Editorial Commentary

Stereotactic body radiation therapy versus surgery for early stage non-small cell lung cancer: clearing a path through an evolving treatment landscape

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An interesting and robust systematic review and meta-analysis comparing outcomes between patients with early stage non-small cell lung cancer (ES-NSCLC) receiving stereotactic body radiation therapy (SBRT) or surgical resection was recently reported by Cao *et al.* (1). After a thorough examination of studies available in the literature comparing these two modalities, 32 studies were ultimately identified as suitable for study inclusion, including the pooled analysis of the STARS and ROSEL randomized trials (2) and 31 observational studies that included SEER (n=6) and NCDB (n=3) analyses. Twenty-three of these studies were used for quantitative analysis, and the investigators performed a quality assessment of all included studies using the Newcastle-Ottawa Scale, indicating an overall moderate quality study score.

The primary endpoint of this analysis was overall survival (OS), with additional secondary clinical endpoints of cancer-specific survival (CSS), disease-free survival (DFS), freedom from locoregional recurrence (FLRR), freedom from distant recurrence (FDR), and perioperative mortality and morbidity (1). Given the heterogeneity of patients between all studies, the authors did an excellent job of assessing all endpoints using unmatched as well as matched cohorts. For the purposes of this editorial, we will focus our comment on those results using only matched cohort analyses to minimize the inherent biases when comparing surgery and SBRT and to avoid generalizations from highly heterogeneous data. In fact, the unmatched analysis for the primary endpoint of OS included 142,293 patients undergoing surgical resection and only 10,333 patients undergoing SBRT. Imbalances between patients selected for surgical resection (younger age, more favorable comorbid status, lesser smoking history, better pulmonary function, etc.) versus for SBRT are well-established (3,4). Given these inherent biases in patient selection, combined with the vast difference in analyzable patient numbers, unmatched cohort outcomes are unlikely to provide added validity to conclusions reached using matched cohort data.

For matched patients, the majority had AJCC 7th Edition stage IA disease (SBRT: IA 72–84%, IB 16–29%; surgery: IA 70–82%, IB 18–34%), with interquartile ages ranging from 71 to 78 years in the SBRT cohort and 68 to 78 years in the surgery cohort (1,5). The study primary endpoint of OS, along with secondary endpoints of CSS, DFS and FLRR, were all strongly in favor of surgical resection (OS: OR 1.71, 95% CI: 1.52–1.94, P<0.00001; CSS: OR 1.78, 95% CI: 1.28–2.48, P<0.0006; DFS: OR 1.83, 95% CI: 1.06–3.16, P=0.03; FLRR: OR 2.91, 95% CI: 1.49–5.71, P=0.002). Of note, insufficient data for matched patients were available to assess distant recurrence rates. As expected, periprocedural mortality was less after SBRT than with surgery (0% SBRT versus 0–8% surgery) (6).

These findings largely mirror the bulk of available literature on this topic. Surgical resection with lobectomy and mediastinal sampling was established as the primary treatment and standard of care for patients with medically operable ES-NSCLC long before the proliferation of lung SBRT, and there are longstanding data demonstrating excellent clinical outcomes with this surgical approach (85–95% local control, 50–80% 5-year survival) (7) and guidelines reflecting this historical standard treatment (8,9).

Radiotherapy was established as a treatment option for medically inoperable or borderline operable patients. Conventionally fractionated definitive radiotherapy (i.e., 1.8–2.0 Gy fractions) to standard doses of 60–70 Gy were delivered, yielding limited 5-year survival rates (17–55%) and local control (30–94%), outcomes that were significantly worse than those achieved with surgery (10,11).

While the relatively poor survival seen after conventionally fractionated radiotherapy was attributed, in part, to the baseline limited life expectancy and worse comorbid status of patients not considered suitable for surgical resection, inferior local control rates spurred interest in alternative radiotherapeutic approaches. As radiation technology rapidly improved, and as it was found that there was improved local control with biological effective doses (BED) ≥100 Gy (12), the use of ablative radiotherapy doses to attempt to achieve complete tumor sterilization proliferated.

SBRT, also termed stereotactic ablative radiotherapy (SABR), allows large, ablative doses of radiation to be delivered with each fraction (most typically 10–34 Gy per fraction over 1 to 5 fractions) directed to a smaller, more conformal treatment volume, thus allowing for a higher tumor-directed BED without a concomitant increase in normal tissue toxicity. Importantly, elective nodal irradiation and even elective margin expansion for microscopic tumor extension are omitted with this approach, which would otherwise make dose escalation to this degree not safely feasible. Early studies of SBRT demonstrated improved local control outcomes compared with conventionally fractioned RT, with short-term control rates similar to those achieved after lobectomy (13,14). However, initial skepticism in SBRT rightfully prevailed given the persistence of poor survival outcomes, limited long-term follow-up, and reports of severe toxicities in select patient populations treated with SBRT (13).

The meta-analysis by Cao *et al.* includes several trials with patients treated with SBRT BED doses of <100 Gy, doses known to be associated with inferior survival; however, numerous newer studies on the long-term results of the efficacy and toxicity of SBRT have more recently been reported. In the inoperable setting, long-term OS rates have notably improved with modern SBRT dose-fractionation regimens and techniques, with 5-year OS rates ranging from 52–56% (15-17). More mature reports in patients with operable disease have also become available, albeit in limited quantity. In a prospective trial from Japan that included 60 operable patients with stage I NSCLC treated with 44–52 Gy in 4 fractions, the 5-year OS was 66% (17). Also from Japan, the phase II Japanese Clinical Oncology Group JCOG 0403 trial treated 64 operable patients with cT1 NSCLC to 48 Gy in 4 fractions and found a 3-year OS of 76.5% (18). Treatment was very well tolerated, with only 8% developing a grade 3 toxicity, and no grade 4–5 toxicities seen. The RTOG 0618 phase II study of SBRT for operable patients with peripheral, biopsy-proven T1–T2 node negative NSCLC ≤5 cm in size treated with 54 Gy in 3 fractions found the 4-year primary tumor control and local control rates were both 96%, and the 4-year OS rate was 56% (19). SBRT was similarly well tolerated, with 8% having grade 3 adverse events, and no grade 4–5 events seen. These survival outcomes in operable patients are in keeping with those seen in surgical series (20). Finally, in the pooled analysis of the STARS and ROSEL phase III trials randomizing patients with operable NSCLC ≤4 cm to receive SBRT with 50–60 Gy in 3–5 fractions (n=31) or surgical resection with mediastinal lymph node dissection (n=27), OS with SBRT at 1 year and 3 years was superior to that with surgery (100% *vs.* 88% and 95% *vs.* 79%, respectively) (2).

The question of local and locoregional control in the comparison of SBRT versus surgery for ES-NSCLC is also worth discussing. This is a heavily nuanced and complex issue given the lack of uniformity and differences in treatment populations in (I) patient and tumor characteristics; (II) regional nodal sampling; (III) pathologic confirmation of primary malignancy; and (IV) endpoint reporting (local tumor failure, in-lobar failure, ipsilateral lobar failure, lobar and regional nodal failure). This is likely reflected to some degree in the systematic review by Cao *et al.*, in which only 6 studies with matched patient data were available to evaluate the endpoint of FLRR. Of these studies, 5 were retrospective series, and 3 of these were database analyses (1).

Literature from prospective studies using modern SBRT dosing have demonstrated tumor control equipoise between surgery and radiation therapy for more uniform patient

populations, both in the medically inoperable and operable setting. For example, in RTOG 0236, a seminal phase II trial in which 55 medically inoperable patients with peripheral, biopsy-proven NSCLC ≤5 cm in size were treated with 54 Gy in 3 fractions, the 5-year rate of local control at the primary tumor site was 92.7% (15). Investigators from MD Anderson Cancer Center performed a similar trial including 65 patients with medically inoperable stage I NSCLC treated with 50 Gy in 4 fractions (16). The estimated local control at 5 years was 91.9%, and the estimated regional control was 89.1%. In the operable setting, the aforementioned combined analysis of the STARS and ROSEL trials demonstrated similar rates of local and regional control for patients receiving SBRT and surgery, with only one local recurrence reported at 3 years in the SBRT arm that was salvaged with lobectomy (2). Our own prior analysis demonstrated 94% local control at 5 years in a large cohort of ES-NSCLC patients all treated with SBRT to BEDs of ≥100 Gy (21). Interestingly, in that analysis, medically operable patients choosing to undergo SBRT had better survival than medically inoperable patients treated with SBRT despite no appreciable differences in patient or tumor characteristics between groups, further underscoring the inherent differences in populations and biases when comparing surgery and SBRT. These are, however, just a few of the growing number of SBRT studies that demonstrate excellent rates of long-term tumor control that mirror the rates in surgical series.

The study of SBRT compared with surgery has also been impacted by additional factors not directly related to biases in patient selection and study heterogeneity. Just as there have been continued advances in surgery for ES-NSCLC, the even younger modality of SBRT has proportionately changed much more in recent years. The technical aspects of SBRT delivery have evolved considerably over the past two decades and continue to be refined as the field continues to understand and optimize this highly technical treatment technique. As the meta-analysis by Cao *et al.* included several studies that treated patients more than two decades ago, the older SBRT treatment techniques used in those studies may have affected the efficacy and quality of SBRT delivery, which in turn may account for the differences identified between the modalities. For example, early SBRT studies did not account for differences in tissue heterogeneity between normal lung tissue and tumor, which affects the amount of irradiation deposited in the tumor (13,22). Additionally, normal tissue dose constraints have since been derived for various dose-fractionation schemas, guidelines have been developed to define optimal tumor doses, metrics have been established to assess rates of radiation dose dissipation surrounding the target volume, and novel delivery techniques have emerged to increase irradiation dose within the target volume while reducing dose outside of the treatment volume.

Furthermore, great strides in recent years have been made in the realm of radiotherapy motion management for thoracic tumors (23). These techniques allow for the delivery of a more precise and accurate treatment by minimizing intrafraction dose variability by controlling for changes in tumor position during the respiratory cycle. Deep inspiratory breath hold, abdominal compression devices, active breathing control, tumor tracking, and respiratory gating are a few examples of modern techniques that can result in improved dose delivery to the tumor volume and decreased planning margin required to compensate for uncertainties due to respiratory motion, which further minimizes normal tissue exposure to radiation and improves the therapeutic ratio of this modality. Increased use of image-guided radiotherapy (IGRT) with cone beam computed tomography (CBCT) has resulted in superior accuracy of tumor positioning and treatment delivery (24). In addition, more frequent use of PET/CT to improve target delineation during radiation treatment planning has allowed for more accurate tumor targeting and more effective treatment (25).

In the meta-analysis under review, toxicity was described in terms of 30-day periprocedural mortality, which was found to be more favorable with SBRT (0%) than with surgery (0–8%) (1). While these outcomes numerically did not differ significantly, the severity of morbidities was clearly illustrated in the increased number of periprocedural deaths that occurred in the surgery group, as well as in the type of morbidity most commonly seen. SBRT patients were more likely to suffer from fatigue, radiation pneumonitis, chest pain, and rib fractures, whereas surgery patients were more likely to experience prolonged air leak, pneumonia, pulmonary embolism, cardiac arrythmia, and myocardial infarction. The reduced toxicity profile with SBRT compared to surgery is reflective of a better understanding of normal tissue tolerance to ablative radiotherapy doses today and is consistent with existing SBRT studies reporting an overall incidence of acute toxicities ranging from 5–40%, with the majority of events being mild and transient in nature (26). This is a necessary consideration when discussing treatment options with particularly frail and elderly ES-NSCLC patients.

This meta-analysis, although reporting interesting and provocative findings in a large-data compilation that affirm the widely-accepted role of surgery as the standard of care for medically operable ES-NSCLC patients, does have additional limitations associated with a meta-analysis that were already acknowledged by the authors (1). Caution must be taken when interpreting data derived from multiple sources with differing study types that are then subjected to a variety of statistical methods to derive a tolerable level of uniformity to allow for reporting on a meaningful endpoint. Also, the strong possibility exists that there was overlap in patients across several studies that were included in this meta-analysis, particularly between database and institutional reports, resulting in an unbalanced weighting of the outcomes for those patients. It is also unclear what impact patients who did not have a tissue diagnosis had on the meta-analysis findings. We fully agree with the authors that pathologic confirmation prior to SBRT should be obtained whenever feasible, and we have contributed to recent guidelines for this (27).

Furthermore, the magnitude of the difference detected between SBRT and surgery was impacted by whether the endpoint was being studied in an unmatched or matched population. In general, the difference detected in each endpoint was smaller in the matched cohorts, suggesting that inherent patient selection bias existed in the included study population; however, it is likely that even within the matched analysis, additional undetected bias remained, affecting the results of these analyses. Additional significant bias in staging likely also existed between surgery and SBRT patients in this meta-analysis. As SBRT patients typically received less extensive or less invasive lymph nodal staging, and up to one-third of patients treated with SBRT for presumed clinical stage I NSCLC are found to have nodal metastases, survival comparisons in such analyses are often biased in favor of surgery, which is in keeping with differences in survival for clinical versus pathologic populations (10).

With several randomized trials comparing surgery to SBRT currently accruing around the world that will provide level 1 evidence, and with an increasing number of studies using modern SBRT maturing and reporting on long-term data, we eagerly await a similar meta-analysis in the coming years that will be able to focus on higher level evidence, more balanced cohorts, and patients treated with more modern and clinically relevant SBRT techniques and doses. Such randomized trials and future meta-analyses ultimately can definitively determine if SBRT and surgery provide equivalent disease control outcomes for operable patients and if the survival benefit historically reported with surgery is primarily due to patient selection biases or an inherent inferiority of SBRT. If efficacy and survival are not inferior with SBRT compared with surgery, and treatment-related morbidity and mortality associated with SBRT remain superior to that of surgery, a continued evolution in the standard treatment paradigm for ES-NSCLC will need to be considered. Until then, we endorse continued collaboration between thoracic surgeons and radiation oncologist to enroll patients onto these important trials (28), and we commend Cao *et al.* on their important analysis that in the interim further supports surgery remaining the standard of care for medically operable ES-NSCLC patients.

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Footnote

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

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