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Commentary: EGFR mutations lung adenocarcinoma—Is the driver removed with the lobe?

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Epidermal growth factor receptor (EGFR) is a receptor that when mutated leads to constitutive activation of growth pathways that drive tumorigenesis. The original discovery of EGFR mutations in lung cancer was based on patients who responded to the tyrosine-kinase inhibitor (TKI), gefitinib.¹ This discovery truly changed the management of patients with non-small cell lung cancer (NSCLC). Now, for patients with advanced NSCLC harboring activating EGFR mutations, EGFR-TKI therapy provides a superior survival benefit over platinum-based chemotherapy. Since the original discovery of EGFR mutations, the value of EGFR mutations is as a biomarker of response to therapy. In contrast, the value of EGFR as a prognostic marker for outcomes after resection of early-stage NSCLC is less clear.^{2,3}

In addition to advances in EGFR-directed therapy, the classifications of NSCLC have evolved. The multidisciplinary efforts by International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society established World Health Organization (WHO) 2015 classifications of NSCLC.^{4,5} These classifications have repeatedly correlated with patient outcome. By the time of the WHO classification, the importance of molecular studies was recognized, but integration into the lung cancer staging had not occurred. Now, the IASLC Lung Cancer Staging Project recommends the development of survival models that incorporated gene mutations as prognostic variables.⁶ This effort will require data from many institutions to develop accurate survival models. In this issue of the *Journal*, Deng and colleagues⁷ report the outcomes of

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CENTRAL MESSAGE

Deng and colleagues report that EGFR mutations were prognostic for patients with surgically resected, lung adenocarcinoma based on specific WHO subtypes of lung adenocarcinoma.

patients with surgically resected EGFR-mutated lung cancers based on the WHO classifications that may contribute to the staging of lung adenocarcinoma.

The authors reviewed the staging and pathologic features of a large cohort of patients who underwent primary surgical resection for lung adenocarcinoma at a single, large center over 7 years. Those who received a TKI were excluded. The recurrence-free survival (RFS) was reported based on pathologic subtype, solid tumor component, and EGFR status. Those with known low-risk features of pure-ground-glass opacity composition and adenocarcinoma in situ, minimally invasive adenocarcinoma, or lepidic-predominate histologic subtypes exhibited 100% RFS; therefore, they were excluded. The authors found a greater prevalence of EGFR mutations in female patients, never-smokers, partially solid, pathologic stage I cancers, and tumors with acinar-predominant, papillary-predominant, or invasive mucinous adenocarcinoma histologic subtypes. On univariate analysis, these groups in addition to tumors that lacked lymphovascular invasion or visceral pleural invasion were found to be prognostic for improved RFS. However, EGFR status was not prognostic. The authors performed additional analyses based on tumor composition, stage, and histologic subtypes and noted that EGFR mutations were prognostic for RFS in radiologically solid tumors, stage II-III disease, and acinar-predominant, papillary-predominant, or invasive mucinous adenocarcinoma subtypes. They also observed that EGFR mutations were an independent predictor for bone and brain metastasis.

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The authors should be commented for undertaking a large study of patients with resected lung adenocarcinoma. They provide critical molecular studies to help clarify the prognostic role of EGFR mutations in resected lung cancer that may benefit the next lung cancer staging system. However, their results suggest that EGFR mutations may be quite specific to certain subtypes. These findings will require additional data for the staging system to establish the role of EGFR mutations.

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Commentary: Epidermal growth factor receptor mutations in resectable lung cancer: What is the prognostic importance?

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CENTRAL MESSAGE

The importance of individual gene mutations including EGFR in resected lung cancer is becoming more important. Further studies are needed to determine optimal therapies.

The landscape of cancer treatment has changed with development of targeted therapeutics to driver mutations. Patients with metastatic cancer are now routinely sequenced for driver mutations, as targeted therapy has become standard of care and prognosis is improved. Despite the success in patients with metastasis, for patients with early-stage

lung adenocarcinoma, little is known about the prognostic or predictive impact of driver mutations. Into this void steps the group from Fudan University in Shanghai.¹ They analyzed 1512 patients with 935 epidermal growth factor receptor (EGFR) mutations. EGFR mutation was more frequent in radiologic part-solid and stage I tumors. The presence of EGFR mutation did not impact survival in the full cohort. However, EGFR mutation strongly predicted worse survival in patients with radiologically solid and histologic acinar/papillary/invasive mucinous

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