

# Respiratory system Pathology- Lung tumors

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# 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

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**95%** of primary lung tumors are **carcinomas**

# HAMARTOMA

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- The most common benign tumor
- It's clonal, so the name hamartoma is a misnomer
- Gross: spherical, small (1 to 4 cm), discrete
- CXR: coin lesion.
- Microscopic: mature cartilage, fat, fibrous tissue, and blood vessels.

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# CARCINOMA OF THE LUNG

- The most important cause of cancer-related deaths in industrialized countries
- The incidence among males is gradually decreasing, but it continues to increase among females BECAUSE the incidence of smoking in women increased markedly over the past half century.

- **peak incidence at 50s & 60s.**
- **At diagnosis:**
  - >50% of pts have distant metastases
  - ¼ have disease in the regional LNs.
- **The prognosis is dismal:**
  - the 5-year survival rate for all stages of lung cancer combined is about 16%
  - Prognosis has not changed over the last 35 yrs; even with disease localized to the lung, the 5-year survival rate is only 45%.

## THE FOUR MAJOR HISTOLOGIC TYPES OF CARCINOMAS OF THE LUNG

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- adenocarcinoma
- squamous cell carcinoma
- small cell carcinoma (a subtype of neuroendocrine carcinoma)
- large cell carcinoma

## Table 13.6 Histologic Classification of Malignant Epithelial Lung Tumors (2015 WHO Classification, Simplified Version)

- ➔ Adenocarcinoma
  - Acinar, papillary, micropapillary, solid, lepidic predominant, mucinous subtypes
- ➔ Squamous cell carcinoma
- ➔ Large cell carcinoma
- Neuroendocrine carcinoma
  - ➔ Small cell carcinoma
  - Large cell neuroendocrine carcinoma
  - Carcinoid tumor
- Mixed carcinomas
  - Adenosquamous carcinoma
  - Combined small cell carcinoma
- Other unusual morphologic variants
  - Sarcomatoid carcinoma
  - Spindle cell carcinoma
  - Giant cell carcinoma

- Squamous cell and small cell carcinomas have the strongest association with smoking
- adenocarcinoma has replaced squamous cell carcinoma as the most common primary lung tumor in recent yrs, because of changes in smoking patterns in US.
- Adenocarcinomas is the most common primary tumors arising in 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.

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# 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 possessing all of the hallmarks of cancer

**Genetic abnormalities**

**carcinogens**

# GENETIC ABNORMALITIES:

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- 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)

# CARCINOGENS:

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

# CIGARETTE SMOKING

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- 90% 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 among 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.
- 11% of heavy smokers develop lung cancer
- Not all individuals exposed to tobacco smoke develop cancer because the mutagenic effect of carcinogens is modified by hereditary (genetic) factors

# ENVIRONMENTAL CARCINOGENS:

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- 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.

# ASBESTOS AND TOBACCO SMOKING

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- SYNERGISTIC INTERACTION:
  - Exposure to asbestos in nonsmokers increases the risk for developing lung cancer **5-fold**.
  - heavy smokers exposed to asbestos the risk is elevated
  - approximately **55-fold**.

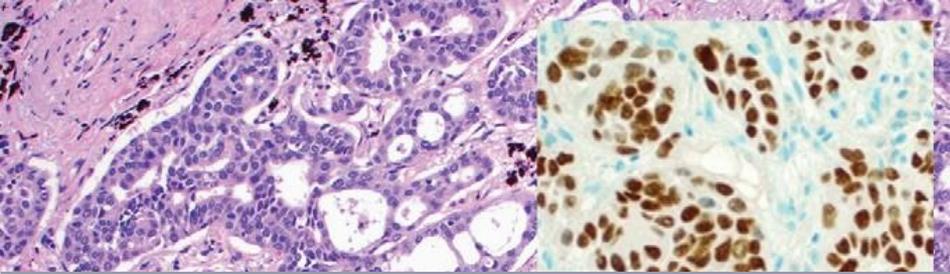
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Some invasive adenocarcinomas of the lung arise through an atypical adenomatous hyperplasia–adenocarcinoma in situ–invasive adenocarcinoma sequence.

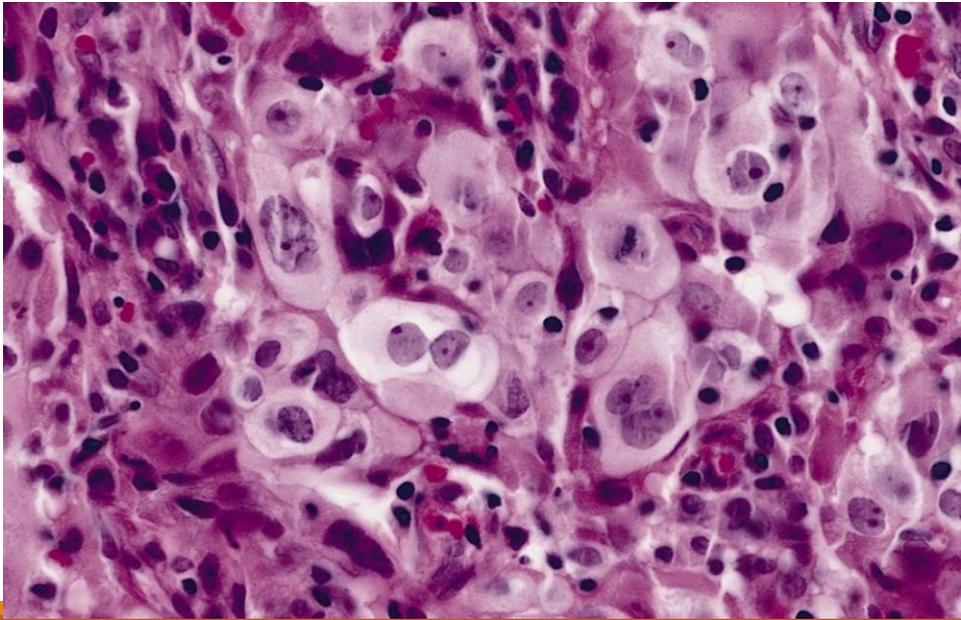
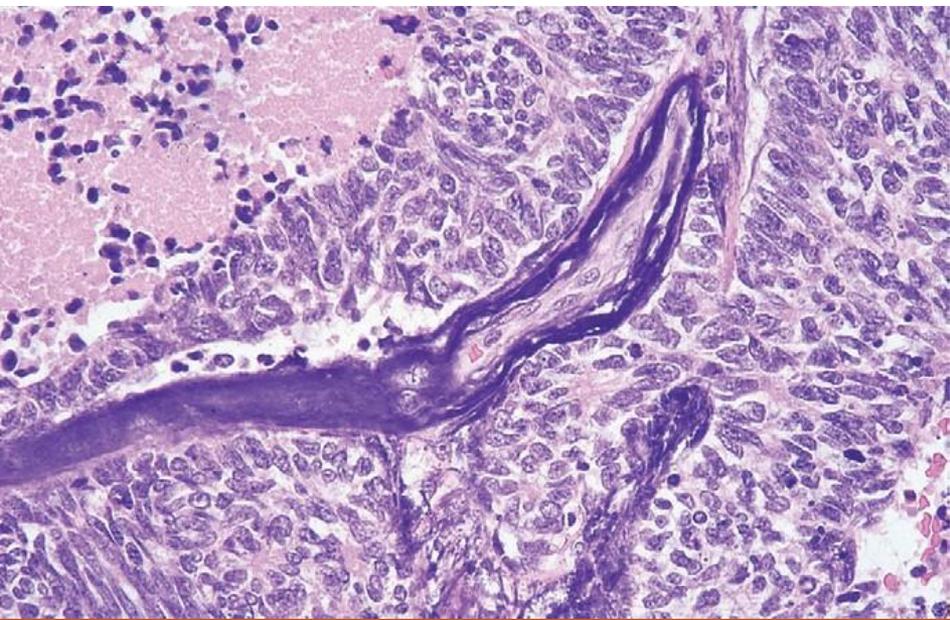
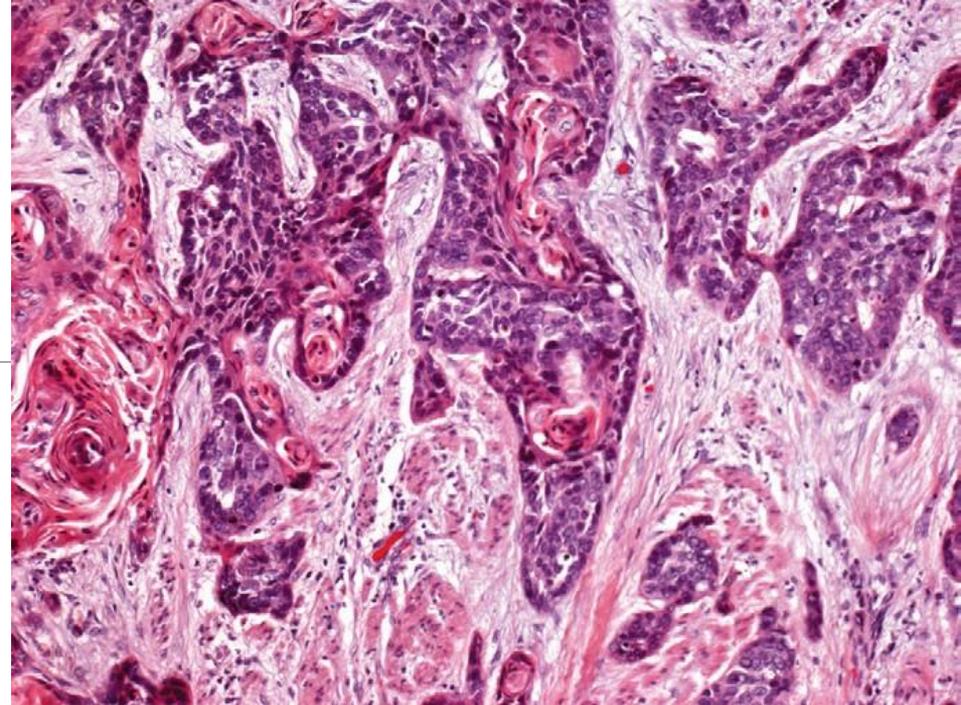
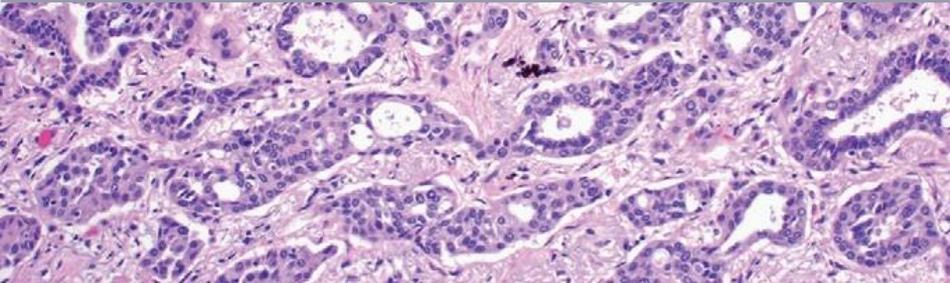
# THE FOUR MAJOR HISTOLOGIC TYPES OF CARCINOMAS OF THE LUNG

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1. **Adenocarcinoma**
2. Squamous Cell Carcinoma
3. Small Cell Carcinoma (a subtype of neuroendocrine carcinoma)
4. Large Cell Carcinoma



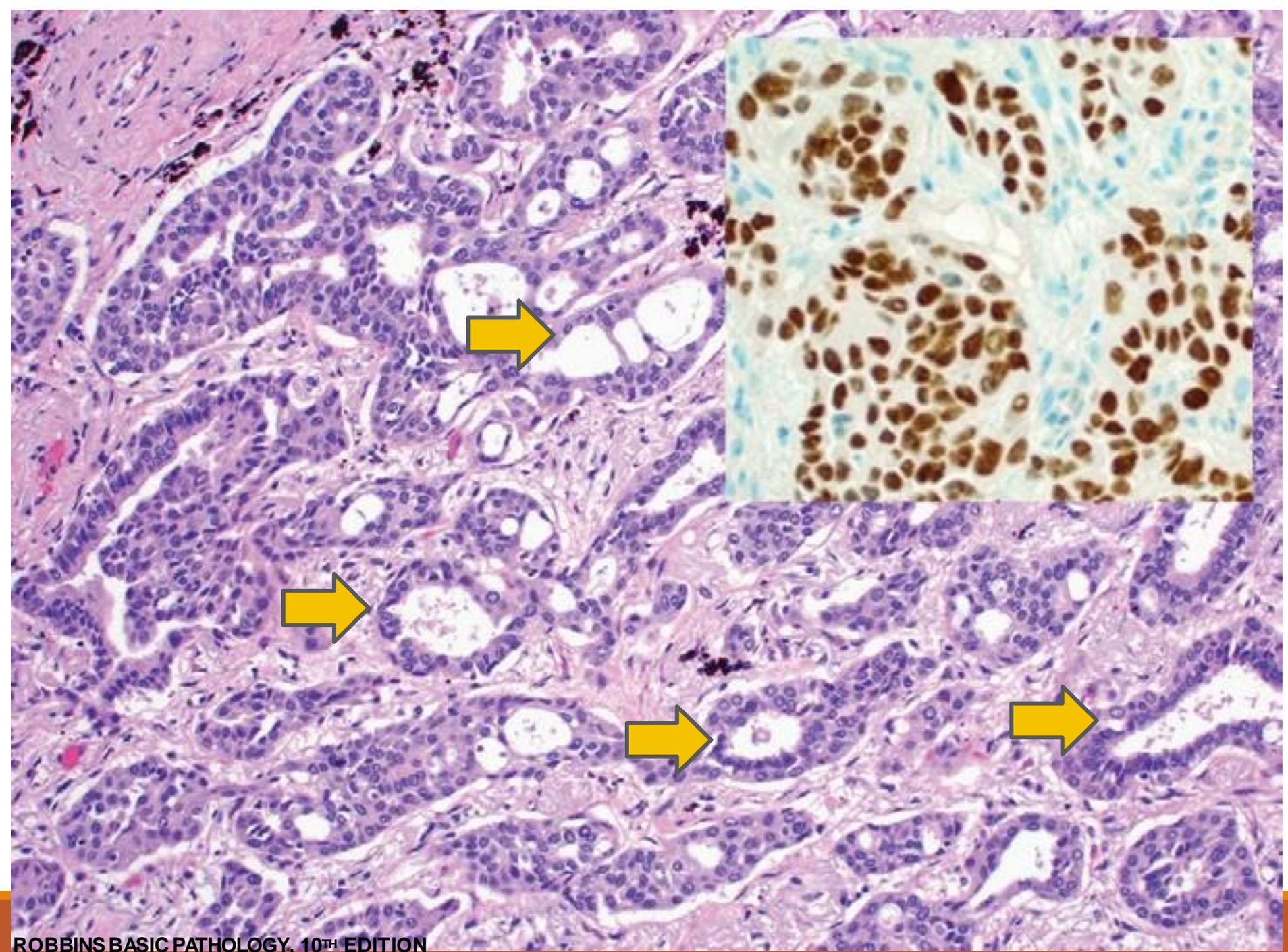
# Adenocarcinoma



# ADENOCARCINOMA:

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1. usually peripherally located, but also may occur closer to the hilum.
2. grow slowly form smaller masses
3. tend to metastasize widely at an early stage



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**1. atypical adenomatous  
hyperplasia (AAH)**

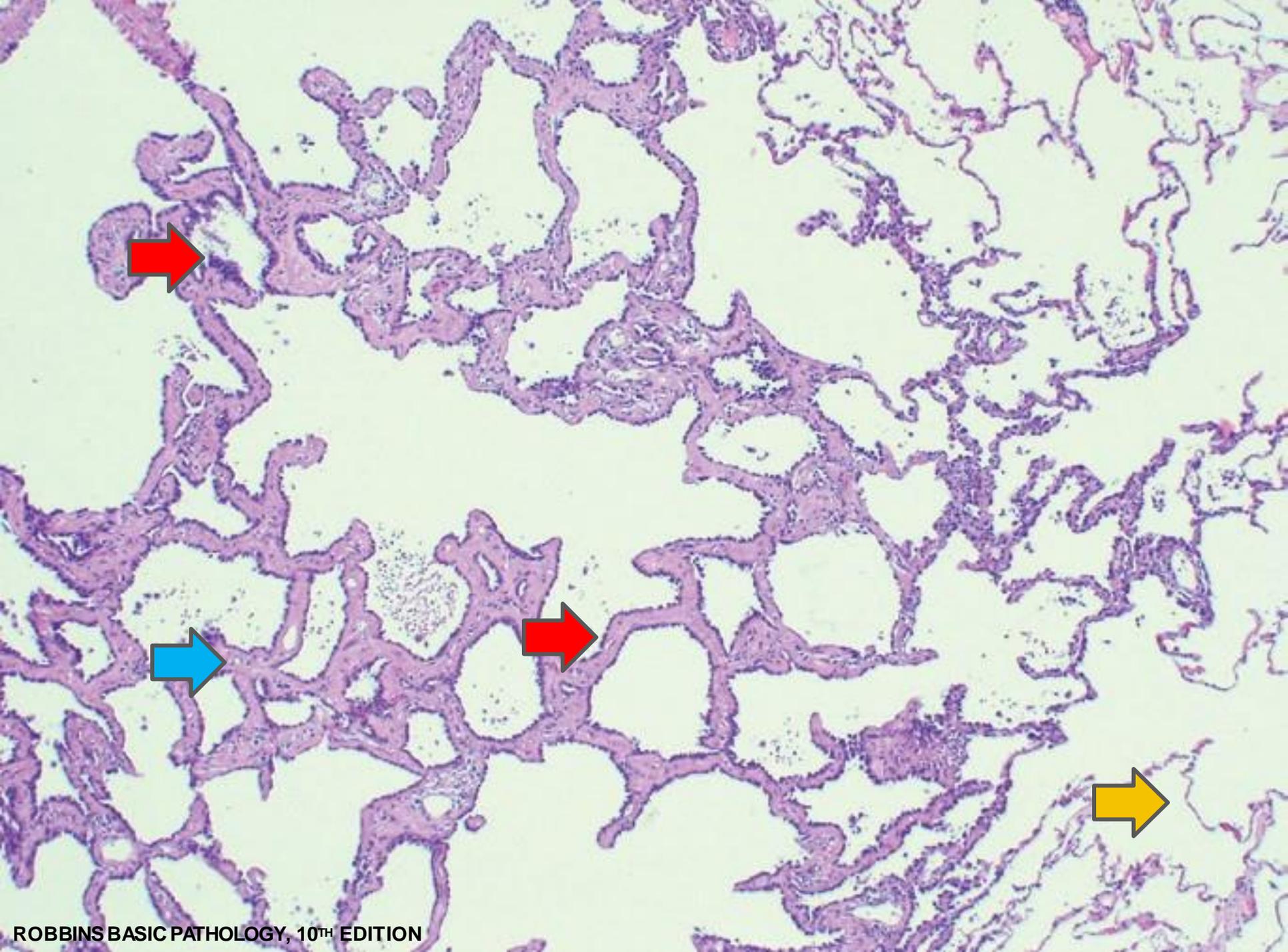
**adenocarcinoma in situ (AIS)**

**Adenocarcinoma,  
minimally invasive or invasive**

# Atypical adenomatous hyperplasia:

well-demarcated focus of epithelial proliferation

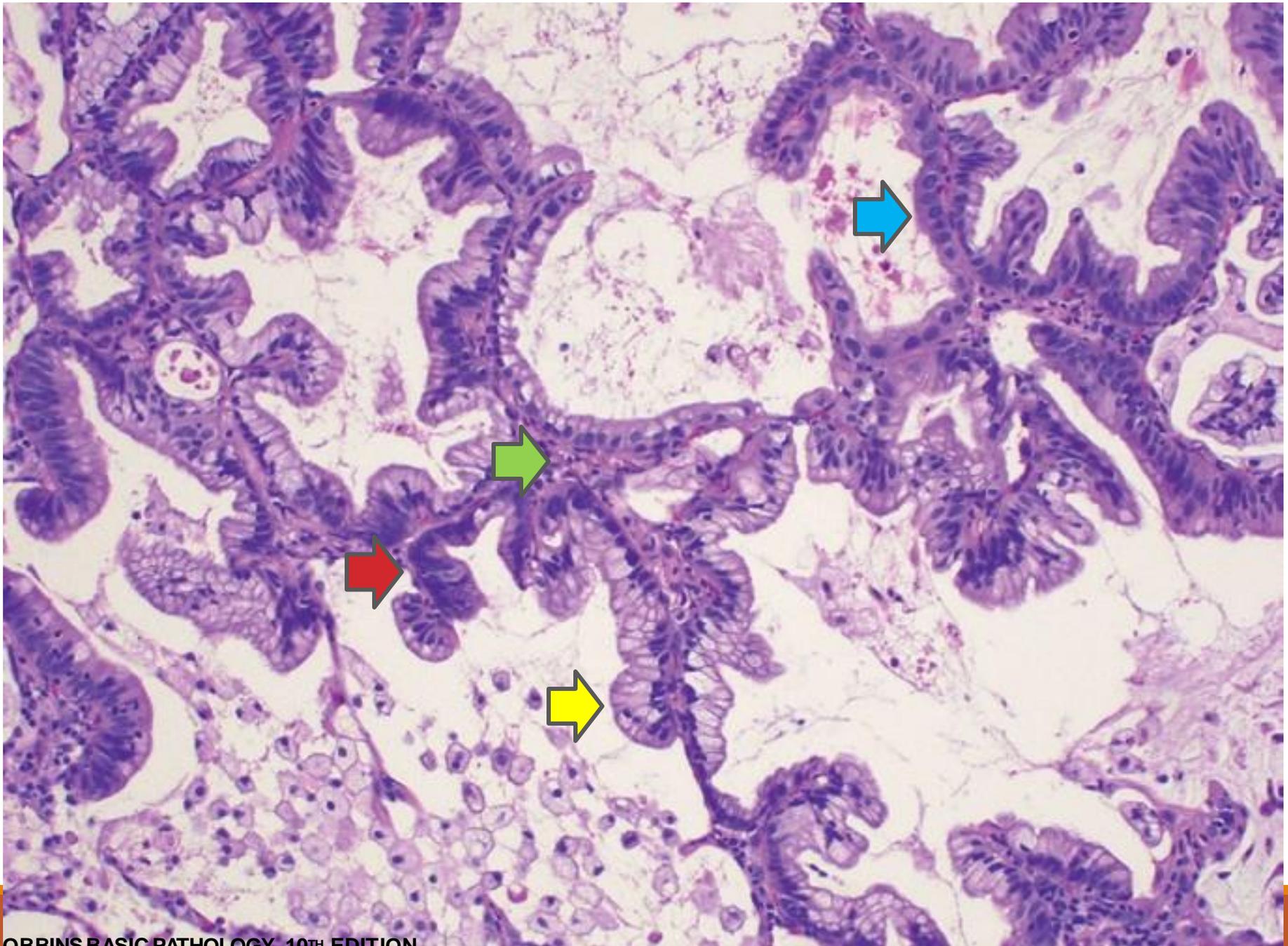
- diameter of <5 mm
- composed of cuboidal to low-columnar cells
- demonstrating nuclear hyperchromasia, pleomorphism, and prominent nucleoli.
- monoclonal and shares many molecular aberrations with adenocarcinomas (e.g., KRAS mutations).



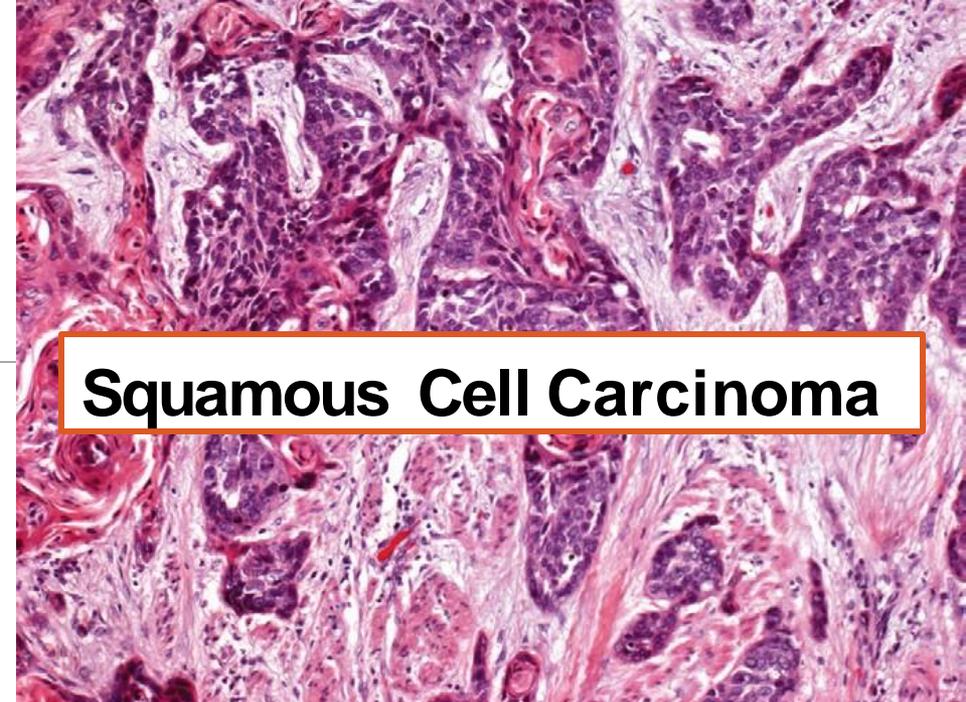
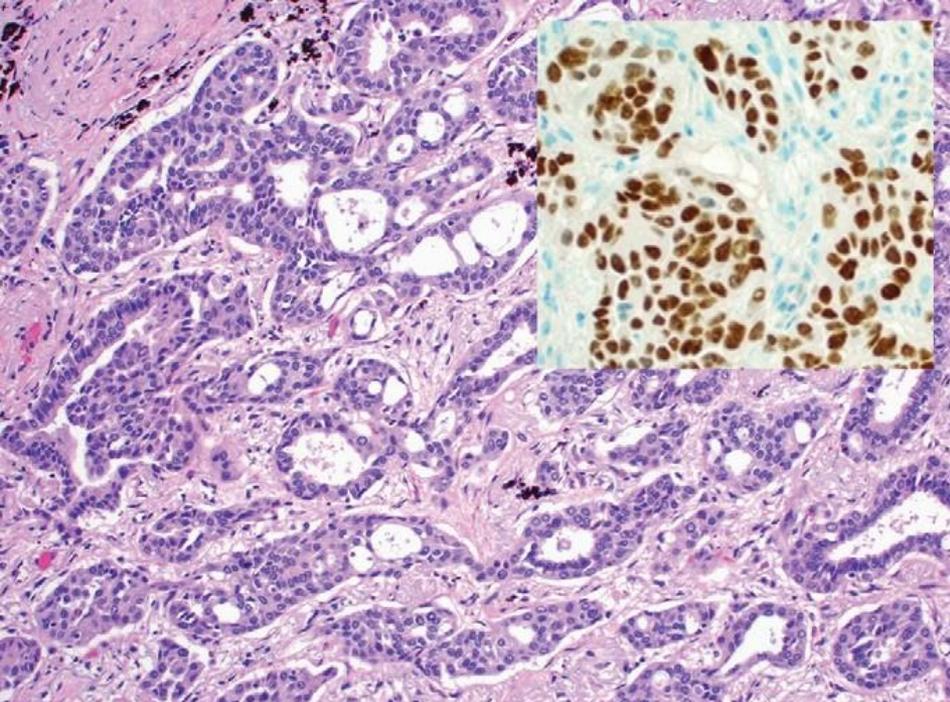
# Adenocarcinoma in situ (AIS):

- formerly bronchioloalveolar carcinoma
- often involves peripheral parts of the lung as a single nodule.
- diameter of <3 cm
- growth along preexisting structures, and preservation of alveolar architecture.

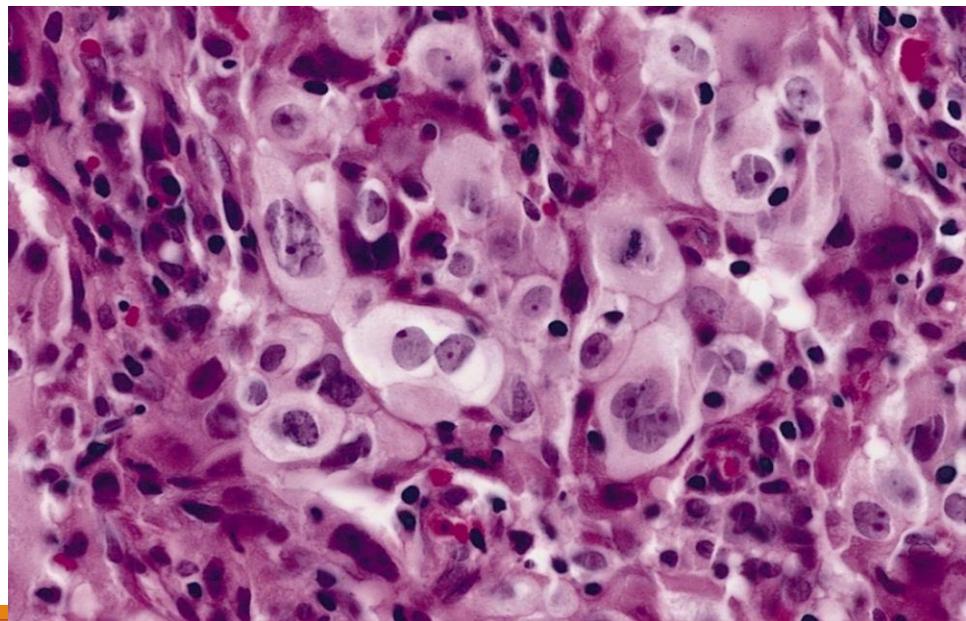
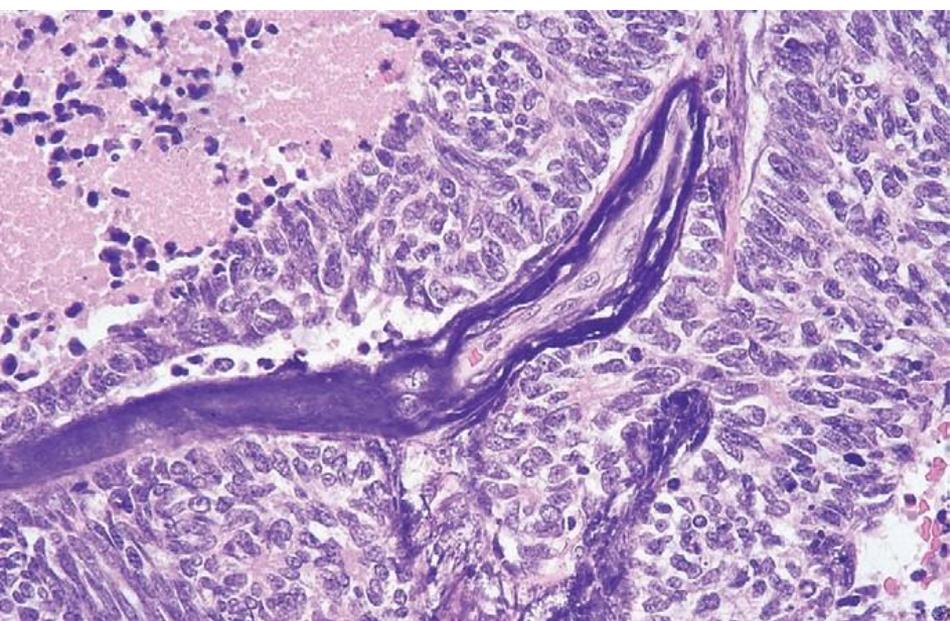
- The tumor cells, which may be nonmucinous, mucinous, or mixed
- grow in a monolayer along the alveolar septa, which serve as a scaffold.



- Minimally invasive adenocarcinoma: <3 cm in diameter with an invasive component of <5 mm
- Invasive adenocarcinoma a tumor of any size with an area of invasion >5 mm.



**Squamous Cell Carcinoma**



# SQUAMOUS CELL CARCINOMAS

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- 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:

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



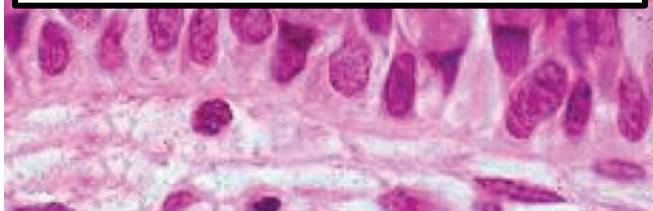
**goblet cell hyperplasia**



**Basal cell hyperplasia**



**Squamous metaplasia**



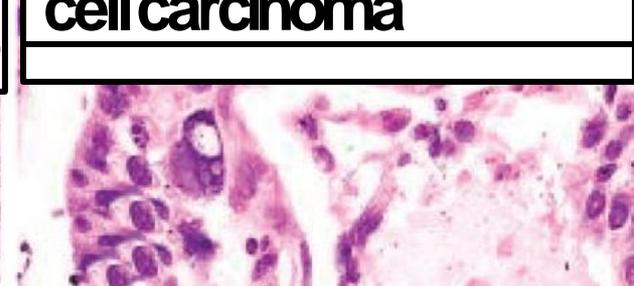
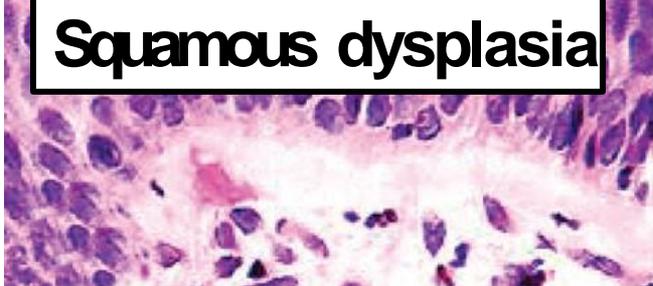
**Squamous dysplasia**



**Carcinoma in situ (CIS)**

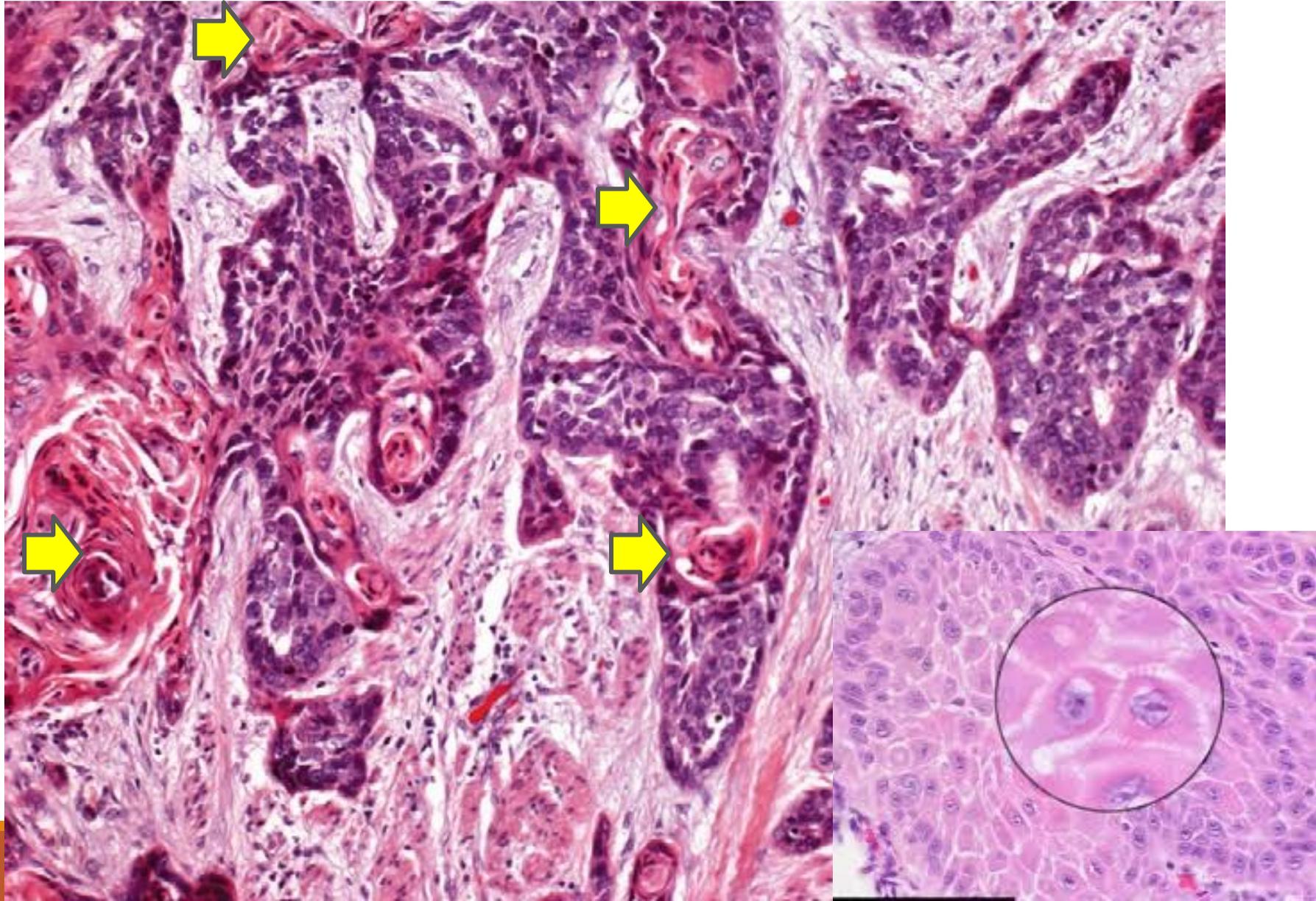


**invasive squamous cell carcinoma**





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



69 year old gentleman, smoker, presented with cough and a 7 kg weight loss over the past 4 months. Physical examination shows finger clubbing. He is afebrile. CXR shows no hilar adenopathy, but there is cavitation within a 3-cm lesion near the right hilum. Labs show elevated serum calcium.

Bronchoscopy shows a lesion occluding the right main bronchus. A surgical procedure with curative intent is attempted. Which of the following neoplasms is most likely to be present in this patient?

- A . Adenocarcinoma in situ
- B. Squamous cell carcinoma
- C. Metastatic renal cell carcinoma
- D. Small cell anaplastic carcinoma

A 57 year old lady presented with chronic nonproductive cough for 4 months along with loss of appetite and a 7 kg weight loss. She does not smoke. On physical examination, no remarkable findings. Her CXR shows a right peripheral subpleural mass. A fine-needle aspiration biopsy is performed, and she undergoes a right lower lobectomy. Microscopically the proliferating cells show glandular differentiation. Which of the following neoplasms did she most likely have?

- A) Adenocarcinoma
- B) Bronchial carcinoid
- C) Hamartoma
- D) Squamous cell carcinoma



**THANK YOU!**