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Stereotactic body radiotherapy versus surgery for early-stage non-small cell lung cancer: an updated meta-analysis involving 29,511 patients included in comparative studies

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ABSTRACT

Objective: To evaluate the efficacy of stereotactic body radiotherapy (SBRT) versus surgery for early-stage non-small cell lung cancer (NSCLC) by means of a meta-analysis of comparative studies. **Methods:** Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and Meta-analysis of Observational Studies in Epidemiology guidelines, searches were performed on PubMed, MEDLINE, Embase, and Cochrane Library for eligible studies. The meta-analysis compared the hazard ratios (HR) for overall survival (OS), cancer-specific survival (CSS), and local control (LC). Subgroup and meta-regression analyses evaluated the association of extent of surgical resection, study publication year, tumor staging, propensity score matching, proportion of chemotherapy use, and proportion of pathological lymph node involvement with CSS and OS. **Results:** Thirty studies involving 29,511 patients were included (surgery group: 17,146 patients and SBRT group: 12,365 patients). There was a significant difference in favor of surgery vs. SBRT in the 3-year OS (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%) and 3-year CSS (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%), but not in the 3-year LC (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%). In the subgroup analysis for OS, no significant difference between surgery and SBRT groups was observed in the T1N0M0 subgroup (HR = 1.26; 95% CI: 0.95-1.68; I^2 = 0%). In subgroup analysis for CSS, no significant difference was detected between the sublobar resection subgroup and the SBRT group (HR = 1.21; 95% CI: 0.96-1.53; I^2 = 16%). **Conclusions:** Surgery generally resulted in better 3-year OS and CSS than did SBRT; however, publication bias and heterogeneity may have influenced these findings. In contrast, SBRT produced LC results similar to those of surgery regardless of the extent of surgical resection. These findings may have important clinical implications for patients with comorbidities, advanced age, poor pulmonary reserve, and other factors that may contraindicate surgery.

Keywords: Carcinoma, Non-Small-Cell Lung/surgery; Radiosurgery; Meta-analysis.

INTRODUCTION

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the world, with 2,206,771 new cases and 1,796,144 deaths in 2020.[(1)] NSCLC represents nearly 87% of lung cancer diagnoses, and only 15% of patients present with early-stage disease.[(2)] The introduction of lung cancer screening into clinical practice, however, will result in more patients being diagnosed with early-stage disease.[(3)] In the National Lung Screening Trial, approximately 70% of lung cancer patients diagnosed by CT screening have stage I NSCLC.[(3)]

Currently, surgery is the standard of care for patients with operable early-stage (stages I or II) NSCLC.[(4)] However, NSCLC usually affects elderly patients. In one study with 27,844 NSCLC patients submitted to surgery, the median age was 67.2 years. In addition, in this population, the incidence of major complications was 9.1%.[(5)] Older age (p < 0.001) and diseases associated with smoking, such as coronary artery disease (p = 0.011) and peripheral vascular disease (p ≤ 0.001), were predictors of morbidity and mortality after surgery.[(5)]

In the last years, encouraging outcomes with stereotactic body radiotherapy (SBRT) in inoperable NSCLC patients have driven the interest in a direct comparison between surgery and SBRT in medically operable patients.[(6)] A standard SBRT course for stage I NSCLC consists of 1-5 treatments over 1 to 2 weeks with a dose per fraction of 10-34 Gy.[(7,8)] The ablative dose per fraction used with SBRT increases patient convenience due to reduced treatment duration, while translating into a higher biologically effective dose (BED), which is likely to produce a better local tumor control rate.[(9)]

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Early randomized trials comparing surgery and SBRT closed prematurely because of low patient accrual.[9] Consequently, several studies and meta-analyses comparing both modalities have been published.[10-14] However, previously published studies lacked methodological rigor, and some key clinical aspects were missing. Therefore, the present study aimed to perform a meta-analysis of studies comparing surgery and SBRT in early-stage NSCLC patients to explore clinical aspects and identify potential differences for guiding future relevant studies.

METHODS

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines, electronic searches were performed in PubMed, Embase, SciELO, and Cochrane Library for eligible studies published before January 1, 2020. The following keywords or medical terms were used: ("non-small cell lung carcinoma" OR "non-small cell lung cancer" OR "non-small cell lung neoplasms" OR "lung adenocarcinoma" OR "lung squamous cell carcinoma" OR "large cell lung cancer") AND ("surgery" OR "lobectomy" OR "sublobar resection" OR "limited resection" OR "sublobectomy" OR "segmentectomy" OR "wedge resection") AND ("stereotactic ablative radiotherapy" OR "stereotactic body radiotherapy" OR "SBRT" OR "SABR"). Only articles in English were included, and reference lists of relevant studies were manually searched for potentially eligible articles.

Study inclusion

We included comparative studies of SBRT and surgery (lobectomy, segmentectomy, or wedge resection) in patients with early-stage (T1-3N0M0) NSCLC. Only studies using an SBRT schedule with a median BED ≥ 100 Gy10 were included in the final meta-analysis. Randomized and observational studies using propensity score analysis or other statistical adjustment methods to reduce bias were included in the meta-analysis. Meta-analyses previously published were additionally included in the quantitative synthesis. Studies without comparisons between SBRT/stereotactic ablative radiotherapy and surgery, case reports, and reviews were excluded.

Outcomes

The outcomes studied in the meta-analysis were 3-year overall survival (OS), cancer-specific survival (CSS), and local control (LC). Studies combining treatments in one of the comparative arms or studies with no data regarding 3-year OS, CSS, and LC were also excluded.

Data collection and quality assessment

Two reviewers (GAV and AGG) independently screened studies and extracted study data using a standardized method, discrepancies being settled by a third reviewer (FKM). The following information was collected: author, year of publication, study design, staging, SBRT dose, fractionation SBRT regimen, clinical characteristics (sex, age, histology, and follow-up), and clinical outcomes.

Statistical analysis

Meta-analysis of the outcomes was performed using ProMeta 3.[15] Hazard ratios (HRs) and respective 95% CIs were used to analyze dichotomous data. Data from survival curves were extracted according to the methods described by Tierney et al.[16] When calculations were not possible or not available, HRs were estimated using the Kaplan-Meier method. We used the iterative algorithm proposed by Guyot et al.[17] to find numeric solutions to the inverted Kaplan-Meier equations. Heterogeneity was estimated using the I^2 index and Cochran's Q statistic. In the presence of heterogeneity using the fixed-effect model, the random-effects model was selected to estimate the outcomes. Sensitivity analysis was conducted by stepwise removal of each included study. Subgroup analysis was performed by separating the studies by type of surgery (lobectomy, sublobar resection, or mixed surgical resection), T staging (T1N0M0, T1-2N0M0, or T1-3N0M0), surgical technique (video-assisted thoracic surgery [VATS] or mixed surgical technique), and use of propensity score matching (yes or no). Meta-regression analysis was performed to determine the effect of different publication years, proportion of chemotherapy use, and proportion of pathological lymph node involvement on CSS and OS. These variables were treated as continuous variables. Publication bias was evaluated using Egger test, and a p-value < 0.05 was considered significant.[18]

RESULTS

A total of 3,632 studies were initially identified. After excluding duplicates and irrelevant publications, 30 studies were selected for the meta-analysis (Figure S1). Three studies had different control groups (lobectomy or sublobar resection); these groups were counted twice as separate cohorts, generating a total of 33 cohorts for quantitative synthesis. Overall, there were 26 retrospective studies with propensity score matching, 1 randomized clinical trial, 1 retrospective study with adjustment for prognostic covariates, and 2 retrospective studies without adjustment for covariates.[9,19-47]

In total, 29,511 patients with early-stage NSCLC were included, 17,146 undergoing surgery and 12,365 being treated with SBRT. Lobectomy, mixed surgical resection, and sublobar resection were compared with SBRT in 11, 10, and 6 studies, respectively. In addition, 3 studies separately compared lobectomy and sublobar resection with SBRT. VATS was employed exclusively in 4 studies; in the remaining studies, both open thoracotomy and VATS were used (Table 1). The SBRT dose ranged from 45 to 60 Gy, in 3 to 12 fractions. Details of study design, number of patients, clinical characteristics, treatment characteristics, and outcomes in the studies included are described in Table S1. Table S2 shows a summary of the characteristics of the previous meta-analyses[10-14] in the literature and of the present meta-analysis.

Considering the studies using propensity score matching to improve treatment group balance, we found that 16 covariates were utilized to generate propensity score models. Age, sex, and educational status were the most common covariates used, whereas tumor staging, tumor location, histology, and PET were the least common (Figure S2). In total, 2 studies used more than 10 covariates in the propensity score model, whereas 9 studies used less than 8 covariates (Figure S3).

Table 1. Summary of the characteristics of all studies included in the meta-analysis.

Variable	Studies, n	Patients, n	Median (range)
Trials and comparative studies			
Randomized trial	1	58	
Retrospective, propensity score matching	26	24,917	
Retrospective, adjustment for prognostic covariates	1	340	
Retrospective, other	2	4,196	
Total		29,511	
SBRT		12,365	
Surgery		17,146	
Patients			
Age			
SBRT			73 (66-82)
Surgery			72 (65-82)
Female sex, %			
SBRT			42 (3-65)
Surgery			40 (3-62)
Histology, %			
Adenocarcinoma			
SBRT			47 (9-100)
Surgery			53 (14-100)
Squamous cell carcinoma			
SBRT			30 (0-46)
Surgery			31 (0-43)
SBRT			
Total dose, Gy			48 (45-60)
Fraction, n			4 (3-12)
Dose per fraction, Gy			14 (5-20)
Median BED > 100	30		
Follow-up period, months			
SBRT			31 (18-58)
Surgery			43 (16-58)
Clinical stage			
T1N0	4	3,334	
T1-2N0	21	24,757	
T1-3N0	4	620	
Stage I	1	800	
Type of surgery[a]			
Mixed	10	772	
Lobectomy	14	6,242	
Sublobar resection	9	10,132	
Surgical technique			
Mixed	26	16,951	
VATS only	4	195	
Chemotherapy, %			
SBRT			1 (0-16)
Surgery			8 (0-15)
Positive lymph node involvement			
SBRT			6.5 (1.0-75.7)
Surgery			11.0 (4.0-37.8)

SBRT: stereotactic body radiotherapy; BED: biologically effective dose; and VATS: video-assisted thoracic surgery. [a]Three studies reported using both lobectomy and sublobar resection.

OS

Thirty studies, with a total of 29,511 patients, compared surgery with SBRT and reported the OS. After quantitative synthesis, the pooled 3-year OS was significantly higher in the surgery group than in the SBRT group (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%); however, there was significant heterogeneity in the studies. When we pooled the data stratified by the extent of surgical resection, the 3-year OS remained higher in the surgery group in comparison with the SBRT group for all subgroups. Significant heterogeneity was noted in the lobectomy subgroup (I^2 = 66%; HR = 1.47; 95% CI: 1.28-1.69), but not in the mixed surgical resection (I^2 = 0%; HR = 1.28; 95% CI: 1.07-1.53) and sublobar resection subgroups (I^2 = 38%; HR = 1.24; 95% CI: 1.06-1.46; Figure 1).

Table 2 presents the results of further subgroup analyses. When we compared VATS and non-VATS procedures or studies that used and did not use propensity score matching, surgery was associated with significantly higher 3-year OS. However, when we stratified patients by T staging, the subgroup of studies including only T1N0M0 patients showed no significant difference in 3-year OS between surgery and SBRT groups (HR = 1.26; 95% CI: 0.95-1.68; I^2 = 0%), with no heterogeneity noted among the studies included. Moreover, in the meta-regression analysis, publication year, proportion of chemotherapy use, and proportion of pathological lymph node involvement had no significant associations with OS (Table 2).

CSS

Sixteen studies involving 11,387 patients reported the CSS at 3 years as an outcome. When compared with SBRT, surgery was associated with higher 3-year CSS (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%), and no significant heterogeneity was detected (Figure 2). In a subgroup analysis stratified by the extent of surgical resection, only lobectomy alone was found to be significantly associated with improved CSS when compared with SBRT (Figure 2 and Table 3). When we assessed sublobar resection, there was no significant difference when compared with SBRT and no significant heterogeneity (HR = 1.21; 95% CI: 0.96-1.53; I^2 = 16%; Figure 2 and Table 3). In additional subgroup analyses, comparison between studies using VATS and no VATS, as well between studies using and not using propensity score matching showed significant benefits of surgery over SBRT regarding 3-year CSS (Table 3). However, in studies including T1N0M0 patients only, no significant differences between surgery and SBRT were observed (HR = 1.12; 95% CI: 0.86-1.46; I^2 = 0%), and there was no heterogeneity. In the meta-regression analysis, publication year, proportion of chemotherapy use, and proportion of pathological lymph node involvement had no relationship with 3-year CSS (Table 3).

LC

Nine studies involving 912 patients reported data on 3-year LC. Surgery and SBRT showed equivalent LC at 3 years (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%) and no heterogeneity (Figure 3).

Publication bias

Publication bias was assessed using the method by Egger et al.[18] A statistical significance for publication bias for OS at 3 years was detected in favor of surgery (p = 0.027; Figure S4).

PROPENSITY SCORE MATCHING

When stratifying the studies by use of propensity score matching, we surprisingly found high heterogeneity (I^2 = 61%). The covariates used for model generation in propensity score matching showed substantial variability among the studies (Figure S2). Several studies did not incorporate clinically essential confounders such as tumor stage, tumor size, clinical performance status, and histology within the propensity score model (only 10% of the studies; Figure S2). Furthermore, the number of covariates used within the generation of the propensity score model was variable. Only 2 studies used more than 10 covariates, whereas 9 used less than 8 parameters (Figure S3). Although propensity score matching can minimize known confounding factors and improve the balance between two groups, it cannot truly ever eliminate them or replicate the results of a randomized study.

DISCUSSION

The present study is the largest meta-analysis examining oncologic outcomes of SBRT versus surgery in early-stage NSCLC. First, our analysis confirmed that surgery improved 3-year OS in comparison with SBRT, with a low degree of heterogeneity. The lobectomy subgroup also showed improved OS compared with the SBRT group; however, there was a high degree of heterogeneity in the pooled result. Second, when we stratified by the type of surgery (VATS or non-VATS), the 3-year OS was better than that in the SBRT group. There was no heterogeneity in the VATS subgroup, indicating that VATS did not compromise the treatment outcome. Third, studies that included only patients with T1N0M0 staging showed no significant differences in OS between surgery and SBRT groups, with no heterogeneity among the pooled studies. These findings failed to show a difference between the two treatments for patients in this population.

CSS is less sensitive to external variables than is OS. Our analysis shows that lobectomy is superior to SBRT for CSS in propensity score matching adjusted and unadjusted studies (neither subgroup showed significant heterogeneity). For patients staged as T1N0M0, there was no significant difference in CSS when comparing SBRT and lobectomy. Similarly, there was no difference in CSS when comparing SBRT and sublobar resection or mixed surgical resection. These findings may have important clinical implications for patients with comorbidities, advanced age, poor

Studies	SBRT	Surgery	HR (95% CI)
Lobectomy subgroup			
Albano et al.[43]	48	64	1.63 (1.12-2.43)
Boyer et al.[29]	468	468	1.80 (1.08-3.20)
Bryant et al.[45]	449	2986	1.38 (1.08-1.78)
Chang et al.[9]	31	31	1.18 (0.98-1.43)
Cornwell et al.[44]	37	37	1.53 (1.05-2.20)
Eba et al.[39]	21	21	1.51 (0.70-3.19)
Hamaji et al.[31]	41	41	2.56 (1.31-5.00)
Lin et al.[47]	45	45	1.00 (0.93-2.80)
Mokles et al.[34]	73	73	1.97 (0.99-3.92)
Rosen et al.[40]	1781	1781	2.00 (1.80-2.30)
Shirvani et al.[30]	251	251	1.00 (0.74-1.38)
Shirvani et al.[22]	99	99	1.41 (0.90-2.31)
Smith et al.[35]	300	300	1.30 (1.01-1.68)
Verstegen et al.[26]	64	64	1.33 (0.68-2.58)
Total subgroup	3706	6241	I^2 = 66%; 1.47 (1.48-1.69)
Mixed subgroup			
Crabtree et al.[20]	57	57	1.62 (0.93-2.80)
Crabtree et al.[28]	56	56	1.63 (0.88-2.97)
Dong et al.[46]	66	66	1.45 (0.54-3.87)
Kasteljin et al.[32]	53	53	1.71 (0.87-3.35)
Miyazaki et al.[42]	27	27	1.07 (0.70-1.10)
Palma et al.[21]	60	60	1.39 (0.93-2.07)
Robison et al.[24]	76	76	0.86 (0.44-1.69)
Van der Berg et al.[36]	197	197	1.07 (0.74-1.74)
Varlotto et al.[25]	77	77	1.28 (1.22-2.38)
Wang et al.[37]	35	35	1.40 (1.09-2.00)
Total subgroup	704	704	I^2 = 0%; 1.28 (1.07-1.53)
Sublobar subgroup			
Bryant et al.[45]	243	243	1.17 (0.90-1.53)
Ezer et al.[33]	362	362	0.98 (0.85-1.28)
Grills et al.[19]	55	55	2.35 (0.95-6.20)
Matsuo et al.[27]	53	53	1.49 (0.90-2.48)
Paul et al.[38]	201	201	1.68 (1.18-2.68)
Puri et al.[23]	5355	5355	1.55 (1.24-2.80)
Shirvani et al.[22]	112	112	1.22 (0.79-1.89)
Smith et al.[35]	243	243	1.01 (0.84-1.30)
Yerokum et al.[41]	1584	1584	1.30 (0.88-1.60)
Total subgroup	8206	8206	I^2 = 38%; 1.24 (1.06-1.46)

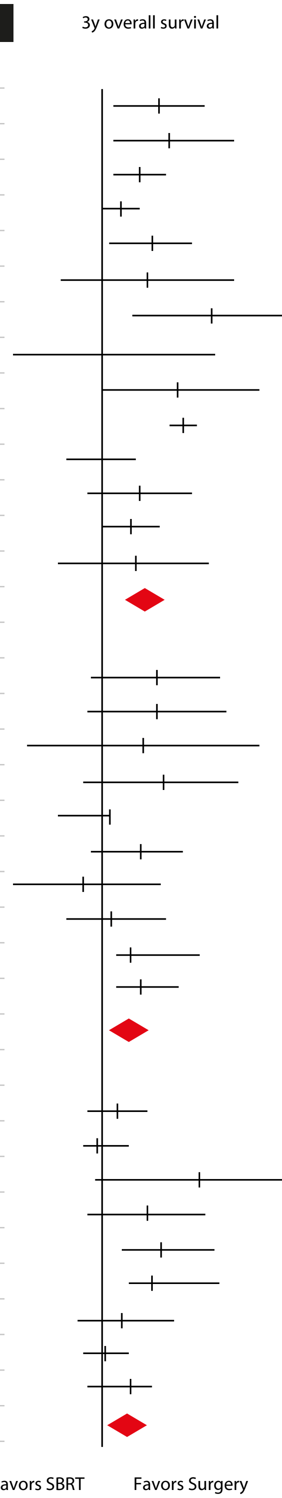

Figure 1. Analyses of 3-year (3y) overall survival comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. The 3y overall survival was significantly higher in all of the surgery subgroups (HR = 1.35; 95% CI: 1.22-1.44; I^2 = 66%). HR: hazard ratio.

pulmonary reserve, and other factors that may contraindicate surgery.

The American Society of Radiation Oncology has recently published a guideline that does not recommend SBRT outside of a clinical trial for patients who are at a low risk for lobectomy.[48] Our findings corroborate this recommendation. Both treatments, even when considering the publication bias in favor

Table 2. Subgroup analyses including categorical and continuous moderator variables for three-year overall survival.

Categorical moderator variable	Number of studies (patients)	HR (95% CI)	p	Heterogeneity	
				I^2, %	p
Type of surgery					
Lobectomy	7 (4,677)	1.47 (1.20-1.69)	<	66	0.0001
Mixed	4 (390)	1.28 (1.07-1.53)	0.001	0	0.658
Sublobar resection	5 (6,320)	1.24 (1.06-1.46)	0.007	38	0.114
			0.009		
VATS					
No	26 (16,951)	1.3 (1.2-1.4)	0.001	66	0.0001
Yes	4 (195)	1.7 (1.2-2.3)	0.002	0	0.528
Propensity score matching					
Yes	26 (24,917)	1.37 (1.23-1.54)	0.001	61	0.001
No	4 (4,594)	1.25 (1.01-1.54)	0.038	38	0.120
T staging					
T1	4 (3,334)	1.26 (0.95-1.68)	0.106	0	0.460
T1-2	21 (24,757)	1.33 (1.18-5.00)	0.0001	68	0.0001
T1-3	4 (620)	1.3 (1.2 -2.0)	0.048	0	0.40
Continuous moderator variable	**Number of studies (patients)**	**Intercept**	**Slope**	**p**	
Publication year					
2010-2019	30 (29,511)	−3.8	0.01	0.916	
Chemotherapy, % (median, 1-8)	12 (19,481)	0.75	−0.02	0.208	
Pathological lymph node involvement, % (median, 6.5-11.0)	8 (8,969)	0.82	−0.042	0.279	

HR: hazard ratio; VATS: video-assisted thoracic surgery; and T: tumor.

of surgery, had good OS and CSS outcomes, making the decision process complex and often dependent on patient desire.[49]

When we compared our meta-analysis results with those of previously published meta-analyses, three[11,12,14] of the five previous meta-analyses showed that surgery provides OS rates superior to those of SBRT. However, these analyses did not appraise publication bias or study heterogeneity. Our meta-analysis has explored study heterogeneity and publication bias, reinforcing the need for new studies with a more robust design, including clear inclusion and exclusion criteria, follow-up protocols, and statistical analyses that adjust for confounding variables, using methods such as propensity score matching and multivariable regression. Given the large sample size in the current study, it is unlikely that the inclusion of further observational studies comparing SBRT with surgery will significantly impact our findings.

Our meta-analysis does have limitations that warrant mention. Our analysis included only 1 small randomized trial, whereas the remaining 29 studies had a retrospective observational design. These are inherent limitations in the literature, although our quantitative synthesis improved the power in detecting the overall effect size. However, these results were significantly influenced by inter-study heterogeneity and publication bias, thereby presenting uncertainty to our pooled results. Similarly, a previous meta-analysis by Chen et al.[10] that reported on 16 comparative studies also found significant heterogeneity and publication bias. The authors identified favorable OS outcomes with surgery in comparison with SBRT (HR = 1.48; 95% CI: 1.26-1.72; $p < 0.001$), but high heterogeneity ($I^2 = 80.5\%$; $p < 0.001$).[10]

We also identified variations in the propensity score analysis for matching across a broad range of baseline variables, such as age, type of surgery, tumor size, histological subtype, tumor location, and others, in order to build two similar groups for comparison. Consequently, the readers must keep in mind that propensity score matching does not replicate randomized trial results, and that even after balancing, all sources of bias cannot be eliminated; unobserved confounders may exist. Lastly, we identified moderate heterogeneity in several of the quantitative syntheses by using random effects modeling.

FINAL CONSIDERATIONS

After pooling the data of 29,511 patients with early-stage NSCLC, surgery has shown to be superior to SBRT regarding OS and CSS outcomes, but no difference was found regarding LC. However, publication bias and heterogeneity may significantly have influenced these findings. Furthermore, there was no significant difference in OS between surgery and SBRT in the T1N0M0 subgroup analysis, the same happening when comparing the sublobar resection subgroup with the SBRT group regarding CSS. SBRT and surgery had similar LC regardless of the extent of surgical resection. Our analyses suggest equivalent outcomes for SBRT in subsets of patients with early-stage NSCLC, and SBRT seems to be a viable option for inoperable

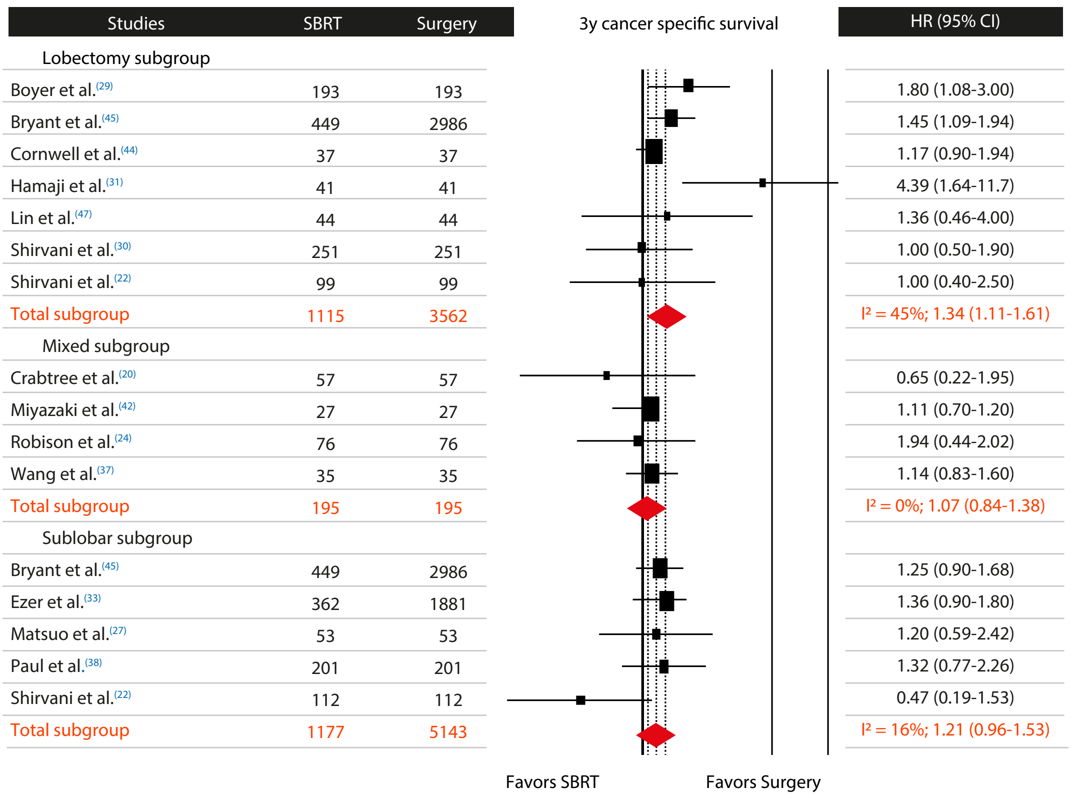

Figure 2. Analyses of three-year (3y) cancer-specific survival comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. The 3y cancer-specific survival was significantly higher in all of the surgery subgroups (HR = 1.23; 95% CI: 1.09-1.37; I^2 = 17%). HR: hazard ratio.

Table 3. Subgroup analyses including categorical and continuous moderator variables for three-year cancer-specific survival.

Categorical moderator variable	Number of studies (patients)	HR (95% CI)	p	Heterogeneity I^2, %	Heterogeneity p
Type of surgery					
Lobectomy	7 (4,677)	1.34 (1.11-1.61)	0.002	45	0.09
Mixed	4 (390)	1.07 (0.84-1.38)	0.573	0	0.77
Sublobar resection	5 (6,320)	1.21 (0.96-1.53)	0.112	16	0.309
VATS					
No	4 (195)	1.26 (1.02-1.54)	0.029	48	0.06
Yes	26 (16,951)	1.24 (1.06-1.44)	0.006	61	0.001
Propensity score matching					
Yes	26 (24,917)	1.15 (1.04-1.20)	0.017	15	0.295
No	4 (4,594)	1.40 (1.18-1.67)	0.0001	0	0.670
T staging					
T1	4 (3,334)	1.12 (0.86-1.46)	0.380	0	0.902
T1-2	21 (24,757)	1.27 (1.10-1.46)	0.001	30	0.145
Continuous moderator variable	**Number of studies (patients)**	**Intercept**	**Slope**	**p**	
Publication year					
2010-2019	30 (29,511)	−102	0.05	0.447	
Chemotherapy, %					
0-20%	12 (19,481)	0.54	−0.05	0.922	
Pathological lymph node involvement, %					
0-22%	8 (8,969)	0.5	−0.02	0.833	

HR: hazard ratio; VATS: video-assisted thoracic surgery; and T: tumor.

patients. These findings may have important clinical implications for patients with comorbidities, advanced age, poor pulmonary reserve, and other factors that may contraindicate surgery.

Studies	SBRT	Surgery	HR (95% CI)
Lobectomy subgroup			
Albano et al.[43]	48	64	0.88 (0.75-1.02)
Chang et al.[9]	31	27	0.97 (0.88-1.02)
Cornwell et al.[44]	37	37	0.92 (0.82-1.02)
Hamaji et al.[31]	41	41	0.79 (0.60-1.06)
Lin et al.[47]	45	45	1.45 (0.23-2.80)
Verstegen et al.[26]	64	64	3.68 (1.09-12.5)
Total subgroup	266	278	0.93 (0.85-1.01), p = 0.08
Mixed subgroup			
Crabtree et al.[28]	56	56	0.98 (0.22-1.95)
Dong et al.[46]	66	61	1.07 (0.70-1.20)
Total subgroup	122	122	0.98 (0.84-1.15), p = 0.809
Sublobar subgroup			
Grills et al.[19]	55	69	3.65 (0.98-13.6)
Total subgroup	55	69	3.65 (0.98-13.6), p = 0.06
Total I²	443	469	I² = 19%; 0.97 (0.93-1.08)

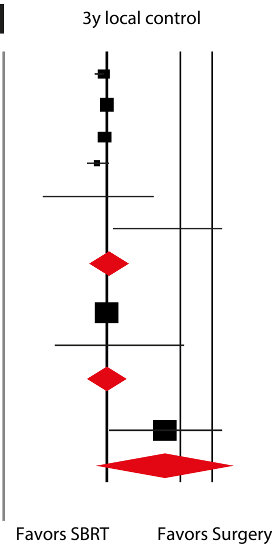

Figure 3. Analyses of 3-year (3y) local control comparing lobectomy, mixed surgical resection, and sublobar resection subgroups with the stereotactic body radiotherapy (SBRT) group. There were no significant differences between the surgery subgroups and the SBRT group (HR = 0.97; 95% CI: 0.93-1.08; I^2 = 19%). HR: hazard ratio.

AUTHOR CONTRIBUTIONS

GAV, AGG, and FYM: conception and planning of the study; interpretation of evidence; drafting and revision of preliminary and final versions; and approval of the final version. MY: interpretation of evidence; and drafting and revision of preliminary and final versions. FKM: conception and planning of the study; interpretation of evidence; and drafting and revision of preliminary and final versions.

CONFLICT OF INTEREST

None declared.

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