Letter to the Editor

Collaborating to assess the role of stereotactic body radiation therapy in medically operable stage I non-small cell lung cancer

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Stokes WA, Rusthoven CG. Surgery vs. SBRT in retrospective analyses: confounding by operability is the elephant in the room. J Thorac Dis 2018;10:S2007-10.

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We appreciate the editorial by Drs. Stokes and Rusthoven about our recent publication that compared the outcomes of patients treated with either a video-assisted thoracoscopic (VATS) lobectomy or stereotactic body radiation therapy (SBRT) for stage I non-small cell lung cancer (NSCLC) at a single Veterans Affairs (VA) medical center (1,2). Their comments shed an important light on the dilemma of "confounding by indication" that can undermine retrospective comparisons of patients who are treated according to guidelines that limits access to one of the treatments (SBRT) to only those who are unfit for the preferred standard of care treatment (lobectomy). We recognize that this may have contributed to our findings that showed better 3-year overall and recurrence-free survival with VATS lobectomy as compared to SBRT in our propensity-matched analysis, especially because the majority of our SBRT patients had been considered medically inoperable. Therefore, we agree with their conclusions that our data, or indeed any retrospective analysis of this nature, cannot rule out a potential role for SBRT in certain operable patients.

We also agree with the comments in Dr. Swanson's related editorial that surgery should remain the standard of care for stage I lung cancer in accordance with guidelines (3). As stated by Dr. Swanson, surgical outcomes with minimally invasive techniques are quite good and remain "the best current treatment" (4). The observed higher recurrence rates with SBRT (40.5% with SBRT versus 8.1% with VATS in our propensity-matched cohorts, at a median follow-up of 3.7 years) may raise appropriate concern about treating potentially operable patients with SBRT, as this difference cannot be easily explained by confounding factors or lead time bias. However, we recognize that it is impossible to know with certainty whether outcomes with SBRT may have been comparable had the groups been instead matched through randomization at baseline.

We also appreciate the comments in both editorials about the surgical outcomes in our propensity-matched cohort (1,3). Although a 90-day mortality of 0% and 3-year overall survival of 85.7% may be considered by some as "better than expected", other modern studies using VATS lobectomy have shown similar outcomes (4). As Dr. Swanson commented (3), data such as ours demonstrate that even in a frail population with extensive comorbidities and poor pulmonary function values, minimally invasive lobectomy offers a safe and excellent option for patients who are appropriately selected and cared for at a tertiary center with high quality perioperative care. Furthermore, the 18.9% of patients in our study who were found to have occult nodal disease via surgical staging of the mediastinum may have especially benefited from a VATS approach, given the option it provided for earlier initiation

of adjuvant systemic therapies, which is not possible when SBRT is delivered to patients who will only declare their unrecognized occult disease after multiple cell doublings (2).

We are well aware of the extent of literature and figurative graveyard of prematurely terminated randomized trials that have aimed to compare these two treatments in a balanced manner. This includes the small and underpowered pooled analysis of two of these trials that had failed to accrue, and included outdated surgical methods with open thoracotomy (5). We believe that the higher survival rate with SBRT in that analysis is meaningless in this setting, and that the honest clinician would readily confess that it serves as an unreliable reference when deciding on patient care. Notwithstanding, the data on SBRT in operable patients has been intriguing enough to continue support and equipoise for the ongoing STABLE-MATES [NCT02468024] and VALOR [NCT02984761] phase III multicenter randomized studies, activated in 2015 and 2017, respectively (6-9). The former study has now exceeded 100 patients enrolled, and the VALOR study was just expanded to recruitment at nine VA medical centers across the US. As a thoracic surgeon and radiation oncologist who work closely together as co-investigators on the VALOR study, we find that randomizing patients to these two disparate treatment choices is indeed feasible—in contrast to Dr. Swanson's opinion. This is likely because of the observed culture of group equipoise at our enrollment sites within the VA, where thoracic surgeons, radiation oncologists, pulmonologists, and medical oncologists have been working collaboratively to support a study that they believe is both valuable and important for our future patients.

For now, until or unless either of these phase III trials show comparable long-term outcomes with SBRT, we believe that the first line treatment option for patients with stage I NSCLC is anatomic surgical resection with staging of the mediastinum. We also believe that the outcomes with VATS approach, whether confounded by anything, should serve as the benchmark for all alternative treatment options. Still, SBRT can be a reasonable option for patients with high operative risk, although such operative risk should be assessed by a thoracic surgeon who specializes in lung resection (4,10). We emphasize this because in recent years, patients and physicians have been increasingly "voting with their feet" with an increasing preference for non-invasive management that might ultimately not be the best option for them (11,12).

In an ideal world, all clinicians who care for patients with cancer would endorse randomized clinical trials, even when they are difficult. We owe it to our patients to work collaboratively to continue seeking ways to improve outcomes, particularly when it comes to enrolling patients into studies that can generate reliable data. In this way, we can best optimize our ability to answer important clinical questions, such as whether SBRT is ever a suitable alternative to surgery in a patient with operable stage I NSCLC.

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Footnote

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