Pathologically, adenocarcinomas typically form glandular structures and produce mucus. *EGFR* mutations are more commonly associated with nonmucinous lung adenocarcinoma, whereas the mucinous subtype is more commonly associated with mutated *KRAS*. The tumor cells typically stain positive for cytokeratin 7 (CK7), thyroid transcription factor 1 (TTF-1), carcinoembryonic antigen (CEA), mucin, and surfactant apoprotein and negative for cytokeratin 20 (CK20). Adenocarcinomas respond poorly to therapy and have a poor prognosis.

Bronchoalveolar cell carcinomas (BAC), a subset of adenocarcinomas, are the most common form of lung cancer found in nonsmokers and young patients. They manifest as lung infiltrates or as a solitary nodule and can be accompanied by bronchorrhea. BAC cells can grow in a lepidic (scaly) pattern and spread along alveolar walls.

Squamous Cell Carcinomas

Squamous cell carcinomas arise from the epithelial layer of the bronchial wall. Normal columnar epithelial cells undergo metaplasia, dysplasia, and then localized carcinoma (*carcinoma in situ*) formation; this can then further extend and invade beyond the bronchial mucosa as it acquires a full malignant invasive phenotype (carcinoma). Because most squamous cell carcinomas arise within central airways (E-Fig. 56-6), the airway lumen may become obstructed, leading to collapse of the lung (atelectasis) or postobstructive pneumonia. Although necrosis and cavity formation can occur in any lung tumor, this feature is more common in squamous cell carcinomas. Because of their slow rate of growth, these tumors have the lowest propensity for metastasis of all types of lung cancer. Pathologically, squamous cell carcinomas can be distinguished from other NSCLCs by the presence of keratinization, pearl formation, and intercellular bridging.

Adenosquamous Carcinomas

Adenosquamous carcinomas constitute between 0.4% and 4% of cases and may have a worse prognosis. They have components of both adenocarcinoma and squamous cell carcinoma, each comprising at least 10% of the tumor.

Large Cell Carcinomas

Large cell carcinomas frequently develop as a peripheral lesion and may be associated with pneumonitis and hilar adenopathy. The two main subtypes are *giant cell carcinoma*, an anaplastic tumor that has a median survival time of less than 1 year; and *clear cell carcinoma*, a tumor that resembles renal cell carcinoma and has fewer malignant features.

NSCLC Not Otherwise Specified

Despite one's best efforts in defining subtype differentiation of a NSCLC through histology and immunophenotyping, there may remain poorly differentiated tumors that defy such classification. These are designated NSCLC-NOS.

Small Cell Lung Carcinoma

SCLC cells are of pulmonary neuroendocrine cell origin and are often associated with paraneoplastic syndromes (Table 56-1). SCLCs typically are perihilar in location, not infrequently originate in the main bronchi, and often have associated malignant adenopathy (E-Fig. 56-7). These tumors have a high propensity for metastasis, most commonly to the thoracic lymph nodes, bones, liver, adrenal glands, and brain. Most patients are already affected with metastatic disease at the time of presentation. SCLC has traditionally been staged as *limited disease* (confined to one hemithorax) or *extensive disease* (distant metastases); although a TNM staging system has recently been suggested. SCLC is an aggressive lung tumor; without treatment, the median survival time of patients with this cancer is less than 5 months. The overall survival at 5 years is 5% and has not improved over the past several decades.

TABLE 56-1 PARANEOPLASTIC SYNDROMES ASSOCIATED WITH LUNG CANCER

SYNDROME	CELL TYPE	MECHANISM
Hypertrophic pulmonary osteoarthropathy and clubbing	All except small cell	Unknown
Hyponatremia	Small cell most common; may be any type	SIADH, ectopic antidiuretic hormone production by tumor
Hypercalcemia	Usually squamous cell	Bone metastases, osteoclast-activating factor, parathyroid hormone–like hormone, prostaglandins
Cushing syndrome	Usually small cell	Ectopic ACTH production
Eaton-Lambert myasthenic syndrome	Usually small cell	Voltage-sensitive calcium channel antibodies in >75%; affects presynaptic neuronal calcium channel activity
Other neuromyopathic disorders	Small cell most common; may be any type	Antineuronal nuclear antibodies, also known as anti-Hu; others unknown
Thrombophlebitis	All types	Unknown

ACTH, Adrenocorticotropic hormone; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Molecular-Genomic Subtypes

Lung cancer is now increasingly regarded as a disease with collections of often very distinct and heterogeneous molecular and genomic subclasses or disease subgroups (Table 56-2). Many of these molecular-genomic alterations can inform the use of targeted therapeutics and predict responses.

Mutant *EGFR*

EGFR mutation testing and targeting therapy are part of routine clinical care of patients with NSCLC worldwide. Specific somatic *EGFR* gene kinase domain–activating mutations, predominantly occurring in lung adenocarcinoma, predict sensitivity and clinical response to the EGFR inhibitors gefitinib and erlotinib. These mutations are usually found in never-smokers or female light smokers with adenocarcinoma. *EGFR* mutations are more prevalent in Asian patients (30%, compared with 7-10% in Caucasians). Molecular tumor selection by profiling is superior to clinical selection.

ALK 2p23 Rearrangement

The *EML4-ALK* fusion in NSCLC is an oncogenic driver fusion-kinase. Oncogenic *ALK*-rearrangements occur in 3% to 7% of NSCLCs, in light smokers (<10 pack-years) or never-smokers. In