Editorial

Stereotactic body radiotherapy for early-stage non-small cell lung cancer has low post-treatment mortality

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Provenance: This is an invited Editorial commissioned by the Section Editor Dr. Lei Deng (Department of Medicine, Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA).

Comment on: Stokes WA, Bronsert MR, Meguid RA, *et al.* Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer. J Clin Oncol 2018;36:642-51.

Submitted Apr 20, 2018. Accepted for publication Apr 26, 2018.
doi: 10.21037/jtd.2018.04.169
View this article at: http://dx.doi.org/10.21037/jtd.2018.04.169

Stereotactic body radiotherapy (SBRT) is increasingly used to treat stage I non-small cell lung cancer (NSCLC). In 2004, less than 0.5% of these cases were managed with SBRT. By 2011, SBRT accounted for 8.7% of cases (1). At Mayo Clinic, local recurrence after SBRT was 4.9% at 2 years (2), comparable to surgical data from Memorial Sloan-Kettering Cancer Center (6% to 10% per person-year in the first 4 years) (3) and the Lung Cancer Study Group randomized trial (10.1% per person-year for sublobar resection, 5.7% per person-year for lobectomy) (4). Despite increased utilization and strong efficacy data, randomized comparisons of SBRT and surgery are lacking. Three randomized trials have been attempted and closed due to slow accrual: STARS, ROSEL, and RTOG 1021/ACOSOG Z4099 (5,6). The STARS and ROSEL trials randomized operable patients to SBRT versus lobectomy with mediastinal lymph node dissection or sampling. Combined analysis of the STARS and ROSEL trials showed 3-year overall survival 95% with SBRT versus 79% with lobectomy (P=0.04) and recurrence-free survival 86% with SBRT versus 80% with lobectomy (P=0.54). However, these findings have not led to SBRT replacing lobectomy as the standard treatment of early NSCLC, at least in part due to the small sample size (N=58) (5). Lobectomy remains the gold standard.

A major argument in favor of SBRT has been reduced treatment-related mortality. Modern surgical series, including minimally invasive surgical techniques, show 30-day perioperative mortality of 1.1% or less for segmentectomy and 1.2% to 4% for lobectomy (7,8). SBRT has been associated with 0.7% treatment-related mortality (9). While not a substitute for well-designed randomized trials, large database analyses may provide insights into difficult clinical questions. The National Cancer Database (NCDB) captures about 70% of newly diagnosed cancers in the United States (10). The recent publication by Stokes *et al.* provides a timely NCDB analysis of "post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small cell lung cancer" (11).

From 2004 to 2013, Stokes *et al.* identified nearly ten-fold more surgical patients than SBRT patients in the NCDB (76,623 *vs.* 8,216 patients). This ratio of surgery to SBRT is not surprising given that surgery is the standard of care for stage I NSCLC. However, 20% of the surgery patients had sublobar resection, which may be considered suboptimal. Furthermore, the NCDB does not provide data on the use of minimally invasive surgical techniques, which increased during the study period (12). Previously, the Lung Cancer Study Group randomized patients to lobectomy versus sublobar resection. Patients who had sublobar resection had 75%

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increased recurrence (P=0.02) and 30% decreased overall survival (P=0.08) compared to lobectomy (4). Although recent data suggest anatomic segmentectomy may have similar overall survival (13) and oncologic outcomes (14) to lobectomy for small (≤2 cm) tumors, lobectomy remains the standard of care until we have the results of ongoing randomized trials: JCOG0802/WJOG4607L (15), STEPS (16), and CALGB 140503 (NCT00499330) (17). Though sublobar resection has uncertain oncologic outcomes compared to lobectomy, Stokes *et al.* demonstrate why surgeons may opt for sublobar resection: perioperative mortality was lower with sublobar resection than with lobectomy. Perhaps some of the patients undergoing sublobar resection in the NCDB could not safely undergo lobectomy. However, Stokes *et al.* found the lowest post-treatment mortality with SBRT, which can be delivered on an outpatient basis and without anesthesia.

Given that lobectomy is the preferred surgical option for stage I NSCLC (18) and SBRT may be equivalent to lobectomy (5), the comparison of lobectomy to SBRT by Stokes *et al.* is particularly relevant. On multivariate analysis, hazard ratio for mortality with lobectomy versus SBRT was 3.7 at 30 days (P<0.001, unadjusted mortality 2.0% *vs.* 0.7%, absolute difference 1.3%, favoring SBRT) and 1.6 at 90 days (P<0.001, unadjusted mortality 3.5% *vs.* 2.9%, absolute difference 0.5%, favoring SBRT). In the absence of additional randomized trials, these data corroborate the findings from the STARS/ROSEL combined analysis (5).

Perhaps not surprisingly, Stokes *et al.* found perioperative mortality increased with increasing age. However, post-treatment mortality after SBRT did not increase proportional to perioperative mortality. In other words, with increasing patient age, SBRT became safer compared to surgery, with a 3.67% absolute difference in mortality for patients over 80 years old at 90 days post-treatment. For patients over 70 years old, post-treatment mortality was significantly less with SBRT than any surgery, including sublobar resection, lobectomy, and pneumonectomy.

In the future, immunotherapy may also be combined with either SBRT or surgery for early-stage NSCLC. Early data show a 45% major pathological response in resected NSCLC treated with neoadjuvant PD-1 blockade (19). Prospective trials combining SBRT with PD-1 or PD-L1 blockade are ongoing: ISABR (NCT03148327), STILE (NCT03383302), C4-MOSART (NCT03431948).

A multidisciplinary approach including opinions from specialists in thoracic surgery, medical oncology, and radiation oncology is advisable for all patients presenting with early-stage NSCLC. Current clinical practice guidelines for stage I NSCLC from the United States National Comprehensive Cancer Network recommend SBRT for "patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation" and allow SBRT as an option for "patients with high surgical risk" (18). We await the results of several randomized trials comparing SBRT to surgery in operable stage I NSCLC: POSTILV (NCT01753414), STABLE-MATES (NCT02468024), SABRTOOTH (NCT02629458), and VALOR (NCT02984761). Until the results of those studies are available, based on the STARS/ROSEL combined analysis (5) and the data presented by Stokes *et al.*, perhaps SBRT should be presented as a reasonable treatment option for patients over 70 years old, especially those who cannot safely undergo lobectomy.

Acknowledgements

None.

Footnote

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

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Cite this article as: Niska JR, Sio TT, Daniels TB, Beamer SE, Jaroszewski DE, Ross HJ, Paripati HR, Schild SE. Stereotactic body radiotherapy for early-stage non-small cell lung cancer has low post-treatment mortality. J Thorac Dis 2018;10(Suppl 17):S2004-S2006. doi: 10.21037/jtd.2018.04.169

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