Pathology of preneoplasia and common lung cancers

Elisabeth Brambilla

INSERM U823 Department of Pathology

CHU Grenoble France

Lung Cancer Classification revised in 1999 (WHO)

- 17 years elapsed since the 1981 WHO classification
- Progress in understanding genetic and molecular basis of carcinogenesis
- Foundation for tumor diagnosis and patient therapy
- Cornerstone of comparative studies: clinical, epidemiologic and biological
- Complemented with clinical and genetic features of entites : **Pathology and geneties (WHO 2004)**

Histological classification of lung tumors (WHO 1999 - 2004)

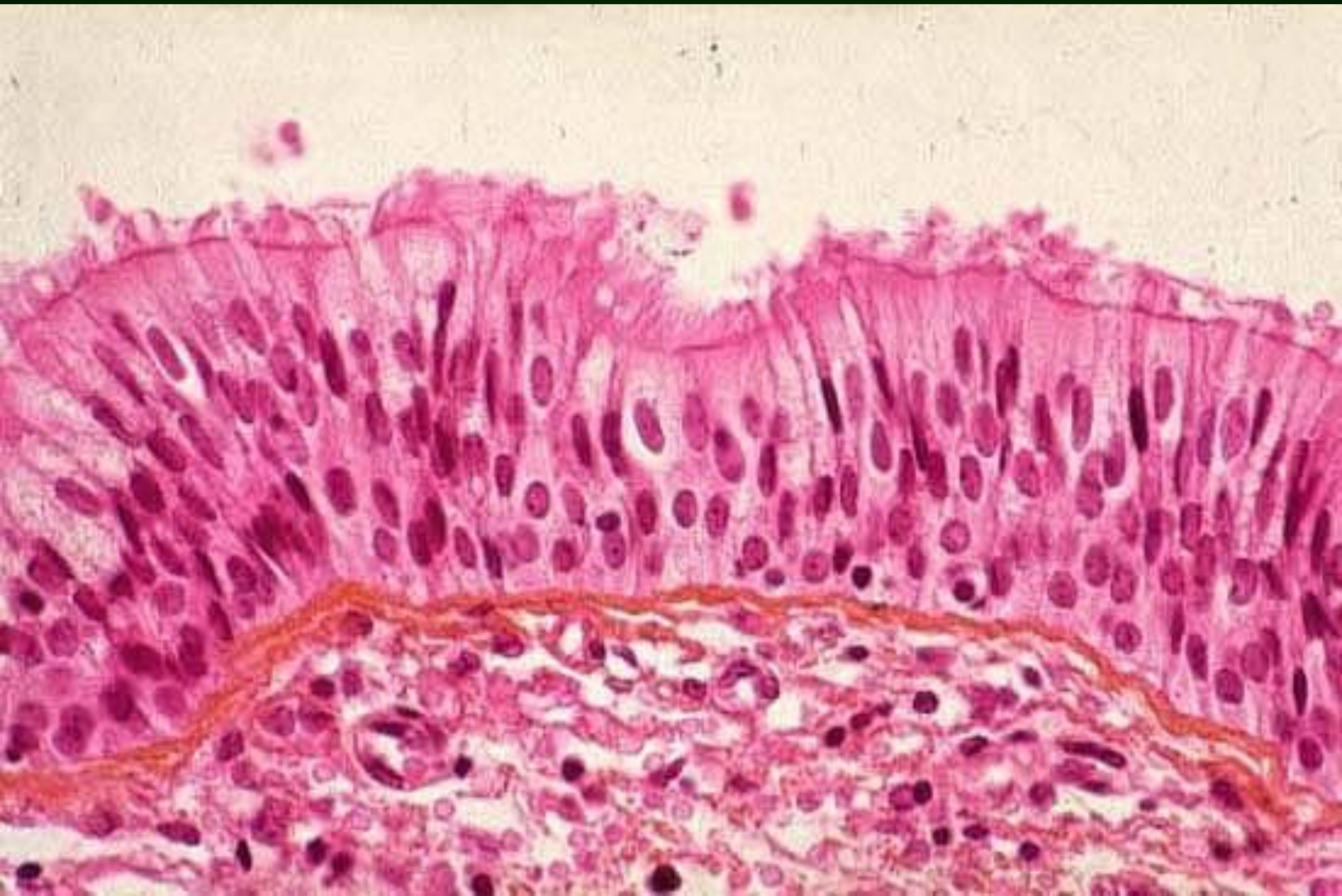
- Squamous Cell Carcinoma
- Small Cell Carcinoma
- Adenocarcinoma
- Large Cell Carcinoma
- Adeno Squamous Carcinoma
- Sarcomatoid carcinoma
- Carcinoid tumors
- Salivary gland tumors
- Preinvasive lesions

Preinvasive lesions

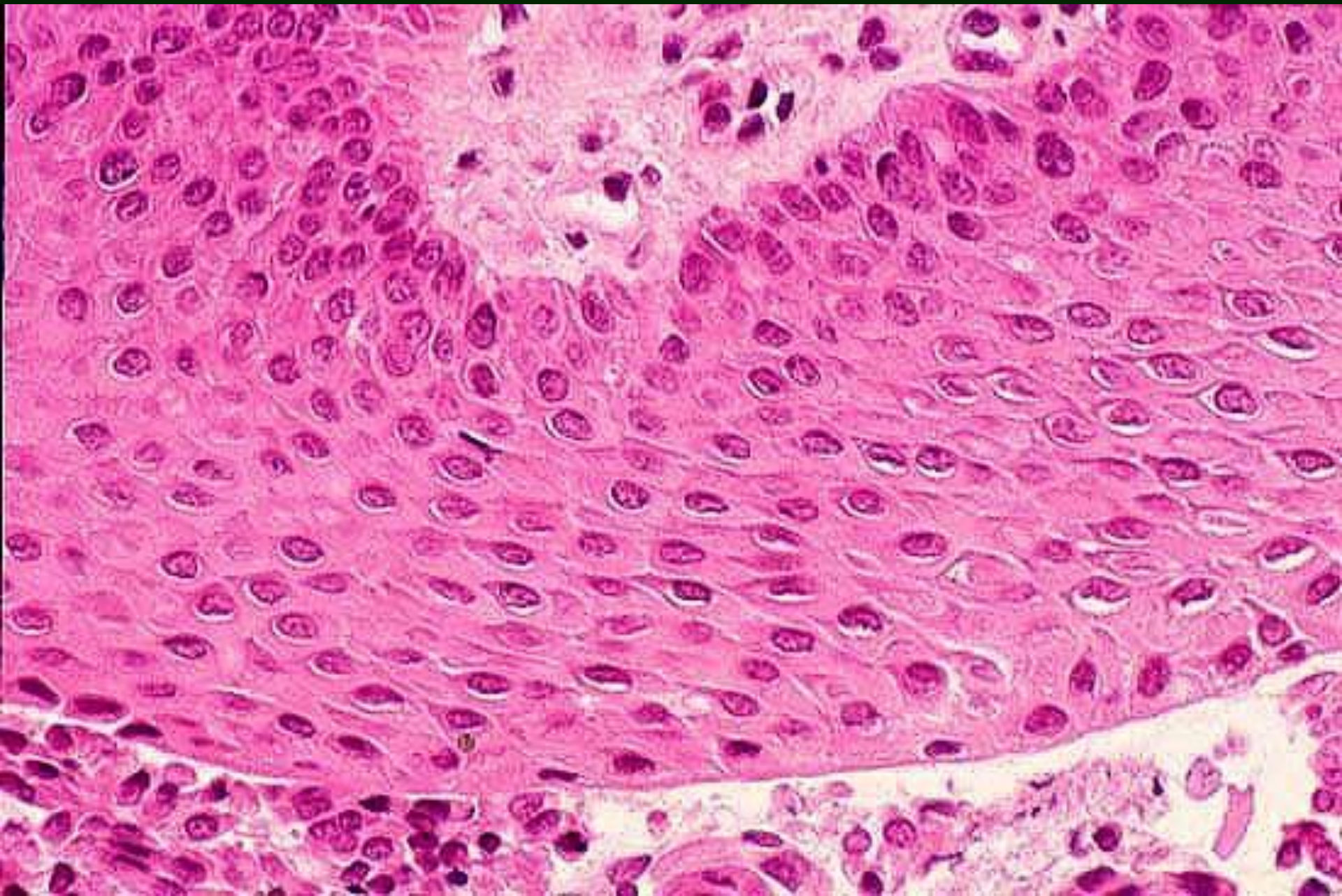
- Squamous dysplasia
  - mild
  - moderate
  - severe
- Carcinoma in situ
- Atypical adenomatous hyperplasia (AAH)
- Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

Normal bronchial epithelium

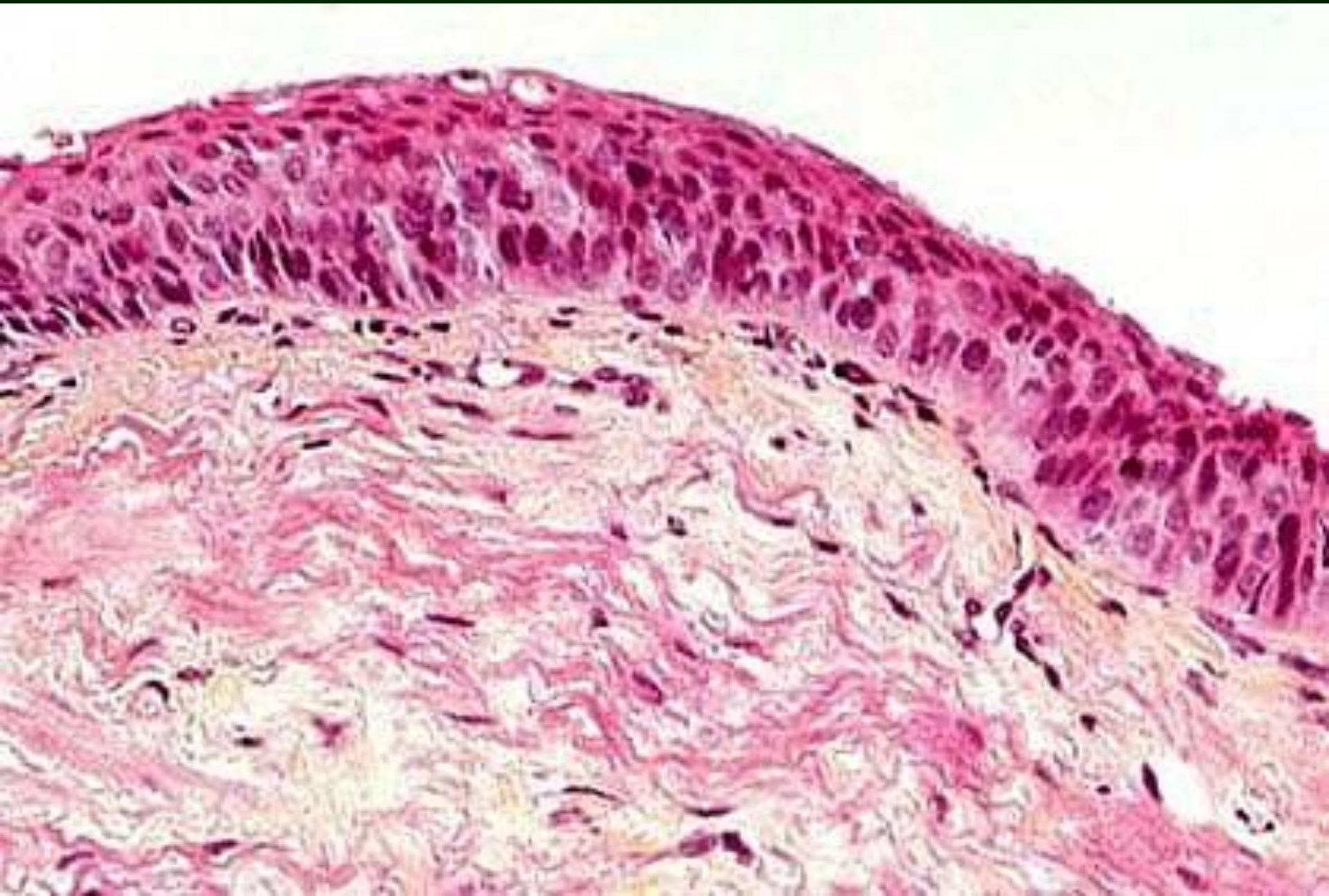
Bronchial epithelium: hyperplasia



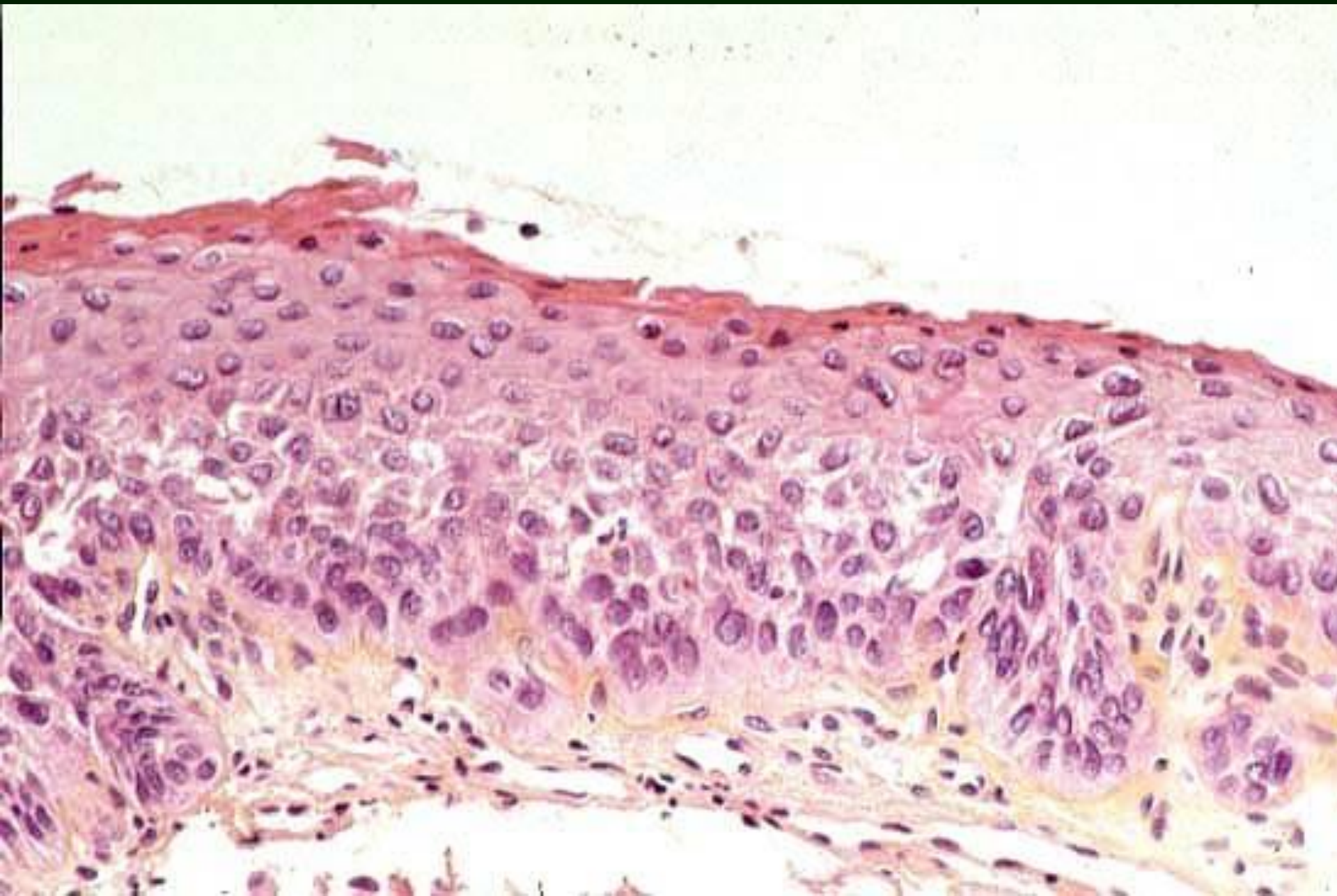
Squamous metaplasia



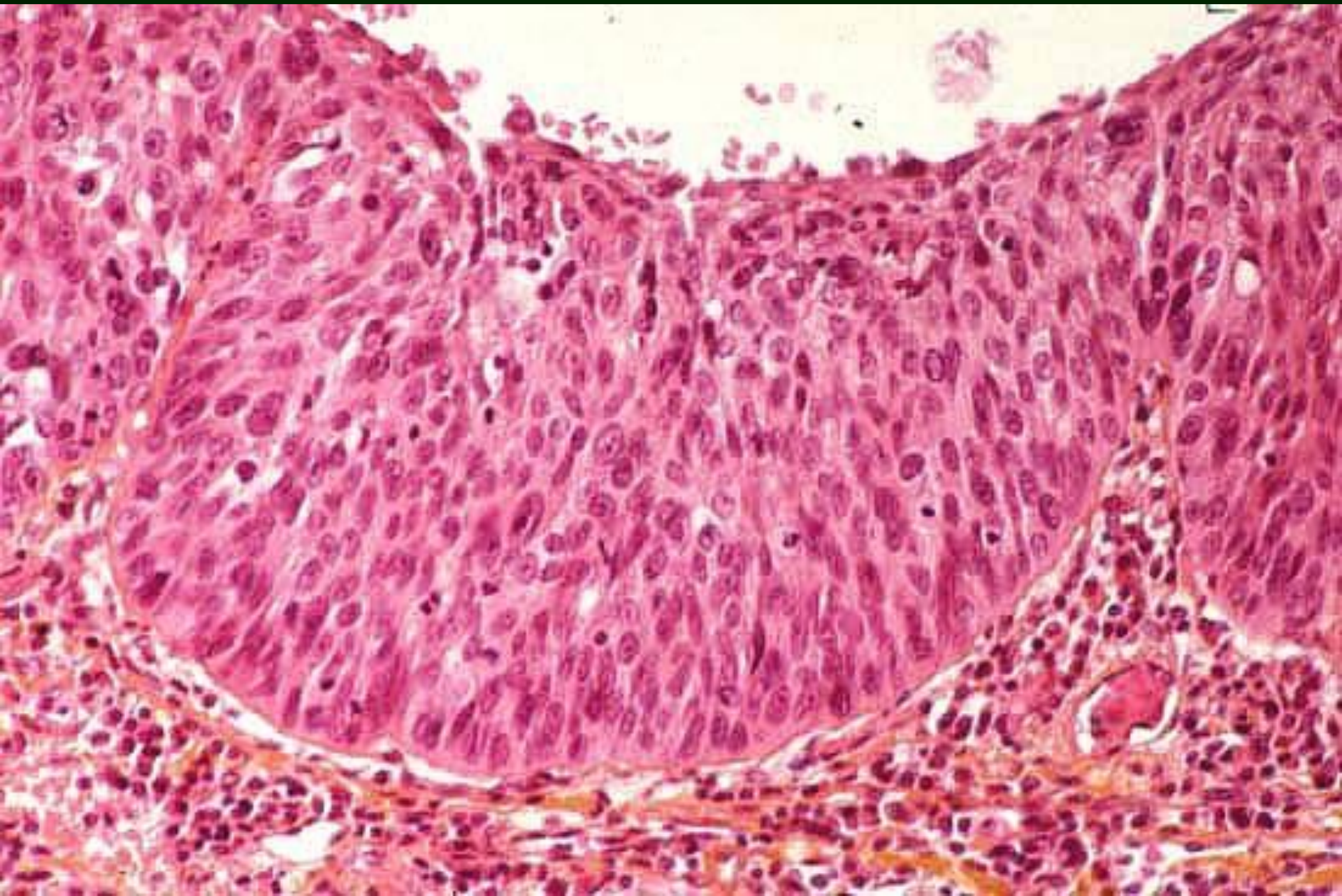
Mild dysplasia



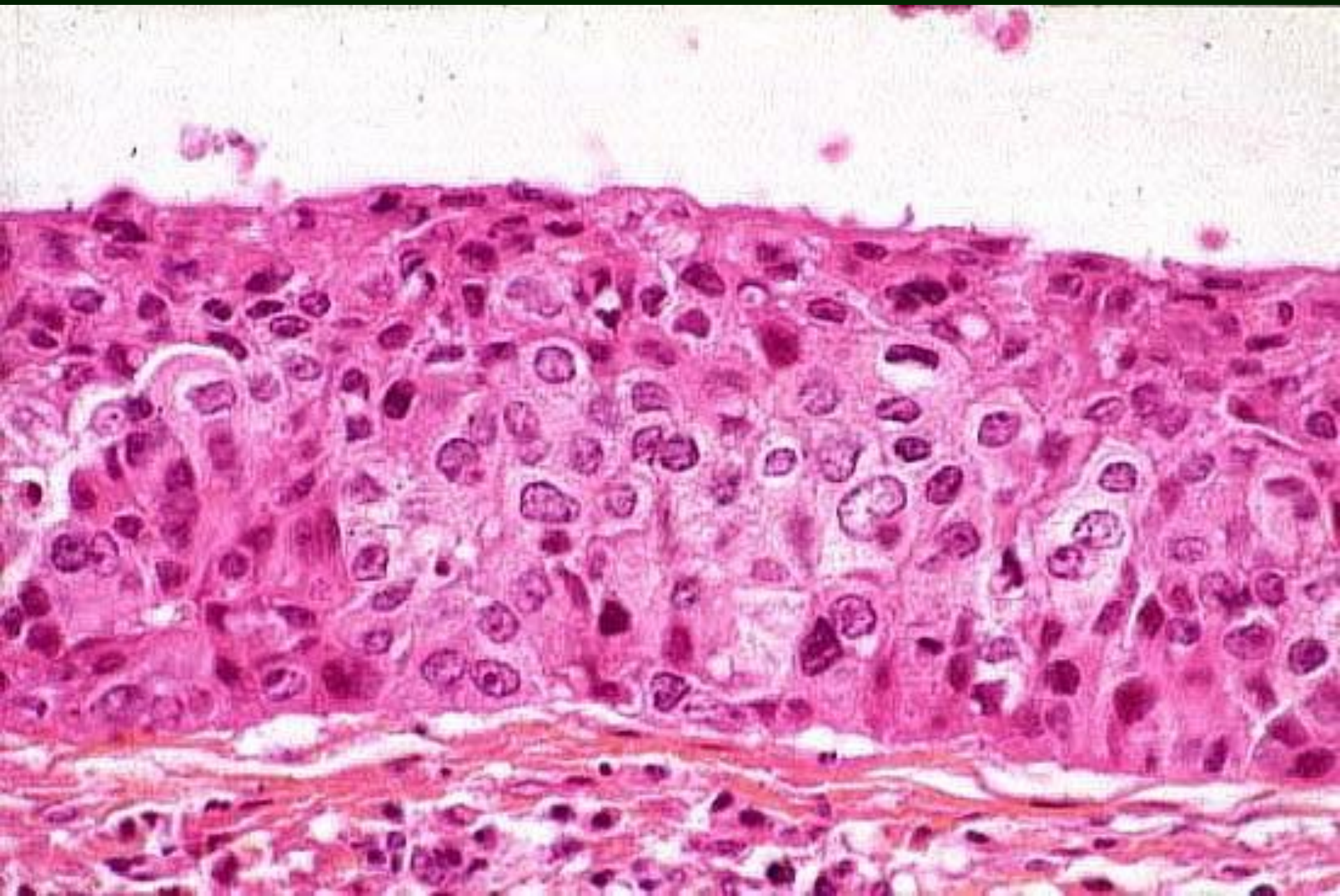
Moderate dysplasia



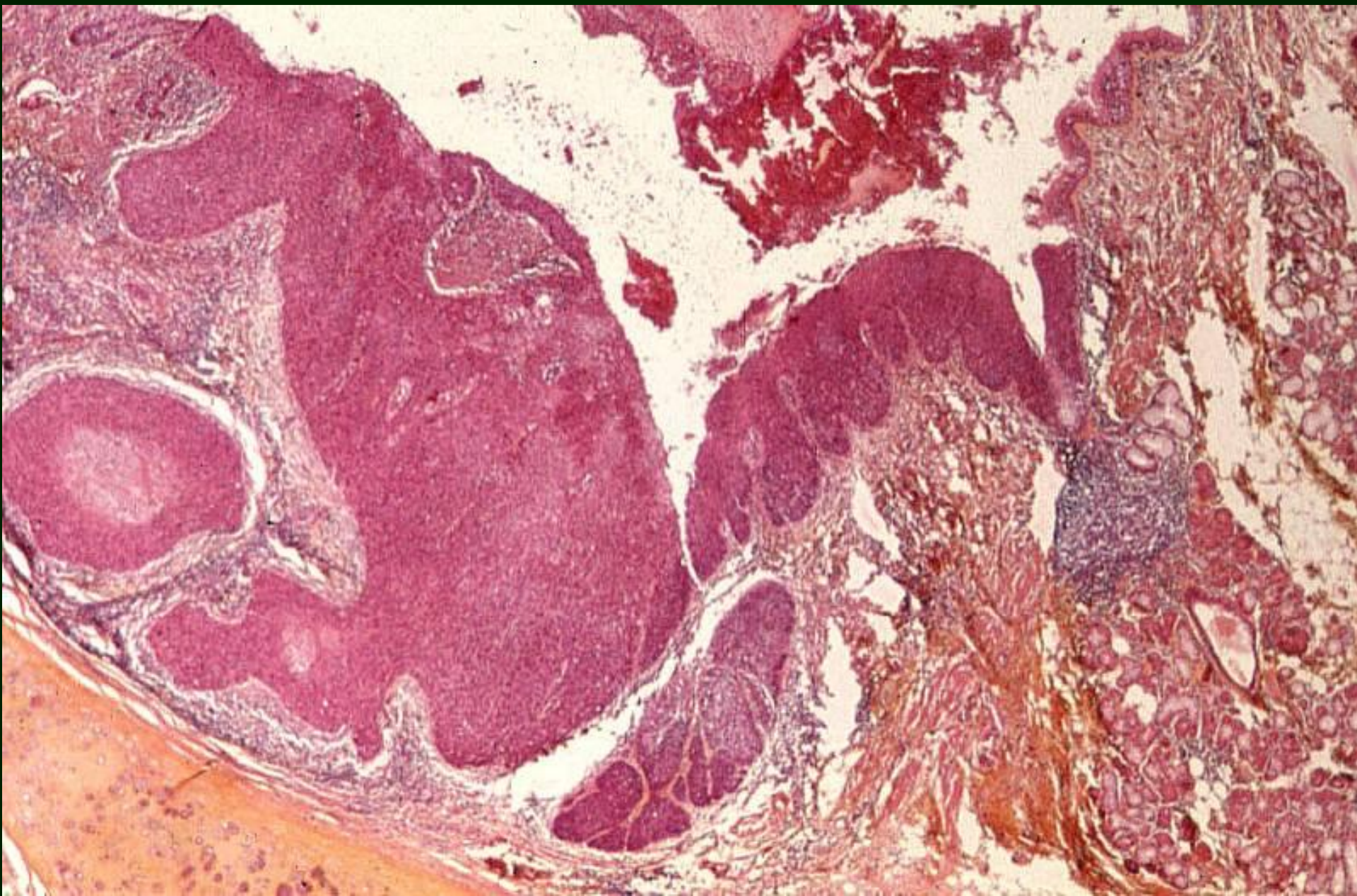
Severe dysplasia



Carcinoma in situ



Invasive carcinoma: T1



Pre- and neoplastic bronchial lesions

Hyperplasia

⇓ ?

Metaplasia

⇓ ?

Dysplasia

⇓⇓ ?

In situ carcinoma

⇓⇓⇓ ?

Invasive carcinoma

Molecular Identity

. **Cell cycle regulation**

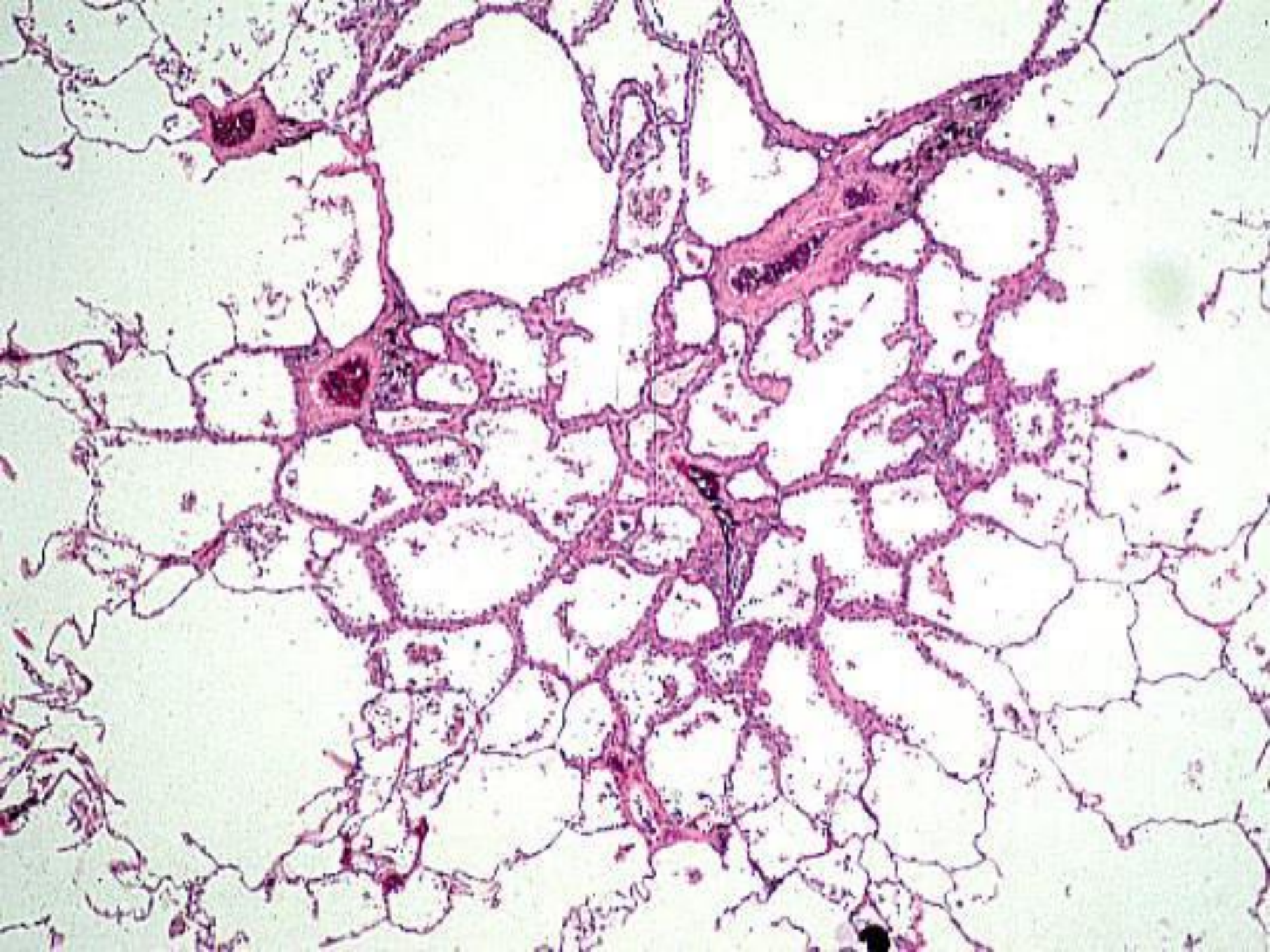
. **Apoptosis / Senescence**

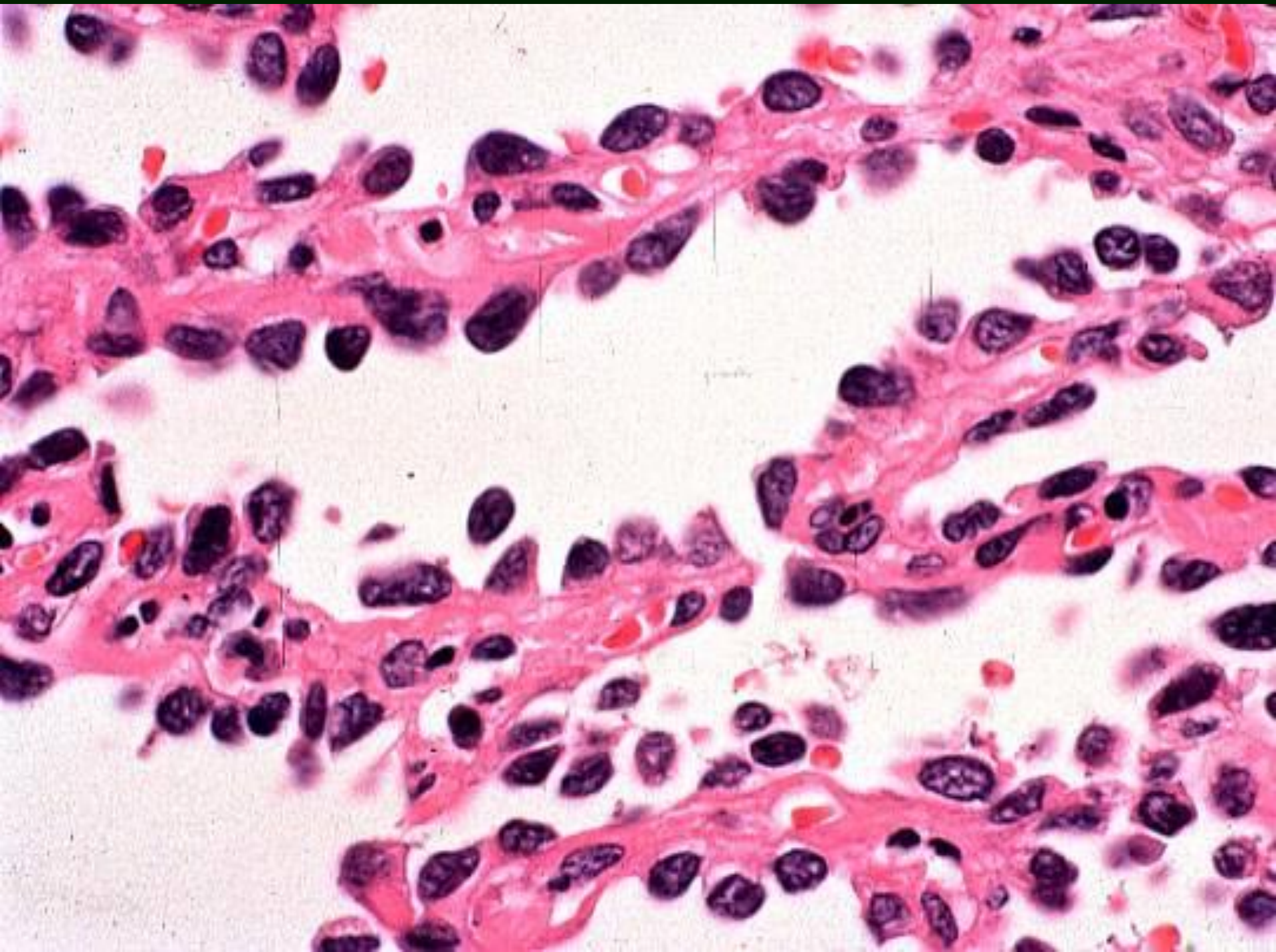
. **Angiogenesis / Migration**

Atypical Alveolar Hyperplasia (AAH)

- A preinvasive lesion for Bronchiolo Alveolar Carcinoma (BAC)
- Focal lesion (1-10 mm) most often less than 3mm
- Slightly atypical epithelial cells covering alveoli and respiratory bronchioles

- Differential diagnosis with BAC
  - size ≥ 5mm
  - no gaps between cells
  - more severe atypia

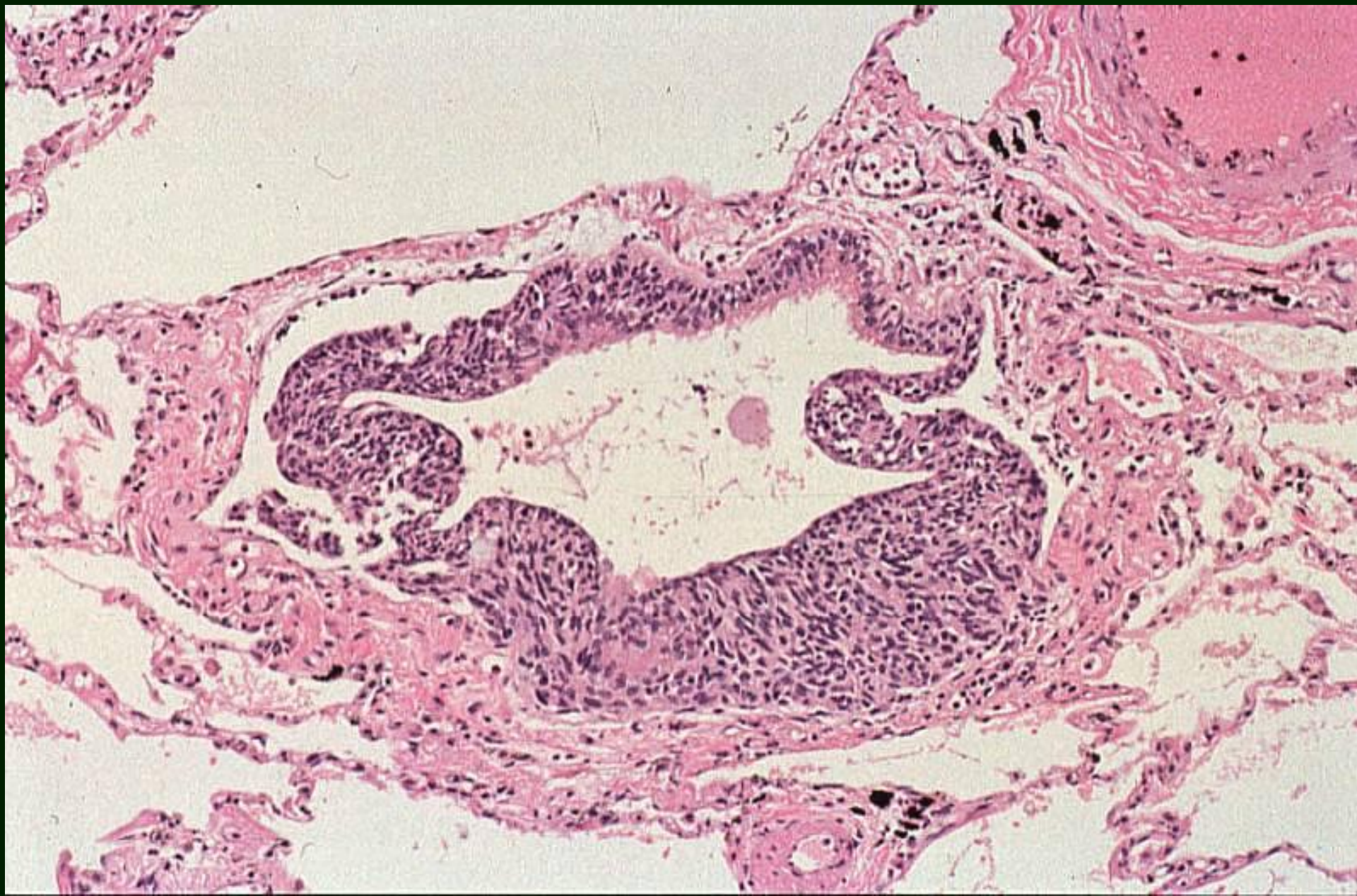




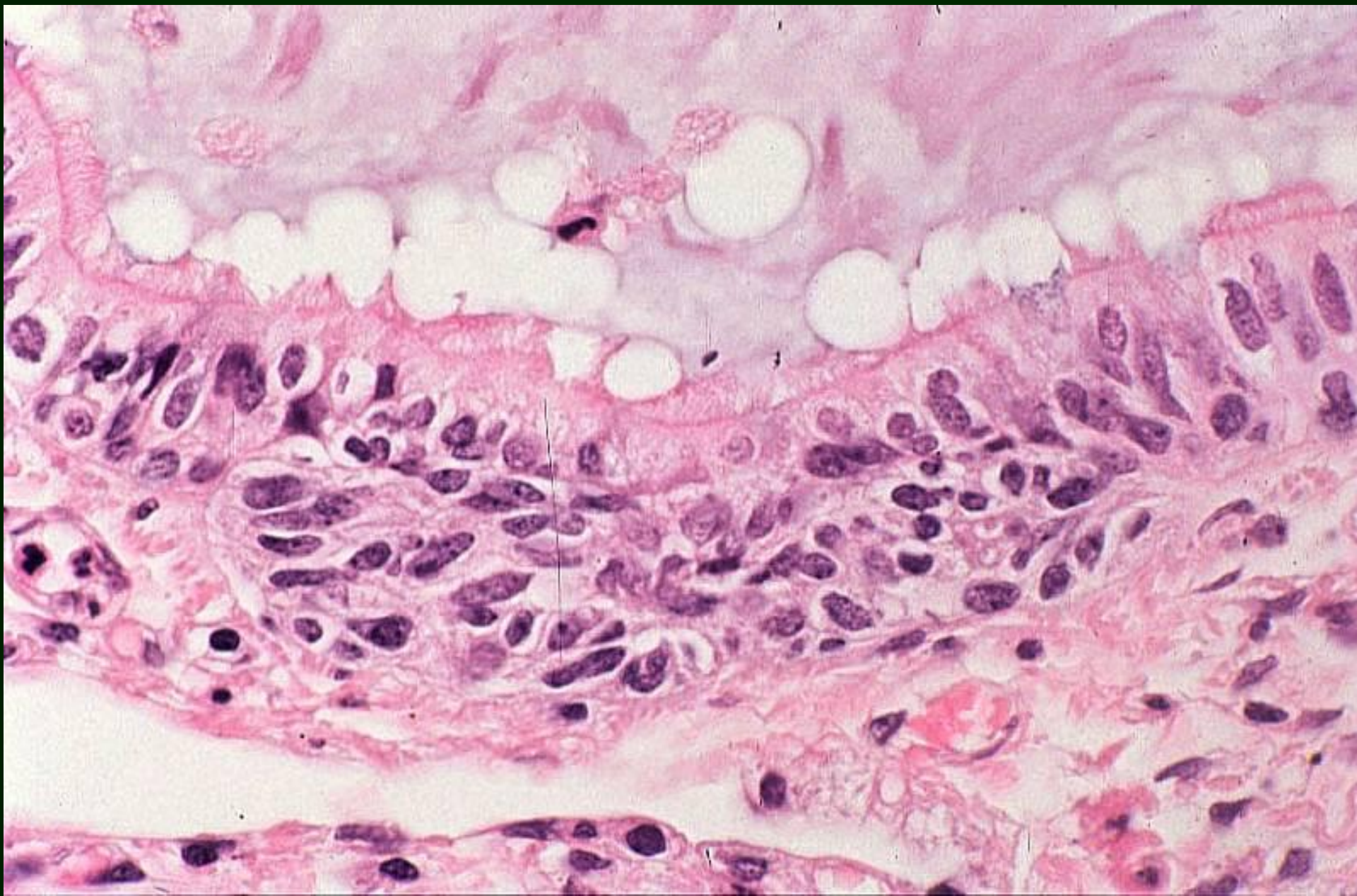
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- A proliferation of neuroendocrine cells confined to the bronchiolar ephithelium
- Scattered single cells, small nodules or linear proliferations
- Often associated with tumourlets

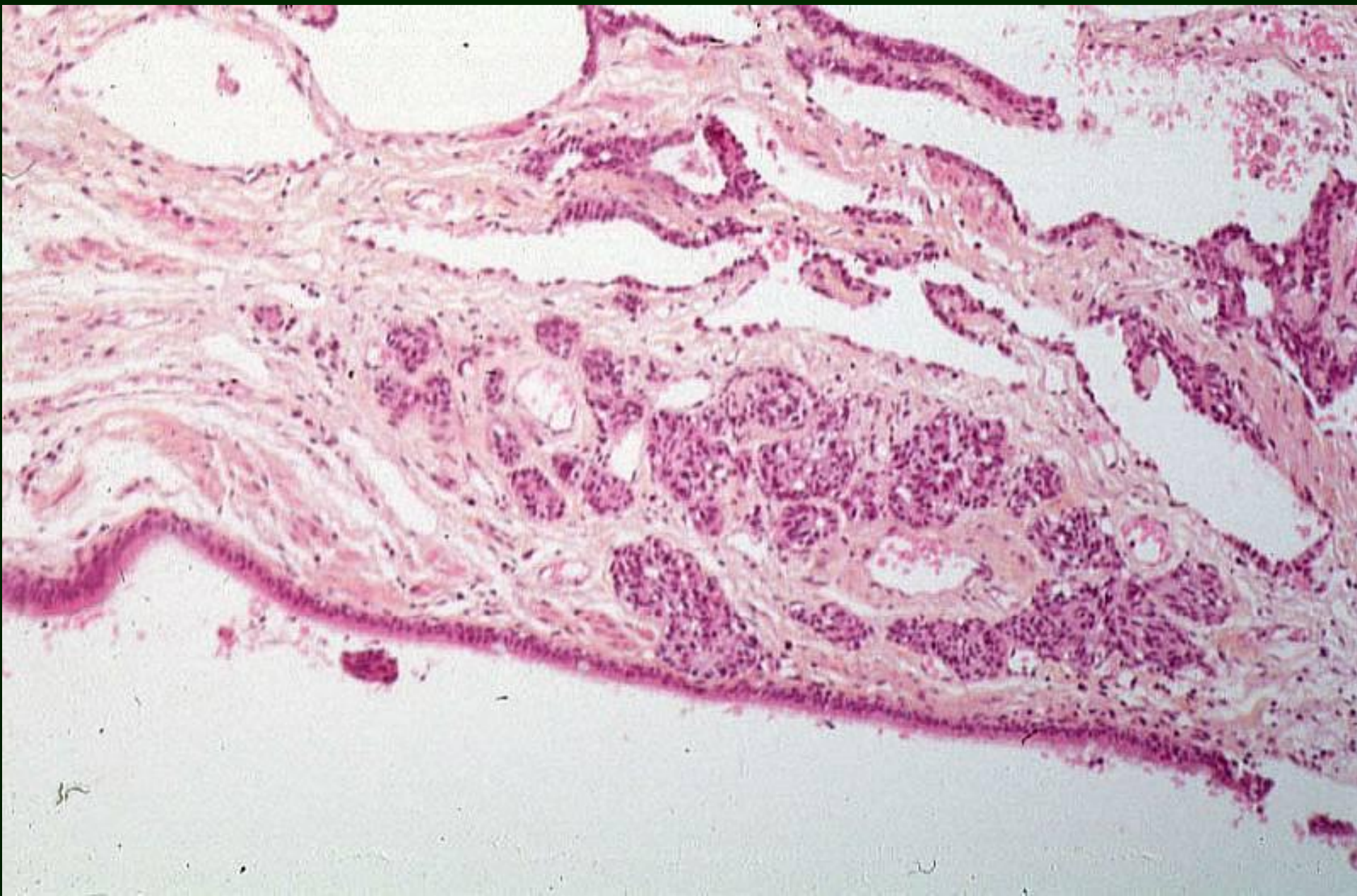
Neuroendocrine hyperplasia



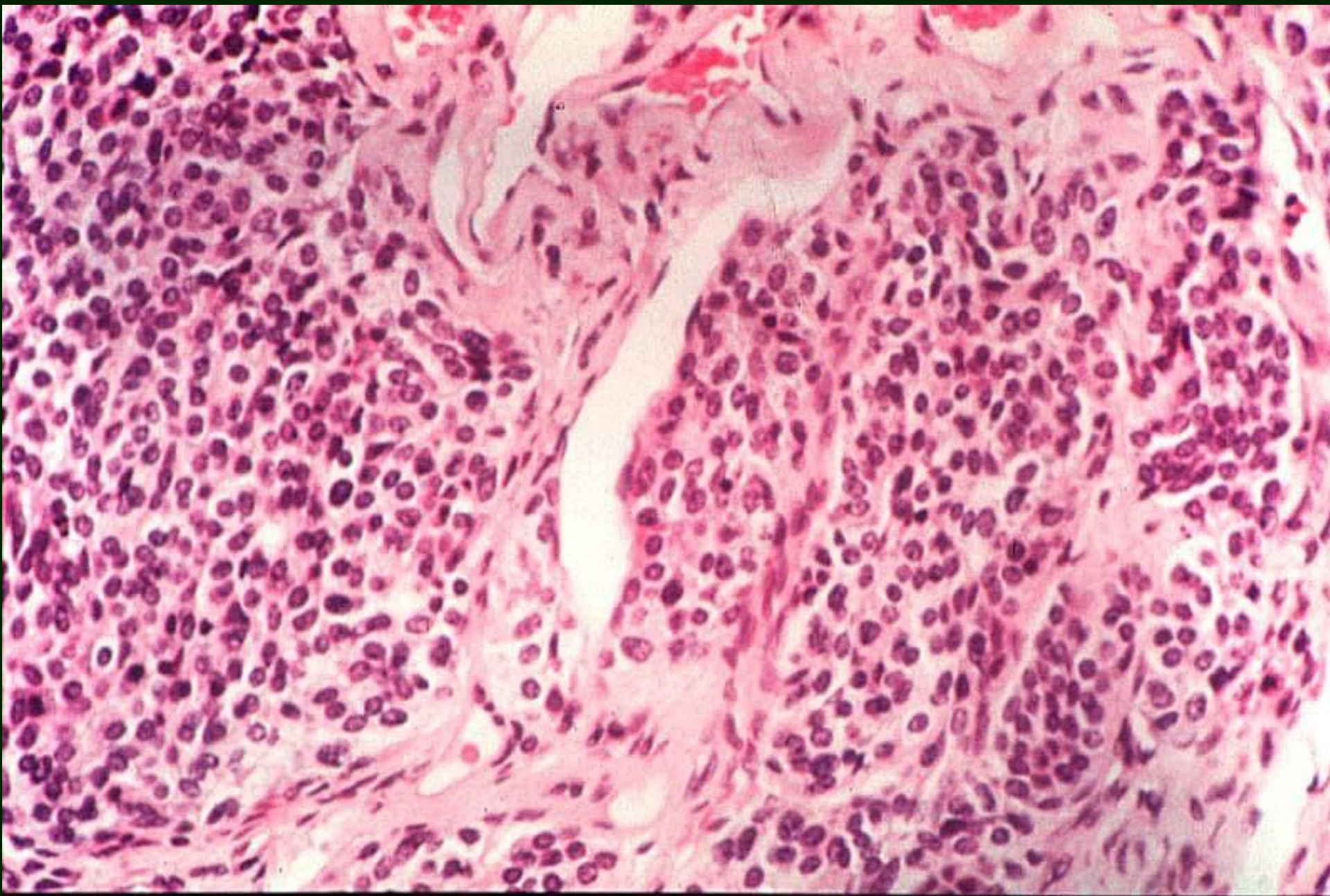
Neuroendocrine hyperplasia



Tumourlet



Tumourlet : less than 5mm > 5mm : carcinoid



Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia

- **Idiopathic: not a simple reaction to lung inflammation of fibrosis**
- **A preneoplastic lesions: some patients develop one or more carcinoid tumors**
- **A subset of patients have obstructive airway disease**

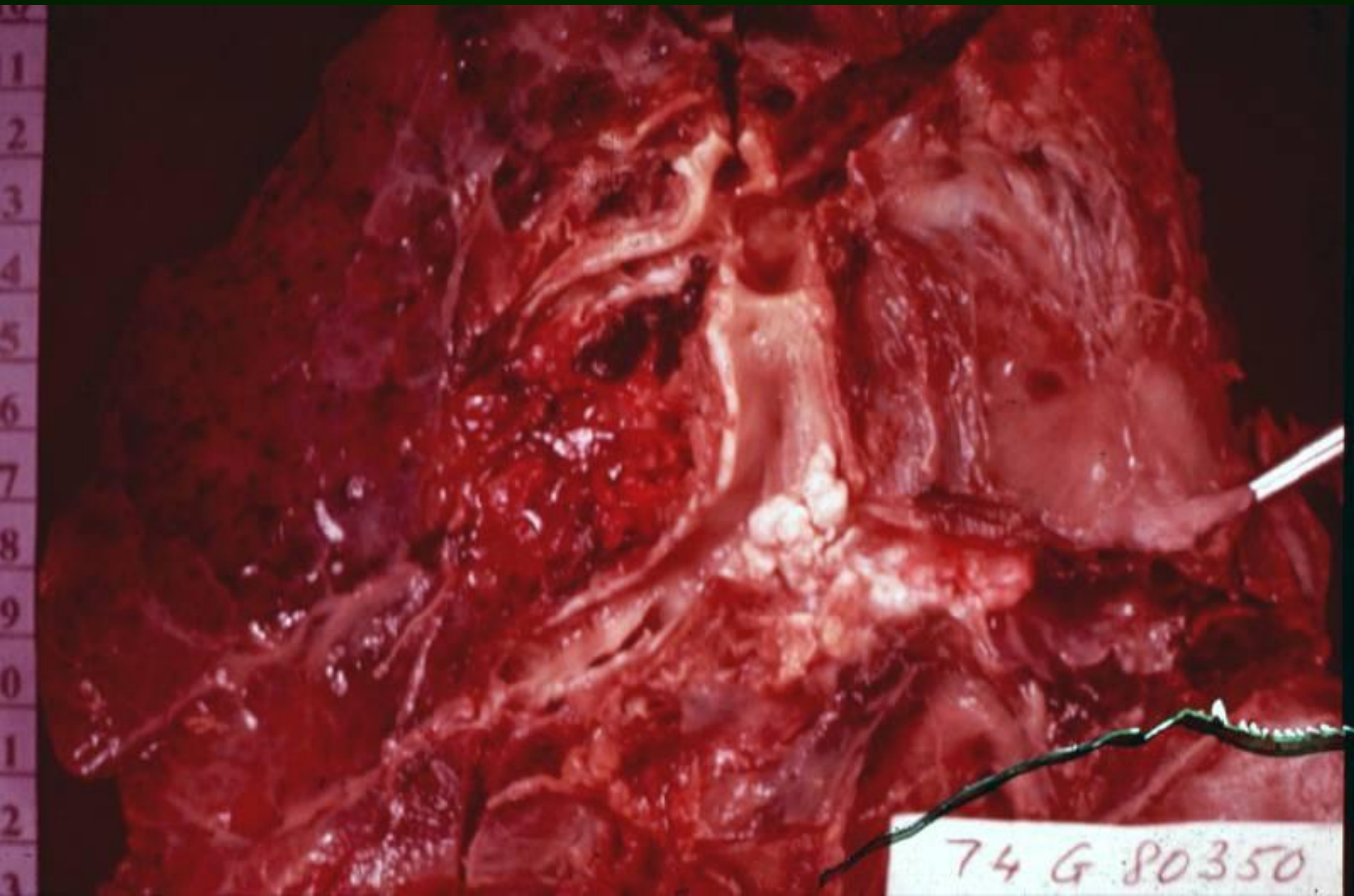
Squamous cell carcinoma

A malignant epithelial tumour showing keratinization and/or intercellular bridges

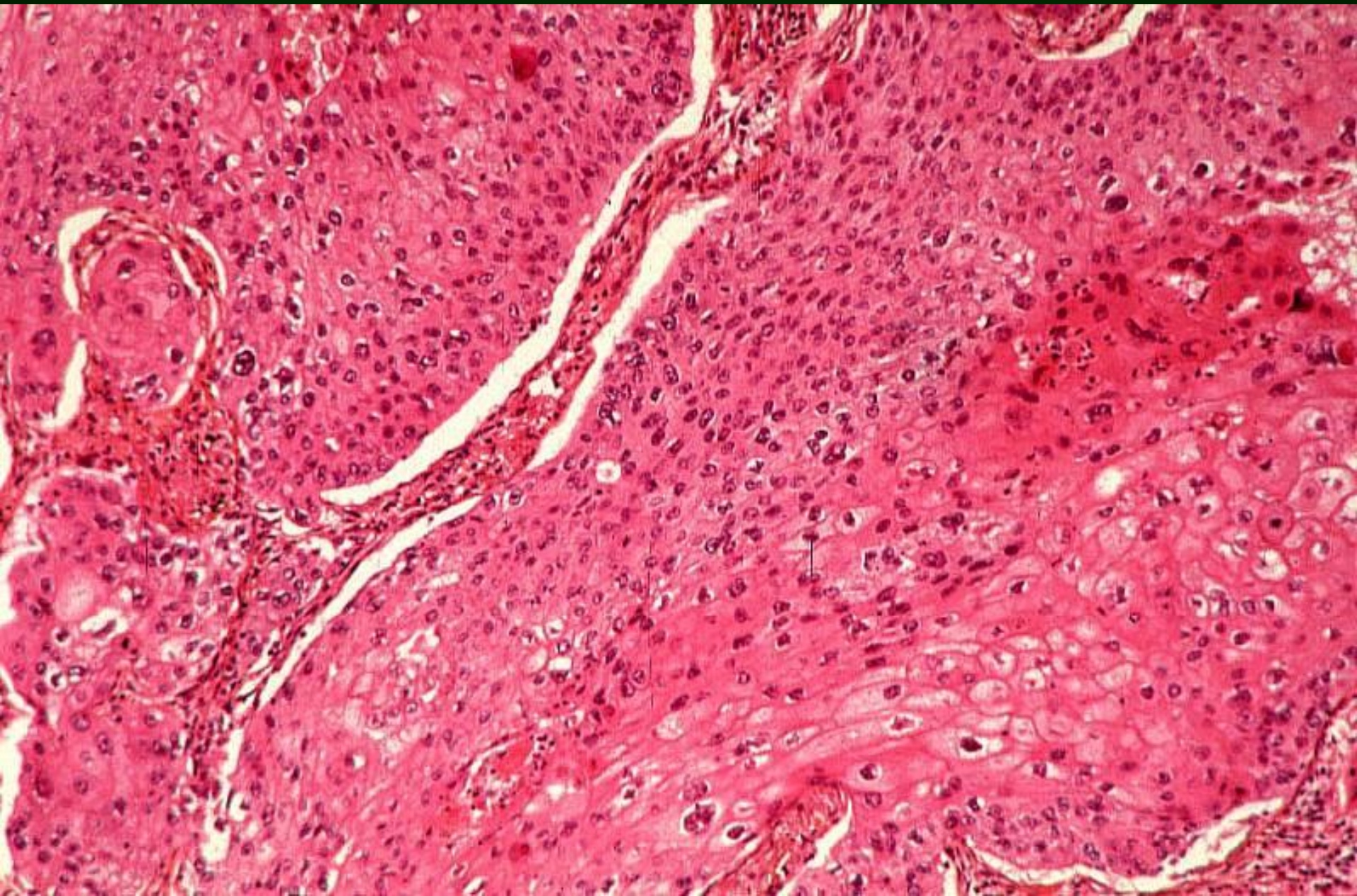
Variants:

- **Papillary**
- **Clear cell**
- **Small cell**
- **Basaloid**

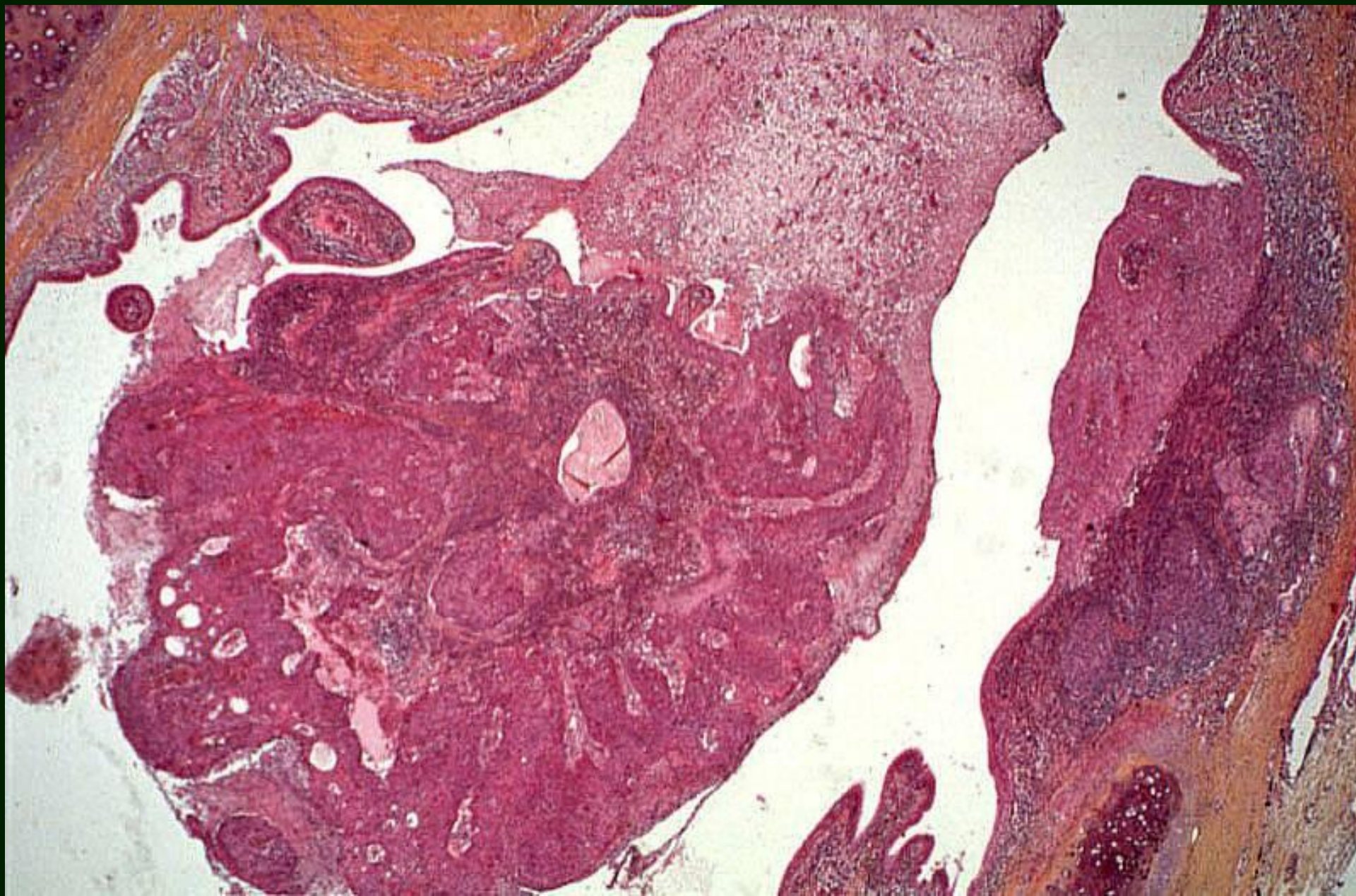
Squamous cell carcinoma



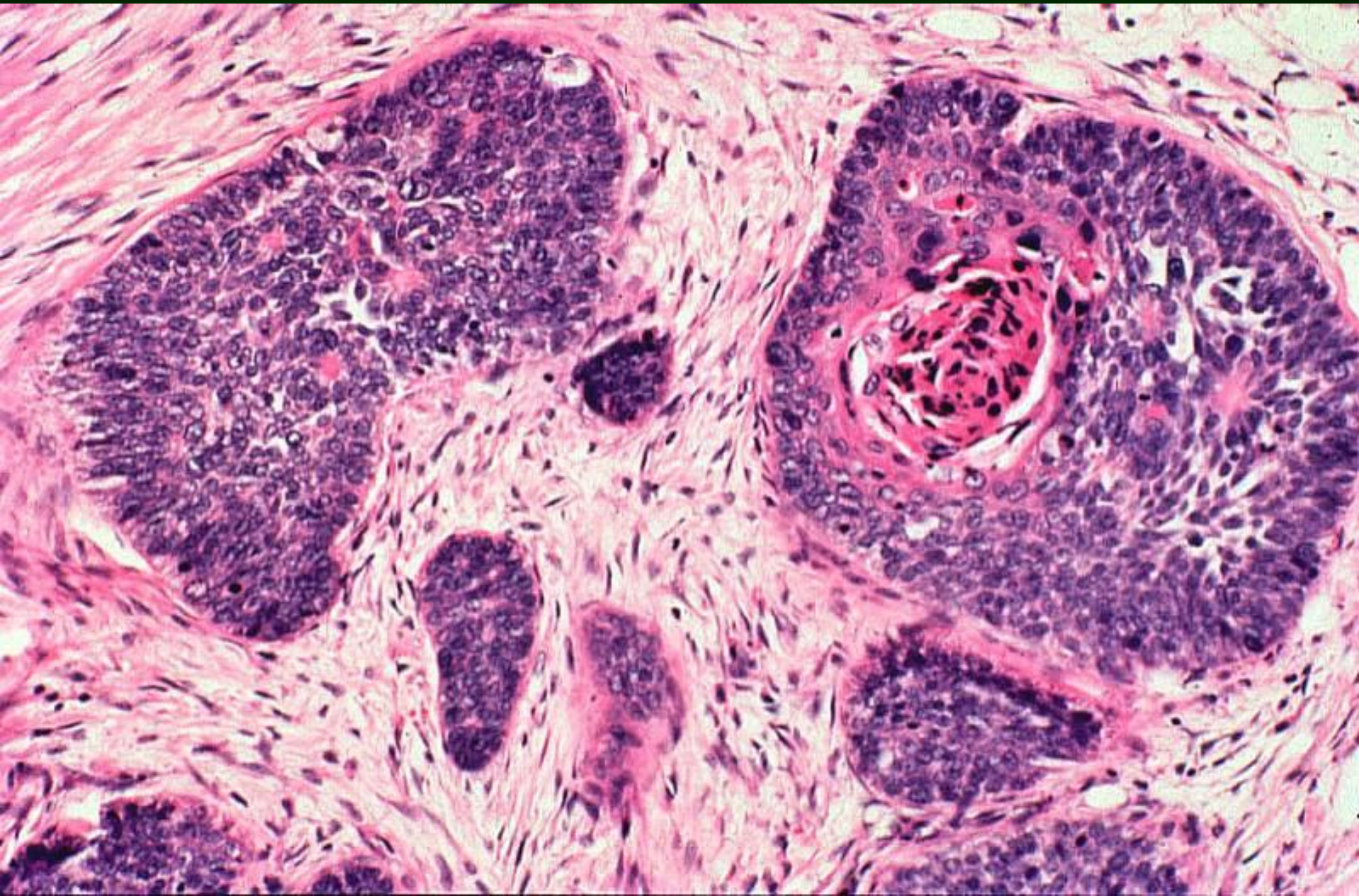
Squamous cell carcinoma



Squamous cell carcinoma: papillary variant

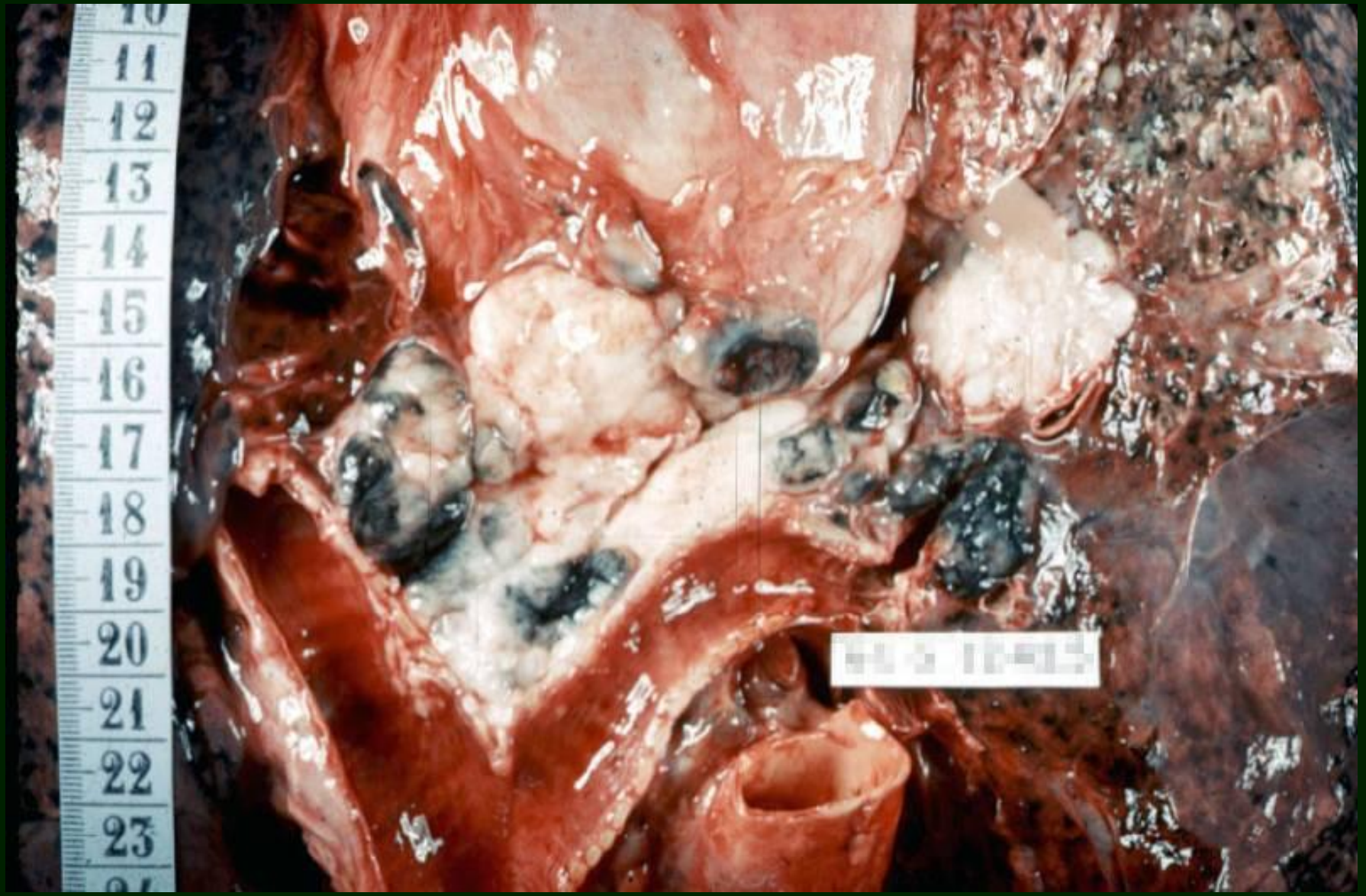


Squamous cell carcinoma: basaloid variant



Small Cell Carcinoma

WHO 1999-2004	WHO 1981
Small Cell Carcinoma	**Small Cell Carcinoma**
Variant • **Combined Small Cell Carcinoma**	**Oat cell** **Intermediate** **Combined**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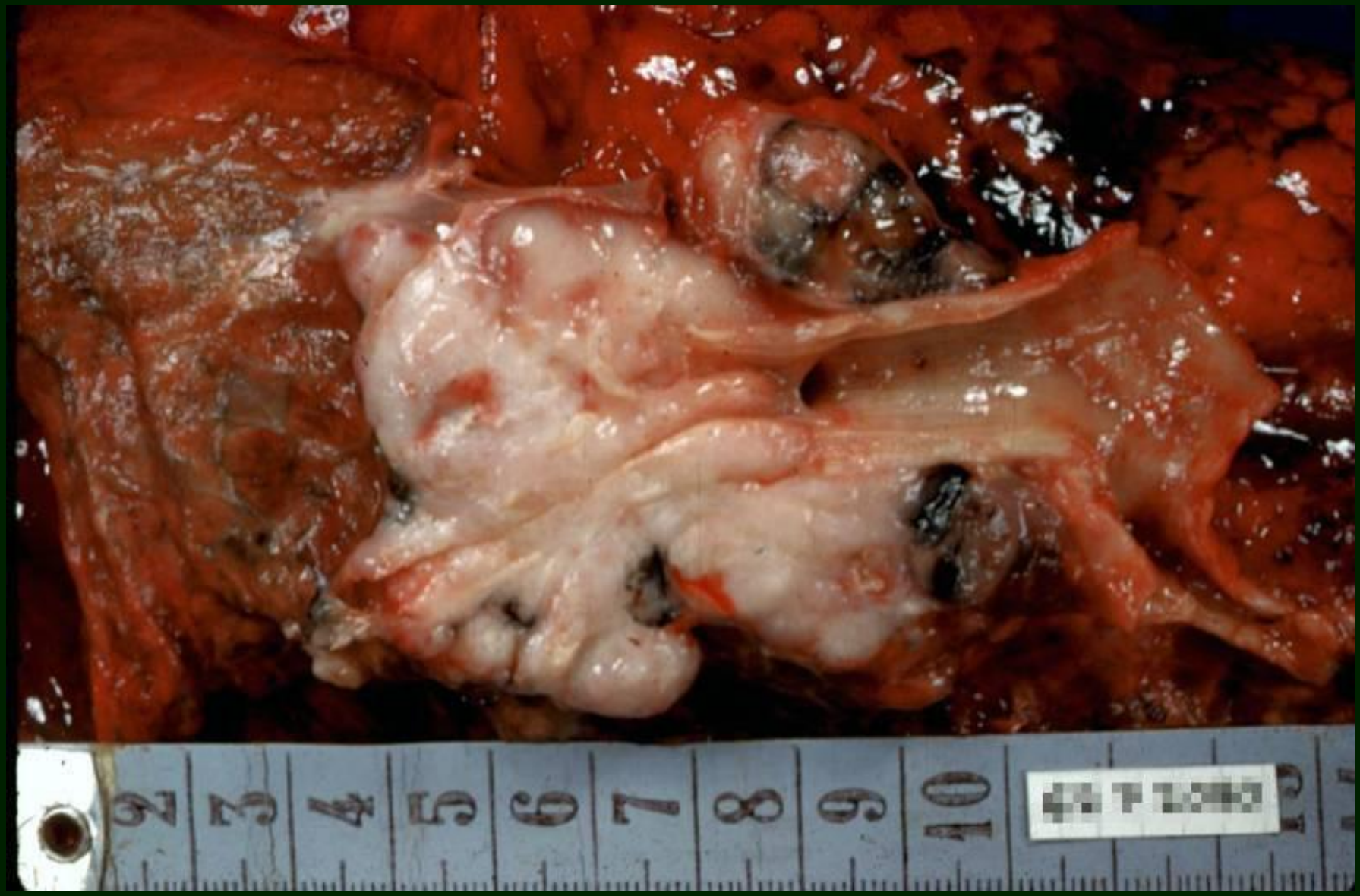
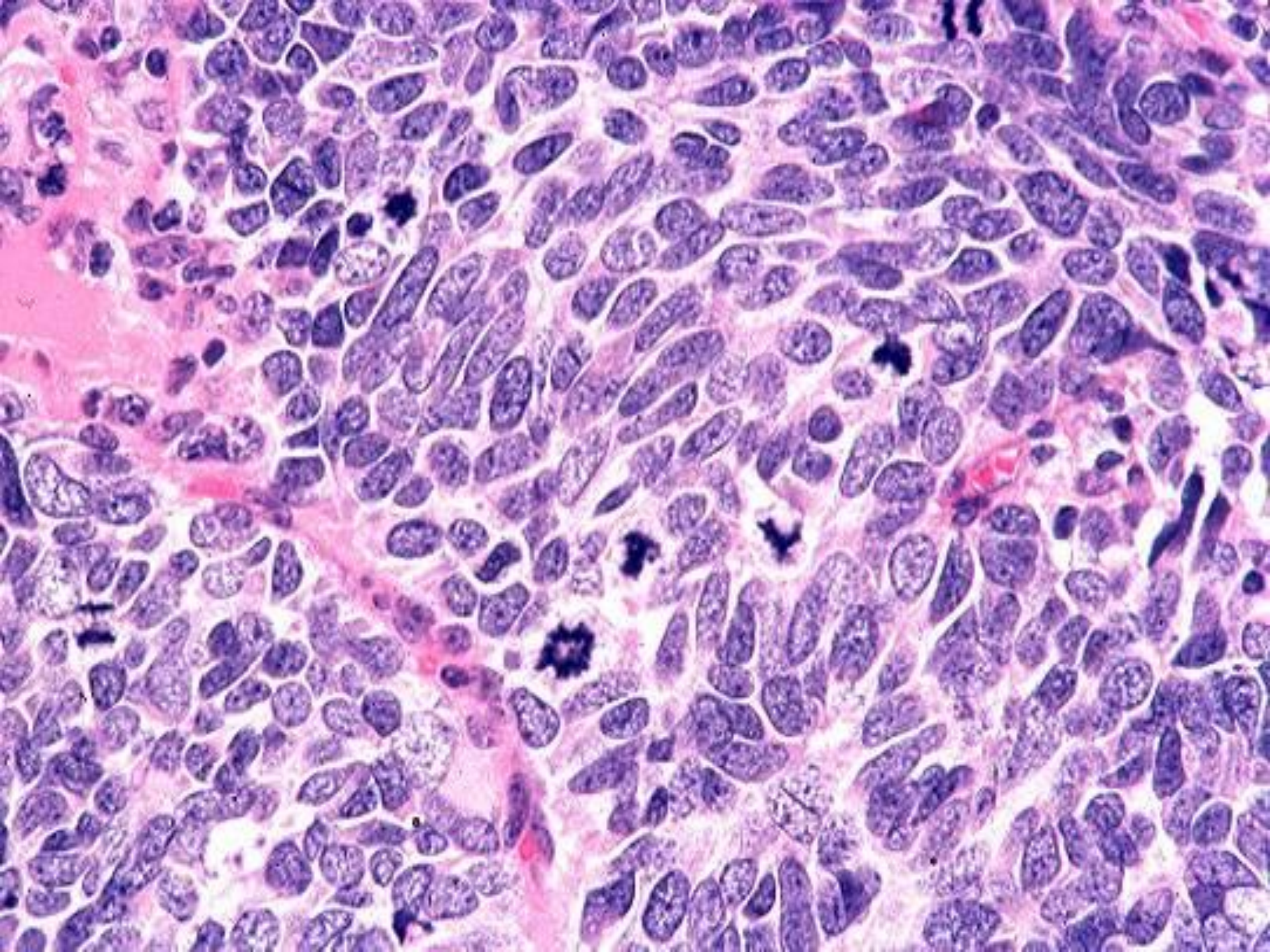
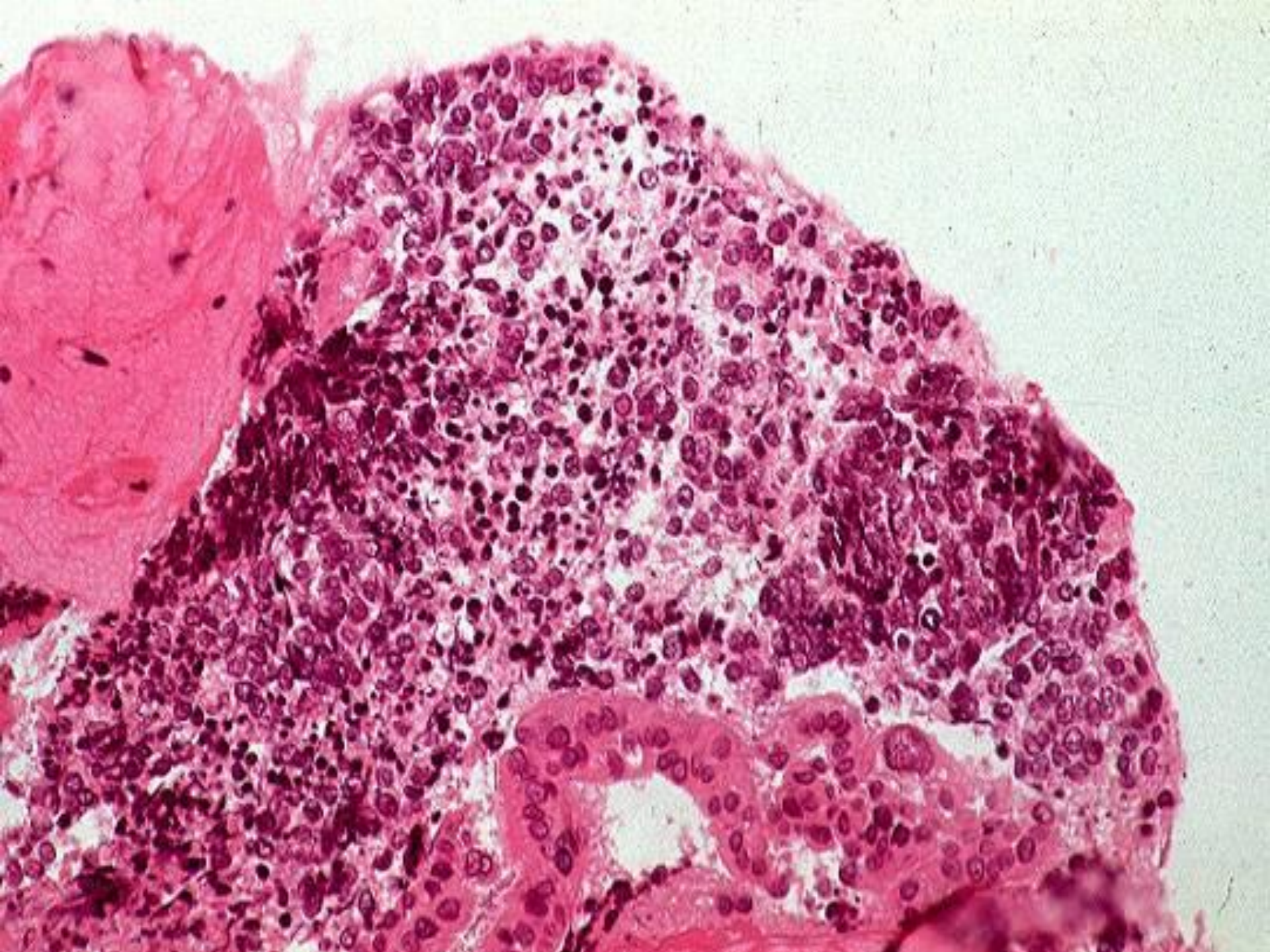
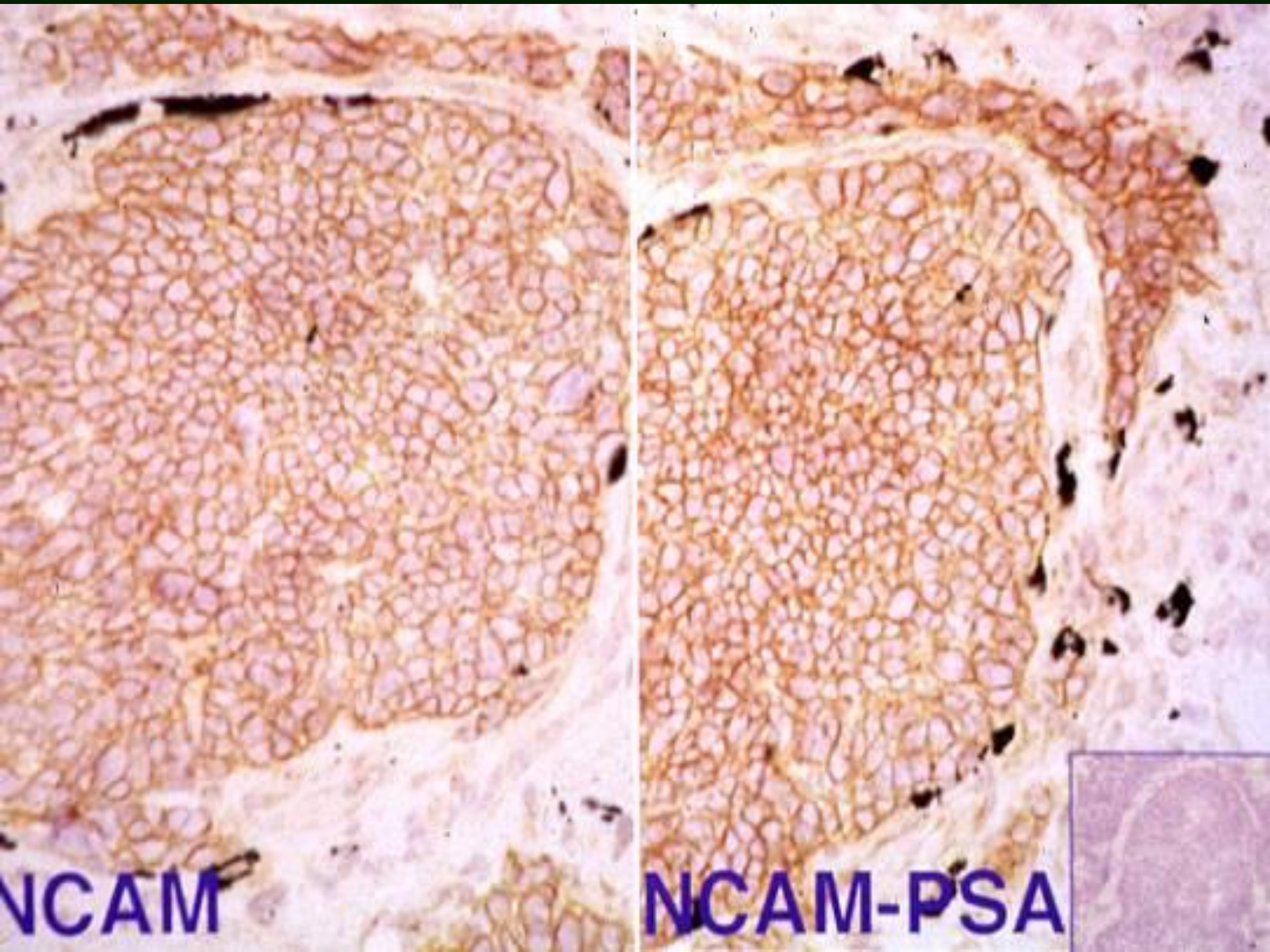
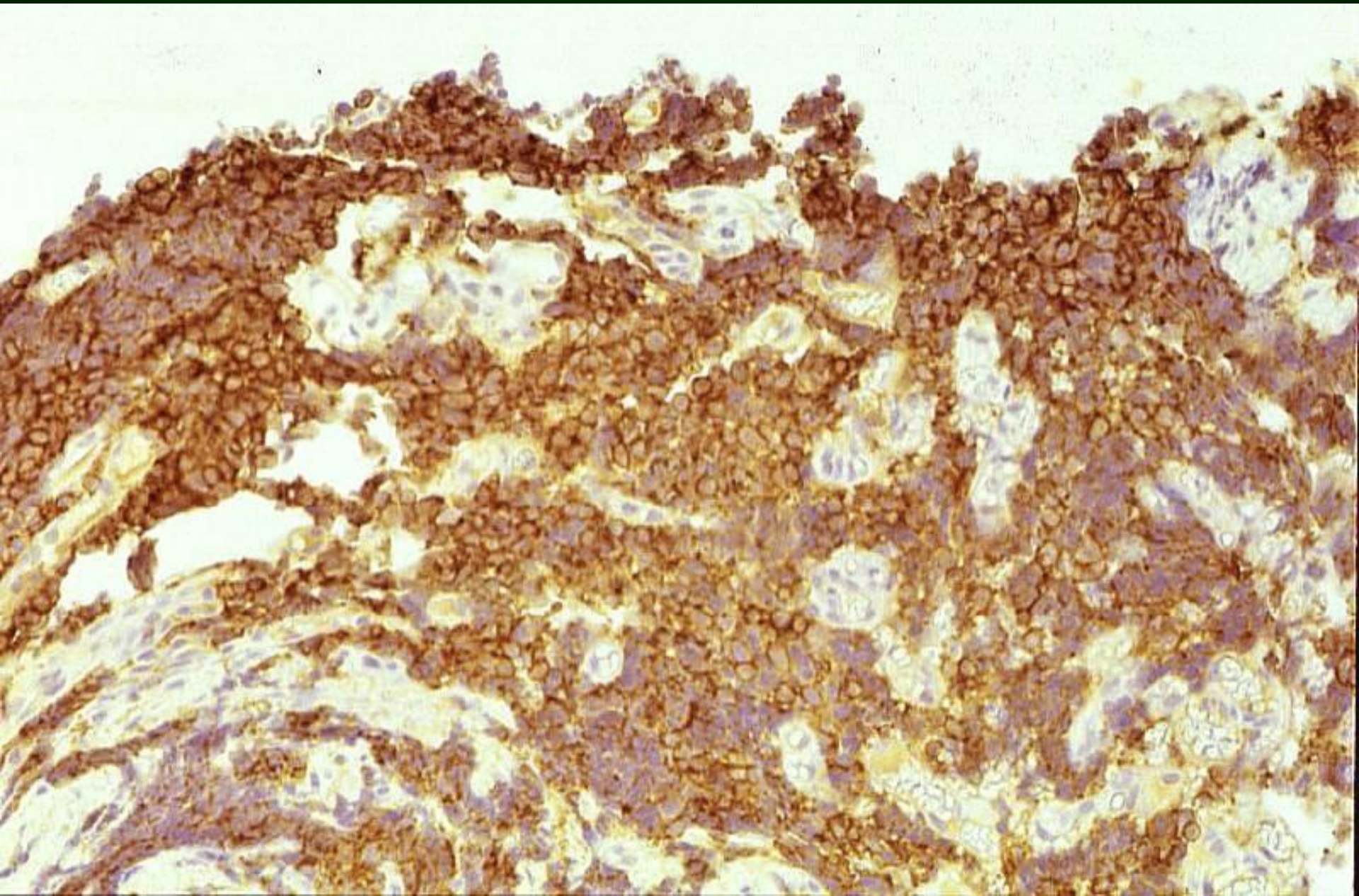




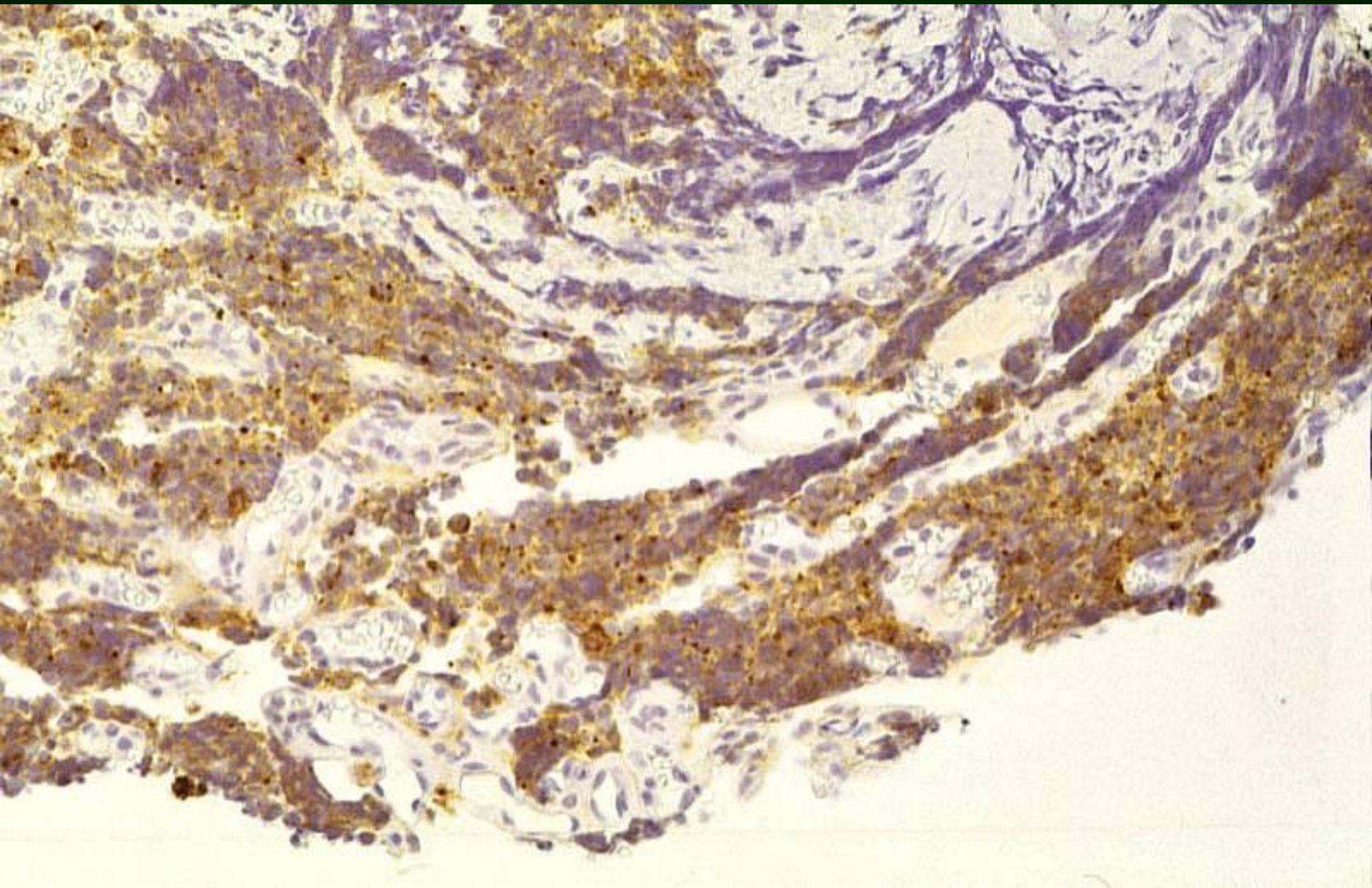



NCAM
NCAM-PSA

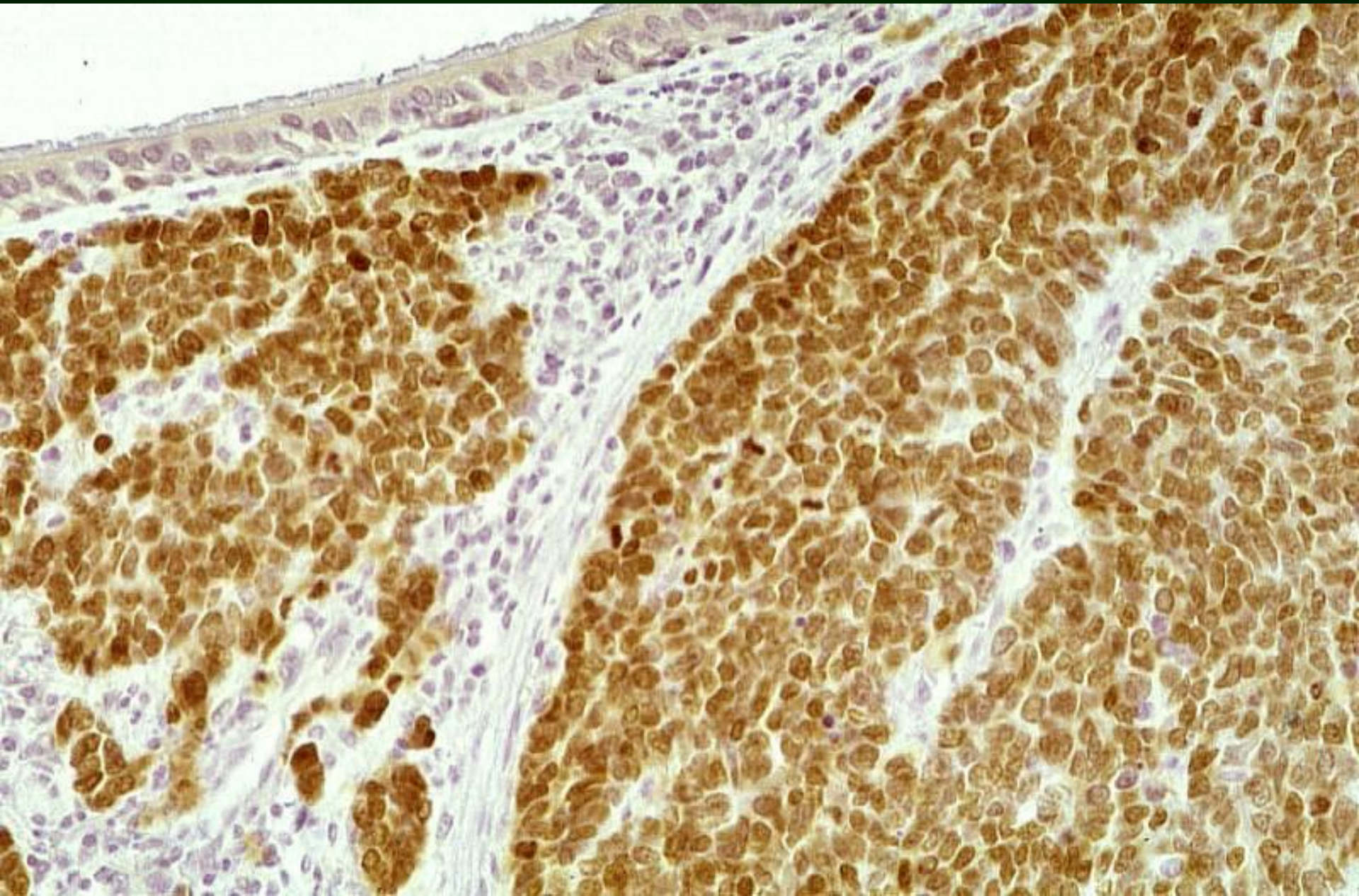
SCLC: NCAM



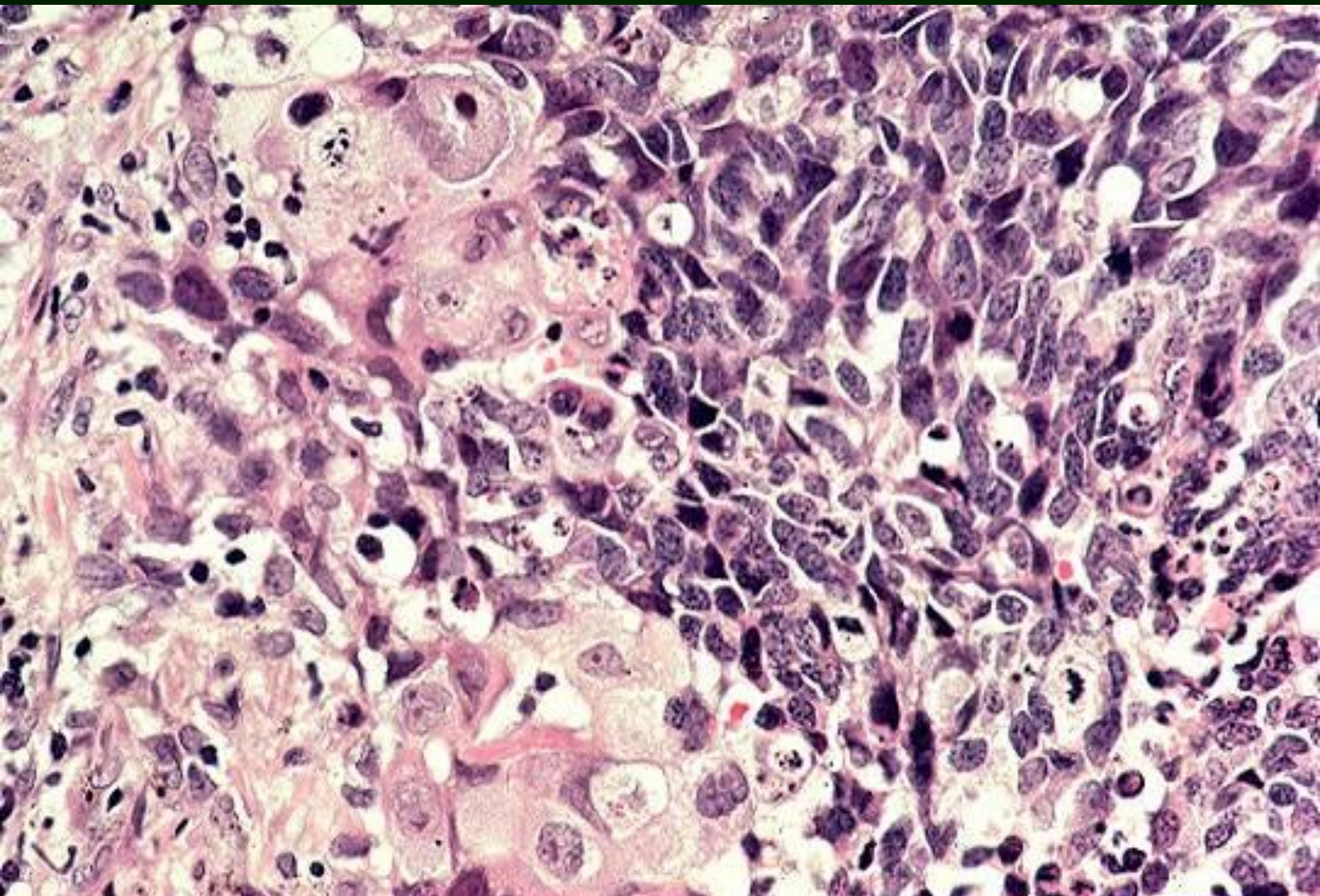
SCLC: Chromogranin



SCLC: TTF1



SCLC combined



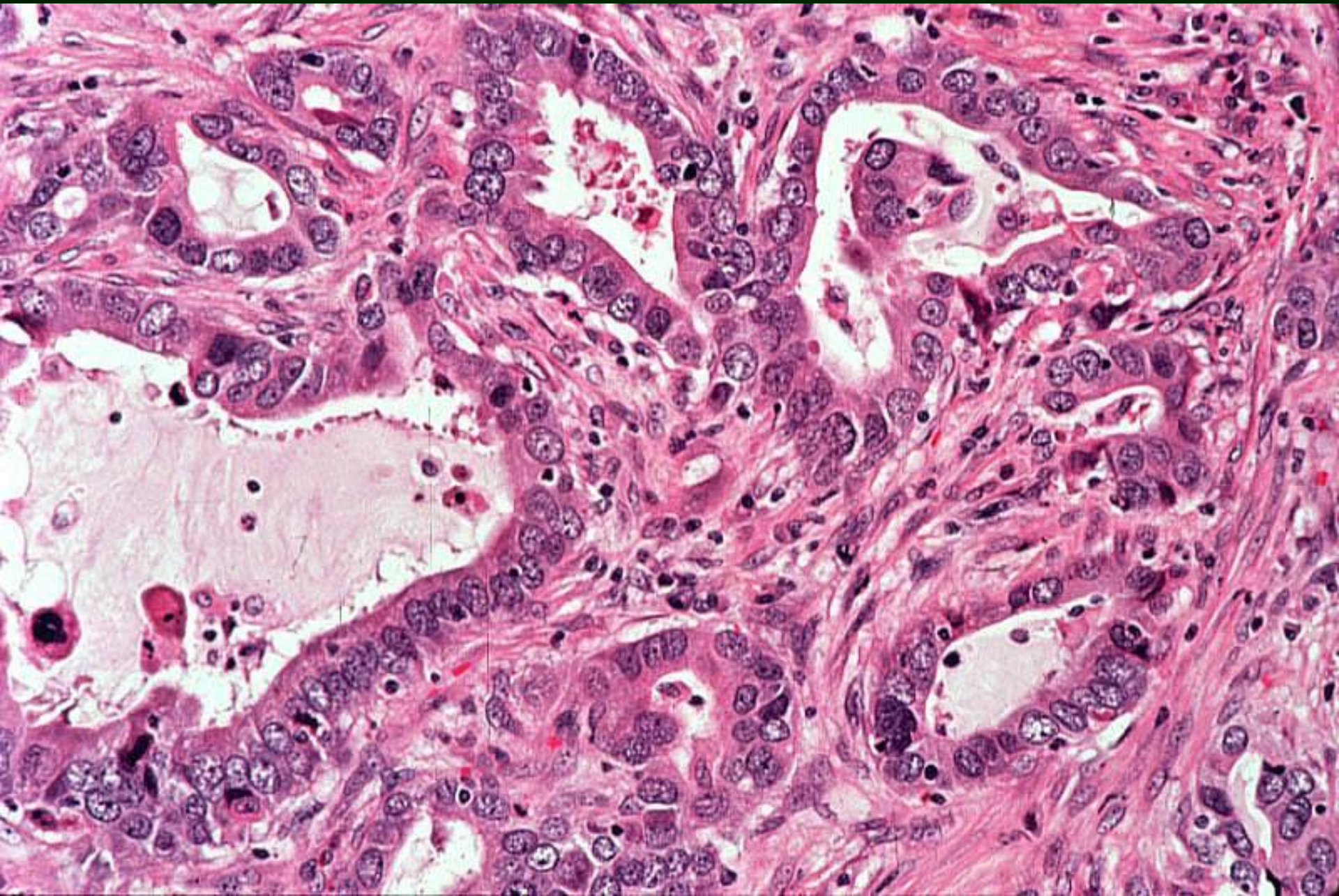
WHO 1999 - 2004	WHO 1981
Adenocarcinoma	**Adenocarcinoma**
. Adenocarcinoma mixed subtype	
. Acinar adenocarcinoma	a. Acinar
. Papillary adenocarcinoma	b. Papillary
. Bronchioloalveolar carcinoma Non-mucinous Mucinous Mixed mucinous - non mucinous	c. Bronchioloalveolar carcinoma
. Solid adenocarcinoma with mucin	d. Solid adenocarcinoma with mucus formation
. Variants:	

Adenocarcinoma

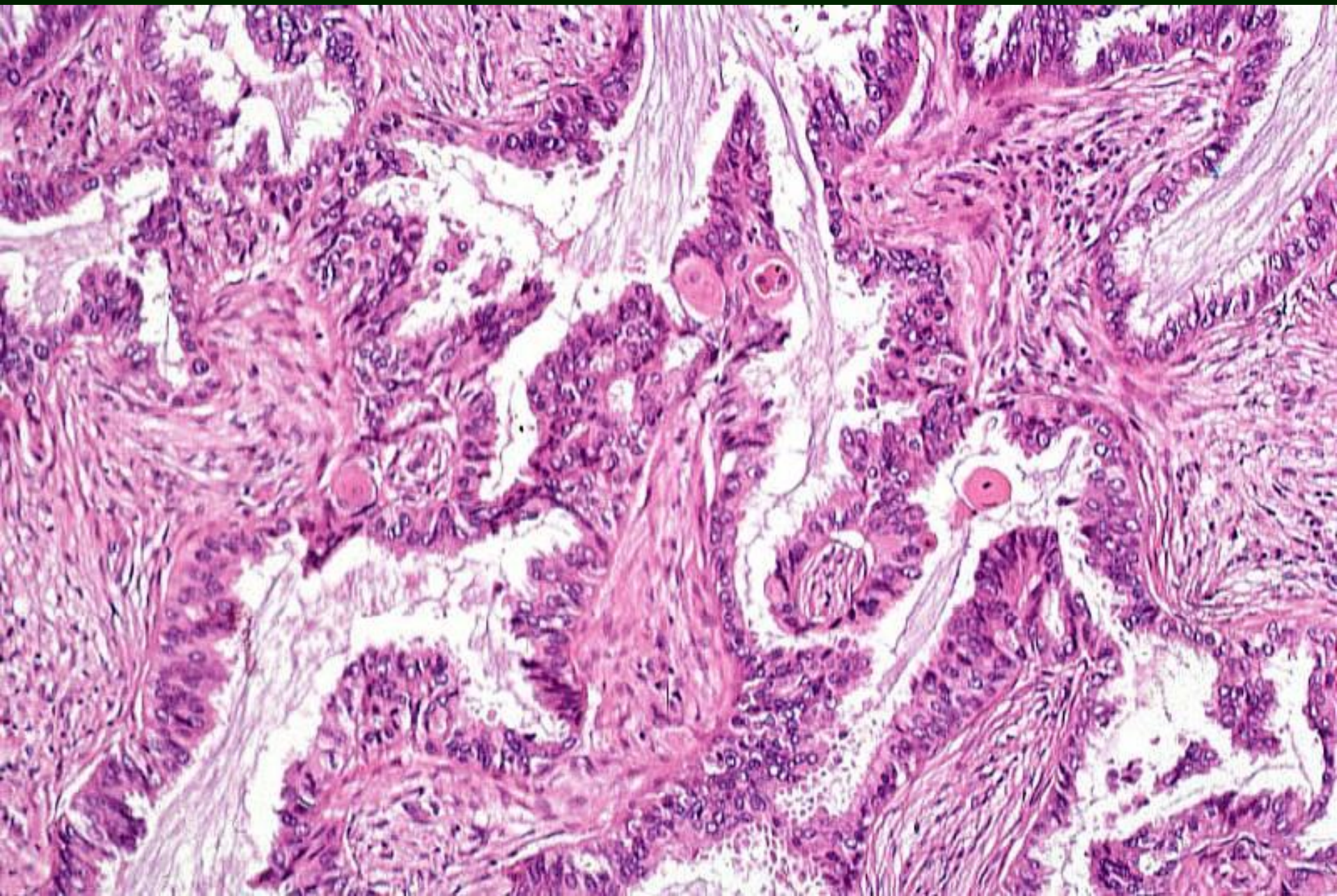
- 85% display mixed histology
  ➔ **Adenocarcinoma mixed type**: more than one subtype

- **Bronchioloalveolar carcinoma**
  restrictive definition: a non invasive tumor

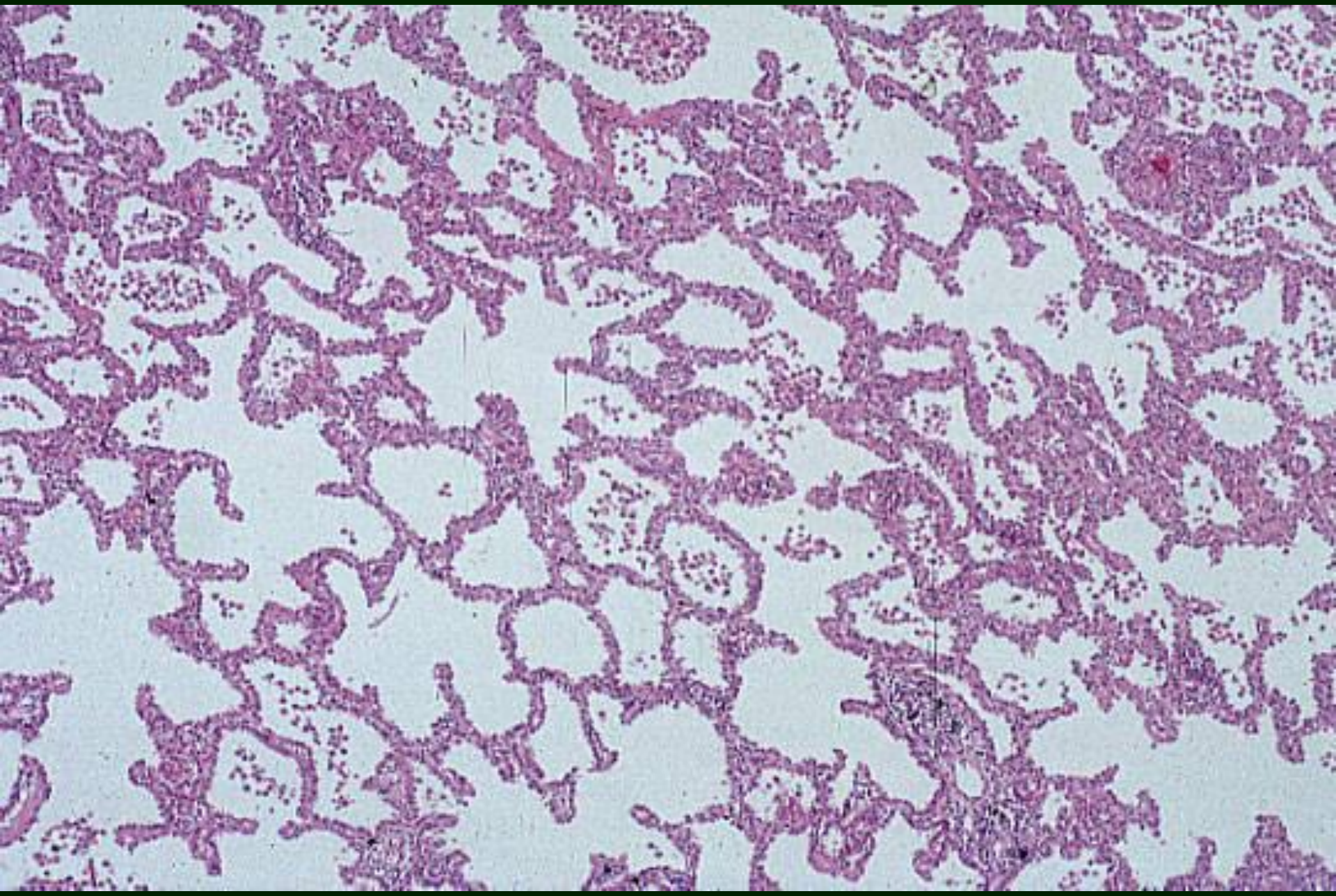
Adenocarcinoma: acinar



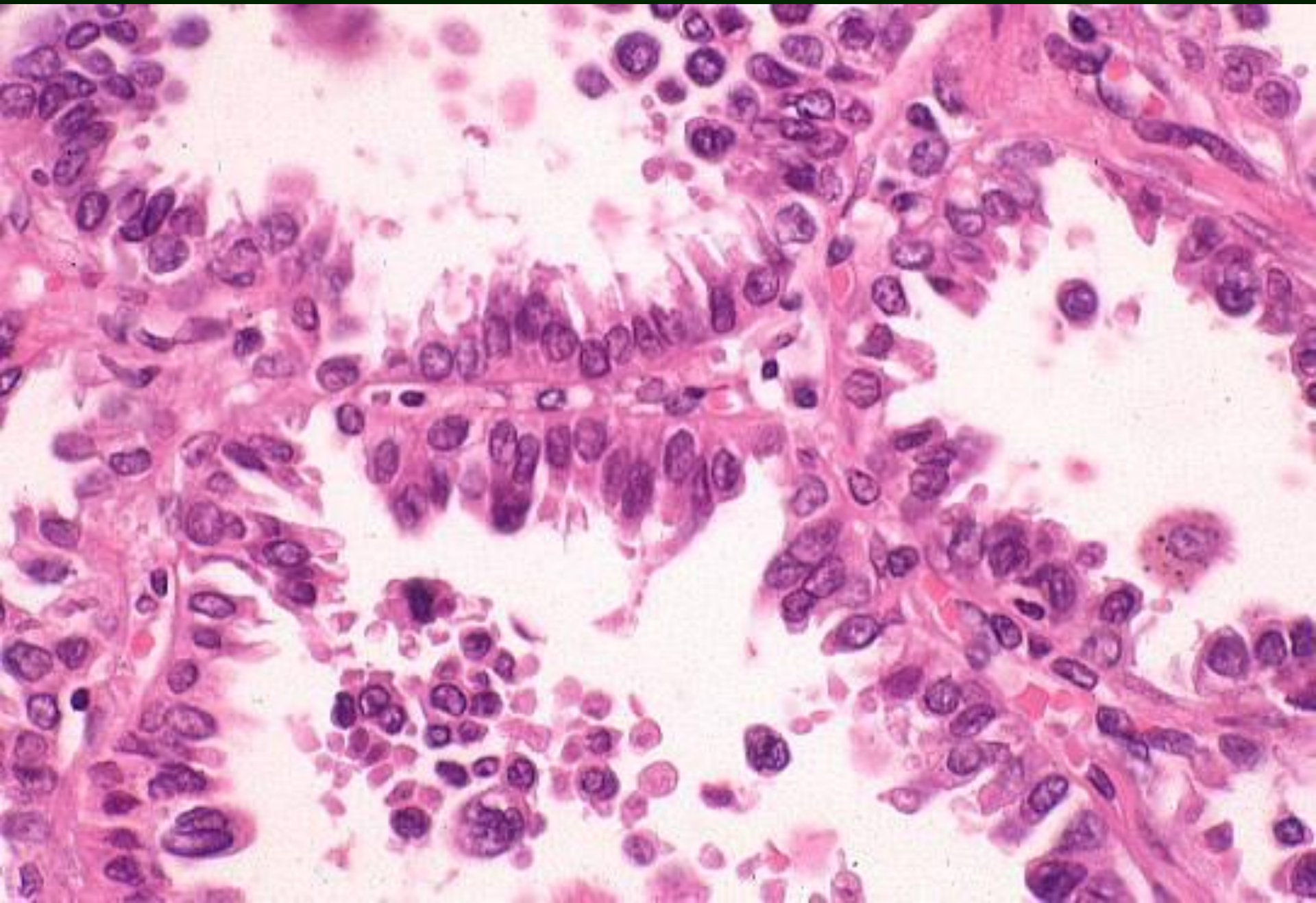
Adenocarcinoma: papillary



Bronchioloalveolar carcinoma (BAC)



BAC : Clara Cell Type



Bronchioloalveolar carcinoma (BAC)

- Pure “lepidic” growth pattern along respected alveolar walls
- No invasion (stromal, vascular, pleural)
- No central scar, no desmoplastic stromal reaction
- No papillary structures in alveolar lumens

➔ Most previously reported BAC are now adenocarcinoma mixed sub type

➔ The diagnosis of BAC cannot be achieved on small biopsies

Bronchioloalveolar carcinoma (non invasive)

Significant association with

- pathological stage I

$p < 0,001$

- absence of lymph node metastasis

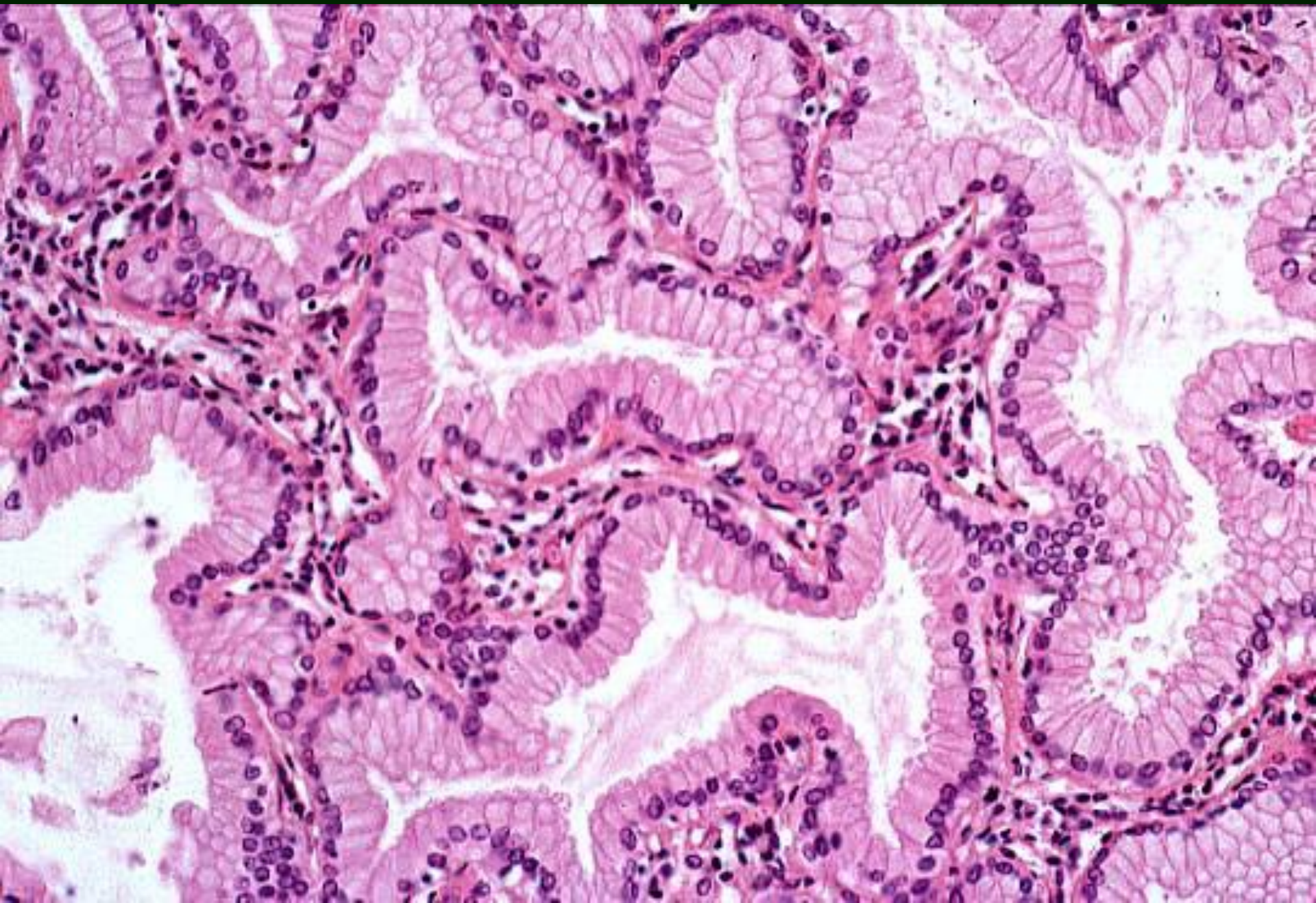
$p < 0,001$

- 5 years patient survival among stage I cases

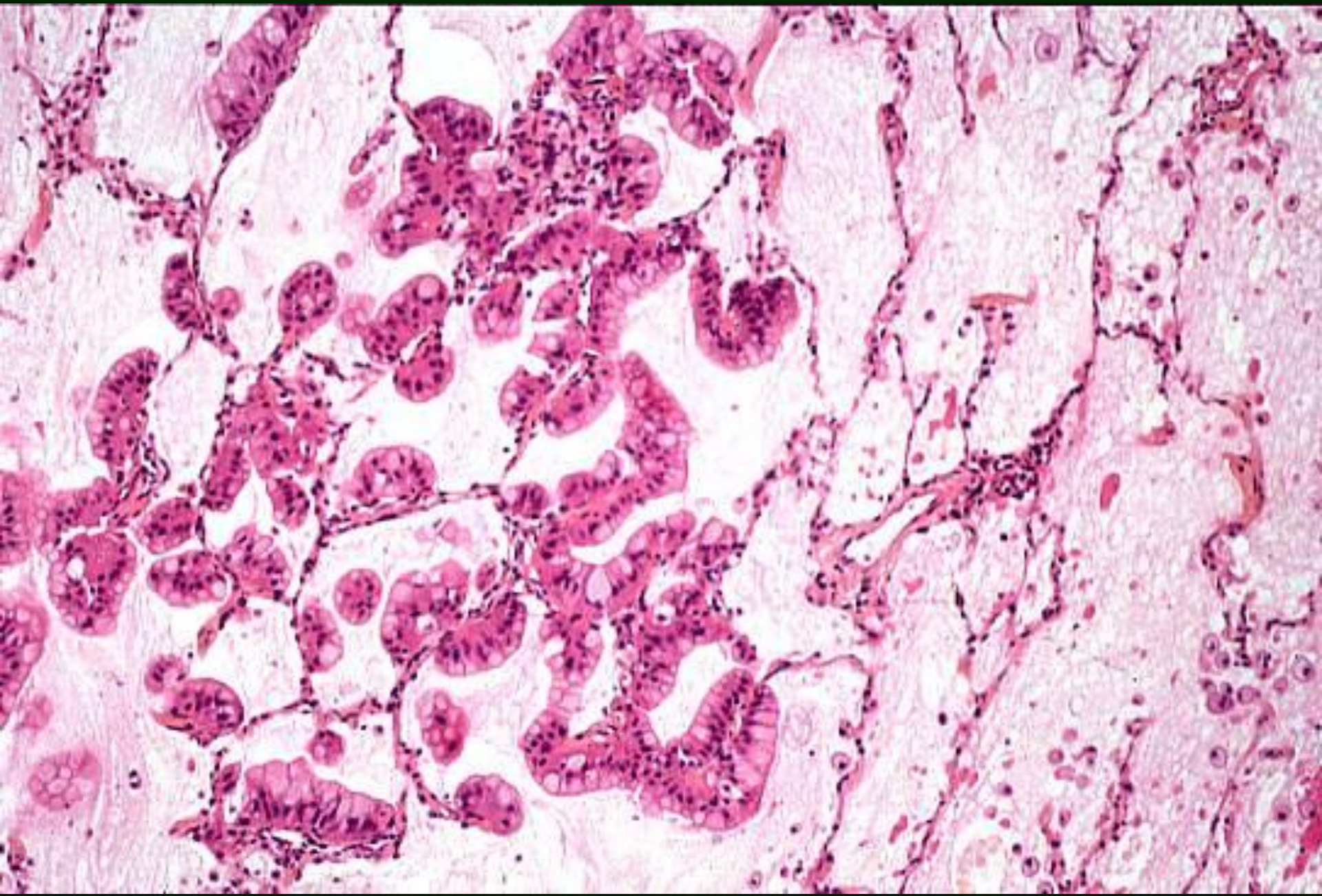
$p < 0,005$

Noguchi M. (type AB-BAC < 2cm) Cancer 1995
Yokose et al Lung Cancer 2000
Suzuki et al Ann Thorac Surg 2002

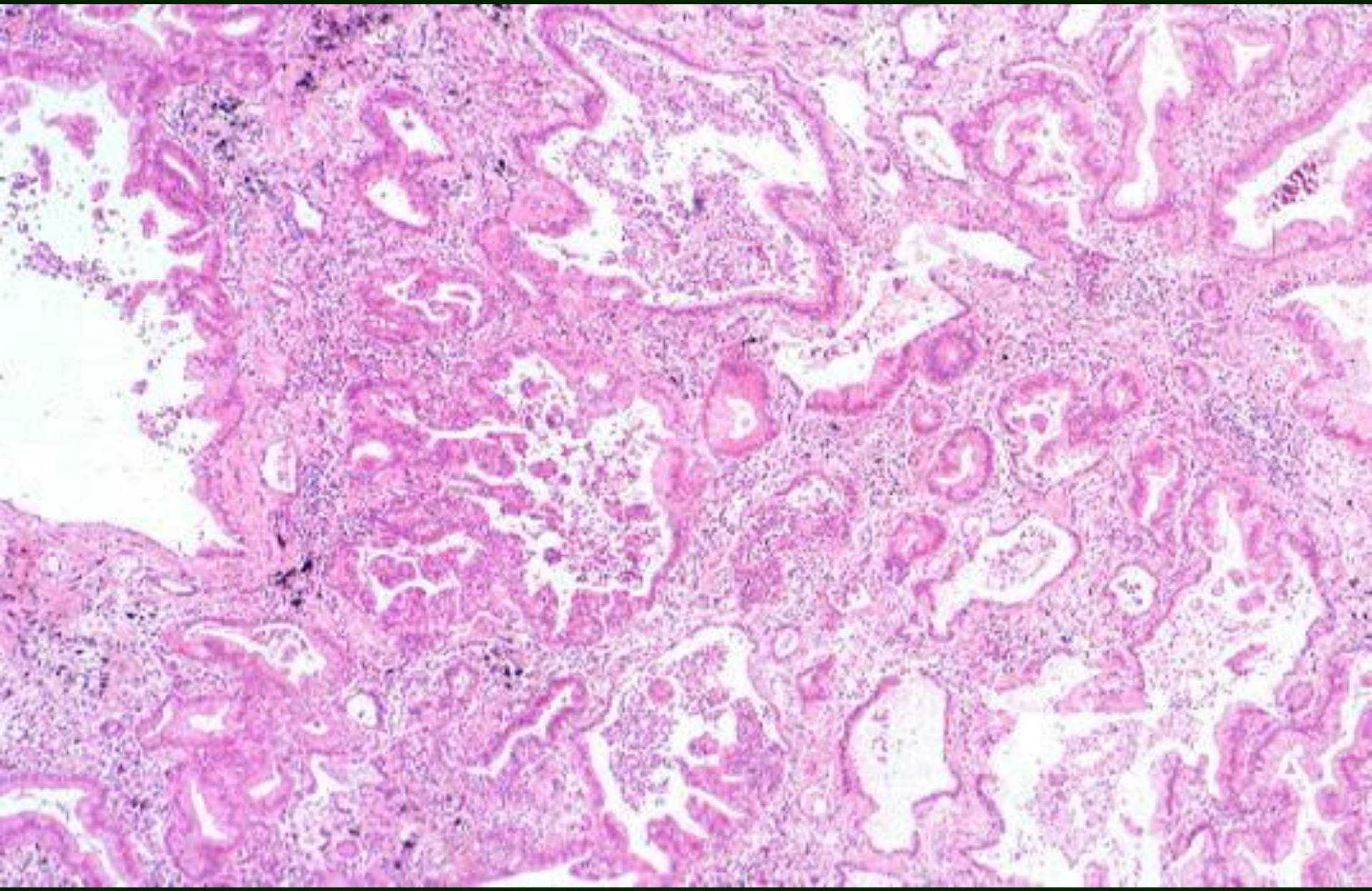
BAC : mucinous type



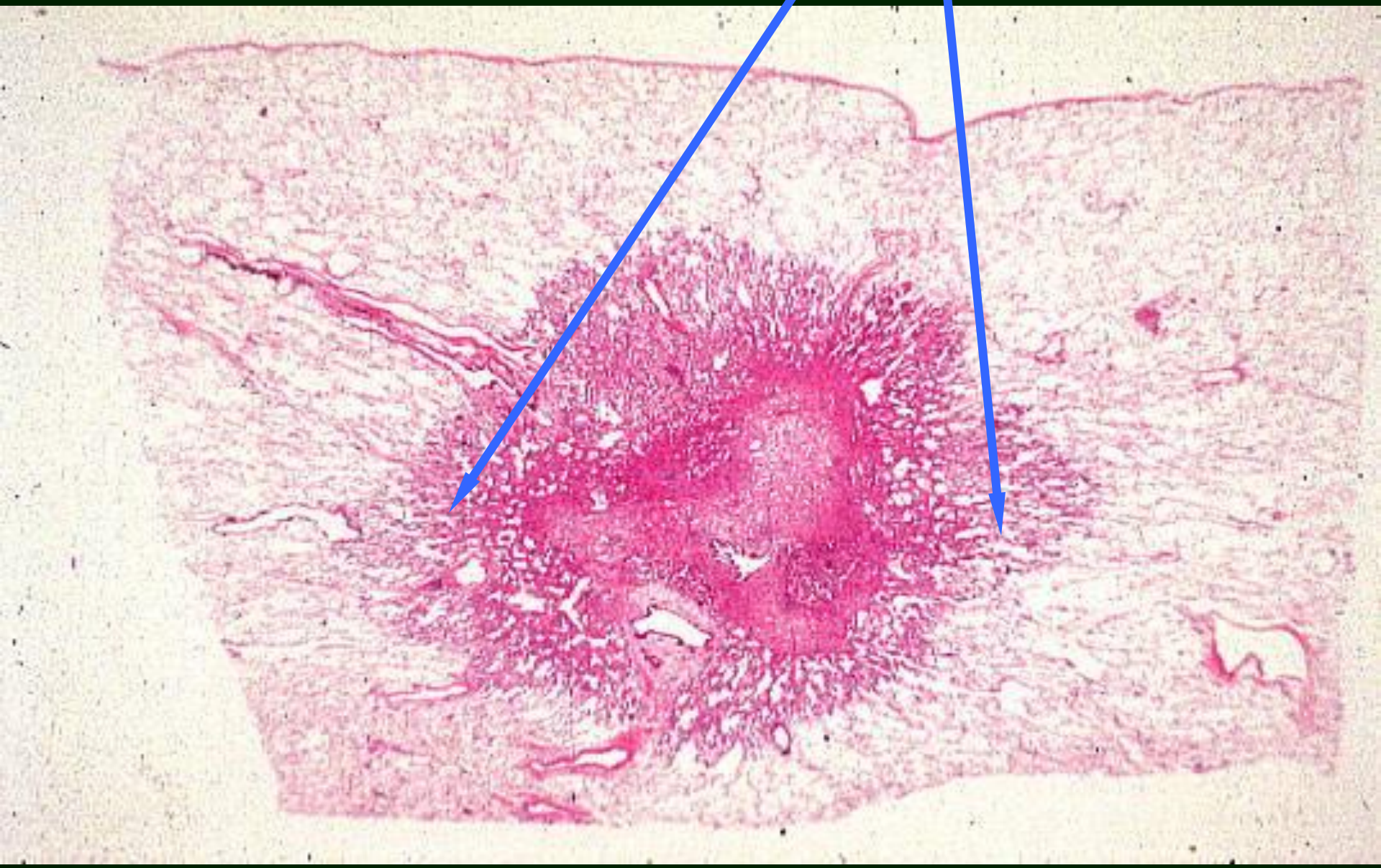
Mucinous BAC : satellite lesion

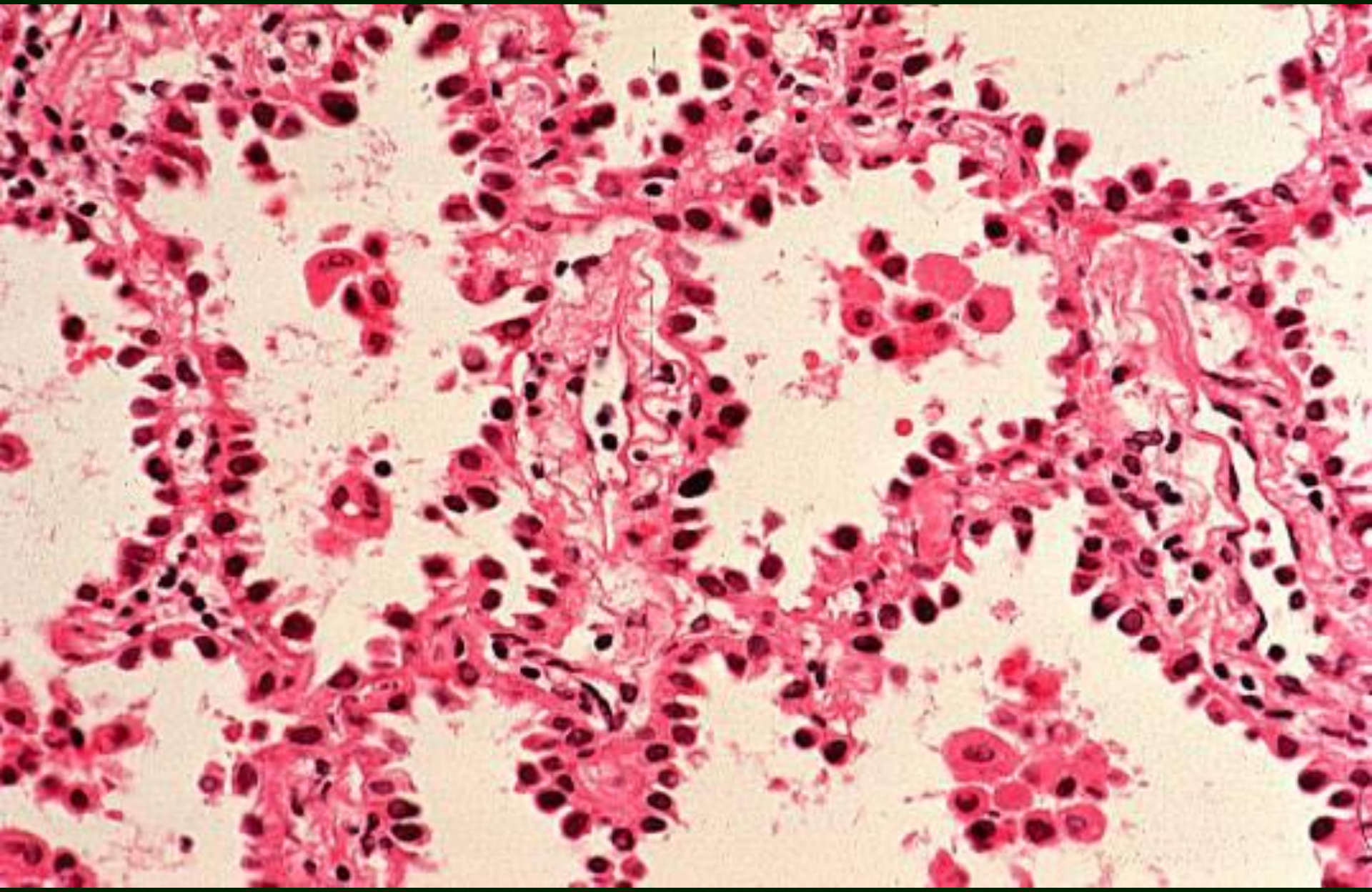


2cm Adenocarcinoma

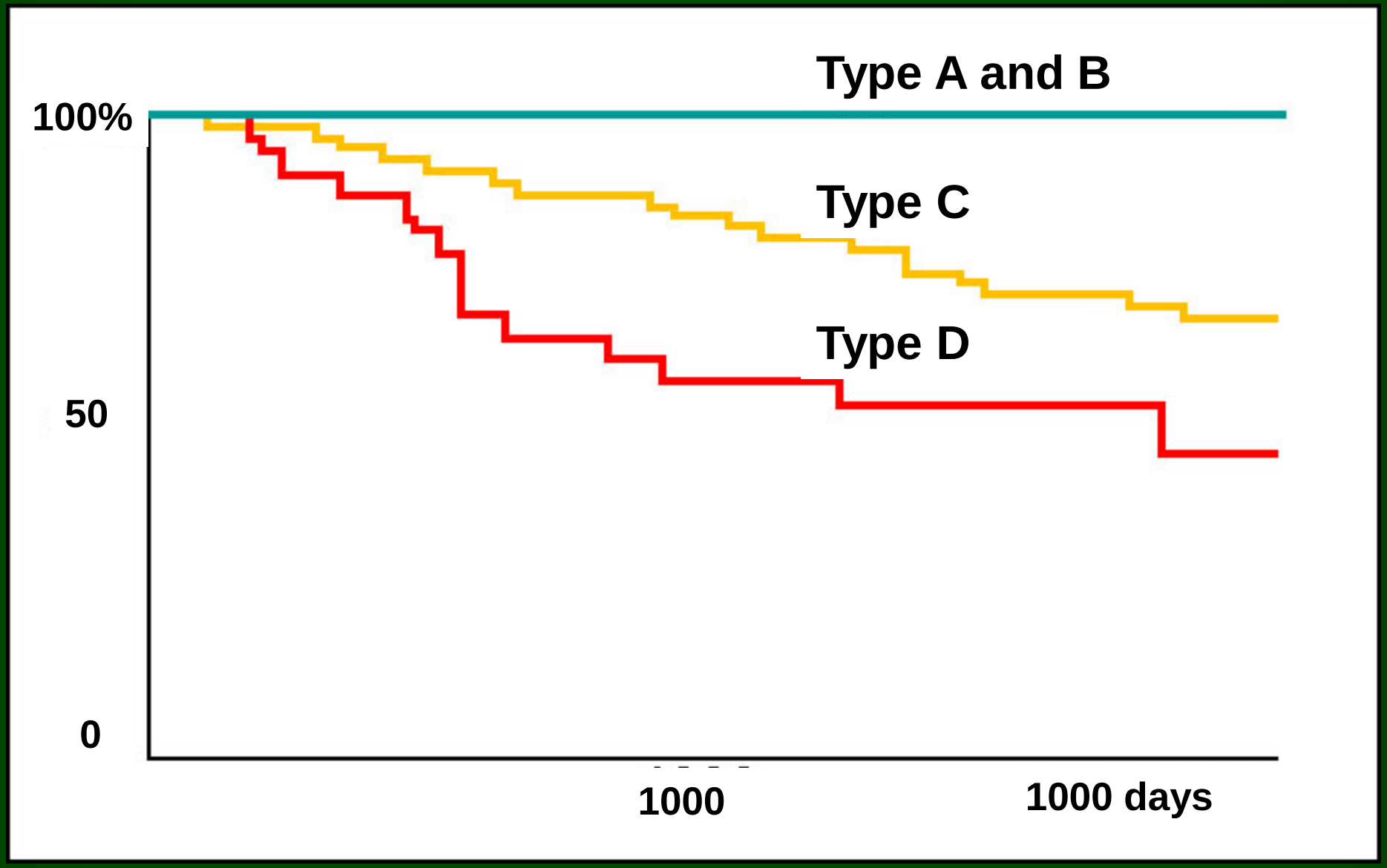


Central scar : Acinous adenocarcinoma





Periphery : BAC component



Noguchi et al 1995

Bronchioloalveolar carcinoma: clinical significance

- **Less than 2 cm BAC can be curable by economic surgical resection:**

  100% - 5 year survival

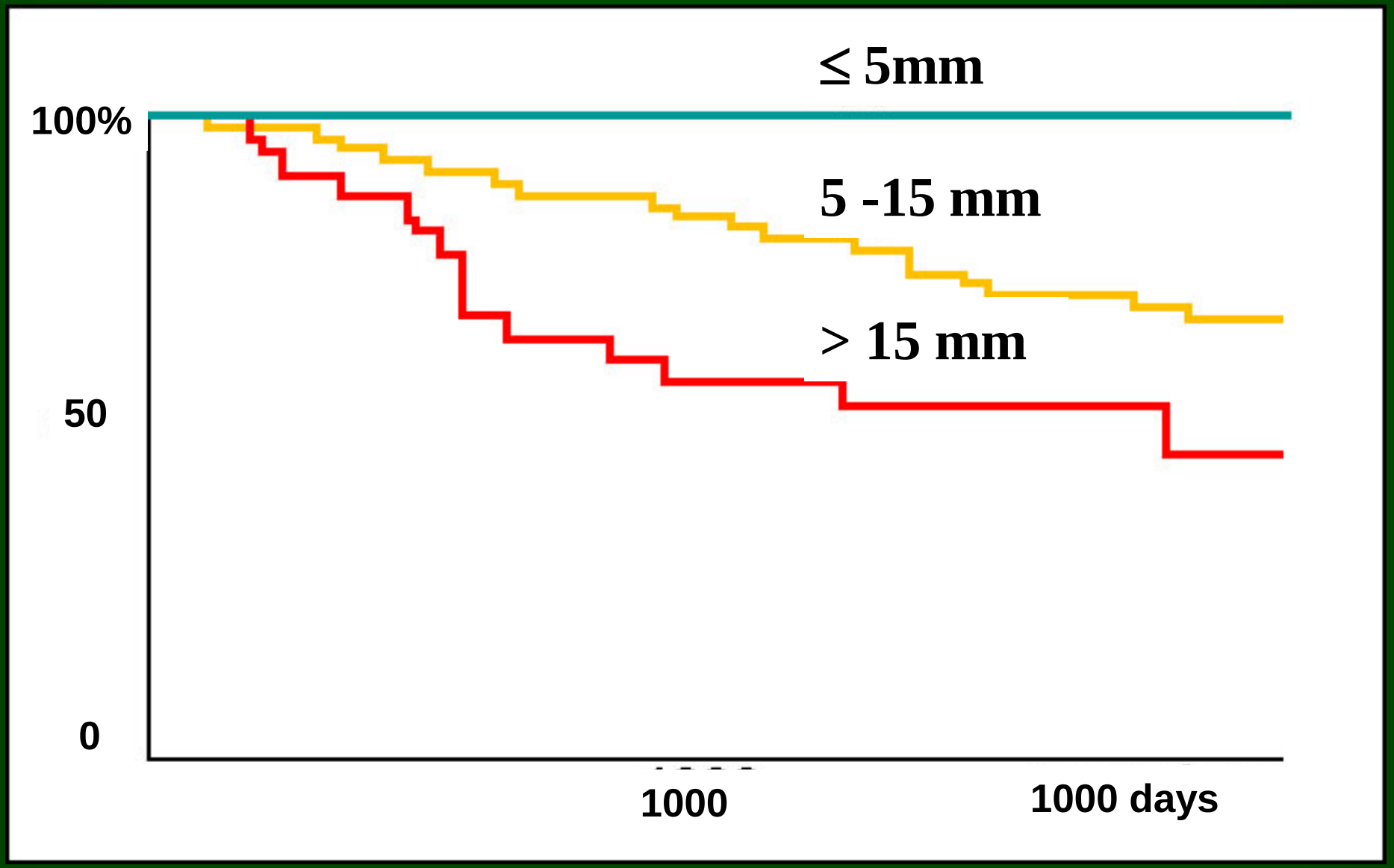
  Noguchi et al Cancer 1995

- **Size of central scar in ADC with peripheral BAC less than 3cm**
  - **< 5mm 100% 5 year survival**
  - **5-15mm 71% 5 year survival**
  - **≥ 15mm 40% 5 year survival**

  independent prognostic factor p = 0.01

  Suzuki et al. Ann Thorac Surg 2000

  Terasaki et al Am. J. Surg. Pathol. 2003



Suzuki et al 2000

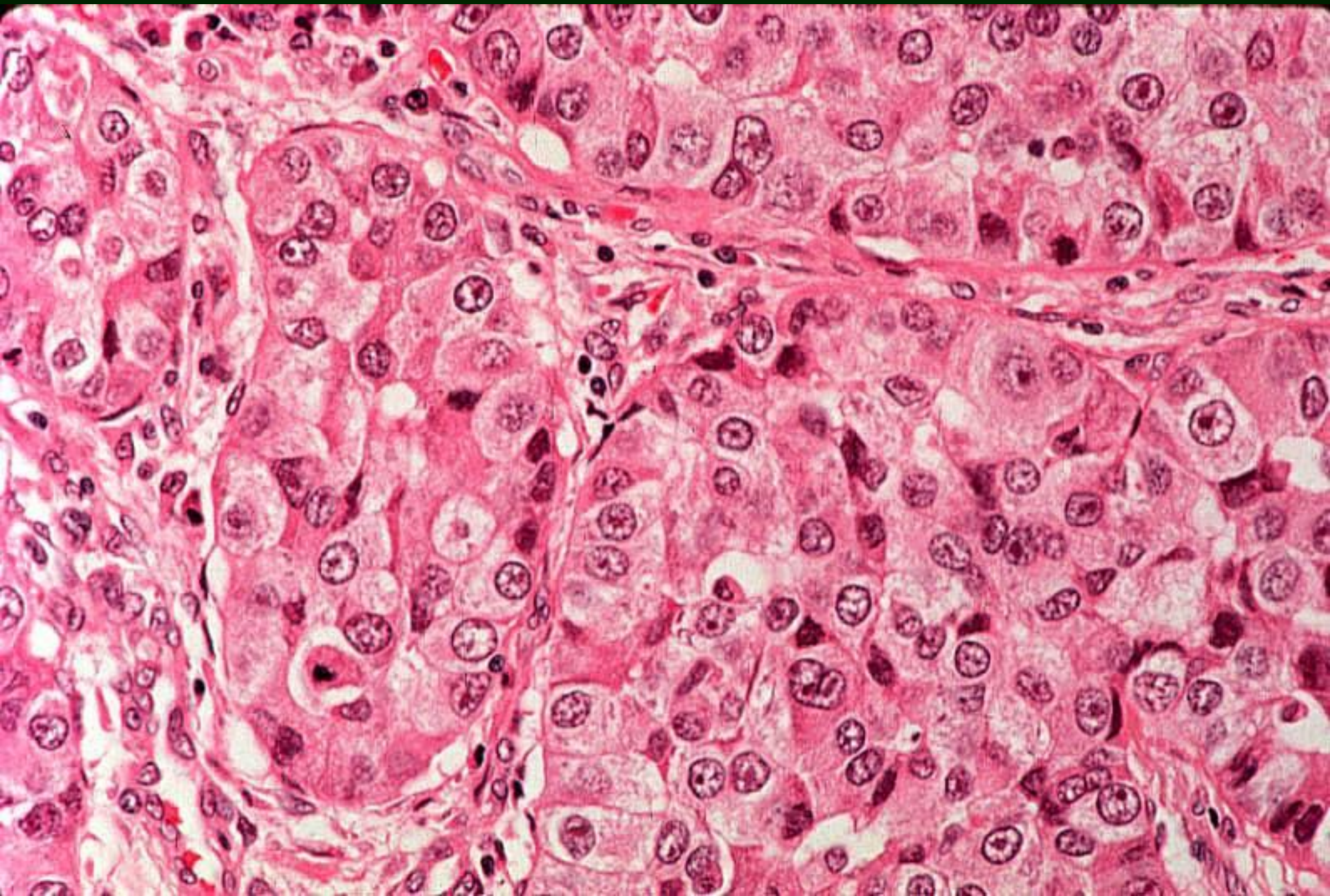
WHO 1999

1.3.4. Large cell carcinoma

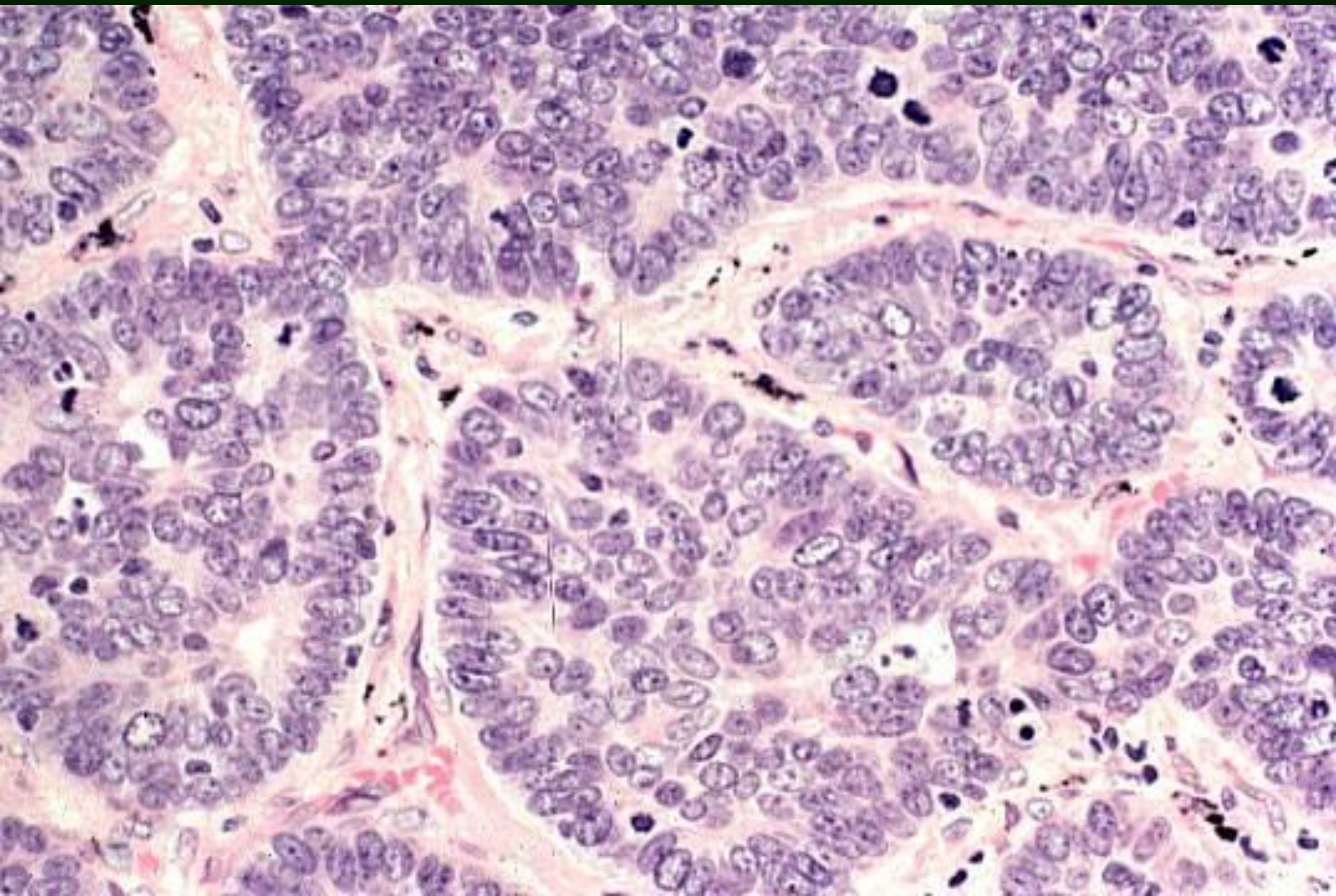
Variants:

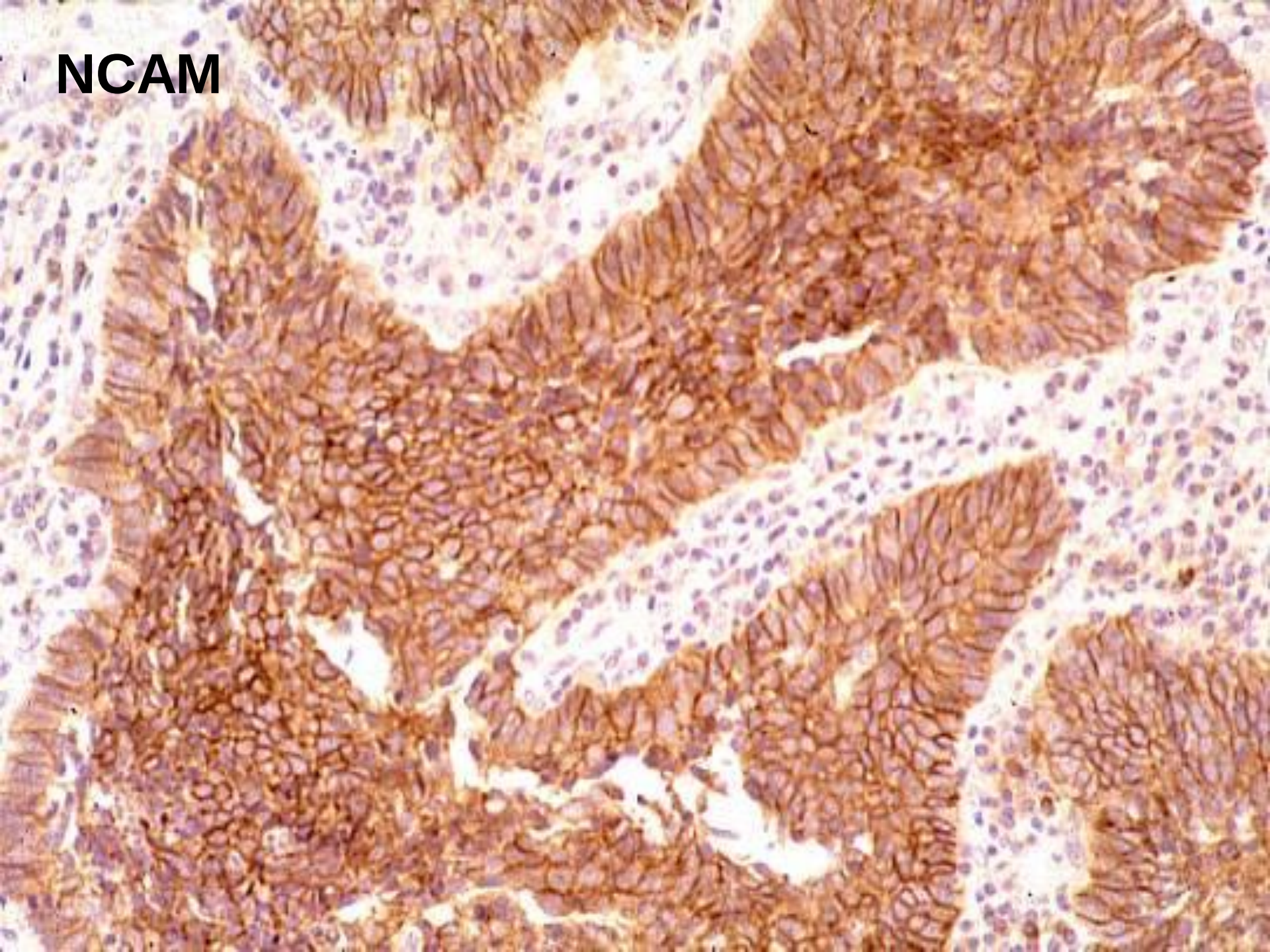
- **1.3.4.1. Large cell neuroendocrine carcinoma**
  Combined large cell neuroendocrine carcinoma
- **1.3.4.2. Basaloid carcinoma**
- **1.3.4.3. Lymphoepithelioma-like carcinoma**
- **1.3.4.4. Clear cell carcinoma**
- **1.3.4.5. Large cell carcinoma with rhabdoid phenotype**

Large cell carcinoma: NOS



Large Cell Neuroendocrine Carcinoma (LCNEC)



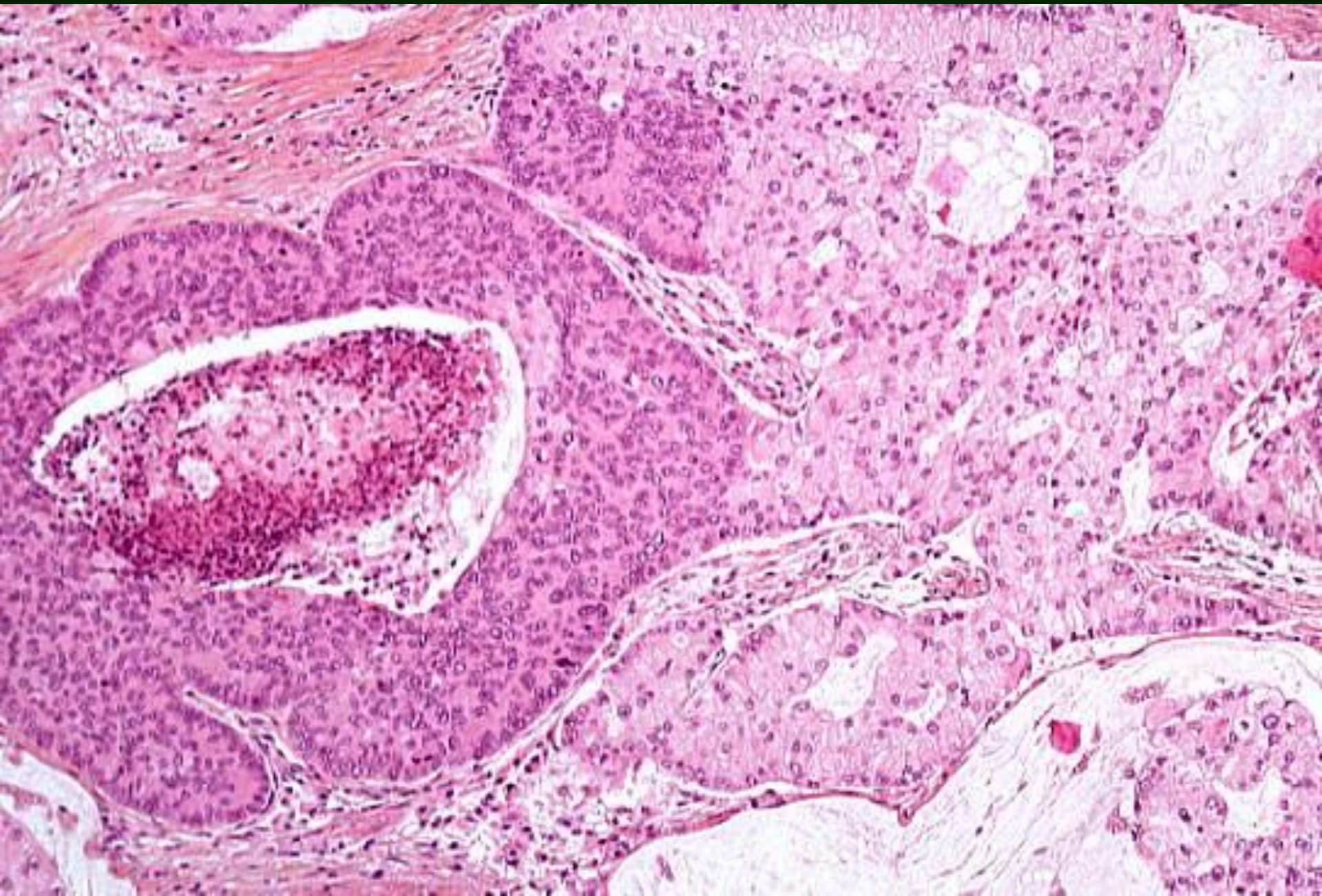

NCAM

Large Cell NEuroendocrine Carcinoma (LCNEC)

- A variant of large cell carcinoma
- A high grade NE tumor
- Characteristic features
  - Neuroendocrine morphology (rosettes ...)
  - Non small cell cytology (≠ SCLC)
  - High mitotic rate ≥ 11 per $2mm^2$

    (≠ Atypical carcinoid)
- 15 - 20% of LCNEC are Combined LCNEC

LCNEC combined



LCNEC: clinical features

- Heavy smokers. Mean age 62 years
- Poor prognosis: 27% - 5 y. survival
  9% - 10 y. survival
- Not significantly different from SCLC
- Surgical resection recommended
- Chemotherapy sensitivity?
  SCLC chemotherapy type ?

Rossi et al JCO 2005

The spectrum of neuroendocrine (NE) proliferation and neoplasms

I - NE cell hyperplasia and tumorlets

- A. NE cell hyperplasia
- B. Tumorlets

II - Tumors with NE morphology

- A. Typical carcinoid
- B. Atypical carcinoid
- C. Large cell neuroendocrine carcinoma
- D. Small cell carcinoma

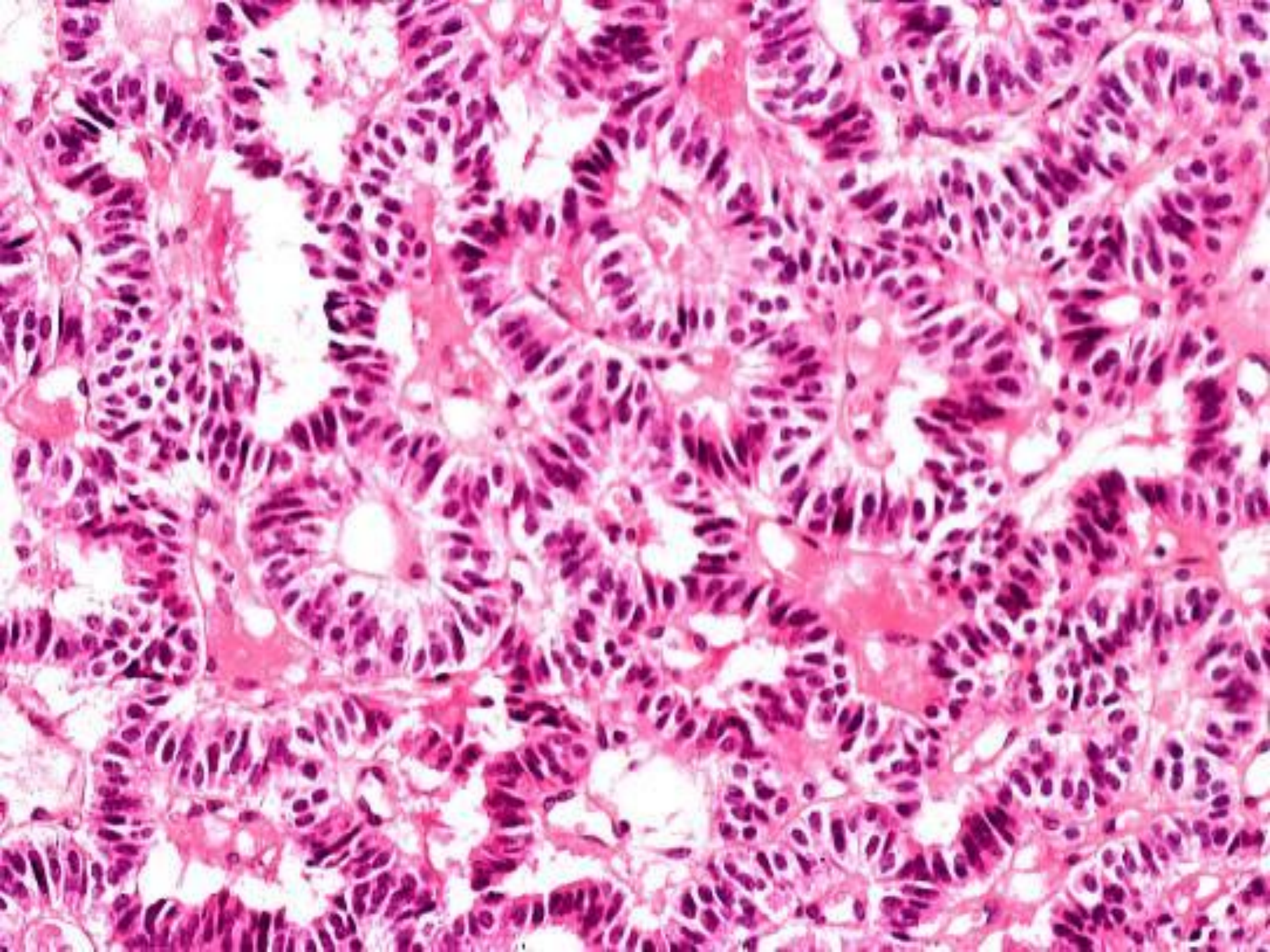
III - Non small cell carcinomas with NE differentiation

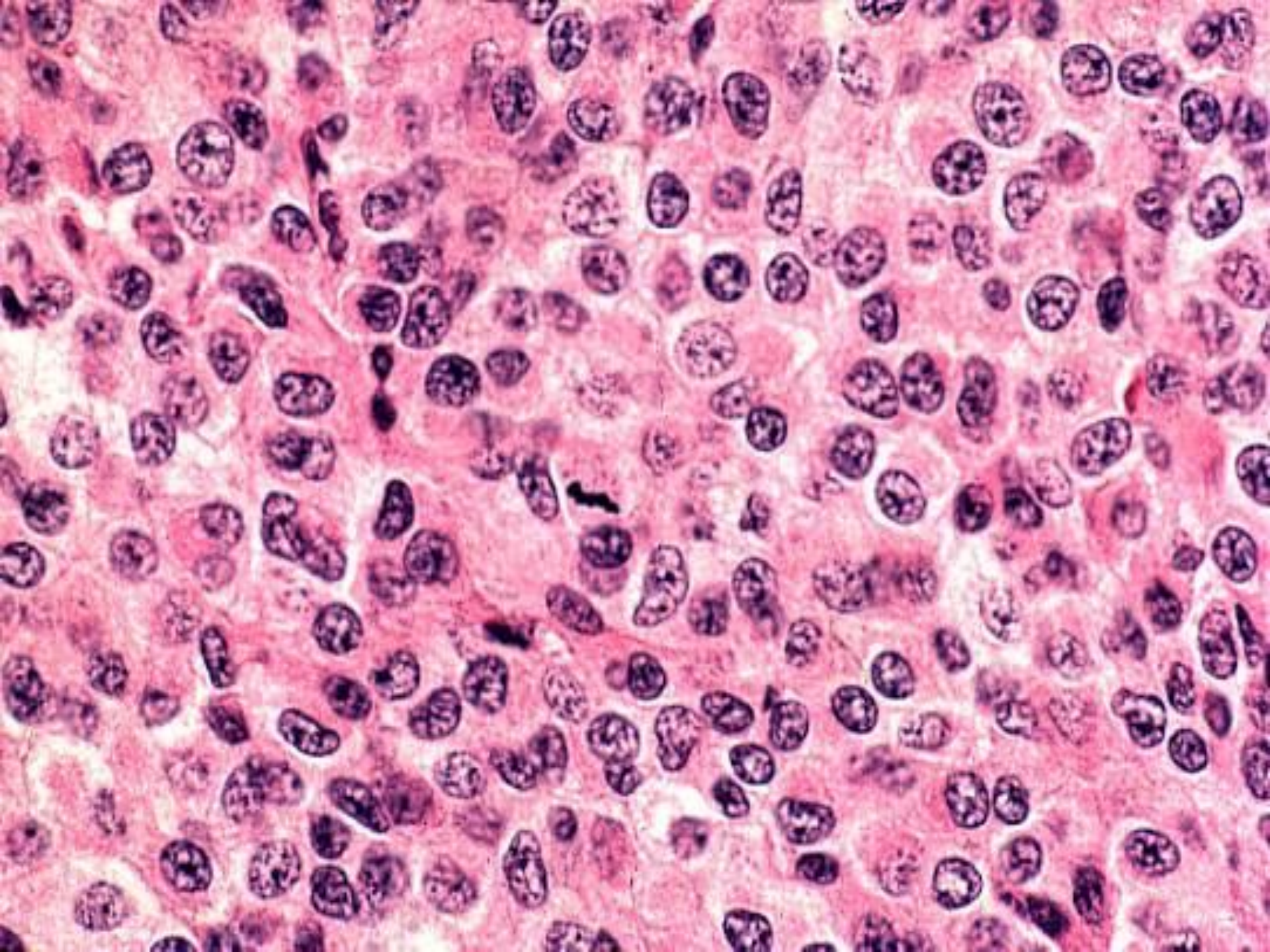
Lung neuroendocrine tumors

- **Carcinoids: Typical carcinoid**
  Atypical carcinoid

➔ **Sharp histopathological definition**

➔ **Significant prognostic differences**



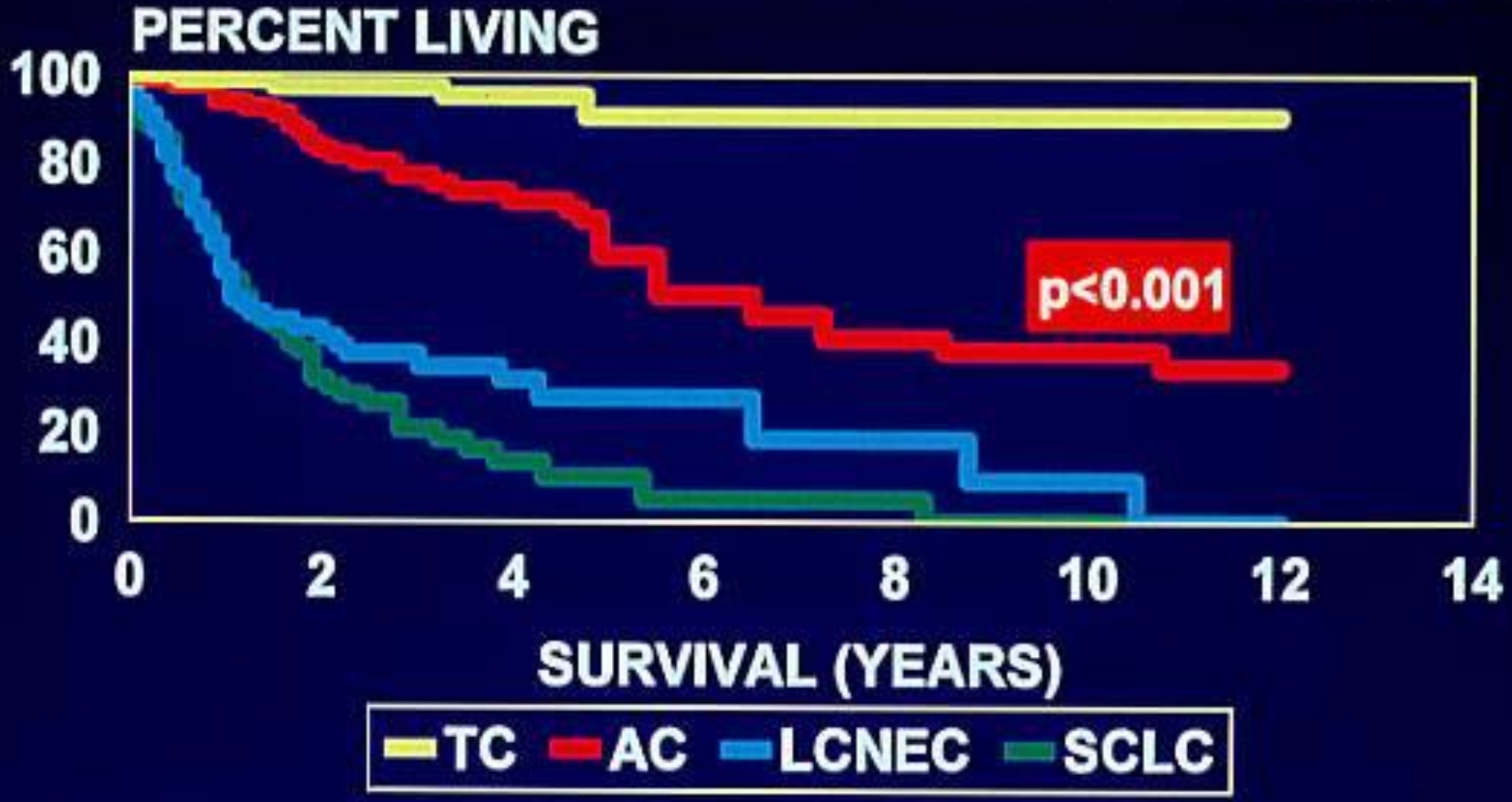


Carcinoids: Typical versus Atypical

	Mitoses	Necrosis	5y. survival	10y. survival
Typical carcinoid	< 2/ 2mm^2	0	87%	87%
Atypical carcinoid	2-10/ 2mm^2	+/-	56%	35%

W.D. Travis Am. J. Surg. Pathol. 1998

PULMONARY NE TUMORS
KAPLAN MEIER SURVIVAL ESTIMATION



AFIP/IASLC NE STUDY 8-97 (N=331; 78 TC, 81 AC, 78 LCNEC, 88 SCLC)

Large cell carcinoma

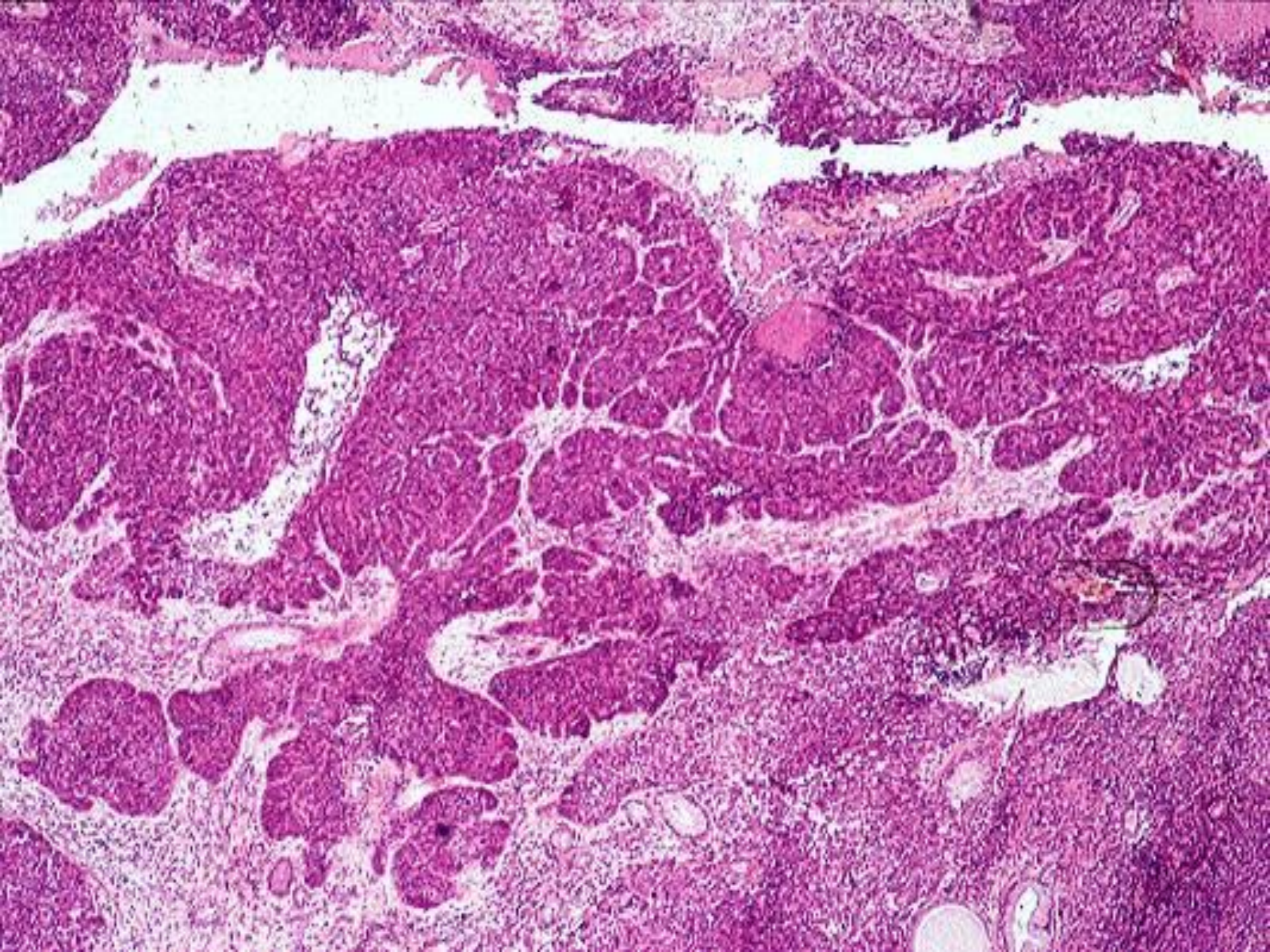
- **Large cell carcinoma :**

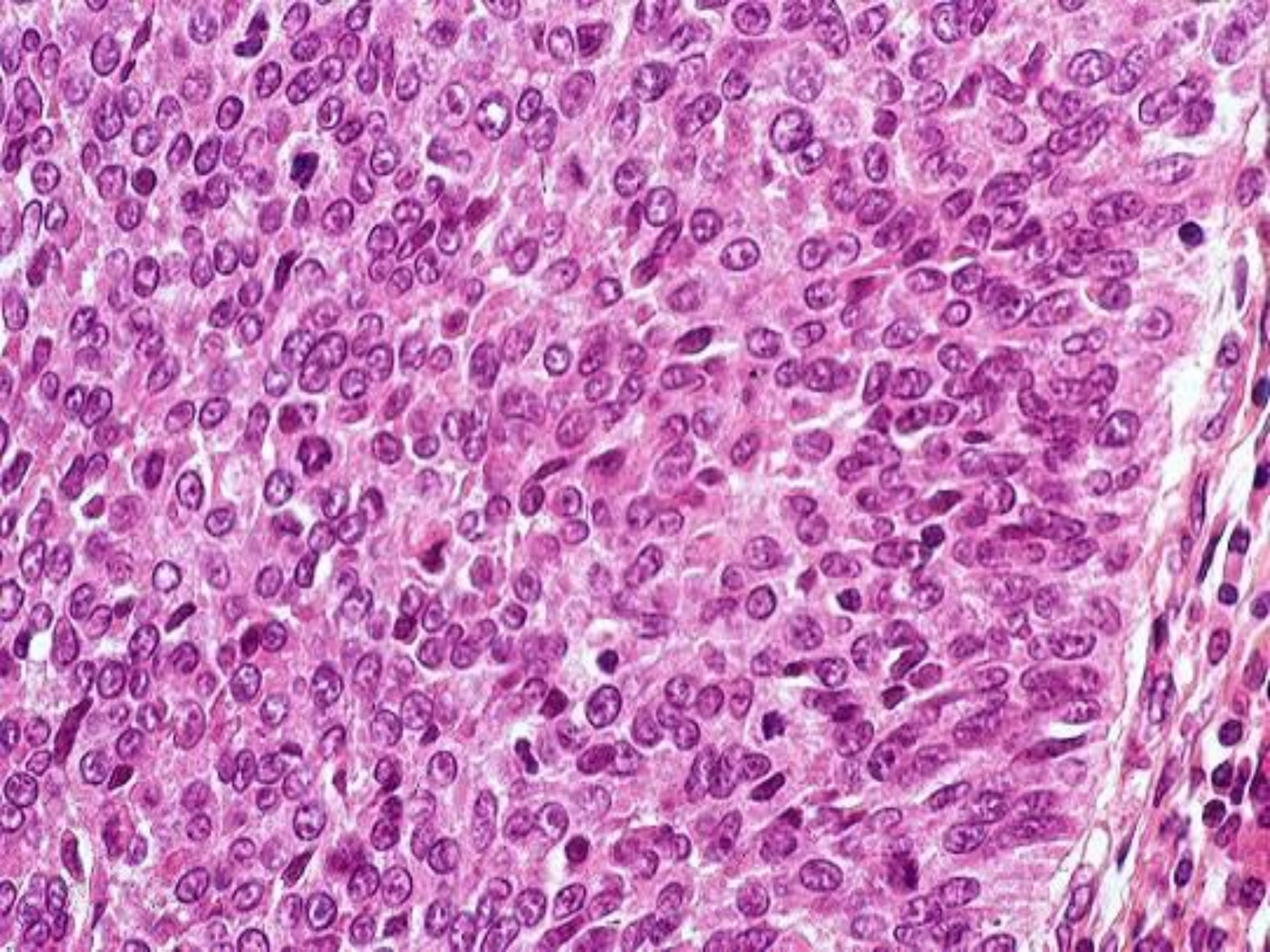
  no clinical significance

- **Two variants with clinical significance**
  - **Large cell neuroendocrine carcinoma (5%)**
  - **Basaloid carcinoma (5%)**

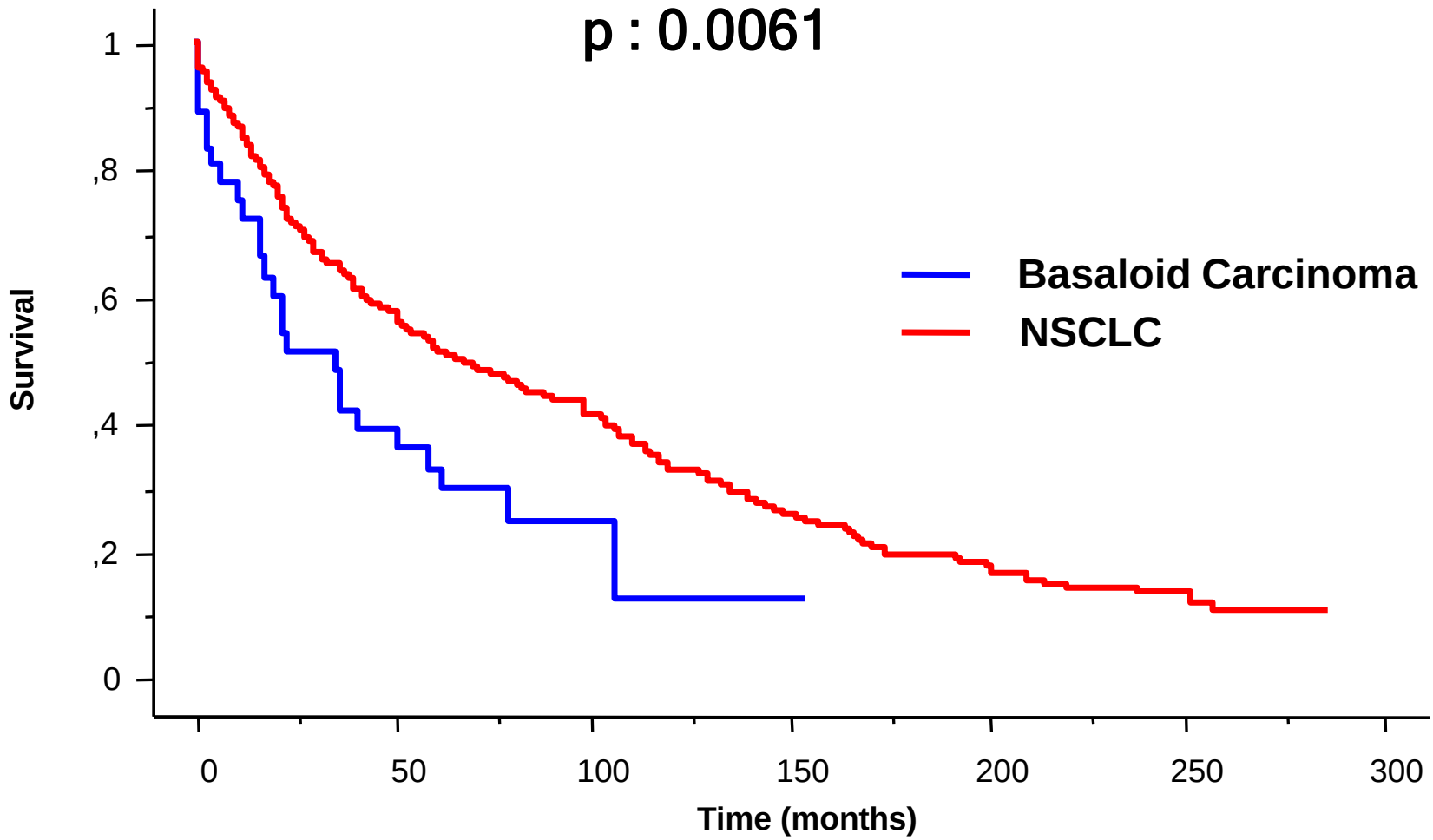
Basaloid carcinoma

- Proliferation of "reserve" stem cells
- No neuroendocrine markers
- High proliferative index
- Poor prognosis





Survival of stage I BC vs NSCLC



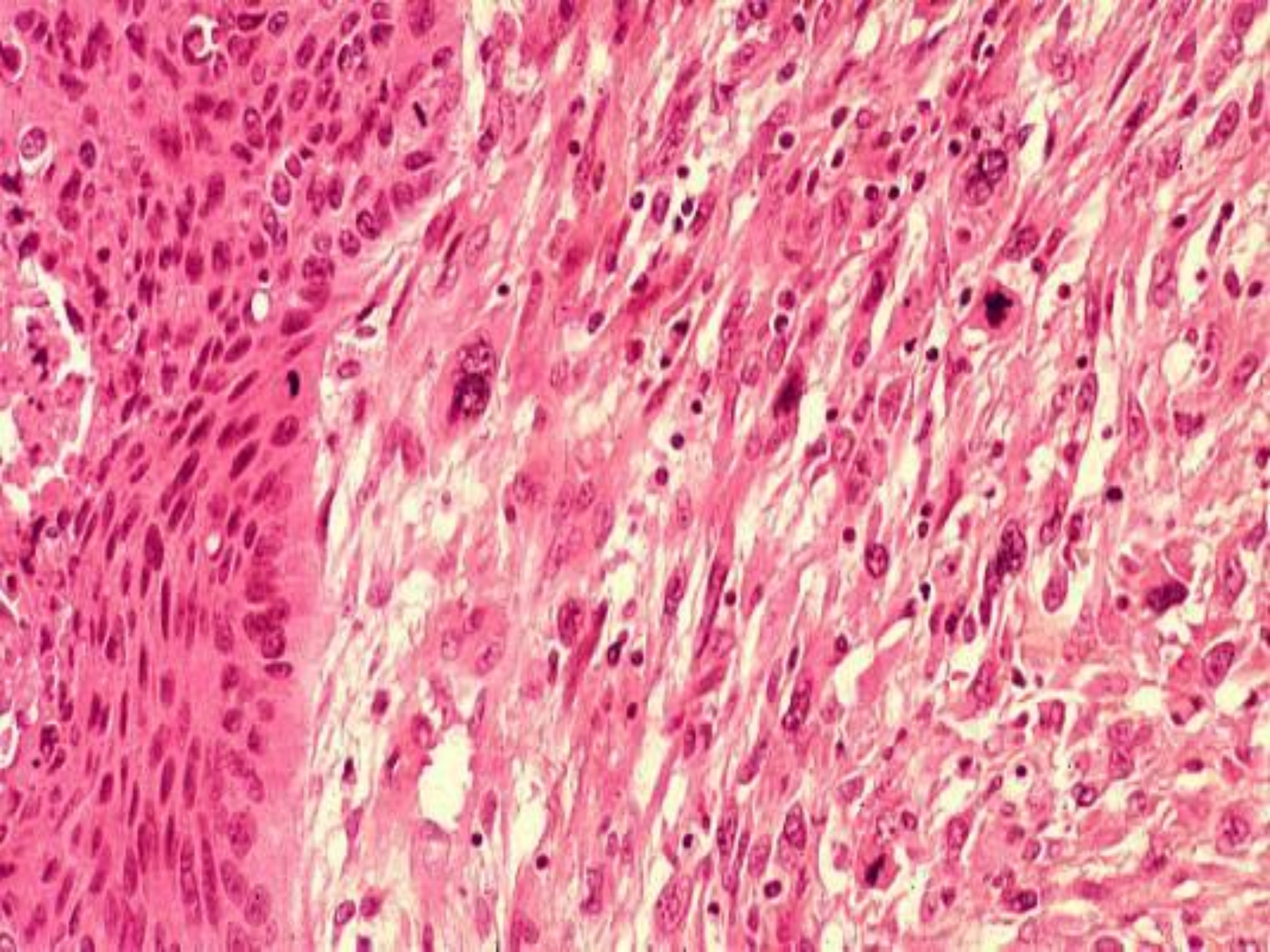
WHO 1999 - 2004

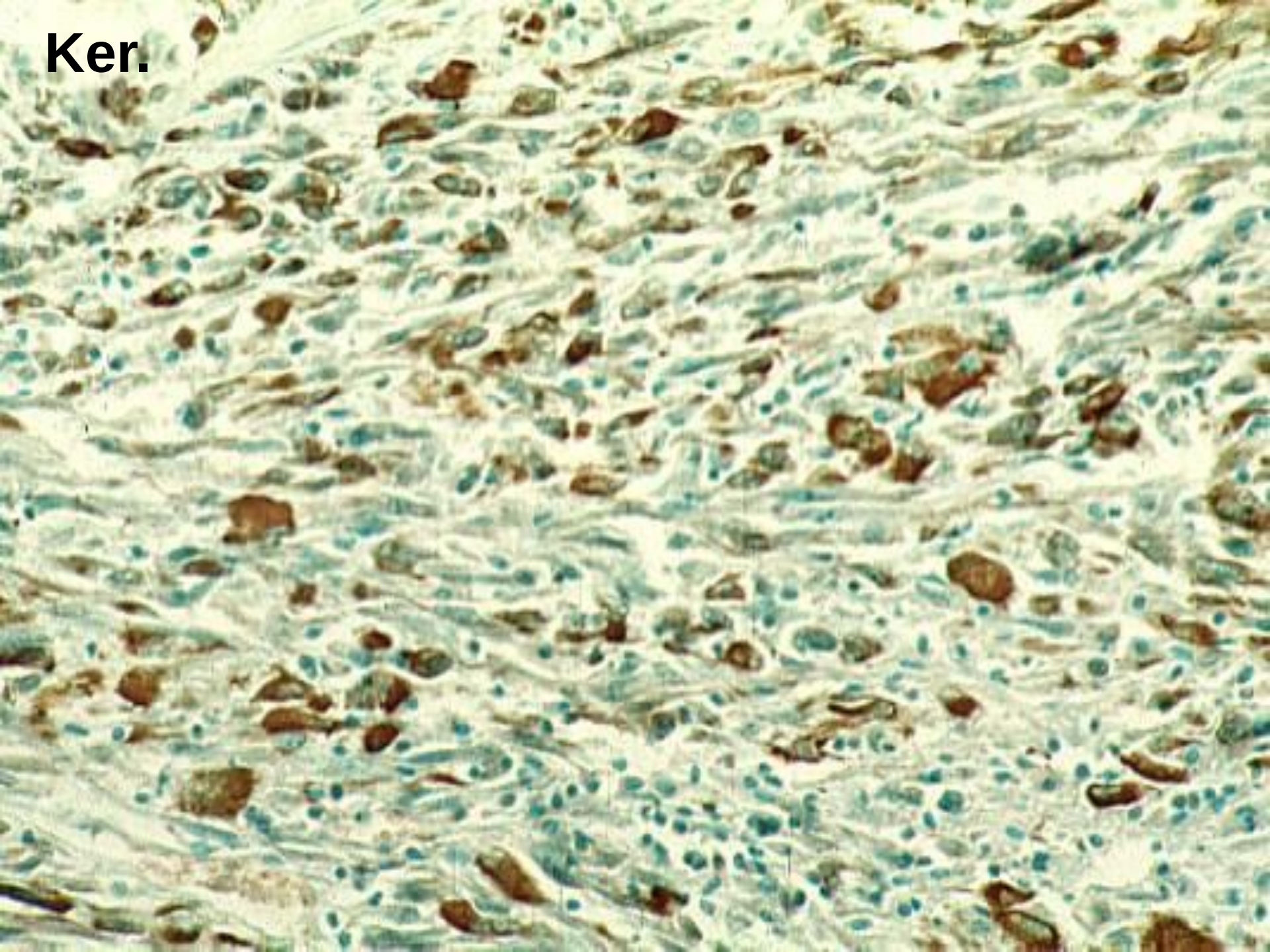
Sarcomatoid carcinomas

- Pleomorphic carcinoma
- Spindle cell carcinoma
- Giant cell carcinoma
- Carcinosarcoma
- Pulmonary blastoma

Sarcomatoid carcinoma

- Express the features of epithelial to mesenchymal transition
- Pleiomorphic carcinoma: 10% of giant or spindle cells
- Large peripheral tumors often invading chest and with endobronchial growth
- Differential diagnosis: sarcoma




Ker.

Pleomorphic Carcinoma (Sarcomatoid carcinoma)

- Poor prognosis
  - median survival: 19 months
  - 47% - 5 year survival at stage I

Rossi et al Am J. Surg Pathol 2003

➔ Disease related survival significantly shorter than NSCLC stage I

Immuno histochemistry
Electron microscopy

↓

Differential diagnosis

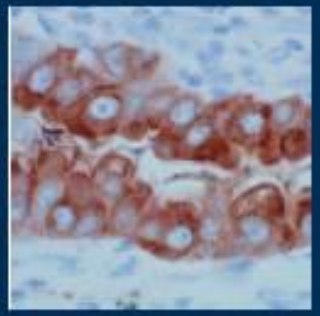
- Large cell Neuroendocrine Carcinoma / Basaloid
- Carcinoma
- Adenocarcinoma / Mesothelioma (calretinin, CK5-6, ACE…)
- Adenocarcinoma / Primitive / Metastatic (TTF1)
- Pleiomorphic carcinoma / Sarcoma (Ck)
- Sarcoma (desmin, E.M.)
- Melanoma (HMB45, S100)

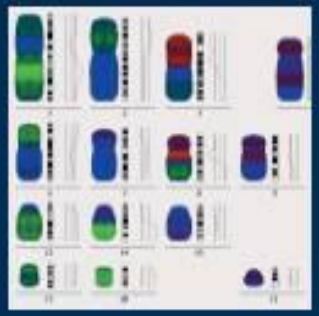
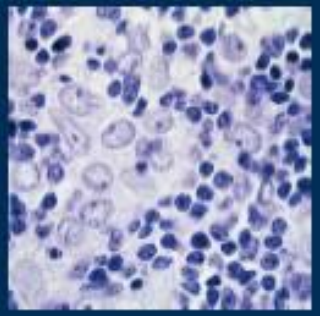
World Health Organization Classification of Tumours

Pathology & Genetics

Tumours of the Lung, Pleura, Thymus and Heart

Edited by William D. Travis, Elizabeth Brambilla, Hans K. Muller-Hermelink & Curtis C. Harris


WHO Classification Tumours of the Lung, Pleura, Thymus and Heart

IARC