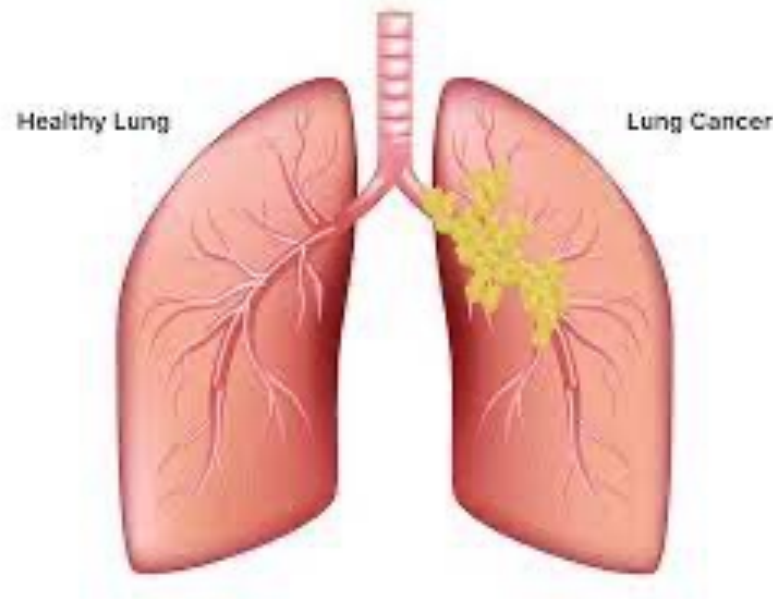
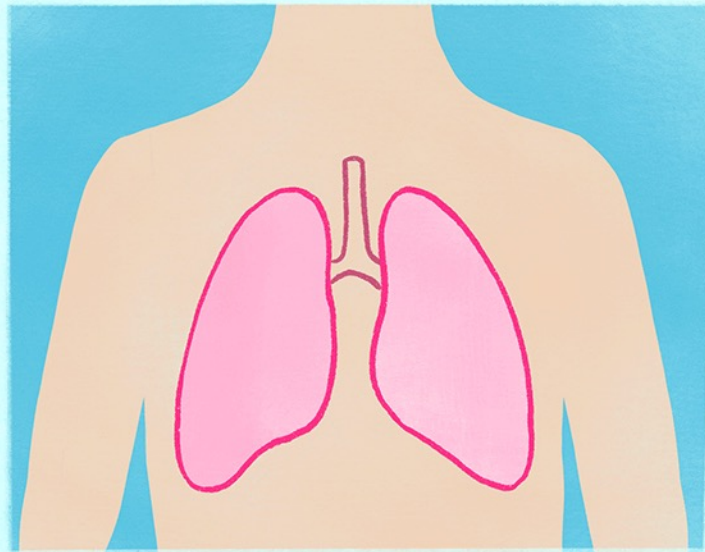


# LUNG TUMORS



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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**

<b>Tumor Classification</b>	
	<b>Adenocarcinoma</b> Lepidic, acinar, micropapillary, papillary, solid (according to predominant pattern) Invasive mucinous adenocarcinoma Minimally invasive adenocarcinoma (nonmucinous, mucinous)
	<b>Squamous cell carcinoma</b> Keratinizing, nonkeratinizing, basaloid
	<b>Neuroendocrine tumors</b> Small cell carcinoma Combined small cell carcinoma Large cell neuroendocrine carcinoma Combined large-cell neuroendocrine carcinoma Carcinoid tumor Typical, atypical
	<b>Other uncommon types</b> 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→

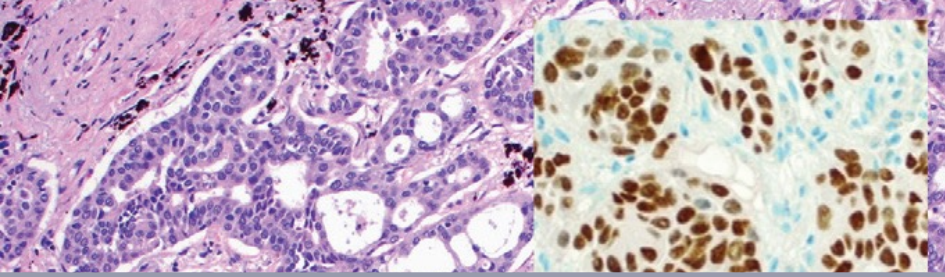
Because the mutagenic effect of carcinogens in smoke is modified by genetic variants

# ENVIRONMENTAL CARCINOGENS:

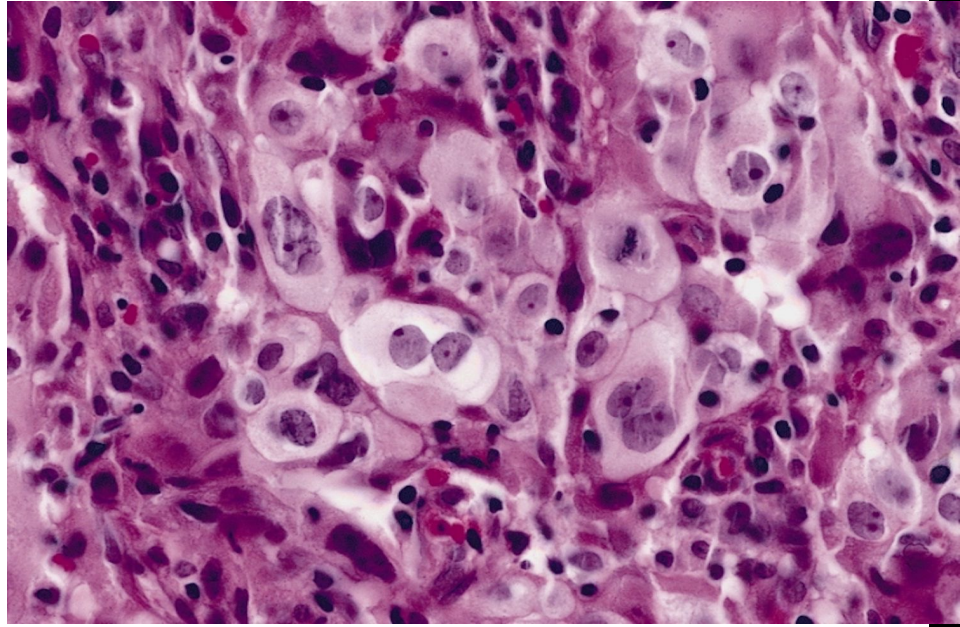
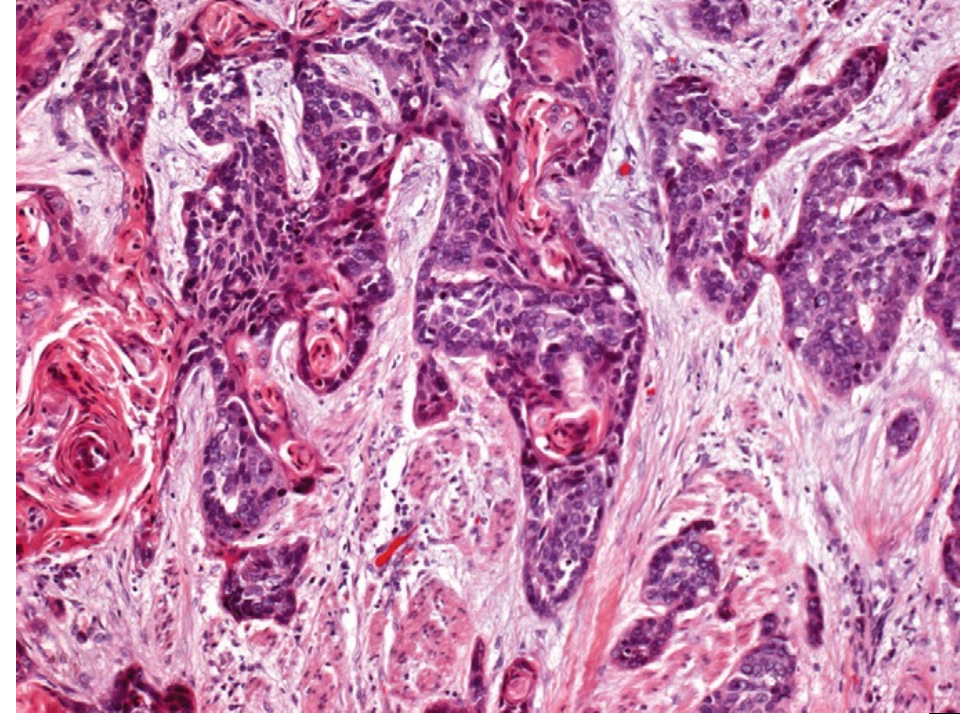
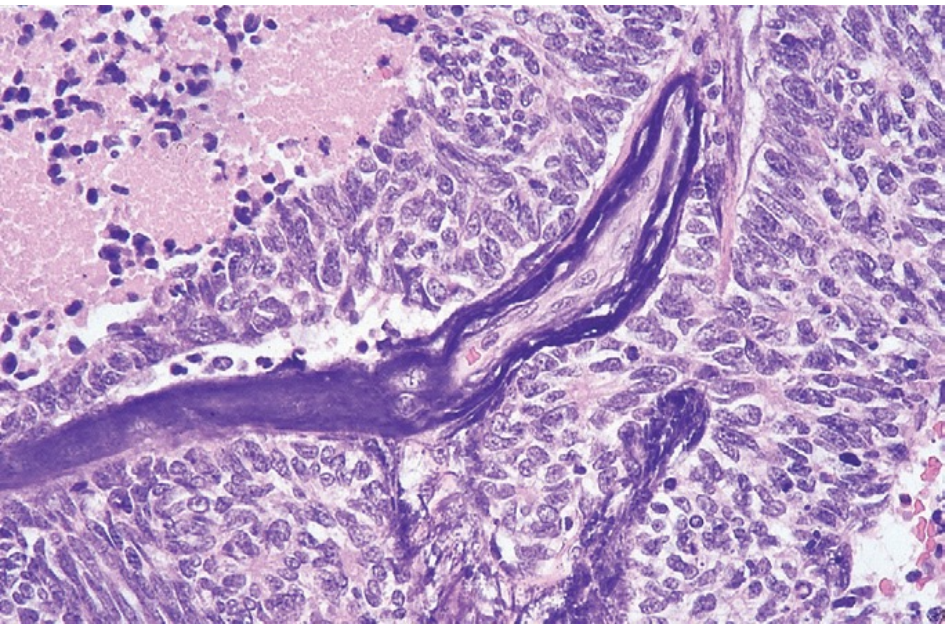
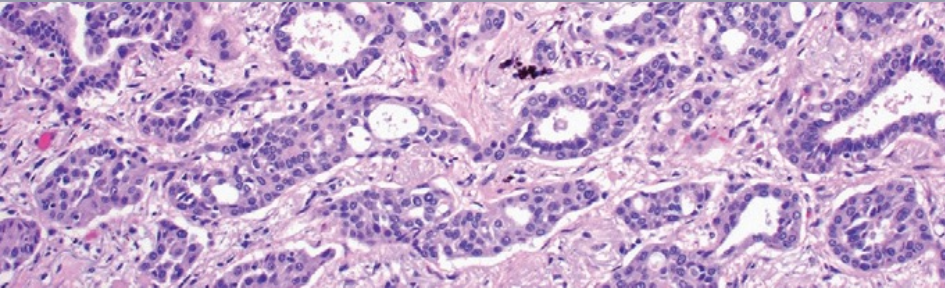
- **Occupational exposures** to some environmental carcinogens may sometimes be responsible for lung cancer **all by themselves**, e.g:
  - **uranium mines**
  - work with **asbestos**
  - inhalation of dusts containing **arsenic, chromium, nickel, or vinyl chloride.**

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





# Adenocarcinoma

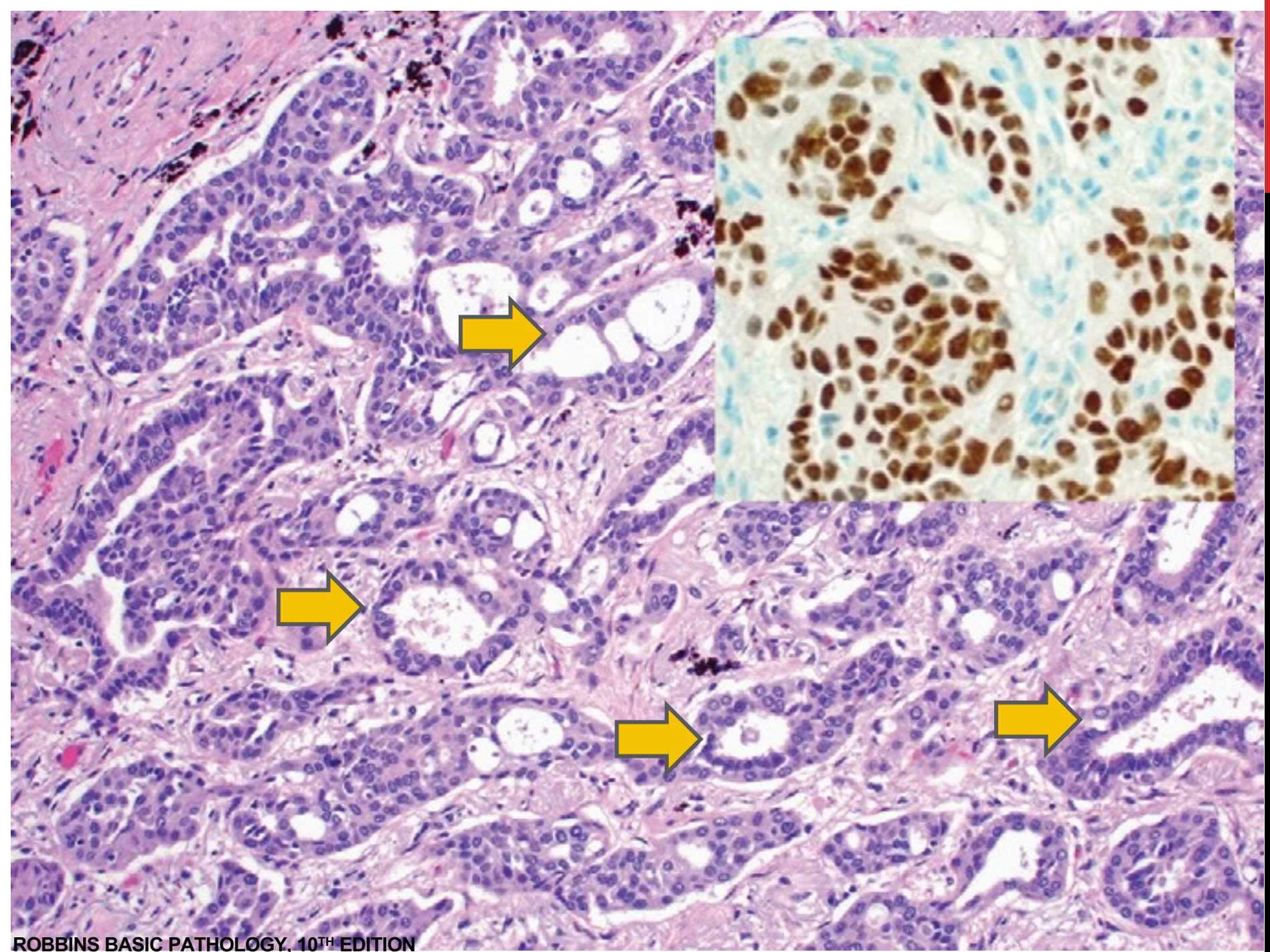


<https://www.verywellhealth.com/large-cell-carcinoma-of-the-lungs-2249356>

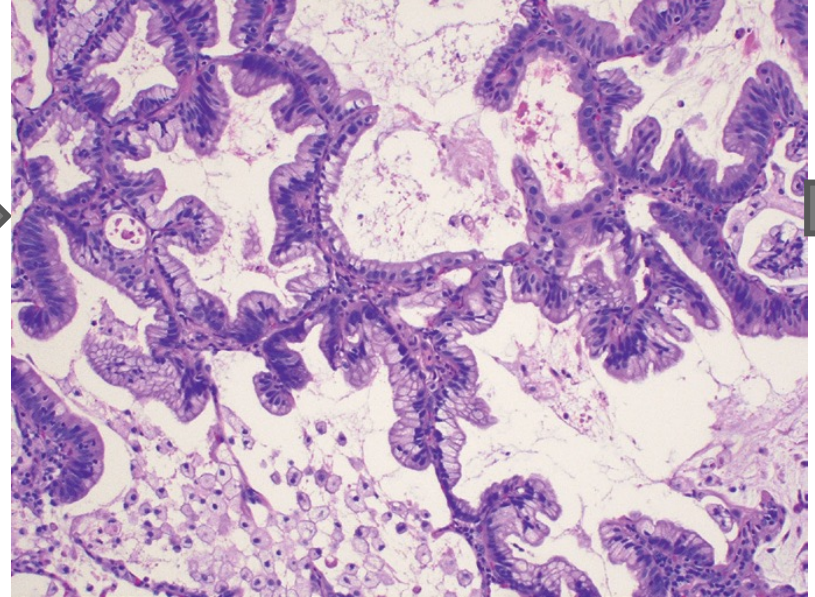
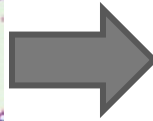
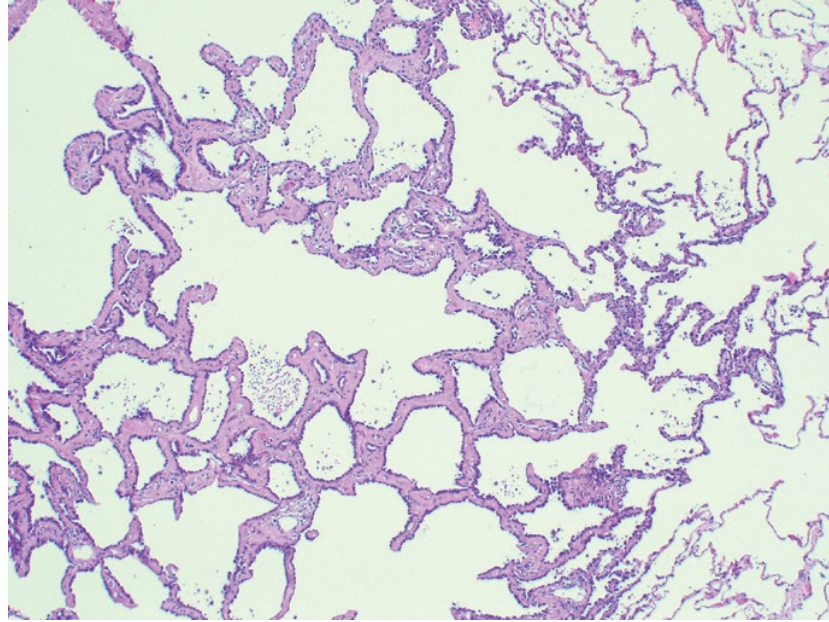


# ADENOCARCINOMA:

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

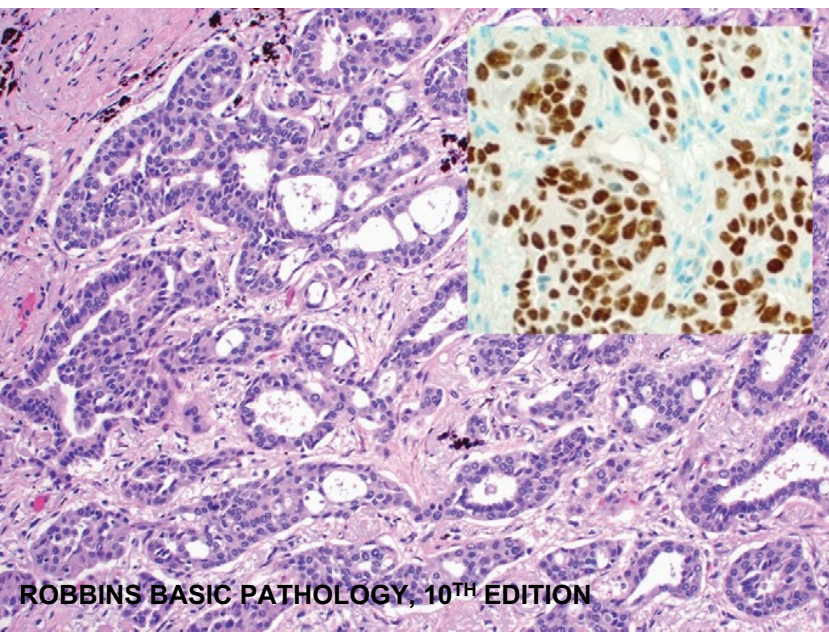






**atypical adenomatous hyperplasia (AAH)**

**adenocarcinoma in situ (AIS)**

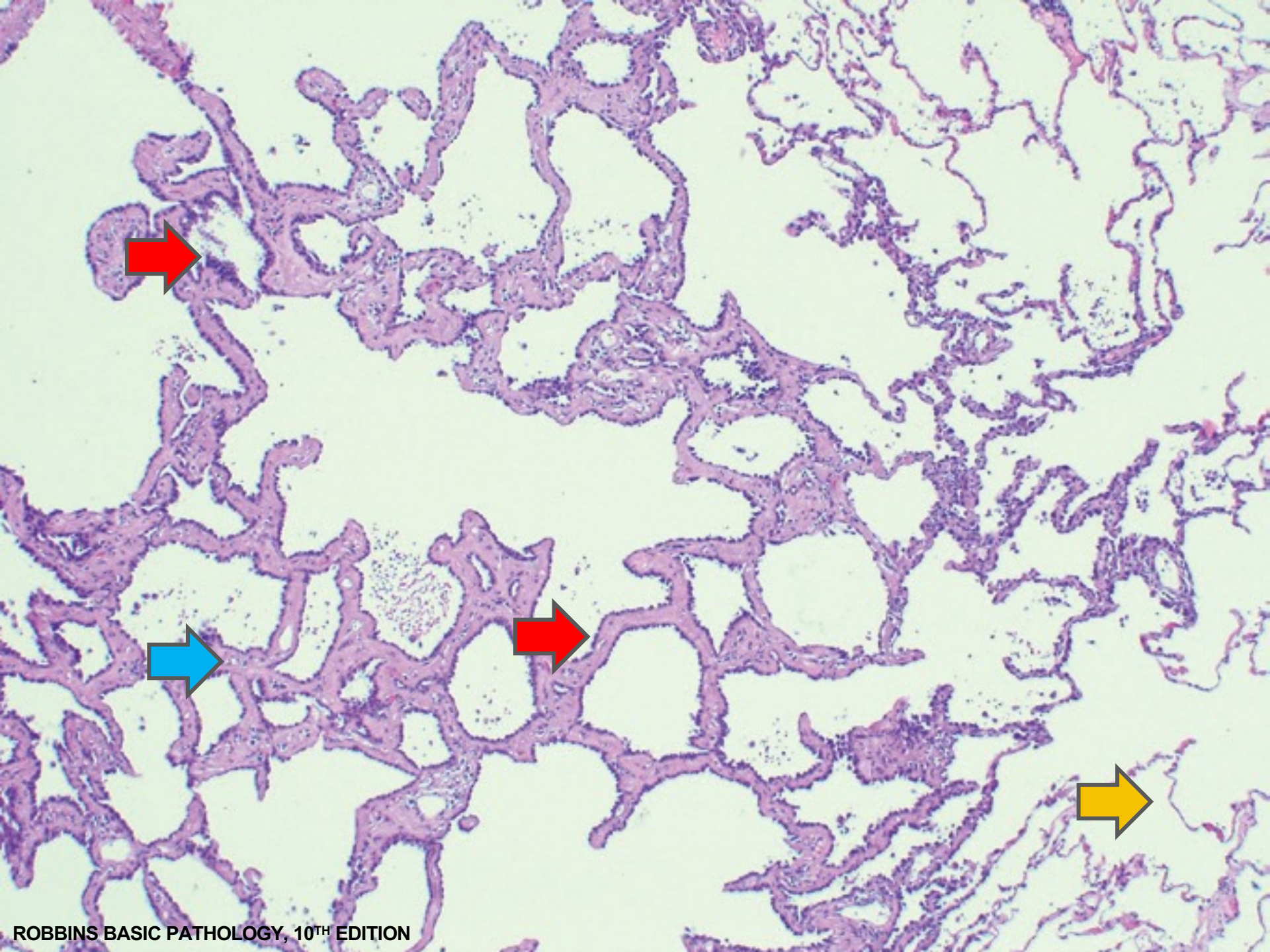


**Adenocarcinoma,  
minimally invasive or invasive**

# Atypical adenomatous hyperplasia:

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

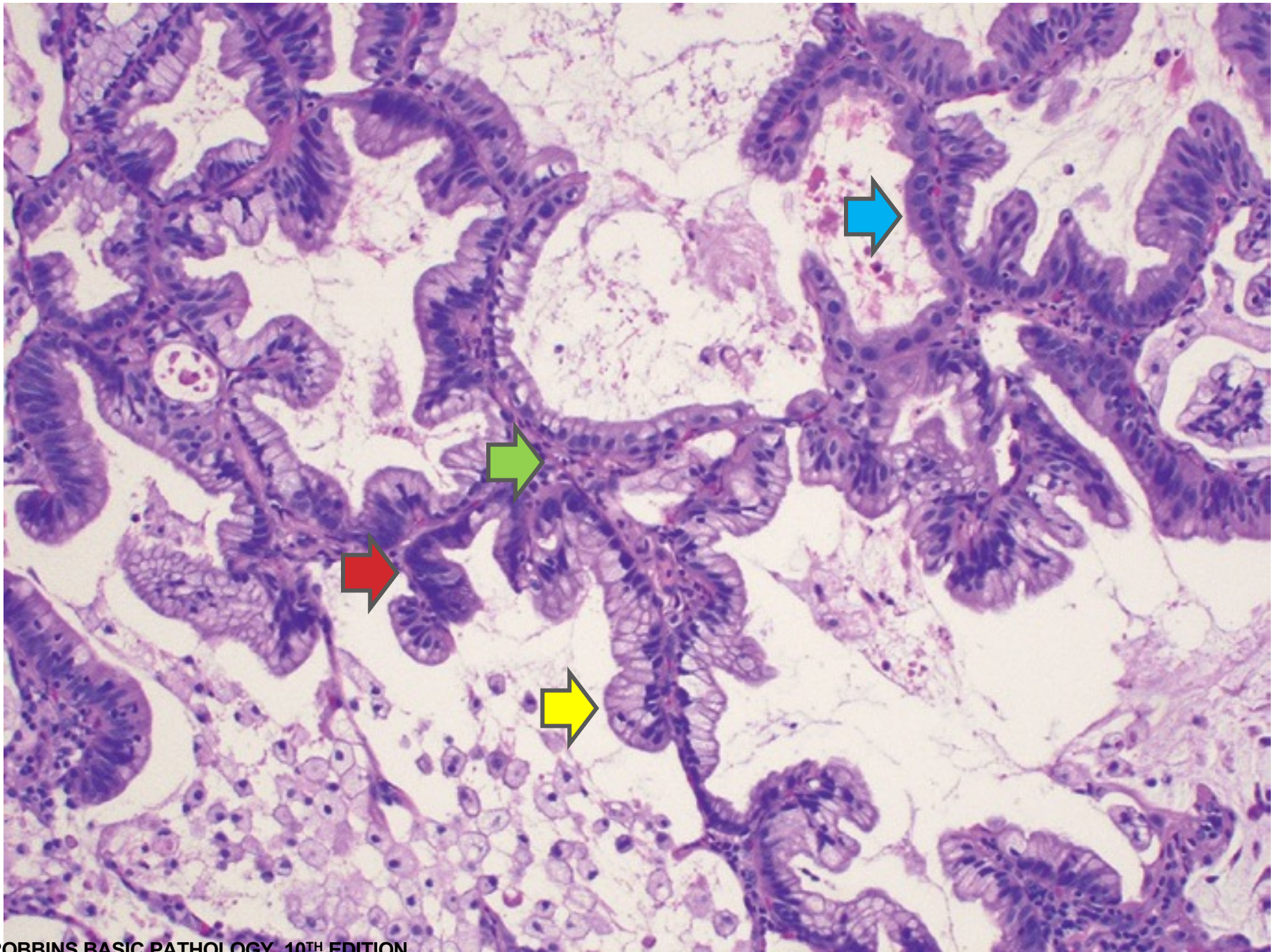




# Adenocarcinoma in situ (AIS):

- 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**





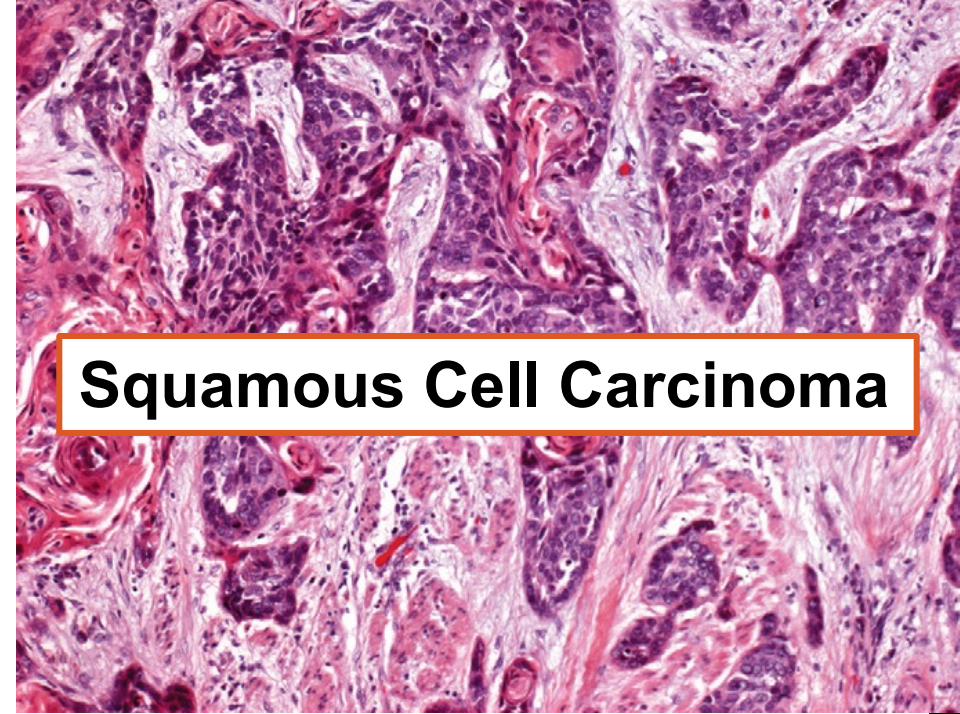
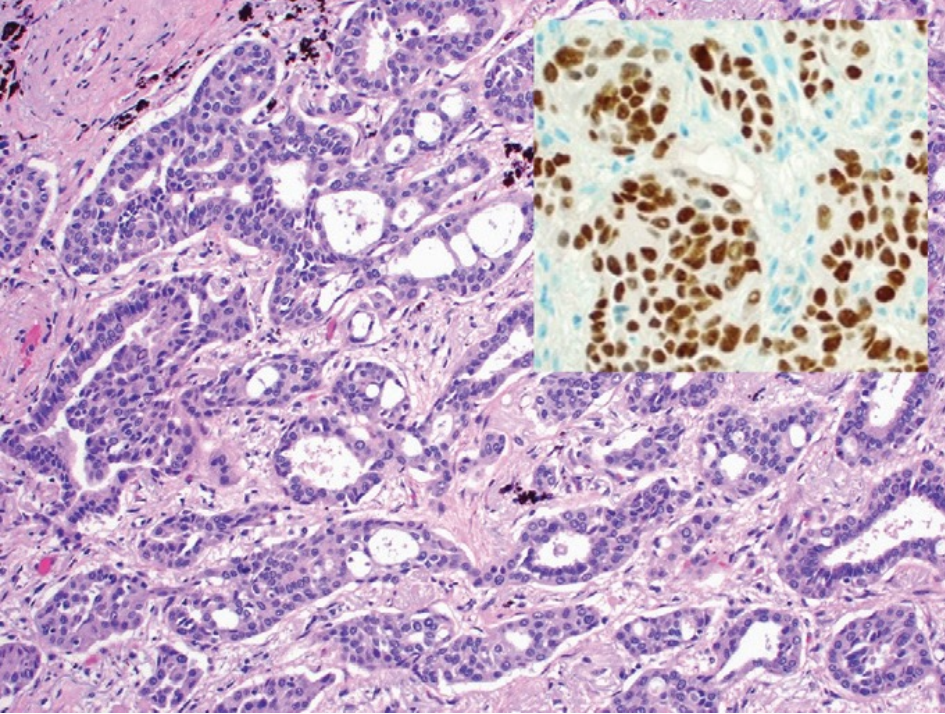
- **microinvasive adenocarcinoma:**

Tumors ( $\leq 3$  cm) with a small invasive component ( $\leq 5$  mm)

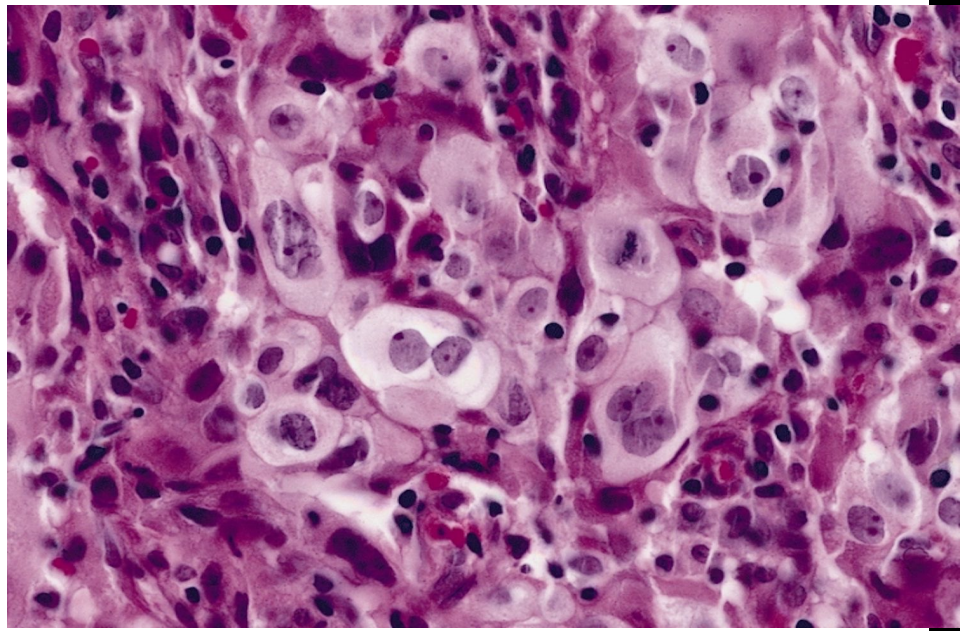
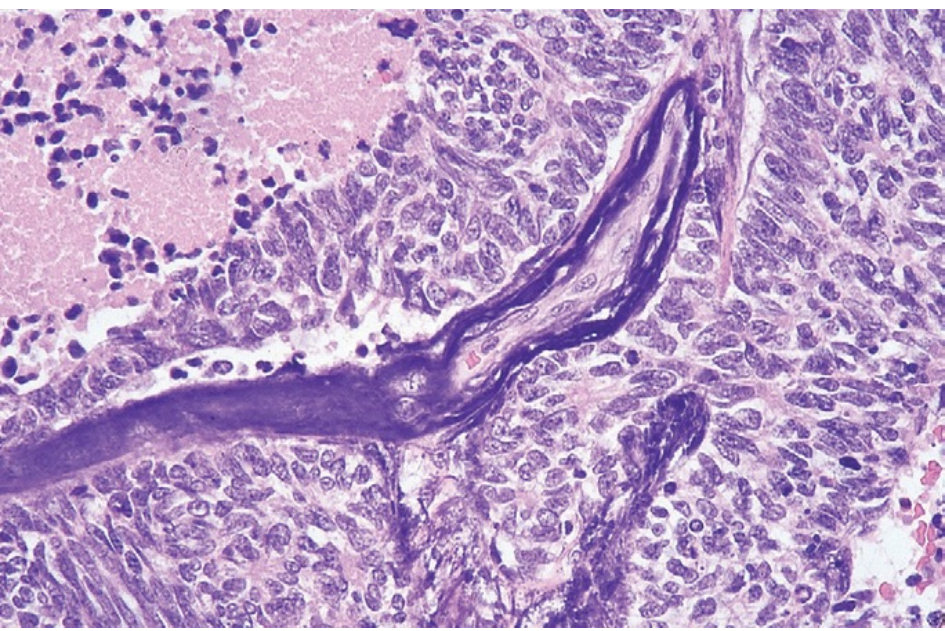
- **Invasive adenocarcinoma:**

- 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

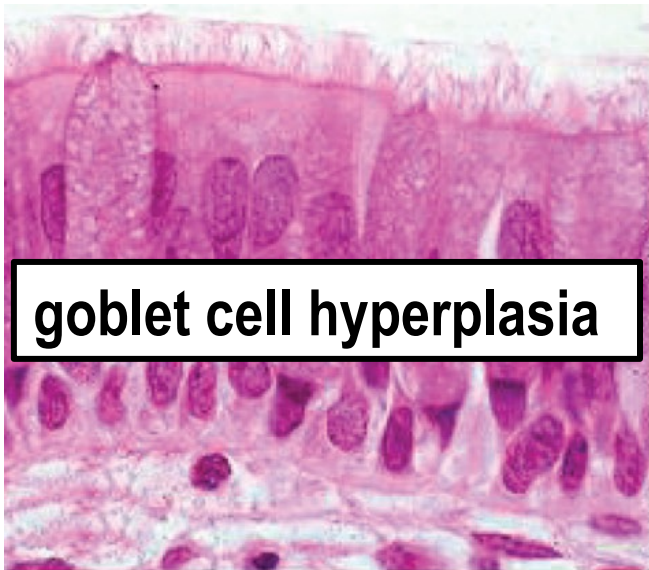
- More common in **men**
- Closely correlated with **smoking history**
- Arise **Centrally in major bronchi** and eventually spread to local hilar nodes and outside the thorax
- Large lesions may undergo **central necrosis**, giving rise to **cavitation**.

- **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.

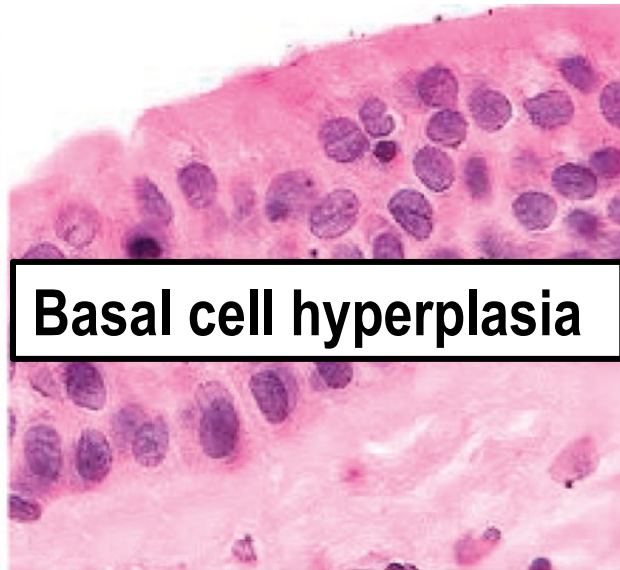
# MORPHOLOGY:

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**



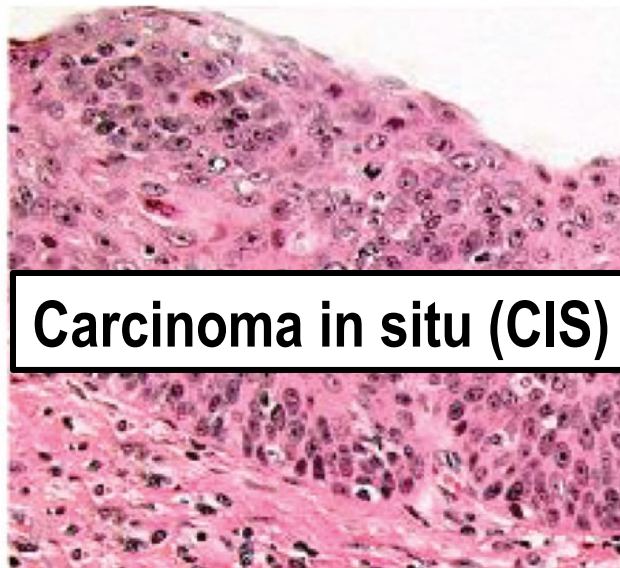
**Basal cell hyperplasia**



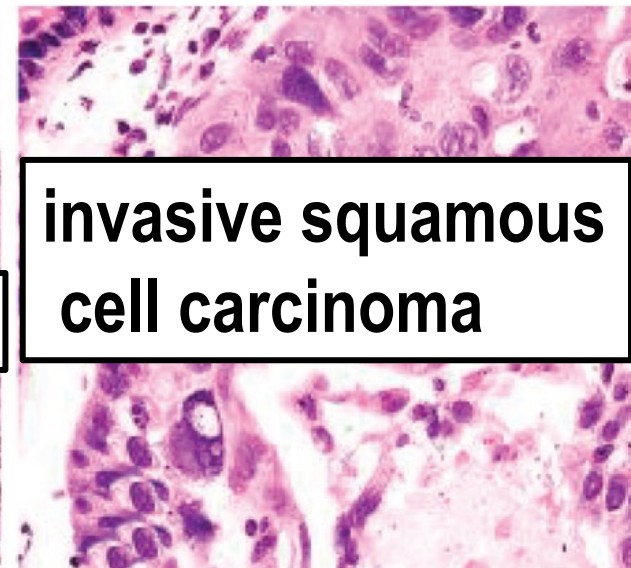
**Squamous metaplasia**



**Squamous dysplasia**



**Carcinoma in situ (CIS)**



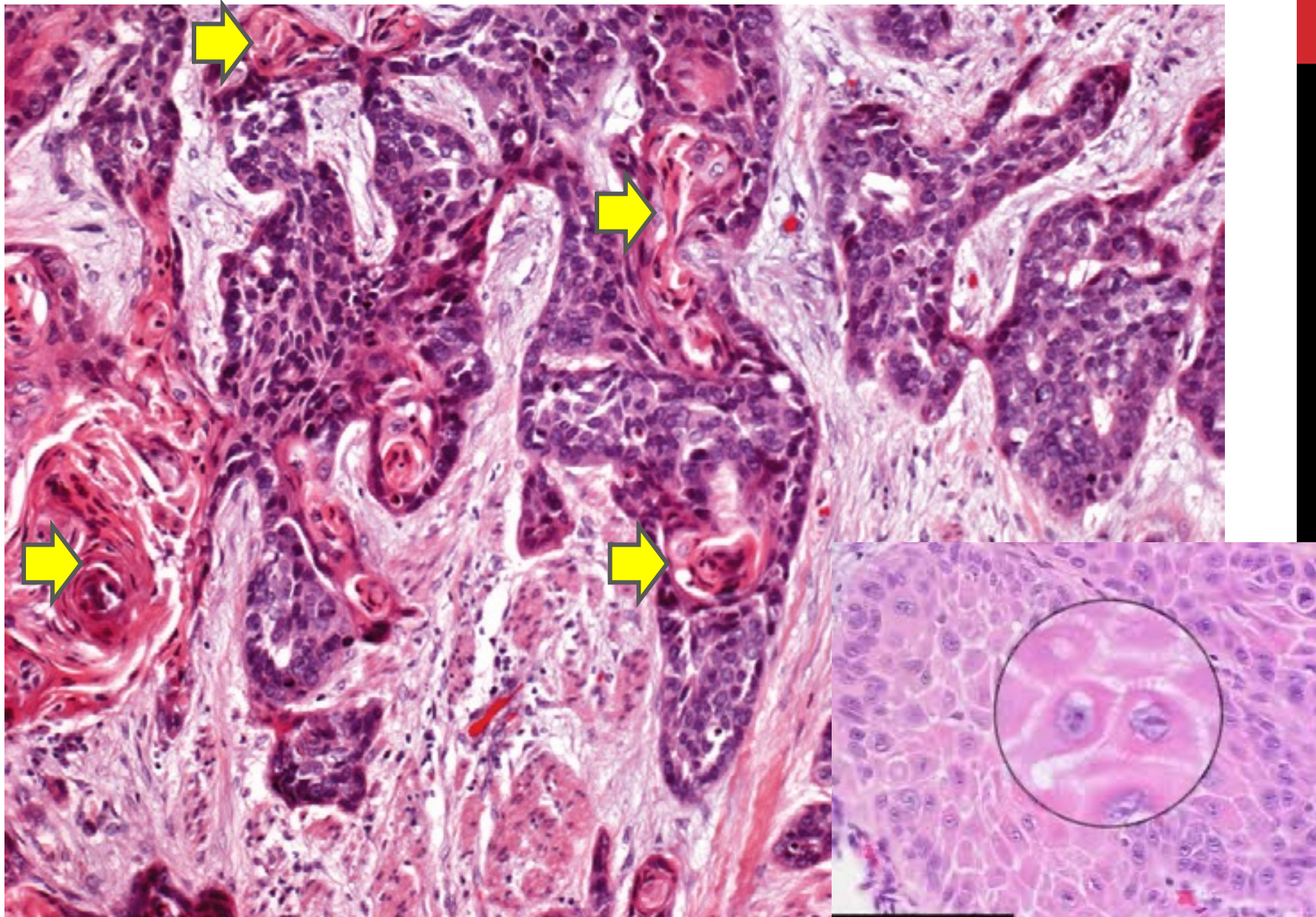
**invasive squamous cell carcinoma**



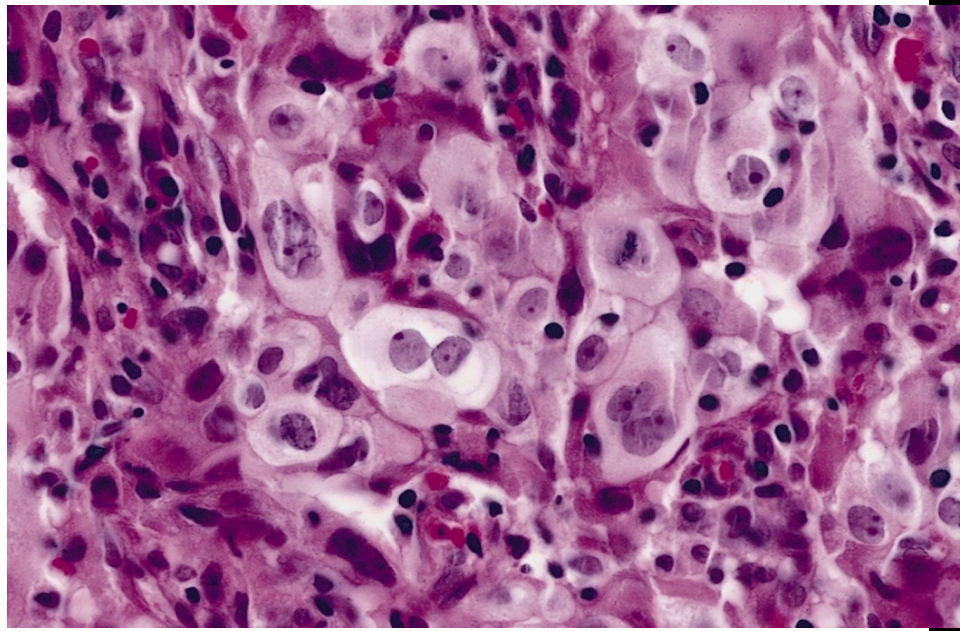
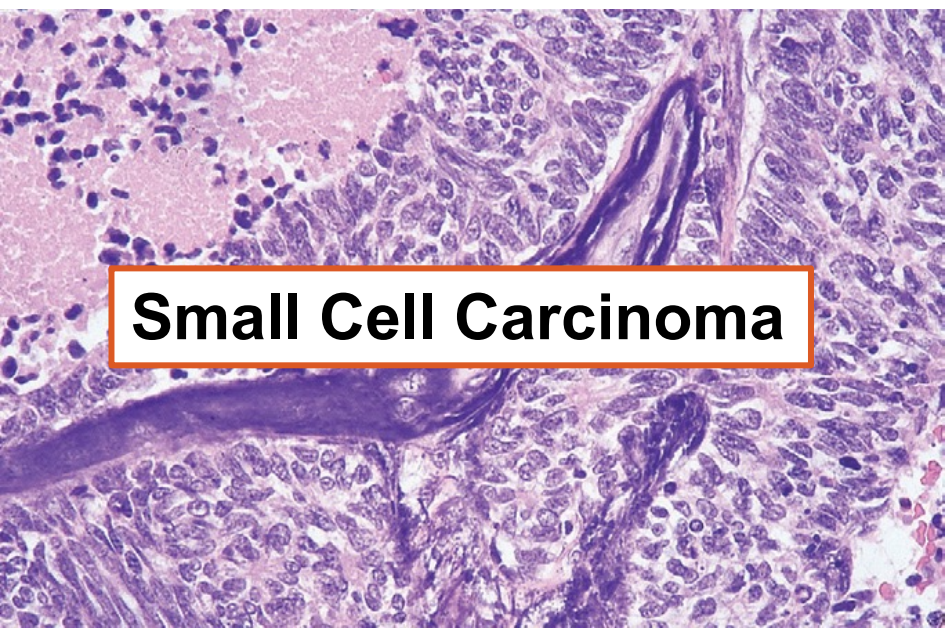
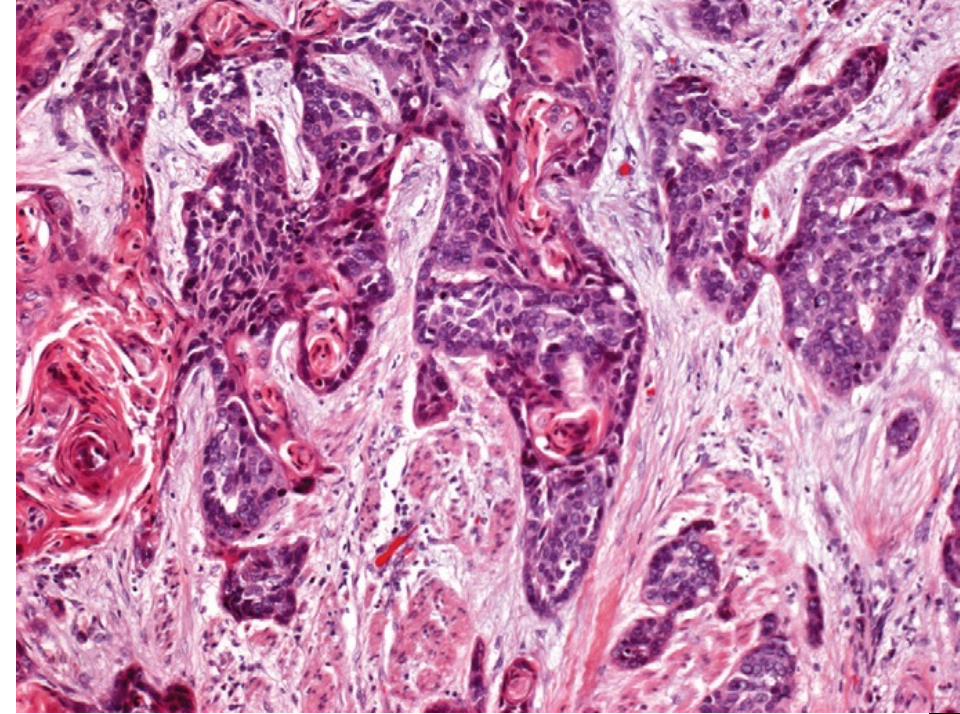
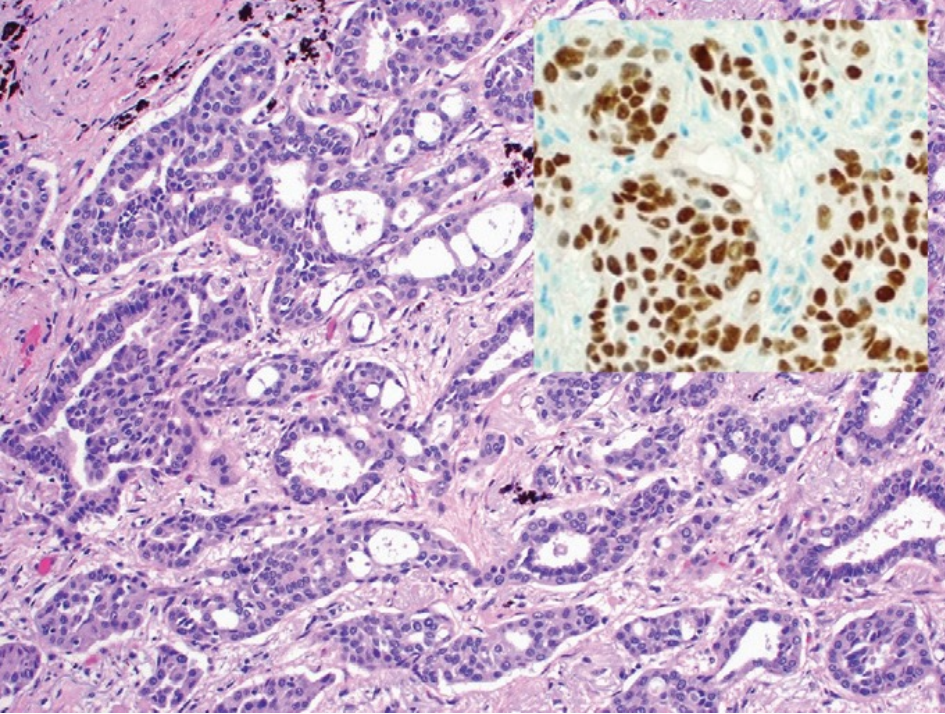




# WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA SHOWING KERATINIZATION AND PEARLS.







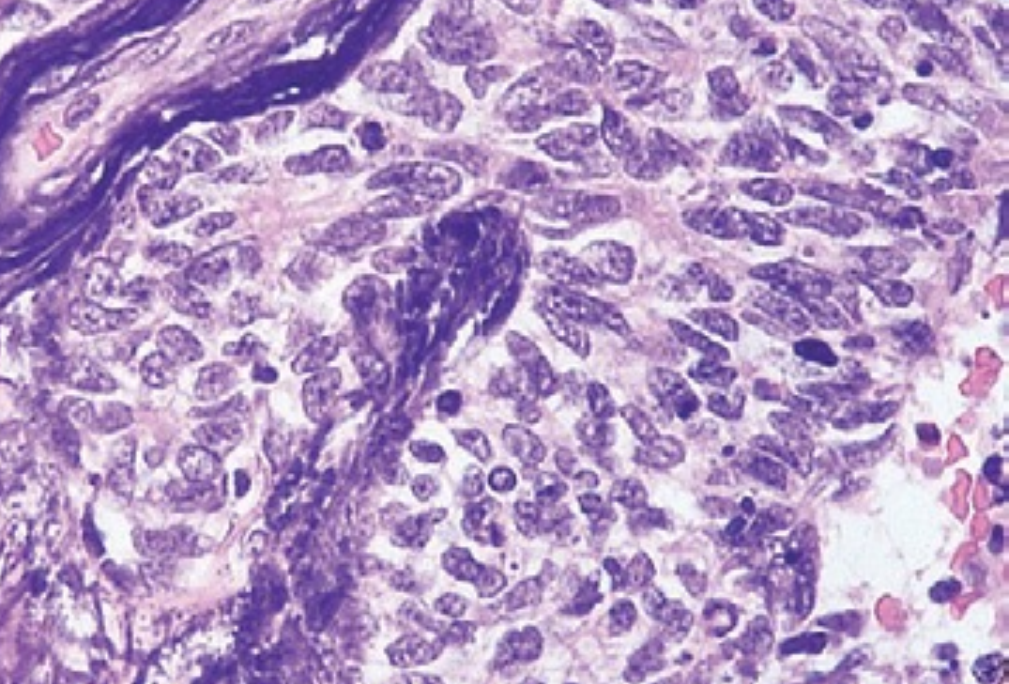
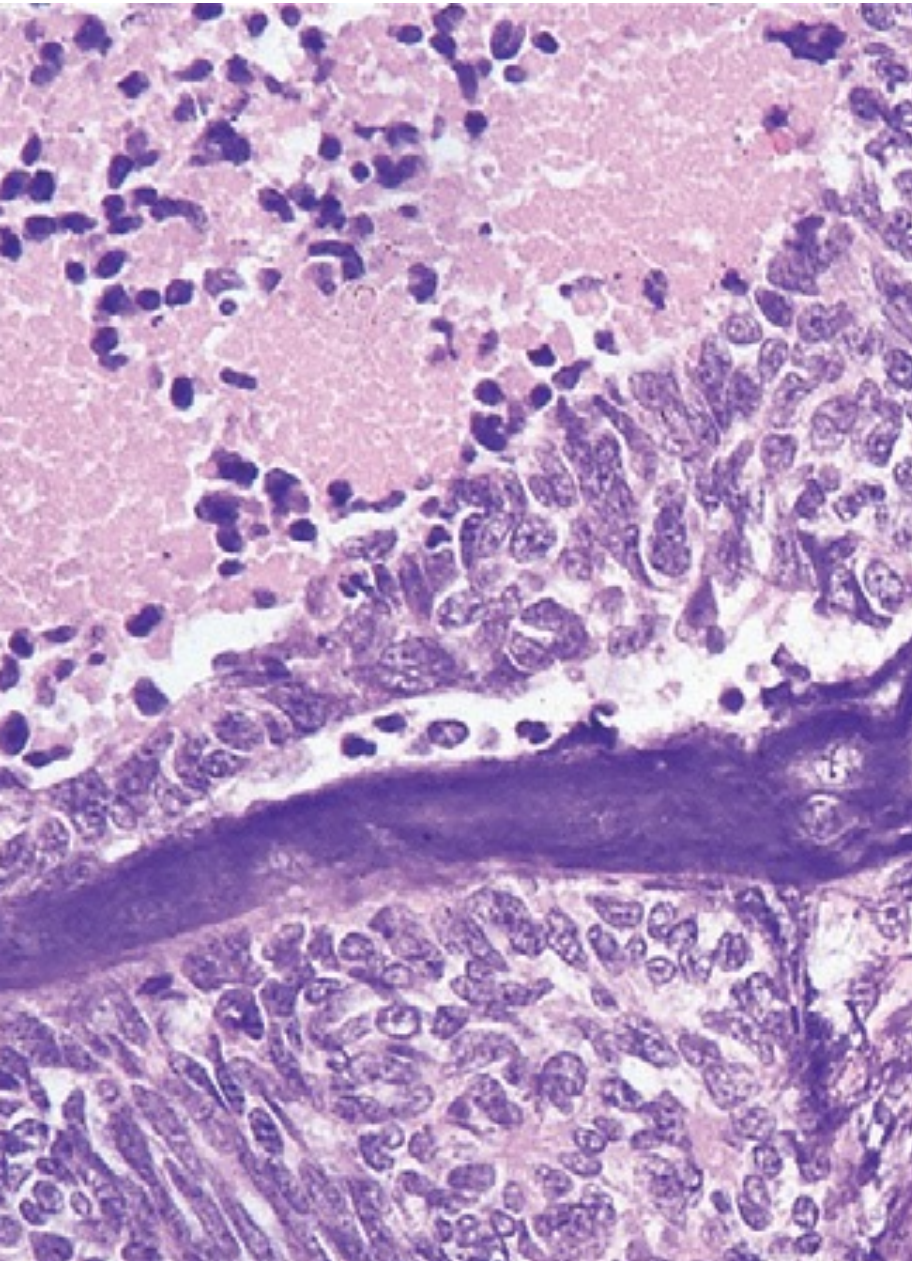
**Small Cell Carcinoma**



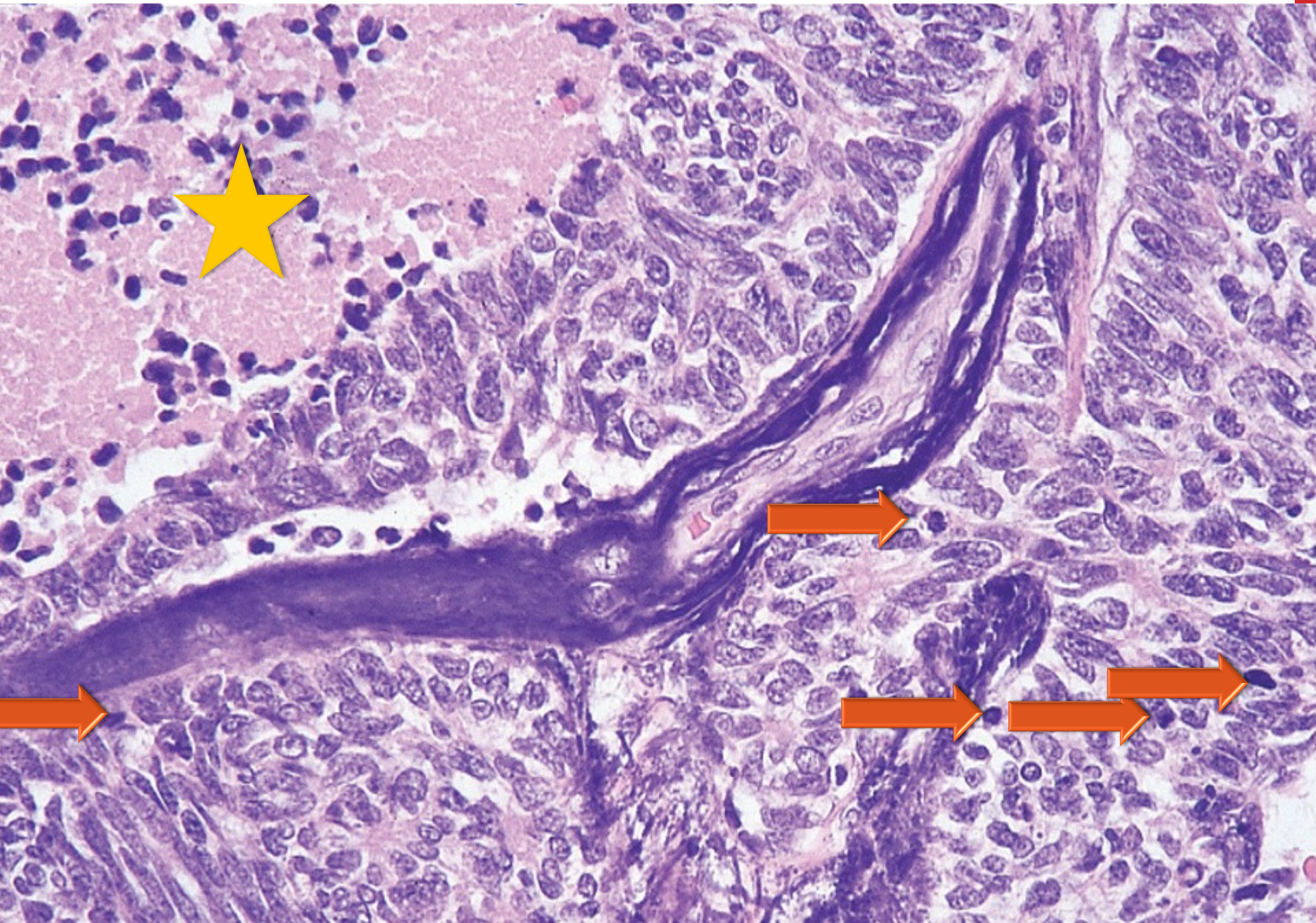
# SMALL CELL LUNG CARCINOMAS (SCLC)

- **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







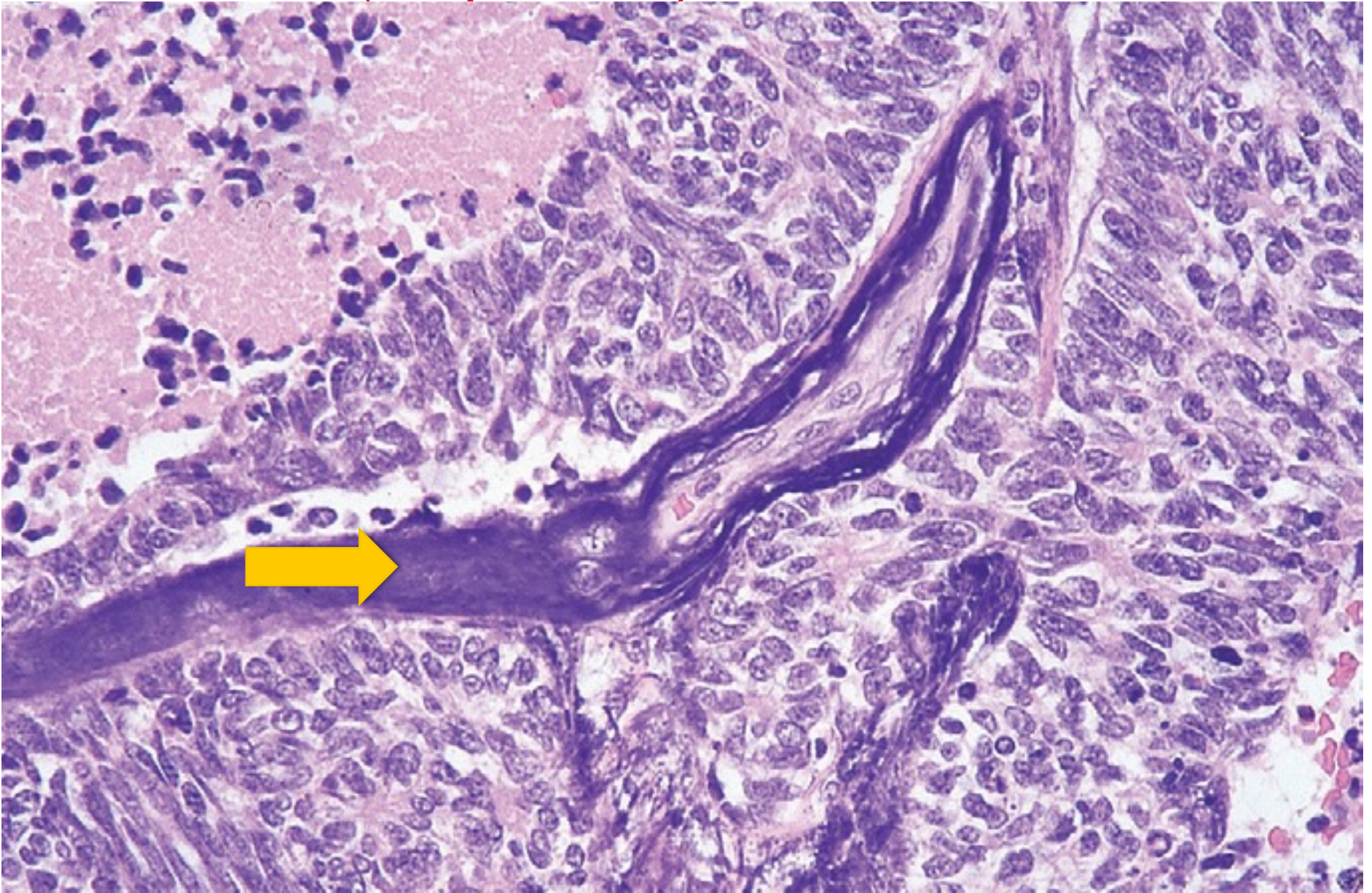


# MORPHOLOGY:

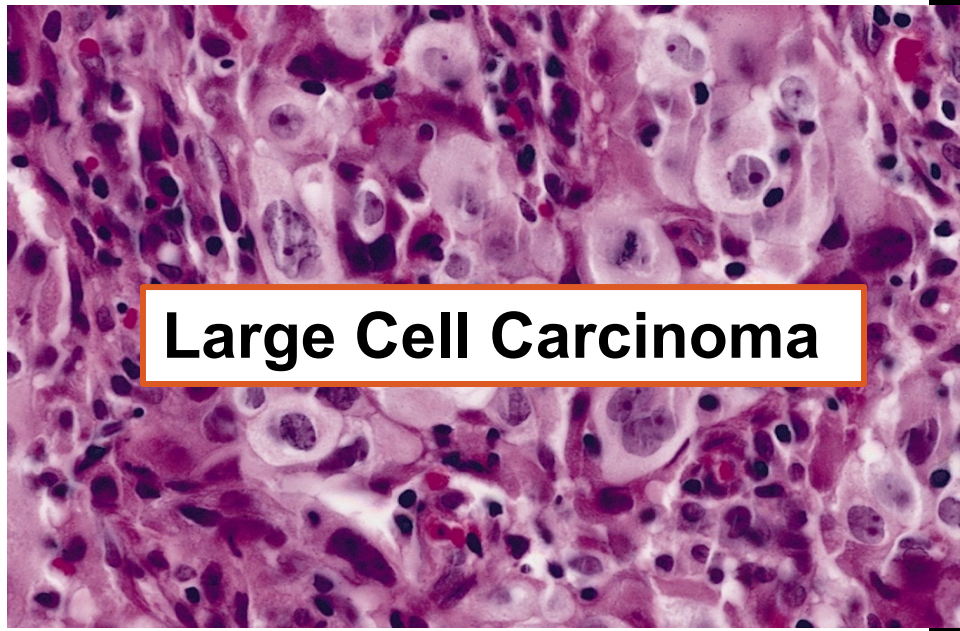
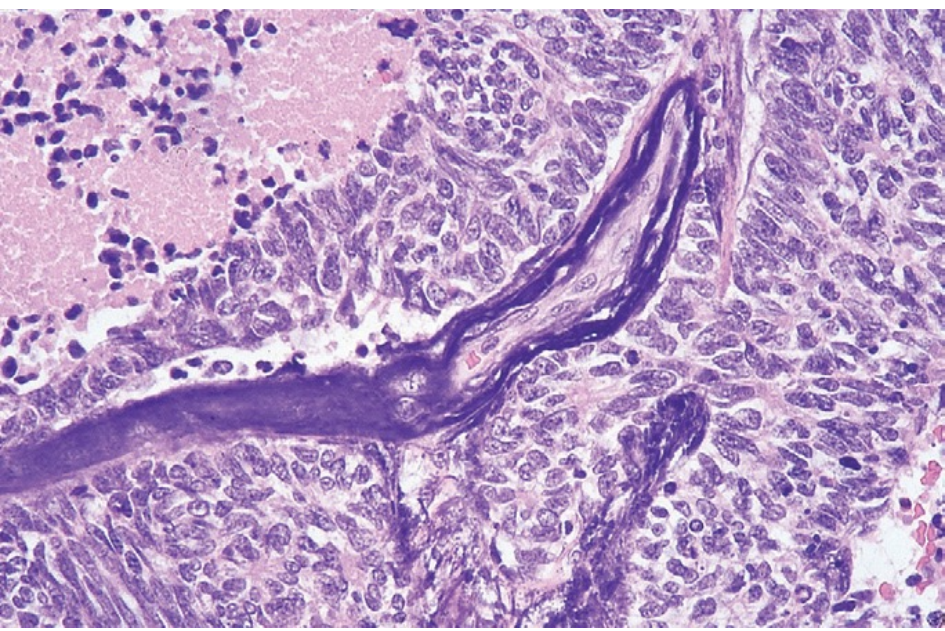
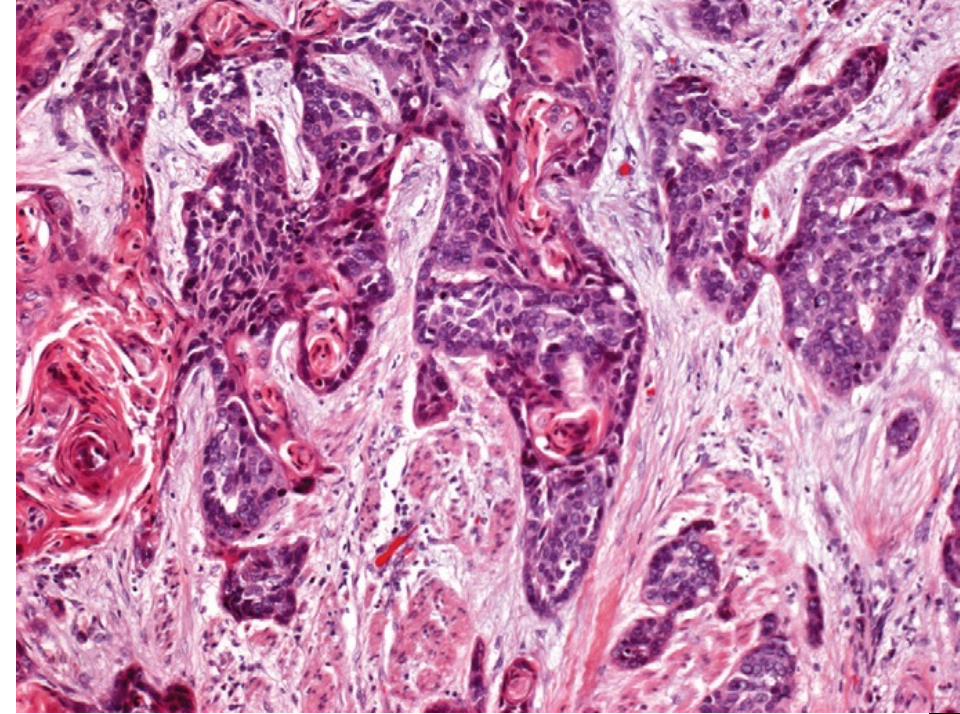
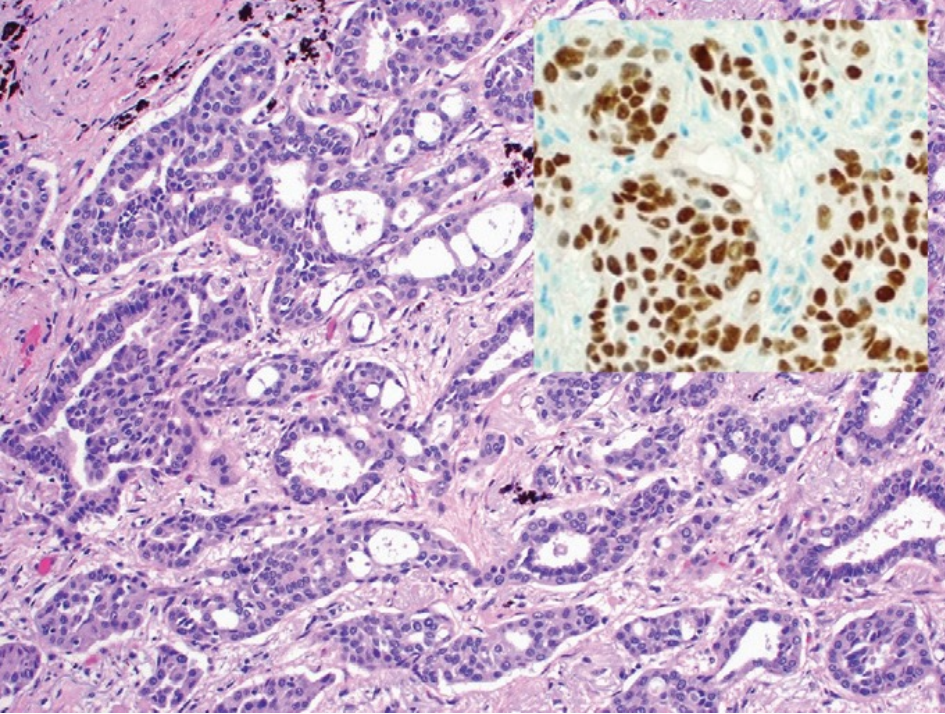
- Fragile tumor cells with “**crush artifact**” in small biopsy specimens
- **Nuclear molding** due to close apposition of tumor cells that have scant cytoplasm
- Express **neuroendocrine markers**



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



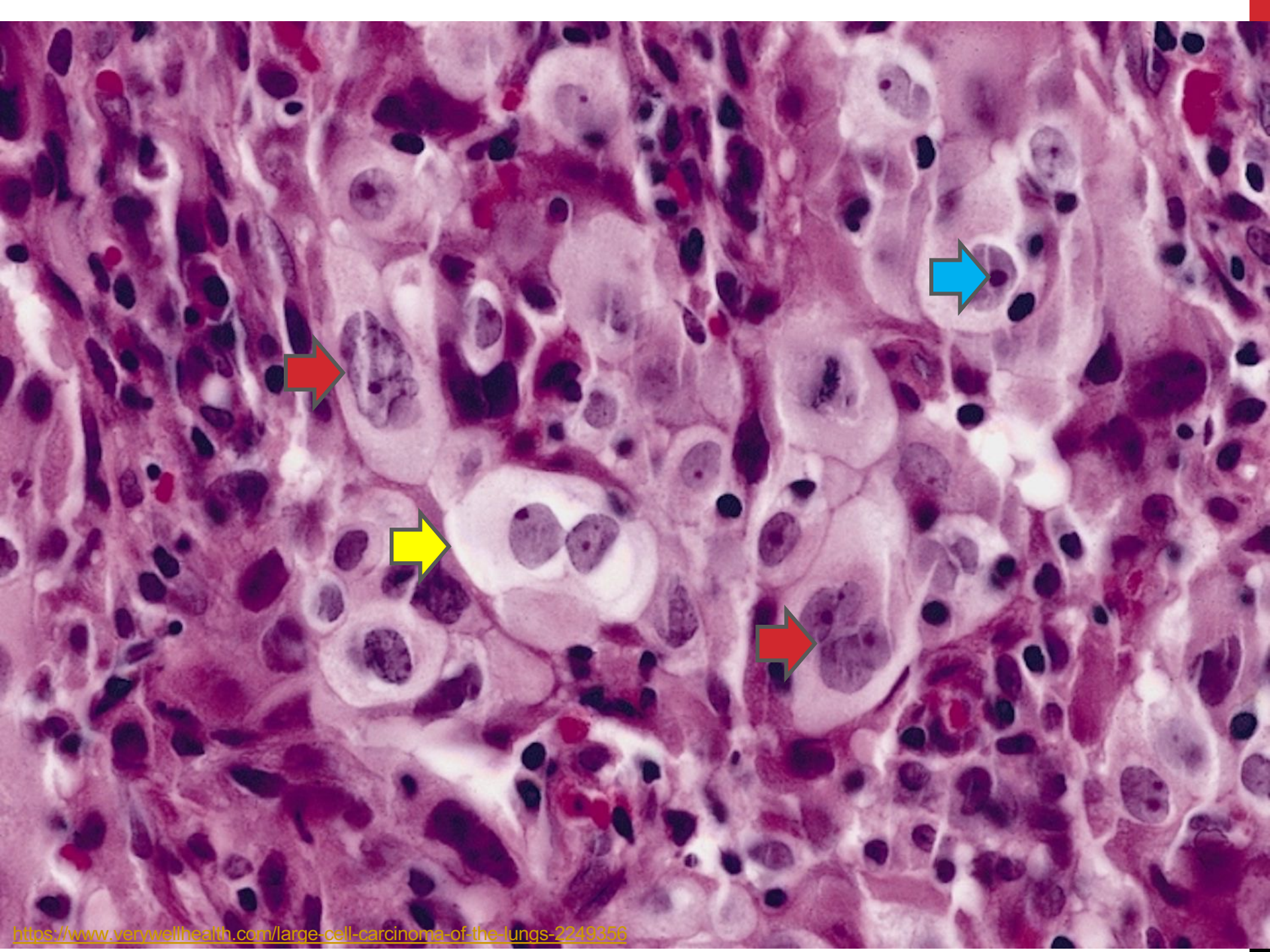






# LARGE CELL CARCINOMAS

- 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!**