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A Systematic Review and Meta-Analysis of Stereotactic Body Radiation Therapy versus Surgery for Patients with Non-Small Cell Lung Cancer

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Abstract

Objective: Stereotactic body radiation therapy (SBRT) is the preferred treatment modality for patients with inoperable early-stage non-small cell lung cancer. However, comparative outcomes between SBRT and surgery for high-risk patients remain controversial. The primary aim of the present meta-analysis was to assess overall survival in matched and unmatched patient cohorts undergoing SBRT or surgery. Secondary endpoints included cancer-specific survival, disease-free survival, disease recurrence, and perioperative outcomes.

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Central Picture:

Kaplan-Meier graph of overall survival using data from matched patients with NSCLC.

Central Message:

In matched patients with early-stage NSCLC, surgery was superior to SBRT in overall survival, cancer-specific survival, disease-free survival, and freedom from disease recurrence.

Perspective Statement:

With a paucity of randomized data, observational studies have utilized propensity score matching to minimize the risk of selection bias to compare surgery versus SBRT in patients with NSCLC. This systematic review and meta-analysis identified superior mid- and long-term clinical outcomes for surgery in both matched and unmatched patient cohorts. However, periprocedural mortality was lower for SBRT.

Methods: A systematic review of relevant studies was performed through online databases using predefined criteria. The most updated studies were selected for meta-analysis according to unmatched and matched patient cohorts.

Results: Thirty-two studies were identified in the systematic review, and 23 were selected for quantitative analysis. Surgery was associated with superior overall survival in both unmatched (odds ratio [OR], 2.49; 95% confidence interval [CI], 2.10–2.94; $p < 0.00001$) and matched (OR, 1.71; 95% CI, 1.52–1.93; $p < 0.00001$) cohorts. Subgroup analysis demonstrated superior overall survival for lobectomy and sublobar resection, compared with SBRT. In unmatched and matched cohorts, cancer-specific survival, disease-free survival, and freedom from locoregional recurrence were superior after surgery. However, SBRT was associated with fewer perioperative deaths.

Conclusions: The current evidence suggests surgery is superior to SBRT in terms of mid- and long-term clinical outcomes; SBRT is associated with lower perioperative mortality. The improved outcomes after surgery, however, may be attributable at least in part to an imbalance of baseline characteristics. Future studies should aim to provide histopathological confirmation of malignancy and compare SBRT with minimally invasive anatomical resections.

INTRODUCTION

Stereotactic body radiation therapy (SBRT) is the preferred treatment modality for patients with medically inoperable early-stage non-small cell lung cancer (NSCLC).^{1, 2} Compared to conventional radiotherapy, SBRT delivers fewer fractions of high-dose radiation per fraction with increased precision, sparing the surrounding normal tissue to maximize the biologically effective dose whilst minimizing toxicity, resulting in improved local control and overall survival.^{3, 4} The accumulating clinical experience with SBRT in prospective trials has led to heightened interest among the oncology community about the comparative outcomes of SBRT versus surgical resection for early-stage NSCLC in operable patients.^{5, 6}

Recently, a retrospective pooled analysis of two prematurely terminated randomized controlled trials suggested that SBRT is better tolerated than surgery and may lead to improved overall survival.⁷ However, several study limitations necessitate caution to avoid overinterpreting these results, and there remains a paucity of robust clinical data to support the above statement, given the heterogeneity of study cohorts.^{8, 9} To address this issue, a number of studies have used propensity score matching to minimize the risk of selection bias.¹⁰ The purpose of the present systematic review and meta-analysis is to assess the clinical outcomes of SBRT versus surgery for patients with early-stage NSCLC. Primary endpoints included overall survival in matched and unmatched cohorts. Secondary endpoints included cancer-specific survival, disease-free survival, freedom from locoregional recurrence, freedom from distant recurrence, and perioperative mortality and morbidity. Each endpoint was assessed using matched and unmatched cohorts to compare relative outcomes, whenever possible. Subgroup analyses of lobectomy and sublobar resection versus SBRT were also performed for overall survival.

METHODS

Literature Search Strategy

A systematic review was performed using EMBASE and Ovid Medline, from their dates of inception to January 2018. To identify all potentially relevant studies, we combined the search terms (“SBRT” or “SABR” or “stereotactic” or “radiosurgery”) and (“NSCLC” or “non-small cell lung” or “carcinoma, non-small cell lung”) and (“surg*” or “resect*” or lobectomy) as either Medical Subject Headings or keywords. All identified articles were then assessed by applying the predefined selection criteria. A summary of search strategies and techniques has been described in detail previously.¹¹

Selection Criteria and Data Appraisal

Eligible studies for selection in the systematic review were those in which comparative overall survival was reported for patients who underwent SBRT or surgical resection for NSCLC. When institutions published duplicate studies with accumulating numbers of patients or increased lengths of follow-up, only the most complete or updated reports were included for meta-analysis. Abstracts, case reports, conference presentations, editorials, expert opinions, and publications not written in English were excluded. Data were extracted from article texts, tables, figures, and supplementary material. Two investigators (D.W. and C.D.C.) independently reviewed each retrieved article. Discrepancies between the two reviewers were resolved by discussion and consensus. To assess the quality of the non-randomized studies, the Newcastle-Ottawa scale was used to evaluate the selection, comparability, and outcomes reported in each study, with 0 – 3 stars indicating poor quality, 4 – 6 stars indicating moderate quality, and 7 or more stars indicating high quality.¹²

Statistical Analysis

When more than four studies provided relevant data on the same predetermined endpoint, meta-analysis was performed by combining the reported clinical outcomes of individual studies using a random effect model. Odds ratio (OR) and standard error were extracted or calculated from each study using methods described by Parma and Tierney.^{13, 14} When calculations were not possible because of inadequate data, ORs were estimated using Kaplan-Meier graphs. I^2 statistic was used to estimate the percentage of total variation across studies attributable to heterogeneity rather than chance. Meta-analysis was performed using Review Manager (version 5.1.2, Cochrane Collaboration, Oxford, United Kingdom). All *P* values were two-sided, and *P* = 0.05 was considered to indicate statistical significance.

Individual patient survival data were reconstructed using Guyot’s iterative algorithm to solve the Kaplan-Meier equations originally used to produce the published graphs.¹⁵ This algorithm used digitalized Kaplan-Meier curve data to find numerical solutions to the inverted Kaplan-Meier equations, and it assumes a constant, noninformative censoring mechanism. The reconstructed patient survival data were then aggregated to form the combined survival curve. Reconstructed Kaplan-Meier analyses were conducted using R (version 3.2.5, R Core Team, Vienna, Austria).

RESULTS

Quantity and Quality of Trials

Applying the predefined inclusion criteria, we identified a total of 2211 records through the electronic search. After identification of additional records through other sources and removal of duplicate studies, 1744 articles remained for screening. Of these, 1698 were excluded on the basis of title and abstract content. After review of the full text of the remaining 46 articles, 32 were found to meet the selection criteria for the systematic review.^{7, 16–46} These included one retrospective pooled analysis of two randomized controlled trials and 31 observational studies, of which 24 provided data on propensity matched populations. By selecting the most complete and updated studies from each institution or database, we identified 23 studies for quantitative meta-analysis. Quality assessment using the Newcastle-Ottawa Scale reported scores that ranged from 5 – 8 points, with a median of 6 points, indicating moderate quality overall. A summary of the study selection process is presented in the PRISMA chart in Supplementary Figure 1, and a summary of each study, with detailed characteristics, is presented in Table 1.

Propensity Score Matching

The systematic review identified 24 studies that used propensity score matching by statistically balancing a number of covariables, which can be categorized into patient characteristics, preoperative risk factors, and tumor characteristics. The most commonly used factors included age; gender; Charlson comorbidity index; performance status; pulmonary function test; size, stage, location, and histologic profile of the tumor; and the preprocedural use of positron emission tomography. A summary of all the chosen covariates for propensity matched studies selected for meta-analysis is presented in Table 2. When individual studies used more than one caliper for comparison between treatment groups, data were derived from the most detailed comparison.

Patient Characteristics

A summary of baseline characteristics of matched patients selected for meta-analysis—including age, gender, SBRT regimen, and surgical procedure details—is presented in Table 3. A summary of these details for unmatched patients is presented in Supplementary Table 1. In brief, the interquartile range of ages for matched patients was 71–78 years for those who underwent SBRT and 68–78 years for those who underwent surgery. Gender variations were noted to be significantly different among studies, with four studies, primarily from military institutions or registries, reporting study populations comprising <10% females.^{25, 26, 33, 46} SBRT regimens varied in dosage and fractions among centers and within each institution, depending on the location, size, and type of the tumor. When resection type was specified, lobectomies accounted for >60% of resections in the studies selected for meta-analysis, with sublobar resections accounting for the majority of the remaining surgical procedures. The use of video-assisted thoracoscopic surgery (VATS) varied among reports, with four studies only reporting on VATS procedures.^{16, 33, 37, 43} A summary of histopathological details and clinical staging for the matched SBRT and surgical patients is presented in Table 4. A summary of these details for unmatched patients is presented in Supplementary Table 2. In brief, adenocarcinoma and squamous cell carcinoma were the most common types of

NSCLC. Up to 70% of patients who underwent SBRT did not have a pretreatment pathological diagnosis of NSCLC.³⁶ However, the proportion of patients who underwent SBRT without histopathological confirmation appeared to differ between European centers and institutions in the United States. Histopathological demonstration of malignancy was confirmed in >90% of surgical patients in all selected studies. In regard to clinical staging, 71% to 84% of matched patients who underwent SBRT had stage IA disease, and 16% to 29% had stage IB disease. For matched patients who underwent surgery, 70% to 82% had stage IA disease, and 18% to 34% had stage IB disease (staged according to the 7th edition of the TNM classification for NSCLC).⁴⁷

Overall Survival

Sixteen studies provided comparative overall survival outcomes on 10,333 patients who underwent SBRT and 142,293 unmatched patients who underwent surgical resection. Fourteen studies reported overall survival for 8946 patients who underwent SBRT and 8942 matched patients who underwent surgery. The unmatched studies demonstrated a significantly superior survival outcome after surgery, compared with SBRT (OR, 2.49; 95% confidence interval [CI], 2.10–2.94; $p < 0.00001$; $I^2 = 86\%$; Figure 1A). When the matched cohorts were compared, overall survival remained superior for surgery, compared with SBRT (OR, 1.71; 95% CI, 1.52–1.93; $p < 0.00001$; $I^2 = 63\%$; Figure 1B). Six studies in which resection type was specified reported unmatched patients who underwent SBRT or lobectomy, demonstrating superior survival outcomes after lobectomy (OR, 2.68; 95% CI, 2.04–3.53; $p < 0.00001$; $I^2 = 84\%$; Supplementary Figure 2). The superiority of lobectomy for overall survival persisted when matched patients from eight studies were compared (OR, 1.61; 95% CI, 1.23–2.12; $p = 0.0006$; $I^2 = 77\%$; Supplementary Figure 3). Six studies compared unmatched patients who underwent SBRT or sublobar resection and found superior outcomes after sublobar resection (OR, 1.54; 95% CI, 1.36–1.75; $p < 0.00001$; $I^2 = 32\%$; Supplementary Figure 4). There was an insufficient number of studies comparing matched patients who underwent SBRT or sublobar resection to conduct a meta-analysis. A reconstructed Kaplan-Meier graph of overall survival, using aggregated data on matched patients who underwent SBRT versus surgery, is shown in Figure 2.

Cancer-Specific Survival

Eight studies provided comparative data on cancer-specific survival for unmatched patients who underwent SBRT or surgery, demonstrating significantly superior outcomes after surgery (OR, 2.44; 95% CI, 1.86–3.19; $p < 0.00001$; $I^2 = 58\%$; Supplementary Figure 5). Eight studies also presented cancer-specific survival data on matched patients, showing superior outcomes after surgery (OR, 1.78; 95% CI, 1.28–2.48; $p = 0.0006$; $I^2 = 51\%$; Figure 1C). A reconstructed Kaplan-Meier graph of cancer-specific survival, using aggregated data on matched patients who underwent SBRT versus surgery, is shown in Figure 3.

Disease-Free Survival

Five studies provided comparative data on disease-free survival for unmatched patients who underwent SBRT or surgery, demonstrating significantly superior outcomes after surgery (OR, 2.13; 95% CI, 1.65–2.75; $p < 0.00001$; $I^2 = 0\%$; Supplementary Figure 6). When the analysis was limited to matched patients, seven studies demonstrated superior disease-free

survival in the surgical cohort (OR, 1.83; 95% CI, 1.06–3.16; $p=0.03$; $I^2=82\%$; Supplementary Figure 7).

Freedom from Disease Recurrence

Six studies provided comparative data on locoregional recurrence for unmatched patients who underwent SBRT or surgery, demonstrating significantly superior outcomes after surgery (OR, 5.44; 95% CI, 1.68–17.56; $p<0.005$; $I^2=87\%$; Supplementary Figure 8). When the analysis was limited to matched patients, six studies demonstrated superior locoregional recurrence rates in the surgical cohort (OR, 2.91; 95% CI, 1.49–5.71; $p=0.002$; $I^2=0\%$; Supplementary Figure 9).

Five studies reported distant recurrence for unmatched patients, showing a nonsignificant trend favoring surgery over SBRT (OR, 1.50; 95% CI, 0.96–2.34; $p=0.07$; $I^2=60\%$). There was an insufficient number of studies comparing matched patients who underwent SBRT versus surgery to conduct a meta-analysis.

Periprocedural Morbidity and Mortality

Periprocedural mortality was defined as death within the same admission or within 30 days of SBRT or surgery. For matched patients, the reported periprocedural mortality was 0% for SBRT and 0% to 8% (interquartile range 0% to 3.25%) for surgery. Periprocedural morbidities varied in nature and frequency after the two treatment modalities. The most commonly reported morbidities after SBRT were fatigue, radiation pneumonitis, chest pain, and rib fractures. The most commonly reported morbidities after surgery were prolonged air leak, pneumonia, pulmonary embolism, cardiac arrhythmia, and myocardial infarction. Summaries of the reported periprocedural mortality and morbidity outcomes for matched and unmatched patients are presented in Supplementary Tables 3 and 4, respectively.

DISCUSSION

Encouraging outcomes of SBRT compared to conventional radiotherapy has led to a paradigm shift in the management of patients with early-stage NSCLC who are considered inoperable surgical candidates.^{3, 48, 49} Although there is currently no class I evidence to compare SBRT with surgical resection, recent guidelines from the American Society of Radiation Oncology, endorsed by the American Society of Clinical Oncology, recommend that SBRT should be considered for all patients with stage I NSCLC who are considered high risk for surgery.^{50, 51} With the increasing prevalence of lung cancer screening programs and an aging population with increased co-morbidities, there is a growing number of ‘high risk’ patients diagnosed with resectable NSCLC.⁵² There is an urgent need to clearly delineate the periprocedural and long-term clinical outcomes of these two modalities to help refine the treatment selection process for this group of patients.

The present systematic review identified 32 comparative studies with overall survival outcomes for SBRT versus surgical resection, and patients from the most updated and complete studies were divided into unmatched and matched cohorts for meta-analysis. Key findings included statistically superior outcomes for surgery for overall survival, cancer-specific survival, disease-free survival, and freedom from locoregional disease recurrence, in

both unmatched and matched cohorts. There was a trend favoring surgery for freedom from distant disease recurrence, but this finding was not statistically significant. After matching was performed, ORs were reduced relative to the unmatched comparisons but remained in favor of surgery. This reduction in the magnitude of benefits after matching suggests that some of the long-term clinical outcomes favoring surgery may result from an imbalance in baseline patient characteristics, preoperative comorbidities, or tumor characteristics, rather than treatment efficacy. Nonetheless, it should be noted that the present study identified the most comparable cohorts in the current literature and demonstrated that surgery remained superior to SBRT for mid- and long-term outcomes when analysis was limited to only matched patients. Subgroup analysis of lobectomy versus SBRT demonstrated superior overall survival outcomes for lobectomy for both unmatched and matched cohorts. Sublobar resection was also superior to SBRT for overall survival, although there was a limited number of studies with matched data. Reporting of perioperative mortality and morbidity outcomes varied widely across studies, with slightly higher perioperative mortality for surgery than for SBRT in both the matched and unmatched cohorts. This is consistent with recent findings of higher mortality at 30 and 90 days for surgery than SBRT.⁵³ In addition, it should be acknowledged that clinical benefits in overall and cancer-specific survival associated with surgery were not apparent until 2 to 4 years after the operation, an important consideration for patients with limited life expectancies. Other important findings from the systematic review include significant variations in patient and tumor characteristics among studies, especially between institutions in Europe and the United States. Histopathological confirmation of NSCLC in the SBRT arm varied widely, between 30% and 100%, with five studies reporting <75% of patients with a confirmed histopathological diagnosis.^{7, 36, 37, 39, 42} It should be noted that two of these studies were the only publications that showed a trend of longer disease-free survival for SBRT than surgery.^{7, 37}

The present study has several limitations. The most important limitation is the lack of level I clinical evidence in the form of randomized controlled trials and the intrinsic patient selection bias present in observational studies. Despite a strong international effort to enroll patients, only 68 of the combined target of 2410 patients (2.8%) were ever successfully enrolled in three planned randomized controlled trials.^{54, 55} Slow accrual of patients may be at least partially attributable to a lack of equipoise for surgeons who still favor surgical resections with well-established long-term clinical data.⁴⁷ Patients allocated to the SBRT arm were often those considered inoperable or high risk, with increased comorbidities that prohibited a surgical resection. The Sublobar Resection Versus Stereotactic Ablative Radiotherapy for Lung Cancer (STABLE-MATES) trial (NCT02468024 on [ClinicalTrials.gov](https://clinicaltrials.gov)) is currently recruiting high-risk patients with peripherally located stage I NSCLC, who are randomized to either SBRT or sublobar resection, with the primary endpoint defined as overall survival and secondary endpoints of progression-free survival and toxicity. In randomized trials that experienced difficulties accruing patients, one method of minimizing potential bias was to compare the two treatment arms using propensity scores. Although this statistical technique can balance selected observed covariates, it does not replace the robustness of randomized trials, owing to a wide range of unobserved covariates.^{10, 56} The closeness of matching, also known as the caliper, differed among studies, depending on the reservoir of potential matches and the number of measured covariates

between treatment groups.⁵⁷ Additional statistical limitations of the present meta-analysis included relatively high heterogeneity identified among studies, potential overlapping of individual patients between institutions and databases, and the intrinsic limitations of the Guyot's method such as assumptions on constant censoring at each time interval. This assumption affects the relative weights of different portions of the curve, particularly as follow-up durations increase and the levels of information is reduced, potentially underestimating the uncertainty in the reconstructed hazard ratios.¹⁵ Other limitations of the current literature included variations in treatment regimens among institutions. Radiation dosages, doses per fraction, and treatment techniques for SBRT differed among centers, and this may have influenced the biological effective dose, treatment delivery precision, and oncologic efficacy. Surgical procedures also differed among studies, with variable portions of patients who underwent lobectomies versus sublobar resections and open thoracotomies versus VATS procedures. Future studies should compare SBRT with the current standard of care for eligible surgical candidates, which is VATS anatomical resection including lobectomy or segmentectomy, with systematic mediastinal lymph node sampling or dissection.⁵⁸ Finally, it should be noted that the follow-up duration for patients who underwent SBRT was relatively short, with only one study with a specified imaging protocol reporting a median follow-up beyond 5 years. Unfortunately, no data for histopathological diagnosis were provided in this study.⁴⁰ Although cancer-specific survival and disease-free survival have been considered to be more appropriate endpoints than overall survival for comparisons of SBRT and surgery in the context of patients with significant medical comorbidities, the inconsistent reporting of histopathological diagnosis, the variations in follow-up imaging, and the relative short-term follow-up duration make these endpoints difficult to interpret.

In conclusion, the present systematic review and meta-analysis of propensity-matched observational studies found surgical resection to be associated with superior overall, cancer-specific, and disease-free survival, compared with SBRT. Locoregional recurrence was also found to be significantly less frequent after surgery than SBRT. However, despite propensity matching, caution should be applied when interpreting these findings, given the potential for unrecognized selection bias inherent in observational studies comparing patients with different baseline characteristics. Indeed, differences in clinical outcomes were significant, although to a smaller degree, when analyses were limited to patient cohorts matched by propensity score or retrospective pooling of randomized trials. Nonetheless, it should be recognized that the present systematic review and meta-analysis represents the best evidence in the current literature, and the key analyses performed demonstrated results that were mostly consistent in both direction and magnitude. Perioperative mortality was higher after surgery than SBRT, and the incidences and types of morbidities varied between the two treatment modalities. To strengthen the existing clinical evidence, future studies on SBRT should aim to confirm histopathological diagnosis before treatment whenever possible and should provide long-term follow-up data with clearly defined imaging protocols. Surgical patients in comparative studies should undergo the current standard of care, which is VATS anatomical resection with systematic lymph node sampling or dissection. Comparing modern techniques of SBRT with the current practice of surgical resection will help refine

the patient selection process and help define the optimal treatment modality for patients with early-stage NSCLC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Glossary of Abbreviations:

CI	confidence interval
NSCLC	non-small cell lung cancer
OR	odds ratio
SBRT	stereotactic body radiation therapy
VATS	video-assisted thoracoscopic surgery

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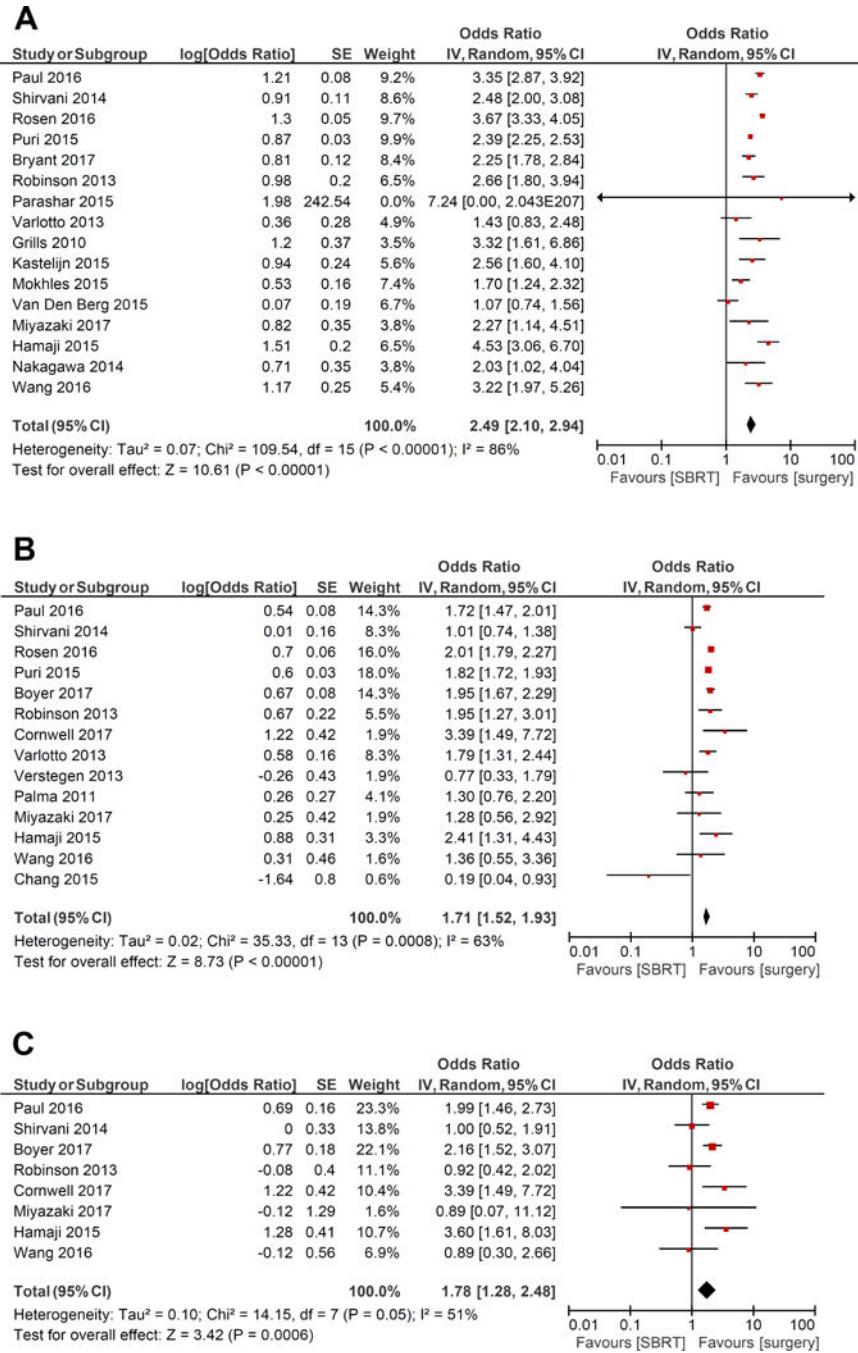


Figure 1. Forest plot of the odds ratio (OR) of overall survival in unmatched patients (A), overall survival in matched patients (B), and cancer-specific survival in matched patients (C) after stereotactic body radiation therapy (SBRT) versus surgery in patients with early-stage non-small cell lung cancer. The estimate of the OR of each study corresponds to the middle of the squares, and the horizontal line shows the 95% confidence interval (CI). On each line, the numbers of events as a fraction of the total number randomized are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR,

is represented by the middle of the solid diamonds. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. SE, standard error.

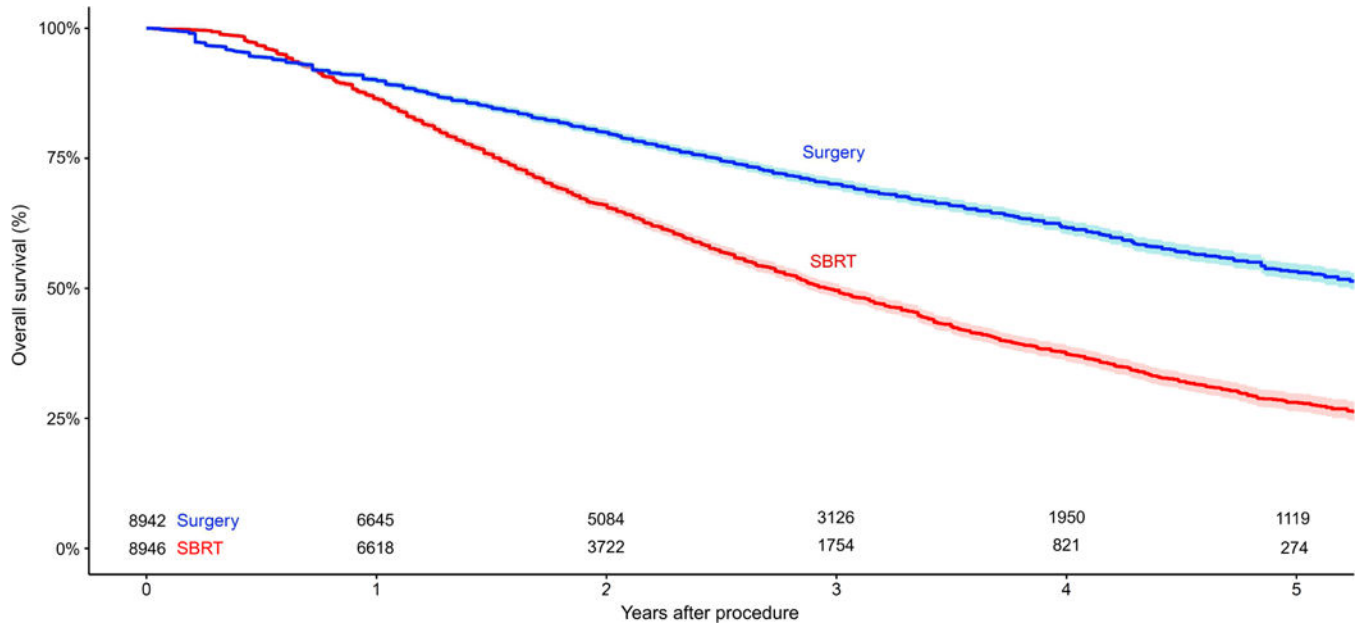


Figure 2. Reconstructed Kaplan-Meier graph of overall survival using aggregated data from matched patients with early-stage non-small cell lung cancer who underwent stereotactic body radiation therapy (SBRT) versus surgery. Shading represents the 95% confidence limits around the central estimate.

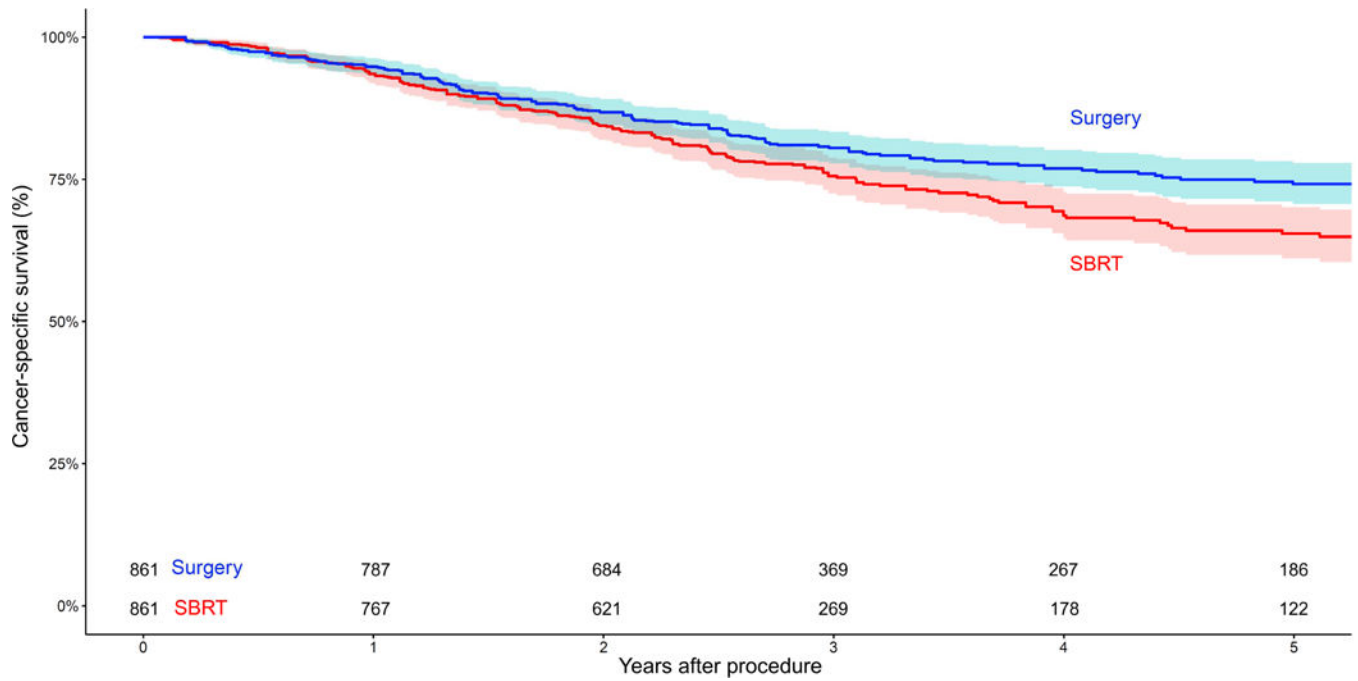


Figure 3. Reconstructed Kaplan-Meier graph of cancer-specific survival using aggregated data from matched patients with early-stage non-small cell lung cancer who underwent stereotactic body radiation therapy (SBRT) versus surgery. Shading represents the 95% confidence limits around the central estimate.

Summary of studies comparing overall survival outcomes between stereotactic body radiation therapy (SBRT) and surgical resection for patients with non-small cell lung cancer

Table 1.

Institution	Author	Study Period	N		Mortality	Morbidity	OS	DFS	CSS	REC
			SBRT	Surgery						
USA SEER	Paul ¹⁴	2007–2012	714	2253			●		●	
	Paul ¹⁴	2007–2012	643	643			●		●	
	Smith ¹⁵	2003–2010	382	1496 ^S 7215 ^L			○			
	Smith ¹⁵	2003–2010	300 243	300 ^S 243 ^L			●			
	Ezer ¹⁶	2002–2009	362	1881		●	○		○	
	Ezer ¹⁶	2002–2009	NS	NS			○		○	
	Yu ¹⁷	2007–2009	383	3852						
	Yu ¹⁷	2007–2009	367	711	○	●	○		○	
	Shirvani ¹⁸	2003–2009	382	8711	○		●		●	
	Shirvani ¹⁸	2003–2009	251	251 ^L			●		●	
	Shirvani ¹⁹	2001–2007	124	6531 ^L 1277 ^S			○		○	
	Shirvani ¹⁹	2001–2007	99 112	99 ^L 112 ^S			○		○	
	Yerokun ²⁰	2008–2011	1778	4517			○			
	Yerokun ²⁰	2008–2011	1584	1584			○			
Rosen ²¹	2008–2012	1781	13652	●		●				
Rosen ²¹	2008–2012	1781	1781	●		●				
Puri ²²	1998–2010	5887	111731	●		●				
Puri ²²	1998–2010	5355	5355	●		●				
VA Cancer Registry	Boyer ²³	2001–2010	3012	8248	●	●	○		○	

Institution	Author	Study Period	N	Mortality	Morbidity	OS	DFS	CSS	REC
	Boyer ²³	2001–2010	468			●		●	
VA Informatics and Computing Infrastructure	Bryant ²⁴	2006–2015	449	●		●		●	
Washington University	Crabtree ²⁵	2004–2010	151	○		○	○		○
	Crabtree ²⁵	2004–2010	56			○	●		○
	Robinson ²⁶	2004–2008	118	●	●	●		●	●
	Robinson ²⁶	2004–2008	76			●		●	●
	Puri ²⁷	2000–2007	76						
	Puri ²⁷	2000–2007	57	○	○	○		○	
Weill Cornell Medical College	Parashar ²⁸	1993–2012	97		●	●	●		○
	Port ²⁹	2001–2012	NR						
	Port ²⁹	2001–2012	23	●	●	○	○		○
	Parashar ³⁰	1999–2010	30		○	○			○
Michael DeBakey VAMC	Cornwell ³¹	2009–2014	56						
	Cornwell ³¹	2009–2014	37	●	●	●	●	●	○
Indiana University	Varlotto ³²	1999–2008	137			●	●		○
	Varlotto ³²	1999–2008	77			●	●		●
William Beaumont Hospital	Grills ³³	2003–2009	55	●	●	●		●	●
Netherlands									
St. Antonius Hospital	Kastelijjn ³⁴	2008–2011	53	●		●	●		●
	Kastelijjn ³⁴	2008–2011	23			○	●		○
VU University Med Center	Verstegen ³⁵	2003–2007	527						
	Verstegen ³⁵	2003–2007	64	●	●	●	●		●
VU and Erasmus University	Mokhles ³⁶	2003–2012	481						
	Mokhles ³⁶	2003–2012	73	○	○	○			○
Erasmus University	Mokhles ³⁷	2001–2011	209			●			●
University of Groningen	van den Berg ³⁸	2007–2010	197			●	●		●

Institution	Author	Study Period	N	Mortality	Morbidity	OS	DFS	CSS	REC
Amsterdam Cancer Registry	Palma ³⁹	2005–2007	81	109					
	Palma ³⁹	2005–2007	60	60	●				
Japan									
Nagasaki University Hospital	Miyazaki ⁴⁰	2008–2014	41	57	●	●		●	○
	Miyazaki ⁴⁰	2008–2014	27	27		●		●	
Kyoto University Hospital	Hamaji ⁴¹	2003–2009	104	413	●	●	●	●	●
	Hamaji ⁴¹	2003–2009	41	41	●	●	●	●	●
	Matsuo ⁴²	2003–2009	115	65	○	○		○	
	Matsuo ⁴²	2003–2009	53	53	○	○		○	○
	Nakagawa ⁴³	2001–2011	35	183	●	●	●		○
Others									
PLA General Hospital, China	Wang ⁴⁴	2002–2010	74	106	●	●	●	●	●
	Wang ⁴⁴	2002–2010	35	35			●	●	●
Multi-institutional	Chang ⁷	2008–2014	31	27	●	●	●		●

CSS, cancer-specific survival; DFS, disease-free survival

L, lobectomy; NCDB, National Cancer Database; OS, overall survival; PLA, People's Liberation Army; REC, locoregional or distant recurrence

S, sublobar resection; SEER, Surveillance, Epidemiology, and End Results; VA, Veterans Affairs; VAMC, Veterans Affairs Medical Center; VU, Vrije Universiteit

W, wedge. Dots denote presented data. Solid dots denote data selected for quantitative analysis. Shaded studies indicate matching of patients by propensity score analysis or retrospective pooling of randomized data.

Table 2.

Summary of covariates used for propensity score matching in comparative studies on stereotactic body radiation therapy versus surgical resection for early-stage non-small cell lung cancer

Study	Patient Characteristics						Pre-Operative Risk Factors						Tumor Characteristics						
	Age	Sex	Race	Education	Income	Insurance	Geography	CCI	ACE	PS	DI	PFT	O ₂ Use	Home Services	Size	Stage	Location	Histology	PET
Paul ¹⁴	●	●	●		●		●			●					●	●		●	●
Smith ¹⁵	●	●	●				●	●		●		●				●			●
Ezer ¹⁶	●	●	●		●		●	●						●	●	●	●	●	●
Yu ¹⁷	●	●	●		●		●			●									●
Shirvani ¹⁸	●	●					●	●	●			●			●	●			●
Rosen ²¹	●	●	●	●	●	●	●	●							●	●	●	●	
Puri ²²	●	●	●		●		●	●							●	●			
Boyer ²³	●		●				●	●			●				●	●	●	●	
Crabtree ²⁵	●								●		●				●	●	●		
Robinson ²⁶															●				
Port ²⁹	●	●																	
Cornwell ³¹		●					●	●			●								
Varlotto ³²	●	●					●	●							●			●	
Kastelijjn ³⁴	●	●							●		●				●	●			
Verstegen ³⁵	●	●					●	●	●		●				●	●	●	●	
Palma ³⁹	●	●													●				
Miyazaki ⁴⁰	●	●					●	●	●		●				●				
Hamaji ⁴¹	●	●					●	●			●				●				
Wang ⁴⁴	●	●					●	●	●		●				●	●	●		

ACE, adult comorbidity evaluation; CCI, Charlson comorbidity index; DI, disability index; PET, pre-treatment position-emission; PFT, pulmonary function tests; PS, performance status; tomography.

Table 3. Summary of baseline patient characteristics and treatment details of matched patients who underwent stereotactic body radiation therapy (SBRT) or surgical resection for early-stage non-small cell lung cancer in studies selected for meta-analysis

Authors	Median Age		Females (%)		Treatment Regimen						Technique (%)		
	SBRT	Sx	SBRT	Sx	SBRT		Lobectomy	Resection Type (%)			VAIS	Open	
					Total Gys	Fractions		Wedge	Sublobar	Other			
Paul ¹⁴	78 ^M	78 ^M	60	62	NR	NR	NR	NR	NR	NR	NR	100	0
Smith ¹⁵	77 ^L 78 ^S	77 ^L 78 ^S	59 ^L 58 ^S	62 ^L 61 ^S	NR	NR	100	100	100	0	0	27 ^L 40 ^S	73 ^L 60 ^S
Shirvani ¹⁸	NS	NS	NS	NS	NR	NR	100	100	NR	NR	NR	NR	NR
Rosen ²¹	76 ^M	75 ^M	57	56	NR	3-5	100	100	0	0	0	NR	NR
Puri ²²	NS	NS	NS	NS	NR	NR	NS	NS	NS	NS	NS	NR	NR
Boyer ²³	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crabtree ²⁵	71 ^M	70 ^M	48	44	45-60	3-6	78	78	9	11	2 ^B	NR	NR
Robinson ²⁶	76	65	45	51	45-54	3-5	94	94	0	0	3 ^B 3 ^P	NR	NR
Cornwell ³¹	66	68	3	3	50-56	4-5	100	100	0	0	0	100	0
Varloto ³²	NR	NR	NR	NR	48-60	3-5	NR	NR	NR	NR	NR	NR	NR
Kastelijjn ³⁴	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Verstegen ³⁵	71 ^M	68 ^M	42	44	54-60	3-12	100	100	0	0	0	100	0
Palma ³⁹	79	79	33	33	32-60	2-8	82	82	15	3 ^P	NR	NR	NR
Miyazaki ⁴⁰	82	82	33	27	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hamaji ⁴¹	73	74	24	22	48-60	4-8	100	100	0	0	0	100	0
Wang ⁴⁴	77 ^M	75 ^M	6	6	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chang ⁷	67	67	55	59	50-54 ^{STARS} 54-60 ^{ROSEL}	3-4 ^{STARS} 4-5 ^{ROSEL}	88	88	4	0	8 [*]	23	77

^B : bilobectomy

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T, lobectomy

M, mean value; NR, not reported

P, pneumonectomy

S, sublobar; Sx, surgery; VATS; video-assisted thoracoscopic surgery.

* VATS biopsy and abortion, 4% each.

Table 4.

Summary of histopathological and clinical staging details of matched patients who underwent stereotactic body radiation therapy (SBRT) or surgical resection for early-stage non-small cell lung cancer in studies selected for meta-analysis

Author	Histopathology – SBRT (%)					Histopathology – Surgery (%)					Clinical Stage – SBRT (%)					Clinical Stage – Surgery (%)				
	A	S	O	U		A	S	O	U		IA	IB	IIA	IIB/IIIA	IA	IB	IIA	IIB/IIIA		
Paul ¹⁴	49	43	8	0	47	43	10	0	70	NR	NR	NR	NR	70	NR	NR	NR	NR		
Smith ¹⁵	NR	NR	NR	NR	NR	NR	NR	NR	82	18	0	0	0	82	18	0	0	0		
Shirvani ¹⁸	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Rosen ²¹	48	33	19	0	50	36	14	0	77	23	0	0	0	77	23	0	0	0		
Puri ²²	NR	NR	NR	NR	NR	NR	NR	NR	76	24	0	0	0	72	28	0	0	0		
Boyer ²³	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Crabtree ²⁵	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	43	NR	NR	NR		
Robinson ²⁶	45	33	21	1	60	33	3	4	74	22	4	0	0	77	20	3	0	0		
Cornwell ³¹	46	41	13	0	41	43	16	0	76	24	0	0	0	81	19	0	0	0		
Varloto ³²	NR	NR	NR	NR	NR	NR	NR	NR	100	0	0	0	0	100	0	0	0	0		
Kastelijjn ³⁴	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Verstegen ³⁵	23	14	16	47	30	11	9	50	61	39	0	0	0	61	38	0	1	0		
Palma ³⁹	NR	NR	NR	NR	NR	NR	NR	NR	65	35	0	0	0	65	35	0	0	0		
Miyazaki ⁴⁰	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR		
Hamajji ⁴¹	54	24	22	0	56	27	17	0	71	29	0	0	0	66	34	0	0	0		
Wang ⁴⁴	48	46	0	6	51	43	6	0	100	0	0	0	0	100	0	0	0	0		
Chang ⁷	52	16	6	26	48	26	4	22	87	13	0	0	0	96	4	0	0	0		

A, adenocarcinoma; L, lobectomy; NR, not reported; O, other type of non-small cell lung cancer; S, squamous cell carcinoma; U, undefined.