Lung Cancer Biomarkers

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KEYWORDS

• Lung cancer • Genotyping • Biomarkers • Molecular targets

KEY POINTS

- The molecular characterization of lung cancer has changed the classification and treatment of these tumors, becoming an essential component of pathologic diagnosis and therapy decisions.
- The success of targeted therapies and new immunotherapy approaches has created a new paradigm of personalized therapy in lung cancer.
- Pathologists should be able to precisely handle tissue adequacy in terms of quantity and quality and maintaining tumor cells for detection of molecular alterations.
- This article focuses on clinically relevant cancer biomarkers as targets for therapy, and potential new targets for drug development.

INTRODUCTION

Lung cancer has shown a decrease in incidence and mortality in recent decades; however, it remains one of the cancers with the highest incidence and ranks first in cancer-related deaths in the United States.[1] An estimated 221,200 new cases and 158,040 deaths are expected to occur in 2015, representing approximately 13% of all cancers diagnosed and 27% of all cancer deaths.[2] Despite advances in early detection and standard treatment, most patients are diagnosed at an advanced stage and have a poor prognosis, with an overall 5-year survival rate of 10% to 15%.[3] Lung cancer is a heterogeneous disease comprising several subtypes with pathologic and clinical relevance.[4] The recognition of histologic subtypes of non–small cell lung carcinoma (NSCLC), namely adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma as the most frequent subtypes, has become important as a determinant of therapy in this disease.[5] In addition, in recent years, the identification of molecular abnormalities in a large proportion of patients with lung cancer has allowed the emergence of personalized targeted therapies and has opened new horizons and created new expectations for these patients.[6] The use of predictive biomarkers to

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identify tumors that could respond to targeted therapies has meant a change in the paradigm of lung cancer diagnosis.[5]

This paradigm change affects all stakeholders in the fight against lung cancer including pathologists. Currently, several multiplex genotyping platforms for the detection of oncogene mutations, gene amplifications, and rearrangement are moving to the clinical setting. Genome-wide molecular investigations using next-generation sequencing (NGS) technologies have been evaluated in the research setting, with promising results. Further investigations in NSCLC are required for a better understanding of the implications of intratumor heterogeneity and the roles of tumor suppressor genes and epigenetic events with no known driver mutations. NGS in the clinical setting will provide comprehensive information cheaper and faster by using small amounts of tissue. Pathologists should be able to precisely handle tissue adequacy in terms of quantity and quality and maintaining tumor cells for detection of molecular alterations. The recent clinical successes of immunotherapy approaches to lung cancer have posed additional challenges to the scientific community and pathologists to develop predictive biomarkers of response to these therapies and have highlighted the need for proper procurement and processing of tissue specimens from patients with lung cancer.

This article focuses on the major predictive biomarkers in NSCLC, with special emphasis on their clinical and molecular importance, and the current status of molecular testing for these biomarkers.

HISTOLOGIC SUBTYPING OF NON–SMALL CELL LUNG CARCINOMA

The advent of molecular profiling and targeted therapy has renewed interest in the classification of NSCLC into major subtypes, such as adenocarcinoma, squamous cell carcinoma, and large cell lung carcinoma.[7] Other subtypes, including sarcomatoid carcinoma and neuroendocrine large cell carcinoma, represent a very minor proportion of the total NSCLC cases.[7] The most recent histologic classification of lung cancer published by the World Health Organization in 2015 incorporates relevant genetics and immunohistochemistry (IHC) aspects of different tumor subtypes (**Fig. 1**).[7] Lung cancers are increasingly diagnosed and staged by transthoracic core needle biopsy and fine-needle aspiration, transbronchial needle aspiration, endobronchial ultrasound-guided transbronchial needle aspiration, and endoscopic ultrasound-guided fine-needle aspiration. It is well established that poorly differentiated adenocarcinoma and squamous cell carcinoma of the lung can appear indistinguishable by routine microscopy, particularly in small biopsy and cytology specimens. In these small specimens, particularly in poorly differentiated tumors, there is a need to integrate morphology with IHC analysis to make a precise diagnosis. This includes the examination of IHC expression of thyroid transcription factor and the novel aspartic proteinase of the pepsin family A (napsin A) for adenocarcinoma and p40 and cytokeratin 5/6 for squamous cell carcinoma.[8] In addition, histochemical staining of mucin is useful for the diagnosis of adenocarcinoma histology. The correct histologic diagnosis of these specimens is important, but it is also imperative to exercise judicial use of the tissue to maximize the yield for molecular testing (**Table 1**).

GENOMIC BIOMARKERS IN NON–SMALL CELL LUNG CARCINOMA

Advances in elucidating the molecular biology of lung cancer have led to the identification of several potential biomarkers that could be relevant in the clinical management of patients with NSCLC.