Respiratory System
RS

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Lung Tumors :

- Although the lungs are the most common site of metastases, primary lung cancer is also common.

- Roughly **95%** of primary lung tumors are **carcinomas**.

- The peak incidence is 50-60 years, M: F = 2:1.
- More than 50% have distant metastasis at the time of diagnosis
- 25% have disease in the regional lymph nodes.
- The 5 years survival for all stages combined is 16%.
- Even with disease localized to the lung, the 5-year survival rate is only 45%.

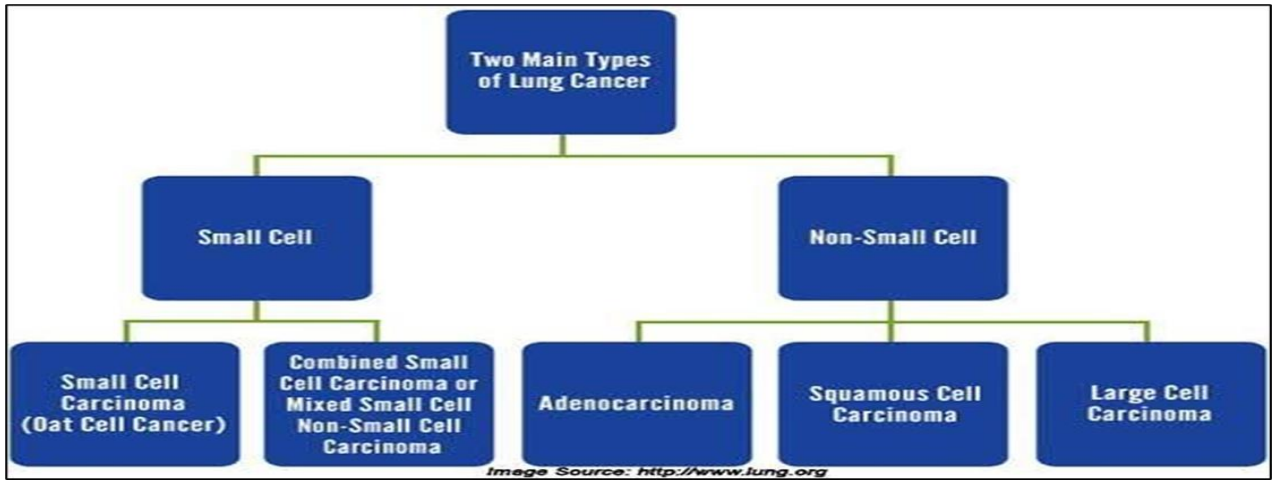
- Adenocarcinoma is the most common primary lung tumor in recent years.
- Adenocarcinomas also are by far the most common primary tumors arising in women, in never-smokers, and in individuals younger than 45 years of age.

For therapeutic purposes : lung cancers were historically classified into :

- Small cell lung cancer (SCLC)

- Non-small cell lung cancer (NSCLC), which includes SqCC., Adenocarcinoma, Large cell ca

- This is because all SCLCs have metastasized at the time of diagnosis & so are not curable by surgery; therefore, they are best treated by chemotherapy with or without radiation.
- In contrast to NSCLC, which usually responds poorly to chemotherapy & is better treated by surgery.

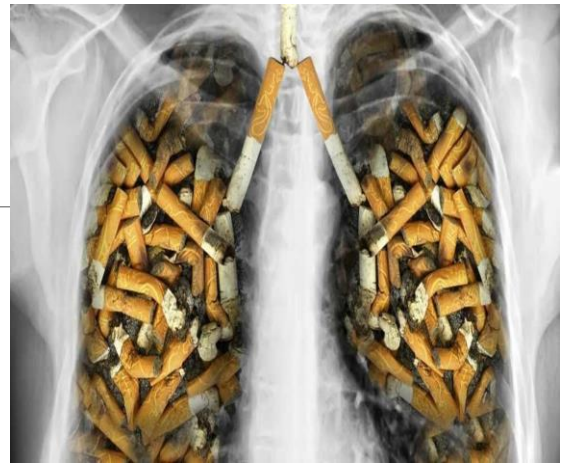


❑ Histologic Classification of Malignant Epithelial Lung Tumors:

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

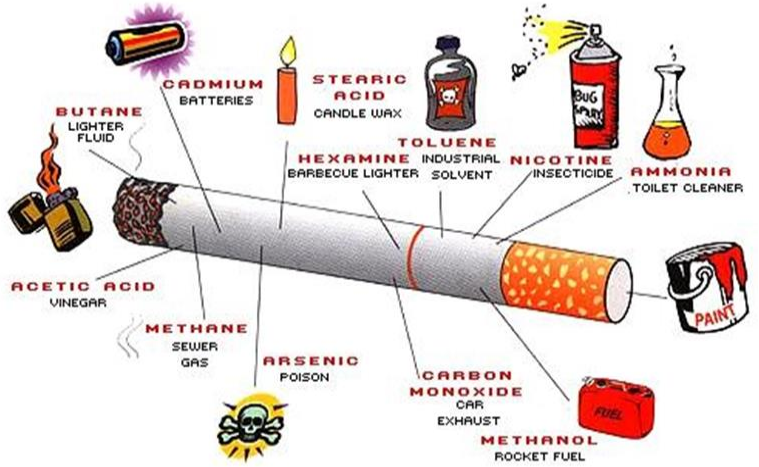
- Adenocarcinoma
  - Acinar, papillary, micropapillary, solid, lepidic predominant, mucinous subtypes
- Squamous cell carcinoma
- Large cell carcinoma
- Neuroendocrine carcinoma
  - Small cell carcinoma
  - Large cell neuroendocrine carcinoma
  - Carcinoid tumor
- Mixed carcinomas
  - Adenosquamous carcinoma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

Etiology & pathogenesis :



1. Cigarette smoking :

- About 90% of lung cancer smokers
- Only 11% of heavy smokers develop lung cancer
- Although cessation of smoking decreases the risk of developing lung cancer over time, it never returns to baseline levels.



2. Occupational hazards:

- Work in uranium mines,with asbestos and inhalation of dust containing arsenic and nickel are associated with increased risk for lung cancer.

3. Genetic Factors:

- Inactivation of the tumor suppressor gene located on the short arm of chromosome 3 is a very early event.
- Whereas P53 mutation or activation of the KRAS oncogene occurs relatively late.
- A subset of adenocarcinomas (about 10% in whites and 30% in Asians), particularly those arising in nonsmoking women, harbor mutations that activate the *epidermal growth factor receptor (EGFR),* a receptor tyrosine kinase.
- Other “targetable” mutations have been described in a low frequency of adenocarcinomas, including ALK, ROS1 or HER2 mutations.
- **RB** and **P53** mutations are very common in **small-cell carcinoma**.

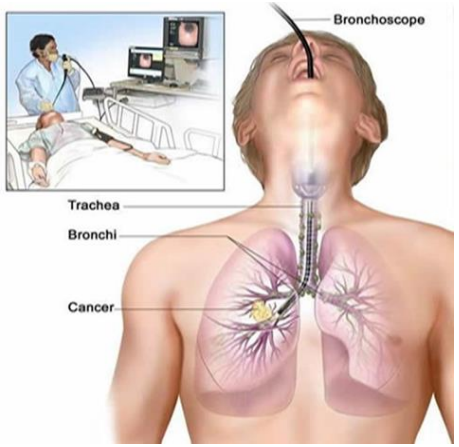
Clinical features of lung cancer:

- Usually insidious.

- Chronic cough and hemoptysis, SOB, and weight loss.

- By the time other symptoms, such as hoarseness, chest pain, and pericardial or pleural effusion appear, the prognosis is poor.

- Too often, the tumor presents with symptoms caused by metastatic sites such as the brain and bone.



Morphology:

- Begin as small lesions that are firm and gray-white.
- Finally, those tumors extend to the pleura & chest wall & involve the intra-thoracic structures.
- More distant spread occurs via the lymphatics or via the hematogenous route.

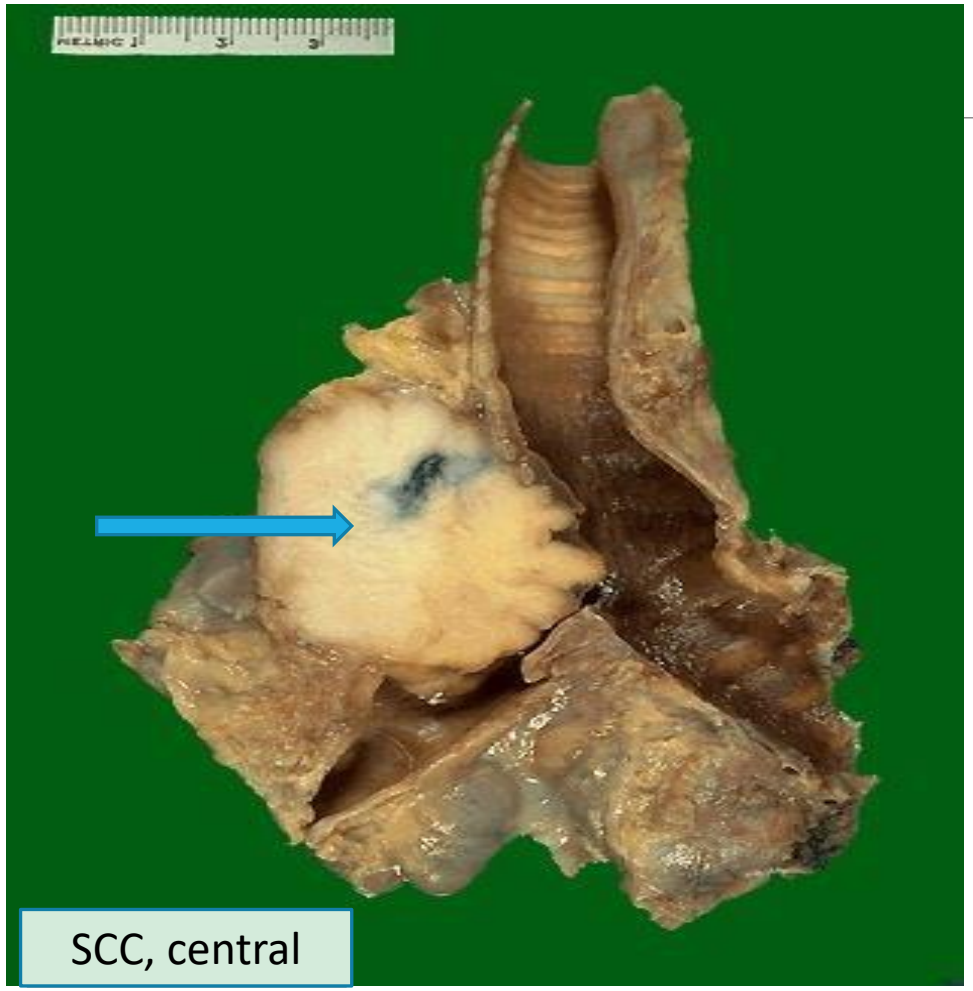
Growth pattern

- ✓ Central masses:

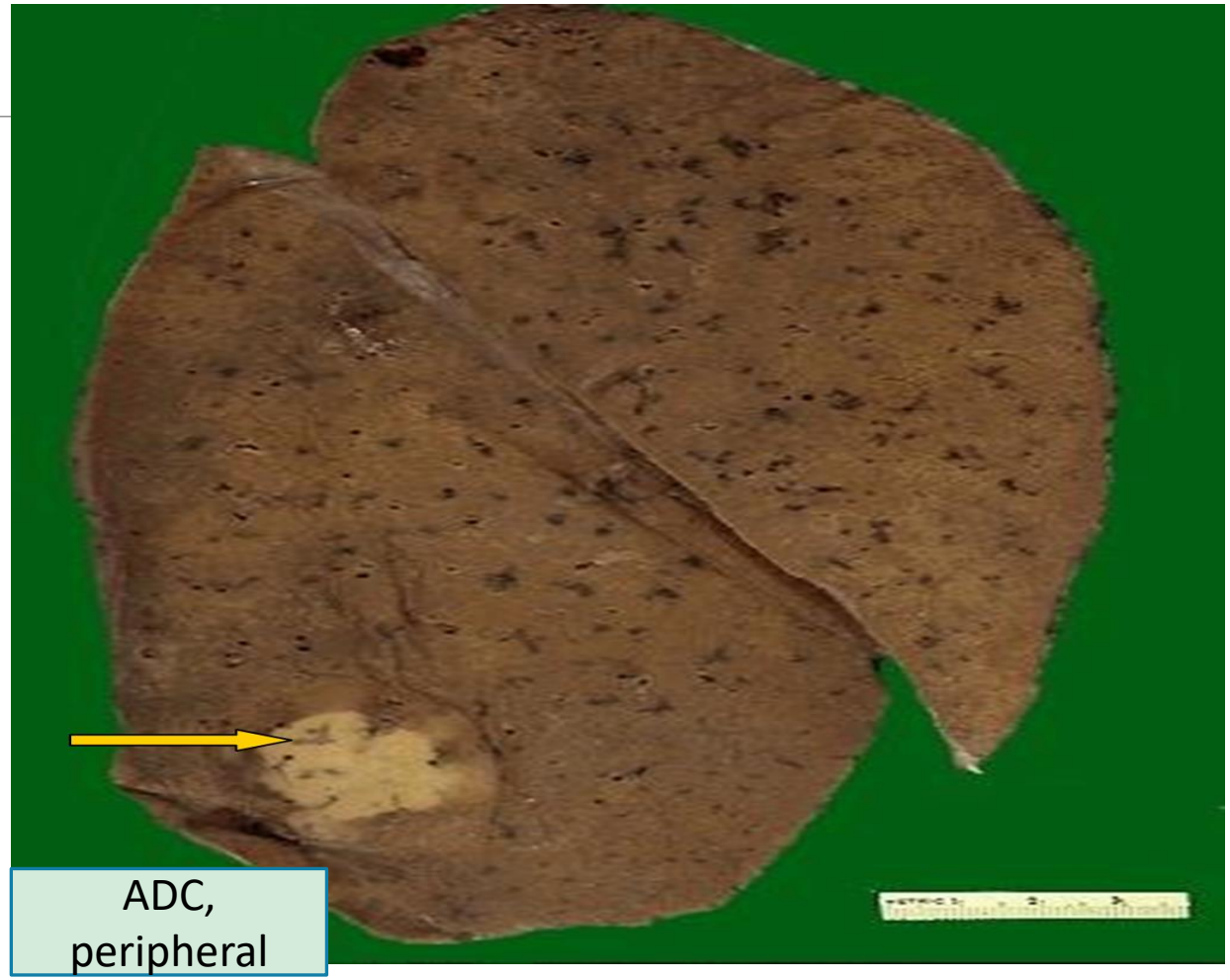
  Typically, squamous cell & small cell CA.

- ✓ Peripheral nodules or masses;

  Typically, adenocarcinomas & large cell carcinomas.



SCC, central



ADC, peripheral

Adenocarcinoma :

- Usually **peripherally** located.
- In general, they **grow slowly** and form smaller masses.
- They tend to **metastasize early**.
- It is **the most common cancer in women & non-smokers.**

Histologically :

- May assume variable growth patterns:

  i. Lepidic.

  ii. Acinar (gland- forming)

  iii. Papillary.

  iv. Micropapillary.

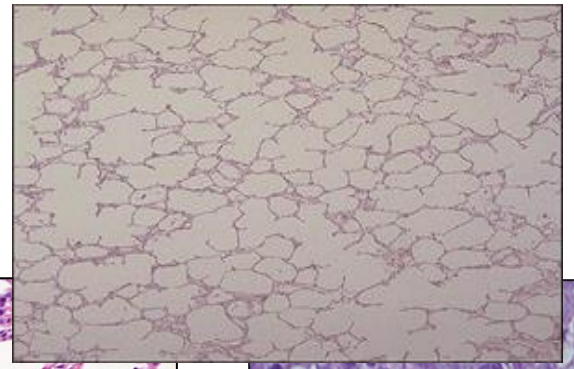
  v. Solid (requires demonstration of intracellular **mucin**).

- Mucinous, which is often multifocal and may manifest as pneumonia-like consolidation.

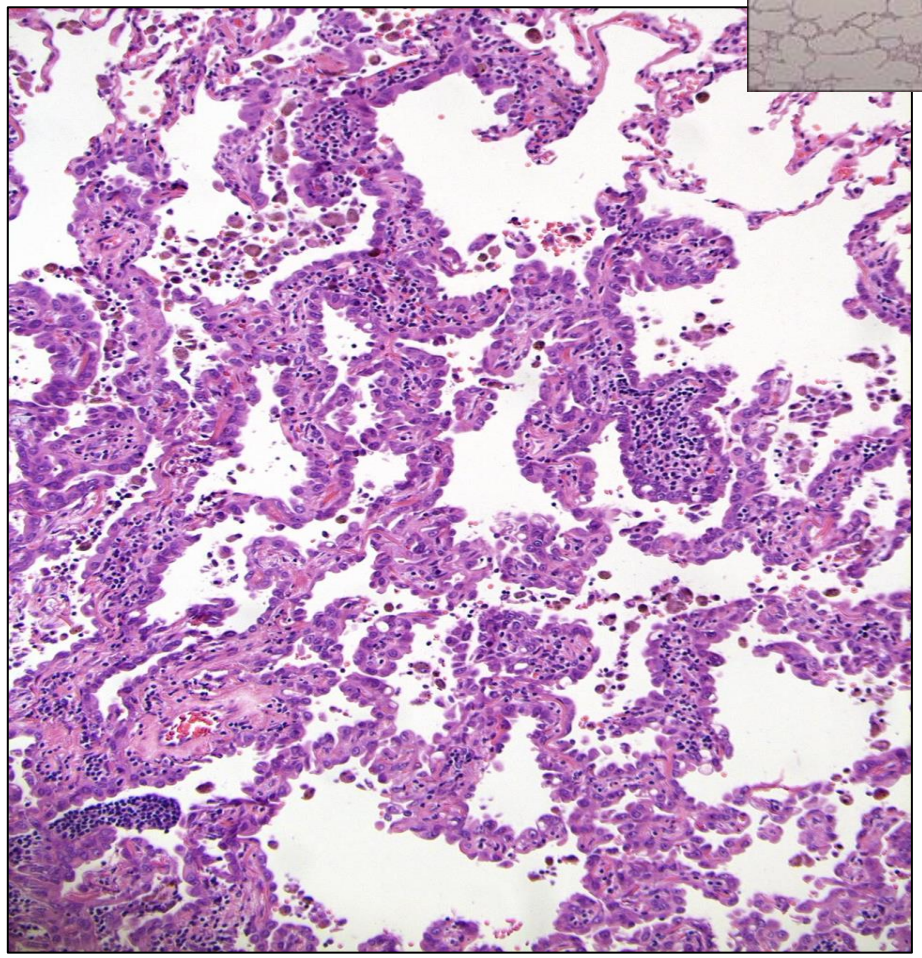
-**The putative precursor for peripheral adenocarcinoma** is atypical adenomatous hyperplasia (AAH) ⟹ AIS ⟹ Minimally invasive adenocarcinoma ⟹ invasive adenocarcinoma

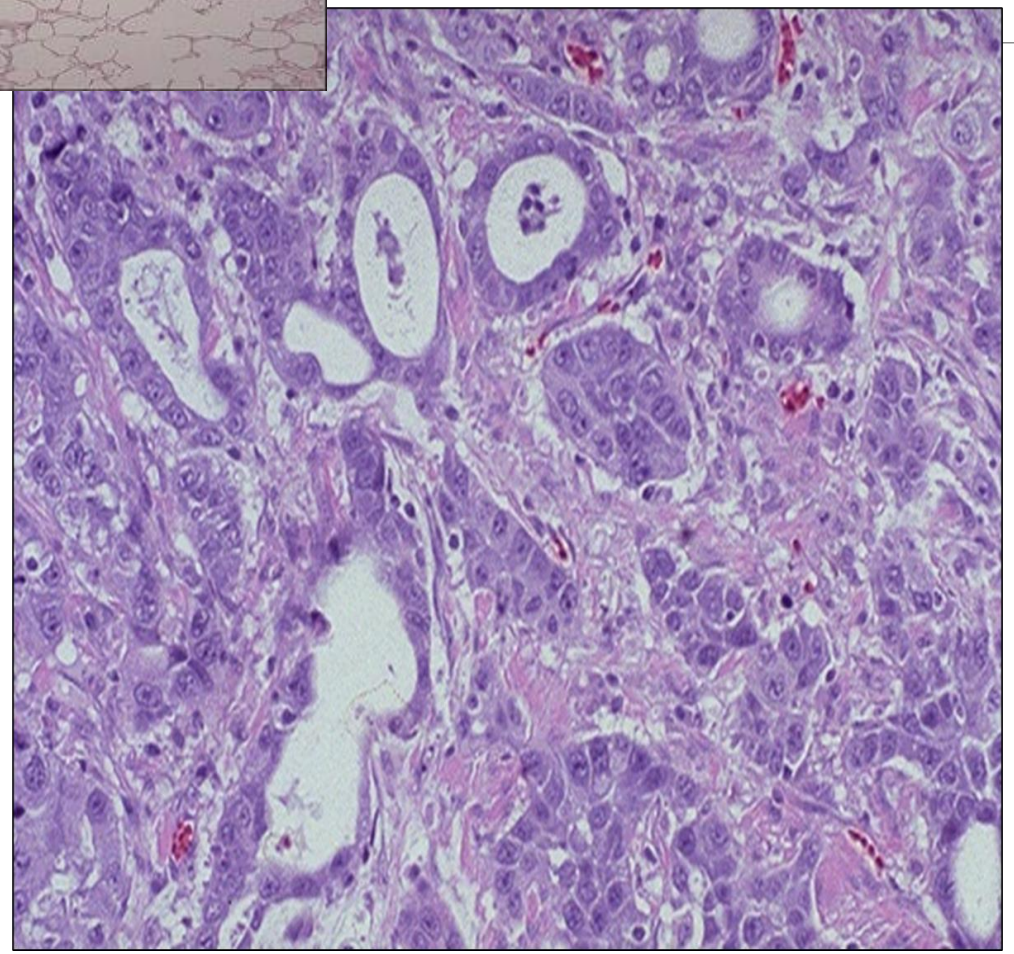
-**TTF-1 +**

Lepidic

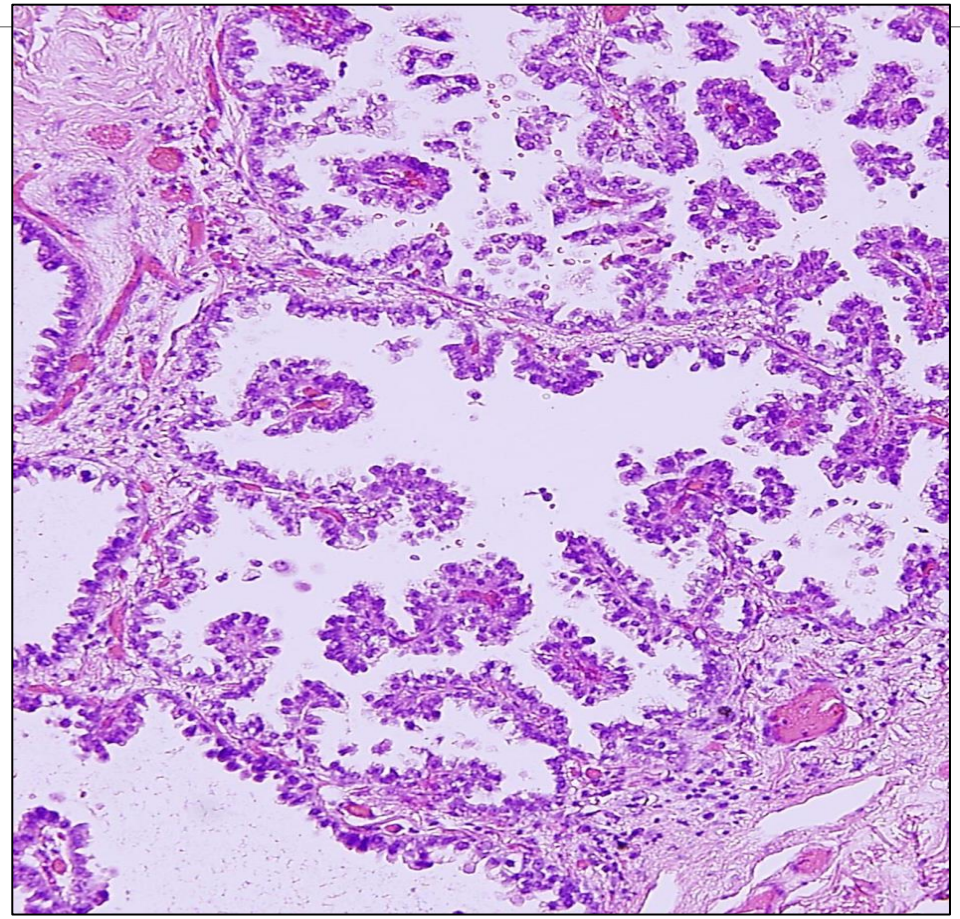


Acinar

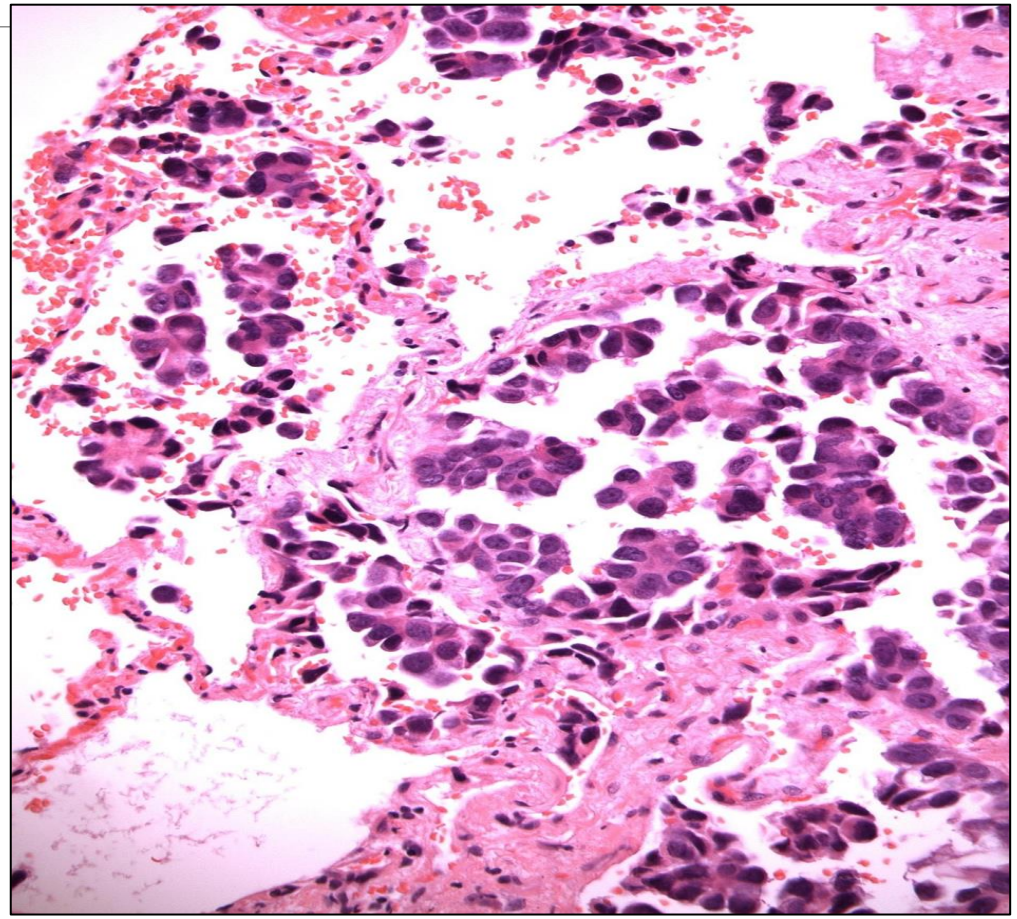




Papillary

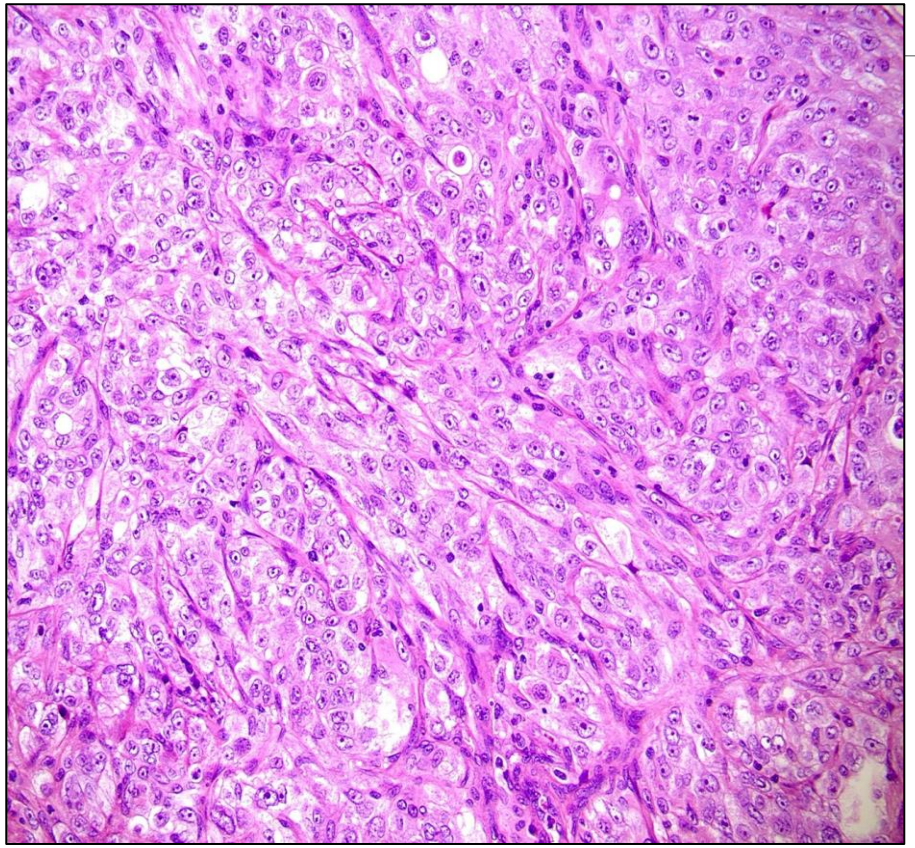


Micropapillary
No fibrovascular core

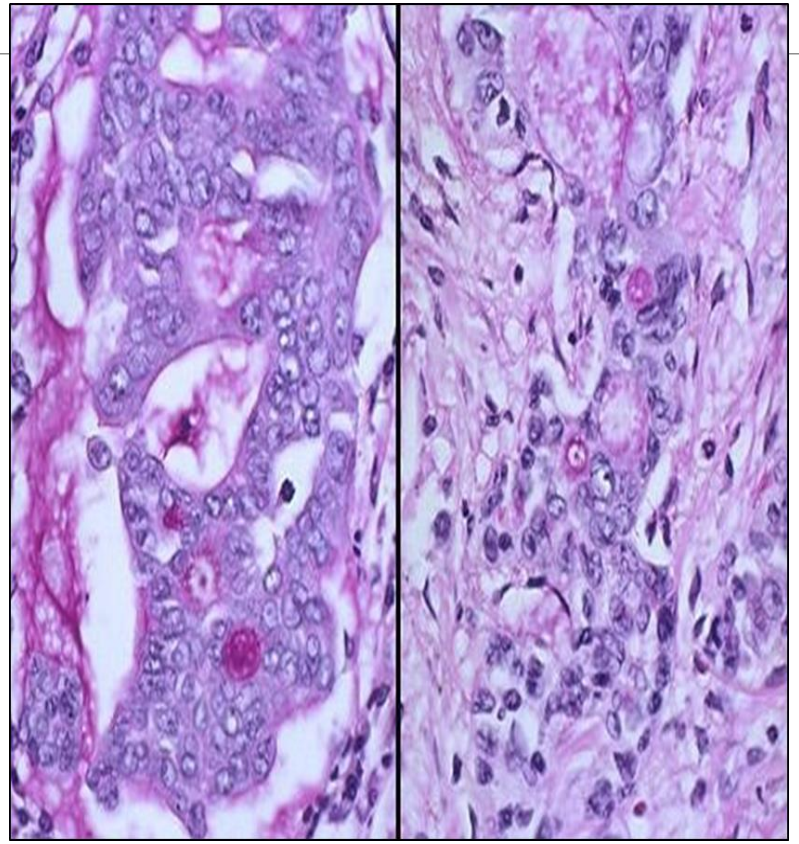


Mucin stains

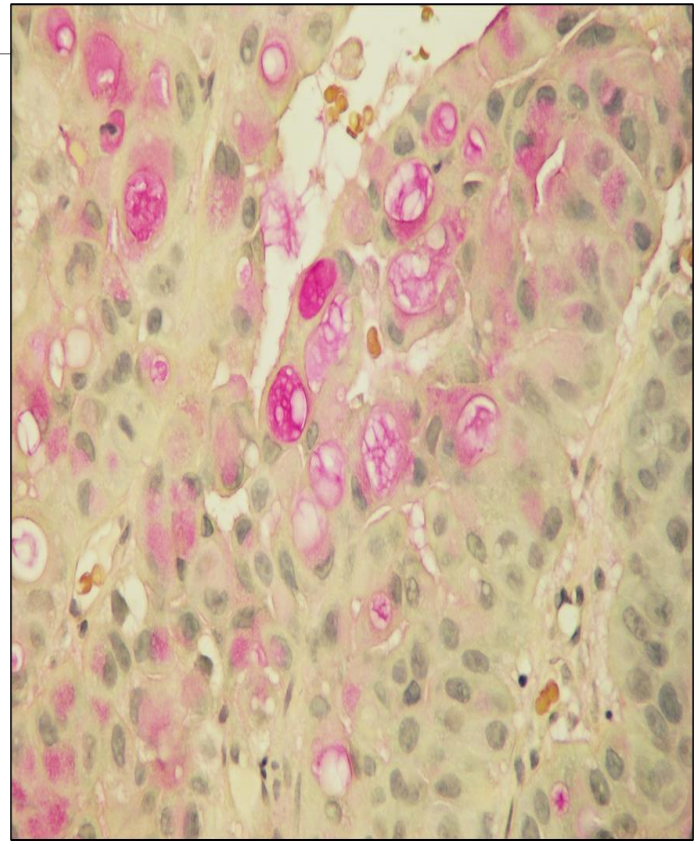
Solid



PAS



Mucicarmine

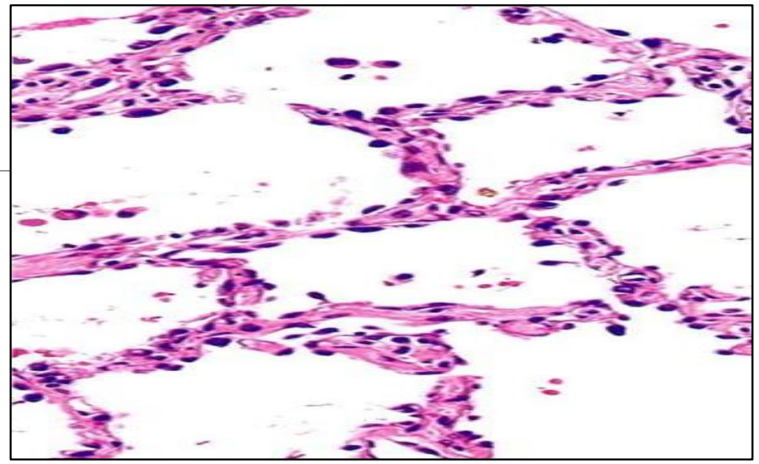


Some Key concepts about adenocarcinoma and its precursor lesions

Atypical Adenomatous Hyperplasia (AAH)

-Well-demarcated focus of epithelial proliferation with nuclear hyperchromasia & pleomorphism

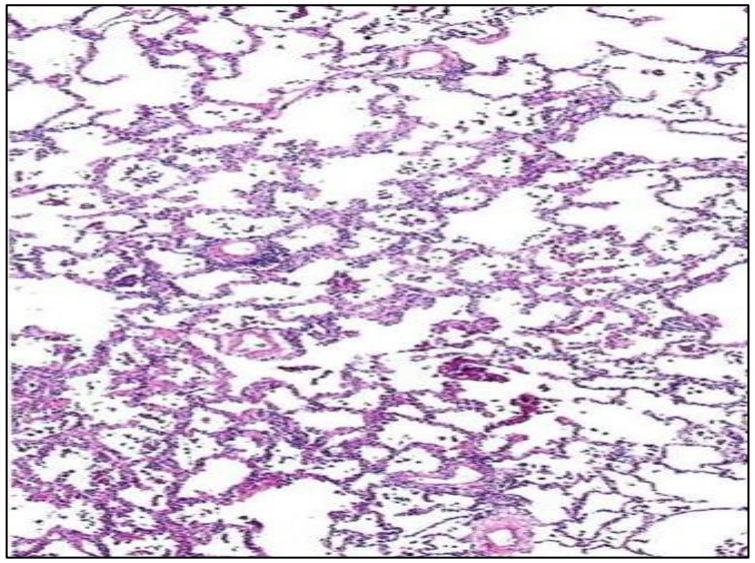
-A diameter of 5 mm or less.



Adenocarcinoma In Situ (AIS)

Formerly bronchioloalveolar carcinoma.

- Tumor ≤ 3.0 cm
- Pure lepidic growth
- No spread through air spaces (STAS)
-No stromal, Lymphovascular invasion (LVI) or pleural invasion



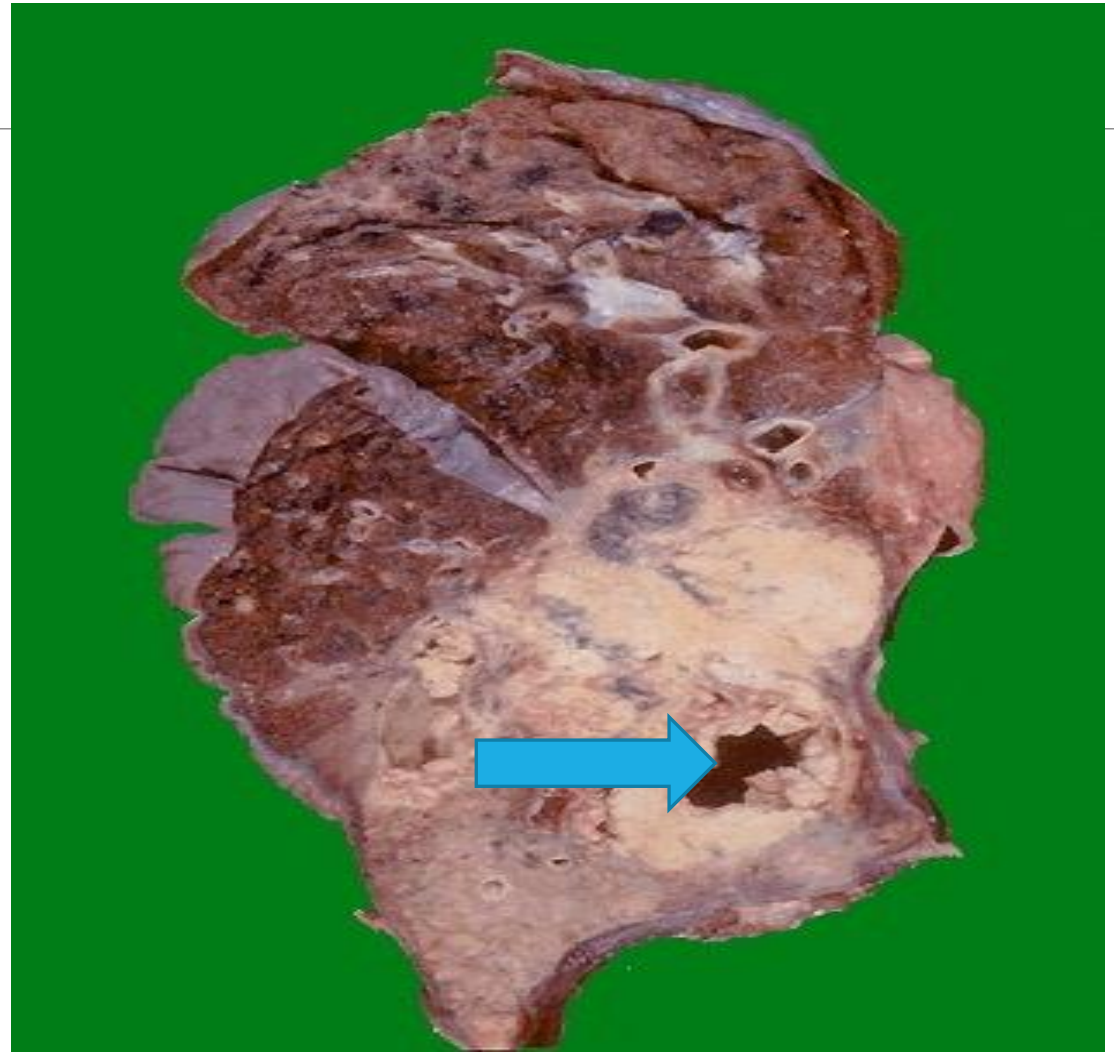
Minimally Invasive Adenocarcinoma (MIA)

- Tumor ≤ 3.0cm
- Predominantly lepidic growth
- Invasive component: ≤ 0.5 cm
- Diagnosis excluded if: Invades pleura or LVI, Tumor necrosis, or STAS

Squamous cell carcinoma :

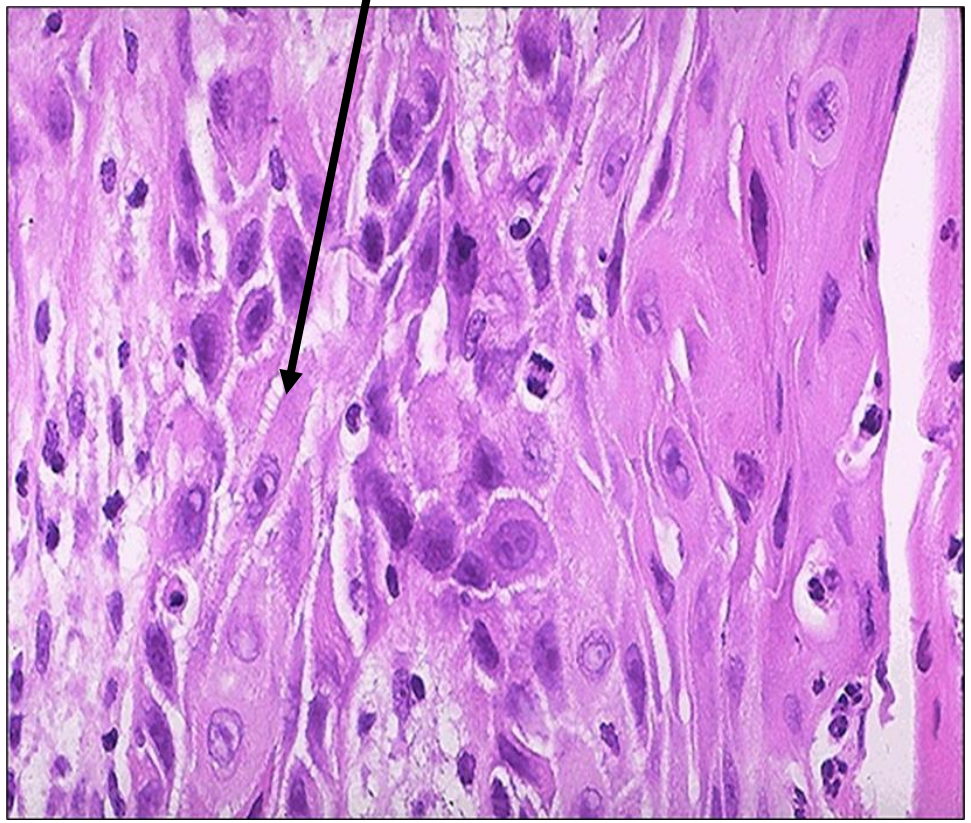
- More common in men, closely related to smoking.
- Arises centrally in major bronchi & spreads to hilar lymph nodes.
- Disseminate outside the thorax later than do other histologic types.
- Large lesions undergo central necrosis & cavitation.
- Preceded by squamous metaplasia, dysplasia & carcinoma in situ

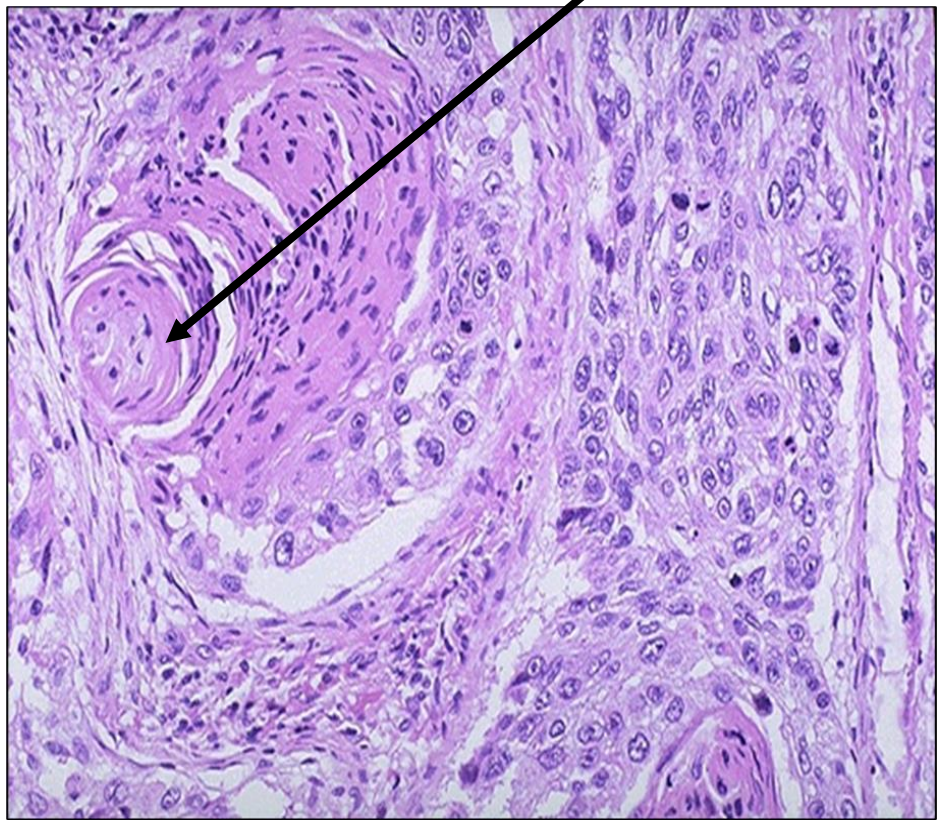
A larger squamous cell carcinoma in which a portion of the tumor demonstrates central cavitation



Histologically :

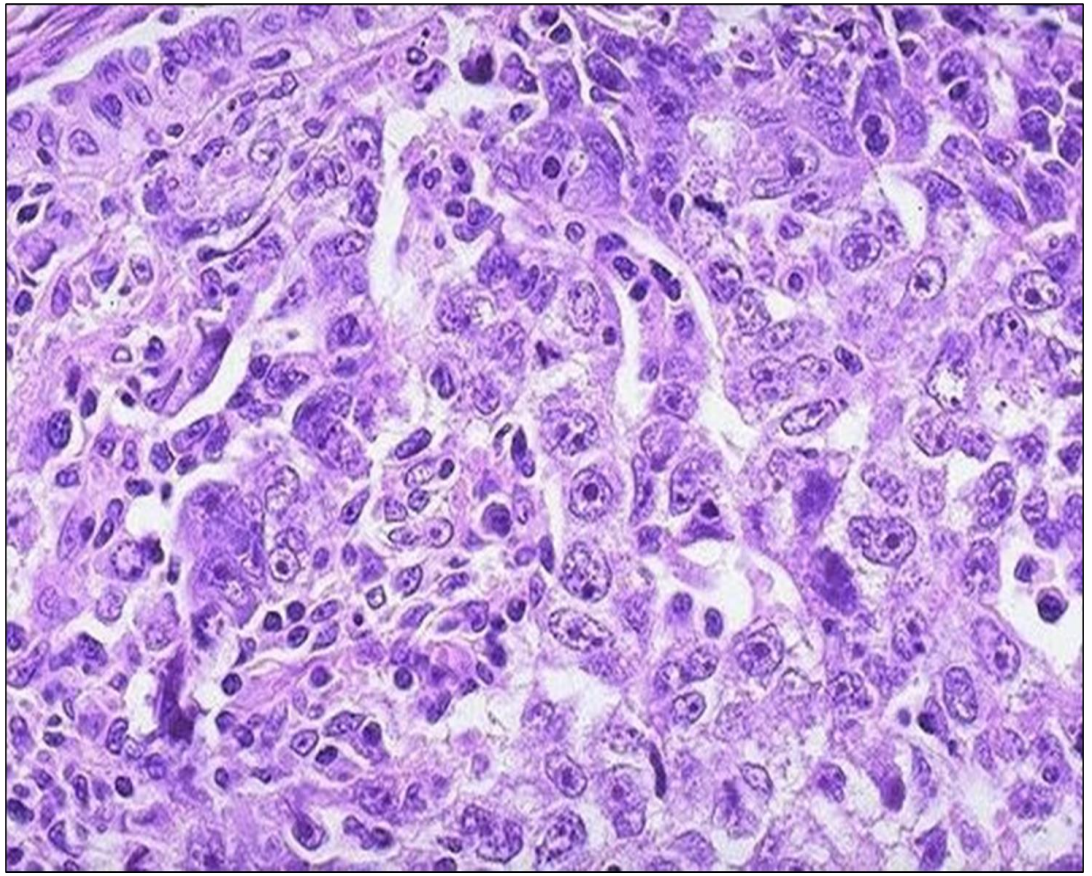
- Ranges from well-differentiated squamous cell carcinoma showing **keratin pearls** & **intercellular bridges** to poorly differentiated.
- **P40+, p63 +**





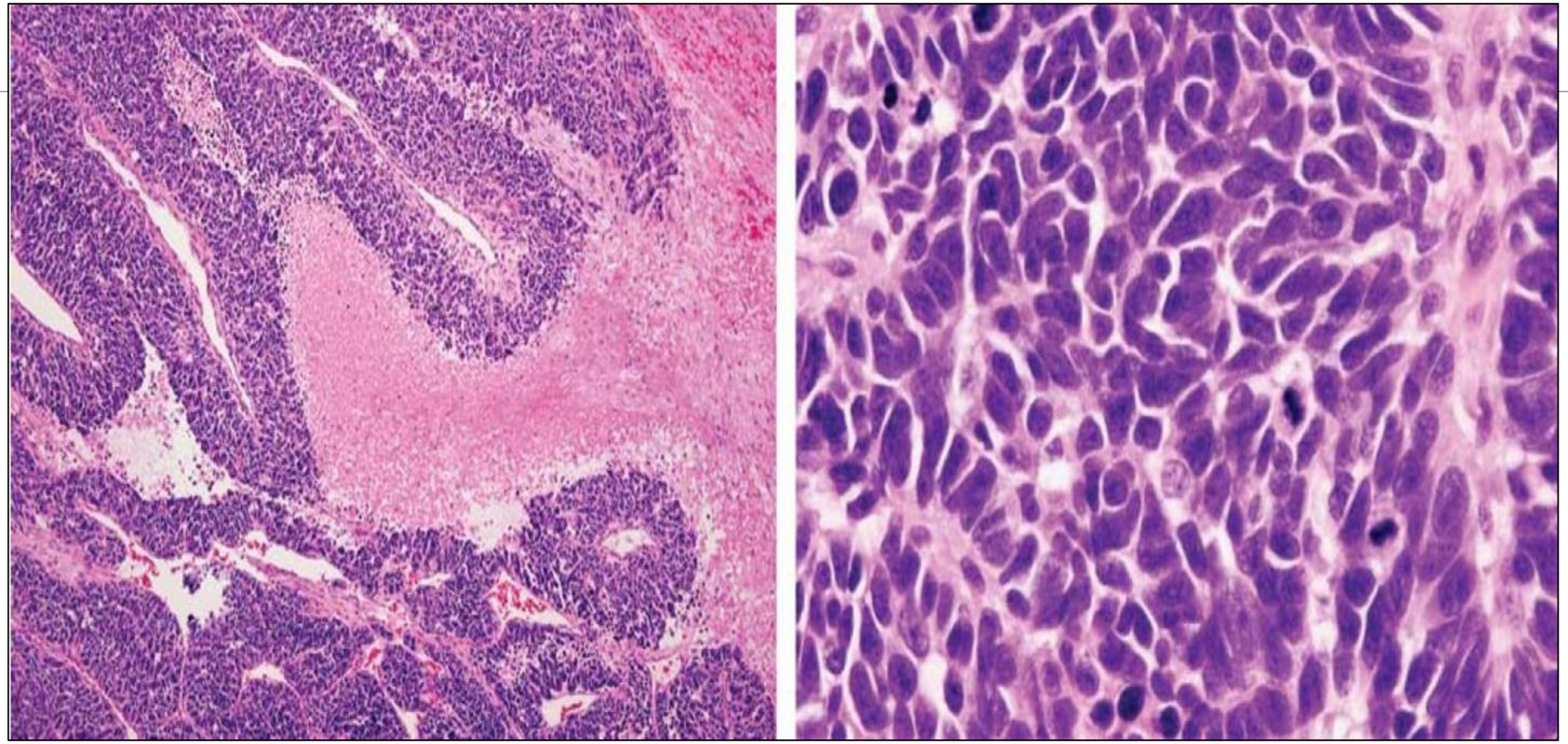
Large cell carcinoma

- Undifferentiated malignant epithelial tumor that **lacks** the **cytological, architectural**, and **IHC features** of small cell ca., squamous cell ca., or adenocarcinoma.
- The cells have **large nuclei**, prominent nucleoli, and a moderate amount of cytoplasm.
- The tumor is highly malignant and tends to be **peripheral** in location.

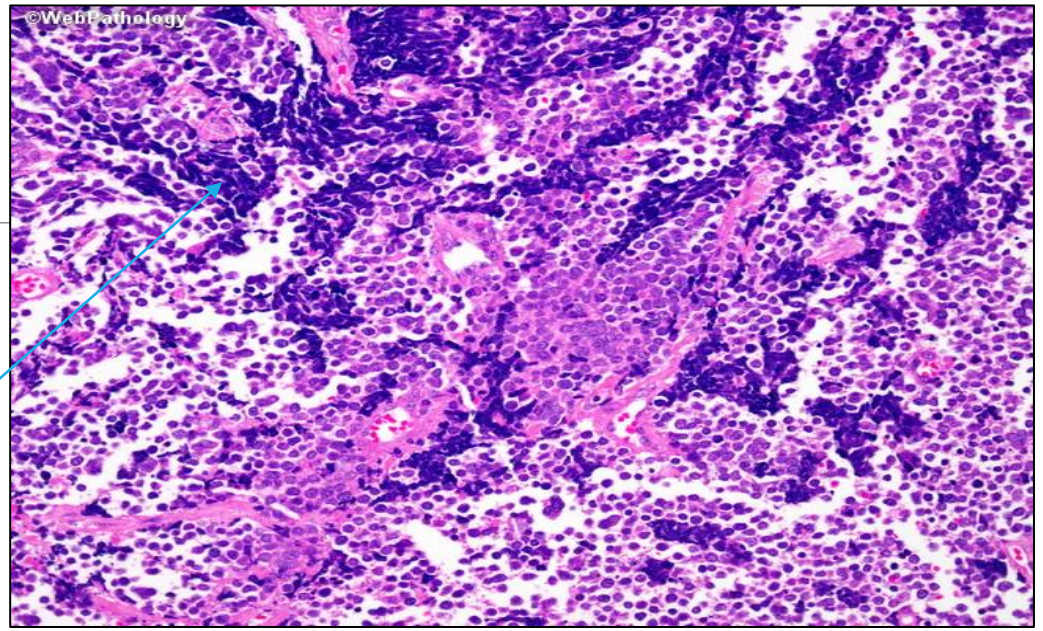


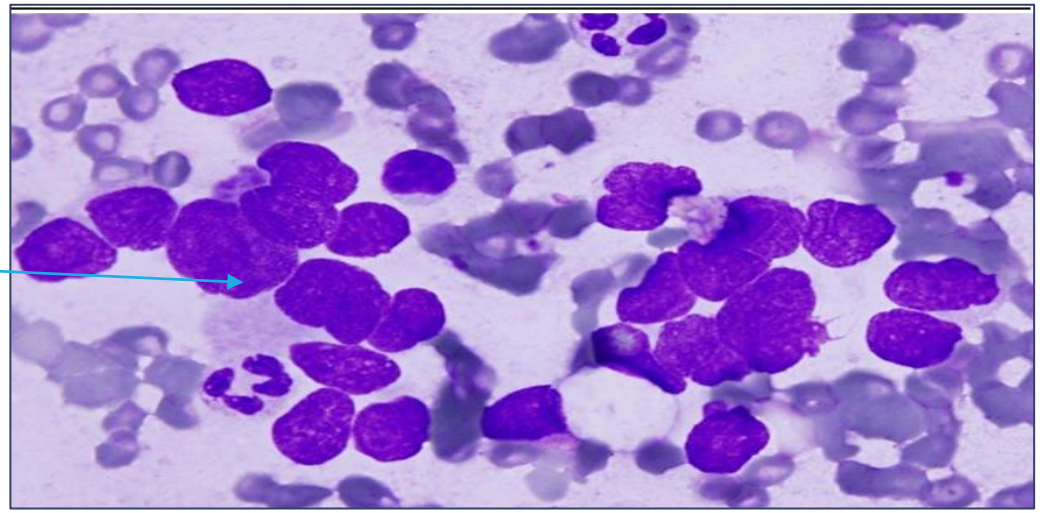
Small cell carcinoma

- Appear as a gray **centrally** located mass with **early involvement of lymph nodes**
- M > F.
- >90% in smokers.
- The tumor is composed of rounded or fusiform cells with **scanty cytoplasm** and finely granular chromatin with a **salt-and-pepper appearance**; **mitotic figures are numerous with necrosis**. The cells show **fragmentation** (it is a small round blue cell tumor)
- The tumor cells are derived from neuro-endocrine cells of the lung.
- **Chromogranin +, synaptophysin +**



- **Cytology:**
  - Crush artifact (the tumor cells are markedly fragile and often show fragmentation and “crush artifact”.
  - Nuclear molding.





Local& secondary effects of lung cancer:

1- Local effects (depend on location):

- **Central** - cough, hemoptysis, obstruction, atelectasis.

- **Peripheral** – incidental or hemoptysis or pneumonia.

2- Regional Invasion

- Recurrent laryngeal nerve ---vocal cord paralysis.
- Phrenic nerve --- diaphragmatic paralysis.
- Esophagus ----bronchoesophageal fistula.

- Late invasion of upper lobe tumors :

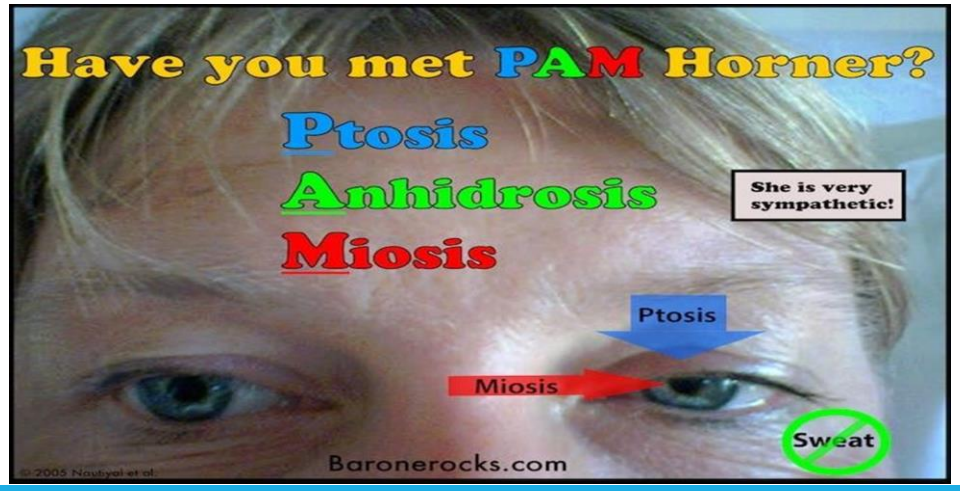
- ✓ SVC compression by tumor ⟹ Superior Vena Cava Syndrome

- ✓ Apical 'Pancoast' tumors (the combination of clinical findings is known as **Pancoast syndrome**):

  Brachial plexus: Pain in the distribution of the ulnar nerve

  Destruction of 1st.& 2nd.ribs ± thoracic vertebrae

  Cervical sympathetic chain invasion: Horner's Syndrome (ptosis, anhidrosis, miosis, and ipsilateral enophthalmos).



3-Extrathoracic Metastases :

- Adrenals, Bone, Brain and Liver

4- Paraneoplastic Syndrome :

3%-10% of patients with cancer develop paraneoplastic syndrome

(1) Hypercalcemia by squamous cell carcinoma
(2) Cushing syndrome.
(3) ADH.
(4) Neuromuscular.
(5) Clubbing of fingers & hypertrophic pulmonary osteoarthropathy

Prognosis

- Squamous cell carcinoma and adenocarcinoma have a more favorable prognosis than SCLC.
- The overall 5 years survival is 16%.
- SCLCs have invariably spread by the time they are detected; **very poor prognosis**
- SCLCs are very sensitive to chemotherapy but **invariably recur.**
- The median survival, even with treatment, remains only 1 year, and only 5% are alive at 10 years.

TNM 8th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T_0	No evidence of tumor
T_{is}	Carcinoma in situ
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T_2	> 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	>3 to ≤4cm
T_{2b}	>4 to ≤5cm
T_3	>5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	> 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

Thank you