Stereotactic Radiotherapy Versus Surgery for Early-Stage Operable Lung Cancer: More Questions Than Answers

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Stereotactic ablative radiotherapy (SABR) is highly controversial compared with surgery for early-stage operable lung cancer. Initial observational data in operable patient cohorts showed that outcomes for SABR were roughly equal to those of surgery, and these data were supported by propensity-matched analyses and preliminary phase II results. Recently, pooled data from 2 closed phase III trials have provided even more data in favor of a possible equivalency between SABR and surgery. However, despite these increasing data supporting the use of SABR for operable patients and the excitement associated with them, several controversies remain. Although, with no active phase III trials, the answer to these concerns may not be known for a while, I hope that mounting evidence supporting SABR in operable patients will lead to larger future phase III trial enrollment to provide answers to this controversial issue.

SABR, also known as stereotactic body radiotherapy (SBRT), has been shown to be an excellent alternative to surgery in medically inoperable patients, with local control rates higher than 90%, minimal treatment morbidity, and essentially no risk of treatment-related mortality. However, multiple studies comparing SABR with various types of surgery have been consistently hampered by the fact that patients in the SABR group often have higher comorbidities, worse lung function, and/or older ages than their surgery-fit counterparts. As a result, nearly all these studies have shown equivalent cancer-specific survival and local control between groups, but with inferior overall survival (OS) in the SABR groups.

One point that remains to be addressed is the issue of patient selection. Early data exploring SABR include 4 reports from Japan that examined relatively large cohorts. Uematsu et al noted a 3-year OS rate for SABR of 86% in 29 medically operable patients with biopsy-proven early-stage lung cancer (n=50, total). This rate in surgical candidates was supported in other data, with an OS rate as high as 88% if a biologically effective dose of 100 Gy or more was administered. In an updated study, 99 of 257 medically operable patients treated with SABR showed double the 5-year OS as compared with inoperable patients (65% vs 35%; P<.0001), although 42 of the 257 patients (16%) received SABR with a biologically effective dose less than 100 Gy and had worse OS. Later publications from the same group further strengthened this evidence, as did population modeling studies. Further data became available using propensity-matched analyses, which were not without corresponding flaws. These demonstrated no difference in outcomes for operable patients.

Unfortunately, despite encouraging early data on SABR for surgically treatable patients in multiple published studies, no phase III data are available, and 3 major phase III trials, the STARS, ROSEL, and ACOSOG Z4099/RTOG 1021 trials, closed due to poor accrual. In addition to very encouraging preliminary results from 2 phase II trials, arguably the strongest data to date comes from a recent pooled analysis of the STARS and ROSEL trials. The number of patients was relatively small (n=31 for SABR; n=27 for lobectomy), but after a follow-up of 40.2 months, no differences were seen in recurrence-free survival or locoregional control. Importantly, the data also display no differences in distant recurrences, the relatively high amounts of which have troubled previous SABR studies. Additionally, patterns of failure analyses demonstrate that distant failures are significantly more common than regional nodal...
failures. Most importantly, the authors found an increase in 3-year OS with SABR (95% vs 79%; \( P = .037 \)), a finding that heretofore has not been found in the literature; the authors did state that the OS difference was present in the 36 STARS patients but not the 22 ROSEL patients.

The presence of more than 2 decades of relatively consistent data has thus been pointing in the same direction, demonstrating that SABR could be equivalent to surgery for operable patients. In fact, serious consideration for SABR versus lobectomy in very elderly but operable patients (the definition of “very elderly” being extremely variable and clinician-dependent) is not uncommon. However, though enthusiasm is mounting along with the data, several issues with existing data that prevent entirely fair comparisons between SABR and surgery must be addressed.

First, there are issues of semantics between existing studies. In some studies, terminology such as *marginally operable* or *borderline operable* is often used. Outcomes for these patients seem to be distinctly closer to those of operable patients, but a central problem in reporting these results is a lack of standardized definition. Thus these classifications represent an elusive oncologic gray area that can potentially skew data. Second, the term *lobar control* has not been used in many studies, but given that many surgeries are lobectomies and that ipsilateral lobar recurrences can happen, the classification of an ipsilateral lobar recurrence could feasibly be counted as local or another type of recurrence. Thus, standardization and distinction between local control and lobar control is important, especially considering that SABR has been noted to have local control rates upward of 90%. It is also predictably difficult to ascertain the presence of new lung nodules as second primary cancers versus metastases.

Other items that can skew outcomes results include the known difficult distinction between postoperative or post-SABR scar tissue versus suspicion of residual or recurrent tumor. Although some centers rarely pursue repeat biopsies, the pursuit of such can lead to predictable biases of reporting outcomes. Analyses have been performed on how best to address these issues, but the issue is currently far from resolved. Additionally, patient treatment despite lack of a biopsy is performed at many centers, particularly in some European centers. It is not uncommon to see data with fewer than half the patients having tissue diagnosis of invasive cancer before treatment. Proceeding without tissue diagnosis means risking that a proportion, albeit small, of patients with preinvasive conditions such as adenocarcinoma in situ will be treated, positively impacting and skewing survival data accordingly. Although reports on how to address the tissue diagnosis issue are available, it is not easy to extrapolate these data to the United States, where risks of PET-positive granulomatous diseases such as histoplasmosis are manyfold more common than in Europe. It is also noteworthy that in light of the OS benefit of SABR in the aforementioned pooled analysis of the STARS and ROSEL trials, many of these patients, per protocol, were not required to have tissue diagnosis.

Yet another issue complicating matters is the renewed interest in surgical sublobar resections for early-stage lung cancer, which have fewer postoperative complications than lobectomies. Some data—although not without flaws—suggest that carefully selected patients with early-stage disease could potentially have relatively equivalent outcomes with this procedure compared with lobectomy. Large-scale analyses are awaited with long-term follow-up comparing sublobar resection with SABR, analyzing outcomes, morbidity, and mortality. Sublobar resection offers an increasingly popular option for some patients, which could hinder enrollment in future phase III trials comparing SABR and lobectomy (the current standard of care for early-stage operable disease).

Although many unresolved questions and concerns remain for treatment of patients with early-stage operable disease, it is difficult to ignore the increasing
number of consistent data supporting the efficacy of SABR in this population. Several other issues will need to be ironed out, such as whether larger tumors (nearing 5 cm) should be managed differently, and whether biologically effective dose-escalation over a higher threshold (eg, 150 Gy) offers improved outcomes. However, clinicians must interpret these data with great caution, not only because much of the evidence is retrospective, but also in light of the fact that completed, large-volume phase III study results may not be available for some time. Until then, the controversy will remain regarding in which subgroups of operable patients SABR is appropriate. At this point, full results of the phase II trials JCOG 0403 and RTOG 0618 are anticipated, and my sincere hope is that more and more promising data for SABR in operable patients encourages placement of these patients into phase III trials to find a definitive answer to this important question in the oncology community.

References