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Segmentectomy or lobectomy for early stage lung cancer: a meta-analysis

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Summary

Early stage lung cancer is routinely treated by lobectomy whenever clinically feasible, whereas the role of segmentectomy is controversial. The purpose of this study was to investigate the benefits of segmentectomy vs lobectomy for early stage lung cancer through a meta-analysis of published data. Eligible studies were identified from MEDLINE through February 2013. The manual selection of relevant studies was based on the summary analysis. We used published hazard ratios (HRs) if available or estimates from the published survival data. Lobectomy was chosen as the reference in all HR calculations. We compared the effect of segmentectomy and lobectomy for Stage I, Stage IA, Stage IA with tumours larger than 2 cm but smaller than 3 cm in size and Stage IA with tumours of 2 cm or smaller in 22 observational studies. The HRs of overall and cancer-specific survival indicated significant benefits of lobectomy for Stage I, Stage IA and Stage IA with tumours larger than 2 cm but smaller than 3 cm at 1.20 (95% confidence interval [CI] 1.04–1.38; *P* = 0.011), 1.24 (95% CI 1.08–1.42; *P* = 0.002) and 1.41 (95% CI 1.14–1.71; *P* = 0.001), respectively. For tumours 2 cm or smaller, segmentectomy provided an effect equivalent to that of lobectomy (HR 1.05; 95% CI 0.89–1.24; *P* = 0.550). No significant publication bias was detected in any part of the analysis. These findings should be interpreted in the context of the inherent limitations of meta-analyses of retrospective studies, including the heterogeneity of patient characteristics.

Keywords: Lung cancer • Segmentectomy • Lobectomy • Survival • Meta-analysis

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality worldwide, with ~1.4 million deaths yearly [1]. Lobectomy with lymph node dissection is the standard surgical treatment for Stage I non-small-cell lung cancer (NSCLC), whereas segmentectomy remains controversial because it lacks supporting data. In 1995, a prospective, multi-institutional, randomized trial reported by the Lung Cancer Study Group (LCSG) compared limited pulmonary resection (wedge resection and segmentectomy) with lobectomy for T1N0M0 NSCLC patients. This study found that limited resection was associated with inferior overall survival (OS) and a higher regional recurrence rate compared with lobectomy [2]. Other studies have also confirmed the results of the LCSG [3–5]. Since then, pulmonary segmentectomy has been applied only to those who are unable to tolerate lobectomy because of limited cardiopulmonary function. However, the unfavourable results for limited resection in the LCSG study may have been related to 40 of the 122 patients who received limited resection undergoing wedge resection, which could have resulted in recurrence and poor outcomes compared with segmental resection [4]. Pulmonary wedge resection, a non-anatomical resection in which the hilar lymph nodes cannot be dissected efficiently, is associated with poor rates of overall and cancer-specific survival (CSS) when compared with segmentectomy, which allows the dissection of the hilar lymph nodes and provides precise staging data that facilitate postoperative treatment [4]. Although lung cancers are increasingly diagnosed at early stages through the widespread use of computed tomography [6], it is unclear whether these patients with very early stage lung cancer should undergo lobectomy, a more aggressive procedure than segmentectomy. Several studies have demonstrated that limited resection, and especially segmentectomy, for Stage I NSCLC may have an effect equivalent to that of lobectomy [5, 7–12]. Additionally, segmentectomy can improve postoperative quality of life by preserving the pulmonary function significantly better than lobectomy [13].

Based on these considerations, we conducted a meta-analysis of published studies to quantitatively review survival data for the segmentectomy of Stage I lung cancer compared with those for standard lobectomy.

MATERIALS AND METHODS

Eligibility criteria

This meta-analysis was limited to studies comparing survival data of pulmonary segmentectomy with those of pulmonary lobectomy. The following eligibility criteria were established before collecting articles. (i) Operative approaches could include thoracotomy, video-assisted thoracoscopic surgery or robotic surgery. (ii) Survival rates for a specific time interval after operation were stated in the article. (iii) Study subjects were limited to clinical Stage I patients. (iv) Median follow-up time was to exceed 1 year. (v) Articles were published or accepted in English in the periodical medical literature from January 1990 to March 2013. (vi) OS or CSS was assessed in detail. (vii) Twenty or more patients were included. (viii) When multiple articles by the same author or the study group analysed the same series of patients, the single most informative article was chosen for the meta-analysis. The exclusion criteria included studies published in letters, reviews and editorials, and papers not published in English.

Collection of published studies

The primary sources of the reviewed studies were MEDLINE abstracts published up to February 2013. The search included the following terms: ('lung neoplasms/surgery' [MESH terms]) and ('segmentectomy' or 'segmental resection') and 'lobectomy' and 'survival'. The computer search was supplemented with manual searches of the reference lists of all retrieved review articles, primary studies and abstracts from meetings. The manual selection of relevant studies was based on the summary analysis. Overlapping or unrelated articles were excluded, and items from manually searched bibliographies were added.

Statistical analysis

OS and CSS were estimated as the hazard ratio (HR) for each study. When possible, the HR and associated variance were obtained directly from each publication or from individual patient data. HRs not reported were calculated by the Parmar and Tierney methods [11, 12]. Because HRs for OS/CSS could not be obtained directly from the data presented in some studies, the Kaplan–Meier survival curves of these studies were analysed to extract the data and to calculate the HR and standard of error for OS/CSS.

HRs and 95% confidence intervals (CIs) were obtained for each study, and the pooled estimate was calculated from an inverse variance-weighted average of the individual studies [13]. χ^2 tests were used to assess statistical heterogeneity. All statistical tests were two-sided, and the significance level was set at 5%. Publication bias was examined using the approach of Egger *et al.* [14], who suggested the presence of significant publication bias when the *P*-value was <0.1. Kaplan–Meier curves were read by Engauge Digitizer version 4.1 (free software downloaded from http://sourceforge.net/projects/digitizer/files/Engauge%20Digitizer/digitizer-4.1/). Data combining and tests of heterogeneity were performed with Stata version 12.0 (StatCorp, College Station, TX, USA). DerSimonian–Laird random-effects analysis [15] was used to combine the HR and 95% CI values to estimate the total effect.

RESULTS

Selected articles and description of the studies

The meta-analysis included 22 observational studies, the characteristics of which are summarized in Table 1. The search on segmentectomy vs lobectomy for lung cancer is illustrated in the flow diagram in Fig. 1. No randomized controlled trials were found. Most of the studies included were based on retrospective data or prospective, non-randomized, controlled studies except for that

Table 1: Characteristics of the included studies

Authors	Publication year	Study design	Stage	No. of seg.	No. of lob.	Survival difference	Reason for segmentectomy
Warren and Faber [3]	1994	RS	I	66	103	LB	Poor cardiopulmonary function and smaller lesions
Okada *et al.* [16]	2001	PS	IA ≤2 cm	68	104	NS	Intentional resection for small lesions of ≤2 cm
Campione *et al.* [17]	2004	RS	IA	21	100	NS	Poor cardiopulmonary function
Keenan *et al.* [8]	2004	RS	I	54	147	NS	Poor pulmonary function
Martin-Ucar *et al.* [10]	2005	MPS	I	17	17	NS	Poor pulmonary function
Watanabe *et al.* [18]	2005	PS	IA ≤2 cm	20	57	NS	Intentional resection for small lesions of ≤2 cm
Okada *et al.* [19]	2005	RS	I	211	496	NS	ND
Okumura *et al.* [20]	2007	RS	IA	84	418	NS	ND
Schuchert *et al.* [21]	2007	PS	I	182	246	NS	ND
Iwasaki *et al.* [22]	2007	RS	IA ≤2 cm	31	55	NS	Intentional resection for small lesions of ≤2 cm
Shapiro *et al.* [7]	2009	RS	I	31	113	NS	Small lesions of ≤2 cm, poor pulmonary function
Kilic *et al.* [5]	2009	PS	I	78	106	NS	Age >75 years
Sugi *et al.* [23]	2010	PS	IA	43	95	NS	Intentional resection for small lesions of ≤2 cm
Whitson *et al.* [24]	2011	RS	I	581	13 892	LB	ND
Nakamura *et al.* [25]	2011	RS	I	38	289	NS	ND
Zhong *et al.* [26]	2012	PS	IA ≤2 cm	39	81	NS	Intentional resection for small lesions of ≤2 cm
Yamashita *et al.* [27]	2012	PS	IA	90	124	NS	ND
Cheng *et al.* [9]	2012	PS	I	32	32	NS	Age ≥70 years, poor pulmonary function
Soukiasian *et al.* [28]	2012	RS	IA	56	178	NS	ND
Yendamuri *et al.* [29]	2012	RS	IA ≤2 cm	311	5142	NS	Intentional resection for small lesions of ≤2 cm
Hamatake *et al.* [30]	2012	RS	IA ≤1 cm	32	77	NS	Intentional resection for small lesions of ≤1 cm
Carr *et al.* [31]	2012	RS	IA	178	251	NS	ND

Seg: segmentectomy; Lob: lobectomy; RS: retrospective study; PS: prospective non-randomized study; NS: not significant; LB: lobectomy better; ND: not described; MPS: matched-pair study.

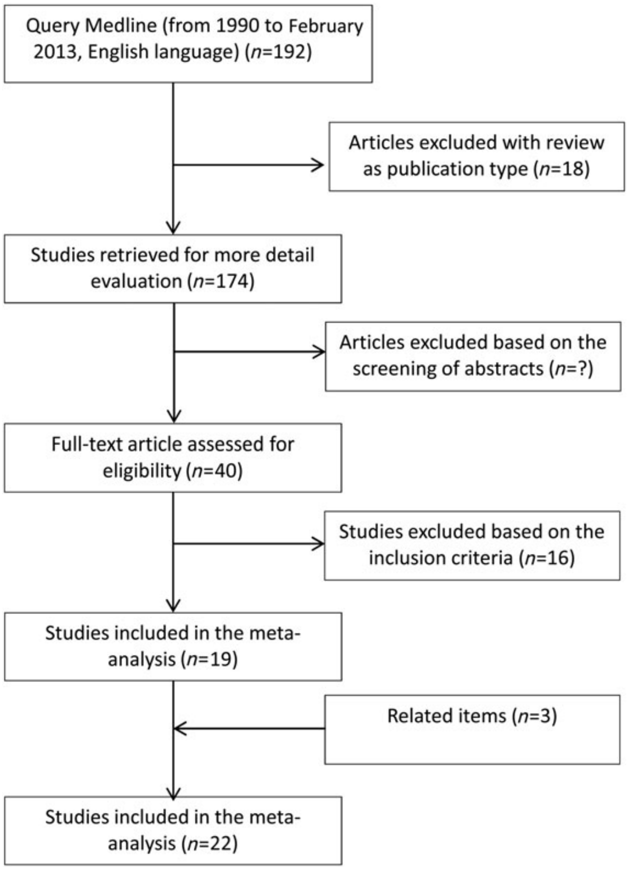

Figure 1: Flow diagram of the search results for segmentectomy vs lobectomy.

by Martin-Ucar *et al.* [10], which was a case-matched study. Cohort sizes ranged from 34 to 14 473 patients. Lobectomy was chosen as the reference in all HR calculations.

Effect of operative approach on the overall survival/cancer-specific survival of Stage I NSCLC patients

Sixteen studies analysed OS and three analysed CSS. Studies from three institutions used stratified analysis and did not provide the results of the whole cohort, and these data were analysed separately [19, 20, 28]. The combined HR of OS was 1.07 (95% CI 0.90–1.28; $P = 0.441$), that of CSS was 1.38 (95% CI 1.20–1.59; $P < 0.001$) and that of OS/CSS was 1.28. In combining the data from univariate analysis, we found that the OS/CSS of patients treated with segmentectomy was inferior to that of patients treated with lobectomy (HR 1.28; 95% CI 1.15–1.42; $P < 0.001$; Fig. 2 and Table 2). The tests for heterogeneity in the subanalysis of OS and CSS showed results of $\chi^2 = 17.25$ ($P = 0.438$, df = 17) and $\chi^2 = 2.34$ ($P = 0.673$, df = 4), respectively, which suggested no significant inconsistency. A *P*-value of 0.770 suggested no evidence of publication bias (Table 2).

Effect of operative approach on the overall survival/cancer-specific survival of Stage IA NSCLC patients

Twelve studies focused on the effect of segmentectomy or lobectomy on the OS of Stage IA patients by univariate analysis, and two focused on the CSS of Stage IA patients. Five studies used stratified analysis and did not provide the results of the whole cohort [3, 20, 24, 31, 32], and these data were analysed separately. The combined HR value in the subanalysis of OS was 1.23 (95% CI 1.07–1.41; $P = 0.003$), that of CSS was 1.35 (95% CI 0.74–2.47; $P = 0.324$) and that of OS/CSS was 1.24. Segmentectomy resulted in inferior OS/CSS compared with that for lobectomy (HR 1.24; 95% CI 1.09–1.41; $P = 0.002$; Fig. 3 and Table 2). The tests for heterogeneity in the subanalysis of OS and CSS gave results of $\chi^2 = 10.25$ ($P = 0.744$, df = 14) and $\chi^2 = 1.45$ ($P = 0.693$, df = 3), respectively, which suggested no inconsistency among the results of the included studies (Fig. 3 and Table 2). A *P*-value of 0.265 suggested a lack of publication bias (Table 2).

Effect of operative approach on the overall survival/cancer-specific survival of Stage IA NSCLC patients with tumours larger than 2 cm but smaller than 3 cm

Six studies focused on the effect of segmentectomy or lobectomy on the OS/CSS of Stage IA NSCLC patients with tumours larger than 2 cm but smaller than 3 cm. These data were analysed separately. The combined HR value in the subanalysis of OS was 1.81 (95% CI 1.21–2.71; $P = 0.004$), that of CSS was 1.27 (95% CI 1.00–1.64; $P = 0.500$) and that of OS/CSS was 1.39. Segmentectomy resulted in inferior OS/CSS compared with that for lobectomy (HR 1.41; 95% CI 1.14–1.71; $P = 0.001$; (Fig. 4 and Table 2). The tests for heterogeneity in the subanalysis of OS and CSS showed the results of $\chi^2 = 1.10$ ($P = 0.578$, df = 2) and $\chi^2 = 1.39$ ($P = 0.497$, df = 2), respectively, suggesting no inconsistency among the results of the included studies (Fig. 4 and Table 2). On the basis of a *P*-value of 0.678, no publication bias existed (Table 2).

Effect of operative approach on the overall survival/cancer-specific survival of Stage IA NSCLC patients with tumours of 2 cm or smaller

Ten studies focused on the effect of segmentectomy or lobectomy on the OS/CSS of Stage IA NSCLC patients with tumours of 2 cm or smaller. One study used stratified analysis and did not provide the results of the whole cohort [29], and these data were also analysed separately. The combined HR value in the subanalysis of OS was 1.05 (95% CI 0.89–1.24; $P = 0.599$), that of CSS was 1.14 (95% CI 0.56–2.32; $P = 0.709$) and that of OS/CSS was 1.05. The rates of OS/CSS with segmentectomy were equivalent to those with lobectomy (HR 1.05; 95% CI 0.89–1.24; $P = 0.550$; Fig. 5 and Table 2). The tests for heterogeneity in the subanalysis of OS and CSS showed the results of $\chi^2 = 4.15$ ($P = 0.843$, df = 8) and $\chi^2 = 0.07$ ($P = 0.876$, df = 1), respectively, which suggested no inconsistency among the results of the included studies (Fig. 5 and Table 2). No publication bias was detected, as indicated by a *P*-value of 0.802 (Table 2).

DISCUSSION

In 1995, a prospective, multi-institutional, randomized trial compared sublobar resection with lobectomy for T1N0M0 NSCLC patients and showed a discouraging outcome for sublobar

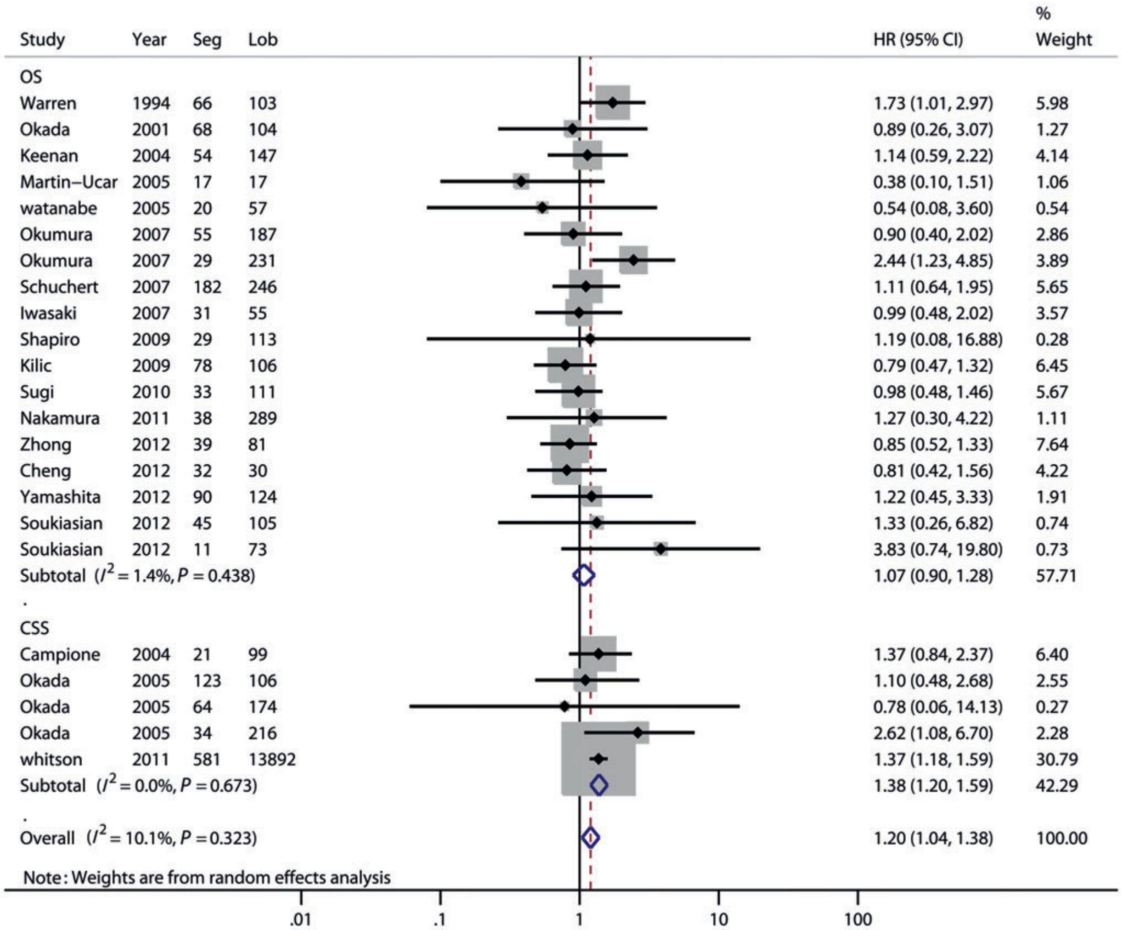

Figure 2: Overall survival/cancer-specific survival estimates for segmentectomy compared with lobectomy for Stage I NSCLC. Seg: segmentectomy; Lob: lobectomy.

resection due to an inferior OS rate and a higher recurrence rate than for lobectomy [2]. Since then, studies comparing the effect of sublobar resection and lobectomy have been limited to retrospective reviews with a small sample size [7, 19, 20, 22]. Advances in minimally invasive surgical techniques, critical care and imaging have caused the issue of sublobar resection, especially segmentectomy, to remerge [24]. The poor prognosis associated with sublobar resection may be due to the use of non-anatomical wedge resection, which does not allow efficient dissection of the pulmonary hilar lymph nodes, whereas anatomical segmentectomy does allow the dissection of these nodes and may be suitable for candidates with small-sized NSCLC. Furthermore, the accurate lymph node staging data available with segmentectomy but not with wedge resection are important for postoperative treatment.

Recently, thoracic surgeons have focused on the evaluation of segmentectomy and lobectomy for patients with small-sized NSCLC, with both encouraging and discouraging outcomes reported (Table 1). Meta-analyses reported by Nakamura *et al.* [33] and Fan *et al.* [34] compared sublobar resection and lobectomy. Nakamura combined differences in survival (survival rate with lobectomy minus that with limited resection) at 1, 3 and 5 years after resection and found no significant differences in survival, suggesting that survival after sublobar resection for Stage I lung cancer is comparable with that after lobectomy [33]. However, their report was based on data published about 10 years ago and much additional data have been published in recent years. Fan *et al.* conducted a meta-analysis to compare the outcomes of segmentectomy with lobectomy for stage I NSCLC patients based on eight published studies, the results showed segmentectomy produced an outcome similar to that with lobectomy [34]; nonetheless, their findings are limited, with many more data reported in recent years. Moreover, these two meta-analyses do not compare segmentectomy with lobectomy using stratified data based on different tumour sizes [33, 34], and it is necessary to conduct a more stratified meta-analysis comparing segmentectomy and lobectomy that is based on updated data.

Meta-analysis is often used in randomized clinical trials (RCTs), but the application of meta-analysis to observational studies is controversial [35]. However, when no RCTs are available, as is the

Table 2: Summary of comparison results

Series	Survival	Comparison of survival			Egger's test	
		HR	95% CI	*P*-value	Bias	*P*-value
I	OS/CSS	1.20	1.04–1.38	0.011	0.12	0.770
IA	OS/CSS	1.24	1.08–1.42	0.002	−0.41	0.265
IA (2–3 cm)	OS/CSS	1.41	1.14–1.71	0.001	0.35	0.678
IA (≤2 cm)	OS/CSS	1.05	0.89–1.24	0.550	−0.15	0.802

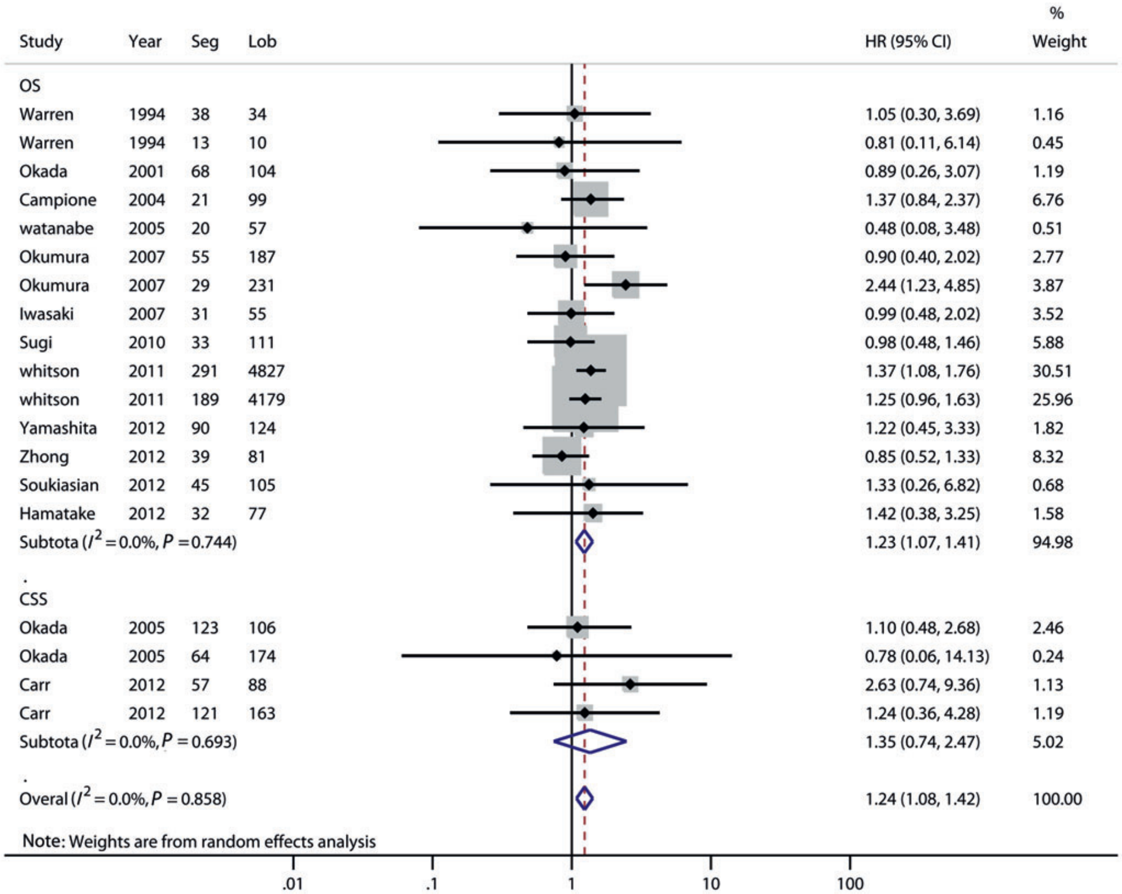

Figure 3: Overall survival/cancer-specific survival estimates for segmentectomy compared with lobectomy for Stage IA NSCLC. Seg: segmentectomy; Lob: lobectomy.

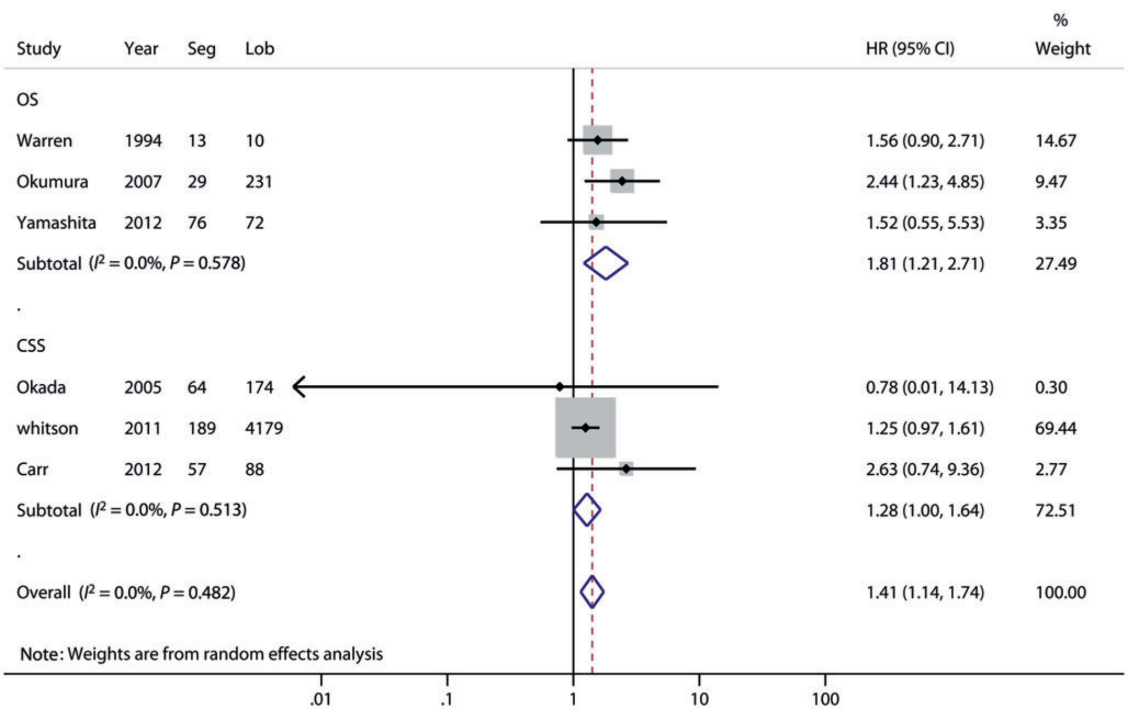

Figure 4: Overall survival/cancer-specific survival estimates for segmentectomy compared with lobectomy for Stage IA NSCLC patients with tumours larger than 2 cm but smaller than 3 cm. Seg: segmentectomy; Lob: lobectomy.

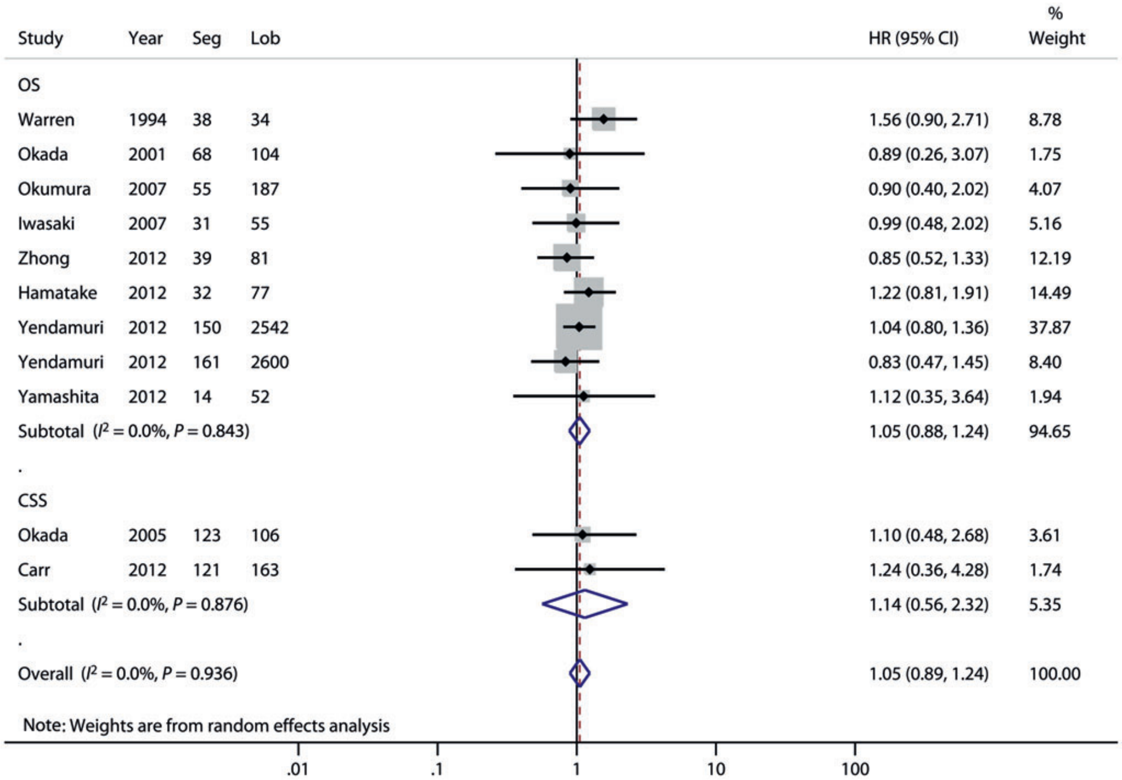

Figure 5: Overall survival/cancer-specific survival estimates for segmentectomy compared with lobectomy for Stage IA NSCLC patients with tumour 2 cm or smaller. Seg: segmentectomy; Lob: lobectomy.

case for segmentectomy in Stage I NSCLC, a meta-analysis of observational studies may be an available method for evaluating efficacy and effectiveness [36]. Performance of this type of meta-analysis may be challenging because of the differences in the baseline characteristics of each study [37]. We addressed this issue by evaluating the statistical heterogeneity of the component studies and by performing subgroup analyses. Admittedly, our meta-analysis covers a mix of small retrospective studies with various indications for segmentectomy, including poor cardiopulmonary function, elderly patients and small lesions, and thus further comparison is needed to clarify which indication provides the largest benefit.

We combined data from 22 studies published from 1990 to 2012 and performed a meta-analysis by combining HRs. Our results indicate that compared with lobectomy, segmentectomy is statistically significantly associated with OS/CSS, with an increased HR for Stage I NSCLC patients. These results are inconsistent with those of Fan *et al*., who found an equivalent effect of segmentectomy and lobectomy on Stage I NSCLC patients in eight studies from 1990 to 2010 [34]. The different outcomes in these two meta-analyses are probably due to the more recent articles included in the present analysis.

To further explore NSCLC candidates who can benefit from segmentectomy, we analysed the effect of segmentectomy or lobectomy on the OS/CSS of patients in three subgroups: Stage IA, Stage IA with tumours larger than 2 cm but smaller than 3 cm and Stage IA with tumours 2 cm or smaller. We found that segmentectomy resulted in inferior survival compared with lobectomy in the subgroups Stage IA and Stage IA with tumours larger than 2 cm but smaller than 3 cm. However, segmentectomy did provide survival similar to that of lobectomy for subgroup Stage IA with tumours 2 cm or smaller. In general, if there are no anatomical contraindications to segmentectomy, a lesion of 2 cm or smaller should be amenable to anatomical segmentectomy. Examination of this issue is currently being undertaken by the Cancer and Leukaemia Group B (CALGB) in a large, randomized, controlled trial (CALGB 140503), which is also using the 2-cm-or-smaller criterion. The CALGB 140503 clinical trial will provide results in several years.

In conclusion, our meta-analysis suggests that segmentectomy provides survival inferior to that following lobectomy for Stage I NSCLC patients, Stage IA patients and Stage IA patients with tumours larger than 2 cm but smaller than 3 cm. However, for Stage IA patients with tumours 2 cm or smaller, segmentectomy had an effect equivalent to that of lobectomy. Based on these results, we recommend segmentectomy for lung cancer patients with tumours 2 cm or smaller but not with tumours larger than 2 cm. However, because of possible bias in the primary studies, heterogeneity between the studies and inherent limitations of the meta-analysis of observational studies, this conclusion should be interpreted cautiously. More evidence is needed to establish the role of segmentectomy in early NSCLC. We expect to explore the answer in future RCTs such as that of CALGB 140503.

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