Classification and Pathology of Lung Cancer

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KEYWORDS

• Lung cancer • Classification • Pathology • Immunohistochemistry
• Molecular testing

KEY POINTS

- Lung cancer classification strives to correlate tumor cell morphology with tumor biological characteristics, thus facilitating therapeutic decision-making and effective prognostic outcome prediction in the era of personalized medicine.
- In small biopsy specimens or cytology specimens, major types of lung cancers are established by morphologic evaluation, that is, adenocarcinoma and squamous cell carcinoma.
- When poorly differentiated carcinomas are encountered, judicious application of immunohistochemical stains facilitates such distinction in most cases.
- In resection specimens, lung adenocarcinomas are further divided into low-grade (lepidic adenocarcinoma), intermediate-grade (acinar and papillary adenocarcinomas), and high-grade (solid and micropapillary adenocarcinomas) types of prognostic significance.
- Analysis of neuroendocrine tumors is initiated by the recognition of neuroendocrine morphology, verified by neuroendocrine marker expression when necessary.

INTRODUCTION

Significant progress has been made in the understanding of lung cancer biology, due in large part to advancement in the understanding of tumor biology and pathogenesis. Acquisition of key somatic mutations acts as a sentinel event in lung carcinogenesis, essential for tumor cell growth and division.[1] Molecular detection of driver mutations in specific histologic types of lung cancer can predict favorable response to targeted therapy. The essence of personalized medicine is to tailor individual lung cancer treatment based on accurate histologic classification and biomarker information. Therefore, characterization of histologic type of lung cancer plays an increasingly pivotal role in the multidisciplinary approach in the diagnosis and management of lung cancer. Recognizing the biological diversity of lung cancer, a comprehensive and accurate tumor classification has been developed, which is important for treatment and prognosis. Pathology of lung cancer has expanded to cover both tissue diagnosis

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and selection of specific subtypes of lung cancers for further molecular testing. Confirmatory histologic diagnosis directs surgical resection of early-stage disease, whereas pathologic classification and molecular testing enable selection of tumor type–tailored adjvuant therapy and genotype-based treatment regimen to improve the survivals of advanced-stage patients.

Lung cancers are traditionally divided into non–small cell carcinoma (NSCC) and small cell carcinoma (small cell lung carcinoma, SCLC), with the former accounting for 80% of the cases and the latter accounting for the remaining 20%. SCLCs behave aggressively and are treated nonsurgically in most cases, whereas NSCCs are managed by a combination of surgery and adjuvant therapy. Recognition of the diversity of NSCC has led to its subclassification, culminating in the 2004 and 2015 World Health Organization (WHO) classifications.[2,3] Major types of NSCC include adenocarcinoma, squamous cell carcinoma (SSC), and large cell carcinoma (LCC). Thus, subtype of NSCC is specified, whereas the designation "NSCC" is only preserved in certain small biopsies and cytology specimens. SCLC is grouped with other tumors exhibiting neuroendocrine differentiation. Since the publication of the last volume, significant update in lung cancer classification has occurred for lung adenocarcinomas based on better understanding of tumor biology. This update is manifested by streamlined classification for small biopsies and cytology specimens, with special emphasis on separating adenocarcinomas from the rest of the lung cancers in order to effectively screen cases responsive to current mutation-driven therapeutic paradigms. More detailed histologic subtyping is used in resection specimens to delineate tissue types of prognostic significance. This article discusses current pathologic classification of lung cancer, with an emphasis on updating readers to the new WHO lung adenocarcinoma classification (**Box 1**).[3] This article thus serves as a springboard for effective surgical and medical treatment modalities discussed in other articles in this series.

ADENOCARCINOMA

Adenocarcinoma is the most common type of lung cancer, accounting for more than 40% of lung cancers, 60% of the NSCC, and more than 70% of surgically resected cases.[3,4] The incidence of adenocarcinoma has risen steadily over the past few decades. Lung adenocarcinoma commonly forms a peripherally located mass with central fibrosis and pleural puckering. It can also have a variety of other gross appearances, including centrally located mass, diffuse lobar consolidation, bilateral multinodular distribution, and pleural thickening. By definition, lung adenocarcinoma is a malignant epithelial neoplasm with glandular differentiation or mucin production. When such morphologic features are recognized, the tumor can be designated as adenocarcinoma, even in small biopsy specimens. Lung adenocarcinoma cells usually express pneumocytic markers. Thyroid transcription factor (TTF-1) and NapsinA are expressed in more than 85% of the lung adenocarcinoma cases and thus can serve as markers of adenocarcinoma or adenocarcinoma differentiation in poorly differentiated tumor and in limited biopsy sampling material (**Fig. 1**).[5–7] Tumor classification based on ancillary tests such as immunohistochemistry (IHC) is designated as "NSCC, favor adenocarcinoma" in a small biopsy specimen. Resection specimens allow a more detailed subclassification. There has been significant refinement in adenocarcinoma classification in recent years based on close pathologic and clinical correlation.[3,8] The major histologic types have been validated to bear prognostic significance delineated by the tumor grade.[9–14] Multiple gene alterations can occur in adenocarcinomas, with approved molecular targeted therapy available to improve patient survival (see later disccusion).