

Review article



Segmentectomy vs. Lobectomy in stage IA non-small cell lung cancer: A systematic review and meta-analysis of perioperative and survival outcomes

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ABSTRACT

While recent randomized controlled trials (RCT) have suggested superior overall survival (OS) outcomes with segmentectomy over lobectomy, questions remain regarding the comparability of these surgical procedures for treating early-stage non-small cell lung cancer (NSCLC). This systematic review and meta-analysis aimed to synthesize existing evidence and to compare the survival outcomes observed for stage IA NSCLC following segmentectomy or lobectomy.

40 studies (38 observational, 2 RCTs) encompassing 103,926 patients were analyzed. Primary outcomes included overall survival (OS), disease-free survival (DFS), local recurrences, harvested lymph nodes, post-operative morbidity, and length of hospital stay. Risk of bias was assessed using established tools, and evidence certainty was evaluated using GRADE.

Non-RCTs showed an OS HR of 1.10 (95 % CI: 0.94–1.30, $p = 0.24$) with low certainty, contrasting with RCTs' HR of 0.82 (95 % CI: 0.66–1.02, $p = 0.7$) with moderate certainty. Local recurrences exhibited OR 1.40 (95 % CI: 0.94–2.08, $p = 0.09$) in non-RCTs with low certainty, and RR 1.61 (95 % CI: 1.12–2.31, $p = 0.01$) in RCTs with low certainty. Non-RCTs showed DFS HR 1.13 (95 % CI: 0.95–1.34, $p = 0.18$) with low certainty, while RCTs

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yielded HR 1.00 (95 % CI: 0.85–1.18, $p = 0.97$) with moderate certainty. Lobectomy resulted in more harvested lymph nodes. Postoperative morbidity and length of hospital stay did not differ significantly.

While definitive evidence for OS, DFS, and postoperative outcomes differences was inconclusive, a potential increase in local recurrences following lobectomy was noted. Further well-designed studies are warranted to enhance evidence and inform clinical practice in stage I lung cancer surgery.

1. Introduction

Surgical resection continues to be the cornerstone of treatment for non-small cell lung cancer (NSCLC) in its early stages, as it guarantees the complete removal of the tumor while minimizing the loss of lung function. Segmentectomy has gained prominence in recent years as a viable substitute for lobectomy among specific patients afflicted with small, early-stage lung cancers or ground-glass opacities. Segmentectomy entails the excision of a more limited segment of the lung in comparison to lobectomy. This size reduction potentially results in enhanced lung function preservation and a diminished likelihood of postoperative complications. The optimal surgical technique for segmentectomy, however, continues to be a matter of debate [1]. The North American Lung Cancer Study Group findings, published twenty-six years ago, demonstrated that lobectomy was associated with a higher overall survival rate for early-stage NSCLC patients than typical or atypical segmentectomy [2]. Lobectomy has since become the procedure of choice for early lung cancers. The Japanese randomised control trial (RCT) JCOG0802/WJOG4607L published in 2022 is the first phase III study to demonstrate the superior overall survival (OS) outcomes of segmentectomy over lobectomy [3].

Furthermore, successful therapeutic approaches for clinical stage T1a N0 NSCLC include sublobar resections such as wedge resection or non-anatomical segmentectomy and anatomical segmentectomy, according to the CALGB 140503 RCT trial published in 2023 [4]. While these findings suggested that sublobar resection may offer patients with early-stage lung cancer an equivalent or higher survival rate than standard lung lobectomy, the locoregional recurrence rate was found to be greater with sublobar resection, with 6.9 % versus 3.1 % locoregional recurrences observed in the JCOG0802/WJOG4607L trial [3]. Moreover, within the CALGB 140503 trial, the sublobar resection group showed a 13.4 % incidence of locoregional recurrences (lung or hilar LN of the index lobe) versus 10 % in the lobectomy group. However, such a difference did not reach statistical significance. Therefore, the oncologic comparability of anatomic segmentectomy and lobectomy in patients with stage I disease remains a subject of ongoing debate within the surgical and oncological communities [5].

This systematic review and meta-analysis aimed to synthesize the evidence about selected perioperative and oncological outcomes associated with segmentectomy and/or lobectomy in stage IA NSCLC.

2. Material and methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [6,7]. A PRISMA checklist was added (Supplementary File 1). The systematic review was registered on the International Prospective Register of Systematic Reviews (PROSPERO): CRD42018105409.

A search technique combined free-text words, suitable MeSH headings, and limitations. MEDLINE (via PubMed), EMBASE (through Ovid), and Cochrane CENTRAL were searched without date or language limitations (Supplemental File 2). Studies that compared segmentectomy and lobectomy in terms of perioperative and/or survival outcomes for stage IA NSCLC were included. Editorials, letters, case reports, expert opinions and reviews were excluded. The outcomes of our query were imported into Rayyan, an application for managing references [8]. When duplicate documents occurred, the most recent record was selected. To ensure the inclusion of pertinent articles for the meta-

analysis, a comprehensive full-text examination was undertaken on papers that appeared to be eligible after an initial screening of titles and abstracts.

Two authors (ACT and MC) independently screened articles from the title and abstracts. Full text of potentially relevant studies was independently retrieved and assessed for final inclusion by two authors, and any disagreement was discussed with a third senior author.

The primary outcome was OS. Secondary outcomes assessed were disease-free survival (DFS), local recurrence, postoperative morbidity (general complications, postoperative air leaks) and length of hospital stay.

We independently extracted the following data: first author's name, geographic region, publication year, study design, overall survival (OS), disease-free survival (DFS), local recurrences, number of harvested lymph nodes, overall postoperative complications, postoperative air leaks, and length of postoperative hospital stay. We independently assessed the risk of bias according to the study design of the included studies. Observational studies were assessed through the Newcastle-Ottawa quality assessment form for cohort studies [9]; RCTs were assessed following criteria suggested by the Cochrane Handbook for Systematic Reviews of Interventions: sequence generation and allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), incomplete outcome data (attrition bias), and selective outcome reporting (reporting bias) [10]. According to the GRADE approach, we assessed the overall certainty of the evidence for primary and secondary outcomes using the five GRADE domains (study limitations, consistency of effect, imprecision, indirectness, and publication bias) [11]. The existing evidence was summarized in a summary of findings table.

2.1. Statistical analysis

The Mantel–Haenszel formula was used for dichotomous variables to produce a pooled effect estimate using risk ratios and their related 95 % confidence intervals (CI). The mean differences (MD) for continuous outcomes were aggregated, weighted by generic inverse variance, and evaluated using a random effects model. Means and standard deviations were determined when results were presented as median, range, and interquartile range. Using the Hazard Ratio (HR) and 95 % CI, we analyzed OS and DFS. If HR data could not be obtained directly from the included studies, we extracted data from Kaplan–Meier curves. We computed the data using the technique described in the scientific literature [12]. The I^2 statistic was employed to measure heterogeneity. This statistic represents the fraction of total variation between studies that can be attributed to heterogeneity instead of random variation. An I^2 statistic of 75 % was considered as proof of heterogeneity. Review Manager 5.4.1 (Nordic Cochrane Centre, Copenhagen, Denmark, <https://community.cochrane.org/help/tools-and-software/revman-5/review-manager-5-download/installation>) was used to produce forest plots.

3. Results

The manual search of reference lists and the electronic database search yielded 146 publications, reduced to 122 records after duplicates were removed. After screening the title and abstracts, 52 were excluded since they were unrelated to this systematic review. Seventy full-text were assessed for eligibility, of which 30 were excluded due to specific reasons: no population of interest ($n = 5$), no intervention of

interest (n = 2), no outcomes of interest (n = 4), no comparison of interest (n = 11), no study design of interest (n = 1) or due to lack of data to meta-analyze (n = 7). Forty studies (38 observational [13–50] and 2 RCTs [3,4]) met our eligibility criteria for 103,926 patients (102,123 in retrospective studies and 1,803 in non RCTs): 12,546 underwent anatomical segmentectomy (11,654 in retrospective studies and 892 in non RCTs), and 91,380 underwent lobectomy (90,469 in retrospective studies and 911 in non RCTs) (Fig. 1). The characteristics of the studies are presented in Table 1.

Fig. 2 provides an overview of the risk of bias for RCTs. Table 2 shows the quality assessment of observational studies following the Newcastle-Ottawa Scale. The existing evidence was summarised in a summary of findings table that provides critical information about the magnitude of the interventions' relative and absolute effects, the amount, and the certainty of available evidence (Supplemental File 3).

3.1. Overall survival

Nineteen non-RCT studies presented OS data and involved 95,427 patients (9,959 received segmentectomies and 85,468 lobectomies) (Fig. 3A). There was high heterogeneity between trials ($I^2 = 84\%$). The combined HR for OS was 1.10 (95 % confidence interval: 0.94 to 1.30, $p = 0.24$; certainty of evidence: very low).

2 RCT studies presented OS data (Fig. 3B) and involved 1803 patients (892 received segmentectomies and 911 lobectomies). There was heterogeneity between trials ($I^2 = 62\%$). The HR for OS was 0.82 (95 % confidence interval: 0.66 to 1.02, $p = 0.07$; certainty of evidence: moderate).

3.2. Disease-free survival

Ten non-RCT studies described data on DFS and involved 2,727 patients (1,936 received segmentectomies and 1,331 lobectomies) (Fig. 4A). There was no heterogeneity between trials ($I^2 = 0\%$). The overall HR for DFS was 1.13 (95 % CI: 0.95 – 1.34, $p = 0.18$; certainty of evidence: very low).

2 RCT studies described data on DFS (Fig. 4B) and involved 1803 patients (892 received segmentectomies and 911 lobectomies). There was no heterogeneity between trials ($I^2 = 0\%$). The overall HR for DFS was 1.00 (95 % CI: 0.85 – 1.18, $p = 0.97$; certainty of evidence: moderate).

3.3. Local recurrences

Twenty non-RCT studies described data on local recurrences (Fig. 5A) and involved 4696 patients (1996 received segmentectomies and 3500 lobectomies). There was a slight heterogeneity between trials ($I^2 = 34\%$). The overall OR was 1.40 (95 % CI: 0.94 – 2.08, $p = 0.09$; certainty of evidence: very low).

2 RCT studies described data on local recurrences (Fig. 5B) and involved 1793 patients (888 received segmentectomies and 905 lobectomies). There was a light heterogeneity between trials ($I^2 = 32\%$). The overall RR for local recurrence was 1.61 (95 % CI: 1.12 – 2.31, $p = 0.01$; certainty of evidence: low).

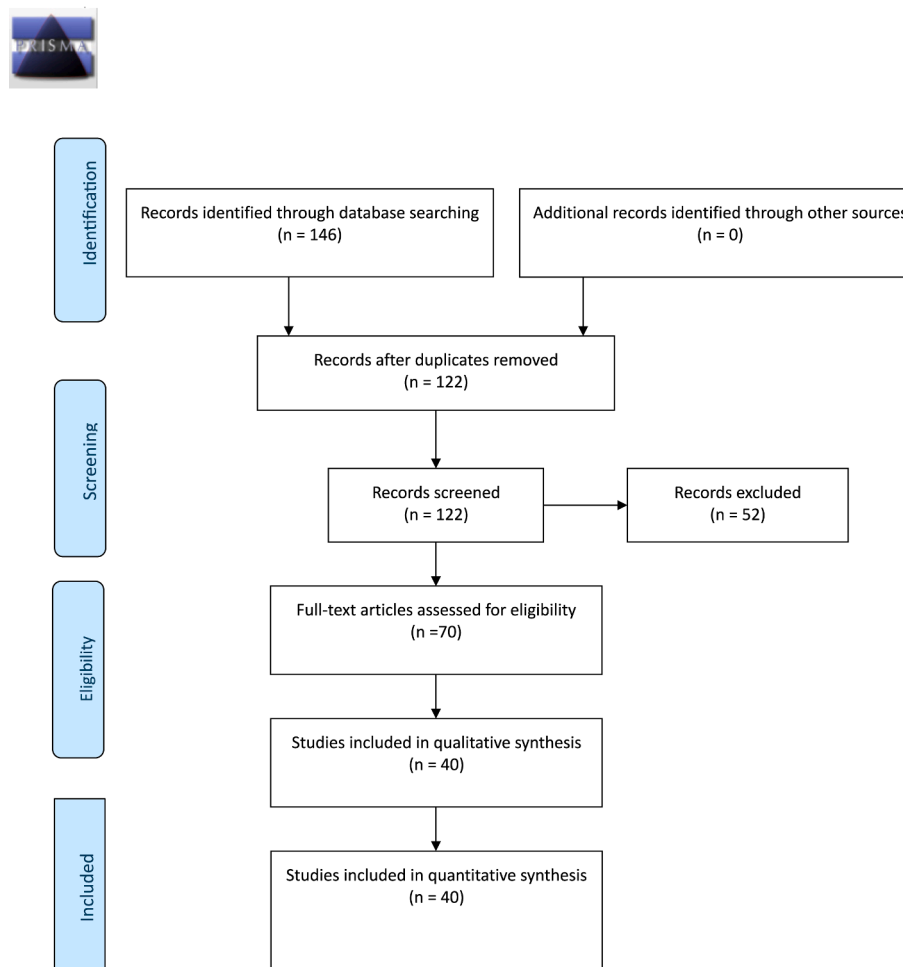


Fig. 1. PRISMA 2020 flow schematic of the search approach used to discover pertinent comparative studies on minimally invasive segmentectomy versus lobectomy.

Table 1

General characteristics of the enrolled studies. RCT = randomised controlled trial; UK = United Kingdom; USA = United States of America.

First author	Year	Reference	Countries	Study Design	Segmentectomy	Lobectomy
Altorki et al.	2023	[4]	North America	RCT	340	357
Carr et al.	2012	[13]	USA	Retrospective	251	178
Dai et al.	2016	[14]	Multicenter	Retrospective	4240	11,520
Darras et al.	2021	[15]	Switzerland	Retrospective	96	92
De Giacomo et al.	2009	[16]	Italy	Restrospective	22	29
Deng et al.	2015	[17]	USA, China	Retrospective	212	2336
Dziedzic et al.	2017	[18]	Poland	Retrospective	233	5911
Echavarría et al.	2016	[19]	USA	Retrospective	43	208
Fiorelli et al.	2016	[20]	Italy	Retrospective	39	51
Hattori et al.	2016	[21]	Japan	Retrospective	225	804
Hwang et al.	2015	[22]	Korea	Retrospective	94	94
Keenan et al.	2004	[50]	USA	Retrospective	54	147
Kilic et al.	2009	[23]	USA	Retrospective	78	106
Koike et al.	2003	[24]	Japan	Retrospective	74	159
Khullar et al.	2015	[25]	USA	Retrospective	1226	19,718
Landreneau et al.	2014	[26]	USA	Retrospective	312	312
Martin-Ucar et al.	2005	[27]	UK	Retrospective	17	17
Moon et al.	2018	[28]	Korea	Retrospective	809	14,549
Nakamura et al.	2011	[29]	Japan	Retrospective	38	289
Nishio et al.	2016	[30]	Japan	Retrospective	164	73
Okada et al.	2006	[31]	Japan	Retrospective	230	260
Okada et al.	2014	[32]	Japan	Retrospective	479	155
Qu et al.	2017	[33]	China	Retrospective	1156	17,748
Read et al.	1990	[34]	USA	Retrospective	107	131
Roman et al.	2019	[35]	UK	Retrospective	64	64
Saji et al.	2022	[3]	Japan	RCT	552	554
Schuchert et al.	2007	[36]	USA	Retrospective	182	246
Sienele et al.	2007	[37]	Germany	Retrospective	49	150
Shapiro et al.	2009	[38]	USA	Retrospective	31	113
Soukiasian et al.	2012	[39]	USA	Retrospective	73	178
Song et al.	2018	[40]	Japan	Retrospective	41	122
Sugi et al.	2010	[41]	Japan	Retrospective	33	111
Tsubokawa et al.	2018	[42]	Japan	Retrospective	52	44
Wang et al.	2013	[43]	Japan	Retrospective	5	14
Whitson et al.	2011	[44]	USA	Retrospective	581	13,892
Yamato et al.	2008	[45]	Japan	Retrospective	153	277
Yamashita et al.	2012	[46]	Japan	Retrospective	90	124
Zhang et al.	2013	[47]	China	Retrospective	26	28
Zhao et al.	2013	[48]	China	Retrospective	36	138
Zhong et al.	2012	[49]	China	Retrospective	39	81

3.4. Number of harvested lymph nodes

Five non-RCT articles reported data on harvested lymph nodes (Fig. 6) and involved 792 patients (360 received segmentectomies and 432 lobectomies). There was a high heterogeneity between trials ($I^2 = 95\%$). A significantly higher number of lymph nodes was harvested in lobectomies (MD = -5.07 , 95% CI: -9.41 – -0.74 , $p = 0.02$; certainty of evidence: very low). These data were not available for RCT.

3.5. Postoperative complications

Thirteen non-RCT articles published data on postoperative complications (Fig. 7) and involved 3323 patients (1289 received segmentectomies and 2034 lobectomies). Significant heterogeneity was observed among the studies ($I^2 = 61\%$). No significant differences in the incidence of postoperative complications were shown between the two groups (OR = 1.06 , 95% CI: 0.78 – 1.44 , $p = 0.71$; certainty of evidence: very low).

Ten non-RCT articles published data on postoperative air leaks (Fig. 8) and involved 4127 patients (777 received segmentectomies and 3350 lobectomies). Mild heterogeneity was observed among the studies ($I^2 = 36\%$). No significant differences in the incidence of postoperative air leaks were shown between the two groups (OR = 1.18 , 95% CI: 0.79 – 1.75 , $p = 0.42$; certainty of evidence: very low). These data were not available for RCT.

3.6. Hospital discharge

Nine non-RCT articles published data on the length of hospital stay (Fig. 9) and involved 1412 patients (472 received segmentectomies and 940 lobectomies). High heterogeneity was observed among the studies ($I^2 = 84\%$). The mean difference in length of hospital stay did not change significantly statistically between the two groups (MD = -0.58 , 95% CI: -1.63 – -0.46 , $p = 0.27$; certainty of evidence: very low). These data were not available for RCT.

4. Discussion

The synthesis of available evidence provides valuable insights into the ongoing controversial debate surrounding the optimal surgical approach (segmentectomy versus lobectomy) for stage IA NSCLC. Our comprehensive analysis of the literature sheds light on critical aspects, facilitating the understanding of the current state of knowledge.

The inconclusive nature of OS outcomes highlights the challenges in drawing definitive conclusions. The high heterogeneity among non-RCT studies may be attributed to variations in patient characteristics, surgical techniques, and institutional practices. The moderate heterogeneity observed in RCT studies, while suggesting potential benefits with segmentectomy, warrants cautious interpretation. In addition, in retrospective studies, there was a significant selection bias where less fit patients, and thus more at risk for various issues, were more frequently subjected to segmentectomy. However, the results of two randomized trials designed for non-inferiority suggest that segmentectomy is superior. Specifically, the JCOG0802/WJOG4607L trial, with OS as its

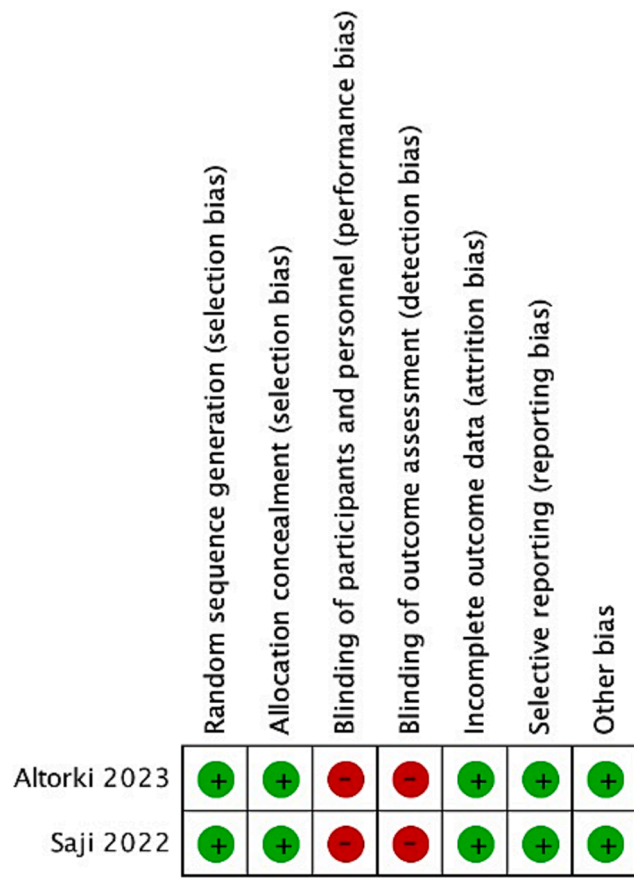


Fig. 2. Risk of bias graph and summary for RCTs. Authors' assessments of each risk of bias item for each study are included. The green and red circles correspondingly represent a low and high risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

endpoint, already indicated such superiority, and this *meta*-analysis further reinforces that conclusion.

The evolving landscape of NSCLC management, including advancements in adjuvant therapies, further complicates the attribution of survival differences solely to the surgical approach.

In non-RCT, there was no trend towards lower local recurrence in lobectomy. On the other hand, in RCT, there was a significant increase in local recurrence rates associated with segmentectomy that deserves additional attention. In the post-hoc analysis of the JCOG0802/WJOG4607L trial, the researchers aimed to investigate the reasons behind the observed better OS associated with segmentectomy over lobectomy. The primary objectives included comparing overall and relapse-free survival, cause of death, and recurrence patterns between the two surgical interventions. Subgroup analyses indicated that higher 5-year OS after segmentectomy was observed in patients aged 70 years or older and males.

Conversely, higher 5-year RFS after lobectomy was noted in younger than 70 years and female patients. The interpretation of these results suggests an improved OS with segmentectomy for pure-solid NSCLC, although outcomes varied based on the patient's age and sex. The study emphasises the need for further research to identify clinically relevant indications for segmentectomy in the radiologically pure-solid NSCLC [51]. The potential disadvantage of segmentectomy in increasing local recurrences aligns with the recent RCT trials, stimulating historical

Table 2

Quality assessment of observational studies following the Newcastle-Ottawa scale form.

First author	Year	Reference	Selection	Comparability	Outcomes
Carr et al.	2012	[13]	☆☆		☆☆
Dai et al.	2016	[14]	☆☆	*	☆☆
Darras et al.	2021	[15]	☆☆	*	*
De Giacomo et al.	2009	[16]	☆☆	*	☆☆
Deng et al.	2015	[17]	☆☆		*
Dziedzic et al.	2017	[18]	☆☆	**	☆☆
Echavarría et al.	2016	[19]	☆☆	*	☆☆
Fiorelli et al.	2016	[20]	☆☆	*	*
Hattori et al.	2016	[21]	☆☆		☆☆
Hwang et al.	2015	[22]	☆☆	*	*
Keenan et al.	2004	[4]	☆☆		*
Kilic et al.	2009	[23]	☆☆	*	*
Koike et al.	2003	[24]	☆☆		☆☆
Khullar et al.	2015	[25]	☆☆	**	☆☆
Landreneau et al.	2014	[26]	☆☆	**	☆☆
Martin-Ucar et al.	2005	[27]	☆☆	**	☆☆
Moon et al.	2018	[28]	☆☆	**	☆☆
Nakamura et al.	2011	[29]	☆☆	*	☆☆
Nishio et al.	2016	[30]	☆☆	*	☆☆
Okada et al.	2006	[31]	☆☆	**	☆☆
Okada et al.	2014	[32]	☆☆	*	*
Qu et al.	2017	[33]	☆☆	**	☆☆
Read et al.	1990	[34]	☆☆		☆☆
Roman et al.	2019	[35]	☆☆	*	☆☆
Schuchert et al.	2007	[36]	☆☆	**	☆☆
Sienel et al.	2007	[37]	☆☆		☆☆
Shapiro et al.	2009	[38]	☆☆		*
Soukiasian et al.	2012	[39]	☆☆		*
Song et al.	2018	[40]	☆☆	*	☆☆
Sugi et al.	2010	[41]	☆☆		☆☆
Tsubokawa et al.	2018	[42]	☆☆	**	☆☆
Wang et al.	2013	[43]	☆☆		*
Whitson et al.	2011	[44]	☆☆	**	☆☆
Yamato et al.	2008	[45]	☆☆		☆☆
Yamashita et al.	2012	[46]	☆☆	*	☆☆
Zhang et al.	2013	[47]	☆☆	**	*
Zhao et al.	2013	[48]	☆☆	*	*
Zhong et al.	2012	[49]	☆☆		☆☆

perceptions favouring lobectomy. However, the underlying mechanisms contributing to this difference require deeper exploration. Factors such as the extent of lymphadenectomy, tumour characteristics, and patient selection criteria may have influenced these outcomes.

The lack of significant differences in DFS between segmentectomy and lobectomy suggests comparable efficacy in preventing disease recurrence. The absence of heterogeneity in non-RCT and RCT studies enhances the reliability of this finding. Nevertheless, the follow-up durations in some studies may limit the ability to capture long-term DFS differences, emphasising the importance of continued surveillance.

The significantly higher number of harvested lymph nodes with lobectomy raises questions about the implications for accurate staging. Although the therapeutic significance of this discrepancy is unknown, staging accuracy is critical for treatment decision-making. Mediastinal lymph nodes should have been routinely dissected in the JCOG0802/WJOG4607L study, with selective dissection authorised and accepted [3]. Literature demonstrated that systematic lymph node dissection produced more metastatic lymph nodes and better oncological outcomes than lobe-specific lymph node dissection [52]. Ongoing research focuses on using tyrosine kinase and immune checkpoint inhibitors as therapeutic agents for resectable NSCLC in neoadjuvant and adjuvant settings. A multimodal approach has emerged as the prevailing method of treatment, specifically in the case of hypermetabolic cancers that have an increased likelihood of developing nodal metastases. As a result, meticulous nodal dissection guarantees accurate staging, essential for

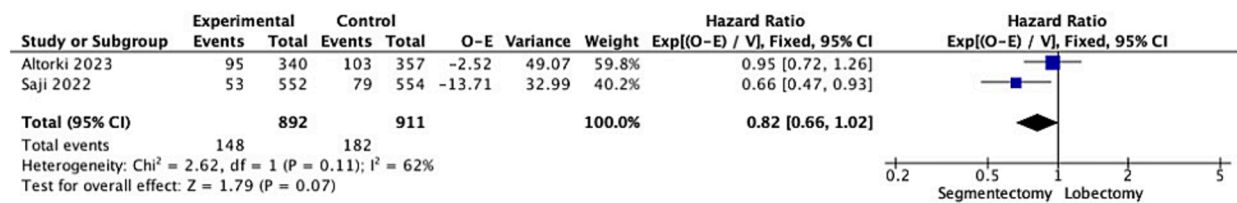
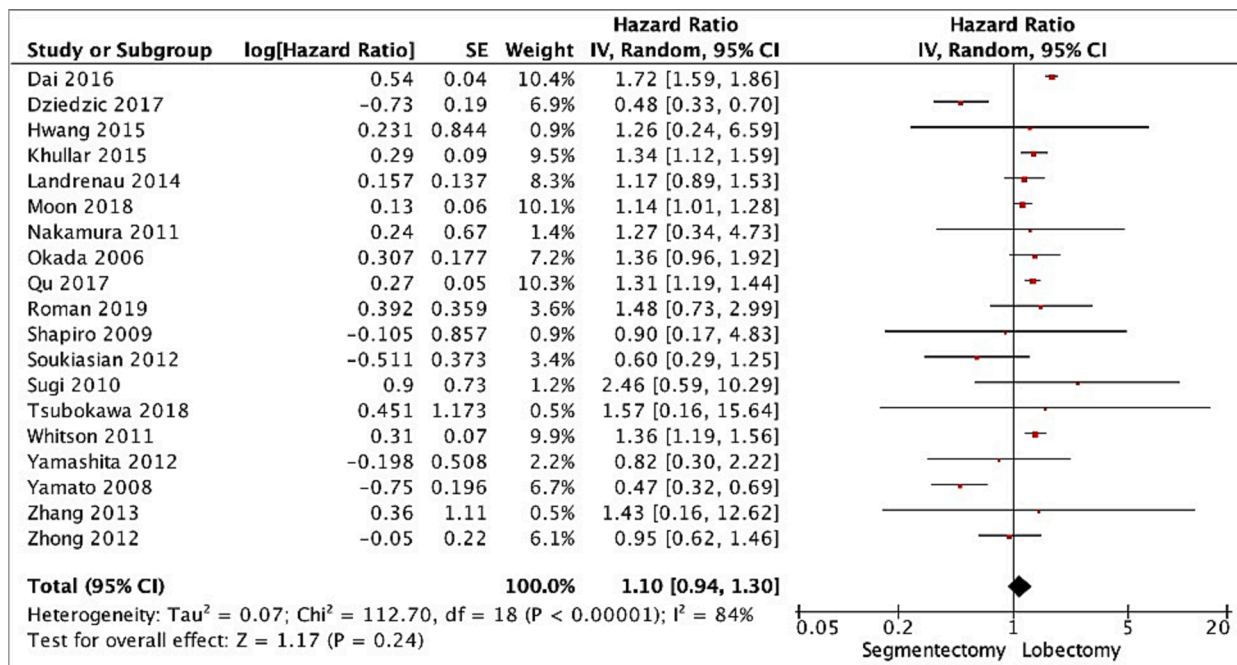


Fig. 3. A. Forest plot for overall survival of the non-randomized controlled studies between segmentectomy and lobectomy. B. Forest plot for overall survival of the randomised controlled studies between segmentectomy and lobectomy. CI = confidence interval; df = degree of freedom; IV = inverse variance; SD = standard deviation.

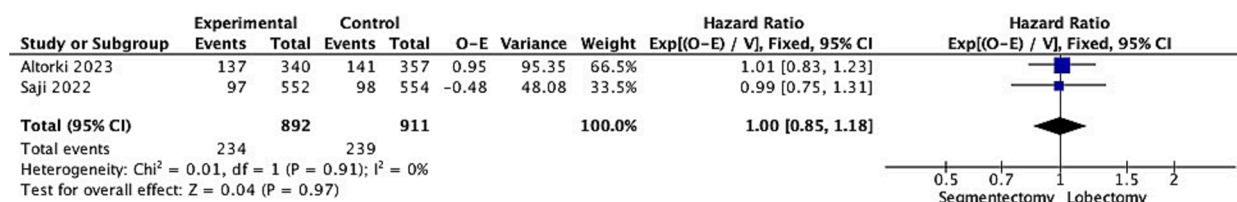
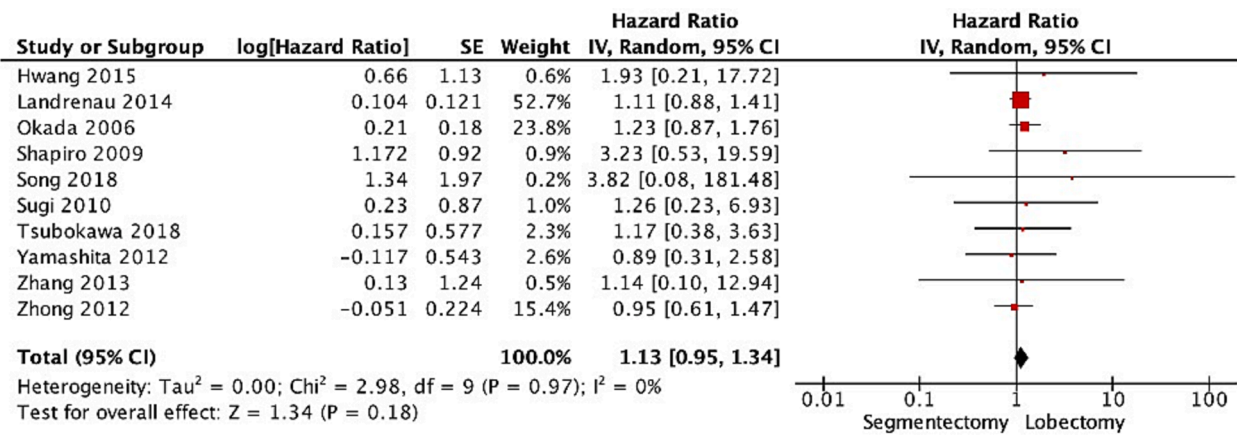


Fig. 4. A. Forest plot for local recurrences of the non-randomized controlled studies between segmentectomy and lobectomy. B. Forest plot for disease-free survival of the randomised controlled studies between segmentectomy and lobectomy. CI = confidence interval; df = degree of freedom; IV = inverse variance; SD = standard deviation.

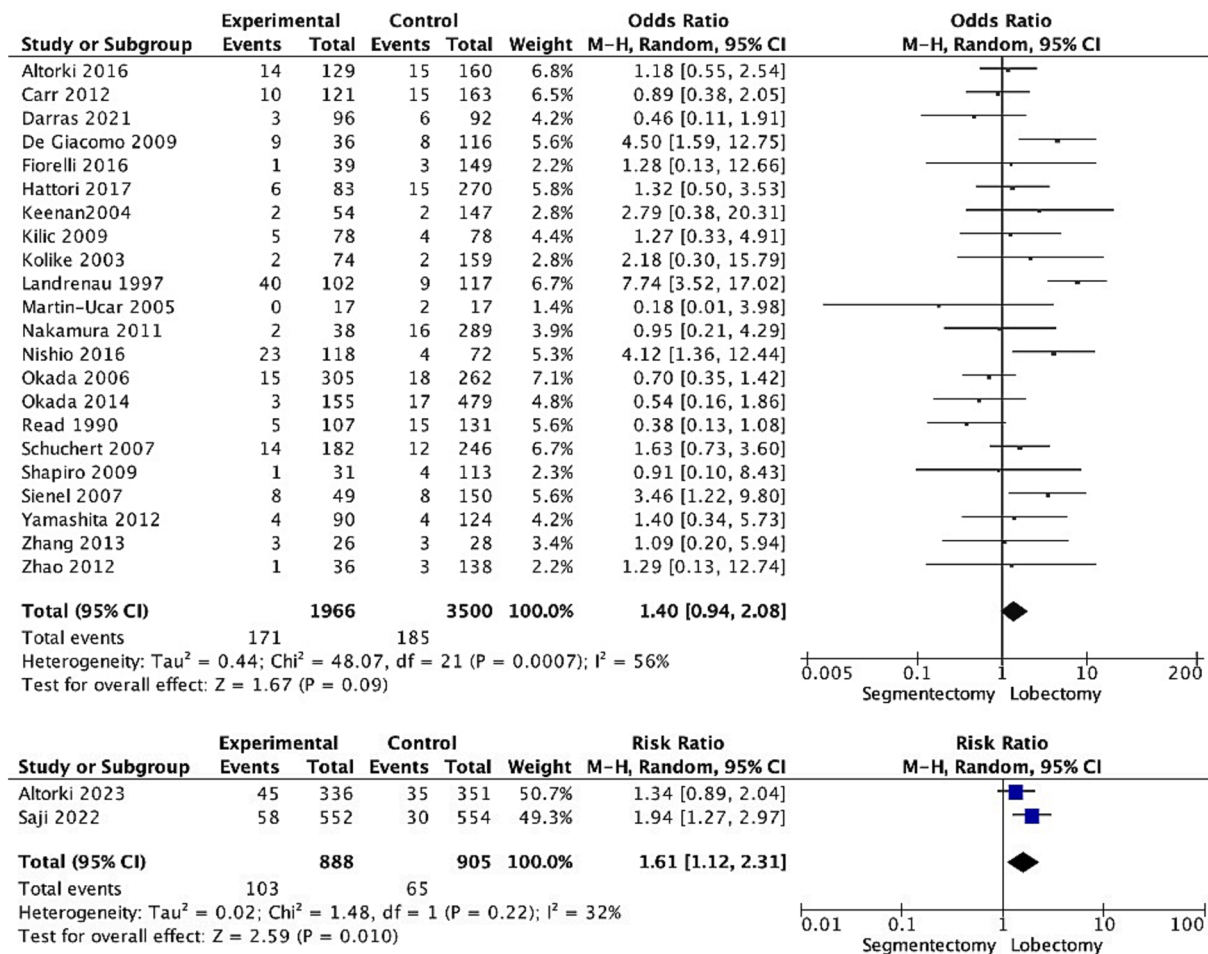


Fig. 5. A. Forest plot for disease-free survival of the non-randomized controlled studies between segmentectomy and lobectomy. B. Forest plot for disease-free survival of the randomised controlled studies between segmentectomy and lobectomy. CI = confidence interval; dF = degree of freedom; IV = inverse variance; SD = standard deviation.

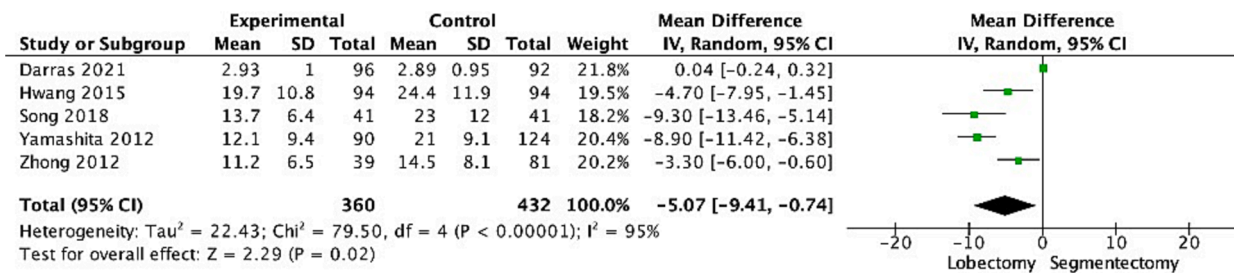


Fig. 6. Forest plot for harvested lymph nodes of segmentectomies and lobectomies. CI = confidence interval; dF = degree of freedom; IV = inverse variance; SD = standard deviation.

adjuvant treatment selection. As novel systemic medicines emerge, erroneous nodal sampling may unnecessarily deny patients access to these efficacious therapies, negatively affecting their chances of survival [53]. Future investigations should delve into the correlation between the number of harvested lymph nodes and long-term outcomes to guide the interpretation of this finding.

The comparable rates of postoperative complications, air leakages, and length of hospital stay between segmentectomy and lobectomy underscore the safety and feasibility of both procedures. The observed heterogeneity in some outcomes may reflect variations in surgical expertise, perioperative care protocols, and patient factors. The overall low certainty of evidence emphasises the need for well-designed prospective studies to refine our understanding of these perioperative

factors.

The randomised study JCOG0802/WJOG4607L suggests that segmentectomies should replace lobectomies as the usual surgical treatment for patients with small (<2 cm) peripheral, clinical stage IA NSCLC. Nevertheless, this evidence cannot leave us safely passing the pillars of the segmentectomies as the gold standard. We suggest two subgroups of Kaplan – Meyer estimates to the trialists: cancer-specific survival and overall survival of the different subtypes of segmentectomies.

Anatomical segmentectomies, removing the segmentary lymphatic pathways, are accepted as radical oncological treatments [3]. As a result, disease-free survival and overall survival of wedge resections should be included in the CALGB140503 outcomes compared to

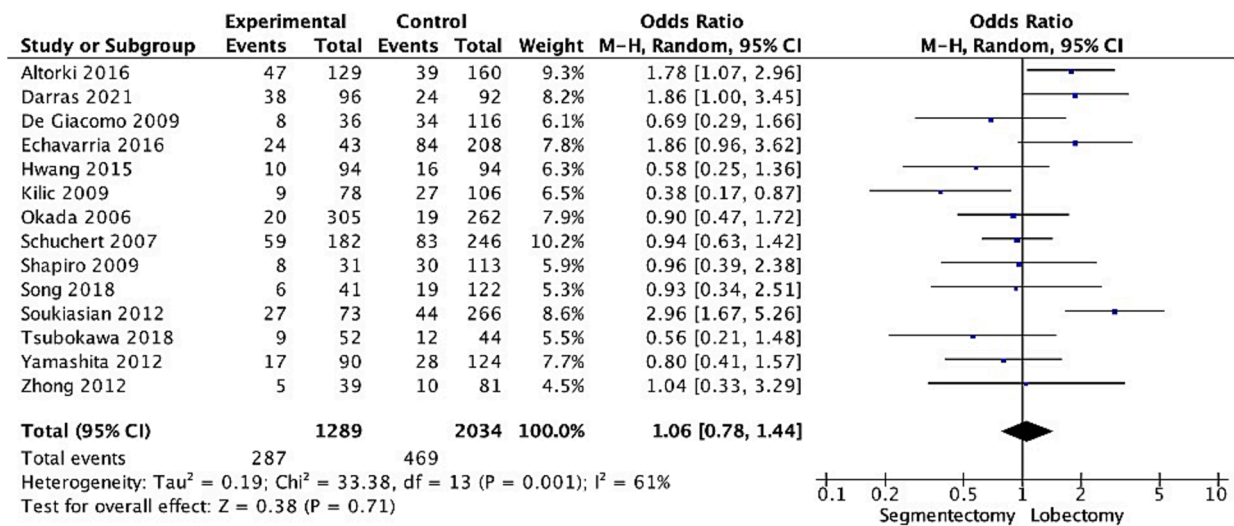


Fig. 7. Forest plot for postoperative complications of the lobectomy compared to segmentectomy. CI = confidence interval; dF = degree of freedom; M – H = Mantel–Haenszel.

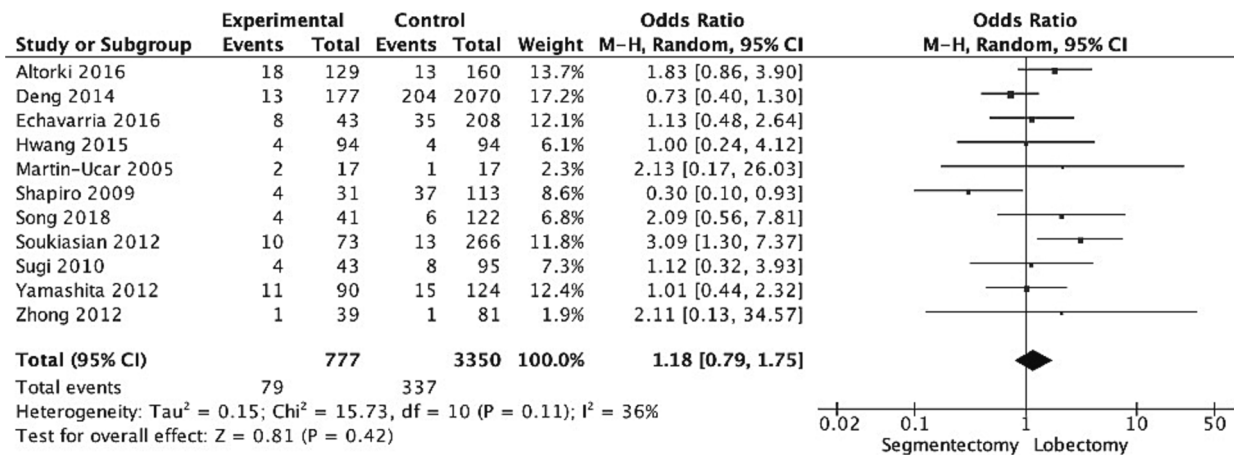


Fig. 8. Forest plot for postoperative air leakages of the lobectomy compared to segmentectomy. CI = confidence interval; dF = degree of freedom; M – H = Mantel–Haenszel.

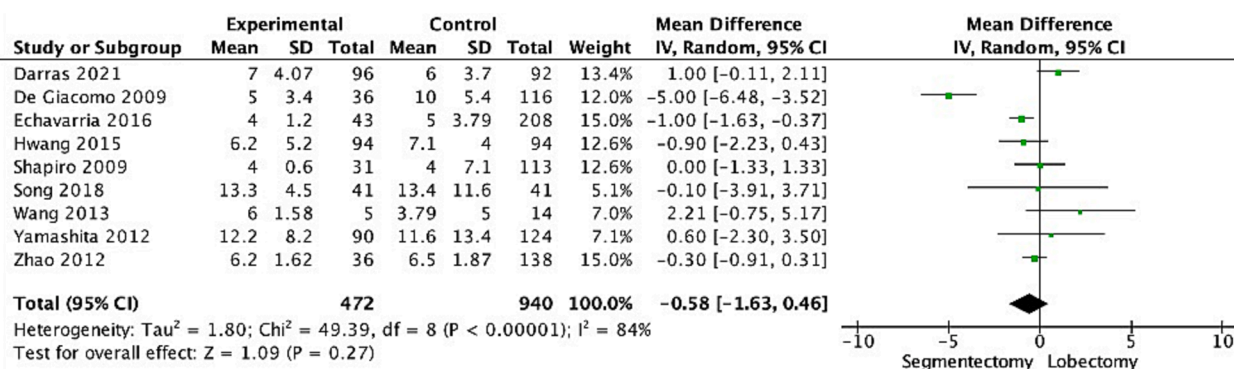


Fig. 9. Forest plot for the length of hospital stay of segmentectomies and lobectomies. CI = confidence interval; dF = degree of freedom; IV = inverse variance; SD = standard deviation.

lobectomies, as this information could alter the clinical practice management of early-stage lung cancer. The findings of this meta-analysis contribute to the evolving paradigm in early-stage NSCLC surgical management. The potential benefits of lobectomy, particularly in

reducing local recurrences, warrant consideration in treatment decision-making. However, the limitations of existing evidence, including heterogeneity and different study designs, necessitate caution in drawing definitive conclusions. Future research should focus on standardised

outcomes reporting, uniform patient selection criteria, and longer follow-up durations to capture late oncological events. Comparative effectiveness research incorporating real-world data may offer valuable insights into the generalizability of findings [5]. Additionally, advancements in imaging modalities, molecular profiling, and adjuvant therapies should be integrated into the assessment of surgical outcomes to provide a comprehensive understanding of the evolving landscape in NSCLC management.

It is essential to acknowledge the limitations of this systematic review and meta-analysis. Despite efforts to include a comprehensive set of studies, the inherent heterogeneity in study designs, patient populations, and surgical techniques introduces challenges in drawing definitive conclusions. The variability in surgical expertise, patient comorbidities, and tumour characteristics across different centres could contribute to the observed outcome heterogeneity. Additionally, the reliance on retrospective observational studies alongside the limited number of available RCTs may introduce selection bias and confounding factors, influencing the validity of the overall findings. The scarcity of high-quality randomised controlled trials directly comparing segmentectomy and lobectomy necessitates cautious interpretation of the presented results. Furthermore, the evolving landscape of lung cancer management, including advancements in imaging, adjuvant therapies, and personalised medicine, introduces temporal considerations. The included studies span several years, during which treatment paradigms and technology changes may impact outcomes.

5. Conclusions

While no conclusive evidence emerged for differences in OS, DFS, and postoperative outcomes, this systematic review and meta-analysis suggests a potential increase in local recurrences following segmentectomy. The heterogeneity observed across various outcomes underscores the need for further well-designed RCT to provide more robust evidence and guide clinical decision-making in the choice between segmentectomy and lobectomy for stage I NSCLC.

CRediT authorship contribution statement

Luca Bertolaccini: Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Antonino Carmelo Tralongo:** Data curation, Formal analysis, Writing – original draft. **Marzia Del Re:** Writing – original draft, Writing – review & editing. **Francesco Fachinetti:** Supervision, Writing – original draft, Writing – review & editing. **Roberto Ferrara:** Writing – original draft, Writing – review & editing. **Tindara Franchina:** Writing – original draft, Writing – review & editing. **Paolo Graziano:** Writing – original draft, Writing – review & editing. **Umberto Malapelle:** Writing – original draft, Writing – review & editing. **Jessica Menis:** Writing – original draft, Writing – review & editing. **Antonio Passaro:** Writing – original draft, Writing – review & editing. **Sara Pilotto:** Writing – original draft, Writing – review & editing. **Sara Ramella:** Writing – original draft, Writing – review & editing. **Giulio Rossi:** Writing – original draft, Writing – review & editing. **Rocco Trisolini:** Writing – original draft, Writing – review & editing. **Michela Cinquini:** Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Francesco Passiglia:** Supervision, Writing – original draft, Writing – review & editing. **Silvia Novello:** Supervision, Writing – original draft, Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.lungcan.2024.107990>.

References

- [1] Y. Shi, S. Wu, S. Ma, Y. Lyu, H. Xu, L. Deng, et al., Comparison between wedge resection and lobectomy/segmentectomy for early-stage non-small cell lung cancer: a Bayesian meta-analysis and systematic review, *Ann. Surg. Oncol.* 29 (3) (2022) 1868–1879.
- [2] R.J. Ginsberg, L.V. Rubinstein, Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung cancer study group, *Ann. Thorac. Surg.* 60 (3) (1995), 615–22; discussion 22–3.
- [3] H. Saji, M. Okada, M. Tsuboi, R. Nakajima, K. Suzuki, K. Aokage, et al., Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial, *Lancet* 399 (10335) (2022) 1607–1617.
- [4] N. Altorki, X. Wang, D. Kozono, C. Watt, R. Landrenau, D. Wigle, et al., Lobar or sublobar resection for peripheral stage IA non-small-cell lung cancer, *N. Engl. J. Med.* 388 (6) (2023) 489–498.
- [5] L. Bertolaccini, L. Spaggiari, Is it time to cross the pillars of evidence in favor of segmentectomies in early-stage non-small cell lung cancer? *Cancers* 15 (7) (2023) 1993.
- [6] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., The PRISMA 2020 statement: an updated guideline for reporting systematic reviews, *BMJ* 372 (2021) n71.
- [7] M.J. Page, D. Moher, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, et al., PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews, *BMJ* 372 (2021) n160.
- [8] M. Ouzzani, H. Hammady, Z. Fedorowicz, A. Elmagarmid, Rayyan—a web and mobile app for systematic reviews, *Syst. Rev.* 5 (1) (2016) 210.
- [9] A. Stang, Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses, *Eur. J. Epidemiol.* 25 (9) (2010) 603–605.
- [10] J.P.T. Higgins, J. Savović, M.J. Page, R.G. Elbers, J.A.C. Sterne, Assessing risk of bias in a randomized trial, *Cochrane Handb. Syst. Rev. Intervent.* (2019) 205–228.
- [11] H. Balslem, M. Helfand, H.J. Schunemann, A.D. Oxman, R. Kunz, J. Brozek, et al., GRADE guidelines: 3. Rating the quality of evidence, *J. Clin. Epidemiol.* 64 (4) (2011) 401–406.
- [12] M.K. Parmar, V. Torri, L. Stewart, Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints, *Stat. Med.* 17 (24) (1998) 2815–2834.
- [13] S.R. Carr, M.J. Schuchert, A. Pennathur, D.O. Wilson, J.M. Siegfried, J.D. Luketich, et al., Impact of tumor size on outcomes after anatomic lung resection for stage IA non-small cell lung cancer based on the current staging system, *J. Thorac. Cardiovasc. Surg.* 143 (2) (2012) 390–397.
- [14] C. Dai, J. Shen, Y. Ren, S. Zhong, H. Zheng, J. He, et al., Choice of surgical procedure for patients with non-small-cell lung cancer ≤ 1 cm or > 1 to 2 cm among lobectomy, segmentectomy, and wedge resection: a population-based study, *J. Clin. Oncol.* 34 (26) (2016) 3175–3182.
- [15] M. Darras, A. Ojanguren, C. Forster, M. Zellweger, J.Y. Perentes, T. Krueger, et al., Short-term local control after VATS segmentectomy and lobectomy for solid NSCLC of less than 2 cm, *Thorac. Cancer* 12 (4) (2021) 453–461.
- [16] T. De Giacomo, M. Di Stasio, D. Diso, M. Anile, F. Venuta, C.G. Furio, Sub-lobar lung resection of peripheral T1N0M0 NSCLC does not affect local recurrence rate, *Scand. J. Surg.* 98 (4) (2009) 225–228.
- [17] B. Deng, S.D. Cassivi, M. de Andrade, F.C. Nichols, V.F. Trastek, Y. Wang, et al., Clinical outcomes and changes in lung function after segmentectomy versus lobectomy for lung cancer cases, *J. Thorac. Cardiovasc. Surg.* 148 (4) (2014) 1186–92 e3.
- [18] R. Dziedzic, W. Rzyman, Lobectomy versus segmentectomy and wedge resection in the treatment of stage I non-small cell lung cancer, *J. Thorac. Dis.* 10 (3) (2018) E234–E235.
- [19] Echavarría, F. Maria, Cheng, M. Anna, C. Velez, O. Frank, et al. Comparison of pulmonary function tests and perioperative outcomes after robotic-assisted pulmonary lobectomy vs segmentectomy. 2016.
- [20] A. Fiorelli, F.P. Caronia, N. Daddi, D. Loizzi, L. Ampollini, N. Ardo, et al., Sublobar resection versus lobectomy for stage I non-small cell lung cancer: an appropriate choice in elderly patients? *Surg. Today* 46 (12) (2016) 1370–1382.
- [21] A. Hattori, T. Matsunaga, K. Takamochi, S. Oh, K. Suzuki, Neither maximum tumor size nor solid component size is prognostic in part-solid lung cancer: impact of tumor size should be applied exclusively to solid lung cancer, *Ann. Thorac. Surg.* 102 (2) (2016) 407–415.
- [22] H. Yoo, C.H. Kang, H.S. Kim, J.H. Jeon, I.K. Park, Y.T. Kim, Comparison of thoracoscopic segmentectomy and thoracoscopic lobectomy on the patients with

- non-small cell lung cancer: a propensity score matching study, *Eur. J. Cardiothorac. Surg.* 48 (2) (2015) 273–278.
- [23] A. Kilic, M.J. Schuchert, B.L. Pettiford, A. Pennathur, J.R. Landreneau, J. P. Landreneau, et al., Anatomic segmentectomy for stage I non-small cell lung cancer in the elderly, *Ann. Thorac. Surg.* 87 (6) (2009), 1662–6; discussion 7–8.
- [24] T. Koike, Y. Yamato, K. Yoshiya, T. Shimoyama, R. Suzuki, Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer, *J. Thorac. Cardiovasc. Surg.* 125 (4) (2003) 924–928.
- [25] O.V. Khullar, Y. Liu, T. Gillespie, K.A. Higgins, S. Ramalingam, J. Lipscomb, et al., Survival after sublobar resection versus lobectomy for clinical stage IA lung cancer: an analysis from the national cancer data base, *J. Thorac. Oncol.* 10 (11) (2015) 1625–1633.
- [26] R.J. Landreneau, D.P. Normolle, N.A. Christie, O. Awais, J.J. Wizorek, G. Abbas, et al., Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis, *J. Clin. Oncol.* 32 (23) (2014) 2449–2455.
- [27] A.E. Martin-Ucar, A. Nakas, J.E. Pilling, K.J. West, D.A. Waller, A case-matched study of anatomical segmentectomy versus lobectomy for stage I lung cancer in high-risk patients, *Eur. J. Cardiothorac. Surg.* 27 (4) (2005) 675–679.
- [28] M.H. Moon, Y.K. Moon, S.W. Moon, Segmentectomy versus lobectomy in early non-small cell lung cancer of 2 cm or less in size: a population-based study, *Respirology* 23 (7) (2018) 695–703.
- [29] H. Nakamura, Y. Taniguchi, K. Miwa, Y. Adachi, S. Fujioka, T. Haruki, et al., Comparison of the surgical outcomes of thoracoscopic lobectomy, segmentectomy, and wedge resection for clinical stage I non-small cell lung cancer, *Thorac. Cardiovasc. Surg.* 59 (3) (2011) 137–141.
- [30] W. Nishio, M. Yoshimura, Y. Maniwa, Y. Kitamura, K. Tane, D. Takenaka, et al., Re-assessment of intentional extended segmentectomy for clinical T1aN0 non-small cell lung cancer, *Ann. Thorac. Surg.* 102 (5) (2016) 1702–1710.
- [31] M. Okada, T. Koike, M. Higashiyama, Y. Yamato, K. Kodama, N. Tsubota, Radical sublobar resection for small-sized non-small cell lung cancer: a multicenter study, *J. Thorac. Cardiovasc. Surg.* 132 (4) (2006) 769–775.
- [32] M. Okada, T. Mimae, Y. Tsutani, H. Nakayama, S. Okumura, M. Yoshimura, et al., Segmentectomy versus lobectomy for clinical stage IA lung adenocarcinoma, *Ann. Cardiothorac. Surg.* 3 (2) (2014) 153–159.
- [33] X. Qu, K. Wang, T. Zhang, H. Shen, W. Dong, Q. Liu, et al., Long-term outcomes of stage I NSCLC ($\leq 3\text{ cm}$) patients following segmentectomy are equivalent to lobectomy under analogous extent of lymph node removal: a PSM based analysis, *J. Thorac. Dis.* 9 (11) (2017) 4561–4573.
- [34] R.C. Read, G. Yoder, R.C. Schaeffer, Survival after conservative resection for T1 N0 M0 non-small cell lung cancer, *Ann. Thorac. Surg.* 49 (3) (1990), 391–8; discussion 9–400.
- [35] M. Roman, S. Labbouz, V. Valtzoglou, A. Ciesla, M. Hawari, E. Addae-Boateng, et al. Lobectomy vs. segmentectomy. A propensity score matched comparison of outcomes. *European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology.* 5 ed. England 2019. p. 845–50.
- [36] M.J. Schuchert, B.L. Pettiford, S. Keeley, T.A. D'Amato, A. Kilic, J. Close, et al., Anatomic segmentectomy in the treatment of stage I non-small cell lung cancer, *Ann. Thorac. Surg.* 84 (3) (2007), 926–32; discussion 32–3.
- [37] W. Sienel, C. Stremmel, A. Kirschbaum, L. Hinterberger, E. Stoelben, J. Hasse, et al., Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins—implications for patient selection for segmentectomy, *Eur. J. Cardiothorac. Surg.* 31 (3) (2007), 522–7; discussion 7–8.
- [38] M. Shapiro, T.S. Weiser, J.P. Wisnivesky, C. Chin, M. Arustamyan, S.J. Swanson, Thoracoscopic segmentectomy compares favorably with thoracoscopic lobectomy for patients with small stage I lung cancer, *J. Thorac. Cardiovasc. Surg.* 137 (6) (2009) 1388–1393.
- [39] H.J. Soukiasian, E. Hong, R.J. McKenna Jr., Video-assisted thoracoscopic trisegmentectomy and left upper lobectomy provide equivalent survivals for stage IA and IB lung cancer, *J. Thorac. Cardiovasc. Surg.* 144 (3) (2012) S23–S26.
- [40] C.Y. Song, T. Sakai, D. Kimura, T. Tsushima, I. Fukuda, Comparison of perioperative and oncological outcomes between video-assisted segmentectomy and lobectomy for patients with clinical stage IA non-small cell lung cancer: a propensity score matching study, *J. Thorac. Dis.* 10 (8) (2018) 4891–4901.
- [41] K. Sugi, S. Kobayashi, M. Sudou, H. Sakano, E. Matsuda, K. Okabe, Long-term prognosis of video-assisted limited surgery for early lung cancer, *Eur. J. Cardiothorac. Surg.* 37 (2) (2010) 456–460.
- [42] N. Tsubokawa, Y. Tsutani, Y. Miyata, Y. Handa, K. Misumi, H. Hanaki, et al., Segmentectomy versus lobectomy for radiologically pure solid clinical T1a-bN0M0 lung cancer, *World J. Surg.* 42 (8) (2018) 2493–2501.
- [43] B.Y. Wang, C.C. Tu, C.Y. Liu, C.S. Shih, C.C. Liu, Single-incision thoracoscopic lobectomy and segmentectomy with radical lymph node dissection, *Ann. Thorac. Surg.* 96 (3) (2013) 977–982.
- [44] B.A. Whitson, S.S. Groth, R.S. Andrade, M.A. Maddaus, E.B. Habermann, J. D'Cunha, Survival after lobectomy versus segmentectomy for stage I non-small cell lung cancer: a population-based analysis, *Ann. Thorac. Surg.* 92 (6) (2011) 1943–1950.
- [45] Y. Yamato, T. Koike, K. Yoshiya, H. Shinohara, S. Toyabe, Results of surgical treatment for small (2 cm or under) adenocarcinomas of the lung, *Surg. Today* 38 (2) (2008) 109–114.
- [46] S. Yamashita, K. Tokuishi, K. Anami, T. Moroga, M. Miyawaki, M. Chujo, et al., Thoracoscopic segmentectomy for T1 classification of non-small cell lung cancer: a single center experience, *Eur. J. Cardiothorac. Surg.* 42 (1) (2012) 83–88.
- [47] L. Zhang, W. Ma, Y. Li, Y. Jiang, G. Ma, G. Wang, Comparative study of the anatomic segmentectomy versus lobectomy for clinical stage IA peripheral lung cancer by video assistant thoracoscopic surgery, *J. Cancer Res. Ther.* 9 Suppl 2 (5) (2013) S106–S109.
- [48] X. Zhao, L. Qian, Q. Luo, J. Huang, Segmentectomy as a safe and equally effective surgical option under complete video-assisted thoracic surgery for patients of stage I non-small cell lung cancer, *J. Cardiothorac. Surg.* 8 (2013) 116.
- [49] C. Zhong, W. Fang, T. Mao, F. Yao, W. Chen, D. Hu, Comparison of thoracoscopic segmentectomy and thoracoscopic lobectomy for small-sized stage IA lung cancer, *Ann. Thorac. Surg.* 94 (2) (2012) 362–367.
- [50] R.J. Keenan, R.J. Landreneau, R.H. Maley Jr., D. Singh, R. Macherey, S. Bartley, et al., Segmental resection spares pulmonary function in patients with stage I lung cancer, *Ann. Thorac. Surg.* 78 (1) (2004), 228–33; discussion 33.
- [51] A. Hattori, K. Suzuki, K. Takamochi, M. Wakabayashi, Y. Sekino, Y. Tsutani, et al., Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer with radiologically pure-solid appearance in Japan (JCOG0802/WJOG4607L): a post-hoc supplemental analysis of a multicentre, open-label, phase 3 trial, *Lancet Respir. Med.* 12 (2) (2024) 105–116.
- [52] Y. Handa, Y. Tsutani, T. Mimae, Y. Miyata, H. Ito, Y. Shimada, et al., Systematic versus lobe-specific mediastinal lymphadenectomy for hypermetabolic lung cancer, *Ann. Oncol.* 28 (12) (2021) 7162–7171.
- [53] M.R. Gooseman, A. Brunelli, Intraoperative lymph node management during non-small cell lung cancer surgery, *Ann. Surg. Oncol.* 28 (12) (2021) 6925–6926.