Editorial

Advances in lung cancer with a focus on ATS 2016 updates

Jinghong Li[1], **Mark M. Fuster**[1,2]

[1]Division of Pulmonary, Critical Care, and Sleep Medicine, Department of Medicine, University of California, La Jolla, CA 92037, USA; [2]VA San Diego Healthcare System, Medical and Research Sections, La Jolla, CA 92093-9111, USA

Correspondence to: Mark M. Fuster. VA San Diego Healthcare System, Medical and Research Sections, La Jolla, CA 92093-9111, USA.
Email: mfuster@ucsd.edu.

Submitted Jun 13, 2016. Accepted for publication Jul 02, 2016.
doi: 10.21037/jtd.2016.07.44
View this article at: http://dx.doi.org/10.21037/jtd.2016.07.44

Lung cancer classification, screening, and staging updates

The 2015 World Health Organization (WHO) classification of tumors of the lung, pleura, thymus and heart has important changes from the 2004 WHO classification (1). The most significant changes include the use of immunohistochemistry to assist the classification and the use of genetic studies with molecular testing to help personalize the treatment for advanced lung cancer patients. The International Association for the Study of Lung Cancer (IASLC) published the lung cancer staging project of the new T staging for subsolid nodules, as part of the 8th edition American Joint Committee on Cancer (AJCC) TNM classification (2). The IASLC has collected an extensive, international database of lung cancer case information from 94,708 patients diagnosed between 1999 and 2010, including tumor sizes, lymph node involvement, and metastasis. The primary tumor categories of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA) were proposed for incorporation into the T (tumor) category for subsolid adenocarcinomas. Accordingly, in the T component of the staging system, the T is category is proposed for AIS, and T1mi is proposed for MIA, recalling that the pathologic microscopic description requires entire-lesion resection (histology) to determine pure lepidic growth in the lesion (AIS) versus minimal invasion (MIA) (3,4).

While recommended low dose CT (LDCT) screening criteria continue to be most broadly accepted according to NLST (i.e., active smokers or former smokers with a threshold of 30 pack-years within the past 15 years) using age cutoffs of 55–80 years (5), there is greater recognition of a subset of pure ground-glass lesions that contribute to over-diagnosis (6), with some controversy as to thresholds for surgical or radio-therapeutic interventions. This notion is especially given risk: benefit considerations with respect to surgical morbidity and mortality weighed against the natural history of such lesions when serial follow-up can be well established in compliant patients. Among ground-glass lesions, appearance and/or growth of a solid component or expansion of any such lesion in the course of follow-up deserves serious consideration for anatomic surgical resection or curative radiotherapy.

The 8th edition AJCC TNM classification, which will be published in late 2016 for patients diagnosed with cancer after January 2017, will incorporate advances made in lung cancer research, staging, diagnosis, and treatment since the 7th edition in October 2009. The revised 8th edition will have improved precision of staging and newly available therapeutic strategies. A special issue was raised to distinguish between a second primary and a metastasis in patients who have more than one focus in the lungs (7). Currently, clinical and pathologic criteria are used, but no definitive consensus is available.

Lung cancer treatment updates

In the past decade, lung cancer research has provided a variety of new biological insights that impact treatment. Non-small cell lung cancer (NSCLC) can be defined at the molecular level according to the oncogenic mutations, with subsequent application of "personalized" or "targeted" therapies. Other than the successful story of tyrosine kinase inhibitor (TKI) therapy for sensitizing mutations in the epidermal growth factor receptor (EGFR), the anaplastic lymphoma kinase (ALK) inversion/fusion as well

as fibroblast growth factor receptor (FGFR) targets have shown promise through novel therapeutics (8,9). Other targets for which small-molecule inhibitors have shown efficacy following appropriate testing include ROS-1, RET, BRAF, MET, and HER2 (10), with the frequency of these (as well as EGFR and ALK targets) significantly higher among never-smokers with adenocarcinoma. However, oncogenic KRAS mutation still does not have an effective targeted therapy.

In the field of immunotherapy, immune checkpoint pathway agents such as anti-PD1 and anti-PD-L1 antibodies show promising results. Anti-PD-1 antibody (nivolumab) was approved for the treatment of advanced NSCLC by the FDA (11). Along with anti-CTLA-4 blockade, recent antibody approaches to block inhibitory signals by these molecules (expressed on T cells) by immunosuppressive ligands on tumor cells and subversive dendritic cells have demonstrated the importance of the tumor microenvironment in tumor biology (12). The greatest advancement in boosting the host response has been demonstrated through blockade of PD-1, resulting in durable survival responses in ~20% of patients with advanced-stage NSCLC that has failed 2nd-line approaches. The most useful biomarker for predicting responsiveness to date has been tumor expression of the PD-1 ligand PD-L1 (by immunohistochemistry on pathologic sampling) (13). However, an emerging predictor of responsiveness is the tumor mutagen burden, which is generally higher in squamous carcinoma (likely due to its association with cigarette-induced hyper-mutagenesis), and higher in individuals with higher expression of mutations within the tumor (14). Moreover, greater neo-antigen (tumor-unique/non-self epitopes) expression as a result of environmental mutagenesis is a parameter that appears to predict responsiveness to approaches that boost T-cell function.

Other advances in immunotherapy are being realized through novel agents interacting with other immune checkpoint pathways that target multiple ligand-receptor pairs during T-cell receptor engagement with dendritic- or tumor cells. Antibody approaches to inhibit T-cell inhibitory inputs (beyond PD-1 or CTLA-4) or even stimulate with agonist-type antibodies pathways that promote T-effector proliferation (OX-40, 4-1BB, CD27) are under development (15). Testing of combination therapies within the immune-checkpoint spectrum (e.g., PD1 and CTLA4 blockade) (16,17) is under investigation, along with considerations of combination with targeted therapies in metastatic lung cancer (e.g., in cases where failure of targeted therapy might not otherwise leave options to improve progression-free or overall survival) (18). Adoptive T-cell therapies through *ex vivo* cytokine-supported expansion and re-infusion into the host, or even the engineering of T cells with chimeric molecules against specific tumor antigens (CAR-T cell therapy) have shown great promise in hematologic malignancies, with ongoing efforts to extend to lung carcinoma and other solid tumors (19).

Acknowledgements

We thank the Thoracic Oncology Assembly of the ATS and speakers that contributed to valuable educational talks at the 2016 symposium.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-60.
2. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: Proposals for Coding T Categories for Subsolid Nodules and Assessment of Tumor Size in Part-Solid Tumors in the Forthcoming Eighth Edition of the TNM Classification of Lung Cancer. J Thorac Oncol 2016;11:1204-23.
3. Tang ER, Schreiner AM, Pua BB. Advances in lung adenocarcinoma classification: a summary of the new international multidisciplinary classification system (IASLC/ATS/ERS). J Thorac Dis 2014;6:S489-501.
4. Rami-Porta R, Bolejack V, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for the Revisions of the T Descriptors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2015;10:990-1003.
5. National Lung Screening Trial Research Team, Church TR, Black WC, et al. Results of initial low-dose computed tomographic screening for lung cancer. N Engl J Med 2013;368:1980-91.
6. Sozzi G, Boeri M, Rossi M, et al. Clinical utility of a plasma-based miRNA signature classifier within computed

tomography lung cancer screening: a correlative MILD trial study. J Clin Oncol 2014;32:768-73.
7. Detterbeck FC, Franklin WA, Nicholson AG, et al. The IASLC Lung Cancer Staging Project: Background Data and Proposed Criteria to Distinguish Separate Primary Lung Cancers from Metastatic Foci in Patients with Two Lung Tumors in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:651-65.
8. Yang JC, Wu YL, Schuler M, et al. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.
9. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-97.
10. Rooney C, Sethi T. Advances in molecular biology of lung disease: aiming for precision therapy in non-small cell lung cancer. Chest 2015;148:1063-72.
11. Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer. N Engl J Med 2015;373:123-35.
12. Anagnostou VK, Brahmer JR. Cancer immunotherapy: a future paradigm shift in the treatment of non-small cell lung cancer. Clin Cancer Res 2015;21:976-84.
13. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. N Engl J Med 2015;372:2018-28.
14. Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015;348:124-8.
15. Linch SN, McNamara MJ, Redmond WL. OX40 Agonists and Combination Immunotherapy: Putting the Pedal to the Metal. Front Oncol 2015;5:34.
16. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-17.
17. Callahan MK, Postow MA, Wolchok JD. CTLA-4 and PD-1 Pathway Blockade: Combinations in the Clinic. Front Oncol 2015;4:385.
18. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell 2015;161:205-14.
19. Fousek K, Ahmed N. The Evolution of T-cell Therapies for Solid Malignancies. Clin Cancer Res 2015;21:3384-92.

Cite this article as: Li J, Fuster MM. Advances in lung cancer with a focus on ATS 2016 updates. J Thorac Dis 2016;8(Suppl 7): S566-S568. doi: 10.21037/jtd.2016.07.44

