

EVOLVING PATHOLOGIC CLASSIFICATION OF LUNG CANCER: FROM BIOPSY TO MOLECULAR TARGETING

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Annotation

Recent advances in molecular diagnostics have transformed the classification and treatment of lung cancer. This article discusses the evolution of histologic classification, the importance of tissue preservation for molecular analysis, and the integration of histopathologic and genomic data for effective patient management.

Keywords: lung cancer, histologic classification, molecular markers, biopsy, EGFR, ALK, adenocarcinoma, precision oncology

Over the past two decades, lung cancer classification has shifted from a purely morphologic system to an integrated histo-molecular approach. This transformation has been driven by the discovery of actionable genetic alterations and the development of targeted therapies. Non-small cell lung cancer (NSCLC), which accounts for approximately 85% of all lung cancers, now requires precise subclassification even in small biopsy or cytologic specimens, as these inform both prognosis and therapeutic strategy.

The 2011 IASLC/ATS/ERS classification of adenocarcinoma marked a significant advance in the understanding of lung cancer pathology. It introduced structured terminology for use in different sample types, eliminated outdated terms such as bronchioloalveolar carcinoma (BAC), and emphasized the need for quantitative subtyping. Each tumor is now classified based on the predominant histologic pattern, with subtypes including lepidic, acinar, papillary, micropapillary, and solid. These patterns carry prognostic implications, with micropapillary and solid subtypes being associated with worse survival.

Molecular diagnostics are now routine in NSCLC management. Testing for EGFR mutations, ALK and ROS1 rearrangements, and PD-L1 expression levels is standard practice in advanced-stage adenocarcinoma. For instance, EGFR mutations are found in 10–15% of Caucasians and up to 50% of Asian patients, and their presence predicts response to TKIs such as gefitinib, afatinib, and osimertinib. Similarly, ALK-positive tumors respond to ALK inhibitors like alectinib or lorlatinib. These targeted therapies offer significantly improved

progression-free survival compared to chemotherapy, reinforcing the importance of accurate histologic and molecular diagnosis.

An emerging challenge in molecular oncology is resistance to targeted therapy. For example, patients with EGFR-mutant tumors may develop a T790M resistance mutation, necessitating the use of third-generation TKIs. In some cases, histologic transformation from adenocarcinoma to small cell carcinoma occurs, highlighting the dynamic nature of lung tumors and the need for re-biopsy and repeat molecular profiling upon progression.

Pathologists are now required to manage limited biopsy material judiciously, balancing the need for histologic diagnosis with preservation of tissue for molecular testing. Immunohistochemistry (IHC) plays an essential role in subtyping poorly differentiated tumors. TTF-1 and p40 help differentiate adenocarcinoma from squamous cell carcinoma, while neuroendocrine markers aid in identifying small cell and large cell neuroendocrine carcinomas.

In rare cases such as adenosquamous carcinoma, which requires at least 10% of both glandular and squamous differentiation, diagnosis cannot be made reliably on small biopsies. Similarly, tumors with ambiguous features may require next-generation sequencing (NGS) to determine the most appropriate classification and therapy. The increasing use of comprehensive NGS panels allows for simultaneous assessment of multiple mutations, improving the efficiency and scope of diagnostic workup.

In summary, the integration of histologic, cytologic, and molecular data has fundamentally changed the classification and management of lung cancer. The ability to identify precise subtypes and actionable mutations ensures that patients receive the most effective and individualized treatment. As technology and knowledge continue to evolve, so too will the pathologic framework guiding the clinical care of lung cancer patients.

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