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What is New in the 2015 WHO Lung Cancer Classification?

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DISCLOSURE

No conflict of interest

Objectives:

- To review the changes in the 2015 lung tumor classification
- To describe the diagnostic criteria for the new entities in lung adenocarcinoma
- To emphasize the importance of molecular profiling in lung cancer

WHO Lung Adenocarcinoma

1967	1981	2004	2015
Acinar	Acinar ADC	Mixed	Lepidic
Papillary	Papillary ADC	Acinar	Acinar
BAC	BAC	Papillary	Papillary
	Solid with mucus	BAC	Micropapillary
		Non-mucinous	Solid
		Mucinous	*Invasive mucinous*
		Mix	*Colloid*
		Solid with mucin	*Fetal*
		Fetal	*Enteric*
		Mucinous (Colloid)	Minimally invasive
		Mucinous cystade	AIS
		Signet-ring	Non-mucinous
		Clear-cell	Mucinous

WHO Lung Adenocarcinoma

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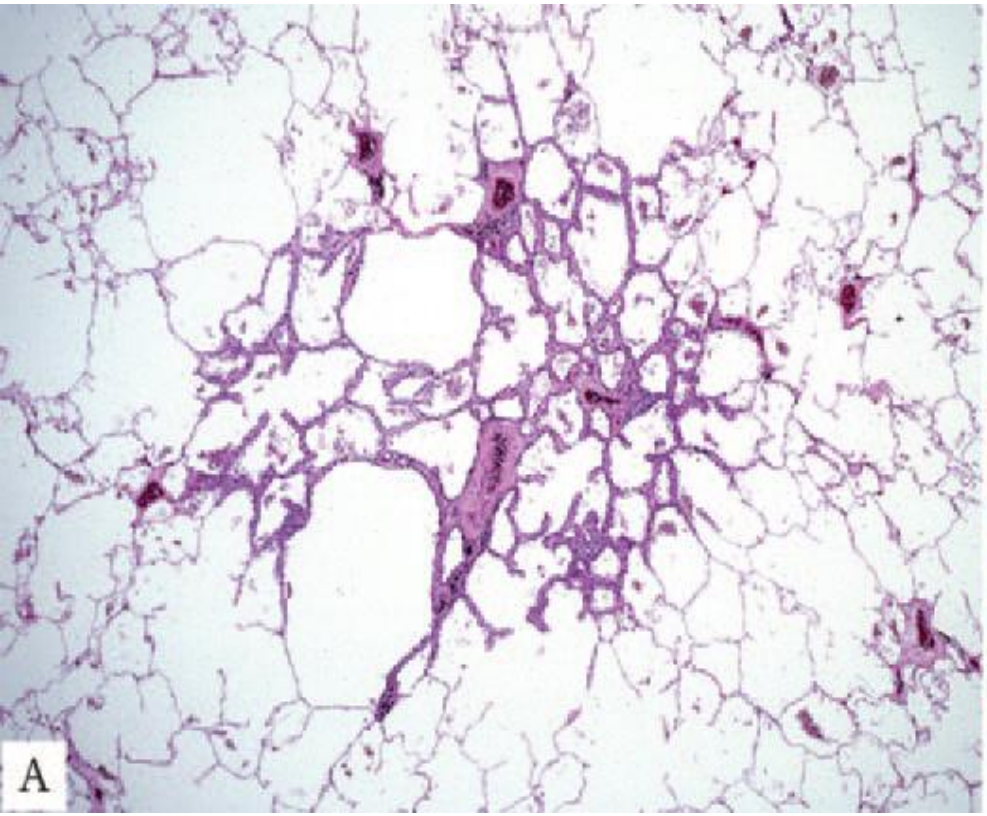
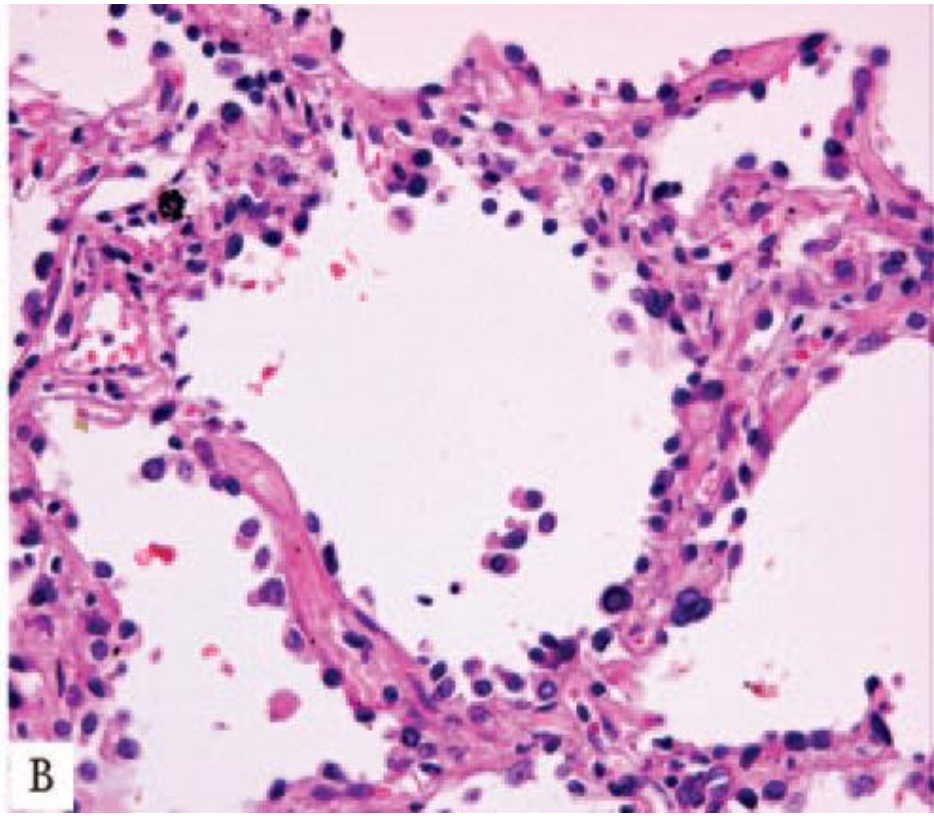
Preinvasive lesions

- For adenocarcinoma
  - Atypical adenomatous hyperplasia
  - Adenocarcinoma in situ
    - Non-mucinous
    - Mucinous
- For squamous cell carcinoma
  - Squamous cell carcinoma in situ
- For neuroendocrine tumors
  - Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Atypical adenomatous hyperplasia





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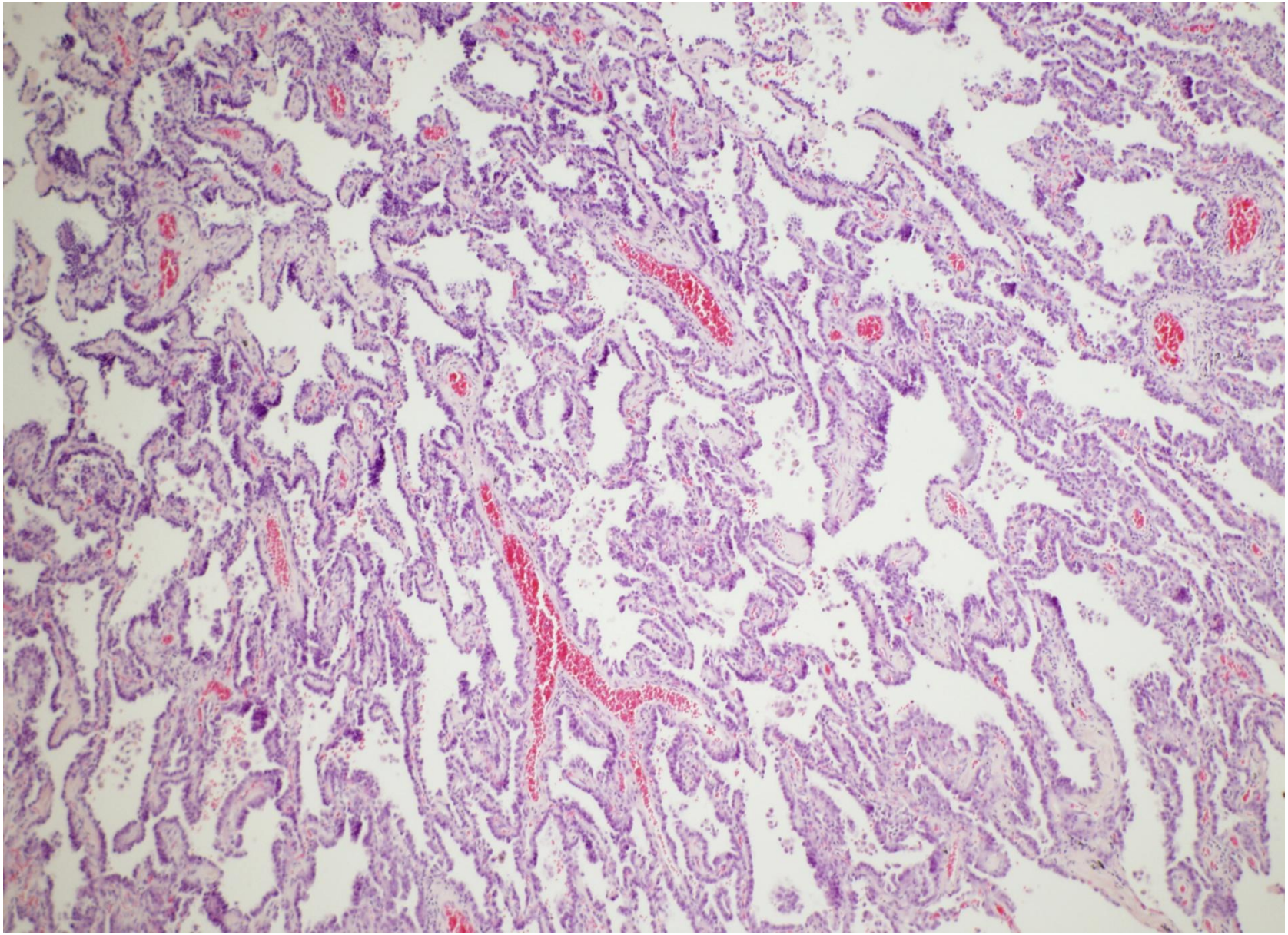
Adenocarcinoma In Situ



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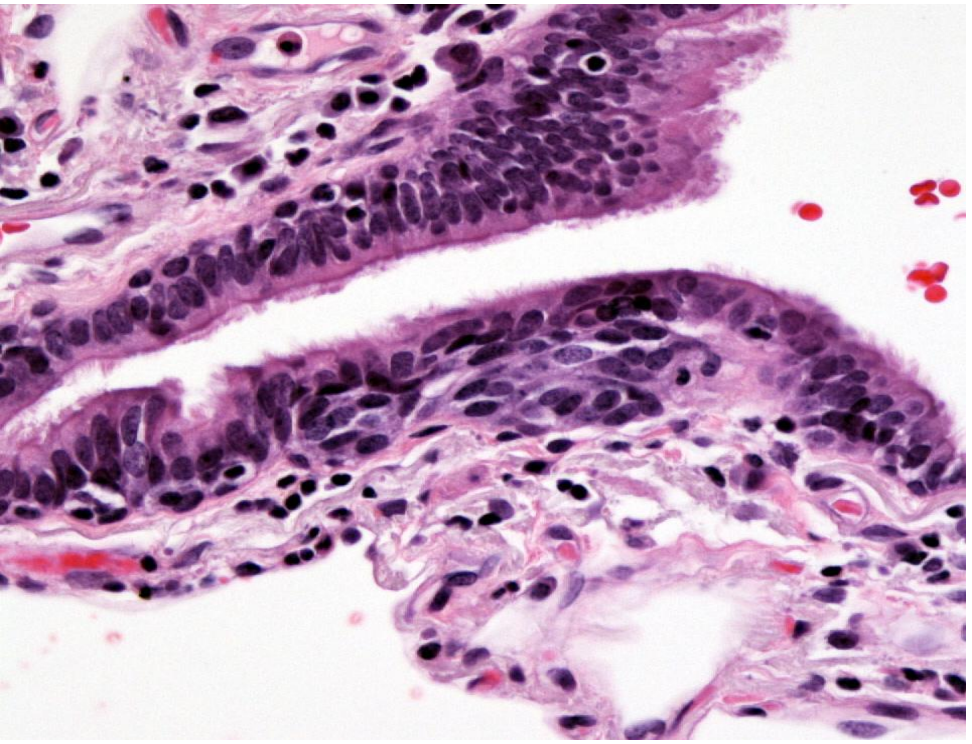
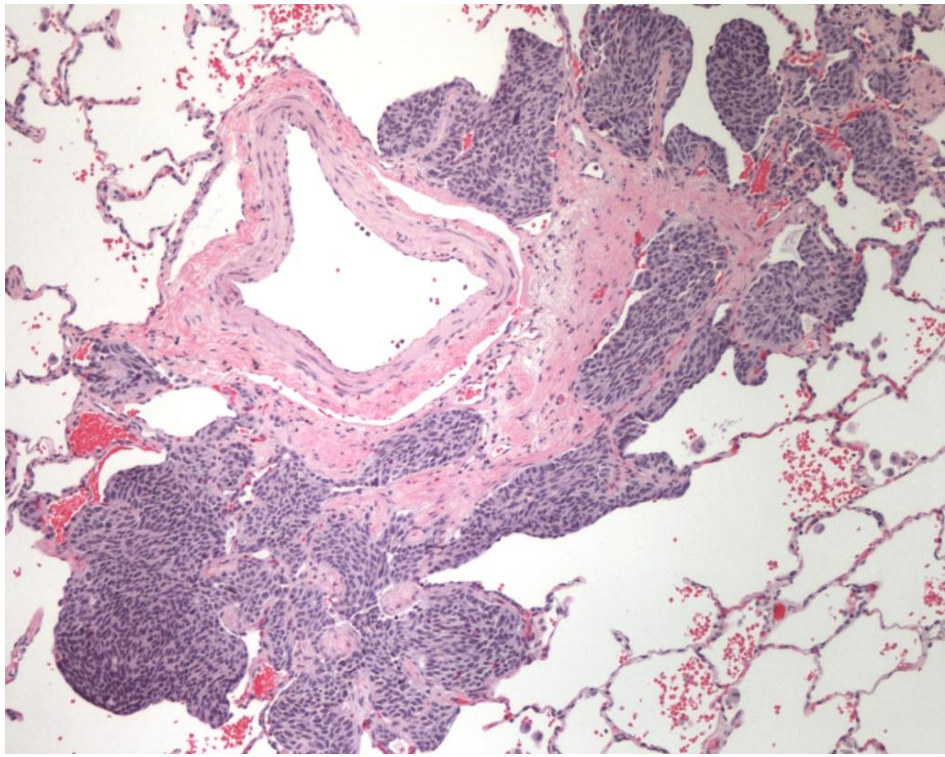
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia





Minimally invasive

- ≤ 3 cm solitary tumor with a predominantly lepidic pattern
- Invasive component ≤ 0.5 cm
- Usually non-mucinous
- Excluded if:
  - invading lymphatc, blood vessels, air spaces or pleura
  - presence of tumor necrosis
  - spread through air spaces

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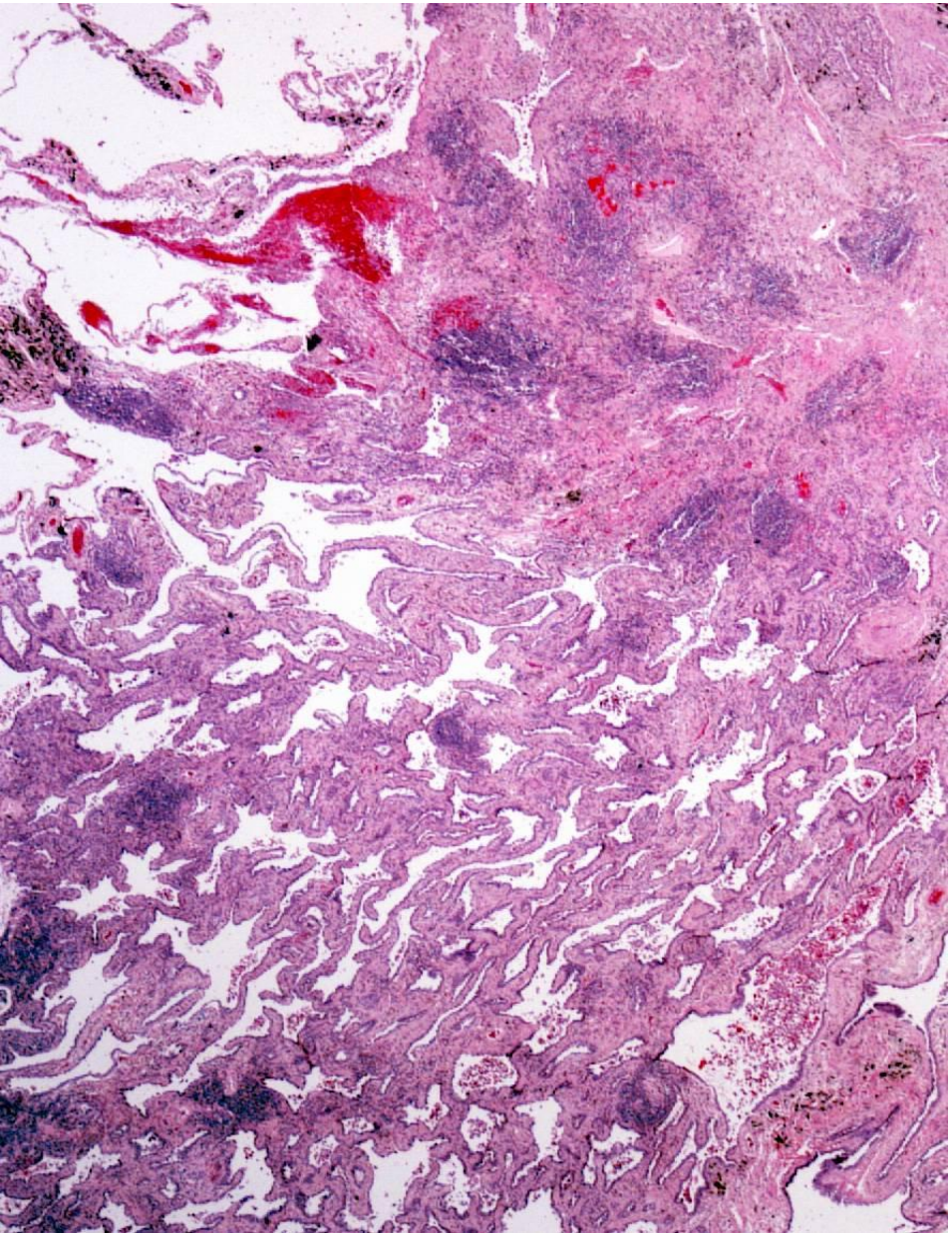
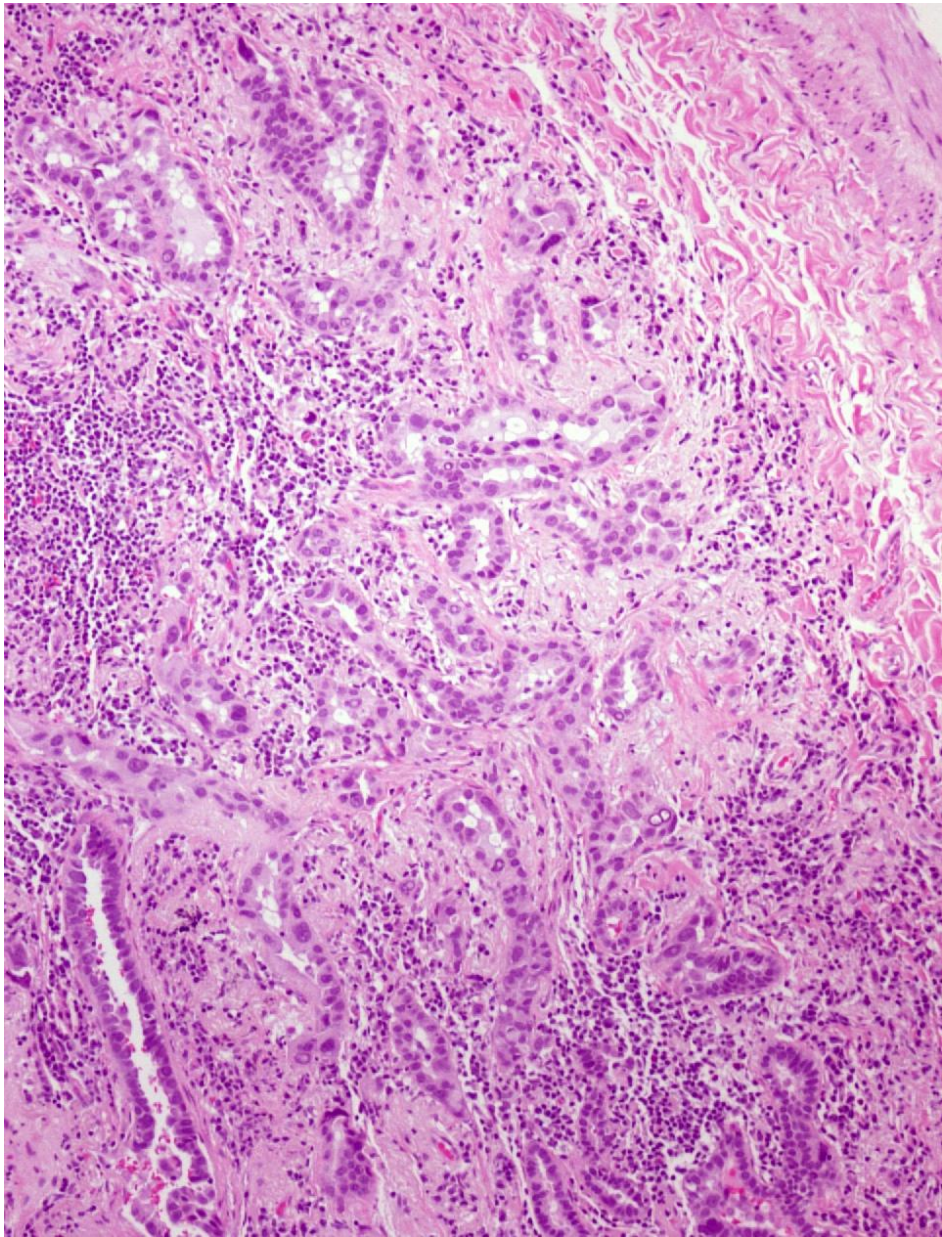
Minimally invasive





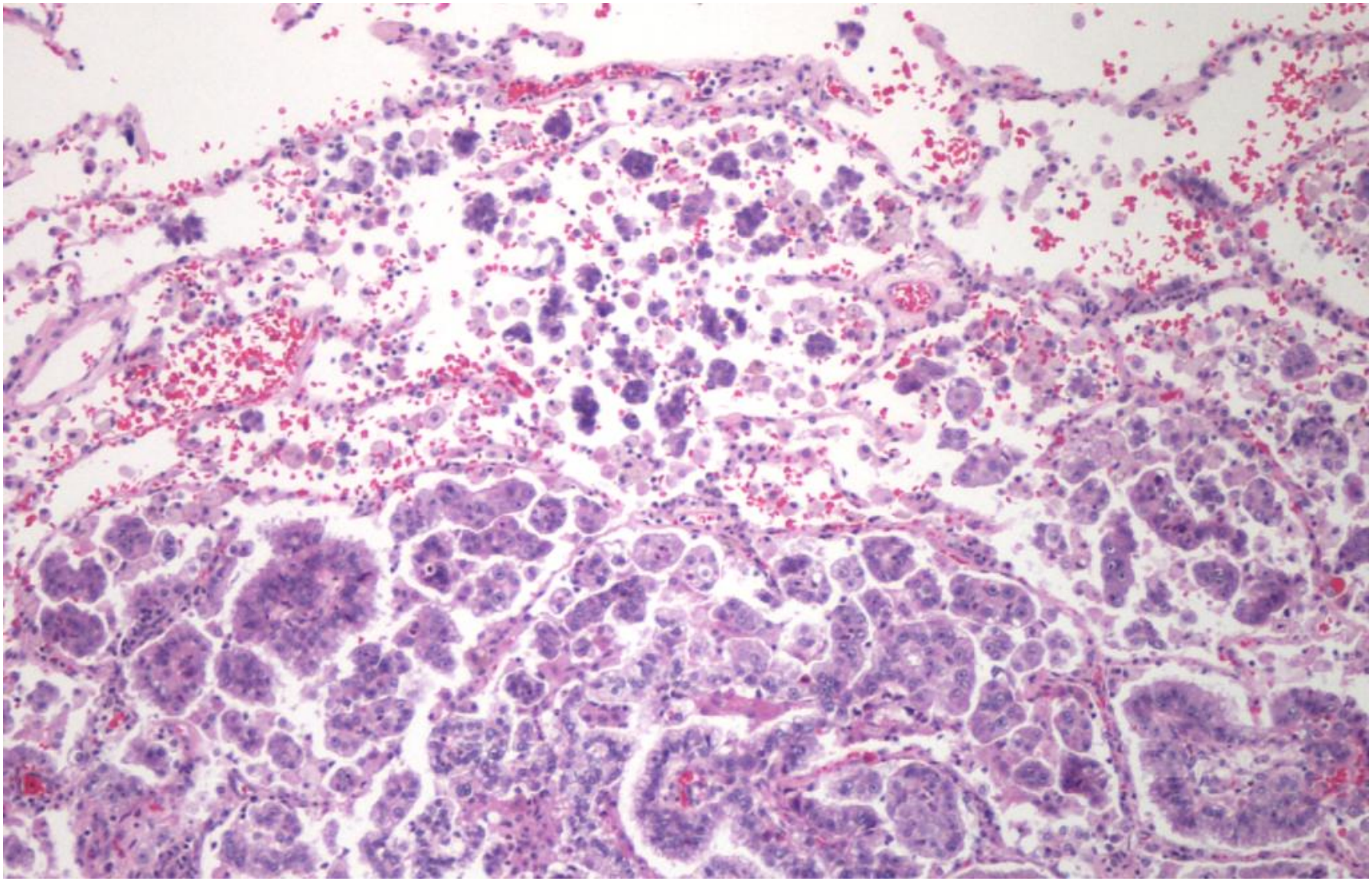
Lepidic adenocarcinoma

- Predominantly lepidic pattern with invasive component > 0.5 cm
- Non-mucinous
- Invasive component:
  - histologic pattern other than lepidic
  - myofibroblastic stroma
  - invading lymphatc, blood vessels, air spaces or pleura
  - presence of tumor necrosis
  - spread through air spaces
- Solitary tumor > 3 cm with lepidic pattern

Micropapillary adenocarcinoma

- Predominantly micropapillary pattern
- Papillary tufts without fibrovascular cores
- Tumor cell clusters may float within the alveolar spaces and/or connected to alveolar walls
- Vascular and stromal invasion is common
- Psammoma bodies may be present

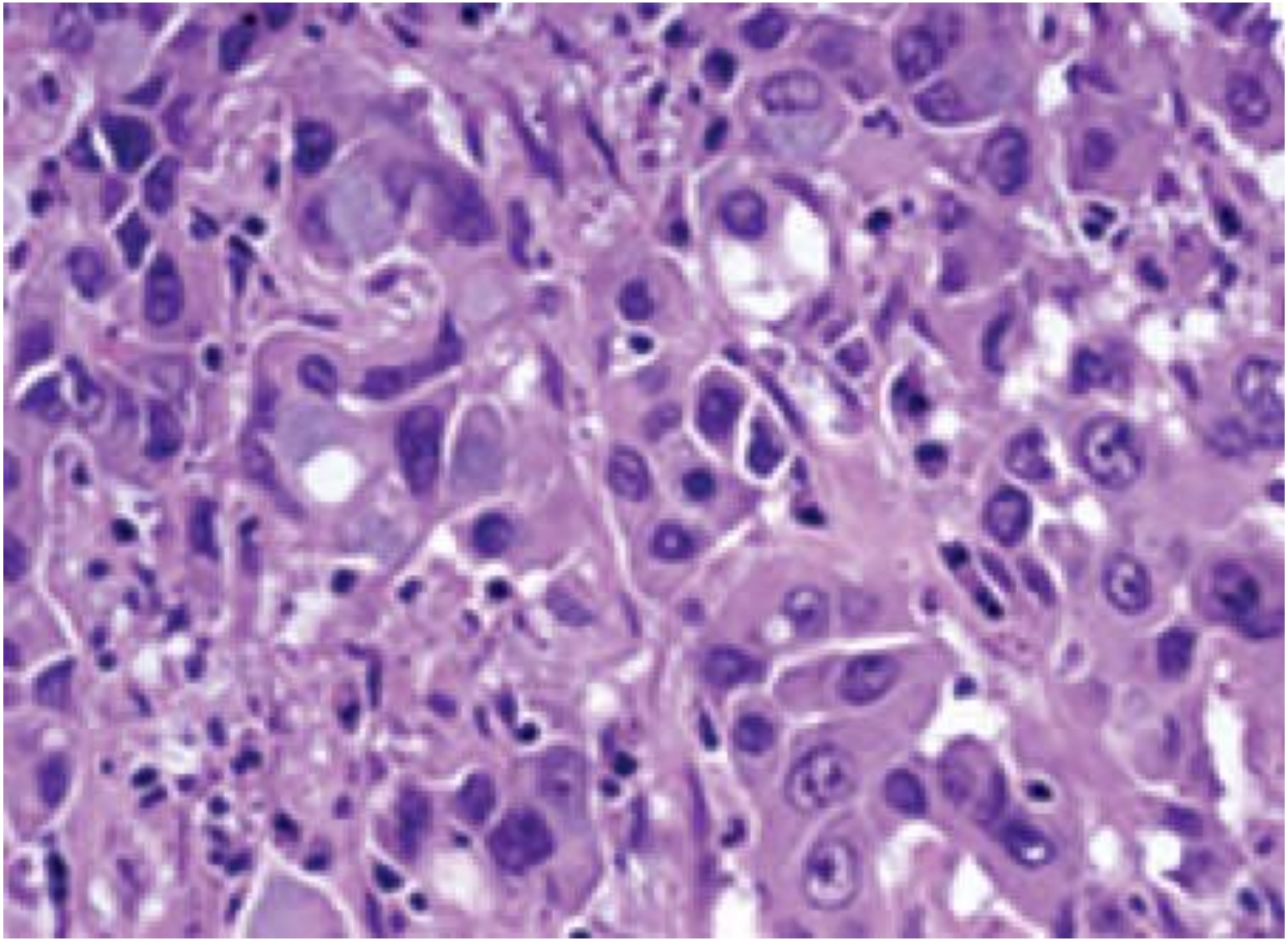
Micropapillary adenocarcinoma



Solid adenocarcinoma

- Predominantly solid pattern
- If 100% solid
  - ≥ 5 tumor cells with intracytoplasmic mucin in each of two high-power fields, or
  - Positive for TTF-1 and/or napsin A
- It must be distinguished from squamous cell carcinoma and large cell carcinoma

Solid adenocarcinoma



Invasive mucinous adenocarcinoma

- Most common a lepidic pattern although other patterns can be seen except for a solid pattern
- It also includes cases formerly classified as mucinous BAC
- Mucinous cells with basally located nuclei
- Nuclear atypia is inconspicuous or absent
- Alveolar spaces often fill with mucin

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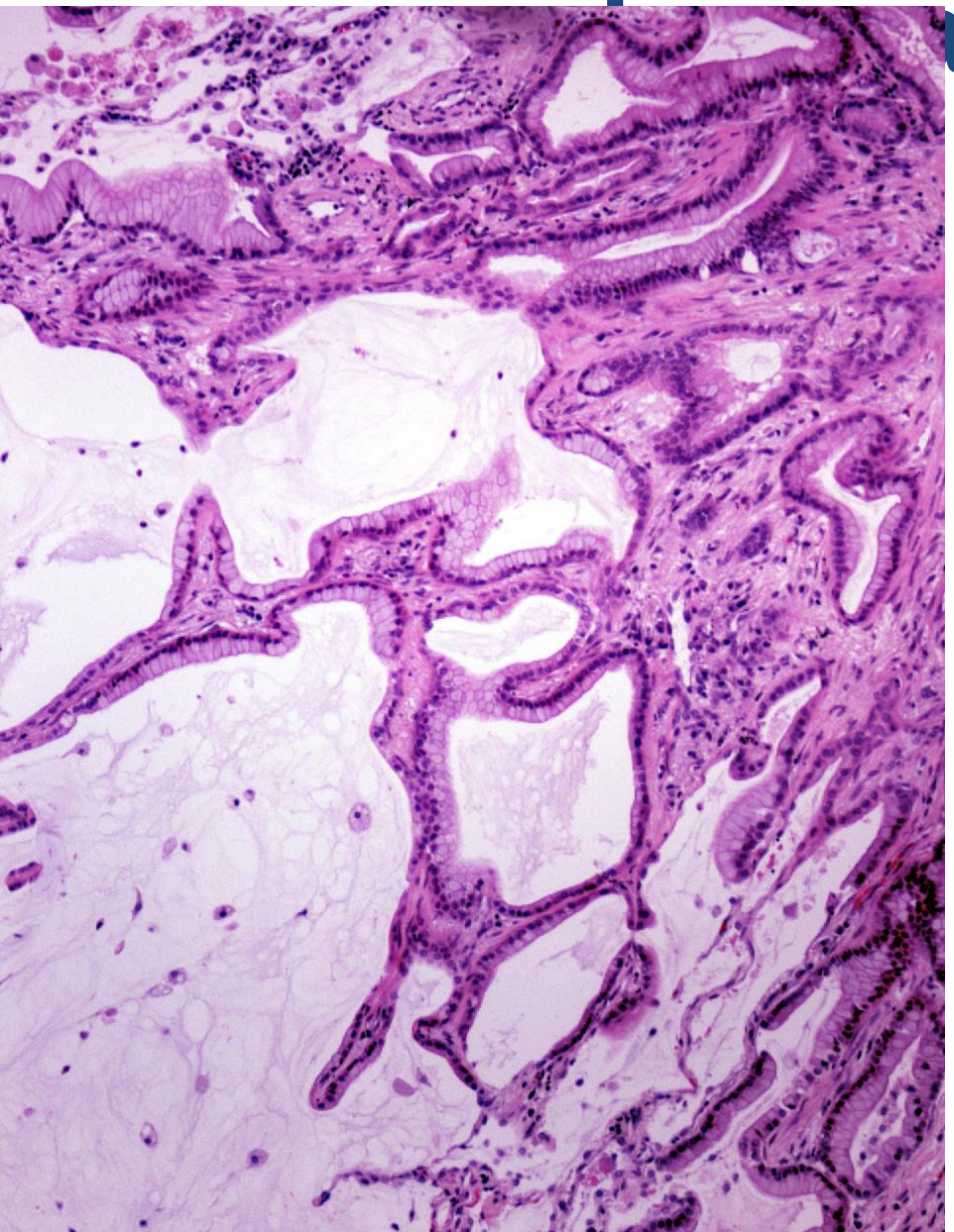
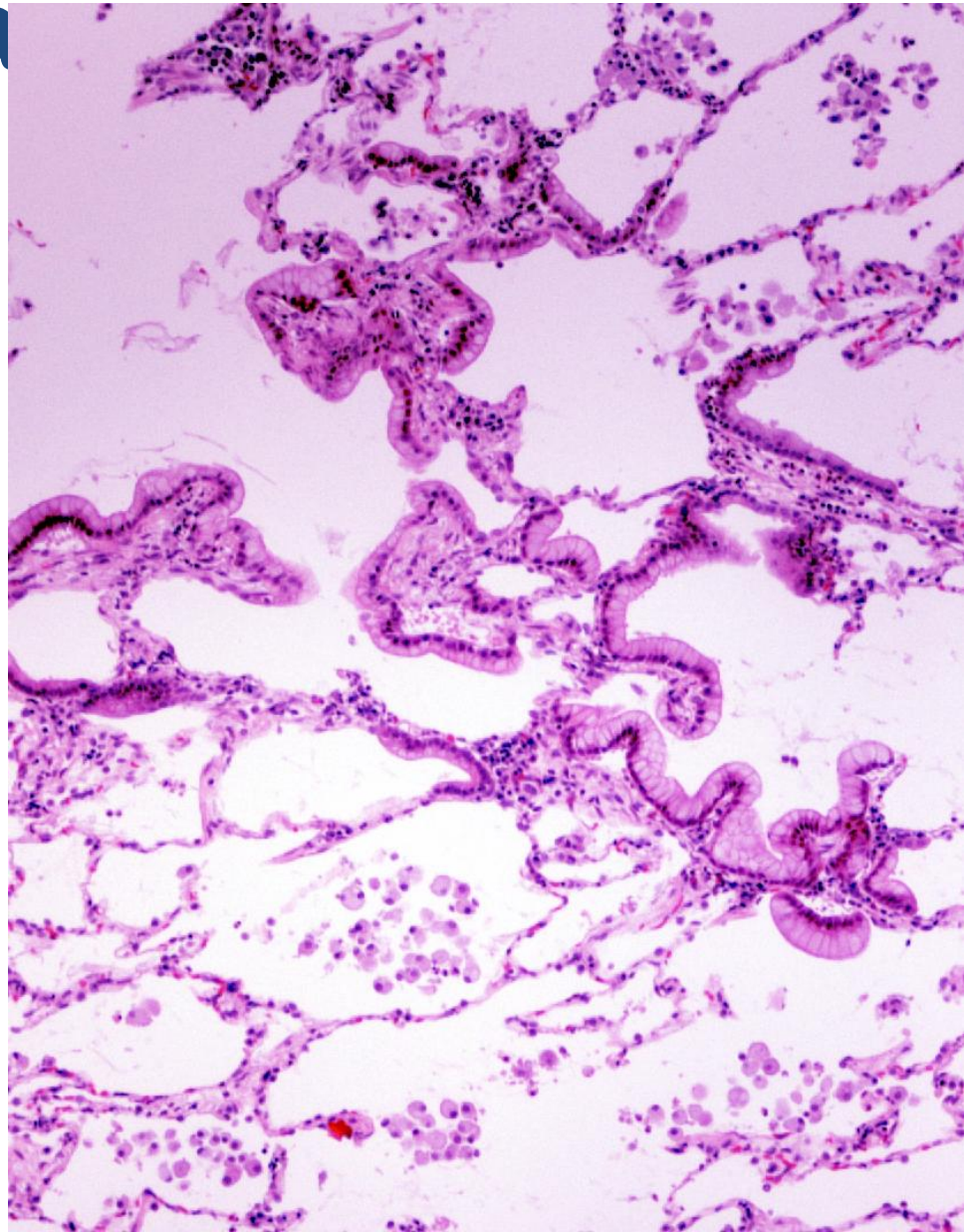
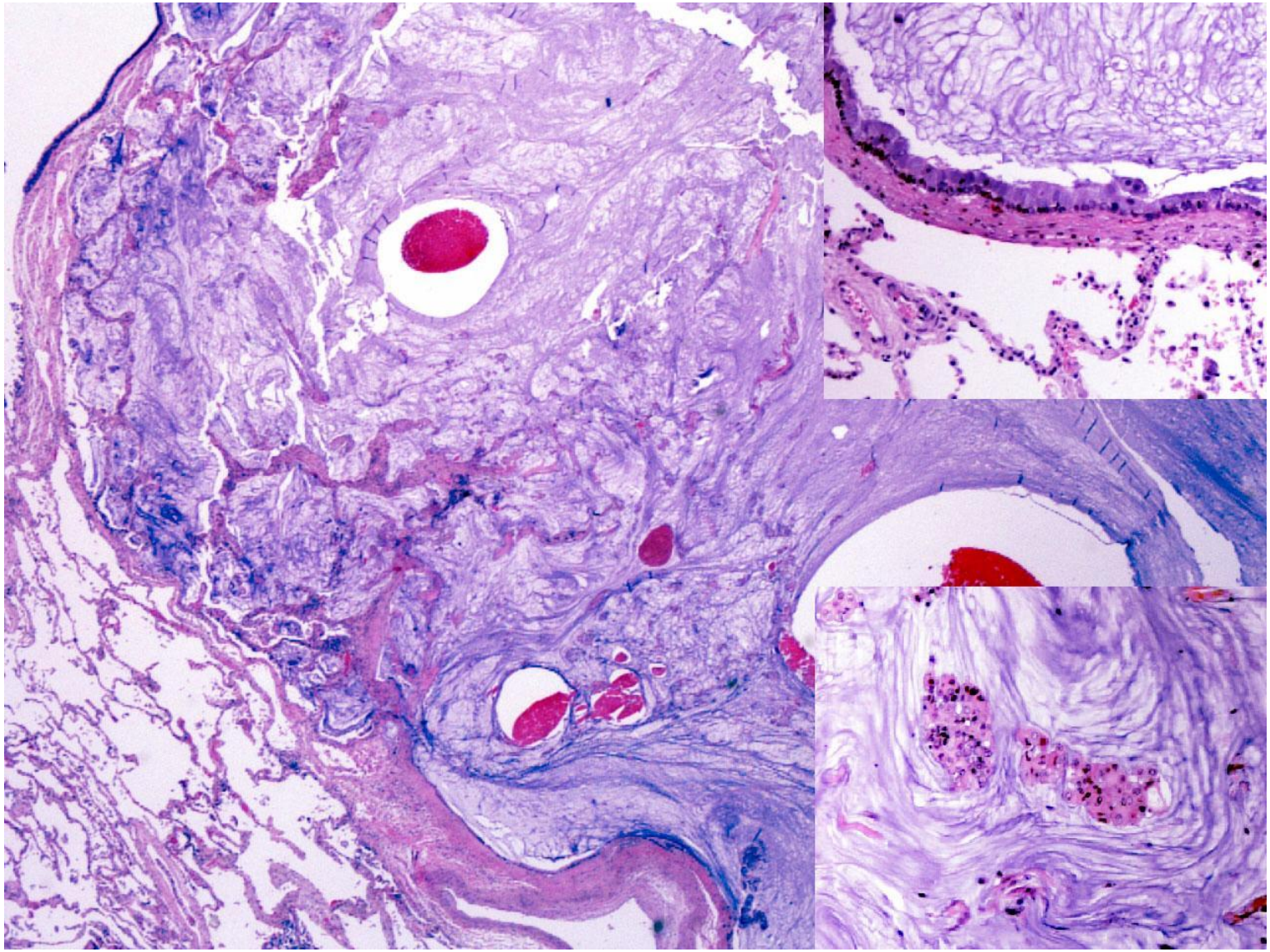
Invasive mucinous adenocarcinoma





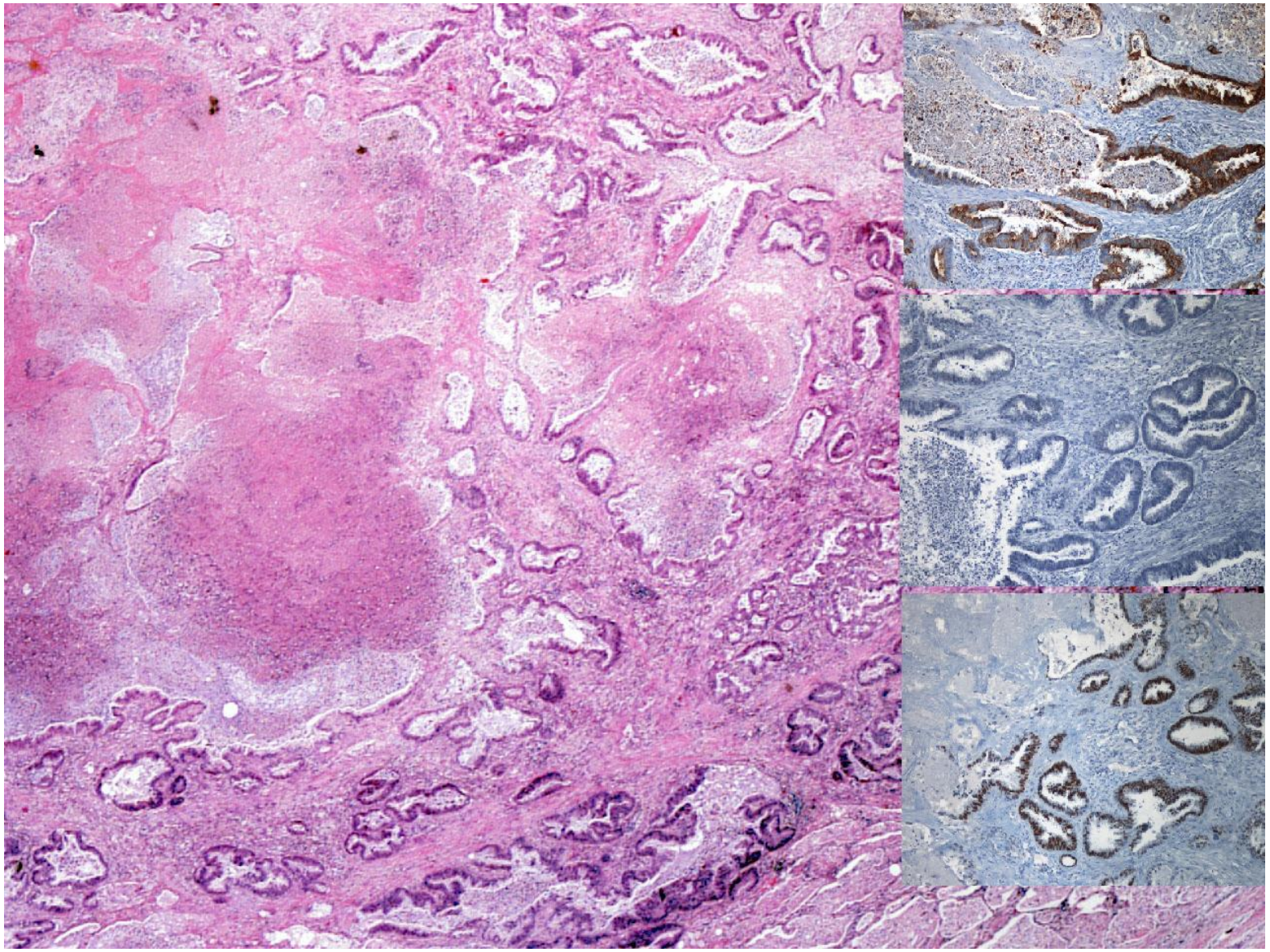
Colloid denocarcinoma



Enteric adenocarcinoma

- It resembles colorectal adenocarcinoma
- The enteric pattern > 50%
- IHC may be identical to or different from colorectal adenocarcinoma (CK7, CK20, CDX2, TTF-1)
- Clinical correlation

Enteric adenocarcinoma



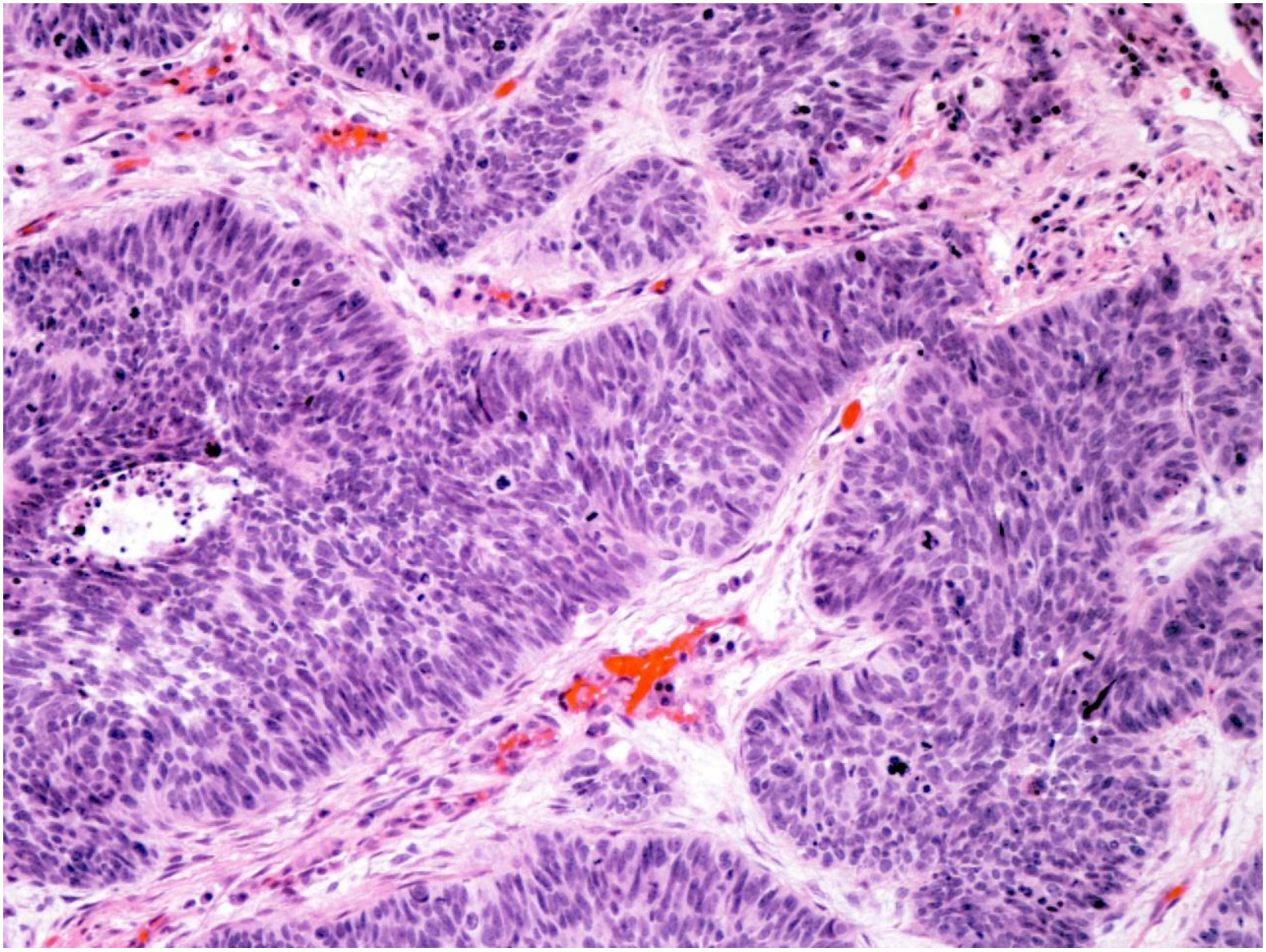
WHO Lung Squamous Cell Carcinoma

1967	1981	2004	2015
Epidermoid	Sq Ca (epidermoid)	Sq Ca	Keratinizing Sq Ca
	Spindle cell	*Papillary*	Non-keratinnizing
		Clear cell	Bsaloid
		Small cell	
		Basaloid	

WHO Lung Squamous Cell Carcinoma

1967	1981	2004	2015
Epidermoid	Sq Ca (epidermoid)	Sq Ca	Keratinizing Sq Ca
	Spindle cell	*Papillary*	Non-keratinnizing
		Clear cell	Bsaloid
		Small cell	
		Basaloid	

Basaloid squamous cell carcinoma



WHO Large Cell Carcinoma

1967	1981	2004	2015
Large cell	Large cell	Large cell	Large cell
	Giant cell	*LCNEC*	
	Clear cell	*Basaloid*	
		Lymphoepithelioma-like	
		Clear cell	
		Rhabdoid	

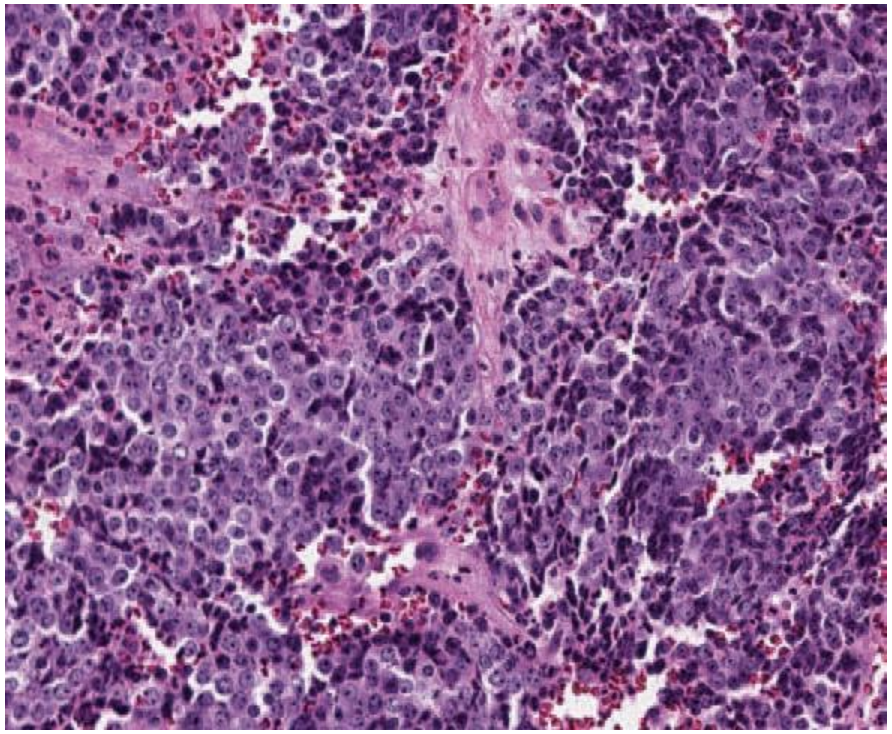
WHO Small Cell Carcinoma

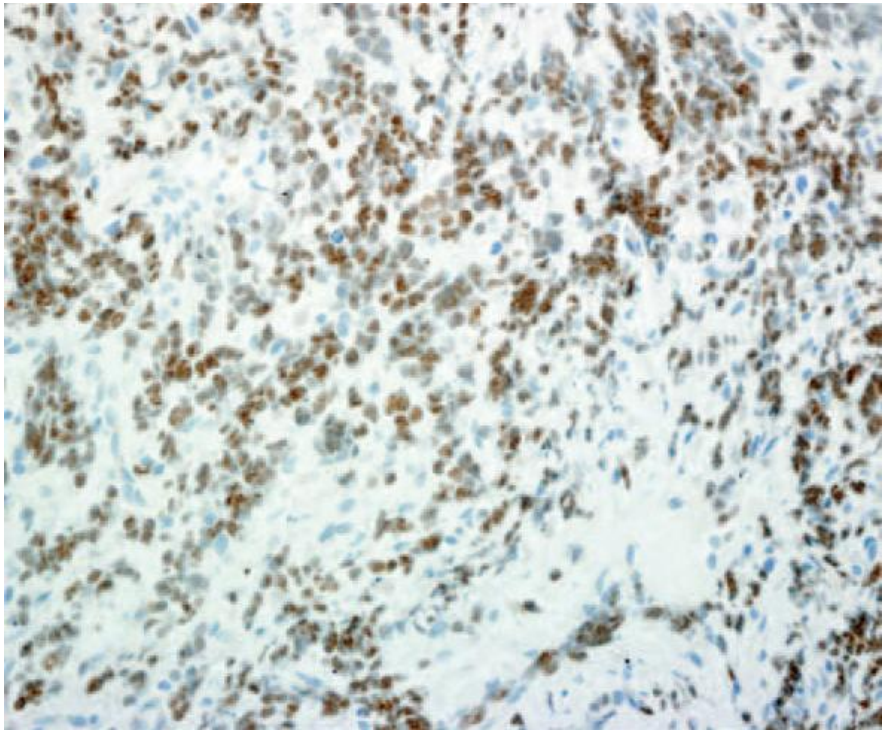
1967	1981	2004	2015
Small cell anaplastic	Small cell *Oat cell* *Intermediate cell* *Combined*	Small cell *Combined*	Small cell *Combined*

NUT carcinoma

- An aggressive tumor with NUT (nuclear protein in testis) gene rearrangement t(15;19), t(15;9)
- Sheets and nests of monomorphic small to intermediate cells
- Abrupt foci of keratinization
- Positive for NUT antibody, CK, P63/P40, CD34
- May also positive for neuroendocrine markers, TTF-1

NUT carcinoma





Sclerosing pneumocytoma

- Previous known as sclerosing hemagioma
- A tumor of pneumocyte origin
- 80% in female, high incidence in East Asian
- A combination of solid, papillary, sclerotic, hemorrhagic patterns
- Two cell types: cuboidal surface cells and stromal round cells
- IHC
  - Surface cells: CK+, CK7 +, TTF-1+, napsin A+, EMA+
  - Round cells: TTF-1+, EMA+, napsin A+/-, CK-

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Sclerosing pneumocytoma

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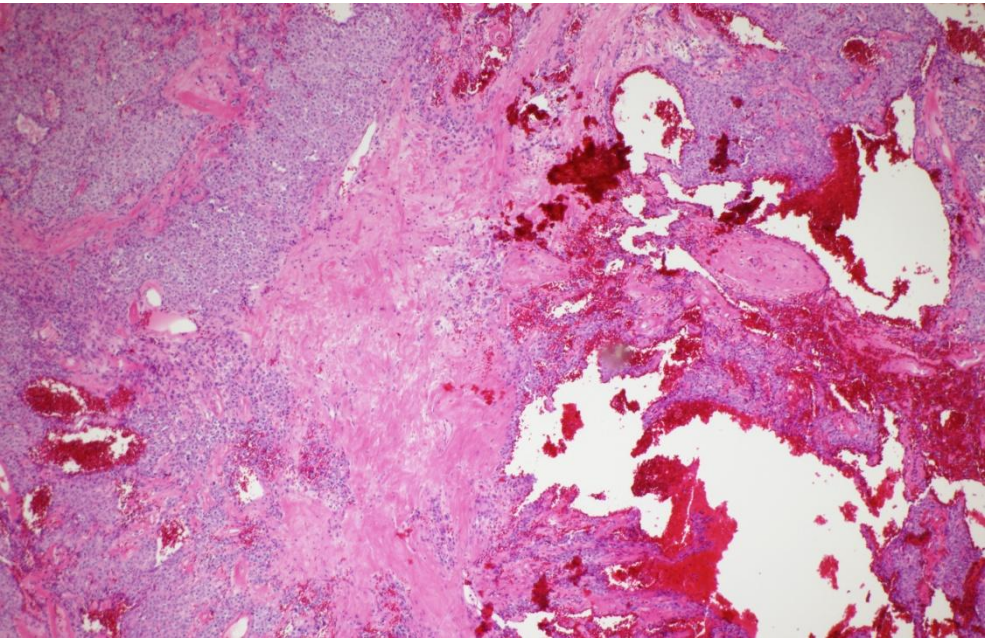
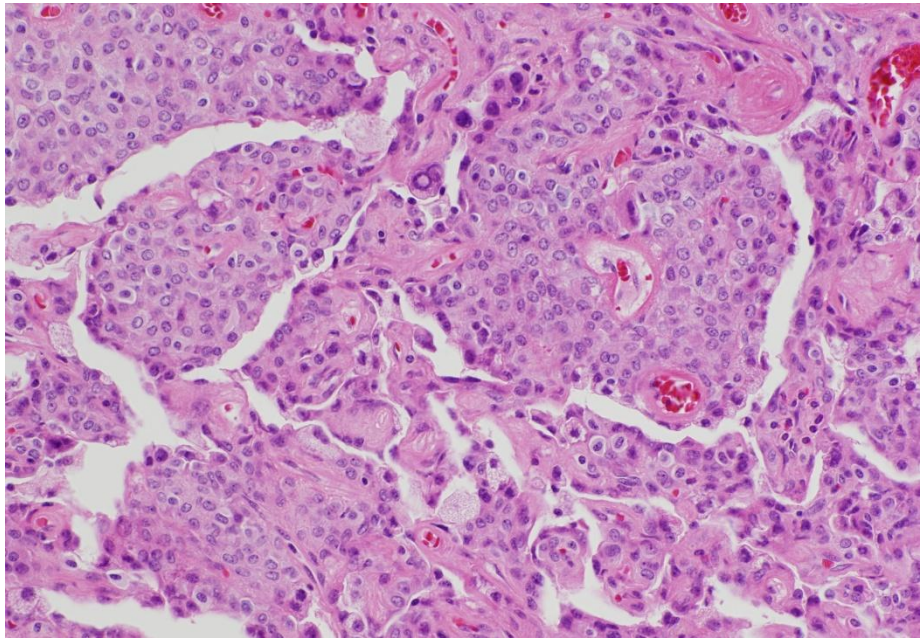
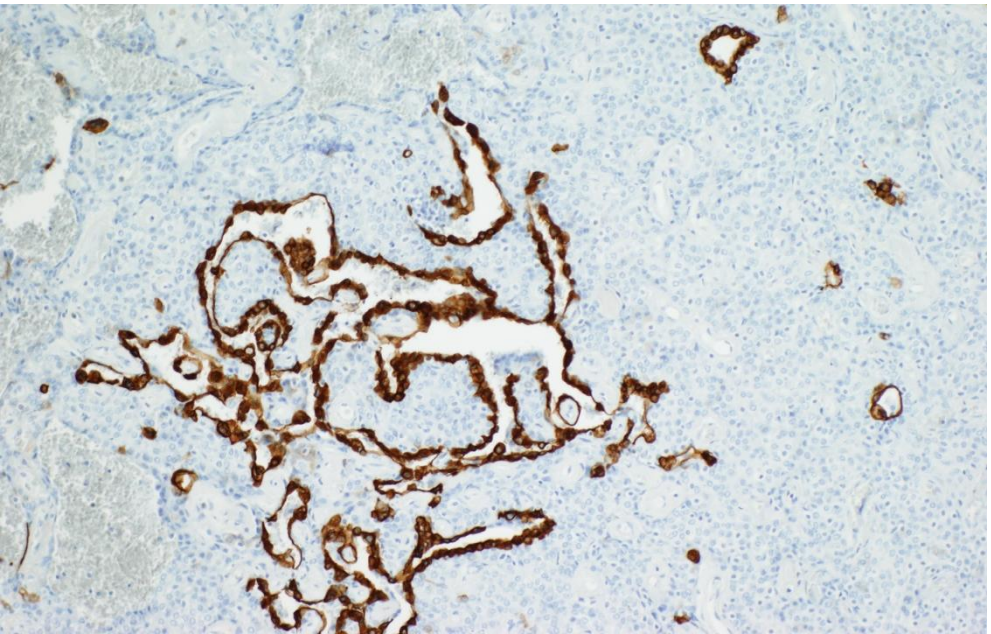
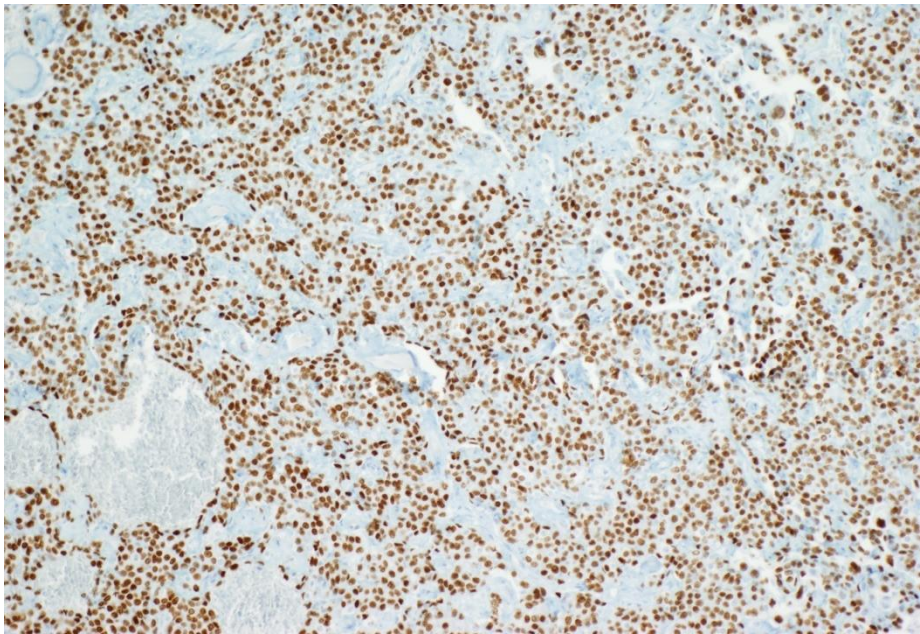




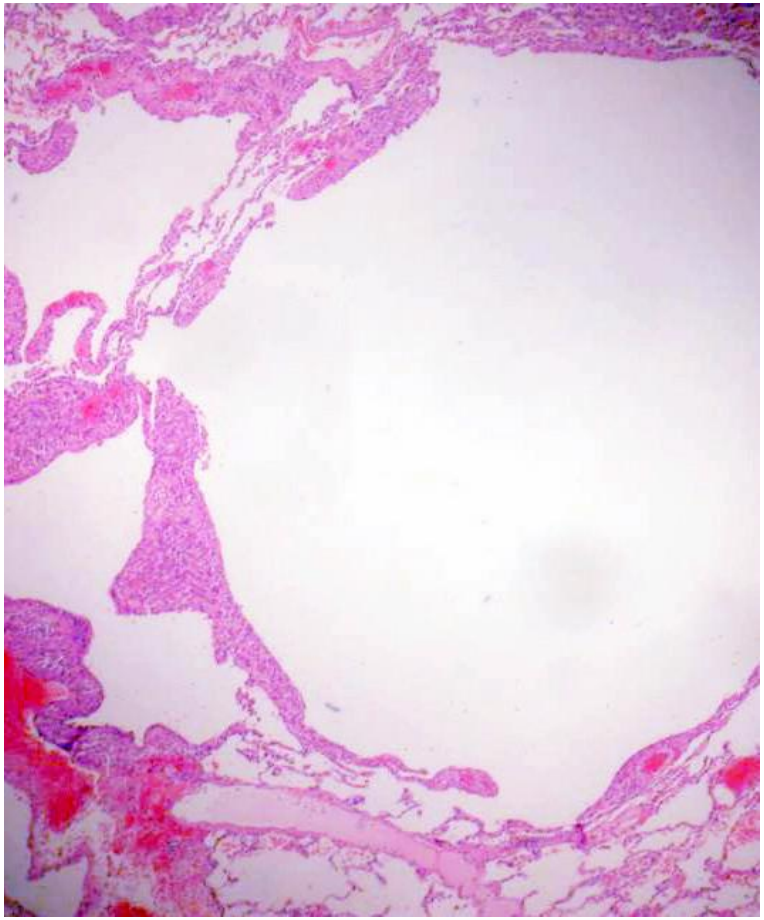


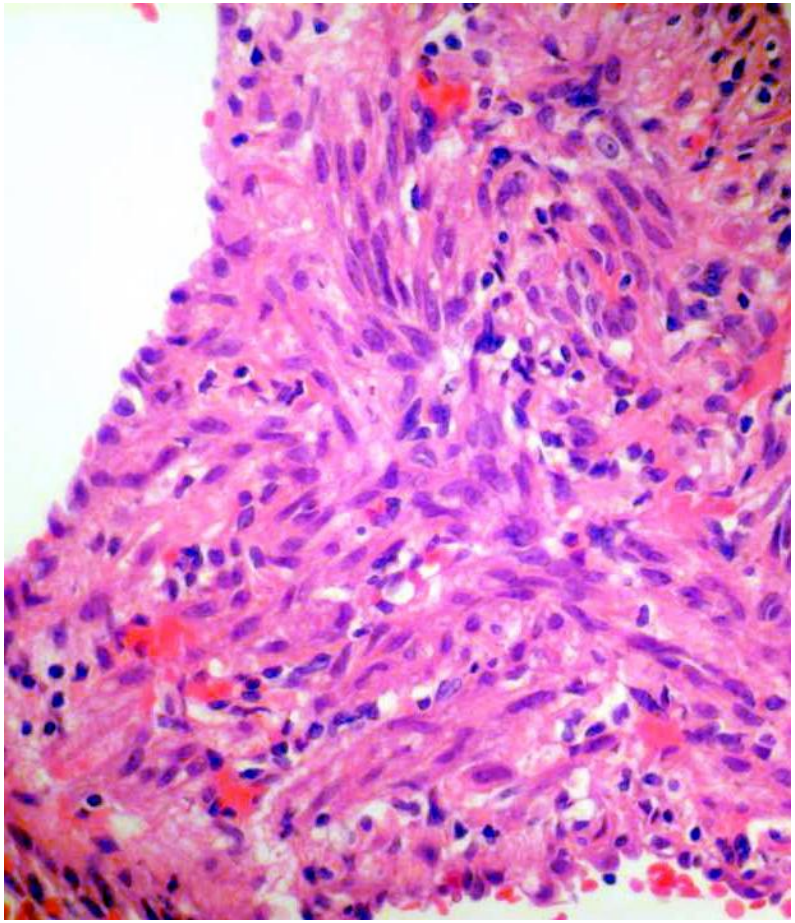


PEComatous tumors

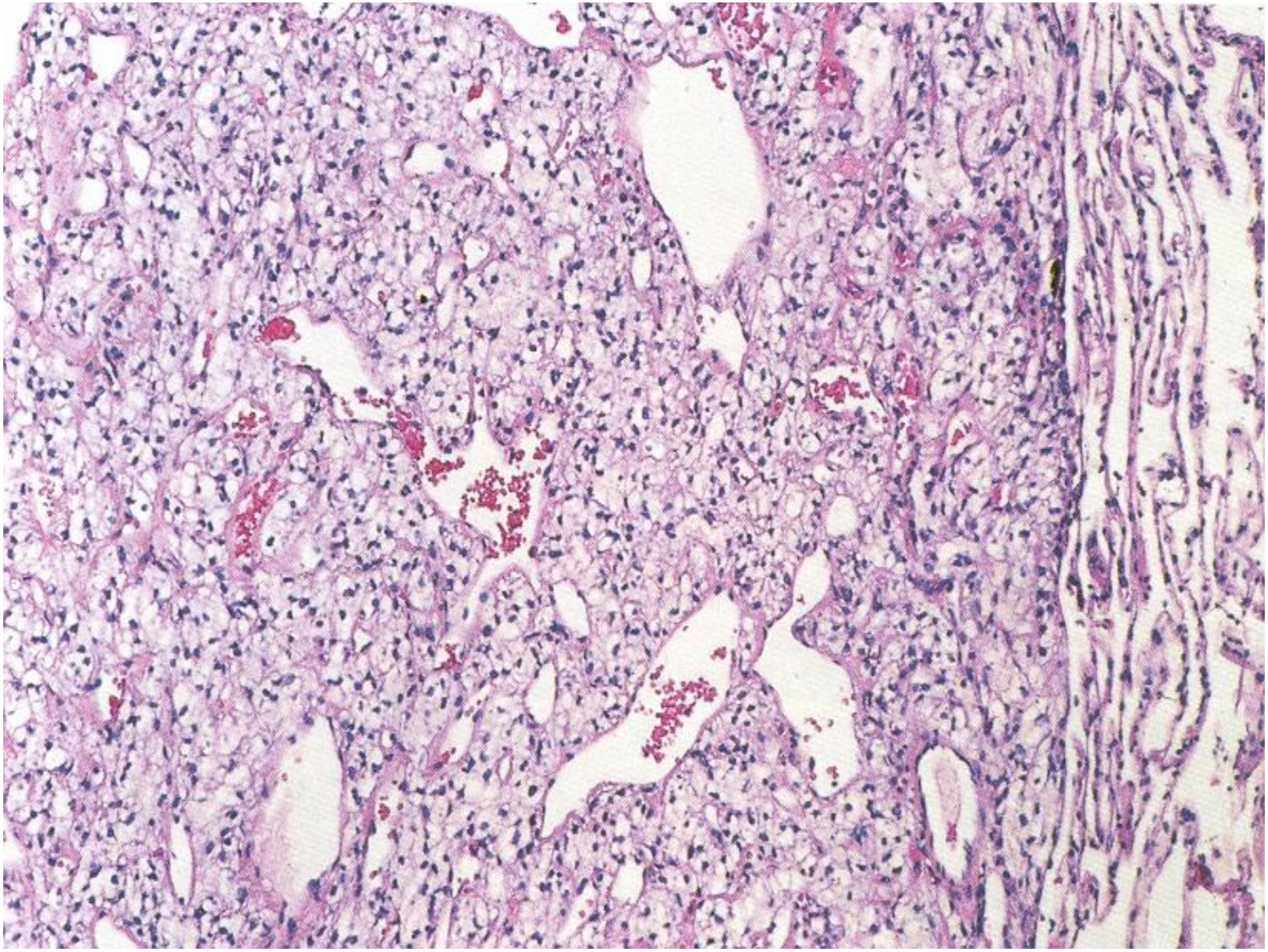
- Arising from perivascular epithelioid cells (PEC)
- Three forms
  - Lymphagioleiomyomatosis (LAM)
  - PEComa (*clear cell tumor*)
    - Benign
    - Malignant
  - A diffuse proliferation with overlapping LAM and PEComa
- IHC
  - LAM: HMB45+, melan A+, α-actin+, ER+, PR+, β-catenin+, S100-
  - PEComa: HMB45+, melan A+ , S100+, PAS/D

Lymphagioleiomyomatosis





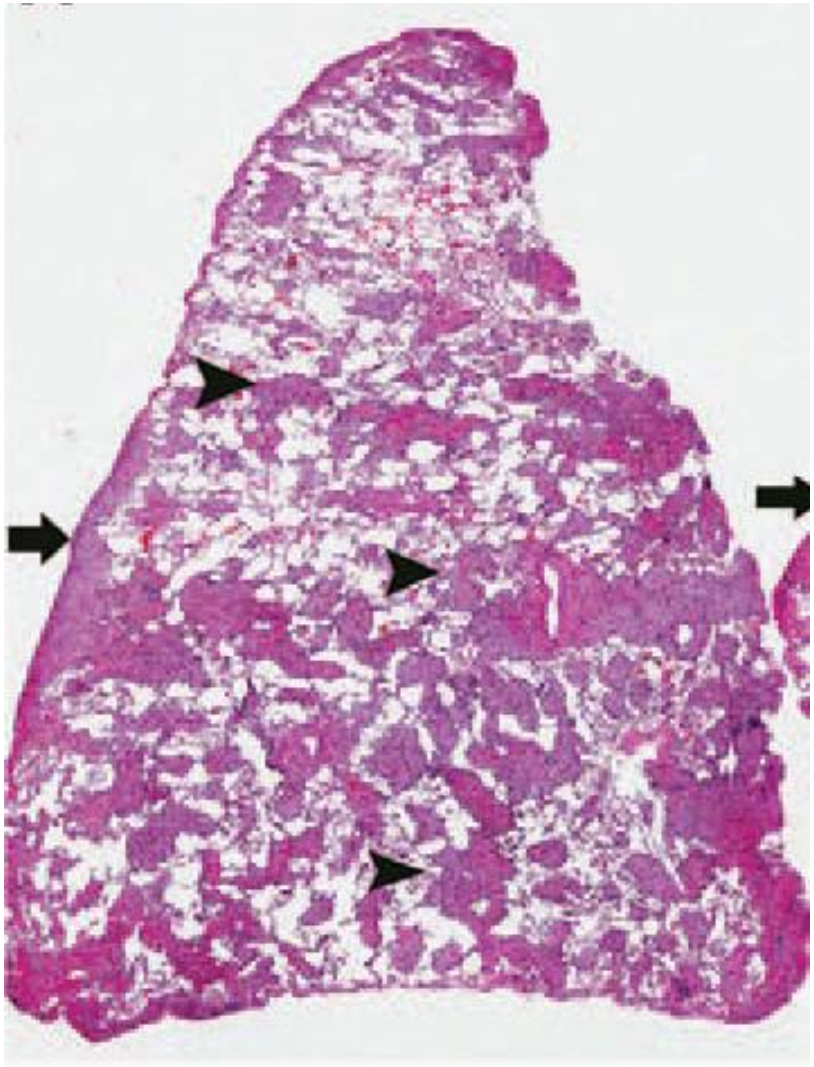
PEComa

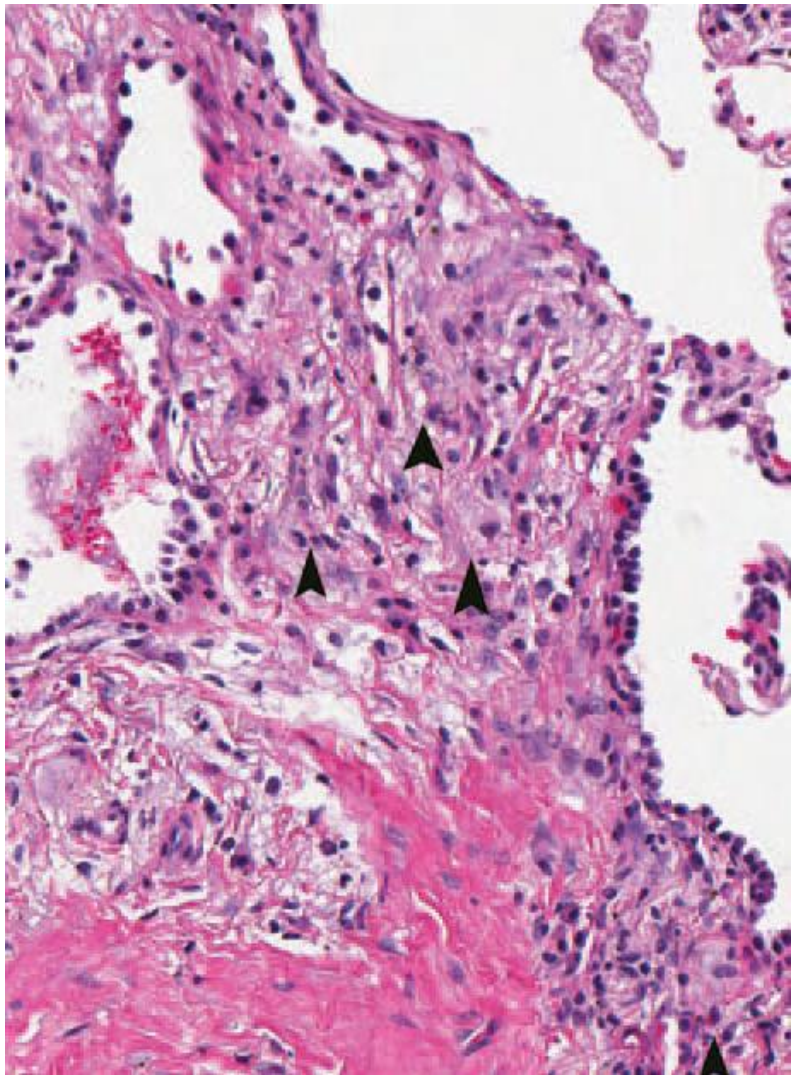


Erdheim-Chester disease

- It is a xanthogranulomatous histiocytosis
- BRAF mutation >50% cases
- Involving skeleton, kidney, heart, lung, CNS
- Foamy histiocytic infiltrate along lymaphatic distribution with fibrosis, inflammatory cells, Touton giant cells
- IHC: CD68, Factor XIIIa, lysozyme, CD4, S100, alpha-antitrypsin, alpha-antichymotrypsin

Erdheim-Chester disease

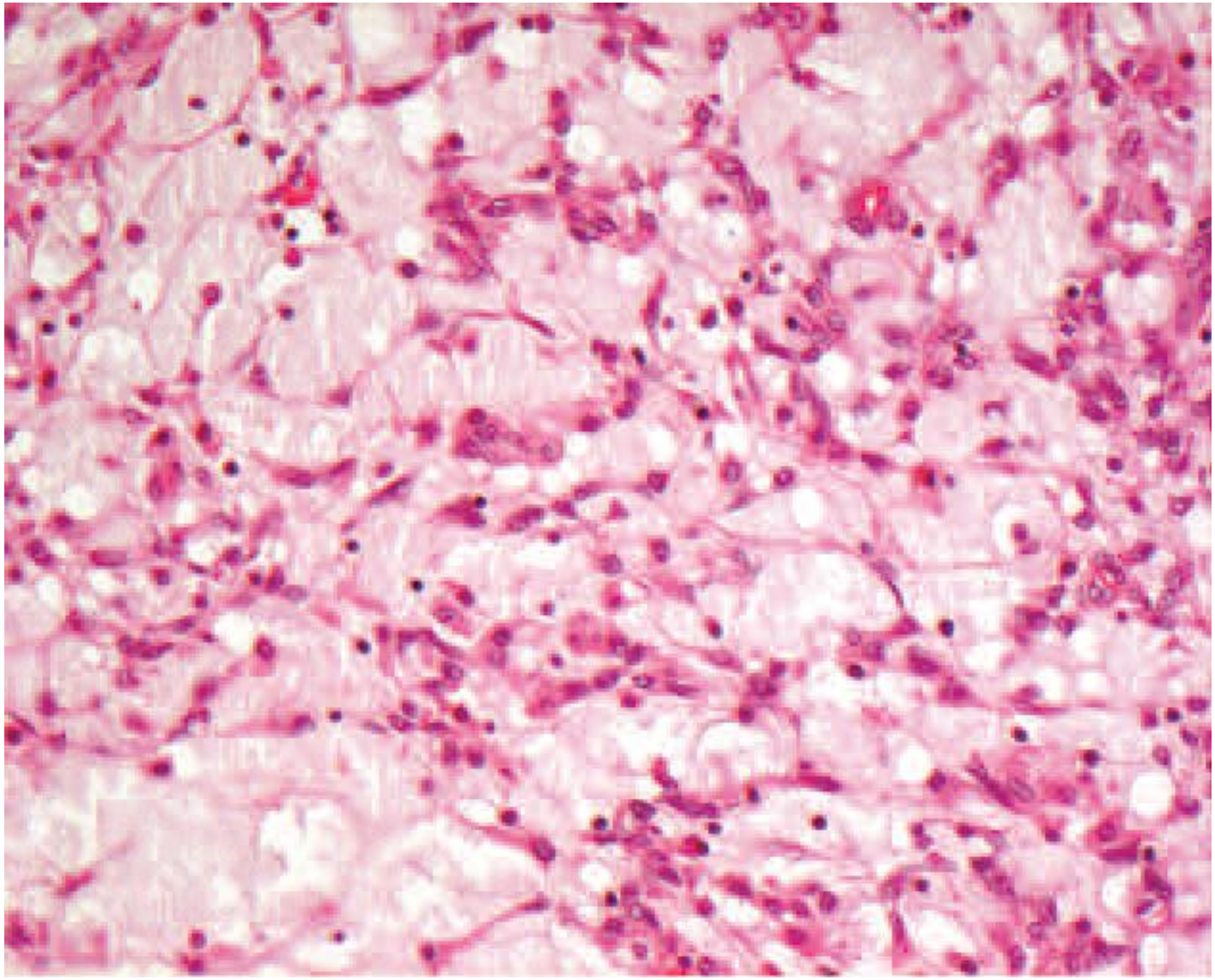




Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation

- Arising in the airways, often seen in young female
- Lobules of lacelike strands, cores of mildly atypical round, spindle or stellate cells with a myxoid stroma
- EMA 60% focal and weak+, others markers-
- EWSR1-CREB1 fusion gene detected by FISH, RT-PCR or direct sequencing

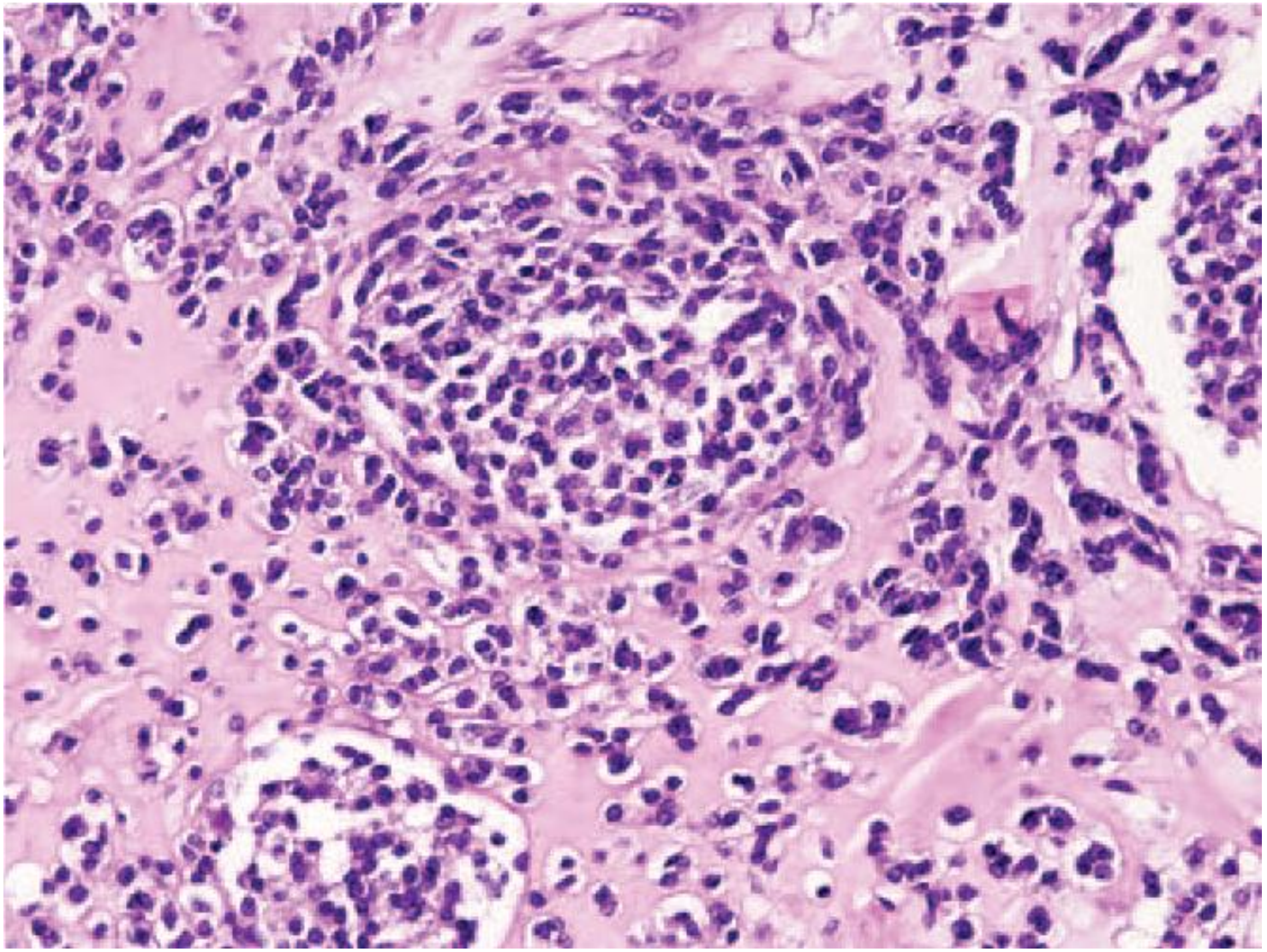
Pulmonary myxoid sarcoma with EWSR1-CREB1 translocation



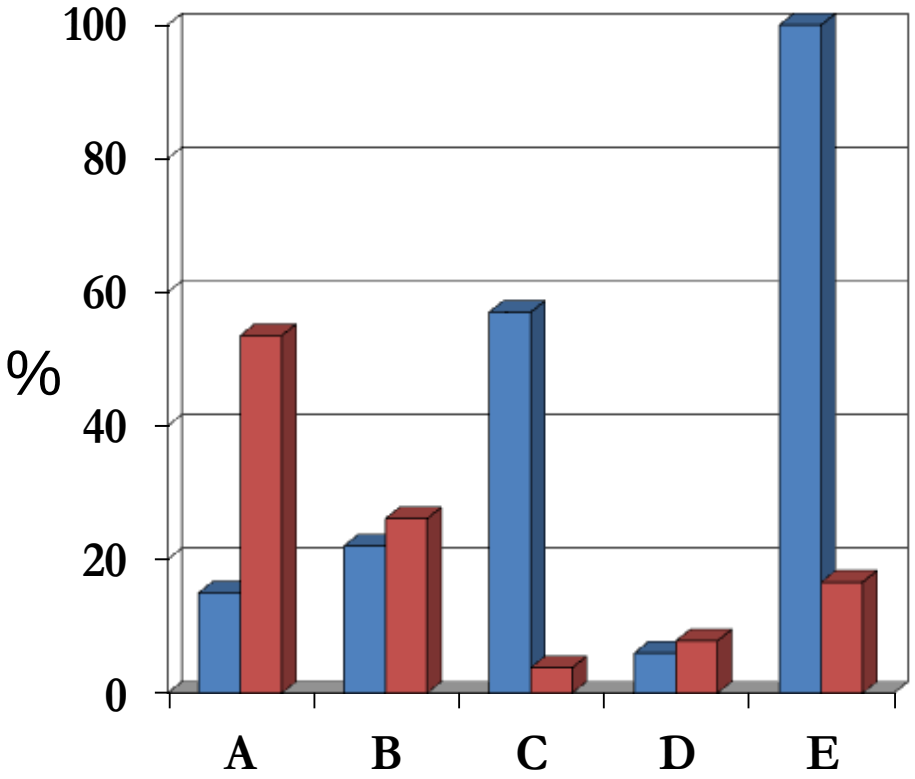
Myoepithelial tumors

- Myoepithelial differentiaiton
- Benign and malignant
- Epithelioid, spindled, or plasmacyotid cells with uniform nuclei, eosinophilic or clear cytoplasm
- Cytoplasmic hyaline inclusions may be present
- Tumor cells arraanged in trabecular and/or reticular patterns with myxoid stroma
- IHC: CK+, S100+, calponin+, GFAP+, actin+, P63/P40+/-, desmin-, CD34-
- EWSR1 gene rearrangement

Myoepithelial tumors

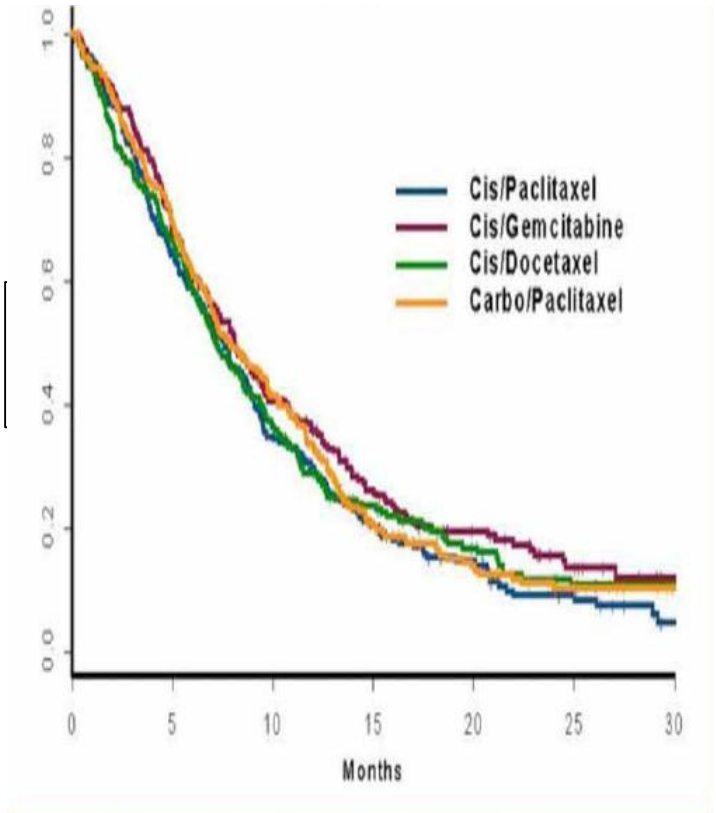


Lung cancer survival rates



Blue – cases Red -5 year survival

A – Localized
B – Regional node metastasis or directly beyond primary site
C - Distant metastasis
D - Unknown stage
E - Overall



Median survival 8 months, 1 year survival 30 %

Schiller JH et al. NEJM Jan. 2002

What do we learn from the history?

- Surgical treatment is effective but has limitations
- Majority of the lung cancer cases with no surgical indications at the time of diagnosis
- Chemotherapy / radiation is palliative
- Solutions
  - Prevention
  - Early detection
  - New modalities

EGFR mutations

- **EGFR mutations**
  - TKIs – gefitinib, erlotinib, afatinib, AZD9291, CO-1686
  - ORR 68%, DCR 86%, median PFS 12 m, OS 23.3 m
  - ↑PFS, quality of life, safety profile, convenience
  - EGFR exon 19 deletion in which afatinib vs chemotherapy median survival 31.7 : 20.7 m $p<0.0001$

- **ALK gene rearrangement**
  - ALK TKI – crizotinib, ceritinib, alectinib
  - In 1st line setting vs chemotherapy: ORR 74% vs 45%, PFS 10.9 vs 7.0 m, but no OS benefit
  - Phase 3 in 2nd line setting vs chemotherapy: ORR 65% vs 20%, PFS 7.7 vs 3.0 m but no OS benefit

Prospective cancer classification