

# Stereotactic body radiation therapy vs. surgery in early-stage non-small cell lung cancer: lessons learned, current recommendations, future directions

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Lung cancer remains the leading cause of cancer-related death in the United States (1). Early stage (T1–T2N0) non-small cell lung carcinoma (NSCLC) accounts for 16% of new diagnoses, a proportion that is expected to rise with the implementation of low-dose CT screening programs (2). Early-stage NSCLC has been definitively managed with either surgery or radiation therapy. Stereotactic body radiation therapy (SBRT), interchangeably known as stereotactic ablative radiotherapy (SABR) is a modality that delivers ablative doses of radiation to extra-cranial targets with a degree of precision and accuracy above what can be reasonably achieved with conventionally fractionated external beam radiotherapy. SBRT is delivered over a limited number of fractions, typically defined as five fractions or fewer. Hypofractionated radiotherapy, consisting of 6–10 fractions, is sometimes included in the SBRT definition.

The last 15 years have seen a dramatic rise in SBRT utilization, including its use for patients with early-stage lung cancer. Large-scale national database results revealed a 33-fold increase in SBRT use for early stage NSCLC, accounting for <0.5% to 8.7% of treated cases over a 8-year span (3). Surveillance Epidemiology and End Results (SEER) data from the same timeframe showed similar trends (4). Utilization is expected to increase, as these series analyzed patients treated between 2003 and 2011, an era that preceded

several landmark publications, including: randomized data for medically operable patients pooled from two smaller trials (5), prospective dose-escalation results for centrally located tumors (6), and efficacy of SBRT for clinically-diagnosed early-stage lung carcinoma (7).

Accordingly, the American Society for Radiation Oncology (ASTRO) developed a set of evidence-based guidelines for the treatment of patients with early-stage NSCLC using SBRT (8). These guidelines were endorsed by the European Society for Radiotherapy & Oncology and the Royal Australian and New Zealand College of Radiologists at the time of publication. The American Society of Clinical Oncology (ASCO) Expert Panel recently endorsed the ASTRO guidelines for the broader oncology community (9). Without question, this formalization is an important step towards wider understanding of the value of SBRT. It provides recommendations by addressing key questions on the appropriateness of SBRT for several challenging clinical scenarios. As a result, a few, but notable, changes were made in the process. One such change is related to the perception of SBRT's appropriateness for medically operable patients.

For high operative risk patients, who ineligible for a lobectomy, but are candidates for a more limited lung resection, ASTRO encourages '*discussions about SBRT as a potential alternative to surgery*', such that '*all clinicians involved*

*in the care of patients with stage I NSCLC should be prepared to interact with operable patients*'. This sentiment is shared by the American College of Surgeons, which emphasize shared decision-making and patient engagement with the informed consent process (10). To clarify this process, ASTRO outlined several points when physicians discuss SBRT with potentially operable patients. Notably, all of these points describe SBRT's potential disadvantages: the omission of pathologic nodal evaluation, possible forfeiture of adjuvant chemotherapy, uncertainties in radiographic follow-up, unnecessary biopsies or false reassurance of disease control, and increased operative risks of post-SBRT salvage surgery. ASTRO values individual patient goals and quality of life preferences in addition to oncologic outcome. The language in ASCO's endorsement specifies that for standard and high operative risk patients, discussions about SBRT may be appropriate among members, or 'within the multidisciplinary cancer care team'. This language is equivocal, suggesting that multi-disciplinary physician contact may be limited to those patients whose appropriateness is externally determined, raising the risk of specialty bias.

ASCO's qualifying statement regarding high operative risk patients with stage I NSCLC referenced the long-term outcomes of Radiation Therapy Oncology Group (RTOG) 0236. Its updated 5-year overall survival (OS) rate was 40% and disease-free survival rate was 26%. RTOG 0236 was landmark study for medically inoperable patients—it validated the use of a technically-demanding modality in the multi-institutional setting; however, its small size (N=49) and enrollment criteria impacts its validity for comparative use to patients eligible for wedge resection. A better-matched comparison with a single-arm trial is RTOG 0618, a prospective study of medically operable patients treated with SBRT to 54 Gy in three fractions, which reported an 84.4% 2-year OS rate, and a 65.4% progression-free survival rate (11). Long-term survival data at 5 years have also been reported institutionally, with significantly more favorable results than RTOG 0236. This includes three multi-institutional reports from Japan with large patient cohorts (range, 60 to 661) which found 5-year OS rates ranging 66–74% (12–14).

Nevertheless, robust randomized data for medically operable patients with early-stage NSCLC is lacking. In its absence, well-designed comparisons between large retrospective cohorts may be informative. Selected studies relevant to the discussion of SABR *vs.* surgery for medically operable patients, not previously discussed by the ASCO

endorsements, are outlined here. Using an administrative database approach, Shirvani *et al.* queried over 9,000 patients who were treated with either lobectomy, sublobar resection, or SBRT from SEER-Medicare linked data. Radiotherapy was an under-represented modality—4.2% of patients treated from 2003 to 2009 received SBRT. Comparisons of SBRT *vs.* lobectomy using propensity matched methods found no difference in either OS (P=0.94) or lung cancer-specific survival (P=0.99). Sensitivity analyses employing a strict match on 20 variables did not change these results. A similar comparison between lobectomy and more limited resections saw inferior outcomes with sublobar resection. Though SABR was not directly compared to sublobar resection, one may reasonably expect favorable outcomes given its equivalence to lobectomy in this analysis.

Zheng *et al.* performed a meta-analysis of 40 SBRT studies and 20 surgical series reporting on 4,850 and 7,701 patients, respectively (15). An operability parameter, based on the proportion of patients in a given study who were offered but declined surgery, was used to aid the comparison between SBRT and surgical patients. After adjusting for age and operability, survival outcomes were not significantly different between SBRT and surgery. In their multivariate mixed effects model, OS numerically favored SBRT [hazard ratio (HR) 0.49 compared to limited lung resection; HR 0.52 compared to lobectomy]. Disease-free survival and local control were similar between SBRT and surgery. Estimates from their fitted regression model with fixed age and operability resulted in 5-year estimated OS of 82%, 66%, and 68% for SBRT, limited lung resection and lobectomy, respectively. It has been hypothesized that substantial residual differences exist after correcting for age and operability, including performance status and expectations over life span, such that more favorable patients were selected for surgery.

Remarkably, much of the data on SBRT outcomes reported patients who were treated in its pioneering era. Notable refinements have since been made to nearly every aspect of SBRT. Treatment planning and target delineation is now routinely based on 4D methods, which obtains CT data over the course of the respiratory cycle divided into 10 phases. Historically, non-4D simulation with asymmetric margins was utilized, as was the case for RTOG 0236. In the same study, verification CTs and portal films to taken at the discretion of the participation institution. Current workflow typically requires cone beam CTs to be obtained with every fraction, raising the standard for image-guidance and accurate dose-delivery (16). Advancements in the physics

and dosimetry of intensity modulated radiation therapy (IMRT) has seen better understanding of the tolerance of normal tissues, and the evolution of static-mode IMRT to arc-based therapy (17). Together, they have the potential to improve the efficacy and tolerability of SBRT over historical standards.

Technical advancements in SBRT, which have paralleled its significant increase in utilization, and clinical relevance, reflect the shared knowledge and expertise that has been gained over the last decade. The ASCO guidelines make no explicit recommendations on preference for the treatment setting. However, as radiation oncologists are presented with challenging cases, perhaps some consideration should be given to the treatment facility. A high-volume facility is linked to provider experience, technical capabilities, and access to strong multi-disciplinary services. Koshy *et al.* utilizing data extracted from the National Cancer Data Base, found treatment at a high-volume center was significantly associated with higher survival rates for patients with inoperable T1–2N0 NSCLC (HR 0.94; P=0.01) than those treated at a low-volume center, even after adjusting for treatment, clinical, and socioeconomic factors (18). The authors theorized that service such as multi-disciplinary tumor boards and patient navigators could plausibly improve survival. Moreover, a high-volume facility may also be a surrogate for provider comfort with the technical aspects of treatment planning, image guidance, normal tissue toxicity, and supportive measures. The experience of chest radiologists interpreting post-SBRT images at a high-volume center may also limit the incidence of unnecessary biopsies in a previously-irradiated lung.

Despite inherent limitations in retrospective analyses, a growing body of evidence supporting SABR has renewed the interest for randomized data comparing surgery to SBRT in medically operable patients. Three early studies in the randomized setting were all prematurely terminated due to insufficient accrual in 2013: Accuray's industry-sponsored STARS; the Dutch ROSEL study; and ACOSOG Z4099/RTOG 1021. These early attempts highlighted the challenges of multi-modality randomizations. Understandably providers may have strong preferences for how patients are treated, and patients would like to retain some control over the decision-making process. Clinical equipoise and increasing public interest as a result of exposure to SBRT have ensured that has remained an area of great interest. To that end, eight randomized clinical trials comparing SBRT to surgery have been activated (8). Most prominent among these include POSTLIV/

RTOG 3502 (NCT01753414), STABLE-MATES (NCT01622621), SABRTooth (NCT02629458), and the Veteran Affairs Lung Cancer Surgery or Stereotactic Radiotherapy (VALOR, NCT02984761). With lessons learned from earlier attempts, ongoing enrollment in the above studies aims to minimize the risk of bias. They are designed to be conducted under close supervision with human research protection monitoring. For instance, under the SABRTooth protocol, potentially eligible patients are introduced to the study by a pulmonologist, and consent to the study may be obtained by a research nurse (19). After randomization, patients only meet with the specialist relevant to their arm of the study.

How SBRT can be best integrated into the current management paradigm of early-stage NSCLC patients is an ongoing debate in search of gold-standard evidence. The recent ASCO endorsement of ASTRO guidelines highlights the importance of this conversation. As it is the result of objective review of the available data, it remains conservative especially in domains where evidence is scarce. The timely completion of the above trials and their long-term results are greatly anticipated. Regardless of outcome, they will have important implications for the management of patients with early-stage NSCLC within the multi-disciplinary setting. Radiation oncologists should play an integral part of this process, one where multi-specialty support will be key to success.

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### Footnote

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

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