

Stereotactic ablative radiotherapy and surgery: two gold standards for early-stage non-small cell lung cancer?

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Abstract: There is growing clinical equipoise between surgery and stereotactic ablative radiotherapy (SABR) in the management of early-stage non-small cell lung cancer (ES-NSCLC). Increasing evidence suggest similar outcomes between these modalities. Through the guidance of a multidisciplinary team, a shared decision making approach in this setting is favoured.

Keywords: Carcinoma; non-small cell lung; comparative effectiveness research; radiosurgery; retrospective studies; thoracic surgical procedures

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Early-stage (T1-T2aN0M0) non-small cell lung cancer (ES-NSCLC) has been successfully treated with surgery for decades, with an anatomic lobectomy established as the treatment of choice for localized disease in operable patients since the 1960s (1). Though sublobar resections via wedge resections or segmentectomies were originally found to be less effective than lobectomies in terms of local control (LC) and overall survival (OS) in the 1990s (2), this concept has been challenged by more recent studies, mostly comprised of elderly patients with compromised pulmonary function (3-5). As such, sublobar resections are currently endorsed by multiple clinical practice guidelines (6,7) as a first-line treatment option for borderline operable patients with poor pulmonary function or multiple comorbidities.

For ES-NSCLC patients who are medically inoperable, non-surgical alternatives such as conventionally fractionated radiotherapy have traditionally been regarded as superior to no treatment, but were not able to achieve similar levels of LC or OS as surgical resection. With the advent of stereotactic ablative radiotherapy (SABR, also known as stereotactic body radiation therapy—SBRT) around the turn of the century, however, radiation oncologists have been able to deliver higher, tumor-ablative doses of radiation (biological effective dose >100 Gy) in fewer fractions with a high degree of accuracy. This has been made possible

through advancements in motion management, image guidance and radiation delivery systems. Early evidence with population-level retrospective time-trend studies on the effectiveness of SABR has demonstrated a correlation of improved OS with the introduction of SABR (8,9). Prospective single-arm clinical trial data on the efficacy of SABR on medically inoperable (10) and operable ES-NSCLC patients (11) have also demonstrated LC and OS rates comparable to historical surgical outcomes (2).

Considering such evidence in the PET-staging era, there has been a sense of growing equipoise that argues for SABR as an alternate to surgery for operable ES-NSCLC (12). Randomized control trial (RCT) evidence based on today's technology and techniques comparing SABR and surgery in operable patients ES-NSCLC would afford the highest level of evidence. Three RCTs have been proposed (ROSEL, STARS, RTOG 1021/ACOSOG Z4099) within the past decade comparing SABR to standard surgical management options for ES-NSCLC, though all have closed prematurely due to poor accrual. This is often the case when treatments offered in a RCT differ significantly from the current paradigm, and both options are otherwise available off study (13,14).

In situations where RCTs are unavailable, other forms of well-controlled, comparative effectiveness research take on the mantle of informing patient and physician decision-

making. Indeed, a number of studies consisting of single-institution retrospective data, which contain inherent biases, have been published regarding the use of SABR in operable ES-NSCLC patients, with mixed results (15,16). Seeking to reduce these biases, the recent study by Shirvani *et al.* (17) is an example of a high-quality, retrospective, SEER-Medicare population-based study that compared the outcomes for surgery and SABR with propensity score-matched analysis. The usage of population-level data overcomes biases from different practice patterns based on geographical location and makes the study results more generalizable. Propensity-score analysis also compensates for confounding by indication via the assignment of propensity scores to individual patients based on their baseline characteristics. Only patients with similar propensity scores from each group are then subsequently compared. Of note, surgical management in this study was stratified into lobectomy and sublobar resection, and lobectomy was used as the standard against which both SABR and sublobar resection were compared. Sublobar resection was not further stratified into segmentectomy and wedge resections due to limitations of the SEER database. This interestingly precluded direct comparison between sublobar resection and SABR, between which currently there is arguably the greatest sense of clinical equipoise (18).

With this approach, Shirvani *et al.* were able to provide valuable insight into the ongoing debate of surgery *vs.* SABR. First of all, the population-level data reiterates the significant differences in baseline characteristics between lobectomy, sublobar resection and SABR patients. For example, compared to lobectomy patients, SABR patients were more likely to be octogenarian, female, have a higher Charlson Comorbidity Index, require supplemental oxygen and have poorer performance. Also, SABR patients were more likely to be PET-staged and much less likely to have received procedure-based mediastinal staging. In unadjusted analyses, lobectomy was shown to have improved OS when compared to sublobar resection or SABR in the long term (>6 months), perhaps related to the older age and higher level of comorbidity in sublobar resection and SABR patients. In a subset analysis, SABR was found to have significantly higher patient OS within 6 months of treatment compared to lobectomy, which highlights the importance of considering treatment related mortality in this context (19).

With propensity-score matched analysis, however, there were no significant differences in OS and disease-specific survival (DSS) between lobectomy and SABR in balanced

populations, though there was a non-statistically significant trend towards improved OS and DSS for lobectomy greater than 12 months after treatment. In terms of lobectomy *vs.* sublobar resection, there was a clear benefit for lobectomy for both OS and DSS with propensity-score matched analysis.

There were some limitations in the Shirvani *et al.* study. The SEER-Medicare database only includes patients using the fee-for-service Medicare services and may not comprehensively include some patients of African-American ethnicity, female gender and/or lower socioeconomic status, as these patients are more likely to seek enrollment in Health Maintenance Organizations (HMOs) (20,21). The database also only includes patients greater than 65 years of age. Data on local and regional control/recurrence and treatment-related toxicity would also have been useful in informing other risk/benefit trade-offs between surgery and SABR. These limitations, however, do not diminish this study's ability to contribute to the growing equipoise of the use of SABR in ES-NSCLC due to its overall large sample size and appropriate statistical analyses. Interestingly, another study with a similar study design using the SEER-Medicare database was published soon after the present study (22). This latter study comprised of a more restricted time period from 2007 to 2009, and performed propensity matching of similar patient factors, but not on tumor factors such as T-stage or histology. The DSS of surgery (lobectomy and sublobar resection were again not differentiated) did not differ from SABR at 24 months, though there was an OS advantage using surgery following 24 months. There was an OS advantage for SABR up to 3 months after treatment, again highlighting treatment-related mortality differences between the two modalities.

There is an increasing body of retrospective evidence that suggests equipoise between SABR and surgery for operable patients with ES-NSCLC. Most recently, ongoing analyses with pooled results from the prematurely-closed RCTs have also shown promising results of comparable outcomes between SABR and surgery in terms of recurrence-free survival, locoregional control and distant control (23). Furthermore, despite the small sample size of this pooled analysis, there was an OS benefit in patients treated with SABR. It is foreseeable that in the near future these studies will lead to increased multidisciplinary discussion of treatment options for ES-NSCLC patients. When there is equipoise on clinical management, shared decision-making is becoming increasingly popular, where the patient is given guidance by experts who are familiar with the pros and cons of each option and attempt to explore the patient's

underlying preferences for cancer treatment in light of the available evidence (24).

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