Original Article

Stereotactic body radiation therapy or surgery for stage I–II non-small cell lung cancer treatment?—outcomes of a meta-analysis

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Background: Stereotactic body radiotherapy (SBRT) has been increasingly recognized as a favourable alternative to surgical resection for early-stage non-small cell lung cancer (NSCLC). Many retrospective analyses compared the efficacy of SBRT with that of surgery for NSCLC. However, the difference in efficacy between SBRT and surgery in patients with early-stage NSCLC remains unclear.

Methods: We searched PubMed, the Cochrane Library, EMBASE and the Chinese Biomedical Literature Database from inception to March 14, 2018, to identify studies comparing SBRT with surgery in the treatment of stage I/II NSCLC. STATA 12.0 software was used to perform the meta-analysis.

Results: A total of 15 studies that carried out propensity score matching (PSM) were included. In this meta-analysis, patients with SBRT had worse overall survival (OS) than those with surgery, but the analysis restricting studies to the same adjustment factors showed that the difference in OS gradually decreased with the increase in comparable matching characteristics between the two groups and that there was eventually no significant difference. Patients treated with SBRT achieved similar cause-specific survival (CSS), local control, regional control, loco-regional control, and distant control compared with surgery. In addition, a separate analysis of 6 studies that compared SBRT with lobectomy also showed that with the increase in comparable matching characteristics between surgery and SBRT, the OS differences gradually decreased, and there was eventually no significant difference.

Conclusions: In this study, we found more favourable OS for stage I/II NSCLC treated with surgery, but when there were increasing numbers of comparable matching characteristics between surgery and SBRT, the differences in the survival rate were reduced to the point that they were not significant. The CSS and recurrence (local, regional, or disseminated) differences between surgery and SBRT were also not significant. Therefore, SBRT has the potential to be an alternative to surgical treatment in patients with stage I/II NSCLC, but these findings need to be confirmed by large-sample, long-term follow-up randomized clinical studies.

Keywords: Meta-analysis; stereotactic body radiotherapy (SBRT); stereotactic ablative radiotherapy (SABR); surgery; stage I/II non-small cell lung cancer (NSCLC)

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Introduction

Lung cancer is the most common type of cancer in China, with an annual incidence of approximately 7,810,001 new cases (1), and it is also the main cause of cancer death in the United States (2). In 2018, 154,050 deaths are estimated to be related to lung cancer (3). Only 18% of all patients with lung cancer are alive 5 years or more after diagnosis (4). Advanced diagnosis has been the main obstacle to the improvement of lung cancer survival rates (5,6). The National Lung Screening Trial (ACRIN Protocol A6654) showed that screening individuals with high-risk factors using low-dose CT decreased the mortality rate from lung cancer by 20% (7). Thus, early diagnosis and treatment of lung cancer are extremely important. Lung cancer is the leading cause of cancer-related deaths worldwide. NSCLC constitutes approximately 80% of lung cancer cases. For early-stage NSCLC, lobectomy with mediastinal node dissection or sampling remains the standard therapy for operable patients (8). However, some patients cannot undergo surgical treatment because of considerable complications or advanced age. Recently, SBRT has been increasingly used for the treatment of early NSCLC. Chang *et al.* (9) reported the results of two phase III clinical trials (STARS and ROSEL) for operable stage I NSCLC, which showed that the 3-year survival rate following treatment with stereotactic ablation radiotherapy (SABR) was higher than that following treatment with surgery (P=0.037). However, Samson *et al.* (10) performed a clinical study focusing on the same inclusion criteria as the STARS and ROSEL trials but with different sample sizes and confirmed that the survival results of small sample studies were highly variable and unreliable. The results of retrospective studies on SBRT and surgery for I/II NSCLC are inconsistent (11,12). Therefore, we carried out a meta-analysis with the aim of comparing the efficacy of SBRT and surgery for stage I/II NSCLC.

Methods

Search strategy

The electronic databases searched included PubMed, The Cochrane Library, EMBASE and the Chinese Biomedical Literature Database from their inception to March 14, 2018. All searches used a combination of advanced retrieval and topic retrieval. References of relevant studies were hand-searched to identify additional relevant publications. The search strategy for PubMed is shown in *Box 1*, and the search strategies for other databases can be found in Appendix 1.

#1. Search "Lung Neoplasms"[Mesh]
#2. Search Pulmonary Neoplasm* [Title/Abstract] OR Lung Neoplasm [Title/Abstract] OR Lung Cancer* [Title/Abstract] OR Pulmonary Cancer* [Title/Abstract]
#3. Search "Radiosurgery"[Mesh]
#4. Search Radiosurgeries [Title/Abstract] OR Stereotactic Radiation Therap* [Title/Abstract] OR Stereotactic Radiation* [Title/Abstract] OR Stereotactic Radiosurger* [Title/Abstract] OR Gamma Knife Radiosurger* [Title/Abstract] OR Stereotactic Body Radiotherap* [Title/Abstract] OR Linear Accelerator Radiosurger* [Title/Abstract] OR LINAC Radiosurger* [Title/Abstract] OR CyberKnife Radiosurger* [Title/Abstract]
#5. Search #1 OR #2
#6. Search #3 OR #4
#7. Search #5 AND #6

Box 1 PubMed search strategy.

Inclusion and exclusion criteria

Studies were included if they met the following criteria: (I) Published in Chinese or English; (II) early-stage NSCLC strictly limited to stage I and II; (III) the type of intervention was stereotactic body radiation therapy, equivalent to SABR and stereotactic radiosurgery. The control was surgical procedures that could be either full anatomical resections, including lobectomy, bilobectomy, and pneumonectomy, or limited lung resection, including sublobar resection, segmentectomy, and wedge resection; (IV) retrospective study design; and (V) outcomes of interest included overall survival (OS), cause-specific survival (CSS), freedom from progression (FFP), recurrence-free survival (RFS), disease-free survival (DFS), local control rate (LCR), regional control rate (RCR), loco-regional control rate (L-RCR) and/or distant control rate (DCR).

Exclusion criteria: (I) For republished literature, if more than one study reported the same measurement for the same clinical trial, only the broader study was selected; if the measurement indicators were different, the corresponding measurement indicators were all included in the analysis; (II) studies with incomplete data or missing information, such as case reports, reviews, notes, letters, commentaries and errata; and (III) studies that included other treatment measures.

Study selection and data collection

Two investigators (L Shao and Y Liao) independently screened the titles and abstracts of potentially relevant

studies. We retrieved the full text of relevant studies for further review by the same two reviewers. A third senior investigator (Q Zhang) resolved any discrepancies between the reviewers. The same paired reviewers extracted study details independently. A third investigator (Q Zhang) reviewed all data entries. We extracted the following data: author, study design, study period, patient characteristics (sex, age, case number, tumour size, stage), interventions (radiation dose and fractionation schedule), sample size, length of follow-up, and outcomes of interest [hazard ratios (HR) with corresponding 95% confidence interval (95% CI) or relevant data for HR and 95% CI calculation].

Quality assessment

We used the Newcastle-Ottawa Scale (NOS) to assess the quality of the included studies (13). This scale judged a study based on three broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively.

Statistical analysis

This meta-analysis was performed with STATA 12.0 software. The endpoint outcomes were considered as a weighted average of individual estimates of the HR in each included study, using the inverse variance method. In a meta-analysis, it is usually required that the corresponding sample statistic of the effect size approximately obey a normal distribution. When the effect indicator of the endpoints of interest is the hazard ratio, the effect size is the logarithm of HR. The lnHR were considered to obey a normal distribution. If the HR and the corresponding 95% CI were reported, the lnHR and the corresponding lnLL and lnUL were used as data points in the pooled analysis. If the HR and 95% CI for surgical treatment to stereotactic radiotherapy were provided, the HR and 95% CI for stereotactic radiotherapy to surgical treatment were calculated using the method described by Tierney *et al.* (14). If the HR or 95% CI was not provided and when the K-M curves were available, survival data were extracted from amplified K-M curves using an open digitizing programme (GetData Graph Digitizer), and the estimates of HR and 95% CI were calculated according to the method described by Tierney *et al.* (14).

A sensitivity analysis was conducted for each study to rule out its predominant influence on the pooled results. Heterogeneity was assessed by the χ^2 test according to the Cochrane systematic review handbook and was investigated using the I^2 statistic. Studies with an I^2 of 25 to 50%, 50% to 75%, or >75% were considered to have low, moderate, or high heterogeneity, respectively. The pooled HRs were first calculated using the fixed-effects model. If there was high heterogeneity among studies, the randomized-effects model was used. A P value less than 0.05 was considered statistically significant.

Results

Overview of literature search and study characteristics

A total of 7,330 studies were identified from the databases, among which 54 were included in the full-text evaluation. Fifteen retrospective studies were included in this meta-analysis (11,12,15-27) (*Figure 1*). All the included studies were of moderate quality at least. *Table 1* shows the basic characteristics of the 15 studies. Among them, 6 studies compared SBRT with lobectomy.

Meta-analysis results

OS

Fifteen studies reported OS (11,12,15-27). The pooled HR showed that surgery was associated with a significantly higher OS than SBRT (HR =1.81; 95% CI, 1.72–1.90; P=0.000; *Figure 2*). The sensitivity analysis demonstrated that the result of OS was relatively stable and credible (*Table S2*). However, the matched baseline characteristics in each study were not consistent (*Table S1*). We restricted studies to the same matched and comparable characteristics, and the results are shown in *Table 2*. The effect estimates of SBRT versus surgery for each of the subgroups were as follows: matched on six characteristics (11,20,23,25,26) (HR =1.769; 95% CI, 1.223–2.559; P=0.002); matched on seven characteristics (11,20,23,25) (HR =1.650; 95% CI, 1.112–2.447, P=0.013); matched on eight characteristics (11,20,23) (HR =1.623; 95% CI, 0.848–3.106; P=0.144); and matched on nine characteristics (11,20) (HR =1.156; 95% CI, 0.623–2.146; P=0.646). The sensitivity analysis demonstrated that some of the results of OS for studies that were restricted to the same matching and comparable characteristics were not stable (*Table S3*).

CSS

Four studies (12,18,23,26) assessed CSS. The forest plot

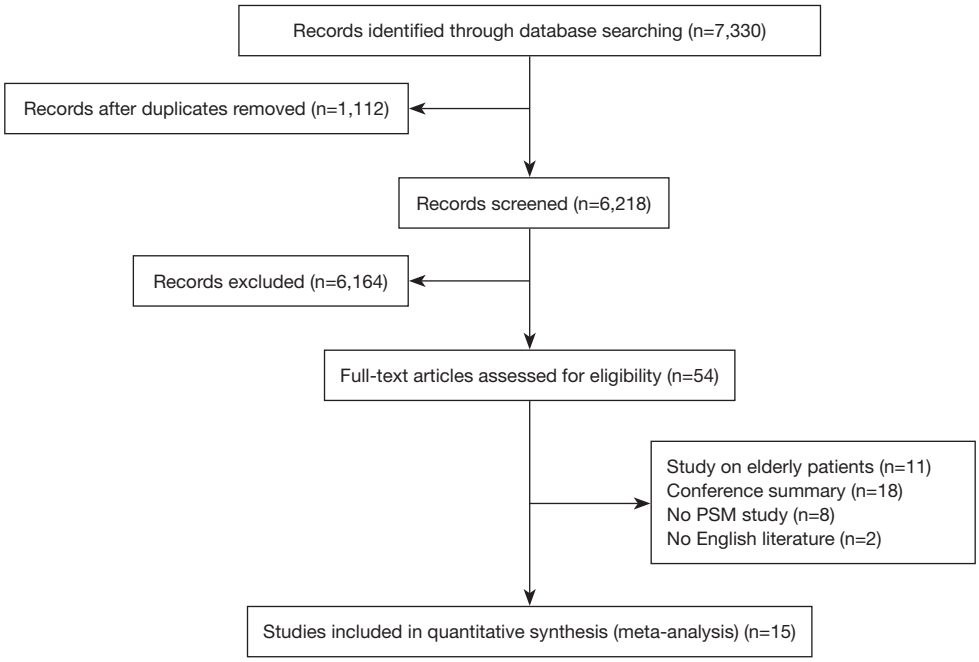

Figure 1 Flow chart of study inclusion. PSM, propensity score matching.

is shown in *Figure 3*. The CSS (HR =1.49; 95% CI, 0.59–3.77; P=0.401) was similar between SBRT and surgery treatments. The sensitivity analysis excluding Hamaji's research (*Table S2*) showed that the HR =0.919; 95% CI, 0.50–1.70, the CSS still similar between SBRT and surgery treatments.

FFP, DFS, or RFS

There were 8 studies that reported FFP, DFS, or RFS according to the definitions in the literature. Four studies defined FFP or DFS as the time from the start of treatment until tumour recurrence or death (22,23,25,26). Surgery showed significantly better outcomes compared with SBRT (HR =2.25; 95% CI, 1.65–3.06; P=0.000; *Figure 4A*). The other four studies (11,15,16,20) defined RFS as freedom from any tumour recurrence, and the pooled results showed that there was no significant difference between surgery and SBRT (HR =0.73; 95% CI, 0.34–1.60; P=0.434; *Figure 4B*). According to the results of the sensitivity analysis, the pooled results are relatively stable and credible (*Table S2*).

LCR, RCR, L-RCR, or DCR

Three studies (12,23,25) reported data on LCR and RCR (*Figure 5*). The pooled analysis showed that SBRT and surgery had similar LCR/RCR, with pooled HRs of 2.22 (95% CI, 0.69–7.17; P=0.184) and 1.23 (95% CI, 0.66–2.29; P=0.517), respectively. Furthermore, four studies reported data on L-RCR (11,15,20,22), six studies (11,12,20,22,23,25) reported data on DCR, and the pooled analysis showed that the differences were not statistically significant, with pooled HRs of 1.11 (95% CI, 0.44–2.77; P=0.830) and 1.32 (95% CI, 0.75–2.31; P=0.341), respectively (*Figure 5*). According to the results of the sensitivity analysis, the pooled results are relatively stable (*Table S2*).

OS comparison between SBRT and lobectomy

Six of the included studies (11,17,20,23,24,26) performed a comparative study of lobectomy and SBRT for stage I/II NSCLC. A pooled analysis of these 6 studies showed that lobectomy had a better survival benefit over SBRT (HR =2.00; 95% CI, 1.45–2.74; P=0.000; *Figure 6*), and the sensitivity analysis also showed similar results (*Table S2*). The pooled results from analyses restricting studies to those with comparable characteristics are shown in *Table 3*, and the effect estimates of SBRT to lobectomy for each subgroup were as follows: matched on three characteristics (11,20,23,24,26) (HR =2.044; 95% CI, 1.150–3.634; P=0.015); matched on six characteristics (11,20,23,26) (HR =1.837; 95% CI, 1.068–3.158; P=0.028); matched on eight characteristics (11,20,23) (HR =1.623; 95% CI,

Table 1 Basic characteristics of the eligible studies.

Study	Research year range	Treatment type	Number of cases	Gender (M/F)	Age [mean] range or SD	Tumour size [cm]	Stage T1/T2	Follow-up time (months)	Dose range (Gy)	The main outcome of interest	NOS	Matching characteristics
Ye *et al.* 2018	Feb 2010–Jun 2016	Surgery	66	46/20	69	2.44±0.89	44/22	27		OS, L-RCR, DCR, PFS	7	abcde*fghi
		SBRT	66	42/24	71	2.49±0.92	45/21	26.5	50 Gy/5 F, 60 Gy/10F			
Varlotto *et al.* 2013	2000–2008	SBRT	77					18.8	60 [48–60] Gy/3 [3–5] F	OS, DFS	8	NA
	1999–2008	Surgery	77					35				
Verstegen *et al.* 2013	2007–	VATS lobectomy	64	36/28	67.95±8.84	2.86±1.24	39/24	16		OS, L-RCR, DCR, PFS	7	abcdjkefl
	Nov 2003–	SABR	64	37/27	70.53±9.91	2.88±1.287	39/25	30	54–60 Gy/3, 5, 8, 12 F			
Rosen *et al.* 2016	2008–2012	Lobectomy	1,781	777/1,004	74.8	2.37	1,374/407	31.6		OS	6	a*bcde*fm*nz¤o
		SBRT	1,781	767/1,014	75.5	2.38	1,371/410	28.6	BED100–200 Gy/3–5 F			
Robinson *et al.* 2013	Jan 2004–Jan 2008	Lobar resection	76	37/39	65 [40–87]	2 [0.8–5.8]	59/17	51.3		OS, LCR, RCR, DCR, CSS	7	a*bcdj*k*ep*q*r*zh
		SBRT	76	42/34	76 [31–93]	2 [1.1–6]	56/20	50.3	45–54 Gy/3–5 F			
Puri *et al.* 2012	Jan 1, 2000–Dec 21, 2006	Surgery	57	34/23	71.54±7.9		40/17			OS, CSS	7	ab*dk*p*q
	Feb 1, 2004–May 5, 2007	SBRT	57	23/34	71.79±10.6		39/18		54 Gy/3 F			
Puri *et al.* 2015	1998–2010	Surgery	5,355	2,382/2,973	74.2±8.4	2.33±1.03	4,099/1,256	27.5		OS	6	abcdjnzβs*
	2003–2010	SBRT	5,355	2,407/2,948	74.3±8.5	2.34±0.95	4,063/1,292	16.6	54 Gy			
Mokhles *et al.* 2015	Jan 2003–Jan 2012	Surgery	73	44/29	67 [39–83]	2.4 [1–6.6]		49		OS, L-RCR, DCR, PFS	7	abcdjkeftl
		SABR	73	42/31	67 [47–89]	2.5 [0.8–7]		28	54–60 Gy/3, 5, 8, 12 F			
Matsuo *et al.* 2014	Jan 2003–Dec 2009	Sublobar resection	53	37/16	76 [50–88]	2 [0.6–5]		63.6		OS, LCR, RCR, DCR, CSS	7	abcjke*l
		SBRT	53	42/11	76 [58–86]	2.2 [1–3.7]		80.4	48, 56, 60 Gy/4, 8 F			

Table 1 *(continued)*

Table 1 *(continued)*

Study	Research year range	Treatment type	No. of cases	Gender (M/F)	Age [mean] range or SD	Tumour size (cm)	Stage T1/T2	Follow-up time (months)	Dose range (Gy)	The main outcome of interest	NOS	Matching characteristics
Kastelijn *et al.* 2015	2008–2011	Surgery	175					31.8		OS, L-RCR, DCR, PFS	7	NA
		SBRT	53					41.5	18 Gy/3 F 12 Gy/5 F 7.5 Gy/8 F			
Hamaji *et al.* 2015	2003–2009	VATS lobectomy	41	32/9	74 [61–86]	2.5 [1.2–4.5]	27/14	54		OS, LCR, RCR, DCR, CSS, RFS	7	abcdjkefguvγw
		SBRT	41	31/10	73 [58–85]	2.5 [1.4–4.5]	29/12	40.7	48, 56, 60 Gy/ 4, 8F			
Eba *et al.* 2016	2002–2004	Lobectomy	21	8/13	73 [67–74]	2.1 [1.8–2.4]	21/0			OS	7	abcx
	2004–2007	SBRT	21	11/10	75 [68–78]	2.3 [1.9–2.6]	21/0		48 Gy/4 F/4–8 D			
Crabtree *et al.* 2014	Jun 2004–Dec 2010	Surgery	56	32/24	70.0±8.1	3.0±1.6	32/24	34		OS, LCR, RCR, DCR, DFS	7	abcdjk ftgzδp*
		SBRT	56	29/27	70.7±10.6	2.5±1.1	40/16	23.4	45–60 Gy/3–6 F			
Cornwell *et al.* 2018	Jul 1, 2009–Dec 31, 2014	VATS lobectomy	37	36/1	68 [63–73]	2.3 [1.7–3.0]		43.2		OS, LCR, RCR, DCR, CSS, RFS	8	abcdjketgy*
		SBRT	37	36/1	66 [63–72]	2.2 [1.6–2.7]		44.4	56 [50–56] Gy/ 4 [4–5] F			
Yerokun *et al.* 2017	2008–2011	Wedge resection	1,584	622/962	73 [67–79]	1.5 [1.3–1.9]	1,584/0			OS	7	abcjefnε
		SBRT	1,584	654/930	73 [67–79]	1.5 [1.3–1.8]	1,584/0					

*The characteristics are significantly different between SBRT and surgery (P<0.05). NA, not applicable; SD, Standard deviation; NOS, Newcastle-Ottawa Scale; OS, overall survival; CSS, cause-specific survival; FFP, freedom from progression; RFS, recurrence-free survival; DFS, disease-free survival; LCR, local control rate; RCR, regional control rate; L-RCR, loco-regional control rate; DCR, distant control rate; SABR, stereotactic ablation radiotherapy; SBRT, stereotactic body radiotherapy. a, age; b, male/female; c, tumour size; d, clinical staging; e, pathological cell type; f, tumour location; g, smoking status; h, SUVmax; i, COPD; j, CCI; k, FEV1; l, WHO performance score; m, pathological grade; n, facility type; o, facility location; p, DLCO; q, ACE score; r, FVC; s, chemotherapy; t, hypertension; u, comorbidities; v, serum CEA, SCC; w, follow-up period; x, C/T ratio; y, mediastinal staging via EBUS; z, race; α, Spanish Hispanic, origin primary payer, median income, high school degree, urban/rural; β, urban location, income >$35,000/year; γ, mortality within 30 days of treatment; δ, weight (lb); ε, insurance status distance to hospital (*Table S1*). There are two studies that did not match any characteristics (16,22) in *Table 1* because the two studies only listed the matching characteristics in the text. However, there is no specific table description, we do not know the specific P value of the comparison of matched characteristics between the SBRT and surgery groups in the propensity-matched patients. The data could not be further analysed, so we expressed the results as NA.

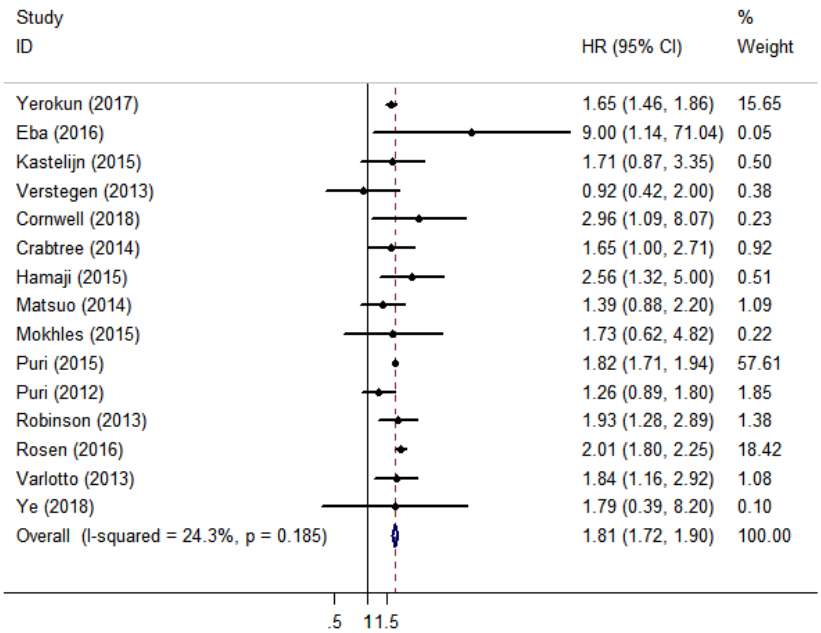

Figure 2 Pooled analysis of OS between SBRT and surgery. OS, overall survival; SBRT, stereotactic body radiotherapy.

Table 2 Pooled analysis of OS between SBRT and surgery in some studies that were restricted to same matching and comparable characteristics.

Matching and comparable basic features	Study number	Surgery N	SBRT N	Heterogeneity		Meta-analysis results		
				I^2 (%)	P	HR (95% CI)	P	Z
Age/sex/tumour size/stage/CCI/FEV1	5	271	271	20.4	0.285	1.769 (1.223–2.559)	0.002	3.03
Age/sex/tumour size/stage/CCI/FEV1/tumour site	4	234	234	22.5	0.276	1.650 (1.112–2.447)	0.013	2.49
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology	3	178	178	48.3	0.144	1.623 (0.848–3.106)	0.144	1.46
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology/WHO performance score	2	137	137	0	0.332	1.156 (0.623–2.146)	0.646	0.46

OS, overall survival; SBRT, stereotactic body radiotherapy; CCI, Charlson Comorbidity Index; FEV1, forced expiratory volume in 1 second.

0.848–3.106; P=0.144); and matched on nine characteristics (11,20) (HR =1.156; 95% CI, 0.623–2.146; P=0.646). The sensitivity analysis of studies that were restricted to the same matched and comparable characteristics showed that the results were not very stable (*Table S3*).

Publication bias

A funnel plot was generated for OS to evaluate publication bias (*Figure 7*). Egger's test (P=0.773) indicated that there was no obvious publication bias.

Discussion

Lung cancer is the world's leading cause of cancer-related death (28). The prevalence of early-stage NSCLC is expected to increase given the current trends in the widespread implementation of computed tomography (CT) screening (7,29). Although lobectomy remains the treatment of choice for early-stage NSCLC, some patients with early-stage NSCLC are not considered candidates for lobar resection because of concomitant severe medical comorbidities or patient preference. SBRT is a non-invasive treatment that delivers precisely targeted ablative doses of

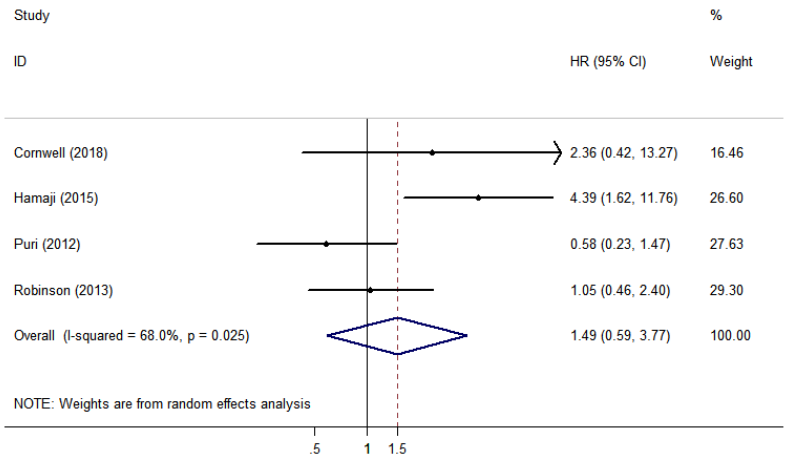

Figure 3 Pooled analysis of CSS between SBRT and surgery. CSS, cause-specific survival; SBRT, stereotactic body radiotherapy.

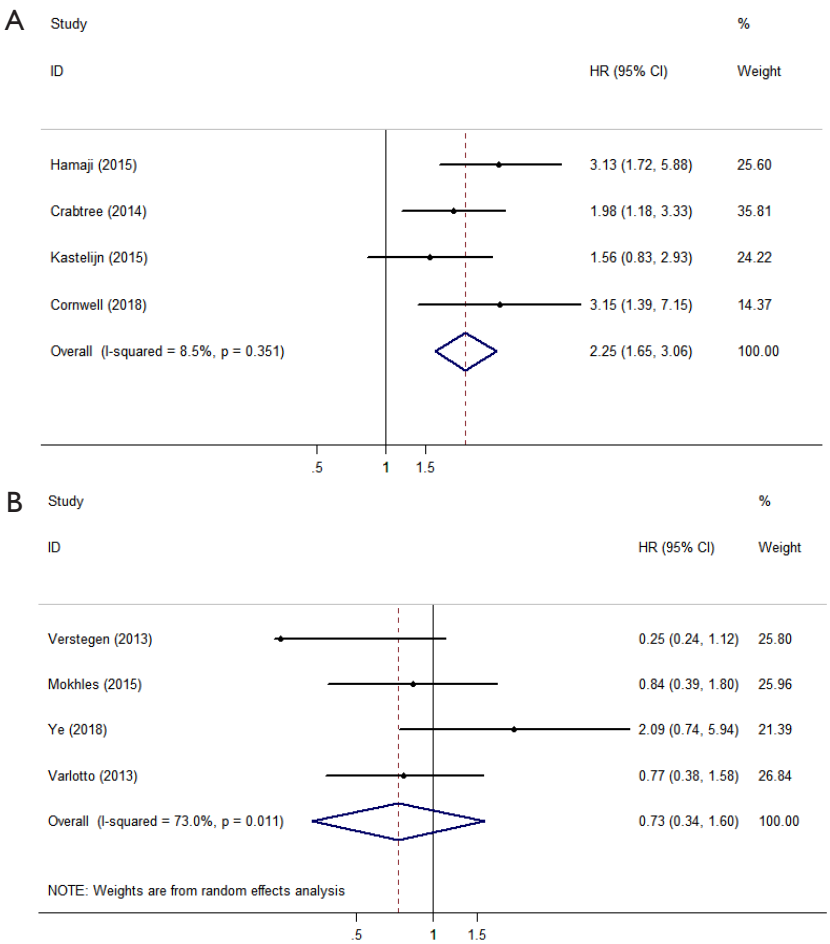

Figure 4 Pooled analysis of FFP or DFS, RFS. (A) Pooled analysis of FFP or DFS between SBRT and surgery; (B) pooled analysis of RFS between SBRT and surgery. FFP, freedom from progression; DFS, disease-free survival; SBRT, stereotactic body radiotherapy; RFS, recurrence-free survival.

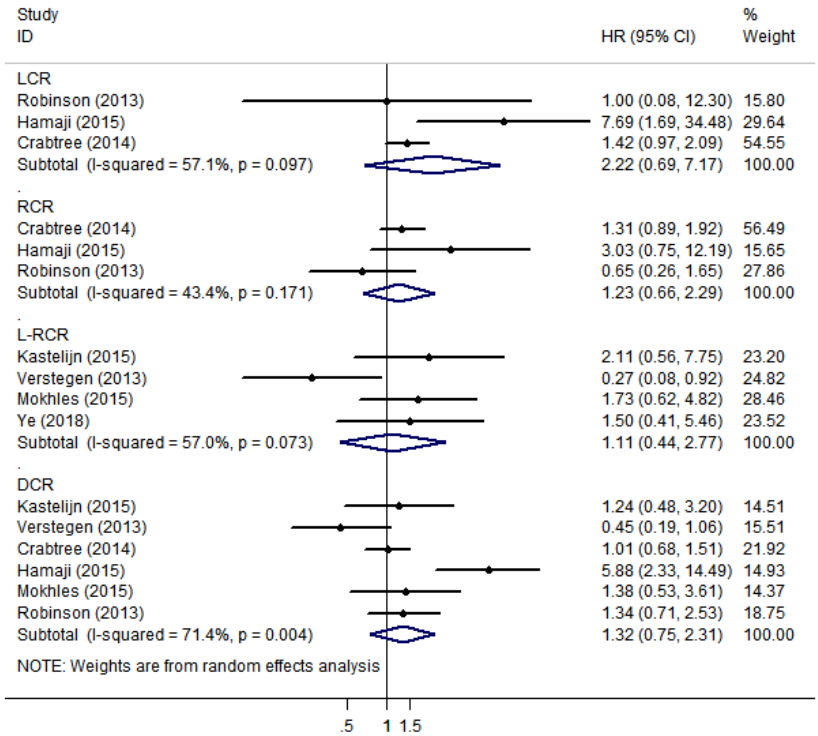

Figure 5 Pooled analysis of LCR, RCR, L-RCR, and DCR between SBRT and surgery. LCR, local control rate; RCR, regional control rate; L-RCR, loco-regional control rate; DCR, distant control rate; SBRT, stereotactic body radiotherapy.

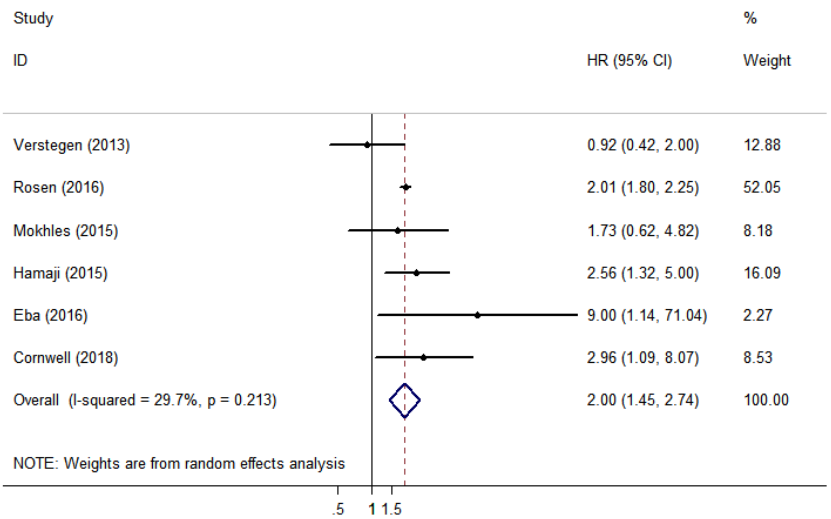

Figure 6 Pooled analysis of OS between SBRT and lobectomy. OS, overall survival; SBRT, stereotactic body radiotherapy.

radiation using the principles of stereotaxis, rigorous patient immobilization and/or tumour tracking, and modern radiotherapy treatment planning. SBRT was initially introduced as an alternative to conventionally fractionated radiation therapy for medically inoperable patients with early-stage NSCLC. SBRT in medically operable patients was first reported in Japan (30), where higher 3-year rates of local control (94%) and OS (86%) were documented

Table 3 Pooled analysis of OS between SBRT and lobectomy in some studies that were restricted to the same matching and comparable characteristics

Matching and comparable basic features	Study number	Lobectomy N	SBRT N	Heterogeneity		Meta-analysis results		
				I^2 (%)	P	HR (95% CI)	P	Z
Age/sex/tumour size	5	236	236	43.6	0.131	2.044 (1.150–3.634)	0.015	2.44
Age/sex/tumour size/stage/CCI/FEV1	4	215	215	39	0.178	1.837 (1.068–3.158)	0.028	2.2
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology	3	178	178	48.3	0.144	1.623 (0.848–3.106)	0.144	1.46
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology/WHO performance score	2	137	137	0	0.332	1.156 (0.623, 2.146)	0.646	0.46

OS, overall survival; SBRT, stereotactic body radiotherapy; CCI, Charlson Comorbidity Index; FEV1, forced expiratory volume in 1 second.

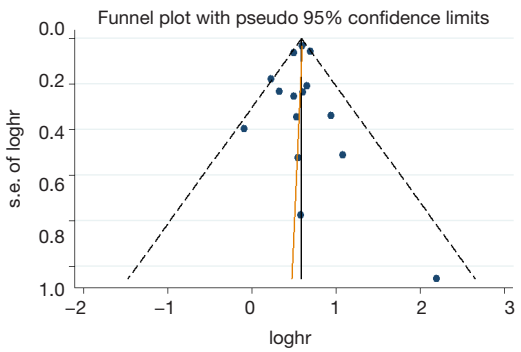

Figure 7 Funnel diagram for OS in the 15 included studies. OS, overall survival.

in patients refusing surgery. Outcomes from SBRT are so promising that there are increasing numbers of studies on the effect of surgery and SBRT for the treatment of early-stage NSCLC. Three randomized clinical trials were carried out, but they were all terminated because of poor accrual (31-33). Retrospective studies have shown that the survival rate of early-stage NSCLC patients treated with SBRT may be worse, better, or not different compared with that of patients treated with surgery (11,17,20).

We included fifteen retrospective studies in this meta-analysis. The baseline characteristics of patients in the surgical treatment group were better than those of patients in the SBRT group; therefore, propensity matching analysis was used to compensate for significant baseline differences between the two groups to achieve an objective analysis of the association between treatment and outcomes. Based on the pooled analysis of these PSM studies, we found that the OS of SBRT for stage I/II NSCLC was inferior to that of surgery (P=0.000), but there were no significant differences in LCR (P=0.184), RCR (P=0.517), L-RCR (P=0.830) or DCR (P=0.341). In addition, the pooled results showed that surgery yielded lower rates of tumour recurrence or death (P=0.000), but there was no significant difference in the rate of absence of tumour recurrence between surgery and SBRT (P=0.434). This further confirmed that surgical treatment of NSCLC was associated with a better survival advantage over SBRT, but there is no difference in recurrence. It is noteworthy that there was no significant difference between surgery and SBRT in the CSS (P=0.401), indicating that patients who undergo SBRT have the same risk of dying from cancer as those undergoing surgery, even though the OS is worse than that associated with surgical treatment. Therefore, compared with surgical treatment, SBRT patients are unhealthier and die more often from non-cancer causes. In the study of Eba *et al.* (24), multivariate analysis of OS showed that age and C/T ratio had a significant impact on OS. In the study by Robinson *et al.* (12), a univariate analysis revealed that ACE-27, CCI, sex, age and FEV1 had significant effects on survival, and a multivariate analysis showed that CCI and age had a significant impact on OS. Research conducted by Varlotto *et al.* (16) showed that OS was significantly correlated with histology, Charlson Comorbidity Index, tumour size, aspirin use, and SBRT/SABR based on a univariate analysis, while a multivariate analysis without propensity score (PS) correction correlated better OS with surgery, lower Charlson Comorbidity Index score, and adenocarcinoma histology. After adjusting for propensity scores, OS correlated only with the Charlson Comorbidity Index. The study by Ye *et al.* (15) showed that COPD (yes/no), sex (male *vs.* female), site (central *vs.* peripheral), age, tumour size, SUVmax, histology, T status, treatment

(SBRT *vs.* surgery) and smoking status were related to OS through the univariate analysis; the multivariate analysis showed that OS was only correlated with tumour size and SUVmax. Based on this finding, and although propensity score matching (PSM) was conducted in each of the included studies, there were significant differences in the matching baseline characteristics (*Table S1*); therefore, we further analysed OS results according to the match of the basic characteristics of the patients in each PSM study. The results are shown in *Table 2* and show that with an increase in matching and comparable basic characteristics between the SBRT and surgical treatment groups, the difference in survival between the two groups gradually decreased, and there was eventually no significant difference. In addition, a separate meta-analysis of 6 studies that compared lobectomy with SBRT for stage I/II NSCLC also yielded similar OS results (*Table 3*). However, according to the sensitivity analysis (*Table S3*), some of the above results changed after deleting a study, indicating that the results were not stable. However, it is worth noting that the number of studies restricted to the same matching and comparable characteristics for analysis was small, and there may be many potential factors affecting the pooled results, more studies need to be involved in the research to validate the results in the future. We further conducted an OS pooled analysis for studies restricted to a single matching and comparable characteristic (*Tables S4*,*S5*). The results show that the pooled HR based on age, pathology, FEV1 and especially WHO performance score (P=0.16) was reduced compared with the pooled HR (1.809) for the entire study. According to the sensitivity analysis, the pooled results are relatively stable and credible (*Tables S4*,*S5*). Therefore, age, pathology, FEV1 and WHO performance score may have significant effects on survival. In the current study, only partial adjustment factors were included in the PSM; however, some of the unmeasured characteristics may be confounders that could affect the results of OS. Chang *et al.* (9) reported the results of a phase III randomized clinical study that balanced the basic characteristics of patients in the surgery and SBRT groups, and the results showed that SBRT had a survival advantage over surgery. In view of the above findings, although SBRT is commonly used to treat medically inoperable patients with early-stage NSCLC, in patients with stage I/II NSCLC, who usually choose surgical treatment, and with better baseline characteristics, such as a better WHO performance score, higher FEV1 and lower CCI, SBRT may be an effective alternative treatment and is worthy of further study.

Compared with SBRT, surgical treatment of stage I/II NSCLC can include the performance of mediastinal lymph node sampling/dissection, can reveal occult nodal disease, and then corresponding patients will receive radiotherapy or chemotherapy to reduce recurrence and distant metastasis. However, in our meta-analysis, we did not find differences in LCR, RCR, L-RCR, or DCR between surgery and SBRT. Several theories have been postulated to explain this phenomenon, including the possible improvement of function of the immune system by radiation that is mediated by T-cell regulation (34,35). The high radiation doses used in SABR may also have resulted in low-dose spillage to the regional nodes, possibly eliminating microscopic disease (36). Surgery-induced oxidative stress may potentiate tumour growth through the local release of cytokines, and growth factors may stimulate tumour growth (37).

The present study has some limitations. Most importantly, this study was based on retrospective trials. To date, three phase 3 random trials have been initiated to compare SBRT with surgery in patients with early-stage NSCLC, but all of them were closed early because of slow accrual. New randomized trials, such as randomized phase III studies of sublobar resection (SR) versus SABR in high-risk patients with stage I NSCLC (STABLe-mates; CT01622621, formerly American College of Surgeons Oncology Group Z4099) and SABRTooth (ISRCTN13029788) (38), are now ongoing, and it is likely to be several years before the results are reported. Second, although all the included studies performed PSM, the matching characteristics of each study were not the same. In addition, propensity matching, although technically feasible, is essentially infeasible because medically inoperable patients who received SBRT have no true counterpart in the surgery cohort. Third, different surgical methods and radiation doses may have different efficacies in the treatment of early NSCLC. Although the surgical treatments and stereotactic radiotherapy doses vary among the studies included in this report, the data provided by each study are limited, making it difficult to conduct further analysis. Fourth, because the results of most studies included in our meta-analysis show that surgery has a significant survival advantage over SBRT, our findings may have potential bias.

Conclusions

In conclusion, compared with SBRT, surgery was associated with more favourable survival for stage I/II NSCLC, but

when increasing numbers of comparable characteristics between surgery and SBRT were matched, the differences in survival gradually decreased until they were no longer significant. There were also no significant differences in CSS and recurrence (local, regional, or disseminated). Therefore, SBRT has the potential to be an alternative to surgical treatment in patients with stage I/II NSCLC, but these findings need to be confirmed by large-sample, long-term follow-up randomized clinical studies.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.07.41). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Chen WQ, Sun KX, Zheng RS, et al. Report of Cancer Incidence and Mortality in Different Areas of China, 2014. Zhonghua Zhong Liu Za Zhi 2018;40:894-9.
2. Torre LA, Siegel RL, Jemal A. Lung cancer statistics. Adv Exp Med Biol 2016;893:1-19.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin 2018;68:7-30.
4. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017.
5. Carney DN. Lung cancer--time to move on from chemotherapy. N Engl J Med 2002;346:126-8.
6. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol 1999;17:1794-801.
7. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
8. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-e313S.
9. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630-7.
10. Samson P, Keogan K, Crabtree T, et al. Interpreting survival data from clinical trials of surgery versus stereotactic body radiation therapy in operable Stage I non-small cell lung cancer patients. Lung Cancer 2017;103:6-10.
11. Verstegen NE, Oosterhuis J W, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. Ann Oncol 2013;24:1543-8.
12. Robinson CG, Dewees TA, Naqa IME, et al. Patterns of Failure after Stereotactic Body Radiation Therapy or Lobar Resection for Clinical Stage I Non–Small-Cell Lung Cancer. J Thorac Oncol 2013;8:192-201.
13. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the Quality of non-randomised studies in meta-analyses. Available online: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
14. Tierney JF, Stewart LA, Ghersi D, et al. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007;8:16.
15. Ye L, Xu F, Shi S, et al. A SUVmax-based propensity matched analysis of stereotactic body radiotherapy versus

surgery in stage I non-small cell lung cancer: unveiling the role of 18F-FDG PET/CT in clinical decision-making. Clin Transl Oncol 2018;20:1026-34.
16. Varlotto J, Fakiris A, Flickinger J, et al. Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery. Cancer 2013;119:2683-91.
17. Rosen JE, Salazar MC, Wang Z, et al. Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer. J Thorac Cardiovasc Surg 2016;152:44-54.e9.
18. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. J Thorac Cardiovasc Surg 2012;143:428-36.
19. Puri V, Crabtree TD, Bell JM, et al. Treatment Outcomes in Stage I Lung Cancer: A Comparison of Surgery and Stereotactic Body Radiation Therapy. J Thorac Oncol 2015;10:1776-84.
20. Mokhles S, Verstegen N, Maat A P, et al. Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis. Lung Cancer 2015;87:283-9.
21. Matsuo Y, Chen F, Hamaji M, et al. Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis. Eur J Cancer 2014;50:2932-8.
22. Kastelijn EA, El Sharouni SY, Hofman FN, et al. Clinical Outcomes in Early-stage NSCLC Treated with Stereotactic Body Radiotherapy Versus Surgical Resection. Anticancer Res 2015;35:5607-14.
23. Hamaji M, Chen F, Matsuo Y, et al. Video-assisted thoracoscopic lobectomy versusstereotactic radiotherapy for stage I lung cancer. Ann Thorac Surg 2015;99:1122-9.
24. Eba J, Nakamura K, Mizusawa J, et al. Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA lung adenocarcinoma: comparison of survival, outcomes in two clinical trials with propensity score analysis (JCOG1313-A). Jpn J Clin Oncol 2016;46:748-53.
25. Crabtree T, Puri V, Robinson C, et al. Analysis of First Recurrence and Survival in Patients with Stage I Non-Small Cell Lung Cancer Treated with Surgical Resection or Stereotactic Radiation Therapy. J Thorac Cardiovasc Surg 2014;147:1183-91.
26. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. J Thorac Cardiovasc Surg 2018;155:395-402.
27. Yerokun BA, Yang CJ, Gulack BC, et al. A national analysis of wedge resection versus stereotactic body radiation therapy for stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2017;154:675-86.e4.
28. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
29. Detterbeck FC, Mazzone PJ, Naidich DP, et al. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e78S-e92S.
30. Uematsu M, Shioda A, Suda A, et al. Computed tomography-guided frameless stereotactic radiotherapy for stage I non-small cell lung cancer: a 5-year experience. Int J Radiat Oncol Biol Phys 2001;51:666-70.
31. Alliance for Clinical Trials in Oncology. Surgery With Or Without Internal Radiation Therapy Compared With Stereotactic Body Radiation Therapy in Treating Patients With High-Risk Stage I Non–Small Cell Lung Cancer. In: ClinicalTrials.gov [Internet]. Bethesda, MD: National Library of Medicine (US); 2000. NLM Identifier: NCT01336894. Available online: https://clinicaltrials.gov/ct2/show/NCT01336894. Accessed September 30, 2016.
32. M.D. Anderson Cancer Center. Randomized Study to Compare CyberKnife to Surgical Resection in Stage I Non–small Cell Lung Cancer (STARS). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. NLM Identifier: NCT00840749. Available online: https://clinicaltrials.gov/ct2/show/NCT00840749. Accessed September 30, 2016.
33. Trial of Either Surgery or Stereotactic Radiotherapy for Early Stage (IA) Lung Cancer (ROSEL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2000. NLMIdentifier: NCT00687986. Available online: https://clinicaltrials.gov/ct2/show/NCT00687986. Accessed September 30, 2016.
34. Schaue D, Ratikan JA, Iwamoto KS, et al. Maximizing tumor immunity with fractionated radiation. Int J Radiat Oncol Biol Phys 2012;83:1306-10.
35. Lee Y, Auh SL, Wang Y, et al. Therapeutic effects of ablative radiation on local tumor require CD8+ T

cells: changing strategies for cancer treatment. Blood. 2009;114:589-95.
36. Timmerman R, Bastasch M, Saha D, et al. Stereotactic body radiation therapy: normal tissue and tumor control effects with large dose per fraction. Front Radiat Ther Oncol 2011;43:382-94.
37. O'Leary DP, Wang JH, Cotter TG, et al. Less stress, more success? Oncological implications of surgery-induced oxidative stress. Gut 2013;62:461-70.
38. Snee MP, McParland L, Collinson F, et al. The SABRTooth feasibility trial protocol: a study to determine the feasibility and acceptability of conducting a phase III randomised controlled trial comparing stereotactic ablative radiotherapy (SABR) with surgery in patients with peripheral stage I non–small cell lung cancer (NSCLC) considered to be at higher risk of complications from surgical resection. Pilot Feasibility Stud 2016;2:5.

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Supplementary

Appendix 1 Search strategies of all databases besides PubMed

EMBASE

#1. 'lung cancer'/exp
#2. "pulmonary neoplasm*": ti, ab, kw OR "lung neoplasm": ti, ab, kw OR "lung cancer*": ti, ab, kw OR "pulmonary cancer*": ti, ab, kw
#3. 'stereotactic radiotherapy'/exp
#4. "Radiosurgeries": ti, ab, kw OR "Stereotactic Radiation Therap*": ti, ab, kw OR "Stereotactic Radiation*": ti, ab, kw OR "Stereotactic Radiosurger*": ti, ab, kw OR "Gamma Knife Radiosurger*": ti, ab, kw OR "Stereotactic Body Radiotherap*": ti, ab, kw OR "Linear Accelerator Radiosurger*": ti, ab, kw OR "LINAC Radiosurger*": ti, ab, kw OR "CyberKnife Radiosurger*": ti, ab, kw
#5. #1 OR #2
#6. #3 OR #4
#7. #5 AND #6

Cochrane Library

#1. MeSH descriptor: [Lung Neoplasms] explode all trees
#2. (pulmonary neoplasm*): ti, ab, kw OR (lung neoplasm): ti, ab, kw OR (lung cancer*): ti, ab, kw OR (pulmonary cancer*): ti, ab, kw
#3. MeSH descriptor: [Radiosurgery] explode all trees
#4. (Radiosurgeries): ti, ab, kw OR (Stereotactic Radiation Therap*): ti, ab, kw OR (Stereotactic Radiation*): ti, ab, kw OR (Stereotactic Radiosurger*): ti, ab, kw OR (Gamma Knife Radiosurger*): ti, ab, kw OR (Stereotactic Body Radiotherap*): ti, ab, kw OR (Linear Accelerator Radiosurger*): ti, ab, kw OR (LINAC Radiosurger*): ti, ab, kw OR (CyberKnife Radiosurger*): ti, ab, kw
#5. #1 OR #2
#6. #3 OR #4
#7. #5 AND #6

CBM

#1. "肺肿瘤"[不加权:扩展]
#2. (((((“肺癌”[常用字段:智能]) OR “非小细胞肺癌”[常用字段:智能]) OR “肺部肿瘤”[常用字段:智能]) OR “支气管肺癌”[常用字段:智能]) OR “肺肿瘤”[常用字段:智能]
#3. “放射外科手术”[不加权:扩展]
#4. ((“立体定向放射治疗”[常用字段:智能]) OR “SBRT”[常用字段:智能]) OR “立体定向放疗”[常用字段:智能]
#5. #1 OR #2
#6. #3 OR #4
#7. #5 AND #6

Table S1 Patient and disease characteristics used for matching in the included studies

Study	Matching characteristics
Ye *et al.* 2018	Age, male/female, tumour size, clinical staging, pathologic cell type*, tumour location, smoking status, SUVmax, COPD
Varlotto *et al.* 2013	NA
Verstegen *et al.* 2013	Age, male/female, tumour size, clinical staging, CCI, FEV1, pathologic cell type, tumour location, WHO performance score
Rosen *et al.* 2016	Age*, male/female, tumour size, clinical staging, pathologic cell type*, tumour location, grade*, facility type, race, spanish hispanic origin, primary payer, median income, high school degree, urban/rural, facility location
Robinson *et al.* 2013	Age*, male/female, tumour size, clinical staging, CCI*, FEV1*, pathologic cell type, DLCO*, ACE score*, FVC*, race, SUVmax
Puri *et al.* 2012	Age, male/female*, clinical staging, FEV1*, DLCO*, ACE score
Puri *et al.* 2015	Age, male/female, tumour size, clinical staging, CCI, facility type, race, urban location, income >$35,000/year, chemotherapy*, median survival*
Mokhles *et al.* 2015	Age, male/female, tumour size, clinical staging, CCI, FEV1, pathologic cell type, tumour location, hypertension, WHO performance score
Matsuo *et al.* 2014	Age, male/female, tumour size, CCI, FEV1, pathologic cell type*, performance status (0:1)
Kastelijn *et al.* 2015	NA
Hamaji *et al.* 2015	Age, male/female, tumour size, clinical staging, CCI, FEV1, pathologic cell type, tumour location, smoking status, comorbidities, serum CEA, serum SCC antigen, mortality within 30 days of treatment, follow-up period
Eba *et al.* 2016	Age, male/female, tumour size, C/T ratio
Crabtree *et al.* 2014	Age, male/female, tumour size, clinical staging, CCI, FEV1, tumour location, hypertension, smoking status, race, weight (lb), DLCO*
Cornwell *et al.* 2018	Age, male/female, tumour size, clinical staging, CCI, FEV1, pathologic cell type, hypertension, smoking status, mediastinal staging via EBUS*
Yerokun *et al.* 2017	Age, male/female, tumour size, CCI, pathologic cell type, tumour location, facility type, insurance status, distance to hospital

*, the characteristics have significant differences between SBRT and surgery ($P<0.05$). NA, not applicable; FEV1, forced expiratory volume in one second; CEA, carcinoembryonic antigen; DLCO, diffusing capacity of lung for carbon monoxide; ACE, adult comorbidity evaluation; FVC, forced vital capacity; SUVmax, maximum standardized uptake value; CCI, Charlson Comorbidity Index; SCC, squamous cell carcinoma.

Table S2 The results of the sensitivity analysis

Study omitted	hr	ul	ll
OS			
Yerokun	1.8400707	1.7465854	1.9385599
Eba	1.8073877	1.7228516	1.8960718
Kastelijn	1.8094635	1.7246432	1.8984553
Verstegen	1.8136526	1.7286876	1.9027938
Cornwell	1.8069048	1.7223189	1.8956448
Crabtree	1.8104978	1.7254543	1.8997327
Hamaji	1.8056992	1.7210512	1.8945105
Matsuo	1.8142195	1.7289299	1.9037163
Mokhles	1.8091191	1.724434	1.897963
Puri	1.7940363	1.6668215	1.9309602
Puri	1.8213148	1.7353703	1.9115158
Robinson	1.8073045	1.722218	1.8965948
Rosen	1.7663994	1.6751817	1.862584
Varlotto	1.8086122	1.7235931	1.8978251
Ye	1.808966	1.7243375	1.8977481
Combined	1.8089472	1.7243604	1.8976834
CSS			
Cornwell	1.3648237	0.44740593	4.1634312
Hamaji	0.91862035	0.49507394	1.7045199
Puri	2.1175666	0.78394288	5.7199168
Robinson	1.75502	0.43099326	7.1465039
Combined	1.4895626	0.58800853	3.7734091
RFS and DFS			
Hamaji	2.0039792	1.3983246	2.8719602
Crabtree	2.408608	1.6349978	3.5482571
Kastelijn	2.5226545	1.7660397	3.6034217
Cornwell	2.1214278	1.5168952	2.9668865
Combined	2.2454038	1.6462356	3.0626468
RFS			
Verstegen	0.99619269	0.5796833	1.7119689
Mokhles	0.71148819	0.23445702	2.159097
Ye	0.55184406	0.26303679	1.1577539
Varlotto	0.73461908	0.23294972	2.3166597
Combined	0.73248023	0.33585692	1.5974877
LRC			
Robinson	2.8066239	0.55296022	14.245398
Hamaji	1.4087356	0.96393794	2.05878
Crabtree	3.5956235	0.5200488	24.860184
Combined	2.2168428	0.68552249	7.1688269
RCR			
Crabtree	1.28017	0.28629088	5.72437
Hamaji	1.0520202	0.55643898	1.9889807
Robinson	1.5083785	0.81575012	2.7890964
Combined	1.2287541	0.65902543	2.2910143
L-RCR			
Kastelijn	0.90567803	0.28358454	2.8924453
Verstegen	1.754505	0.88387251	3.4827282
Mokhles	0.93215638	0.26229578	3.3127315
Ye	1.0030768	0.28693643	3.5065713
Combined	1.1059231	0.44077615	2.7748005
DCR			
Kastelijn	1.3352301	0.68837976	2.5899065
Verstegen	1.5862026	0.90612304	2.7767076
Crabtree	1.4209255	0.66007811	3.0587735
Hamaji	1.0237905	0.73714757	1.4218956
Mokhles	1.3104142	0.67754769	2.5344126
Robinson	1.3211111	0.64130294	2.7215447
Combined	1.3150553	0.7484743	2.3105276
Lobectomy *vs.* SBRT OS			
Verstegen	2.0371864	1.8275077	2.2709227
Rosen	2.0443203	1.1500962	3.6338234
Mokhles	2.0352147	1.3764541	3.0092535
Hamaji	1.8959923	1.2384275	2.9027023
Eba	1.9469334	1.4940101	2.5371647
Cornwell	1.9151517	1.3214743	2.7755408
Combined	1.9953141	1.452325	2.7413137

hr, hazard ratio; ul, upper CI limit; ll, lower CI limit; OS, overall survival; CSS, cause-specific survival; FFP, freedom from progression; RFS, recurrence-free survival; DFS, disease-free survival; LCR, local control rate; RCR, regional control rate; L-RCR, loco-regional control rate; DCR, distant control rate; SABR, stereotactic ablation radiotherapy.

Table S3 The results of sensitivity analysis for some studies that were restricted to the same matching and comparable characteristics

Study omitted	hr	ll	ul
SBRT *vs.* surgery			
Age/sex/tumour size/stage/CCI/FEV1			
Cornwell	1.6495802	1.1118855	2.4472978
Crabtree	1.8368011	1.0681913	3.1584585
Hamaji	1.579457	1.0551697	2.3642497
Mokhles	1.782833	1.1317002	2.8086004
Verstegen	2.0083621	1.4169319	2.8466566
Combined	1.7689382	1.2226687	2.5592725
Age/sex/tumour size/stage/CCI/FEV1/tumour site			
Crabtree	1.6228749	0.84796333	3.1059396
Hamaji	1.4343506	0.97291517	2.1146364
Mokhles	1.6216862	0.9721716	2.7051458
Verstegen	1.9035183	1.3119954	2.7617338
Combined	1.6495802	1.1118855	2.4472977
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology			
Hamaji	1.1559277	0.62260908	2.1460795
Mokhles	1.5628695	0.57187903	4.2711153
Verstegen	2.27895	1.3025346	3.9873126
Combined	1.6228749	0.84796335	3.1059396
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology/ WHO performance score			
Verstegen	1.732	0.62119561	4.8291135
Mokhles	0.917	0.42207512	1.9922732
Combined	1.1559276	0.62260911	2.1460795
SBRT *vs.* lobectomy			
Age/sex/tumour size			
Verstegen	2.5995011	1.6162257	4.1809793
Mokhles	2.1960237	1.0460625	4.6101642
Hamaji	1.9456136	0.8923775	4.2419405
Eba	1.8368011	1.0681913	3.1584585
Cornwell	1.8996218	0.93906474	3.8427203
Combined	2.0443205	1.1500961	3.6338233
Age/sex/tumour size/stage/CCI/FEV1			
Verstegen	2.4252729	1.4882857	3.9521639
Mokhles	1.8709387	0.90483546	3.8685613
Hamaji	1.5760972	0.78540981	3.1627851
Cornwell	1.6228749	0.84796333	3.1059396
Combined	1.836801	1.0681913	3.1584586
Age/sex/tumour size/stage/CCI/FEV1/tumour site/pathology			
Verstegen	2.27895	1.3025346	3.9873126
Mokhles	1.5628695	0.57187903	4.2711153
Hamaji	1.1559277	0.62260908	2.1460795
Combined	1.6228749	0.84796335	3.1059396
Age/sex/tumoursize/stage/CCI/FEV1/tumour site/pathology/ WHO performance score			
Verstegen	1.732	0.62119561	4.8291135
Mokhles	0.917	0.42207512	1.9922732
Combined	1.1559276	0.62260911	2.1460795

hr, hazard ratio; ul, upper CI limit; ll, lower CI limit; CCI, Charlson Comorbidity Index; FEV1, forced expiratory volume in one second.

Table S4 Pooled analysis of OS between SBRT and surgery in some studies that were matched and comparable with respect to a single characteristic

Matched and comparable	Study number	Heterogeneity		Meta-analysis results		
		I^2	P	HR 95% CI	P	Z
Age	11	28.90%	0.17	1.685 (1.502–1.892)	0.000	8.87
Sex	12	23.30%	0.215	1.814 (1.672–1.968)	0.000	14.33
Tumour size	12	23.30%	0.215	1.814 (1.672–1.968)	0.000	14.33
Tumour site	7	38.30%	0.137	1.793 (1.542–2.084)	0.000	7.59
Pathology	7	4.20%	0.394	1.665 (1.494–1.856)	0.000	9.21
FEV1	6	12.50%	0.335	1.630 (1.255–2.117)	0.000	3.66
CCI	8	13.80%	0.322	1.775 (1.681–1.875)	0.000	20.56
WHO performance score	3	0	0.56	1.302 (0.901–1.882)	0.16	1.41
Stage	10	25.60%	0.207	1.831 (1.653–2.027)	0.000	11.64

OS, overall survival; SBRT, stereotactic body radiotherapy; CCI, Charlson Comorbidity Index; FEV1, forced expiratory volume in one second.

Table S5 Sensitivity analysis for OS between SBRT and surgery in some studies that matched and compared a single characteristic

Study omitted	hr	ll	ul
WHO performance score			
Matsuo	1.1559277	0.62260908	2.1460795
Mokhles	1.2482964	0.84137028	1.8520312
Verstegen	1.4418236	0.94897151	2.1906402
Combined	1.3021361	0.90105694	1.8817441
CCI			
Verstegen	1.7811882	1.6861216	1.8816148
Puri	1.6464717	1.475185	1.837647
Mokhles	1.7331141	1.5635493	1.9210681
Matsuo	1.7591522	1.6143737	1.9169145
Hamaji	1.7368838	1.5980154	1.8878198
Crabtree	1.7366304	1.5642656	1.9279879
Cornwell	1.7380165	1.5949125	1.8939604
Yerokun	1.782964	1.587473	2.0025289
Combined	1.744878	1.6019877	1.9005136
FEV1			
Verstegen	1.754642	1.3294036	2.3159022
Mokhles	1.6232841	1.2388787	2.1269646
Matsuo	1.7603524	1.2806404	2.4197586
Crabtree	1.6226661	1.1938679	2.2054746
Cornwell	1.5605381	1.1904382	2.0456996
Hamaji	1.5022434	1.1308502	1.9956095
Combined	1.6301331	1.2552573	2.1169636
Pathology			
Verstegen	1.6849387	1.5099949	1.880151
Robinson	1.6445134	1.3653029	1.9808236
Mokhles	1.6844364	1.4025178	2.0230231
Matsuo	1.7211684	1.4475336	2.0465298
Hamaji	1.645655	1.4742202	1.8370256
Cornwell	1.6536372	1.4825866	1.8444222
Yerokun	1.730846	1.3010579	2.3026092
Combined	1.6711456	1.4659635	1.905046
Tumour site			
Ye	1.7877356	1.5173078	2.1063612
Rosen	1.6519463	1.4746035	1.8506172
Verstegen	1.8348652	1.6249032	2.0719573
Mokhles	1.7890148	1.5162021	2.1109152
Hamaji	1.760498	1.5058082	2.0582657
Crabtree	1.8011726	1.5160294	2.1399472
Yerokun	1.9698706	1.7690516	2.1934862
Combined	1.7928256	1.5420132	2.0844334
Tumour size/sex			
Yerokun	1.8682752	1.7224461	2.0264506
Eba	1.8133087	1.6874046	1.948607
Verstegen	1.827387	1.7110267	1.9516605
Cornwell	1.8080132	1.6648475	1.9634902
Crabtree	1.8175399	1.663331	1.9860457
Hamaji	1.8048924	1.6622403	1.9597869
Matsuo	1.8289365	1.6869751	1.982844
Mokhles	1.8129864	1.6601011	1.9799514
Puri	1.7996904	1.5719037	2.0604858
Robinson	1.8072671	1.6516297	1.9775708
Rosen	1.7636899	1.6402458	1.8964244
Ye	1.8124709	1.6599579	1.9789964
Combined	1.8141657	1.6722329	1.9681452
Age			
Yerokun	1.6628933	1.3799418	2.0038629
Eba	1.6912272	1.5269233	1.8732109
Verstegen	1.7187033	1.5561492	1.8982375
Cornwell	1.6729795	1.4894521	1.8791207
Crabtree	1.6797321	1.4780302	1.9089595
Hamaji	1.666374	1.4838452	1.8713557
Matsuo	1.7038975	1.5108503	1.9216111
Mokhles	1.6779509	1.4815413	1.9003987
Puri	1.5947312	1.3609457	1.8686769
Puri	1.7457726	1.5927151	1.9135388
Ye	1.6781578	1.4827392	1.8993316
Combined	1.6854631	1.5018507	1.8915234
Stage			
Verstegen	1.8585182	1.7230624	2.0046227
Cornwell	1.8199849	1.6401489	2.0195391
Crabtree	1.8321621	1.6365567	2.0511467
Hamaji	1.8151941	1.6352527	2.0149362
Mokhles	1.8243045	1.6318126	2.0395031
Puri	1.7718397	1.4668602	2.1402283
Puri	1.8623133	1.7650927	1.9648887
Robinson	1.8146738	1.6156299	2.0382395
Rosen	1.7402323	1.5199064	1.992497
Ye	1.8234518	1.6317147	2.037719
Combined	1.830589	1.653334	2.0268475

hr, hazard ratio; ul, upper CI limit; ll, lower CI limit; OS, overall survival; SBRT, stereotactic body radiotherapy; CCI, Charlson Comorbidity Index; FEV1, forced expiratory volume in one second.