Updates in Lung Cancer Cytopathology

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KEYWORDS

• Non–small cell lung cancer (NSCLC) • Adenocarcinoma • Cytology • Ancillary testing • Minimally invasive • PD-L1 • Biomarker

Key points

- The diagnosis, staging, and selection of therapy for patients with lung cancer are increasingly reliant on cytology and small biopsy specimens obtained via minimally invasive means.
- Combining cytomorphologic features with immunohistochemical testing can provide the accurate and specific lung cancer diagnosis required for clinical decision making.
- Molecular testing for a growing number of targetable genomic alterations is standard of care for patients diagnosed with advanced stage non–small cell lung cancer.
- PD-L1 is an evolving biomarker for the selection of patients for immune checkpoint inhibitor therapy.

ABSTRACT

Lung cancer diagnosis and ancillary testing are increasingly relying on cytology and small biopsy specimens obtained via minimally invasive means. Paired with traditional immunohistochemical characterization of tumors, biomarker testing and comprehensive genomic profiling are becoming essential steps in the workup of lung cancer to identify targetable alterations and guide optimal therapy selection. Recent advances in immune checkpoint inhibitor therapy have led to an increasingly complex and unresolved landscape for tumor PD-L1 testing. The prevalence and importance of lung cancer cytology specimens are growing, with more required by the cytopathologist in directing the care of patients with lung cancer.

OVERVIEW

Despite the advances in targeted therapeutic options over the past decade, lung cancer remains by far the leading cause of cancer-related death in the United States. Most patients with lung cancer present at an advanced stage and as such are not surgical candidates.[1] For these patients, the only diagnostic materials obtained are generally small biopsy and increasingly cytology specimens, due in part to technological advances in minimally invasive sampling techniques used by interventional pulmonology and interventional radiology. Furthermore, refinements in immunohistochemistry (IHC) and ancillary molecular testing have improved the diagnostic accuracy as well as prognostic/predictive information that can be gleaned from these pulmonary cytology specimens. In this regard, the cytopathologist is becoming an increasingly important member of the clinical team in directing the care of patients with lung cancer.

Pulmonary cytopathology is both a broad and a constantly evolving field. Much has been written on the subject, including a previous *Surgical Pathology Clinics* article only a few years ago.[2] In this brief review, the author focuses on recent updates in the field, including specimen acquisition, diagnostic workup, and molecular/ancillary testing. In truth,

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not much has changed with respect to the cytomorphologic features of lung cancer cytology, but what has evolved is how these samples are obtained and the ancillary testing now required for most lung carcinoma specimens.

MINIMALLY INVASIVE TISSUE SAMPLING TECHNIQUES

In patients with suspected lung cancer based on clinical risk factors (such as smoking history) and radiologic imaging findings (computed tomographic [CT] or PET-CT scans), a tissue sample is necessary for confirmation. As stated in the most recent lung cancer guidelines from the American College of Chest Physicians, "it is recommended that the diagnosis of lung cancer be established by the least invasive and safest method."[3] This diagnostic process has increasingly relied on either bronchoscopic or transthoracic CT-guided sampling modalities, generating cytology aspirates and/or small tissue biopsy specimens. The sampling modality in part depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient comorbidities, and the local expertise and equipment availability in a given practice.[4] Especially for disease limited to the thorax, bronchoscopic sampling techniques (such as endobronchial ultrasound–transbronchial needle aspiration [EBUS-TBNA]) are generally recommended as the preferred choice for mediastinal staging and sampling of central lesions as well as for more peripheral lesions when coupled with radial EBUS or navigational guidance.[3–5] Alternatively, CT-guided transthoracic needle biopsies can be used for peripheral lung lesions, although they harbor a higher risk of pneumothorax. Regardless of the minimally invasive sampling technique used, the acquisition of sufficient cellular tumor material is critically important, with rapid onsite specimen evaluation potentially helpful in ensuring adequate material is obtained and appropriately triaged in such situations.[6] As shall be discussed, in this era of personalized medicine, the definition of "adequate" has evolved to cover not only material for diagnosis but frequently also tumor subtyping by IHC and ancillary/molecular testing for therapy selection.[7]

DIAGNOSTIC WORKUP OF LUNG CARCINOMA

All diagnoses of lung cancer should be made according to the most recent 2015 World Health Organization (WHO) classification system, which incorporates the most recent International Association for the Study of Lung Cancer (IASLC), American Thoracic Society, European Respiratory Society (ERS) pathologic classification of lung cancer with particular attention given to cytology and small biopsy specimens.[5,8,9] In practice, these pathologic entities can pose diagnostic challenges when evaluated on limited cytologic samples or ones with suboptimal cellular preservation or visualization. Thus, a risk-based categorization schema that is used in many areas of cytology has been recently proposed by the Papanicolaou Society of Cytopathology.[10] These standardized terminology and nomenclature guidelines for respiratory cytology are much in line with the WHO classification and follow the familiar "Nondiagnostic–Negative (for malignancy)–Atypical–Neoplastic–Suspicious for malignancy–Malignant" framework already codified by the cytopathology community.

Most lung cancers encountered on a daily basis include lung adenocarcinoma, squamous cell carcinoma, and the neuroendocrine tumors, both carcinoid tumors and the high-grade neuroendocrine carcinomas: small cell carcinoma and large cell neuroendocrine carcinoma (LCNEC). Admittedly, these tumors can display a broad spectrum of cytomorphologic features depending on the degree of differentiation, preceding treatment effects, or to a lesser extent the cytologic preparation method used, but classic cytologic exemplars of these tumors are illustrated in **Fig. 1**. In the modern-day workup of lung cancer, the cytology community is well aware that a diagnosis of "non–small cell lung carcinoma (NSCLC)" is no longer sufficient, given the divergent pattern of driver mutations and therapeutic strategies for lung adenocarcinoma as compared with squamous cell carcinoma or other tumors falling under the umbrella of NSCLC. Further subclassification is needed. For NSCLC, if the cytomorphologic features are not clear, a limited IHC panel of generally mutually exclusive markers is recommended, composed of thyroid transcription factor 1 (TTF-1) or novel aspartic proteinase A (Napsin-A) for adenocarcinoma versus p40 or cytokeratin 5/6 (CK5/6) for squamous cell carcinoma.[8] For squamous cell carcinoma, p40 (N-terminal truncation isoform of p63) has been shown to be more specific with similar sensitivity as compared with p63, and as such, is a preferred first-line squamous marker.[11,12] If neuroendocrine features are present or there are suggestive clinical or radiologic findings, only then is it recommended to perform neuroendocrine markers (synaptophysin and chromogranin, and if needed the more sensitive but less specific CD56). If the cytomorphology and immunohistochemical staining profile remains ambiguous, then a cytologic diagnosis of NSCLC-