Perioperative pharmacotherapy for lung resection: “Going for the gold”?

Valerie W. Rusch, MD

From the Department of Surgery, Thoracic Service, Memorial Sloan-Kettering Cancer Center, New York, NY.

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

Received for publication Sept 22, 2015; accepted for publication Sept 23, 2015; available ahead of print Oct 27, 2015.

Address for reprints: Valerie W. Rusch, MD, Department of Surgery, Miner Family Chair in Intrathoracic Cancers, Vice Chair, Clinical Research, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10065 (E-mail: ruschv@mskcc.org).

J Thorac Cardiovasc Surg 2016;151:18-9

0022-5223/\$36.00

Copyright © 2016 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.09.092>

This issue of the *Journal* includes 3 articles that address potential ways to reduce perioperative morbidity and improve long-term outcomes after resection of non-small cell lung cancer (NSCLC). The retrospective review by Medeiros and colleagues¹ suggests that metformin treatment in 138 patients with diabetes and stage I or II NSCLC is associated with a better progression-free survival. The retrospective analysis by Litle and coworkers² and the prospective cohort study by Agzarian and associates³ suggest that the risk of venous thromboembolism (VTE) after NSCLC resection may be in the range of 12% despite adherence to prophylaxis guidelines, and that VTE often occurs after discharge from the hospital. The latter 2 studies indicate the need for additional prospective studies to confirm the true incidence of VTE and to determine whether continued prophylaxis after discharge from the hospital is warranted.

During the past 3 decades, there has been a steady decline in operative mortality associated with lung cancer resection, even in patients with locally advanced NSCLC requiring complex multimodality therapy.⁴ In a large prospective clinical trial performed by the American College of Surgeons, operative mortality after resection of clinical stage I NSCLC was 2%, and operative morbidity was 38%.⁵ This decline may be related to changes in NSCLC epidemiology (eg, more peripheral tumors, fewer current smokers) but also reflects improved patient selection and attention to preoperative patient preparation. The advent of minimally invasive resection techniques, both video-associated thoracoscopic surgery and robotic surgery, has also improved surgical safety, especially in high-risk patient populations.^{6,7} Because operative mortality has decreased to very low levels, it is now appropriate to investigate whether we can further reduce operative morbidity. In fact, given current concerns about health care costs and quality, it is imperative that we focus on this issue. In the language of the Olympics, it is time that we “go for the gold.”

Determining how best to reduce morbidity for an operation (most frequently a lobectomy) that already has become

Valerie W. Rusch, MD

Central Message

Interventions to reduce operative morbidity will require well-structured, large multicenter prospective trials.

See Article page 37.

See Editorial Commentary page 45.

quite safe will require prospective studies, preferably randomized clinical trials. Agzarian and associates³ should be congratulated for planning a randomized trial for VTE prophylaxis in Canada on the basis of their initial cohort study. Such trials need to be very carefully designed, with appropriate stratification and meaningful end points. For example, the VTE risk of an otherwise healthy 60-year-old patient with stage I NSCLC undergoing a video-assisted thoracoscopic surgical lobectomy is likely to be different from that of an elderly sedentary patient with medical comorbidities, or of a patient with locally advanced NSCLC who is receiving induction chemotherapy. In this era of rising health care costs, it will not be enough to generalize across the entire lung cancer patient population. We will need to know which of these patients really need extended prophylaxis, and figuring that out for a low frequency event will require very large multicenter trials. The implementation of a new lung cancer staging system in early 2017 will facilitate even more precise tumor stage stratification than what we have currently.⁸⁻¹⁰

Whereas studies of adverse events such as VTE can be based on straightforward clinical parameters, the article by Medeiros and colleagues¹ on metformin treatment raises different issues. A recent meta-analysis showed that

metformin use is associated with lower all-cause and cancer-specific mortalities among patients with concurrent diabetes and malignancies such as breast, colorectal, ovarian, and endometrial cancers.¹¹ There is less information available with respect to lung cancer, but it is thought that the effect of metformin may be mediated via the mechanistic target of rapamycin pathway, which is known to be important in NSCLC.¹² Our increasing ability to study tumor biology through high-throughput molecular platforms (ie, next generation sequencing) offers the opportunity to gain insight into the fundamental mechanisms underlying the effects of a drug such as metformin. This type of question needs to be answered through carefully structured studies—both retrospective and prospective—correlating clinical, pathologic, and molecular findings by means of bioinformatics. If the key molecular abnormalities are of low frequency, large multicenter correlative studies will also be required to identify these.¹³ In vitro and in vivo studies would be advisable to elucidate the mechanisms of drug action before we launch into large-scale therapeutic trials.

Analyses of large multicenter and risk-adjusted clinical databases, such as the Society of Thoracic Surgeons and the American College of Surgeons National Surgical Quality Improvement Program databases, can identify operative morbidities that require further study. We can effectively design interventions to reduce operative morbidity further, but such design will require large well-structured, multicenter, prospective trials.

References

1. Medeiros RA, Clark J, Holoubeck S, Kubasiak JC, Pithadia R, Hamid F, et al. Metformin exposure is associated with improved progression free survival in early stage non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2016 [Submitted].
2. Hachey KJ, Hewes PD, Porter LP, Ridyard DG, Rosenkranz P, McAneny D, et al. Caprini venous thromboembolism risk assessment permits selection for postdischarge prophylactic anticoagulation in patients with resectable lung cancer. *J Thorac Cardiovasc Surg*. 2016;151:37-44.e1.
3. Agzarian J, Hanna WC, Schneider L, Schieman C, Finley CJ, Peisakhovich Y, et al. Incidence of pulmonary embolism (PE) and deep vein thrombosis (DVT) following major lung resection: a prospective cohort study. *J Thorac Cardiovasc Surg*. 2016 [In press].
4. Barnett SA, Rusch VW, Zheng J, Park BJ, Rizk NP, Plourde G, et al. Contemporary results of surgical resection of non-small cell lung cancer after induction therapy: a review of 549 consecutive cases. *J Thorac Oncol*. 2011;6:1530-6.
5. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE II, Landreneau RJ, et al; ACOSOG Z0030 Study Group. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg*. 2006;81:1013-9; discussion 1019-20.
6. Ceppa DKP, Kosinski AS, Berry MF, Tong BC, Harpole DH, Mitchell JD, et al. Thoracoscopic lobectomy has increasing benefit in patients with poor pulmonary function: a Society of Thoracic Surgeons Database analysis. *Ann Surg*. 2012;256:487-93.
7. Farivar AS, Cerfolio RJ, Vallières E, Knight AW, Bryant A, Lingala V, et al. Comparing robotic lung resection with thoracotomy and video-assisted thoracoscopic surgery cases entered into The Society of Thoracic Surgeons Database. *Innovations (Phila)*. 2014;9:10-5.
8. Rami-Porta R, Bolejack V, Crowley J, Ball D, Kim J, Lyons G, et al. IASLC Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for revisions of the T descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10:990-1003.
9. Asamura H, Chansky K, Crowley J, Goldstraw P, Rusch VW, Vansteenkiste JF, et al. IASLC Staging and Prognostic Factors Committee, Advisory Boards and Participating Institutions. Proposals for the revision of the N descriptors in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol*. September 3, 2015 [Epub ahead of print].
10. Goldstraw P, Crowley J, Rami-Porta R, Rusch VW, Postmus PE, et al; The International Association for the Study of Lung Cancer Staging and Prognostic Factors Committee, Advisory Board Members and Participating Institutions. IASLC Prognostic Factors Committee. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the eighth edition of the TNM classification of malignant tumors. *J Thorac Oncol*. 2015. In press.
11. Zhang Z, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. *Diabetes Obes Metab*. 2014;16:707-10.
12. Frankenberger CA, Seder CW, Lund N, Medeiros RA, Liptay MJ, Bonomi P, et al. Identification of a meta-gene network associated with metformin sensitivity and recurrence in stage I non-small cell lung cancer. *J Thorac Oncol*. 2015;10(9 Suppl 2):S382.
13. Kris MG, Johnson BE, Berry LD, Kwiatkowski DJ, Iafrate AJ, Wistuba II, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *J Am Med Assoc*. 2014;311:1998-2006.