Rrespiratory Block

Lung Cancer

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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 tumors with special emphasis on small cell carcinoma and bronchial carcinoid
- Is aware that the lung is a frequent site for metastatic neoplasms

Introduction

- 95% of primary lung tumors are carcinomas
- Remaining 5% span a miscellaneous group that includes
  - carcinoids
  - mesenchymal malignancies (e.g., fibrosarcoma, leiomyomas)
  - lymphomas
  - benign lesions
- Primary lung cancer is a common disease BUT metastatic tumors are more common than the primary tumors.

Epidemiology

Carcinoma of the lung is the most important cause of cancer-related deaths in industrialized countries

- Accounts for >30% of cancer deaths in men
- Accounts for >25% of cancer deaths in women

- Incidence of lung cancer is declining in men but increasing in women
- Peak incidence is at 55 to 65 years of age

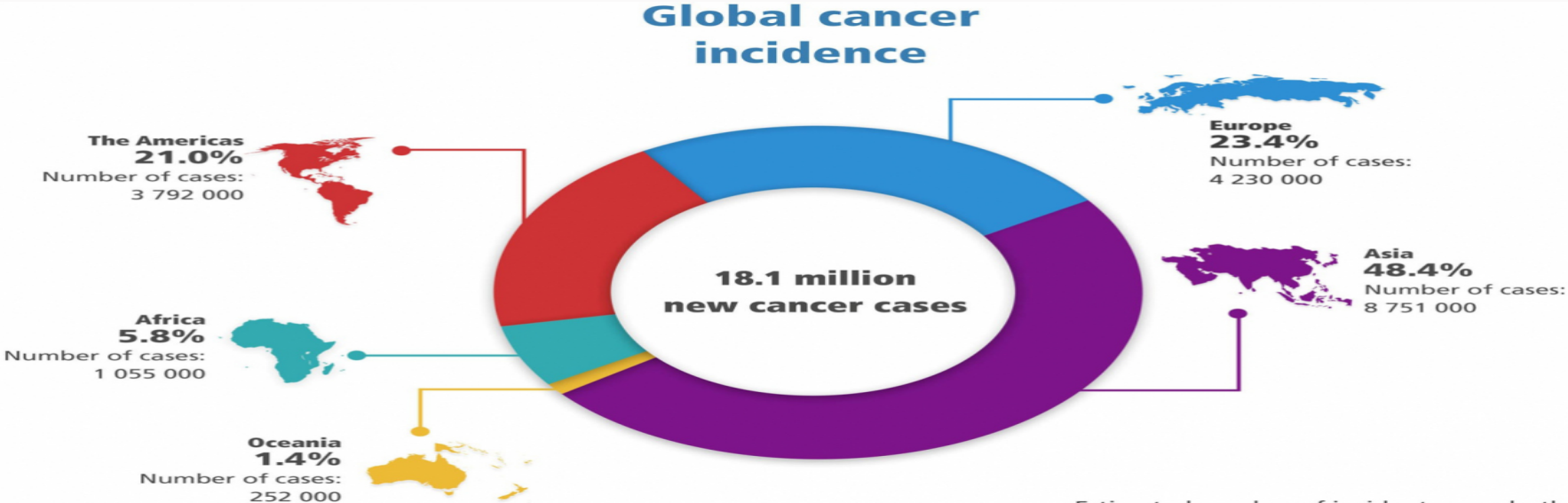
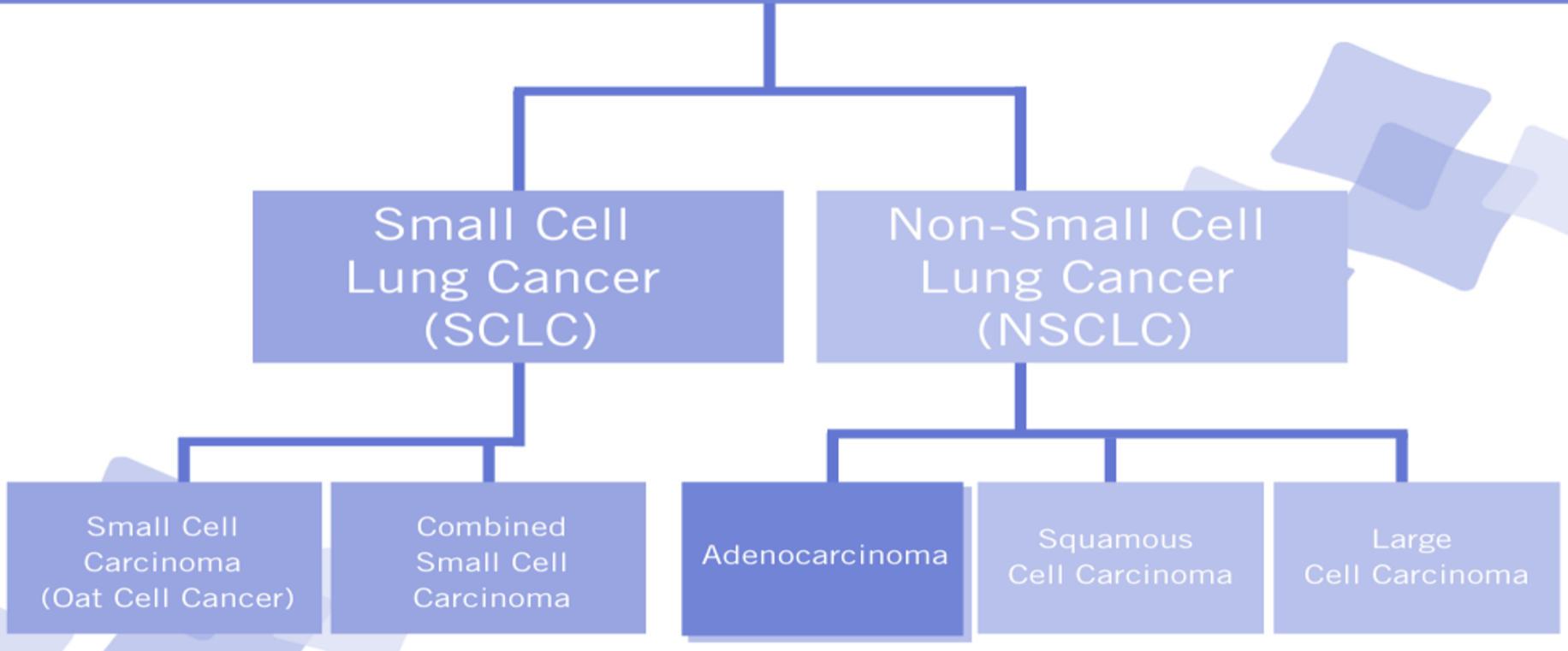


Table 13.6 Histologic Classification of Malignant Epithelial Lung Tumors (2015 WHO Classification, Simplified Version)

- 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

LCFA
Lung Cancer Foundation of America

TWO MAIN TYPES OF LUNG CANCER

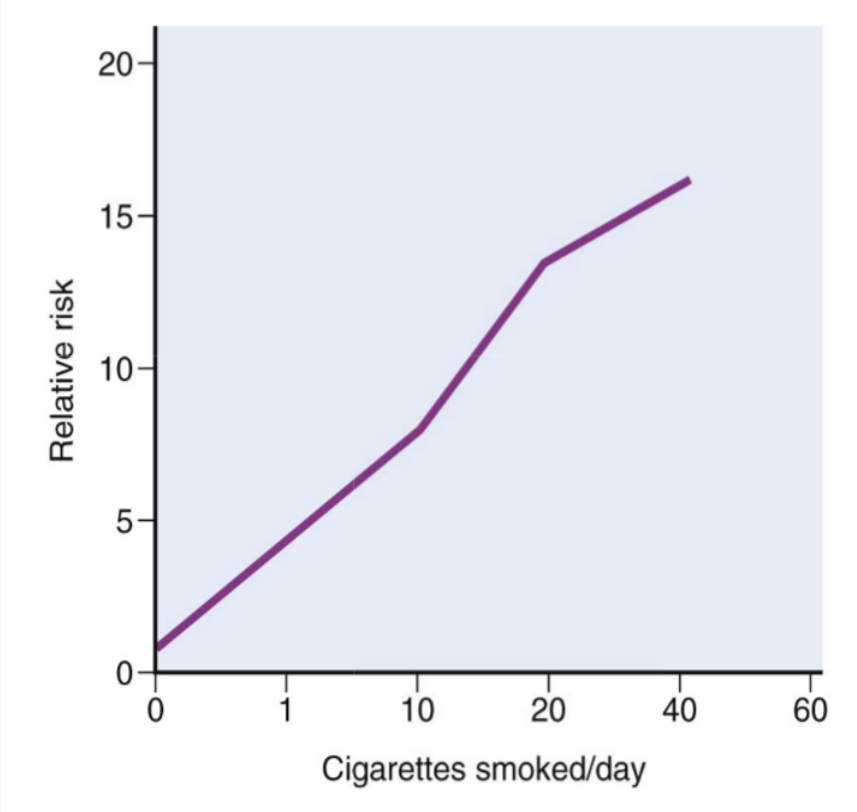


Etiology and Pathogenesis

- 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
- 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

Etiology and Pathogenesis

- 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



Etiology and Pathogenesis

- For unclear reasons, women are more susceptible to carcinogens in tobacco smoke than men
- Female smokers have a much greater risk of death from lung cancer and COPD in recent years than female smokers 20 or 40 years ago
- Female smokers today smoke more like men than women in previous generations, beginning earlier in adolescence and, until recently

Smoking and Cancer

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

Etiology and Pathogenesis

- **Radiation**:. All types of radiation may be carcinogenic and increase the risk of developing lung cancer. radium and uranium workers are at risk

- **Asbestos**: increased incidence of cancer with asbestos exposure, especially in combination with cigarette smoking

- Industrial exposure to **nickel and chromates, coal, mustard gas, arsenic, iron** etc.
- **Air pollution**: May play some role in increased incidence. Indoor air pollution especially by radon

- **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

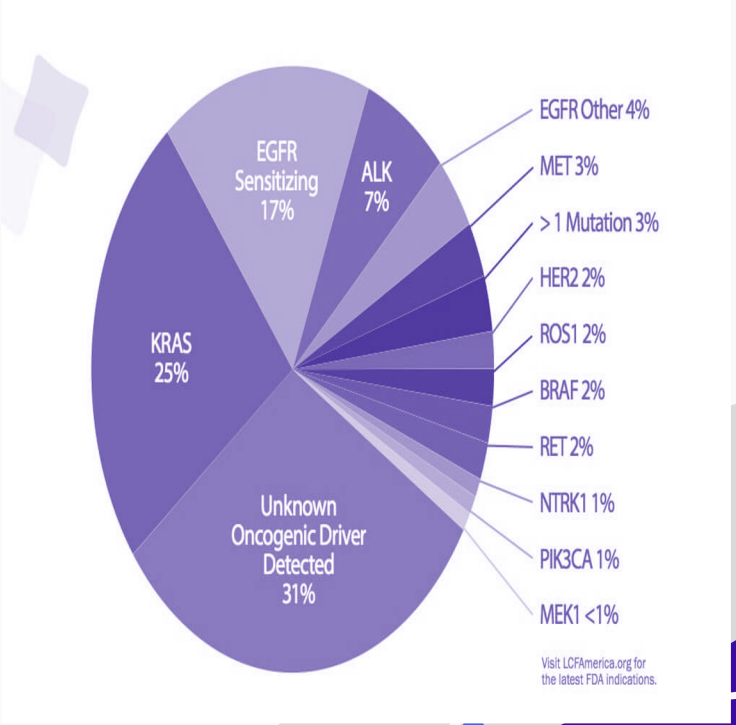
(2) Atypical adenomatous hyperplasia can lead to:
Adenocarcinoma

(3) Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia can lead :
Neuroendocrine tumors

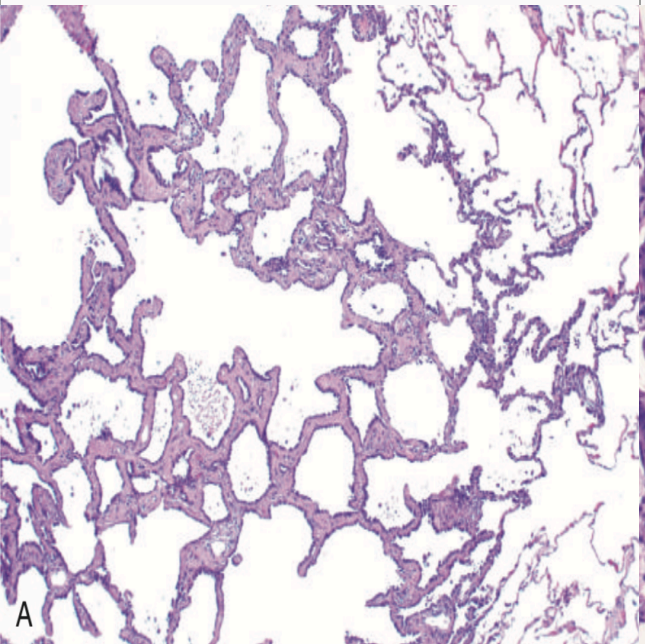
It should be noted that the term "precursor" does not imply that progression to invasion will occur in all cases

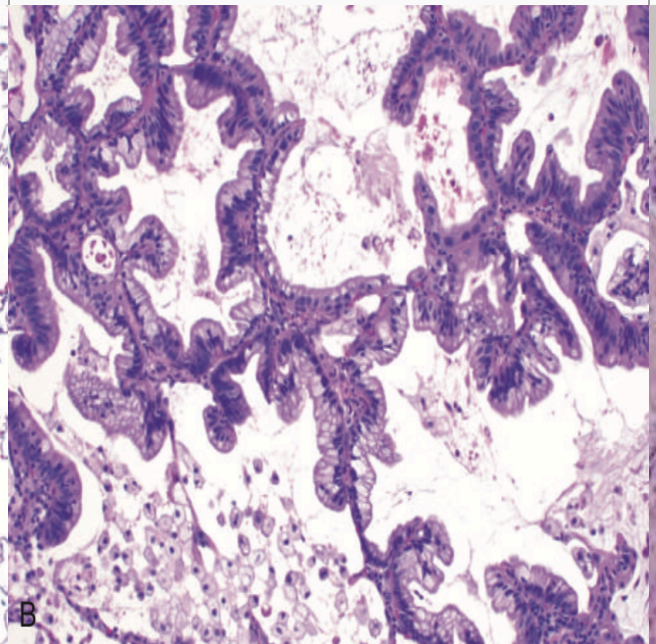
ADENOCARCINOMA

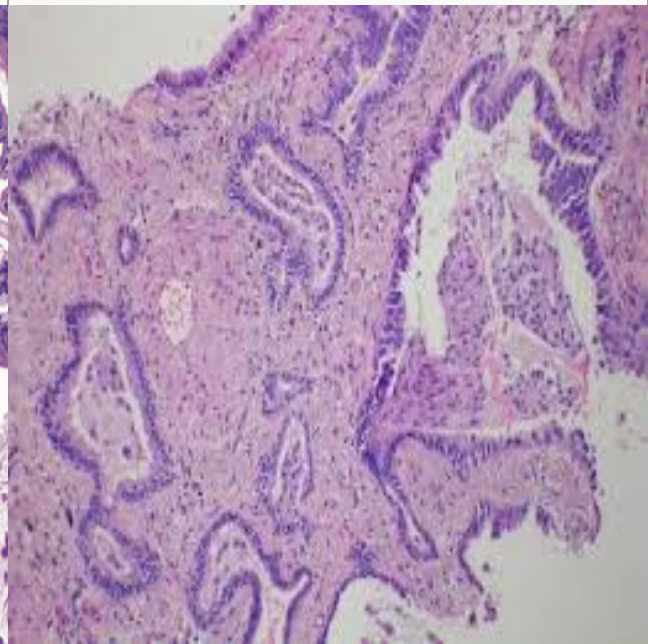
- Adenocarcinomas is now the most frequent histologic carcinoma
- More common in young women
- About 10% in whites
-
- 30% in Asians, particularly those arising in non-smoking women, harbor mutations that activate the *epidermal growth factor receptor (EGFR)*
- EGFR and KRAS mutations can occur and in 30% of adenocarcinomas
- Usually, peripheral located tumors and arising from the peripheral airways and alveoli

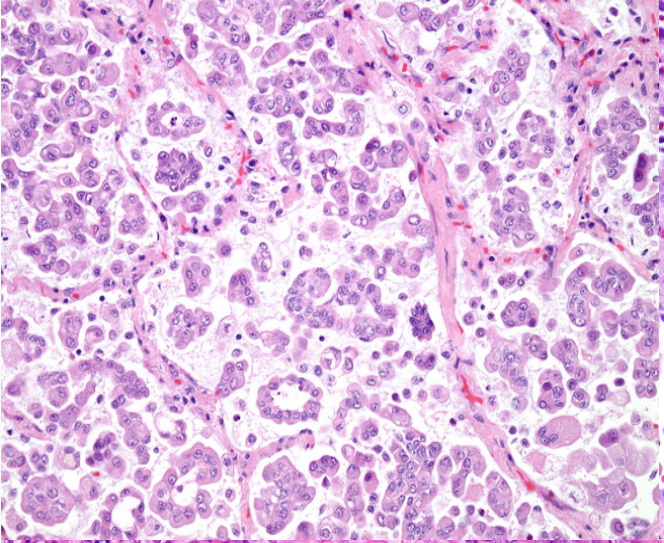
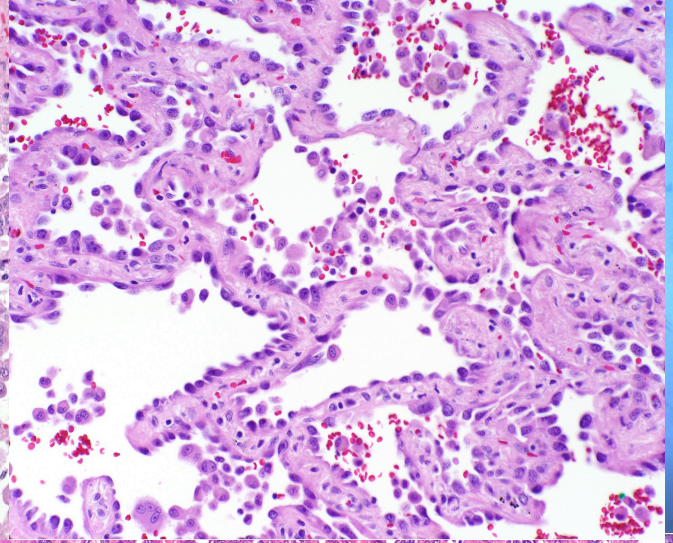


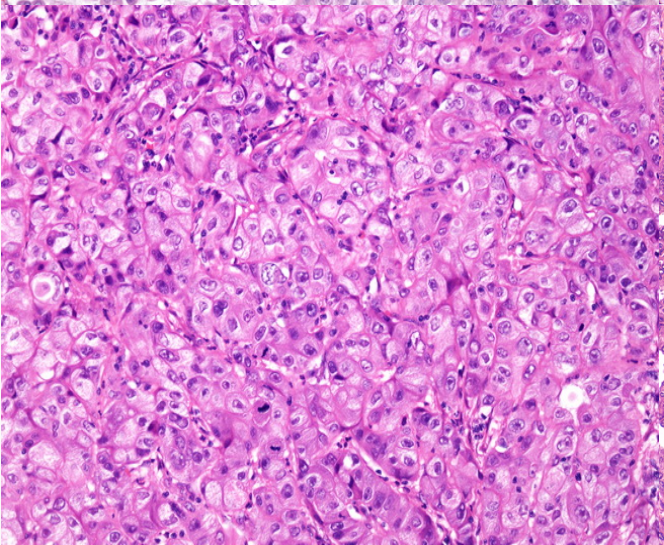
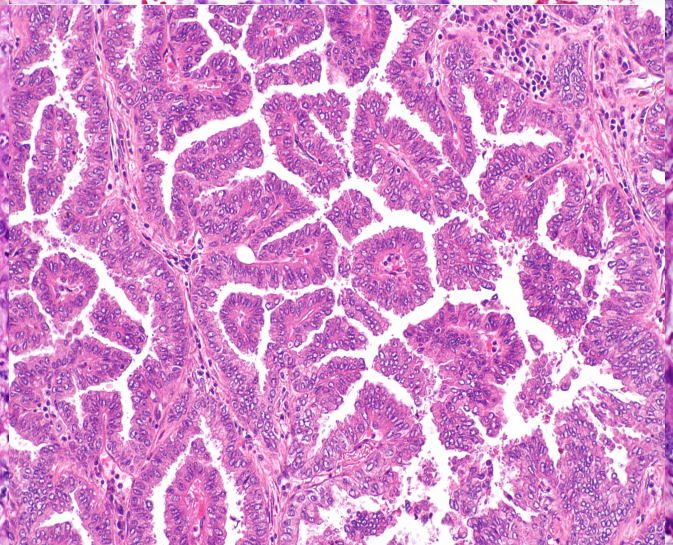
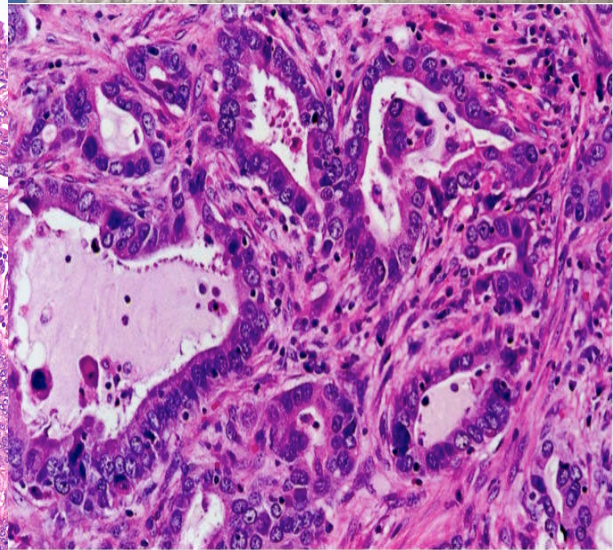
Atypical adenomatous hyperplasia	Adenocarcinoma in situ (AIS)	Minimally invasive adenocarcinoma (MIA)
Small lesion (≤5 mm) characterized by dysplastic pneumocytes lining alveolar walls that are mildly fibrotic	Lesion that is less than 3 cm and is composed entirely of dysplastic cells growing along preexisting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





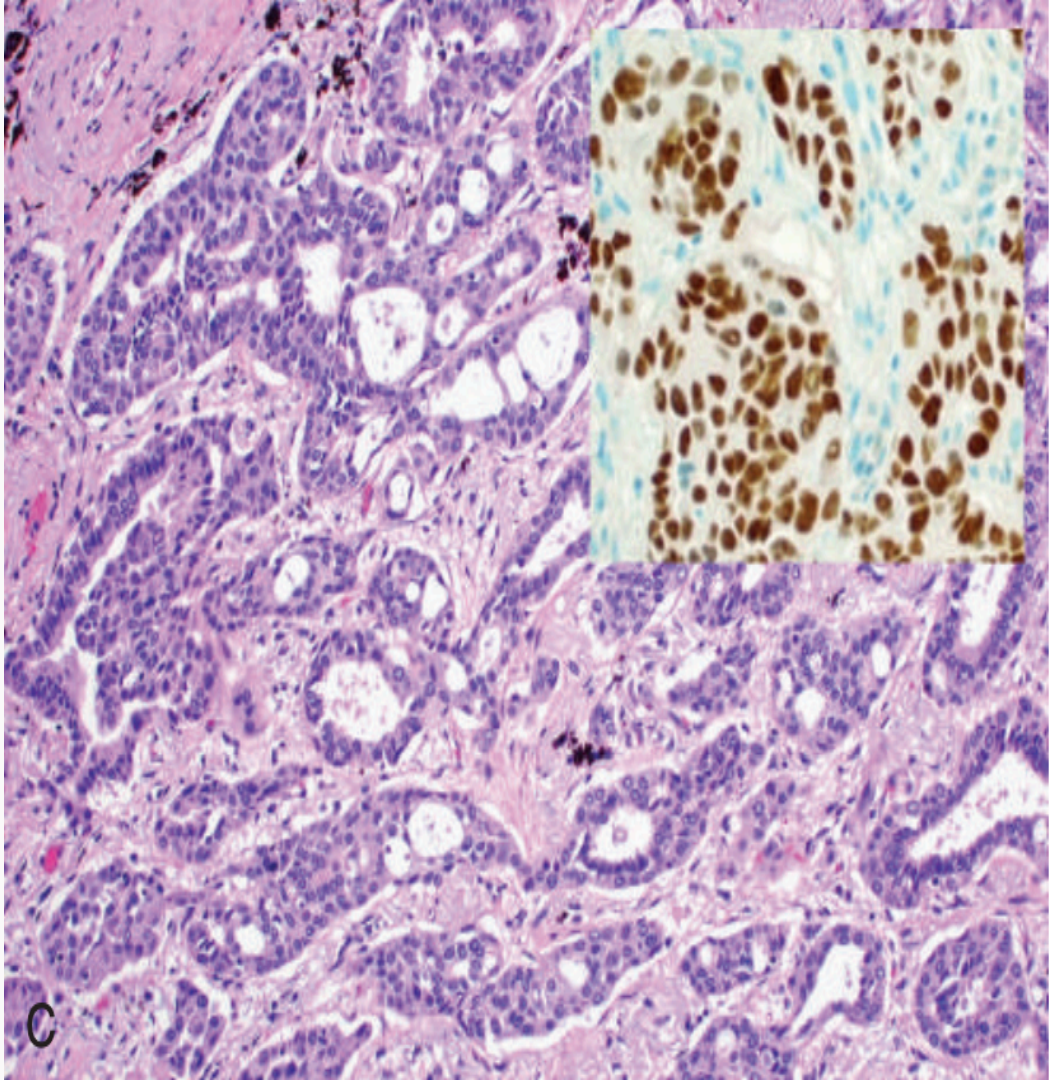


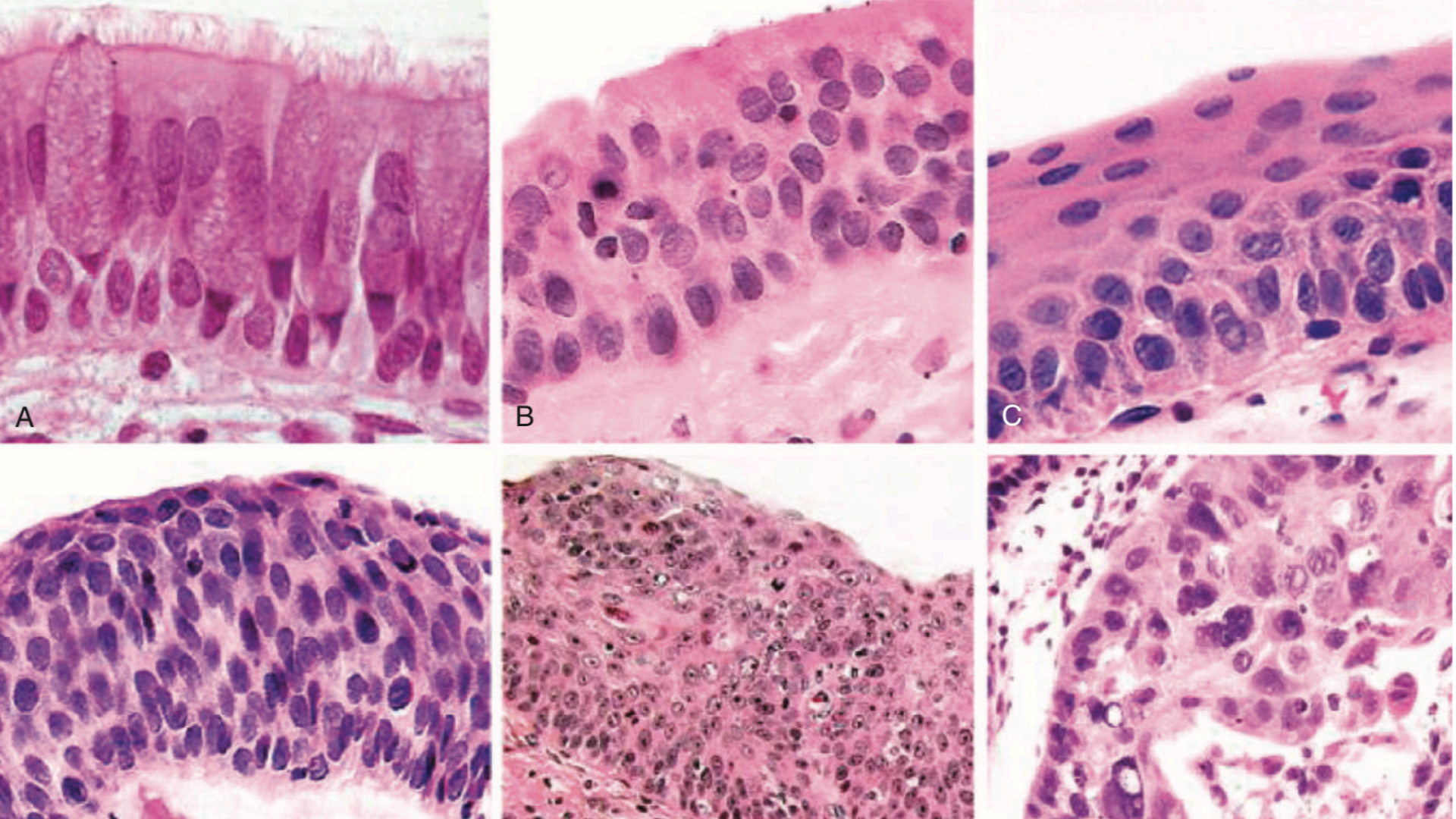
- IHC: TTF-1 positive

- Targeted therapies, such as EGFR inhibitor therapy for adenocarcinomas with EGFR mutations, can be effective

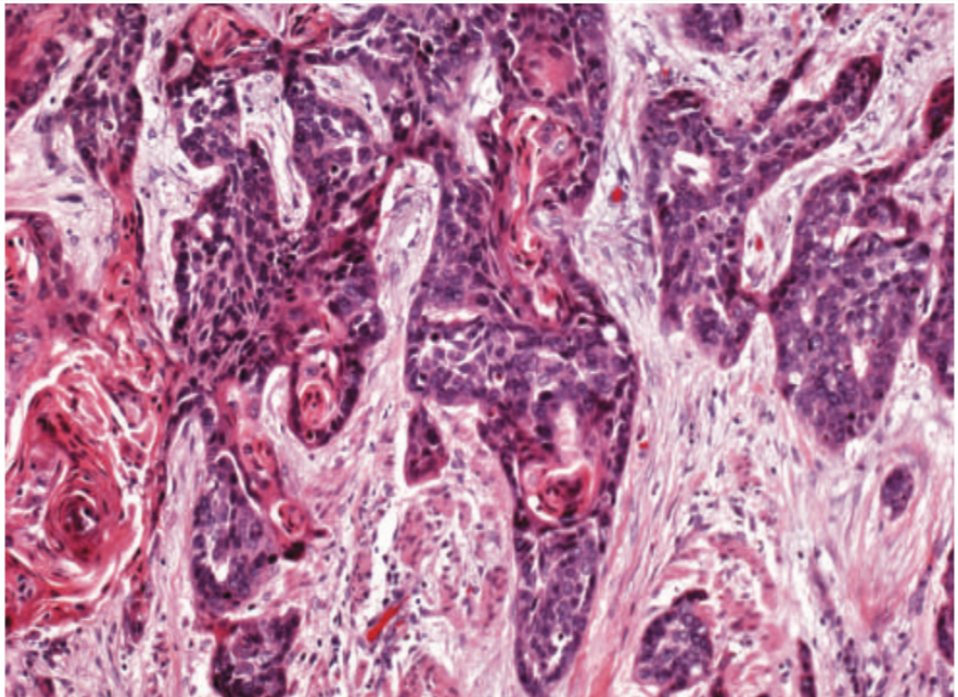


SQUAMOUS CELL CARCINOMA

- More common in men than in women
- Closely correlated with a smoking history
- Large lesions may undergo central necrosis, giving rise to cavitation
- Squamous cell carcinomas often are preceded by the development, over years, of squamous metaplasia or dysplasia in the bronchial epithelium, which then transforms to carcinoma in situ
- Eventually, the small neoplasm reaches a symptomatic stage, when a well-defined tumor mass begins to obstruct the lumen of a major bronchus, often producing distal atelectasis and infection

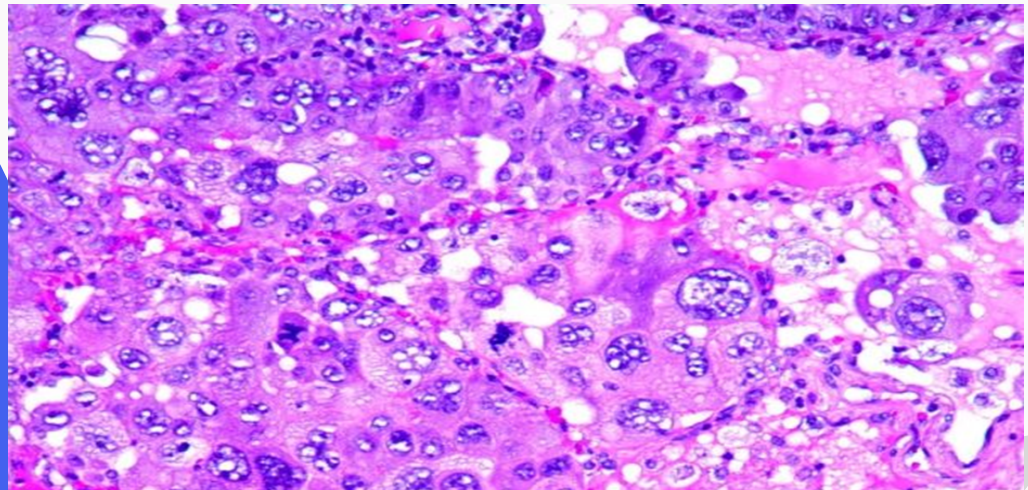

A
B
C

These tumors range from well- differentiated squamous cell neoplasms showing keratin pearls and intercellular bridges to poorly differentiated neoplasms exhibiting only minimal squamous cell features



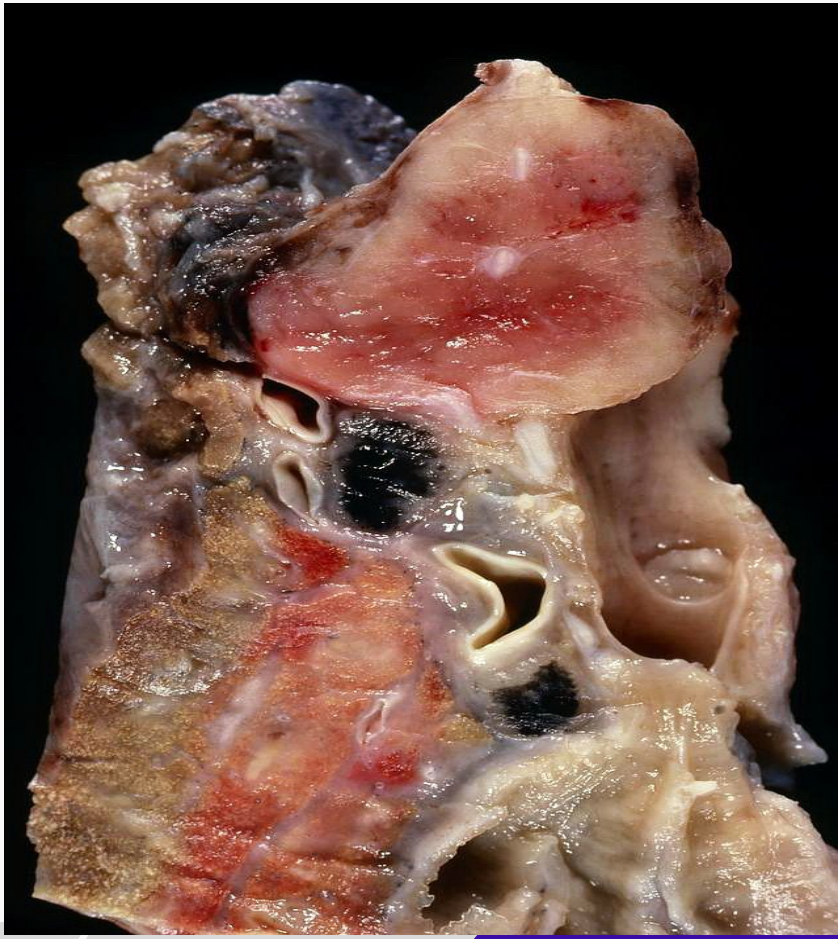
LARG CELL CARCINOMA

- **Frequency: 10 %**
- Strongly associated with smoking
- Large-cell carcinoma are usually located peripherally
- These group of carcinomas are undifferentiated
- Uundifferentiated malignant epithelial tumors that lack the cytologic features of neuroendocrine carcinoma and show no evidence of glandular or squamous differentiation
- The cells typically have large nuclei, prominent nucleoli, and moderate amounts of cytoplasm.
- Poor prognosis



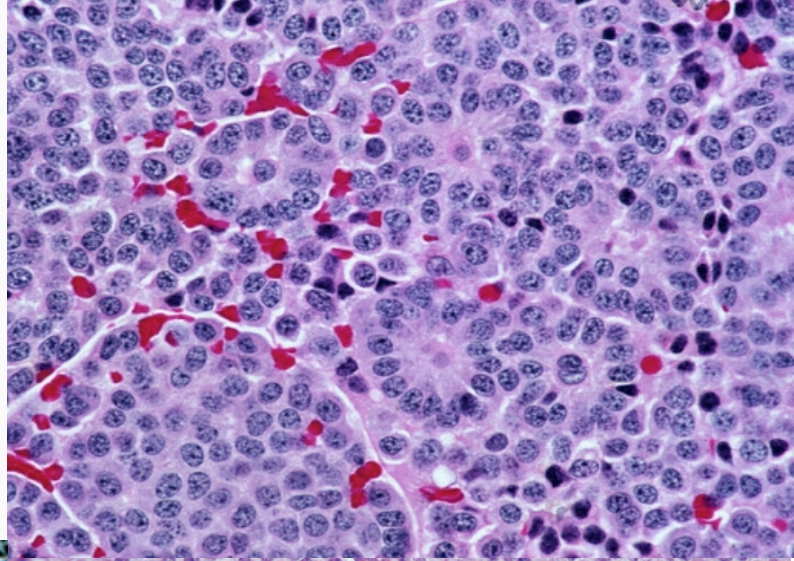
Carcinoid tumor

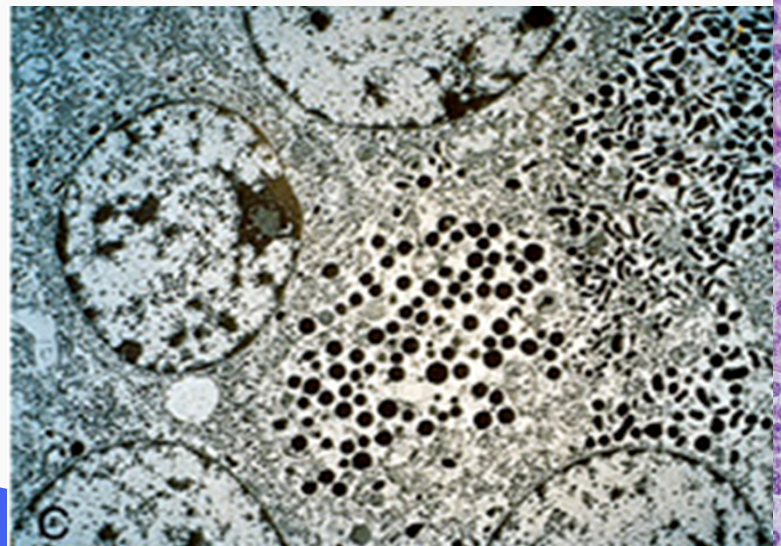
- Malignant tumors composed of cells that contain dense-core neurosecretory granules in their cytoplasm
- These neoplasms account for 2% of all primary lung cancers
- It shows no sex predilection and are not related to cigarette smoking or other environmental factor
- Usually seen in adults
- Can be 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)
- Low malignancy, Often respectable and curable.
- Spreads by direct extension into adjacent tissue
- Mainly seen as endobronchial lesions

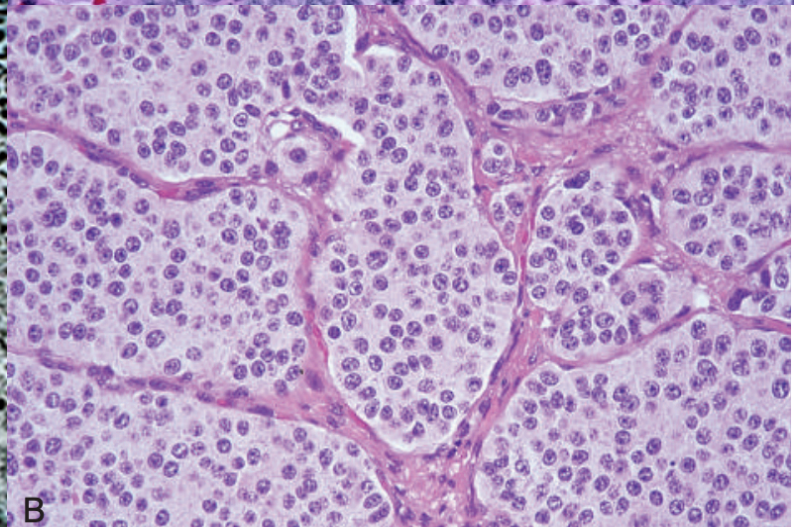


Two types:

1. typical carcinoids: are composed of nests of uniform cells that have regular round nuclei with “salt-and-pepper” chromatin, absent or rare mitoses and little pleomorphism
2. Atypical carcinoid: tumors display a higher mitotic rate and small foci of necrosis. These tumors have a higher incidence of lymph node and distant metastasis than typical carcinoids



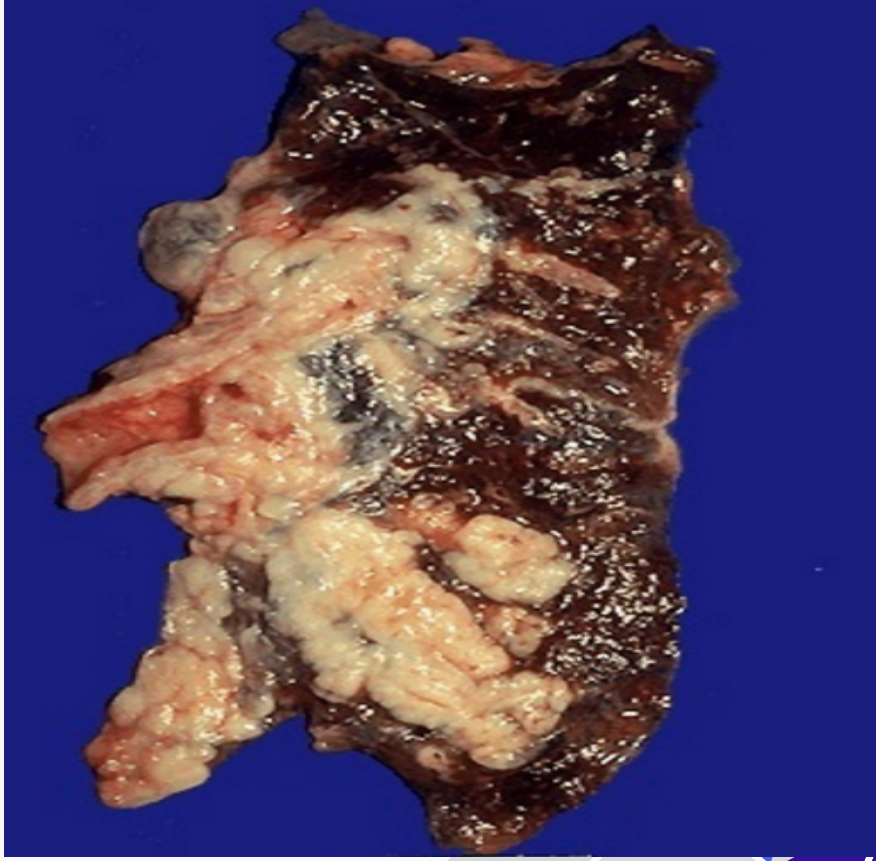


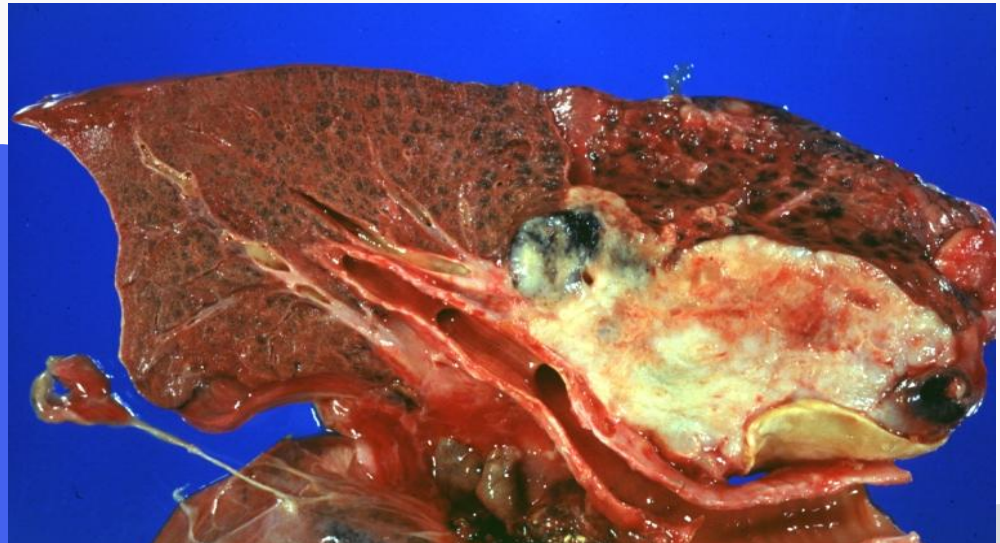


SMALL CELL CARCINOMA

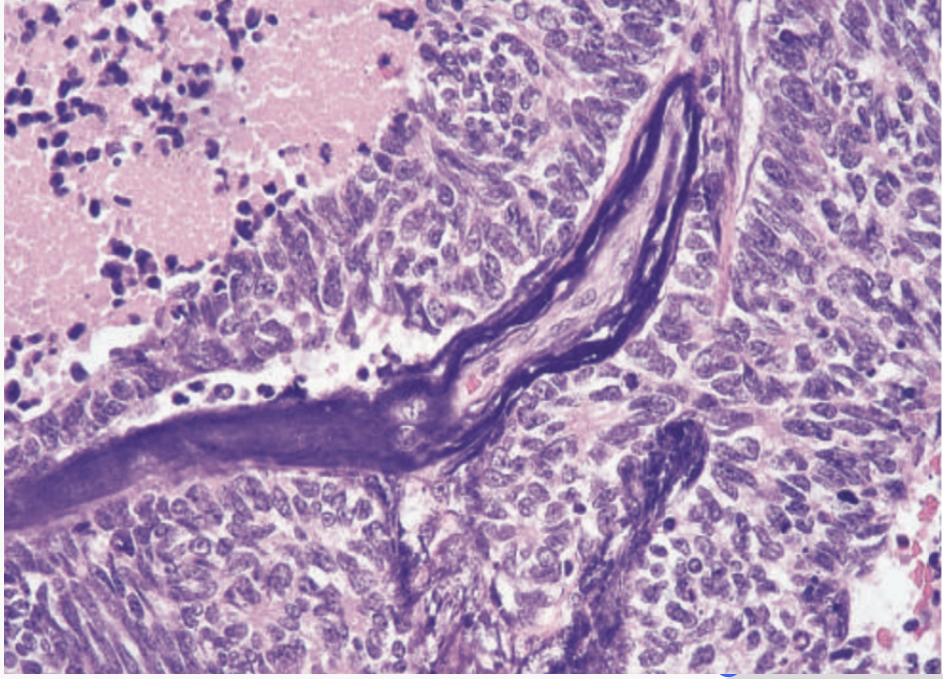
- SCLC are a type neuroendocrine tumors arising from neuroendocrine cells. More common in men
- Highly malignant and aggressive tumor, poor prognosis, rarely respectable
- Strongly associated with cigarette smoking. 95% of patients are smokers
- Chemotherapy responsive
- least likely form to be cured 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

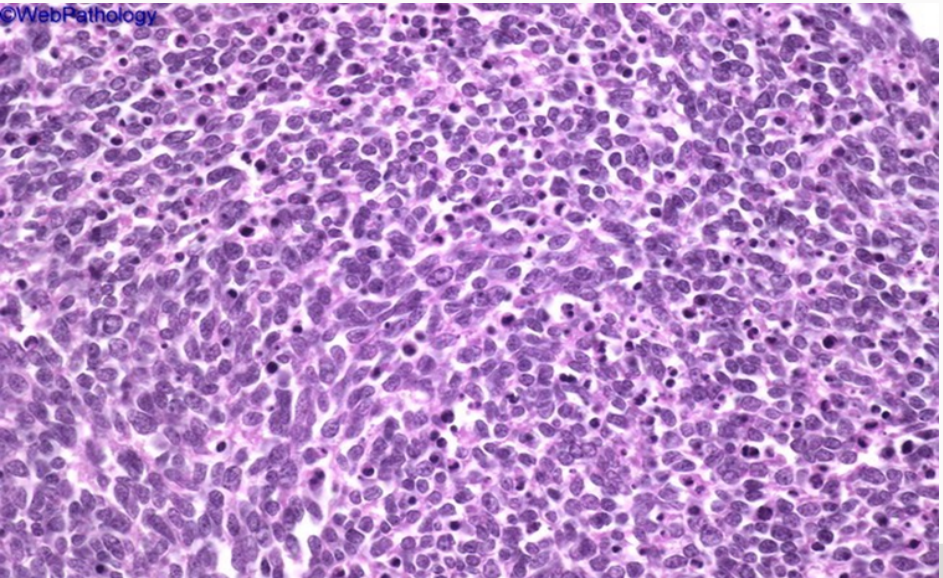
Centrally located perihilar mass with early metastases (Early involvement of the hilar and mediastinal nodes)





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





Lambert-Eaton Myasthenic Syndrome (LEMS)

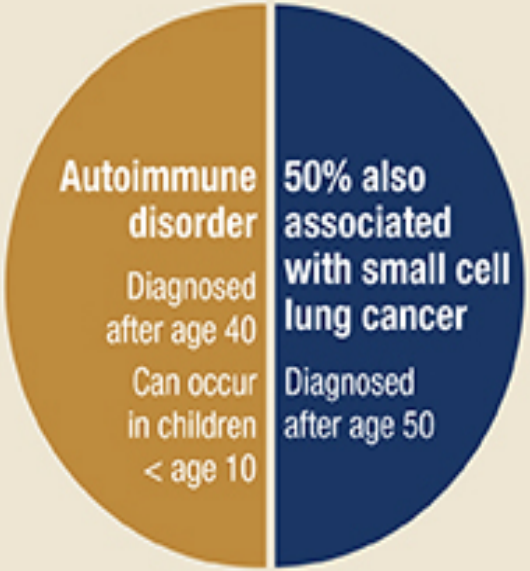
A rare autoimmune disorder where the immune system mistakenly attacks the body's own tissues.

These figures illustrate muscles most often affected by LEMS. Red is most affected to yellow least affected.

Symptoms

- Muscle weakness, fatigue and pain
- Difficulty walking and reduced reflexes
- Weakness in the muscles of the eyes, face and throat
- Speech impairment
- Swallowing problems

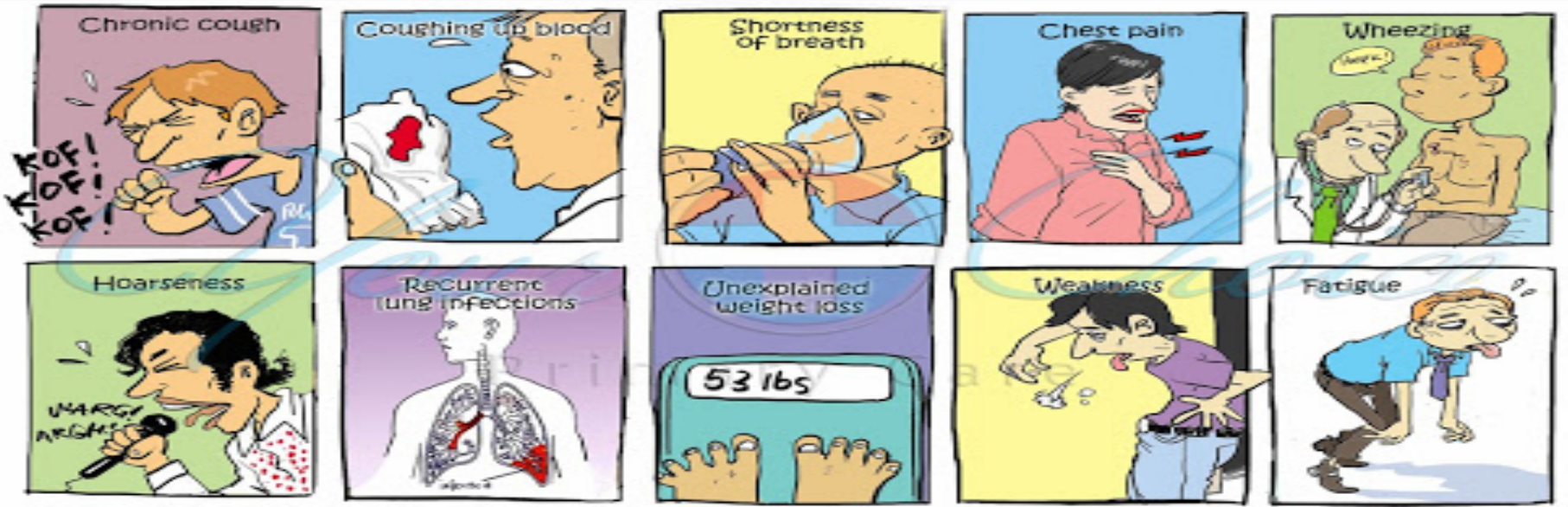
Two Groups of LEMS Patients



The estimated prevalence of LEMS in the U.S. is approximately 3,000 patients.

Clinical picture

- 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
- Symptoms due to metastatic spread



Clinical picture

- **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
- **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
  - Pancoast tumor is often accompanied by destruction of the first and second ribs and thoracic vertebrae. It often coexists with **Horner syndrome**
- **Horner syndrome:** invasion of the cervical thoracic sympathetic nerves and it leads to ipsilateral enophthalmos, miosis, ptosis, and facial anhidrosis
- **Hoarseness from recurrent laryngeal nerve paralysis**
- **Pleural effusion, often bloody**

Paraneoplastic syndrome

- **Paraneoplastic syndromes** of lung cancer, are extrapulmonary, remote effects of tumors.
- 3% to 10% of lung cancers develop paraneoplastic syndromes.
- **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

Complications and spread

- Bronchiectasis
- Obstructive pneumonia
- Pleural effusion
- Superior vena cava syndrome

Prognosis:

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

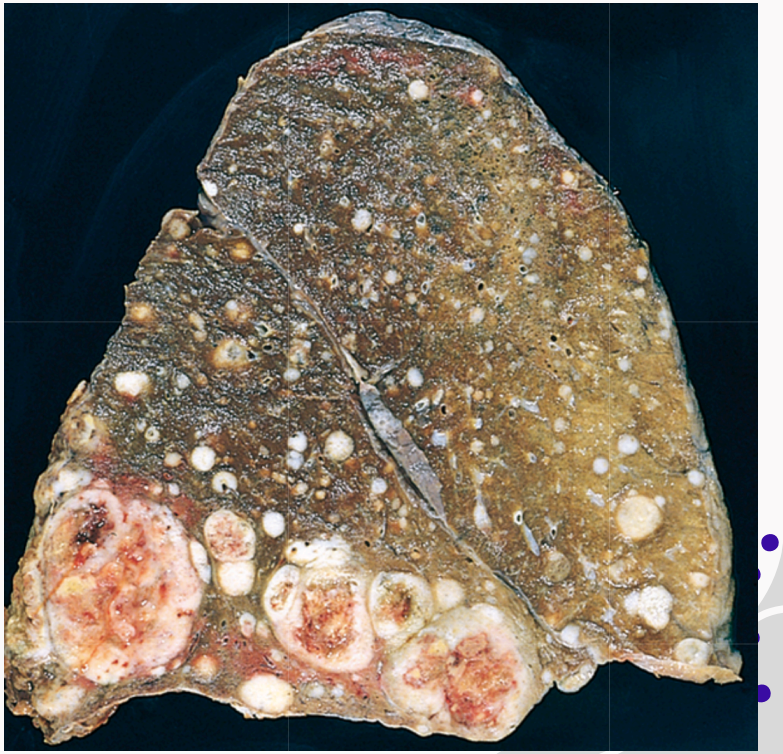
Complications and spread

- **Lymphatic spread**
  - successive chains of nodes (scalene nodes)
  - involvement of the supraclavicular node (Virchow's node)
- Extend into the **pericardial or pleural spaces**. Infiltrate the superior vena cava
- A tumor may extend directly into the **esophagus**, producing obstruction, sometimes complicated by a fistula
- **Phrenic nerve invasion** usually causes diaphragmatic paralysis
  - May invade the brachial or cervical sympathetic plexus (Horner's Syndrome)
- **Distant metastasis** to liver (30-50%), adrenals (>50%), brain (20%) and bone (20%)

Feature	Small Cell Lung Carcinoma	Non–Small Cell Lung Carcinoma
Histology		
	Scant cytoplasm; small, hyperchromatic nuclei with fine chromatin pattern; nucleoli indistinct; diffuse sheets of cells	Abundant cytoplasm; pleomorphic nuclei with coarse chromatin pattern; nucleoli often prominent; glandular or squamous architecture
Neuroendocrine Markers		
For example, dense core granules on electron microscopy; expression of chromogranin, synaptophysin, and CD56	Present	Absent
Epithelial Markers		
Epithelial membrane antigen, carcinoembryonic antigen, and cytokeratin intermediate filaments	Present	Present
Mucin	Absent	Present in adenocarcinomas
Peptide hormone production	Adrenocorticotropic hormone, anti-diuretic hormone, gastrin-releasing peptide, calcitonin	Parathyroid hormone–related peptide (PTH-rp) in squamous cell carcinoma
Tumor Suppressor Gene Abnormalities		
3p deletions	>90%	>80%
RB mutations	~90%	~20%
p16/CDKN2A mutations	~10%	>50%
TP53 mutations	>90%	>50%
Dominant Oncogene Abnormalities		
KRAS mutations	Rare	~30% (adenocarcinomas)
EGFR mutations	Absent	~20% (adenocarcinomas, nonsmokers, women)
ALK rearrangements	Absent	4%–6% adenocarcinomas, nonsmokers, often have signet ring morphology
Response to chemotherapy and radiotherapy	Often complete response but recur invariably	Incomplete

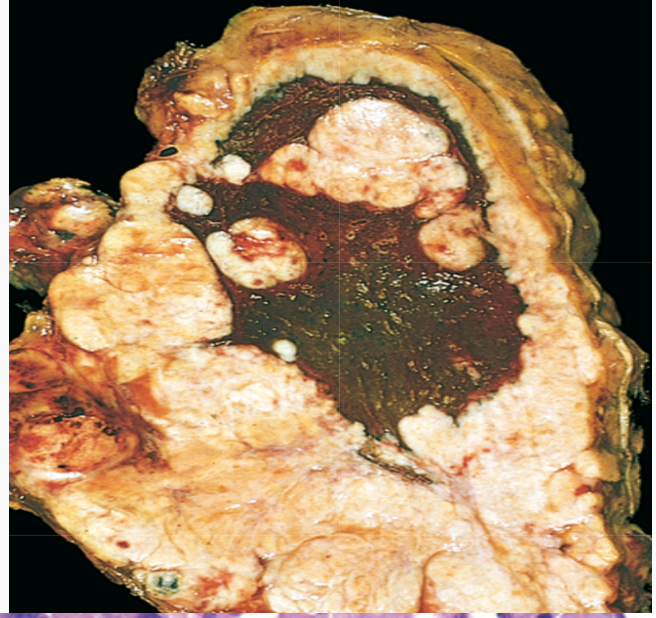
Metastatic Carcinoma of the lung

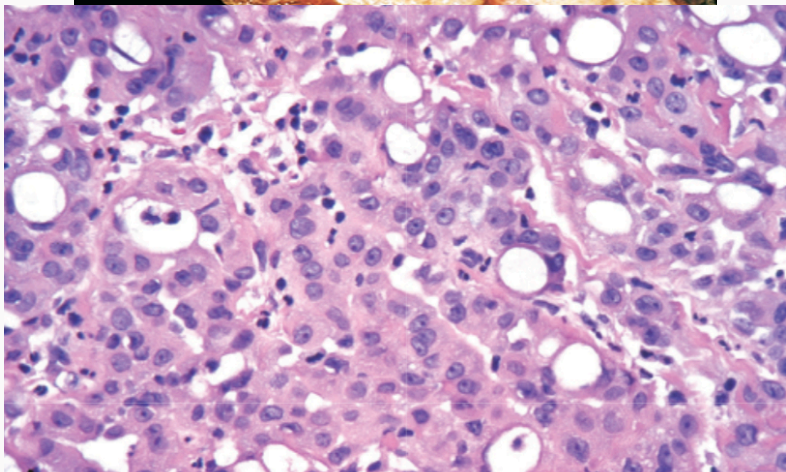
- **Pulmonary Metastases are More Common than Primary Lung Tumors**
- Metastatic tumors in the lung are typically multiple and circumscribed. When large nodules are seen in the lungs radiologically, they are called cannon ball metastases
- The common primary sites are the breast, stomach, pancreas, and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



Mesothelioma

- Malignant tumor of mesothelial cells lining the pleura
- Highly malignant neoplasm
- Most patients (70%) have a history of exposure to asbestos
- Smoking is not related to mesothelioma
- The average age of patients with mesothelioma is 60 years
- Three main histological variants: epithelioid, spindle cell, biphasic
- 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





Summery

- The three major histologic subtypes are adenocarcinoma (most common), squamous cell carcinoma, and small cell carcinoma, each of which is clinically and genetically distinct.
- Adenocarcinomas are the most common cancers overall and are especially common in women and in non-smokers.
- Precursor lesions include atypical adenomatous hyperplasia and adenocarcinoma in situ for adenocarcinomas and squamous dysplasia for squamous cancer.
- Tumors 3 cm or less in diameter characterized by pure growth along pre-existing structures without stromal invasion are called adenocarcinoma in situ.
- SCLCs are best treated with chemotherapy, because almost all are metastatic at presentation. The other carcinomas may be curable by surgery if limited to the lung.
- Targeted therapies, such as EGFR inhibitor therapy for adenocarcinomas with EGFR mutations, can be effective, an excellent example of personalized cancer therapy. Immunotherapies are under development and show promise.
- Lung cancers commonly cause a variety of paraneoplastic syndromes.

Protect your self