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Less is more in solid-dominant lung cancer? Sublobar resection versus lobectomy for solid-dominant stage IA non-small-cell lung cancer: A meta-analysis study

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Abstract. Although lobectomy is well established as the standard surgical procedure for stage IA non-small-cell lung cancer (NSCLC), sublobar resection is increasingly preferred, particularly in intentional segmentectomy for radiologically less-invasive small NSCLC. However, the indication for sublobar resection of radiologically pure solid or solid-dominant NSCLC remains controversial, owing to its invasive pathological characteristics. Therefore, the present meta-analysis was conducted to compare the efficacy of sublobar resection with lobectomy for treating solid-dominant stage IA NSCLC. An electronic search was conducted using four online databases from their dates of inception to April 2017. The hazard ratio (HR) was used as a summary statistic for censored outcomes and the odds ratio (OR) was used as the summary statistic for dichotomous variables. A total of nine studies met the selection criteria, including a total of 2,265 patients (1,728 patients underwent lobectomy, 425 segmentectomy and 112 wedge resection). From the available data, patients treated with a sublobar resection had a higher risk of local recurrence compared with patients treated with lobectomy [OR=1.89; 95% confidence interval (CI), 1.02-3.50; P=0.04]. However, no obvious difference in local recurrence was found in a subgroup analysis of segmentectomy compared with lobectomy (OR=1.19; 95% CI, 0.68-2.10; P=0.61). Sublobar resection was not associated with a significantly negative impact on distant recurrence (OR=1.09; 95% CI, 0.55-2.16; P=0.796). Patients in the sublobar resection group had no significant differences in recurrence-free survival (RFS; HR=1.43; 95% CI, 0.76-2.69; P=0.27) and overall survival (OS; HR=0.96; 95% CI, 0.75-1.23; P=0.77) compared with those in the lobectomy group. In the subgroup analysis of anatomic segmentectomy compared with lobectomy, there was no significant difference in RFS, with mild inter-study heterogeneity. The current meta-analysis suggested that segmentectomy had a comparable oncologic efficacy to lobectomy for solid-dominant stage IA NSCLC. Therefore, segmentectomy may be a feasible alternative in selected cases of solid-dominant stage IA NSCLC. However, these findings should be confirmed by prospective randomized controlled trials in the future.

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Abbreviations: NSCLC, non-small-cell lung cancer; HR, hazard ratio; OR, odds ratio; RFS, recurrence-free survival; OS, overall survival; CT, computer tomography; GGO, ground-glass opacity; DFS, disease-free survival; RCT, randomized control trial

Key words: lobectomy, non-small-cell lung cancer, sublobar resection, segmentectomy, solid

Introduction

Lobectomy has been the standard procedure for lung cancer resection since the widespread acceptance of the 1995 Lung Cancer Study Group (LCSG) randomized trial of lobectomy compared with limited resection for stage IA non-small-cell lung cancer (NSCLC) (1). However, lung cancer screening with low-dose computed tomography (CT) and widespread use of spiral CT imaging has contributed to the identification and diagnosis of early-stage NSCLC (2,3). In the past decade, the number of patients presenting with very small and peripheral lung cancers has markedly increased. Meanwhile, a growing population of older patients with significant medical comorbidities that preclude major operations are being diagnosed with early lung cancer. These factors have led to the popularity of sublobar resection in recent years.

Early lung cancer presents as a wide area of ground-glass opacity (GGO) on CT scans, which is likely to be less invasive adenocarcinoma associated with a good prognosis (4-6). Therefore, these patients are considered to be feasible candidates for sublobar resections, i.e. segmentectomy or wedge resection, as confirmed by the prospective JCOG 0201 study in Japan (4).

However, radiologically solid-dominant lung cancer has been regarded as a different, highly invasive category of lung cancer (7,8). Thus, sublobar resection for lung cancer with a solid-dominant appearance on thin-section CT scans, namely invasive lung cancer, remains controversial (9,10). A total of three multi-center, prospective, randomized studies focused on this issue are currently ongoing, and the data have not yet been published (11-13).

Segmentectomy, rather than wedge resection, is preferred for patients with stage IA NSCLC as it is an anatomical resection involving more extensive lymph node dissection (14-16). Whether sublobar resection, particularly segmentectomy, is comparable to lobectomy in terms of oncologic outcomes in radiologically solid (i.e. invasive) NSCLC remains unknown.

This meta-analysis investigated whether sublobar resection has comparable oncologic outcomes to lobectomy in lung cancer with a solid-dominant appearance. The evaluated outcomes were local recurrence, distant recurrence, recurrence-free survival (RFS) and overall survival (OS).

Materials and methods

Search strategies. Systematic computerized searches of the PubMed, Embase and Cochrane Library databases and Google Scholar were performed from their dates of inception to April 2017. The following search terms were used: 'non-small-cell lung cancer (NSCLC)/lung cancer' and 'lobectomy/sublobectomy/segmentectomy/limited resection/sublobar resection' and 'recurrence/prognosis/survival' and 'solid'. The search was limited to English and the Abstract/Title. The citation lists of all retrieved articles were scanned to identify other potentially relevant publications.

Study selection. The following criteria were used for study inclusion. i) Either completed randomized controlled trials (RCTs) or retrospective observational studies that compared sublobar resection/segmentectomy with lobectomy in treating patients with clinical stage IA NSCLC, according to the 7th edition of TNM classification (17). ii) Nodules were peripheral with 'solid or solid-dominant appearance' on thin-section CT. The solid component was defined as an area of increased opacification that completely obscured the underlying vascular markings. GGO was defined as an area of slight, homogeneous increase in density that did not obscure the underlying vascular markings (9). In the current study, a solid tumor was defined as a tumor exhibiting only consolidation without GGO, while a solid dominant tumor was defined as a tumor in which the ratio of the maximum diameter of consolidation to the maximum tumor diameter was >50% on thin-section CT. iii) The primary outcomes of interest in this study were OS, disease-free survival (DFS)/RFS, and local or distant recurrence rate. Only studies that reported at least one of the outcomes were included. iv) The most recent or completed study was chosen if the studies were based on overlapping patients.

The exclusion criteria were as follows: i) Stage IA lung cancer was characterized as GGO-dominant or its nature was not described on CT; ii) papers that were not published in English; and iii) case reports, abstracts, conference reports, reviews and experiments.

Statistical analysis. The meta-analysis was performed in accordance with the recommendations of the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines (18,19). The hazard ratio (HR) was used as a summary statistic for censored outcomes (OS and RFS), as previously described (20). An HR >1 represented a survival benefit favoring the sublobar resection/segmentectomy group. The odds ratio (OR) was used as the summary statistic for dichotomous variables. An OR <1 favored the sublobar resection/segmentectomy group. The pooled OR/HR and 95% confidence intervals (CIs) were graphically presented as forest plots. The effect measure OR/HR was calculated by a fixed effects model (using the Mantel-Haenszel method) or a random effects model (using the DerSimonian and Laird method) based on the heterogeneity among studies (21,22).

The heterogeneity of the included studies was detected using the Cochran test. Random effects models were used if high heterogeneity was detected among the studies (P<0.1 or I^2 >50%). Otherwise, fixed effects models were used. To combine the data, an HR with 95% CI was used, which were directly obtained from the original articles. When the HR was not directly reported in the original articles, it was estimated, as previously described (23). A funnel plot and the Egger test were used to investigate possible publication bias (24). Statistical significance was set at P<0.05.

Analyses were performed using STATA version 13.0 software (Stata Corporation).

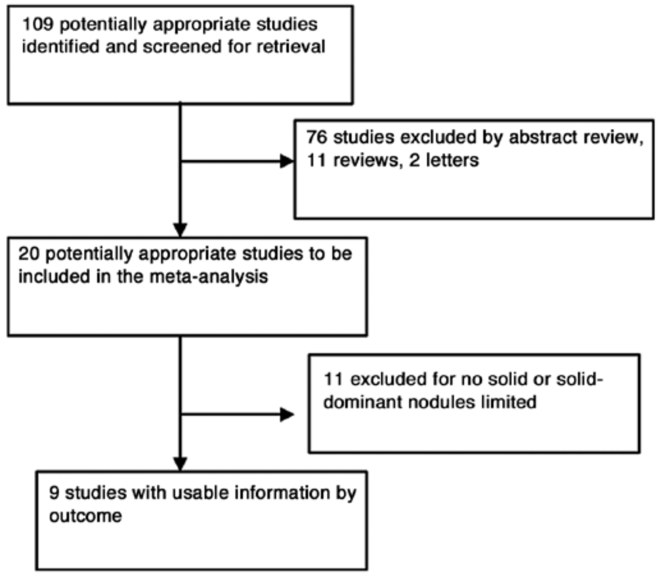

Figure 1. Flow diagram of the study selection procedure.

Results

Literature Search and Study Characteristics. A total of 109 publications were identified using the predefined search strategy (Fig. 1). Eighty-nine studies were excluded after screening the titles and abstracts, and full texts of the remaining 20 studies were retrieved. These included 11 reviews, two letters and 76 studies, which were either wedge resection/sublobar resection versus lobectomy or insufficient data for the specified endpoints. Eleven were excluded due to lack of definite solid or solid-dominant nodules reporting. Finally, nine studies that met the inclusion criteria were included in the meta-analysis (Fig. 1). Study characteristics are summarized in Table I. The combined study population

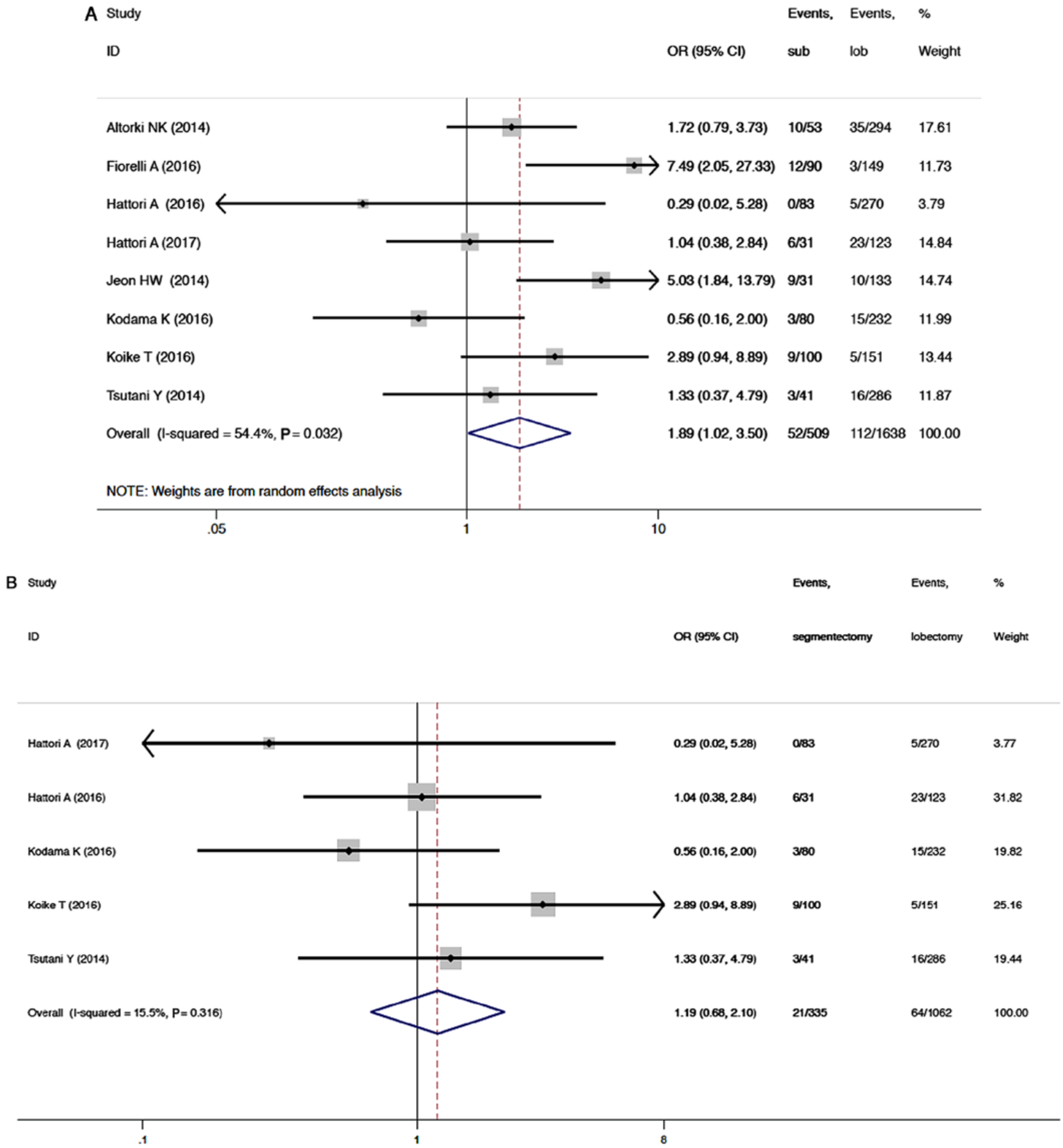

Figure 2. Local recurrence after (A) sublobar resection vs. lobectomy and (B) local recurrence after segmentectomy vs. lobectomy for early-stage solid-dominant NSCLC. Squares are point estimates of the treatment effect (HR, OR and WMD), with 95% CIs indicated by the horizontal bars. Diamonds are the summary estimate from the pooled studies with 95% CI. NSCLC, non-small-cell lung cancer; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

from the included studies was 2,265 patients with 1,728 lobectomies, 425 segmentectomies and 112 wedge resections. All studies were retrospective studies. Seven studies reported several pathological types of NSCLC, whereas two studies only included adenocarcinoma. In four studies, sublobar resection involved segementectomy and wedge resection, but in the other five studies, sublobar resection only referred to segmentectomy. Five studies described intentional sublobar resection, three compromised procedure and one had both categories.

Primary outcome measures

Local and Distant Recurrence. Eight studies reported local recurrence in the sublobar resection and lobectomy groups, providing a total sample size of 2,147 patients for evaluation. Meta-analysis of the data showed that patients treated with a sublobar resection were inferior to patients treated with lobectomy, with a pooled OR of 1.89 (95% CI, 1.02-3.50; P=0.04; Fig. 2A). There was moderate inter-study heterogeneity (P=0.03; I^2=54%).

Table I. General characteristics of the enrolled studies.

Author, year	Refs.	Institution	Study period	Total patients	Including criteria	Extent of resection			Stage[a]	Tool of staging	Outcomes	Selection category of sub
						Lob	Seg	WR				
Hattori *et al*, 2017	(25)	Juntendo University School of Medicine	2008-2014	353	Solid-dominant	270	83		cT1aN0M0	PET-CT	RFS OS	Intentional
Hattori *et al*, 2016	(26)	Juntendo University School of Medicine	2008-2013	154	Solid-dominant and pure solid	123	31		cT1bN0M0	PET-CT	RFS OS	Intentional
Altorki *et al*, 2014	(27)	I-ELCAP database	1993-2011	347	Solid nodules	294	16	37	cIA	PET-CT	10-year Kaplan-Meier	Intentional
Tsutani *et al*, 2014	(28)	Hiroshima University, Kanagawa Cancer Center, Cancer Institute Hospital, and Hyogo Cancer Center, Japan	2005-2010	327	≥50% solid component	286	41		cIA	PET-CT	RFS	Intentional
Koike *et al*, 2016	(29)	Niigata University Hospital and Niigata Cancer Center Hospital	1998-2009	251	Without GGO	151	100		cT1aN0M0	CT	OS DFS	Intentional (n=74) and compromised (n=26)
Fiorelli *et al*, 2016	(30)	Multicenter	2006-2016	239	Solid-dominant and pure solid	149	39	51	cT1a,b-2aN0M0	PET-CT	OS DFS	Compromised
Kodama *et al*, 2016	(31)	Osaka Medical Center cancer registry database	1997-2010	312	Solid and part-solid	232	80		cT1aN0M0	CT, PET-CT	OS RFS	Intentional
Jeon *et al*, 2014	(32)	Seoul St. Mary's Hospital	2001-2010	164	Without GGO	133	12	19	cIA	CT, PET-CT	OS DFS	Compromised
Inoue *et al*, 2010	(33)	Osaka University Hospital, Osaka, Japan	1992-2007	118	Solid or solid dominant	90	23	5	cIA	CT, PET-CT	DFS	Compromised

[a]Staging is according to the TNM Classification of Malignant Tumors, Seventh Edition, published by the International Union Against Cancer and the American Joint Committee on Cancer.

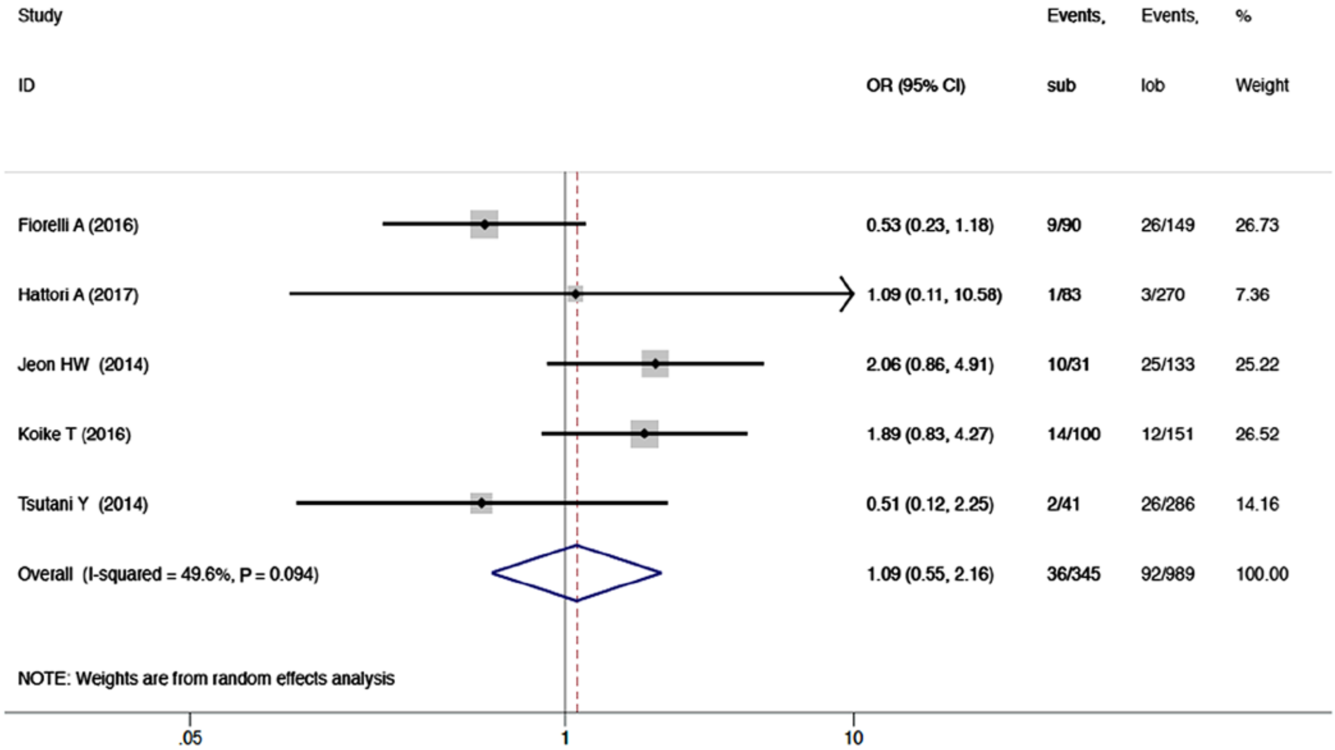

Figure 3. Distant recurrence after sublobar resection vs. lobectomy for early-stage solid-dominant NSCLC. Squares are point estimates of the treatment effect (HR, OR and WMD), with 95% CIs indicated by the horizontal bars. Diamonds are the summary estimate from the pooled studies with 95% CI. NSCLC, non-small-cell lung cancer; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

However, in subgroup analysis of anatomic segmentectomy versus lobectomy, there was no obvious difference in local recurrence between the two groups (OR=1.19; 95% CI, 0.68-2.10; P=0.61; Fig. 2B). Inter-study heterogeneity was not significant in subgroup analysis (P=0.316; I^2=15.5%).

Sublobar resection was not associated with a significant negative impact on distant recurrence based on five reports (1,334 patients) as compared to lobectomy. The OR was 1.09 (95% CI, 0.55-2.16; P=0.796; I^2=49.6%; Fig. 3).

RFS and OS. For RFS, eight eligible studies that included a total of 1918 patients were pooled. Given the significant heterogeneity among studies (I^2=74.1%), a random-effects model was used to pool the HR of the studies. As seen in Fig. 4A, the combined HR for the eight studies was 1.43 (95% CI, 0.76-2.69; P=0.27). Both in intentional and compromised sublobar resection groups, there are similar combined HR (1.40 vs. 1.44) in RFS. Accordingly, there was no statistical difference in RFS between sublobar resection (both intentional and compromised sublobar resection) and lobectomy group. In subgroup analysis of anatomic segmentectomy versus lobectomy, there was no statistical difference in RFS (HR=1.40; 95% CI, 0.79-2.48; P=0.244; Fig. 4B). Furthermore, inter-study heterogeneity was not obvious in subgroup analysis (P=0.253; I^2=25.2%).

For OS, eight studies with a total of 1938 patients were included in the quantitative analysis. The combined HR for the eight studies was 0.96 (95% CI, 0.75-1.24; P=0.77; Fig. 5) with a random-effects model, indicating that sublobar resection was associated with similar OS as lobectomy. There was minor heterogeneity between studies (I^2=37.3%; P=0.13).

Publication Bias. The results of the Egger test did not suggest any evidence of publication bias in local and distant recurrence (P=0.933, P=0.699; respectively). For RFS and OS, the funnel plots provided no evidence of overt publication bias. The Egger test also showed no significant publication bias in RFS (P=0.774) and OS (P=0.557).

Discussion

Lobectomy is widely recommended as the standard treatment for patients with stage IA NSCLC who can tolerate the procedure (1). Recently, sublobar resection (including wedge resection and segmentectomy) was suggested as an alternative surgical treatment for early-stage NSCLC (34-45). A number of meta-analyses have reported that sublobar resection or segmentectomy have comparable oncologic outcomes to lobectomy in patients with stage IA NSCLC (46-48). The most favorable subset consists of radiologically non-invasive lung cancer, usually defined as a consolidation/tumor (C/T) ratio <0.5 on thin-section CT (4,49,50). Recently, several studies have compared the efficacy of sublobar resection with lobectomy for treating solid-dominant stage IA NSCLC, which is conventionally an unfavorable indication for sublobar resection (51,52). Therefore, this meta-analysis involving nine studies and 2,265 patients was conducted to examine the efficacy of sublobar resection for the treatment of solid-dominant stage IA NSCLC.

According to this meta-analysis, sublobar resection had a higher local recurrence rate than lobectomy in solid-dominant NSCLC. However, there was no significant difference between the local recurrence rates of segmentectomy and lobectomy.

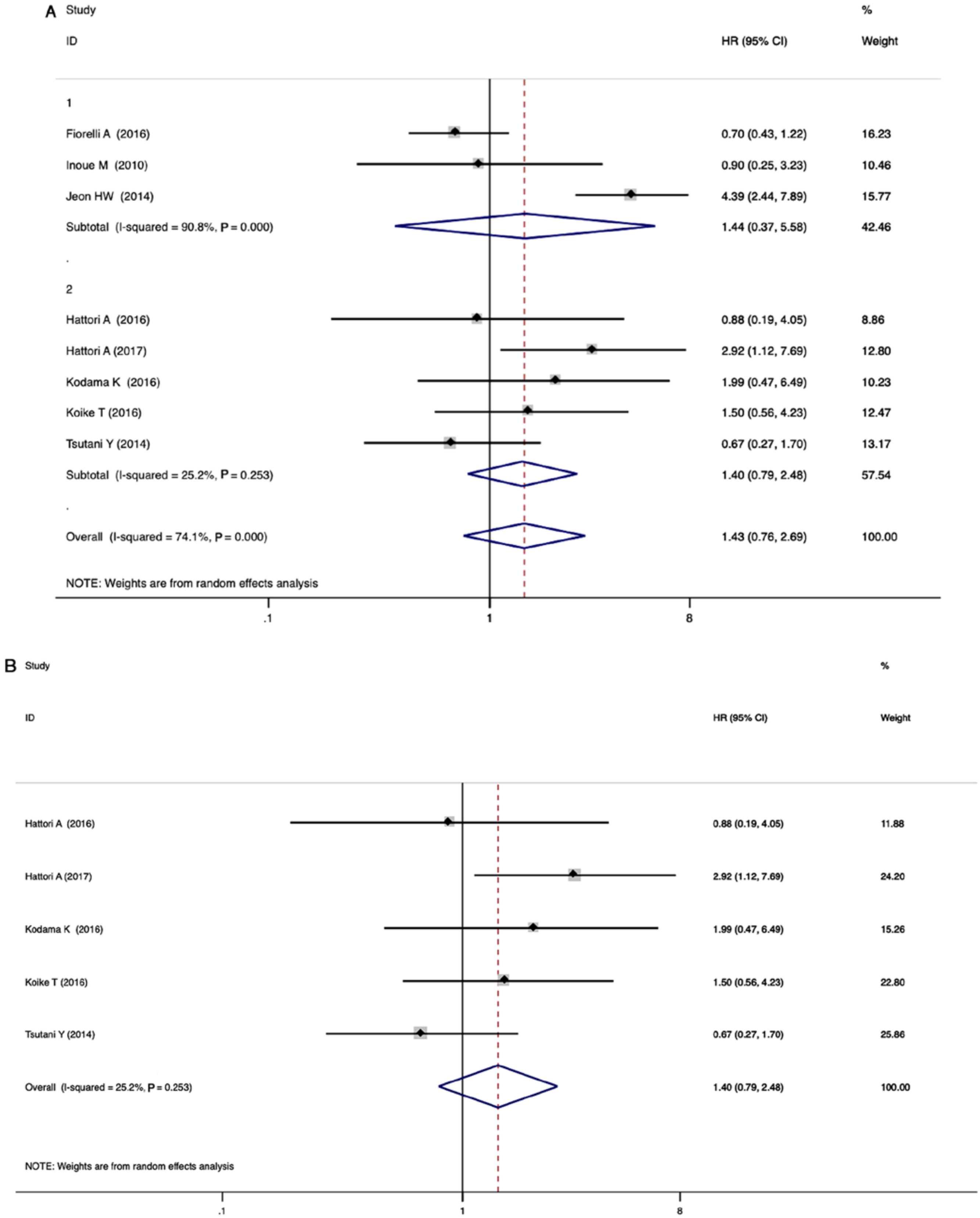

Figure 4. Recurrence-free survival after sublobar resection vs. lobectomy for early-stage solid-dominant NSCLC. (A) Compromised sublobar resection group. (B) Intentional sublobar resection group. Squares are point estimates of the treatment effect (HR, OR and WMD), with 95% CIs indicated by the horizontal bars. Diamonds are the summary estimate from the pooled studies with 95% CI. NSCLC, non-small-cell lung cancer; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

Moreover, the distant recurrence risk was comparable between sublobar resection and lobectomy. The RFS and OS values of patients with solid-dominant tumors who underwent sublobar resection were similar to those of patients who underwent

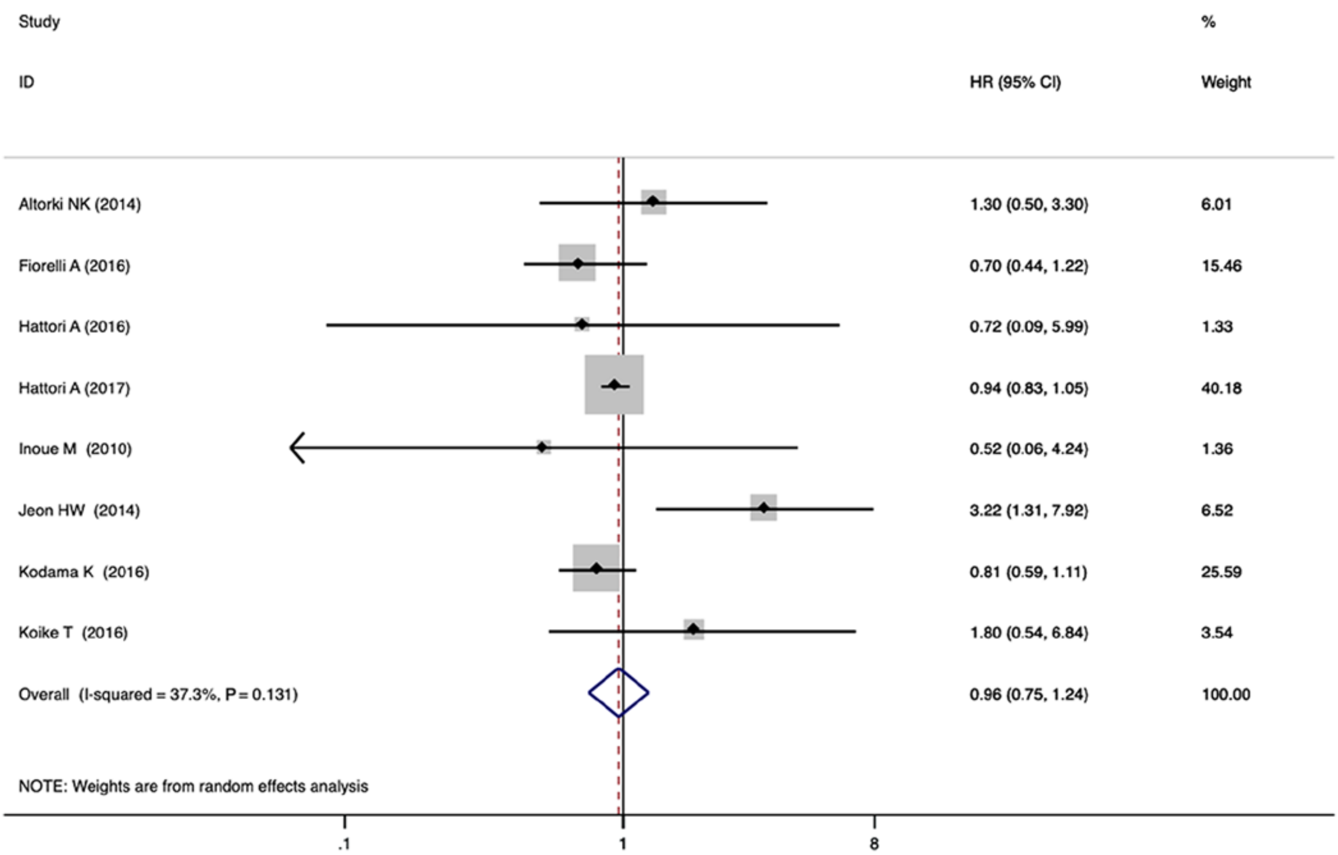

Figure 5. Overall survival after sublobar resection vs. lobectomy for early-stage solid-dominant NSCLC. Squares are point estimates of the treatment effect (HR, OR and WMD), with 95% CIs indicated by the horizontal bars. Diamonds are the summary estimate from the pooled studies with 95% CI. NSCLC, non-small-cell lung cancer; CI, confidence interval; HR, hazard ratio; OR, odds ratio.

lobectomy. Despite the obvious heterogeneity between studies in RFS, studies with intentional sublobar resection had no obvious heterogeneity. The subgroup analysis showed that segmentectomy was equivalent to lobectomy with respect to RFS, with no obvious heterogeneity. The results indicated that anatomic segmentectomy with systemic lymph node dissection may be an alternative surgical procedure for solid-dominant stage IA NSCLC. These findings should be confirmed in prospective studies, such as JCOG 0802/WJOG4607L (11,12) and NCT00499330 (13).

In comparing with other meta-analyses, the present study selected patients with radiologically solid-dominant early stage NSCLC. Up to now, the use of segmentectomy in radiologically solid-dominant early stage NSCLC has been controversial. Given the lack of solid evidence, it is necessary to summarize the relevant studies prior to the results of several large RCTs being delivered. This analysis suggested segmentectomy had comparable oncologic efficacy to lobectomy for solid-dominant stage IA NSCLC. This may be a novel concept.

The present meta-analysis had several limitations. First, the meta-analysis was based on retrospective cohort studies and the level of evidence was relatively low compared with that for RCTs. The number of studies was limited. In addition, not all studies were of high quality, which introduced a potential bias. Second, even though subgroup analyses were conducted, heterogeneity persisted in the meta-analysis, primarily due to the use of wedge resection in four studies. Numerous studies have highlighted the technical and oncological differences between wedge resection and segmentectomy (14-16). Segmentectomy is an anatomic resection frequently accompanied by hilar and mediastinal lymph node sampling or dissection. It is inappropriate to combine the two oncologically-distinct procedures of wedge resection and segmentectomy in radiologically-invasive stage IA lung cancer. Moreover, heterogeneity was also observed in solid part ratio (pure solid or solid-dominant type), tumor size (T1a or T1b) and the accuracy of clinical staging. Third, publication bias is a major concern in all meta-analyses. Although the present analysis did not show publication bias, it should be noted that this meta-analysis could not completely exclude biases. For example, intentional sublobar resection had a different compromised selection criteria, which may lead to bias. Finally, some of the included studies reported a relatively short follow-up duration. Therefore, RCTs with longer follow-up durations are needed to precisely compare segmentectomy (not including wedge resection) with lobectomy in solid-dominant stage IA NSCLC.

The current meta-analysis suggested that lobectomy and sublobar resection for solid-dominant stage IA NSCLC were equivalent with respect to distant recurrence, RFS and OS, but the outcome for local recurrence with sublobar resection was inferior to that with lobectomy. Nevertheless, segmentectomy had comparable oncologic efficacy to lobectomy for solid-dominant stage IA NSCLC. Therefore, segmentectomy with systemic node dissection/sampling may be a feasible alternative in selected solid-dominant (not pure-solid) stage IA NSCLC cases, such as smaller peripheral neoplastic nodules (53), air bronchogram (54) and lower SUVmax (10,55,56). However, these findings should be confirmed by prospective randomized controlled trials in the future.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JG participated in the literature search, performed the statistical analysis, and drafted the manuscript. ZR, JL and BW participated in the literature search. YL and CL participated in the study design. XT conceived the study, participated in its design and coordination, and helped to draft the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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