

Weighing the relative importance of short-term versus long-term outcomes when comparing surgery versus stereotactic body radiation therapy (SBRT) for early-stage non-small cell lung cancer

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Lung cancer continues to be the leading cause of cancer death in the United States, with an estimated 234,030 new cases and 154,050 deaths expected in 2018 alone (1). Approximately one-sixth of new cases are early-stage (T1-2N0) non-small cell lung cancer (NSCLC), a proportion which is anticipated to grow with increased use of low-dose CT lung cancer screening programs (2). While lobectomy has traditionally been considered the standard of care for definitive management of early stage NSCLC, alternative treatment strategies have increased in popularity. Of these, the primary non-surgical modality has been stereotactic body radiation therapy (SBRT), which has seen an exponential increase in popularity over the past decade. By some estimates, SBRT is currently the primary treatment modality for nearly 10% of early-stage NSCLC (3).

Initially, SBRT was considered primarily for patients who were either unwilling to have surgery or deemed to be medically unfit for surgery. As SBRT has increased in popularity, the American Society of Clinical Oncology (ASCO) and the American Society for Radiation Oncology (ASTRO) have published broader guidelines for the use of SBRT for early-stage NSCLC (4,5). In these newer guidelines, both societies recommend consideration of SBRT for patients with early-stage disease who are considered to be at “high operative risk”. While the

definition of “high” remains unclear, the ASTRO guidelines do specify that risk should be assessed by a thoracic surgeon who specializes in lung resection. Similarly, the ASCO guidelines stress the importance of shared decision-making between the patient and the multidisciplinary medical team, emphasizing discussions about efficacy and risks of the various treatment options.

The contribution by Stokes *et al.*, “Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer”, reports that short-term mortality (assessed at 30 and 90 days post-treatment) was moderately increased with surgery versus SBRT for patients with early-stage NSCLC, and that these differences increased as a function of patient age. The authors, utilizing the National Cancer Database (NCDB), concluded that these data allow for improved shared decision-making between patients and their providers when determining treatment strategies. As a corollary, they emphasize the importance of these findings by asserting that for some individuals, short-term outcomes may be more important than long-term survival.

Stokes and colleagues quote 30-day mortality rates of 2.0% and 1.77% for patients undergoing lobectomy and sublobar resection, respectively. These figures, based on the authors' analysis of registry data from the NCDB, are

somewhat higher than similar statistics reported in the more robust STS General Thoracic Surgery Database (1.6% and 0.6% for lobectomy and sublobar, respectively) (6). Interestingly, the 0.6% 30-day mortality for sublobar resection in the STS database is lower than the 0.73% 30-day mortality for SBRT in the NCDB. Regardless of these nuanced differences in post-treatment outcomes, scrutinizing short-term mortality outside the context of long-term survival is somewhat misguided. To make an extreme example of such logic, one might argue that placebo has the lowest 30-day mortality in the treatment of NSCLC, yet such an approach should still not be recommended as therapy.

While an assessment of short-term risks should undoubtedly factor into the shared decision-making process for patients with early-stage NSCLC, it is important to note that the vast majority of these patients are seeking curative-intent treatment. Consequently, discussion of perioperative risks, while important, should not overshadow discussions of long-term survival, which most would consider the top priority for this population of patients facing two relatively low-risk treatment options. Lobectomy with mediastinal lymph node assessment remains the gold standard for definitive treatment of NSCLC in medically operable patients (7). This is primarily based on data from a randomized controlled trial comparing lobectomy to sublobar resection, wherein lobectomy was found to have lower local recurrence rates with a trend towards superior long-term survival (8).

One of the key advantages to lobectomy is that the approach affords assessment of regional and mediastinal lymph nodes at the time of surgery. In a study that we recently published, which also utilized the NCDB, 9.3% of patients treated with lobectomy for clinical stage IA (cT1aN0) NSCLC were found to have node-positive disease at the time of surgery (9). The extent of nodal upstaging would only be expected to increase with the inclusion of clinical T1-T2a patients in the study by Stokes *et al.* While it remains plausible that SBRT offers similar local control of an early-stage tumor compared to a sublobar resection, the primary downside to SBRT is that it does not allow for pathologic assessment of hilar and mediastinal lymph nodes. Notably, in our aforementioned NCDB study, we examined patients undergoing sublobar resection for early-stage NSCLC and found that lymph node sampling at the time of surgery was associated with superior long-term survival (9).

Despite these findings, recent studies have reported SBRT being increasingly utilized in potentially operable

patients, with 5-year survival outcomes approaching those of surgical resection (10-14). As clinical interest in SBRT has increased, so too have efforts to more rigorously investigate the role of SBRT among patients with early-stage disease who are deemed medically fit for surgery. Specifically, these including the veteran affairs lung cancer surgery or stereotactic radiotherapy (VALOR, NCT02984761), STABLE-MATES (NCT01622621), SABRTooth (NCT02629458) and POSTLIV/RT0G 3502 (NCT01753414), the results of each being eagerly awaited.

The current study attempts to compare post-procedural mortality among patients treated with either surgery or SBRT for early-stage NSCLC. The authors present short-term mortality rates for the two treatment modalities, and provide age-stratified estimates. These estimates allow for more informed discussions regarding the risks and benefits of various treatment options, but fall short of offering meaningful perspective relative to the known long-term survival of each approach. While a full understanding of short-term risks is essential for shared decision-making, we assert that absolute mortality differences on the order of 1% can only offer meaningful information to patients when they are considered in the context of long-term survival.

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Footnote

Conflicts of Interest: Dr. TA D'Amico serves as a consultant for Scanlan, Inc. PJ Speicher has no conflicts of interest to declare.

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