Advance in predictive and prognostic marker assessments in lung cancer

Lung cancer is the leading cause of cancer death worldwide and represents 19% of all cancer-related deaths (1). In the US, the majority, about 60% of patients, present with stage IV disease, and the 5-year overall survival (OS) rate is 4.5% for stage IV and 18% for all stages. Even those who presented with stage I tumors, 45% will die at 5 years (2). Thus, there have been multiple efforts to improve the survival of not only patients with advanced disease, but also those with early stage tumors.

In the last 2 decades, we have observed rapid advance in personalized medicine with development of multiple targeted agents including tyrosine kinase inhibitors and chemotherapeutics, and more recently immune checkpoint inhibitors, leading to a paradigm shift in advanced lung cancer treatment (3). Implementation of advanced molecular testing including next generation sequencing and plasma genotyping in clinic will facilitate not only identification of biomarkers that predict response to the targeted agents (predictive biomarker testing) (Sholl) but also discovery of new molecular targets (Farago & Azzoli) (4). In addition, several immunohistochemistry (IHC) assays for predictive biomarkers have already been implemented in routine pathology practice. In particular, IHC for ALK and PD-L1 plays a significant role in predictive biomarker testing, and ROS1 IHC is now considered as an effective screening method (Mino-Kenudson) (3,5).

We have also witnessed significant changes in the histologic classification and staging of lung tumor in less than a decade (6,7). They were meant to adapt the histologic classification to the biology of tumors that will lead to more accurate treatment decision-making, and to improve risk stratification for recurrence and prognosis that will assist identifying patients with early stage tumors who may benefit from adjuvant therapy. Among the lung tumor subtypes, the classification of adenocarcinoma and that of neuroendocrine tumors have evolved to a large extent (6). For the adenocarcinoma, a histologic type-based classification that recognizes five histologic patterns and four variants has been proposed to classify resected tumors into a few groups of prognostic significance. In addition, the concept of air space "invasion" characterized by spread through air spaces (STAS) has been introduced to discriminate patients with a high-risk of recurrence from those without (Warth). Among the adenocarcinoma variants, invasive mucinous adenocarcinoma comprises a decent minority of lung adenocarcinomas (8), and appears to have distinct clinicopathologic and molecular features and response to therapy (Cha & Shim). For the neuroendocrine tumors, the biological differences between typical and atypical carcinoid tumors and high-grade neuroendocrine carcinomas have been clarified, although there appear to be some outliers (Pelosi and colleagues). Further, subclassification of high-grade neuroendocrine carcinomas, in particular, that of large cell neuroendocrine carcinoma is now extensively investigated (Hiroshima & Mino-Kenudson). Last but not least, proposals to revise the tumor, node, and metastasis (TNM) staging criteria for lung cancer put forth by the International Association for the Study of Lung Cancer (IASLC) took effect on January 1, 2017, in the staging guidelines for the Union for International Cancer Control (UICC) and will take effect on January 1, 2018, for the American Joint Committee on Cancer (AJCC) (7). Of those, the tumor (T) stage criteria for patients who present with synchronous, multiple pulmonary sites of involvement will facilitate distinguishing multiple primary lung cancers that are biologically independent and staged as individual cancers from intrapulmonary metastases, although the differentiation is often challenging (Schneider & Dacic).

In his focused issue of *Translational Lung Cancer Research*, the above important topics are discussed in depth. Hopefully, the readers will enjoy the collection of timely articles and apply valuable pieces of information to their daily practice.

Acknowledgements

None.

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Dr. Mari Mino-Kenudson

Mari Mino-Kenudson

Department of Pathology, Massachusetts General Hospital & Harvard Medical School,
Boston, MA, USA. (Email: mminokenudson@partners.org)

doi: 10.21037/tlcr.2017.08.04

View this article at: http://dx.doi.org/10.21037/tlcr.2017.08.04