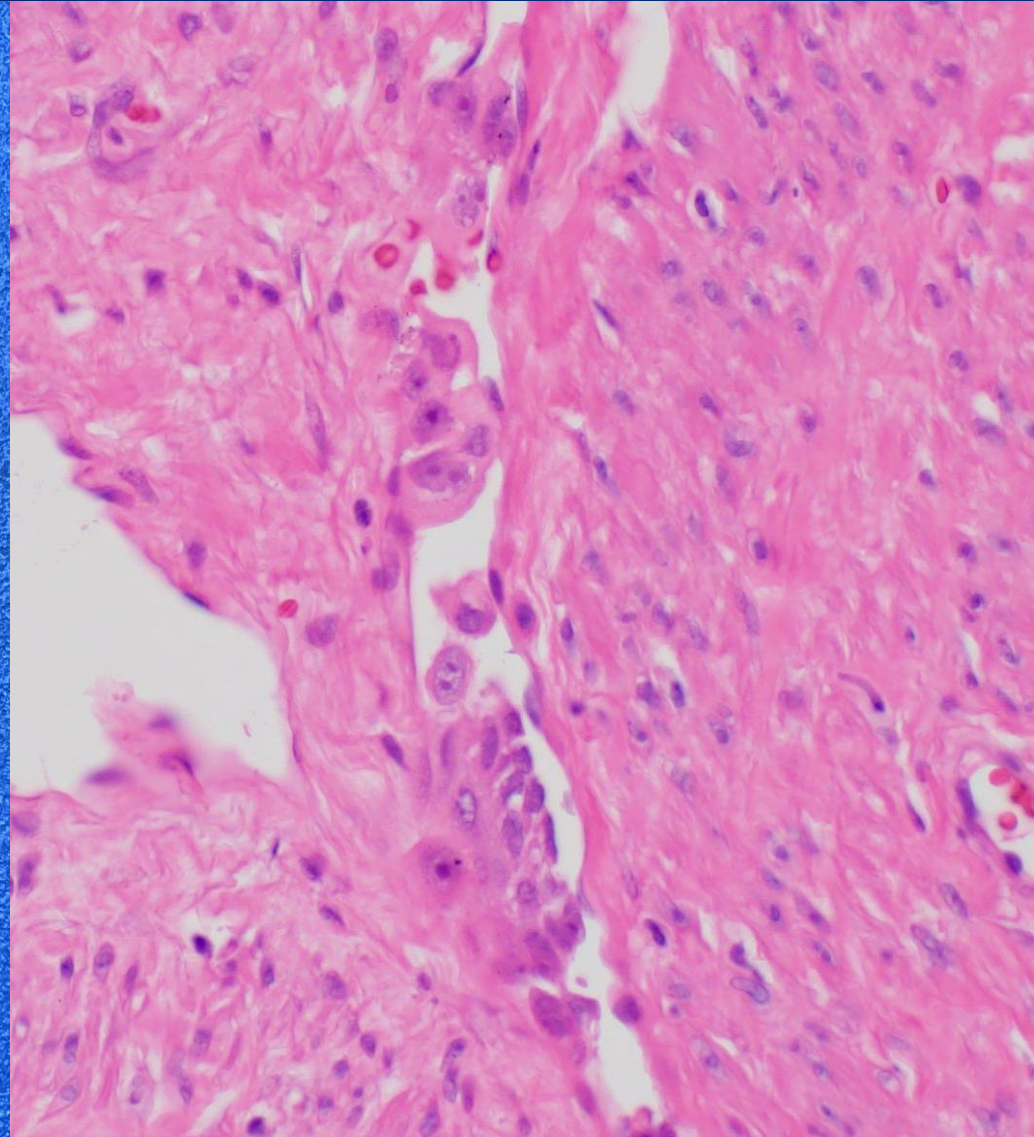


# Uterus, bilateral FT and Ovaries



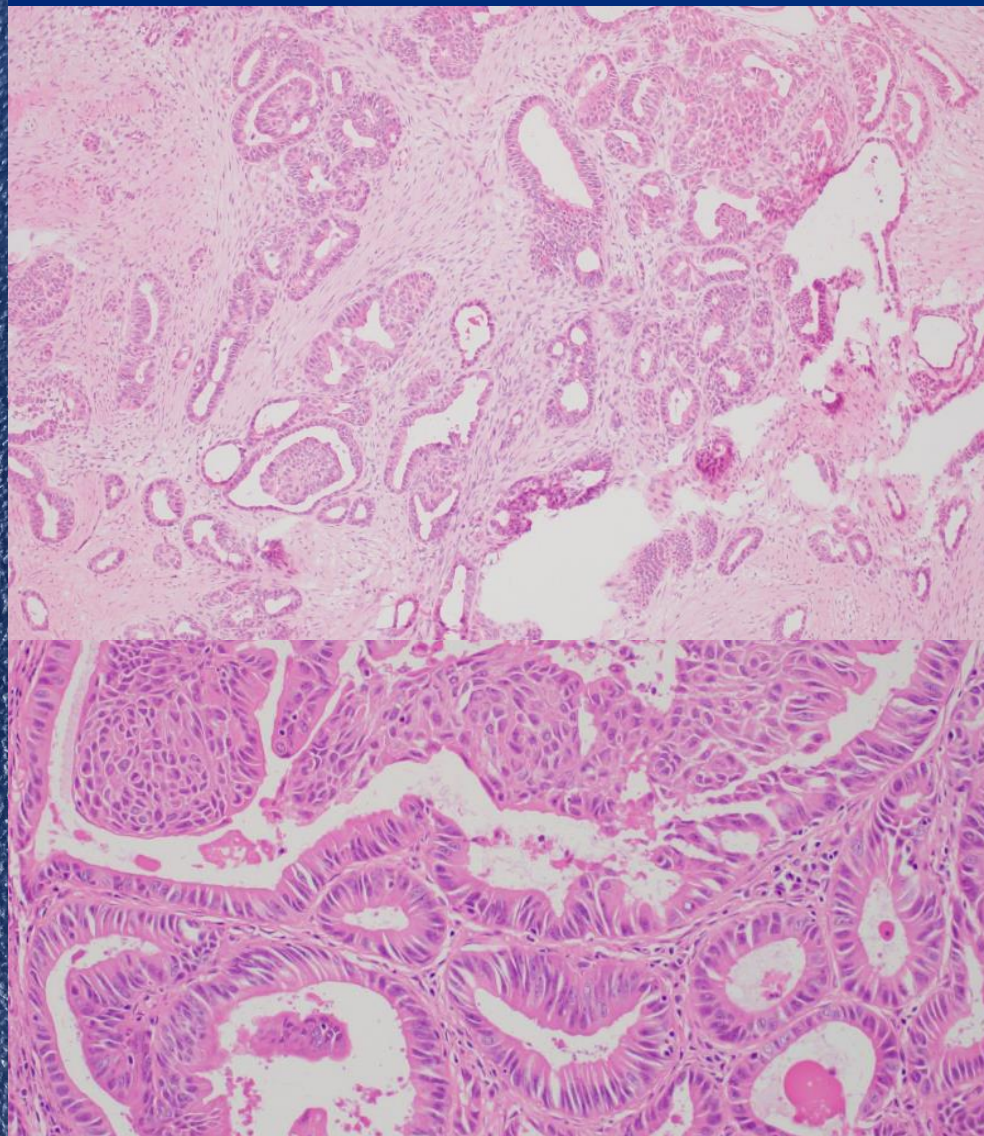


# Endometrium, Cervix, LVSI





# Ovaries





# Ovarian Tumors

## Favor Primary

- Unilateral
- Large
- Confined to ovary
- Expansile growth pattern
- No signet ring cells
- Mixed mucinous and serous epithelium

## Favor MT

- Bilateral
- <10 cm
- +Ovarian surface, extra-ovarian
- Multinodular
- + Signet ring cells
- Colonic appearing epithelium



# Ovarian Tumors

## Favor Synchronous

- Unilateral
- Superficial myometrial invasion
- Low histologic grade in both sites
- Expansile growth
- No lymphovascular invasion (LVI)
- Ovarian endometriosis

## Favor MT

- Bilateral
- Deep myometrial invasion
- High histologic grade in both sites
- Multinodular growth
- + LVI
- No ovarian endometriosis





## Case 10: Friday night/ holiday eve

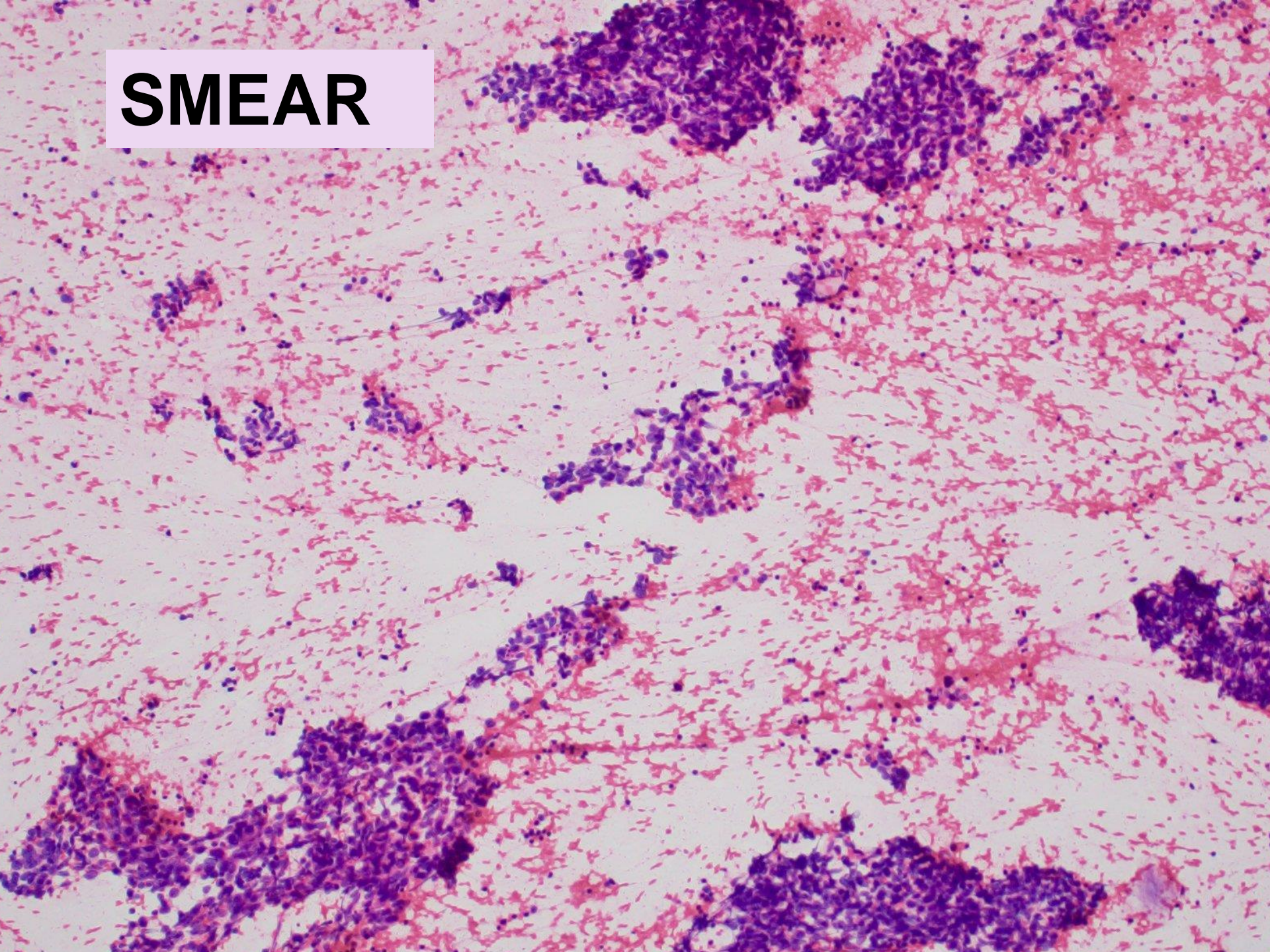
- 40 yo male, heavy smoker
- Remote history of melanoma
- Acute/ progressive shortness of breath
- Large mediastinal mass
- Treatment needs to be started asap

# Clinical Differential

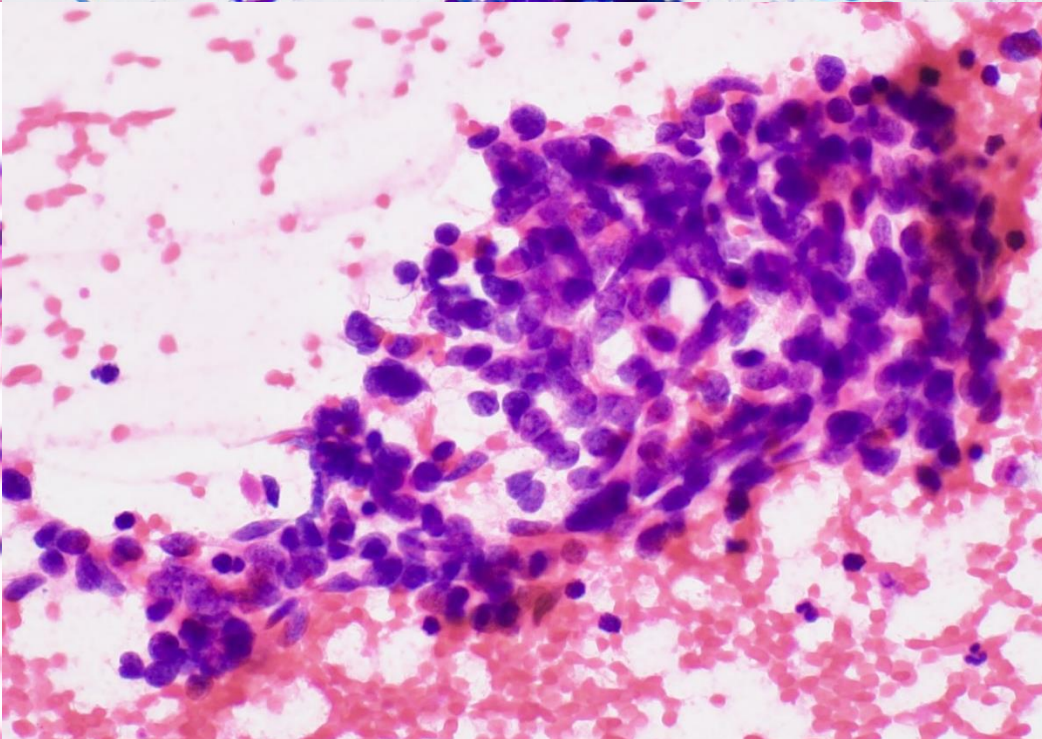
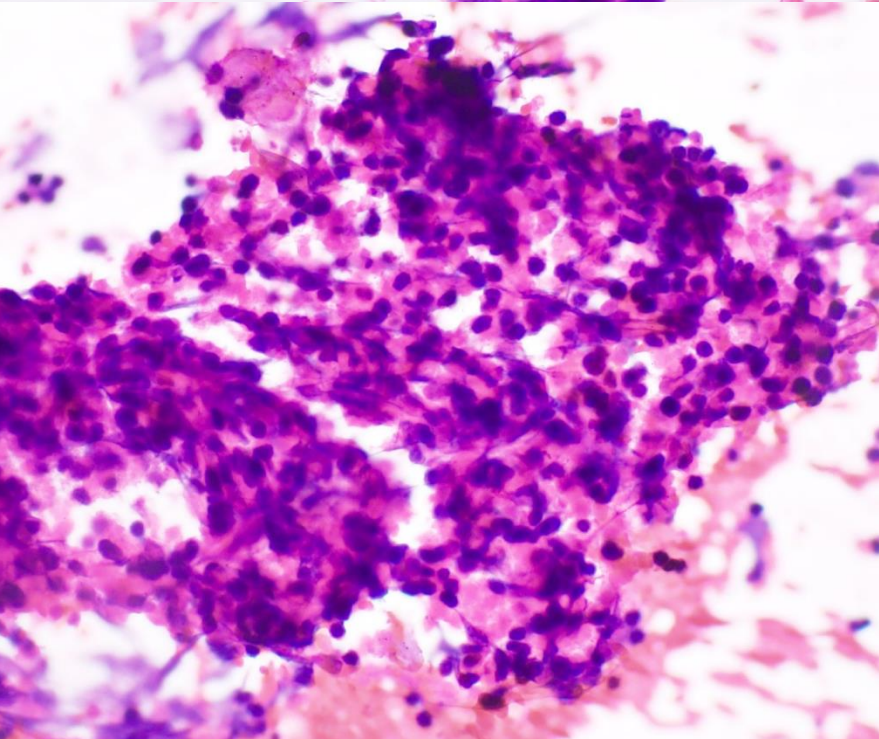
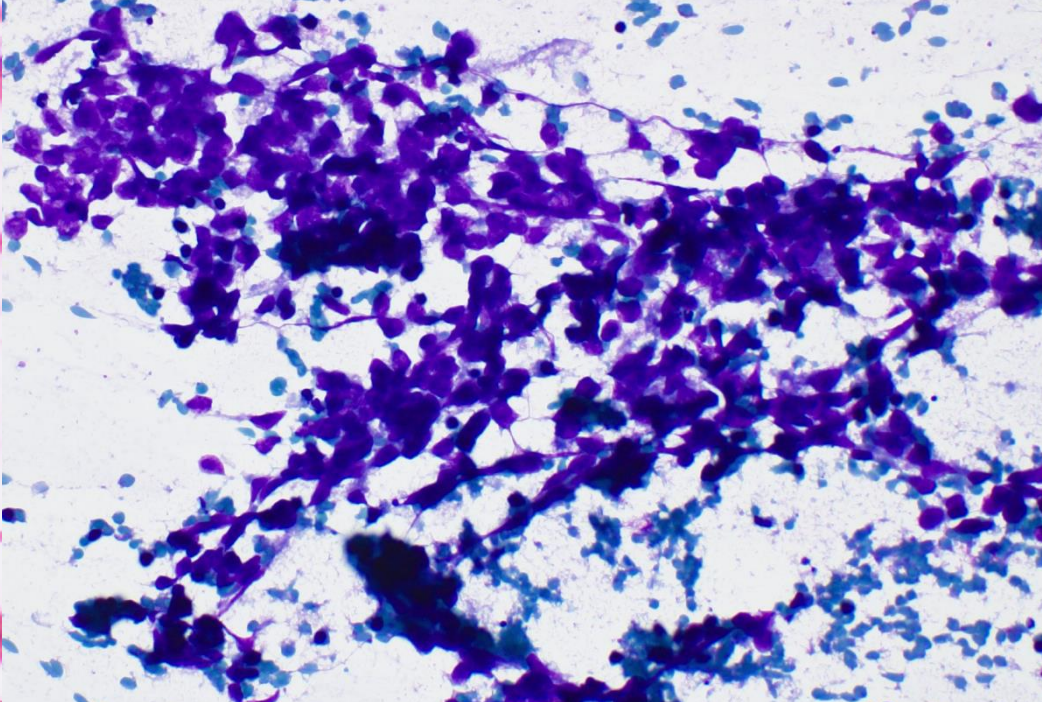
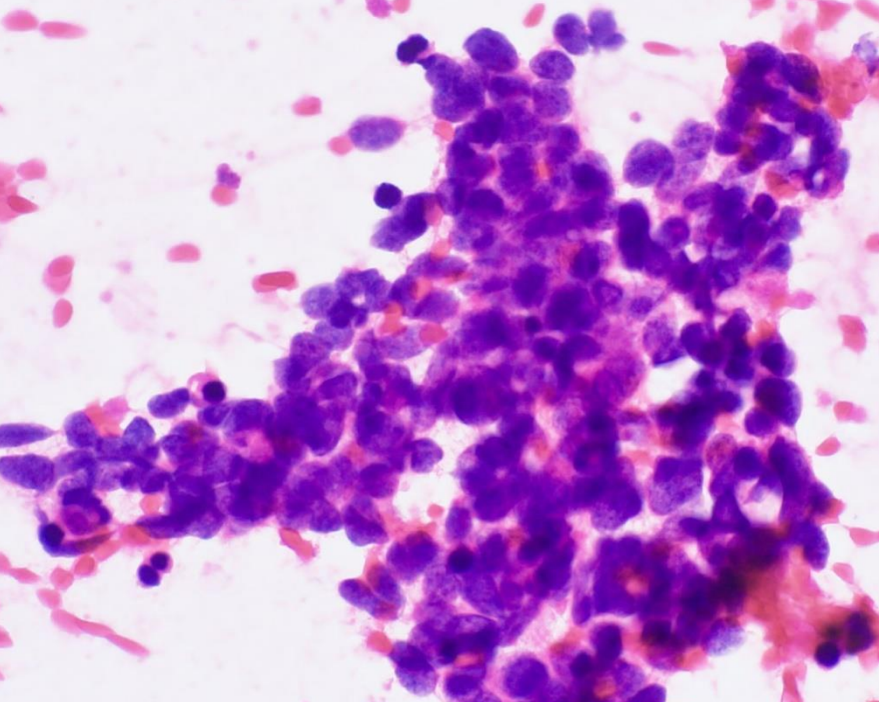
- Carcinoma
- Lymphoma
- Melanoma
- Germ cell tumor



# SMEAR

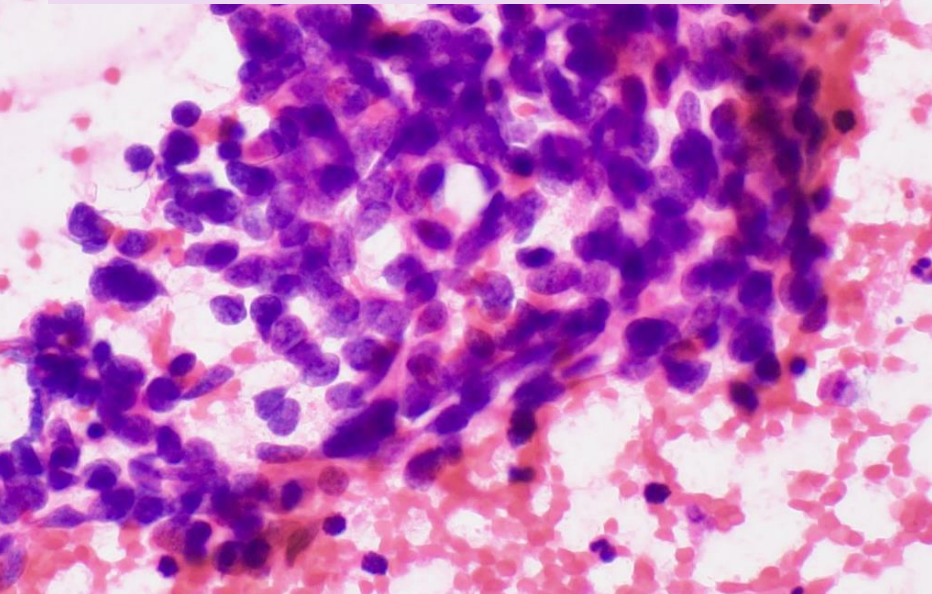




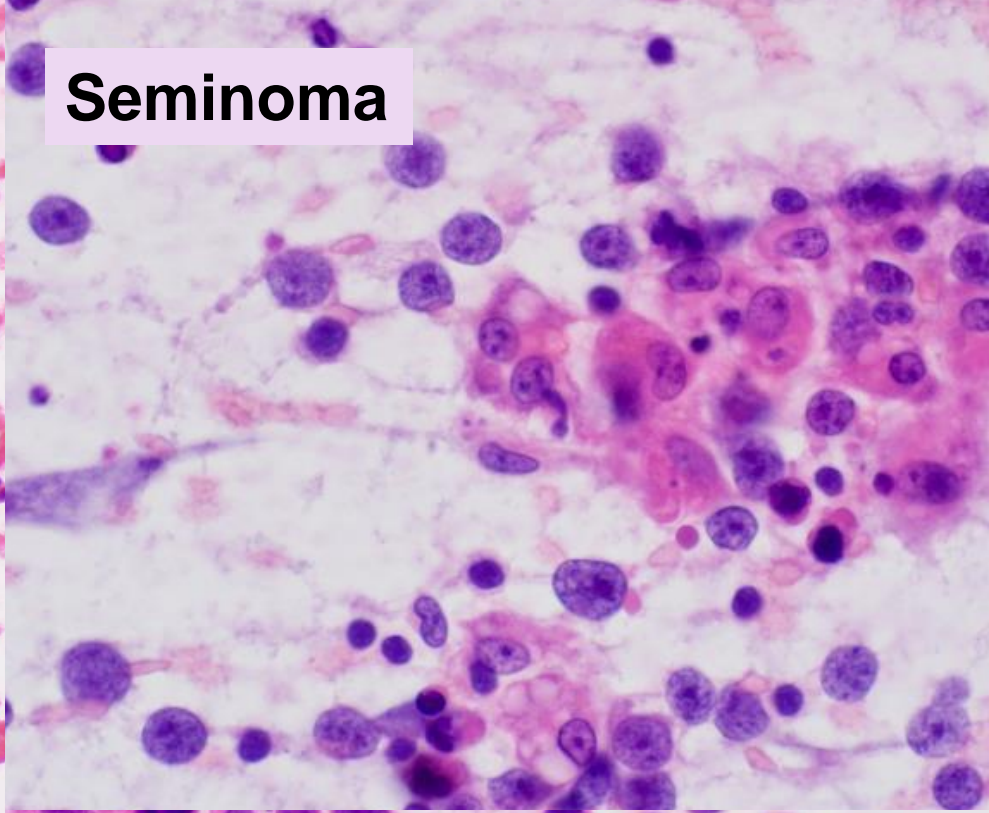




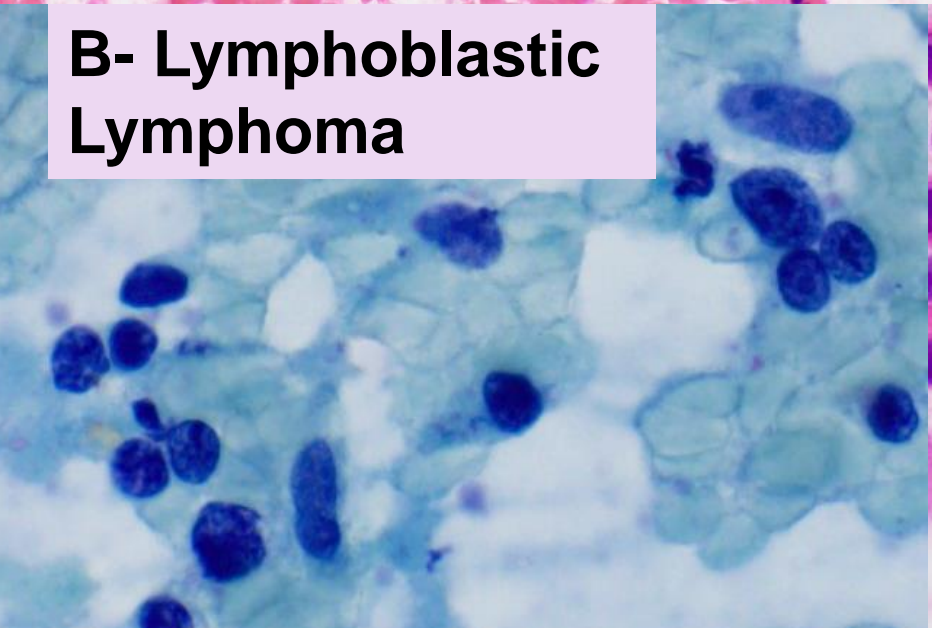
**Our case:  
Favor CA, Small Cell type**



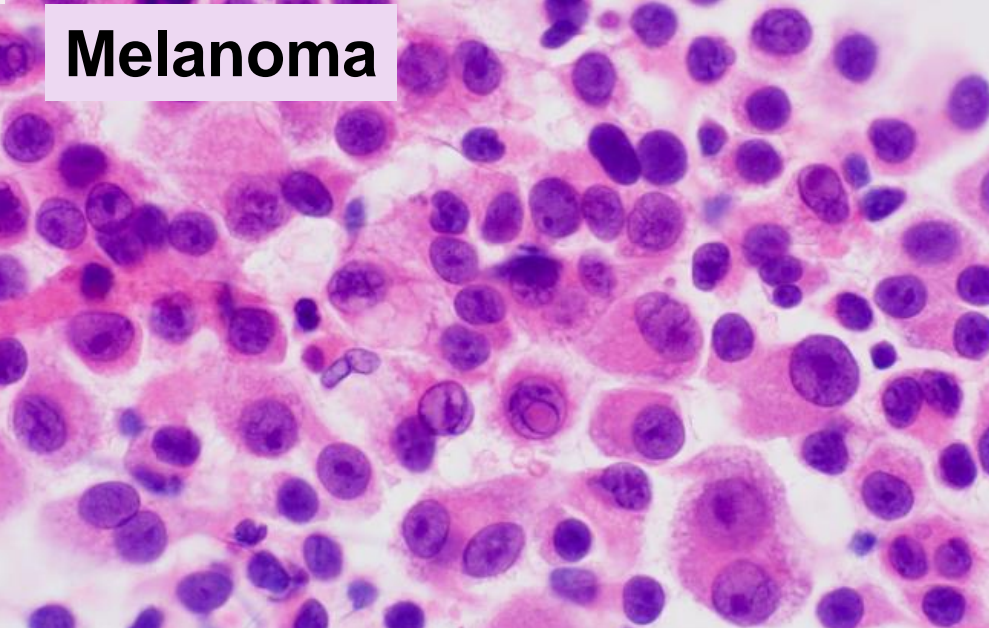
**Seminoma**



**B- Lymphoblastic  
Lymphoma**

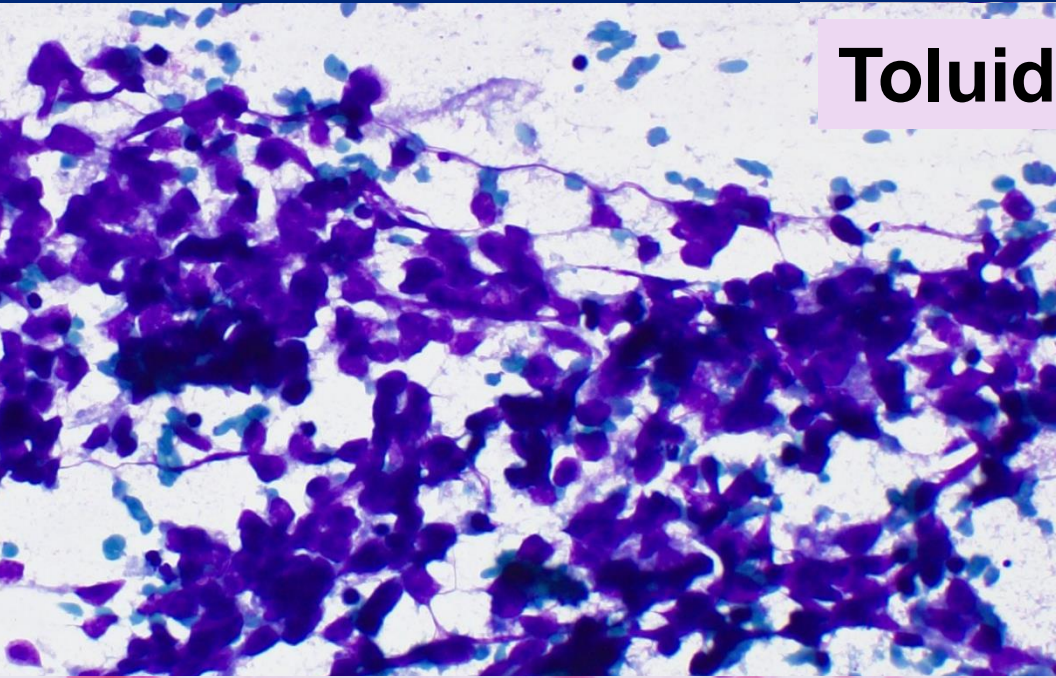


**Melanoma**

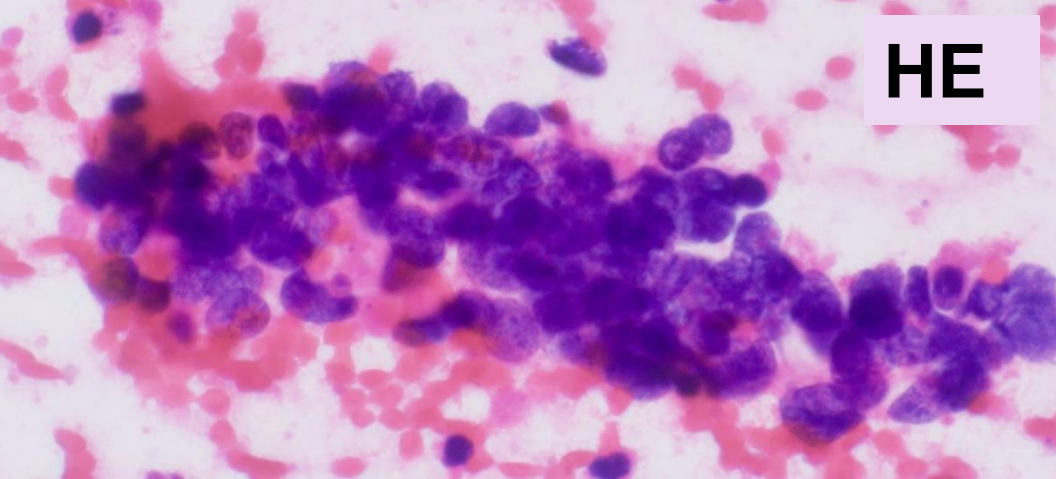




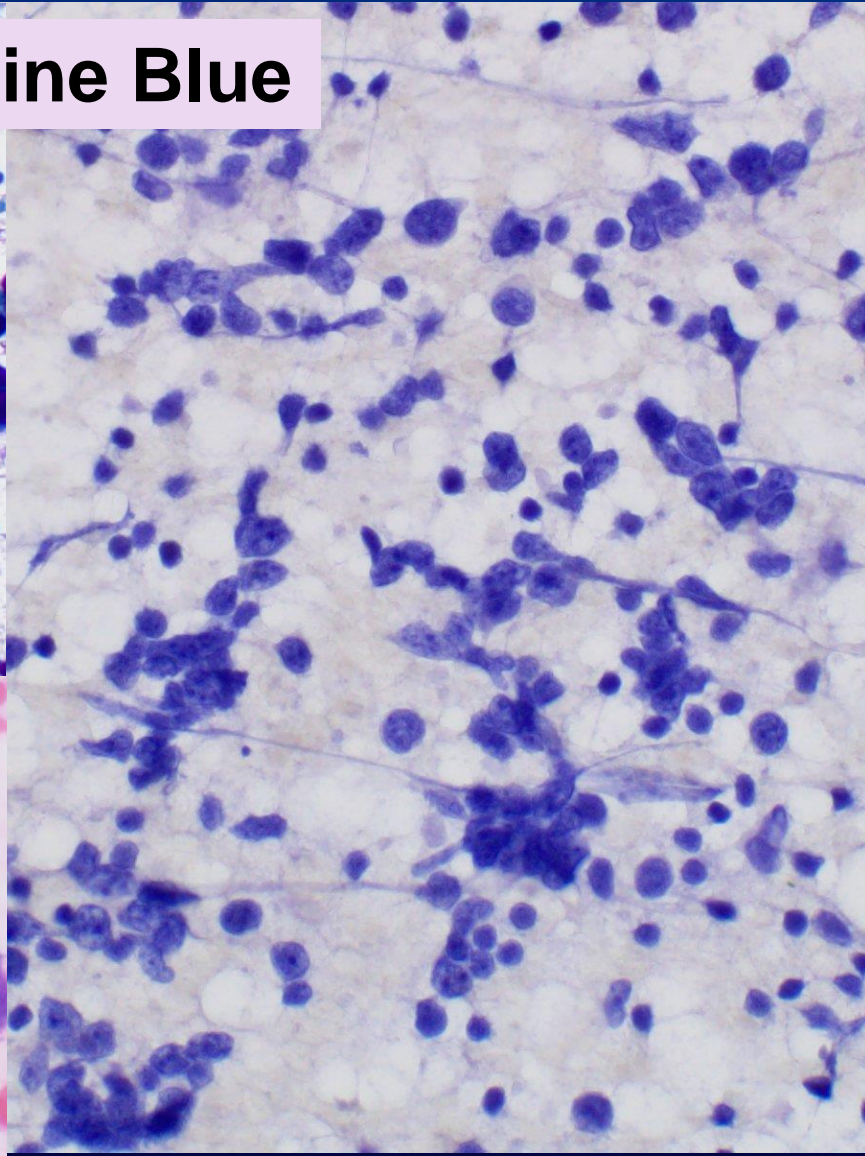
# Small Cell CA vs DLBCL



Toluidine Blue



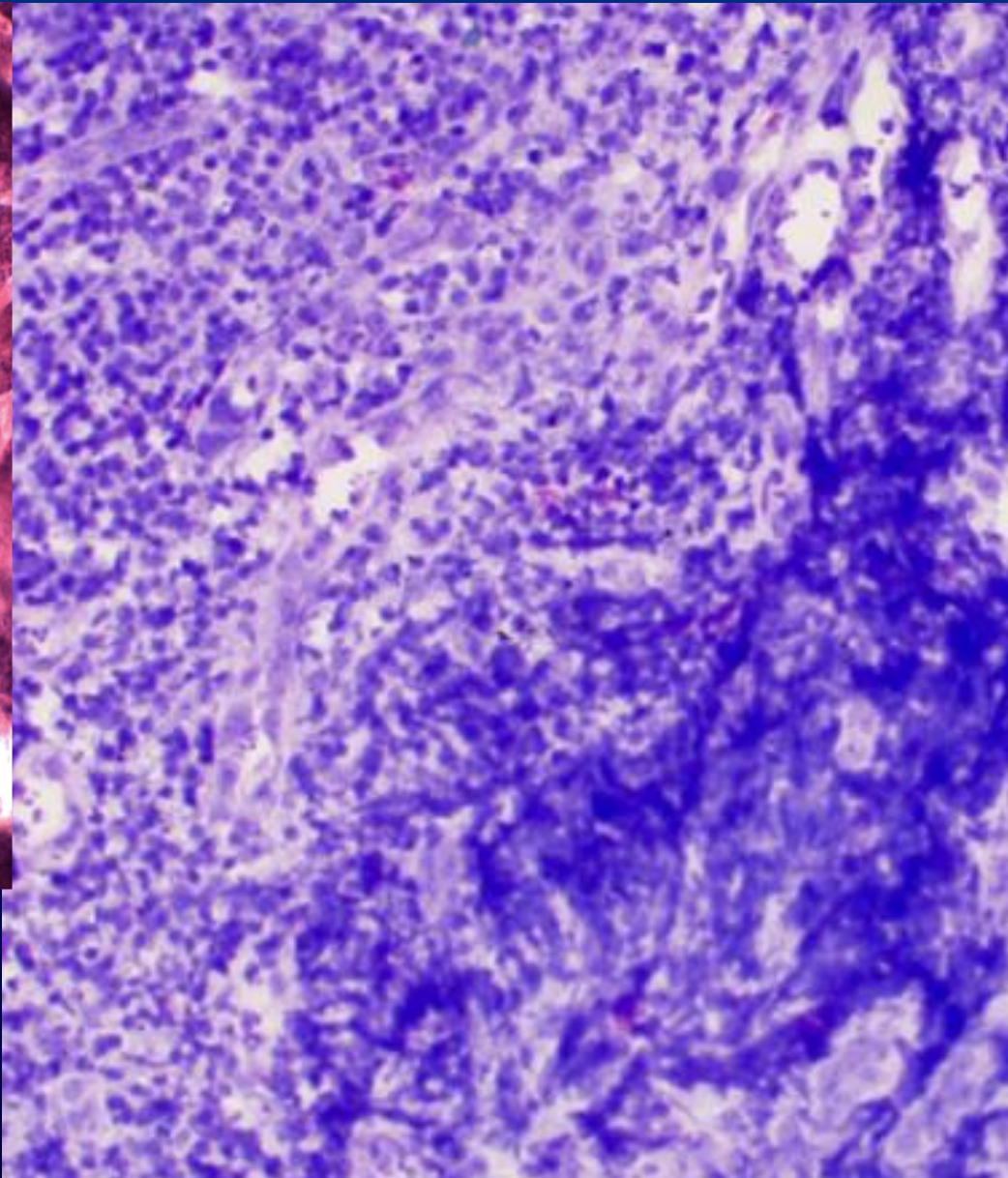
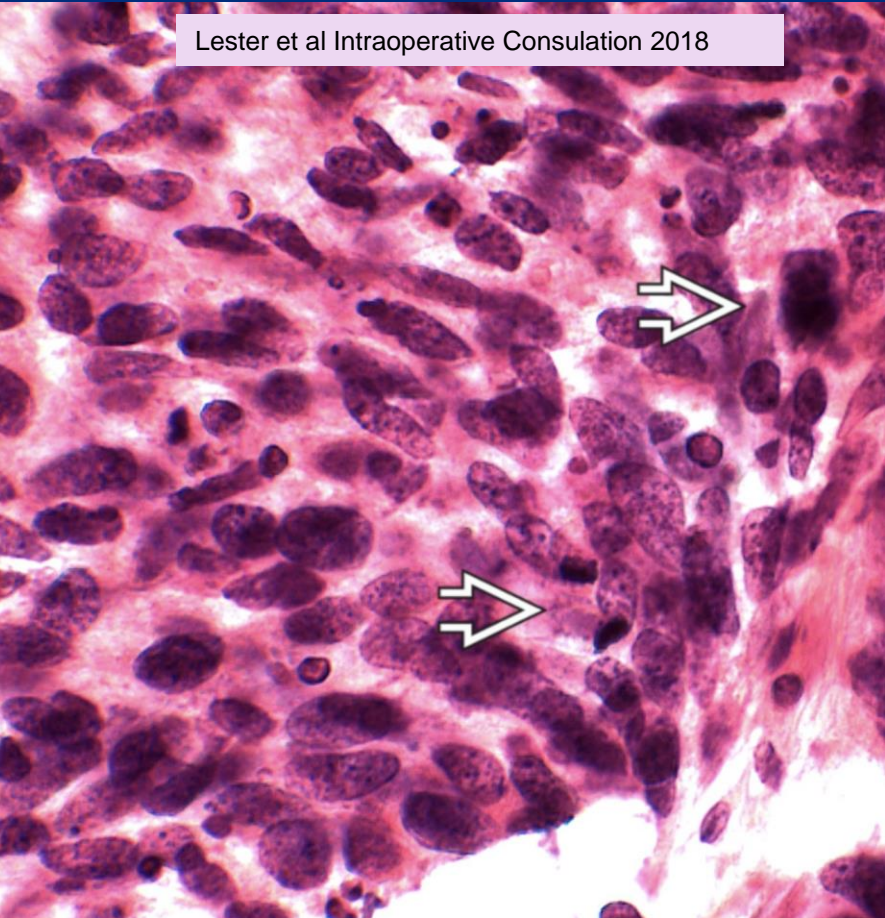
HE





# MT Small cell to LN vs crushed Lymphocytes FS

Lester et al Intraoperative Consultation 2018



**Favor Small Cell:**

N 3-4x larger than lymphocytes  
+necrosis, molding, mitosis

# How Can We Improve?

- Years before FS:
  - Cytology
  - Grossing
- Day before/ day of:
  - **REDUCE STRESS** by being better prepared



# How Can We Improve?

- Years before FS:
  - Cytology
  - Grossing
- Day of/ before FS:
  - Look up history
  - Pull slides
- FS day:
  - Keep organized
  - High volume: prioritize (SLN, closest MG), backup
  - Clear communication
  - Documentation

# New Job?

- Find out:
  - Specimen types
  - Specific expectations/requests



# Difficult FS?

- Determine how much information you need to provide so that the appropriate care is delivered:
  - ?RCC vs Neoplastic
  - ?Low Grade vs High Grade
  - ?MT vs primary
  - ?Lymphoma
- Defer for permanents ok, but assure that “lesional tissue obtained”, if not:
  - Request more tissue

# ALWAYS Know:

- What is the FS goal?
- What will the surgeon do with that information?



# ALWAYS Know:

- What is the FS goal?
  - Diagnosis? Obtain diagnostic tissue
- What will the surgeon do with that information?
  - Is he/ she going to/ need to act on it TODAY?

# References

- Khalifa MA. Intraoperative assessment of the Whipple resection specimen. *J Clin Pathol* 2007 (60): 575-980.
- Volmar KE et al. Florid von Brunn Nests Mimicking Urothelial Carcinoma. A Morphologic and Immunohistochemical Comparison to the Nested Variant of Urothelial Carcinoma. *Am J Surg Pathol* 2003 (27): 1243- 1252.
- USCAP e-learning: Interactive Microscopy Session: Common and Challenging Diagnostic Dilemmas on Frozen Section Service. October 4-7, 2019.
- Medeiros F et al. Intraoperative Frozen Section Consultation in Gynecologic Pathology. *Methods Mol Biol.* 1180: 209-220
- Buza N. Frozen Section Diagnosis of Ovarian Epithelial Tumors. Diagnostic pearls and Pitfalls. *Arch Pathol Lab Med* 2019 (143): 47-64.
- Wong KS et al. Utility of Birefringent Crystal Identification by Polarized Light Microscopy in Distinguishing Thyroid From Parathyroid Tissue on Intraoperative Frozen Sections. *Am J Surg Pathol* 2014; 38: 1212-1219.
- McHale T. Potential Pitfalls in the Frozen Section Evaluation of Parenchymal Margins in Nephron Sparing Surgery. *Am J Clin Pathol* 2002; 118: 903-910.



# References

- Zhu X et al. Frozen section diagnosis of gastrointestinal poorly cohesive and signet-ring cell adenocarcinoma: useful morphologic features to avoid misdiagnosis [published online ahead of print, 2020 Mar 25]. *Virchows Arch*. 2020;10.1007/s00428-020-02799-4. doi:10.1007/s00428-020-02799-4
- Lester et. Al. Diagnostic Pathology: Intraoperative Consultation. Elsevier, Second Ed. 2018
- Kumar S. The Role of Frozen Section in Surgical Staging of Low Risk Endometrial Cancer. *PLoS One*. 2011;6(9):e21912. doi:10.1371/journal.pone.0021912
- Calhoun B- USCAP Evening Specialty Conference 2016  
[http://handouts.uscap.org/2016\\_brea\\_calho\\_1.pdf](http://handouts.uscap.org/2016_brea_calho_1.pdf)
- Cacciato Insilla. Deep endometriosis with pericolic lymph node involvement: A case report and literature review. *World J Gastroenterol* 2014 June 7; 20(21): 6675-6679
- Kubik MW. Intraoperative Margin Assessment in head and Neck Cancer: A Case of Misuse and Abuse? *Head and Neck Pathology* 2020 (14): 291-302.
- Theisen BK. Pancreatic Frozen section nightmares. *Diagnostic Histopathology* June 2016: 236-242.
- Zarbo RJ et al. Interinstitutional comparison of frozen section consultation. *Arch Pathol Lab Med* 1991; 115:1187-1194

"Follow these precepts and you will revolutionize your life. Read this book!"

—Steven Pressfield, author of *The War of Art* and *Gates of Fire*

# THE OBSTACLE IS THE WAY



**RYAN HOLIDAY**

Bestselling author of *Trust Me, I'm Lying*