Curing Operable Stage I Non-Small Cell Lung Cancer With Stereotactic Ablative Body Radiotherapy: The Force Awakens

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Disclosures of potential conflicts of interest may be found at the end of this article.

In this study, the median overall survival (OS) was 23.6 months for surgery and 22.2 months for chemoradiotherapy ($p = .24$), despite a significantly longer median progression-free survival (PFS) of 12.8 months versus 10.5 months, respectively ($p = .017$). There was an 8% rate of treatment-related death in the surgical arm versus 2% in the chemoradiotherapy arm.

In a contemporaneous European study (European Organisation for Research and Treatment of Cancer [EORTC]-08941 [4]) comparing radiotherapy with surgery after induction chemotherapy, OS did not differ between arms ($p = .596$). In this case, there was no difference in PFS either ($p = .605$). The results of INT-0139 and EORTC-08941 thus began to erode the authority of the one piece of level II evidence in favor of surgery for nonmetastatic NSCLC. Chemoradiotherapy alone was now acknowledged—to the surprise of many—as a curative treatment option in stage IIIA disease [5]. More recently, these findings have gathered further support from a German cooperative group study [6] that, although unable to complete recruitment (256 of a planned 500 patients were enrolled), reported no difference in OS ($p = .34$) or PFS ($p = .75$) between the surgery and chemoradiotherapy arms.

If radiotherapy could now cure the same proportion of patients with locally advanced disease as surgery, what might be possible by using modern radiotherapy techniques in patients with stage I NSCLC? A recent provocative publication by Chang et al. [7] suggests that stereotactic ablative body radiotherapy (SABR) may indeed achieve outcomes similar to those seen with surgery in node-negative disease. SABR is one of the modern success stories of the management of early-stage lung cancer. The SABR technique is typically delivered in abbreviated courses of up to five outpatient sessions, dramatically reducing the inconvenience of long courses of conventionally fractionated RT. Population-based data from The Netherlands indicates that the survival of elderly patients with stage I lung cancer improved significantly after 2005 [8], a finding attributed to the increasing availability of SABR for these patients.

In this paper, we review the data addressing the role of SABR in patients with operable NSCLC. We interpret the
available evidence, despite its limitations, as at least indicating that SABR for peripheral stage I NSCLC is not only well-tolerated, safe, and associated with negligible mortality but also possibly equally effective as surgery in operable cases. We would argue that a state of clinical equipoise exists, and that, in spite of the impediments, the time is ripe for an adequately powered study to settle the question of surgery or SABR once and for all.

Randomized Data Comparing Surgery With SABR

The current paucity of high-level evidence reflects the challenges of randomly assigning patients between two treatments provided by competing medical specialties. Health care systems that reward clinicians according to the number of procedures they perform discourage them to submit their patients to the process of randomization and subsequent possible threat of reassignment to an alternate competing modality of treatment. Furthermore, radiotherapy and surgery are such vastly differing treatments that patients may themselves have strong preferences for one or the other depending on their preconceptions of which one may be more effective, more toxic, or both.

It is little wonder, then, that the scientific landscape is a graveyard of failed phase III trials. The American College of Surgeons Oncology Group in collaboration with the Radiation Therapy Oncology Group devised the Z4099/1021 randomized phase III study of sublobar resection versus SABR in high-risk operable patients with stage I NSCLC. This study had a target accrual of 420 patients in a noninferiority design and, despite being open in more than 35 centers, was closed after 24 months because of poor accrual in 2013. The Dutch Radiosurgery Or Surgery for operable Early stage non-small cell Lung cancer (ROSEL) study randomly assigned patients with operable stage IA NSCLC of any risk to surgery or SABR and was also terminated because of poor accrual in 2013. This study had a noninferiority design with a required sample size of 960 but managed to recruit only 22 patients. Similarly, the industry-sponsored study Stereotactic Radiotherapy vs. Surgery (STARS) compared CyberKnife (Accuray, Sunnyvale, CA, http://www.accuray.com) SABR to surgery and had an ambitious target sample size of 1,030 patients. However, it closed after recruitment of only 36 patients. A modified protocol is open for recruitment at the MD Anderson Cancer Center in Houston, TX, with a relatively modest accrual target of 80 patients (ClinicalTrials.gov ID NCT02357992).

Fortunately, the principal investigators of the prematurely terminated STARS and ROSEL studies pooled their data for analysis so that their efforts were not entirely wasted. The results of this pooled analysis of 58 patients significantly challenged the surgical paradigm [7]; the estimated overall survival at 3 years was 95% in the SABR group compared with 79% in the surgery group (hazard ratio [HR], 0.14; log-rank

Comparative Data of Surgery Versus SABR

Given the dearth of randomized evidence comparing SABR and surgery, several investigators have attempted comparative effectiveness studies addressing both modalities of treatment. However, comparison of surgical cohorts with radiotherapy cohorts is challenging because of inherent biases resulting from differences in patient comorbidity and staging of disease extent. In an effort to compensate for these and other biases, the authors have used strategies such as propensity-score matching, match-pair analysis, Markov modeling, cost-effectiveness, and meta-analytic methods.

Three Surveillance, Epidemiology, and End Results (SEER) database comparative effectiveness studies have been performed using propensity matching to limit treatment selection bias based on patient characteristics. Shirvani et al. [9] analyzed data from 10,923 patients aged ≥66 years with stage I NSCLC treated from 2001 to 2007 from the SEER database. SABR was associated with a lower risk for death at 6 months (HR, 0.48), whereas lobectomy had better long-term survival in fit patients (HR, 0.71). A second analysis from this group based on patients treated between 2003 and 2009 [10] also indicated similar survival on propensity score-matching analysis for surgery and SABR (HR, 1.01). These findings of lower risk for early mortality but inferior long-term survival with SABR compared with surgery in an unadjusted population were further confirmed in an additional SEER database analysis [11] using a narrower time window (from 2007 to 2009). Overall mortality was lower with SABR versus surgery at 3 months (2.2% vs. 6.1%), but by 24 months overall mortality was higher with SABR (40.1% vs. 22.3%). Additionally, two meta-analyses of nonrandomized data have directly compared SABR and surgery. In a systematic review of 45 publications of stage I NSCLC from 2006 to 2013, there was no difference in survival at 2 years (70% vs. 68%) or local control for 3,201 SABR patients and 2,038 surgery patients [12]. In an analysis of data from 2000 to 2012, 40 studies of SABR with 4,850 patients and 23 studies of surgery with 7,071 patients were included. The mean unadjusted overall survival at 5 years with SABR was 41.2% compared with 66.1% with lobectomy. After adjustment for age and proportion of operable patients, SABR and surgery had similar estimated overall and disease-free survival [13]. In general, the main conclusion from the 12 comparative effectiveness studies published to date is that there are similar outcomes when comparing SABR and surgery, especially after taking into

SABR Versus Surgery for Stage I NSCLC

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account competing risks for death associated with advanced age and increased comorbidities [14].

**Single-Arm Studies of SABR in Operable Patients**

Although comparative effectiveness studies have attempted to compensate for imbalances between SABR and surgical cohorts, outcomes from noncomparative single-arm studies in operable patients receiving SABR are also informative. A major bias of comparative effectiveness analyses is that they exclude clinically node-negative patients who are pathologically upstaged to N1 status in the surgical cohorts, defeating the intention-to-treat principle in stage I patients and thus inevitably favoring the surgical comparator arm [15]. In addressing the largely retrospective literature of patients who are receiving SABR but are medically operable, patient survival is considerably higher than typically reported for inoperable patients, with evidence summarized in Table 1. A key factor in the interpretation of these outcomes is the relatively elderly patient cohorts reported, with median ages uniformly in the seventh decade of life.

Despite this, impressive 3-year overall survival rates were reported, ranging from 76% to 86%; when reported, 5-year OS ranged from 51% to 72%. Treatment-related mortality rates in this elderly cohort ranged from 0% to 0.5%, except for a study in which 2 patients (1.1%) died of causes that could not be excluded as resulting from treatment. By comparison, data from the National Lung Cancer Audit of 10,991 patients from the U.K. undergoing surgery from 2004 to 2010 indicates that

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**Figure 1.** Clinical outcomes of the pooled Radiosurgery or Surgery for Operable Early-Stage Non-Small Cell Lung Cancer/Stereotactic Radiotherapy vs. Surgery study analysis [7]. (A): Overall survival by treatment arm. (B): Time to local recurrence by treatment arm. Abbreviations: SABR, stereotactic ablative body radiotherapy; E, events; N, number of patients.
enroll patients on the trial, reasons given included the due to poor patient accrual [19]. When 94 NSABP investigators surgery plus adjuvant radiation. The trial risked early closure mastectomy, breast conserving surgery, or breast conserving Breast Project (NSABP)-B06 study. Initially the trial was opened diverse randomization arms is the National Surgical Adjuvant decision-making control they desire.

In light of the failure of recent randomized trials to recruit, it is an opportune time to reflect about why this has occurred. There is no doubt that the question is of major interest to patients, clinicians, and health care funders. Stage I NSCLC is common and is likely to become more so with the introduction of screening programs. The population that could benefit is large. Yet it is estimated that up to half of all phase III oncologic trials close because of inadequate accrual. Analyses of causes for poor accrual demonstrate that major barriers to enrollment are “patient dislike of randomization” and “loss of control over the decision making process” [17, 18]. Ironically, it is only through being informed by the knowledge obtained from randomized studies that the patient achieves the informed decision-making control they desire.

A previous success story of overcoming the challenge of diverse randomization arms is the National Surgical Adjuvant Breast Project (NSABP)-B06 study. Initially the trial was opened using a classical trial design, with patients randomized to total mastectomy, breast conserving surgery, or breast conserving surgery plus adjuvant radiation. The trial risked early closure due to poor patient accrual [19]. When 94 NSABP investigators were mailed a questionnaire and asked why they chose not to enroll patients on the trial, reasons given included the “doctor-patient relationship would be affected by the randomization” and concerns about obtaining informed consent in which the options were amputation or retention of the breast [20]. The study was amended, with prerandomization performed on all eligible patients before explanation of a patient’s allocated treatment arm and then obtaining of informed consent. The patients maintained their right to accept or decline the allocated treatment, a method originally described by Zelen [21]. Within a year after the protocol was amended, monthly patient accrual doubled and the trial was not only successfully completed but also practice-changing [19, 22].

Several further phase III studies comparing surgery to SABR for early-stage NSCLC are underway, using a variety of randomization techniques. The STABLE-MATES trial from the United States (ClinicalTrials.gov ID NCT02414334) is recruiting, with a projected sample size of 272 patients. This study also addresses the high-risk operable cohort but is using Zelen’s prerandomization method, described in the preceding paragraph, with an expected target of 218 patients. The SABRTOOTH trial (ISRCTN 13029788) is a U.K. multicenter, 2-group individually randomized controlled study of patients with peripheral stage NSCLC considered at higher risk from surgery. To maximize impartiality, information regarding the treatment arms is provided before randomization by the respiratory physician, and consent is subsequently taken by a trained research nurse. The patient is then referred to the radiation oncologist or thoracic surgeon after randomization. The final expected sample size is 690 patients. The Veterans Affairs VALOR (Lung cancer surgery Or stereotactic Radiotherapy) trial is a further study planned for the near future, in this case using a superiority study design.

**Patient Autonomy**

At present it is clear that patients (and likely referring clinicians) with stage I NSCLC are not appropriately aware of SABR as a treatment option. A recent qualitative study of patients undergoing lung surgery in the U.K. found that “there was desire to ‘get rid of cancer’ and perception of no alternative to surgery.” Despite being aware of radiotherapy and chemotherapy as treatments for cancer, the majority reported that surgery was the only treatment option that had been discussed [23]. In a U.S. study from Los Angeles, of 102 patients treated with SABR, 56% had no prior knowledge of SABR before meeting a radiation oncologist. Among a subset of 39 who had had prior lung surgery, 80% were more satisfied with SABR than surgery and 90% would have rather had SABR than surgery as it was performed for their previous stage I NSCLC [24]. The very definition of “operable” is fiendishly

| Author, Year [Reference] | Design            | Patients (n) | Median age (yr) | Treatment-related mortality rate (%) | 3-yr OS (%) | 5-yr OS (%) |
|--------------------------|-------------------|--------------|----------------|--------------------------------------|-------------|-------------|
| Uematsu et al., National Defense Medical College, Tokozawa, Japan, single institution, 2001 [31] | Retrospective | 29 | 71 | 0 | 86 |
| Lagerwaard et al., VU University, single institution, 2011 [32] | Retrospective | 177 | 76 | 30-day rate, 0; potentially 1.1 overall | 85 | 51 |
| Nagata et al., Ishikura et al., JCOG 0403, multi-institutional, 2010–2011 [33, 34] | Prospective phase II | 64 | 79 | 0 | 76 |
| Timmerman et al., RTOG 0618, 2013 [35] | Prospective phase II | 26 | 72 | 0 | 77 |
| Onishi et al., Japan, multi-institutional, 2011 [36] | Retrospective | 87 | 74 | 0 | 80 | 62–72 |
| Komiyama et al., Japan, multi-institutional, 2015 [37] | Retrospective | 661 | 75 | 0.5 | 79 |

Abbreviations: JCOG, Japan Clinical Oncology Group; OS, overall survival; RTOG, Radiation Therapy Oncology Group.
nebulous and obfuscates patient choice by conveying the sense of primacy for the surgical approach, a presumption that may not be warranted. In the future, as an increasingly educated public becomes aware of SABR, it is likely that more patients will seek SABR as a noninvasive alternative to surgery and become less accepting of randomization.

**The Debate Continues**

The debate will continue until further randomized clinical trials are completed. Criticisms regarding the small sample size of the only reported randomized evidence to date by Chang et al. [7] are understandable. Predictably, the surgical community has reacted defensively and has dismissively relegated these findings to no more than that of “an unplanned publication” and “discovery” of an interesting survival trend [25]. Others have called for prospective registry-based comparisons [26]; however, this strategy circumvents the intention-to-treat principle because registries will likely record only those stage I cases that are pathologically node-negative in the surgical group as compared with those who are clinically node negative in the SABR arm. A universal criticism is the small final sample size of the pooled analysis in question. Somewhat ironically, the very evidence that established surgery as the standard of care—the Hammersmith trial [1]—had an identical sample size of 58 patients!

History has demonstrated that the natural evolution of investigation and treatment of disease is toward less invasive and aggressive approaches. In the context of breast cancer, we have transitioned from Halstedian mastectomy to lumpectomy and breast irradiation, although this approach initially met significant resistance as described earlier in this paper. Cardiothoracic surgery has seen nodal assessment by endobronchial ultrasonography largely supersede mediastinoscopy [27, 28] and percutaneous coronary intervention become more prevalent at the expense of surgical coronary artery bypass [29]. Now, transcatheter aortic valve implantation is being evaluated in place of surgical aortic valve replacement [30]. It is little wonder, then, that the topic of SABR for operable patients has evoked such charged responses within the cardiothoracic community. However, undeterred by preconceptions and without rancor, we need to urgently establish what is best for our patients. There is a very real risk that noninvasive intervention with SABR may pervade clinical management without definitive high-level evidence to support it. Even if SABR proves to be as effective as surgery for stage I NSCLC, surgery will still play a key role in the context of patients who prefer surgery, whose disease recurs after SABR and can be surgically salvaged, and others whose tumors may be too large or anatomically unsuitable for SABR. The oncological community has an ethical obligation to successfully complete randomized studies of surgery versus SABR for the benefit of our patients while clinical equipoise still exists.

**Conclusion**

Surgery remains the standard of care for peripheral stage I NSCLC. However, the available body of evidence is highly suggestive that SABR has survival outcomes similar to those of surgery. Notwithstanding the limited information on patient-reported outcomes and quality of life, SABR compares favorably to surgery because it is noninvasive and associated with relatively few treatment-related complications. A new era of much-needed studies with novel randomization methods is upon us, and provided they are supported without prejudice by all specialty groups involved, we hope this contentious issue will be finally resolved.

“...a stand can be made against invasion by an army; no stand can be made against invasion by an idea.” *Histoire d’un Crime* (1877) pt. 5, sect. 10

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