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.

References

1. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004; 350:2129-39.
2. Jeon JH, Kang CH, Kim HS, Seong YW, Park IK, Kim YT. Prognostic and predictive role of epidermal growth factor receptor mutation in recurrent pulmonary adenocarcinoma after curative resection. *Eur J Cardiothorac Surg*. 2015;47:556-62.
3. Ito M, Miyata Y, Tsutani Y, Ito H, Nakayama H, Imai K, et al. Positive EGFR mutation status is a risk of recurrence in pN0-1 lung adenocarcinoma when combined with pathological stage and histological subtype: a retrospective multi-center analysis. *Lung Cancer*. 2020;141:107-13.
4. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, 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.
5. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6:244-85.
6. Giroux DJ, Van Schil P, Asamura H, Rami-Porta R, Chansky K, Crowley JJ, et al. The IASLC lung cancer staging project: a renewed call to participation. *J Thorac Oncol*. 2018;13:801-9.
7. Deng C, Zhang Y, Ma Z, Fu F, Deng L, Li Y, et al. Prognostic value of epidermal growth factor receptor gene mutation in resected lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2021;162:664-74.e7.

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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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adenocarcinomas and in patients with pathologic stage II/III cancers. Interestingly, patients with EGFR-mutant tumors developed more frequent brain and bone metastases than patients with wild-type EGFR tumors. Clearly, the large Chinese centers are leading the way in helping to analyze these patients.

Although these data begin to illuminate the issue, many questions remain unanswered. First and most obvious is whether EGFR-mutant patients with stage I lung cancer with radiologically solid and/or acinar/papillary/invasive tumors should be treated in the adjuvant setting with targeted EGFR inhibition. Second, should the adjuvant treatment of patients with stage II and III contain conventional chemotherapy, targeted inhibition, or both? Recent results from ADAURA, which compared osimertinib versus placebo in surgically resected stage IB-IIIa disease, showed improvement in disease-free survival in the treatment group.² Although overall survival data were not yet mature, the benefit in stage IB disease was lower (hazard ratio, 0.5; 95% confidence interval [CI], 0.25-0.96) compared with stage II (0.17; 95% CI, 0.008-0.31) and stage III (0.12 m; 95% CI, 0.007-0.2), thus tempering our enthusiasm from using it in this setting. Several other trials, such as ADJUVANT, showed improvement in disease-free survival when gefitinib was compared with chemotherapy, but overall survival was not improved.³ However, if, as the Fudan study demonstrates, subsets of patients with stage I disease have inferior prognosis, investigating EGFR tyrosine kinase inhibitor is warranted. The ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing

Trial) trial in the United States is ongoing, with overall survival as a primary end point. Next, what is the best local treatment for tumors with low-risk features and EGFR mutation? Would stereotactic body radiation therapy be appropriate for some of these tumors? Perhaps an analysis of subgroups that rarely have occult lymph node metastasis would be helpful in this regard. Also, regarding the metastasis findings, is there a group of patients who should be treated with prophylactic brain radiation or at least more frequent central nervous system surveillance imaging? Finally, what is the impact of co-mutations? We know that mutations in RB1 and P53 identify a poor prognostic subset of EGFR-mutated patients at least in metastatic disease. Prognostic value of co-mutations must also be analyzed in these subgroups.

All in all, the data from Fudan represent a great first step in using sequencing information to plan therapies that improve survival. Involvement of multidisciplinary teams of medical, radiation, and thoracic surgical oncologists will be key to answering further questions.

References

1. Deng C, Zhang Y, Ma Z, Fu F, Deng L, Li Y, et al. Prognostic value of epidermal growth factor receptor gene mutations in resected lung adenocarcinoma. *J Thorac Cardiovasc Surg.* 2021;162:664-74.e7.
2. Herbst RS, Tsuboi M, John T, Grohe C, Majem M, Goldman JW, et al. Osimertinib as adjuvant therapy in patients with stage IB-IIIa EGFR mutation positive NSCLC after complete tumor resection: ADAURA. Presented at: ASCO, June 2020.
3. Wu Y, Zhong W-Z, Wang Q, Mao W, Xu S-T, Wu L, et al. Adjuvant gefitinib versus chemotherapy for resected N1-2 NSCLC with EGFR mutation—final overall survival analysis of the randomized phase III trial. Presented at: ASCO, June 2020.