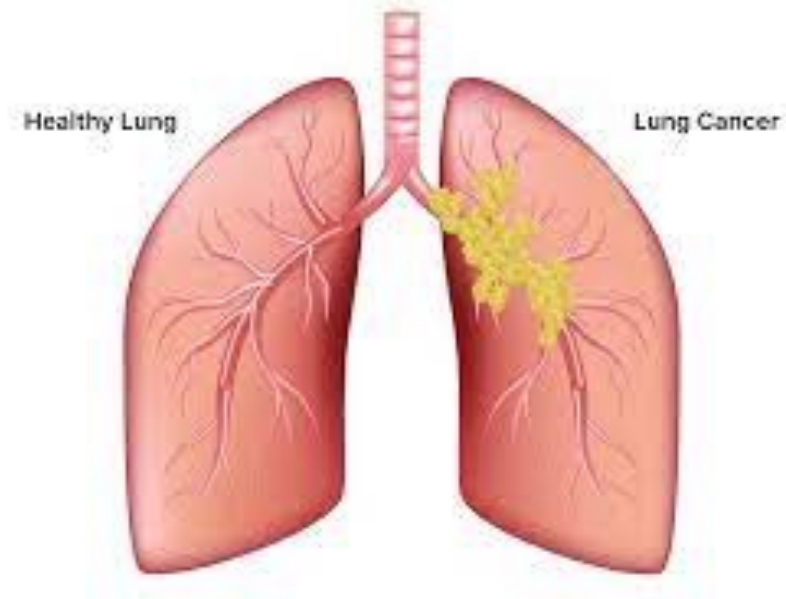
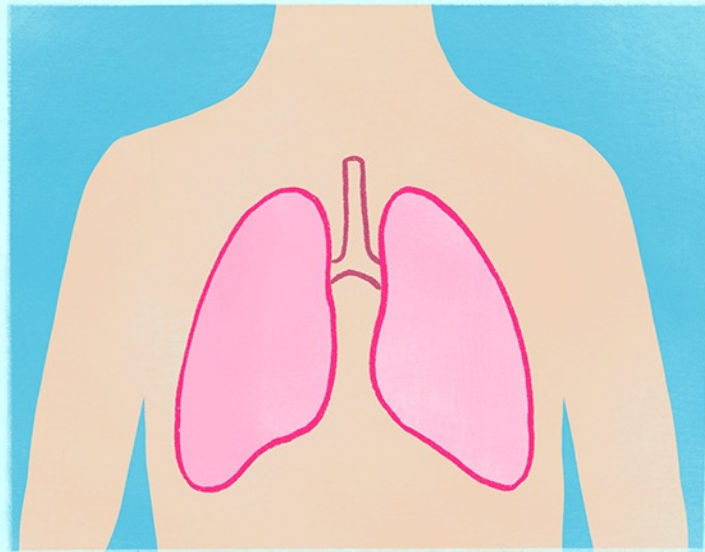


LUNG TUMORS



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DERMATOPATHOLOGIST & NEUROPATHOLOGIST

Metastatic vs. Primary Lung Cancer



Metastatic Lung Cancer

originated from a different part of the body and spread to the lungs



Primary Lung Cancer

originated in the lungs

90- 95% of primary lung tumors are **carcinomas**
5% are carcinoid tumors,
2- 5% are mesenchymal and other neoplasms.





CARCINOMA OF THE LUNG

- **the most frequently diagnosed cancer in the world**
- **the most common cause of cancer mortality worldwide**
- lung cancer is strongly linked to cigarette smoking:
 - changes in smoking habits greatly influence lung cancer incidence, mortality & the prevalence of the various histologic types of lung cancer.
 - The incidence among females is increasing **BECAUSE** the incidence of smoking in women increased markedly over the past half century.
- **peak incidence: 65 and 74 years.**

THE FOUR MAJOR HISTOLOGIC TYPES OF CARCINOMAS OF THE LUNG

- 1. Adenocarcinoma (50%)**
- 2. Squamous Cell Carcinoma (20%)**
- 3. Small Cell Carcinoma (a subtype of neuroendocrine carcinoma) (15%)**
- 4. Large Cell Carcinoma (2)**

Table 15.9 Histologic Classification of Malignant Epithelial Lung Tumors

Tumor Classification	
	<i>Adenocarcinoma</i> Lepidic, acinar, micropapillary, papillary, solid (according to predominant pattern) Invasive mucinous adenocarcinoma Minimally invasive adenocarcinoma (nonmucinous, mucinous)
	<i>Squamous cell carcinoma</i> Keratinizing, nonkeratinizing, basaloid
	<i>Neuroendocrine tumors</i> Small cell carcinoma Combined small cell carcinoma Large cell neuroendocrine carcinoma Combined large-cell neuroendocrine carcinoma Carcinoid tumor Typical, atypical
	<i>Other uncommon types</i> Large cell carcinoma Adenosquamous carcinoma Sarcomatoid carcinoma Pleomorphic, spindle cell, giant cell carcinoma, carcinosarcoma, pulmonary blastoma Others such as lymphoepithelioma-like carcinoma and NUT carcinoma Salivary gland-type tumors

- **S**quamous cell and **S**mall cell carcinomas **have the strongest association with S**moking
- **Adenocarcinomas is the most common primary tumors arising in men & women, in never-smokers, and in individuals younger than 45 years of age.**

- Old designation to small cell lung cancer (**SCLC**) and non–small cell lung cancer (**NSCLC**)
- **NSCLC** includes adenocarcinoma, squamous and large cell carcinoma, and large cell neuroendocrine carcinomas

- **SCLCs:**

- virtually all cases have metastasized by the time of diagnosis
- not curable by surgery.
- best treated by chemotherapy, +/- radiation therapy.

- **NSCLCS:**

- more likely to be Resectable
- Respond poorly to chemotherapy
- targeted therapy nowadays for adenocarcinoma and SqCC.

ETIOLOGY AND PATHOGENESIS

PATHOGENESIS:

Accumulation of **genetic abnormalities** after exposure to **carcinogens** resulting in a stepwise accumulation of driver mutations → transformation of benign progenitor cells in the lung into neoplastic cells having all of the hallmarks of cancer

Genetic abnormalities

carcinogens

GENETIC ABNORMALITIES:

- Inactivation of tumor suppressor genes located on chromosome **3** (3p) as an **early event**
- mutations in **TP53** tumor suppressor gene and **KRAS** oncogene as a **late event**
- mutations that activate the *epidermal growth factor receptor (EGFR)* → (adenocarcinomas arising in nonsmoking women)

CARCINOGENS:

- **cigarette smoking**
- **environmental carcinogens**

CIGARETTE SMOKING

- **80 %** in active smokers or those who stopped recently.
- linear correlation between the frequency of lung cancer and pack-years of cigarette smoking.
- **habitual heavy smokers** (two packs a day for 20 years) have **60X** more risk than nonsmokers.
- For unclear reasons, **women are more susceptible to carcinogens** in tobacco smoke than men.

- Although smoking cessation decreases the risk over time, it never returns to baseline levels
- smoking of pipes, cigars and passive smoking increases the risk.
- The long-term effects of electronic cigarette “vaping” are not known.
- Chewing tobacco causes oral cancers and can lead to nicotine addiction
- Secondhand smoke, or environmental tobacco smoke: increased the risk

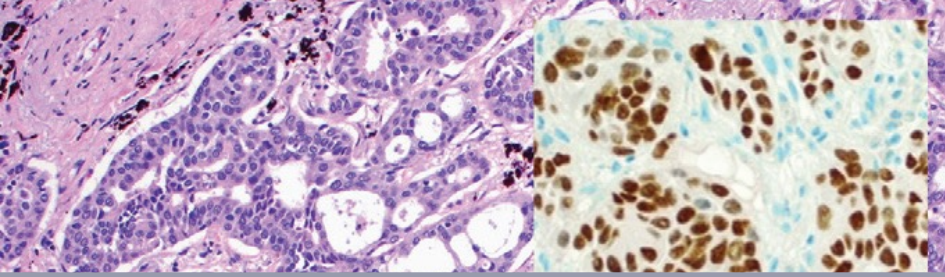
- lung cancer develops in only 10% to 15% of smokers→

Because the mutagenic effect of carcinogens in smoke is modified by genetic variants

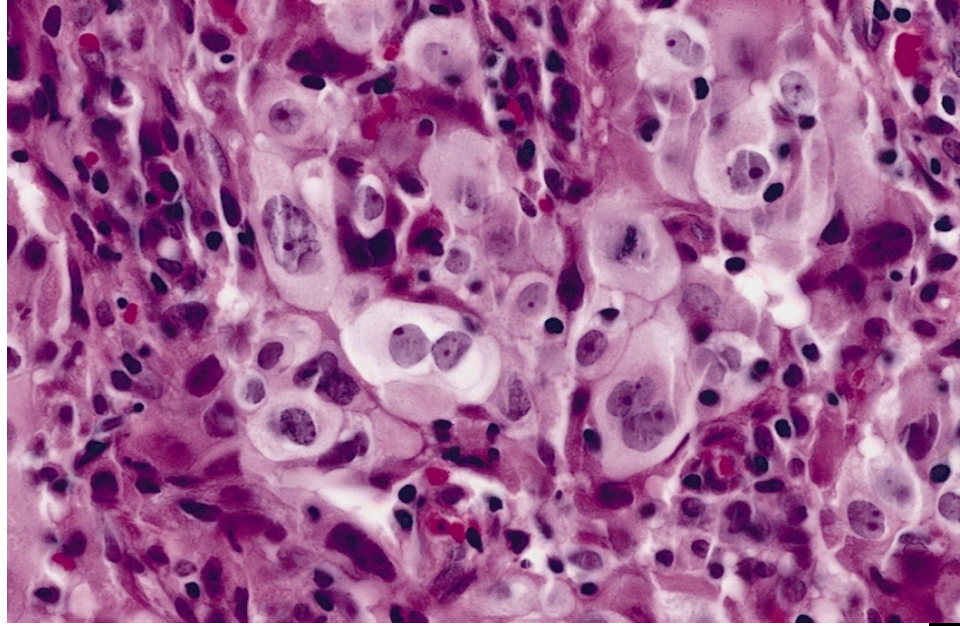
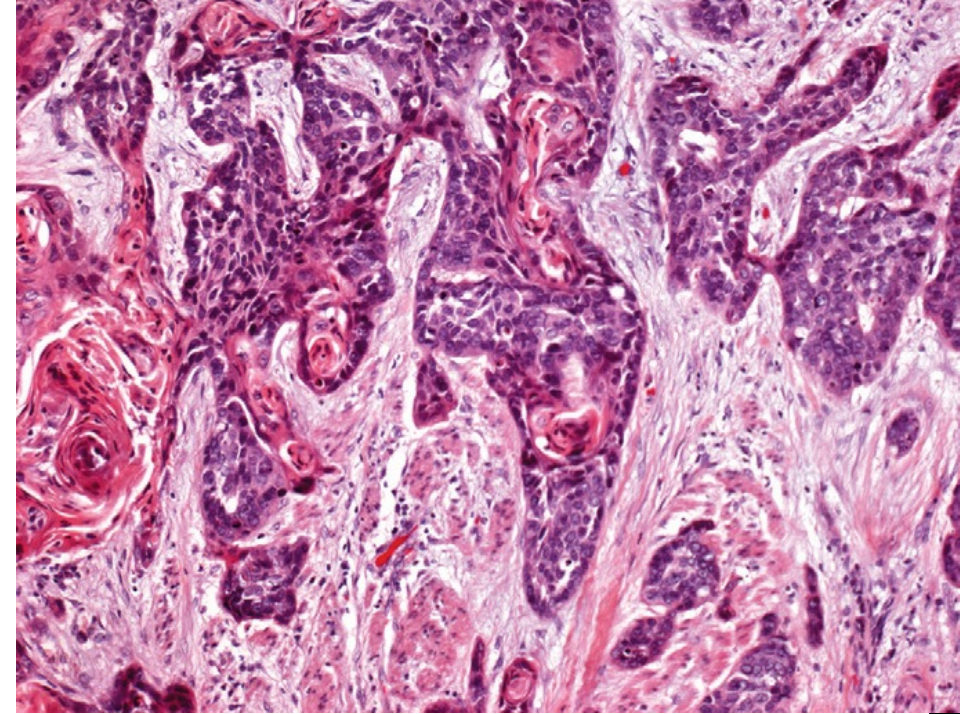
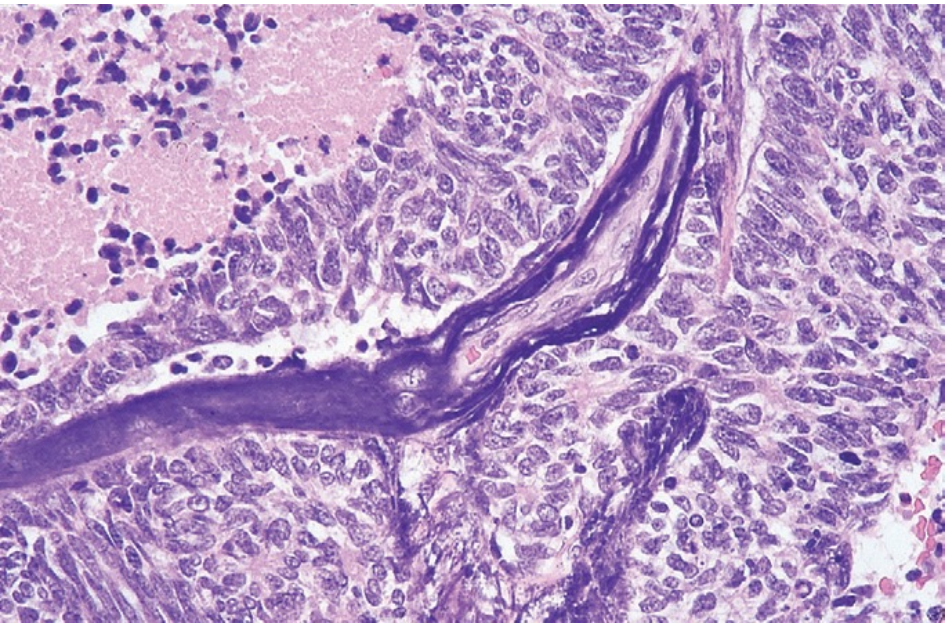
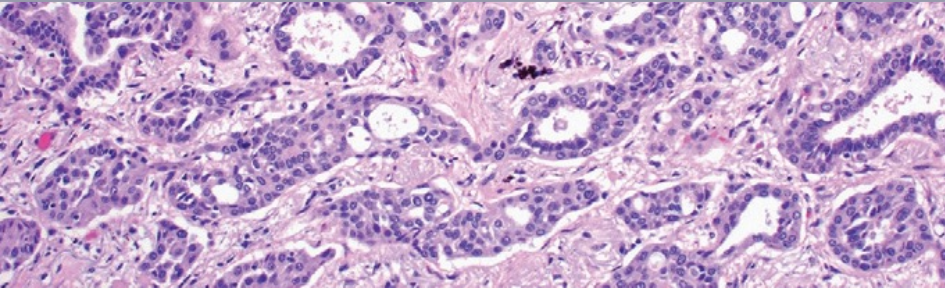
ENVIRONMENTAL CARCINOGENS:

- **Occupational exposures** to some environmental carcinogens may sometimes be responsible for lung cancer **all by themselves**, e.g:
 - **uranium mines**
 - work with **asbestos**
 - inhalation of dusts containing **arsenic, chromium, nickel, or vinyl chloride.**

Some invasive adenocarcinomas of the lung arise through an **atypical adenomatous hyperplasia–adenocarcinoma in situ–invasive adenocarcinoma sequence.**



Adenocarcinoma



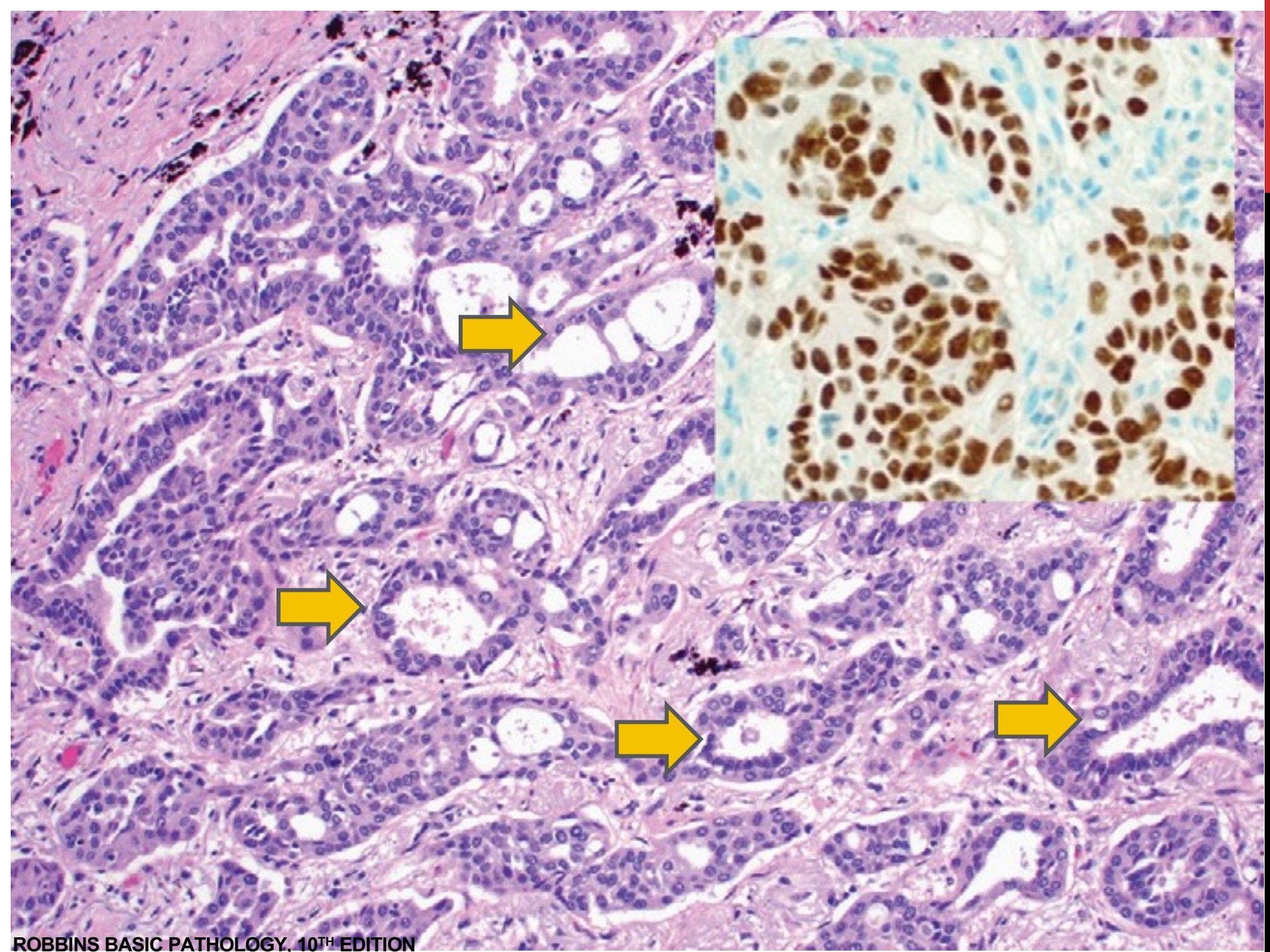
<https://www.verywellhealth.com/large-cell-carcinoma-of-the-lungs-2249356>

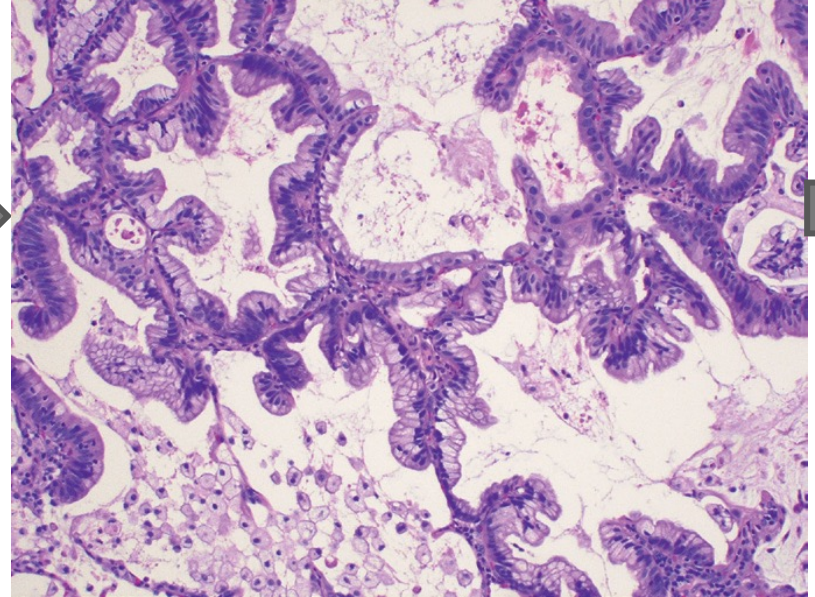
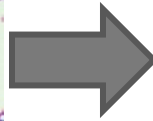
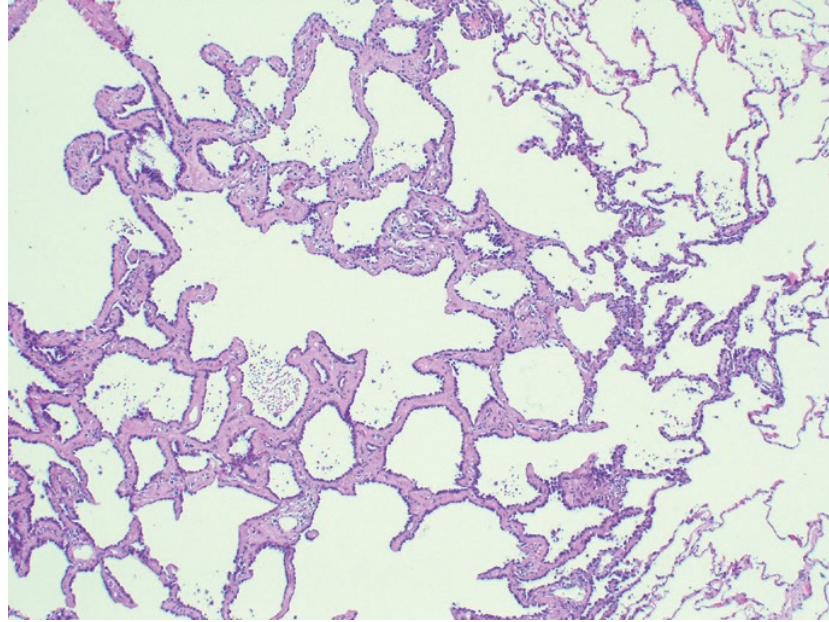
ADENOCARCINOMA:

- usually **peripherally located**
- grow slowly
- form smaller masses
- tend to metastasize widely at an early stage

MORPHOLOGY, MICROSCOPIC:

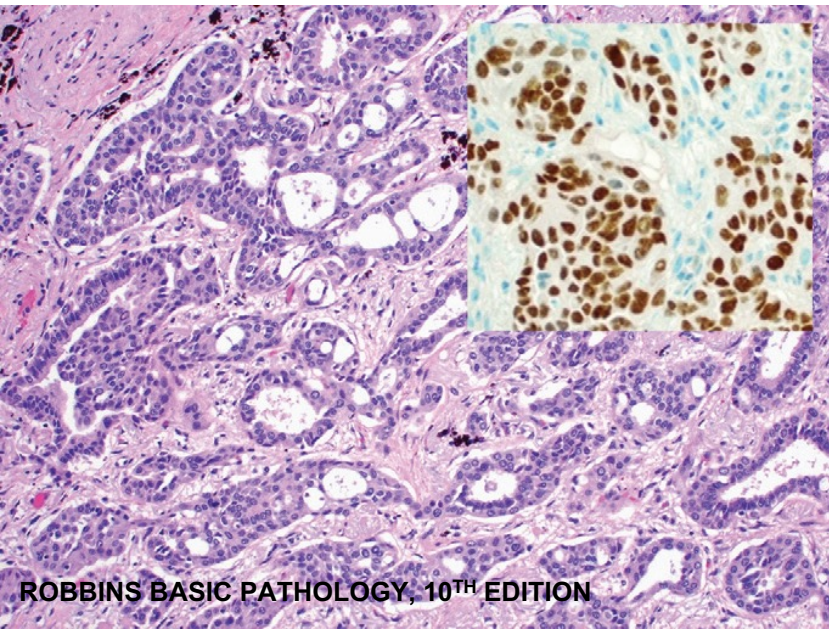
- variety of growth patterns
- including **acinar (gland-forming); papillary; mucinous and solid types**





atypical adenomatous hyperplasia (AAH)

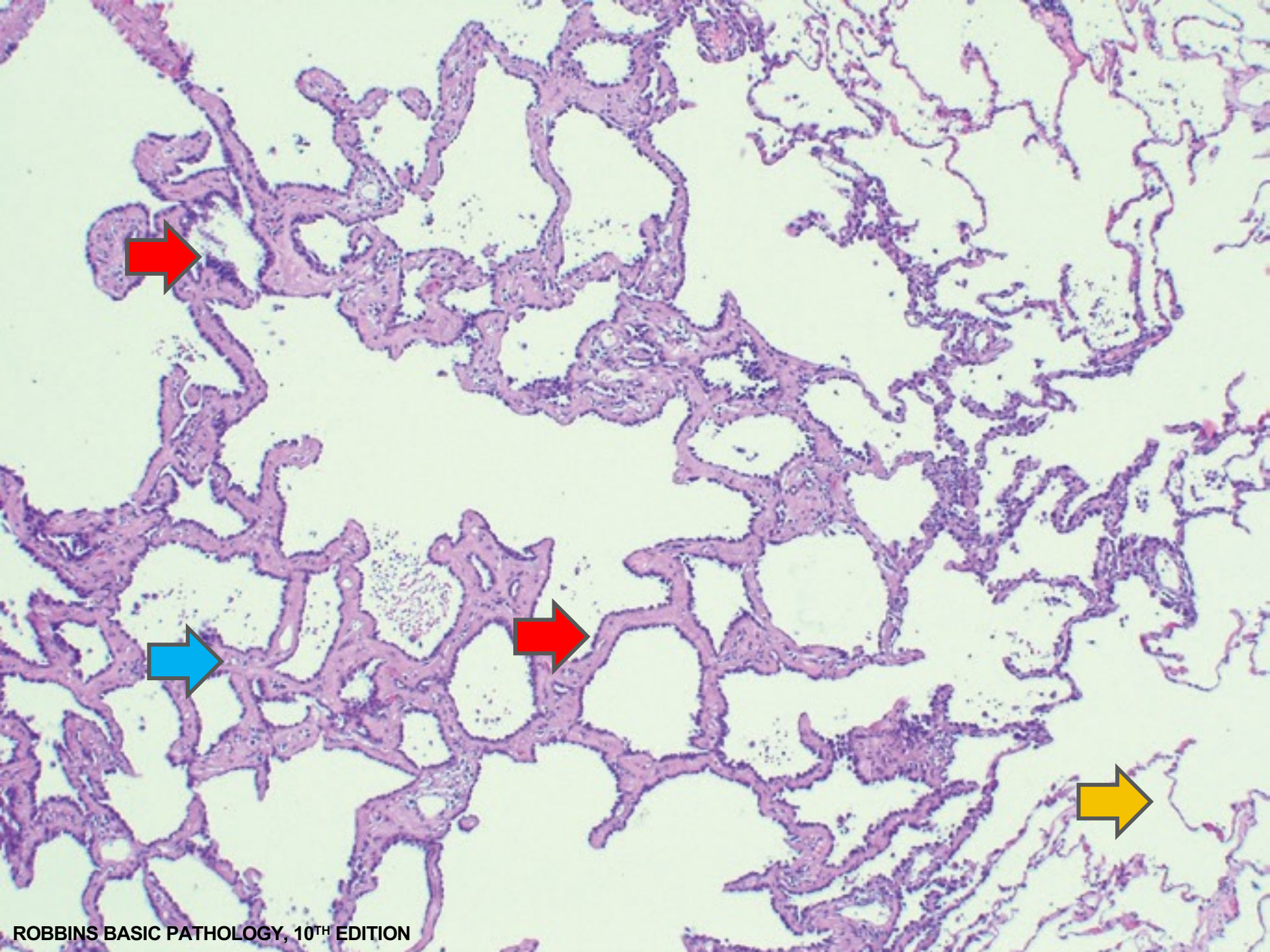
adenocarcinoma in situ (AIS)



**Adenocarcinoma,
minimally invasive or invasive**

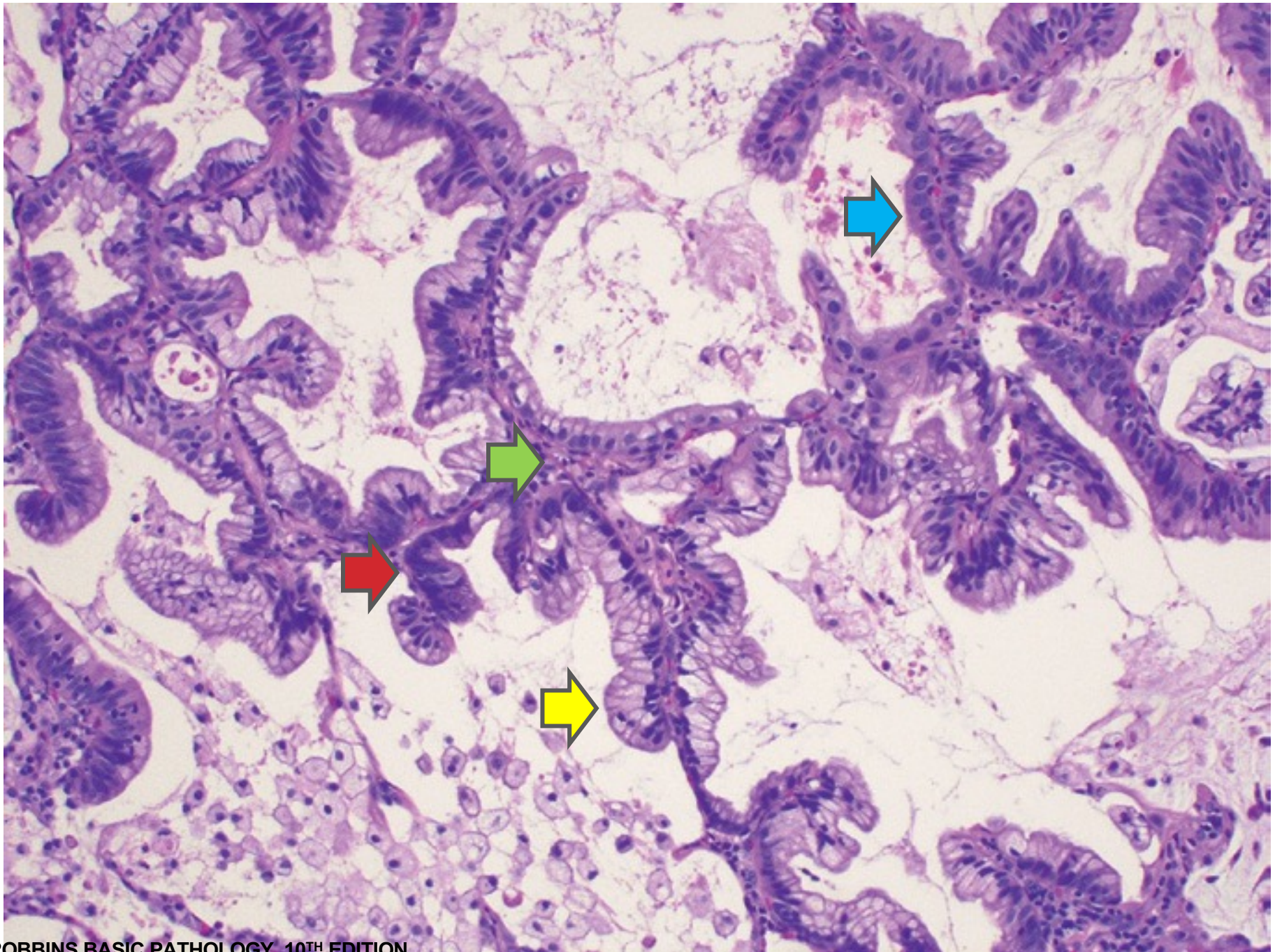
Atypical adenomatous hyperplasia:

- **small precursor lesion (≤ 5 mm) characterized by dysplastic pneumocytes lining alveolar walls that are mildly fibrotic**
- demonstrating nuclear hyperchromasia, pleomorphism, and prominent nucleoli.
- **can be single or multiple**



Adenocarcinoma in situ (AIS):

- diameter of <3 cm, composed entirely of dysplastic cells growing along pre-existing alveolar septa which serve as a scaffold.
- growth along preexisting structures, and preservation of alveolar architecture.
- **No destruction of alveolar architecture**
- **No stromal invasion**
- **No desmoplasia**

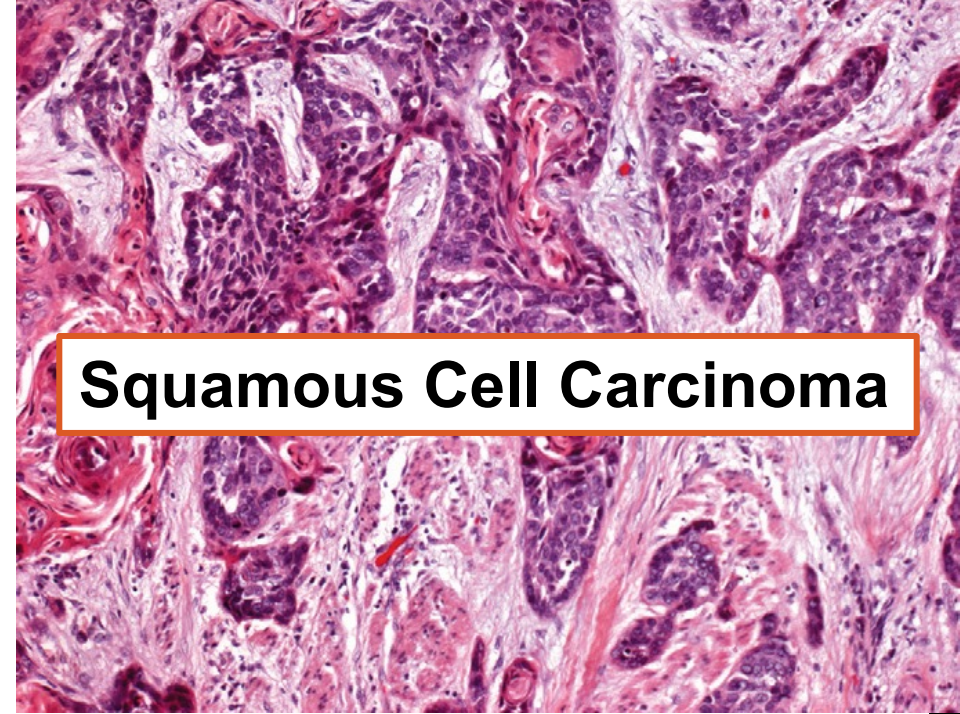
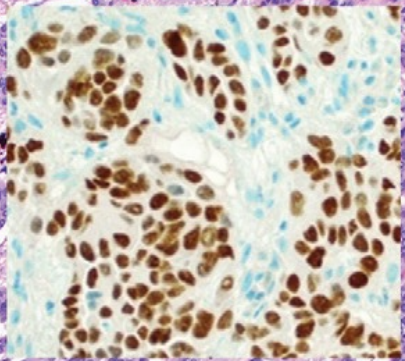
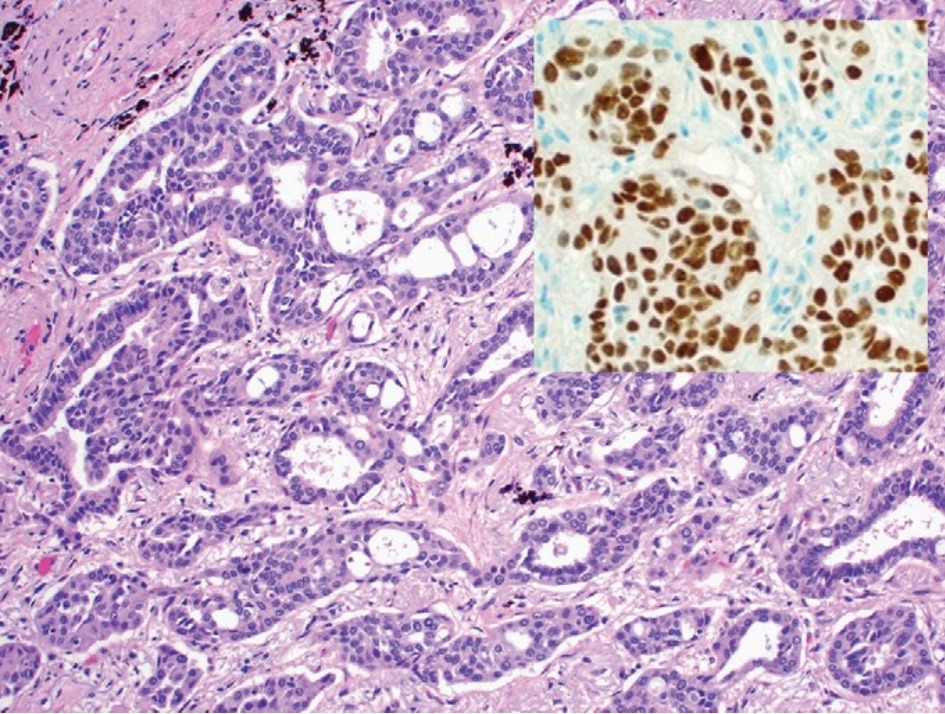


- **microinvasive adenocarcinoma:**

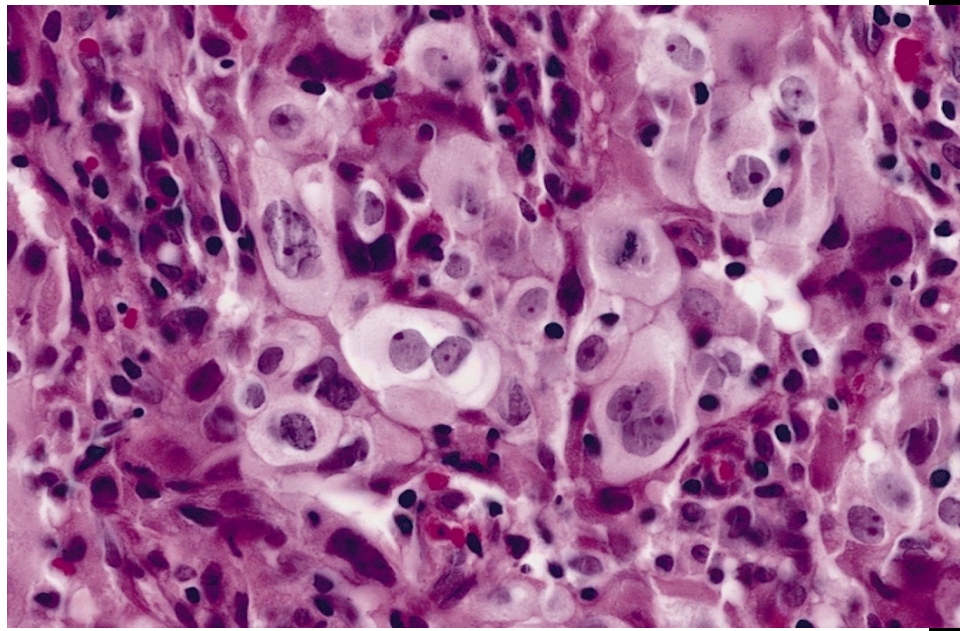
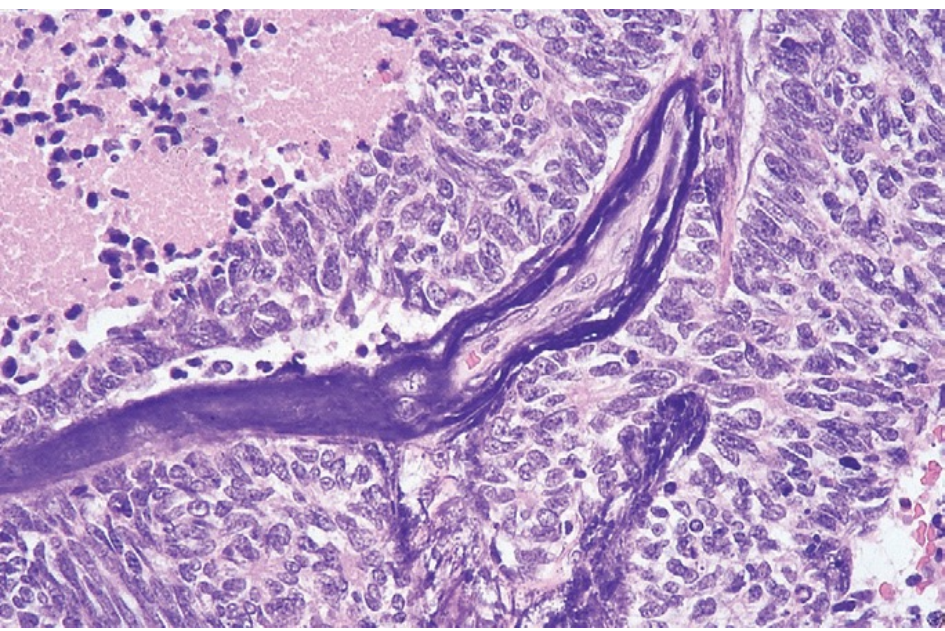
Tumors (≤ 3 cm) with a small invasive component (≤ 5 mm)

- **Invasive adenocarcinoma:**

- invasive malignant epithelial tumor with glandular differentiation or mucin production by the tumor cells.
- a tumor of any size with an area of invasion >5 mm.



Squamous Cell Carcinoma



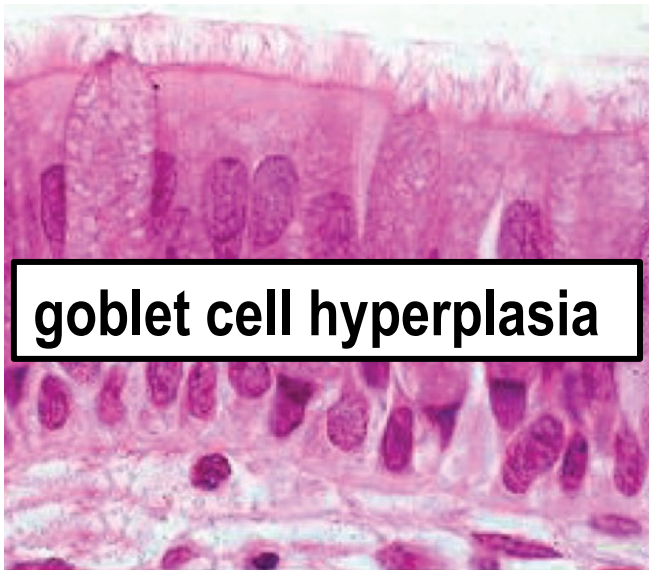
SQUAMOUS CELL CARCINOMAS

- More common in **men**
- Closely correlated with **smoking history**
- Arise **Centrally in major bronchi** and eventually spread to local hilar nodes and outside the thorax
- Large lesions may undergo **central necrosis**, giving rise to **cavitation**.

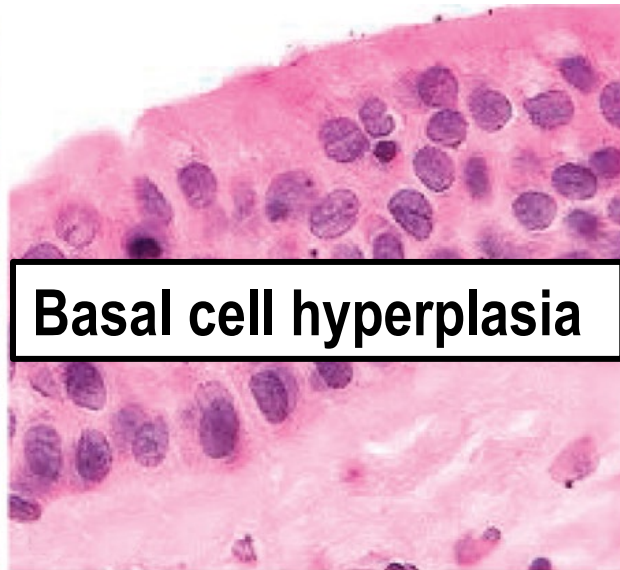
- **Preneoplastic lesions:**
 - **squamous metaplasia or dysplasia** in the bronchial epithelium → **carcinoma in situ** → **Squamous cell carcinoma**
 - the lesion is asymptomatic until reaches a symptomatic stage when it begins to obstruct the lumen of a major bronchus, +/- atelectasis and infection.

MORPHOLOGY:

Ranges from **Well differentiated squamous cell neoplasms** showing keratin pearls and intercellular bridges to **Poorly differentiated neoplasms** with only minimal residual squamous cell features.



goblet cell hyperplasia



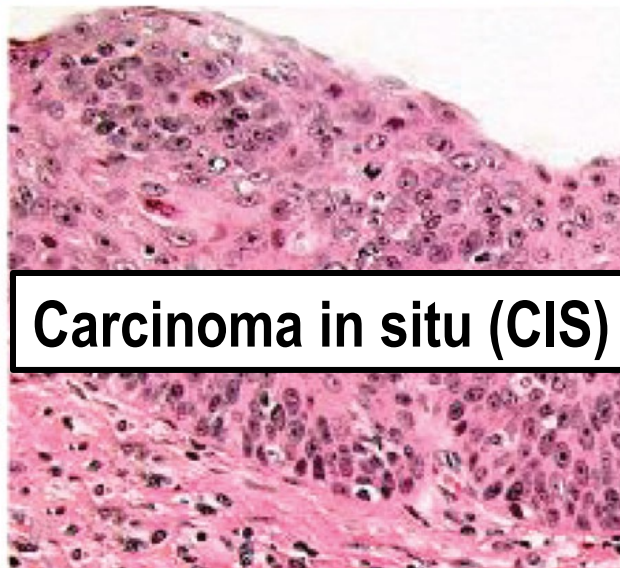
Basal cell hyperplasia



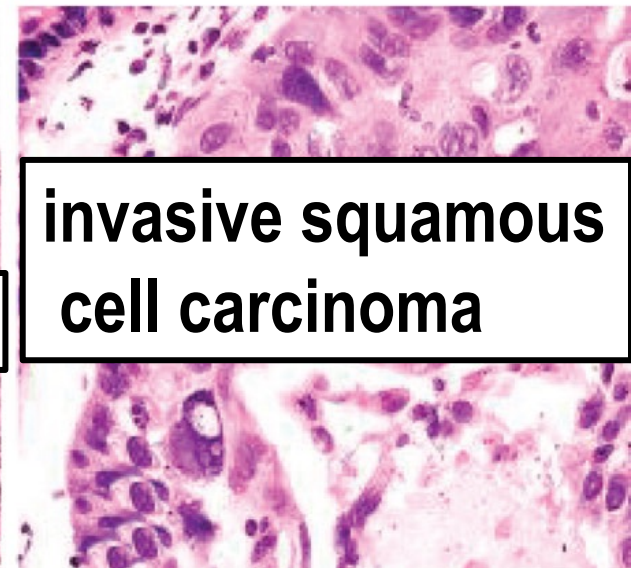
Squamous metaplasia



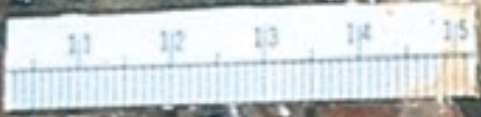
Squamous dysplasia



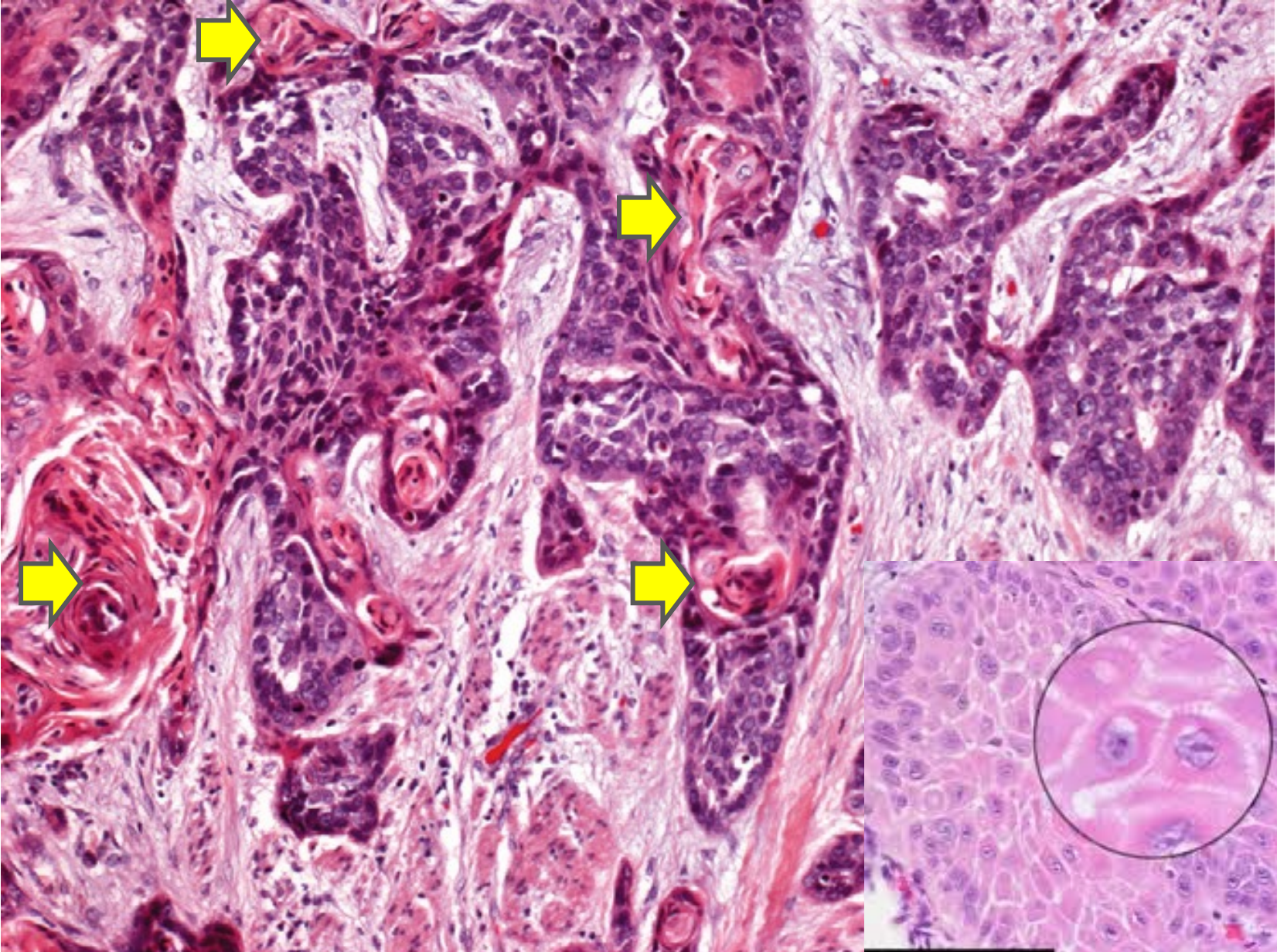
Carcinoma in situ (CIS)

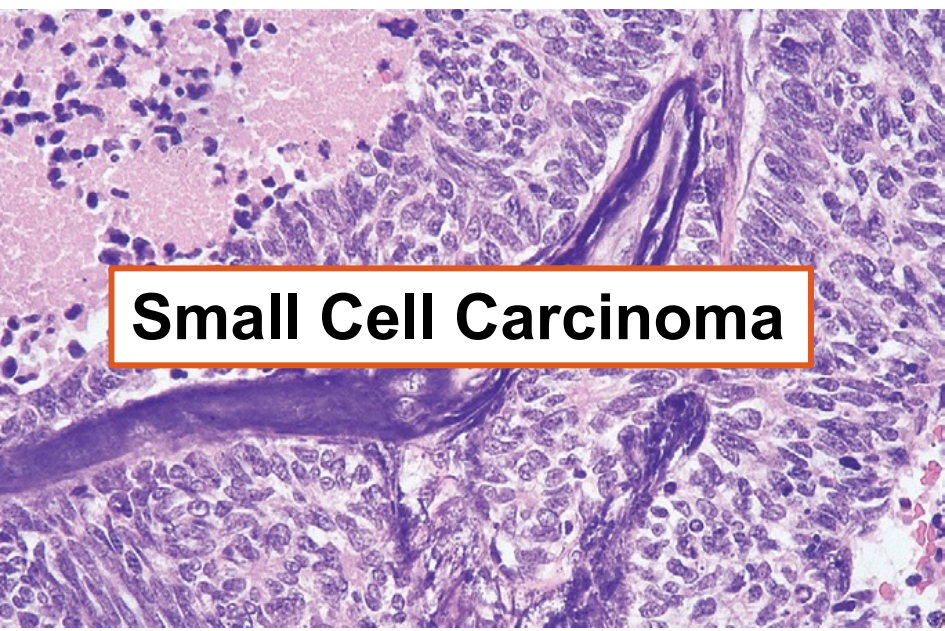
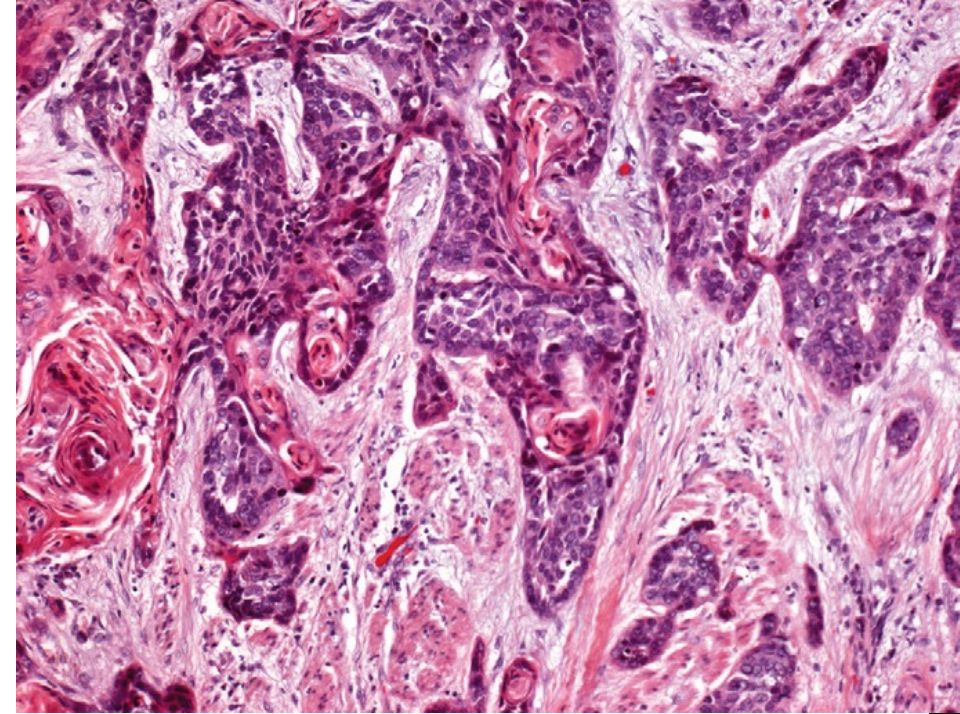
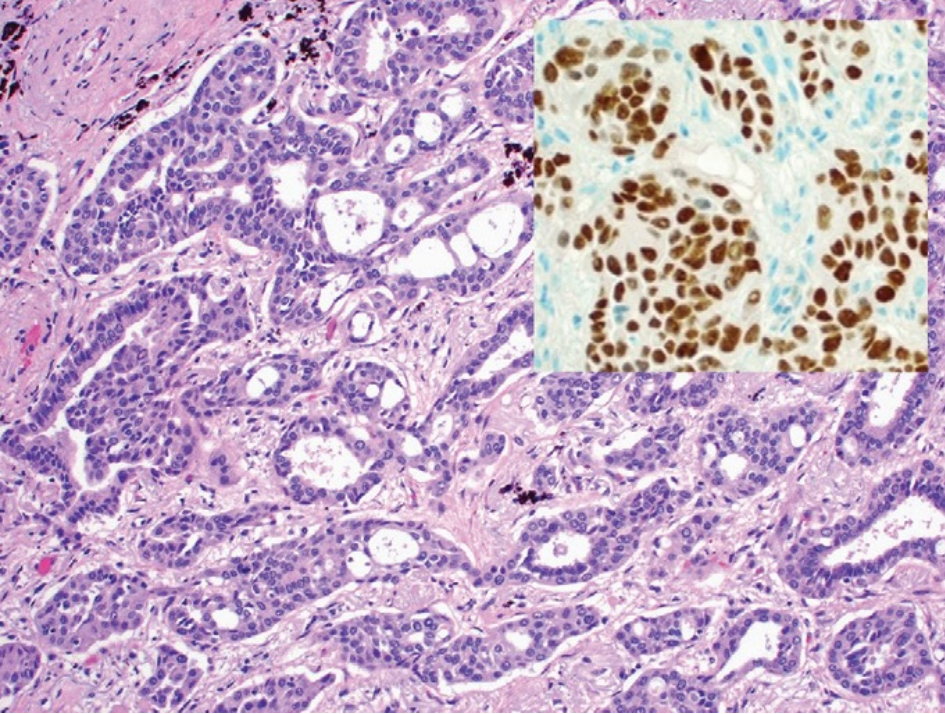


invasive squamous cell carcinoma

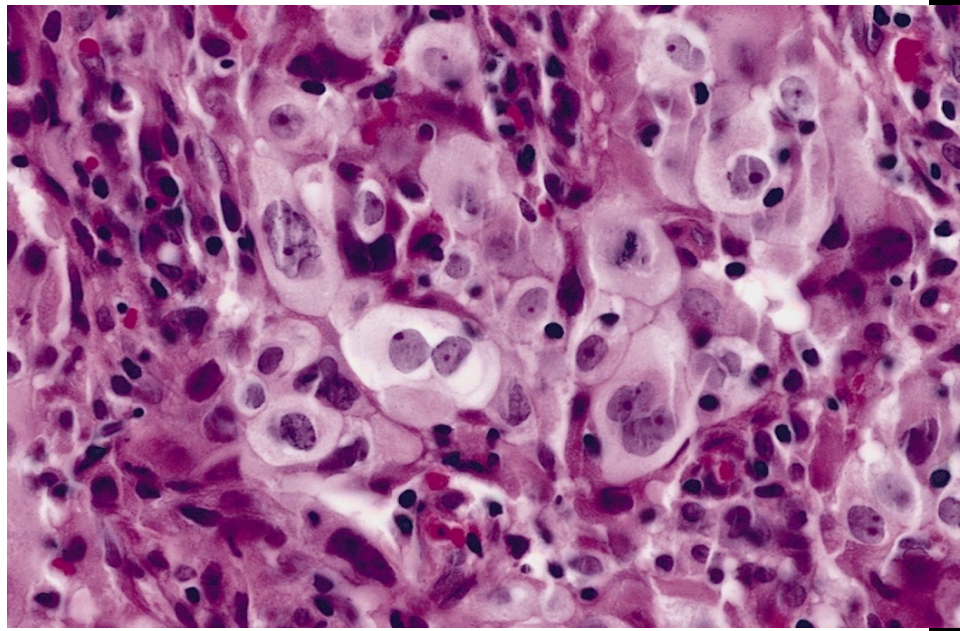


WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA SHOWING KERATINIZATION AND PEARLS.





Small Cell Carcinoma

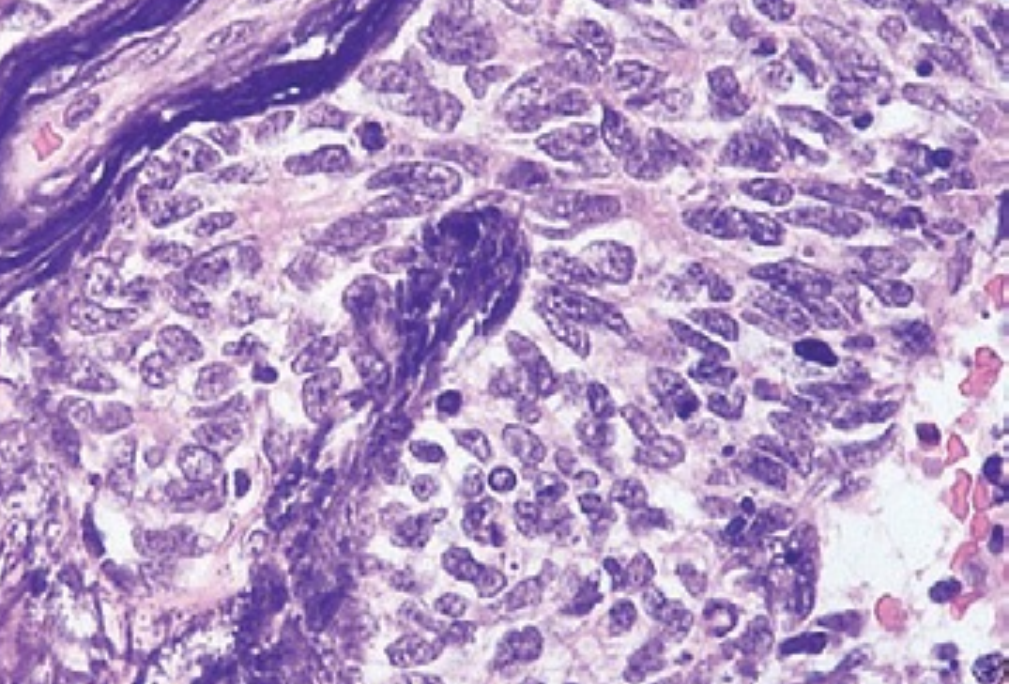
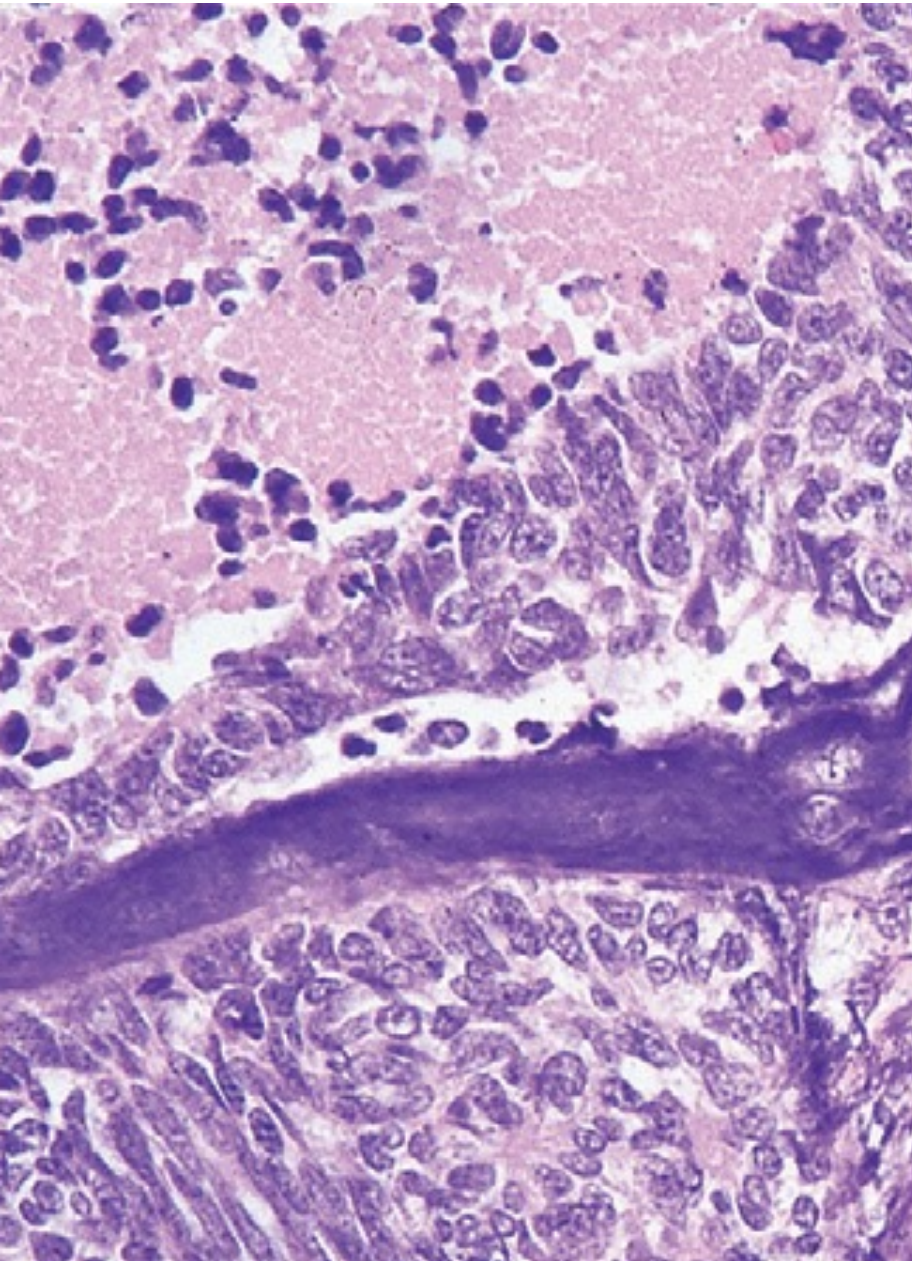


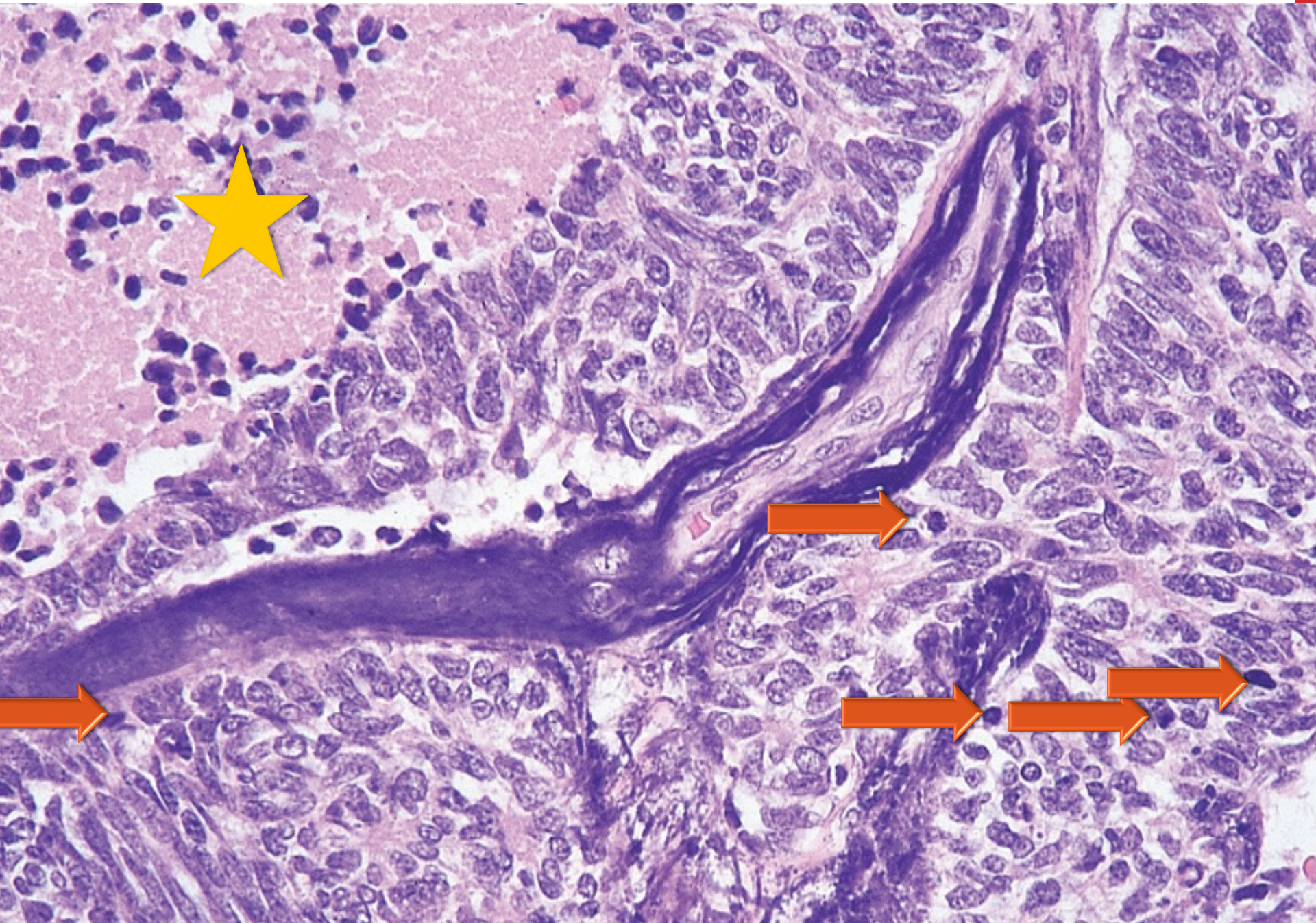
SMALL CELL LUNG CARCINOMAS (SCLC)

- **the most aggressive lung tumors**, metastasizing widely;
 - By the time of diagnosis, most will have metastasized to hilar and mediastinal lymph nodes.
- may arise in major bronchi or in the periphery of the lung.
- No known pre-invasive phase
- In the 2015 WHO Classification, SCLC is grouped together with large cell neuroendocrine carcinoma

MORPHOLOGY:

- **Pale grey tumor**
- **Small tumor cells:**
 - Round to fusiform, scant cytoplasm, finely granular chromatin a salt and pepper appearance
 - Cells are twice the size of resting lymphocytes.
- **Frequent mitotic figures**
- **Necrosis invariably present, can be extensive.**

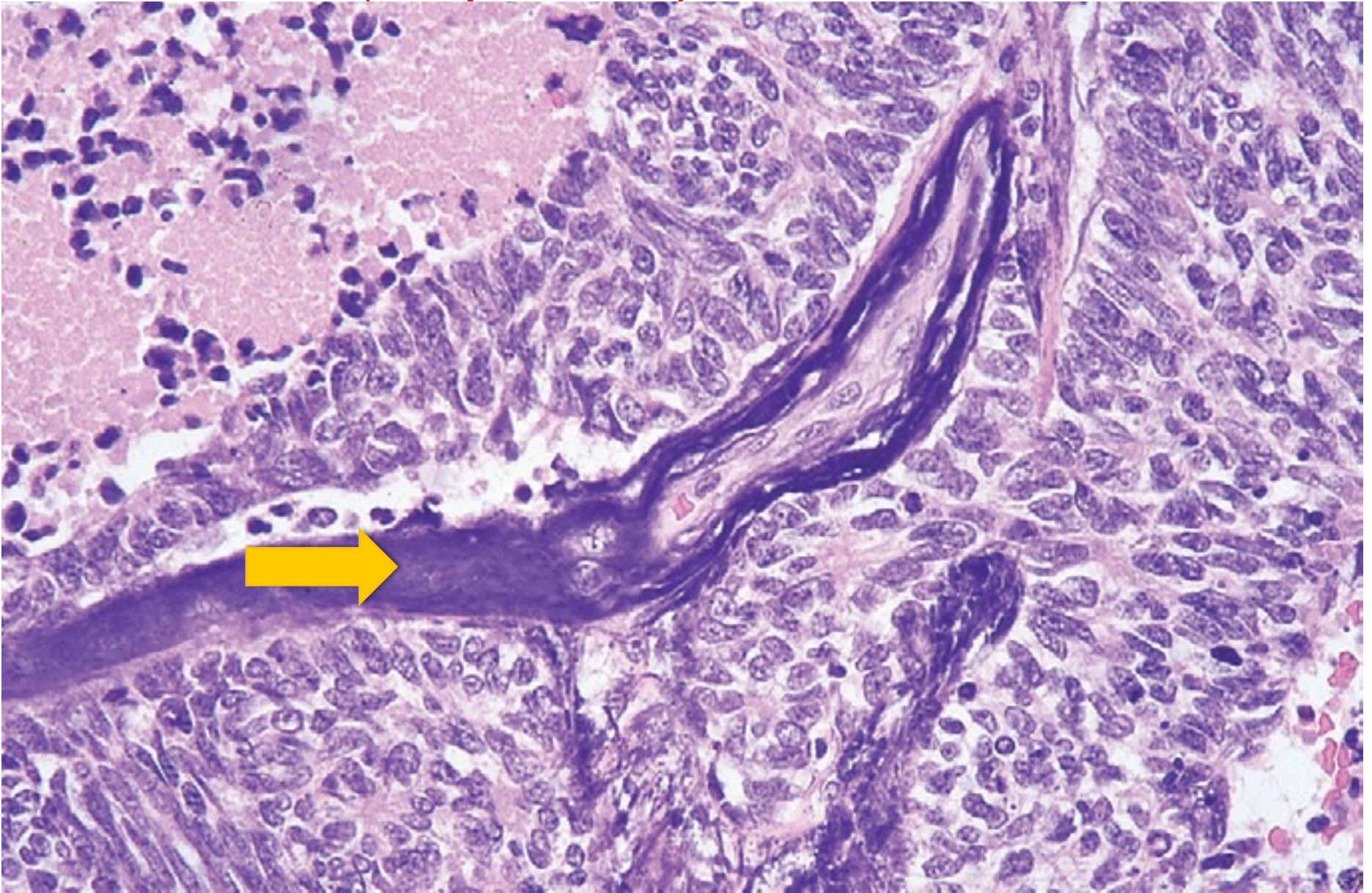


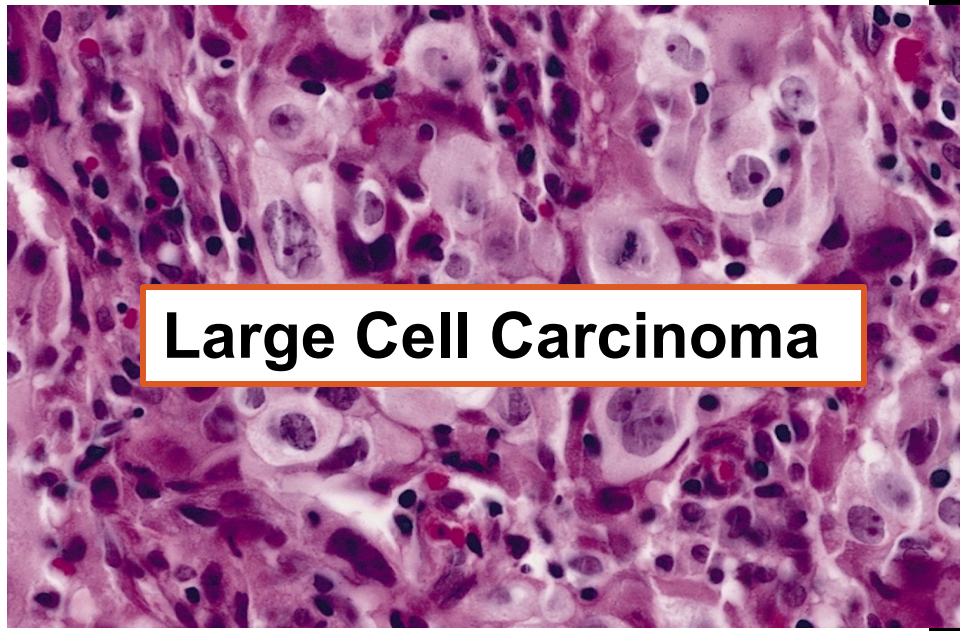
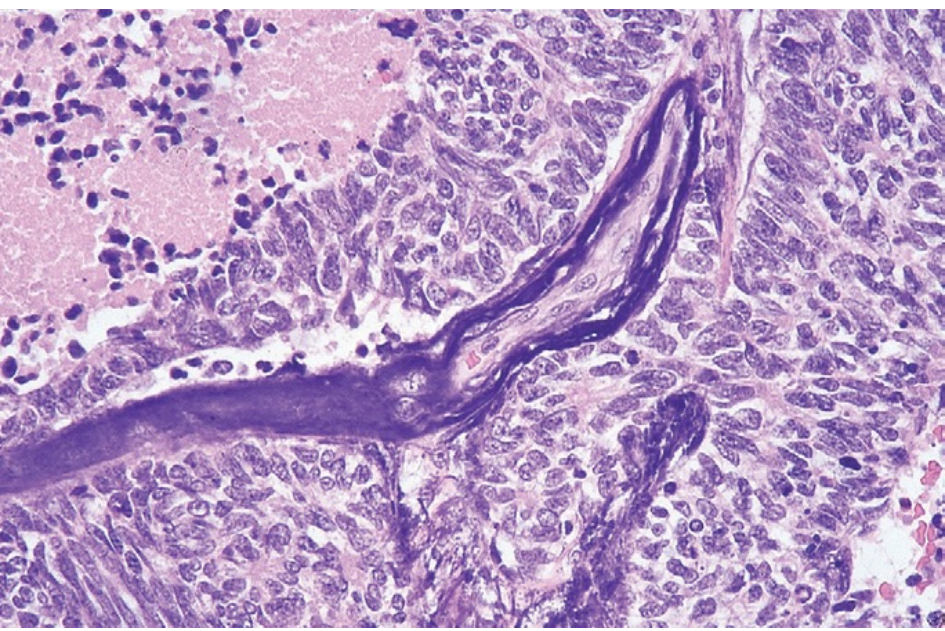
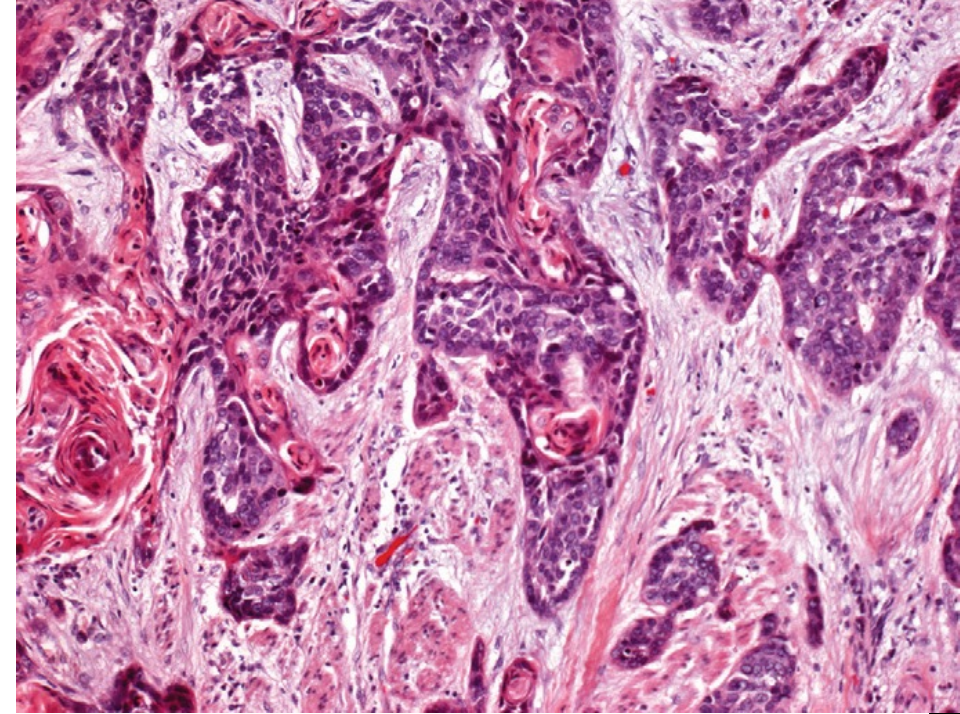
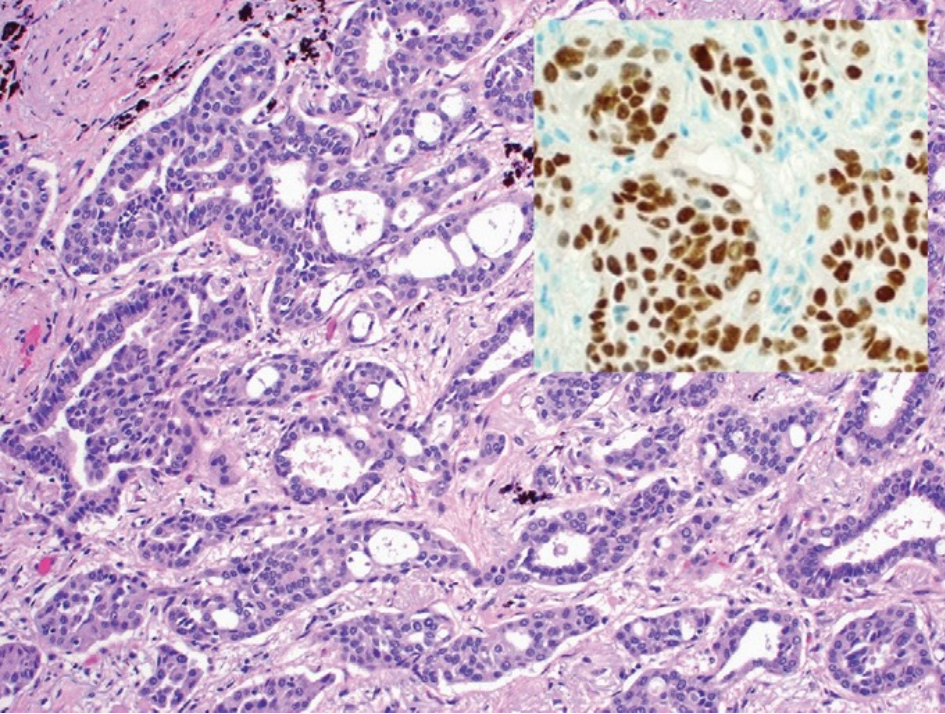


MORPHOLOGY:

- Fragile tumor cells with “**crush artifact**” in small biopsy specimens
- **Nuclear molding** due to close apposition of tumor cells that have scant cytoplasm
- Express **neuroendocrine markers**

basophilic staining of vascular walls due to accumulation of the DNA of necrotic tumor cells (**Azzopardi effect**).

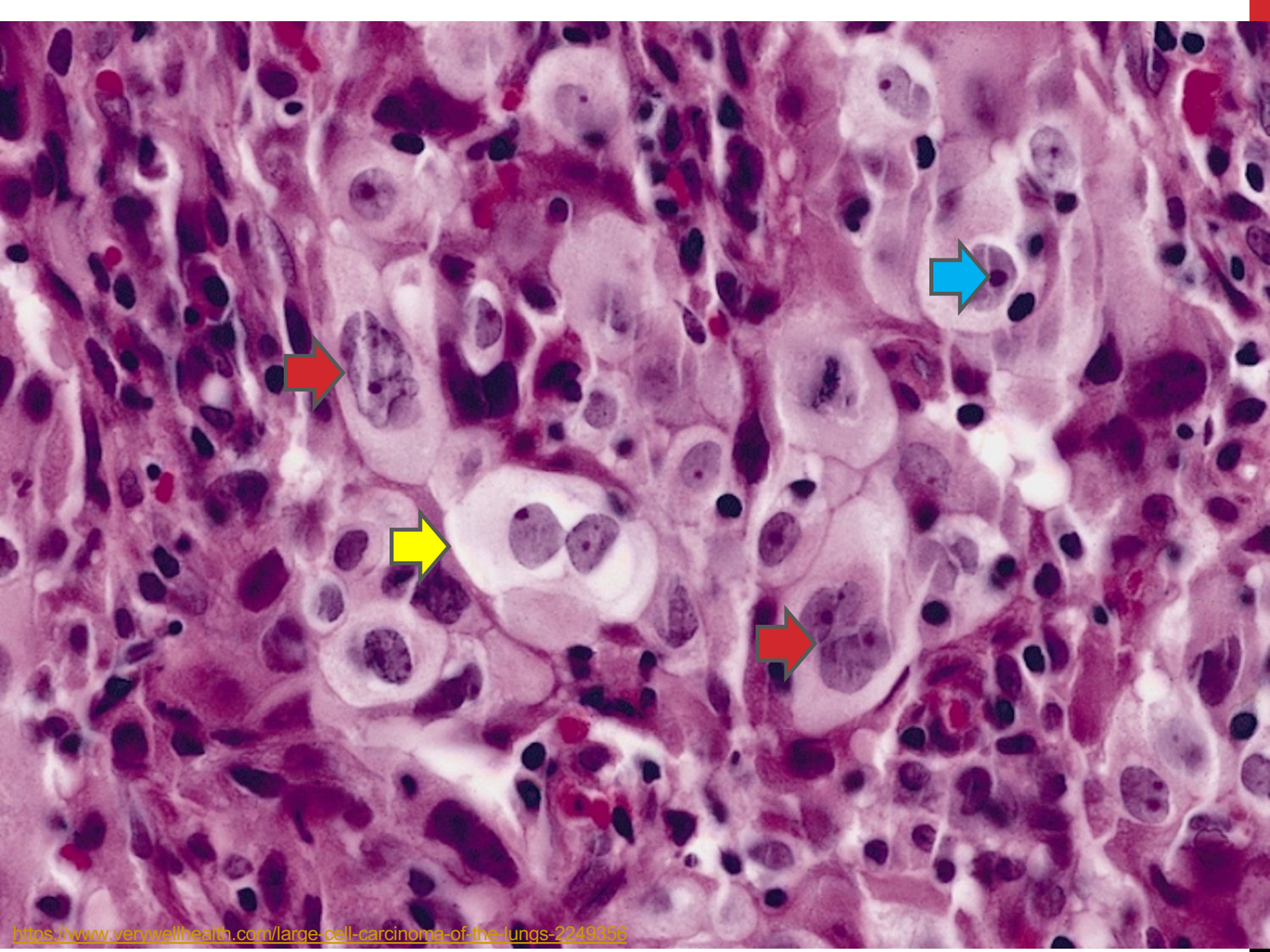




Large Cell Carcinoma

LARGE CELL CARCINOMAS

- Are undifferentiated malignant epithelial tumors.
- Lack cytologic features of small cell carcinoma and have no glandular or squamous differentiation.
- Large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.



Mixed patterns:

- e.g., adenosquamous carcinoma, mixed adenocarcinoma, small cell carcinoma

- **4% to 5% of all lung carcinomas**

THANK YOU!