Lobectomy *vs.* sublobectomy for stage I non-small-cell lung cancer: a meta-analysis

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Background: Although lobectomy is widely regarded as the treatment of choice for early-stage non-small-cell lung cancer (NSCLC), sublobectomy (segmentectomy and wedge resection) has emerged as an alternative modality over the years. Only a handful of studies has compared the treatment effects of these two surgical interventions. This study aimed to analyze the treatment effects between lobectomy and sublobectomy on the survival outcomes of patients with stage I NSCLC systematically.

Methods: PubMed, Embase, and the Cochrane Library were systematically searched from their inception up to February 2019 for studies that compared the survival outcomes of lobectomy and sublobectomy. Studies that reported the diagnosis of stage I NSCLC by imaging or pathophysiology, lobectomy as intervention, sublobectomy as control, and overall survival (OS) and disease-free survival (DFS) as outcomes were included. The mean OS and DFS rates were calculated using the fixed-effects model.

Results: A total of 12 studies that included 4,373 patients with stage I NSCLC were included in the meta-analysis. The patients who underwent lobectomy showed a significant improvement in OS than those who underwent sublobectomy (P=0.025). These results differed when stratified by publication year (before 2010 and after 2010), study design (prospective and retrospective), country (Eastern and Western), control (segmentectomy and wedge), and study quality (high and low), but no significant differences were observed in DFS. These results were not altered in the sensitivity and subgroup analyses.

Conclusions: Stage I NSCLC patients who undergo sublobectomy display poor OS, whereas the DFS is similar for both methods.

Keywords: Lobectomy; meta-analysis; non-small-cell lung cancer (NSCLC); sublobectomy

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide (1). According to the global epidemiological data, over 2 million individuals were affected in 2018 (2). Non-small-cell lung cancer (NSCLC) accounts for approximately 80% of all diagnosed lung cancers; of these, poor prognosis and non-availability of curative treatment worsen the condition in about 75% of patients with metastatic or advanced-stage NSCLC (3-5). The long-term prognosis of patients with early-stage NSCLC is reportedly satisfactory, with 5-year survival rates after resection of over 70% (6-8). High-resolution computed tomography (CT) imaging and low-dose spiral CT imaging help to detect early lung adenocarcinoma (9,10). The Chinese Health Commission's 2018 guidelines for the diagnosis and treatment of primary lung cancer classifies the imaging examination as an additional diagnostic modality and suggests histopathological examinations. A biopsy can guide the choice of treatment based on histologic type, molecular profiling, tumor involvement, and, more importantly, the patient's health condition (11).

Although the therapeutic modalities against lung tumors include various methods such as chemotherapy, targeted therapy, immunotherapy, and radiotherapy, surgery remains the treatment of choice since it improves survival rates and reduces treatment-induced adverse effects. Currently, lobectomy remains the standard treatment strategy for patients with early-stage NSCLC (12). Nevertheless, limited resection is often the alternative surgical technique for patients who are not suitable for lobectomy due to advanced age, severely compromised pulmonary function, or other comorbidities (13). Besides, limited resection in early-stage NSCLC is associated with improved lung function preservation and low risk of morbidity and disability, crucial for patients with borderline preoperative cardiopulmonary function (14,15). Currently, segmentectomy and wedge resection are the most common limited resection approaches available. Segmentectomy is an anatomical resection with extensive lymph node dissection, while wedge resection removes the lung tumor and normal lung parenchyma from the margin surrounding the lung (16). Sublobectomy is preferred for tumors ≤2 cm combined with adenocarcinoma in situ, ≥50% ground-glass appearance on CT, or a long doubling radiologic surveillance time (≥400 days) (17).

Only a handful of studies have compared the treatment effects of lobectomy and sublobectomy in lung cancer management. Therefore, the present systematic review and meta-analysis aimed to compare the survival outcomes between these two surgical techniques in patients with stage I NSCLC. We present the following article in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) reporting checklist (available at http://dx.doi.org/10.21037/atm-20-460).

Methods

Data sources, search strategy, and selection criteria

Scholarly databases like PubMed, Embase, and the Cochrane Library were thoroughly searched from their inception up to February 2019 for potential studies, using the following core search terms and strategy: ("lung cancer" OR "NSCLC") AND ("segmentectomy" OR "segmental resection" OR "lobectomy") AND ("sublobar" OR "sublobectomy" OR "wedge") AND "stage I." No language or publication status restrictions were applied. A manual search of the reference lists of the identified relevant articles was also performed.

Two authors independently performed the literature search and study selection. Inconsistencies were settled by group discussions. The inclusion criteria were (I) diagnosis: imaging or pathological confirmation of stage I NSCLC; (II) intervention: lobectomy; (III) control: sublobectomy (segmentectomy and wedge resection); (IV) outcomes: overall survival (OS) and disease-free survival (DFS); and (V) study design: prospective or retrospective.

Data collection and quality assessment

Two authors independently assessed the abstracts and collected the following key information: first authors' surname, publication year, country, study design, sample size, mean age, percentage male, tumor stage, follow-up period, OS, and DFS. The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) based on selection (representative of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and no outcomes were present at the start of the study), comparability (based on the design or analysis), and outcomes (outcome assessment, and adequate follow-up duration and rate) (18). Two authors assessed the studies' quality, and any disagreement was resolved by a third author referring to the original article. The PRISMA statement was used to report the findings (19).

Statistical analysis

The treatment effects of lobectomy *vs.* sublobectomy on OS and DFS were studied based on the hazard ratio (HR) and 95% confidence interval (CI) in each study. Moreover, the pooled HR and 95% CI for OS and DFS were calculated using the fixed-effects model (20,21). The multivariate HR values were considered from the included studies. Heterogeneity among included studies was tested using the I-square method and P value for Q statistic, and I-square >50.0% or P<0.10 indicated significant heterogeneity (22,23). Sensitivity analyses for OS and DFS

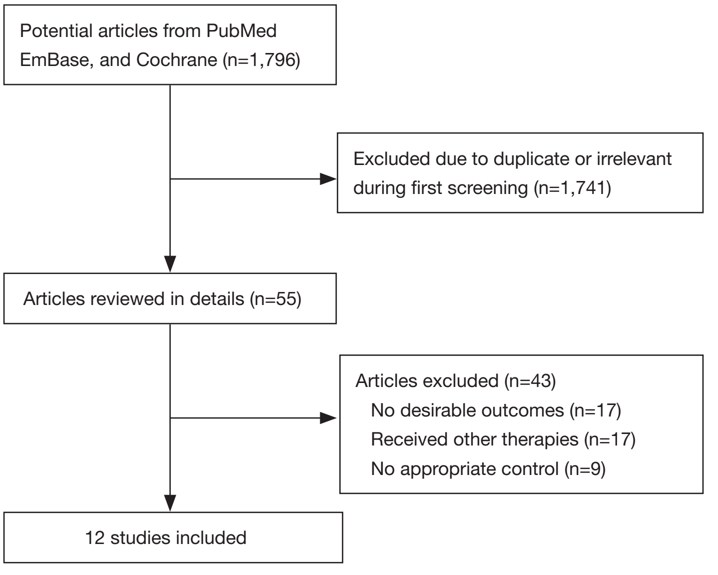

Figure 1 Schematic of the literature search and study selection processes.

were conducted to evaluate the pooled results' stability (24). Subgroup analyses for OS and DFS were conducted based on the publication year, country, mean age, percentage male, control, study quality, and study design. Moreover, P values between subgroups were calculated using interaction tests (25). Publication biases for OS and DFS were evaluated using funnel plots and Egger and Begg tests (26,27). All reported P values were two-sided, and P values <0.05 were regarded as statistically significant. Statistical analyses were performed using STATA software (version 12.0; Stata Corporation, College Station, TX, USA).

Results

Literature search

The electronic searches of databases such as PubMed, Embase, and the Cochrane Library retrieved 1,796 records; 1,741 were duplicates or irrelevant and were excluded. The remaining 55 studies were evaluated, and 43 studies were excluded due to a lack of sufficient data, having chemotherapy or radiotherapy as treatment, or no appropriate control. Finally, 12 studies were selected for the quantitative meta-analysis (28-39). A manual search of the reference lists of the retrieved studies did not yield any further studies. The study selection process's schematic is presented in *Figure 1*, and the baseline characteristics of the included studies are shown in *Table 1*.

Study characteristics

A total of 12 studies published between 2005 and 2017 and 4,373 patients with stage I NSCLC were included in the final analysis. Six studies were conducted in Japan, three in China, two in the USA, and one in Poland. The sample size of the selected studies ranged from 73 to 1,241. The age of the included patients ranged from 58.9 to 72.0 years, and the proportion of males ranged between 32.9% and 74.1%. Seven studies included patients with stage Ia NSCLC, and the remaining five studies included patients with stage Ia or Ib NSCLC. The NOS assessment of quality revealed that three studies had eight stars, five studies had seven stars, and the remaining four studies had six stars.

OS

A total of 11 studies reported an effect of lobectomy *vs.* sublobectomy on OS. The summary results indicated that lobectomy was associated with a significant OS improvement compared with sublobectomy (HR: 0.67; 95% CI: 0.47–0.95; P=0.025; *Figure 2*). Significant heterogeneity was detected across the included studies. Sensitivity analyses indicated that the pooled conclusion was altered due to marginal 95% CI (Tables S1,S2).

Table 1 Baseline characteristic of studies included in the systematic review and meta-analysis

Study	Publication year	Country	Study design	Sample size	Mean age (years)	Percentage male (%)	Tumor stage	Follow-up period	Study quality
Okada (28)	2005	Japan	Retrospective	1,241	65.0	71.0	Ia (≤20; 20–30) and Ib (≥30)	61 months (12–225 months)	6
Okada (29)	2006	Japan	Prospective	567	63.6	55.2	Ia (≤20)	>5 years	7
Yamato (30)	2008	Japan	Retrospective	523	65.2	50.3	Ia (≤20)	65 months	8
Shapiro (31)	2009	US	Retrospective	144	68.1	43.1	Ia (≤30)	21.5 months	7
Sugi (32)	2010	Japan	Prospective	159	63.9	39.6	Ia (≤30)	5 years	8
Nakamura (33)	2011	Japan	Prospective	411	69.6	53.0	I	37 months	8
Soukiasian (34)	2012	US	Retrospective	73	72.0	32.9	Ia and Ib	5 years	6
Yamashita (35)	2012	Japan	Retrospective	214	68.4	53.3	Ia	30 months	7
Zhong (36)	2012	China	Retrospective	120	64.5	57.5	Ia	25 months	6
Zhao (37)	2013	China	Retrospective	174	58.9	36.8	I	10.9 months	7
Zhang (38)	2013	China	Retrospective	54	62.5	74.1	Ia	3 years	6
Dziedzic (39)	2017	Poland	Retrospective	693	63.3	58.5	I	36.9 months	7

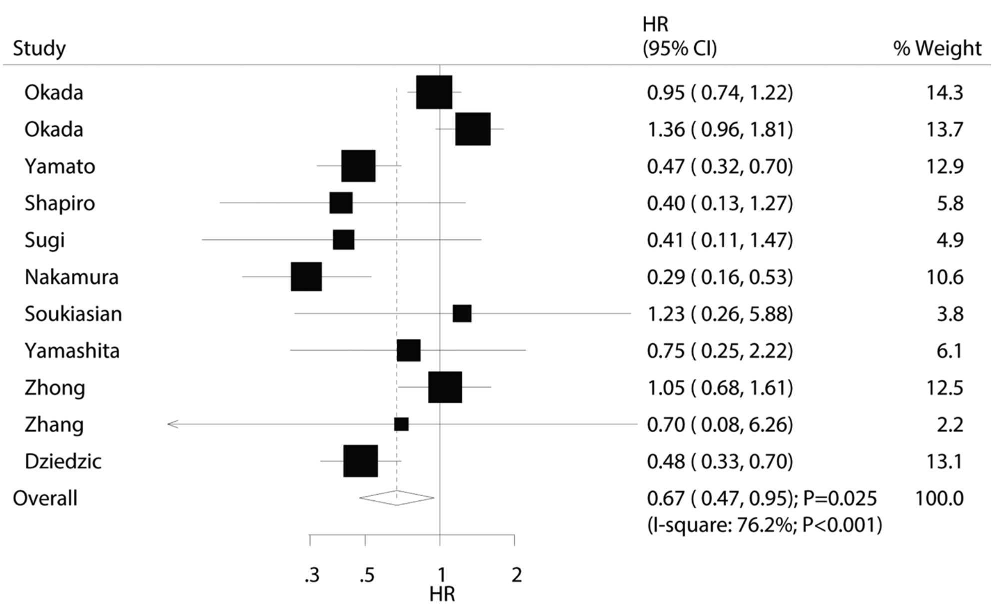

Figure 2 Lobectomy *vs.* sublobectomy on overall survival (OS) for patients with stage I non-small cell lung cancer (NSCLC).

DFS

A total of eight studies reported an effect of lobectomy *vs.* sublobectomy on DFS. Overall, no significant difference was detected between lobectomy and sublobectomy for DFS (HR: 1.07; 95% CI: 0.88–1.29; P=0.496; *Figure 3*). No evidence of heterogeneity was observed. The results were not altered by the sequential exclusion of each study (Tables S1,S2).

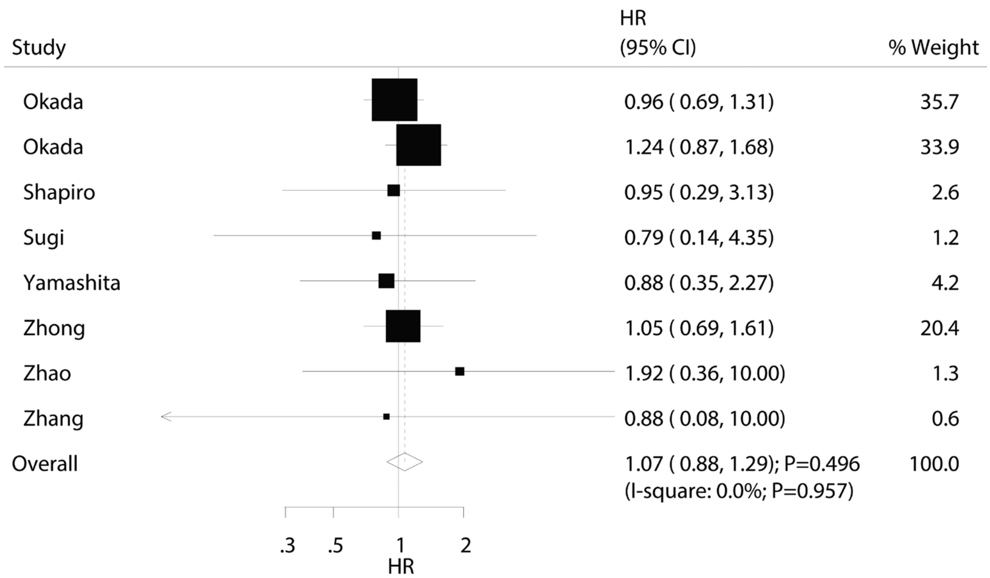

Figure 3 Lobectomy *vs.* sublobectomy on disease-free survival (DFS) for patients with stage I non-small cell lung cancer (NSCLC).

Subgroup analyses

Subgroup analyses for OS and DFS based on publication year, country, mean age, percentage of male, control, study quality, and study design were conducted to identify the source of heterogeneity and the treatment effects in patients with specific characteristics. We found that lobectomy, compared with wedge resection, was associated with a significant improvement in OS when the study was published in or after 2010, in Western countries, when the mean age of the patients was ≥65.0 years, when the study was of good quality, and when study design was prospective (Tables S3,S4). Moreover, the subgroup analyses for DFS based on the predefined factors were consistent with the overall analysis in all subsets, and no significant differences were detected between lobectomy and sublobectomy (Tables S3,S4).

Publication bias

Potential publication bias for OS and DFS could not be excluded by reviewing the funnel plots (*Figure 4A,B*), but no potential publication biases were detected for OS (P value for Egger: 0.327; P value for Begg: 0.755) and DFS (P value for Egger: 0.789; P value for Begg: 0.902).

Discussion

This quantitative meta-analysis involving 4,373 patients with stage I NSCLC from 12 studies evaluated the OS and DFS between lobectomy and sublobectomy. Lobectomy was significantly associated with an improvement in OS compared with sublobectomy, but no significant difference was detected in DFS. The treatment effect between lobectomy and sublobectomy on OS was affected by publication year (before 2010 and after 2010), country (Eastern and Western), control (segmentectomy and wedge), study quality (high and low), and study design (prospective and retrospective). In contrast, the predefined factors did not yield any significant impact on the DFS.

A previous meta-analysis of eight studies also demonstrated that lobectomy resulted in a significant improvement in OS compared with sublobectomy, whereas no significant difference was detected for DFS. Moreover, it pointed out that the significant difference in OS was the primary focus compared to wedge resection (40). Nevertheless, the stratification of treatment effects of these surgical techniques by patients' characteristics was unclear. Another meta-analysis of nine studies reported that segmentectomy was associated with a significant improvement in OS and cancer-specific survival compared with wedge resection. In contrast, no significant difference was detected for DFS (41). Even the 2014 meta-analysis of 12 studies indicated that sublobectomy could lower OS in patients with stage 1a NSCLC (42). Of note, several included studies in the present analysis reported conflicting

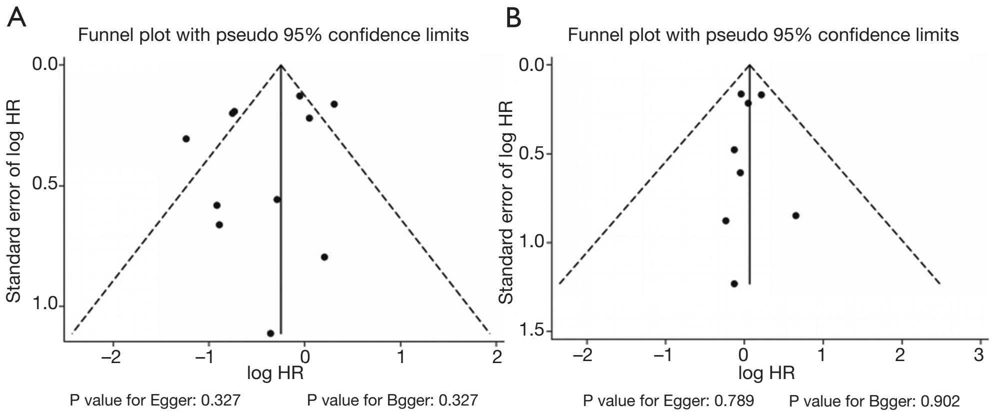

Figure 4 Funnel plot for (A) overall survival (OS) and (B) disease-free survival (DFS).

results. A non-randomized study by Okada *et al.* involving patients with peripheral cT1N0M0 NSCLC of ≤2 cm indicated that the OS and DFS were similar between lobar and sublobar resections (29). A study also pointed out that the extended segmentectomy was associated with an improved treatment margin (43). Intriguingly, another comparative study in elderly patients also highlighted no significant difference between the OS and DFS rates in stage 1 tumors <2 cm (44). A retrospective study of 73 patients with stage I NSCLC suggested that segmentectomy by video-assisted thoracoscopic surgery was comparable to video-assisted thoracoscopic lobectomy, but no significant difference was detected in morbidity or mortality (34). The treatment effect could be attributed to disease staging and comorbidities. Zhong *et al.* reported that segmentectomy was safe in 120 patients with stage Ia NSCLC, and the survival outcome was comparable to that of lobectomy (36). Moreover, the results could be attributed to the tumor diameters ≤20 mm without nodal involvement. Although several other studies reported no significant difference between lobectomy and sublobectomy on OS, they provided a potentially beneficial trend of lobectomy on OS (28,31,32,35,38).

Furthermore, no significant difference was observed between lobectomy and sublobectomy on DFS, and all the included studies reported similar results. This might vary due to the low incidence of disease relapse and varied follow-up duration among the included studies. Moreover, the width of resection margin, lymph node dissection, or sampling and segment localization could affect local recurrence frequency, and these factors varied among the included studies (45,46).

Different prognostic factors may help to stratify overall prognosis estimates and help choose appropriate surgical intervention in each patient. They provide details on the expected outcomes of a population having unique disease characteristics. Subgroup analyses indicated that publication year, country, control, study quality, and study design could bias the treatment effect on OS by both surgical methods. This phenomenon could be attributed to several interconnected factors. First, the publication year was significantly associated with early diagnosis, disease stage, and background therapies. Second, different countries have different diagnosis and medical levels, which could affect the prognosis. Control strategy could affect the net treatment effect of lobectomy. Lastly, of the 12 studies included, only three received eight stars in the NOS assessment. The study quality and study design were significantly correlated with the reliability and evidence level of individual studies.

The present meta-analysis included several recent studies, and the results have a profound value of evidence on the choice of surgical treatment against lung cancer. Nevertheless, it has several limitations. First, all the included non-randomized studies and uncontrolled confounders could affect the treatment effects between lobectomy and sublobectomy. Second, the treatment effects stratified by patients' characteristics were not considered due to unavailable data. Third, unpublished data were not available, which might be associated with a high false-positive rate. Finally, the analysis was based on the pooled results; data were not available from the included studies, which restricted the detailed analysis based on the patients' disease status.

Conclusions

This meta-analysis indicates a similar DFS between lobectomy and sublobectomy for patients with stage I NSCLC. Lobectomy was associated with a significant improvement in OS compared with sublobectomy. Nonetheless, the results should be substantiated by further prospective randomized controlled trials.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at http://dx.doi.org/10.21037/atm-20-460

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-460). 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.

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Supplementary

Table S1 Sensitivity analysis for OS

Excluding study	HR and 95%CI	P value	Heterogeneity (%)	P value for heterogeneity
Okada	0.63 (0.41–0.96)	0.030	76.6	<0.001
Okada	0.60 (0.43–0.85)	0.003	67.0	0.001
Yamato	0.71 (0.49–1.02)	0.066	74.0	<0.001
Shapiro	0.69 (0.48–0.99)	0.045	77.8	<0.001
Sugi	0.69 (0.48–0.99)	0.041	78.1	<0.001
Nakamura	0.75 (0.54–1.04)	0.085	70.8	<0.001
Soukiasian	0.65 (0.46–0.94)	0.021	78.4	<0.001
Yamashita	0.66 (0.46–0.96)	0.029	78.5	<0.001
Zhong	0.63 (0.43–0.93)	0.019	77.5	<0.001
Zhang	0.67 (0.47–0.96)	0.027	78.5	<0.001
Dziedzic	0.71 (0.49–1.02)	0.066	73.9	<0.001

Table S2 Sensitivity analysis for DFS

Excluding study	HR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity
Okada	1.13 (0.89–1.44)	0.301	0.0	0.967
Okada	0.99 (0.78–1.25)	0.936	0.0	0.990
Shapiro	1.07 (0.88–1.30)	0.482	0.0	0.919
Sugi	1.07 (0.88–1.30)	0.475	0.0	0.926
Yamashita	1.08 (0.89–1.31)	0.452	0.0	0.931
Zhong	1.07 (0.87–1.33)	0.517	0.0	0.916
Zhao	1.06 (0.87–1.29)	0.551	0.0	0.955
Zhang	1.07 (0.88–1.30)	0.490	0.0	0.918

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Table S3 Subgroup analysis for OS

Factors	Group	HR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity	P value between groups
Publication year	Before 2010	0.78 (0.47–1.29)	0.336	84.4	<0.001	0.005
	2010 or after	0.59 (0.37–0.93)	0.025	59.5	0.022	
Country	Eastern	0.72 (0.48–1.07)	0.101	78.5	<0.001	0.005
	Western	0.49 (0.35–0.70)	<0.001	0.0	0.480	
Mean age (years)	≥65.0	0.57 (0.35–0.94)	0.028	74.3	0.002	0.069
	<65.0	0.80 (0.46–1.39)	0.428	79.2	0.001	
Percentage male (%)	≥50.0	0.70 (0.47–1.02)	0.065	82.2	<0.001	0.288
	<50.0	0.52 (0.25–1.11)	0.091	0.0	0.472	
Control	Segmentectomy	0.85 (0.66–1.08)	0.187	3.5	0.406	<0.001
	Wedge	0.32 (0.23–0.44)	<0.001	0.0	0.619	
Study quality	High	0.54 (0.33–0.91)	0.020	82.4	<0.001	0.006
	Low	0.98 (0.79–1.21)	0.819	0.0	0.954	
Study design	Prospective study	0.68 (0.56–0.83)	0	0	0.648	<0.001
	Retrospective study	0.67 (0.59–0.76)	<0.001	0	1.000	

Table S4 Subgroup analysis for DFS

Factors	Group	HR and 95% CI	P value	Heterogeneity (%)	P value for heterogeneity	P value between groups
Publication year	Before 2010	1.08 (0.86–1.36)	0.492	0.0	0.538	0.838
	2010 or after	1.03 (0.72–1.49)	0.853	0.0	0.943	
Country	Eastern	1.07 (0.88–1.30)	0.482	0.0	0.919	0.844
	Western	0.95 (0.29–3.12)	0.933	–	–	
Mean age (years)	≥65.0	0.95 (0.71–1.28)	0.738	0.0	0.985	0.305
	<65.0	1.16 (0.90–1.50)	0.236	0.0	0.915	
Percentage male (%)	≥50.0	1.07 (0.88–1.30)	0.514	0.0	0.842	0.964
	<50.0	1.09 (0.47–2.53)	0.843	0.0	0.729	
Study quality	High	1.18 (0.88–1.58)	0.263	0.0	0.889	0.373
	Low	0.99 (0.77–1.28)	0.941	0.0	0.942	
Study design	Prospective study	1.04 (0.89–1.20)	0.638	0	0.619	0.079
	Retrospective study	1.08 (0.99–1.17)	0.080	0	0.999	

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