MAYO CLINIC

WHO 2021 THORACIC TUMOR UPDATES

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DISCLOSURES

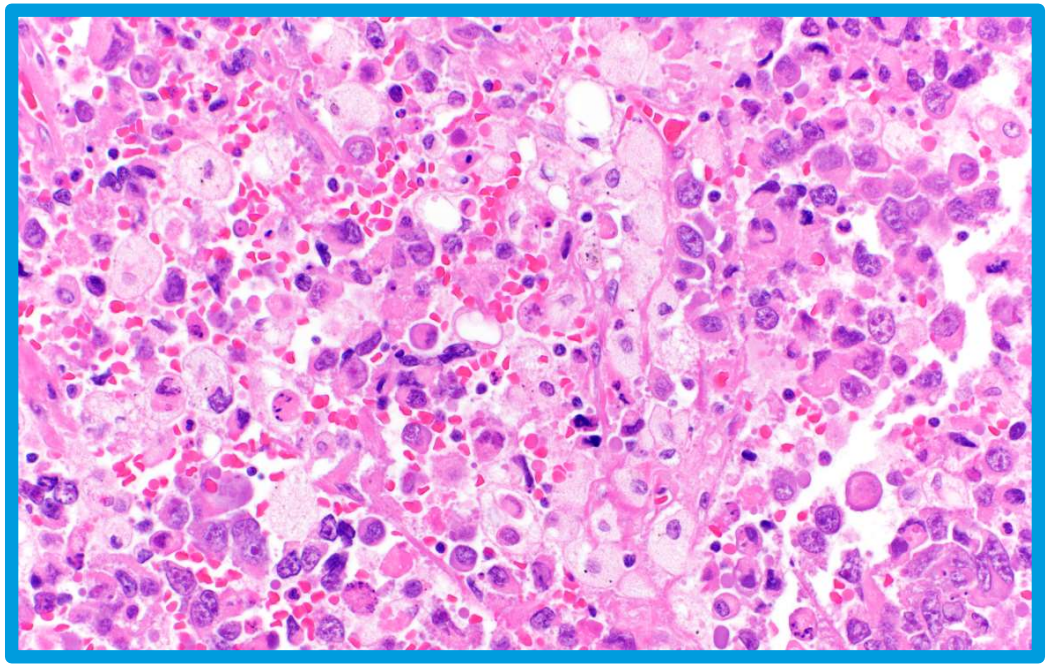
- No relevant financial relationships with ineligible companies to disclose by Dr. Yasmeen M. Butt.

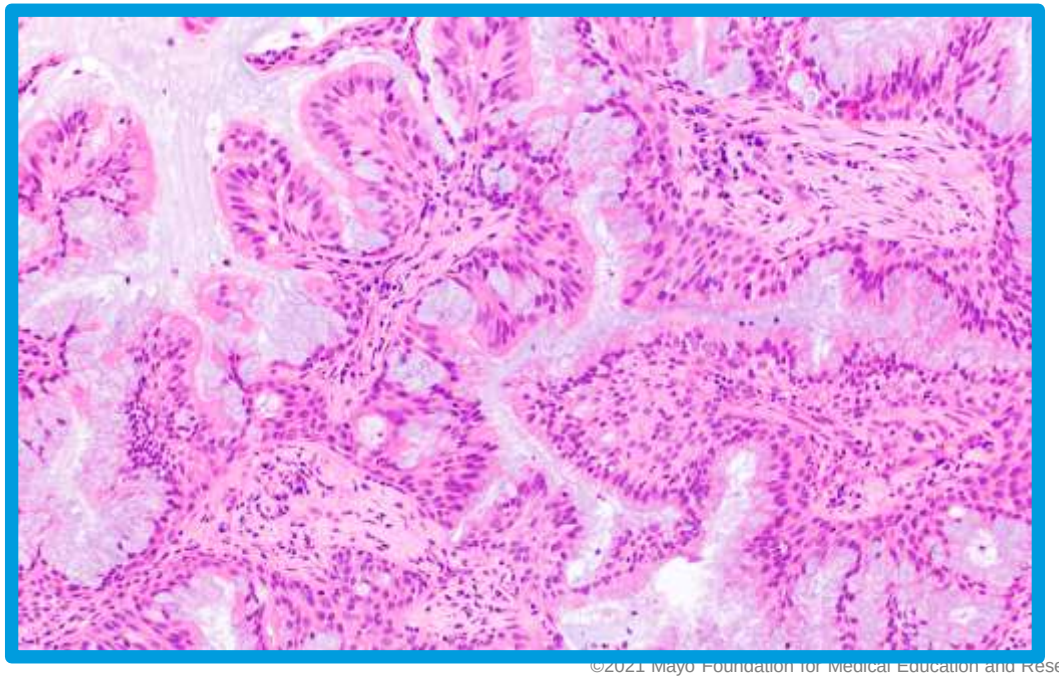
LEARNING OBJECTIVES

- List WHO 2021 grading criteria for pulmonary adenocarcinoma
- Describe spread through air spaces (STAS) and summarize its significance
- Formulate a differential diagnosis for high grade thoracic malignancies that includes new entities
- Be able to grade epithelioid mesotheliomas according to new criteria
- Be aware of new terminology for bronchiolar adenomas.

2021 UPDATES: NEW ENTITIES

- Overall, histopathologic classification remains intact from 4th edition
- Thoracic *SMARCA4*-deficient undifferentiated tumor
- Bronchiolar adenoma/ciliated muconodular papillary tumor (new adenoma subtype)





2021 UPDATES: RE-CLASSIFIED/RE-NAMED

- Lymphoepithelioma-like carcinoma → lymphoepithelial carcinoma (EBV + and EBV -)
- Enteric adenocarcinoma → enteric-type adenocarcinoma
- Pleomorphic carcinoma (replaces giant cell and spindle cell carcinoma)
- Carcinoid tumor NOS terminology

IASLC HISTOPATHOLOGIC GRADING SCHEME FOR NON-MUCINOUS LUNG ADENOCARCINOMA

Grade	Differentiation	Patterns
1	Well-differentiated	Lepidic-predominant with no or <20% high-grade pattern
2	Moderately differentiated	Acinar or papillary-predominant with no or <20% high-grade pattern
3	Poorly differentiated	Any tumor with ≥ 20% high-grade pattern (solid, micropapillary, cribriform, or complex glandular pattern*)

*Fused glands or single cells infiltrating in a desmoplastic stroma

Suggestion that a 5% cutoff may be appropriate for this grading system

Moreira AL et al. Journal of Thoracic Oncology 2020:15:1599-610

TISSUE MANAGEMENT: GENERAL RECOMMENDATIONS

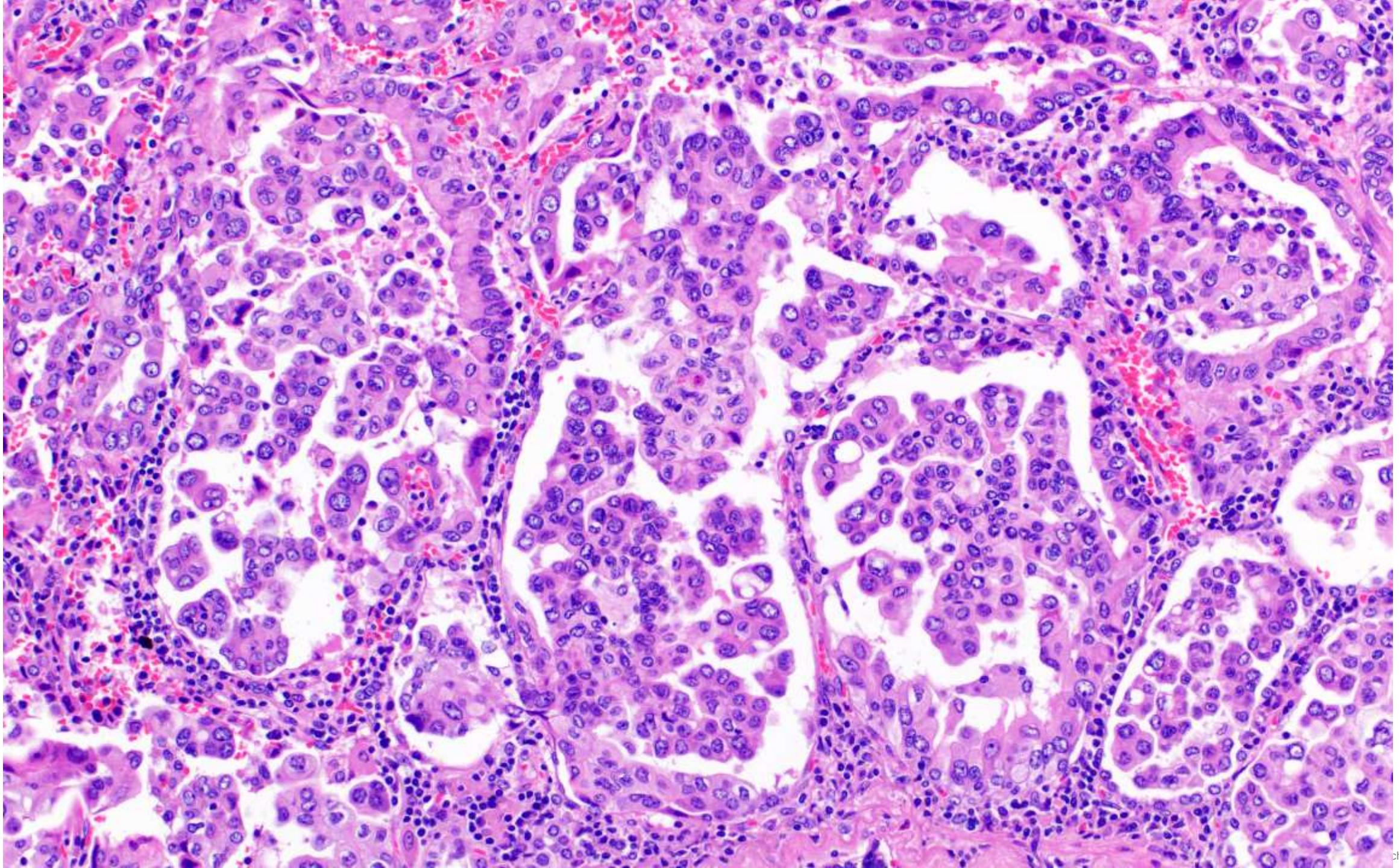
- Separate cores into different blocks
- Don’t ink cores
  - A dab of hematoxylin before processing works!
- Don’t exhaust the block in ‘gray-zone’ cases (especially those that are ground glass on imaging)
  - 2-3 deeper sections in challenging cases ok
  - Preserve remaining tissue for molecular
- Limited panel (if needed), TTF-1, p40

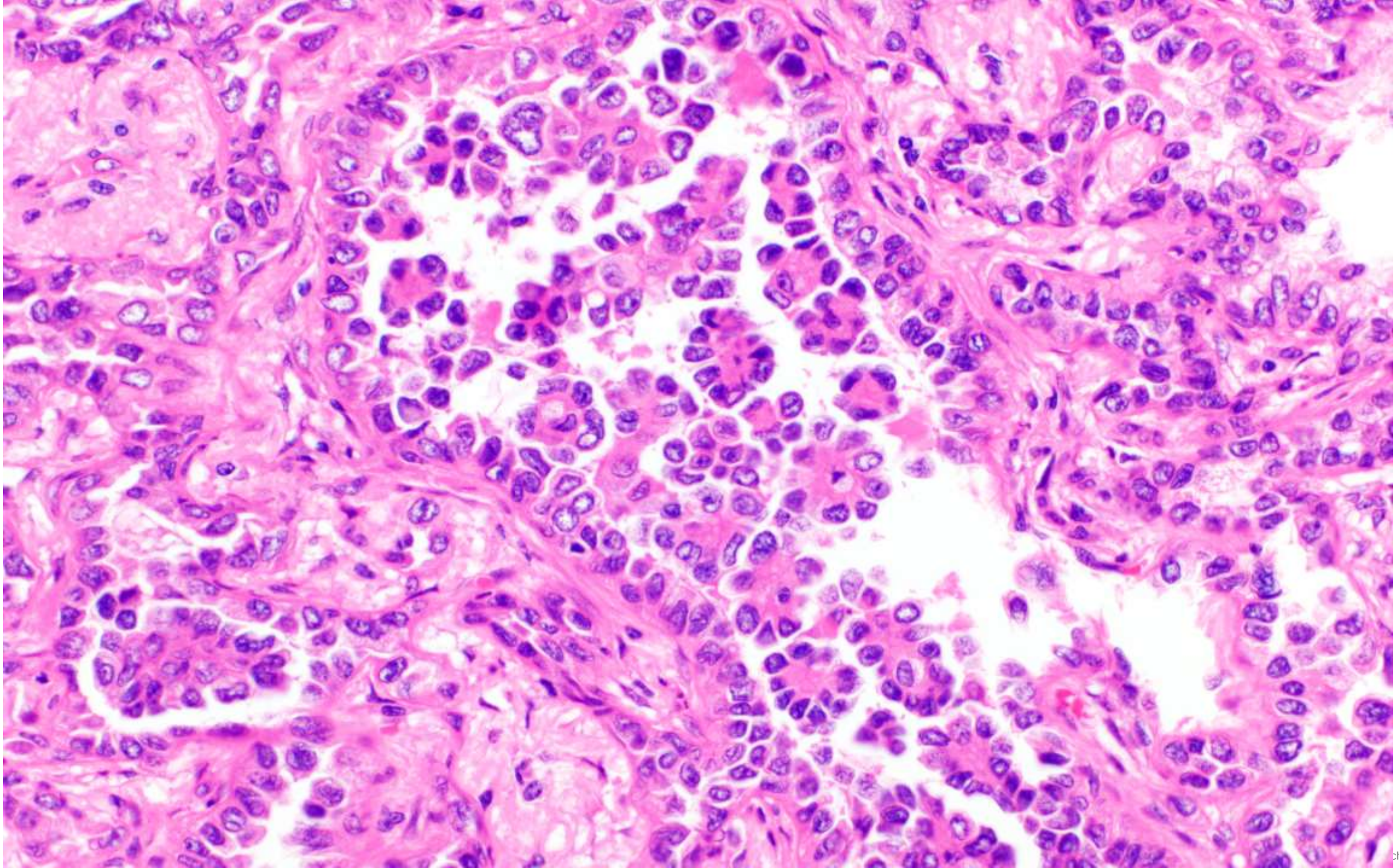
MICROPAPILLARY PATTERN: EXPANDED

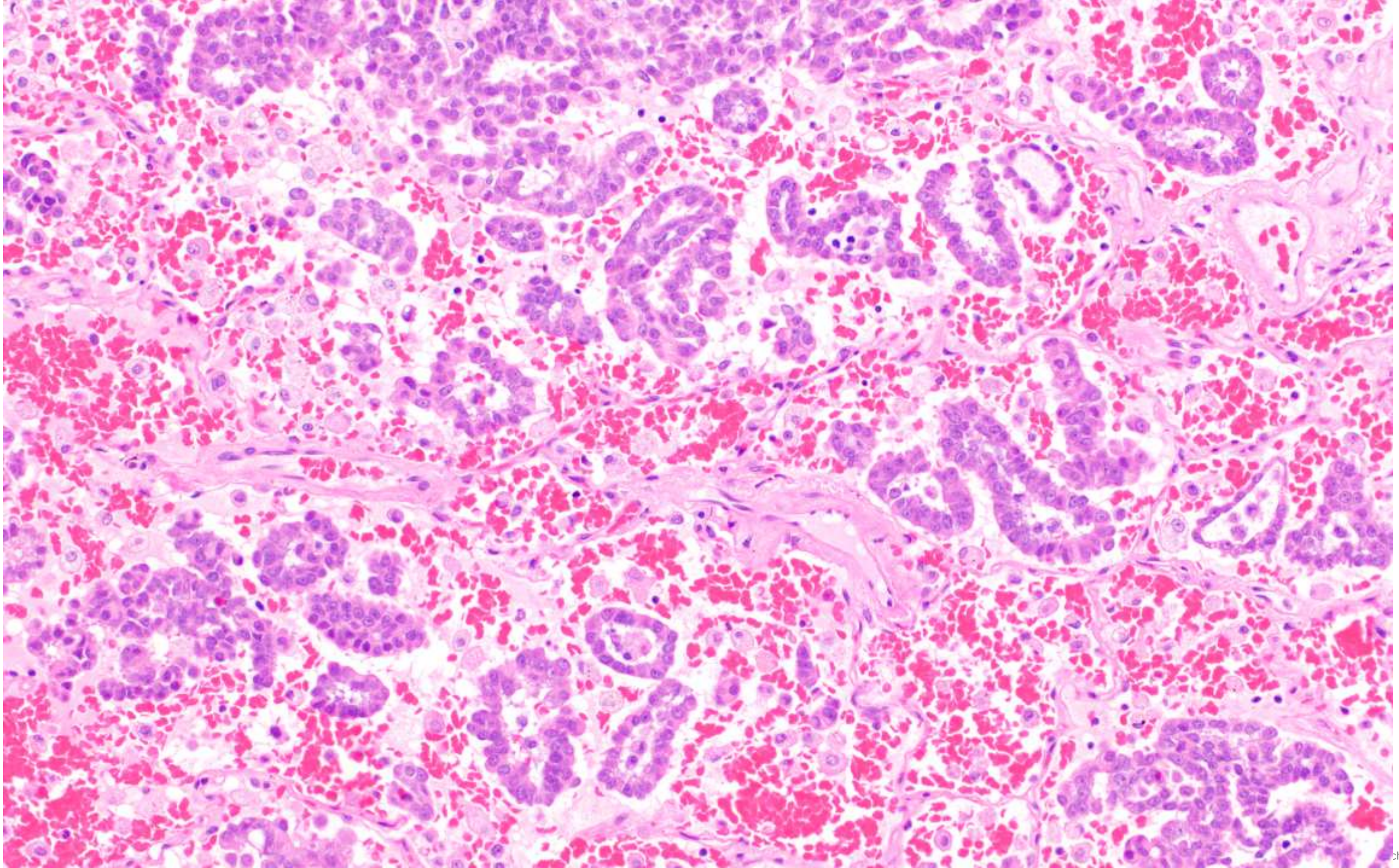
- Classical/Floret
- Filigree
  - Delicate lace-like narrow stacks
  - At least 3 nuclei piled outwards (avoids tangential cut issues)
  - No fibrovascular cores

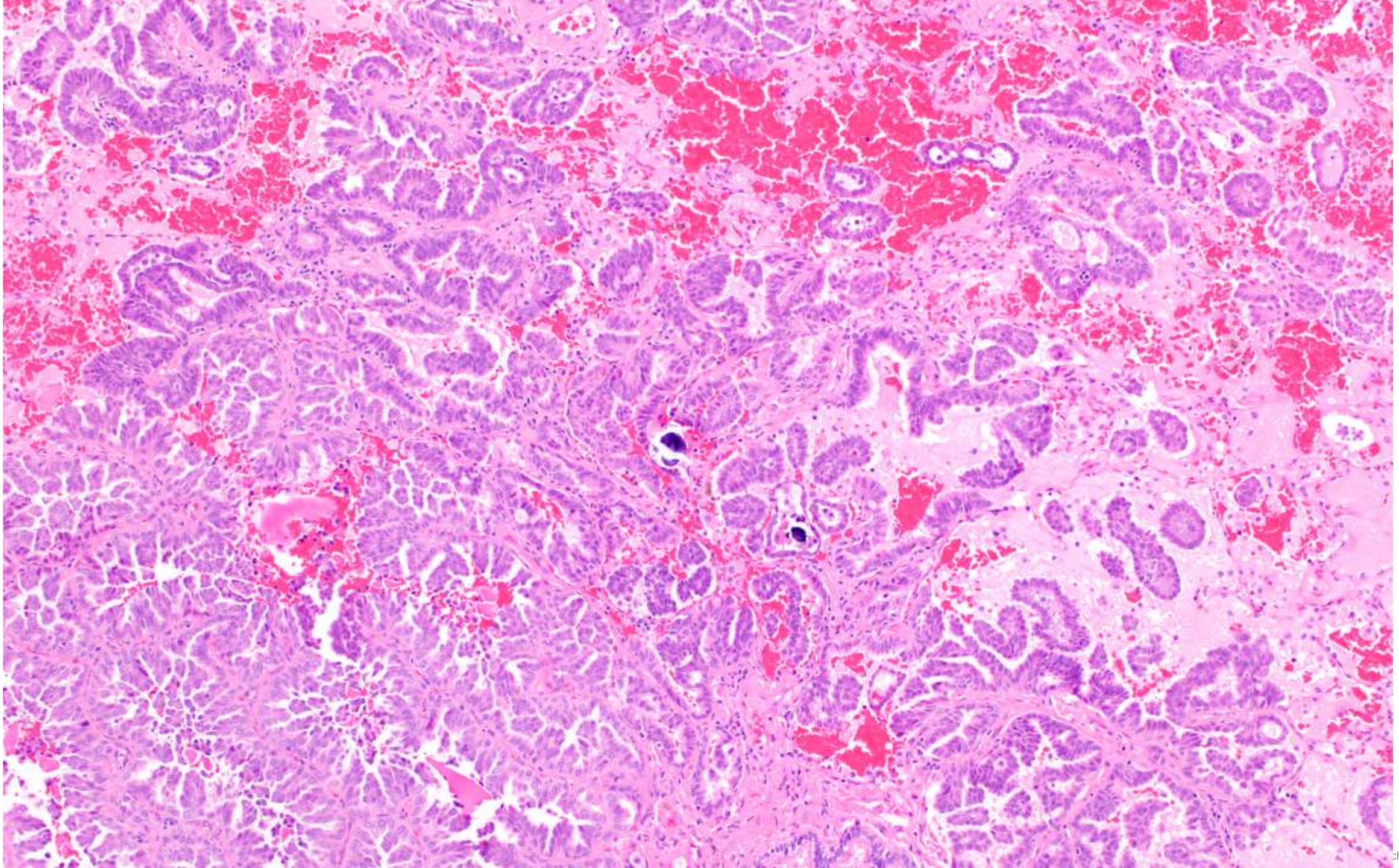
MICROPAPILLARY SPECTRUM

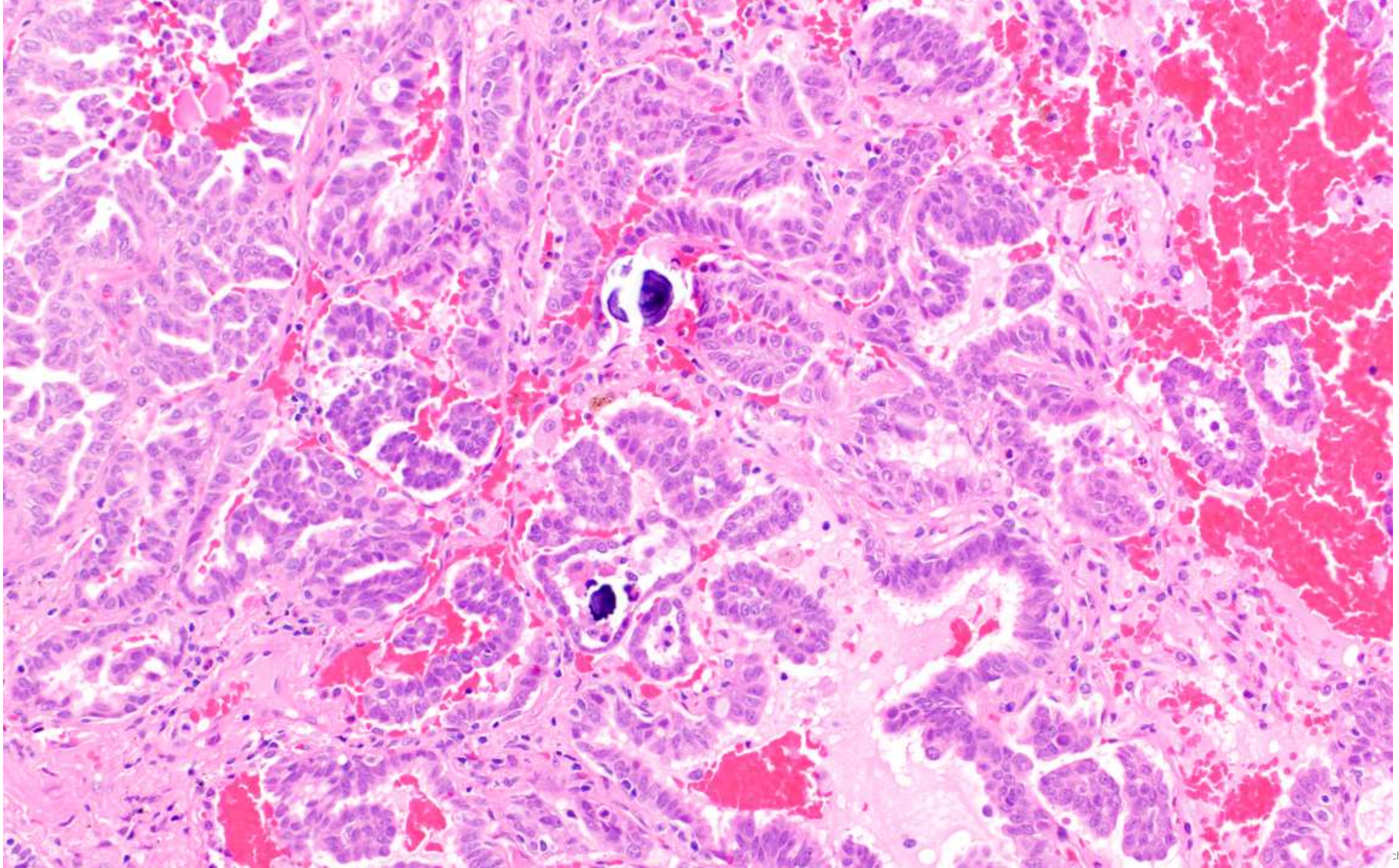
- Stromal pattern
  - Nests of micropapillary cells infiltrating in the stromal
- Airspace MP in acinar/papillary
  - Default should be MP
- Rings
- Single cells
- Psammoma bodies not uncommon (might be clue that MP is overlooked)

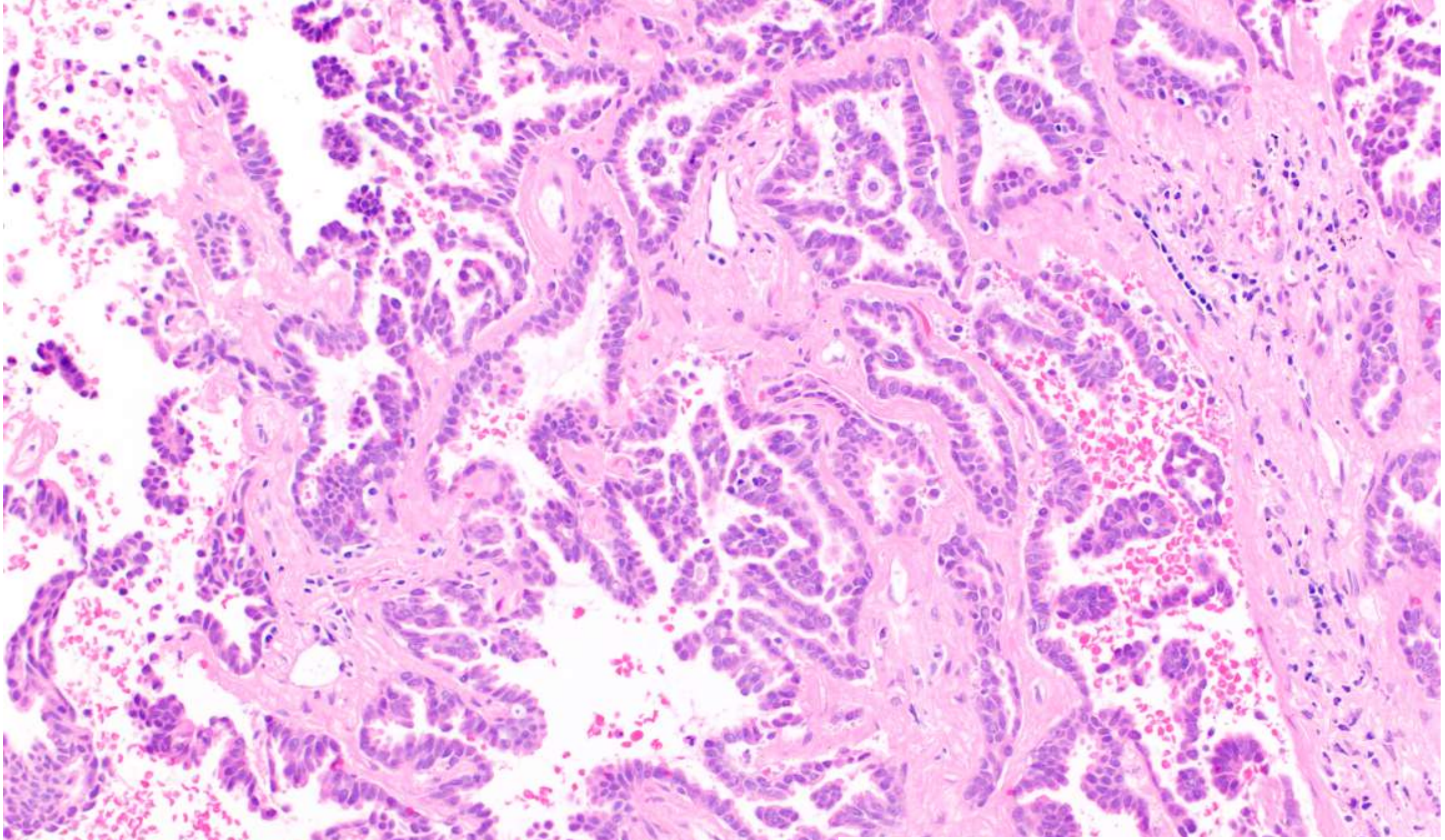




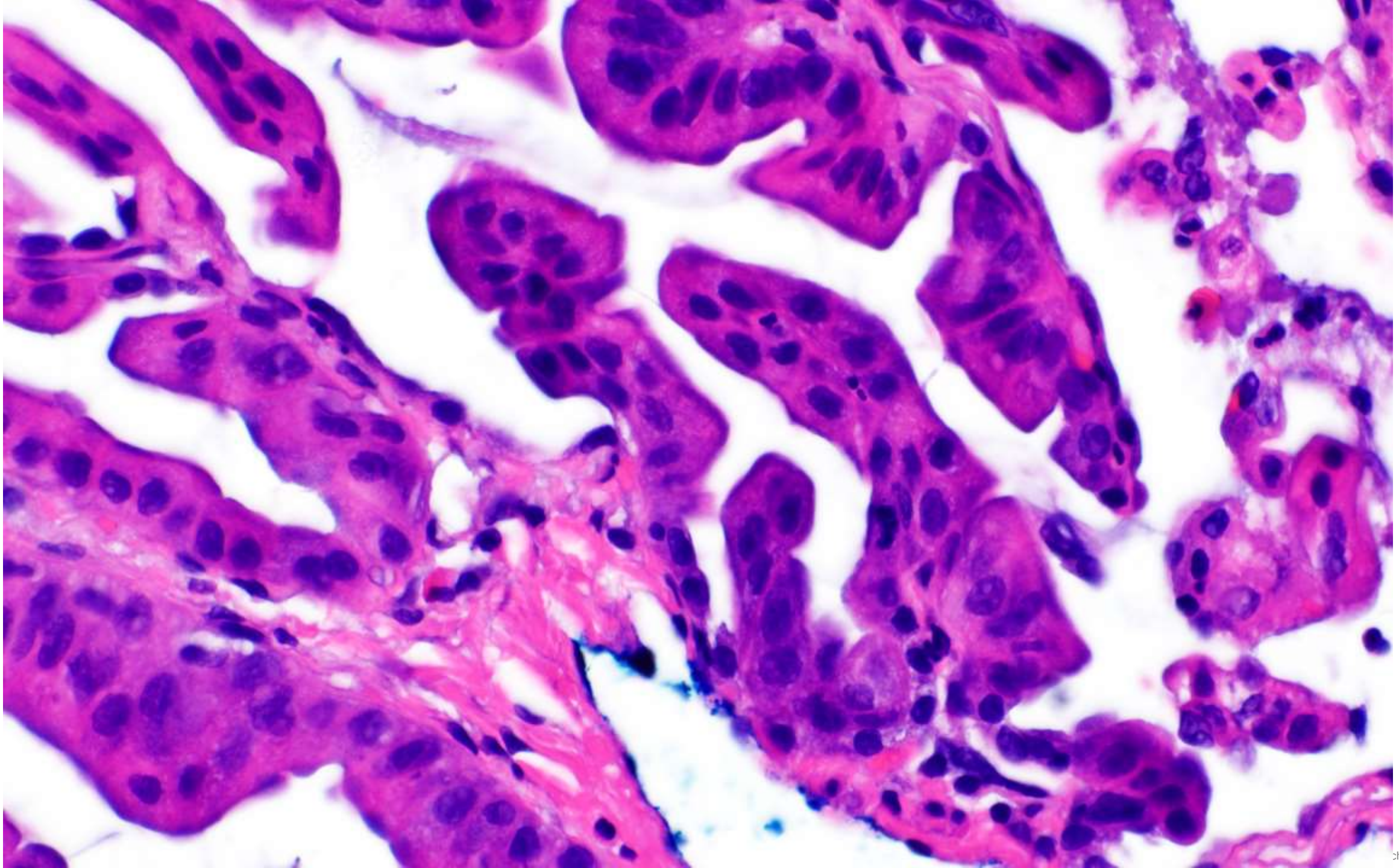


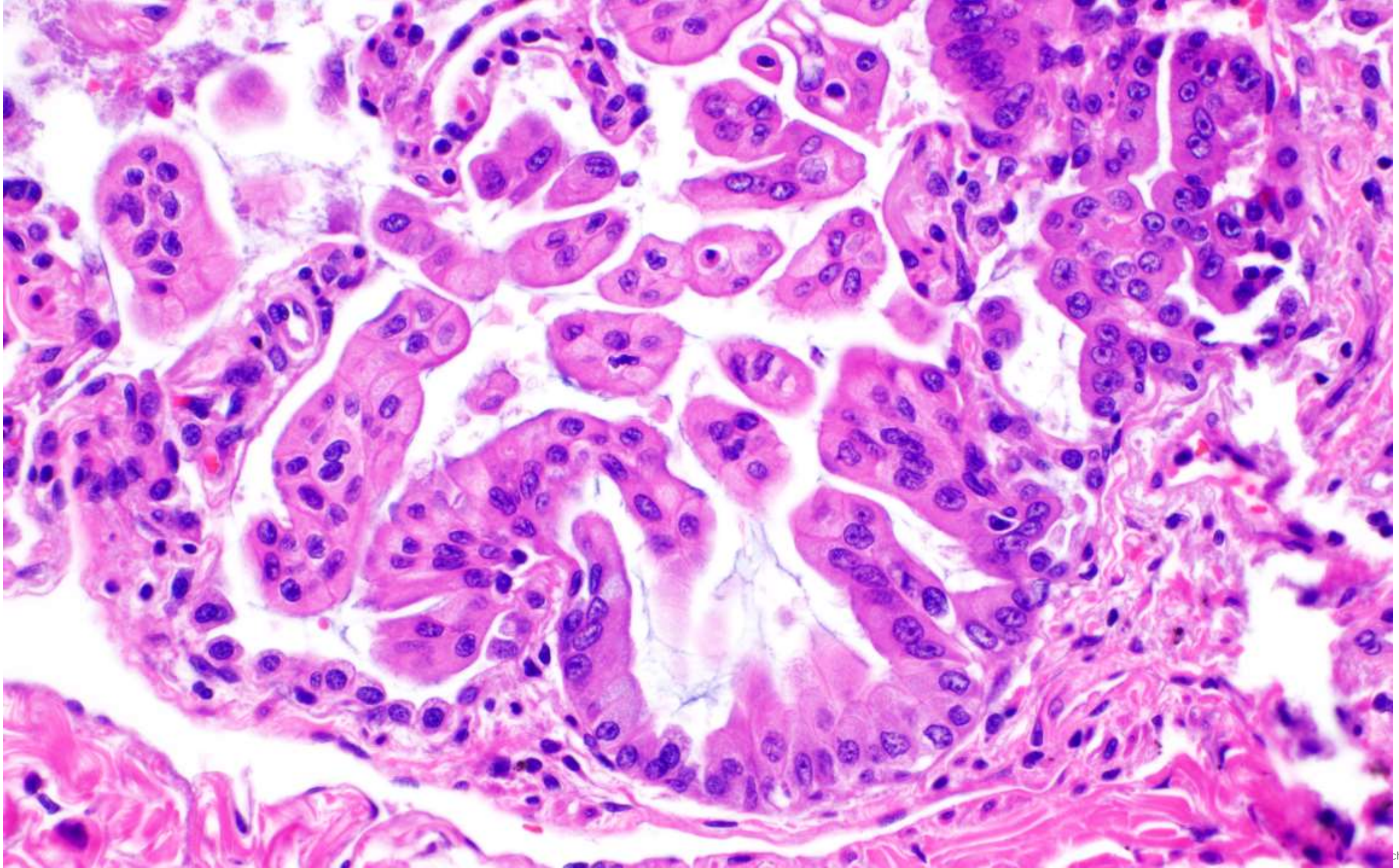


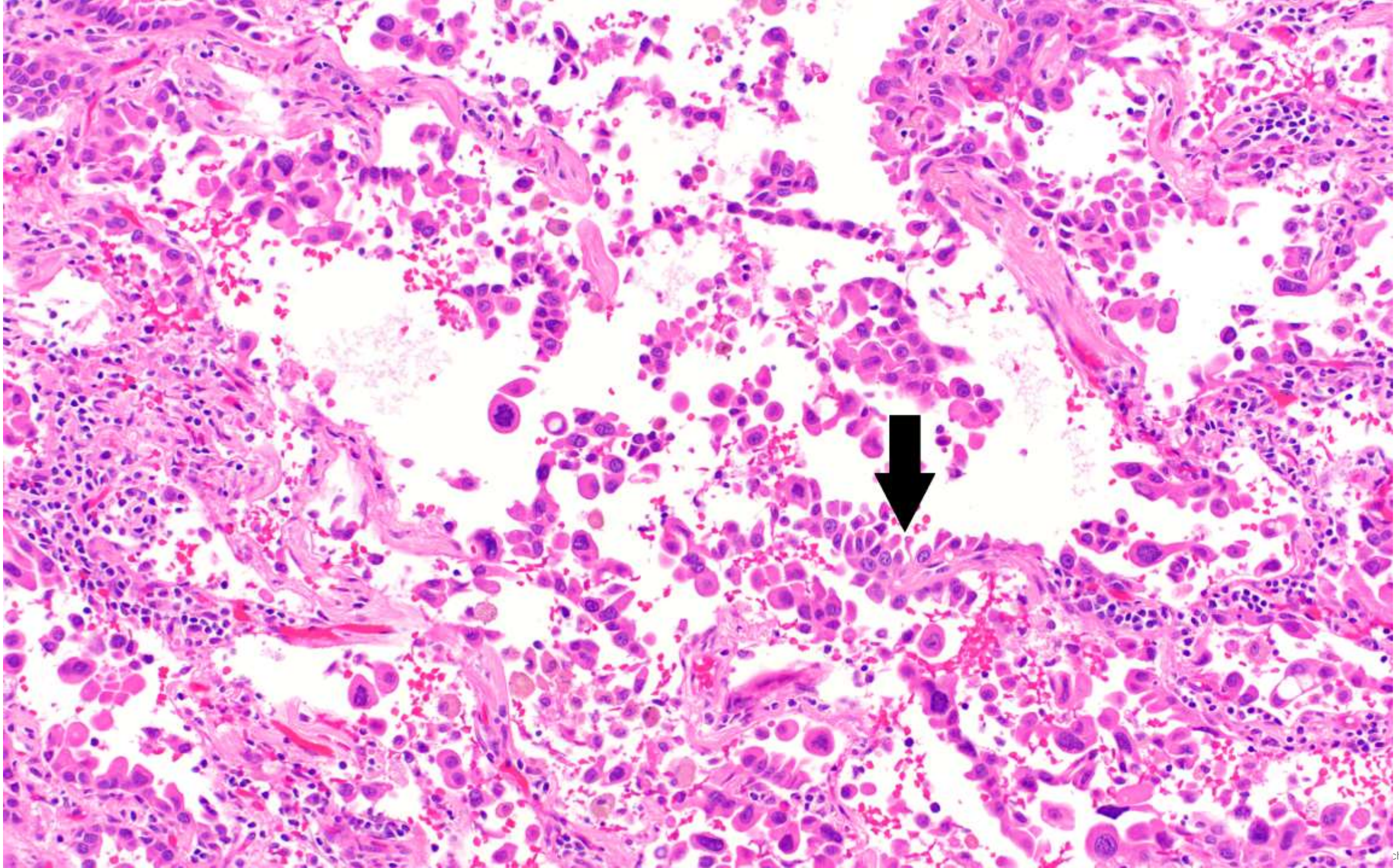


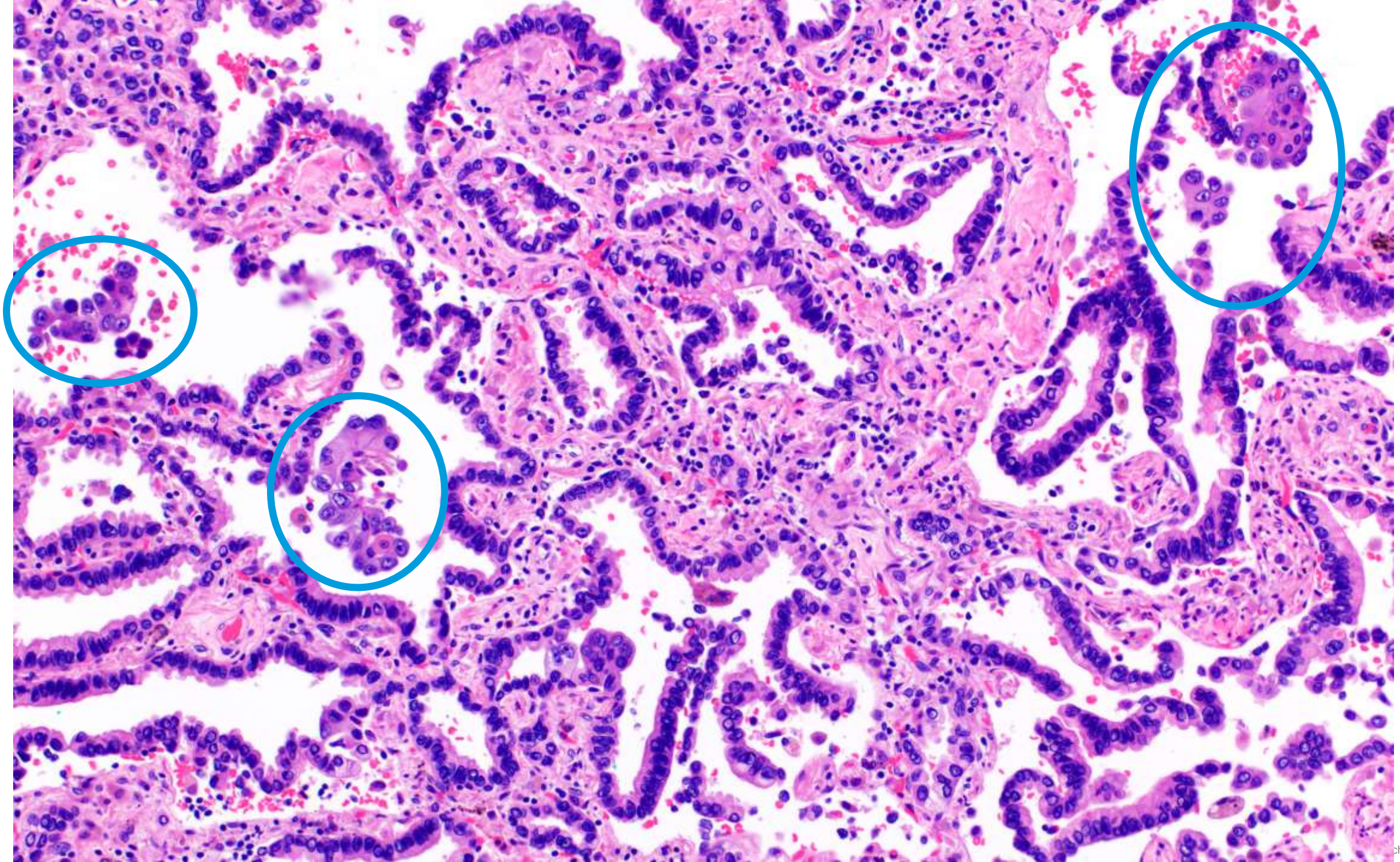


Sneaky micropapillary filigree pattern



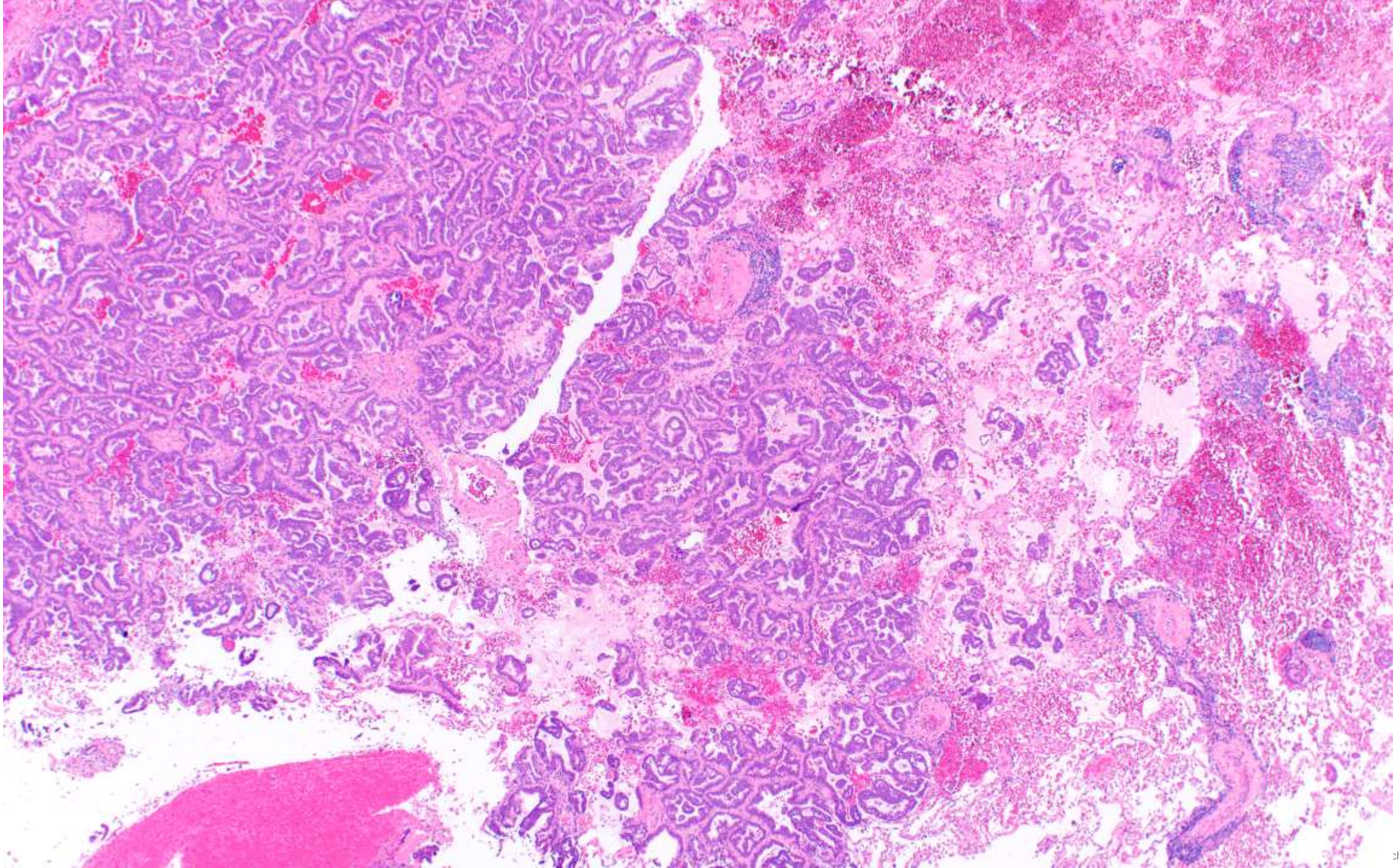


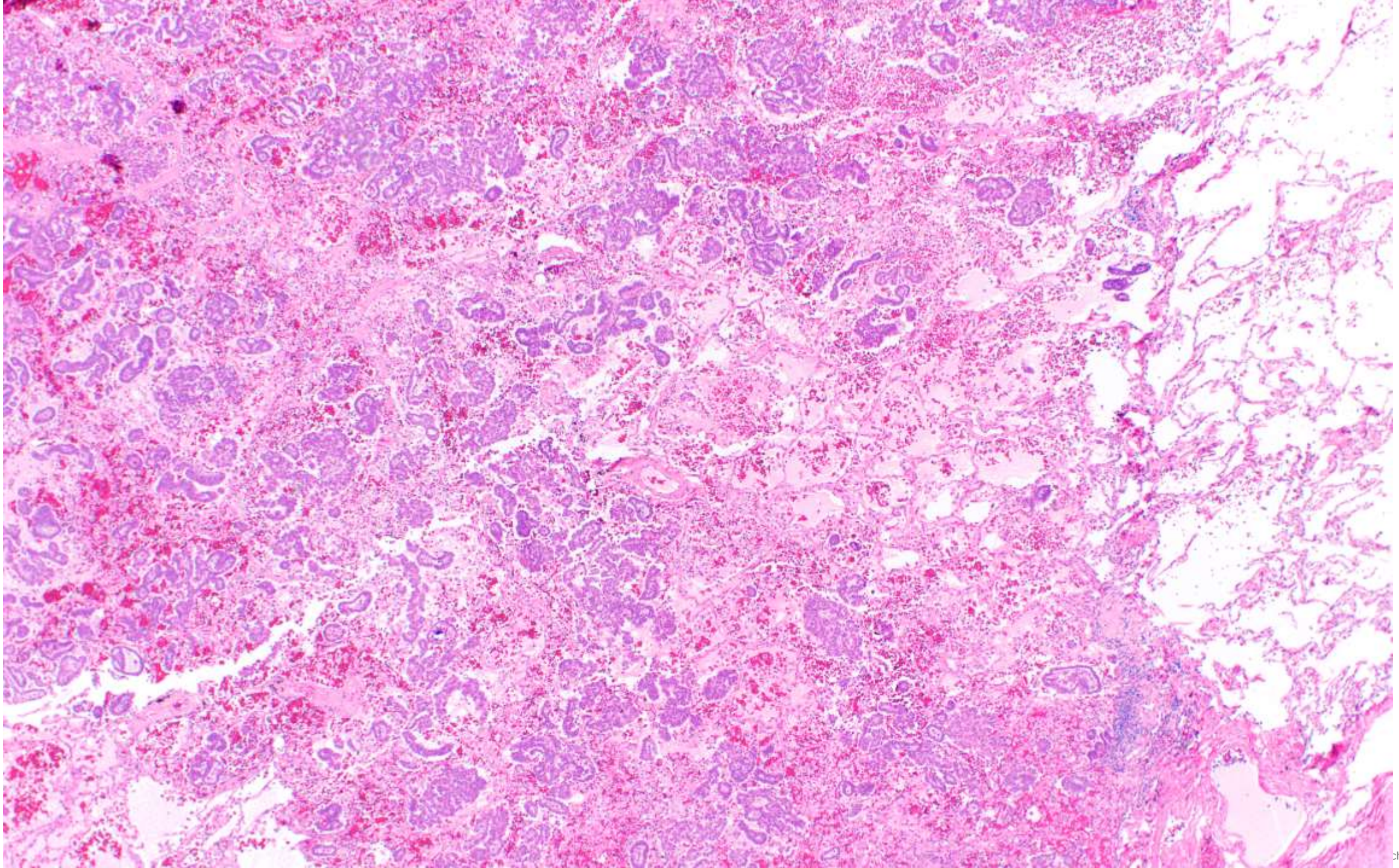


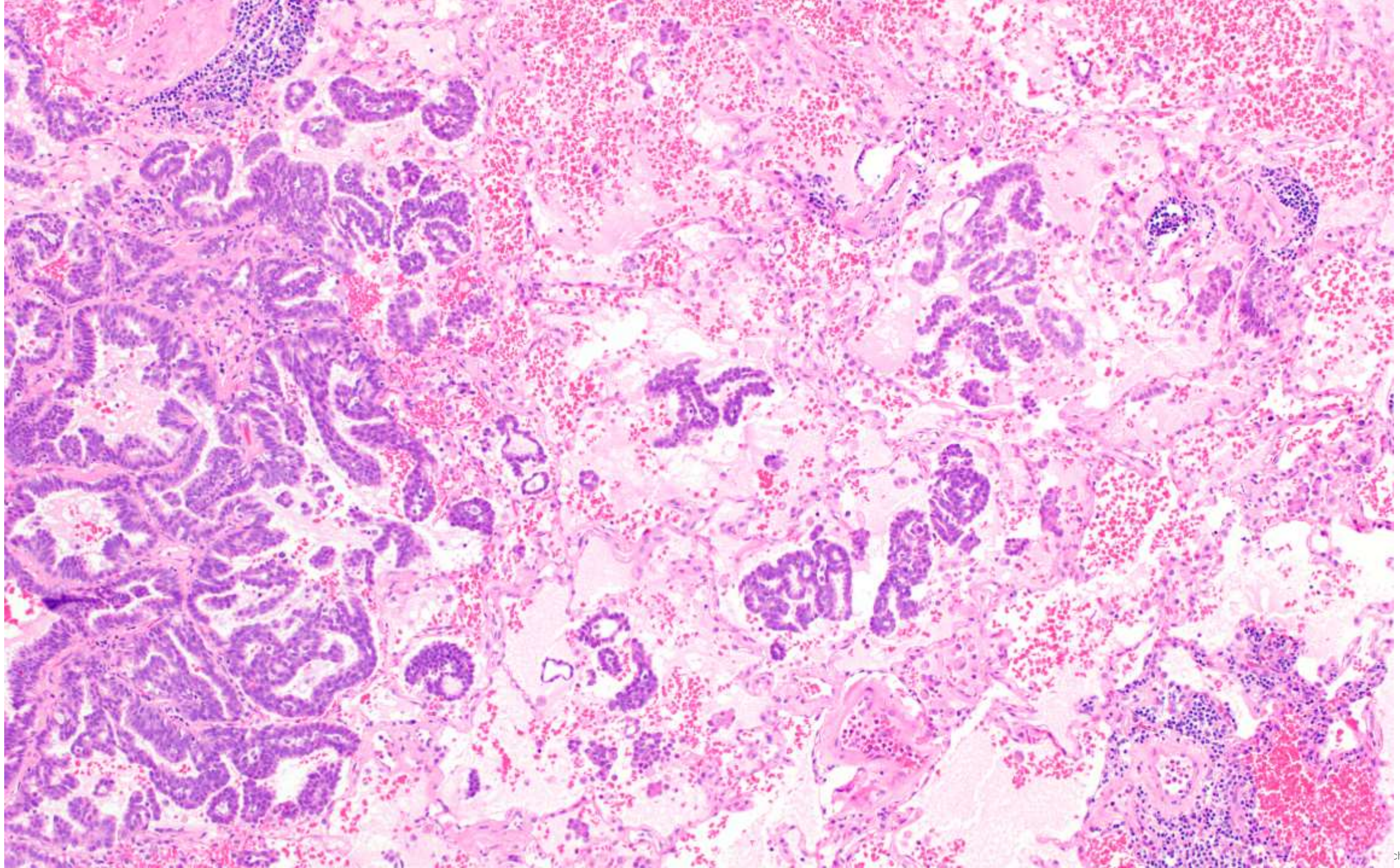


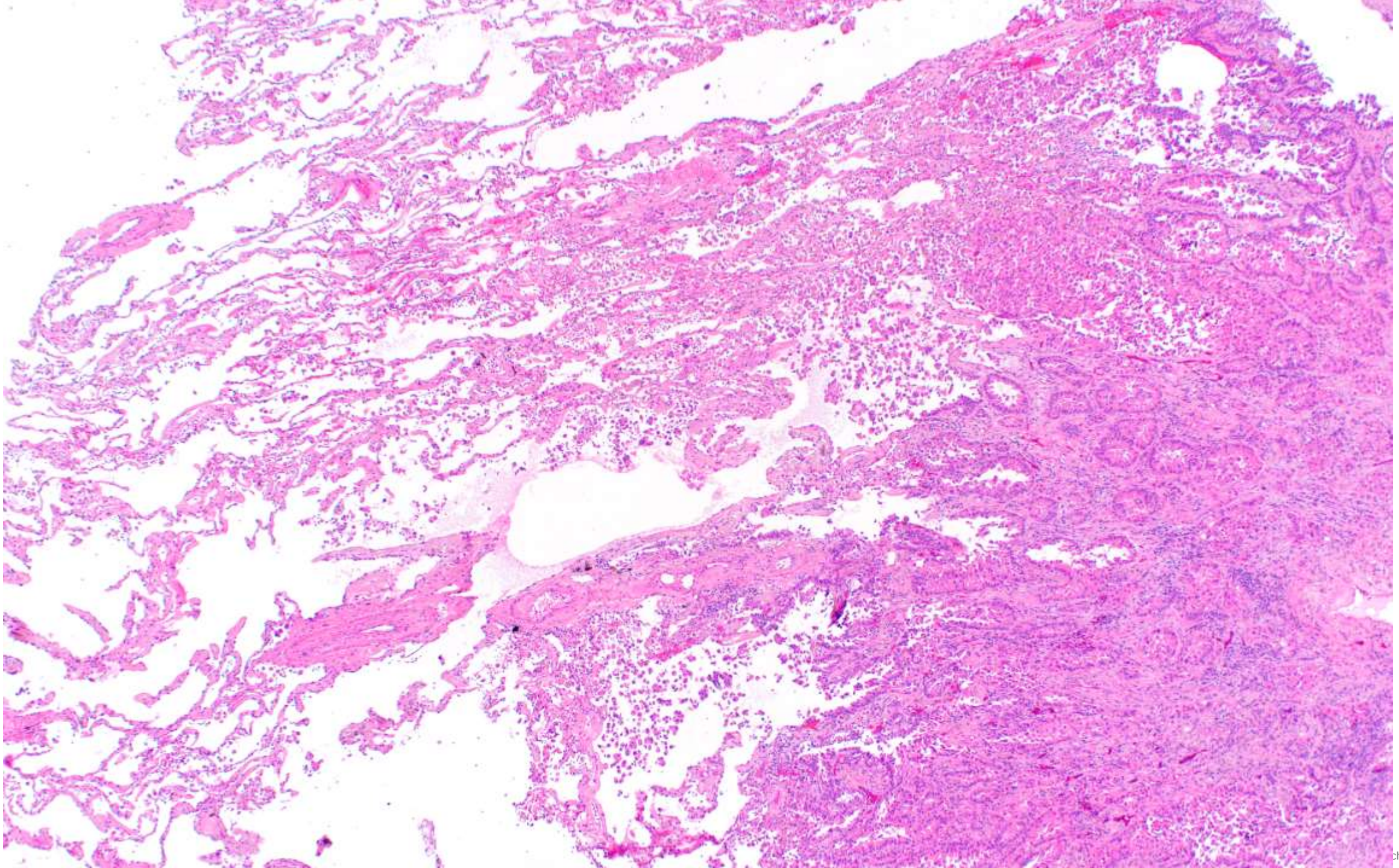
STAS (SPREAD THROUGH AIR SPACES)

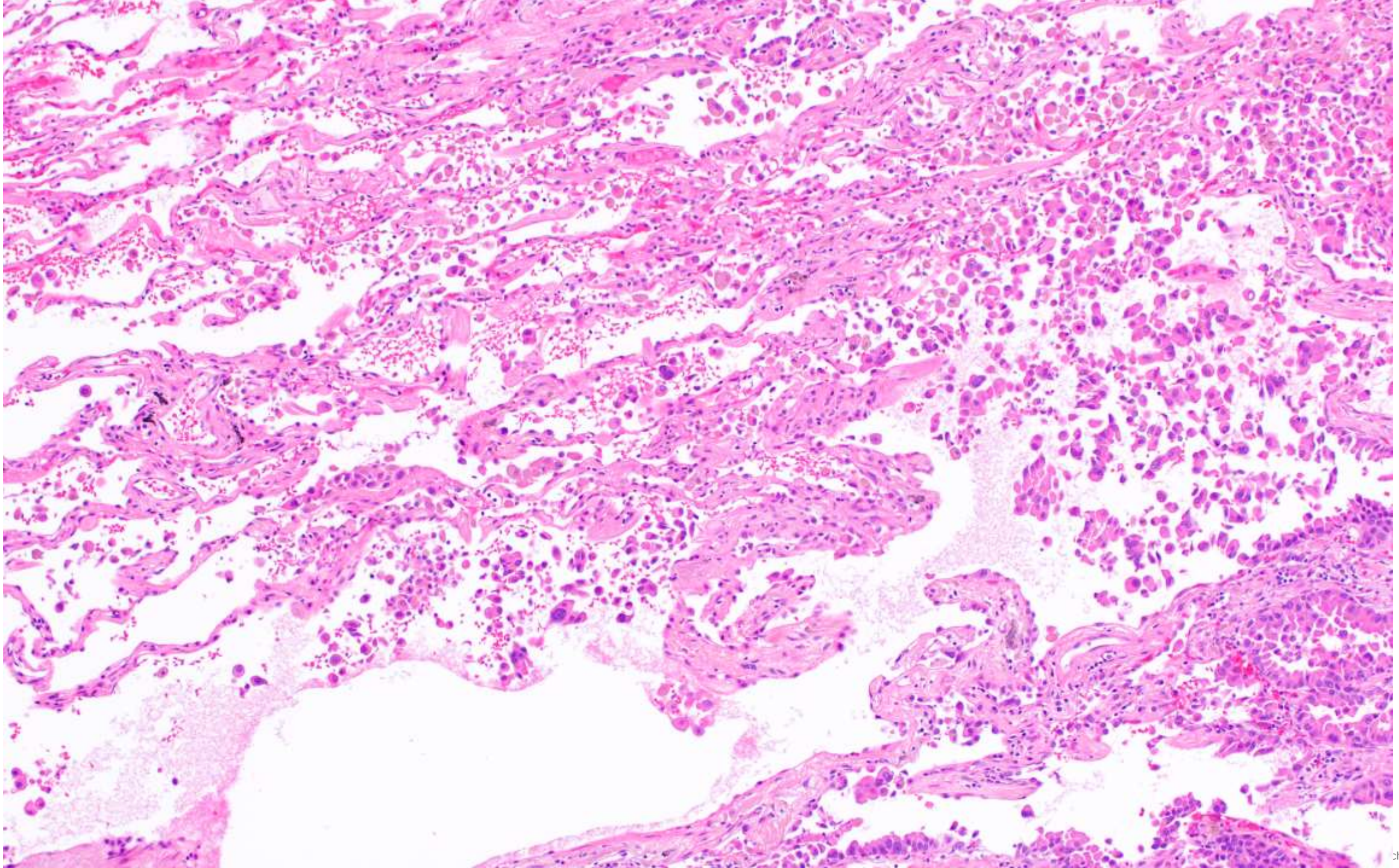
- Manifestation of tumor spread (*not* included in tumor size)
- Tumor cells within airspaces in the lung parenchyma beyond the edge of the main tumor
- Predictor of worse clinical outcome, especially in limited resections







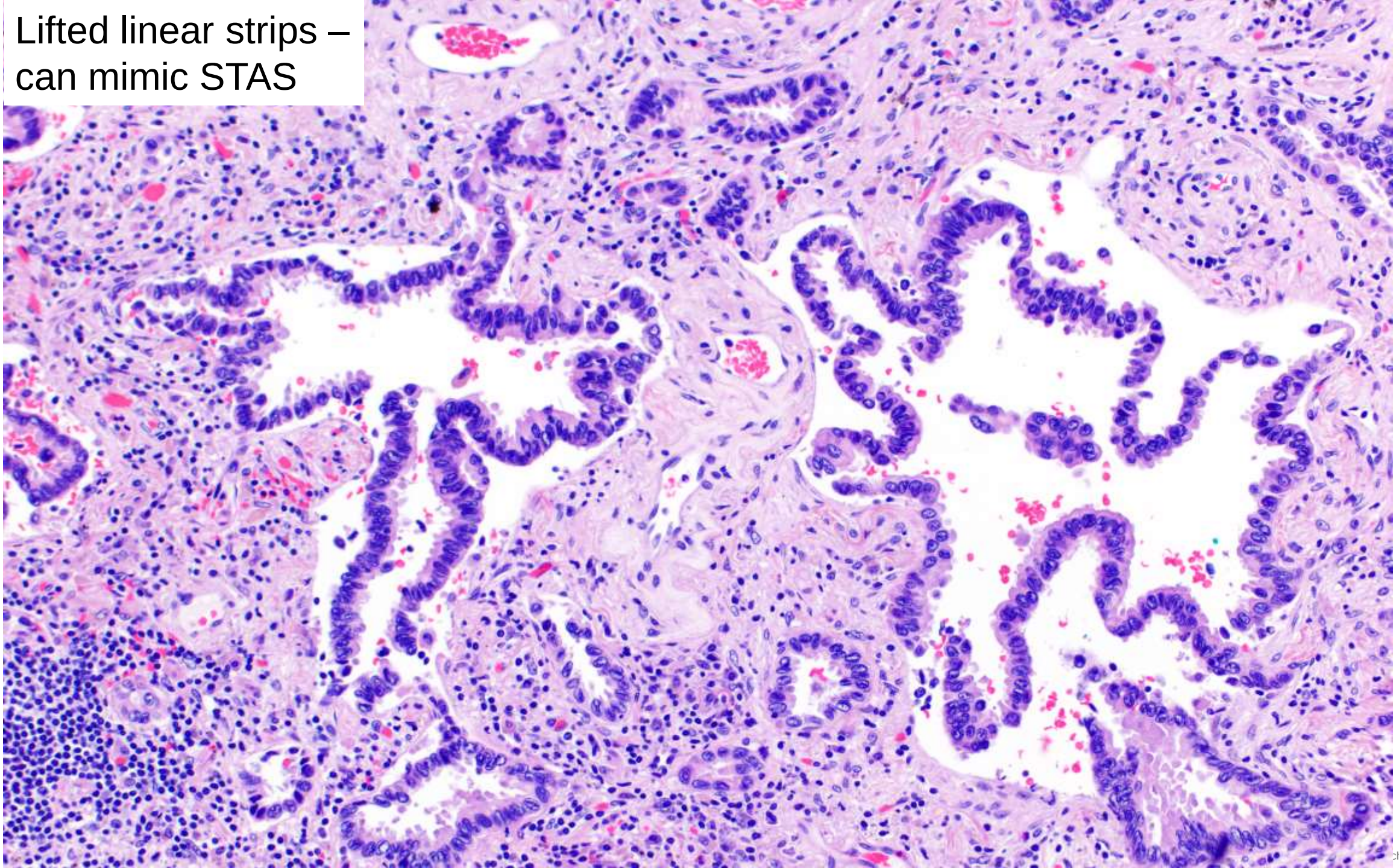


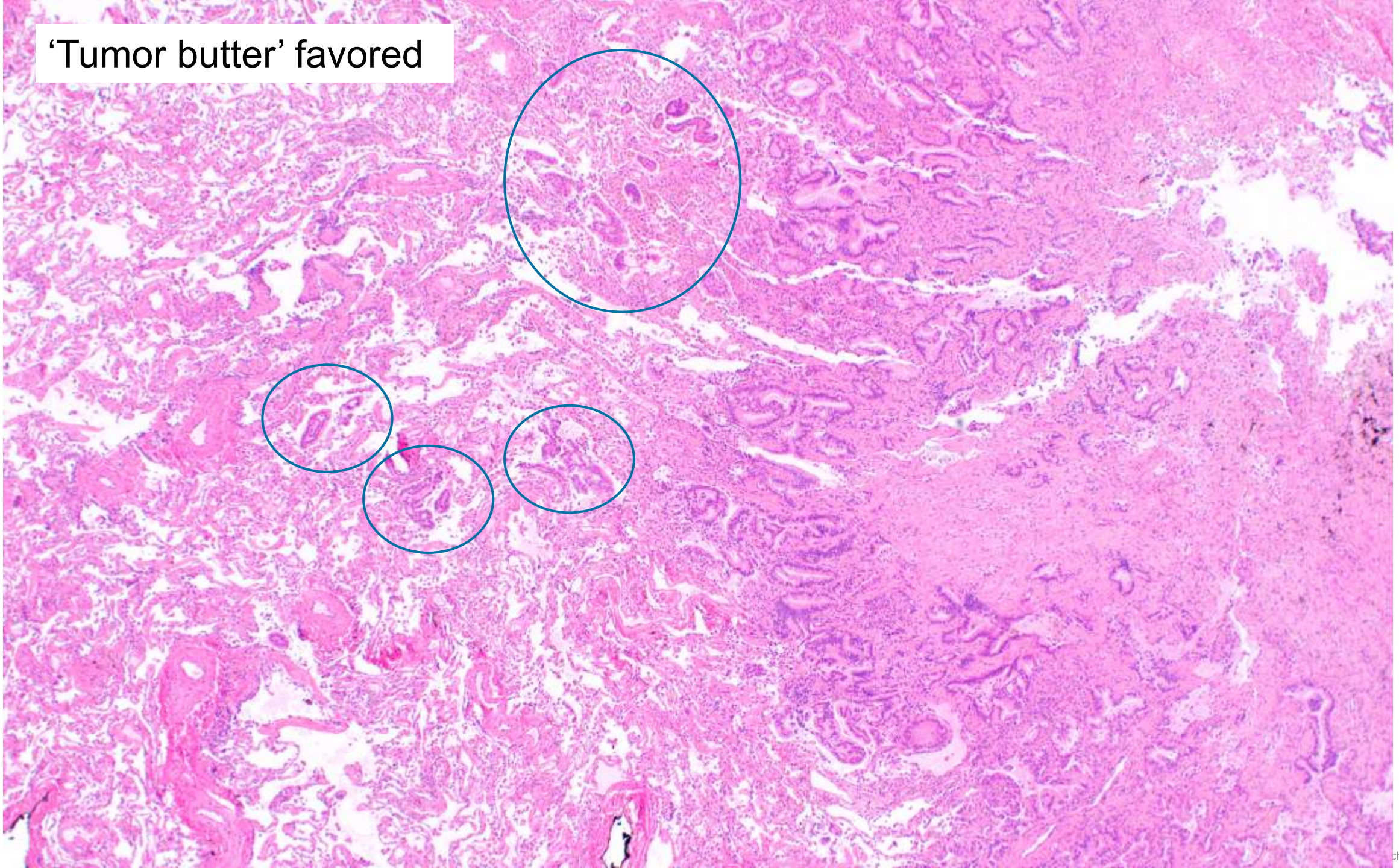


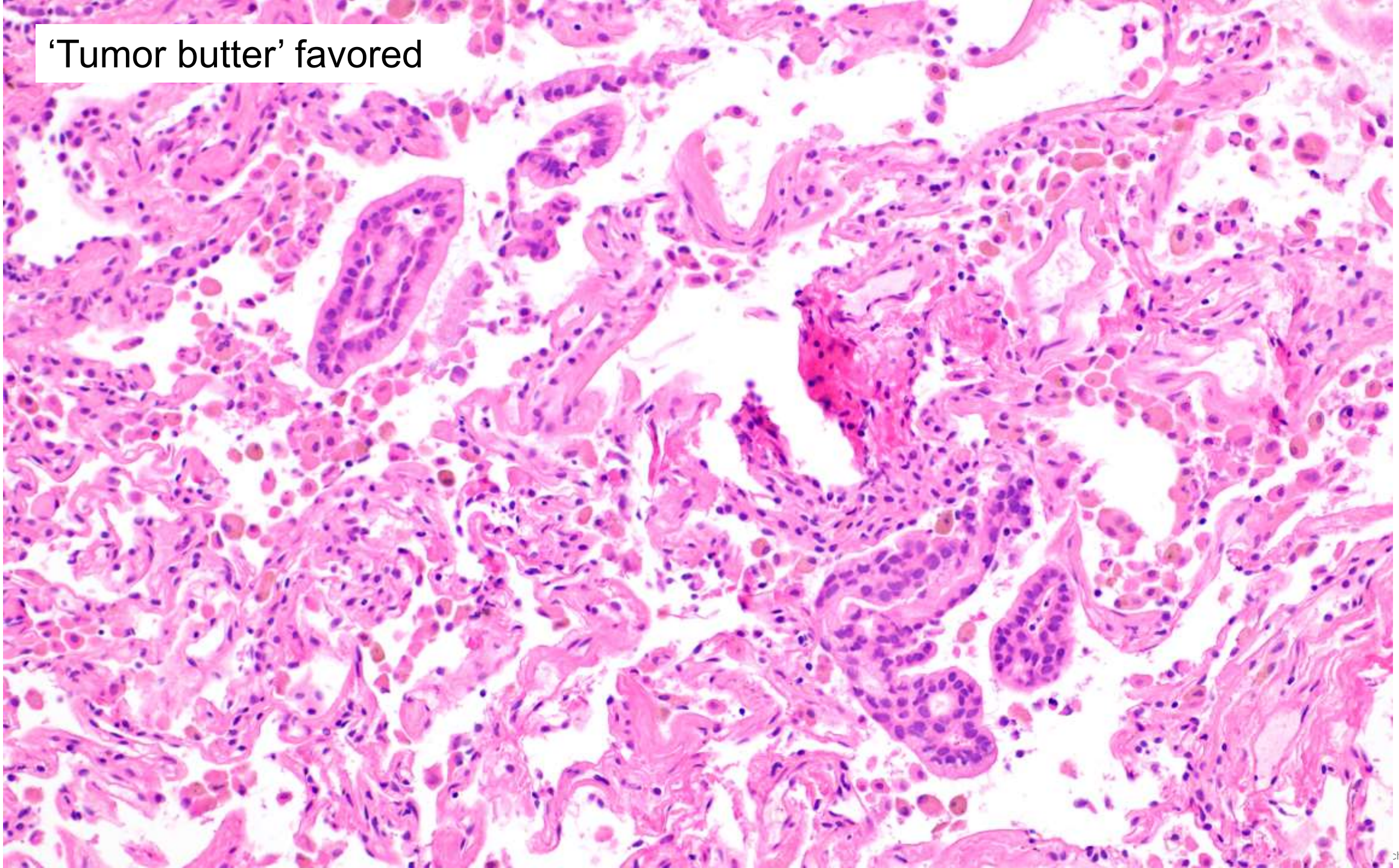
STAS - CAVEATS

- Not recommended to report amount/size or distance of STAS from main tumor
- Artifacts
  - ‘Tumor butter’
  - Lifted linear strips of tumor
  - Lack of continuous spread from tumor to edge – clue to an artifact

Lifted linear strips – can mimic STAS




‘Tumor butter’ favored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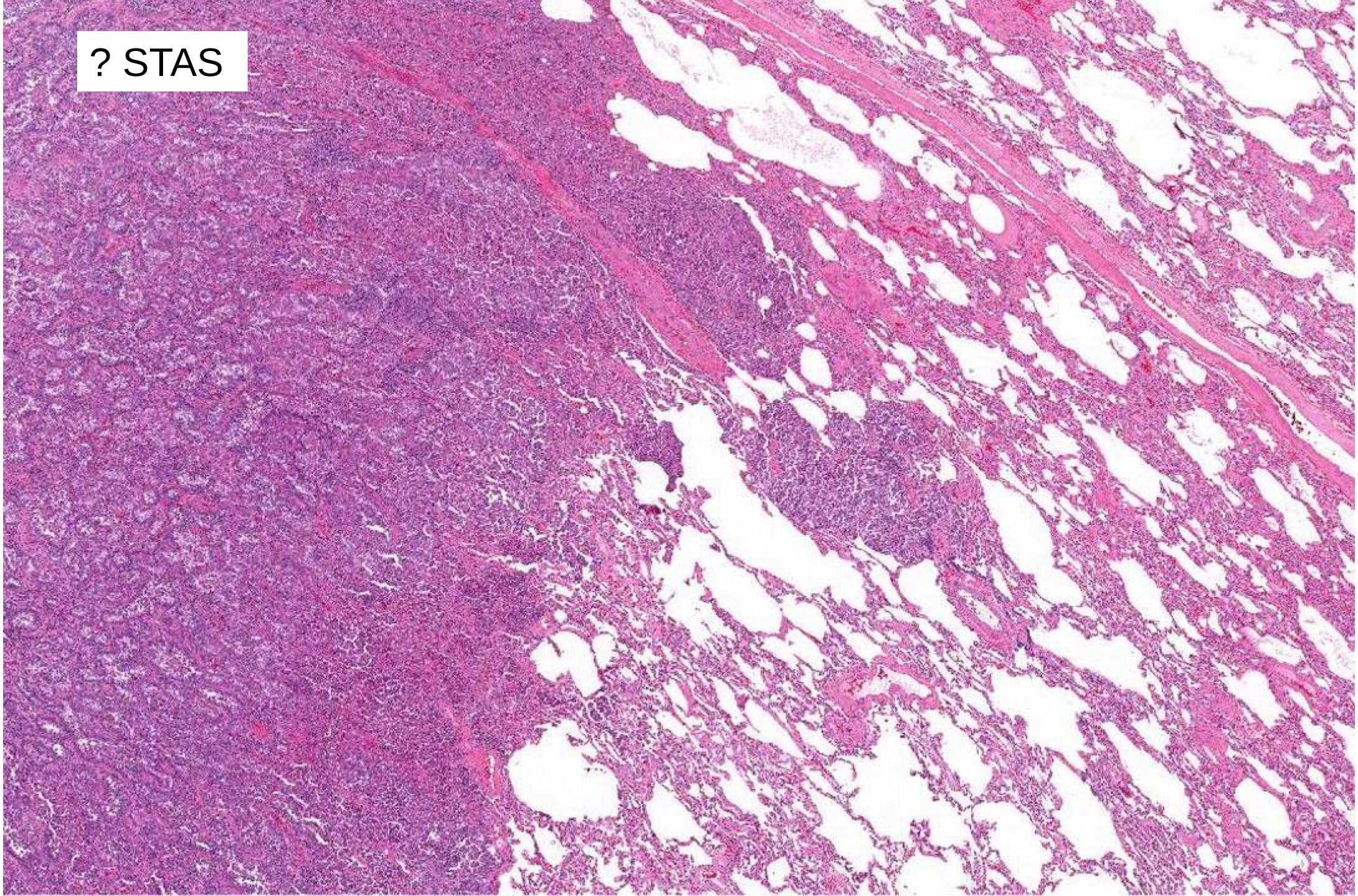
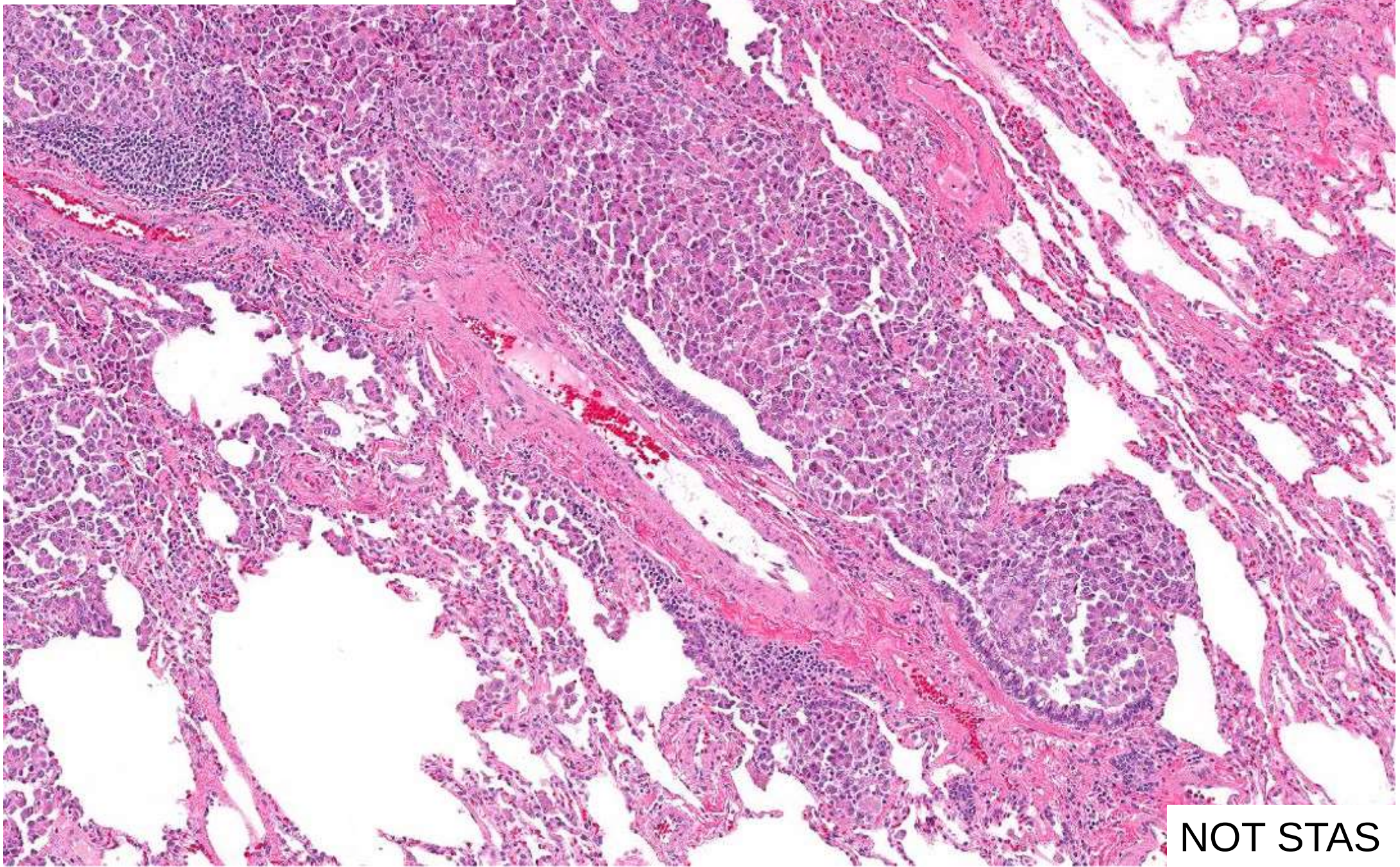

? STAS

Deeper levels – connects!



NOT STAS

NEUROENDOCRINE LESIONS

- Neuroendocrine tumors (NET)
  - Carcinoid tumor, NOS – for small bx, metastases or limited sampling
  - Typical Carcinoid/NET, Grade 1 (<2 mitoses per 2 mm^2)
  - Atypical Carcinoid/NET, Grade 2 (2-10 mitoses per 2 mm^2)
- Neuroendocrine carcinomas
  - Small cell carcinoma
    - Combined small cell carcinoma
  - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma

CARCINOID TUMOR, NOS

In situations where the features are of a typical carcinoid

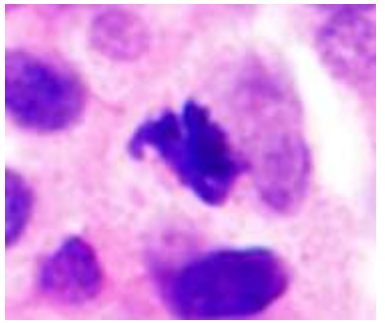
- Terminology used in 3 settings
  - Distinction between typical and atypical carcinoids
    - Report mitotic count
    - Report presence/absence of necrosis
    - Ki-67 (if available, not required, but is desirable)
  - Metastatic carcinoids
  - Situation where only limited slides from a case are available (consults, transfer of care)

KI-97

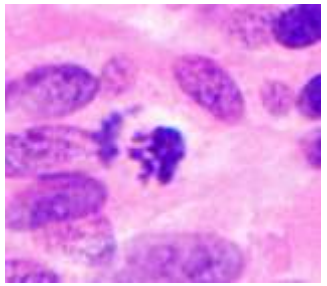
- Useful in carcinoids versus SCLC or LCNEC (small crushed biopsies)

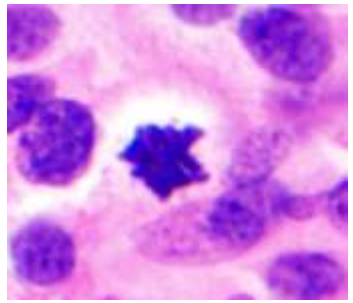
- Carcinoids and small cell ca and Large NECA are genetically different (not new, but important to recall)

COUNTING MITOSES



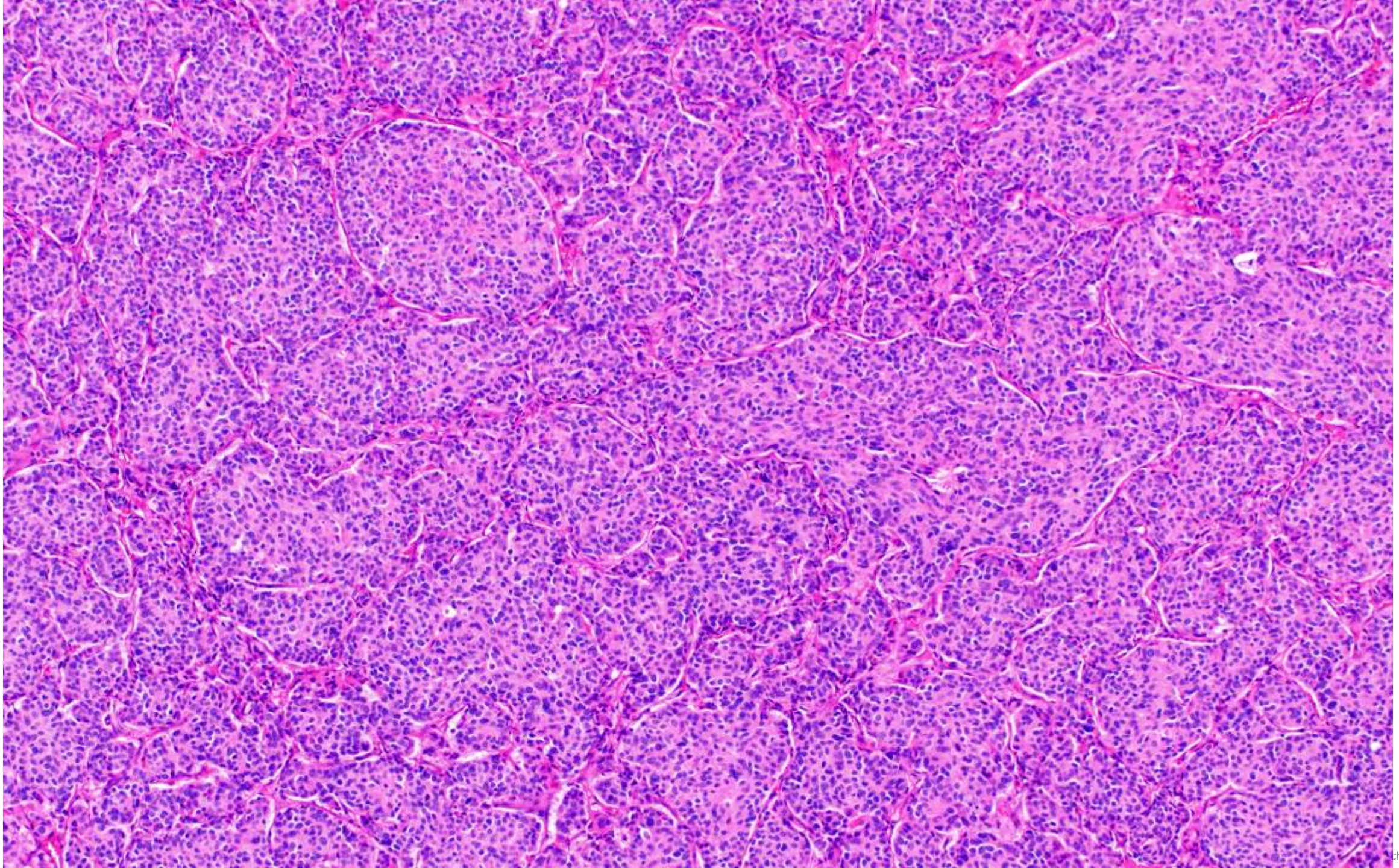
- Count in areas of highest mitotic activity and the highest concentration of viable tumor cells (Ki-67 can be useful here in resection cases)
- 2 mm^2 (not 10 HPF)
- If near the cutoff, count at least 3 sets of 2 mm^2 and the mean used RATHER than the single highest rate
- Only definitive mitoses should be counted

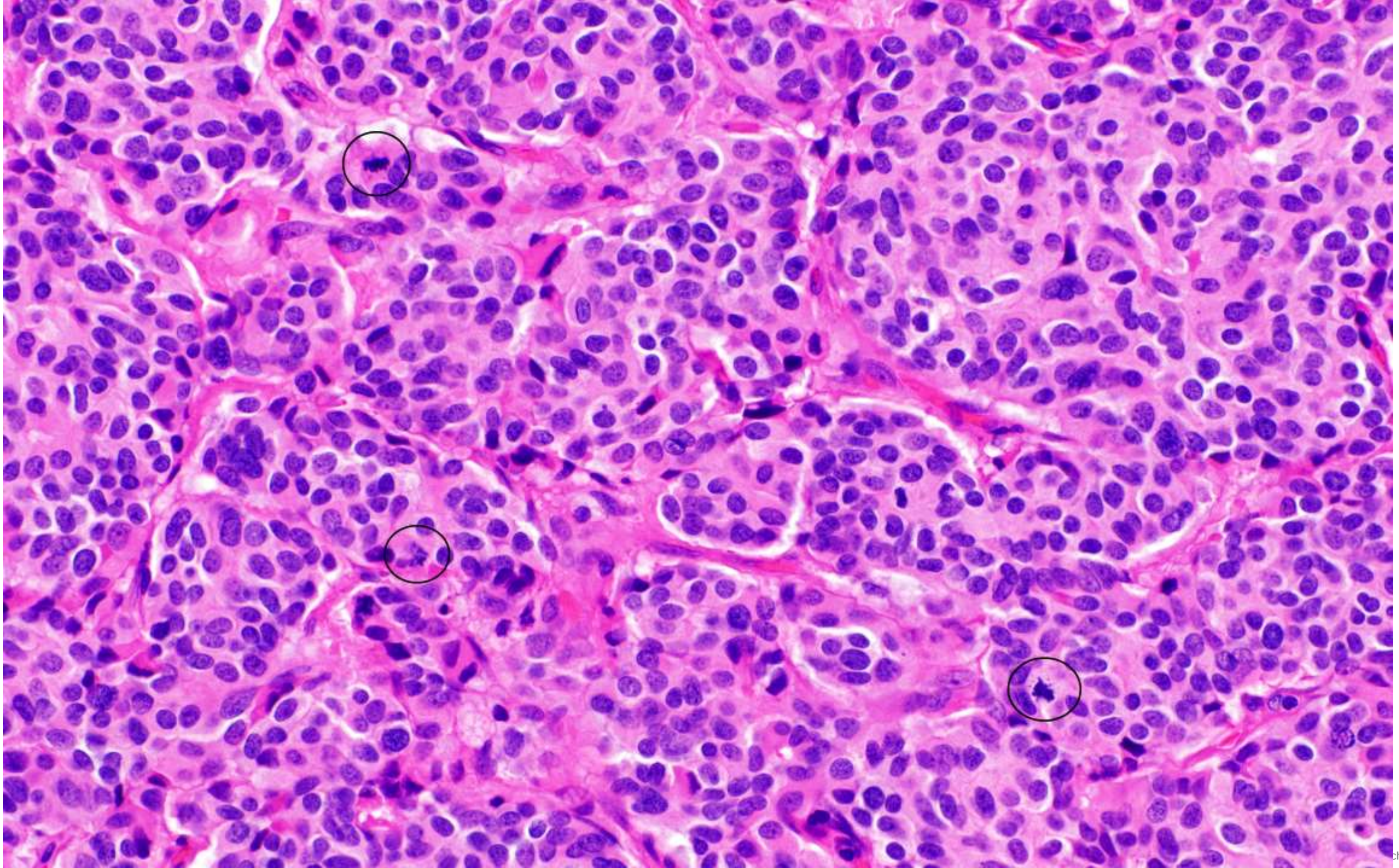


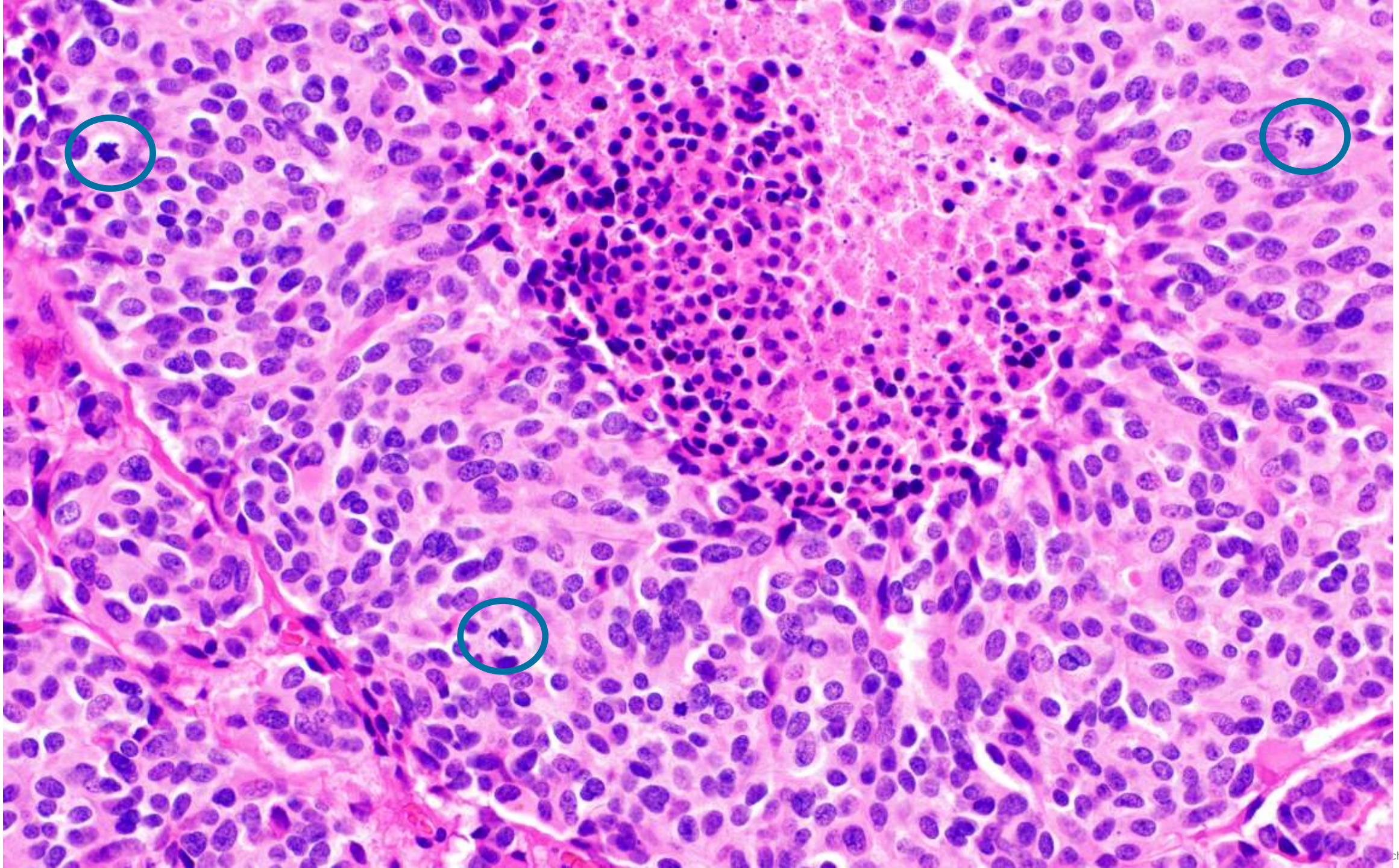


CARCINOID TUMORS WITH ELEVATED MITOTIC COUNTS

- Still not formally recognized in WHO (rare)
- Generally, correspond to the Grade 3 NET of the pancreas (PanNET) – felt to have insufficient data to add to the lung WHO
- 2021: Suggest that these have carcinoid features







NEW GRADING CRITERIA

- Epithelioid mesothelioma
  - Low-grade
  - High-grade
  - Favorable/unfavorable architectural patterns, cytologic features, and stromal features

GRADING OF PLEURAL EPITHELIOID MALIGNANT MESOTHELIOMA

- **Nuclear atypia score**
  - 1 (mild)
  - 2 (moderate)
  - 3 (severe)
- **Mitotic count**
  - 1 (low, ≤ 1 per 2mm^2)
  - 2 (intermediate, 2-4 per 2mm^2)
  - 3 (high, 5+ per 2mm^2)
- **SUM of above**
  - 2 or 3 = nuclear grade I
  - 4 or 5 = nuclear grade II
  - 6 = nuclear grade III
- **Necrosis**: present/absent

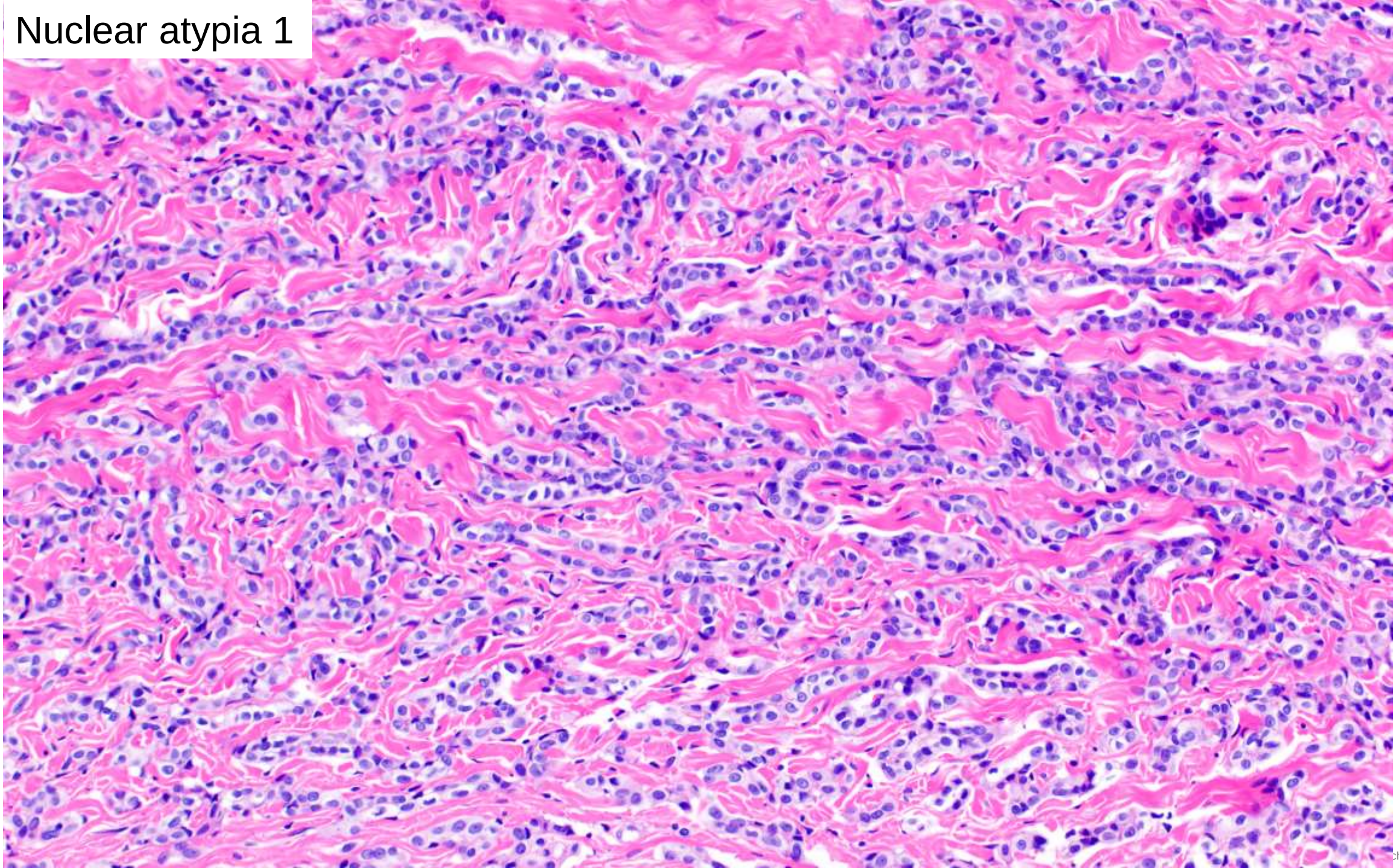
- **Low-grade** = Nuclear grade I and II without necrosis
- **High-grade** = Nuclear grade II with necrosis, Nuclear grade II with or without necrosis

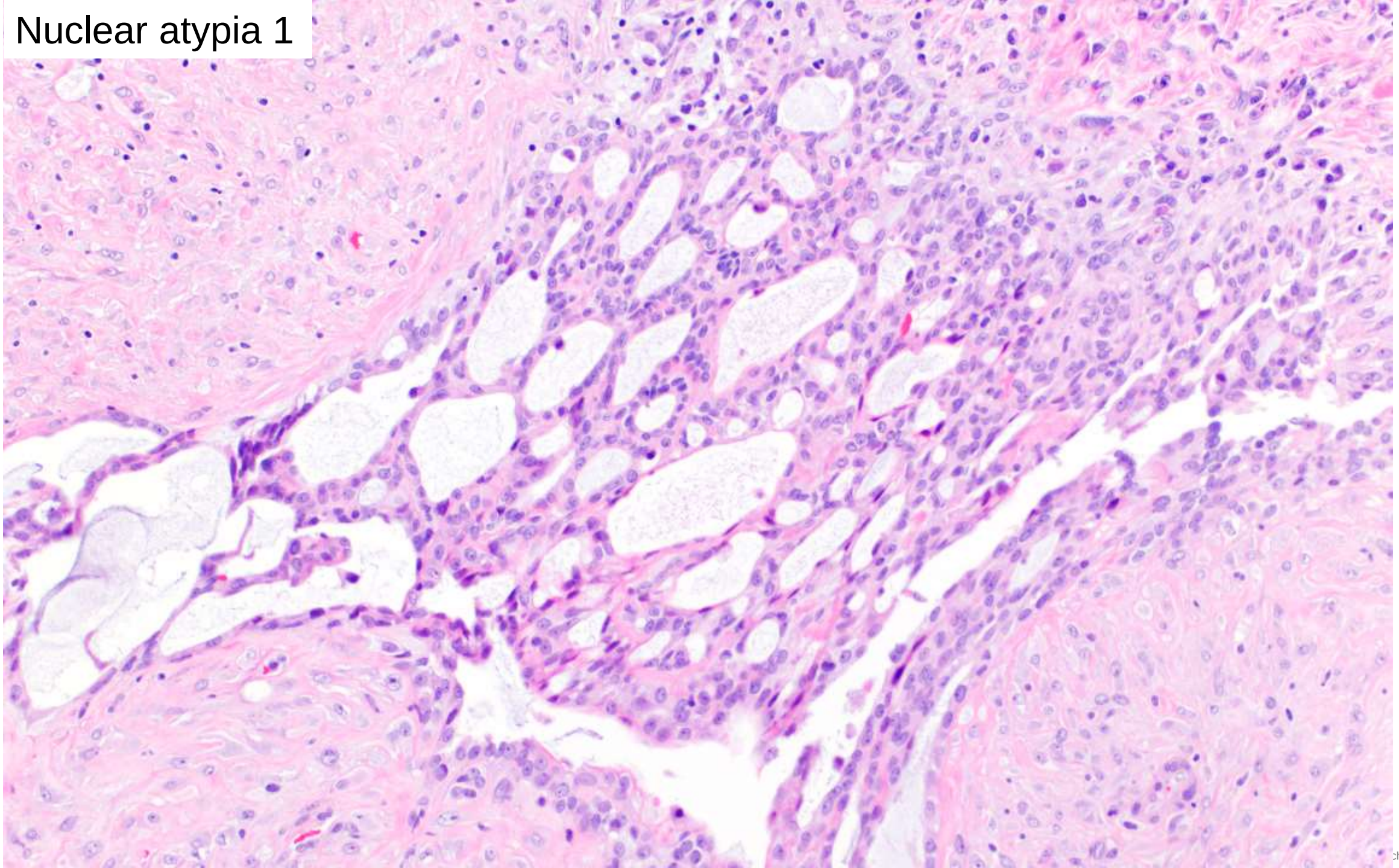
HISTOLOGIC CLASSIFICATION

- Unfavorable architectural patterns
  - Solid (≥ 50%)
  - Micropapillary
- Unfavorable cytologic features
  - Rhabdoid
  - Pleomorphic
  - Severe nuclear atypia

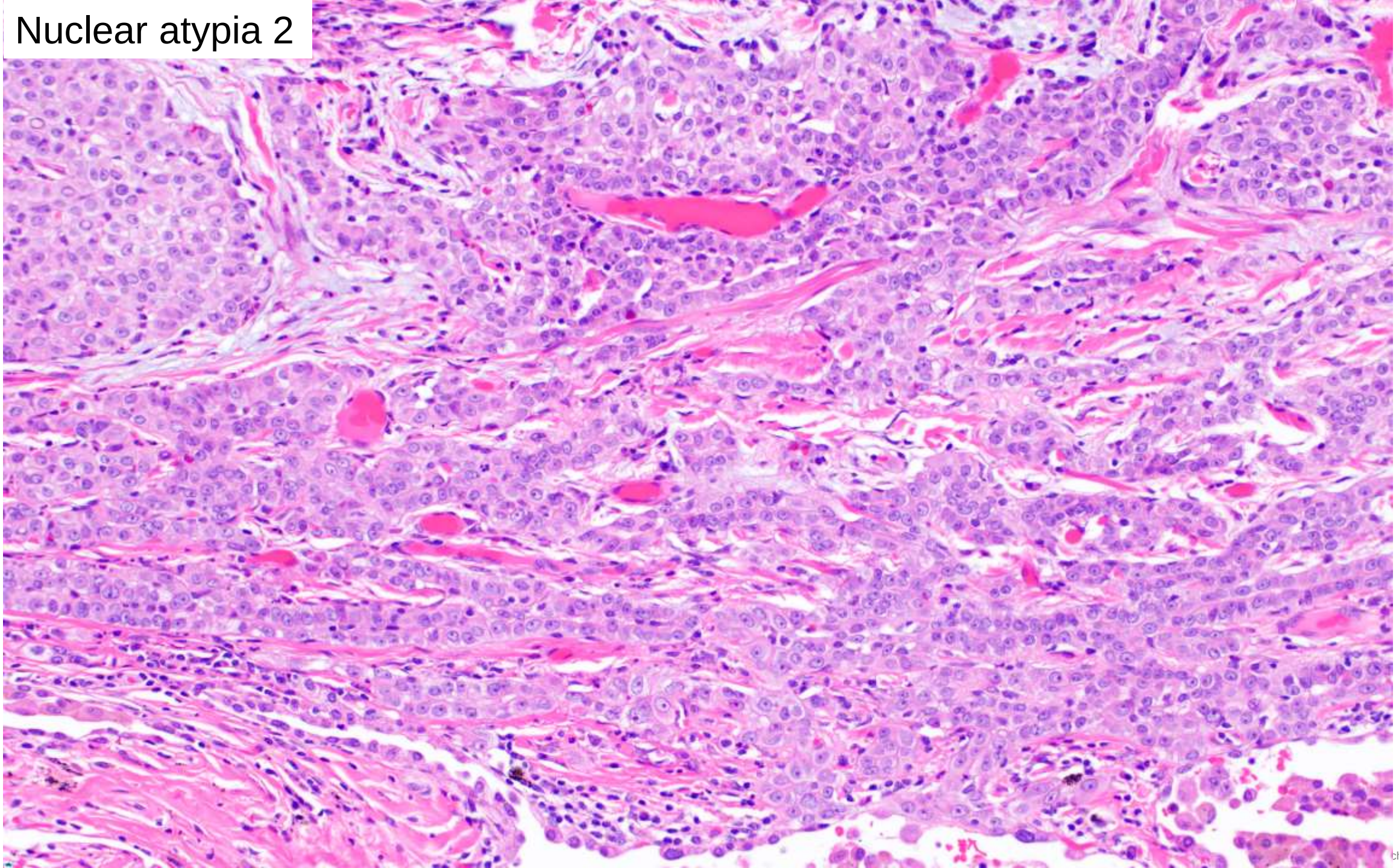
HISTOLOGIC CLASSIFICATION

- Favorable architectural patterns
  - Tubulopapillary
  - Trabecular
  - Adenomatoid
- Favorable cytologic features
  - Lymphohistiocytoid
  - Low nuclear grade
- Favorable stroma features
  - Myxoid (≥ 50% of tumor with less than 50% solid pattern contains myxoid stroma)

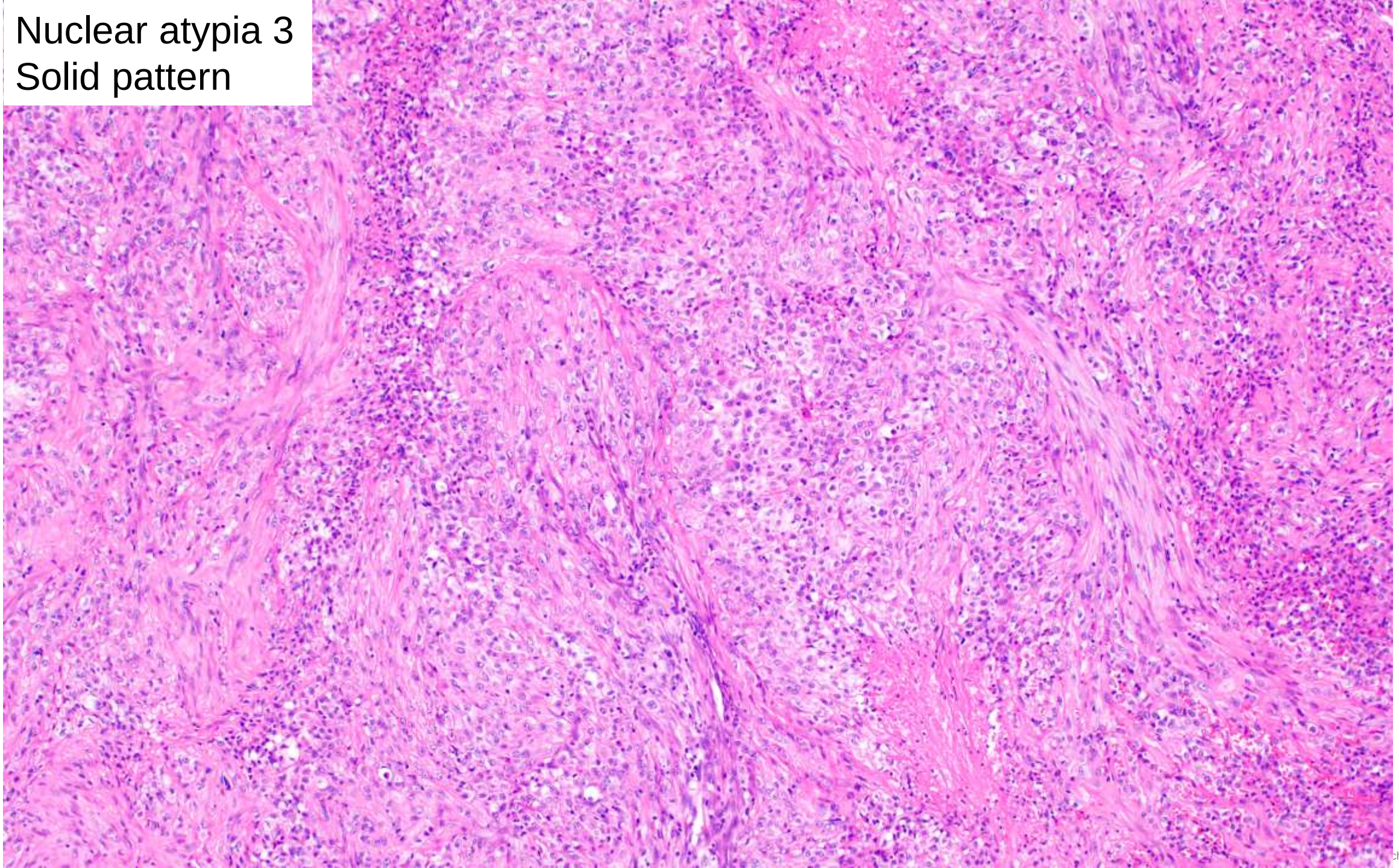

Nuclear atypia 1

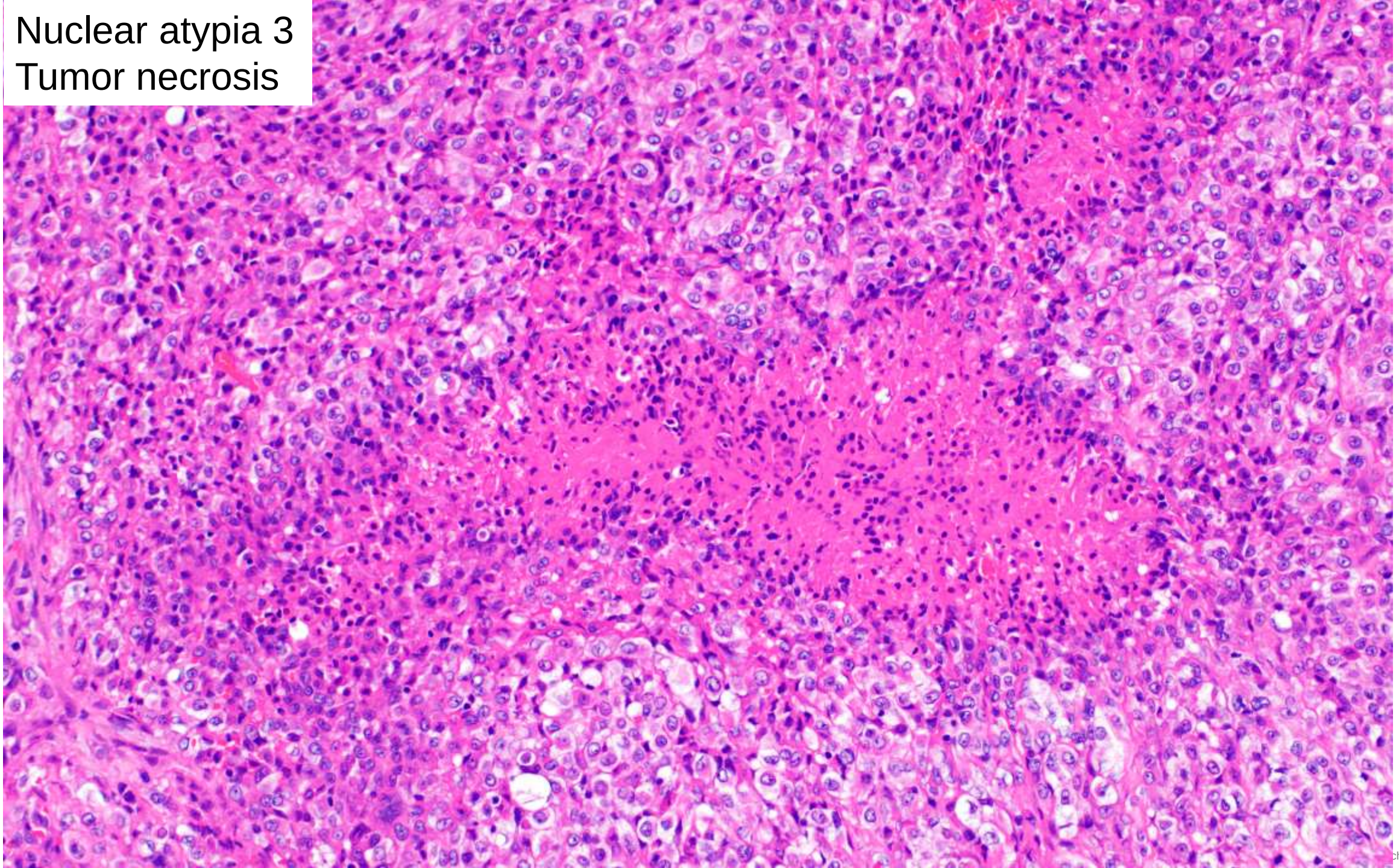

Nuclear atypia 1

Nuclear atypia 2

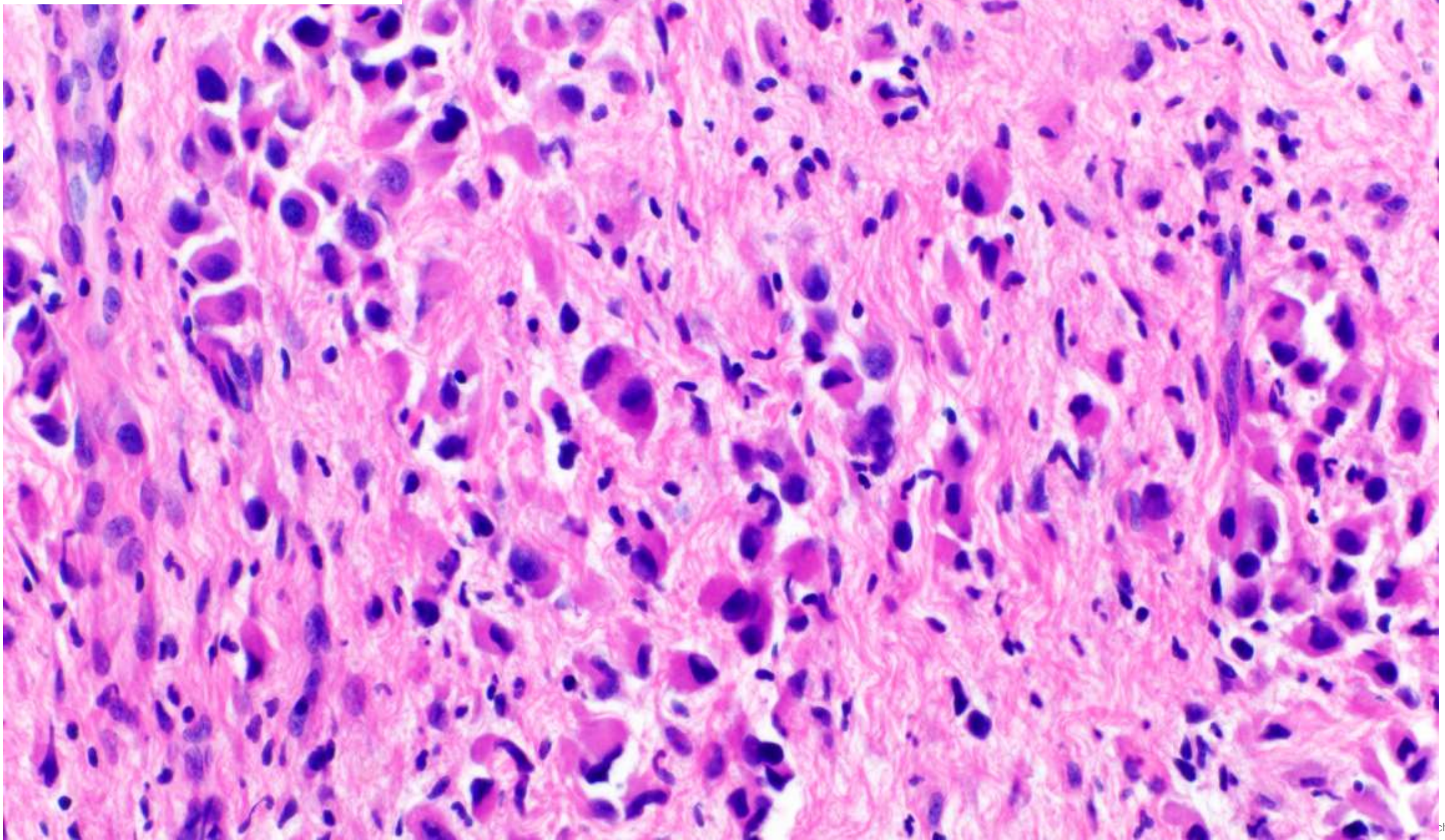


Nuclear atypia 3
Solid pattern

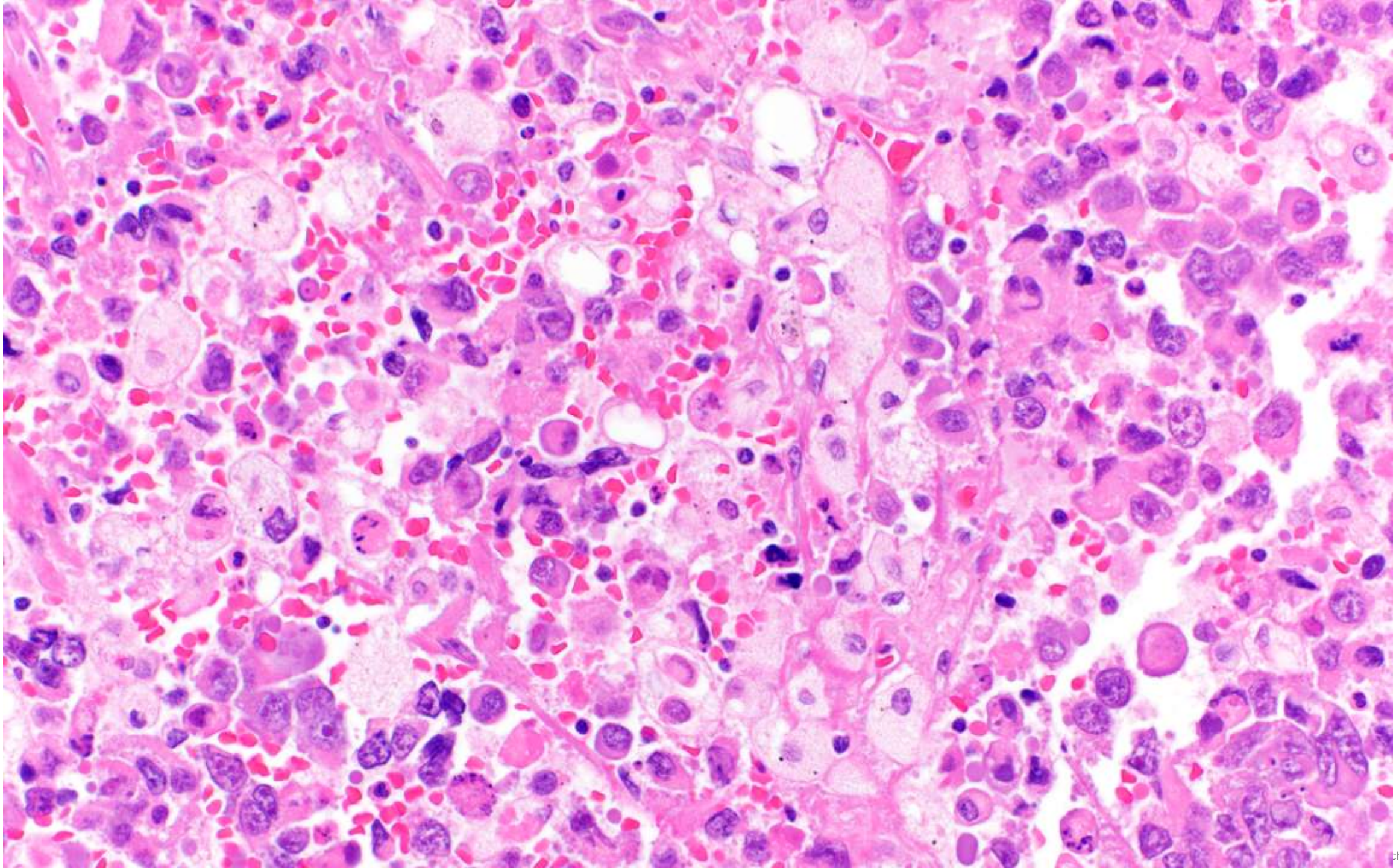


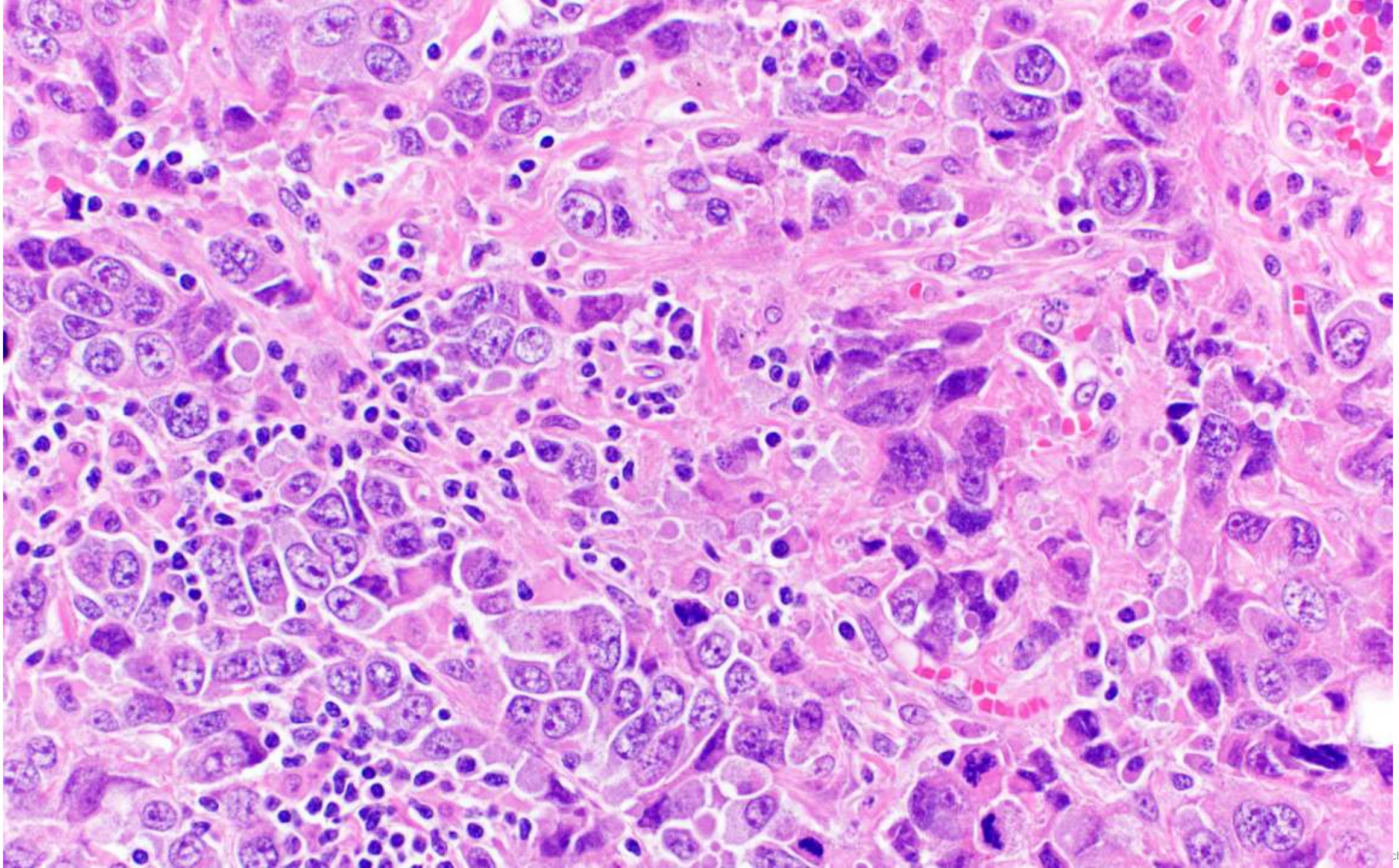

Nuclear atypia 3
Tumor necrosis

Rhabdoid phenotype



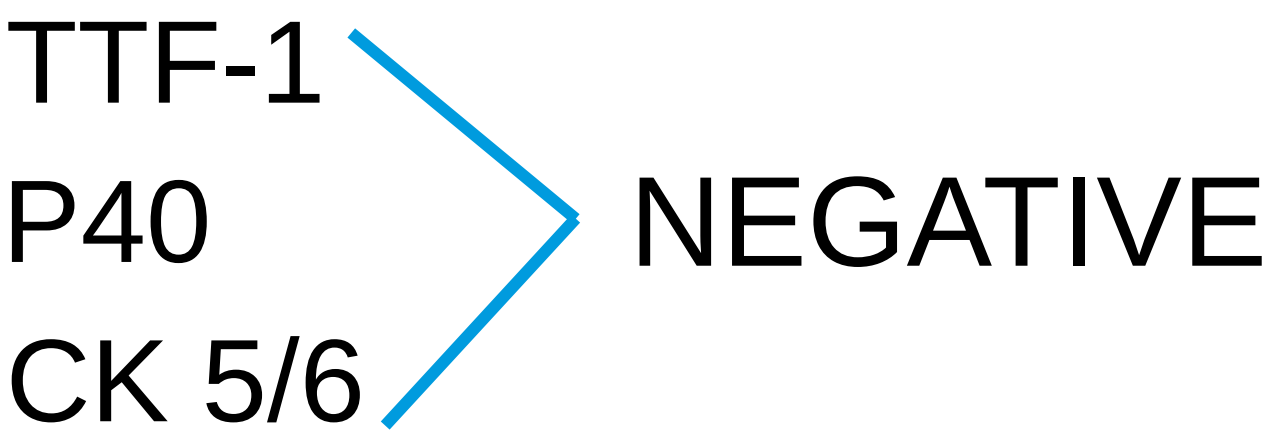
NOW, FOR A CASE!



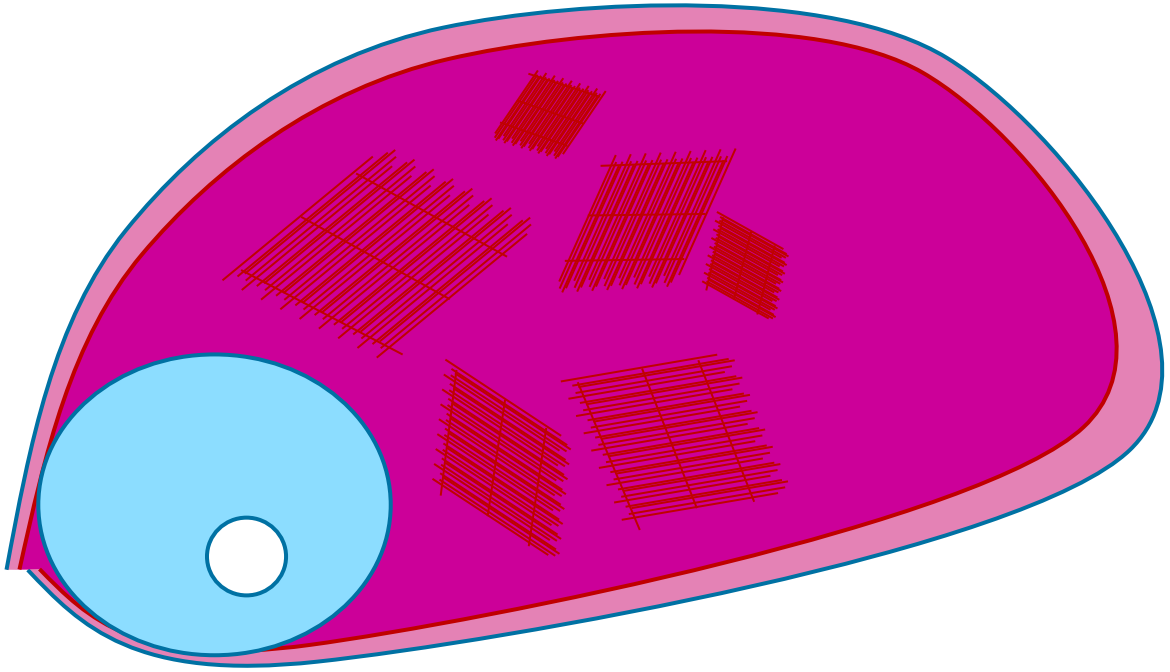


POORLY DIFFERENTIATED CARCINOMA

Initial workup



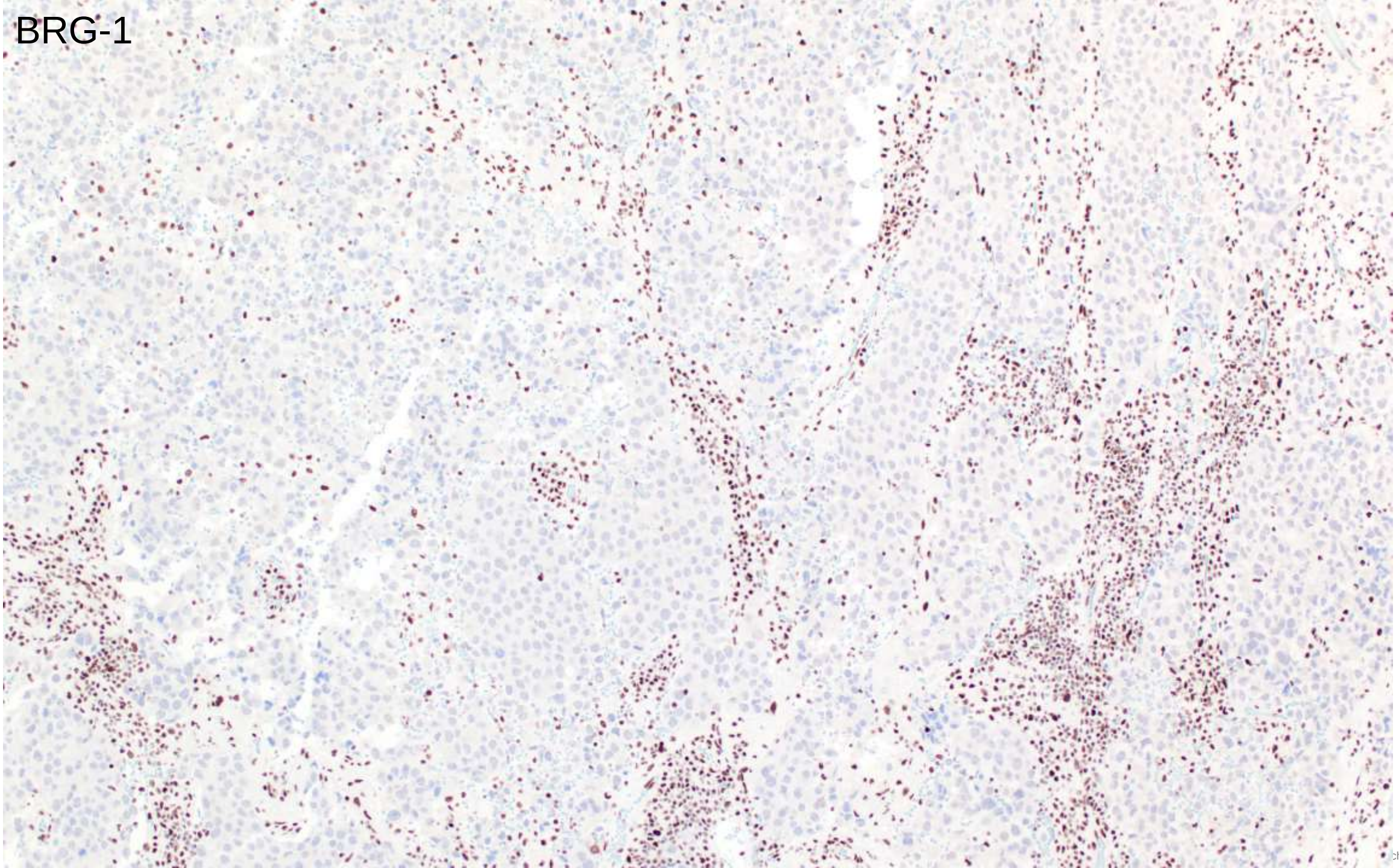
DDX for tumors with “rhabdoid” cytology



Muscle--Rhabdomyosarcoma
Kidney--Rhabdoid tumor (and other sites!)
Skin--Rhabdoid melanoma
Lung--Sarcomatoid carcinoma

WHAT NEXT?

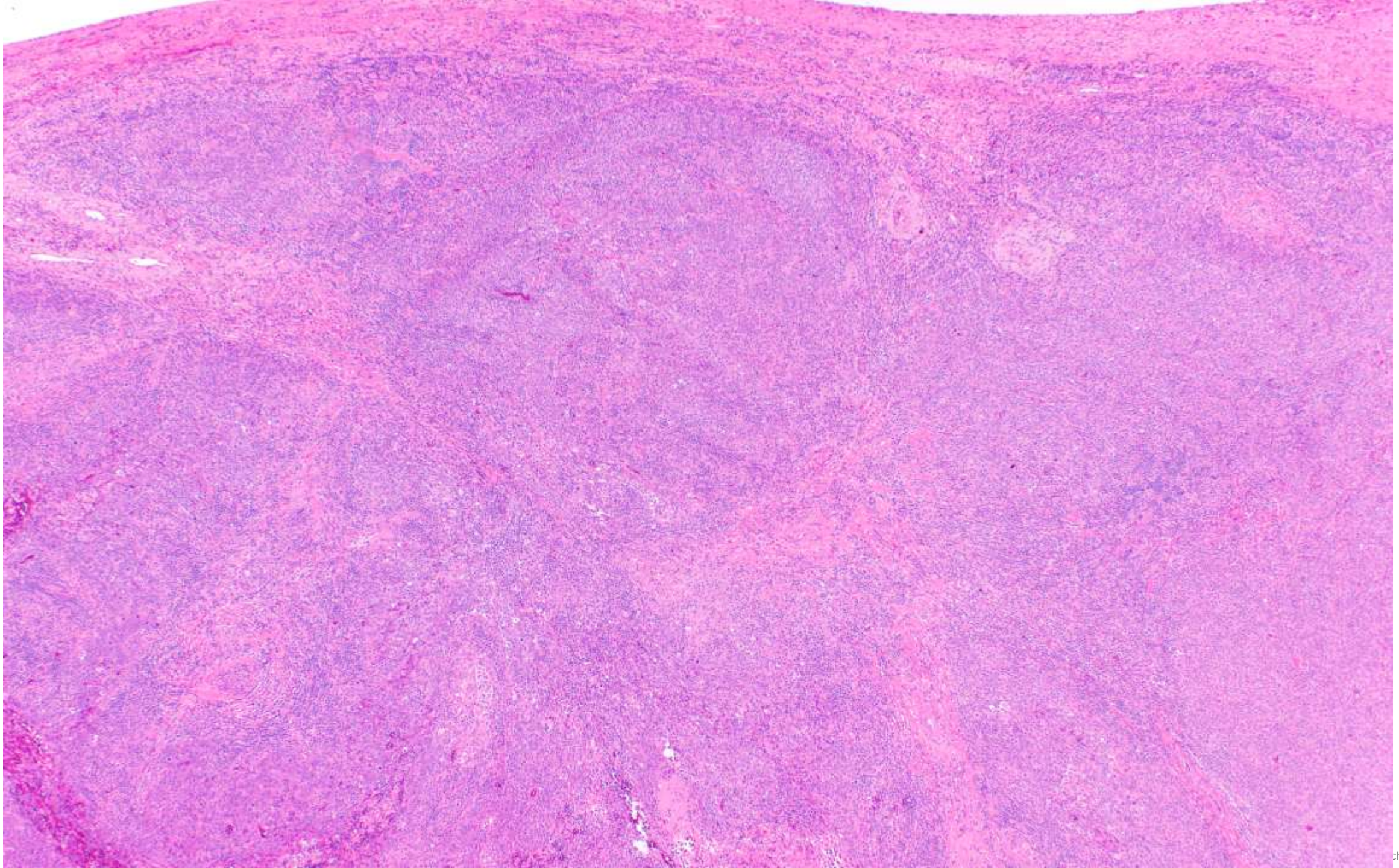
- Most primary lung tumors are carcinomas
- Repeat the markers, maybe in another lab, expand keratin markers
- Do vascular, melanoma, lymphoma markers
- Think about metastases
- Think about tumors with unusual IHC patterns!
  - Thoracic *SMARCA4*-deficient undifferentiated tumor (CK +/-; CD34+, BRG1 lost, INI1 retained)
  - NUT carcinoma (CK focal, TTF1 neg, NUT pos)

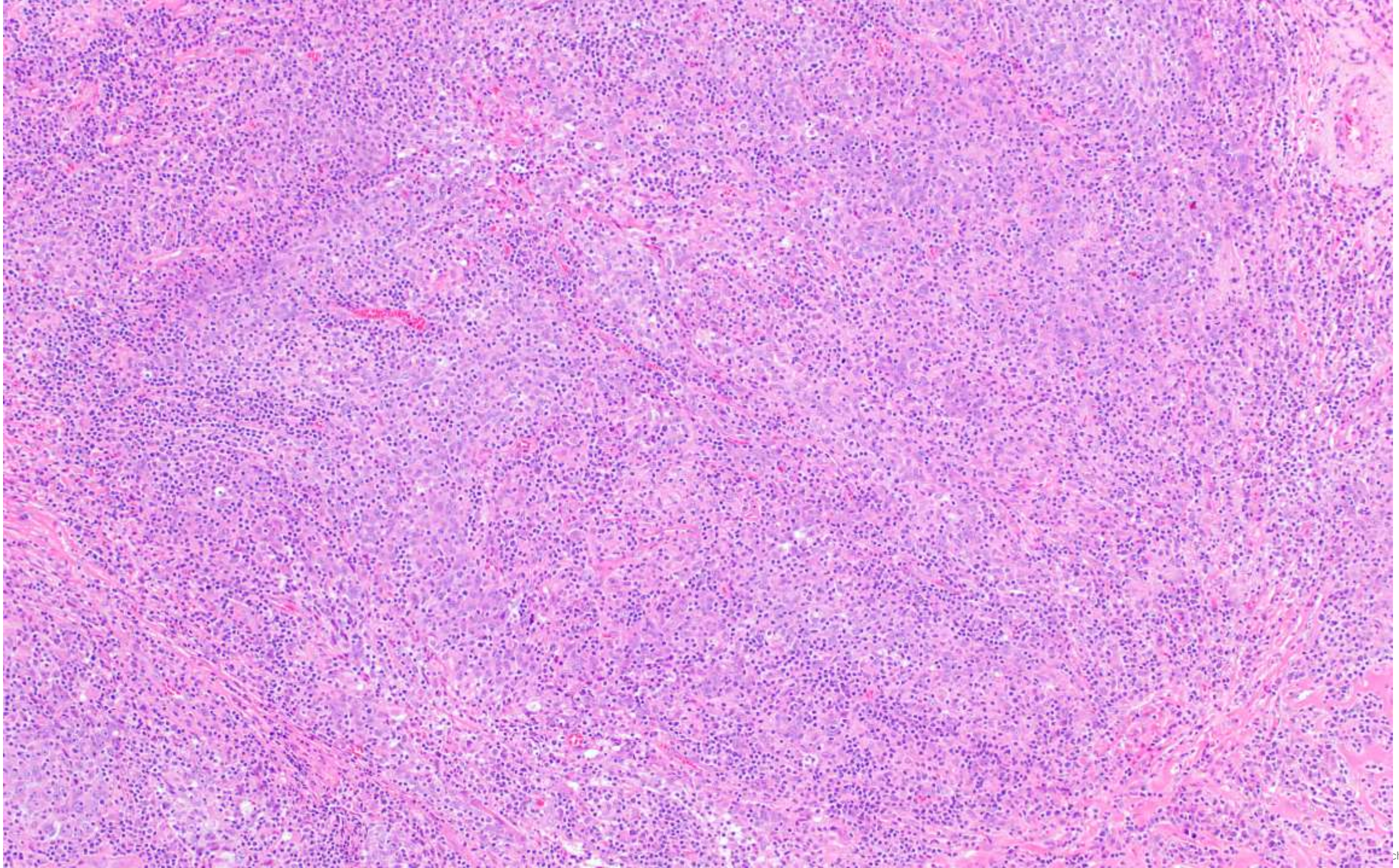

BRG-1

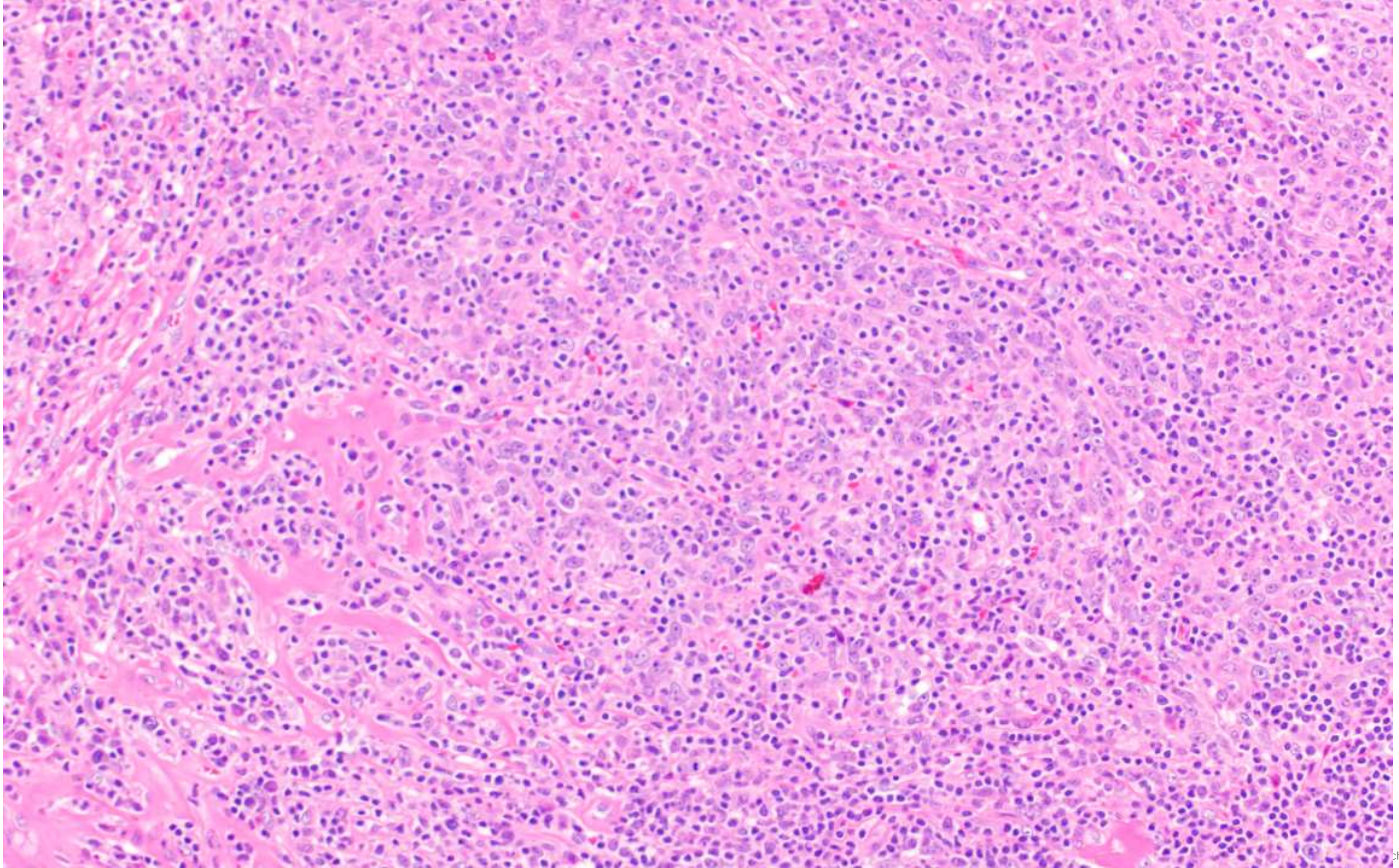
THORACIC *SMARCA4*-DEFICIENT UNDIFFERENTIATED TUMOR

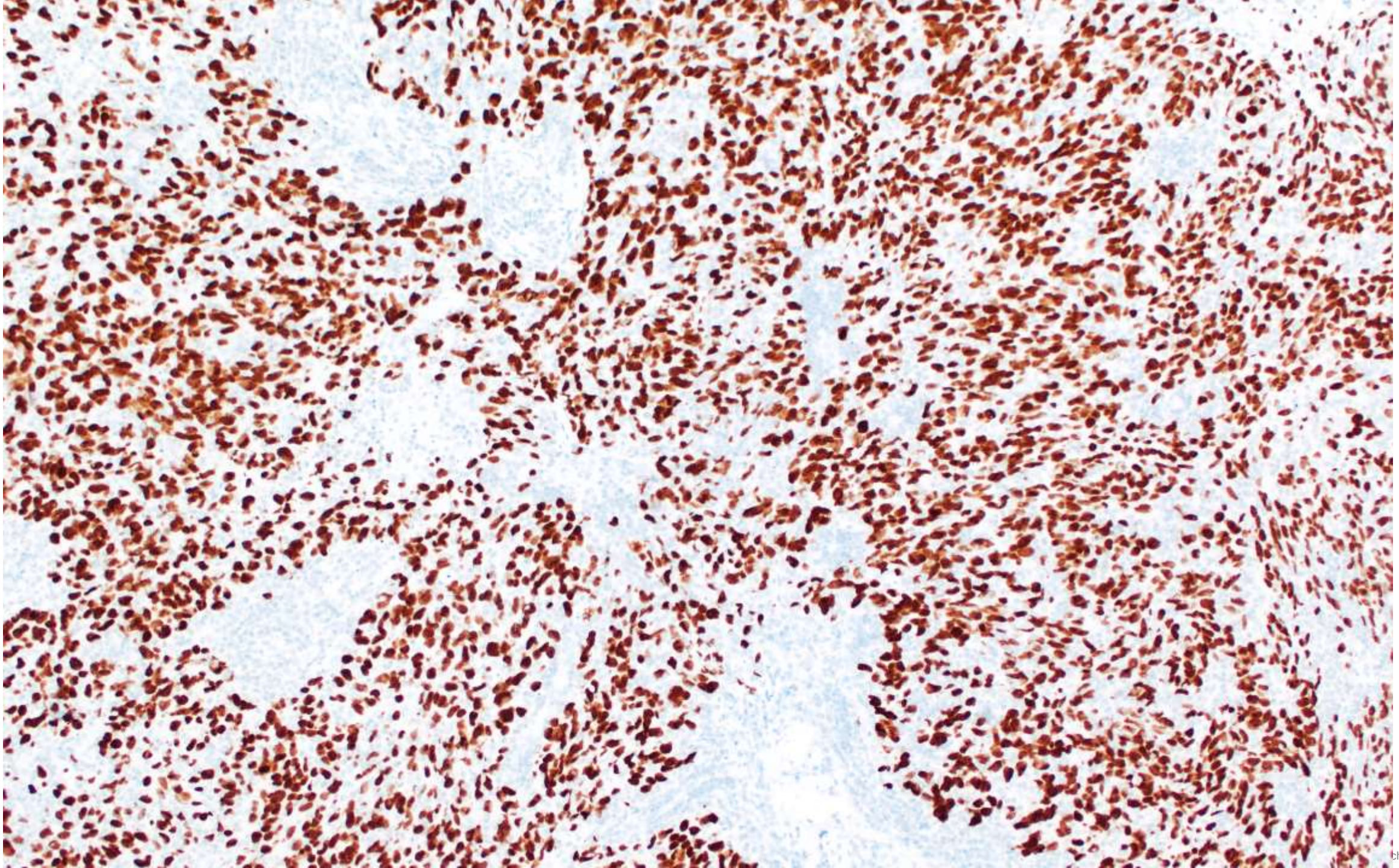
- Undifferentiated high-grade rhabdoid malignancy
- Adults (median age 56, range 19-84), smoking
- Loss of *SMARCA4* (BRG1), member of SWI/SNF chromatin remodeling complex
- IHC
  - Variable: keratins, CD34, Sox 10, SALL4, CD34, Synaptophysin
  - Occasionally TTF-1, p63, p40, WT-1 positivity

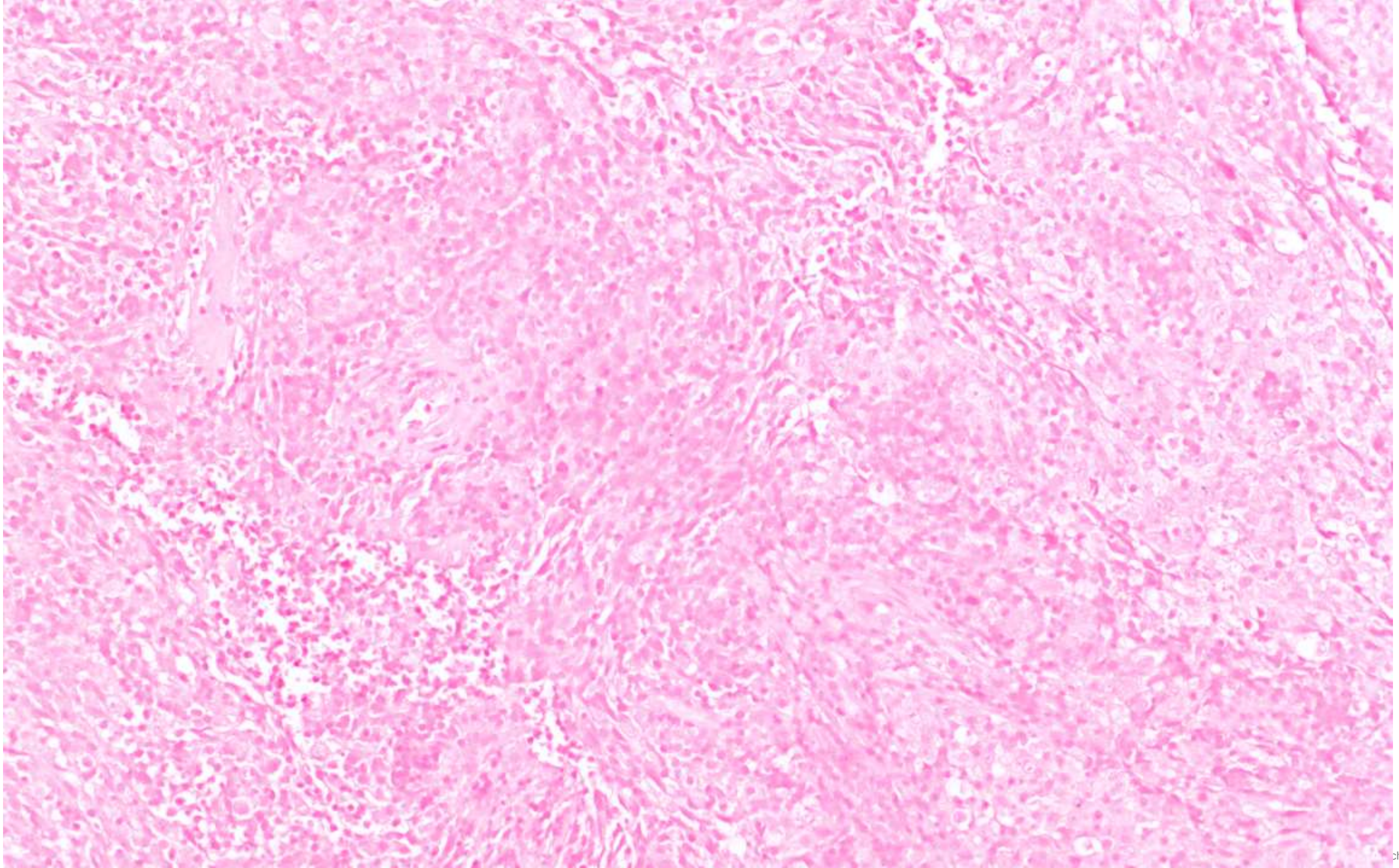
NOW, FOR ANOTHER CASE!







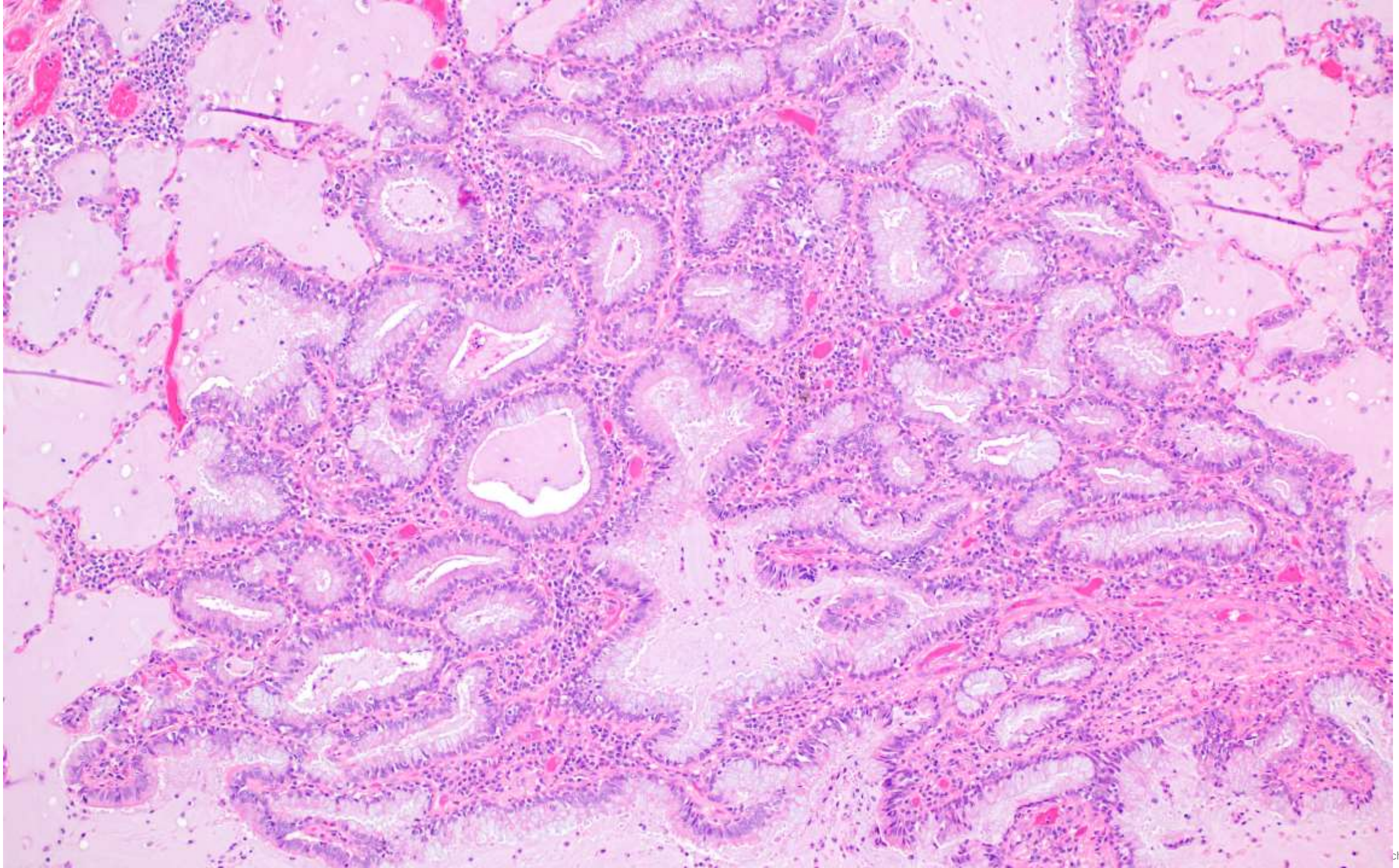


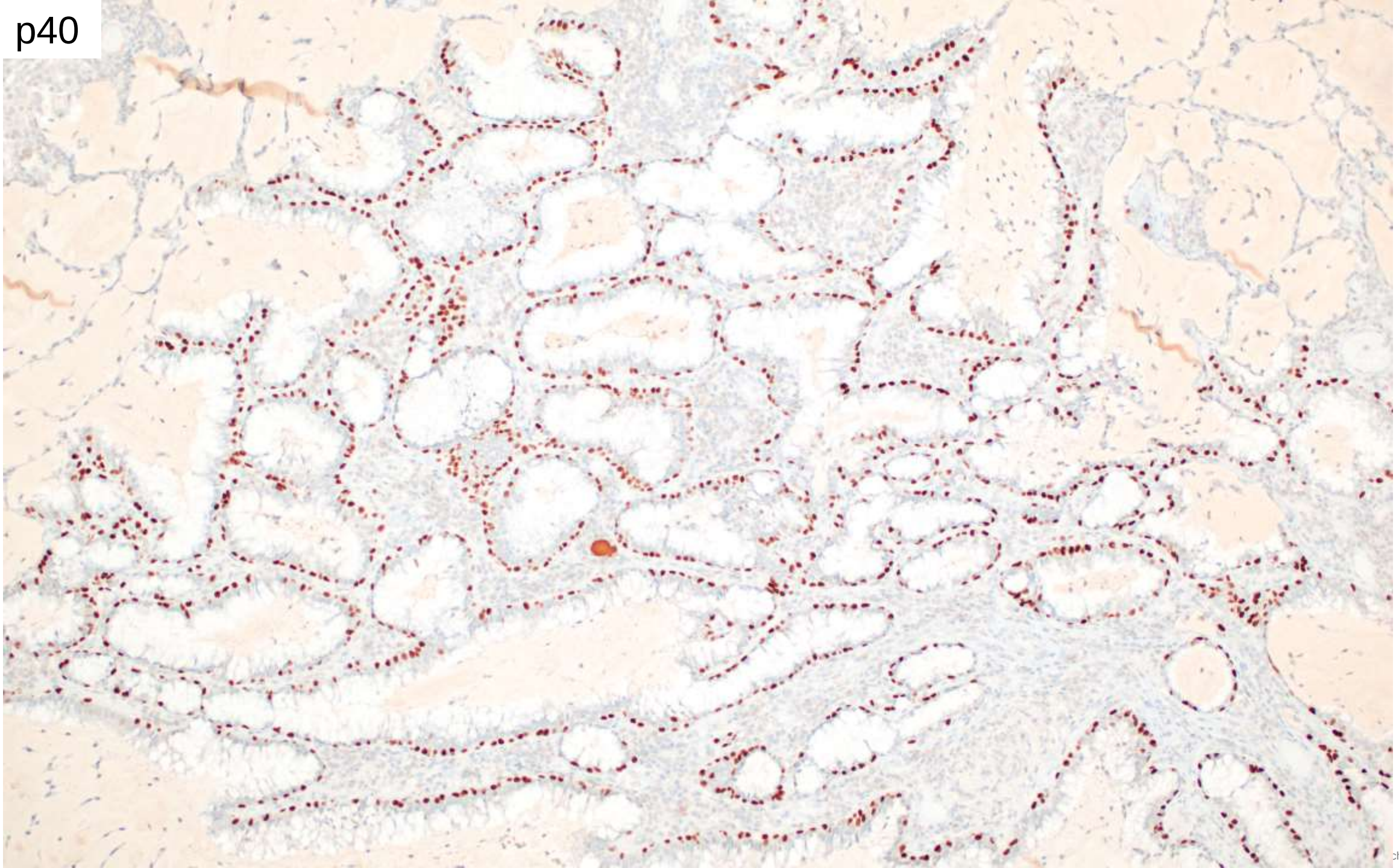


NOW, WITHOUT EBV POSITIVITY

- Lymphoepithelioma-like carcinoma →
- **Lymphoepithelial carcinoma (EBV + and EBV -)**

- Bronchiolar adenoma (ciliated muconodular papillary tumor)
- New in the adenoma category

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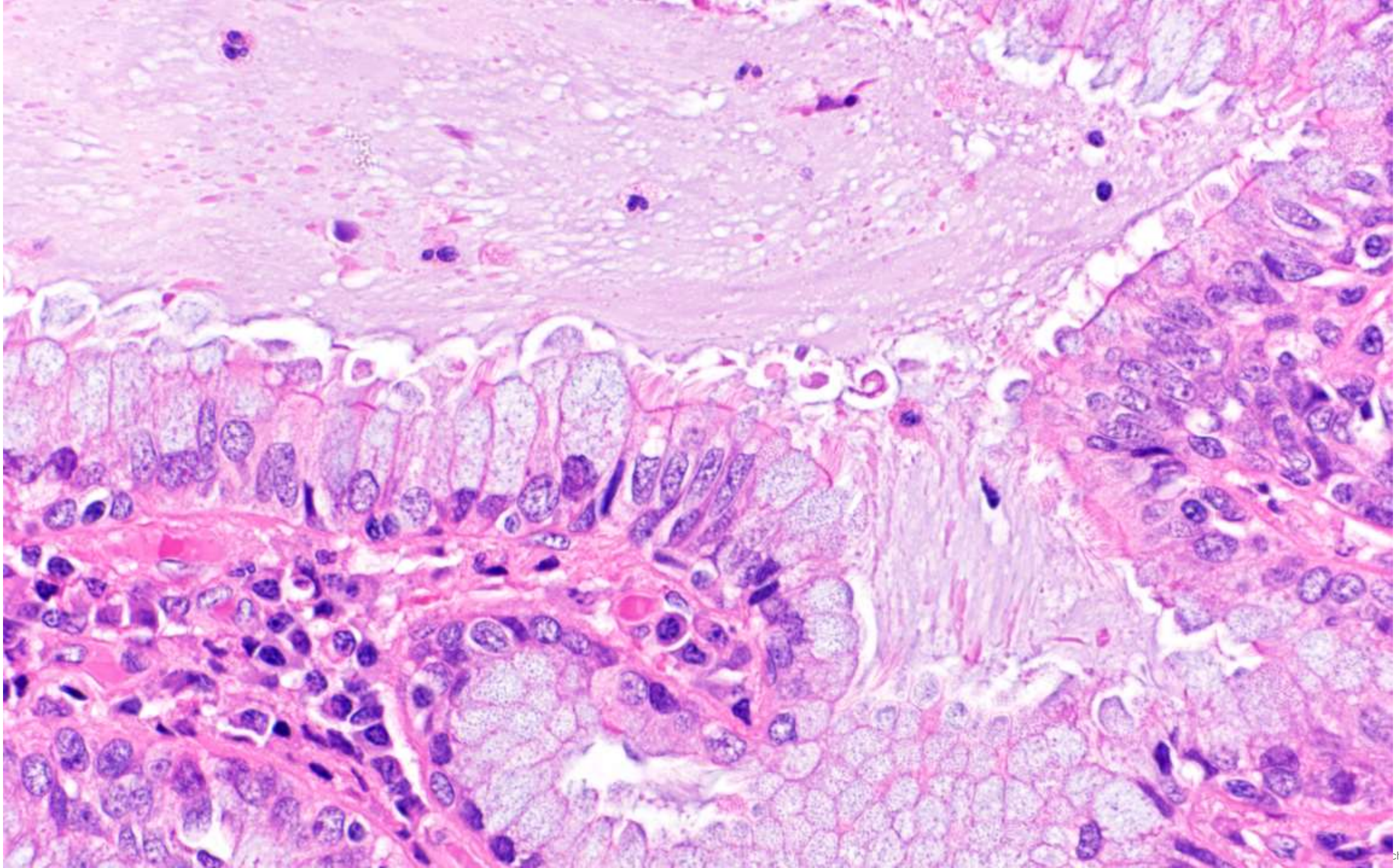

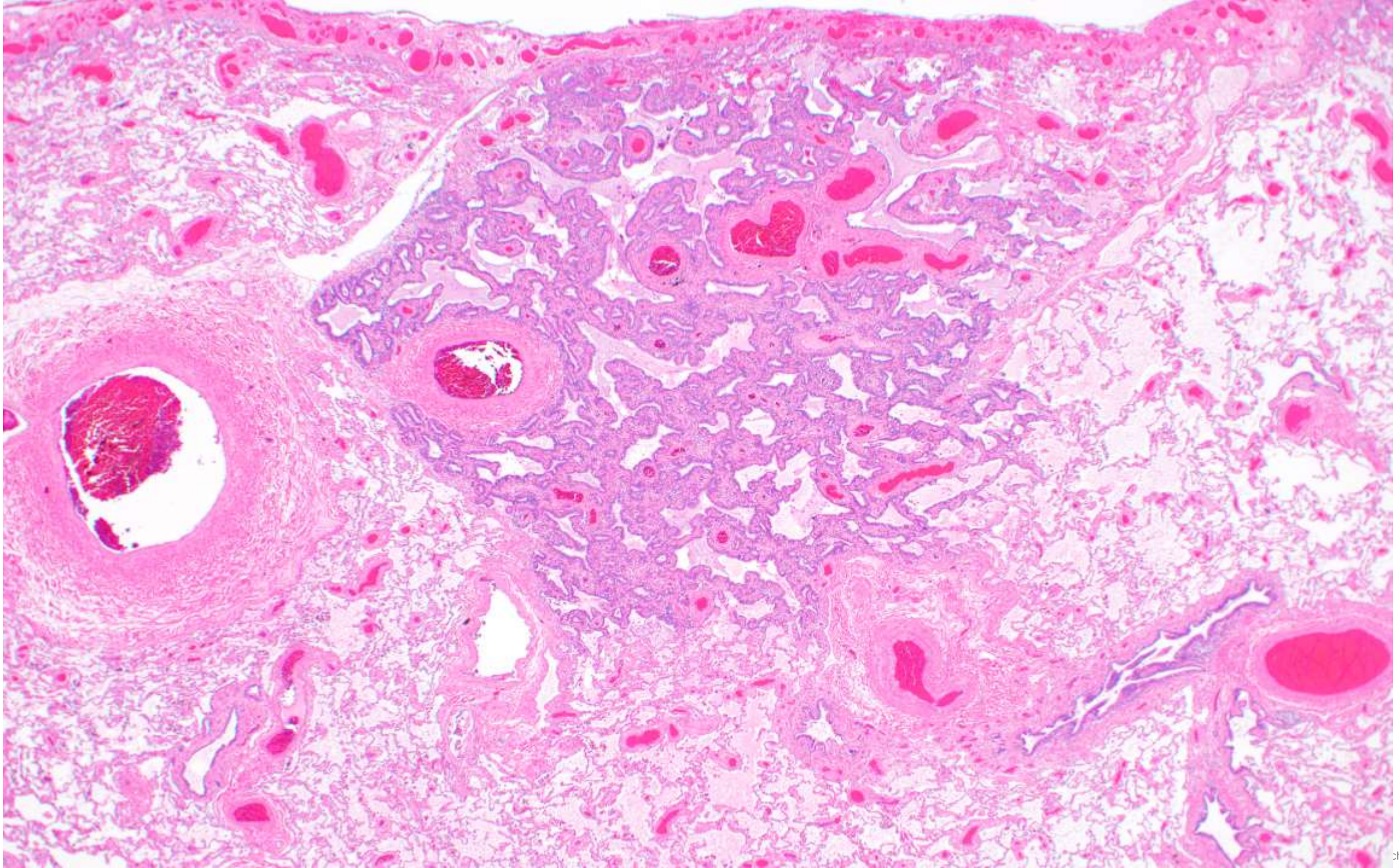

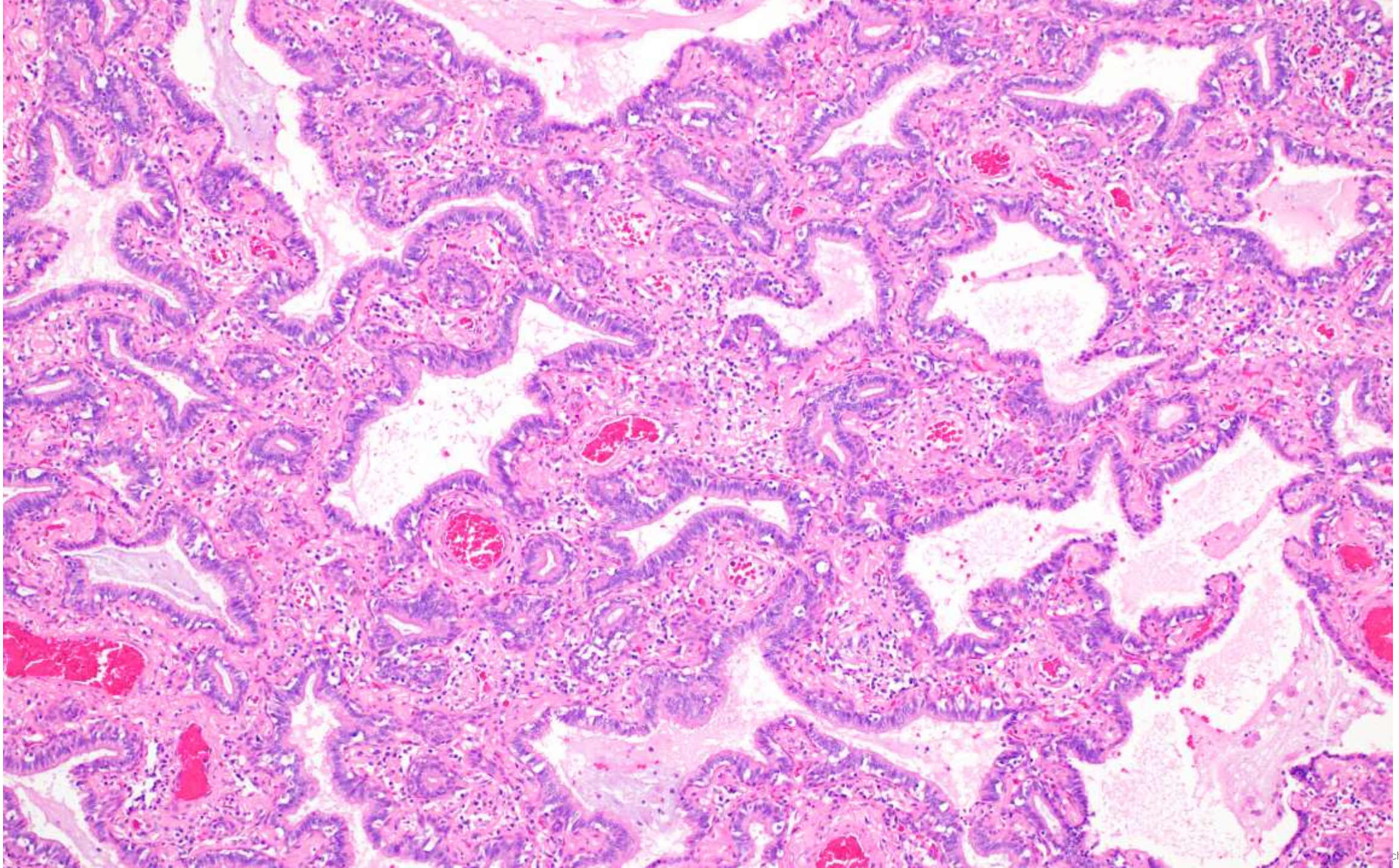

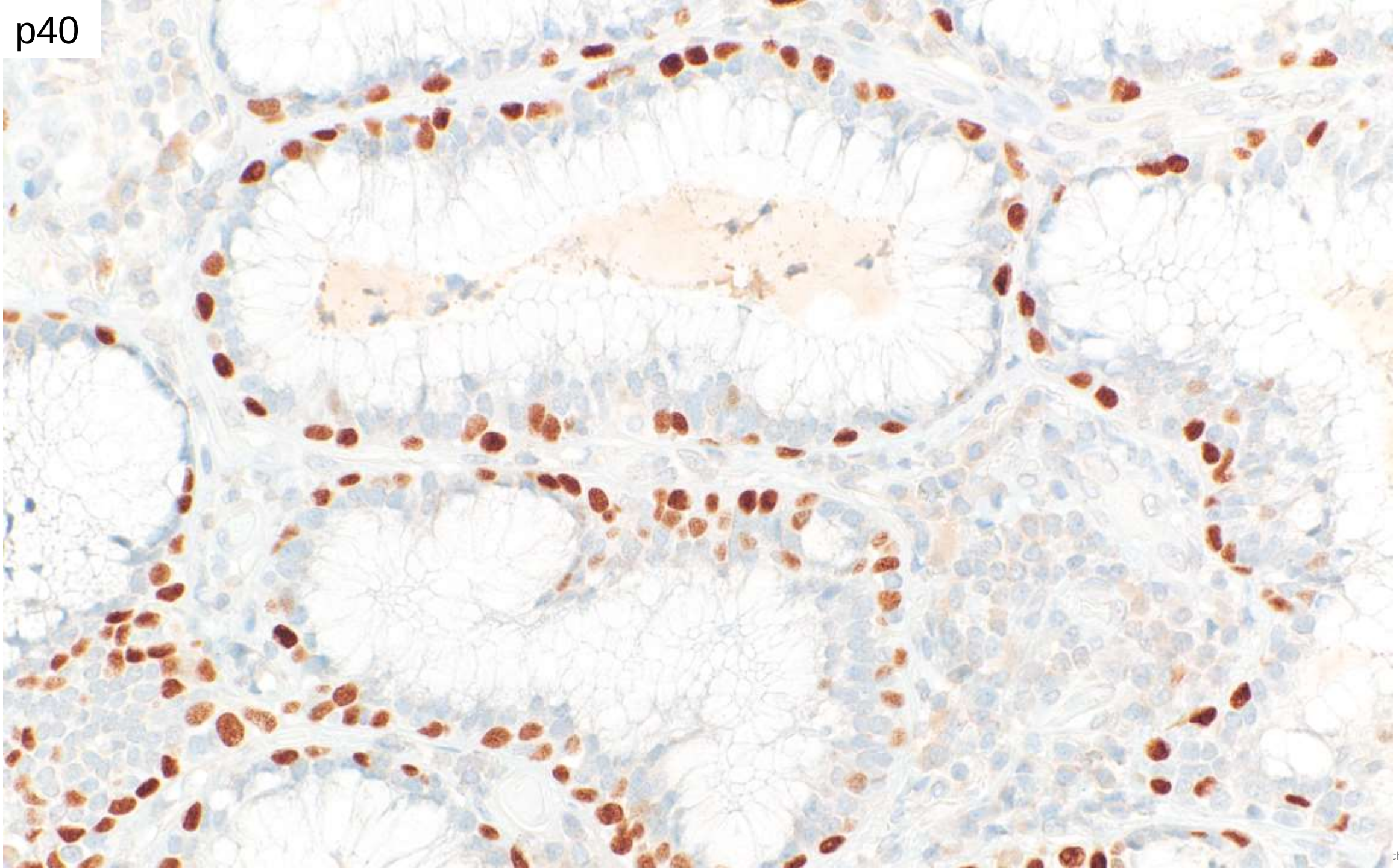
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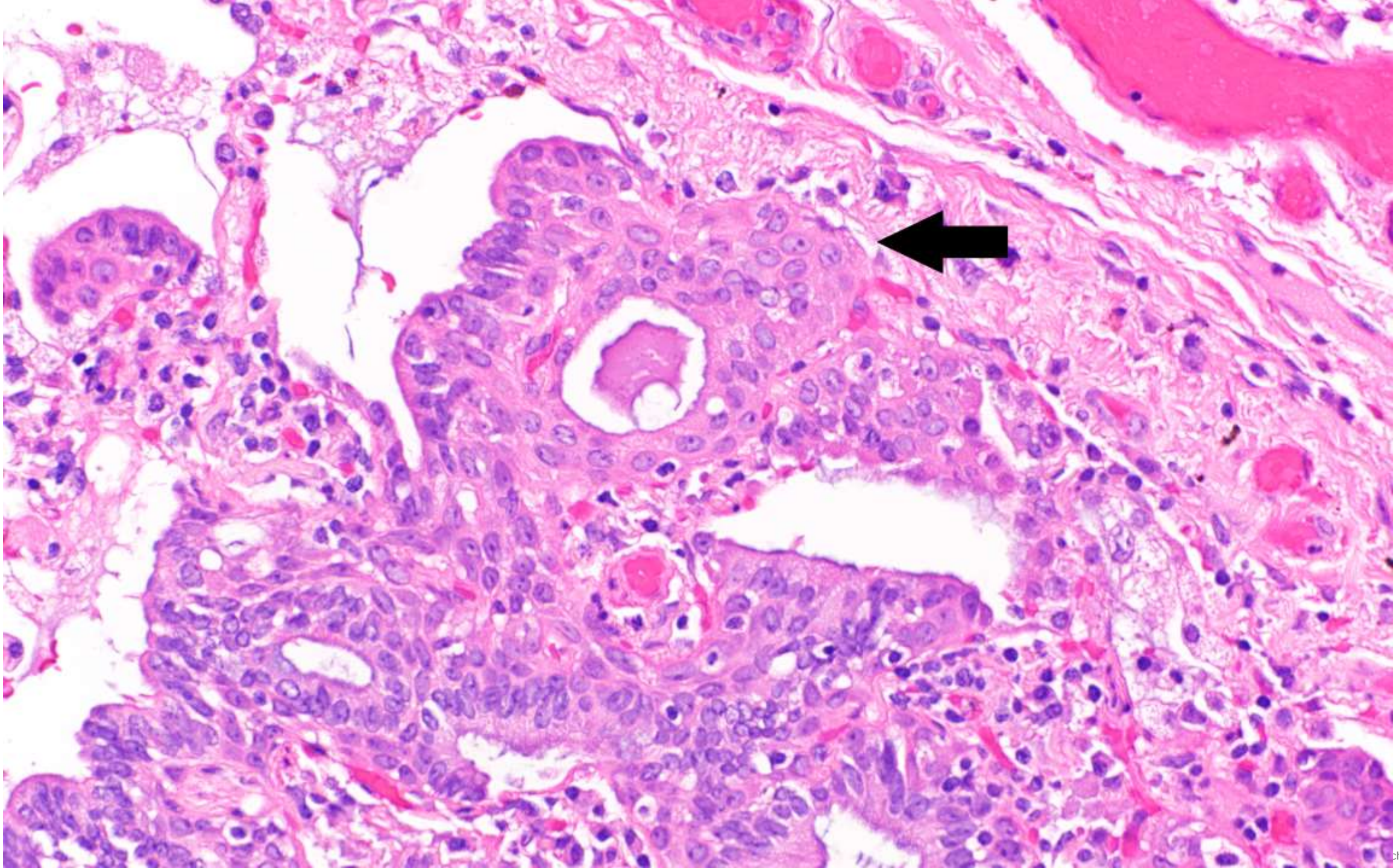

THANK YOU!
QUESTIONS?