Original Article

Segmentectomy versus lobectomy for stage I non-small cell lung cancer: a systematic review and meta-analysis

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Background: In recent years, many factors have revamped the interest in segmentectomies as preferred procedure for stage I non-small cell lung cancer (NSCLC). The aim of this systematic review and meta-analysis is to compare the outcomes of segmentectomy versus lobectomy regarding overall survival (OS) in the surgical treatment of stage I NSCLC, as stated in the conclusions of the largest studies conducted in this field and reported to date.

Methods: The searching strategy was developed in EMBASE, MEDLINE and Cochrane CENTRAL from 1990 until December 2016. The meta-analysis was performed with the combination of the reported survival outcomes of the individual studies using a random effect model. The OS of the lobectomy group was compared with the segmentectomy group alone. The hazard ratio (HR) and standard error were extracted or calculated for each study using the Kaplan-Meier method.

Results: Regarding the results, most of these studies were based on the retrospective data. The size of the cohorts varied from 17 to 11,520, with a total number of 24,542 patients. The pooled HR was 1.04 [95% confidence interval (CI), 0.92–1.18; P=0.50].

Conclusions: The survival in the segmentectomy group was not inferior to patients treated with lobectomy. In conclusion, the current meta-analysis disclosed that segmentectomies produce similar survival compared to lobectomy for patients with stage I NSCLC. To establish the role of segmentectomy in early NSCLC, more evidence is needed, in particular, a large numbered, prospective, randomised trials, which should dissolve the uncertainties and the questions raised by retrospective data.

Keywords: Lung cancer; segmentectomy; lobectomy; overall survival (OS); hazard ratio (HR); meta-analysis

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Introduction

Traditionally, the management of patients with stage I non-small cell lung cancer (NSCLC) includes lobectomy associated to complete lymph node dissection through a conventional thoracotomy or thoracoscopic approach. Conversely, sublobar resections are considered the treatment of choice in patients with a compromised cardiorespiratory status (1).

In recent years, along with the line of what already happened in breast surgery, many factors have revamped the interest in sublobar resections, segmentectomies

in particular, as preferred procedures for early lung cancers. In fact, with the technical advances in thoracic imaging and the use of low-dose computed tomography in screening programs as well as more accurate patient selection strategies, thoracic surgeons will likely encounter a significant increase in the number of small peripheral lesions in clinical practice (2).

The main advantage of the segmentectomy over lobectomy is that it is an anatomical resection with a parenchyma sparing-effect. However, whether anatomic segmentectomy is comparable with lobectomy about oncologic outcomes in patients with stage I disease is still debated in the medical and surgical community. The aim of this systematic review and meta-analysis is to compare the results of segmentectomy versus lobectomy regarding overall survival (OS) in the surgical treatment of early stage (stage I) NSCLC, as stated in the conclusions of the largest studies conducted in this field and reported and reported to date.

Methods

Search strategy and selection criteria

A search strategy using a combination of free-text words, relevant MeSH terms and appropriate filters was designed; the searching strategy was developed in EMBASE (via Ovid), MEDLINE (via PubMed) and Cochrane CENTRAL from 1990 until December 2016, without imposing any language or time restrictions (see section "Search history" in Supplementary). Records identified through our search strategy were imported into reference management software. The eligibility criteria were: stage I NSCLC patients; segmentectomy without wedge resection; comparison of recurrence-free survival, OS between lobectomy and segmentectomy. Two authors worked independently to assess each identified study based on the eligibility criteria; when multiple studies contained overlapping data, a most informative study was included. Letters, editorials, case reports, and reviews were excluded. Disagreements were discussed and resolved by consensus. Data extracted included study characteristics, baseline patient characteristics primary and secondary outcomes. We selected papers in the meta-analysis that also included wedge resections, but only when the OS was distinguished in the two groups of surgical techniques of sublobar resection (wedge and segmentectomy). The Cochrane's Collaboration Tool was used to assess the risk of bias for the primary outcome for included studies (3). The risk of bias due to incomplete outcome data was evaluated at an outcome level, while the risk of bias due to sequence generation, allocation concealment, blinding, selective reporting or funding was assessed at study level. The risk of bias was assessed by two independent reviewers and disagreements were settled by discussion and consensus [see section "Risk of bias assessment of the primary outcome (immediate success)" in Supplementary]. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42016040153. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used to improve the report of this systematic review (*Table S1*) (4).

Data analysis

The meta-analysis was performed by combining the reported survival outcomes of the individual studies using a random effect model. The OS of the lobectomy group was compared with the segmentectomy group alone. The hazard ratio (HR) and standard error were extracted or calculated from each study using Kaplan-Meier graphs with methods reported in the literature (5,6). Confidence intervals (CI) were set to 95%. Heterogeneity was measured using χ^2 test and I^2. Values of $P<0.10$ or $I^2>50\%$ represented substantial heterogeneity. The publication bias was assessed for the primary outcome with a Funnel plot, both visually and formally with Egger's test ($P<0.10$ suggests strong asymmetry). Data analysis was performed using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark).

Role of the funding source

There was no source of financing for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The flow diagram of the study selection process was shown in *Figure 1*. The search strategy identified 154 records. Following deduplication, 98 records were screened at the title and abstract level, and six were excluded as irrelevant. The remaining 92 records were assessed in the full text. Of those, 27 were included in the systematic review (7-21) and meta-analysis (22-33).

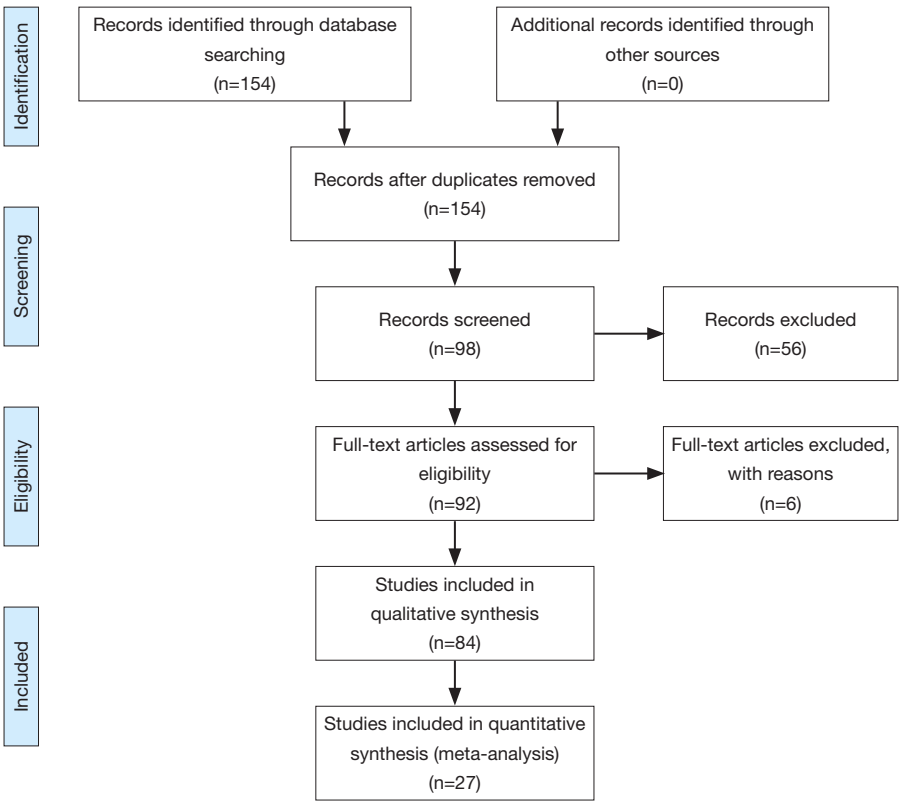

Figure 1 Summary of search strategy performed to identify relevant comparative studies on lobectomy versus segmentectomy for early stage not small cell lung cancer (PRISMA 2009 flow diagram). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Baseline characteristics of patients were well balanced in each study. Study characteristics are presented in *Table 1* and the quality assessment in *Table 2*. Most of these qualified studies were based on the retrospective data. The size of the cohorts varied from 17 to 11,520, with a total number of 24,542 patients. In all HR calculations, the lobectomy was chosen as the reference. None of the included trials was blinded. However, lack of blinding was not considered likely to influence the primary outcome due to its objective nature. Hence, all studies were at low risk of bias despite being open label. Similarly, the risk of bias was low for all other domains. Hence, all trials were at low overall risk of bias. The pooled HR was 1.04 (95% CI, 0.92–1.18; P=0.50). The segmentectomy group was not inferior to patients treated with lobectomy. The Cochrane tests for heterogeneity showed that χ^2=25.04 degree of freedom =26 (P=0.52); I^2=0%, which did not suggest a significant inconsistency and heterogeneity between the selected studies. The combined HR displayed in this figure suggested there was no statistical significance between segmentectomy and lobectomy on OS (*Figure 2*). The funnel plot showed no publication bias (*Figure 3*).

The whole group of papers was then divided in two subgroups regarding the methodology of the study: the first group comprehends the observational studies (24/27), the second the randomized studies (3/27). The HR for retrospective study (HR =1.01; 95% CI, 0.88–1.16, P=0.49) and for randomized clinical trial were not both significant (HR =1.21; 95% CI, 0.89–1.63, P=0.48) (*Figures 4* and *5*).

Discussion

The refinement of the diagnostic pathway for NSCLC and the recent consolidation of minimally invasive techniques for lobectomy and segmentectomy have revived the debate about whether segmentectomies should be applied to all patients with early stage NSCLC as intentional resection and not only as compromised procedure in patients with limited cardiopulmonary reserves. To better understand what has been published in the literature until today and to have a current state of the art, we combined data from 26 studies published from 1990 to 2016 and performed

Table 1 General characteristics of the enrolled studies

Author	Year	Sample size	Segmentectomy	Lobectomy	Study design	Gender distribution	Countries of the study	Funding sources
Read (7)	1990	244	107	131	Retrospective	242 males (99%), 2 females (1%)	USA	Not mentioned
Warren (8)	1994	173	68	105	Retrospective	115 males (66.7%), 58 females (33.3%)	USA	Not mentioned
Ginsberg (9)	1995	247	122	125	Prospective randomized	Not mentioned	USA	Not mentioned
Kodama (10)	1997	123	46	77	Retrospective	Not mentioned	Japan	Not mentioned
Bando (11)	2002	213	74	132	Retrospective	45 males (60.8%), 29 females (39.2%)	Japan	Not mentioned
Okada (12)	2001	1,272	919	258	Retrospective	Not mentioned	Japan	Not mentioned
Koike (13)	2003	223	74	159	Prospective randomized	38 males (51.3%), 36 females (48.7%)	Japan	Not mentioned
Keenan (14)	2004	201	54	147	Retrospective	175 males (87%), 26 females (13%)	USA	Not mentioned
Watanabe (15)	2005	77	20	57	Retrospective	Not mentioned	Japan	Not mentioned
Martin-Ucar (16)	2005	34	17	17	Retrospective	22 males (64.7%), 12 females (35.3%)	UK	None
Iwasaki (17)	2007	86	31	55	Retrospective	Not mentioned	Japan	Not mentioned
Okumura (18)	2007	1,385	144	1,241	Retrospective	Not mentioned	Japan	Not mentioned
Sienel (19)	2007	199	49	150	Retrospective	141 males (70.8%), 58 females (29.2%)	Germany	Not mentioned
Yamato (20)	2008	523	153	277	Retrospective	263 males (50.2%), 260 females (49.8%)	Japan	Not mentioned
Kilic (21)	2009	184	78	106	Retrospective	82 males (44.6%), 102 females (55.4%)	USA	Not mentioned
Sugi (22)	2010	144	33	111	Intervention study	63 males (43.7%), 96 females (56.3%)	Japan	Not mentioned
Nakamura (23)	2011	411	38	289	Retrospective	218 males (53%), 193 females (47%)	Japan	Not mentioned
Yendamuri (24)	2011	3,478	797	2,681	Retrospective	1,203 males (34.6%), 2,275 females (65.4%)	USA	Not mentioned
Hamatake (25)	2012	143	32	67	Retrospective	62 males (43.3%), 81 females (56.7%)	Japan	None
Cheng (26)	2012	164	64	120	Retrospective	149 males (90.8%), 35 females (9.2%)	China	None
Soukiasian (27)	2012	251	73	178	Retrospective	Not mentioned	USA	Not mentioned
Yamashita (28)	2012	214	90	124	Retrospective	114 males (53.3%), 100 females (46.7%)	Japan	None
Zhong (29)	2012	120	39	81	Retrospective	69 males (57.5%), 51 females (42.5%)	China	Not mentioned
Tsutani (30)	2014	481	98	383	Retrospective	Not mentioned	Japan	Not mentioned
Landreneau (31)	2014	624	312	312	Retrospective (propensity matched)	Not known	USA	None
Dai (32)	2016	15,760	4,240	11,520	Retrospective	6,286 males (40%), 9,474 females (60%)	China, USA, Denmark, Hong Kong (China), Taiwan, Italy, UK	None
Razi (33)	2016	1,170	119	1,051	Retrospective	Not known	USA	None

Table 2 Assessment of methodological quality of the selected papers

Item	Yes	No	NA
Was an a priori design provided?	27/27		
Was there duplicate study selection and data extraction?			27/27
Was a comprehensive literature search performed?			27/27
Was the status of publication (i.e., grey literature) used as an inclusion criterion?			27/27
Was a list of studies (included and excluded) provided?			27/27
Were the characteristics of the included studies provided?			27/27
Was the scientific quality of the included studies assessed and documented?			27/27
Was the scientific quality of the included studies used appropriately in formulating conclusions?			27/27
Were the methods used to combine the findings of studies appropriate?			27/27
Was the likelihood of publication bias assessed?		27/27	
Was the conflict of interest stated?	7/27	20/27	

NA, not applicable.

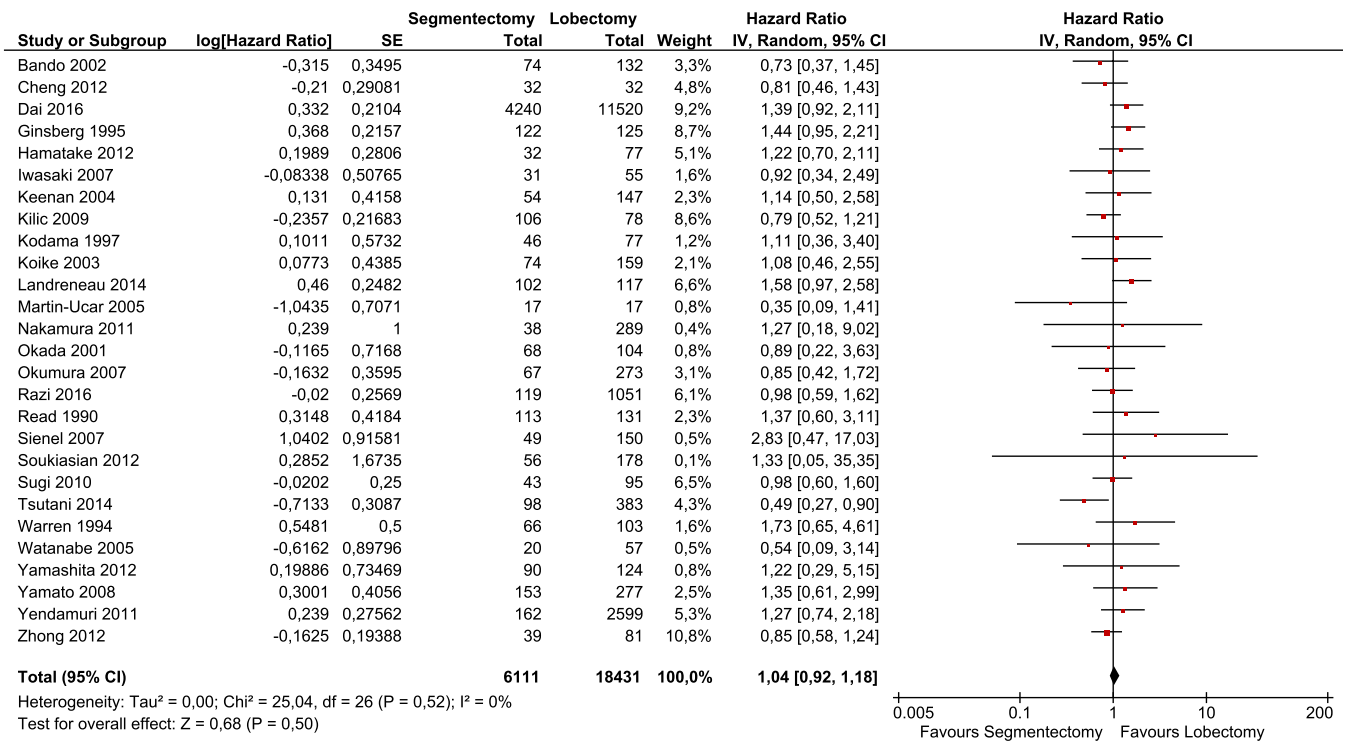

Figure 2 Forest plot of HR for overall survival impact of operative approach (segmentectomy versus lobectomy) of stage I NSCLC patients. The pooled HR displayed in this figure when compared with segmentectomy suggested that there was not a significant benefit of lobectomy on HR of stage I patients (7-21) (HR 1.04; 95% CI, 0.92–1.18, P=0.50) (22-33). HR, hazard ratio; NSCLC, non-small cell lung cancer; CI, confidence interval; df, degree of freedom; SE, standard error.

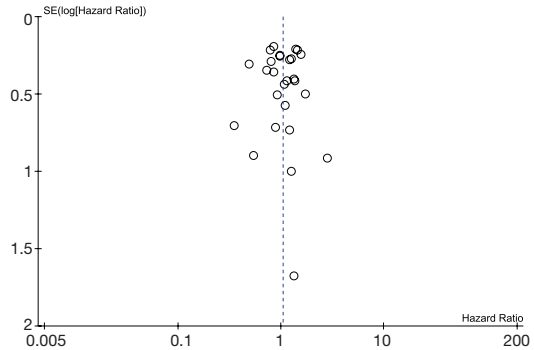

Figure 3 Funnel plot of this analysis. This figure presents the publication bias (segmentectomy versus lobectomy in stage I NSCLC patients). NSCLC, non-small cell lung cancer.

a meta-analysis by combining the OS in the lobectomy and segmentectomy groups for patients with stage I NSCLC. Overall, the patients in the lobectomy group did not have a better survival than the patients treated with segmentectomy. In particular, a significant benefit of lobectomy over segmentectomy on OS in patients with stage IA disease could not be confirmed.

Other meta-analyses also support these findings. As an example, Cao *et al.* stated that patients intentionally selected for segmentectomies to treat early-stage, peripheral NSCLC had overall disease-free survival outcomes that were not significantly different to those undergoing lobectomies. Conversely, patients who

			Segmentectomy	Lobectomy		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Bando 2002	-0,315	0,3495	74	132	4,0%	0,73 [0,37, 1,45]	
Cheng 2012	-0,21	0,29081	32	32	5,8%	0,81 [0,46, 1,43]	
Dai 2016	0,332	0,2104	4240	11520	11,1%	1,39 [0,92, 2,11]	
Hamatake 2012	0,1989	0,2806	32	77	6,2%	1,22 [0,70, 2,11]	
Iwasaki 2007	-0,08338	0,50765	31	55	1,9%	0,92 [0,34, 2,49]	
Keenan 2004	0,131	0,4158	54	147	2,8%	1,14 [0,50, 2,58]	
Kilic 2009	-0,2357	0,21683	106	78	10,4%	0,79 [0,52, 1,21]	
Kodama 1997	0,1011	0,5732	46	77	1,5%	1,11 [0,36, 3,40]	
Landreneau 2014	0,46	0,2482	102	117	8,0%	1,58 [0,97, 2,58]	
Martin-Ucar 2005	-1,0435	0,7071	17	17	1,0%	0,35 [0,09, 1,41]	
Nakamura 2011	0,239	1	38	289	0,5%	1,27 [0,18, 9,02]	
Okada 2001	-0,1165	0,7168	68	104	1,0%	0,89 [0,22, 3,63]	
Okumura 2007	-0,1632	0,3595	67	273	3,8%	0,85 [0,42, 1,72]	
Razi 2016	-0,02	0,2569	119	1051	7,4%	0,98 [0,59, 1,62]	
Read 1990	0,3148	0,4184	113	131	2,8%	1,37 [0,60, 3,11]	
Sienel 2007	1,0402	0,91581	49	150	0,6%	2,83 [0,47, 17,03]	
Soukiasian 2012	0,2852	1,6735	56	178	0,2%	1,33 [0,05, 35,35]	
Tsutani 2014	-0,7133	0,3087	98	383	5,1%	0,49 [0,27, 0,90]	
Warren 1994	0,5481	0,5	66	103	2,0%	1,73 [0,65, 4,61]	
Watanabe 2005	-0,6162	0,89796	20	57	0,6%	0,54 [0,09, 3,14]	
Yamashita 2012	0,19886	0,73469	90	124	0,9%	1,22 [0,29, 5,15]	
Yamato 2008	0,3001	0,4056	153	277	3,0%	1,35 [0,61, 2,99]	
Yendamuri 2011	0,239	0,27562	162	2599	6,5%	1,27 [0,74, 2,18]	
Zhong 2012	-0,1625	0,19388	39	81	13,0%	0,85 [0,58, 1,24]	
Total (95% CI)			**5872**	**18052**	**100,0%**	**1,01 [0,88, 1,16]**	

Heterogeneity: Tau² = 0,00; Chi² = 22,51, df = 23 (P = 0,49); I² = 0%
Test for overall effect: Z = 0,18 (P = 0,85)

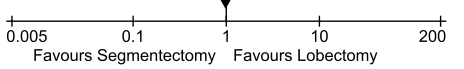

Figure 4 Forest plot of hazard ratio for overall survival impact of operative approach (segmentectomy versus lobectomy) of stage I NSCLC patients in the retrospective studies of our analysis. NSCLC, non-small cell lung cancer.

			Segmentectomy	Lobectomy		Hazard Ratio	Hazard Ratio
Study or Subgroup	log[Hazard Ratio]	SE	Total	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ginsberg 1995	0,368	0,2157	122	125	50,3%	1,44 [0,95, 2,21]	
Koike 2003	0,0773	0,4385	74	159	12,2%	1,08 [0,46, 2,55]	
Sugi 2010	-0,0202	0,25	43	95	37,5%	0,98 [0,60, 1,60]	
Total (95% CI)			**239**	**379**	**100,0%**	**1,21 [0,89, 1,63]**	

Heterogeneity: Tau² = 0,00; Chi² = 1,45, df = 2 (P = 0,48); I² = 0%
Test for overall effect: Z = 1,22 (P = 0,22)

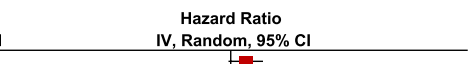

Figure 5 Forest plot of hazard ratio for overall survival impact of operative approach (segmentectomy versus lobectomy) of stage I NSCLC patients in the randomized studies of our analysis. NSCLC, non-small cell lung cancer.

underwent "compromise" segmentectomies due to medical comorbidities or cardiopulmonary limitations showed a significantly worse OS than lobectomies (34).

Other published meta-analysis suggested that segmentectomy may not have superior oncologic outcomes for all patients with early stage lung cancer, but only for the subgroups of patients with tumors smaller than 2 cm (35) or for patients in stage IA (36).

This study presents some limitations. An ideal meta-analysis should be performed using individual patient data, but they may not always be available or practical. Therefore, the majority of meta-analyses are performed using summary data, which is a well-accepted form of analysis.

This study did not include any data about additional chemotherapy or radiotherapy regimens, which might have affected the survival of some patients. Also, since most of the retrospective studies did not describe with accuracy whether the stage was clinical or pathological, it is reasonable to conclude that the authors of the papers subjected to meta-analysis have selected the surgical method mainly based on the clinical stage. Similarly, the comparison between procedures in patients who can tolerate the lobectomy should be more compelling. In fact, most studies did not take into consideration systematic, or sampling lymphadenectomy is emphasising the current technical differences in lymph node management and anatomical approach. In this setting, segmentectomies are more often accompanied by hilar and mediastinal lymph node sampling than dissection (34).

Another potentially critical issue as a source of bias results from the fact that many studies comparing segmentectomy and lobectomy for stage IA NSCLC did not take into consideration the appearance of the nodule on chest CT, i.e., pure solid, part-solid or pure ground-glass opacity (GGO).

The current meta-analysis disclosed that segmentectomies produce similar survival compared to lobectomy for patients with stage I NSCLC. Considering heterogeneity among studies and most of the data from retrospective studies, the results of the meta-analysis should be interpreted with caution.

More evidence is needed to establish what is the role of segmentectomy in early NSCLC, in particular, a large numbered, prospective, randomised trials, which should dissolve the uncertainties and the questions raised by retrospective data. Otherwise, propensity score matching method is required in a retrospective study, since the patients' selection bias could be incredibly high in such data accumulation.

Currently, two prospective, randomised, multi-institutional phase III trials are being conducted by the Cancer and Leukemia Group B (CALGB 140503) and the Japan Clinical Oncology Group (JCOG 0802) to establish the effectiveness of intentional sublobar resections for small peripheral tumours (2 cm) (37-39). The results will likely provide significant contributions to the role of intentional resection for peripheral stage IA tumours.

In conclusion, our analysis seems to support the concept that rigorously selected patients with early-stage NSCLC may be subjected to segmentectomies rather than lobectomies with similar survival outcomes and the benefit of preserving lung function.

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Footnote

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

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Supplementary

Search history

(I) Medline; exp LUNG NEOPLASMS/SU [SU=surgery]; 180503 results.
(II) Medline; (segmentectom* OR "limit* resect*" OR sublobar).ti,ab; 3516 results.
(III) Medline; (intention* OR compromis*).ti,ab; 146950 results.
(IV) Medline; 1 AND 2 AND 3; 72 results.
(V) Medline; (lung OR pulmo*).ti,ab; 749424 results.
(VI) Medline; 2 AND 3 AND 5; 86 results.
(VII) Medline; 6 [Limit to: (Document Status In Data Review or In Process)]; 2 results.
(VIII) EMBASE; exp LUNG TUMOR/su [su=Surgery]; 22940 results.
(IX) EMBASE; (segmentectom* OR "limit* resect*" OR sublobar).ti,ab; 4856 results.
(X) EMBASE; (intention* OR compromis*).ti,ab; 188421 results.
(XI) EMBASE; 8 AND 9 AND 10; 52 results.

Risk of bias assessment of the primary outcome (immediate success)

We assessed the risk of bias utilising the Cochrane Collaboration risk of bias tool for sequence generation, allocation concealment, blinding, selective reporting, incomplete outcome data and other sources of bias (sponsorship bias). The risk of bias for sequence generation, allocation concealment, blinding, selective outcome reporting and sponsor bias were assessed at study level. The risk of bias for incomplete outcome data was evaluated at outcome level. We then determined the overall risk of bias.

Sequence generation

- Low risk of bias, if randomization was generated by a computer or a table of random numbers.
- High risk of bias, if the method of randomization was inadequate (i.e. "quasi-randomized").
- Unclear risk of bias, if the method of randomization was not described.

Allocation concealment

- Low risk of bias, if the method of allocation involved an independent central unit or consecutively numbered sealed envelopes.
- High risk of bias, if allocation sequence was known to the investigators or conducted with an inadequate method.
- Unclear risk of bias, if the method of allocation concealment was not described.

Blinding of participants and personnel

- Low risk of bias if the study had a double-blind design and unlikely that the blinding could have been broken, or if no blinding or incomplete blinding but the review authors judge that the outcome is not likely to be influenced by the lack of blinding.
- High risk of bias, if the study was open-label and the outcome is likely to be affected by the lack of blinding, or if blinding of the main study participants and personnel attempted but likely that the blinding could have been broken, and the outcome is likely to be influenced by the lack of blinding.
- Unclear risk of bias, if there was insufficient information to permit judgment of 'Low risk' or 'High risk'.

Selective outcome reporting

- Low risk of bias if the trial provided data about immediate success and recurrence for the follow-up period.
- High risk of bias if data about instant success and recurrence for the given follow-up period were reported with inadequate detail for the data to be included in the meta-analysis or if it was reported only for a subset of the randomised population.
- Unclear risk of bias, if there was insufficient information to assess whether the risk of bias of selective outcome reporting was present.

Incomplete outcome data

- Low risk of bias, if attrition rate was balanced between treatment arms and relatively low (below 20%), reasons for discontinuation were described, an intention-to-treat analysis was performed and an appropriate method of imputation of missing outcome data was applied.
- High risk of bias, if withdrawal rates were unbalanced between treatment arms or more than 20%, or reasons for drop-outs were not clearly described, or an inappropriate analysis was performed (i.e. per protocol analysis), or an inappropriate imputation method (i.e. last

observation carried forward method) was used to handle missing data.

- ❖ Unclear risk of bias, if it was not clear whether there were any drop-outs or reasons for these withdrawals were not clear, or no method of imputation of missing data was mentioned.

Other bias (sponsor bias)

- ❖ Low risk of bias, if the trial did not receive commercial funding.
- ❖ High risk of bias, if the trial received commercial funding.
- ❖ Unclear risk of bias, if the source of funding was unclear.

Overall risk of bias

- ❖ The overall risk was considered high in the presence of high bias in any domain, or low when low for all domains.
- ❖ In all other cases, the overall risk of bias was deemed unclear.

Table S1 PRISMA 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both	1–2
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	6–7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	6–7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	/
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	7–8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (I) simple summary data for each intervention group; (II) effect estimates and confidence intervals, ideally with a forest plot	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	7–8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	7
Additional analysis	23	Give results of additional analyses, if done [e.g., sensitivity or subgroup analyses, meta-regression (see item 16)]	/
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	8–9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	9–10
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	11

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