EGFR mutational status in lung adenocarcinoma: Staging implications or continuous evolution?

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication July 16, 2017; accepted for publication July 31, 2017; available ahead of print Sept 1, 2017.

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J Thorac Cardiovasc Surg 2017;154:1766-7
0022-5223/\$0.00

Published by Elsevier Inc. on behalf of The American Association for Thoracic Surgery
<http://dx.doi.org/10.1016/j.jtcvs.2017.07.053>

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Central Message

Given the rapid advancement in actionable knowledge in the molecular biology of lung cancer, additional subclassifications in the staging systems may remain in a state of constant evolution.

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Patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) mutations (EGFR-mut) have longer progression-free survivals than do those with wild-type EGFR (EGFR-wt).¹ The prognosis of EGFR-mut in earlier stage disease and whether mutational subtypes have prognostic significance is not as clear.² In their study in this issue of the *Journal*, Takamochi and colleagues³ examined whether EGFR-mut (and if so, which specific EGFR-mut) genotypes have prognostic value after resection for lung adenocarcinoma. They reviewed 939 patients and found that EGFR-mut was associated with longer 5-year overall survival than was EGFR-wt. The individual mutations (exon 21 L858R point mutation [L858R] vs exon 19 deletion [19-del]) were not associated with different survivals.

Takamochi and colleagues³ are to be commended for several strengths. First, the number of patients with adequate testing ($n = 939$) who had adenocarcinoma (45% EGFR-mut) is noteworthy. Second, exclusion of perioperative therapy helped determine the prognostic role of EGFR-mut without tyrosine kinase inhibitor (TKI) treatment. Takamochi and colleagues³ contradict a negative meta-analysis, in which they correctly note that most studies were small and underpowered. Of the 16 studies, however, the largest 2 report that EGFR-mut genotypes were associated with survival advantages. D'Angelo and colleagues report an overall survival advantage in stage I to III adenocarcinoma with EGFR mutations.⁴ A significant percentage received adjuvant cytotoxic chemotherapy and EGFR-TKI. In 307 patients, one of these studies reported that EGFR-mut was independently associated with improved overall survival and disease-free survival. No patients received adjuvant TKI or cytotoxic therapy. Despite differences in demographics, staging, and adjuvant treatment, the conclusions of testing and stratification according to EGFR status are relatively similar.

The ENSURE study (A Study of Erlotinib [Tarceva] Versus Gemcitabine/Cisplatin as First-line Treatment in Patients With Non-Small Cell Lung Cancer With EGFR Mutations) reported a progression-free survival advantage with 19-del compared with L858R for patients treated with erlotinib versus cytotoxic chemotherapy.⁵ A small, retrospective study found improved overall survival with 19-del versus L858R.⁶ Takamochi and colleagues³ reported that among 222 patients (53%) with L858R and 161 patients (39%) with 19-del, no survival advantages were observed. Fourteen patients (3.3%) of the EGFR-mut genotypes had T790 mutations, which were often associated with additional mutations. The molecular biology underlying EGFR-mut has several clinical implications. First, TKI resistance develops in all patients. The first-generation TKIs reversibly bind to the tyrosine kinase domain, whereas the third-generation TKIs irreversibly bind with more than 100 times the affinity. As studies are reported with third-generation TKIs, the treatment implications and the prognostic value of individual mutations will likely change. Takamochi and colleagues³ speculate that “complex oncogenic processes” with multiple mutations are more common in EGFR-wt tumors, unlike EGFR-mut tumors, which rely on a specific driver mutation. Indeed, lung adenocarcinoma has the third highest number of mutations in tumor-normal pair.⁷ In addition, a lower frequency of neopeptides was observed in patients with

adenocarcinoma who had never smoked than in those who were smokers.⁸ The implication is that chronic exposure to smoking results in thousands of somatic mutations that likely affect multiple oncogenic pathways, reducing the chance that targeting a single mutation will be effective.

Takamochi and colleagues³ recommend that EGFR status be considered in future staging guidelines. Given the rapid advancement in TKI therapy and the increases in actionable knowledge in the molecular biology of lung cancer, additional subclassifications in the staging systems may remain in a state of constant evolution that will rarely, if ever, be adequately reflected in staging guidelines.

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