Time to take a step beyond the “high-risk features”

Thomas Ng, MD,^a and Angela Taber, MD^b

From the ^aDepartment of Surgery, The Warren Alpert Medical School of Brown University, Providence, RI; and the ^bDivision of Hematology/Oncology, The Warren Alpert Medical School of Brown University, Providence, RI.

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

Received for publication April 4, 2018; accepted for publication April 9, 2018; available ahead of print May 4, 2018.

Address for reprints: Thomas Ng, MD, 2 Dudley St, Suite 470, Providence, RI 02905 (E-mail: tng@usasurg.org).

J Thorac Cardiovasc Surg 2018;156:794-5

0022-5223/\$36.00

Copyright © 2018 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2018.04.037>

Thomas Ng, MD (left), and Angela Taber, MD (right)

Central Message

Published studies identify poor prognostic factors in resected early-stage lung cancer; however, this must be furthered by identifying the patient population who will benefit from adjuvant therapy.

See Article page 785.

The study by Okiror and colleagues¹ published in this month's *Journal* focuses on the importance of lymphovascular invasion in resected lung cancer. From a single institution, 524 patients with resected stage T1-3N0-2 are retrospectively evaluated. After multivariable Cox regression analysis, lymphovascular invasion continued to be associated with overall survival, along with parietal pleural invasion, age, and N2 disease; surprisingly T staging was not associated with overall survival. Weaknesses of this study include its retrospective nature, the heterogeneous study population, the failure to account for important prognostic factors, and the short follow-up time. Despite these limitations, and despite findings of other investigators who have already shown lymphovascular invasion to be predictive of survival, this study by Okiror and colleagues¹ has relevance, because it serves as a reminder that identifying “high-risk features” of resected lung cancer should only be the initial step. This knowledge needs to be used during the development of clinical trials, with the goal of identifying the patient population who will benefit from adjuvant therapy.

Cure continues to elude patients with lung cancer, including those with early-stage disease. Recent data from the eighth edition of the TNM staging system for lung cancer proposed by the International Association for the Study of Lung Cancer showed 5-year overall survivals for pathologically staged node-negative cancers sized 2 to 3 cm and sized 3 to 4 cm to be 80% and 73% respectively.² Because recurrence continues to be an issue despite curative resection of pathologically determined N0 disease, adjuvant chemotherapy is aimed at improving outcomes by treating presumed occult micrometastatic disease. Benefit from adjuvant therapy is seen only in patients with node-positive disease, however, because published clinical trials have been unable to show definitive benefit in patients with pathologic N0 disease, perhaps because these trials fail to stratify for “high-risk features” a priori in their design.³⁻⁷ The current ongoing randomized trials, Adjuvant Lung Cancer Enrichment Marker Identification

and Sequencing Trial (ALCHEMIST) and IMpower010, evaluate the role of targeted molecular therapy and immunotherapy after lung cancer resection but do not address the continued knowledge gap regarding the role of standard platinum-based adjuvant therapy in early-stage lung cancer.

In resected early-stage lung cancer, “poor prognostic factors” is synonymous with the term “high-risk features.” A large amount of literature has been published identifying factors associated with poor survival, beyond the T and N descriptors, including standard uptake value, grade (solid and micropapillary histologic types), spread through air space, and lymphovascular invasion, to name a few. It is important to incorporate the knowledge of these “high-risk features” into the design of adjuvant trials if we are to identify the patient population who will benefit from postoperative chemotherapy; this may be especially true for patients with resected early-stage lung cancer, an area in which there is the opportunity for survival improvement, even though published evidence does not suggest that adjuvant therapy has benefit in N0 disease.

References

1. Okiror L, Harling L, Toufektzian L, King J, Routledge T, Harrison-Phipps K, et al. Prognostic factors including lymphovascular invasion on survival for resected non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2018;156:785-93.
2. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Boards, and Participating Institutions; International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the

- forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39-51.
3. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J, International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350:351-60.
 4. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al; National Cancer Institute of Canada Clinical Trials Group, National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. *N Engl J Med*. 2005;352:2589-97.
 5. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, González-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIa non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 2006;7:719-27.
 6. Strauss GM, Herndon JE II, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the cancer and leukemia group B, radiation therapy oncology group, and north central cancer treatment group study groups. *J Clin Oncol*. 2008;26:5043-51.
 7. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE collaborative group. *J Clin Oncol*. 2008;26:3552-9.