Help! How do I Diagnose and Stage this Lung Cancer?

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Disclosures

Dr. Tazelaar has no relevant disclosures to the topics being presented

Objectives/Outline

At the end of the lecture, participants should be able to

1. **Have an understanding of the current WHO classification for lung adenocarcinoma and how it differs from previous classifications**
2. **Should be able to successfully navigate the traps in making a diagnosis of adenocarcinoma on small biopsies**
3. **Will know how to report lung cancer in accordance with AJCC 8th edition**

Pathologic Classification of Lung Cancer

WHO 2004

- Light microscopy
- Use of limited special stains e.g mucin
- No terminology for small biopsies/cytology

WHO 2015

- Light microscopy & Immunohistochemistry
- Small specimen guidelines
- Personalized therapies

Adenocarcinoma Classification in Resection Specimens

- Pre-invasive lesions
- Minimally invasive
- Invasive
- Variants of invasive

Some Key Points

- No more BAC
- All invasive tumors are appended with “predominant”
  - Implies semiquantitative recording of patterns -- 5% increments
- Invasion now identified by pattern as well as by presence of desmoplasia

Diagnostic Categories on Small Biopsies/Cytology Specimens

- Describe morphologic adca patterns present e.g. acinar, lepidic, colloid
- Pure lepidic tumor? State invasion cannot be excluded
- If ADCA NOT present, should be supported by special stains, e.g. mucin or IHC

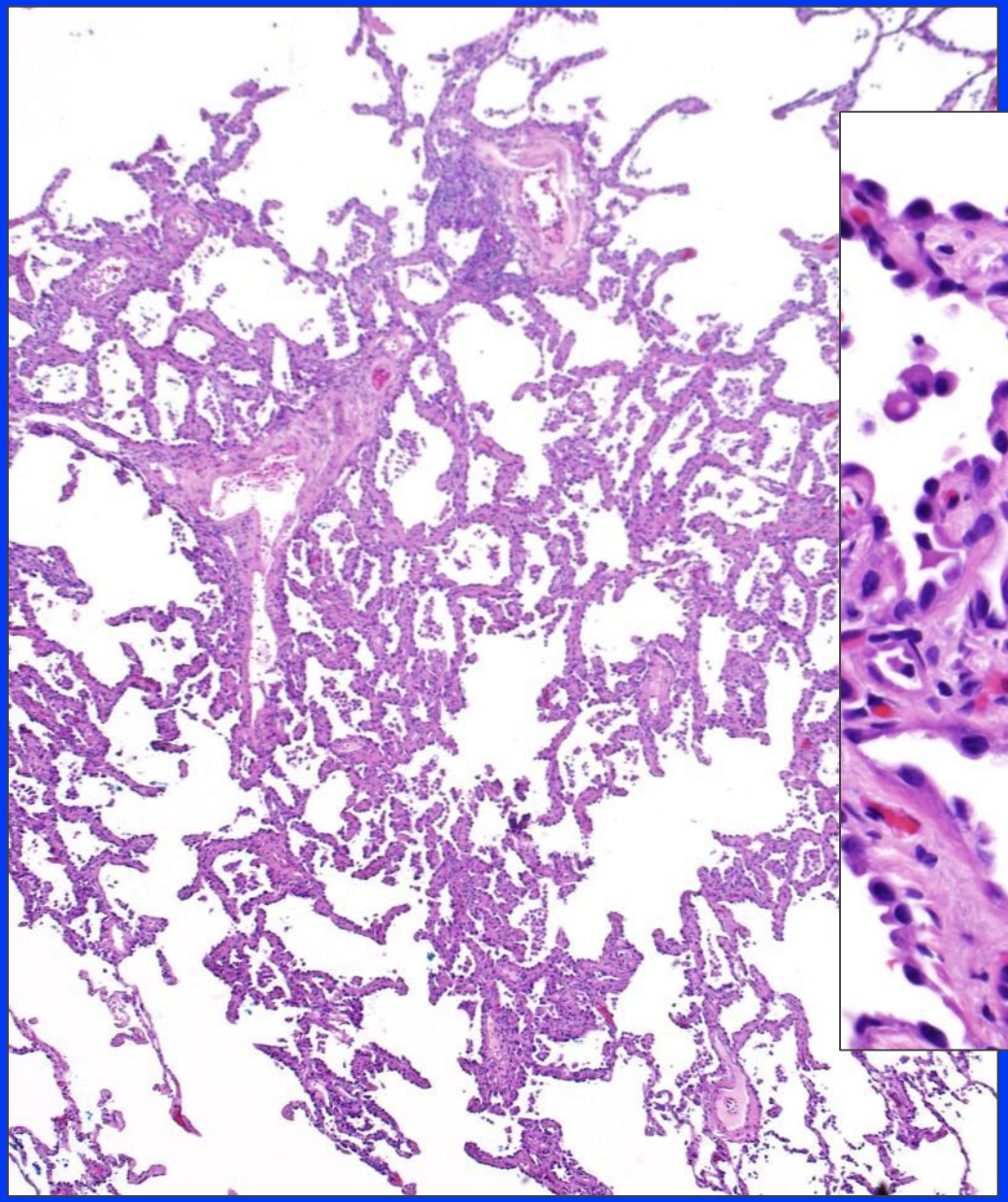
Atypical Adenomatous Hyperplasia

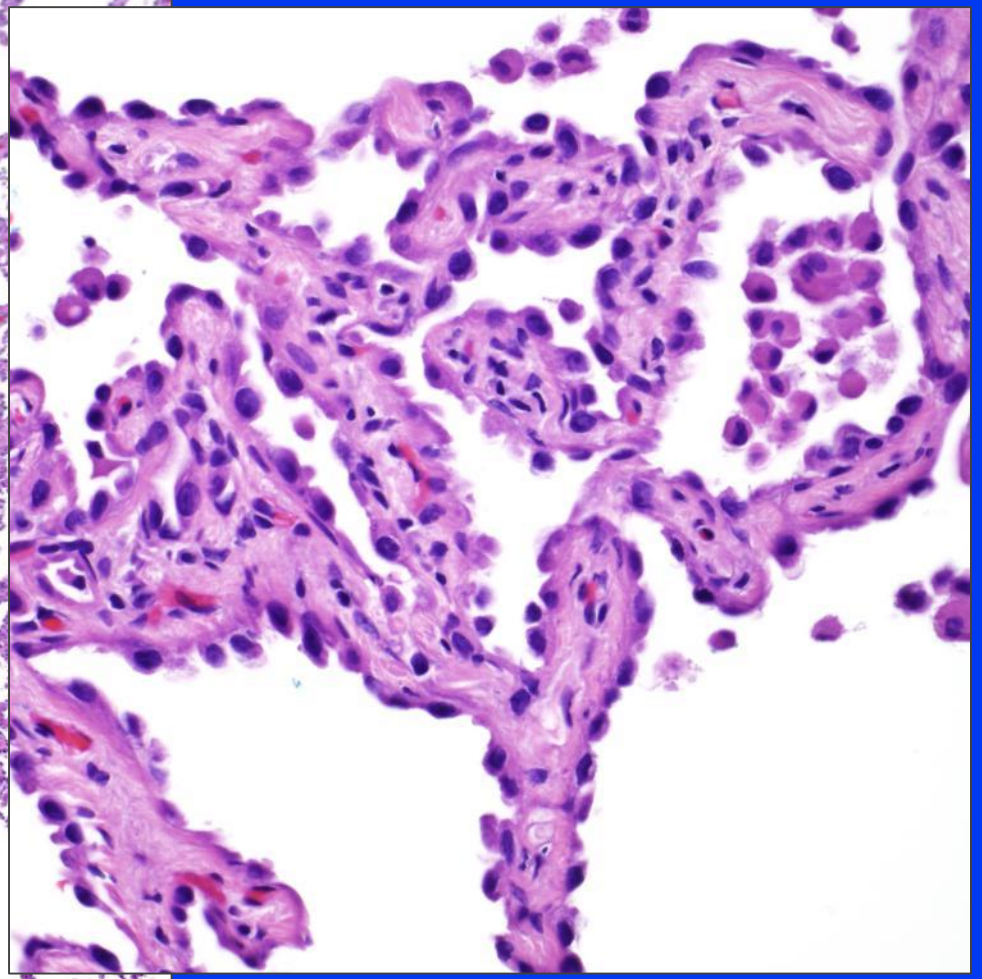
Localized small proliferation of

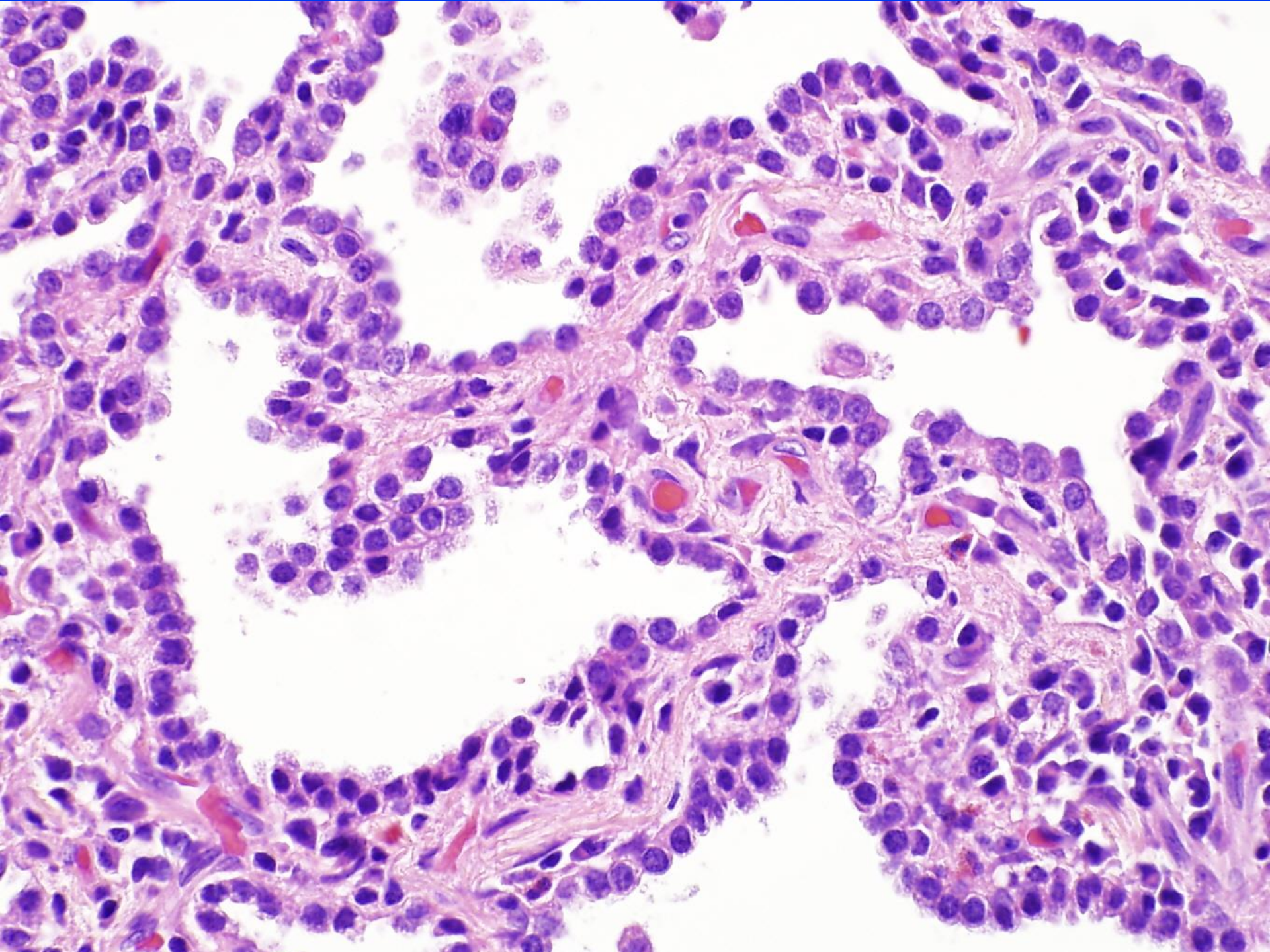
- ***Mild to moderately*** atypical cells
- Lining involved alveoli and sometimes respiratory bronchioles…
- ***Usually less than 5 mm in diameter (not absolute!)***
- Double nuclei rare
- Alveolar walls may be thickened
- Pseudopapillae and tufts *may* be present

<u>Diagnosis reserved for resection specimens</u>

Atypical Adenomatous Hyperplasia



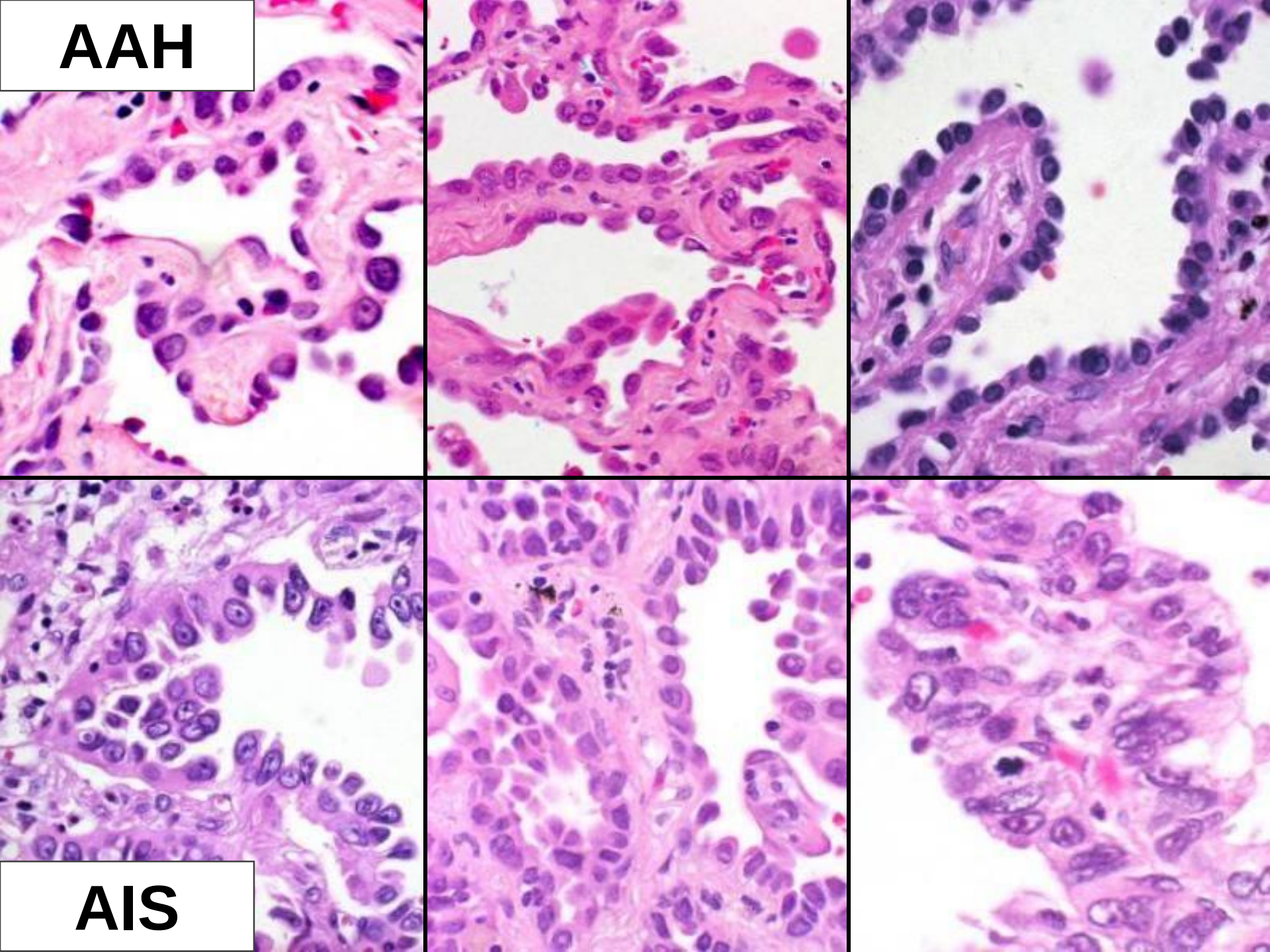




AAH vs AIS

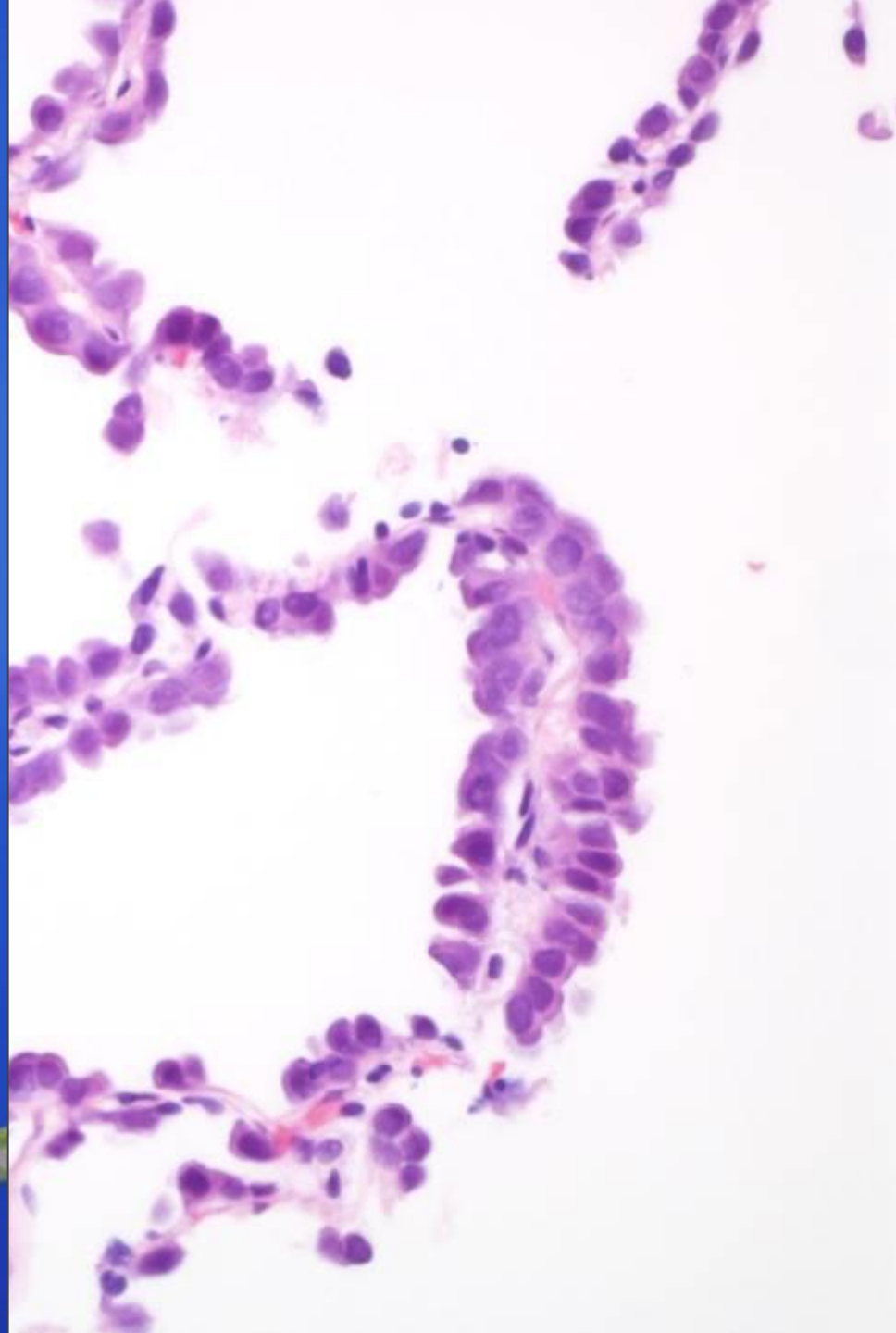
- AIS has "…malignant epithelial cells"
- AAH has "...mild to moderately atypical cells"

AAH	AIS
Polymorphous cells with ciliated and goblet cells	Monotonous population
No nuclear or cell border overlapping	Densely packed with overlapping nuclei
Blends into surrounding lung	Sharply demarcated


AAH
AIS

Adenocarcinoma in Situ/AIS

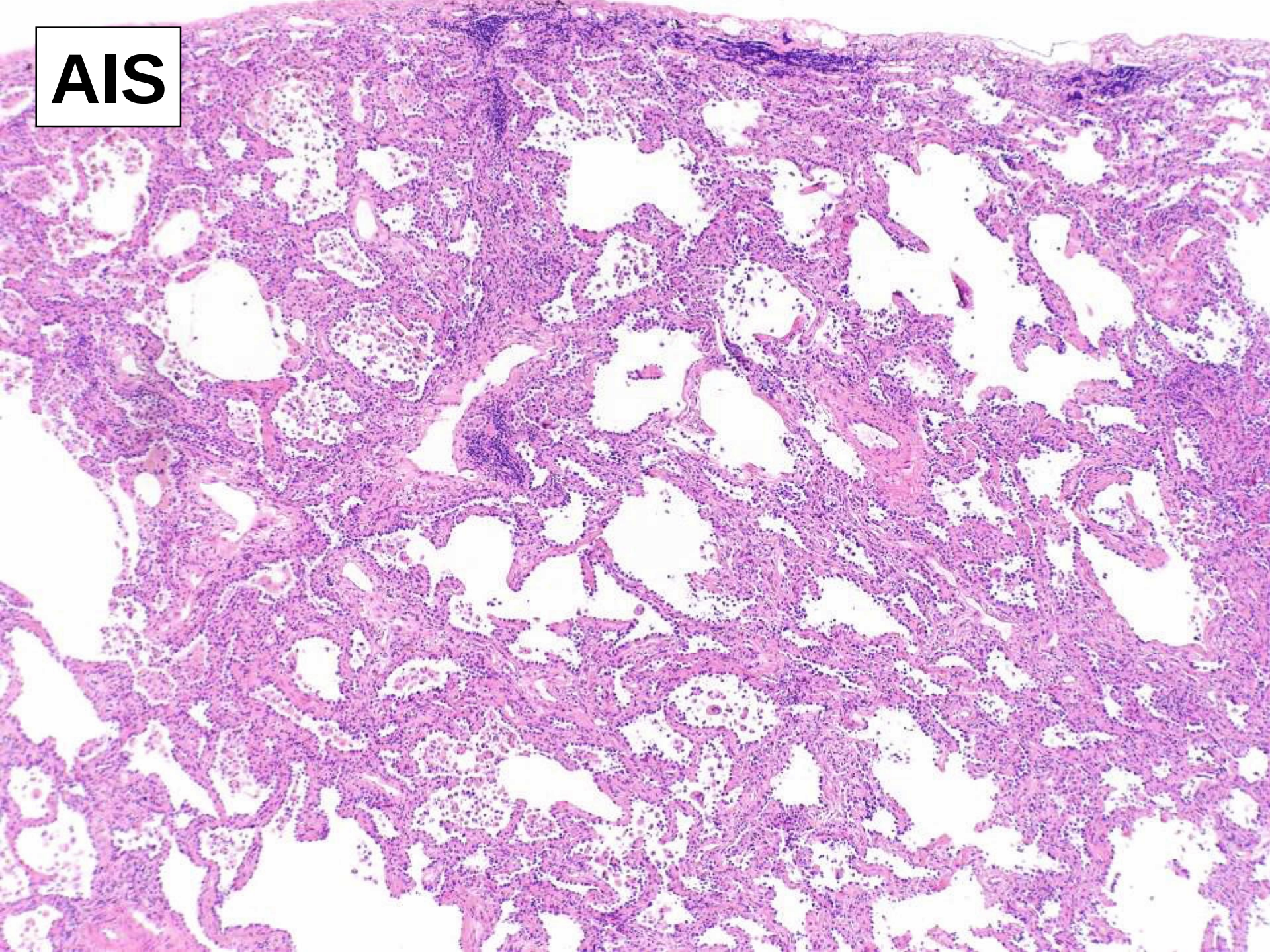
- *Pure* lepidic growth ≤ 3 cm
- 100% disease free survival
- Diagnosis cannot be made on cytologic or biopsy specimens
- Very rare in mucinous tumors

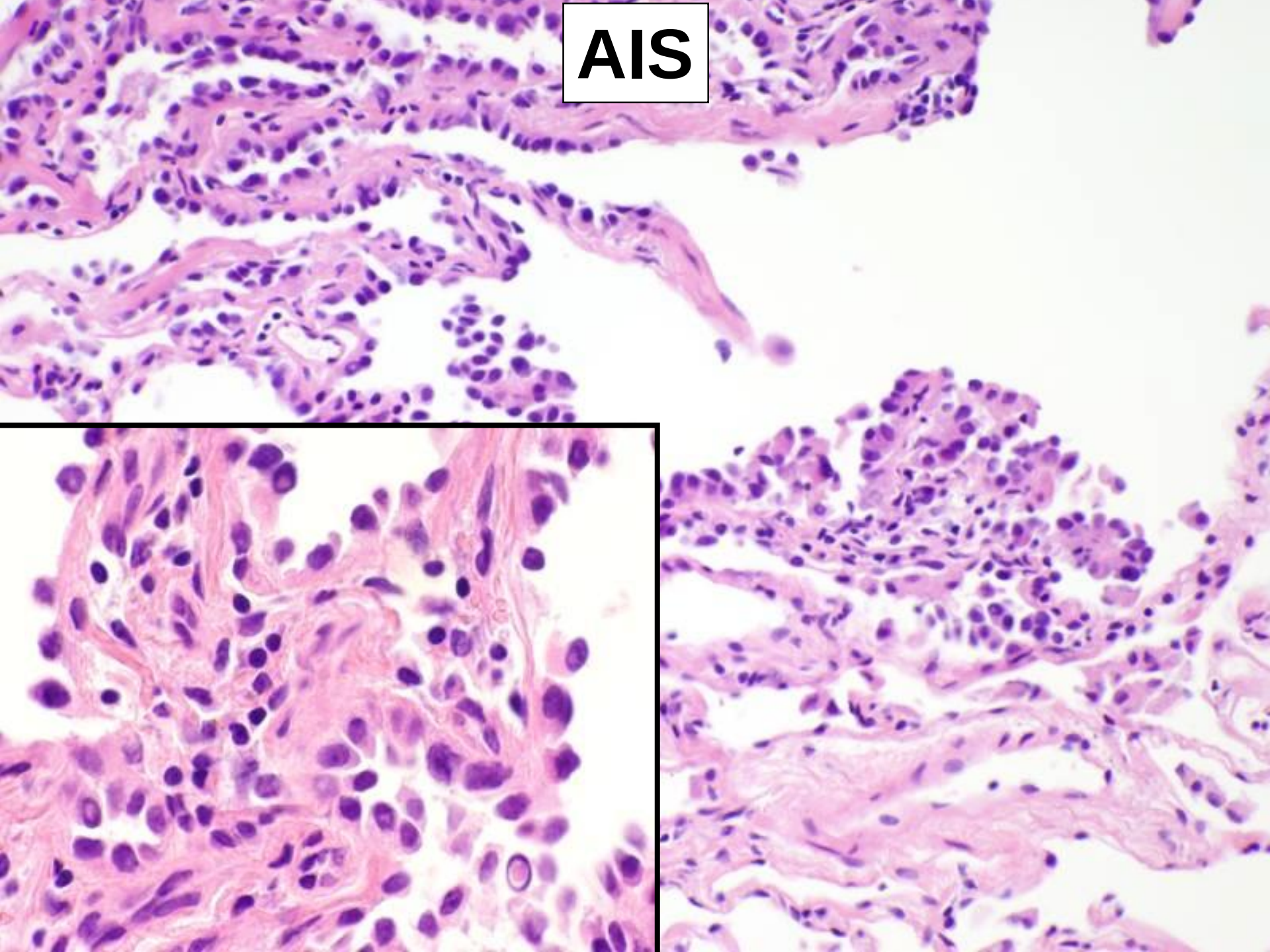


Whence Lepidic?

- ***Neologism*** **of Dr. John Adami in 1902 at the Toronto Pathological Society**
- **Term applied to tumors that appeared to be derived from surface lining cells (as opposed to *hylic* (from connective tissue)**

Jones, KD Arch Pathol Lab Med 2013;137:1822-24


AIS

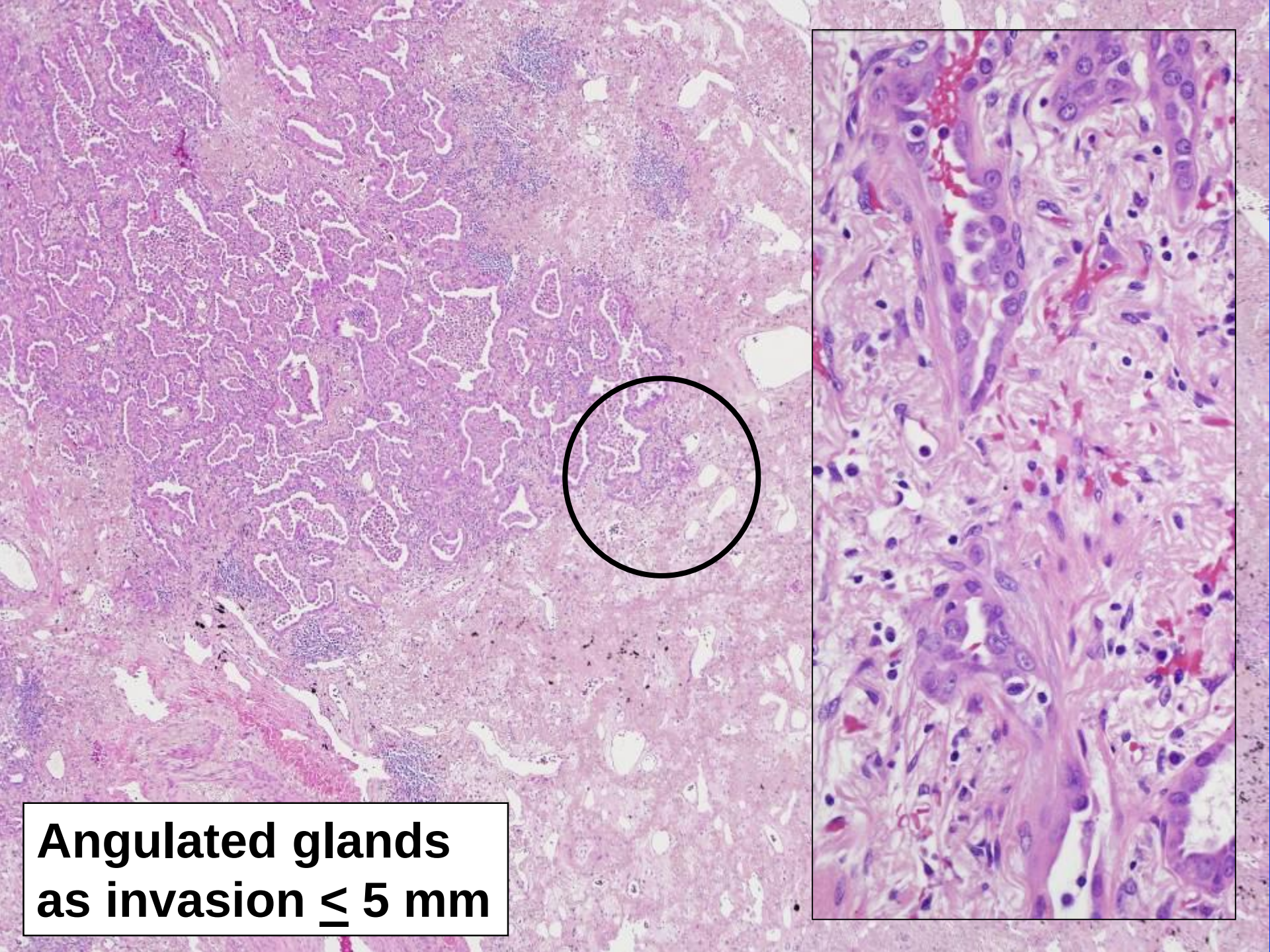

AIS

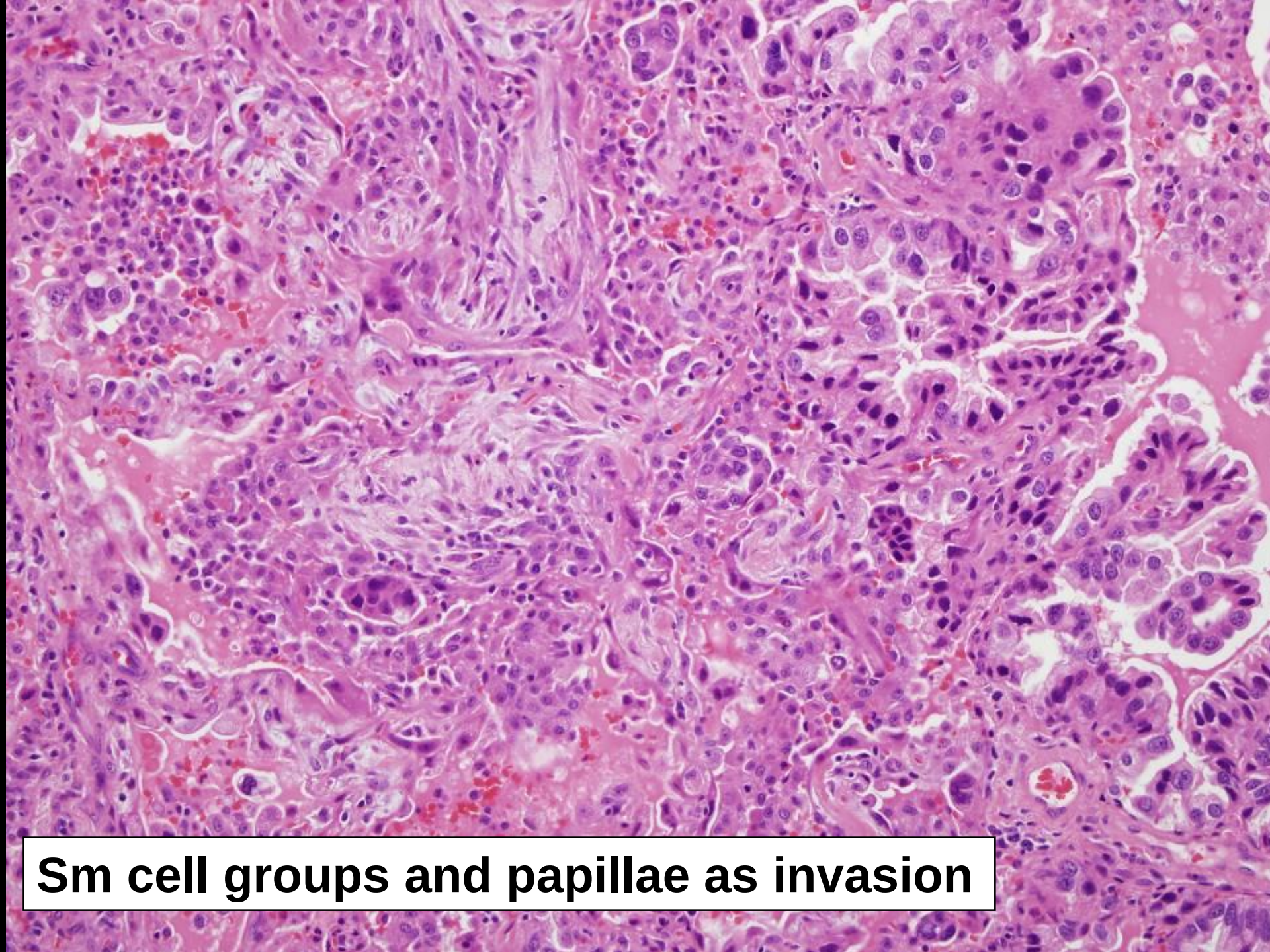
Minimally Invasive Adeno (MIA)

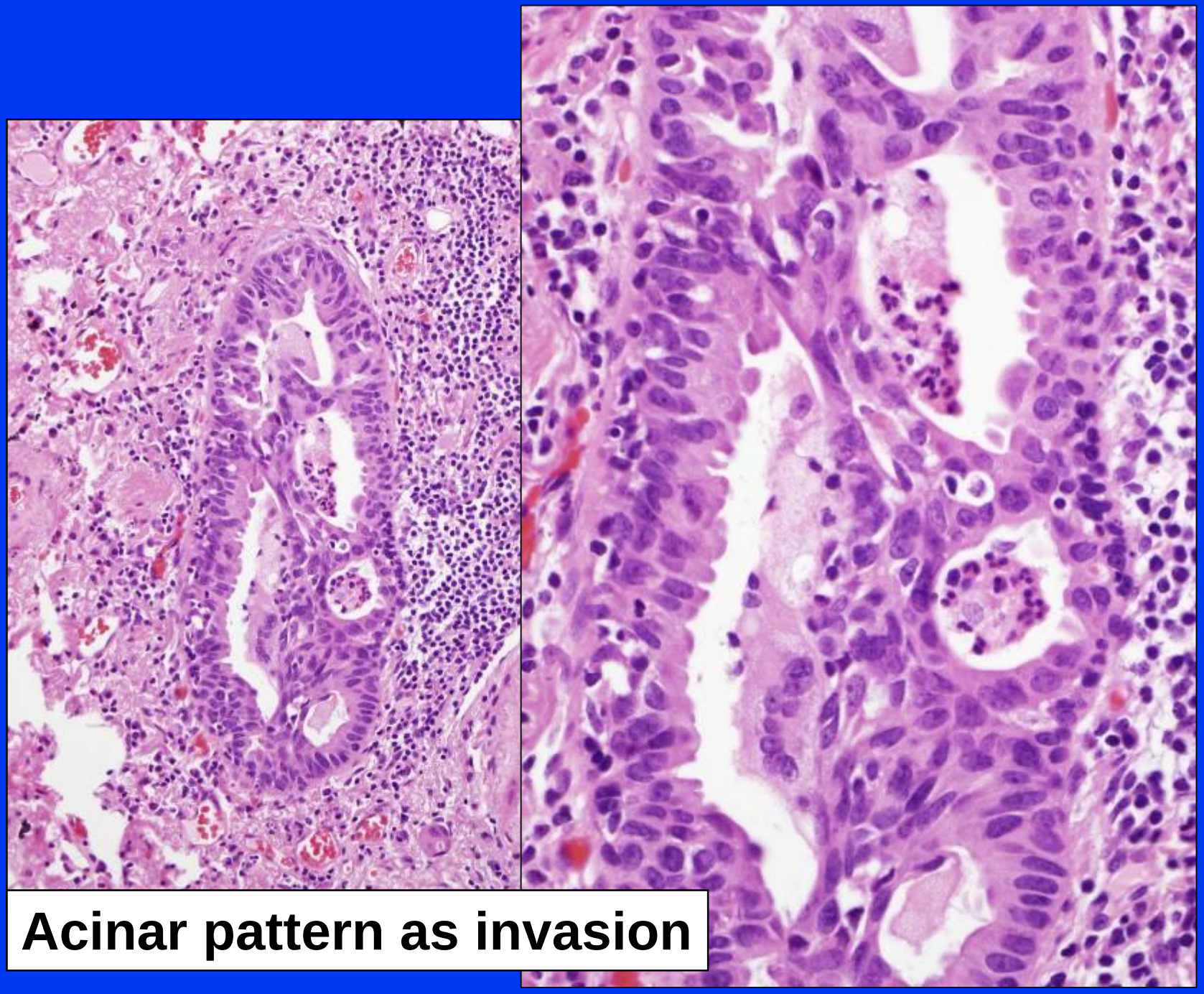
- Lepidic growth, ≤ 3 cm, ≤ 5 mm of invasion
- If multiple areas of micro-invasion present, the largest area focus should be ≤ 5 mm (do not add foci)
  - Estimate % invasive and multiply by tumor size
- No necrosis, lymphovascular or pleural invasion

Defining Invasion

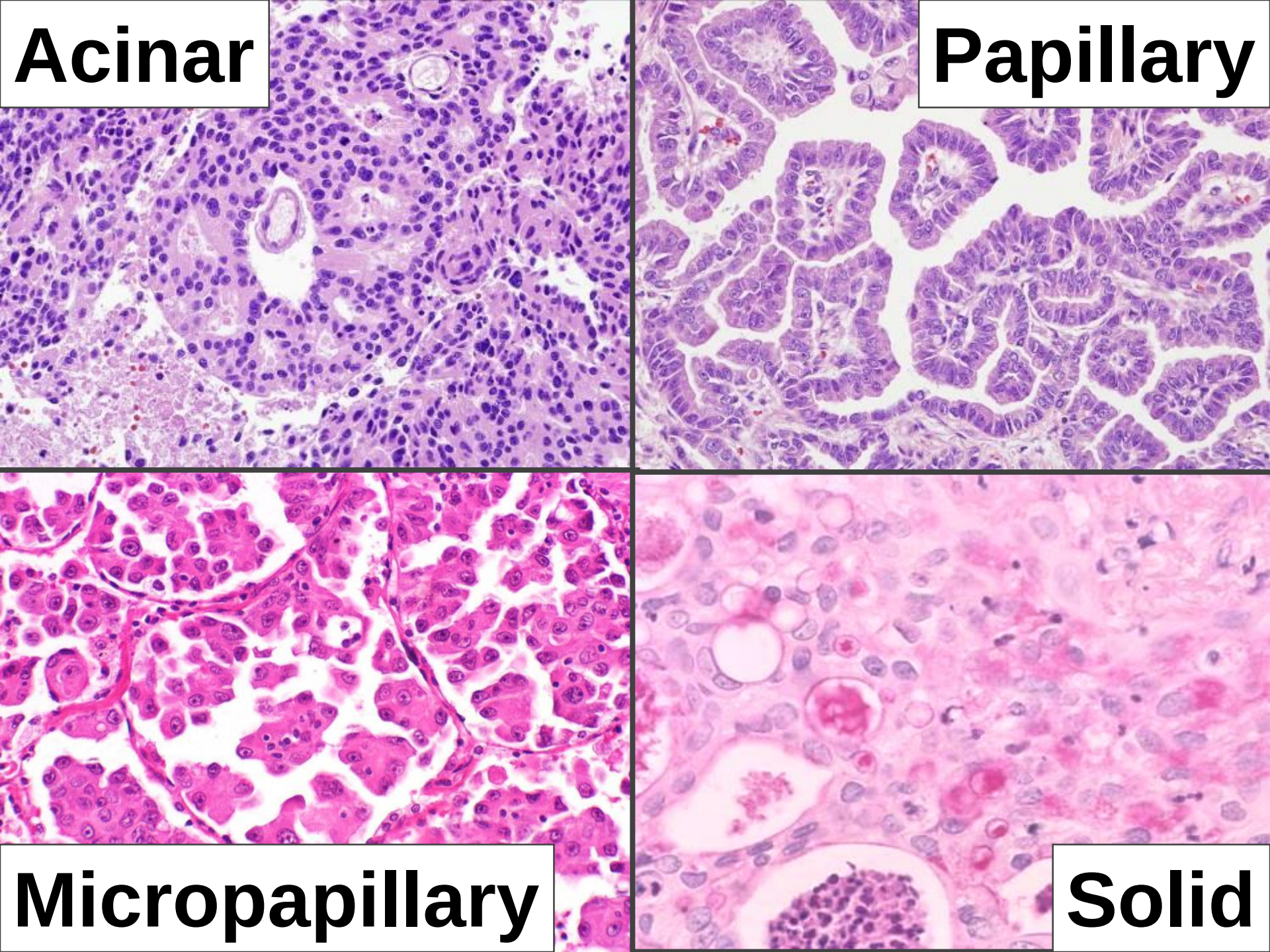
- Does not equate with alveolar collapse/ septal widening or sclerosis
- Requires
  - Angulated glands or single cells infiltrating stroma with stromal desmoplasia
  - Destruction of elastica (VVG, laminin)
  - Presence of histologic type other than lepidic pattern e.g. acinar, micropapillary


Angulated glands
as invasion ≤ 5 mm


Sm cell groups and papillae as invasion

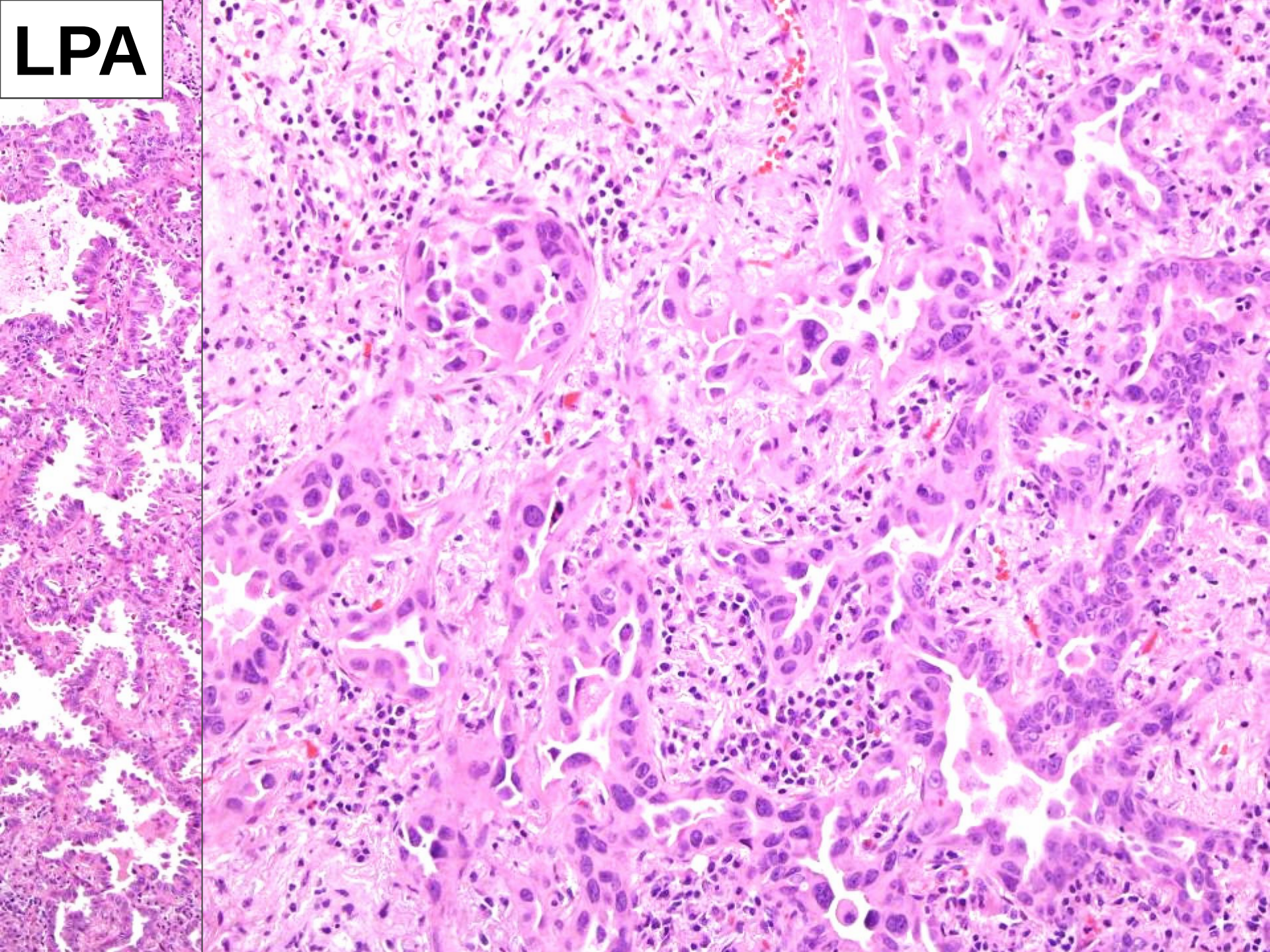


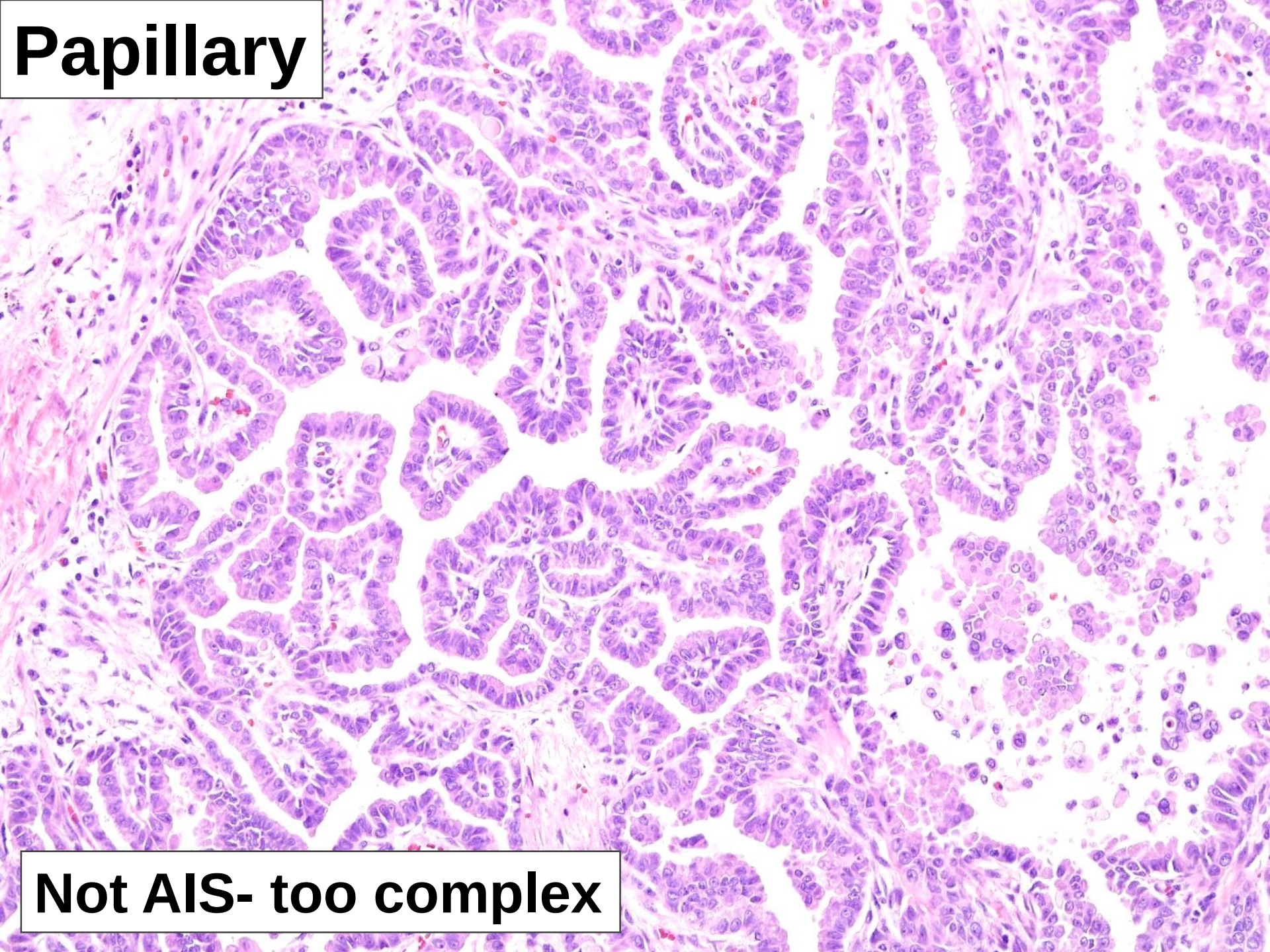
Acinar pattern as invasion


Acinar
Papillary
Micropapillary
Solid

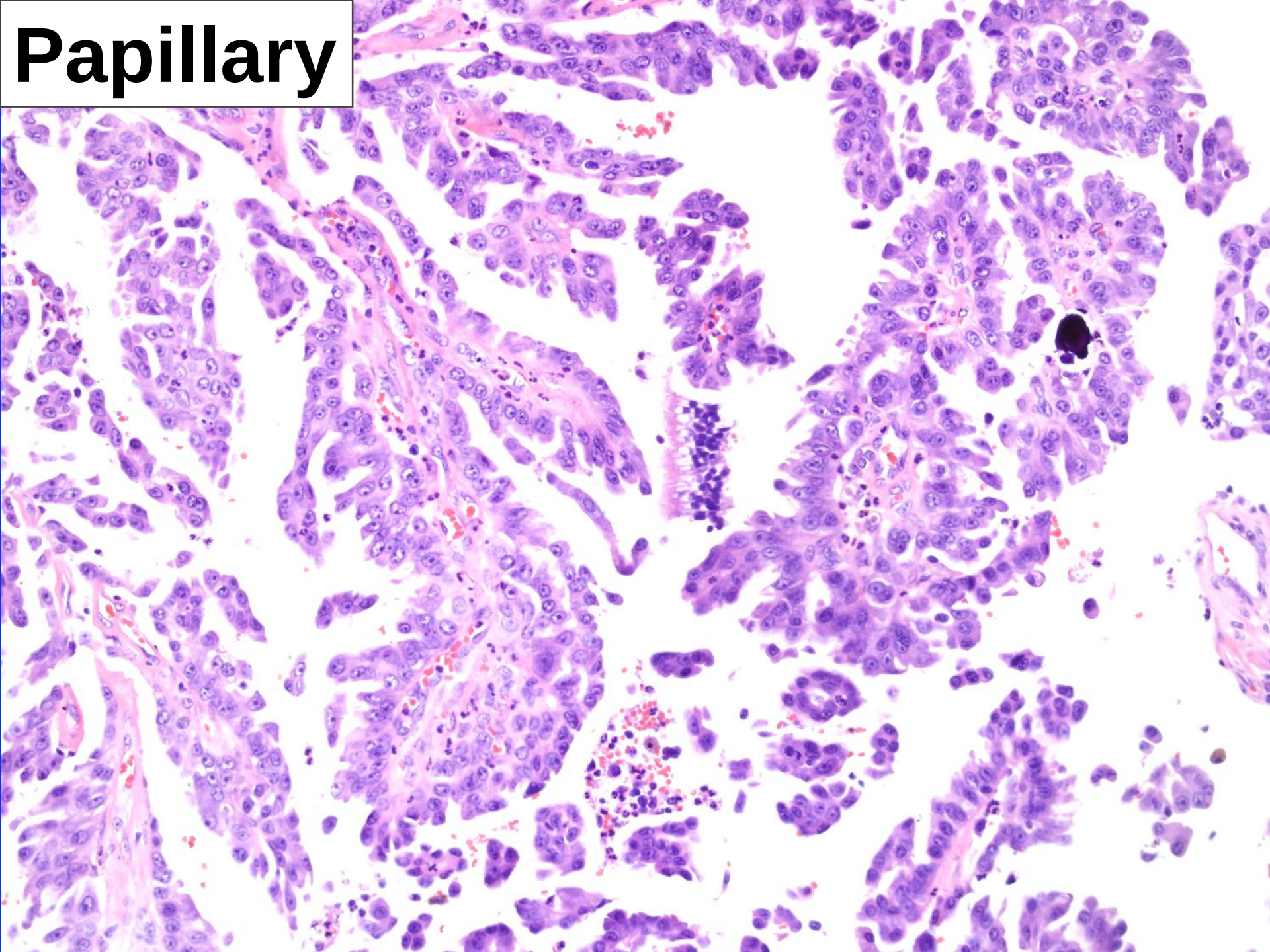
Lepidic Predominant Adenocarcinoma

- Non mucinous histology
- Lepidic growth in majority of tumor
- Invasion > 5 mm in at least one focus
- Lymphatic, vascular, or pleural invasion may be present
- Necrosis may be present

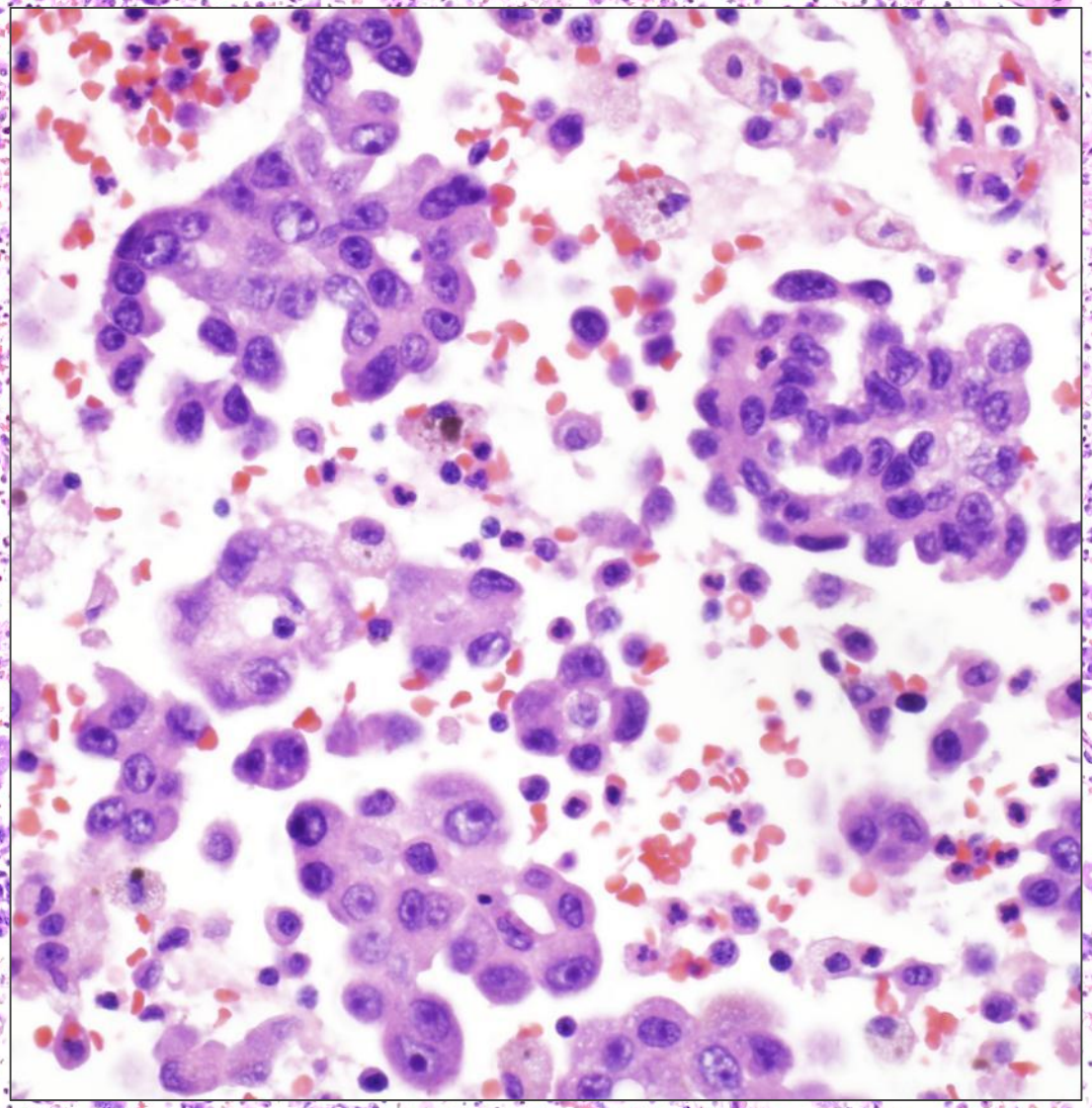

LPA


Papillary
Not AIS- too complex

Papillary



Micropapillary

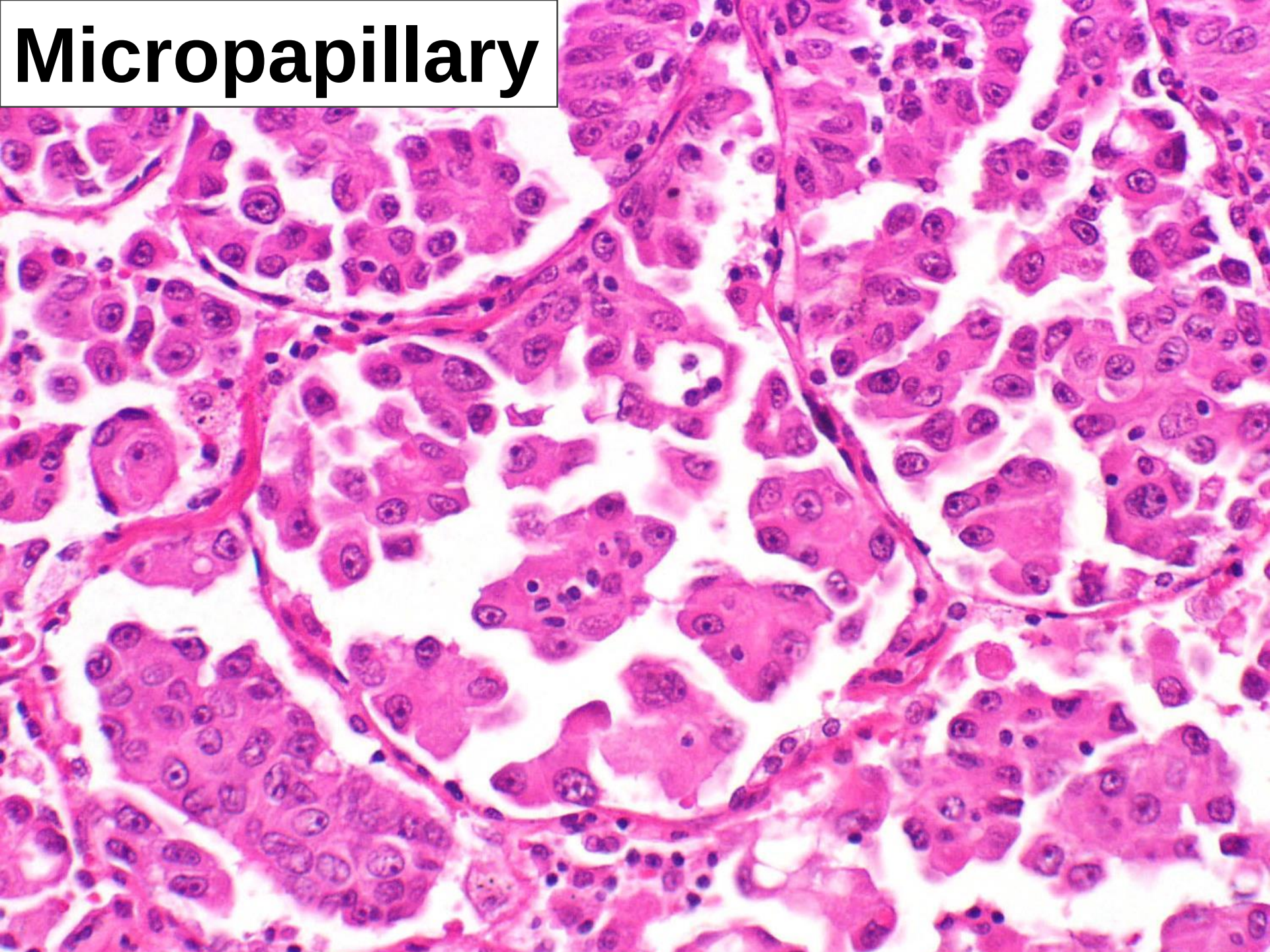


Criteria for Micropapillary

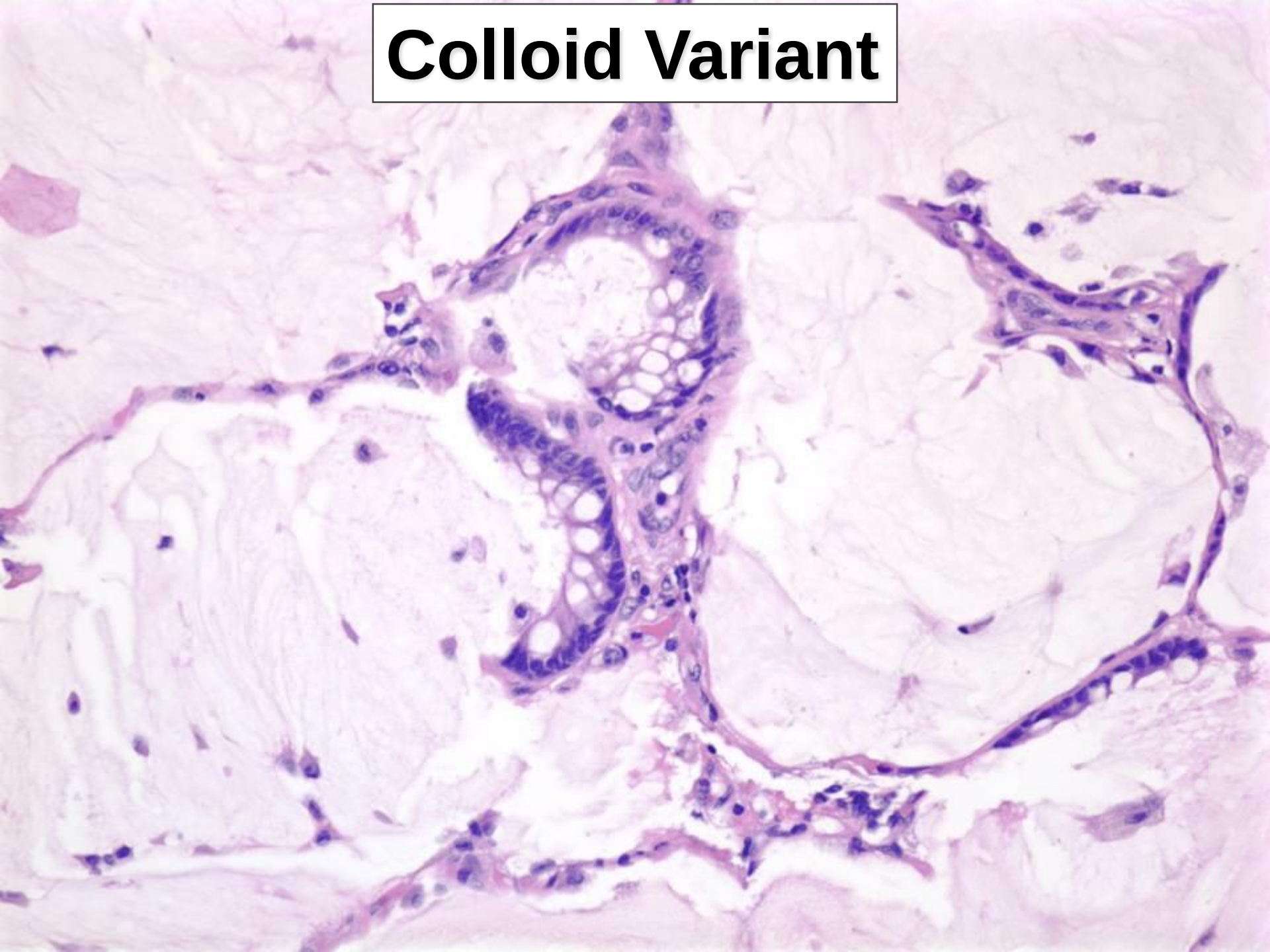
- Epithelial nest anastomosis /confluence
- Multiple nests in same alv. space
- Small/medium tumor nest size (1-12 cells)
- Intracytoplasmic vacuoles

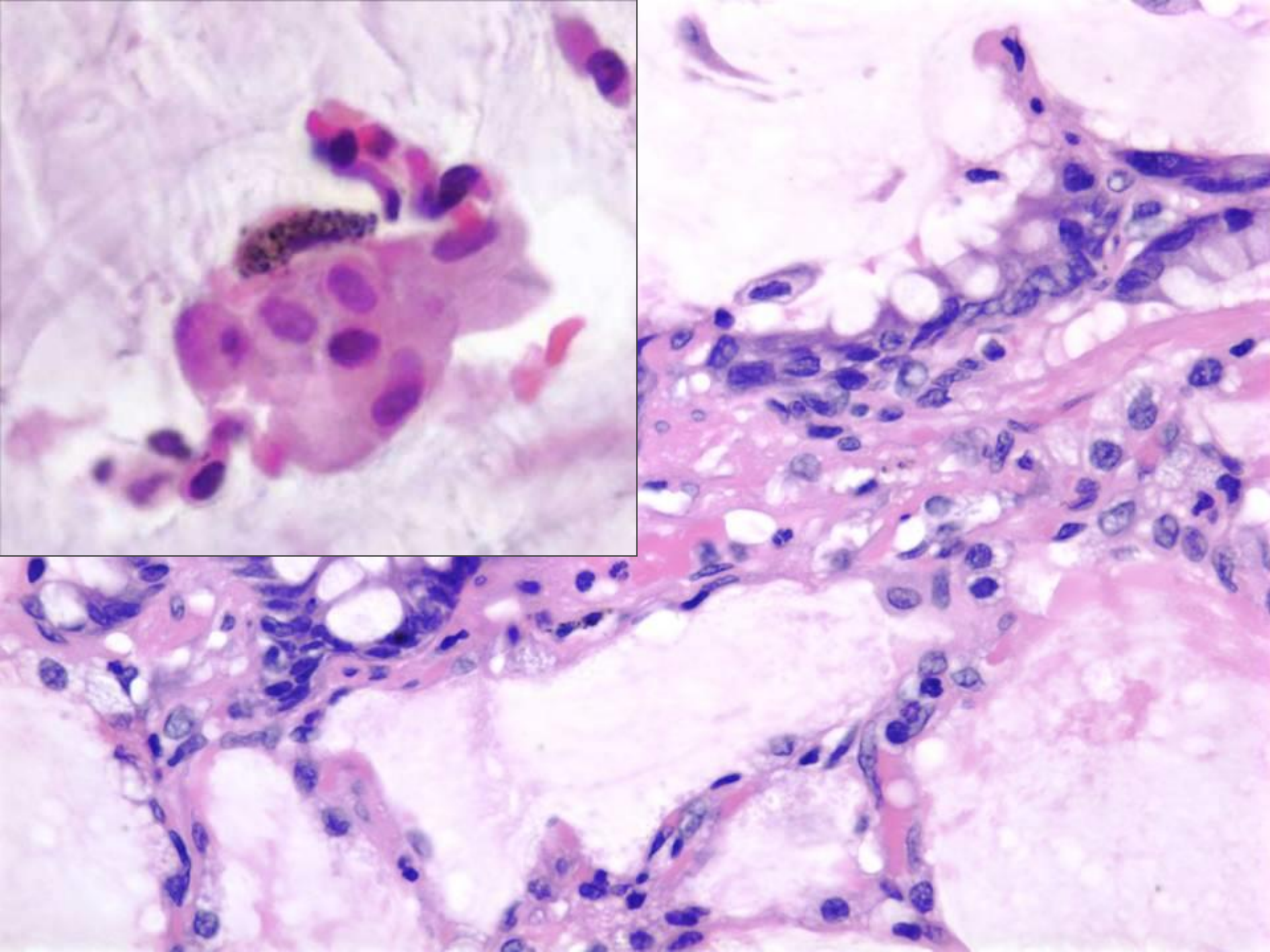
Monroig-Bosque PC et al. Mod Pathol 2018 31(S2):741

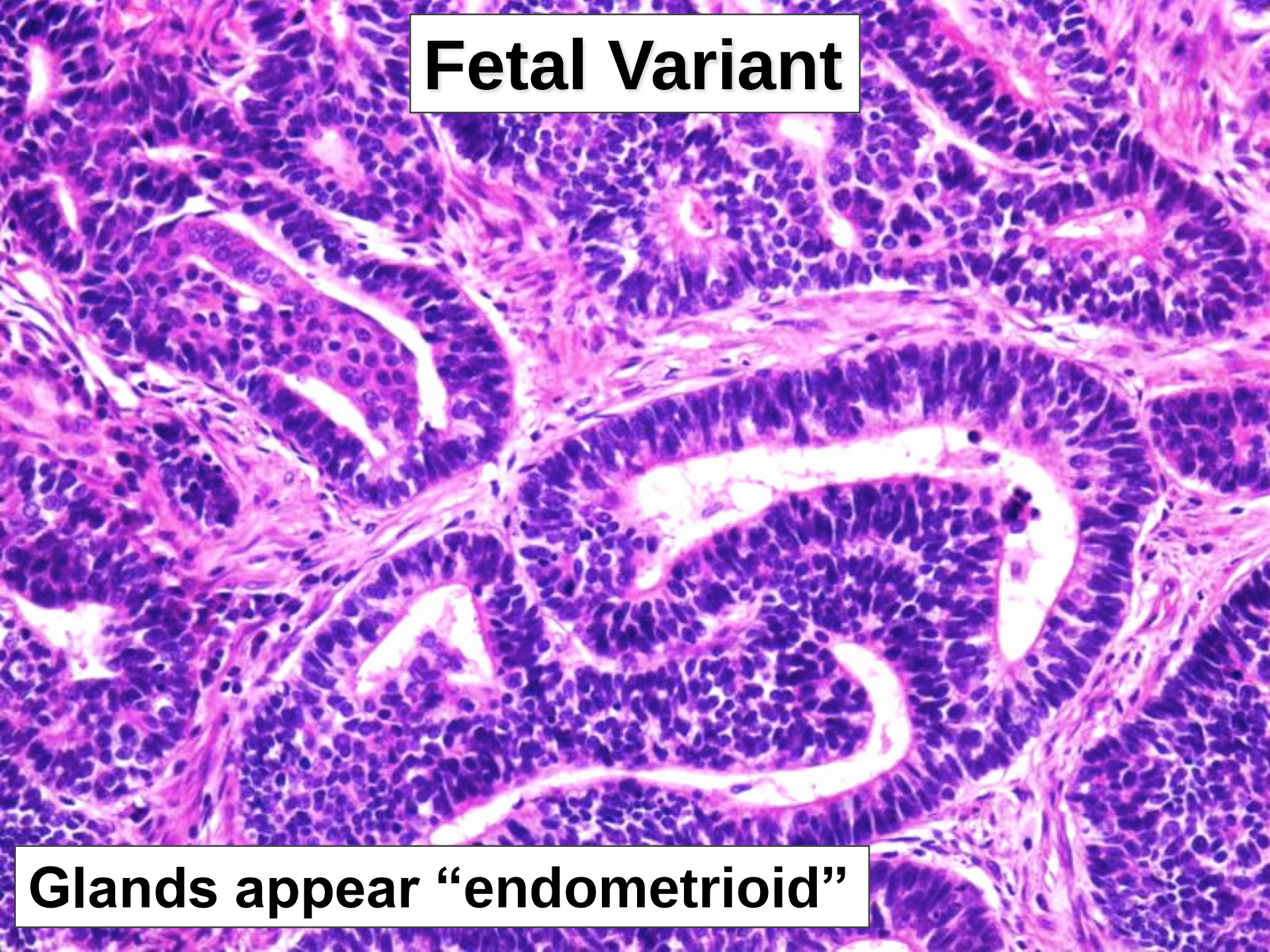
Micropapillary



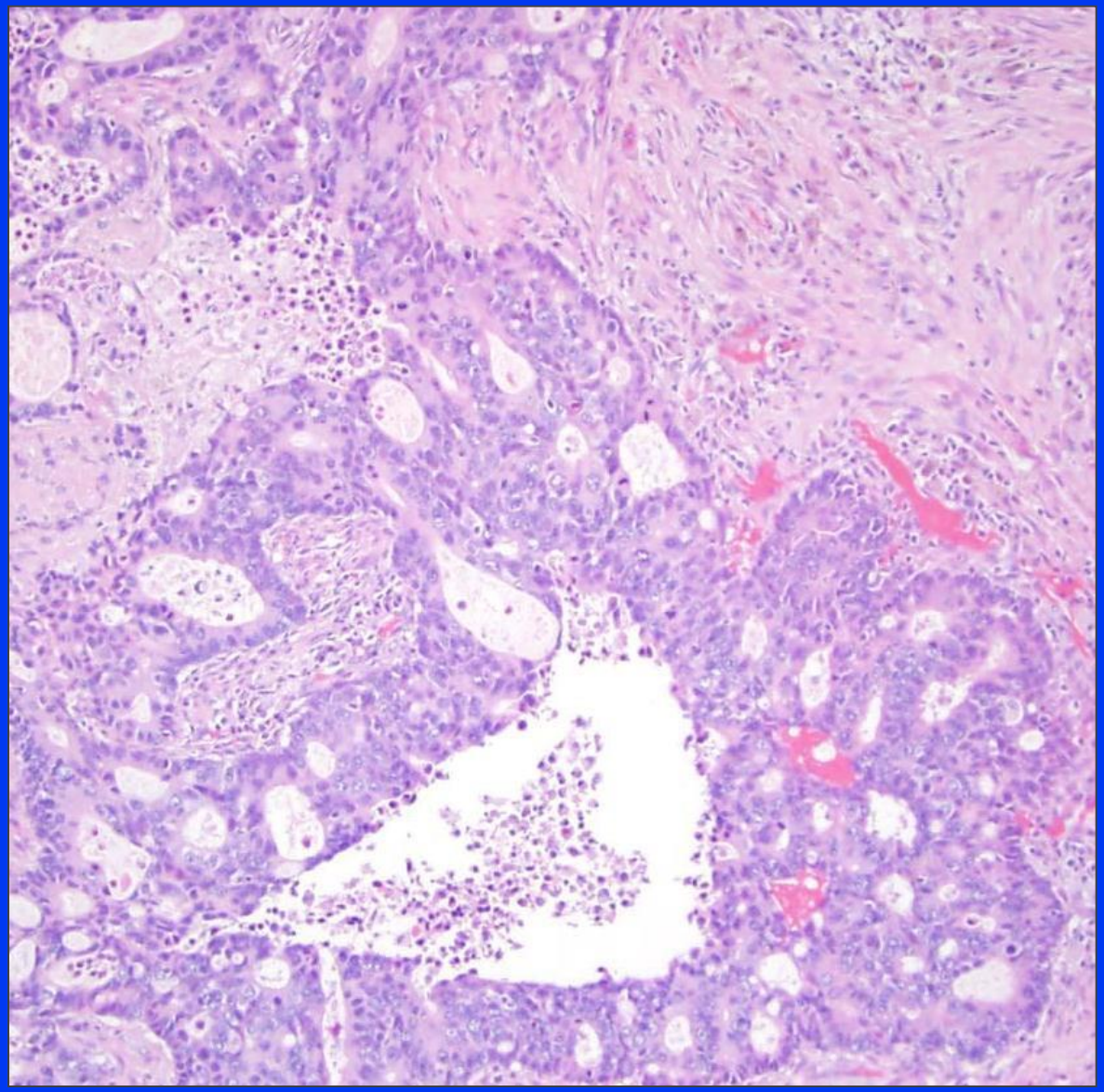
Colloid Variant

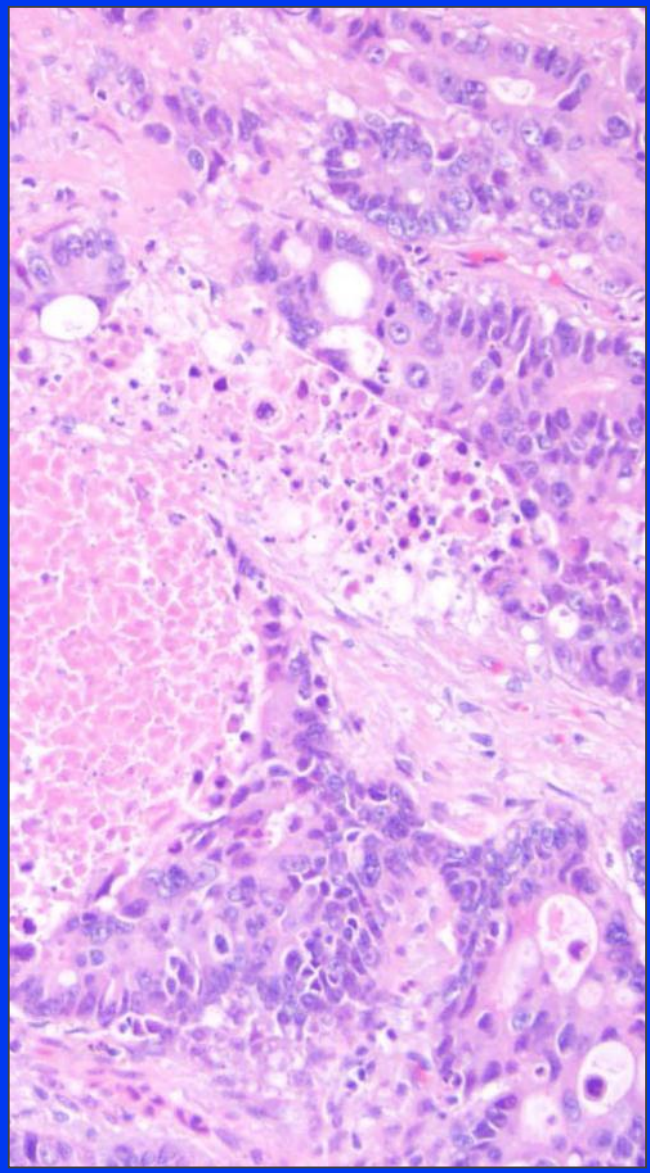





Fetal Variant
Glands appear “endometrioid”

Enteric Variant





Courtesy of Dr. Lindsay Schmidt, Ann Arbor, MI

Small Biopsy and Cytology Diagnosis

On small biopsies and cytology specimens, sub-classification is recommended whenever possible e.g. squamous, adca

Guidelines for Diagnosis

Look for desmosomes, mucin or glands. If absent…

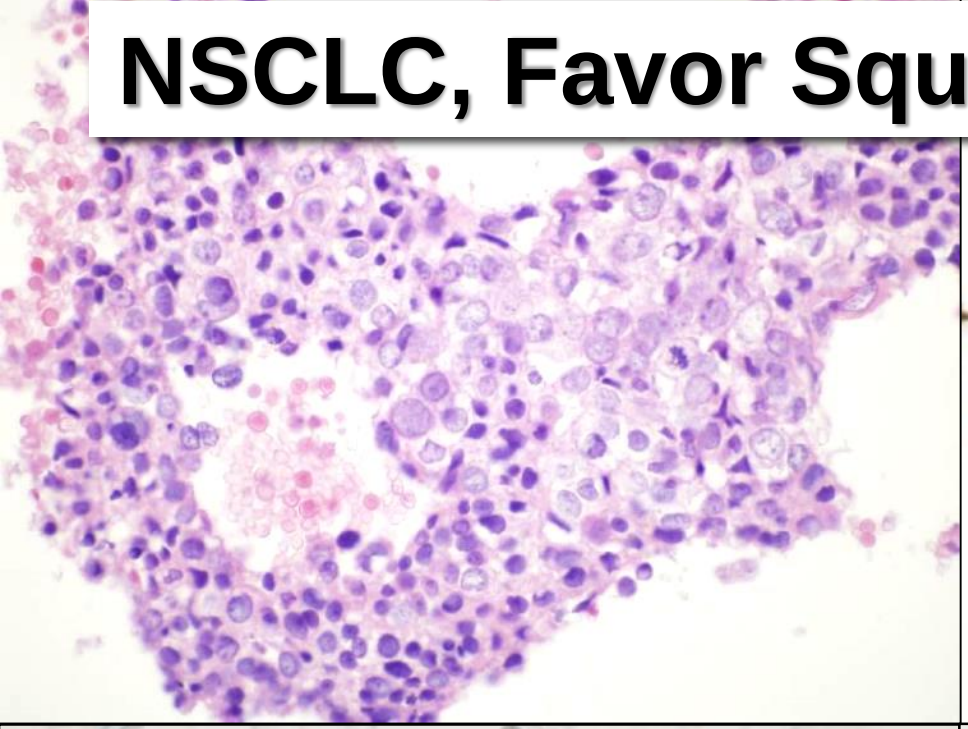
WHO Recommendation for Small Biopsies and Cytology

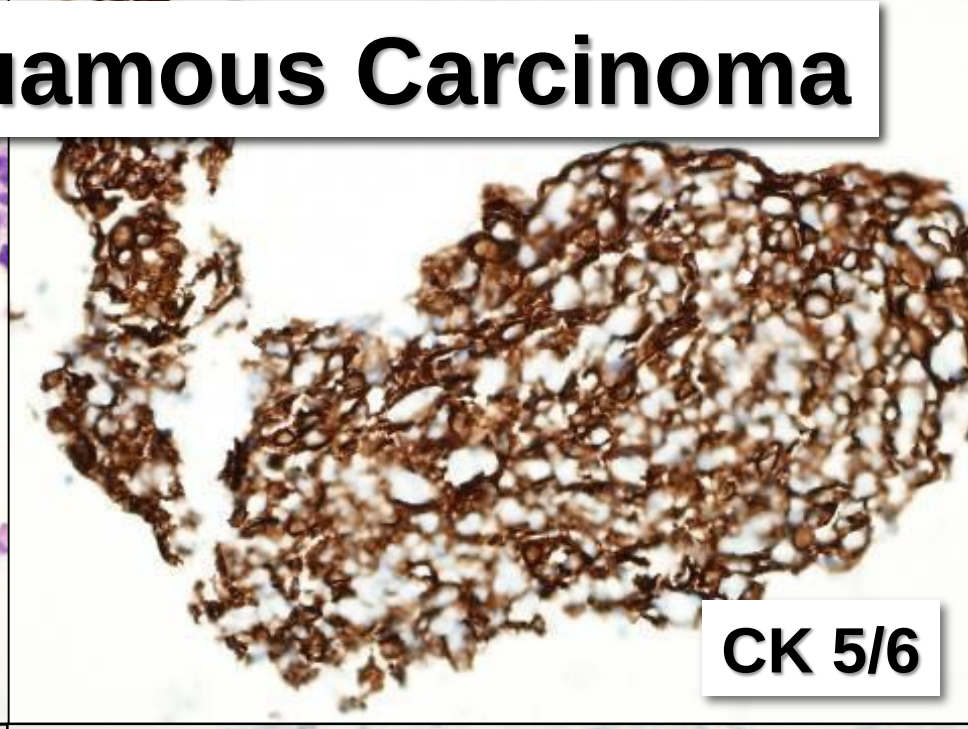
- Perform limited IHC panel
  - ✧ TTF-1
  - ✧ p40
- Conserve tissue for potential molecular testing
  - ✧ Split samples into multiple blocks

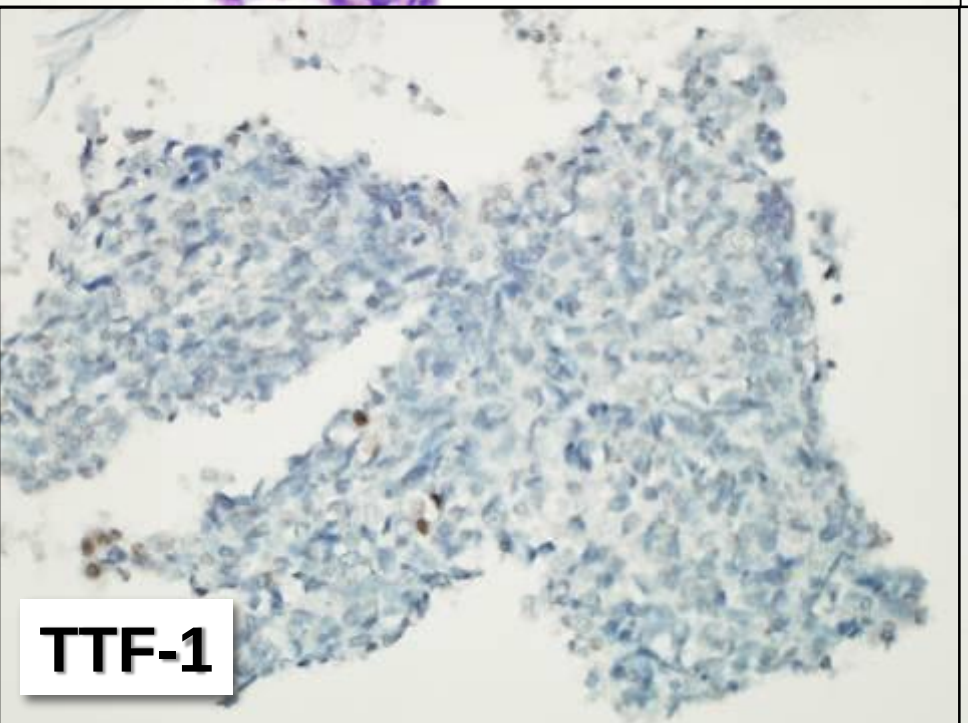
Small Biopsy and Cytology Diagnosis

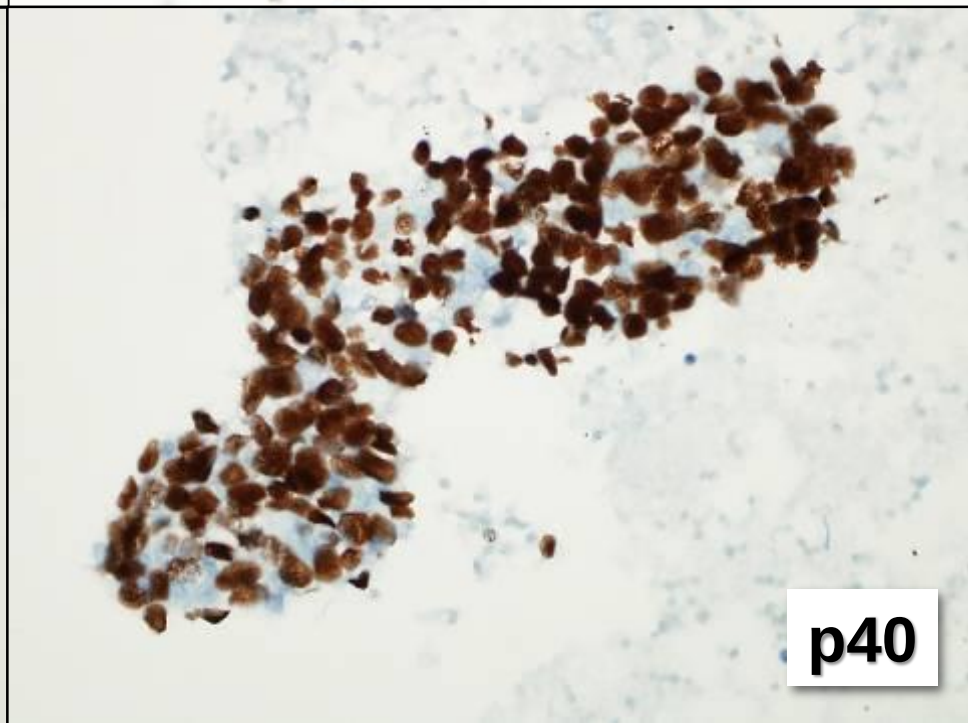
- Diagnostic categories when clear differentiation absent
  - NSCLC, favor Adca (+ TTF regardless of other markers)
  - NSCLC, favor Sqca (+ and – markers all favor)
  - NSCLC NOS – diagnose sparingly

NSCLC, Favor Squamous Carcinoma









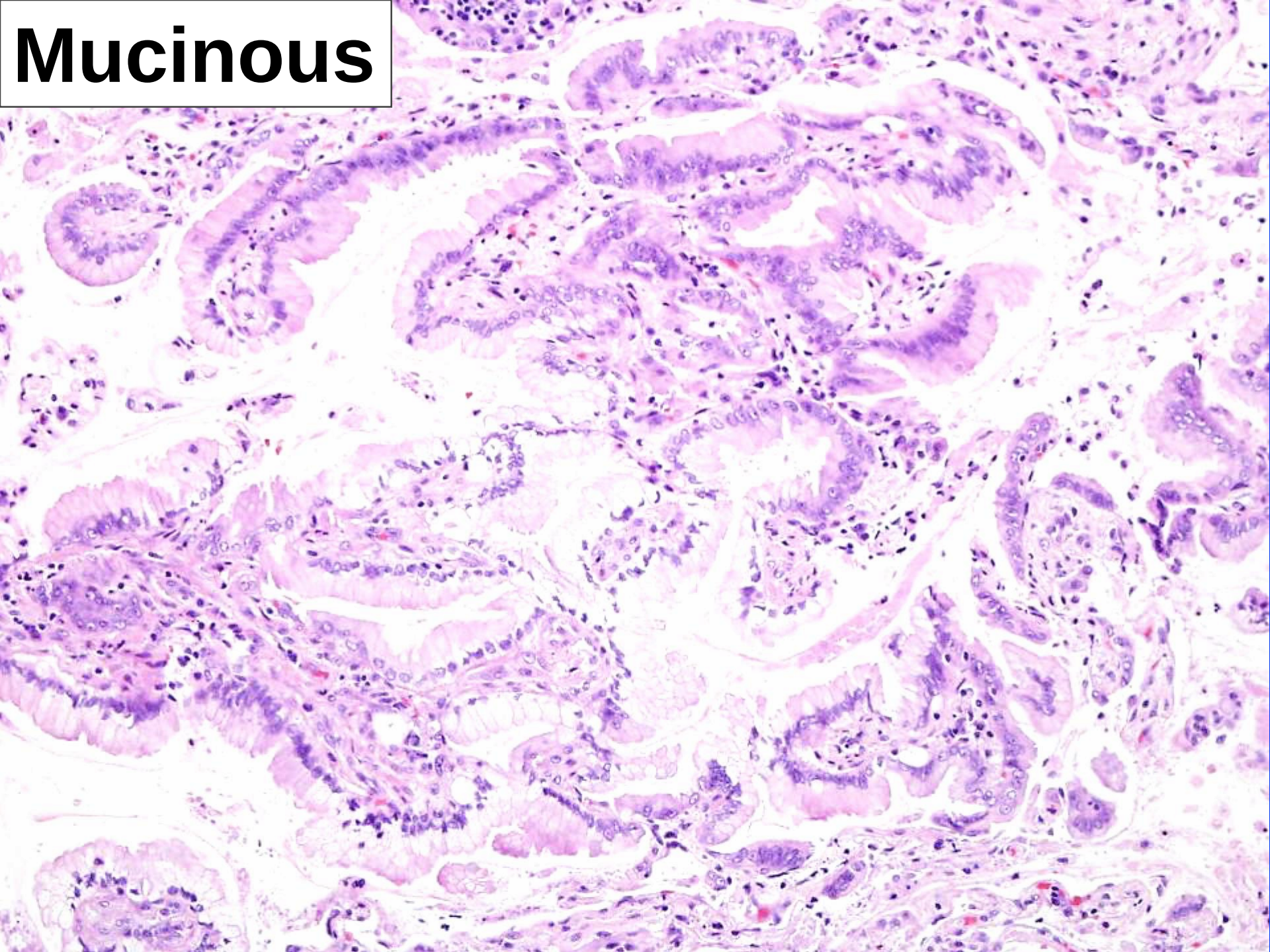
Additional Caveats

- Adca may appear pseudosquamous
- Densely eosinophilic cytoplasm or sharp intercytoplasmic borders in the absence of frank keratinization, pearls or intercellular bridges is ***insufficient*** for squamous cell
- Many *EGFR* mutated cases of squamous carcinoma, likely represent adenosquamous ca or pseudosquamous ca

Predominant Pattern	Grade
AIS/MIA	Low
Lepidic	Intermediate
Papillary	
Acinar	
Mucinous	High
Colloid	
Solid	
Micropapillary	

Sica G. et al. Am J Surg Pathol 2010;34:1155–1162

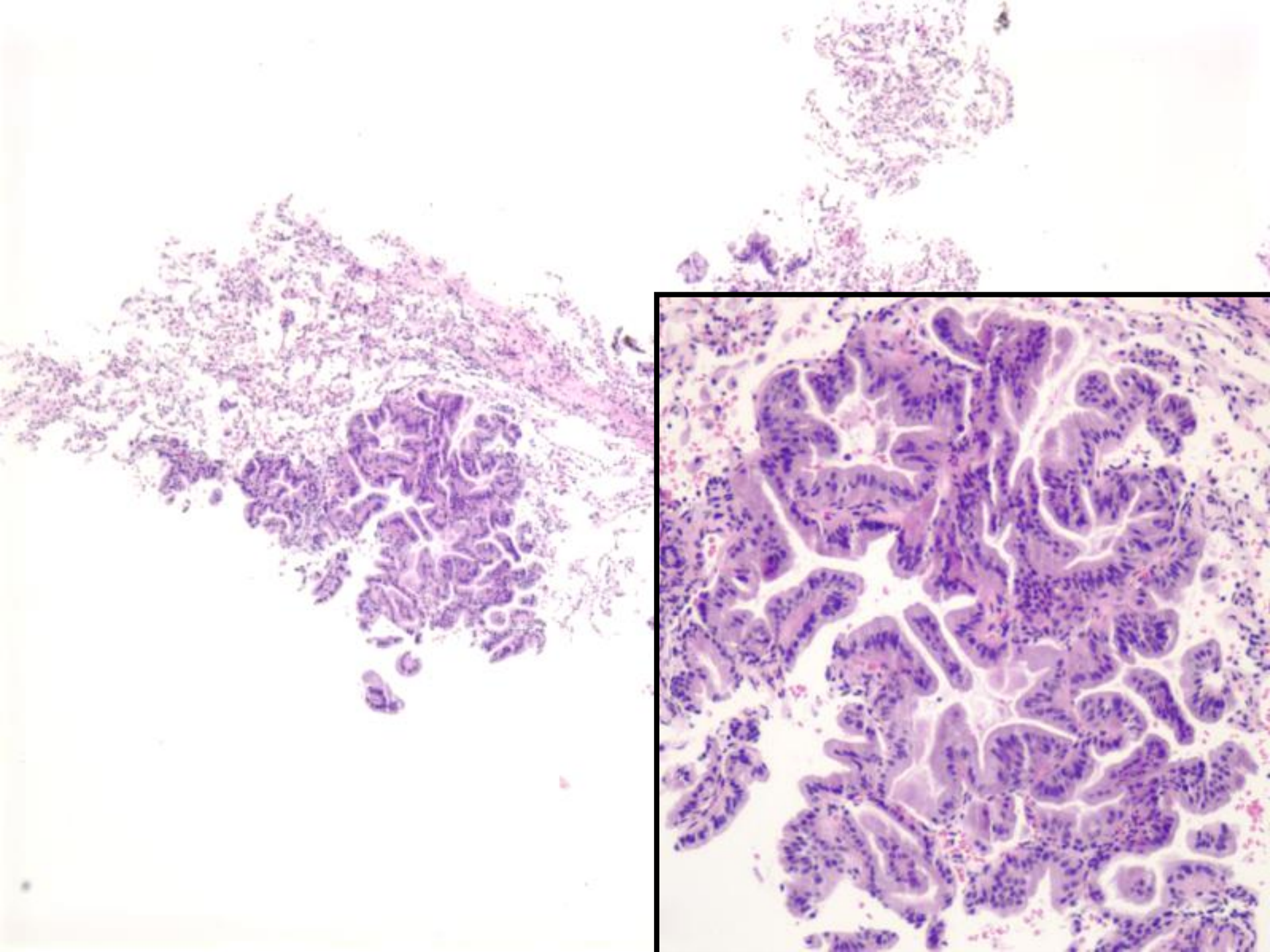
Mucinous

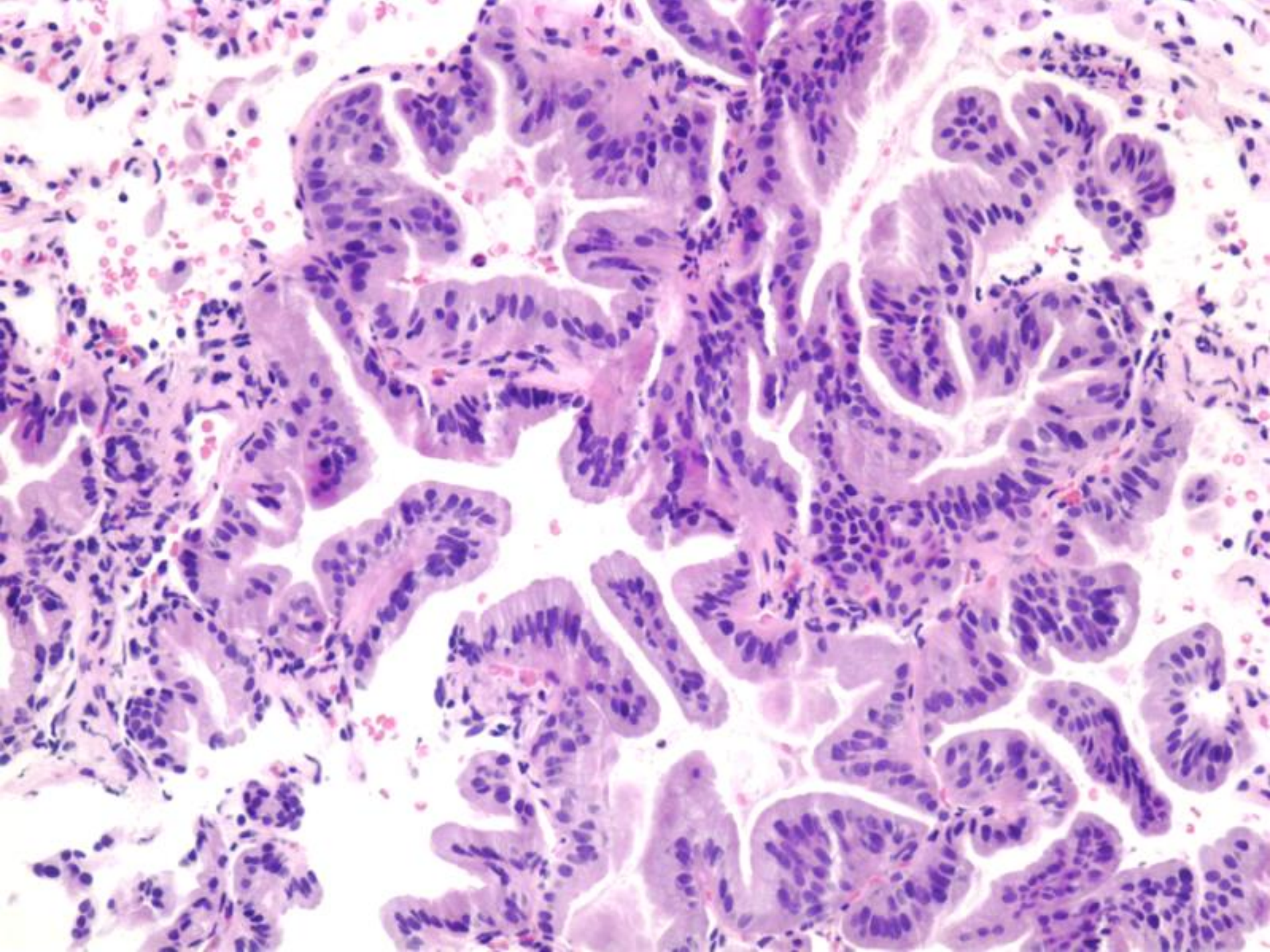


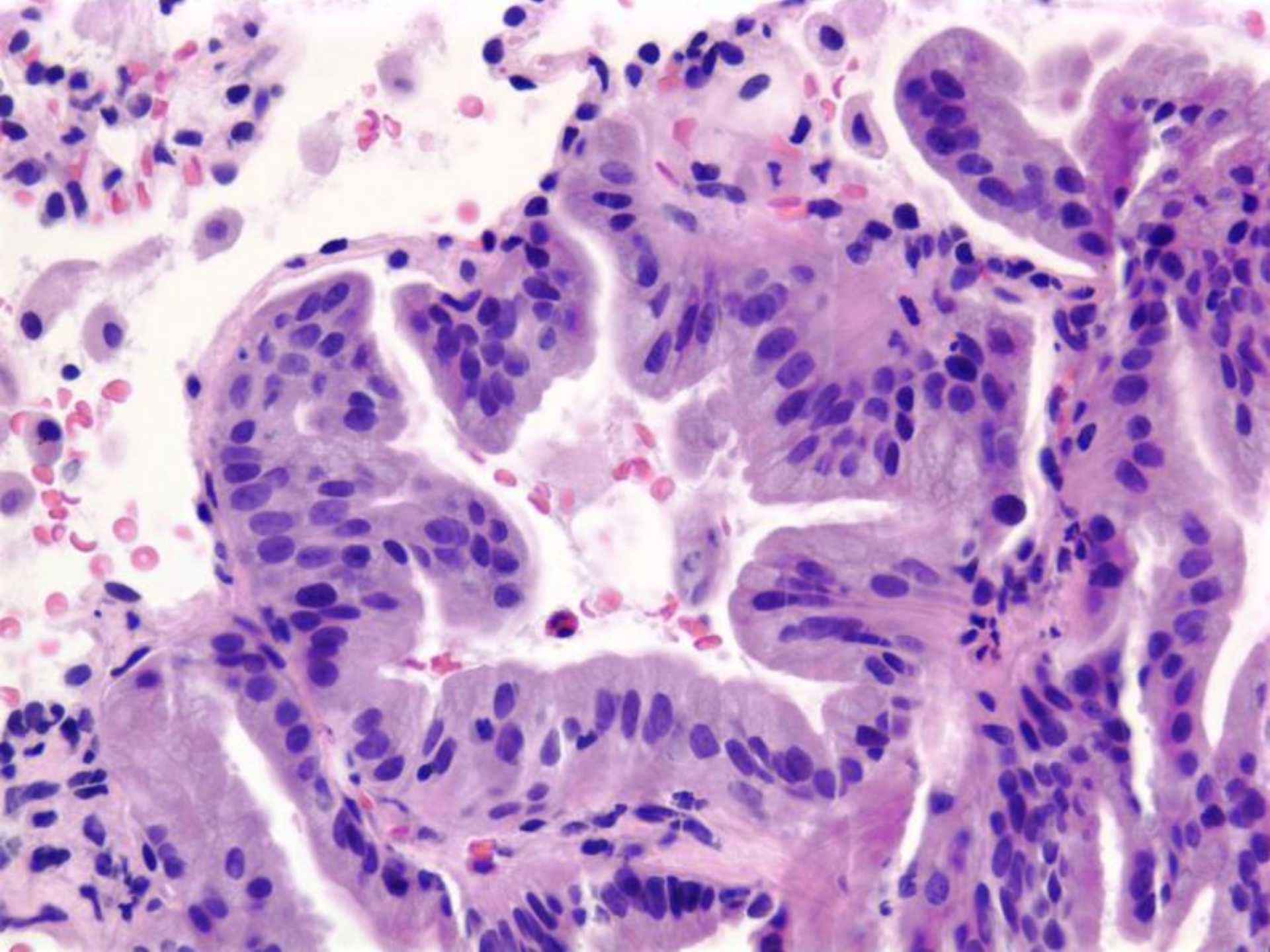
Diagnosis of ADCA on Needle or Transbronchial Biopsy

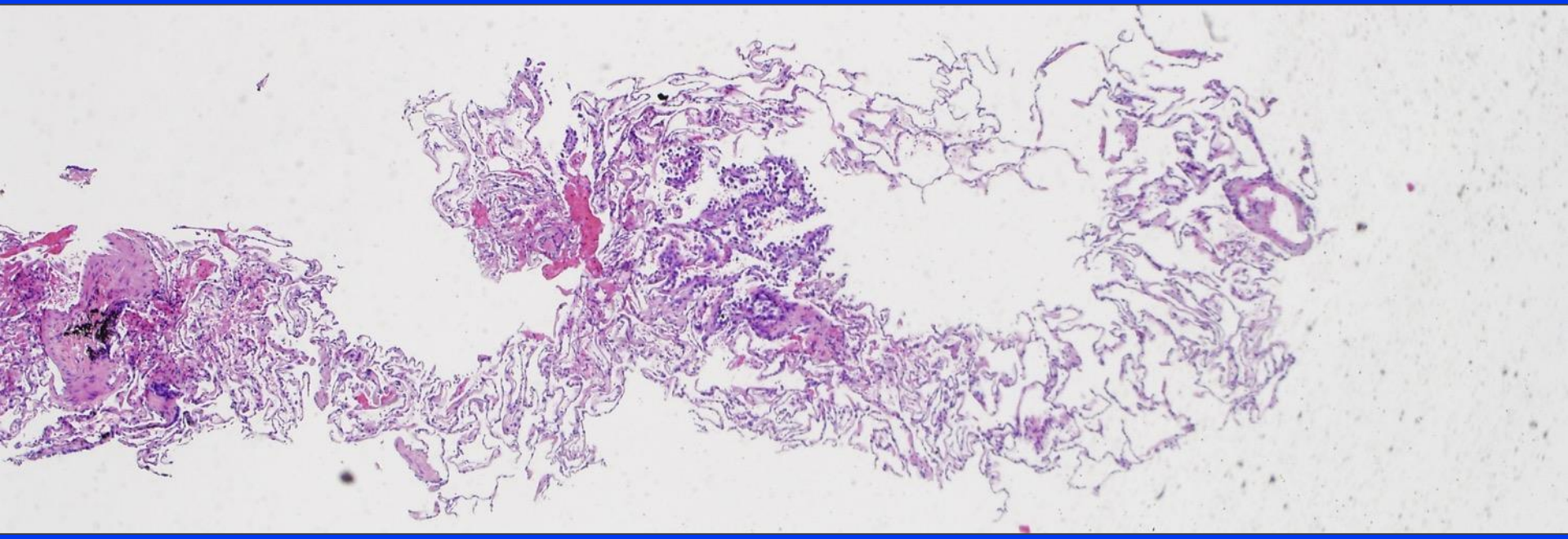
What features suggest adca?

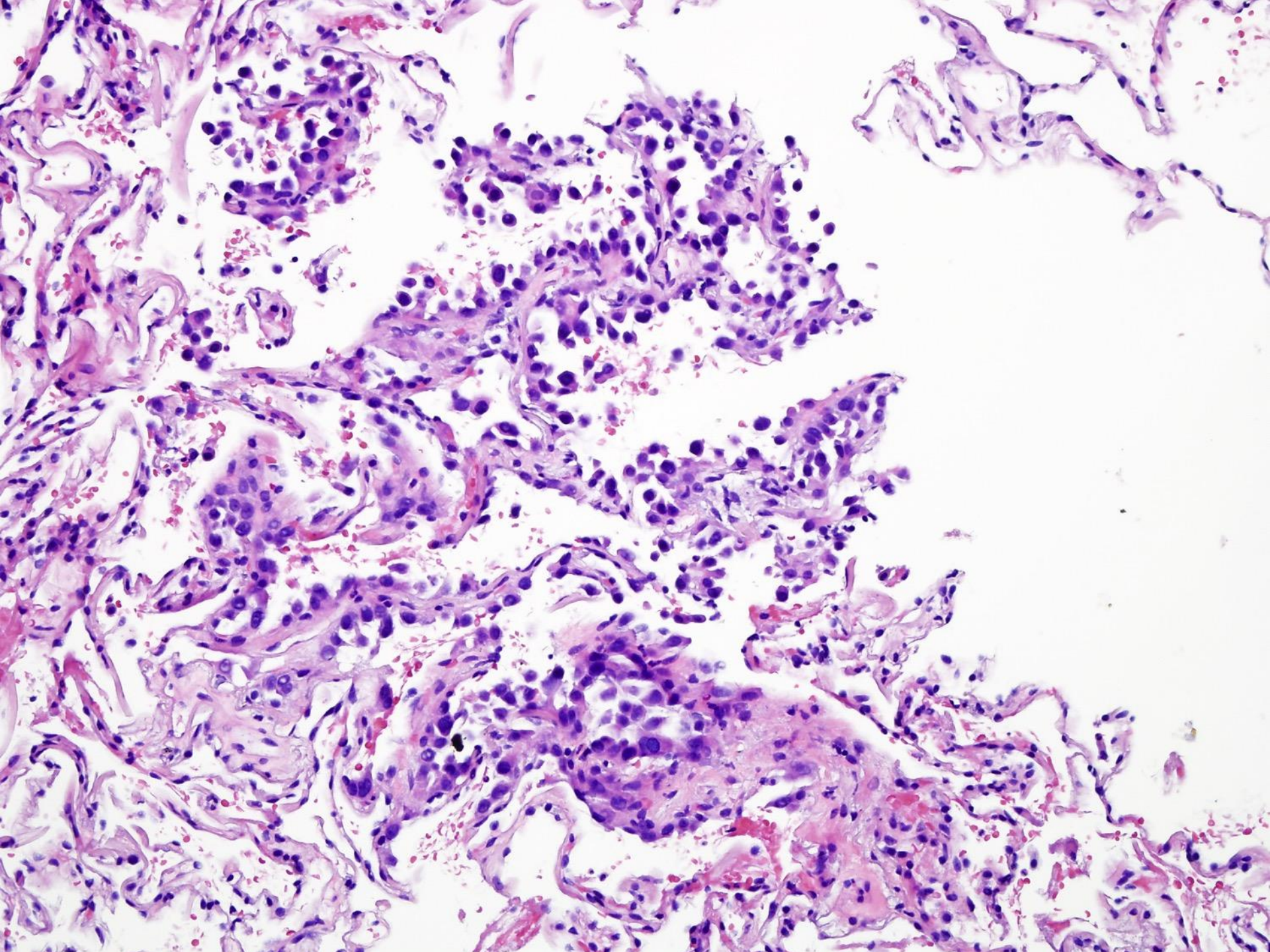
- Large cell size
- Monotony of cell population
- Subtle nuclear pleomorphism
- Uniform population of mucinous cells
- Lack of cilia

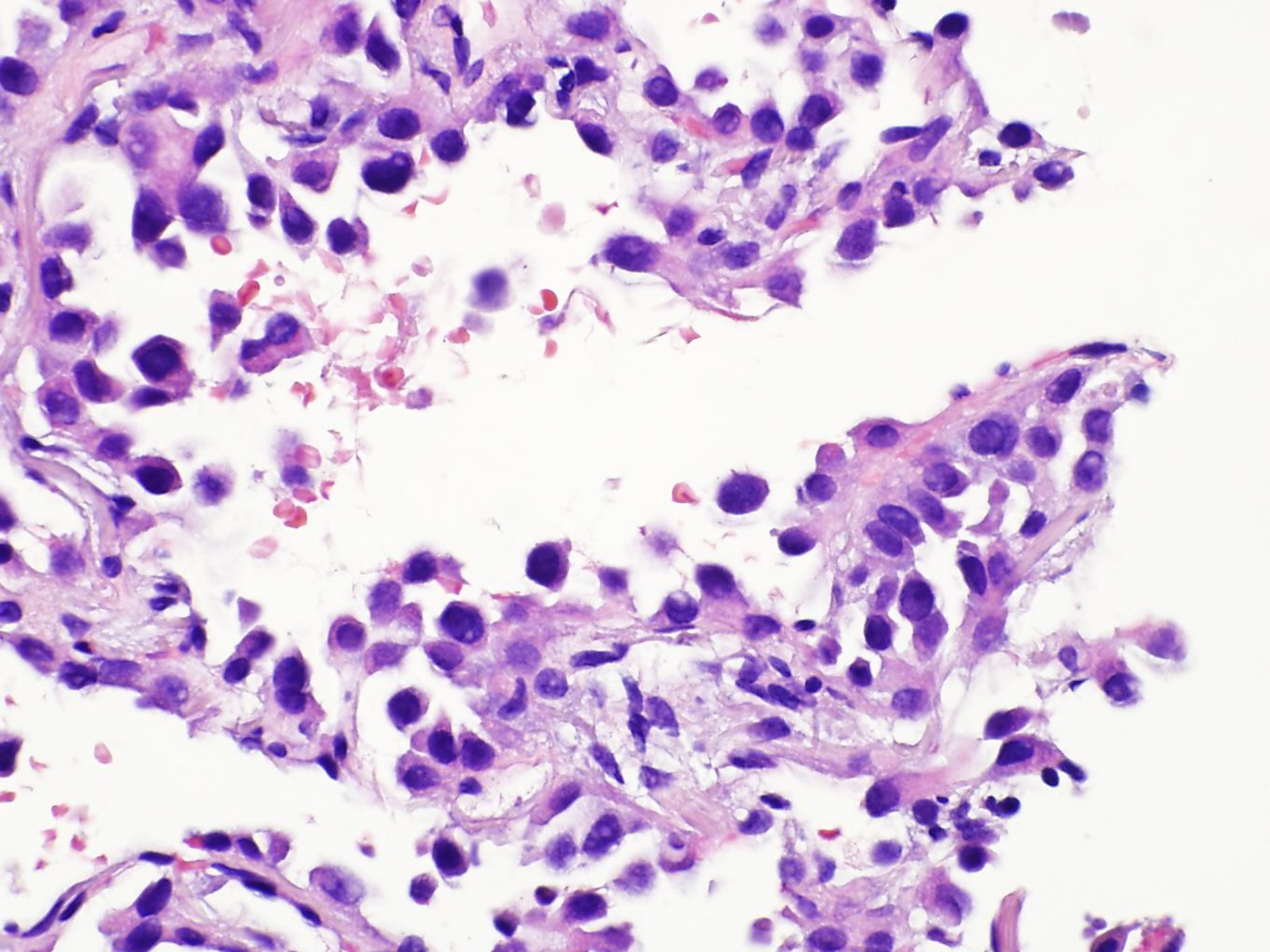


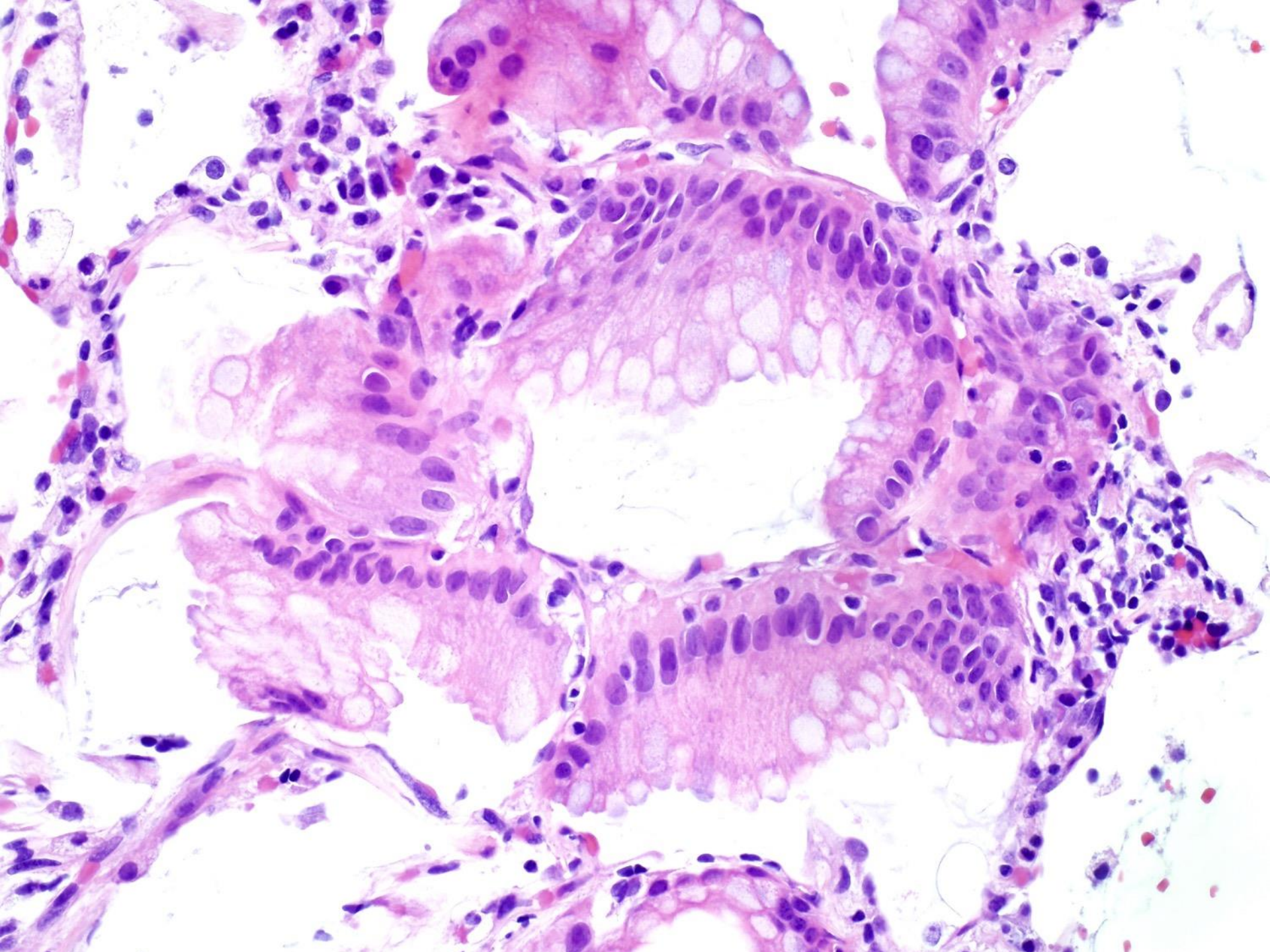


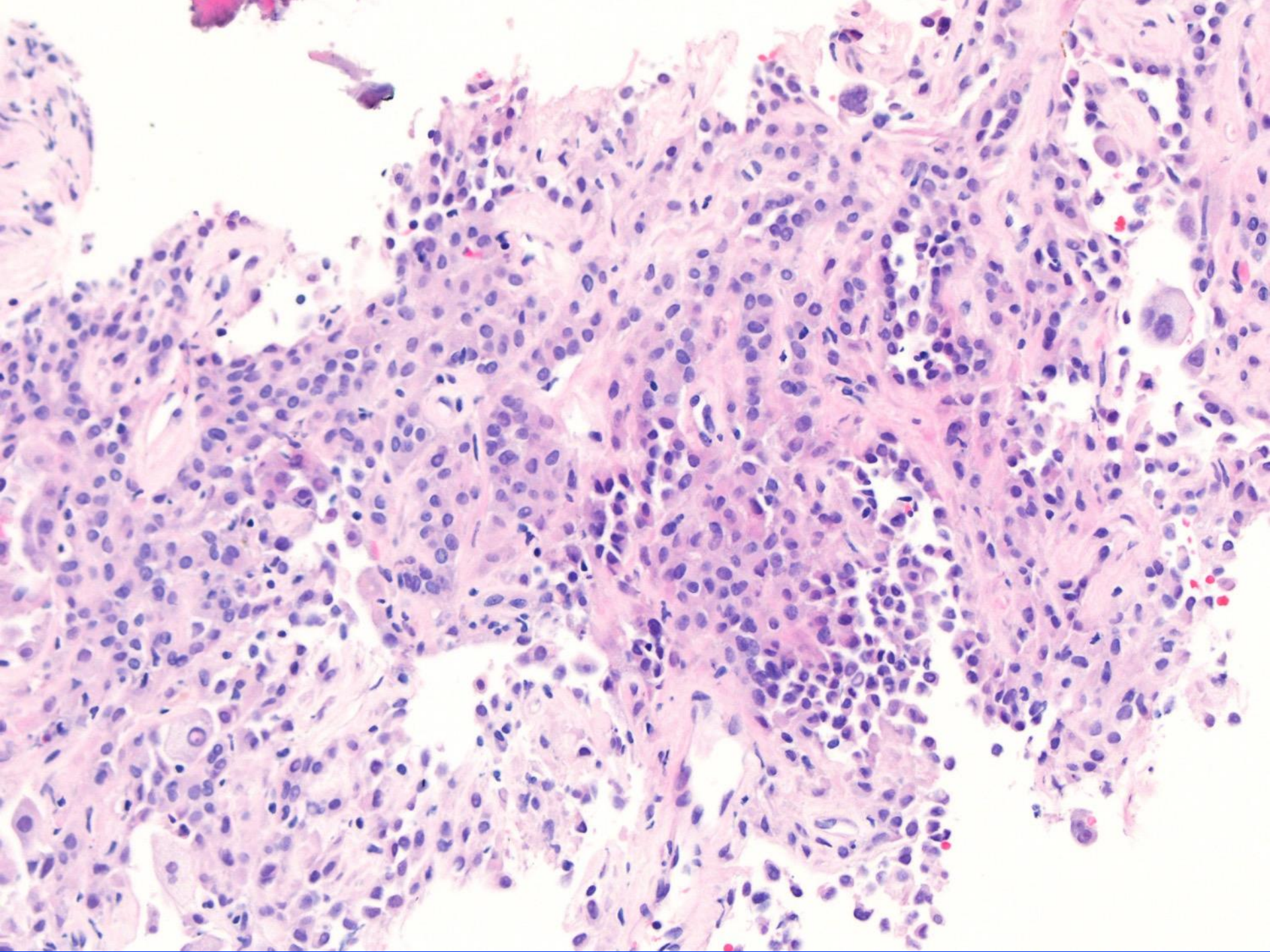


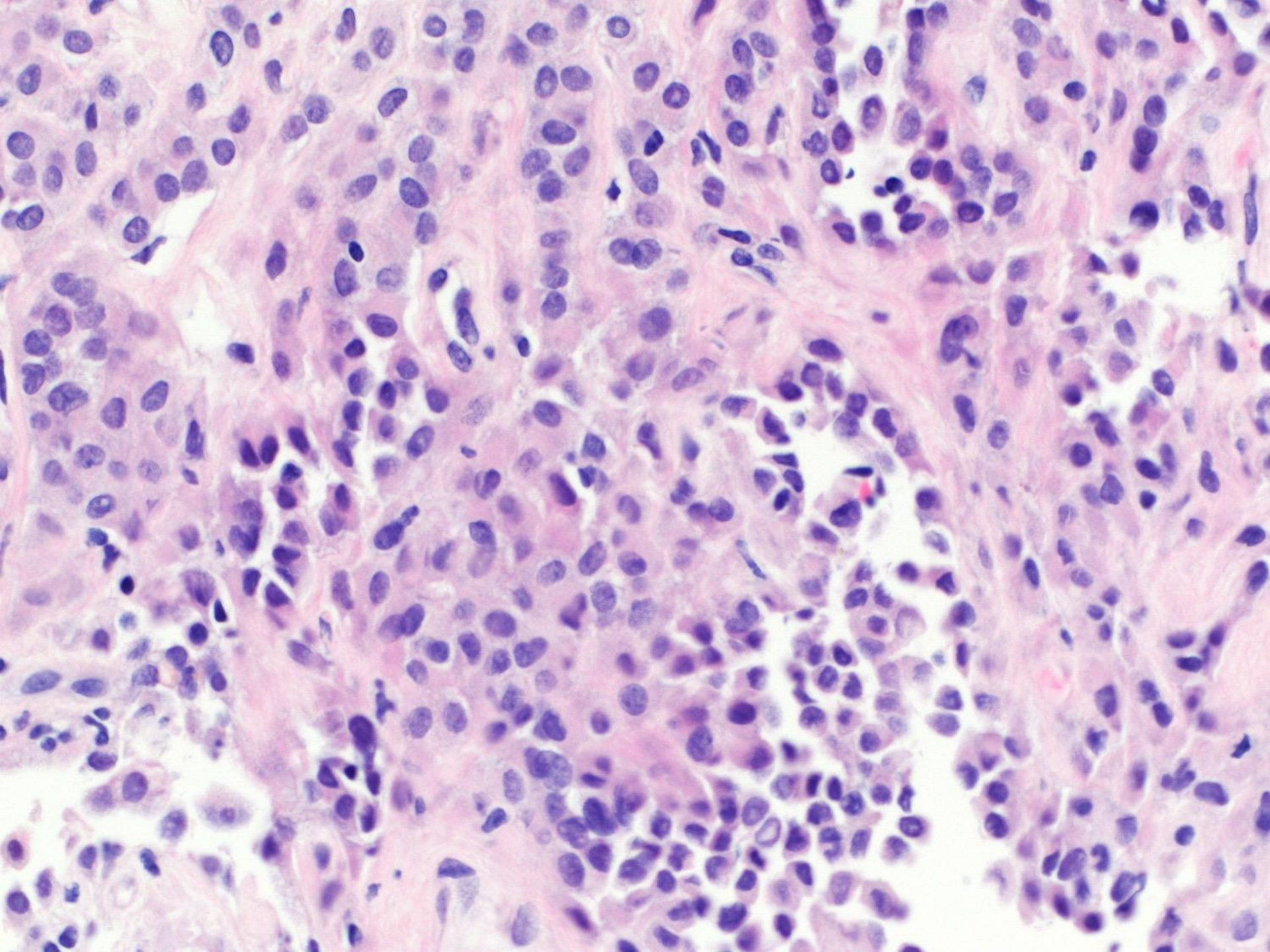


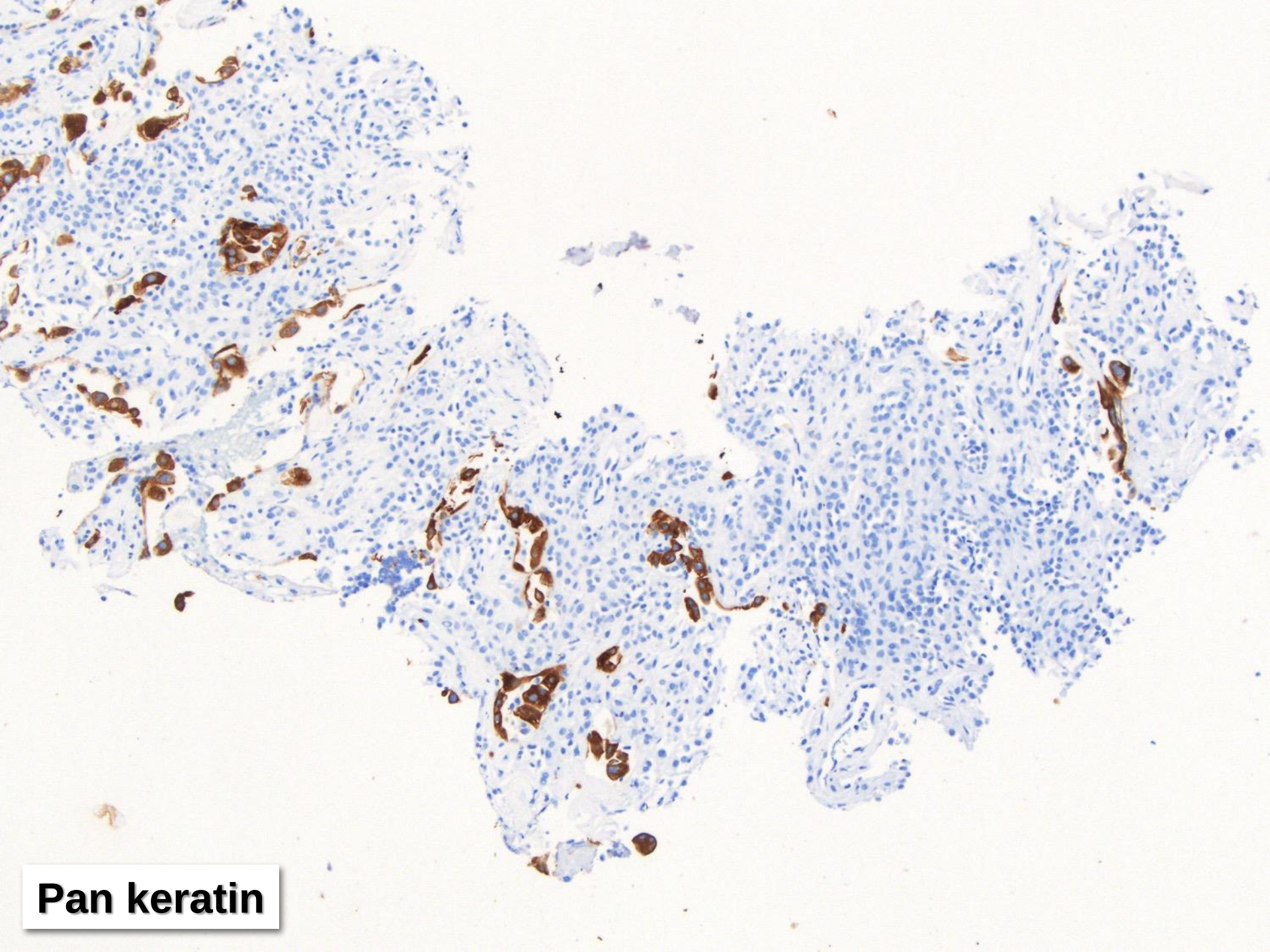


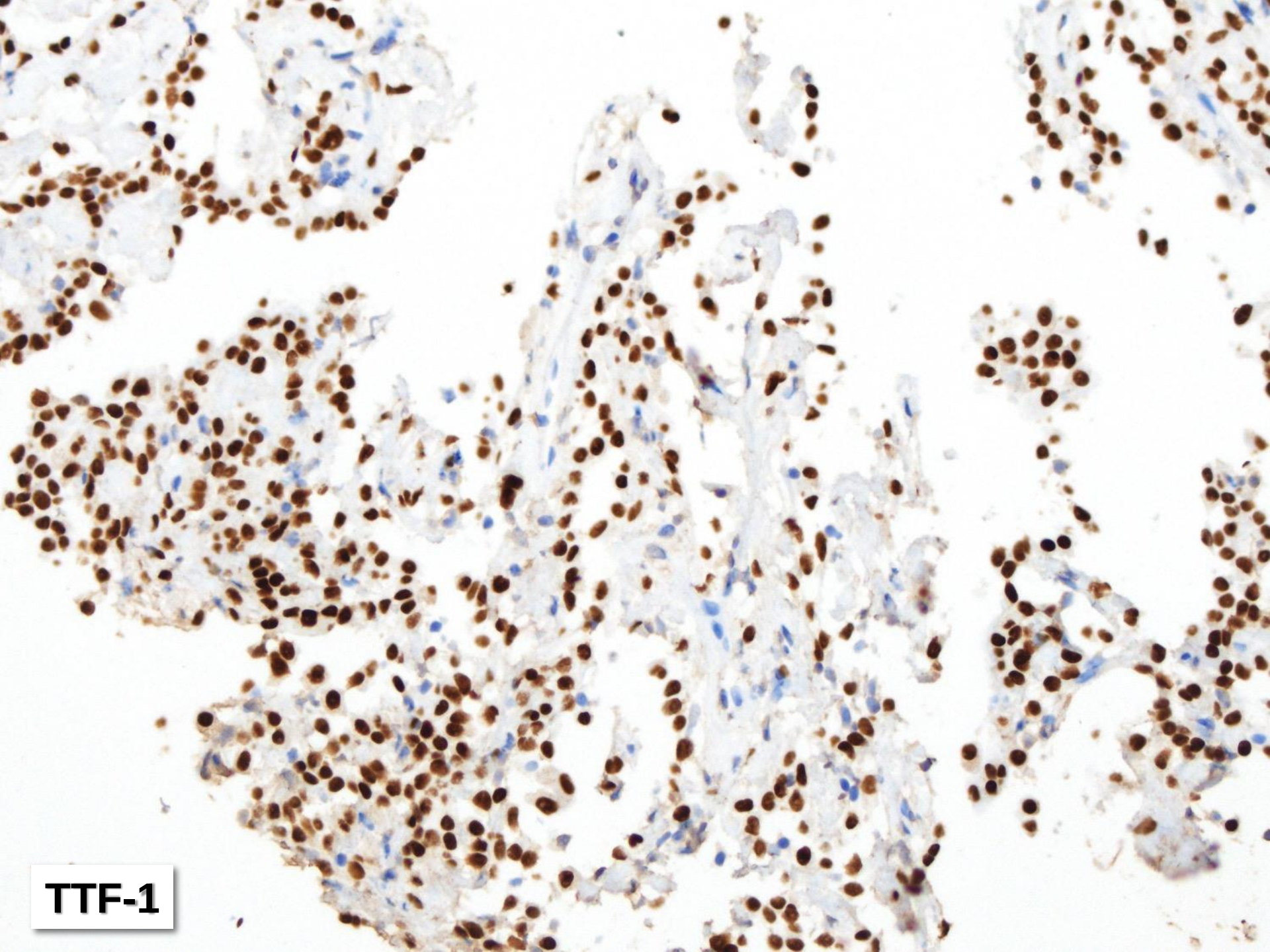




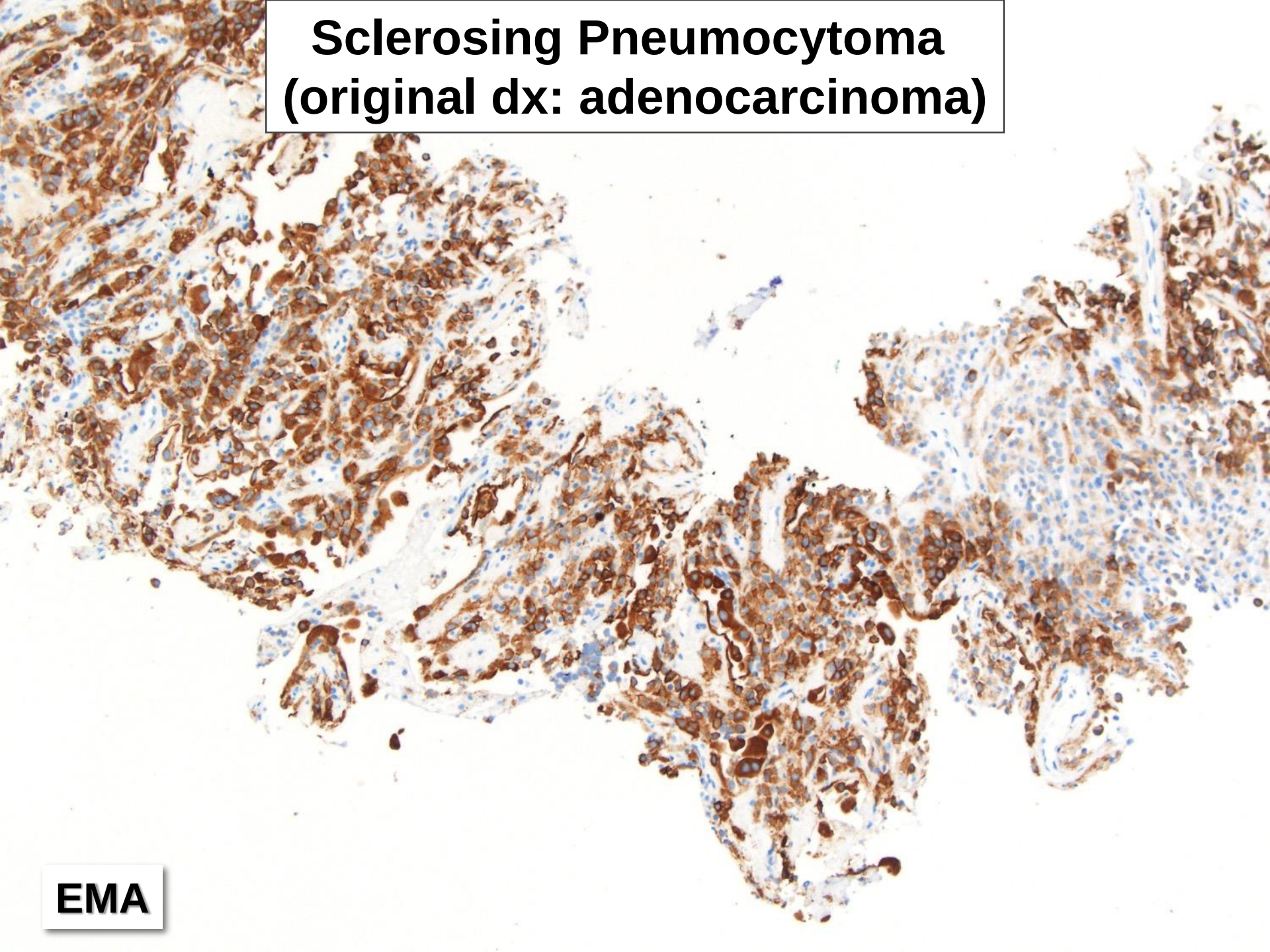





Pan keratin


TTF-1

Sclerosing Pneumocytoma (original dx: adenocarcinoma)

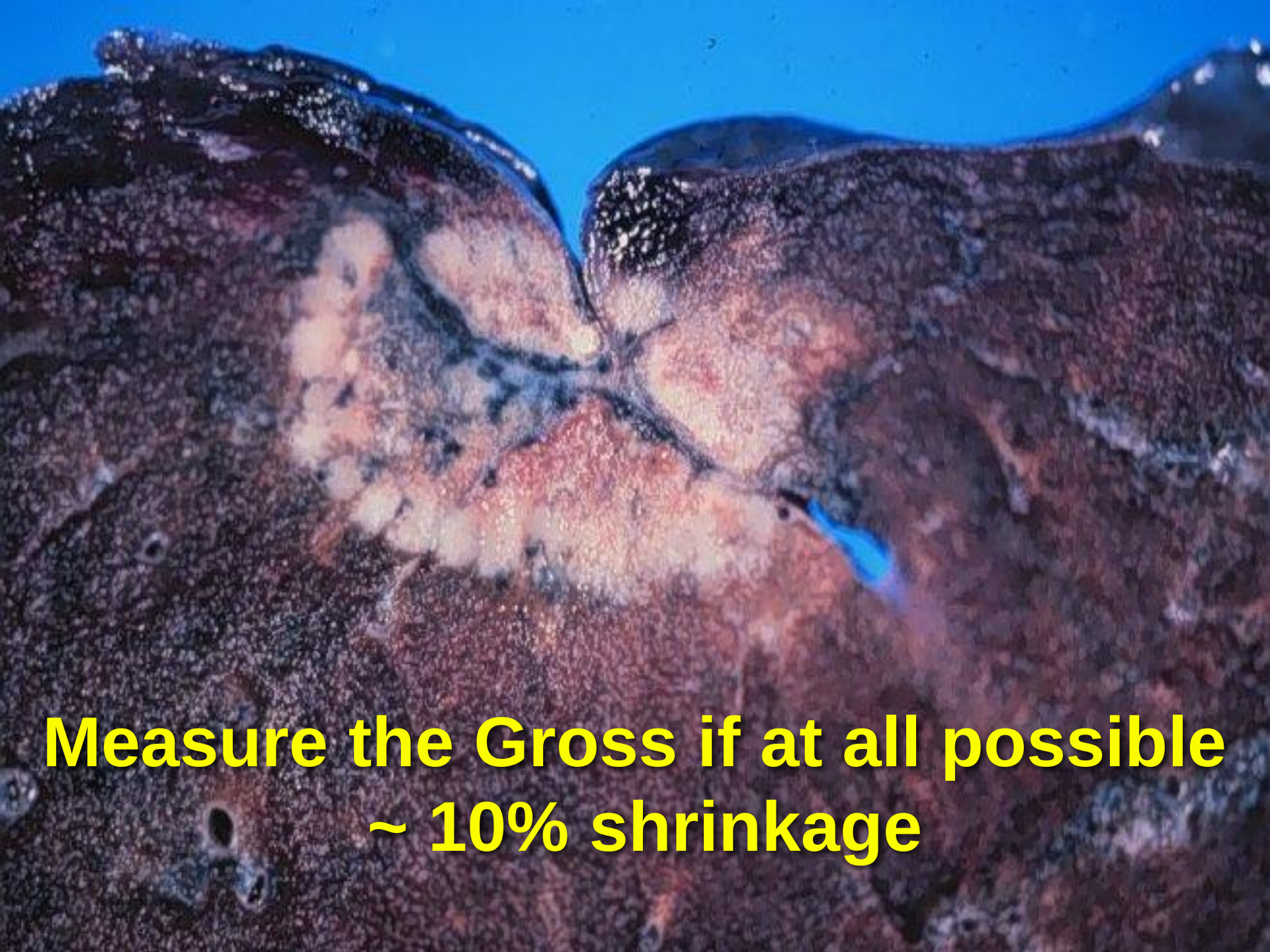


EMA

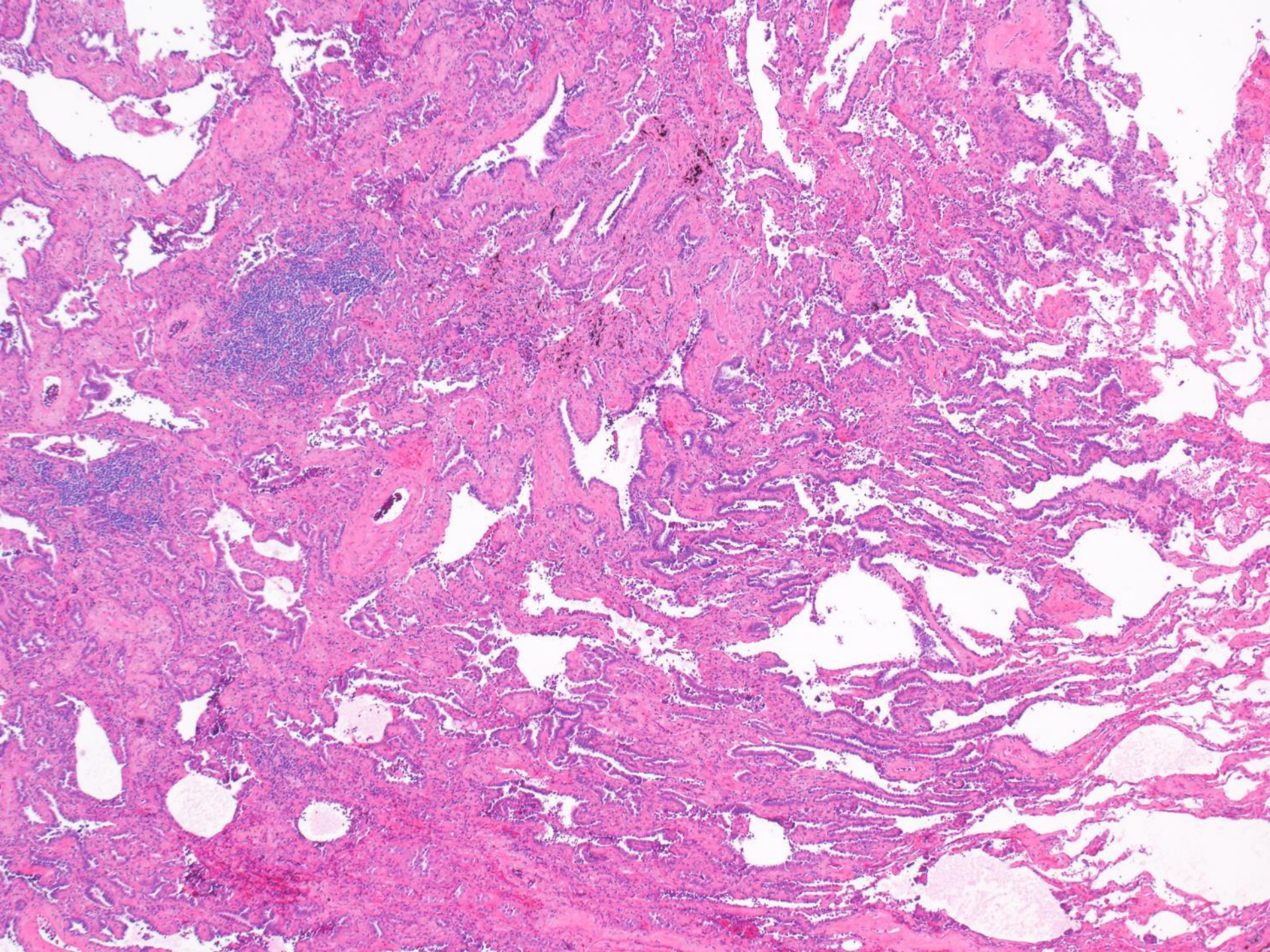
AJCC 8th Edition: Guiding Principles

- Large retrospective data set: 70,967 NSCLC and 6,189 SCLC
- Data limited for sub-solid and multiple lung cancers
- Clinical and pathology T,N,M match
- Radiologic info necessary for pT

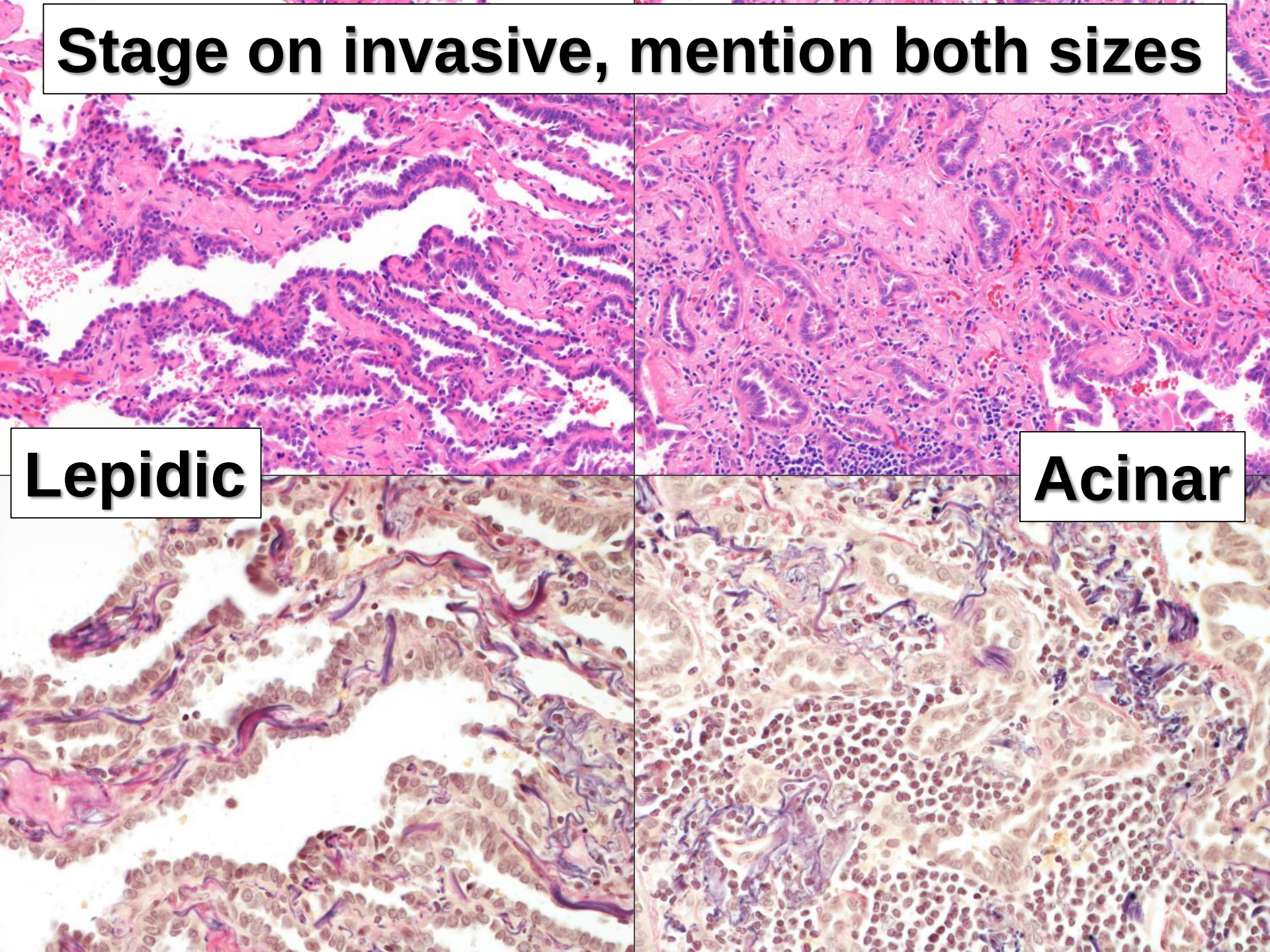
7th ed.	8th ed.
T0 No primary tumor	T0 No primary
Tis CIS	Tis CIS (SCIS-AIS)
	Tmi ≤ 5 mm
T1 ≤ 3 cm not in main bronchus and no pleural invasion	T1 ≤ 3cm not in main bronchus and no pl. invasion
T1a ≤ 2 cm	T1a ≤ 1 cm
T1b > 2 < 3 cm	T1b > 1 ≤2 cm
	T1c > 2 ≤ 3cm


Measure the Gross if at all possible
~ 10% shrinkage

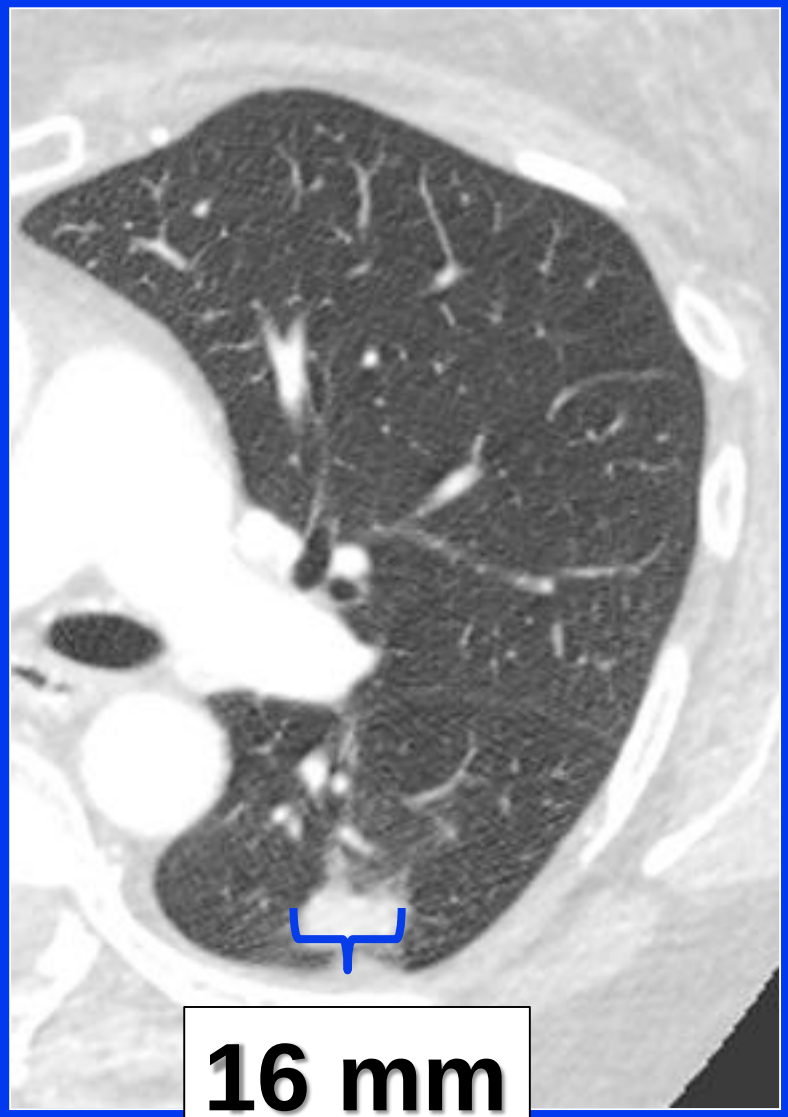
Part Solid (presumed invasive), Part GG (presumed lepidic)

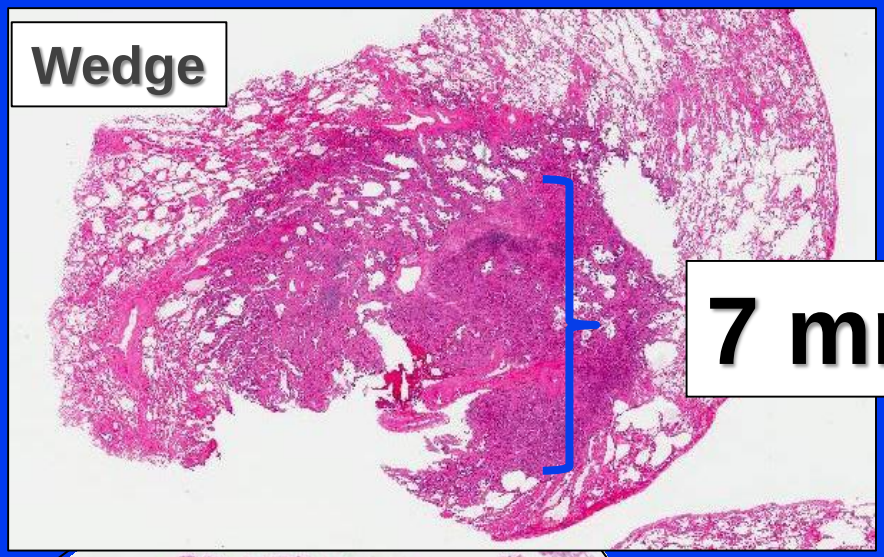


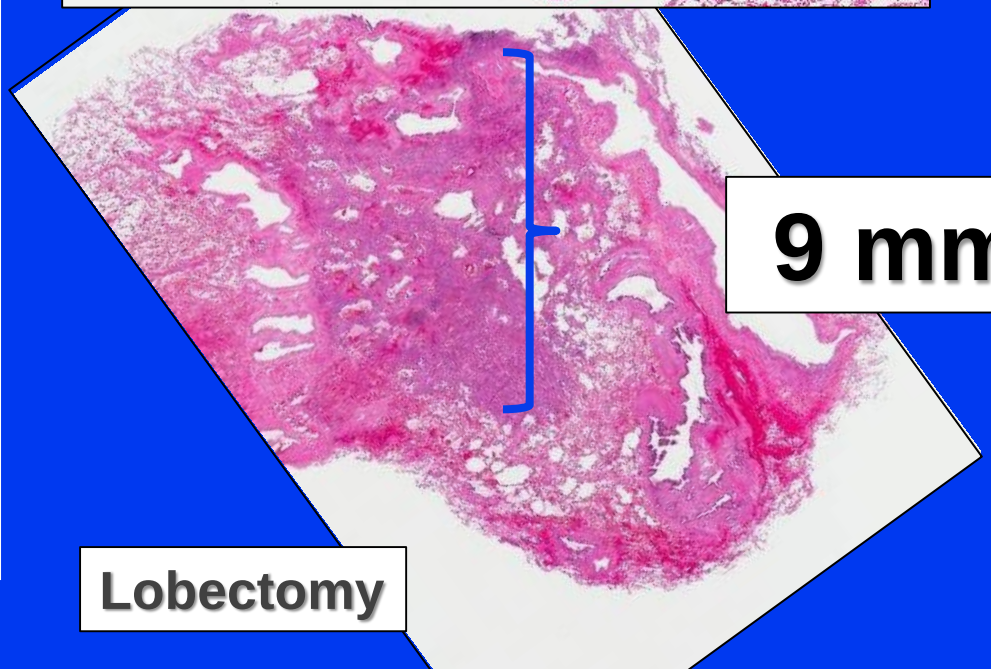
Stage on invasive, mention both sizes



Part Solid, Part GG







7th ed.

T2 > *3* ≤ *7 cm* OR w/ any of:

pleural invasion, *main bronchus* ≥ *2 cm from carina,* atelectasis/obst. pneumonia to hilum

T2a > 3cm ≤ 5cm

T2b > 5cm ≤ 7cm

8th ed.

T2 > *3* ≤ *5 cm* OR w/ any of:

pleural invasion, main bronchus, atelectasis/obst. pneumonia to hilum, part or all of lung

T2a > 3 cm ≤ 4 cm

T2b > 4 cm ≤ 5 cm

T2 due to atelectasis or obstructive pneumonia that extends to the hilar region, involving all or part of the lung

7th ed.

T3 > 7cm OR invasion into par. pl. or pericard, diaph., chest wall, mediastinal pl, in main bronchus < 2cm from carina, atelectasis/obstructive pneumonia of entire lu or separate tumor nodule same lobe

8th ed.

T3 > 5cm ≤ 7cm OR invasion into parietal pleura or pericardium, chest wall, or separate tumor nodule in same lobe

7th ed.

T4 any size with invasion of heart, trachea, esophagus, vertebra or separate tumor nodule in other ipsilat lobe

8th ed.

T4 > 7cm or any size with invasion of diaphragm, heart, trachea, esophagus, vertebra or separate tumor nodule in other ipsilat lobe

7th ed.

T4 any size with invasion of heart, trachea, esophagus, vertebra or separate tumor nodule in other ipsilat lobe

8th ed.

T4 > 7cm or any size with invasion of diaphragm, heart, trachea, esophagus, vertebra or separate tumor nodule in other ipsilat lobe

8th ed. Nodal Status

N0 No regional LN met

N1 Met in ipsilateral peribronchial and/or hilar LN and intrapulmonary LN including direct extension

N2 Met in ipsilateral mediastinal and/or subcarinal LN

N3 Met in contralateral hilar or mediastinal, ipsilateral or contralateral scalene or supraclavicular LN

7th ed.

M0 No distant mets

M1 Distant mets

M1a Separate tumor nodule (s) in contralateral lu, tumor with pl nodule(s) or malignant pl effusion

M1b Distant mets

8th ed.

M0 No distant mets

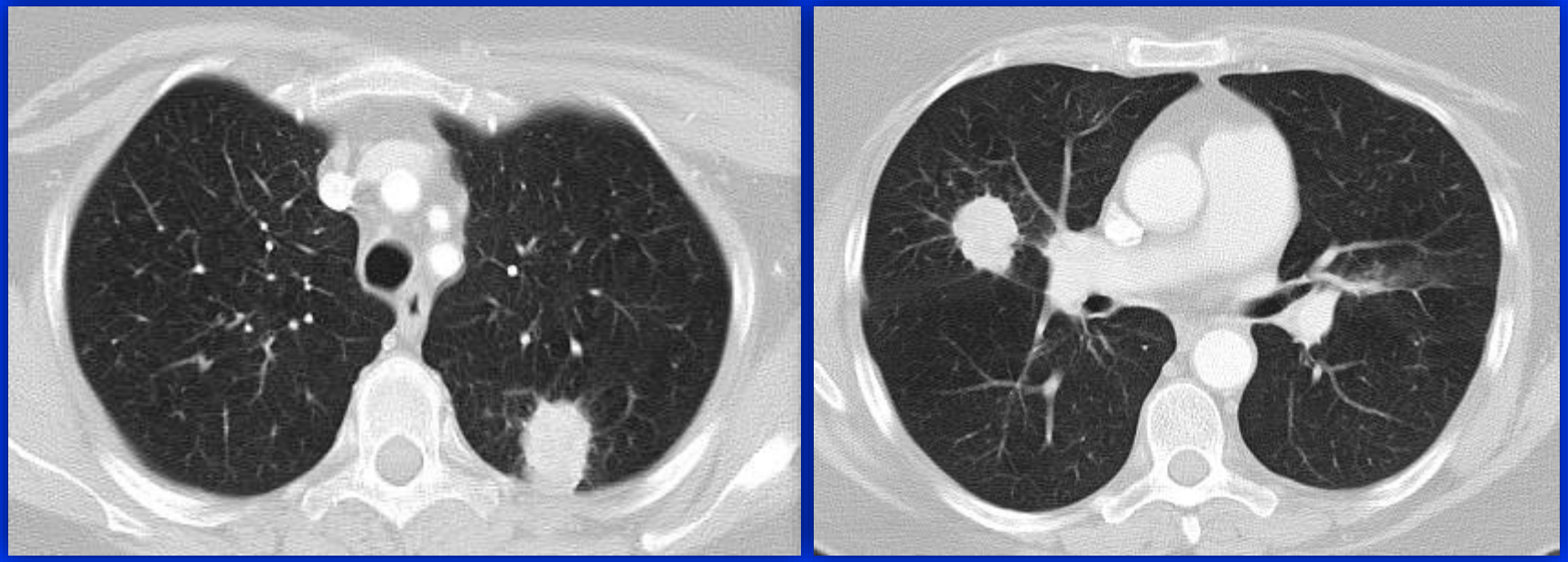
M1 Distant metastasis

M1a Any of: pl. /pericard effusion, or pl pericard nodule(s), contralateral/bilateral nodule (s), > 1 of above

M1b Single met in single organ

M1c Multiple mets in single or multiple organs

Staging of Multiple Tumors



First need to determine if the tumor nodules are separate primaries or intrapulmonary metastasis

Multiple Lung Carcinomas

3 different clinical scenarios with 3 different staging schemes

1. **Multiple *solid* tumor nodules**
2. **Multiple nodules with *ground glass or lepidic* features**
3. **Pneumonic involvement**

Pathologic criteria* requires resection

May be considered separate primary tumors
Clearly different histologic types (ie SQCC and AD)
Clearly different with comprehensive histologic assessment
SQCC arising from CIS

May be considered intrapulmonary metastasis
Exactly matching breakpoints on CGH

***Relative arguments* to favor separate primary tumors (consider with clinical factors)**
Different patterns of biomarkers (molecular signature)
Absence of nodal or systemic metastasis

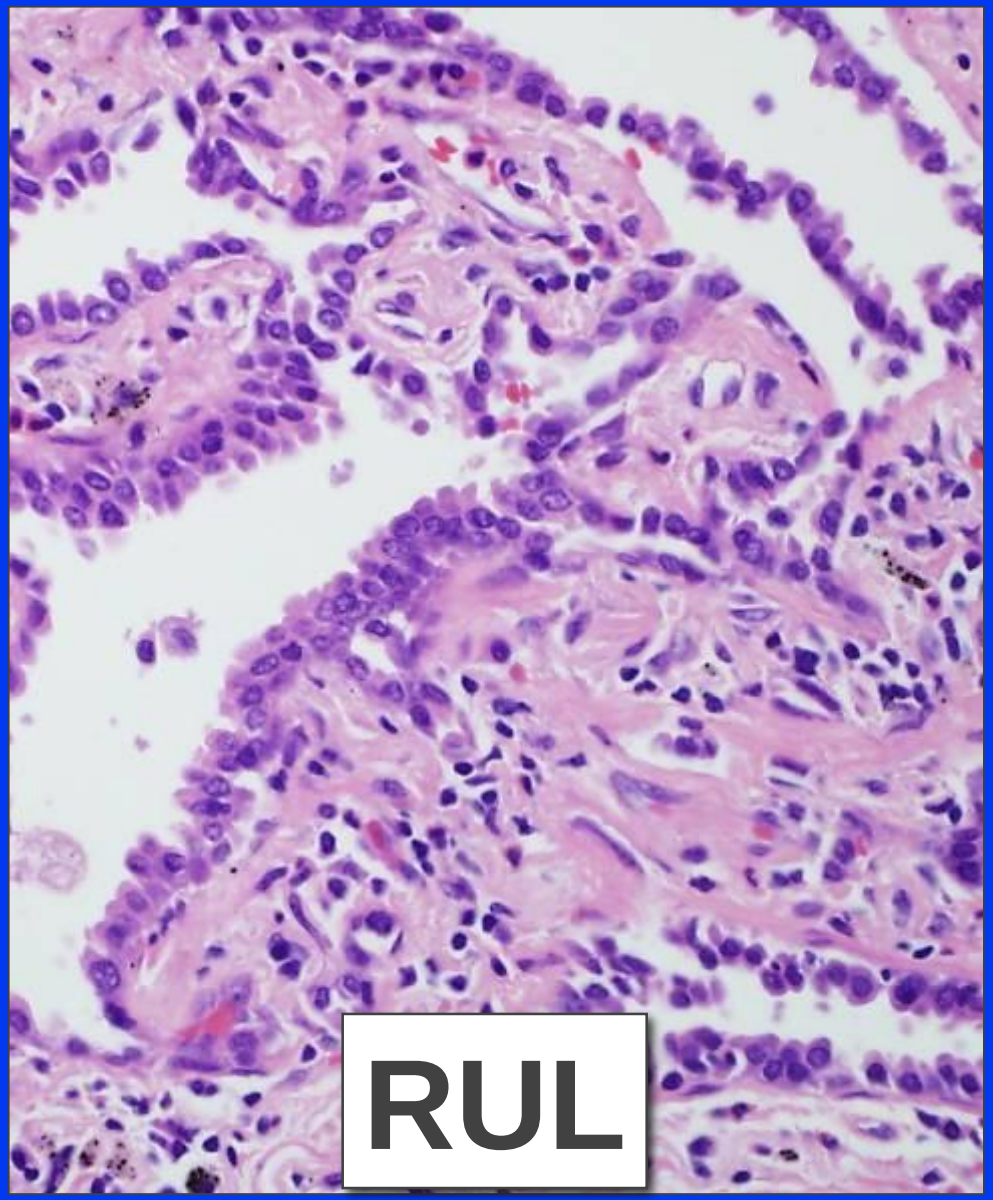
***Relative arguments* to favor intrapulmonary metastasis**
Matching appearance of comprehensive histologic assessment
The same biomarker pattern
Significant nodal or systemic metastases

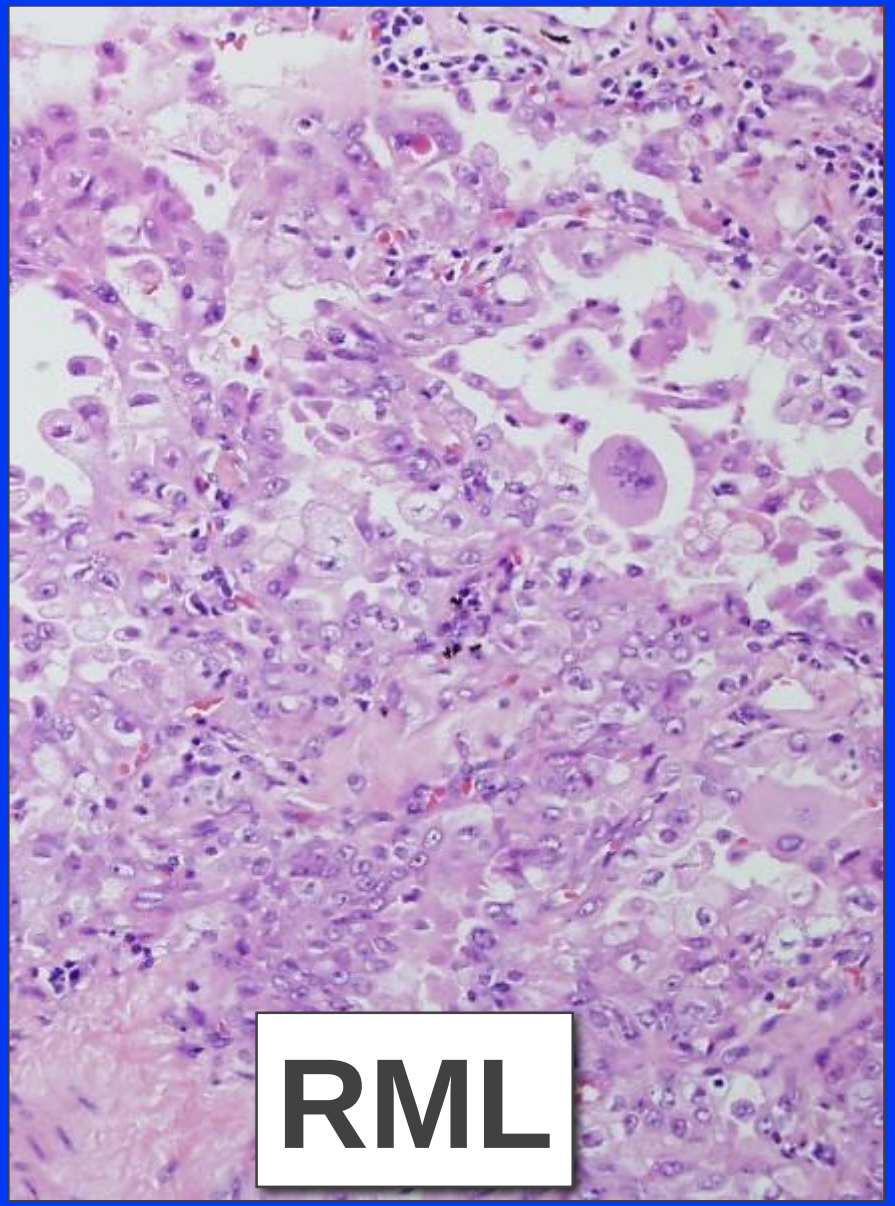
Comprehensive Assessment

- Histologic subtype
  - AD, SQCC, SCLC, Sarcomatoid….
- Relative proportion of AD patterns -5% increments
  - Acinar, papillary, lepidic, solid…
- Grade
- Cytologic and stromal features
- No interobserver comparison

Girard et al Am. J Surg Pathol 2009; 33:1752-64

Comprehensive Histologic Assessment





Case	Tumor 1	Tumor 2	Prediction
Case 1 Reviewer 1	AD Cribriform 80% Acinar 10% Solid 10%	AD Acinar 50% Lepidic 40% Papillary 10%	Independent 1aries
Case 1 Reviewer 2	AD Solid 50% Cribriform 50%	AD Papillary 40% Acinar 30% Lepidic 10% Cribriform 10% Solid 10%	Independent 1aries
Case 2 Reviewer 1	AD Acinar 70% Lepidic 30%	MIA	Independent 1aries
Case 2 Reviewer 2	AD Acinar 50% Papillary 50%	AD Lepidic 70% Acinar 30%	Independent 1aries
Case 3 Reviewer 1	AD Solid 45% Acinar 35% Lepidic 20%	AD Acinar 70% Lepidic 20% Solid 10%	Independent 1aries
Case 3 Reviewer 2	AD Acinar 50% Solid 20% Lepidic 20% Cribriform 10%	AD Acinar 40% Lepidic 30% Solid 20% Papillary 10%	Metastasis

Murphy et al JCO 2014; 32:4050

Reproducibility in Determining Lineage

- Agreement on predominant pattern in 12/16 (75%)
- When in doubt, share
- NGS breakpoints- able to accurately classify tumors predicted to be independent primaries or metastases.

Murphy et al JCO 2014; 32:4050

Molecular Profiling Summary

- CGH recommended
- NGS
  - Same mutations can be present in different tumor types
  - Correlation with histology key

Dacic S Arch Pathol Lab Med 2017:923-6

Interobserver Variation Among Pathologists Using Comprehensive Subtyping

- 126 tumors from 48 pts
- Classified by 17 pulmonary pathologists
- Kappa = 0.6 for second primary vs intrapulmonary mets
- Predominant type, nuclear pleomorphism, cell size, acinar formation, nucleolar size, mitotic rate

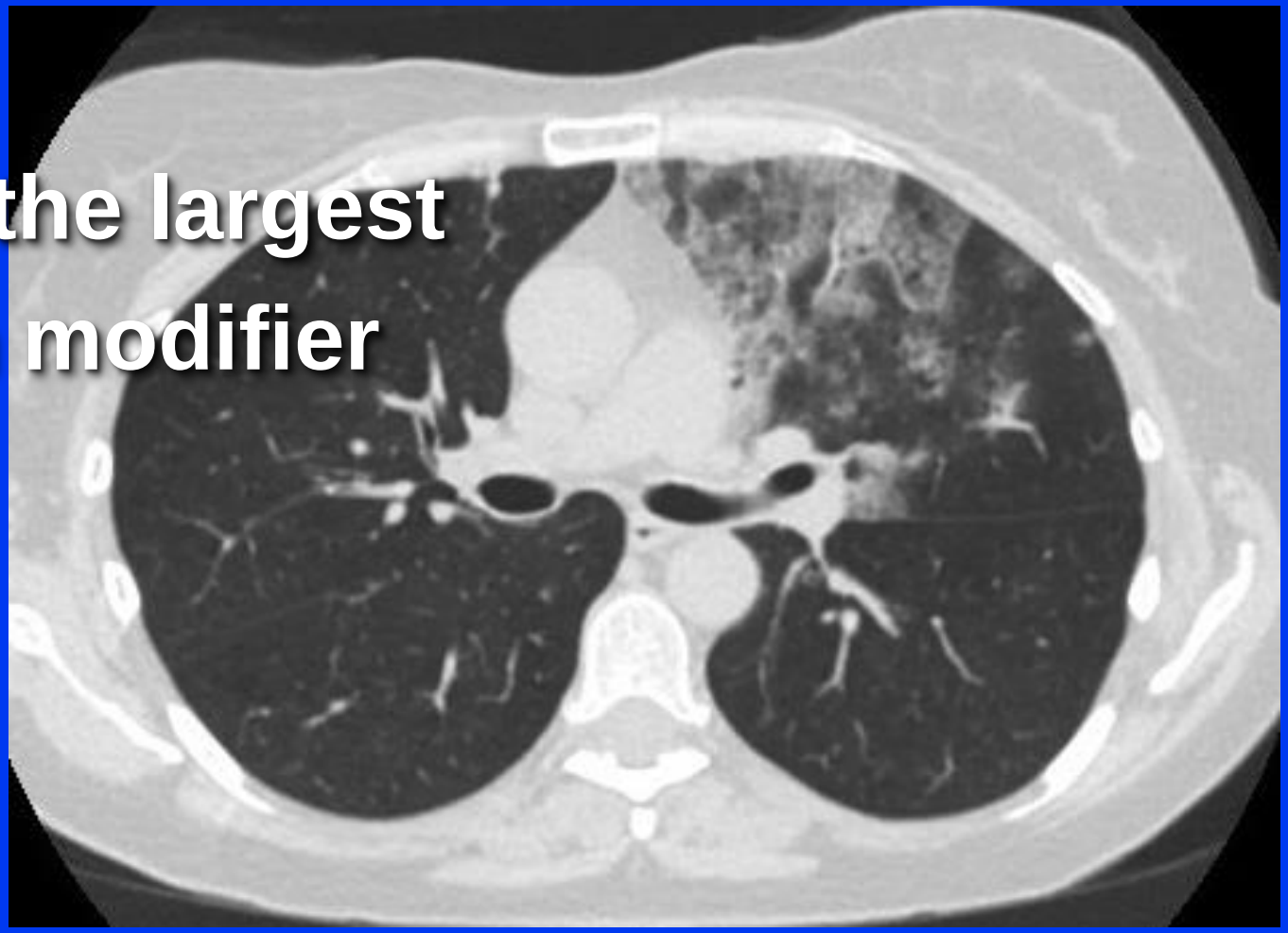
Nicholson AG et al. Histopathology JTO 2018; 205-217

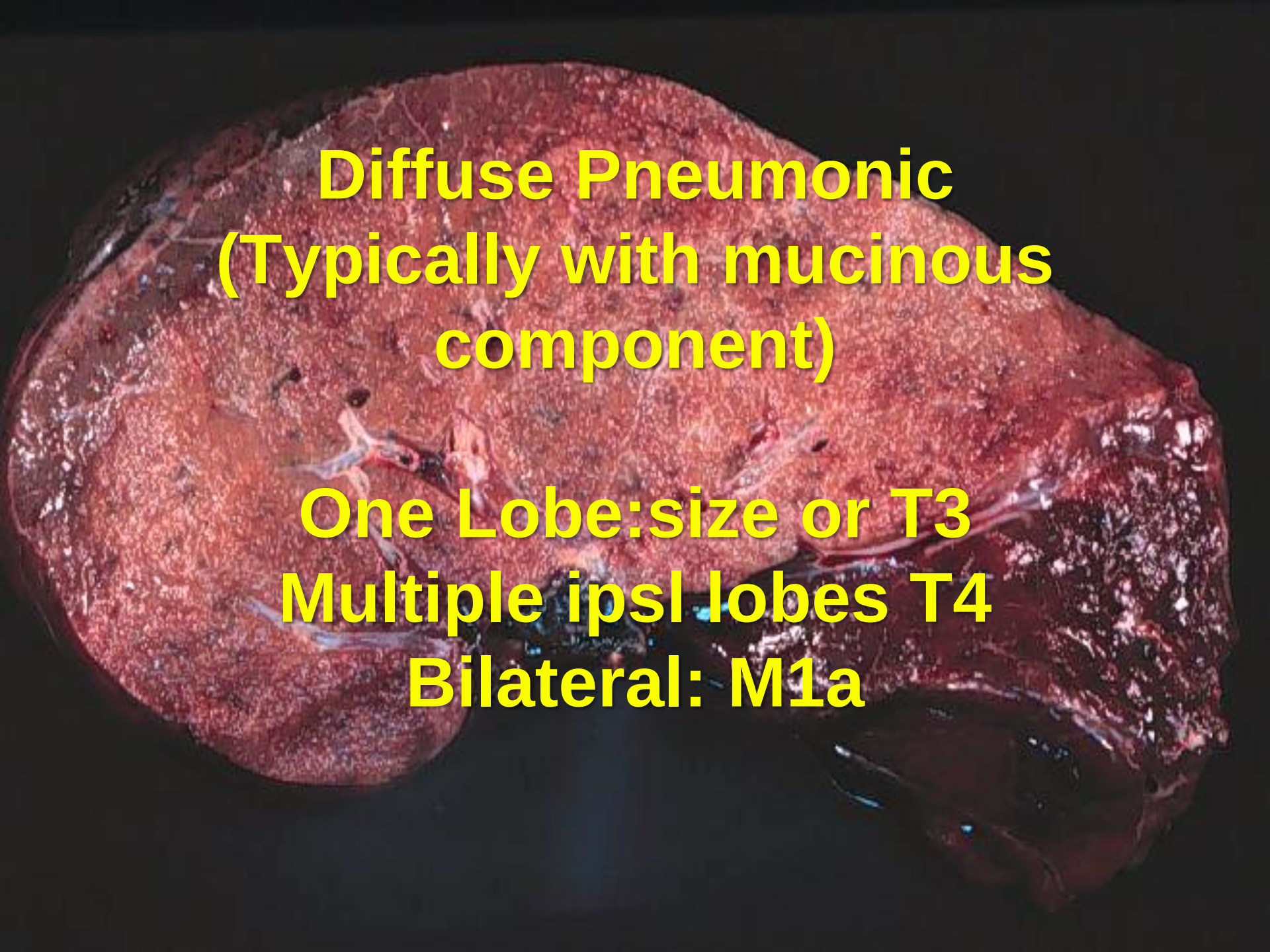
T4 Cancer- if same histology

- 1º superior segment RLL
- Tumor nodule RUL-met

Multiple Ground Glass or Lepidic Predominant Tumors (non-mucinous)

- Stage the largest
- Add m modifier




Diffuse Pneumonic
(Typically with mucinous component)
One Lobe:size or T3
Multiple ipsl lobes T4
Bilateral: M1a

…A long way from Liebow

- No more BAC
- AIS and MIA
- Doing less, and more, with less
- Importance of comprehensive assessment and predominant subtypes
- 8th Edition clarifies a number of complex issues…but…


Thank you