

TUMORS OF THE LUNG



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Objectives

- Know the **epidemiology of lung cancer**
- Is aware of the new classification of bronchogenic carcinoma which include: squamous carcinoma, adenocarcinoma, small cell and large cell (anaplastic) carcinomas.
- Understand the predisposing factors of bronchogenic carcinoma.
- Understands the clinical features and gross pathology of bronchogenic carcinoma. Know the precursors of squamous carcinoma (squamous dysplasia) and adenocarcinoma (adenocarcinoma in situ and atypical adenomatous hyperplasia).
- Have a basic knowledge about neuroendocrine tumours with special emphasis on small cell carcinoma and bronchial carcinoid.
- Is aware that the lung is a frequent site for metastatic neoplasms.

Lung Tumors

- Most lung tumors are malignant.
- Primary lung cancer is a common disease BUT metastatic tumors are more common than the primary tumors.
- The most common benign lesions are hamartomas.

Epidemiology

1. Primary lung cancer is the most common fatal cancer in both men and women worldwide.
 - a. Accounts for >30% of cancer deaths in men
 - b. Accounts for >25% of cancer deaths in women
2. Incidence of lung cancer is declining in men but increasing in women.
3. Peak incidence is at 55 to 65 years of age.

Classification of bronchogenic carcinoma

Malignant epithelial tumors/ bronchogenic carcinoma

- I. **Non-Small Cell Lung Carcinoma (NSCC)**
 1. Squamous cell carcinoma
 2. Adenocarcinoma
 3. Large cell carcinoma
- II. **Small cell lung carcinoma (SCC)**
- III. **Combine patterns**
- IV. **Carcinoid tumor**
- V. **Others**

Malignant mesothelial tumor

Malignant mesothelioma

- Epithelial
- Fibrous (spindle cell)
- Biphasic

➤ Miscellaneous malignant tumor

- Carcinosarcoma
- Pulmonary blastoma
- Melanoma
- Lymphoma
- Others

Classification of Malignant epithelial tumors of lung

I. Non-Small Cell Lung Carcinoma (NSCC)

1. Squamous cell carcinoma (SqCC)
2. Adenocarcinoma, including bronchioloalveolar carcinoma
3. Large cell carcinoma

II. Small cell lung carcinoma (SCC)


III. Combine patterns

- Most frequent patterns:
 - Mixed squamous cell ca and adenocarcinoma.
 - Mixed squamous cell ca and SCC.

IV. Carcinoid tumors

V. Others

Both small cell carcinoma and carcinoids are neuroendocrine tumors as both arise from the neuroendocrine cells normally present in the lung

- 
- Adenocarcinoma (38%)
 - Squamous cell carcinoma (20%)
 - Small cell carcinoma (14%)
 - Large cell carcinoma (3%)
 - Other (25%)

Bronchogenic carcinoma

- Bronchogenic carcinoma is a malignant neoplasm of the lung arising from the epithelium of the lung.
- is a common cause of cancer death in both men and women.
- For therapeutic purposes, bronchogenic carcinoma are classified into:
 1. **Non- Small cell lung carcinoma (NSCC)** which includes squamous cell, adenocarcinomas, and large-cell carcinomas.
 2. **Small cell lung carcinoma (SCC)**

Lung Cancer Pathology

www.TheBestOncologist.com

Non-Small Cell
85%

Small Cell
15%

Large cell
carcinoma

Adenocarcinoma

Squamous cell
carcinoma

Bronchogenic carcinoma

It is important to differentiate NSCC from SCC because treatments are different.

NSCC therapy

- Surgical - offers the best chance for curing.
- Radiation - controls local disease.
Radiation therapy is most commonly used to palliate symptoms.
- Chemotherapy – not effective.

SCC therapy

- Chemotherapy is very effective because small cell carcinomas are highly responsive to chemotherapy

Predisposing factors of bronchogenic carcinoma

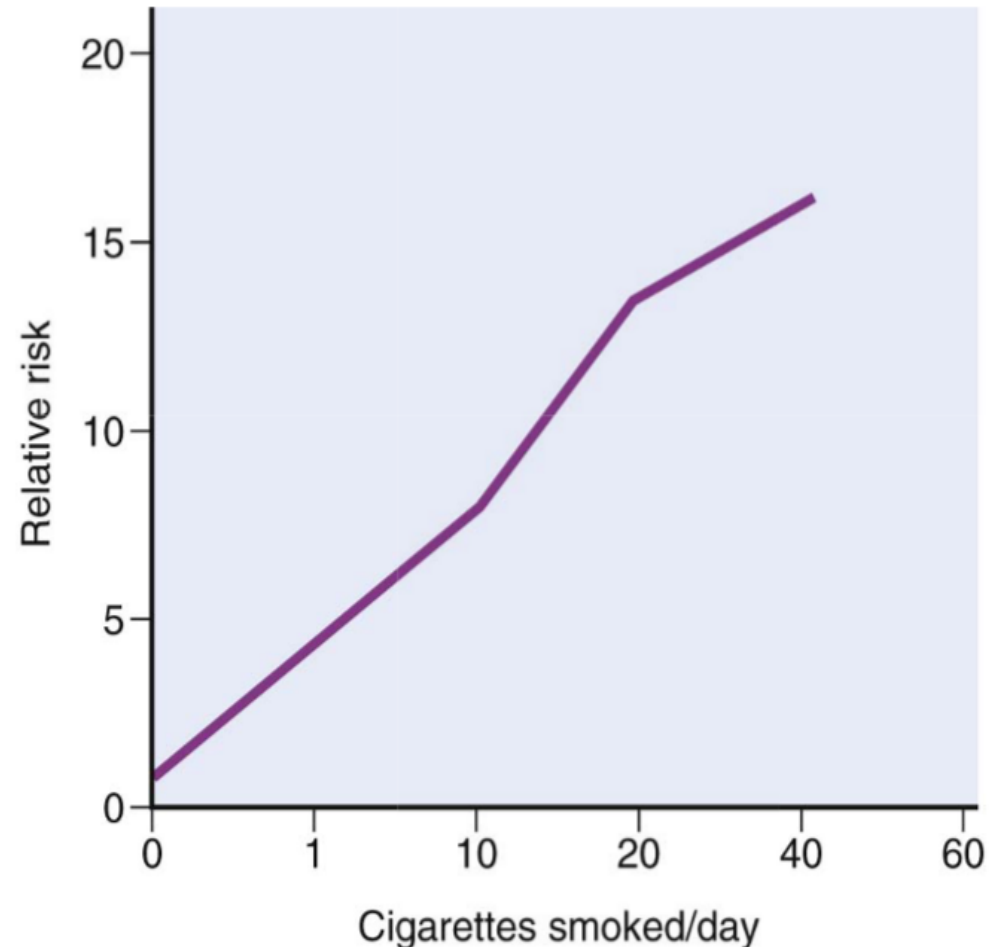
1. Tobacco smoking:

- Some 85% of lung cancers occur in cigarette smokers. Most types are linked to cigarette smoking, but the strongest association is with squamous cell carcinoma and small cell carcinoma
- The nonsmoker who develops cancer of the lung usually has an adenocarcinoma.
- is directly proportional to the number of cigarettes smoked daily and the number of years of smoking.
- Cessation of cigarette smoking for at least 15 years brings the risk down.
- Passive smoking increases the risk to approximately twice than non-smokers.
- Cigarette smokers show various histologic changes, including squamous metaplasia of the respiratory epithelium which may progress to dysplasia, carcinoma in situ and ultimately invasive carcinoma

Predisposing factors

1. Tobacco smoking:

- The risk of lung cancer is determined by the number of cigarettes smoked
- The risk is 20 to 40 times greater among habitual heavy smokers



Smoking and Cancer

Study: "If Women Smoke Like Men, They Will Die Like Men"

Female smokers have a much greater risk of death from lung cancer and chronic obstructive lung disease in recent years than female smokers 20 or 40 years ago, reflecting changes in smoking behavior according to an article published in New England Journal of Medicine.

Female smokers today smoke more like men than women in previous generations, beginning earlier in adolescence and, until recently, smoking more cigarettes per day.

Predisposing factors of bronchogenic carcinoma

Other causes

2. **Radiation:** All types of radiation may be carcinogenic and increase the risk of developing lung cancer. Radium and uranium workers are at risk
3. **Asbestos:** increased incidence of cancer with asbestos exposure, especially in combination with cigarette smoking.
4. Industrial exposure to **nickel and chromates, coal, mustard gas, arsenic, iron** etc.
5. **Air pollution:** May play some role in increased incidence. Indoor air pollution especially by radon.
6. **Scarring:** sometimes old infarcts, wounds, scar, granulomatous infections are associated with adenocarcinoma.

Precursor Lesions

- Three types of precursor epithelial lesions are recognized:
 - (1) Squamous dysplasia and carcinoma in situ can lead to:
Squamous cell carcinoma
 - (2) Atypical adenomatous hyperplasia can lead to:
Adenocarcinoma
 - (3) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia can lead to:
Neuroendocrine tumors
- It should be noted that the term "precursor" does not imply that progression to invasion will occur in all cases.

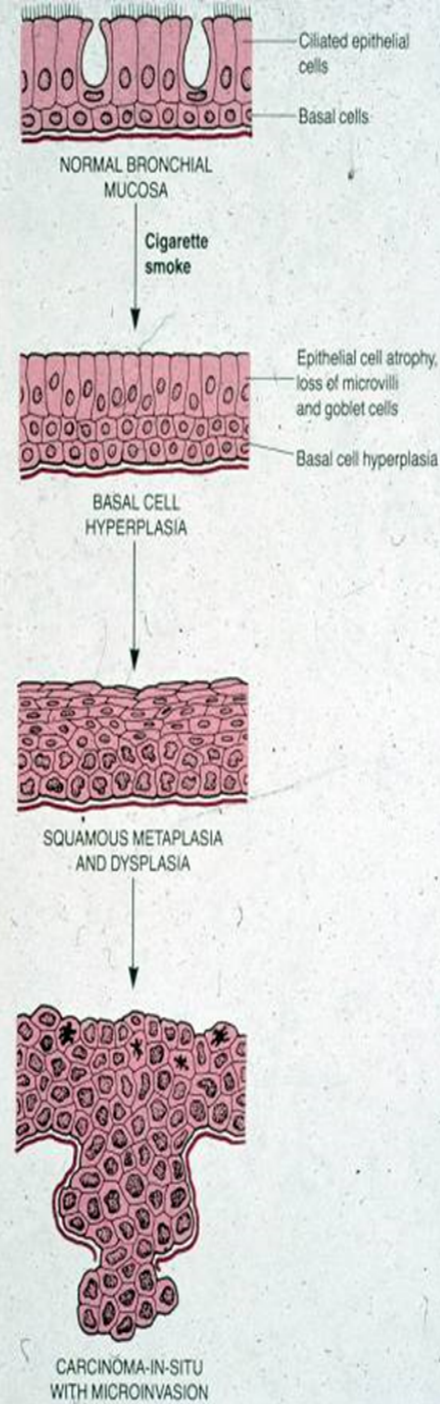
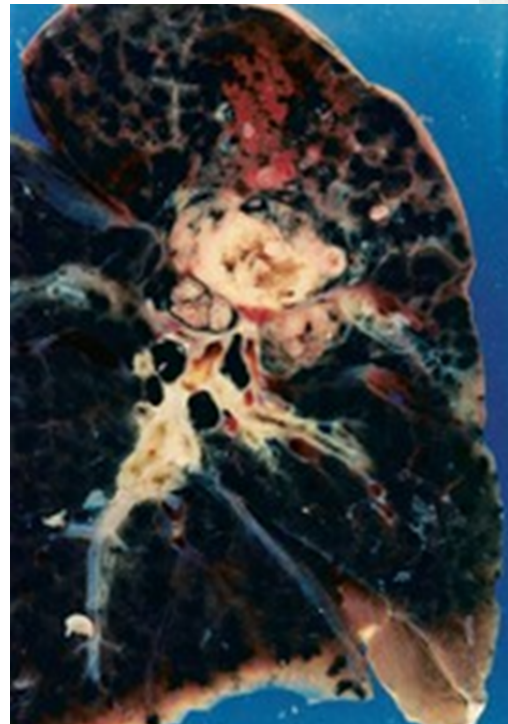
Squamous cell carcinoma

- Second most common bronchogenic carcinoma
- Strong association with smoking (25 times risk)
- Before Males>Females, now incidence in female rising because of smoking.
- This type of cancer is preceded by years of progressive mucosal changes of respiratory epithelium to squamous metaplasia to dysplasia to CA in situ to invasive SCC.

SqCC arise in the central airways (centrally located). So they appear as a hilar mass. Frequently cavitate

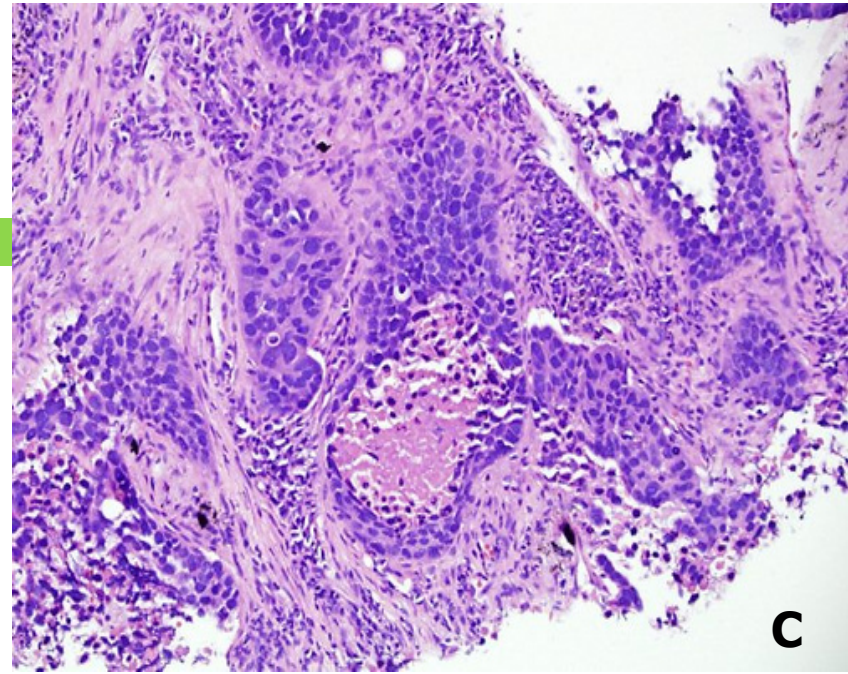
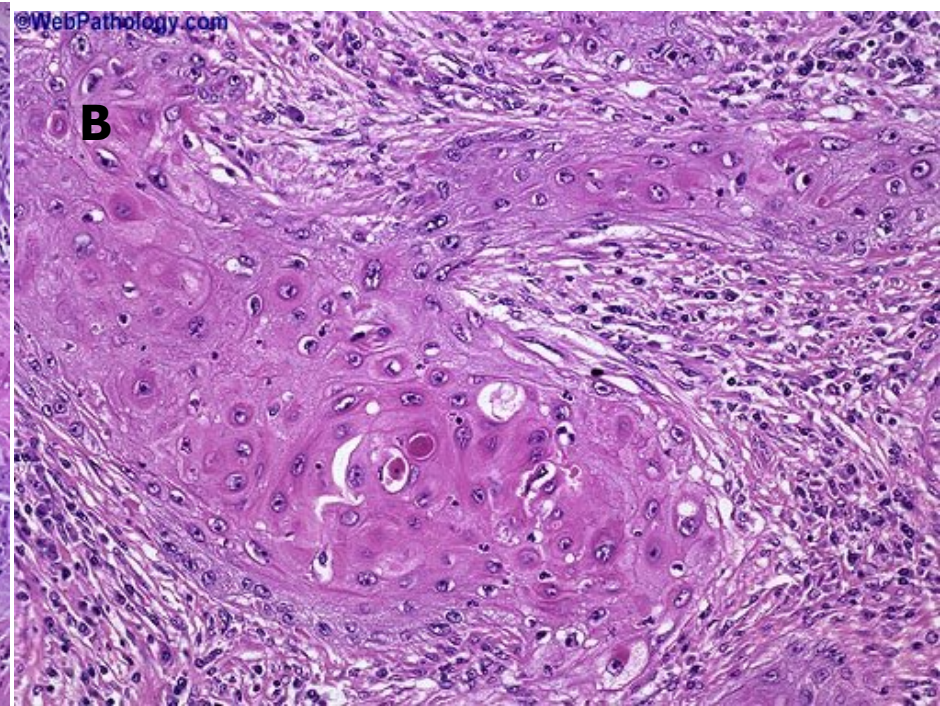
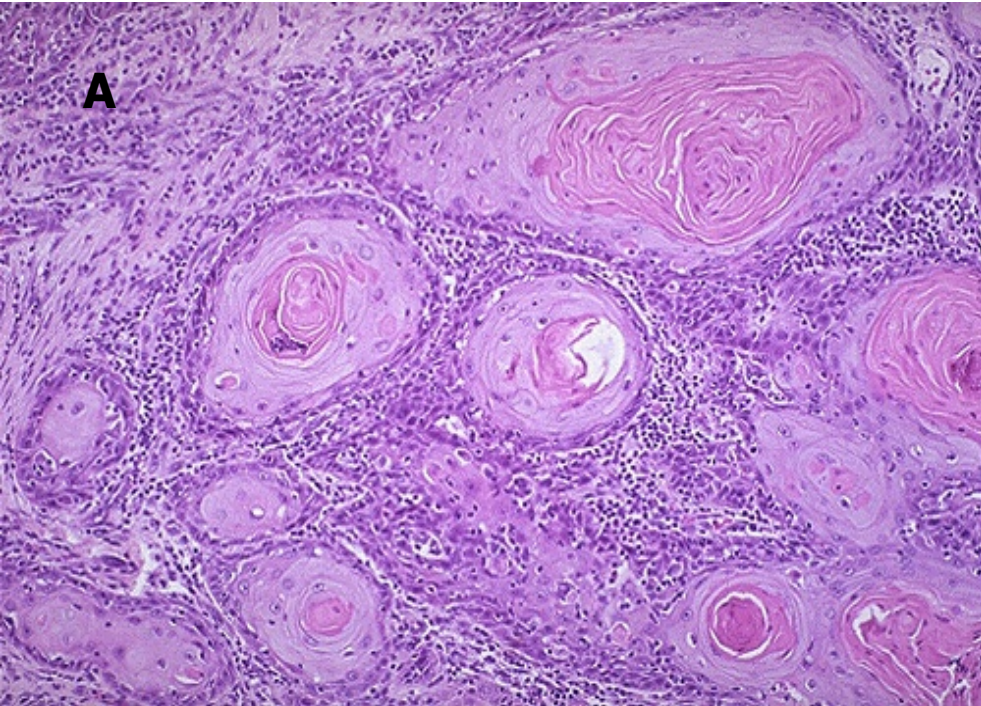
Tumor cells secrete a parathyroid hormone (PTH)- like peptide leading to hypercalcemia.

Poor prognosis



Squamous cell carcinoma (SqCC)

- Histologically, these tumors are graded according to degree of squamous differentiation and tumors ranges from:
 - well-differentiated squamous cell carcinoma (A),
 - moderately differentiated SqCC (B) to
 - poorly differentiated SqCC (C).

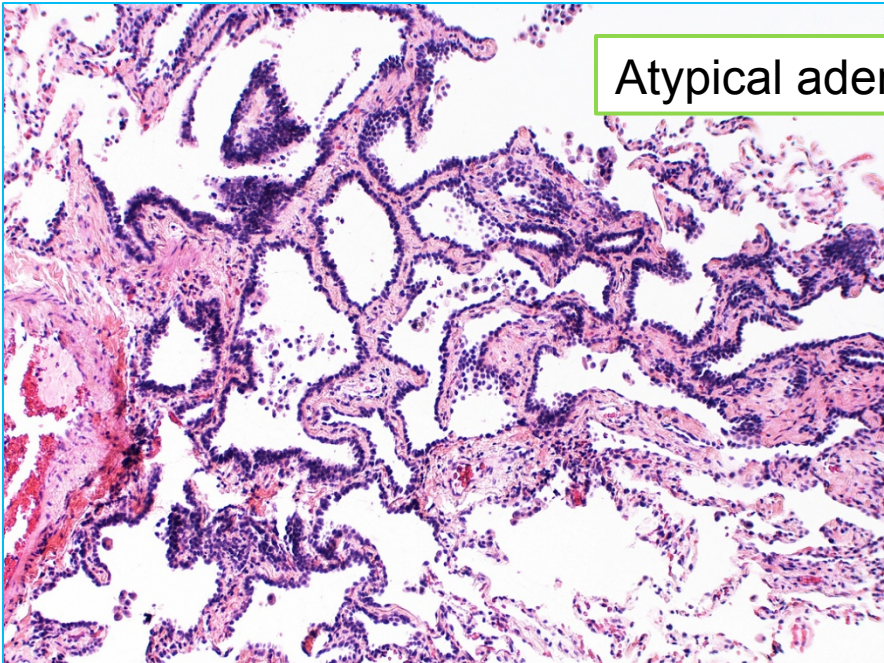


Adenocarcinomas

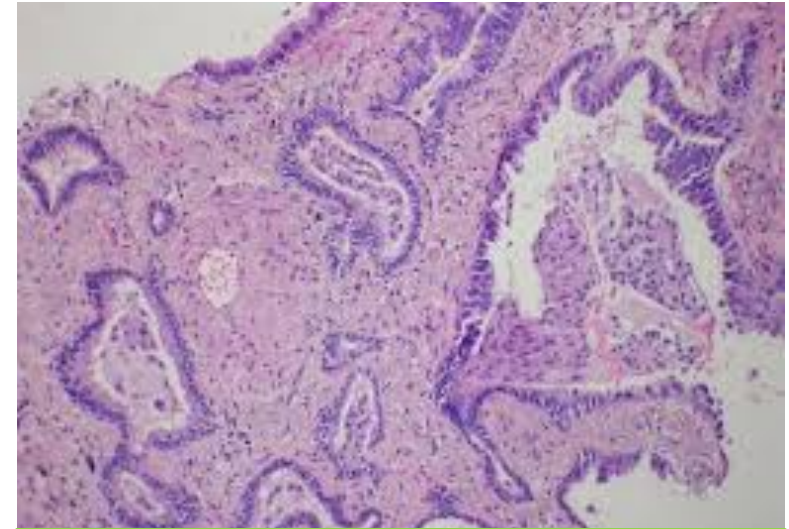
- Adenocarcinomas is now the most frequent histologic subtype of bronchogenic carcinoma; more common in women.
- They do not have a clear link to smoking history
- Most often they are associated with pulmonary scars
- They are classically peripheral tumors arising from the peripheral airways and alveoli.

Adenocarcinoma Precursor Lesions

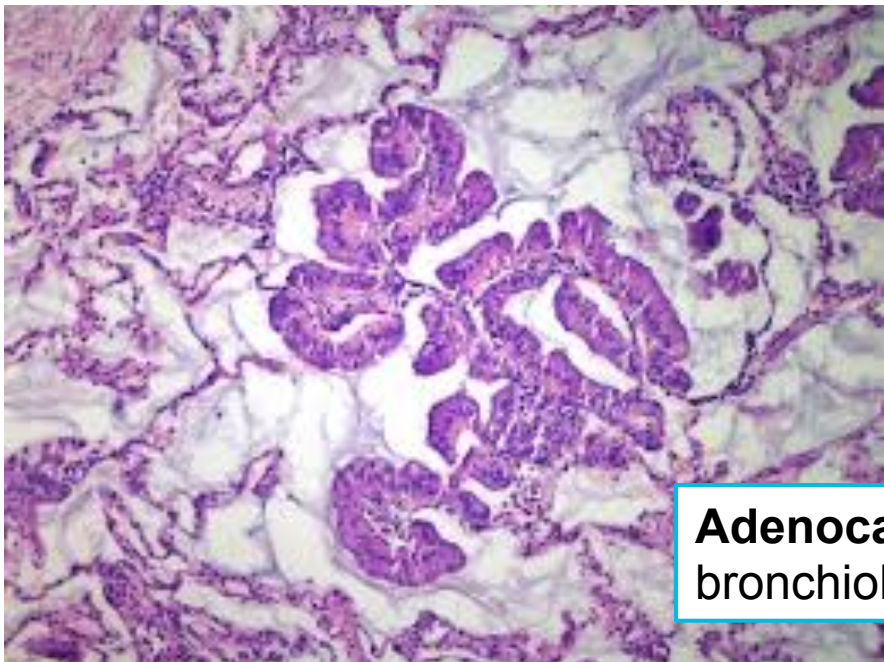
- **Atypical adenomatous hyperplasia** is a small lesion (≤ 5 mm) characterized by dysplastic pneumocytes lining alveolar walls that are mildly fibrotic
- **Adenocarcinoma in situ; AIS** (formerly called bronchioloalveolar carcinoma) is a lesion that is less than 3 cm and is composed entirely of dysplastic cells growing along preexisting alveolar septae, no growth patterns other than lepidic and no feature of necrosis or invasion
- Minimally invasive adenocarcinoma of lung (**MIA**) ≤ 3 cm, describes small solitary adenocarcinomas with either pure lepidic growth or predominant lepidic growth with ≤ 5 mm of stromal invasion.



Atypical adenomatous hyperplasia



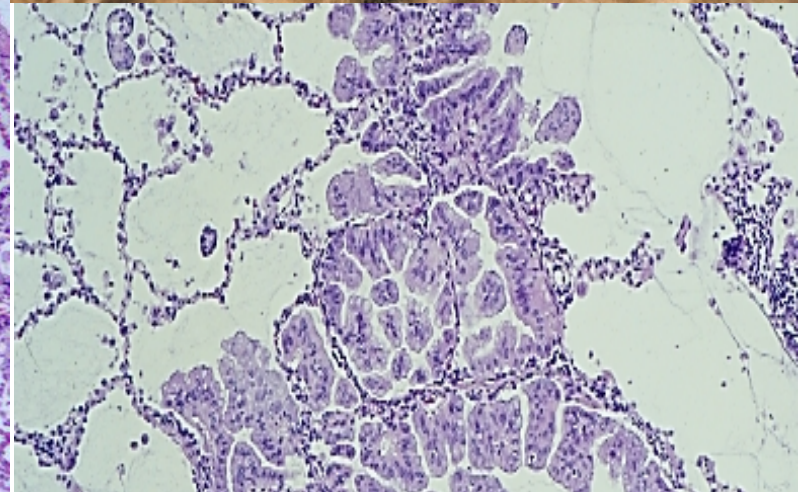
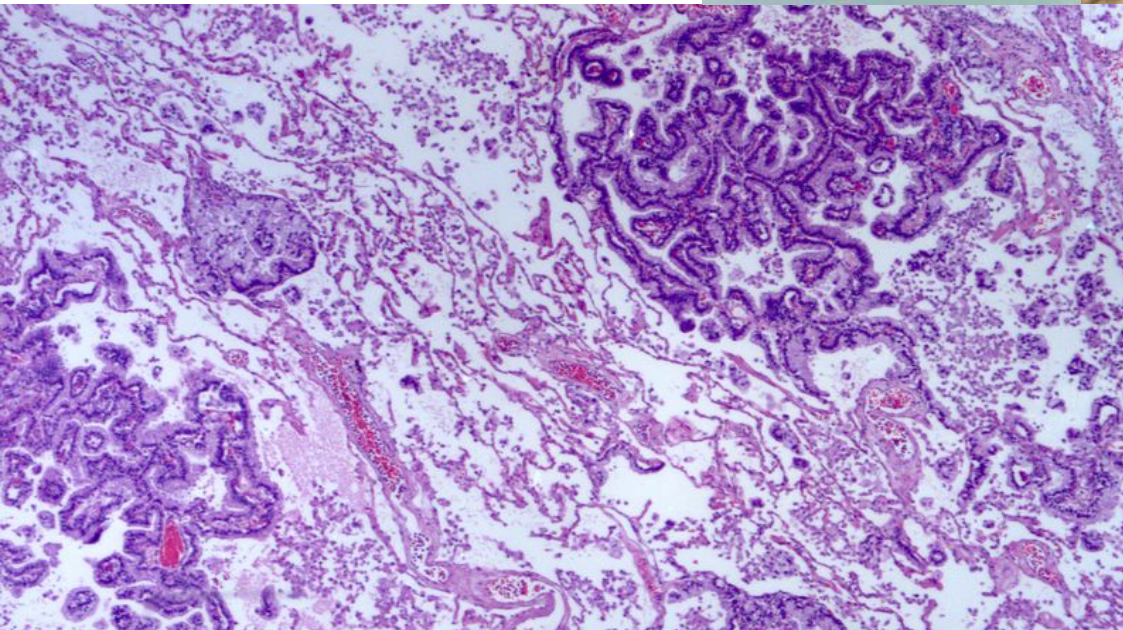
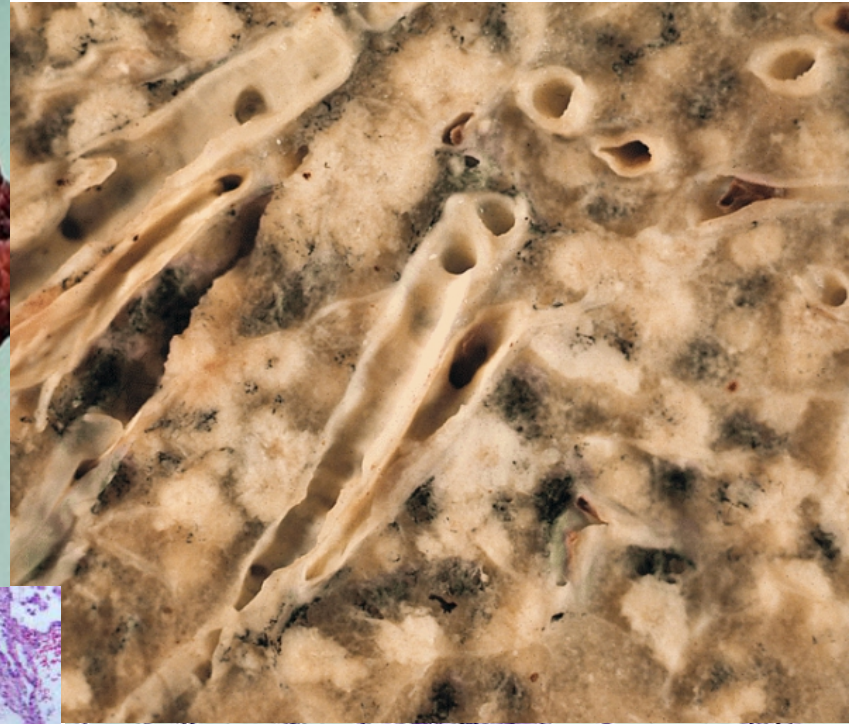
Minimally invasive adenocarcinoma of lung



Adenocarcinoma in situ (formerly called bronchioloalveolar carcinoma)

Adenocarcinoma in situ (formerly called bronchioloalveolar CA)

Malignant cells grow along alveolar septae

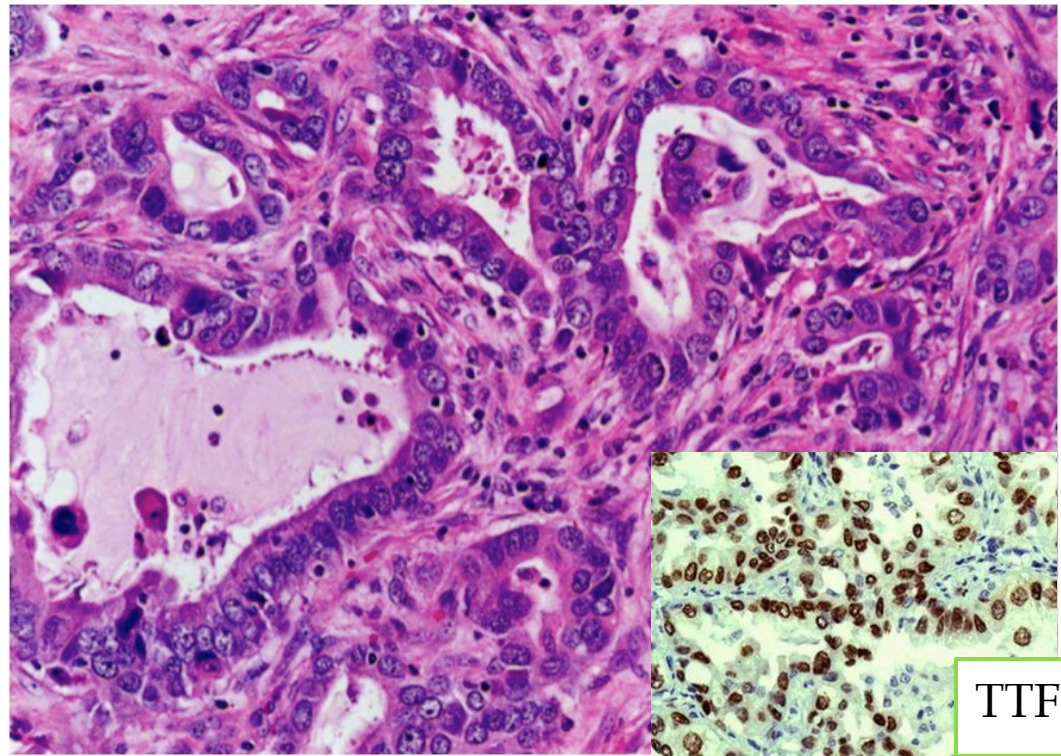


referred to as adenocarcinoma in situ according to the new classification of lung cancers

Adenocarcinomas

More common in patients under the age of 40, women and non-smokers.
Tend to metastasize widely at early stage

- The hallmark of adenocarcinomas is the tendency to form glands that may or may not produce mucin.
- Peripheral adenocarcinomas are sometimes associated with pulmonary scars (from a previous pulmonary inflammation/infection) and therefore is also referred to as scar carcinoma.
- Rarely cavitate



TTF1

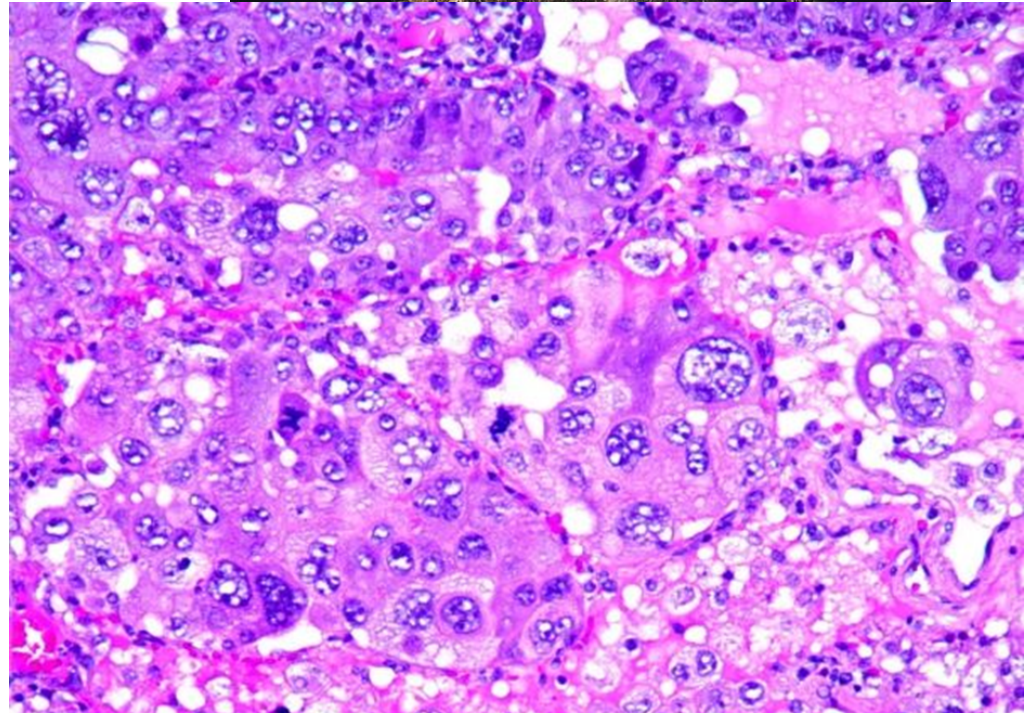
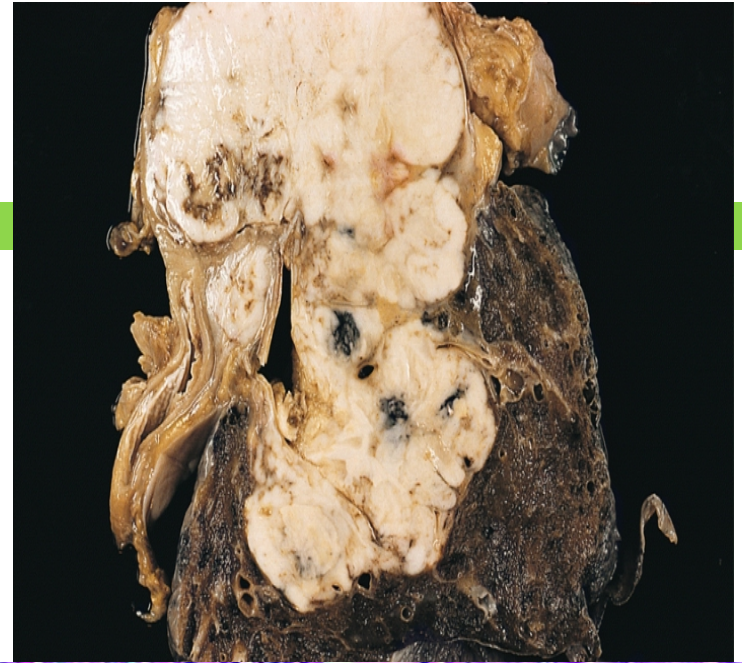
Adenocarcinoma

Associated with hypertrophic pulmonary osteoarthropathy
“Clubbing of the fingers”



Large Cell Carcinoma

- **Frequency: 10 %**
- strongly associated with smoking
- Large-cell carcinoma are usually located peripherally. These group of carcinomas are undifferentiated. They made up of large and anaplastic cells. They may exhibit neuroendocrine or glandular differentiation markers when studied by immunohistochemistry or electron microscopy.
- Poor prognosis.

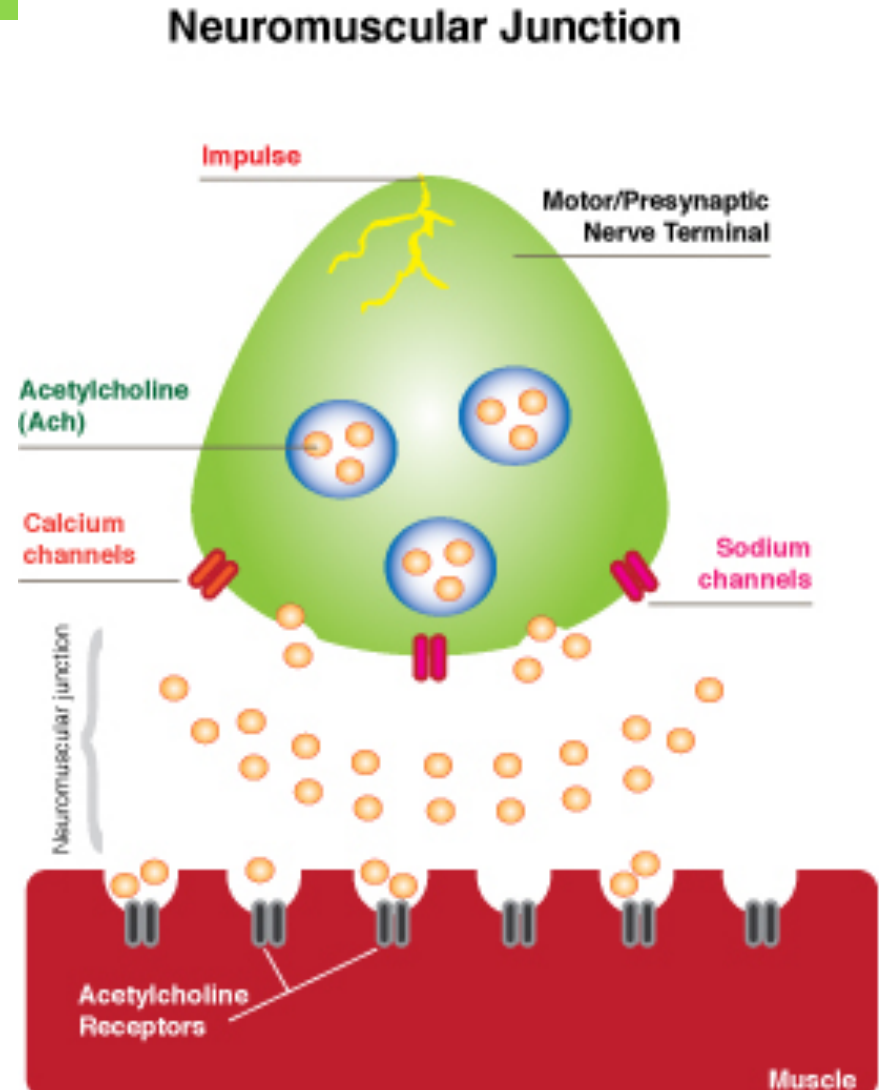


Small cell carcinomas

- SCLC are a type neuroendocrine tumors arising from neuroendocrine cells. More common in men.
- Highly malignant and aggressive tumor, poor prognosis, rarely resectable.
- Strongly associated with cigarette smoking. 95% of patients are smokers
- Centrally located perihilar mass with early metastases (Early involvement of the hilar and mediastinal nodes)
- Chemotherapy responsive
- least likely form to be cured by surgery; usually already metastatic at diagnosis
- Ability to secrete a host of polypeptide hormones like ACTH, antidiuretic hormone (ADH), calcitonin, gastrin-releasing peptide and chromogranin.
- It may be associated with paraneoplastic syndrome, Cushing's, and Eaton-Lambert syndrome

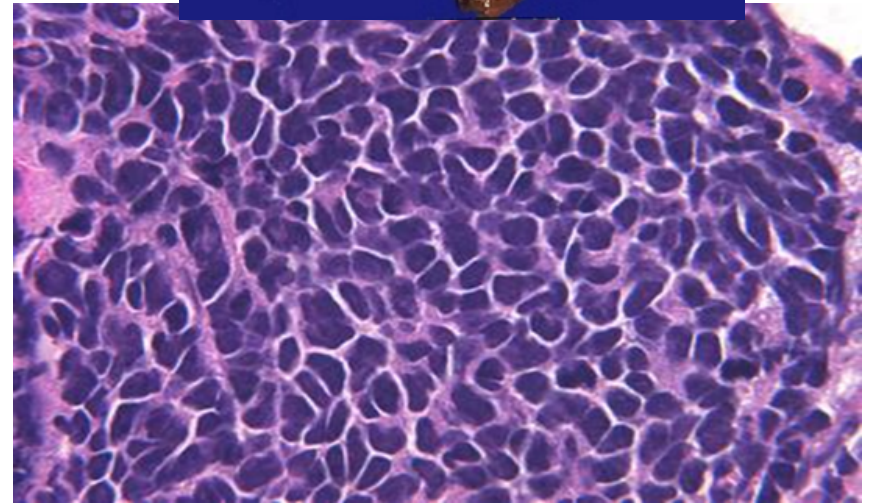
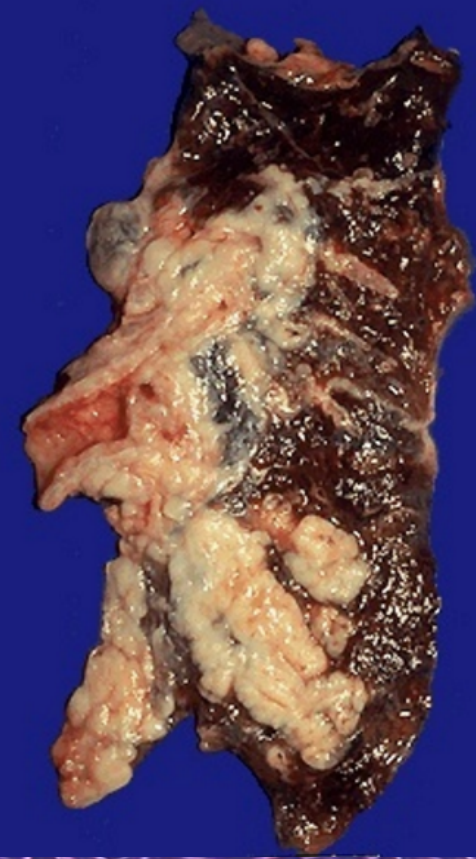
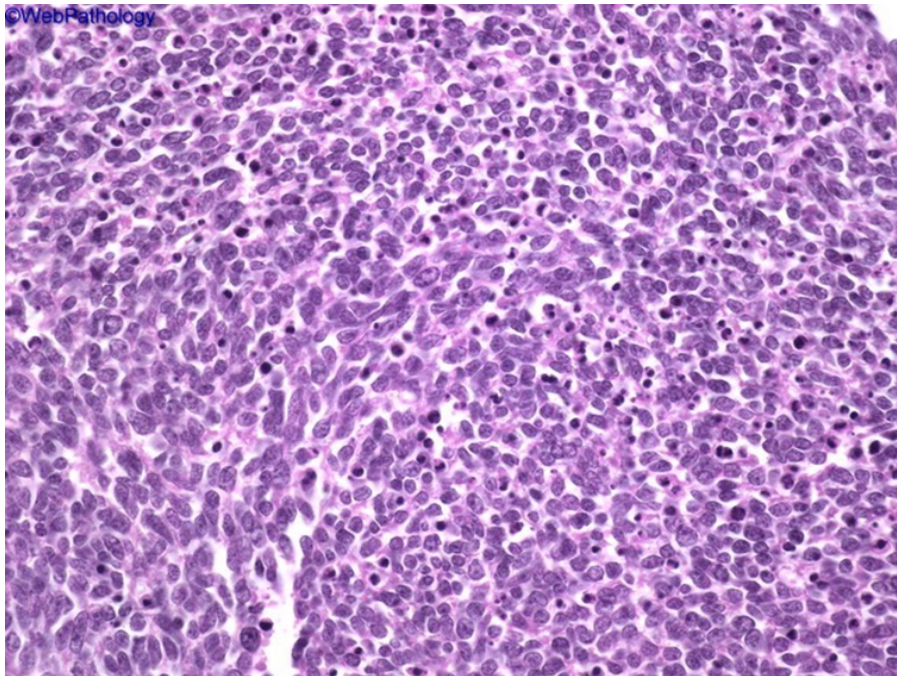
Eaton-Lambert syndrome

- is an autoimmune disease
- a disease in which the immune system attacks the body's own tissues.
- The attack occurs at the connection between nerve and muscle (the neuromuscular junction) and interferes with the ability of nerve cells to send signals to muscle cells.



Small cell carcinomas

- Microscopically composed of small, dark, round to oval, lymphocyte-like cells with little cytoplasm.
- Electron microscopy: dense-core neurosecretory granules.



Bronchogenic carcinoma site

Central tumors

- Squamous cell CA
- Small cell CA

Peripheral tumors

- Adenocarcinoma
 - bronchial derived
 - bronchioloalveolar ca
- Large cell carcinoma

Molecular genetics in lung cancer

Most common oncogenes—
KRAS, *MYC* family, *HER-2/neu*, *BCL-2*, *EGFR*
(epidermal growth factor receptor found in pulmonary adenocarcinoma, if certain mutation is positive, will respond to anti-tyrosin kinase)

b. Most common suppressor genes—*p53* (most common), *RB1*, *p16*

Clinical features of bronchogenic carcinoma

- Can be silent or insidious lesions
- chronic cough and expectoration, hemoptysis, and bronchial obstruction, often with atelectasis.
- Hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion(bloody).
- Symptoms due to direct or metastatic spread.

| Clinical Feature | Pathologic Basis |
|------------------------------------|---|
| Cough (50%-75%) | Involvement of central airways |
| Hemoptysis (25%-50%) | Hemorrhage from tumor in airway |
| Chest pain (20%) | Extension of tumor into mediastinum, pleura wall |
| Pneumonia, abscess, lobar collapse | Airway obstruction by tumor |
| Lipoid pneumonia | Tumor obstruction; accumulation of cellular foamy macrophages |
| Pleural effusion | Tumor spread into pleura |
| Hoarseness | Recurrent laryngeal nerve invasion |
| Dysphagia | Esophageal invasion |
| Diaphragm paralysis | Phrenic nerve invasion |
| Rib destruction | Chest wall invasion |
| SVC syndrome | SVC compression by tumor |
| Horner syndrome | Sympathetic ganglia invasion |
| Pericarditis, tamponade | Pericardial involvement |

Bronchogenic CA may manifest by the following syndromes:

- a) **Superior vena cava syndrome:** invasion leads to obstruction of venous drainage which leads to dilation of veins in the upper part of the chest and neck resulting in swelling and cyanosis of the face, neck, and upper extremities
- b) **Pancoast tumor (superior sulcus tumor):** Apical neoplasms may invade the brachial sympathetic plexus to cause severe pain, numbness and weakness in the distribution of the ulnar nerve.
- c) The combination of clinical findings is known as **Pancoast syndrome.**
- d) Pancoast tumor is often accompanied by destruction of the first and second ribs and thoracic vertebrae. It often coexists with **Horner syndrome**
- e) **Horner syndrome:** invasion of the cervical thoracic sympathetic nerves and it leads to ipsilateral enophthalmos, miosis, ptosis, and facial anhidrosis.
- f) **Paraneoplastic syndrome**

Paraneoplastic syndrome

- **Extrapulmonary, remote effects of tumors.**
- **3% to 10% of lung cancers develop paraneoplastic synd.**

Small cell carcinomas

ACTH (leading to Cushing's syndrome)
ADH (water retention and hyponatremia)

Carcinoid tumors produce serotonin and bradykinin leading to carcinoid syndrome (flushing, wheezing, diarrhea, and cardiac valvular lesions)

Squamous cell carcinomas may secrete parathyroid hormone-like peptide and prostaglandin E that lead to hypercalcemia

Adenocarcinomas can lead to hematologic manifestations

Other endocrine syndromes associated with primary lung carcinomas e.g. gonadotrophin production leading to gynecomastia, calcitonin production leading to hypocalcemia, hyperglycemia, thyrotoxicosis, and skin pigmentation

Complications of bronchogenic carcinoma

- Bronchiectasis
- Obstructive pneumonia
- Pleural effusion
- Metastasis

Prognosis:

- NSCLC have a better prognosis than SCLC.
- Outlook is poor for most patients.

Spread of bronchogenic carcinoma

1. Direct extension into:

- a. The pericardial or pleural spaces.
- b. A tumor may extend directly into the esophagus, producing obstruction, sometimes complicated by a fistula.
- c. Phrenic nerve invasion usually causes diaphragmatic paralysis
- d. May invade the brachial or cervical sympathetic plexus
- e. Infiltrate the superior vena cava.

2. Lymphatic spread.

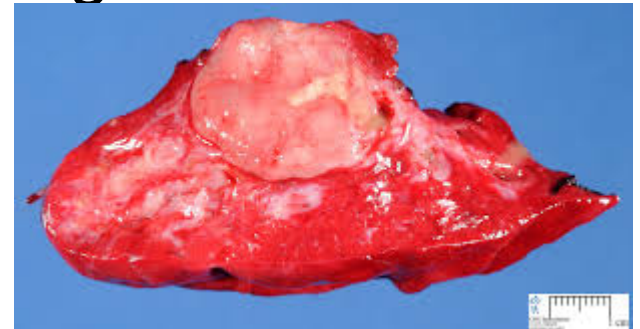
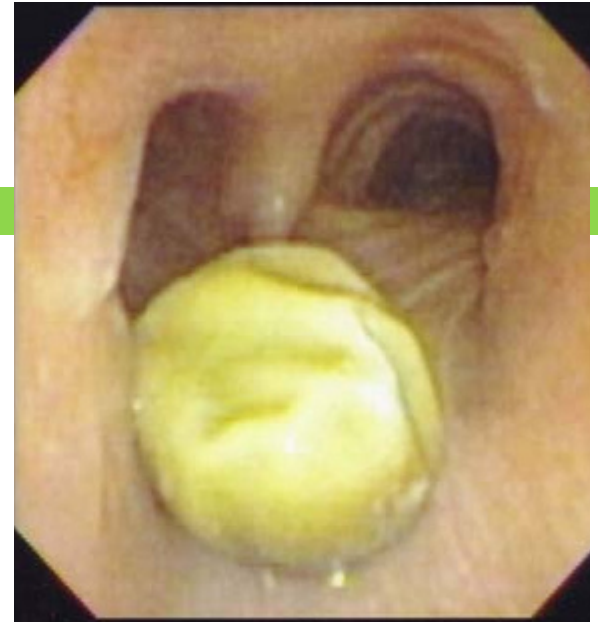
successive chains of nodes (scalene nodes).

involvement of the supraclavicular node (Virchow's node).

3. **Distant metastasis** to liver (30-50%), adrenals (>50%), brain (20%) and bone (20%).

Carcinoid tumor

- Carcinoid tumors of the lung are neuroendocrine neoplasms
- These neoplasms account for 2% of all primary lung cancers,
- It shows no sex predilection, and are not related to cigarette smoking or other environmental factor.
- Usually seen in adults
- Can be central or peripheral in location.
 - **Tumor cells** produce serotonin and bradykinin leading to carcinoid syndrome
- Can occur in patients with Multiple Endocrine Neoplasia (MEN-I)

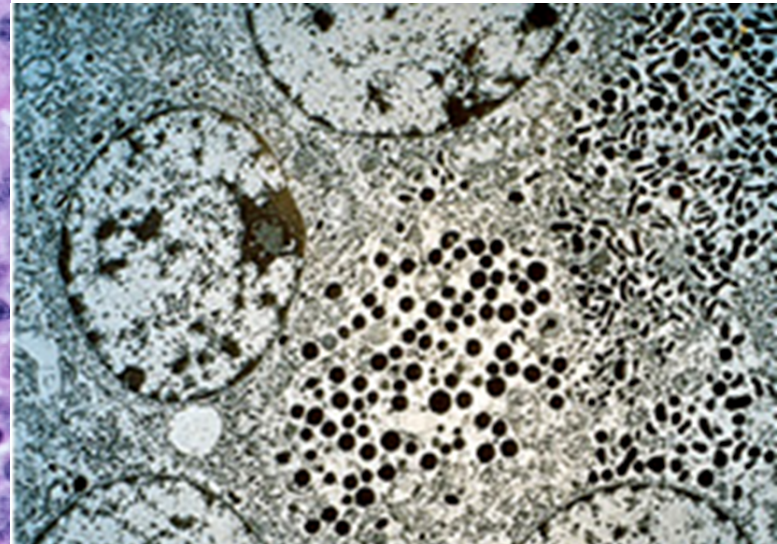
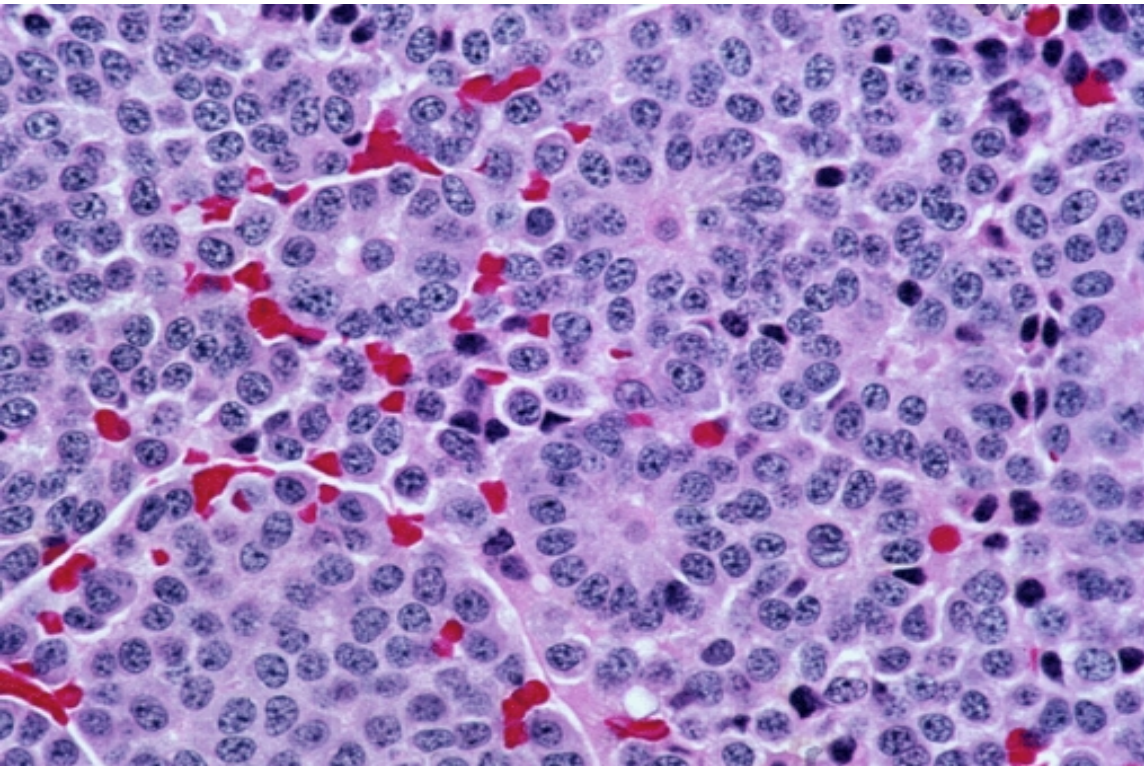


Morphology of typical carcinoid tumors

- Composed of uniform cuboidal cells that have regular round nuclei with few mitoses and little or no anaplasia.
- Electron microscopy: dense-core neurosecretory granules

Prognosis:

Low malignancy, Often resectable and curable. Spreads by direct extension into adjacent tissue



Mesothelioma

- Malignant tumor of mesothelial cells lining the
- Highly malignant neoplasm
- Most patients (70%) have a history of exposure
- Smoking is not related to mesothelioma
- The average age of patients with mesothelioma is 60 years.
- Pleural mesotheliomas tend to spread locally within the chest cavity, invading and compressing major structures.
- Metastases can occur to the lung parenchyma and mediastinal lymph nodes, as well as to extrathoracic sites e.g. liver, bones, peritoneum etc.
- Treatment is largely ineffective and prognosis is poor: few patients survive longer than 18 months after diagnosis



Carcinoma metastatic to the lung

- Pulmonary Metastases are More Common than Primary Lung Tumors
- Metastatic tumors in the lung are typically multiple and circumscribed. When large nodules are seen in the lungs radiologically, they are called cannon ball metastases .
- The common primary sites are the breast, stomach, pancreas, and colon.

