

# Early stage lung cancer survival after wedge resection and stereotactic body radiation

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**Background:** The comparative effectiveness of stereotactic body radiation therapy (SBRT) and wedge resection in the treatment of early stage lung cancer is still under debate. This meta-analysis compares the 5-year overall survival (OS) of wedge resection and SBRT in patients with stage I non-small cell lung cancer (NSCLC).

**Methods:** Original research articles published between 1995 and 2017 were identified through the National Library of Medicine and National Institutes of Health PubMed database and through the reference lists of reviewed articles. Data were processed and analyzed in R (version 3.4.2) and a summary estimate that accounted for the sample size of each study was calculated. The combined percent survival was calculated using random effect models. Funnel plots were used to assess publication bias. Heterogeneity was tested using the Q statistic and the I<sup>2</sup> statistic.

**Results:** There were 16 studies totaling 1,984 patients with stage I NSCLC treated with wedge resection. The meta-estimate was 74% (95% CI, 66–81%), with significant heterogeneity across studies (Q =172.46, P<0.0001; I<sup>2</sup>=91.30%). Thirty-six studies including 3,309 patients with stage I NSCLC treated with SBRT/SABR produced a meta-estimate of 44% (95% CI, 38–50%), with significant heterogeneity (Q =423.55, P<0.0001; I<sup>2</sup>=91.74%). Two articles directly comparing stage I NSCLC patients treated with wedge resection to patients treated with SBRT both reported higher 5-year OS after wedge resection.

**Conclusions:** SBRT is a treatment option reserved to medically inoperable patients, but could be an alternative to surgery in medically operable patients who prefer a less invasive treatment. More standardized methods for data collection and reporting are necessary to allow better comparisons across published studies.

**Keywords:** Comparative effectiveness; surgery; radiotherapy; meta-analysis; epidemiology

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## Introduction

Lung cancer accounted for 27% of all cancer deaths in the United States of America (USA) in 2014, and is the leading cause of death among cancers in both men and

women in the USA (1). Survival however depends largely on stage of diagnosis, and as screening and early cancer-detection become more widely accepted, lung cancer can be diagnosed more frequently at earlier stages with a marked increase in overall survival (OS) rates (1).

Surgical resection has been emphasized as the standard of care and the most effective treatment for early stage non-small cell lung cancer (NSCLC) (2,3). Although more than 80% of lung cancers are classified as NSCLC and are thus candidates for surgery, approximately 25% of these patients do not undergo surgery (4,5). Some of these patients are judged to be inoperable due to medical conditions and comorbidities, while other patients refuse surgery (2). As an alternative, radiation therapy was developed as an additional treatment for NSCLC (2,6,7).

Stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiotherapy (SABR), was developed in order to provide a minimally invasive treatment that improves accuracy, local control and survival rates (8-10). SBRT delivers high radiation doses to immobilized patients under controlled conditions using guided focused beams. This approach has become widely accepted and adapted as an effective alternative treatment for early stage NSCLC (10-15). A meta-analysis comparing various radiotherapeutic approaches for stage I NSCLC reported that SBRT resulted in higher 5-year OS compared to conventional radiotherapy (16).

The comparative effectiveness of SBRT versus surgery in early stage lung cancer is still a topic of debate. A systematic review examining 2-year survival and local control following SABR in NSCLC patients reported equivalent short-medium term survival outcomes to surgery, and put forth SABR as an alternative to surgery (10). Two randomized controlled trials [STARS (17) and ROSEL (18)] attempted to compare SBRT and surgery in the treatment of NSCLC. However, both trials have been closed early due to low recruitment. A pooled analysis of these two trials suggested a better 3 years survival with SBRT in comparison to surgery (19), although a meta-analysis comparing the effectiveness of SBRT and surgical resection in stage I NSCLC concluded that 3-year survival of sublobar resection and SBRT is comparable for stage I NSCLC patients (14). Although surgery is the recommended treatment for early stage NSCLC, those who support SBRT suggest that, once patients' characteristics such as age, comorbidities, performance and overall health are taken into account, SBRT can be considered a comparable treatment to limited resection.

Recently, wedge resection has become an alternative type of limited surgery performed on small (<1 cm), peripheral nodes, and in patients with comorbidities who cannot tolerate the resection of a larger part of the lung, or even

a complete lobe (20). In these special cases, both wedge resection and SBRT can be considered as less invasive and effective treatment approaches for patients who cannot undergo a larger surgical treatment. Published studies comparing wedge resection and SBRT in the treatment of NSCLC are very limited (21,22).

Given the relevance of determining the most beneficial long-term treatment, the primary objective of this meta-analysis was to compare 5-year OS of wedge resection and SBRT in patients with stage I NSCLC.

## Methods

### *Search strategy and selection criteria*

Original research articles reporting 5-year OS of patients with stage I lung cancer undergoing SBRT or wedge resection were identified through the National Library of Medicine and National Institutes of Health PubMed database. The following keywords were included in the search strategy: "Stage I", "lung cancer", "SBRT", "surgical resection" and "SABR". Research published between 1995 and 2017 was included, and the references of selected articles were searched for additional publications. Articles were first screened by title and abstract, and then by full-text if appropriate.

Studies were considered eligible if they met the following inclusion criteria (*Figure 1*): (I) patients were diagnosed with stage I lung cancer; (II) data on 5-year OS were provided or could be extrapolated from published results; (III) patients were treated with SBRT or SABR, which are equivalent radiation treatment strategies; (IV) the total dose was administered in 5 fractions or less for domestic studies; (V) the majority of patients were treated with a total dose of >40 Gy; (VI) staging was performed with at least a computed tomography (CT) scan; (VII) surgical procedure was a wedge resection, regardless of whether it was performed via open thoracotomy or video-assisted thoracic surgery (VATS); (VIII) data were reported in English. There was no minimum sample size for inclusion. Studies were excluded according to the following reasons: (I) reviews, meta-analyses, editorials, commentaries, SEER re-analyses, conference abstracts; (II) lack of key information for calculation of 5-year survival; (III) patients with lung cancer more advanced than stage I; and (IV) surgical procedure other than wedge resection.

### Data extraction

All relevant characteristics were extracted from each article and recorded including author names, year of publication, duration of study, country of study, number of patients treated with SBRT or wedge resection, gender, median or mean age, histology, tumor stage, 5-year survival, median and range of follow-up, the dose/fraction radiation criteria, and if the study was performed on operable or inoperable patients. The primary endpoint of this study was 5-year OS. Data extraction was performed by two independent researchers (SR and WL-C). Data extraction was then performed independently using a standardized data extraction form. Disagreements were resolved by a third reviewer (ET) according to a predefined protocol. The NIH's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used to determine the quality of included studies (23).

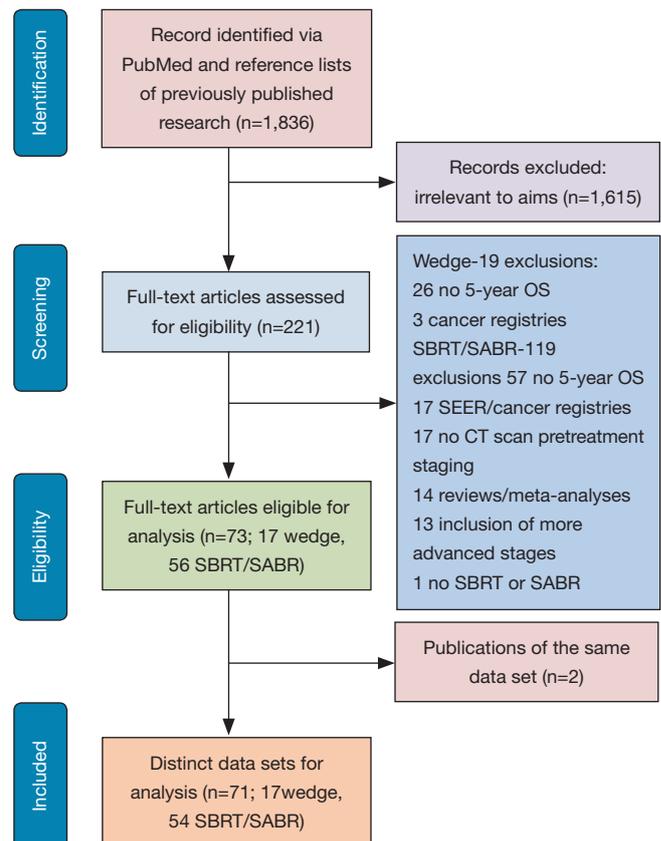
### Data analysis and statistical considerations

Data were processed and analyzed in R (version 3.4.2; R Foundation for Statistical Computing, Vienna, Austria), and a summary estimate that accounted for the sample size of each study was calculated. The combined percent survival was calculated using random effect models. Funnel plots were created in order to assess publication bias (*Figure S1*). Heterogeneity was tested using the Q statistic and the  $I^2$  statistic, with  $I^2 < 25\%$ ,  $25\%$  to  $50\%$  and  $> 50\%$  representing a low, moderate and high degree of heterogeneity, respectively (24,25). Where necessary, median age was converted to mean age (26).

## Results

### Search results and characteristics of studies

The PubMed search yielded 1,836 potential articles. After screening titles and abstracts, 221 articles were found to be relevant and were reviewed in full text, which resulted in the exclusion of an additional 148 articles. Twenty-nine articles on wedge resection were further excluded due to the absence of 5-year OS data ( $n=26$ ) and the inclusion of data from cancer registries ( $n=3$ ). In total, 119 articles on radiotherapy were further excluded due to the lack of 5-year OS data ( $n=57$ ), stemming from cancer registries and SEER data ( $n=17$ ), lacking baseline staging with at least CT scan ( $n=17$ ), reviews and meta-analyses ( $n=14$ ), including advanced cancer stages ( $n=13$ ), and reporting



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart for search and selection strategy.

on conventional radiation therapy ( $n=1$ ; *Figure 1*). This left 73 articles including 71 distinct data sets which were utilized in the present meta-analysis (*Tables 1, 2*, and <http://jtd.amegroups.com/public/addition/jtd/supp-jtd.2018.09.140-1.pdf>).

### Wedge resection

There were 16 studies including 1,984 patients with stage I NSCLC treated with wedge resection for which 5-year OS was available (21,22,27-40) (*Figure 2*). The sample size of the studies ranged from 14–746 patients. In studies that reported age ( $n=9$ ) and gender ( $n=10$ ), the average age was 70 years and the frequency of males was 53%. The range of 5-year OS was 44–100%; the meta-estimate was 74% (95% CI, 66–81%; *Figure 2*), with significant heterogeneity across studies ( $Q = 172.46$ ,  $P < 0.0001$ ;  $I^2 = 91.30\%$ ). Results from a sensitivity analysis, in which five articles with outlier

**Table 1** Description of the studies on wedge resection included in the meta-analysis

Author, year	n	Mean age (years)	Gender (male)	Histology	Stage	Treatment	5-year OS	Median (range) follow-up (months)	Quality assessment***
Harpole, 1995	75	63	46 (61%)	AC, AVCC, LCU, SCC	I	Stapled Wedge	61%	61 [1–169]	10/12
Landreneau, 1997	102	68 (Open); 71 (VATS); 70 (Overall)	NR	NR	I	Open wedge (41%); VATS wedge (59%)	Open: 58%; VATS: 65%; overall: 62%,	Open: 29 (NR); VATS: 24 (NR)	8/12
Watanabe, 2005	14	60.4	5 (36%)	AC (100%)	Ia	Wedge	100%	36 [8–79]	8/12
Okada, 2006	30	NR	NR	NR	Ia	Wedge	95%	>5 years	10/12
Yamato, 2008	93	NR	NR	AC (100%)	I	Wedge	70.6%	65 (mean)	10/12
Hsu, 2009	41	NR	NR	AC, SCC, other	Ib	Wedge	44%	103.6 [12–129]	10/12
Sugi, 2010	15	NR	NR	NR	Ia	Wedge	95.2%	All patients, 5 years	9/12
Grills, 2010	69	74**	38 (55%)	AC (65%), SCC (25%), ASCC (10%)	I	Wedge (VATS (52%), open thoracotomy (20%), converted to open thoracotomy (28%))	51%	30 (NR)	10/12
Nakamura, 2011	55	NR	NR	AC, SCC, other	Ia	Wedge (VATS)	71.2% (Ia)	NR	10/12
Stefani, 2012	82	70.1	55 (67%)	AC (67%), non-AC (33%)	Ia	Wedge	63%	49 [3.1–179]	10/12
Tamura, 2014	149	67	90 (60.4%)	AC (85%), SCC (13%), other (2%)	Ia	Thoracotomy (24.2%), mini-thoracotomy (20.1%), VATS (55.7%)	72%	58 [12–127]	10/12
Maurizi, 2015	182	70	129 (71%)	AC (62%), SCC (16%), other (22%)	I	Wedge	70.4%	31 [2–133]	10/12
Altorki, 2016	160	74	68 (43%)	AC (76%), SCC (20%), other (4%)	I	Thoracotomy (26%), VATS (74%)	68%	34 [19–48]	10/12
Wang, 2017	746	NR	290 (39%)	AC (100%)	I	Wedge	83.6%	18.96 [0.07–71.7]	10/12

\*\* , mean estimated from median; \*\*\*, number of yes/number of relevant questions from the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. NR, not reported; AC, adenocarcinoma; AVCC, alveolar cell carcinoma; LCU, large cell undifferentiated carcinoma; SCC, squamous cell carcinoma; ASCC, adenosquamous cell carcinoma; VATS, video-assisted thoracic surgery; OS, overall survival.

**Table 2** Description of the studies comparing wedge resection and SBRT included in the meta-analysis

Author, Year	n	Mean age (years)	Male gender (%)	Histology	Stage	Operability	5-year OS	Median (range) follow-up (months)	Modality (dose x fraction)	Total dose group***	Quality assessment****
Varlotta, 2013	SBRT (n=137); Wedge (n=48); match (n=17)	SBRT: 73.3; Wedge: 67.5; match (NR)	SBRT: 66 (48%); Wedge: 24 (50%); match (NR)	SBRT: AC (28%), SCC (28%), unspecified (43%); Wedge: ACC (54%), SCC (38%), unspecified (8%); match: NR	I	Inoperable (SBRT)	Unmatched: SBRT: 21%; Wedge: 65%; match: SBRT/ SABR: 31.7%; Wedge: 86.3	SBRT: (18.8); Wedge: (NR); Match: (NR)	SBRT: mean dose: 60 Gy in 3 fractions; range: 48 to 60 Gy in 3 to 5 fractions	2***	10/12 (Wedge); 10/13 (SBRT)
Parashar, 2015	SBRT (n=97); Wedge (n=123)	Overall: 77 (40-96)**	SBRT: 41 (39%); Wedge: 53 (43%)	AC, SCC, small cell carcinoma, other, missing	I	Inoperable (SBRT)	SBRT: 89.6%; Wedge: 97.7%	SBRT [24]; Wedge: [25]	Median dose 48 Gy (range, 30-60 Gy) over 4 fractions (range, 3-5)	1***	10/12 (Wedge); 10/13 (SBRT)

\*\*, mean estimated from median; \*\*\*, estimated from the majority of patients. Total dose group: <50 Gy =1, ≥50 Gy =2; \*\*\*\*, number of yes/number of relevant questions from the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. NR, not reported; AC, adenocarcinoma; AVCC, alveolar cell carcinoma; LCU, large cell undifferentiated carcinoma; SCC, squamous cell carcinoma; ASCC, adenocarcinoma; NSC, non-small cell cancer; BAC, bronchoalveolar carcinoma; SBRT, stereotactic body radiation therapy; OS, overall survival.

results were removed, indicated heterogeneity still existed ( $Q = 22.22$ ,  $P = 0.0140$ ;  $I^2 = 55.00\%$ ; *Figure S2*).

### SBRT

Thirty-six studies including 3,309 patients with stage I NSCLC treated with SBRT/SABR reported 5-year OS (<http://jtd.amegroups.com/public/addition/jtd/supp-jtd.2018.09.140-1.pdf>). The study size ranged from 20-257 patients. The average age in studies that reported it ( $n = 31$ ) was 75 years, and the average percent of males was 56% ( $n = 32$ ). The range of 5-year OS was 17.0-89.6%, with a meta-estimate of 44% (95% CI, 38-50%; *Figure 3*). There was significant heterogeneity when pooling results ( $Q = 423.55$ ,  $P < 0.0001$ ;  $I^2 = 91.74\%$ ). Thirteen articles treated the majority of patients with <50 Gy, and among these, the pooled 5-year survival estimate was 48% (95% CI, 36-60%) (15,41-51). The remaining 23 articles treated the majority of patients with ≥50 Gy, and their pooled 5-year survival estimate was 42% (95% CI, 36-48%; data not shown) (11,12,21,52-71).

There were 10 studies consisting of 907 patients that reported the 5-year OS of medically operable patients undergoing SBRT (11,12,15,47-50,52,58,65). The meta-survival estimate (*Figure 3*) was 57% (95% CI, 50-64%), with significant heterogeneity ( $P < 0.0001$  and  $I^2 = 79.31\%$ ).

Twenty-five studies consisting of 1,960 patients reported the 5-year OS of medically inoperable patients undergoing SBRT (21,22,41-45,48,49,52-57,59,60,63,64,66,68-71) (*Figure 3*). The OS was 40% (95% CI, 33-48%) with statistically significant heterogeneity ( $Q = 257.92$ ,  $P < 0.0001$ ;  $I^2 = 91.75\%$ ). Three studies had both operable and inoperable patients (48,49,52), and four articles did not report if the patients were operable or inoperable (46,51,61,62). Results from a sensitivity analysis among inoperable patients receiving SBRT reported high heterogeneity among studies ( $Q = 105.23$ ,  $P < 0.0001$ ;  $I^2 = 80.04\%$ ; *Figure S3*).

### Analysis according to stage

Among studies of wedge resection, there were six that specifically included stage IA, consisting of 345 patients (29,30,32,34,35,39). The percent survival was 83% (95% CI, 65-95%) with statistically significant heterogeneity ( $Q = 24.43$ ,  $P = 0.0002$ ;  $I^2 = 79.53\%$ ; *Figure 4*). For SBRT, there were 6 articles including stage IA lung cancer, on 228 patients (11,41,46,48,50,53). The percent survival was 67% (95% CI, 57-76%) with statistically significant

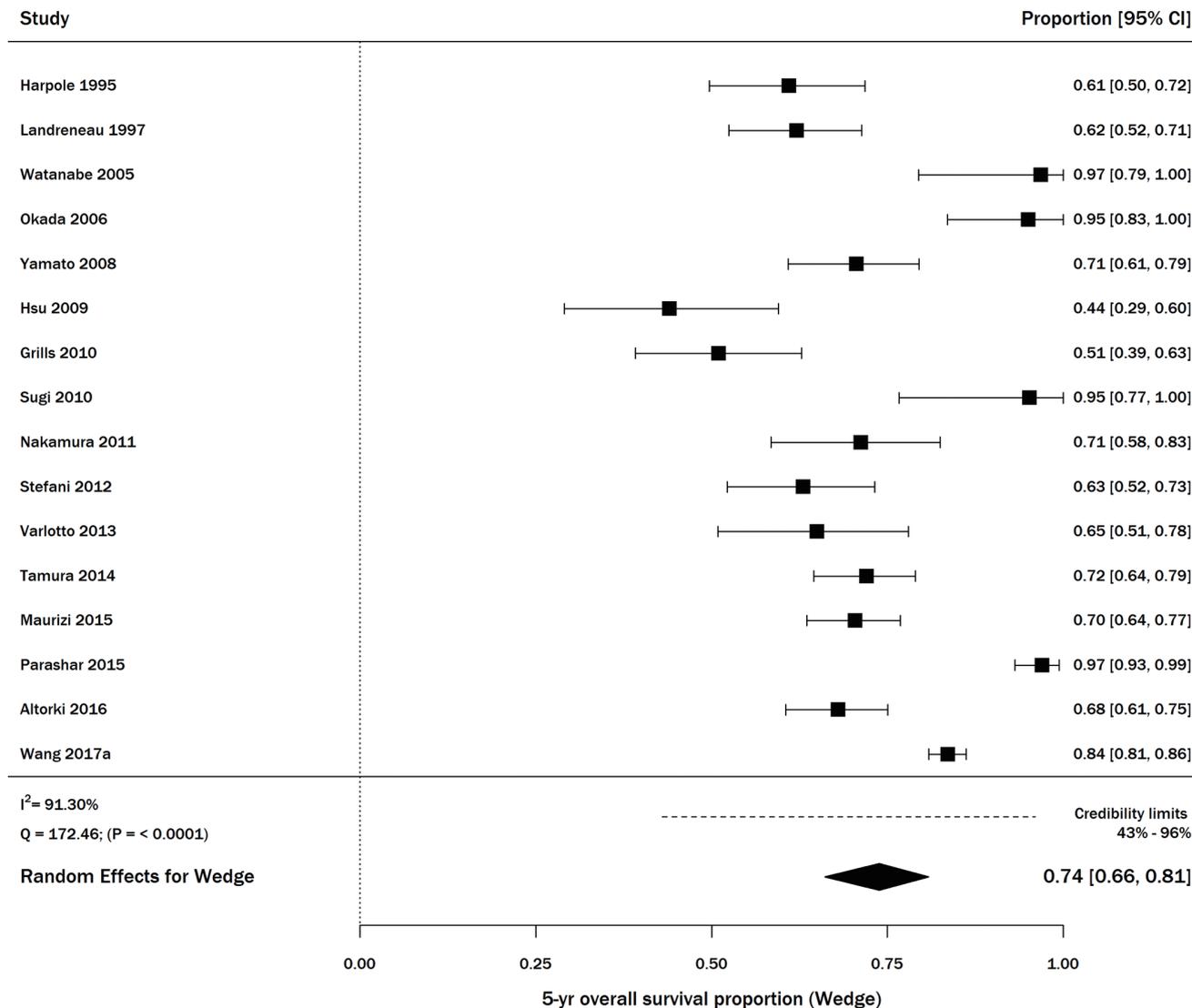


Figure 2 Five-year survival after wedge resection.

heterogeneity ( $Q = 16.45, P = 0.0057; I^2 = 69.61\%$ ; Figure 4).

**Direct comparison of wedge resection vs. SBRT**

Two articles compared stage I NSCLC patients treated with wedge resection to patients treated with SBRT (Table 2) (21,22). In the first article, 48 patients (50% male) were treated with wedge resection with an average age of 67.5 years, while 137 patients (48% male) were treated with SBRT with a mean age of 73.3 years (21). The comorbidities index was higher for SBRT patients [average score = 4.2 (range, 3–10)] than for patients treated with wedge resection [average score = 3 (range, 1–6)].

Preoperative lung function was better in patients treated with surgery compared to SBRT [forced expiratory volume in one second (FEV1) of 71% and 49%, diffusing capacity of the lung for carbon monoxide (DLCO) of 56% and 46%, respectively]. Prior to matching, the 5-year OS was higher following wedge resection (~65%) than after SBRT (~21%). After propensity matching (n=17), 5-year OS remained significantly lower ( $P = 0.0003$ ) for patients treated with SBRT (31.7%) compared to wedge resection (86.3%).

The second publication included 123 patients (43.1% male) treated with wedge resection and 97 patients (39.2% male) treated with SBRT (22). Lung function and information on comorbidities were not reported in this

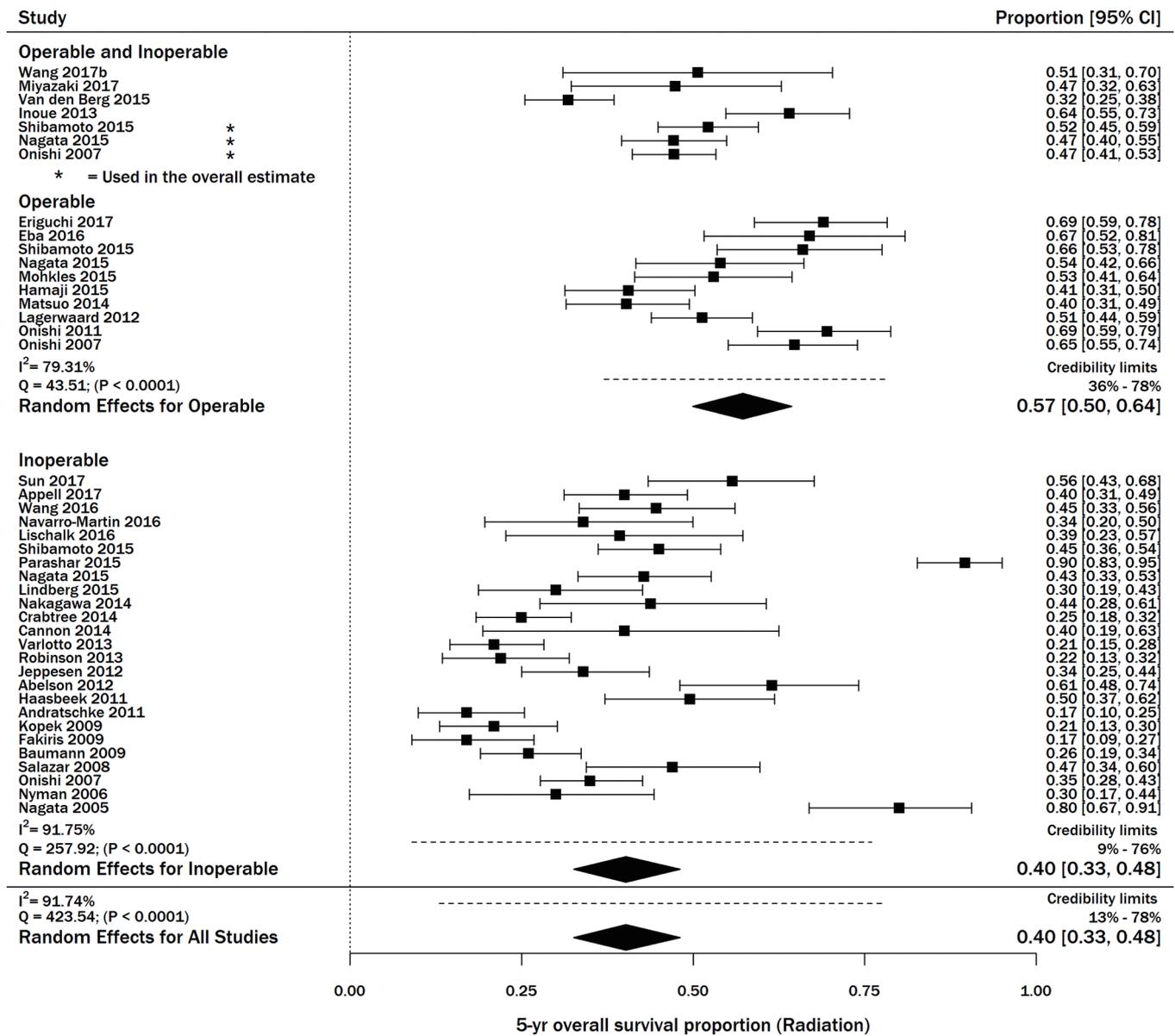


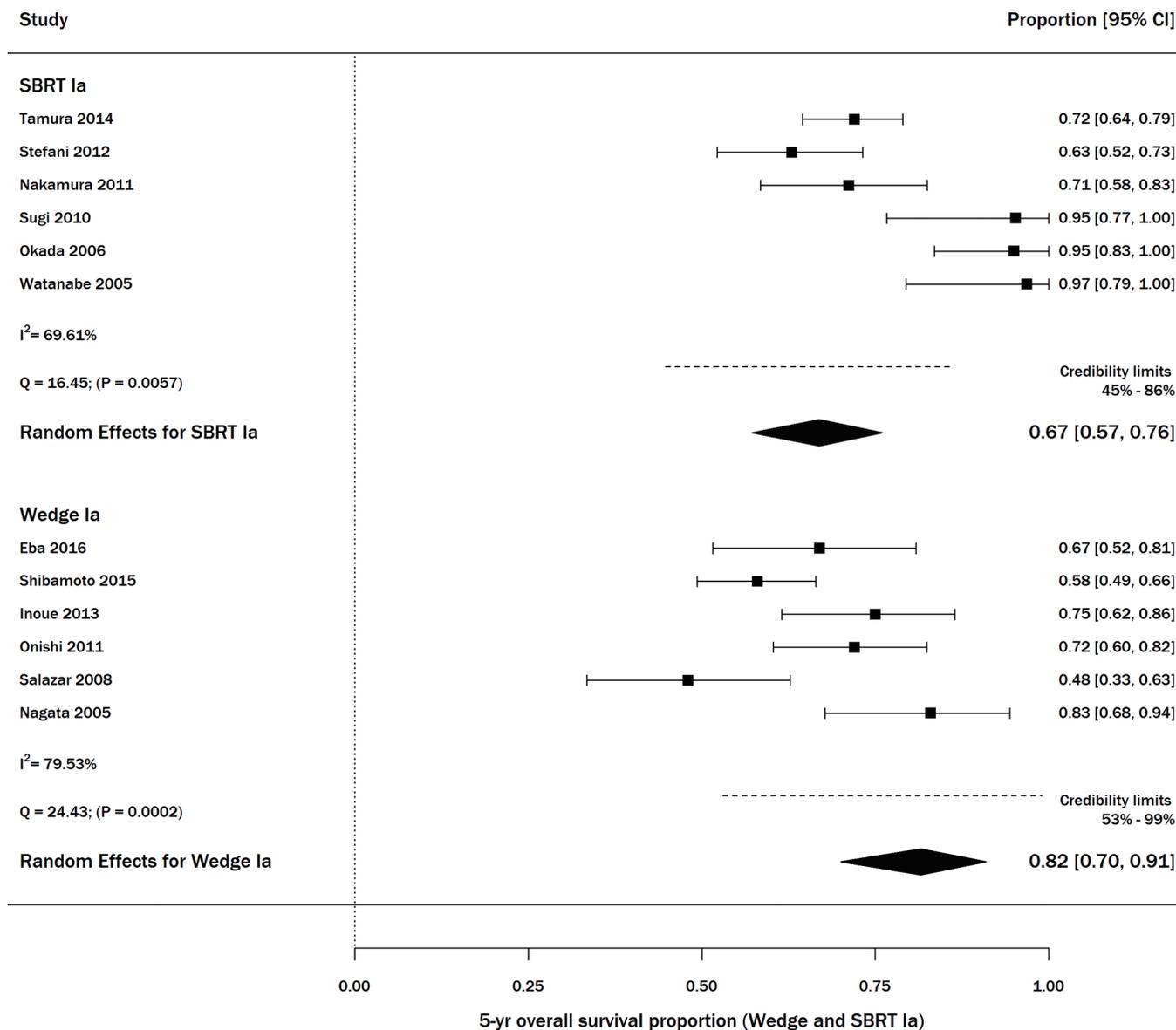
Figure 3 Five-year survival after SBRT for operable and inoperable patients. SBRT, stereotypic body radiation therapy.

article. The 5-year OS was significantly different ( $P=0.02$ ) between wedge resection (97.7%) and SBRT (89.6%).

### Discussion

In the present study, 5-year survival in stage I lung cancer was compared between patients treated with wedge resection or SBRT. This study suggests that wedge resection overall generated significantly higher survival rates than SBRT treatment. It is apparent that studies on SBRT

included older patients and patients who are less likely to be operable compared to studies on wedge resection. Patients eligible for SBRT are staged clinically, while surgical patients are staged pathologically, and this may contribute to the difference in outcomes between the two groups. The included publications indicate that SBRT is used in patients who cannot afford surgery because of age or comorbidities, as well as in high-risk and medically inoperable patients; these patients may have worse OS because of their own prognostically negative baseline characteristics. These



**Figure 4** Five-year survival of stage IA patients treated with wedge resection and SBRT. SBRT, stereotypic body radiation therapy.

aspects have to be taken into account when comparing the survival rates between SBRT and wedge resection in retrospective studies.

The present analysis shows that long-term survival for medically operable patients treated with SBRT was significantly higher than the survival observed for medically inoperable patients. From this data, we assessed that patients who would be fit for surgery have a much higher chance of survival when treated with SBRT versus patients who are not candidates for surgery. If a patient who is judged operable refuses to undergo surgery, he/she can be considered for

SBRT as an effective, less invasive treatment option.

Another conclusion deriving from this meta-analysis is that the medical status of the patient is very important when assessing survival rates of stage I NSCLC, and when comparing SBRT to surgical resection. There were only 10 studies out of the 36 SBRT studies that reported the 5-year survival of operable patients specifically (11,12,15,47-50,52,58,65), and additional studies on medically operable patients should be conducted to have a larger sample size and provide more definite conclusions. Also very few studies [6 studies for wedge resection (11,41,46,48,50,53) and 6

studies for SBRT (29,30,32,34,35,39)] reported enough information to assess the outcomes of each treatment based on staging. When comparing stage IA patients treated with either wedge or SBRT, improved overall survival was observed with both treatments, although wedge was superior to SBRT. More studies should be conducted on the effectiveness of these treatments in stage IA NSCLC.

To date, only two observational studies directly compared clinical outcomes of SBRT and wedge resection in stage I NSCLC (21,22). The two studies yielded very different conclusions: Parashar *et al.* reported high survival rates for both procedures (22), while Varlotto *et al.* indicated very poor 5-year survival rates for SBRT, around 32% in the matched population (21). This result is likely due to the unequal distribution of patient characteristics; patients in the SBRT group had more comorbidities and worse pulmonary function than patients in the wedge resection group. These findings confirm that comorbidities, pulmonary function, prior medical history and performance status are important factors influencing the OS.

The STARS and ROSEL trials were two independent, randomized trials comparing SBRT and surgery in patients with operable stage I NSCLC (17,18). Unfortunately, both trials were closed early due to low accrual. A pooled analysis of these two trials found that patients in the SBRT group had a higher 3-year OS than patients in the surgery group, 95% and 79%, respectively (72). The authors mentioned that lower survival after surgery might be associated with a worsening of comorbidities related to the surgical reduction of lung function. The results of this pooled analysis should be interpreted with caution because only a very small portion of the intended sample size (2.3–3.5%) was enrolled before the trials were closed and follow-up was limited (19).

### Limitations

This study has some limitations, the most prominent of which was heterogeneity and the lack of consistency in reporting information in articles spanning over 12 years, from 2005–2017. Study populations were heterogeneous, and their description and characterization were very minimal, which prevented any further in-depth analysis of covariates associated with outcomes. Additionally, many possible confounders such as age, gender, clinical stage, histology, comorbidities, pulmonary function and performance status were missing from many of the studies, which prevented a thorough comparison across procedures. Many studies did not report the location (central or peripheral) of

tumors, which influences SBRT regimes and thus survival. Additionally, the biological effective dose (BED) was not always mentioned, which limited the ability to conduct sub-analyses of the survival of patients receiving high doses of radiation (BED >100 Gy). Furthermore, there was variability in the prescribed dose regimes for SBRT studies between studies conducted in the USA, where Medicare defines SBRT as 5 fractions or less, and those conducted internationally. This limits the comparability among SBRT articles.

There was a dearth of studies directly comparing wedge and SBRT, and only two studies included a direct comparison of wedge and SBRT patients (21,22). Another main limitation was that many of the available studies from the initial search limited their follow-up to 2–3 years, and did not provide clear 5-year OS data. Given the excellent curability rates of stage I NSCLC, longer follow-ups are necessary in order to fully evaluate the success of each procedure, and make more definite conclusions about the benefits of wedge and SBRT.

### Conclusions

This meta-analysis comparing long-term survival after wedge resection and SBRT in the treatment of stage I NSCLC suggests that wedge resection has higher survival rates. Medically operable patients treated with SBRT have better survival than non-operable patients. More standardized methods for data collection and data reporting are necessary in order to allow comparisons across published studies on wedge and SBRT treatment.

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors have complied with all ethical standards in publishing.

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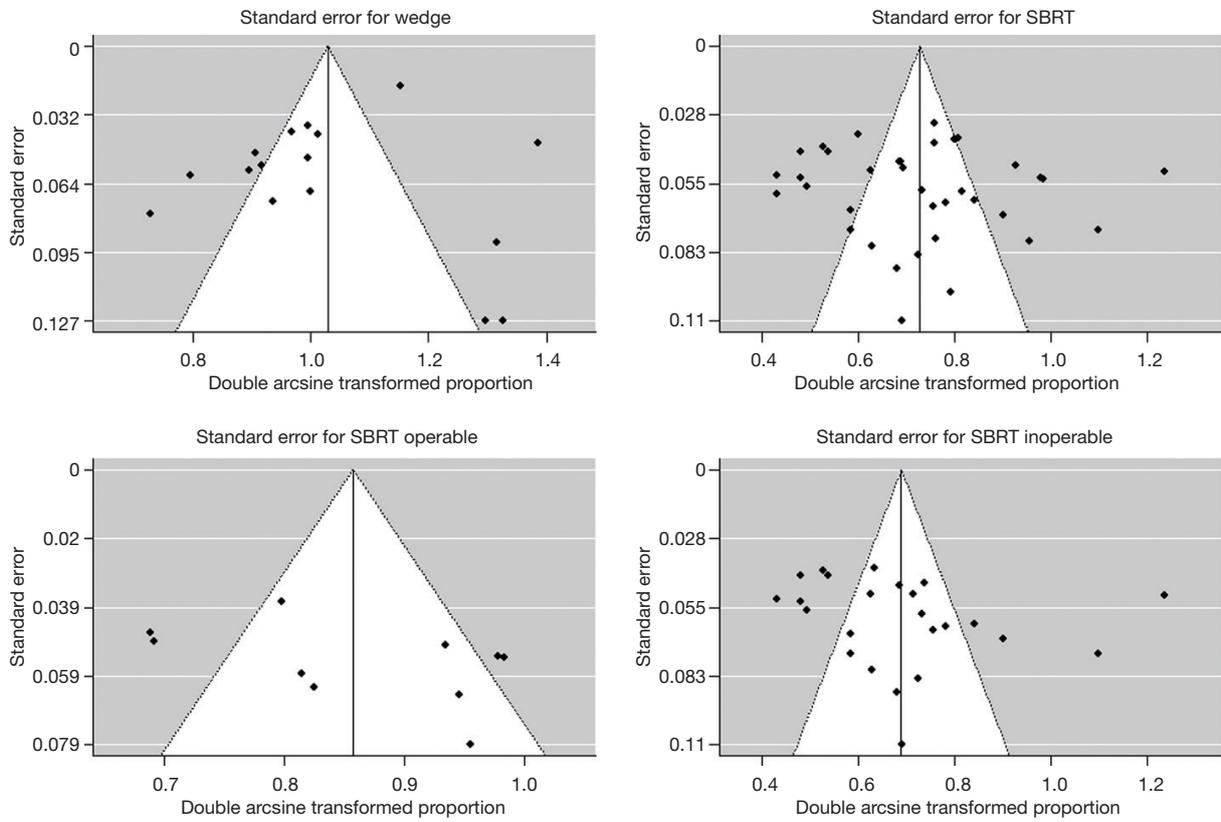


Figure S1 Funnel plots to assess publication bias. SBRT, stereotactic body radiation therapy.

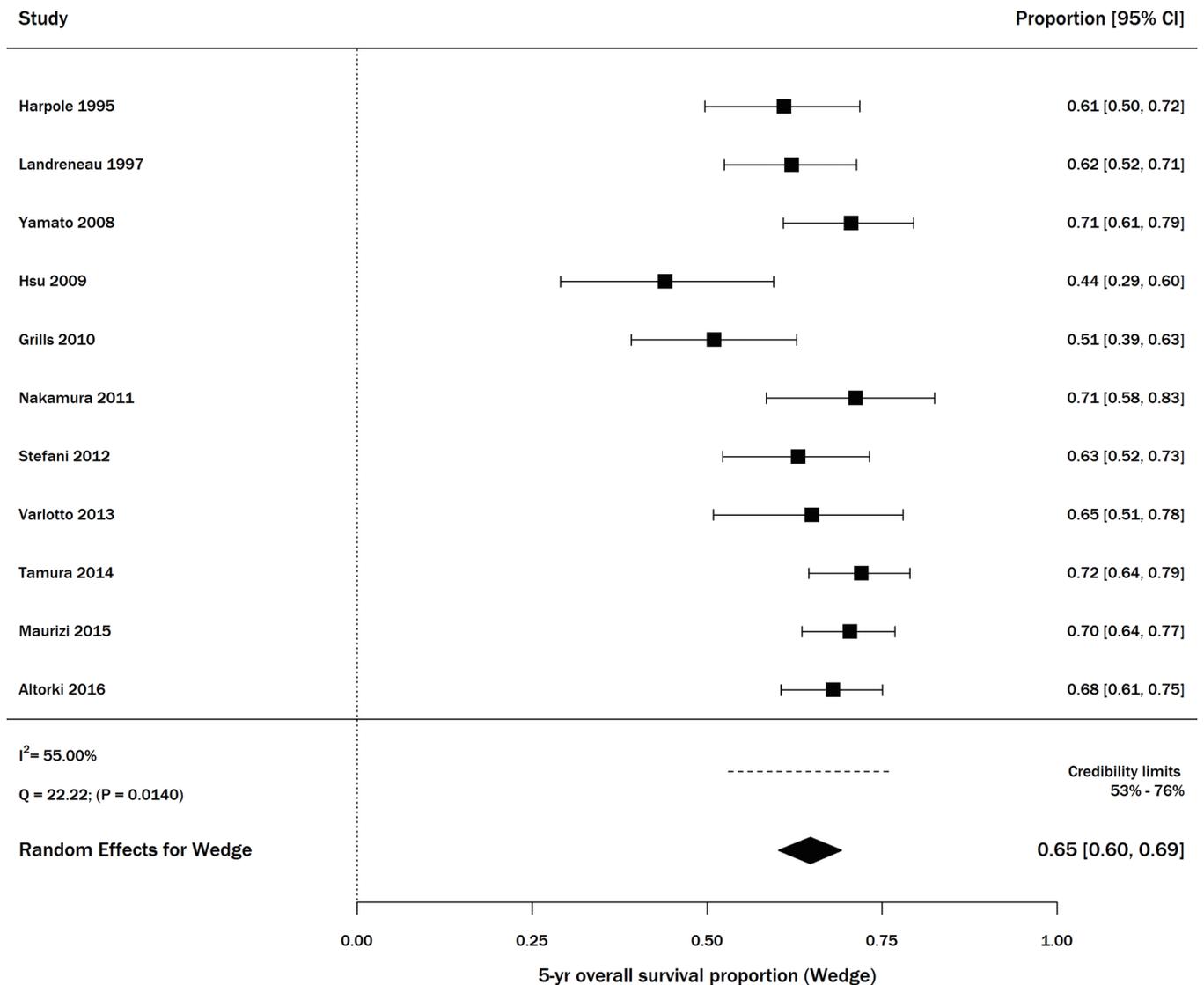
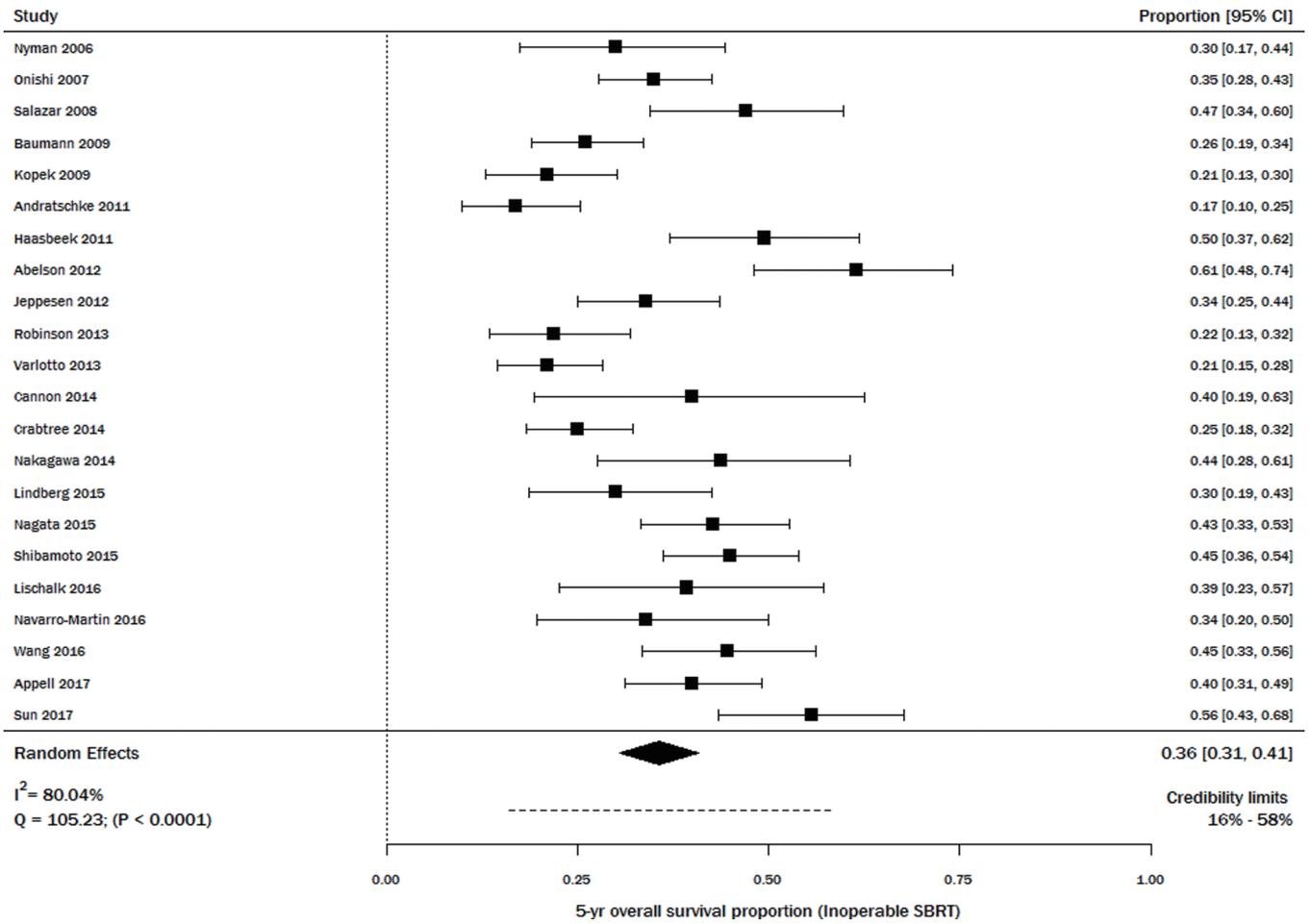


Figure S2 Sensitivity analysis of 5-year overall survival of wedge resection studies.



**Figure S3** Sensitivity analysis of 5-year overall survival of inoperable SBRT studies. SBRT, stereotactic body radiation therapy.