

## PULMONARY NEOPLASMS

### What's Important For You to Know?

- Lung metastases are more common than primary lung cancers.
- Are there any other causes of lung cancer besides smoking? (Does the Surgeon General know about them?)
- Occupational causes of lung cancer.
- The association of certain oncogenes with certain types of lung cancer.
- Pay attention to: the "Big Four" histologic types of lung cancer (small cell, squamous cell, adenocarcinoma and large cell bronchogenic carcinomas).
- Pay attention to: clinical features of lung cancer (local spread, Pancoast's and Horner's syndromes).
- Pay attention to: paraneoplastic syndromes in lung cancer.
- Concepts and significance (but not the details) of staging for lung cancer.
- Bronchial carcinoids.

**Case Study:** A 64-year-old 3-Star Admiral developed a spastic hemiparesis involving the right upper and right lower limbs 3 weeks prior to admission to hospital. He also experienced difficulty in concentrating and displayed serious memory lapses. He gave a 60 pack/year cigarette smoking history. The patient was admitted for a "stroke" evaluation. Physical examination disclosed no evidence of congestive cardiac failure or of edema. Serum electrolytes demonstrated a low sodium level (122 mEq/L). The patient's plasma osmolality was low (265 mosmol/Kg H<sub>2</sub>O) whereas his urine osmolality was elevated (480 mosmol/kg H<sub>2</sub>O). Despite intensive treatment and several hospital admissions, his condition steadily deteriorated. Eventually, he became disoriented and developed convulsions and coma.

### Lung Metastases:

A variety of benign and malignant neoplasms can originate in the lung. However, it should be noted that ***metastatic lung tumors are much more common than primary lung neoplasms.*** The most common primary sites for metastatic lung neoplasms are: **breast, stomach, prostate and ovary.**

### Primary Lung Tumors:

- The vast majority ( $\pm$  90-95%) of primary lung tumors are malignant epithelial neoplasms. These are collectively designated **bronchogenic carcinomas.**
- + 1-2% of primary lung neoplasms are **bronchial carcinoids.**
- + 2-5% of primary lung tumors are of mesenchymal origin -- **lymphomas, fibromas, leiomyomas, lipomas, fibrosarcomas, leiomyosarcomas, etc.**
- **Bronchial hamartoma** refers to a benign tumor which exhibits disorganized, aberrant differentiation of bronchial tissues. It is best regarded as a developmental abnormality, and is composed of islands of hyaline cartilage,

blood vessels, smooth muscle cells, adipose tissue, and loose connective tissue, interspersed with clefts lined by ciliated, respiratory type epithelium.

**Bronchogenic Carcinoma (Lung Cancer):** Bronchogenic carcinoma is the leading cancer killer in the U.S. for both males and females. The incidence rate has increased 15-fold for males and 7-fold for females over the past 50 years. **Currently, there are approximately 170,000 new cases of lung cancer diagnosed annually in the U.S., accounting for  $\pm$  13% of all cancer diagnoses** Of these, 90,200 are predicted for males and 79,200 are predicted for females during 2002. For males, the age-adjusted death rate for lung cancer rose from 19.9/100,000 in 1950 to 72.3/100,000 in 1994. For females, the age-adjusted death rate rose even more dramatically: from 4.5/100,000 in 1950 to 33.4/100,000 in 1994. **Since 1992, the incidence rate has been declining for men (at  $\pm$  1.9% per year) but not for women (where it has been increasing at  $\pm$  0.8% per year).** Since 1987, more women have died from lung cancer than from breast cancer, peaking at 43.4/100,000. **Although, historically, lung cancer has had a strong male preponderance, currently the male : female ratio of new cases is  $\pm$  1.14 : 1.** Overall, lung cancer accounts for 27.9% of all cancer deaths. **The peak incidence of lung cancer occurs in the 40-70 year age group.** Less than 2% of cases occur below the age of 40.

#### **Etiology of Lung Cancer:**

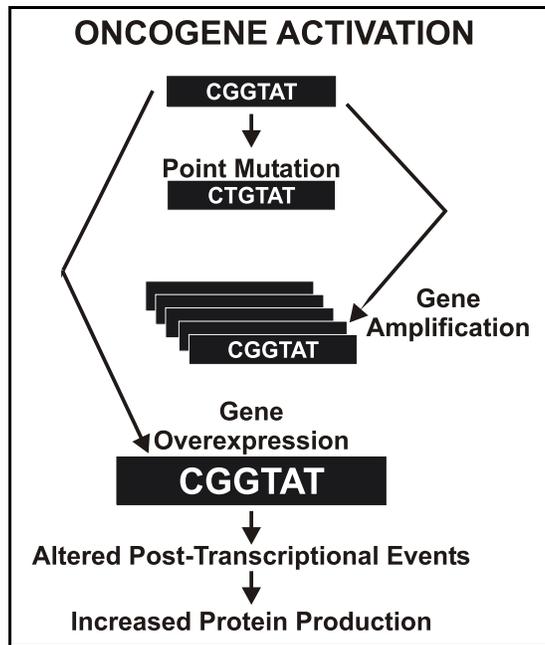
- **Cigarette smoking is the leading cause of lung cancer!** There is a good statistical correlation between the frequency of lung cancer, the tendency to inhale, and the number of cigarette pack-years:
  - Lung cancer risk increases  $\pm$  20-fold in people who smoke more than 40 cigarettes per day.
  - Smokers have a 10-fold greater chance of dying from lung cancer than non-smokers.
  - Smokers who quit for longer than 10 years have a similar risk of developing lung cancer as that of non-smokers.
  - **Tobacco smoke contains at least 55 known carcinogens** including **initiators** (e.g., benzo[a]pyrene), **promoters** (e.g., phenol derivatives), and **radioactive elements** (e.g.,  $^{210}\text{Po}$ ). Precancerous changes (atypical squamous metaplasia, dysplasia and carcinoma-in-situ) are noted in the bronchial epithelium of  $\pm$  10% of smokers (versus less than 1% of non-smokers). Experimental exposures of animals to tobacco smoke have, however, failed to induce appropriate respiratory cancers in rodents (except for laryngeal tumors in hamsters).
  - **The issue of environmental tobacco smoke (ETS) and the causation of lung cancer (in non-smoking spouses and co-workers of smokers) has generated considerable debate.** The EPA and the AMA have published reports which indicate that environmental tobacco smoke is causally associated

with lung cancer and may account for  $\pm 3,000$  excess deaths annually in the U.S. **However, epidemiologic studies suggest that there is only a slightly increased risk of contracting lung cancer from ETS.**

- **What about radon?** Radon is a ubiquitous radioactive gas which has been linked epidemiologically to an increased incidence of lung cancer among underground miners. Inhaled,  $\alpha$ -emitting “**radon daughters**” (which are radioactive uranium decay products) become attached to environmental aerosols  $\Rightarrow$  deposit on the bronchial epithelium. **It is well recognized that radon exposure can cause lung cancer in underground miners.** The EPA estimated that  $\pm 5,000 - 20,000$  Americans die of lung cancer each year from indoor exposure to radon. How? – indoor radon exposure results from the seepage of radioactive uranium decay products from underground rocks through the foundations of homes. In one study,  $\pm 25\%$  of U.S. homes surveyed in 17 states had “unsafe” radon levels. One epidemiologic study has suggested that the effects of indoor radon and cigarette smoking may be synergistic in the induction of lung cancer. This finding has not been supported by other studies.

Recognized Pulmonary Carcinogens	Occupations Associated with an Increased Risk of Lung Cancer
<ul style="list-style-type: none"> <li>● Polycyclic aromatic hydrocarbons</li> <li>● Radon</li> <li>● Asbestos fibers</li> <li>● Heavy metals (As, Cr, Ni, Sb, Cd and Co)</li> <li>● Silica</li> <li>● Chloromethyl ethers</li> <li>● Mustard gas (World War I)</li> </ul>	<ul style="list-style-type: none"> <li>● Uranium miners</li> <li>● Coke oven workers</li> <li>● Smelters</li> <li>● Rubber workers</li> <li>● Welders</li> <li>● Iron and steel foundry workers</li> <li>● Insulators</li> </ul>
<p><b>Putative Pulmonary Carcinogens</b></p>	
<ul style="list-style-type: none"> <li>● Beryllium</li> <li>● Man-made mineral fibers (glasswool and rockwool)</li> <li>● Vinyl Chloride monomer</li> </ul>	

**Oncogenes and Suppressor Genes in Lung Cancer:** As has been noted with other cancers (such as gastrointestinal malignancies and breast cancers), **there is evidence of dominant oncogene activation in bronchogenic carcinoma.** Thus, tumor explants from lung cancer patients and cultured lung cancer cell lines have demonstrated activation of certain oncogenes via diverse mechanisms, including point mutations, gene amplification, and gene overexpression due to post-translational mechanisms. Although many instances of oncogene activation have been observed in lung cancer, **activation of c-myc** frequently is noted in **small cell carcinomas** as is **K-ras activation in adenocarcinomas.** In addition to dominant oncogene activation, it is likely that tumor suppressor gene deletions may play a role in lung carcinogenesis. Notably, **homozygous loss of the p53 gene** has been found in  $\pm 50\%$  of **bronchogenic carcinomas**, and **loss of heterozygosity of the Rb gene** and of **suppressor gene markers on chromosome 3p** has been detected in **small cell carcinomas.** However, the precise clinical significance of many of these findings remains to be determined.



ONCOGENE ACTIVATION IN LUNG CANCER	
Mechanisms of Activation	Oncogenes Involved
Gene amplification	c-myc L-myc N-myc c-erbB-1 c-erbB-2
Protein overexpression without gene amplification	c-myc L-myc N-myc c-erbB-1 c-erbB-2
Point mutation	K-ras

**Features of Bronchogenic Carcinomas:** Most of these tumors originate in the lining epithelium of the bronchi close to the hilum of the lung. ***Cigarette smoking is most closely linked to the development of squamous cell carcinoma, small cell carcinoma, and large cell carcinoma*** — the relationship to adenocarcinoma is less obvious. ***All lung cancers are aggressive, invasive and widely metastasizing neoplasms*** → may spread to any organ, especially the liver, adrenals, brain and bones. These cancers also have the ability to synthesize bioactive hormones and other products.

**Histologic Varieties of Bronchogenic Carcinomas:**

- **Adenocarcinoma** (including bronchioloalveolar carcinoma) — ± 30-35%.
- **Squamous cell carcinoma** — ± 25-30%.
- **Small cell carcinoma** — ± 15-25%.

- **Large cell carcinoma** —  $\pm$  10-15%.
- **Combined cell patterns** (e.g., squamous cell + adenocarcinoma, or small cell + squamous cell carcinoma) —  $\pm$  5-10%.
- **Pleomorphic carcinoma** (mixed carcinoma + sarcomatoid pattern) — very rare (< 0.5% ).

***From a clinical standpoint, the most important distinction is between small cell and non-small cell carcinomas***, since small cell carcinomas are initially responsive to appropriate chemotherapeutic regimens. Also, ***K-ras mutations are associated with a bad prognosis for non-small cell carcinomas***.

● **Adenocarcinomas:** These neoplasms are relatively more frequent in women than in men, and frequently arise in a peripheral location of the lung. **They are the most common type of lung cancer in non-smokers**. An association with cigarette smoking is not clear-cut. Some adenocarcinomas may arise within an area of pulmonary fibrosis (e.g., an old infarct, asbestosis, or healed tuberculosis) -- **such neoplasms are referred to as scar cancers**. It should be noted, however, that adenocarcinomas, *per se*, can evoke a strong desmoplastic host response to the tumor. Thus, in some cases, it may be difficult to determine whether or not the scar preceded the development of the cancer. Distant organ metastases are noted in > 50% of cases (especially within the brain). Adenocarcinomas also have a poor prognosis →  $\pm$  10-12% five-year survival rate. The histologic features are heterogeneous:

■ The most common pattern of adenocarcinoma is the **acinar variety** -- regular glands lined by columnar cells with basal nuclei. Mucus production may be scanty or abundant.

■ **Papillary adenocarcinomas** have a single layer of cuboidal or columnar cells on a core of fibrous tissue.

■ **Solid adenocarcinomas** with mucin formation are poorly differentiated neoplasms with scanty glandular formation and scanty intracellular mucin.

■ **Bronchioloalveolar carcinomas:** These neoplasms represent  $\pm$  10-25% of bronchogenic adenocarcinomas. Although there is some debate about their histogenesis, they are considered a **subtype of bronchogenic adenocarcinoma**. They are often solitary, peripheral tumors but may be multicentric. **The solitary type is amenable to surgical resection** (if < 2 cm in size, surgical resection is curative). **The multicentric type has the same prognosis as other lung cancers**. Electron microscopy studies have shown that **the cell of origin** in these tumors may be either the **bronchiolar mucin secreting cell**, the **type II pneumocyte**, or the **Clara cell**. Histologically, these tumors show either well-differentiated, mucin-containing columnar cells lining alveolar spaces without invading the underlying stroma, or papillary formations composed of mucin-containing columnar cells on a fibrous tissue core, resembling adenocarcinomas.

● **Squamous Cell Carcinomas:** These tumors are more common in males than in females, and are strongly associated with cigarette smoking. Arise centrally in the major or segmental bronchi and spread to local hilar nodes (in  $\pm$  70-90% of cases), distant lymph nodes (in  $\pm$  50-60% of cases), or other viscera. **Often, the development of**

***squamous cell carcinoma in cigarette smokers is preceded by multicentric atypical squamous metaplasia, dysplasia, or carcinoma-in-situ over a period of many years.*** These changes are analogous to those seen in the cervix prior to the development of invasive carcinoma in that organ. Squamous cell carcinomas have a dismal prognosis → ± 5-8% five-year survival rate. The histologic appearances may vary:

■ **Well-differentiated squamous cell carcinomas** exhibit formation of intercellular bridges as well as characteristic, eosinophilic keratin “pearls,” surrounded by onion skin layers of squamous cells.

■ **Poorly differentiated squamous cell carcinomas** show scanty or no features of squamous cell differentiation. They may be difficult to differentiate from some small cell carcinomas.

● **Small Cell Carcinomas:** These are very aggressive, early metastasizing neoplasms. They tend to be more common in males than in females and are strongly associated with cigarette smoking. The tumors are usually centrally located, and appear to arise from pluripotential basal cells of the bronchial epithelium. The tumor cells exhibit neuroendocrine differentiation. **On electron microscopy, they contain dense-core neurosecretory granules, and immunohistochemical stains demonstrate the presence of neuroendocrine markers** (e.g., chromogranin and synaptophysin). Small cell carcinomas are commonly associated with paraneoplastic syndromes, and have a very bad prognosis → ± 5-8% five-year survival. Histologically, there are two main morphologic types of small cell carcinoma:

■ **Oat cell type**, comprising lymphocyte-like cells with virtually no cytoplasm.

■ **Intermediate cell type**, composed of spindle-shaped or polygonal cells with abundant cytoplasm.

● **Large Cell Carcinomas:** These are very anaplastic cancers that tend to occur in smokers. They may arise in either a central or peripheral location and tend to metastasize rapidly and widely. Also, they have an extremely grave prognosis → ± 2-3% five-year survival rate. **Large cell carcinomas are undifferentiated or poorly differentiated neoplasms which show no evidence of glandular, squamous, or neuroendocrine differentiation.** Two variants of large cell carcinoma include:

■ **Giant cell carcinoma** — huge, poorly cohesive cells with eosinophilic cytoplasm.

■ **Clear cell carcinoma** — cells with clear cytoplasm containing glycogen.

**Clinical Features of Bronchogenic Carcinomas:** The clinical presentation of bronchogenic carcinoma is extremely variable. Some patients have symptoms referable to local tumor invasion whereas, in other patients, the initial presentation may stem from the effects of metastatic involvement (e.g., cerebral involvement may simulate the features of a primary tumor of the central nervous system). ± 10-15% of lung cancers are discovered by chance (on cytologic or radiographic screening) — **typically, a “coin lesion” is evident on chest radiographs.**

● Local symptoms include cough, chest pain, weight loss and hemoptysis.

- Local tumor invasion and obstruction may produce any of the following:
  - Recurrent laryngeal nerve paralysis → hoarseness.
  - Phrenic nerve paralysis → diaphragmatic paralysis.
  - Esophageal invasion → dysphagia.
  - Superior vena caval obstruction → edema.
  - **Pancoast syndrome** -- apical lung tumors can infiltrate the spinal (C8-T2) nerves (→ shoulder pain) and cervical sympathetic nerves (→ **Horner's syndrome**, characterized by absence of sweating, drooping of the eyelid, and pupil constriction on the affected side).
  - Pericardial or pleural effusions; bronchial obstruction → atelectasis, bronchopneumonia, and/or lung abscess formation.
- **Paraneoplastic syndromes** occur in ± 10-15% of cases -- tumor-related effects which are *not* due to the effects of invasion or metastases. Examples include:
  - **Hypercalcemia** (due to ectopic secretion by tumor cells of either parathormone, a parathyroid hormone-like peptide, or prostaglandin E). This is seen especially with squamous cell carcinomas.
  - **Cushing's syndrome** (due to ectopic secretion of ACTH by tumor cells). This occurs especially in association with small cell carcinomas.
  - **Inappropriate release of ADH** → sodium and water retention → altered mental status changes). This is associated with small cell carcinomas.
  - **Hypocalcemia** (possibly due to ectopic secretion of calcitonin by tumor cells).
  - **Gynecomastia** (due to ectopic secretion of gonadotrophins by tumor cells).
  - **Clubbing** of the fingers and toes as well as pulmonary hypertrophic osteoarthropathy.
  - **Migratory thrombophlebitis** (due to secretion of thromboplastic substances by tumor cells).
  - **Cerebellar degeneration.**
  - **Neuropathies and myopathies (Lambert-Eaton syndrome).**
  - **Leukoencephalopathy.**

**Clinical Staging of Lung Cancer:** As with other cancers, an **International TNM Staging System** is used, based on the size of the **Tumor**, and on whether or not there is involvement of Lymph **N**odes and Distant **M**etastases, at the time of presentation. For further details, consult Table 16-10 (p. 745) of *Robbins: Pathologic Basis of Disease* (6th edition, 1999) by Cotran, Kumar and Collins. Non-small cell carcinomas < 4 cm in diameter are more readily treated by surgery. **Small cell carcinomas are not**

**amenable to surgical resection, and are best treated by chemotherapy.** Overall, bronchogenic carcinomas have a very poor overall five-year survival rate ( $\pm$  14% for all stages combined). In contrast, the survival rate for early stage (i.e., stage I - II) disease is about 49%. **However, only approximately 15% of lung cancers are discovered early enough to be resectable.**

● **Neuroendocrine tumors:** These represent a wide spectrum of lung tumors that manifest neuroendocrine differentiation. In order of biological aggressiveness, they comprise the following tumors: small cell bronchogenic carcinomas > large cell neuroendocrine carcinomas > atypical bronchial carcinoids > typical bronchial carcinoids. **All these neoplasms contain dense-core neurosecretory granules on E.M. and usually express one or more neuroendocrine differentiation markers** (e.g., chromogranin-A, synaptophysin, CD15, neuron-specific enolase, serotonin, calcitonin, or bombesin).

● **Bronchial carcinoids:** These tumors, are all neuroendocrine neoplasms that originate from **Kulchitsky cells** in the bronchial mucosa, and represent  $\pm$  1-2% of all primary lung tumors. Typical carcinoids have no relationship to cigarette smoking. They occur equally in both genders, and occur most frequently under 40 years of age. Bronchial carcinoids usually present as finger-like or spherical polypoid masses which either project into the bronchial lumen, or fan out into the surrounding peribronchial tissue, producing a "collar-stud" lesion.  $\pm$  50% are asymptomatic. In the remainder of cases, their clinical effects are mainly referable to their intraluminal growth pattern  $\rightarrow$  cough, hemoptysis, bronchiectasis, emphysema and atelectasis.  $\pm$  5-55% metastasize to the regional lymph nodes or to the liver  $\rightarrow$  hepatomegaly. A small number of bronchial carcinoids that metastasize to the liver produce a **systemic carcinoid syndrome** (intermittent diarrhea, flushing, and cyanosis) — due to the release of serotonin and kallikrein from the tumor cells. Histologically, three main varieties are noted:

■ **Typical carcinoids** have an "organoid" pattern composed of tumor cells arranged in cords, clusters, and/or tubules. The tumor cells are round or polyhedral, and have abundant cytoplasm. Necrosis is not a feature, and mitoses are rare. Lymph node metastases are comparatively rare.

■ **Atypical carcinoids** display similar features to classic carcinoids. However, necrosis and mitotic figures are prominent. They are more common in smokers than in non-smokers. Regional lymph node metastases are quite common. Their biologic behavior is intermediate between that of classic carcinoids and large cell neuroendocrine carcinomas.

■ **Large cell neuroendocrine carcinomas** have the most tumor mitoses of all the carcinoids. Morphologically, these tumors resemble large cell bronchogenic carcinomas but demonstrate neuroendocrine differentiation. **Almost all patients with large cell neuroendocrine carcinomas are smokers.**