LEC 4
Dr. Asseel M. Ghazi

LUNG TUMORS

Although lungs frequently are the site of metastases from cancers arising in extrathoracic organs, primary lung cancer is also a common disease.

Roughly 95% of primary lung tumors are carcinomas; the remaining 5% constitute a miscellaneous group that includes carcinoids, mesenchymal malignancies (e.g., fibrosarcomas, leiomyomas), lymphomas, and a few benign lesions.

The most common benign tumor is a spherical, small (3 to 4 cm), discrete "**hamartoma**" that often shows up as a so-called coin lesion on chest radiographs.

It consists mainly of mature cartilage, but this is often admixed with fat, fibrous tissue, and blood vessels in various proportions.

Clonal cytogenic abnormalities have been demonstrated, indicating that it is a benign neoplasm, although still commonly referred to as **hamartoma**.

Carcinomas

Carcinoma of the lung (also known as "lung cancer") is without doubt the single most important cause of cancer related deaths in industrialized countries.

It has long held this position among males in the United States, accounting for about one third of cancer deaths in men, and has become the leading cause of cancer deaths in women as well.

These statistics undoubtedly reflect the causal relationship of cigarette smoking and lung cancer.

The four major histologic types of carcinomas of the lung are adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma .

Of these, squamous cell and small cell carcinomas show the strongest association with smoking.

Adenocarcinomas also are by far the most common primary tumors arising in women, in never-smokers, and in persons younger than 45 years.

• Until recently, carcinomas of the lung were classified into two broad groups: small cell lung cancer (SCLC) and non–small cell lung cancer (NSCLC), with the latter including adenocarcinomas and squamous and large cell carcinomas.

***Adenocarcinoma and squamous cell and large cell carcinoma are collectively referred to as non–small cell lung carcinoma (NSCLC).**

usually responded poorly to chemotherapy; however, now therapies are available that target specific mutated gene products present in the various subtypes of NSCLC, mainly in adenocarcinomas.

ETIOLOGY AND PATHOGENESIS

Smoking-related carcinomas of the lung arise by a stepwise accumulation of a multitude of genetic abnormalities (estimated to be in the thousands for small cell carcinoma) that result in transformation of benign progenitor cells in the lung into neoplastic cells.

More important, it seems that certain genetic changes, such as loss of chromosomal material , can be found even in benign bronchial epithelium of persons with lung cancer, as well as in the respiratory epithelium of smokers **without** lung cancer, suggesting that large areas of the respiratory mucosa are mutagenized after exposure to carcinogens **(“field effect”).** On this fertile soil, those cells that accumulate additional mutations ultimately develop into cancer.

MORPHOLOGY

Carcinomas of the lung begin as small mucosal lesions that typically are firm and gray-white.

They may arise as intraluminal masses, invade the bronchial mucosa, or form large bulky masses pushing into adjacent lung parenchyma.

Some large masses undergo cavitation secondary to central necrosis or develop focal areas of hemorrhage. Finally, these tumors may extend to the pleura, invade the pleural cavity and chest wall, and spread to adjacent intrathoracic structures.

More distant spread can occur by way of the lymphatic's or the hematogenous route.

Squamous cell carcinomas are more common in men than in women and are closely correlated with a smoking history; they tend to **arise centrally in major bronchi** and eventually spread to local hilar nodes, but they disseminate outside the thorax later than do other histologic types.

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,** a phase that may last for several years . By this time, atypical cells may be identified in cytological smears of sputum or in bronchial lavage fluids or brushings, although the lesion is asymptomatic and undetectable on radiographs. 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.

Simultaneously, the lesion invades surrounding pulmonary substance.

On histologic examination, these tumors range from well differentiated squamous cell neoplasms showing keratin pearls and intercellular bridges to poorly differentiated neoplasms exhibiting only minimal residual squamous cell features.

Adenocarcinomas may occur as central lesions like the squamous cell variant but usually are more **peripherally located,** many with a central scar.

Adenocarcinomas are the most common type of lung cancer in women and nonsmokers.

In general, adenocarcinomas grow slowly and form smaller masses than do the other subtypes, but they tend to metastasize widely at an early stage.

On histologic examination, they may assume a variety of forms, including **acinar (gland-forming)** , **papillary, mucinous** and **solid types.**

The putative precursor of peripheral adenocarcinomas is thought to be **atypical adenomatous hyperplasia** (AAH)

which progresses to adenocarcinoma in situ (formerly bronchioloalveolar carcinoma), minimally invasive adenocarcinoma (tumor less than 3 cm and invasive component

measuring 5 mm or less), and invasive adenocarcinoma (tumor of any size that has invaded to depths greater than 5 mm).

On microscopic examination, AAH is recognized as a well-demarcated focus of epithelial proliferation (with a thickness of 5 mm or less) composed of cuboidal to low-columnar cells, which demonstrate cytologic atypia of variable degree such as nuclear hyperchromasia, pleomorphism, prominent nucleoli, but not to the extent seen in adenocarcinoma.

Large cell carcinomas are undifferentiated malignant epithelial tumors that lack the cytologic features of small cell carcinoma and have no glandular or squamous differentiation.

The cells typically have large nuclei, prominent nucleoli, and a moderate amount of cytoplasm.

Large cell carcinomas probably represent squamous cell or adenocarcinomas that are so undifferentiated that they can no longer be recognized by means of light microscopy.

On ultrastructural examination, however, minimal glandular or squamous differentiation is common.

These cancers are composed of tumor cells with a round to fusiform shape, scant cytoplasm, and finely granular chromatin.

Mitotic figures frequently are seen.

Necrosis is invariably present and may be extensive.

The tumor cells are markedly fragile and often show fragmentation and “crush artifact” in small biopsy specimens.

These cancers, when advanced, often extend into the pleural or pericardial space, leading to inflammation and effusion.

Clinical Course

Carcinomas of the lung are silent, insidious lesions that in many cases have spread so as to be unresectable before they produce symptoms.

In some instances, chronic cough and expectoration call attention to still localized, resectable disease.

By the time hoarseness, chest pain, superior vena cava syndrome, pericardial or pleural effusion, or persistent segmental atelectasis or pneumonitis makes its appearance, the prognosis is grim.

Too often, the tumor presents with symptoms emanating from metastatic spread to the brain (mental or neurologic changes), liver (hepatomegaly), or bones (pain). Although the adrenals may be nearly obliterated by metastatic disease, adrenal insufficiency (Addison disease) is uncommon, because islands of cortical cells sufficient to maintain adrenal function usually persist.

Overall, NSCLCs carry a better prognosis than SCLCs.

When NSCLCs (squamous cell carcinomas or adenocarcinomas) are detected before metastasis or local spread, cure is possible by lobectomy or pneumonectomy.

SCLCs, on the other hand, have invariably spread by the time they are first detected, even if the primary tumor appears small and localized. Thus, surgical resection is not a viable treatment.

They are very sensitive to chemotherapy but invariably recur.

Median survival even with treatment is 1 year.

It is variously estimated that 3% to 10% of all patients with lung cancer develop clinically overt ***paraneoplastic syndromes.***

These include (1) hypercalcemia caused by secretion of a parathyroid hormone–related peptide (osteolytic lesions may also cause hypercalcemia, but this would not be a paraneoplastic syndrome ; (2) Cushing syndrome (from increased production of adrenocorticotropic hormone); (3) syndrome of inappropriate secretion of antidiuretic hormone; (4) neuromuscular syndromes, including a myasthenic syndrome, peripheral neuropathy, and polymyositis; (5) clubbing of the fingers and hypertrophic pulmonary osteoarthropathy; and (6) coagulation abnormalities, including migratory thrombophlebitis, nonbacterial endocarditis, and disseminated intravascular coagulation.

Hypercalcemia most often is encountered with squamous cell neoplasms, the hematologic syndromes with adenocarcinomas.

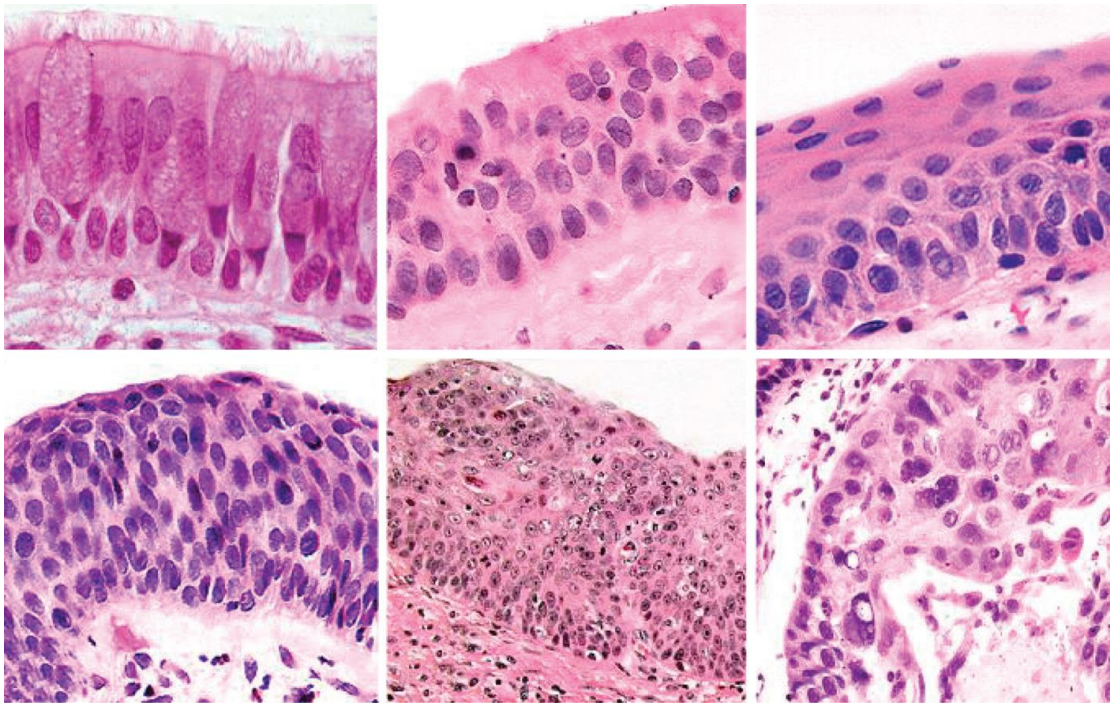
• Smoking is the most important risk factor for lung cancer;

in women and nonsmokers, adenocarcinomas are the most common cancers.

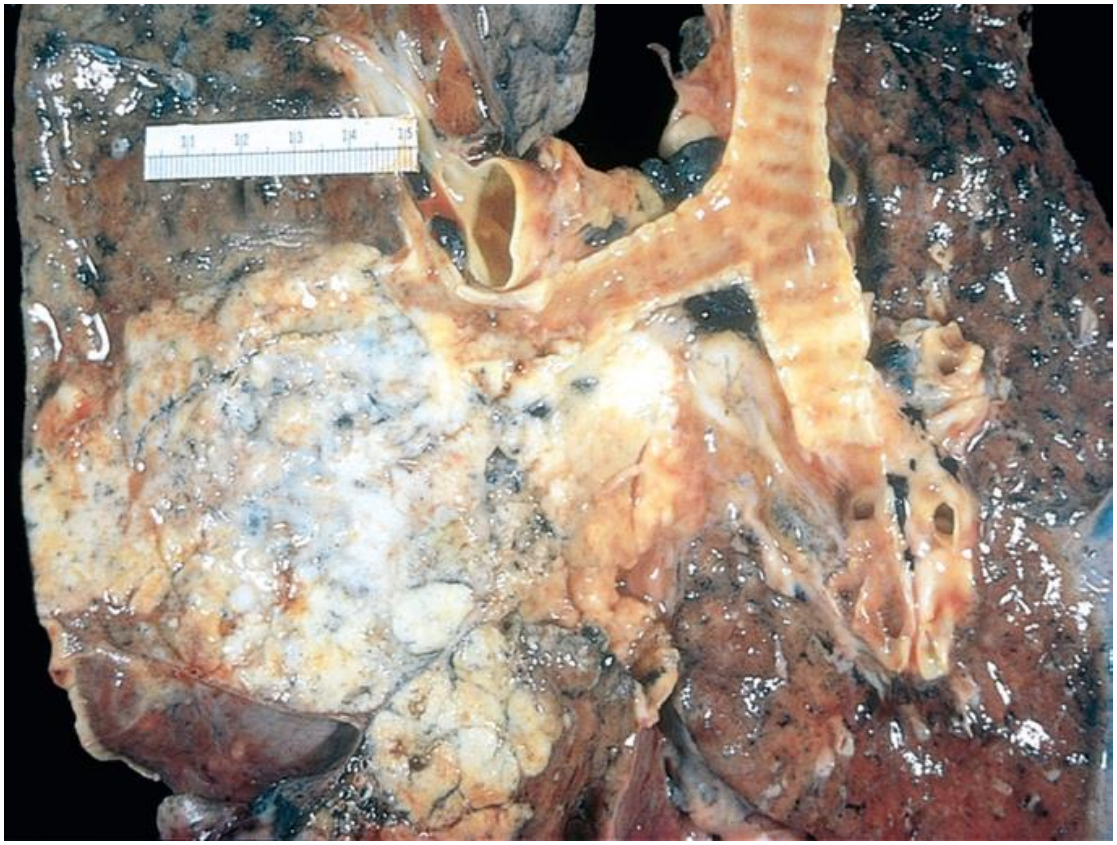
• Precursor lesions include squamous dysplasia (for squamous cancer) and atypical adenomatous hyperplasia and adenocarcinoma in situ (formerly bronchioloalveolar carcinoma) (for some adenocarcinomas).

• Tumors 3 cm or less in diameter characterized by pure growth along preexisting structures (lepidic pattern) without stromal invasion are now called adenocarcinoma in situ.

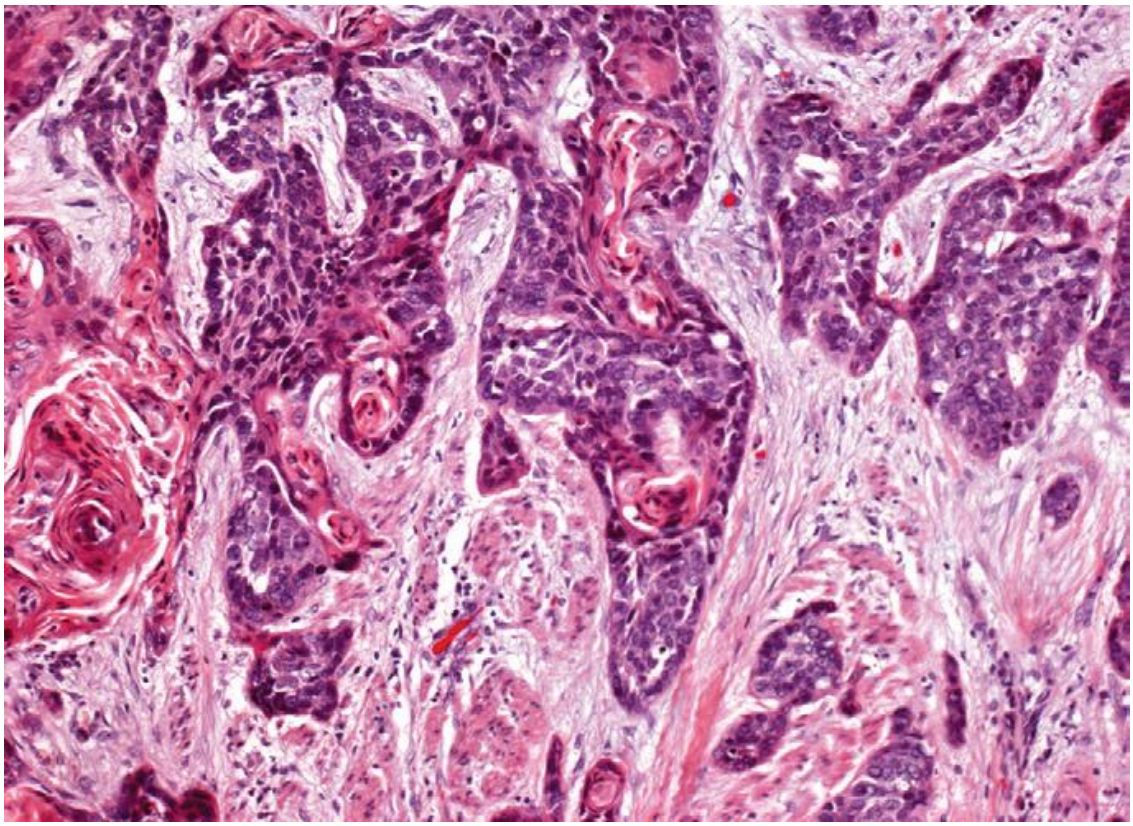
• Lung cancers, particularly SCLCs, can cause *paraneoplastic syndromes.*



Precursor lesions of squamous cell carcinomas that may antedate the appearance of invasive tumor by years. **A–C,** Some of the earliest (and "mild") changes in smoking-damaged respiratory epithelium include goblet cell hyperplasia (**A**), basal cell (or reserve cell) hyperplasia (**B**), and squamous metaplasia (**C**). **D,** More ominous changes include the appearance of squamous dysplasia, characterized by the presence of disordered squamous epithelium, with loss of nuclear polarity, nuclear hyperchromasia, pleomorphism, and mitotic figures. **E** and **F,** Squamous dysplasia may, in turn, progress through the stages of mild, moderate, and severe dysplasia. Carcinoma in situ (CIS) (**E**) is the stage that immediately precedes invasive squamous carcinoma (**F**). Apart from the lack of basement membrane disruption in CIS, the cytologic features of CIS are similar to those in frank carcinoma. Unless treated, CIS eventually progresses to invasive cancer.



Squamous cell carcinoma usually begins as a central (hilar) mass and grows contiguously into the peripheral parenchyma as seen here.



Well-differentiated squamous cell carcinoma showing keratinization and pearls.