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.

"There is one thing stronger than all the armies in the world, and that is an idea whose time has come." *Nation*, April 15, 1943

SURGERY AS THE STANDARD OF CARE

For more than half a century, surgery has been entrenched as the standard of care for patients with early-stage operable non-small cell lung cancer (NSCLC). The evidence underpinning this practice is the trial performed at the Hammersmith Hospital in London between 1954 and 1958, in which 58 patients without clinical or plain radiographic evidence of mediastinal involvement were randomly assigned to radiotherapy (RT) or surgery [1]. Nineteen of the patients had "oat cell or anaplastic carcinomas," and the remainder had squamous cell or adenocarcinoma. At 1 year the survival favored the patients allocated to radiotherapy (64% vs. 43%), but at 4 years only 7% of the radiotherapy patients were alive compared with 23% treated by surgery. The survival advantage was confined to the subset of 37 patients with squamous histology and was statistically significant ($p = .05$). It would be almost another 30 years, in the U.K. at least, before the curative potential of radiotherapy in NSCLC would be investigated again. In the meantime, the outcomes after surgery steadily improved because of advances in staging, preoperative assessment, surgical technique, and postoperative care. The surgeon could accurately stage the patient and establish completeness of resection. When this was achieved, locoregional progression was uncommon, occurring at a rate of approximately 2% per year in patients randomly assigned to lobectomy in a trial for peripheral stage I non-small cell lung cancer [2].

However, in patients with more locally advanced NSCLC, the benefits of local control achieved through surgery are offset by a not insignificant risk for early mortality. This was sufficiently severe in one recent trial comparing induction chemoradiation and surgery versus chemoradiotherapy for stage IIIA disease (intergroup trial [INT] 0139 [3]) that it negated any survival advantage that might have resulted from the better local control observed in the surgical treatment arm.

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 $p = .037$) (Fig. 1A). The 3-year rate of freedom from local recurrence was similar at 96% versus 100% ($p = .44$) (Fig. 1B), respectively. There were clear differences in toxicity profiles; 3 (10%) patients in the SABR group had grade 3 treatment-related adverse events and no grade 4 events, whereas 1 (4%) patient in the surgical group died of postoperative complications and 12 (44%) patients experienced grade

3–4 treatment-related adverse events. The authors concluded, "SABR is better tolerated and might lead to better overall survival." Although the former claim is difficult to dispute because SABR is a noninvasive outpatient procedure with consistently low reported rates of treatment-related morbidity or mortality, the latter conclusion is at best hypothesis generating. The dissemination of these results into routine clinical practice is hampered by the failure of both trials to meet recruitment targets and thus an inability to confidently reject a type I error. Additionally, 14 of the patients proceeded to treatment without histological confirmation of malignancy, 8 of whom received SABR.

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
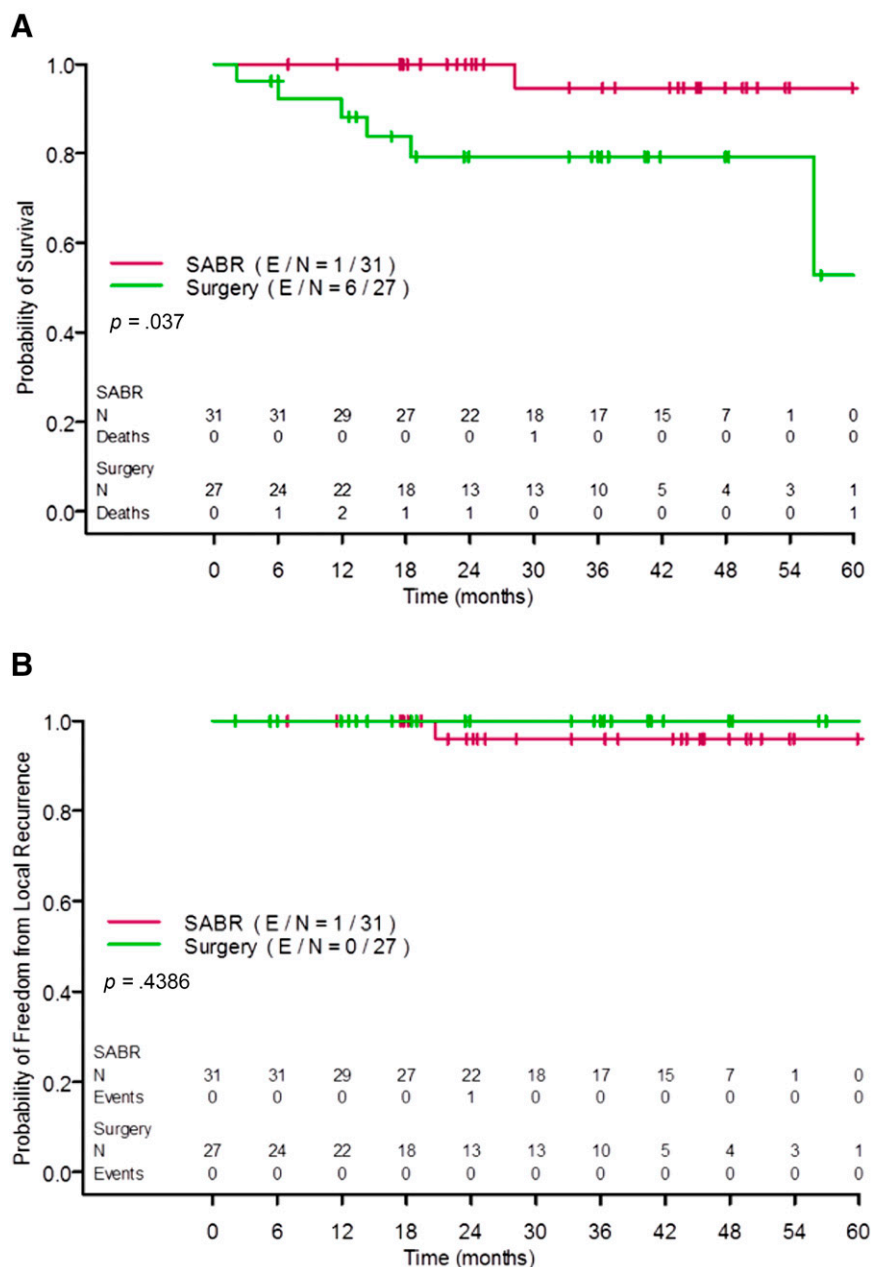
Figure 1. Clinical outcomes of the pooled Radiosurgery or Surgery for Operable Early-Stage Non-Small Cell Lung Cancer/Stereotactic Radiotherapy vs. Surgery study analysis [7]. **(A):** Overall survival by treatment arm. **(B):** Time to local recurrence by treatment arm.
Abbreviations: SABR, stereotactic ablative body radiotherapy; E, events; N, number of patients.

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

Table 1. Overall survival and treatment-related mortality in patients with operable stage I lung cancer treated with stereotactic ablative body radiotherapy

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.

age is strongly predictive of postoperative mortality even after adjustment for demographic characteristics, stage, and patient comorbidity ($p < .001$) [16]. Overall, 7.3% of patients aged 70–74 years and 8.2% of those aged 75–79 years died within 90 days of surgery.

FUTURE STUDIES ADDRESSING SURGERY VERSUS SABR

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 (ClinicalTtrials.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

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

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: Shankar Siva

REFERENCES

1. Morrison R, Deeley T, Cleland W. The treatment of carcinoma of the bronchus: A clinical trial to compare surgery and supervoltage radiotherapy. Lancet 1963;281:683–684.

2. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Ann Thorac Surg 1995;60:615–622; discussion 622–623.

3. Albain KS, Swann RS, Rusch VW et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomised controlled trial. Lancet 2009;374:379–386.

4. van Meerbeeck JP, Kramer GW, Van Schil PE et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442–450.

5. Bryant AS, Rudemiller K, Cerfolio RJ. The 30-versus 90-day operative mortality after pulmonary resection. Ann Thorac Surg 2010;89:1717–1722; discussion 1722–1723.

6. Eberhardt WEE, Pöttgen C, Gauler TC et al. Phase III study of surgery versus definitive concurrent chemoradiotherapy boost in patients with resectable stage IIIa(N2) and selected IIIb non-small-cell lung cancer after induction chemotherapy and concurrent chemoradiotherapy (ESPATUE). J Clin Oncol 2015;33:4194–4201.

7. Chang JY, Senan S, Paul MA et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: A pooled analysis of two randomised trials. Lancet Oncol 2015;16:630–637.

8. Palma D, Visser O, Lagerwaard FJ et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: A population-based time-trend analysis. J Clin Oncol 2010;28:5153–5159.

9. Shirvani SM, Jiang J, Chang JY et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060–1070.

10. Shirvani SM, Jiang J, Chang JY et al. Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly. JAMA Surg 2014;149:1244–1253.

11. Yu JB, Soulos PR, Cramer LD et al. Comparative effectiveness of surgery and radiosurgery for stage I non-small cell lung cancer. Cancer 2015;121:2341–2349.

12. Solda F, Lodge M, Ashley S et al. Stereotactic radiotherapy (SABR) for the treatment of primary non-small cell lung cancer; systematic review and

comparison with a surgical cohort. Radiother Oncol 2013;109:1–7.

13. Zheng X, Schipper M, Kidwell K et al. Survival outcome after stereotactic body radiation therapy and surgery for stage i non-small cell lung cancer: A meta-analysis. Int J Radiat Oncol Biol Phys 2014;90: 603–611.

14. Louie AV, Rodrigues GB, Palma DA et al. Measuring the population impact of introducing stereotactic ablative radiotherapy for stage I non-small cell lung cancer in Canada. *The Oncologist* 2014;19:880–885.

15. Blackstone EH, Lauer MS. Caveat emptor: The treachery of work-up bias. J Thorac Cardiovasc Surg 2004;128:341–344.

16. Powell HA, Tata LJ, Baldwin DR et al. Early mortality after surgical resection for lung cancer: an analysis of the English National Lung cancer audit. Thorax 2013;68:826–834.

17. Schroen AT, Petroni GR, Wang H et al. Preliminary evaluation of factors associated with premature trial closure and feasibility of accrual benchmarks in phase III oncology trials. Clin Trials 2010;7:312–321.

18. Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. JAMA 2004;291:2720–2726.

19. Fisher B, Bauer M, Margolese R et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med 1985;312:665–673.

20. Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering eligible patients in a randomized clinical trial of surgery for breast cancer. N Engl J Med 1984;310:1363–1367.

21. Torgerson DJ, Roland M. What is Zelen's design? BMJ 1998;316:606.

22. Schaffner K. Ethically optimizing clinical trials. In: Kadane JB, ed. Bayesian Methods and Ethics in a Clinical Trial Design. Hoboken, NJ: John Wiley & Sons, Inc., 1996:19–63.

23. Powell HA, Jones LL, Baldwin DR et al. Patients' attitudes to risk in lung cancer surgery: A qualitative study. Lung Cancer 2015;90:358–363.

24. Shaverdian N, Wang P-C, Steinberg M et al. The patient's perspective on stereotactic body radiation therapy (SBRT) vs. surgery for treatment of early stage non-small cell lung cancer (NSCLC). Lung Cancer 2015;90:230–233.

25. Meyers BF, Puri V, Broderick SR et al. Lobectomy versus stereotactic body radiotherapy for stage I non-small cell lung cancer: Post hoc analysis dressed up as level-1 evidence? J Thorac Cardiovasc Surg 2015;150:468–471.

26. Jones DR. Do we know bad science when we see it? J Thorac Cardiovasc Surg 2015;150:472–473.

27. Ernst A, Anantham D, Eberhardt R et al. Diagnosis of mediastinal adenopathy-real-time endobronchial ultrasound guided needle aspiration versus mediastinoscopy. J Thorac Oncol 2008;3: 577–582.

28. Yasufuku K, Pierre A, Darling G et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. J Thorac Cardiovasc Surg 2011;142:1393–1400.e1391.

29. Bravata DM, Gienger AL, McDonald KM et al. Systematic review: the comparative effectiveness of percutaneous coronary interventions and coronary artery bypass graft surgery. Ann Intern Med 2007; 147:703–716.

30. Cao C, Ang SC, Indraratna P et al. Systematic review and meta-analysis of transcatheter aortic valve implantation versus surgical aortic valve replacement for severe aortic stenosis. Ann Cardiothorac Surg 2013;2:10–23.

31. Uematsu M, Shioda A, Suda A et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: A 5-year experience. Int J Radiat Oncol Biol Phys 2001; 51:666–670.

32. Lagerwaard FJ, Verstegen NE, Haasbeek CJ et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage i non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348–353.

33. Nagata Y, Hiraoka M, Shibata T et al. A phase II trial of stereotactic body radiation therapy for operable T1N0M0 non-small cell lung cancer: Japan Clinical Oncology Group (JCOG0403). Int J Radiat Oncol Biol Phys 2010;78:S27–S28.

34. Ishikura S, Ito Y, Hiraoka M. JCOG Radiation Therapy Study Group: History and achievements. Jpn J Clin Oncol 2011;41:1241–1243.

35. Timmerman RD, Paulus R, Pass HI et al. Rtog 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients. Presented at: ASCO Annual Meeting; May 31–June 4, 2013; Chicago, IL.

36. Onishi H, Shirato H, Nagata Y et al. Stereotactic body radiotherapy (SBRT) for operable stage I non–small-cell lung cancer: Can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81: 1352–1358.

37. Komiyama T, Onishi K, Shioyama HY et al. Japanese multi-institutional study of stereotactic body radiotherapy for 661 medically operable patients with stage I non-small cell lung cancer. Presented at: International Association for the Study of Lung Cancer, 16th World Conference; September 6–9, 2015; Denver, CO. Oral 19.05.

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