Editorial Commentary

Encouraging early outcomes in cancer and leukemia group B (CALGB)/Alliance 140503: patient selection, not extent of resection, is the key to perioperative success

Kyle G. Mitchell, Mara B. Antonoff

Department of Thoracic and Cardiovascular Surgery, University of Texas MD Anderson Cancer Center, Houston, TX, USA

Correspondence to: Mara B. Antonoff, MD. Assistant Professor, Department of Thoracic and Cardiovascular Surgery, University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Email: MBAntonoff@MDAnderson.org.

Provenance: This is an invited article commissioned by the Section Editor Song Xu, MD, PhD (Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin, China; Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Comment on: Altorki NK, Wang X, Wigle D, *et al.* Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med 2018;6:915-24.

Submitted Feb 19, 2019. Accepted for publication Mar 01, 2019.
doi: 10.21037/atm.2019.03.12
View this article at: http://dx.doi.org/10.21037/atm.2019.03.12

After the Lung Cancer Study Group published its seminal trial in 1995, anatomic lobectomy was established as the gold standard surgical therapy for patients with resectable non-small cell lung cancer (NSCLC) (1). However, the increasing utilization of low-dose helical computed tomography (CT) as a screening strategy in high-risk patients and the resultant increase in the frequency of diagnosis of smaller, more peripheral lesions has reinvigorated interest in the oncologic merits of sublobar resection (2). A host of retrospective studies have suggested that sublobar resection provides equivalent locoregional disease control while sparing lung parenchyma (3-5). Consequently, sublobar resection is frequently offered to patients with marginal pulmonary function or to those whose comorbidities render them to be otherwise borderline surgical candidates. A critical determinant in the preoperative decision-making process is the postoperative morbidity profile associated with each operation. In fact, this lack of clarity with regard to oncologic outcomes and postoperative morbidity has in part spurred the expansion of less-invasive local therapeutic techniques to some operable patients with peripheral, node-negative tumors. As a consequence, it is clear that greater elucidation of the therapeutic benefits, as well as the associated perioperative morbidity profile, associated with each extent of resection is in desperate need.

To address this question, Dr. Altorki and colleagues have embarked on a multicenter, international randomized controlled trial (CALGB/Alliance 140503) that randomized 697 patients with peripheral cT1aN0 NSCLC to undergo either lobectomy or sublobar resection with segmentectomy or non-anatomic wedge resection (6). All patients underwent confirmation of node-negative disease by either preoperative invasive mediastinal staging or pre-randomization nodal sampling. Randomization was performed intraoperatively, with the operative approach [video-assisted thoracoscopic surgery (VATS), robotic-assisted thoracoscopic surgery (RATS), or thoracotomy], as well as the extent of resection for patients randomized to sublobar resection (segmentectomy versus wedge resection), left to the operating surgeon's discretion. The primary outcome of this non-inferiority trial is disease-free survival, and data regarding oncologic outcomes (enrollment completed in March 2017) are currently immature. Here, the authors report an unplanned, post-hoc, intention-to-treat analysis of perioperative outcomes of patients enrolled in the trial (6).

Importantly, this "real world" study reflects contemporary practice, as 80% of patients in the trial underwent thoracoscopic resection, and 21% of the study cohort were treated at community hospitals. Two key points are immediately apparent: first, pulmonary resection is safe;

and second, perioperative outcomes after sublobar resection seem to be equivalent to those following lobectomies. The well-balanced cohorts included 340 patients randomized to undergo sublobar resection, of whom a majority (59%) underwent nonanatomic wedge resection, 38% underwent segmentectomy, and 3% were converted intraoperatively to lobectomy. Rates of 30- and 90-day mortality observed in this study (0.9% and 1.4%, respectively) are commendable and compare favorably to those published in other trials and large database analyses (7-9). No differences were noted between patients who underwent sublobar resection and those who underwent lobectomy in terms of 30-day mortality (0.6% versus 1.1%), 90-day mortality (1.2% versus 1.7%), or major (grade 3–4) complications (any grade 3–4 adverse event: sublobar resection 14% versus lobectomy 15%; cardiovascular: sublobar 1% versus lobectomy 2%; pulmonary: sublobar 7% versus lobectomy 10%). However, although rates of prolonged air leak were approximately equivalent in both groups (sublobar resection 7% versus lobectomy 9%), patients who underwent lobectomy were noted to have higher rates of supraventricular arrhythmias (12% versus sublobar resection 7%). Critically, the only determinants of major postoperative morbidity or mortality on multivariable analysis were patient age [odds ratio (OR) 1.31 for each decade of increase] and pulmonary function [FEV_1 (forced expiratory volume in one second) (% predicted) OR 0.98], suggesting that patient selection, rather than the extent of parenchymal resection, is the primary determinant of short-term postoperative outcomes in the modern era.

Although this multicenter trial is well designed and aims to address an urgent clinical question, the present report is limited by its exploratory and post-hoc nature. Furthermore, the authors are in some ways victims of their own perioperative successes: because the study was powered for its primary endpoint of disease-free survival (rather than postoperative morbidity and mortality) and the frequency of postoperative adverse events was low, the size of the study cohort included may well be insufficient to detect any differences that may exist between sublobar and lobar resection. Moreover, the lack of further stratification according to extent of sublobar resection (i.e., segmentectomy versus wedge resection) further complicates the interpretation of these results. Ultimately, a definitive account of the equivalence of these operations (or lack thereof) requires an adequately powered trial with clear analytic distinction between nonanatomic wedge resection, segmentectomy, and lobectomy. Despite these limitations, this multicenter effort constitutes an urgently-needed trial, and the present report provides high quality data to aid clinical decision making. Ultimately, the perioperative outcomes observed in CALGB/Alliance 140503 demonstrate that major morbidity and mortality after lung resection for small peripheral lesions is uncommon, and these outcomes appear to be equivalent between patients undergoing lobectomy and those undergoing sublobar resection. The lung cancer community at large eagerly awaits this trial's long-term results.

Acknowledgements

None

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
3. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. J Thorac Cardiovasc Surg 2014;147:754-62; Discussion 762-4.
4. Wisnivesky JP, Henschke CI, Swanson S, et al. Limited resection for the treatment of patients with stage IA lung cancer. Ann Surg 2010;251:550-4.
5. Kates M, Swanson S, Wisnivesky JP. Survival following lobectomy and limited resection for the treatment of stage I non-small cell lung cancer ≤1 cm in size: a review of SEER data. Chest 2011;139:491-6.
6. Altorki NK, Wang X, Wigle D, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med 2018;6:915-24.
7. Allen MS, Darling GE, Pechet TT, et al. 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.
8. Fernandez FG, Kosinski AS, Burfeind W, et al. The society of thoracic surgeons lung cancer resection risk model: higher quality data and superior outcomes. Ann Thorac Surg 2016;102:370-7.
9. Rosen JE, Hancock JG, Kim AW, et al. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. Ann Thorac Surg 2014;98:1953-60.

Cite this article as: Mitchell KG, Antonoff MB. Encouraging early outcomes in cancer and leukemia group B (CALGB)/Alliance 140503: patient selection, not extent of resection, is the key to perioperative success. Ann Transl Med 2019;7(Suppl 1):S50. doi: 10.21037/atm.2019.03.12

