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HISTOLOGIC SUBTYPES OF LUNG CANCER AND THEIR CLINICAL IMPLICATIONS

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Annotation

Lung cancer is the leading cause of cancer-related deaths globally. Accurate histologic classification is vital in diagnosis, prognosis, and therapeutic decision-making. This article explores the major histologic subtypes of lung cancer, highlights their clinical and molecular characteristics, and emphasizes the role of precise diagnosis in the era of personalized therapy.

Keywords: lung cancer, adenocarcinoma, squamous cell carcinoma, histology, EGFR, molecular testing, targeted therapy.

Lung cancer continues to be the most prevalent cause of cancer-related mortality worldwide, particularly among men. Its early diagnosis and effective management rely heavily on accurate histologic classification, which has evolved substantially over recent decades. Among the major histologic types, adenocarcinoma, squamous cell carcinoma, small cell carcinoma, and large cell carcinoma are the most frequently encountered, each with unique clinical, morphologic, and molecular features that influence treatment strategy and prognosis.

Adenocarcinoma is currently the most common histologic subtype, especially among non-smokers and women. It is often located peripherally in the lung and is associated with several driver mutations such as EGFR, ALK, ROS1, and KRAS. The 2011 IASLC/ATS/ERS classification introduced new concepts such as adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), refining the understanding of tumor invasiveness and guiding surgical management. Subtypes like lepidic predominant adenocarcinoma and micropapillary adenocarcinoma show significant differences in prognosis, with the latter being linked to worse outcomes. Patients with EGFR mutations, for instance, benefit significantly from tyrosine kinase inhibitors (TKIs) such as osimertinib, highlighting the importance of molecular testing.

Squamous cell carcinoma, strongly associated with smoking, traditionally presented as a central tumor, but recent data indicate an increasing proportion in peripheral locations. It is characterized histologically by intercellular bridges and keratinization. Unlike adenocarcinoma,

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squamous cell carcinoma typically lacks EGFR mutations and is not eligible for treatments such as pemetrexed or bevacizumab. Subtypes include basaloid and papillary variants, although their clinical significance remains under investigation.

Small cell carcinoma, a high-grade neuroendocrine tumor, is aggressive and rapidly progressive. Most commonly found in heavy smokers, it is often associated with paraneoplastic syndromes like SIADH and Cushing's syndrome. Small cell carcinoma may appear as a pure form or in combination with non-small cell components. Despite its high initial response to chemotherapy and radiotherapy, recurrence is common, and long-term survival is rare.

Large cell carcinoma is a poorly differentiated subtype that lacks the histologic features of adenocarcinoma or squamous carcinoma. It used to comprise about 10% of lung cancers, but the proportion has decreased with improved diagnostic techniques. Large cell neuroendocrine carcinoma, a subtype, shares biologic behavior with small cell carcinoma and has a similarly poor prognosis.

Preinvasive lesions play an increasingly important role in early detection strategies. Atypical adenomatous hyperplasia (AAH), adenocarcinoma in situ (AIS), and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) are recognized precursors to invasive disease. Bronchial squamous dysplasia and carcinoma in situ (CIS) represent early stages of squamous carcinogenesis. These lesions demonstrate a progression of molecular changes, including p53 mutation, 3p loss, and telomerase reactivation, which correlate with increasing dysplasia and risk of invasion.

In conclusion, the histologic classification of lung cancer has become an essential part of modern oncologic practice. It provides critical information for treatment selection, including the use of targeted therapies based on molecular alterations. As diagnostic capabilities expand, particularly in small biopsies and cytologic samples, integrating histopathology with molecular data will continue to improve outcomes for lung cancer patients.

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