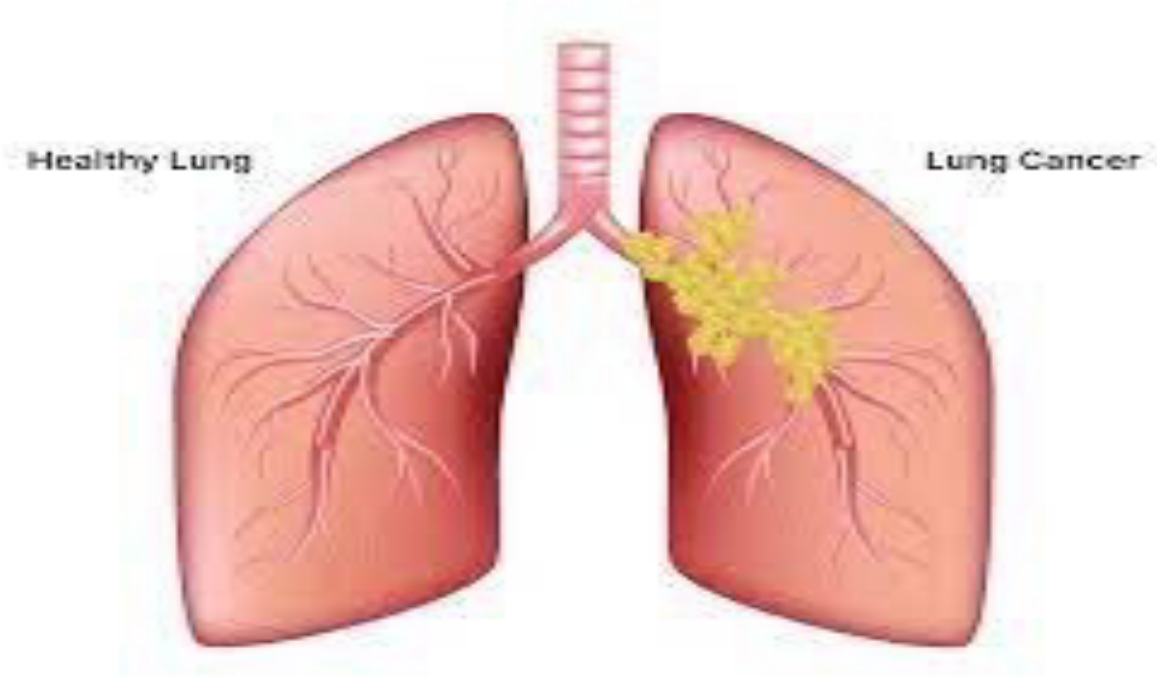
النادي الطلابي
كلية الطب

Pathology RS

Done By Dana Alkhateeb

Corrected By Samah Freihat

LUNG TUMORS



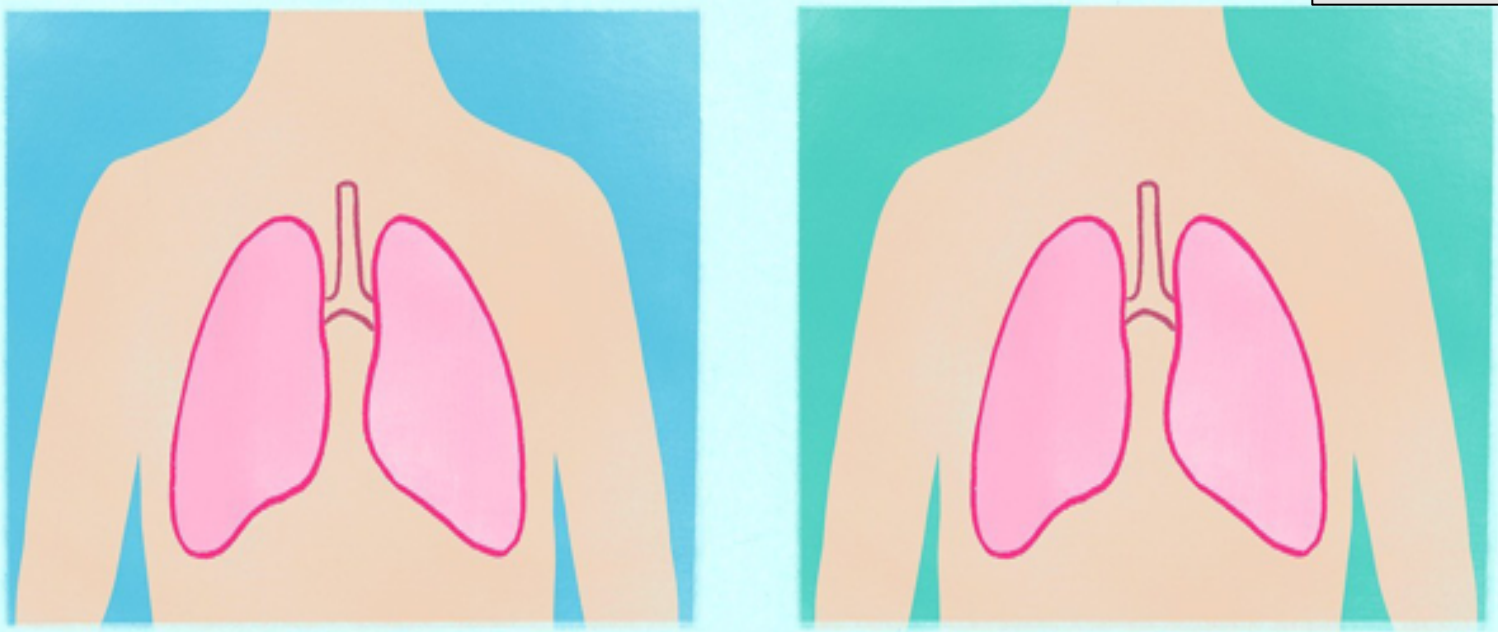
MARAM ABDALJALEEL, MD

DERMATOPATHOLOGIST &NEUROPATHOLOGIST

Metastatic or secondary lung tumors are tumors arising outside the lungs and travel through the bloodstream, lymphatics or directly to the lung
The most common cancers that spread to the lung are (breast, renal, colorectal ,head & neck, testicular, soft tissue sarcoma like osteosarcoma and melanoma)

Metastatic vs. Primary Lung Cancer

Can be benign or malignant



Metastatic Lung Cancer

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

Primary Lung Cancer

originated in the lungs

verywell

https://www.verywellhealth.com/metastatic-cancer-2249129

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

The remaining 5% are carcinoid, mesenchymal tumors like fibrosarcoma , lymphomas and few benign lesions

HAMARTOMA

- The most common benign tumor
- It's clonal, so the name hamartoma is a misnomer

Benign neoplasm , the name hamartoma implies a developmental anomaly which is a misnomer

- Gross: spherical, small (1 to 4 cm), discrete
- CXR: coin lesion.
- Microscopic: mature cartilage, fat, fibrous tissue, and blood vessels.

CARCINOMA OF THE LUNG

- The most important cause of cancer-related deaths in industrialized countries

  This accounts for about one third of cancer deaths in men and considered as the leading cause of cancer deaths in women

- 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.

  Since 1987 more women are dying from lung cancer than from breast cancer

- 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

1. adenocarcinoma
2. squamous cell carcinoma
3. small cell carcinoma (a subtype of neuroendocrine carcinoma)
4. large cell carcinoma

In some cases there is a combination of histologic patterns like you may find small cell carcinoma with adenocarcinoma

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**

  There is some association with adenocarcinoma

- **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

This classification has been recently replaced by 2015 WHO classification

The reason behind this old classification is the presence of these short features :

- **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.

that target specific oncoproteins

In addition, new immunotherapy approaches are now approved for a subset of the NSCLCs and also are being tested for the SCLCs

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

So what we need?

Accumulation of

Genetic abnormalities

After being exposed to

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)***

That stimulates downstream progress pathways is seen in a subset of adenocarcinoma especially those are associated with non smoker women

CARCINOGENS:

- cigarette smoking
- environmental carcinogens

CIGARETTE SMOKING

The most important Because there is a strong evidence that cigarette smoking and to lesser extent other environmental carcinogens are the main culprit responsible for the mutations

- **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.

Passive smoking (close proximity to smokers) increases the risk for developing lung cancer

مش مضطرين ندخن معكم لو سمحتوا

- Although smoking cessation **decreases** the risk over time, it **never** returns to baseline levels

The resulting genetic changes can persist for many years in the bronchial epithelium of a former smoker

- **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:

- **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

- **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.

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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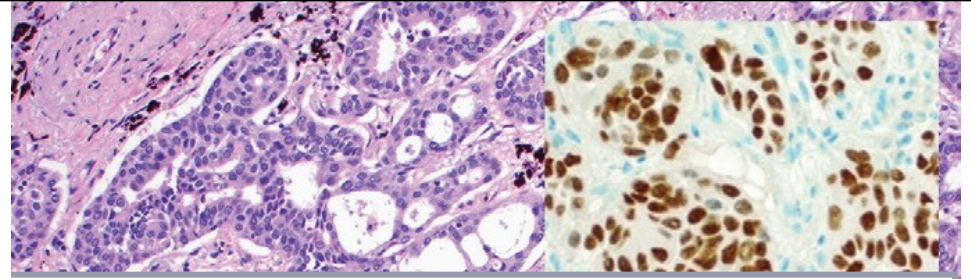
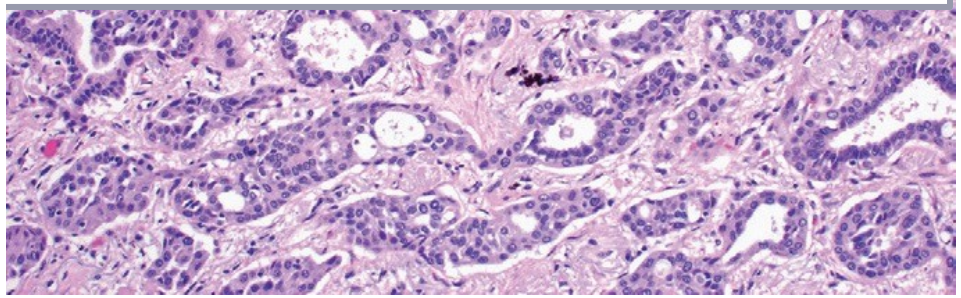
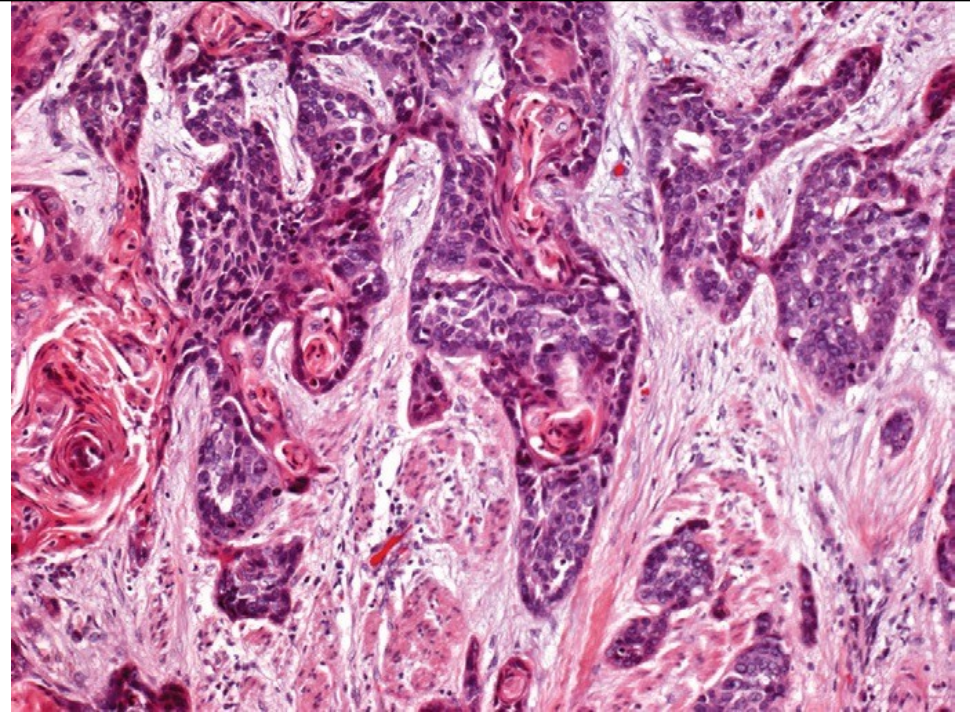
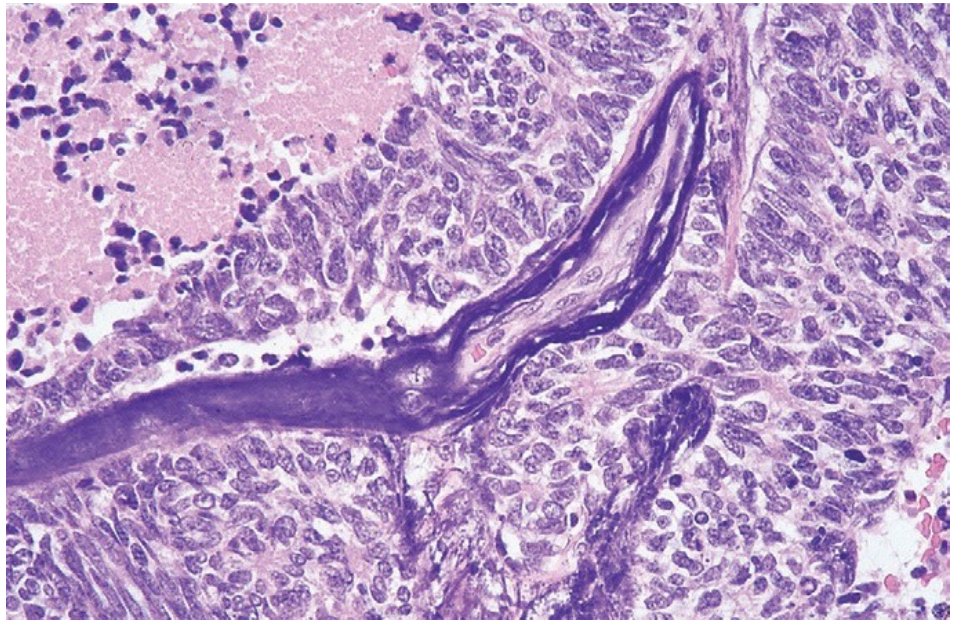
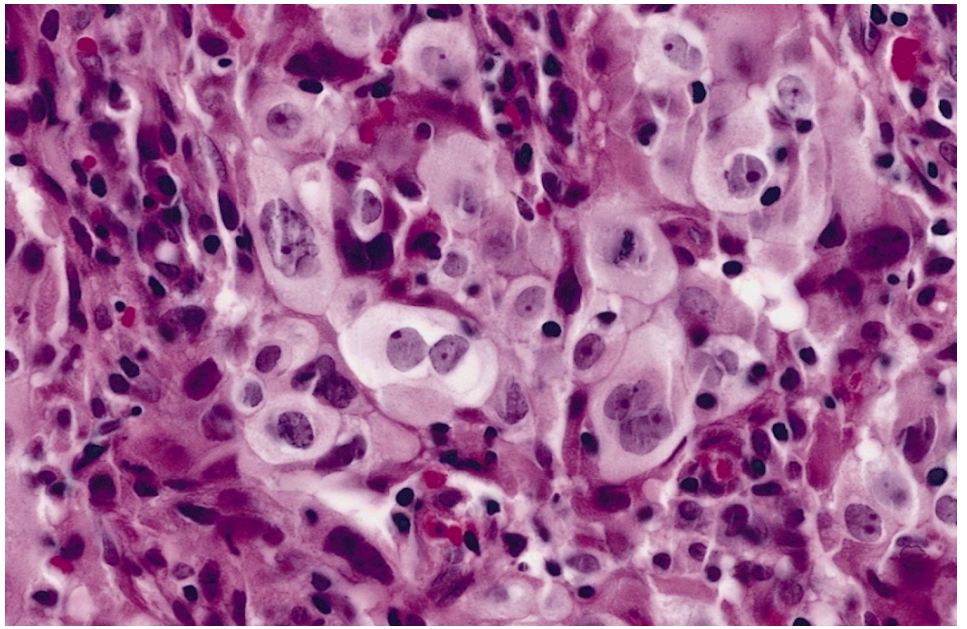
Adenocarcinoma











ROBBINS BASIC PATHOLOGY, 10TH EDITION

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

ADENOCARCINOMA:

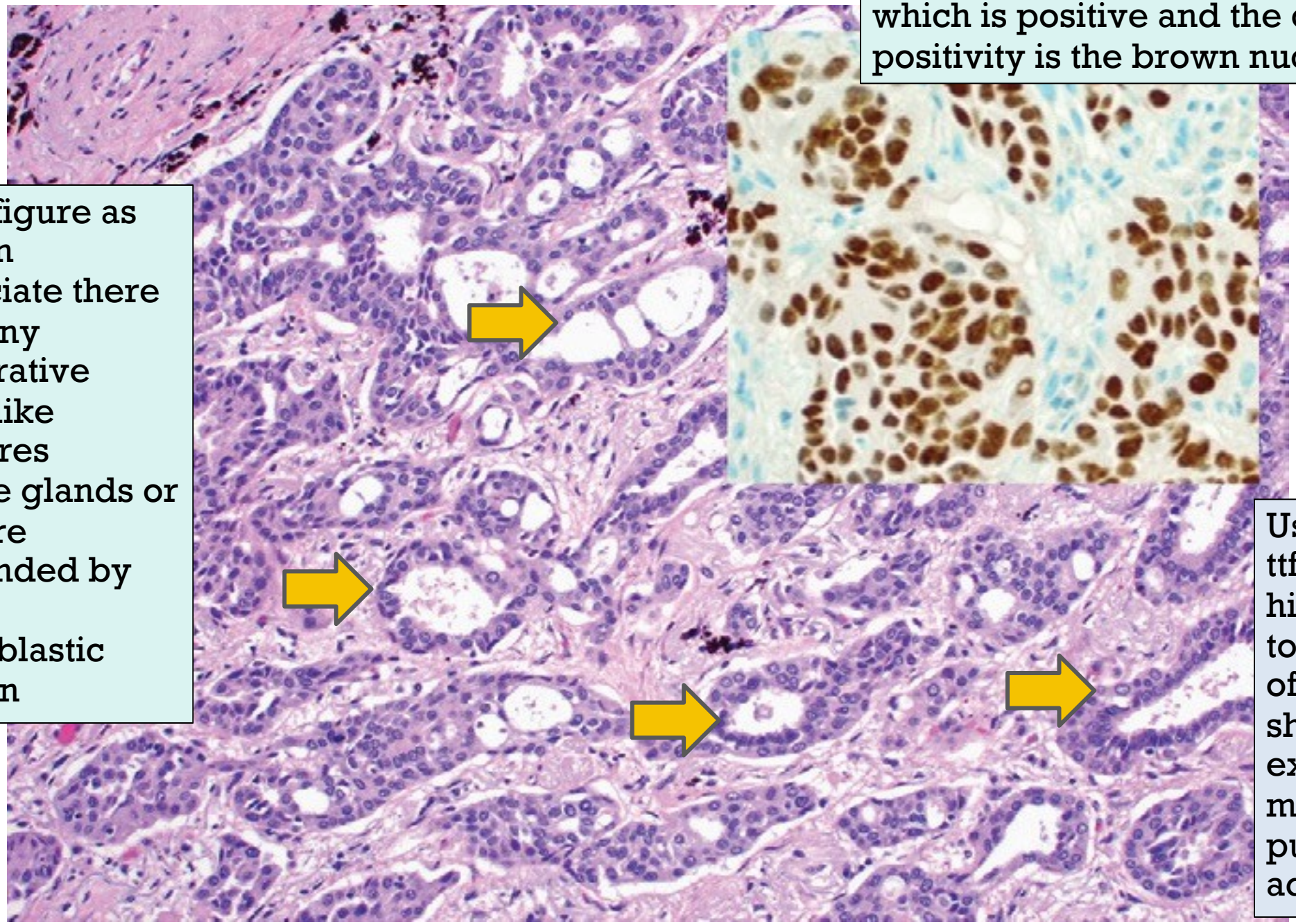
- usually **peripherally located,** but also may occur closer to the hilum.
- grow slowly
- form smaller masses
- tend to metastasize widely at an early stage

MORPHOLOGY, MICROSCOPIC:

- variety of growth patterns

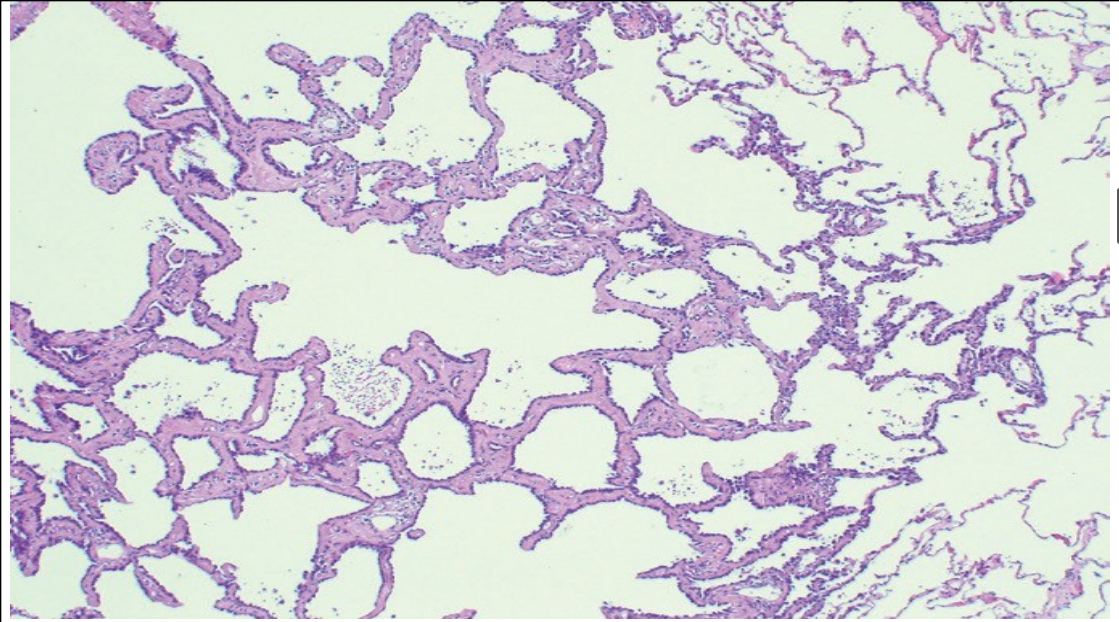
- including **acinar (gland-forming)**; **papillary; mucinous and solid types**

Shows thyroid transcription factor 1 (ttf 1) which is positive and the clue for the positivity is the brown nuclear staining

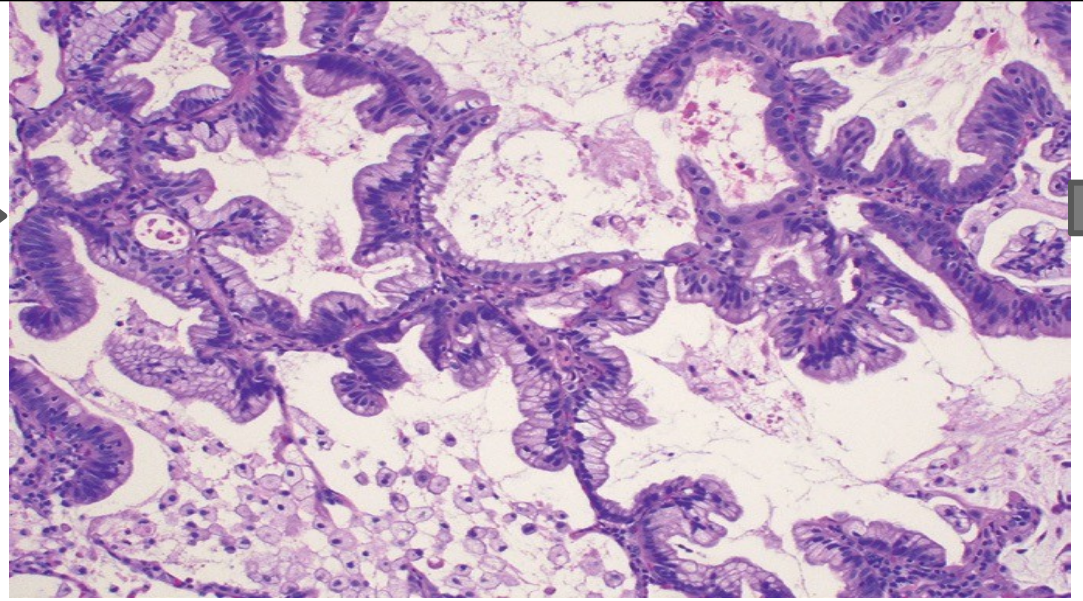


In this figure as you can appreciate there are many proliferative gland-like structures
* These glands or acini are surrounded by dense desmoblastic reaction

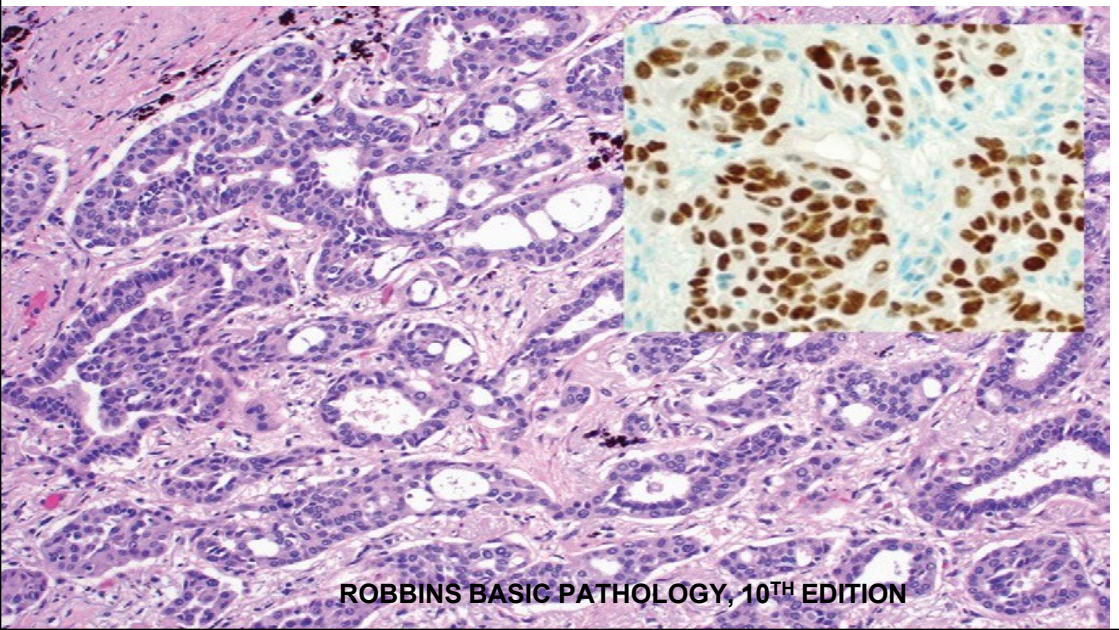
Usually we use the ttf 1 immune stain in histopathology lab to highlight tumors of lung origin and it shows positive expression in the majority of pulmonary adenocarcinomas



atypical adenomatous hyperplasia (AAH)



adenocarcinoma in situ (AIS)



Adenocarcinoma,
minimally invasive or invasive

Atypical adenomatous hyperplasia:

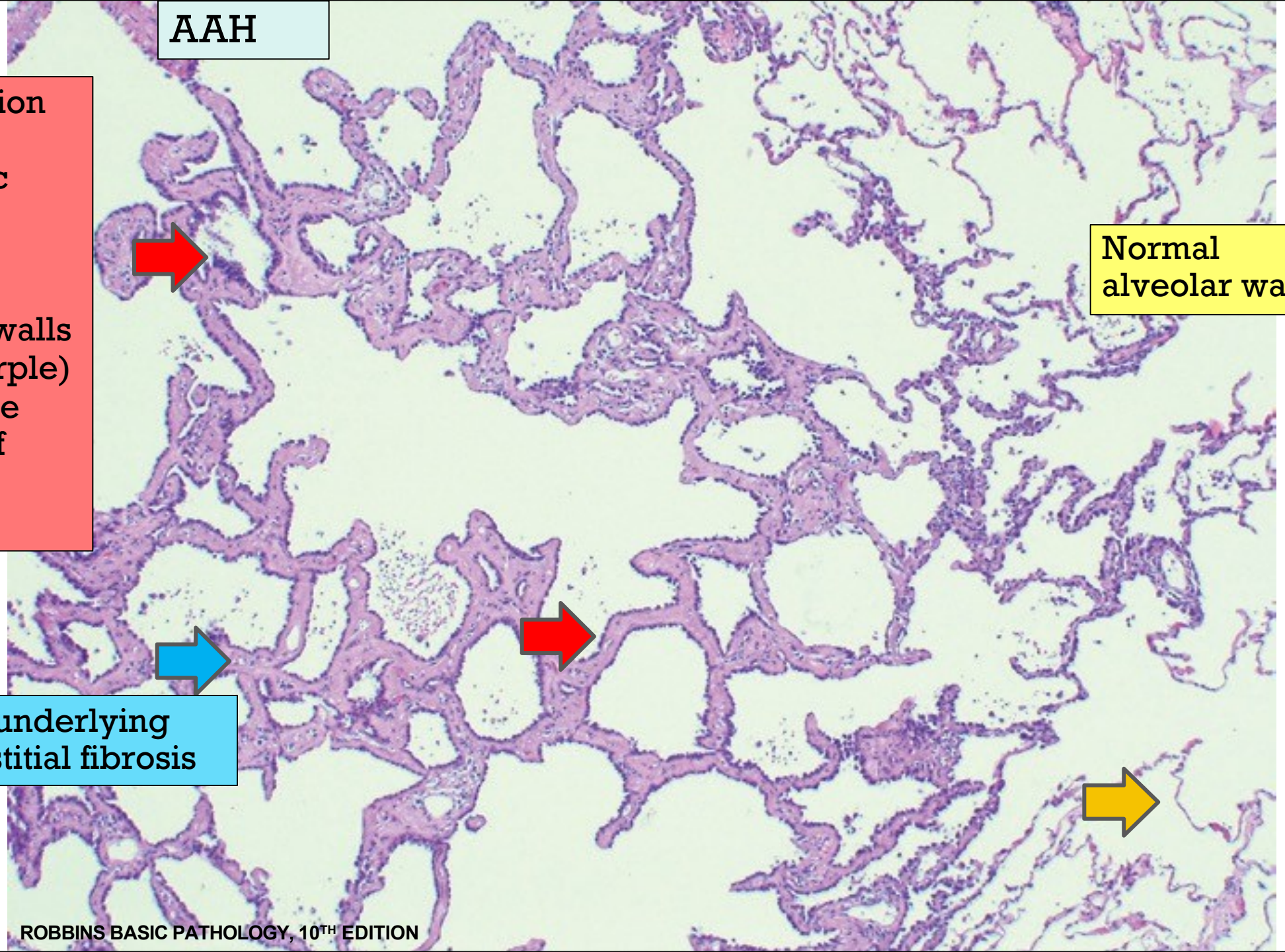
Precursor of lesion of adenocarcinoma

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).

AAH

Proliferation of hyper chromatic cuboidal epithelial lining of alveolar walls (blue purple) With some degree of cytologic atypia



Normal alveolar walls

Mild underlying interstitial fibrosis

ROBBINS BASIC PATHOLOGY, 10TH EDITION

Adenocarcinoma in situ (AIS):

- formerly **bronchioloalveolar carcinoma**
- often involves **peripheral parts** of the lung as a single nodule.
- diameter of **≤3 cm** Key feature of diagnosis
- **growth along preexisting structures,** No destruction of the underlying structures **and preservation of alveolar architecture.**

Does not demonstrate destruction of the alveolar architecture or stromal invasion with desmoplasia like what we see in invasive carcinoma because destruction of the underlying structures or the presence of desmoplastic reaction means invasion and infiltration and AIS is not an infiltrative tumor

- The tumor cells, which may be nonmucinous, mucinous, or mixed

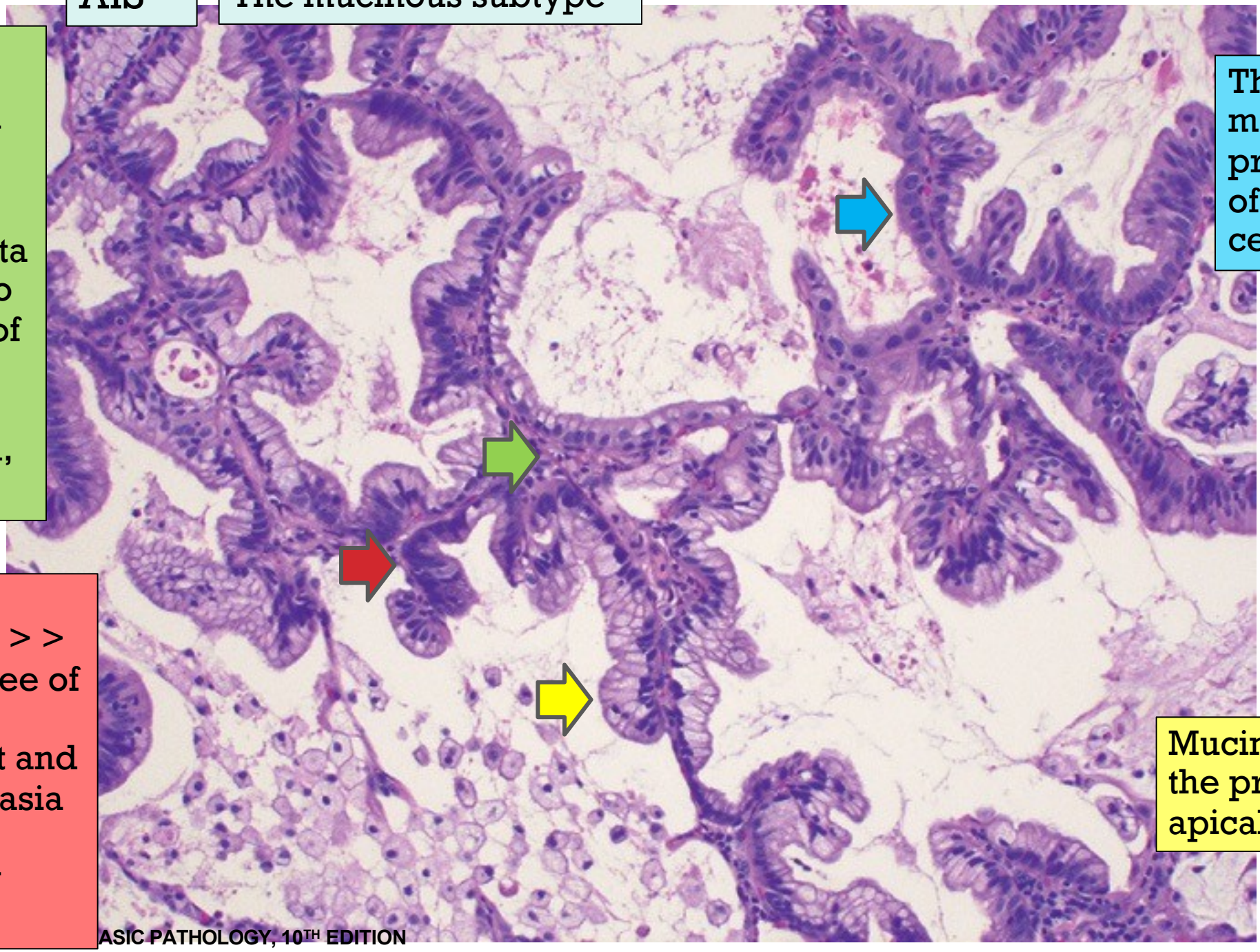
- grow in a monolayer along the alveolar septa, which serve as a **scaffold.**

By definition adenocarcinoma in sito does not demonstrate destruction of alveolar structures or stromal invasion with desmoplasia , if these features are present then the diagnosis should be invasive adenocarcinoma

AIS

The mucinous subtype

These cells are proliferating along a preexisting alveolar septa so there is no destruction of the alveolar septa, no desmoplasia, no invasion



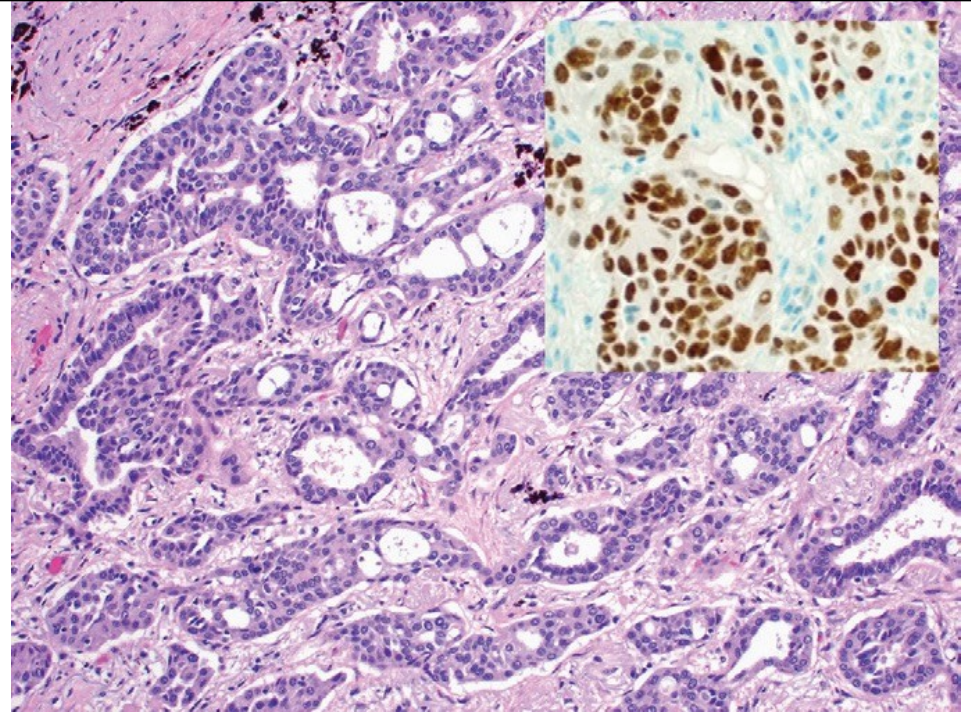
There is monolayer proliferation of atypical cells

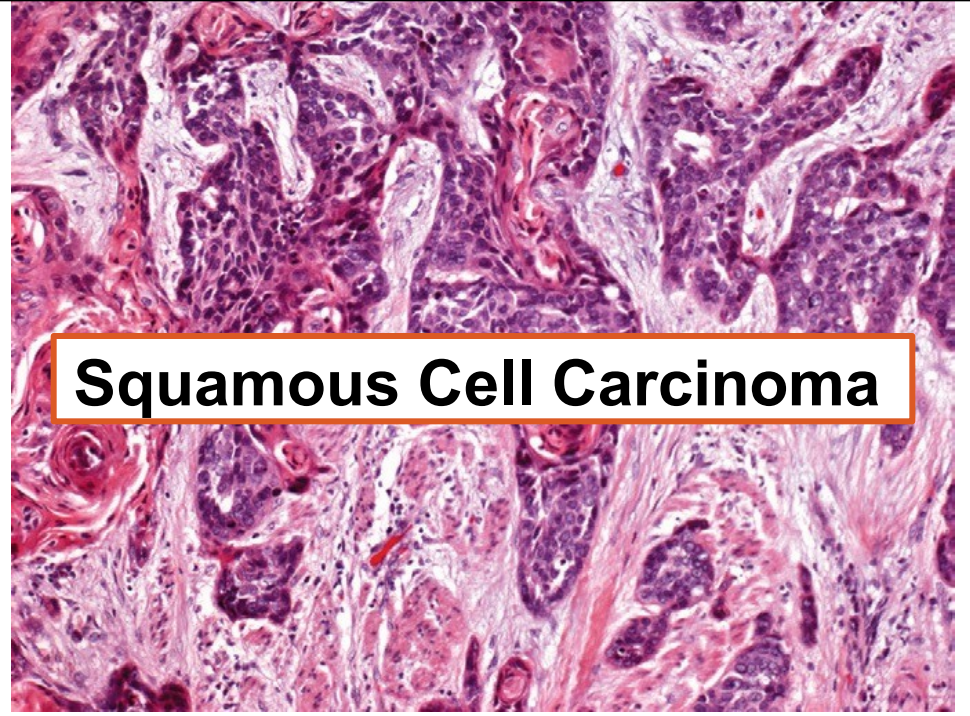
Atypical proliferation > > certain degree of nuclear enlargement and hyperchromasia in these proliferating cells

Mucinous type >> the presence of apical mucin

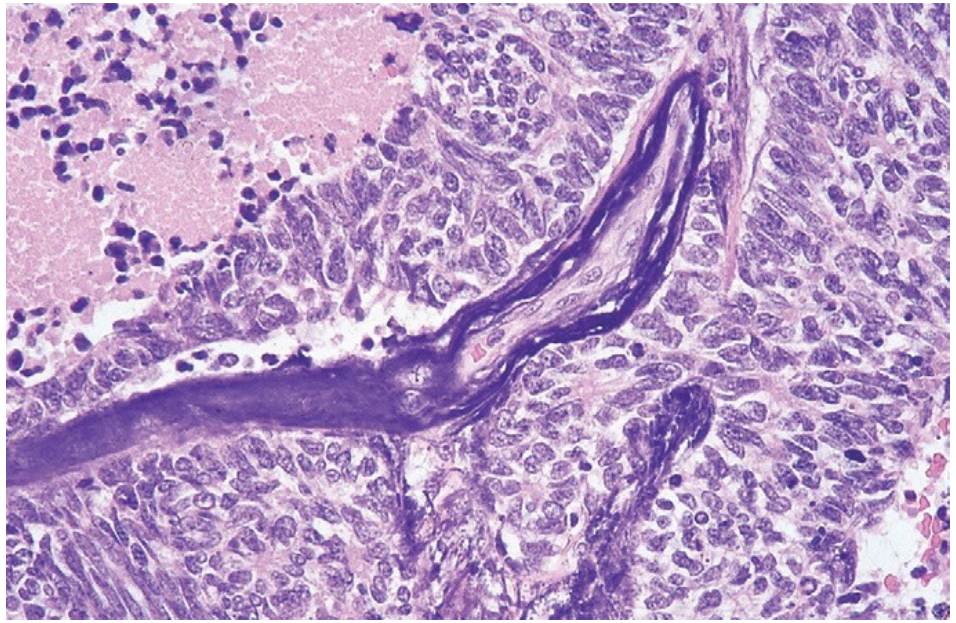
- **Minimally invasive adenocarcinoma**: **<3 cm** in diameter with an invasive component of **<5 mm**

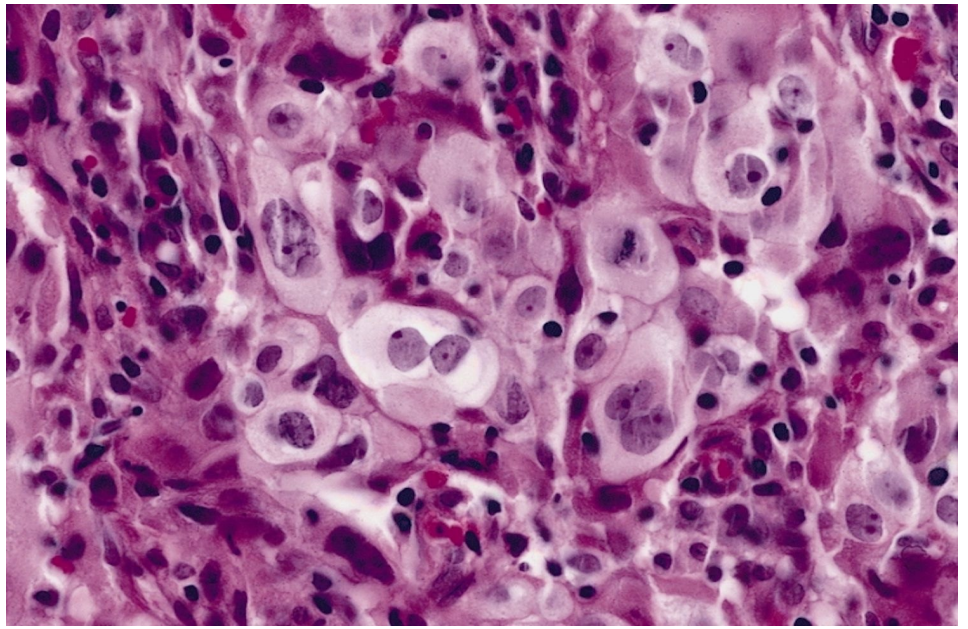
- **Invasive adenocarcinoma** a tumor of any size with an area of invasion **>5 mm.**





Squamous Cell Carcinoma





ROBBINS BASIC PATHOLOGY, 10TH EDITION

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

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**

    May last for several years

    Undetectable on radiographs

  - the lesion is asymptomatic until reaches a symptomatic stage when it begins to obstruct the lumen of a major bronchus, +/- atelectasis and infection.

    Distal

MORPHOLOGY:

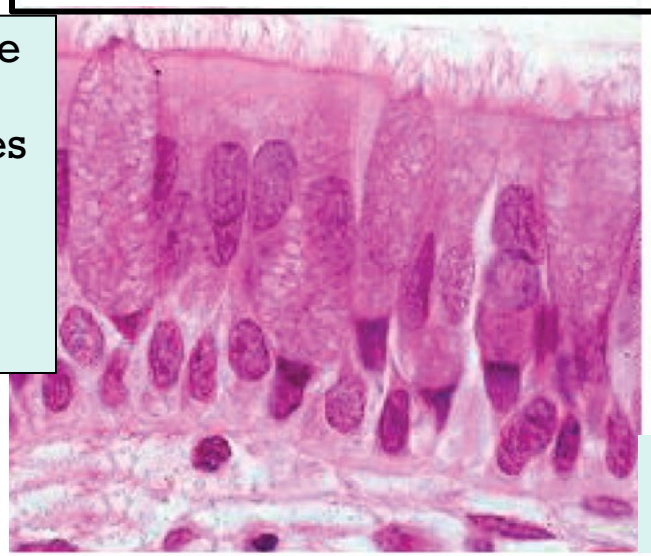
Ranges from **Well differentiated squamous cell neoplasms** showing keratin pearls and intercellular bridges to **Poorly differentiated neoplasms** with only minimal residual squamous cell features.

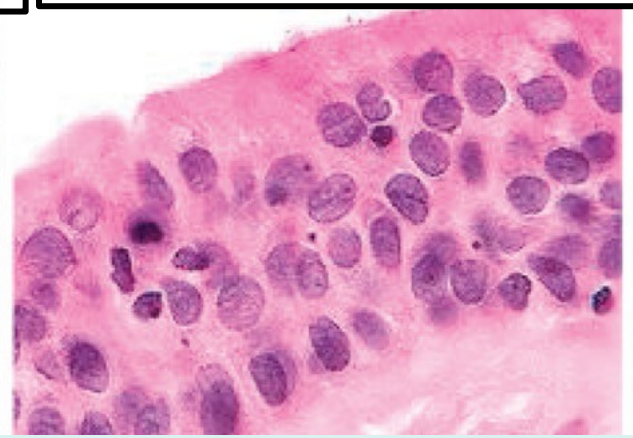
a: goblet cell hyperplasia

b:Basal cell hyperplasia

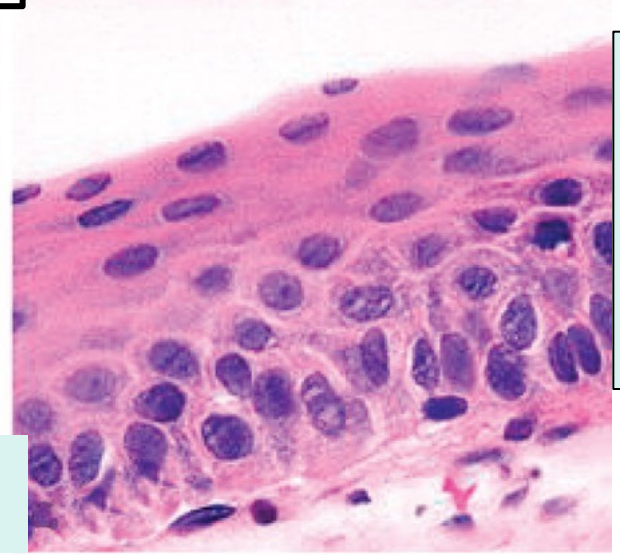
c:Squamous metaplasia

A: One of the earliest and mild changes in smoking damage respiratory epithelium





B :Is another smoking adaptive response

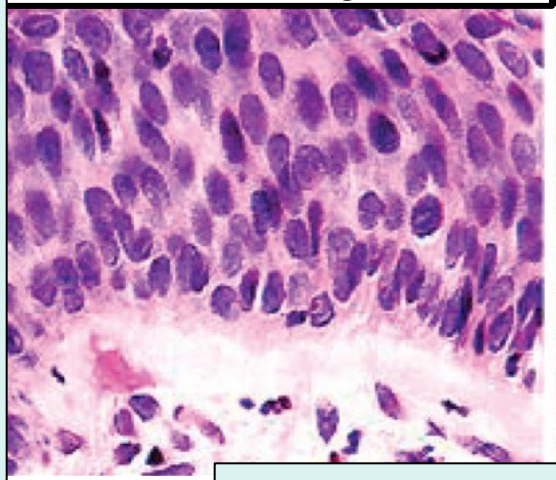


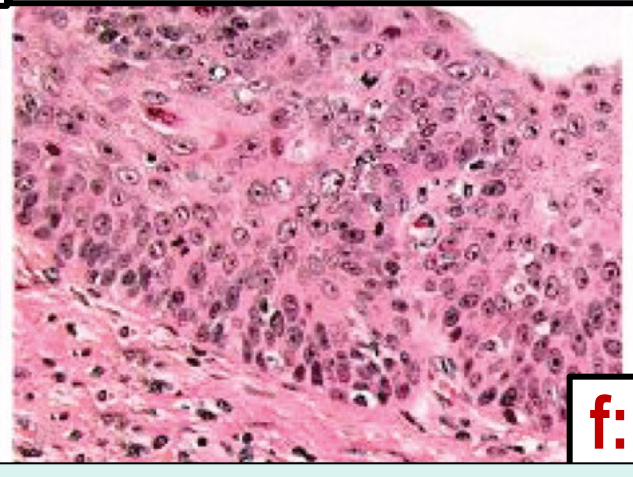
C:The ciliated pseudo stratified columnar epithelium is replaced by squamous epithelium

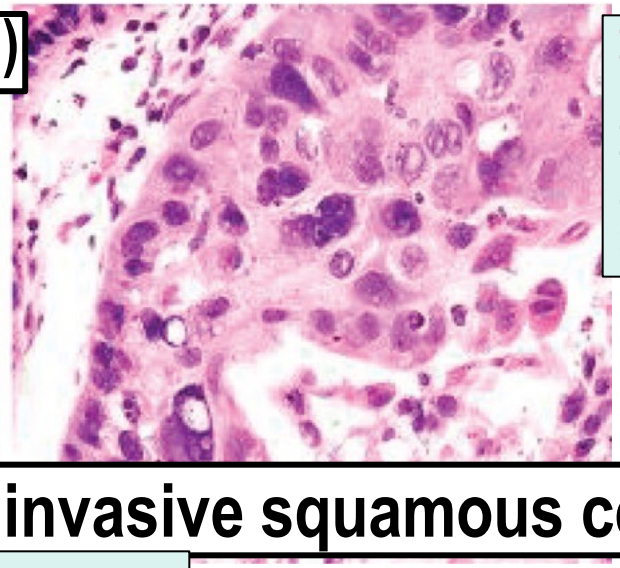
D:Squamous dysplasia

E:Carcinoma in situ (CIS)

D:Characterized by the presence of disorderd squamous epithelium, loss of nuclear polarity , nuclear hyperchromasia pleomorphis & mitotic figures
Mild >> moderate >> severe







F:Cytologic atypia & basement membrane invasion

f:invasive squamous cell carcinoma

E: Full thickness of squamous epithelium showing cytologic atypia and lacking basement membrane destruction so this stage happens immediately before invasive squamous carcinoma

These lesions Range from well , moderately , poorly differentiated

Gross appearance of Squamous cell carcinoma involving the lung

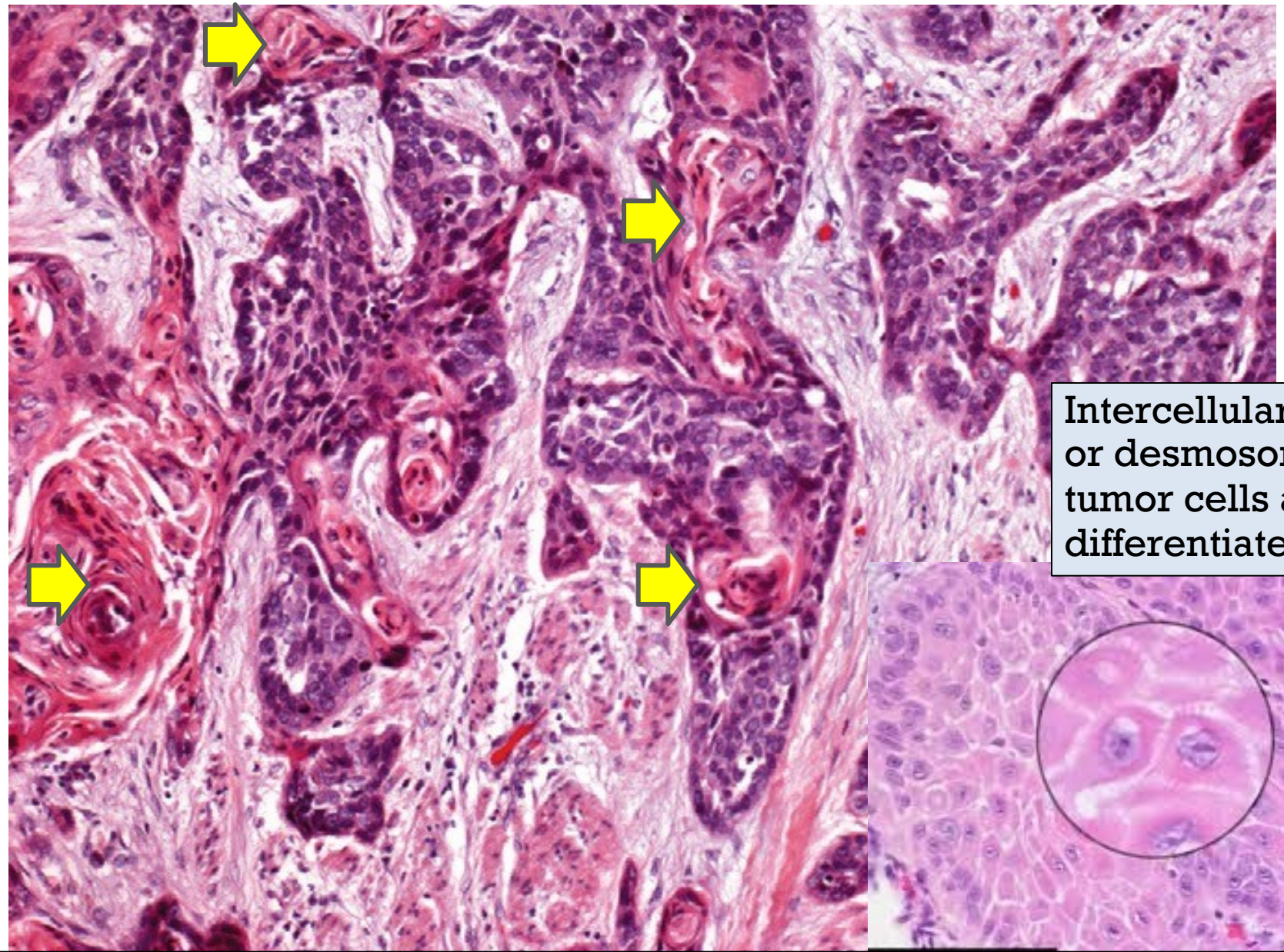
There is brilliant white central area accounting for the lung carcinoma that starts centrally and growths to the peripheral lung parenchyma

ROBBINS BASIC PATHOLOGY, 10TH EDITION

WELL-DIFFERENTIATED SQUAMOUS CELL CARCINOMA SHOWING KERATINIZATION AND PEARLS.

The presence of intercellular bridges or desmosomes & keratinization are considered features of well differentiation since normal squamous epithelium shows both

In this figure we can appreciate the presence of keratin pearls



Intercellular bridges spines or desmosomes between the tumor cells are seen in well differentiated tumors

I recommend to try solving the cases after finishing the lung tumors concept (after lec 8)

https://baytowncrimestoppers.com/baytowns-most-wanted/unsolved-crimes/

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

Strong association with squamous cell carcinoma

Squamous cell carcinoma can undergo central necrosis & cavitation

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Squamous cell carcinoma is most likely to produce paraneoplastic hypercalcemia

Centrally located

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?

Localized squamous cell carcinoma may be be cured by surgery

A Adenocarcinoma in situ

B Squamous cell carcinoma

C Metastatic renal cell carcinoma

Maybe associated with hypercalcemia but metastatic lesions are usually multiple not solitary & well circumscribed

D Small cell anaplastic carcinoma

Never localized enough to be cured by surgery usually the patient presents to you in advanced stage less likely to be associated with hypercalcemia

https://baytowncrimestoppers.com/baytowns-most-wanted/unsolved-crimes/

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?

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FOR YOUR QUESTIONS:

M.ABDALJALEEL@JU.EDU.JO, M. Teams

Or E-learning

THANK YOU!