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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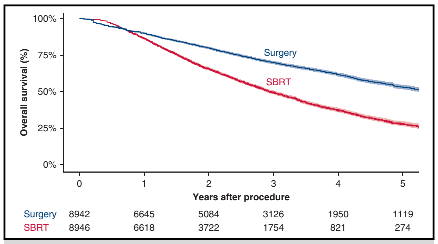
ABSTRACT

Objective: Stereotactic body radiation therapy is the preferred treatment modality for patients with inoperable early-stage non–small cell lung cancer. However, comparative outcomes between stereotactic body radiation therapy 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 stereotactic body radiation therapy or surgery. Secondary end points included cancer-specific survival, disease-free survival, disease recurrence, and perioperative outcomes.

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, 2.49; 95% confidence interval, 2.10-2.94; $P < .00001$) and matched (odds ratio, 1.71; 95% confidence interval, 1.52-1.93; $P < .00001$) cohorts. Subgroup analysis demonstrated superior overall survival for lobectomy and sublobar resection compared with stereotactic body radiation therapy. In unmatched and matched cohorts, cancer-specific survival, disease-free survival, and freedom from locoregional recurrence were superior after surgery. However, stereotactic body radiation therapy was associated with fewer perioperative deaths.

Conclusions: The current evidence suggests surgery is superior to stereotactic body radiation therapy in terms of mid- and long-term clinical outcomes; stereotactic body radiation therapy is associated with lower perioperative mortality. However, the improved outcomes after surgery may be due at least in part to an imbalance of baseline characteristics. Future studies should aim to provide histopathologic confirmation of malignancy and compare stereotactic body radiation therapy with minimally invasive anatomical resections. (J Thorac Cardiovasc Surg 2019;157:362-73)



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

With a paucity of randomized data, observational studies have used 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.

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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 with conventional radiotherapy, SBRT delivers

Abbreviations and Acronyms

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

fewer fractions of high-dose radiation per fraction with increased precision, sparing the surrounding normal tissue to maximize the biologically effective dose while 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 2 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 over-interpreting 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 end points included overall survival in matched and unmatched cohorts. Secondary end points included cancer-specific survival, disease-free survival, freedom from locoregional recurrence, freedom from distant recurrence, and perioperative mortality and morbidity. Each end point 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.

MATERIALS AND 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 2 reviewers were resolved by discussion and consensus. To assess the quality of the nonrandomized studies, the Newcastle-Ottawa scale was used to evaluate the selection, comparability, and outcomes reported in each study, with 0 to 3 stars indicating poor quality, 4 to 6 stars indicating moderate quality, and 7 or more stars indicating high quality.[12]

Statistical Analysis

When more than 4 studies provided relevant data on the same predetermined end point, 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 Tierney and colleagues[13] and Parma and colleagues.[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, UK). All *P* values were 2 sided.

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 numeric 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 1 retrospective pooled analysis of 2 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 to 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 Figure E1, and a summary of each study, with detailed characteristics, is presented in Table 1.

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TABLE 1. Summary of studies comparing overall survival outcomes between stereotactic body radiation therapy and surgical resection for patients with non–small cell lung cancer

Institution	Author	Study period	*N*		Mortality	Morbidity	OS	DFS	CSS	REC
			SBRT	Surgery						
USA										
SEER	Paul[16]	2007-2012	714	2253			●		●	
	Paul[16]*	2007-2012*	643*	643*	*	*	●*	*	●*	*
	Smith[17]	2003-2010	382	1496^{S} 7215^{L}			○			
	Smith[17]*	2003-2010*	300* 243*	300^{S}* 243^{L*}	*	*	●*	*	*	*
	Ezer[18]	2002-2009	362	1881		●	○		○	
	Ezer[18]*	2002-2009*	NS*	NS*	*	*	○*	*	○*	*
	Yu[19]	2007-2009	383	3852						
	Yu[19]*	2007-2009*	367*	711*	○*	●*	○*	*	○*	*
	Shirvani[20]	2003-2009	382	8711	○		●		●	
	Shirvani[20]*	2003-2009*	251*	251^{L*}	*	*	●*	*	●*	*
	Shirvani[21]	2001-2007	124	6531^{L} 1277^{S}			○		○	
	Shirvani[21]*	2001-2007*	99* 112*	99^{L}* 112^{S*}	*	*	○*	*	○*	*
NCBD	Yerokun[22]	2008-2011	1778	4517			○			
	Yerokun[22]*	2008-2011*	1584*	1584*	*	*	○*	*	*	*
	Rosen[23]	2008-2012	1781	13652	●		●			
	Rosen[23]*	2008-2012*	1781*	1781*	●*	*	●*	*	*	*
	Puri[24]	1998-2010	5887	111731	●		●			
	Puri[24]*	1998-2010*	5355*	5355*	●*	*	●*	*	*	*
VA Cancer Registry	Boyer[25]	2001-2010	3012	8248	●	●	○		○	
	Boyer[25]*	2001-2010*	468*	468*	*	*	●*	*	●*	*
VA Informatics and Computing Infrastructure	Bryant[26]	2006-2015	449	4069	●		●		●	
Washington University	Crabtree[27]	2004-2010	151	458	○		○	○		○
	Crabtree[27]*	2004-2010*	56*	56*	*	*	○*	●*	*	○*
	Robinson[28]	2004-2008	118	260	●	●	●		●	●
	Robinson[28]*	2004-2008*	76*	76*	*	*	●*	*	●*	●*
	Puri[29]	2000-2007	76	462						
	Puri[29]*	2000-2007*	57*	57*	○*	○*	○*	*	○*	*
Weill Cornell Medical College	Parashar[30]	1993-2012	97	123^{W}		●	●	●		○
	Port[31]	2001-2012	NR	NR						
	Port[31]*	2001-2012*	23*	38^{W*}	●*	●*	○*	○*	*	○*
	Parashar[32]	1999-2010	30	17		○	○			○
Michael DeBakey VAMC	Cornwell[33]	2009-2014	56	127						
	Cornwell[33]*	2009-2014*	37*	37*	●*	●*	●*	●*	●*	○*
Indiana University	Varlotto[34]	1999-2008	137	132^{L} 48^{S}			●	●		○
	Varlotto[34]*	1999-2008*	77*	77*	*	*	●*	●*	*	●*
William Beaumont Hospital	Grills[35]	2003-2009	55	69	●	●	●		●	●

(Continued)

TABLE 1. Continued

Institution	Author	Study period	N SBRT	N Surgery	Mortality	Morbidity	OS	DFS	CSS	REC
Netherlands										
St. Antonius Hospital	Kastelijn[36]	2008-2011	53	175	●		●	●		●
	Kastelijn[36]*	2008-2011*	23*	23*	*	*	○*	●*	*	○*
VU University Med Center	Verstegen[37]	2003-2007	527	86						
	Verstegen[37]*	2003-2007*	64*	64*	●*	●*	●*	●*	*	●*
VU and Erasmus University	Mokhles[38]	2003-2012	481	96						
	Mokhles[38]*	2003-2012*	73*	73*	○*	○*	○*	*	*	○*
Erasmus University	Mokhles[39]	2001-2011	209	216			●			●
University of Groningen	van den Berg[40]	2007-2010	197	143			●	●		●
Amsterdam Cancer Registry	Palma[41]	2005-2007	81	109						
	Palma[41]*	2005-2007*	60*	60*	●*	*	●*	*	*	*
Japan										
Nagasaki University Hospital	Miyazaki[42]	2008-2014	41	57	●	●	●		●	○
	Miyazaki[42]*	2008-2014*	27*	27*	*	*	●*	*	●*	*
Kyoto University Hospital	Hamaji[43]	2003-2009	104	413	●		●	●	●	●
	Hamaji[43]*	2003-2009*	41*	41*	●*	*	●*	●*	●*	●*
	Matsuo[44]	2003-2009	115	65	○		○		○	
	Matsuo[44]*	2003-2009*	53*	53*	○*	*	○*	*	○*	○*
Tenri and Kurashiki Hospitals	Nakagawa[45]	2001-2011	35	183	●	●	●			○
Others										
PLA General Hospital, China	Wang[46]	2002-2010	74	106	●	●	●	●	●	●
	Wang[46]*	2002-2010*	35*	35*	*	*	●*	●*	●*	●*
Multi-institutional	Chang[7]*	2008-2014*	31*	27*	●*	●*	●*	●*	*	●*

Dots denote presented data. Solid dots denote data selected for quantitative analysis. Asterisks indicate matching of patients by propensity score analysis or retrospective pooling of randomized data. *OS*, Overall survival; *DFS*, disease-free survival; *CSS*, cancer-specific survival; *REC*, locoregional or distant recurrence; *SBRT*, stereotactic body radiation therapy; *SEER*, Surveillance, Epidemiology, and End Results; *S*, sublobar resection; *L*, lobectomy; *NCDB*, National Cancer Database; *VA*, Veterans Affairs; *W*, wedge; *VAMC*, Veterans Affairs Medical Center; *VU*, Vrije Universiteit; *PLA*, People's Liberation Army.

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 1 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 Table E1. In brief, the interquartile range of ages for matched patients was 71 to 78 years for those who underwent SBRT and 68 to 78 years for those who underwent surgery. Gender variations were noted to be significantly different among studies, with 4 studies, primarily from military institutions or registries, reporting study populations comprising less than 10% female participants.[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 more than 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 4 studies only reporting on VATS procedures.[16,33,37,43] A summary of histopathologic 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 Table E2. 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 pathologic diagnosis of NSCLC.[36]

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

	Patient characteristics							Preoperative risk factors							Tumor characteristics				
Study	Age	Sex	Race	Education	Income	Insurance	Geography	CCI	ACE	PS	DI	PFT	O_2 Use	Home services	Size	Stage	Location	Histology	PET
Paul[16]	●	●	●		●		●				●				●	●		●	●
Smith[17]	●	●	●					●		●			●			●			●
Ezer[18]	●	●	●		●			●						●	●	●	●	●	●
Yu[19]	●	●	●		●		●				●								●
Shirvani[20]	●	●						●		●			●		●	●			●
Rosen[23]	●	●	●	●	●	●	●	●							●	●	●	●	
Puri[24]	●	●	●		●		●	●							●	●			
Boyer[25]	●		●				●	●				●				●		●	
Crabtree[27]	●								●			●			●	●	●		
Robinson[28]																●			
Port[31]	●	●																●	
Cornwell[33]		●						●				●							
Varlotto[34]	●	●						●							●			●	
Kastelijn[36]	●	●								●		●			●	●			
Verstegen[37]	●	●						●		●		●			●	●	●	●	
Palma[41]	●	●														●			
Miyazaki[42]	●	●						●		●		●			●				
Hamaji[43]	●	●						●				●			●				
Wang[46]	●	●						●		●		●				●	●		

CCI, Charlson comorbidity index; *ACE*, adult comorbidity evaluation; *PS*, performance status; *DI*, disability index; *PFT*, pulmonary function tests; *PET*, pretreatment position emission.

However, the proportion of patients who underwent SBRT without histopathologic confirmation appeared to differ between European centers and institutions in the United States. Histopathologic demonstration of malignancy was confirmed in more than 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; $P < .00001$; $I^2 = 86\%$; Figure 1, *A*). When the matched cohorts were compared, overall survival remained superior for surgery compared with SBRT (OR, 1.71; 95% CI, 1.52-1.93; $P < .00001$; $I^2 = 63\%$; Figure 1, *B*). 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; $P < .00001$; $I^2 = 84\%$; Figure E2). The superiority of lobectomy for overall survival persisted when matched patients from 8 studies were compared (OR, 1.61; 95% CI, 1.23-2.12; $P = .0006$; $I^2 = 77\%$; Figure E3). 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; $P < .00001$; $I^2 = 32\%$; Figure E4). 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;

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

	Median age		Female (%)		Treatment regimen							
					SBRT		Resection type (%)				Technique (%)	
								Sublobar				
Authors	SBRT	Sx	SBRT	Sx	Total Gys	Fractions	Lobectomy	Wedge	Segmentectomy	Other	VATS	Open
Paul[16]	78^{M}	78^{M}	60	62	NR	NR	NR	NR	NR	0	100	0
Smith[17]	77^{L} 78^{S}	77^{L} 78^{S}	59^{L} 58^{S}	62^{L} 61^{S}	NR	NR	100	100		0	27^{L} 40^{S}	73^{L} 60^{S}
Shirvani[20]	NS	NS	NS	NS	NR	NR	100	NR	NR	NR	NR	NR
Rosen[23]	76^{M}	75^{M}	57	56	NR	3-5	100	0	0	0	NR	NR
Puri[24]	NS	NS	NS	NS	NR	NR	NS	NS	NS	NS	NR	NR
Boyer[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crabtree[27]	71^{M}	70^{M}	48	44	45-60	3-6	78	9	11	2^{B}	NR	NR
Robinson[28]	76	65	45	51	45-54	3-5	94	0	0	3^{B} 3^{P}	NR	NR
Cornwell[33]	66	68	3	3	50-56	4-5	100	0	0	0	100	0
Varlotto[34]	NR	NR	NR	NR	48-60	3-5	NR	NR	NR	NR	NR	NR
Kastelijn[36]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Verstegen[37]	71^{M}	68^{M}	42	44	54-60	3-12	100	0	0	0	100	0
Palma[41]	79	79	33	33	32-60	2-8	82	15		3^{P}	NR	NR
Miyazaki[42]	82	82	33	27	NR	NR	NR	NR	NR	NR	NR	NR
Hamaji[43]	73	74	24	22	48-60	4-8	100	0	0	0	100	0
Wang[46]	77^{M}	75^{M}	6	6	NR	NR	NR	NR	NR	NR	NR	NR
Chang[7]	67	67	55	59	$50\text{-}54^{STARS}$ $54\text{-}60^{ROSEL}$	$3\text{-}4^{STARS}$ $4\text{-}5^{ROSEL}$	88	4	0	8*	23	77

SBRT, Stereotactic body radiation therapy; *Sx*, surgery; *VATS*, video-assisted thoracoscopic surgery; *M*, mean value; *NR*, not reported; *L*, lobectomy; *S*, sublobar; *B*, bilobectomy; *P*, pneumonectomy. *VATS biopsy and abortion, 4% each.

$P < .00001$; $I^2 = 58\%$; Figure E5). 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; $P = .0006$; $I^2 = 51\%$; Figure 1, *C*). 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; $P < .00001$; $I^2 = 0\%$; Figure E6). When the analysis was limited to matched patients, 7 studies demonstrated superior disease-free survival in the surgical cohort (OR, 1.83; 95% CI, 1.06-3.16; $P = .03$; $I^2 = 82\%$; Figure E7).

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; $P < .005$; $I^2 = 87\%$; Figure E8). When the analysis was limited to matched patients, 6 studies demonstrated superior locoregional recurrence rates in the surgical cohort (OR, 2.91; 95% CI, 1.49-5.71; $P = .002$; $I^2 = 0\%$; Figure E9).

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; $P = .07$; $I^2 = 60\%$). 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%-3.25%) for surgery. Periprocedural morbidities varied in nature and frequency after the 2 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

TABLE 4. Summary of histopathologic and clinical staging details of matched patients who underwent stereotactic body radiation therapy or surgical resection for early-stage non–small cell lung cancer in studies selected for meta-analysis

	Histopathology – SBRT (%)				Histopathology – surgery (%)				Clinical stage – SBRT (%)				Clinical stage – surgery (%)			
Author	A	S	O	U	A	S	O	U	IA	IB	IIA	IIB/IIIA	IA	IB	IIA	IIB/IIIA
Paul[16]	49	43	8	0	47	43	10	0	70	NR	NR	NR	70	NR	NR	NR
Smith[17]	NR	NR	NR	NR	NR	NR	NR	NR	82	18	0	0	82	18	0	0
Shirvani[20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rosen[23]	48	33	19	0	50	36	14	0	77	23	0	0	77	23	0	0
Puri[24]	NR	NR	NR	NR	NR	NR	NR	NR	76	24	0	0	72	28	0	0
Boyer[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crabtree[27]	NR	NR	NR	NR	NR	NR	NR	NR	NR	29	NR	NR	NR	43	NR	NR
Robinson[28]	45	33	21	1	60	33	3	4	74	22	4	0	77	20	3	0
Cornwell[33]	46	41	13	0	41	43	16	0	76	24	0	0	81	19	0	0
Varlotto[34]	NR	NR	NR	NR	NR	NR	NR	NR	100	0	0	0	100	0	0	0
Kastelijn[36]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Verstegen[37]	23	14	16	47	30	11	9	50	61	39	0	0	61	38	0	1
Palma[41]	NR	NR	NR	NR	NR	NR	NR	NR	65	35	0	0	65	35	0	0
Miyazaki[42]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hamaji[43]	54	24	22	0	56	27	17	0	71	29	0	0	66	34	0	0
Wang[46]	48	46	0	6	51	43	6	0	100	0	0	0	100	0	0	0
Chang[7]	52	16	6	26	48	26	4	22	87	13	0	0	96	4	0	0

SBRT, Stereotactic body radiation therapy; *A*, adenocarcinoma; *S*, squamous cell carcinoma; *O*, other type of non–small cell lung cancer; *U*, undefined; *NR*, not reported.

arrhythmia, and myocardial infarction. Summaries of the reported periprocedural mortality and morbidity outcomes for matched and unmatched patients are presented in Tables E3 and E4, respectively.

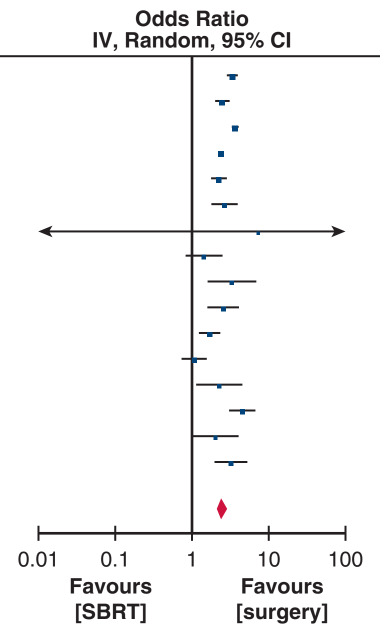
DISCUSSION

Encouraging outcomes of SBRT compared with 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 comorbidities, 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 2 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

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Paul 2016	1.21	0.08	9.2%	3.35 [2.87, 3.92]
Shirvani 2014	0.91	0.11	8.6%	2.48 [2.00, 3.08]
Rosen 2016	1.3	0.05	9.7%	3.67 [3.33, 4.05]
Puri 2015	0.87	0.03	9.9%	2.39 [2.25, 2.53]
Bryant 2017	0.81	0.12	8.4%	2.25 [1.78, 2.84]
Robinson 2013	0.98	0.2	6.5%	2.66 [1.80, 3.94]
Parashar 2015	1.98	242.54	0.0%	7.24 [0.00, 2.043E207]
Varlotto 2013	0.36	0.28	4.9%	1.43 [0.83, 2.48]
Grills 2010	1.2	0.37	3.5%	3.32 [1.61, 6.86]
Kastelijn 2015	0.94	0.24	5.6%	2.56 [1.60, 4.10]
Mokhles 2015	0.53	0.16	7.4%	1.70 [1.24, 2.32]
Van Den Berg 2015	0.07	0.19	6.7%	1.07 [0.74, 1.56]
Miyazaki 2017	0.82	0.35	3.8%	2.27 [1.14, 4.51]
Hamaji 2015	1.51	0.2	6.5%	4.53 [3.06, 6.70]
Nakagawa 2014	0.71	0.35	3.8%	2.03 [1.02, 4.04]
Wang 2016	1.17	0.25	5.4%	3.22 [1.97, 5.26]
Total (95% CI)			**100.0%**	**2.49 [2.10, 2.94]**

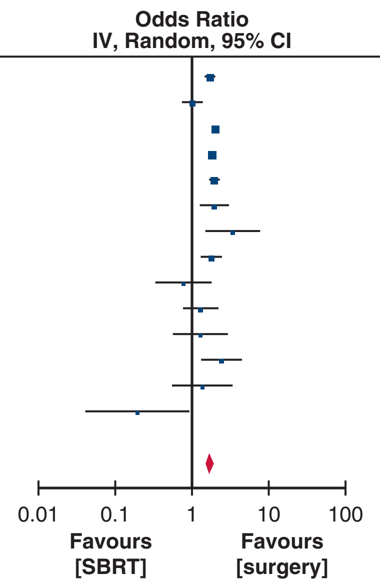
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 109.54$, df = 15 ($P < .00001$); $I^2 = 86\%$
Test for overall effect: Z = 10.61 ($P < .00001$)



A

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Paul 2016	0.54	0.08	14.3%	1.72 [1.47, 2.01]
Shirvani 2014	0.01	0.16	8.3%	1.01 [0.74, 1.38]
Rosen 2016	0.7	0.06	16.0%	2.01 [1.79, 2.27]
Puri 2015	0.6	0.03	18.0%	1.82 [1.72, 1.93]
Boyer 2017	0.67	0.08	14.3%	1.95 [1.67, 2.29]
Robinson 2013	0.67	0.22	5.5%	1.95 [1.27, 3.01]
Cornwell 2017	1.22	0.42	1.9%	3.39 [1.49, 7.72]
Varlotto 2013	0.58	0.16	8.3%	1.79 [1.31, 2.44]
Verstegen 2013	–0.26	0.43	1.9%	0.77 [0.33, 1.79]
Palma 2011	0.26	0.27	4.1%	1.30 [0.76, 2.20]
Miyazaki 2017	0.25	0.42	1.9%	1.28 [0.56, 2.92]
Hamaji 2015	0.88	0.31	3.3%	2.41 [1.31, 4.43]
Wang 2016	0.31	0.46	1.6%	1.36 [0.55, 3.36]
Chang 2015	–1.64	0.8	0.6%	0.19 [0.04, 0.93]
Total (95% CI)			**100.0%**	**1.71 [1.52, 1.93]**

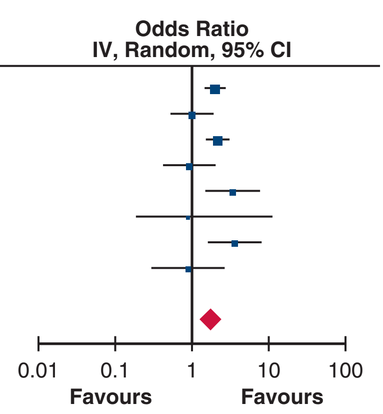
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 35.33$, df = 13 ($P = .0008$); $I^2 = 63\%$
Test for overall effect: Z = 8.73 ($P < .00001$)



B

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Paul 2016	0.69	0.16	23.3%	1.99 [1.46, 2.73]
Shirvani 2014	0	0.33	13.8%	1.00 [0.52, 1.91]
Boyer 2017	0.77	0.18	22.1%	2.16 [1.52, 3.07]
Robinson 2013	–0.08	0.4	11.1%	0.92 [0.42, 2.02]
Cornwell 2017	1.22	0.42	10.4%	3.39 [1.49, 7.72]
Miyazaki 2017	–0.12	1.29	1.6%	0.89 [0.07, 11.12]
Hamaji 2015	1.28	0.41	10.7%	3.60 [1.61, 8.03]
Wang 2016	–0.12	0.56	6.9%	0.89 [0.30, 2.66]
Total (95% CI)			**100.0%**	**1.78 [1.28, 2.48]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 14.15$, df = 7 ($P = .05$); $I^2 = 51\%$
Test for overall effect: Z = 3.42 ($P = .0006$)



C

FIGURE 1. Forest plot of the OR of overall survival in unmatched patients (A), overall survival in matched patients (B), and cancer-specific survival in matched patients (C) after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number randomized are shown for both

THOR

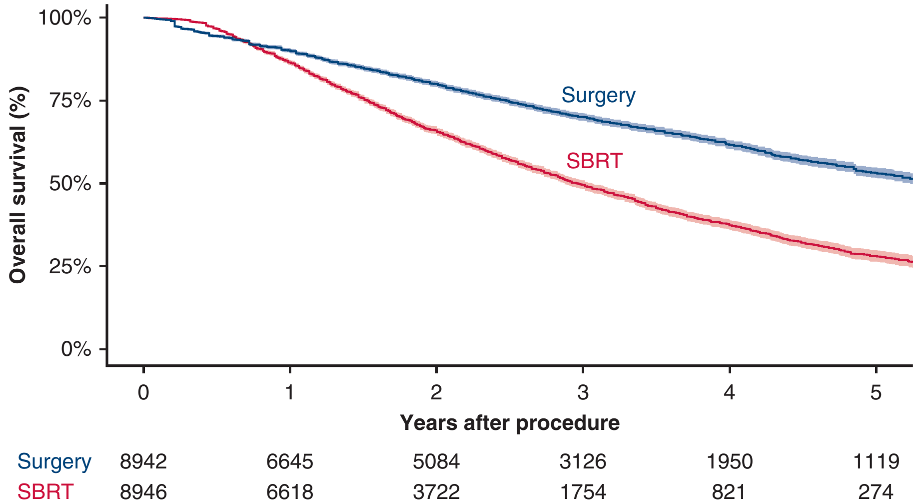


FIGURE 2. Reconstructed Kaplan–Meier graph of overall survival using aggregated data from matched patients with early-stage NSCLC who underwent SBRT versus surgery. Shading represents the 95% confidence limits around the central estimate. *SBRT*, Stereotactic body radiation therapy.

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. Histopathologic confirmation of NSCLC in the SBRT arm varied widely, between 30% and 100%, with 5 studies reporting less than 75% of patients with a confirmed histopathologic diagnosis.[7,36,37,39,42] It should be noted that 2 of these studies were the only publications that showed a trend of longer disease-free survival for SBRT than surgery.[7,37]

Study Limitations

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 3 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) is currently recruiting high-risk patients with peripherally located stage I NSCLC, who are randomized to SBRT or sublobar resection, with the primary end point defined as overall survival and secondary end points of progression-free survival and toxicity. In randomized trials that experienced difficulties accruing patients, one method of minimizing potential bias was to compare the 2 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

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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

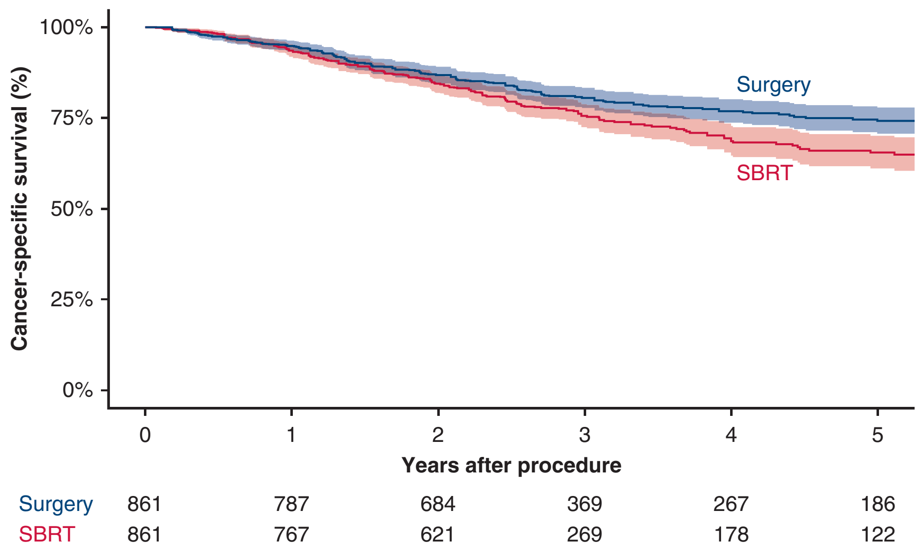


FIGURE 3. Reconstructed Kaplan–Meier graph of cancer-specific survival using aggregated data from matched patients with early-stage NSCLC who underwent SBRT versus surgery. Shading represents the 95% confidence limits around the central estimate. *SBRT*, Stereotactic body radiation therapy.

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 anatomic 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 1 study with a specified imaging protocol reporting a median follow-up beyond 5 years. Unfortunately, no data for histopathologic diagnosis were provided in this study.[40] Although cancer-specific survival and disease-free survival have been considered to be more appropriate end points than overall survival for comparisons of SBRT and surgery in the context of patients with significant medical comorbidities, the inconsistent reporting of histopathologic diagnosis, the variations in follow-up imaging, and the relative short-term follow-up duration make these end points difficult to interpret.

CONCLUSIONS

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 2 treatment modalities. To strengthen the existing clinical evidence, future studies on SBRT should aim to confirm histopathologic 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 anatomic 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.

Conflict of Interest Statement

A.R. has received funding from Varian Medical Systems, Boehringer Ingelheim, Pfizer, and AstraZeneca. All other authors have nothing to disclose with regard to commercial support.

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Key Words: stereotactic body radiation therapy, surgery, non–small cell lung cancer, survival, meta-analysis

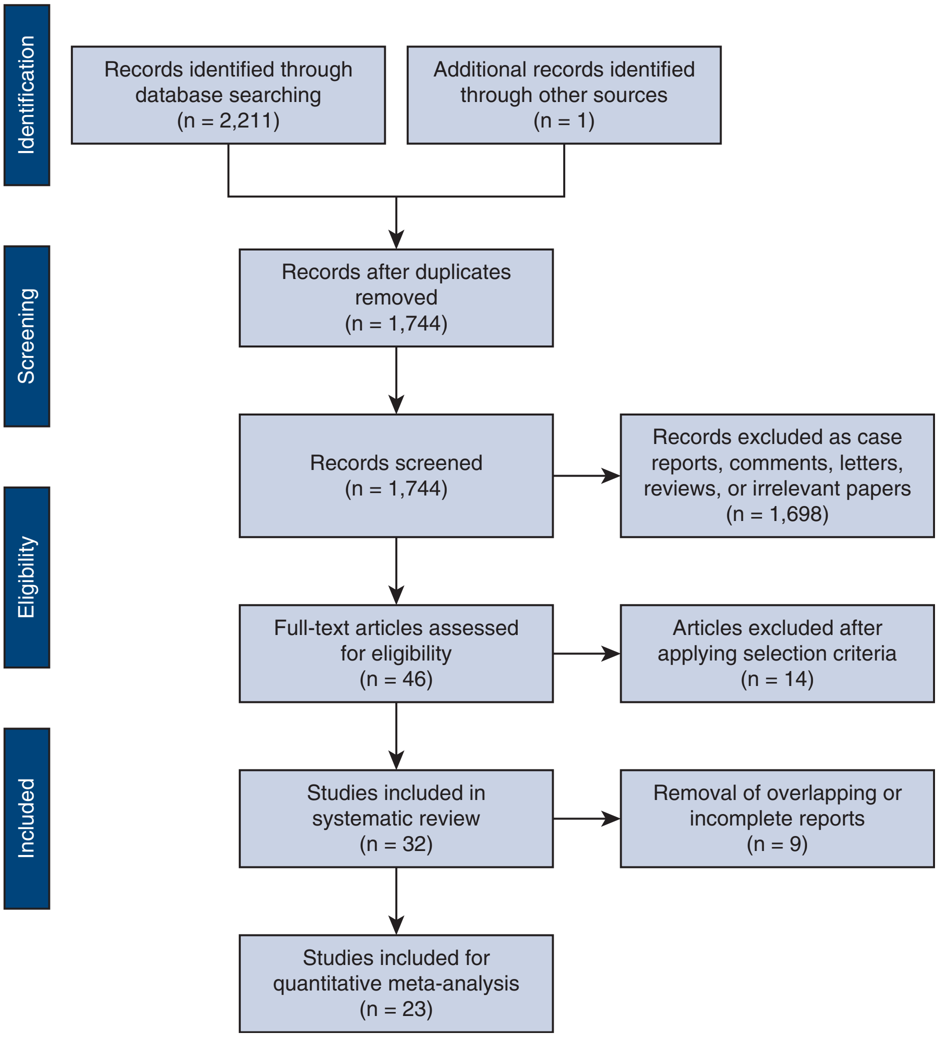

FIGURE E1. PRISMA flow chart summarizing the literature search strategy in the systematic review of SBRT versus surgical resection for patients with early-stage NSCLC.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Shirvani 2014	0.91	0.11	20.0%	2.48 [2.00, 3.08]
Rosen 2016	1.3	0.05	22.2%	3.67 [3.33, 4.05]
Bryant 2017	0.81	0.12	19.6%	2.25 [1.78, 2.84]
Robinson 2013	0.98	0.2	15.6%	2.66 [1.80, 3.94]
Varlotto 2013	0.36	0.28	11.9%	1.43 [0.83, 2.48]
Hamaji 2015	1.51	0.31	10.8%	4.53 [2.47, 8.31]
Total (95% CI)			**100.0%**	**2.68 [2.04, 3.53]**

Heterogeneity: $Tau^2 = 0.09$; $Chi^2 = 31.76$, df = 5 ($P < .00001$); $I^2 = 84\%$
Test for overall effect: Z = 7.06 ($P < .00001$)

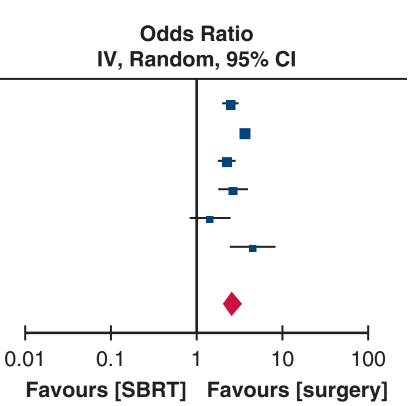

FIGURE E2. Forest plot of the OR of overall survival in unmatched patients after SBRT versus lobectomy in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Smith 2015	0.24	0.13	16.9%	1.27 [0.99, 1.64]
Shirvani 2014	0.01	0.16	15.7%	1.01 [0.74, 1.38]
Boyer 2017	0.67	0.08	18.6%	1.95 [1.67, 2.29]
Robinson 2013	0.67	0.22	13.3%	1.95 [1.27, 3.01]
Cornwell 2017	1.22	0.42	7.1%	3.39 [1.49, 7.72]
Varlotto 2013	0.58	0.16	15.7%	1.79 [1.31, 2.44]
Hamaji 2015	0.88	0.31	10.0%	2.41 [1.31, 4.43]
Chang 2015	–1.64	0.8	2.6%	0.19 [0.04, 0.93]
Total (95% CI)			**100.0%**	**1.61 [1.23, 2.12]**

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 30.30$, df = 7 ($P < .0001$); $I^2 = 77\%$
Test for overall effect: Z = 3.43 ($P = .0006$)

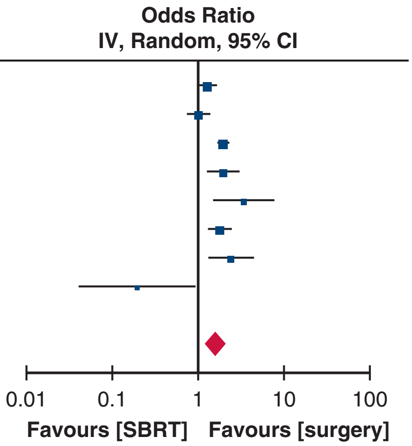

FIGURE E3. Forest plot of the OR of overall survival in matched patients after SBRT versus lobectomy in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Shirvani 2014	0.31	0.1	23.4%	1.36 [1.12, 1.66]
Puri 2015	0.48	0.03	50.6%	1.62 [1.52, 1.71]
Bryant 2017	0.37	0.12	18.6%	1.45 [1.14, 1.83]
Parashar 2015	1.08	239.05	0.0%	2.94 [0.00, 8.887E203]
Varlotto 2013	0.36	0.28	4.7%	1.43 [0.83, 2.48]
Grills 2010	1.2	0.37	2.8%	3.32 [1.61, 6.86]
Total (95% CI)			**100.0%**	**1.54 [1.36, 1.75]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 7.36$, df = 5 ($P = .19$); $I^2 = 32\%$
Test for overall effect: Z = 6.89 ($P < .00001$)

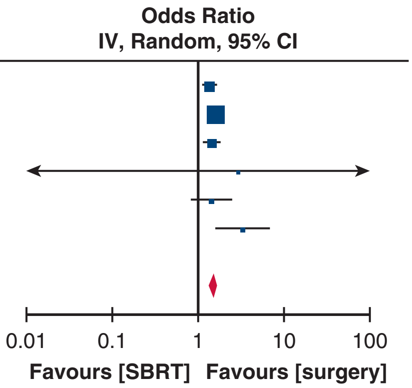

FIGURE E4. Forest plot of the OR of overall survival in unmatched patients after SBRT versus sublobar resection in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Paul 2016	0.95	0.14	21.3%	2.59 [1.97, 3.40]
Shirvani 2014	1.06	0.19	18.0%	2.89 [1.99, 4.19]
Bryant 2017	0.8	0.12	22.6%	2.23 [1.76, 2.82]
Robinson 2013	0	0.34	10.3%	1.00 [0.51, 1.95]
Grills 2010	1.2	0.89	2.2%	3.32 [0.58, 19.00]
Miyazaki 2017	1.04	1.04	1.7%	2.83 [0.37, 21.72]
Hamaji 2015	1.55	0.25	14.4%	4.71 [2.89, 7.69]
Wang 2016	0.52	0.36	9.6%	1.68 [0.83, 3.41]
Total (95% CI)			**100.0%**	**2.44 [1.86, 3.19]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 16.54$, df = 7 ($P = .02$); $I^2 = 58\%$
Test for overall effect: Z = 6.44 ($P < .00001$)

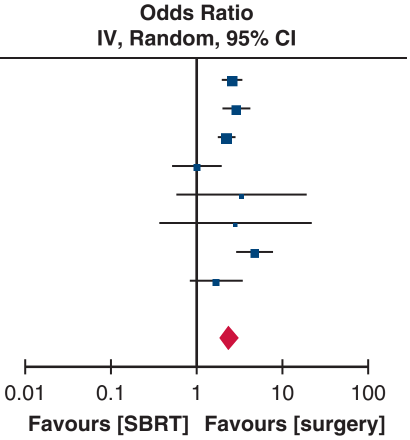

FIGURE E5. Forest plot of the OR of cancer-specific survival in unmatched patients after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Parashar 2015	0.79	0.24	29.2%	2.20 [1.38, 3.53]
Kastelijn 2015	0.83	0.22	34.8%	2.29 [1.49, 3.53]
Van Den Berg 2015	0.19	0.59	4.8%	1.21 [0.38, 3.84]
Hamaji 2015	0.9	0.29	20.0%	2.46 [1.39, 4.34]
Wang 2016	0.42	0.39	11.1%	1.52 [0.71, 3.27]
Total (95% CI)			**100.0%**	**2.13 [1.65, 2.75]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.04$, df = 4 ($P = .73$); $I^2 = 0\%$
Test for overall effect: Z = 5.82 ($P < .00001$)

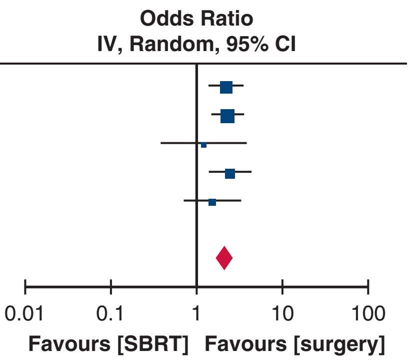

FIGURE E6. Forest plot of the OR of disease-free survival in unmatched patients after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Crabtree 2014	0.71	0.29	15.5%	2.03 [1.15, 3.59]
Cornwell 2017	1.39	0.37	14.0%	4.01 [1.94, 8.29]
Varlotto 2013	–0.02	0.4	13.4%	0.98 [0.45, 2.15]
Verstegen 2013	–0.57	0.38	13.8%	0.57 [0.27, 1.19]
Hamaji 2015	1.35	0.19	17.1%	3.86 [2.66, 5.60]
Wang 2016	1.12	0.23	16.5%	3.06 [1.95, 4.81]
Chang 2015	–0.35	0.62	9.7%	0.70 [0.21, 2.38]
Total (95% CI)			**100.0%**	**1.83 [1.06, 3.16]**

Heterogeneity: $Tau^2 = 0.42$; $Chi^2 = 33.01$, df = 6 ($P < .0001$); $I^2 = 82\%$
Test for overall effect: Z = 2.16 ($P = .03$)

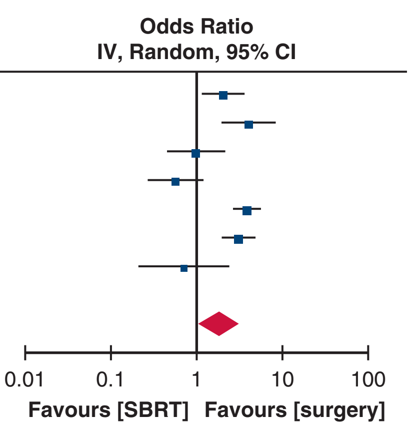

FIGURE E7. Forest plot of the OR of disease-free survival in matched patients after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Robinson 2013	2.73	1.03	13.2%	15.33 [2.04, 115.44]
Grills 2010	1.85	1.68	8.0%	6.36 [0.24, 171.18]
Kastelijin 2015	0.49	0.49	19.0%	1.63 [0.62, 4.26]
Van Den Berg 2015	0.92	0.42	19.6%	2.51 [1.10, 5.72]
Hamaji 2015	3.6	0.4	19.8%	36.60 [16.71, 80.16]
Wang 2016	0.97	0.34	20.3%	2.64 [1.35, 5.14]
Total (95% CI)			**100.0%**	**5.44 [1.68, 17.56]**

Heterogeneity: $Tau^2 = 1.64$; $Chi^2 = 37.41$, df = 5 ($P < .00001$); $I^2 = 87\%$
Test for overall effect: Z = 2.83 ($P = .005$)

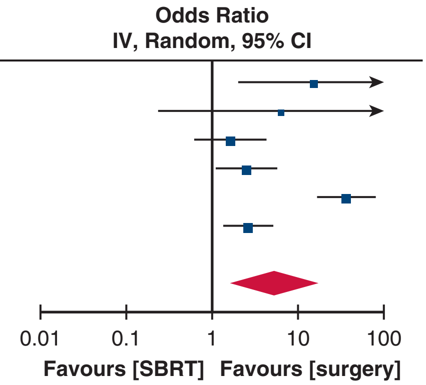

FIGURE E8. Forest plot of the OR of freedom from locoregional recurrence in unmatched patients after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

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Study or Subgroup	log [Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
Robinson 2013	1.37	0.99	12.0%	3.94 [0.57, 27.40]
Varlotto 2013	2.08	1.99	3.0%	8.00 [0.16, 395.57]
Verstegen 2013	–0.63	0.92	14.0%	0.53 [0.09, 3.23]
Hamaji 2015	1.54	0.52	43.7%	4.66 [1.68, 12.93]
Wang 2016	0.85	0.7	24.1%	2.34 [0.59, 9.23]
Chang 2015	1.63	1.91	3.2%	5.10 [0.12, 215.62]
Total (95% CI)			**100.0%**	**2.91 [1.49, 5.71]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.77$, df = 5 ($P = .45$); $I^2 = 0\%$
Test for overall effect: Z = 3.11 ($P = .002$)

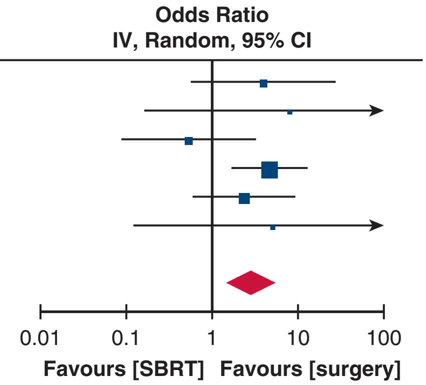

FIGURE E9. Forest plot of the OR of freedom from locoregional recurrence in matched patients after SBRT versus surgery in patients with early-stage NSCLC. The estimate of the OR of each study corresponds to the middle of the squares, and the *horizontal line* shows the 95% CI. On each line, the numbers 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; *CI*, confidence interval; *SBRT*, stereotactic body radiation therapy.

TABLE E1. Summary of baseline patient characteristics and treatment details of unmatched patients who underwent stereotactic body radiation therapy or surgical resection for early-stage non–small cell lung cancer in studies selected for meta-analysis

	Median age		Female (%)		Treatment regimen							
					SBRT		Resection type (%)				Technique (%)	
								Sublobar				
Authors	SBRT	Sx	SBRT	Sx	Total Gys	Fractions	Lobectomy	Wedge	Segmentectomy	Other	VATS	Open
Paul[16]	79^{M}	79^{M}	61	61	NR	NR	71	25	4	0	100	0
Smith[17]	NR	NR	NR	NR	NR	NR	83	17		0	NR	NR
Shirvani[20]	NS	NS	63	53^{L} 54^{S}	NR	NR	83	17		0	NR	NR
Rosen[23]	76^{M}	67^{M}	57	55	NR	3-5	100	0	0	0	NR	NR
Puri[24]	75	68	55	55	47-61	NR	74	24		2^{P}	NR	NR
Boyer[25]	72^{M}	67^{M}	1	3	NR	NR	75	20		3^{P}	14	86
Bryant[26]	NR	NR	3	4	NR	NR	82	18		0	NR	NR
Crabtree[27]	74^{M}	66^{M}	47	54	45-60	3-6	76	11	7	4^{P} 2^{B}	NR	NR
Robinson[28]	76	66	44	46	45-54	3-5	91	0	0	3^{B} 6^{P}	14	86
Cornwell[33]	70	64	2	8	NR	4-5	100	0	0	0	100	0
Varlotto[34]	73	69	52	43	48-60	3-5	73	27		0	NR	NR
Grills[35]	78	74	60	62	48-60	4-5	0	100	0	0	52	48
Kastelijn[36]	72^{M}	67^{M}	64	38	54-60	3-8	80	3	0	5^{B} 10^{P} 2^{SV}	41	59
Verstegen[37]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mokhles[39]	74	65	35	34	45-60	5-20	76	3	0	7^{B} 14^{P}	NR	NR
van den Berg[40]	77	67	27	33	60	3-12	77	12	0	8^{B} 3^{P}	6	94
Palma[41]	NS	NS	29	29	32-60	2-8	NR	NR	NR	NR	NR	NR
Miyazaki[42]	82	83	29	30	48-60	4-10	60	21	19	0	NR	NR
Hamaji[43]	77	66	28	43	48-60	4-8	100	0	0	0	100	0
Nakagawa[45]	80^{M}	78^{M}	29	33	48-60	4-8	84	2	13	1^{P}	NR	NR
Wang[46]	83^{M}	73^{M}	12	8	54-60	3-8	60	40		0	51	49

SBRT, Stereotactic body radiation therapy; *Sx*, surgery; *VATS*, video-assisted thoracoscopic surgery; *M*, mean value; *NR*, not reported; *L*, lobectomy; *S*, sublobar; *P*, pneumonectomy; *B*, bilobectomy; *SV*, sleeve resection.

TABLE E2. Summary of histopathologic and clinical staging details of unmatched patients who underwent stereotactic body radiation therapy or surgical resection for early-stage non–small cell lung cancer in studies selected for meta-analysis

	Histopathology – SBRT (%)				Histopathology – surgery (%)				Clinical stage – SBRT (%)				Clinical stage – surgery (%)			
Author	A	Sq	O	U	A	Sq	O	U	IA	IB	IIA	IIB/IIIA	IA	IB	IIA	IIB/IIIA
Paul[16]	49	43	8	0	49	27	24	0	70	30	0	0	67	33	0	0
Smith[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shirvani[20]	47	26	27	0	58^{S} 61^{L}	32^{S} 31^{L}	10^{S} 8^{L}	0	80	20	0	0	77^{S} 88^{L}	23^{S} 12^{L}	0	0
Rosen[23]	48	33	19	0	69	26	5	0	77	23	0	0	70	30	0	0
Puri[24]	NR	NR	NR	NR	NR	NR	NR	NR	76	24	0	0	72	28	0	0
Boyer[25]	24	42	26	9	50	38	10	2	51	49	0	0	55	45	0	0
Bryant[26]	39	45	0	16	58^{S} 57^{L}	33^{S} 32^{L}	NS	9^{S} 11^{L}	81	19	0	0	88^{S} 73^{L}	11^{S} 27^{L}	0	0
Crabtree[27]	NR	NR	NR	NR	NR	NR	NR	NR	73	27	0	0	59	36	3	2
Robinson[28]	46	32	21	1	59	34	3	4	72	24	4	0	53	32	9	6
Cornwell[33]	43	41	16	0	65	26	9	0	75	25	0	0	74	26	0	0
Varlotto[34]	28	28	43	0	61	31	8	0	100	0	0	0	100	0	0	0
Grills[35]	62	33	0	5	65	25	10	0	71	29	0	0	81	19	0	0
Kastelijn[36]	9	9	12	70	59	33	8	0	72	14	7	7	53	21	14	12
Verstegen[37]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mokhles[39]	10	11	19	60	40	36	24	0	53	35	11	1	45	26	19	10
Van Den Berg[40]	NR	NR	NR	NR	NR	NR	NR	NR	64	36	0	0	58	42	0	0
Palma[41]	NR	NR	NR	NR	NR	NR	NR	NR	90	10	0	0	39	61	0	0
Miyazaki[42]	32	22	0	46	70	NR	NR	NR	80	20	0	0	72	28	0	0
Hamaji[43]	52	33	15	0	74	17	9	0	72	28	0	0	71	29	0	0
Nakagawa[45]	54	34	11	0	60	34	7	0	80	20	0	0	75	25	0	0
Wang[46]	38	46	3	13	73	23	4	0	100	0	0	0	100	0	0	0

SBRT, Stereotactic body radiation therapy; *A*, adenocarcinoma; *Sq*, squamous cell carcinoma; *O*, other type of non–small cell lung cancer; *U*, undefined; *NR*, not reported; *S*, sublobar; *L*, lobectomy.

TABLE E3. Summary of perioperative morbidity and mortality outcomes in matched patients who underwent stereotactic body radiation therapy or surgical resection for early-stage non–small cell lung cancer in studies selected for meta-analysis

	Mortality (%)		Surgical morbidity (%)					SBRT morbidity (%)			
Author	SBRT	Surgery	Air leak	Pneumonia	PE	Cardiac arrhythmia	MI	Rib fracture	Pneumonitis	Chest pain	Fatigue
Paul[16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shirvani[20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rosen[23]	NR	3	NR	NR	NR	NR	NR	NR	NR	NR	NR
Puri[24]	NR	3	NR	NR	NR	NR	NR	NR	NR	NR	NR
Boyer[25]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crabtree[27]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Robinson[28]	0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Cornwell[33]	0	0	0	0	0	5	0	0	8	11	0
Varlotto[34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kastelijn[36]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Verstegen[37]	0	2	0	0	0	0	0	0	2	1	0
Palma[41]	2	8	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miyazaki[42]	NR	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hamaji[43]	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang[46]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chang[7]	0	4	0	7	0	4	0	3	NR	NR	3

SBRT, Stereotactic body radiation therapy; *PE*, pulmonary embolism; *MI*, myocardial infarction; *NR*, not reported.

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TABLE E4. Summary of perioperative morbidity and mortality outcomes in unmatched patients who underwent stereotactic body radiation therapy or surgical resection for early-stage non–small cell lung cancer in studies selected for meta-analysis

	Mortality (%)		Surgical morbidity (%)					SBRT morbidity (%)			
Author	SBRT	Surgery	Air leak	Pneumonia	PE	Cardiac arrhythmia	MI	Rib fracture	Pneumonitis	Chest pain	Fatigue
Paul[16]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Smith[17]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Shirvani[20]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Rosen[23]	NR	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Puri[24]	NR	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Boyer[25]	NR	NR	NR	13	NR	NR	NR	NR	1	NR	NR
Bryant[26]	1	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Crabtree[27]	1	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Robinson[28]	0	2	4	0	0	12	2	NR	8	0	0
Cornwell[33]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Varlotto[34]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Grills[35]	0	0	0	3	0	6	0	12	20	0	27
Kastelijn[36]	0	2	NR	NR	NR	NR	NR	NR	NR	NR	NR
Verstegen[37]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mokhles[38]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
van den Berg[40]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Palma[41]	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Miyazaki[42]	NR	0	12	7	0	6	0	0	17	0	0
Hamaji[43]	0	0	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nakagawa[45]	3	1	NR	NR	NR	NR	NR	NR	NR	NR	NR
Wang[46]	0	2	NR	NR	NR	NR	NR	NR	NR	NR	NR

SBRT, Stereotactic body radiation therapy; *PE*, pulmonary embolism; *MI*, myocardial infarction; *NR*, not reported.

THOR