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Sleeve Lobectomy Versus Pneumonectomy for Non-Small Cell Lung Cancer: A Meta-Analysis

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Abstract: *Background:* Sleeve lobectomy (SL) presents an attractive option compared to pneumonectomy (PN) for patients with central or locally advanced non-small cell lung cancer (NSCLC). This study aimed to assess the advantages of SL over PN for NSCLC via a meta-analysis. *Methods*: We performed a systematic review and cumulative analysis of comparative studies that reported both postoperative and survival outcomes for SL and PN. This was accomplished through a thorough search of electronic databases, including PubMed, EMBASE, and the Cochrane library, from inception to April 2023. *Results*: A total of 5727 patients (SL: 1945; PN: 3782) from thirty-one studies were analyzed. The meta-analysis focused on perioperative mortality, local recurrence, and overall survival. The SL group exhibited a significantly lower rate of perioperative mortality (OR = 0.43, 95% CI = 0.32–0.60, $P < 0.0001$). However, no significant difference was observed in local recurrence rates between SL and PN (OR = 1.25; 95% CI, 0.92 to 1.69; $P = 0.16$). Additionally, the survival rates at 1 year and 5 years in the SL cohort (1-year: 0.14, 95% CI: 0.12 to 0.17, $p < 0.0001$; 5-year: 2.15, 95% CI: 1.77 to 2.61, $p < 0.0001$) along with the survival in patients with pN0 or pN1 at 5 years (OR = 0.13, 95% CI 0.04 to 0.22; $P = 0.006$) were notably superior compared to those undergoing PN. *Conclusions*: Sleeve lobectomy should be regarded as a viable alternative to pneumonectomy for treating NSCLC.

Keywords: Non-small cell lung cancer; Sleeve lobectomy; Pneumonectomy; Meta-analysis

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1. Introduction

Lung cancer is the main cause of cancer-related mortality in many parts of the world, and is associated with dismal prognosis in part due to lymphatic spread and early metastasis [1]. Even with the generous improvements in multimodality therapy, surgical resection remains the most effective method to control non-small cell lung cancer (NSCLC), through the complete removal of the lung tumor and the nearby lymph nodes. Pneumonectomy (PN) has traditionally been considered the gold standard for the treatment of central or locally advanced NSCLC [2]. However, PN is the most extensive pulmonary resection and a challenge for surgeons. It is associated with a high occurrence of postoperative complications and poor quality of life resulting from cardiopulmonary dysfunction postoperatively [3].

Sleeve lobectomy (SL) is a surgical technique designed to preserve lung parenchyma while fully removing tumors that infiltrate the bronchial openings and the main bronchus. It was first introduced by Price-Thomas in 1947and first performed by Allison in 1952 [4]. Since this pioneering study, a growing body of evidence suggests SL as an alternative to PN for NSCLC patients. There have been reports that SL has an advantage in terms of better preservation of lung function without increasing postoperative mortality, even in patients who have undergone chemotherapy or neoadjuvant radiation therapy [2,5]. Moreover, some preliminary reports showed that locoregional recurrences and long-term survival of SL are comparable to PN [6–8]. Despite the multitude of reported equal outcomes in retrospective observational studies or meta-analyses that included patients operated on many years ago, the controversy of SL within the thoracic community has continued [9,10]. This controversy may be attributed to the more demanding techniques and, therefore the need for more experience in addition to the possibility of increased risk of locoregional tumor dissemination. Nevertheless, SL is increasingly used for central or locally advanced NSCLC by thoracic surgeons.

The purpose of this study was to carry out an updated systematic review and meta-analysis based on the earliest to most recent published studies to determine whether SL is an adequate modality for central or locally advanced disease. Through comparison of mortality, locoregional recurrences, and survival between SL and PN. A meta-analysis conducted in accordance with the timeline of publication updates the treatment effect estimate whenever new research findings are released. This approach allows for monitoring the gradual accumulation of evidence over time.

2. Methods

2.1. Search strategy

A systematic electronic search was conducted utilizing PubMed, EMBASE, and the Cochrane Library, spanning from their establishment up until April 2023. The search was restricted to articles published in English. To ensure a thorough collection of relevant studies, we employed a combination of terms, including "sleeve lobectomy," "pulmonary artery reconstruction," "pulmonary artery-sleeve resection," as well as "bronchoplastic resection," "bronchoplasty," "bronchovascular sleeve resection," "sleeve lung resections," and "pneumonectomy" along with "non-small cell lung cancer" or the abbreviation "NSCLC" across all fields. Two researchers, Xuewei Chen and Xin Zhang, executed the literature search independently and subsequently verified their results against one another. The analysis also incorporated unpublished data, those available solely in abstract form, and articles that were not full-length. Furthermore, the reference lists of all identified articles were examined to uncover additional relevant studies.

2.2. Study eligibility

Eligible studies for this systematic review and meta-analysis included patient cohorts that underwent SL and PN. In cases where institutions released duplicate studies with larger patient numbers or extended follow-up periods, only the most comprehensive reports were considered for quantitative evaluation at each time point. All included publications focused exclusively on human subjects. Abstracts, case reports, conference presentations, editorials, and expert opinions were not included. Review articles were excluded to avoid potential publication bias and the possibility of result duplication. Additionally, studies with fewer than 10 patients in both comparable groups were also disregarded.

2.3. Data extraction and critical appraisal

The full-text articles were reviewed, and data were extracted by two independent authors (Junjun Fu and Xuewei Chen). Discrepancies between the two reviewers were resolved by discussion and consensus. Extracted data included: publication details (first author, study country of origin, publication year, and sample size), patient clinical characteristics and demographics, histologic type of tumor, and distribution of tumor stage. Outcomes included perioperative mortality, locoregional recurrences, overall survival, and the difference of survival at 1 and 5 years between the 2 groups. The results were reviewed by two senior investigators (Yingxin Chen and Xuewei Chen).

2.4. Statistical analysis

We conducted a meta-analysis to evaluate clinical outcomes, using the odds ratio (OR) as the principal metric. These values were sourced directly from the original articles when available. In cases where the hazard ratio (HR) and 95% confidence interval (CI) were not provided, we employed Engauge Digitizer version 4.1 (http://sourceforge.net/projects/digitizer/) to extract data from Kaplan-Meier curves. The outcomes for each trial with dichotomous data were represented as odds ratios (OR) along with 95% confidence intervals. A significance level of $p < 0.05$ was established for all evaluated outcomes. Data pooling for the meta-analysis was executed using both fixed-effect and random-effect models. When outcomes from both models were available, we reported the statistics from the random-effects model. To determine statistical heterogeneity for each analysis, the chi-squared (χ^2) and I^2 tests were employed. The I^2 statistic was utilized to convey the proportion of total variation among studies attributed to heterogeneity rather than random chance, and standard heterogeneity tests were conducted. An I^2 value exceeding 50% indicated considerable heterogeneity. Fixed-effects models were applied when no heterogeneity was detected ($p > 0.10$, or $p \leq 0.10$ but $I^2 \leq 50\%$); in contrast, the random-effects model was utilized otherwise. Sensitivity analyses were carried out to assess the robustness of the meta-analysis results based on study quality. We evaluated publication bias using Egger's method and illustrated it with Begg's funnel plot. Throughout all analyses, a 2-tailed p-value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Review Manager 5.4 software

3. Results

3.1. Literature search and study characteristics

From our initial literature search, a total of 1347 studies were obtained from PubMed, EMBASE and Cochrane Library. **Figure 1** illustrates the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart for study inclusion and exclusion. After manually screening the titles and abstracts, 1315 articles were excluded (review articles, abstracts, experimental research, duplicate reports and studies irrelevant to the current research objectives). The remaining 32 relevant studies were acquired for full-text review and full assessment, leaving 30 studies that met the inclusion criteria and were included in the final meta-analysis (**Figure 1**).

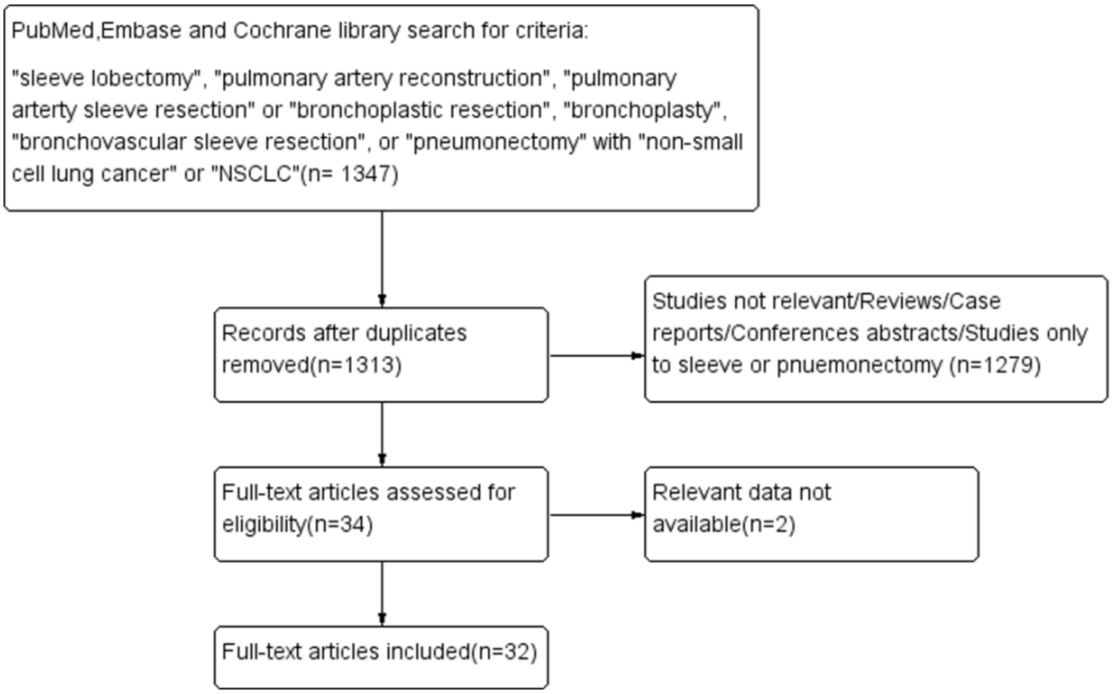

Figure 1. The flow diagram for study selection in this meta-analysis.

Among the 30 studies that were published, one was prospective while the remaining 29 were retrospective. No randomized controlled trials have been documented. Within these studies, comparisons were made involving 5,697 patients diagnosed with NSCLC, of which 1,933 underwent sleeve lobectomy (SL) and 3,764 had pneumonectomy (PN). The baseline characteristics from all included clinical trials can be found in **Table 1**. A significant difference was observed in the stage distribution between the SL group and the PN group (stages I, 32.1%; II, 38.6%; and III, 29.3% for SL; stages I, 19.6%; II, 33.2%, and III, 47.2% for PN, $p < 0.001$), with a higher proportion of early-stage NSCLC (stages I and II) in the SL group. The sex ratio between the two groups showed no significant variation (male/female, 81.2%/18.6% for SL, and 81.6%/18.4% for PN). Information regarding age distributions for the two surgical approach groups was not reported in the available literature. Nonetheless, the average age was similar across the groups (63.4 years for SL; 62.1 years for PN, $P = 0.06$).

Assessment of perioperative mortality rates was reported in all thirty studies (**Figure 2**). The overall mortality rate was 2.56% in the SL group and 6.04% in the PN group. The meta-analysis showed lower mortality in the SL group compared with the PN group (OR = 0.43, 95% CI = 0.32–0.60, $P < 0.0001$) and there was no heterogeneity among the pooled studies.

Table 1. Summary of the main characteristics of the included studies

Authors	Country	Year	Study design	Number		Mean age		Male/female		Stage I		Stage II		Stage III/IV	
				SL	*PN*	*SL*	*PN*	*SL*	*PN*	*SL (%)*	*PN (%)*	*SL (%)*	*PN (%)*	*SL (%)*	*PN (%)*
Gaissert	USA	1996	R	72	56	63.4	60.8	56/16	42/14	29(40.3)	9(16.1)	31(43.0)	25(44.6)	12(16.7)	22(39.3)
Yoshino	Japan	1997	R	29	29	60.6	58.2	26/3	23/6	9(31.0)	9(31.0)	12(41.4)	12(41.4)	8(27.6)	8(27.6)
Suen	USA	1999	R	58	142	63.7	66.5	41/17	81/61	18(31.0)	37(26.1)	28(48.3)	46(32.4)	12(20.7)	59(41.5)
Okada	Japan	2000	R	60	60	60.9	60.6	52/8	53/7	U	U	U	U	U	U
Ghiribelli	Italy	2002	R	38	127	65.0	62.4	36/2	102/25	16(42.1)	29(22.8)	10(26.3)	43(33.9)	12(31.6)	55(43.3)
Martin	UK	2002	P	38	81	65.0	63.0	27/11	63/18	10(26.3)	10(12.3)	16(42.1)	32(39.5)	12(31.6)	39(48.2)
Deslauriers	Canada	2004	R	184	1046	60.0	60.7	152/32	827/219	82(44.6)	164(15.7)	72(39.1)	361(34.5)	30(16.3)	521(49.8)
Bagan	France	2005	R	66	151	60.7	58.2	58/8	138/13	40(60.6)	35(23.2)	14(21.2)	35(23.2)	12(18.2)	81(53.6)
Ludwig	Germany	2005	R	116	194	62.0	59.0	U	U	31(26.7)	32(16.5)	41(35.4)	52(26.8)	44(37.9)	110(56.7)
Kim	Korea	2005	R	49	49	58.7	58.1	44/5	46/3	14(28.6)	24(49.0)	20(40.8)	13(26.5)	15(30.6)	12(24.5)
Lausberg	Germany	2005	R	171	63	62.1	60.9	136/35	56/7	33(19.3)	7(11.1)	80(46.8)	32(50.8)	58(33.9)	24(38.1)
Jiménez	Spain	2006	R	35	220	62.0	62.0	34/1	205/15	U	U	U	U	U	U
Takeda	Japan	2006	R	62	110	61.1	59.3	46/16	92/18	26(41.9)	24(21.8)	19(30.7)	14(12.7)	17(27.4)	72(65.5)
Kawaguchi	Japan	2008	R	26	34	68.0	59.0	18/8	30/4	7(26.9)	7(20.6)	8(30.8)	11(32.4)	11(42.3)	16(47.0)
Melloul	Switzerland	2008	R	69	78	U	U	U	U	15(21.7)	28(35.9)	30(43.5)	21(26.9)	24(34.8)	29(37.2)
Balduyck	Belgium	2008	P	10	20	65.3	63.3	U	U	2(20.0)	3(15.0)	1(10.0)	9(45.0)	7(70.0)	8(40.0)
Hanagiri	Japan	2009	R	24	72	65.1	64.7	18/ 6	61/11	5(20.8)	5(6.9)	8(33.3)	13(18.1)	11(45.9)	54(75.0)
Xie	China	2009	R	93	571	U	U	74/19	482/89	U	U	U	U	U	U
Parissis	Ireland	2009	R	79	129	64.5	65.5	54/25	91/38	U	U	U	U	U	U
Park	Korea	2010	R	105	105	61.3	62.2	99/ 6	98/7	44(41.9)	43(41.0)	32(30.5)	36(34.3)	29(27.6)	26(24.7)
Gomez-Caro	Spain	2011	R	55	21	63.5	62.4	51/ 4	18/3	33(60.0)	7(33.3)	20(36.4)	13(61.9)	2(3.6)	1(4.8)
Bölükbas	Germany	2011	R	31	29	73.6	74.2	25/ 6	25/4	5(16.1)	2(6.9)	17(54.8)	10(34.5)	9(29.1)	17(58.6)
Lee	Korea	2011	R	19	20	62.1	64.3	15/ 4	16/4	5(26.3)	8(40.0)	8(42.1)	5(25.0)	6(31.6)	7(35.0)
Maurizi	Italy	2013	R	39	39	63.0	59.2	28/ 11	30/9	17(43.6)	6(15.4)	10(25.6)	15(38.5)	8(20.5)	18(46.1)
Berry	USA	2014	R	35	52	63.5	60.9	21/ 14	36/16	0	0	22(62.9)	32(61.5)	13(37.1)	20(38.5)
Cusumano	Italy	2014	R	51	68	63.0	59.7	28/23	54/14	27(52.9)	26(38.2)	11(21.6)	18(26.5)	13(25.5)	24(35.3)
Pan	China	2014	R	70	35	72.9	72.8	63/ 7	33/2	14(20.0)	5(14.3)	35(50.0)	9(25.7)	21(30.0)	21(60.0)
Tagawa	Japan	2015	R	151	54	63.8	62.8	122/ 29	42/12	43(28.5)	2(3.7)	47(31.1)	7(13.0)	60(39.7)	44(81.5)
Andersson	Finland	2015	R	40	67	61.5	60.0	29/ 11	49/18	8(20.0)	16(23.9)	19(47.5)	26(38.8)	13(32.5)	25(37.3)
Ma	China	2016	R	58	42	58.5	57.8	50/8	40/2	0	0	30(51.7)	18(42.9)	28(48.3)	24(57.1)
Higuchi	Japan	2018	R	12	18	68.7	66.1	12/0	16/2	3	3	5	6	4	9
Total				1945	3782	63.6	62.2	1451/335	2833/639	536	541	647	914	491	1301
R:Retrospective P:Prospective J:Unknown				5727											

R: Retrospective, P: Prospective, U: Unknown

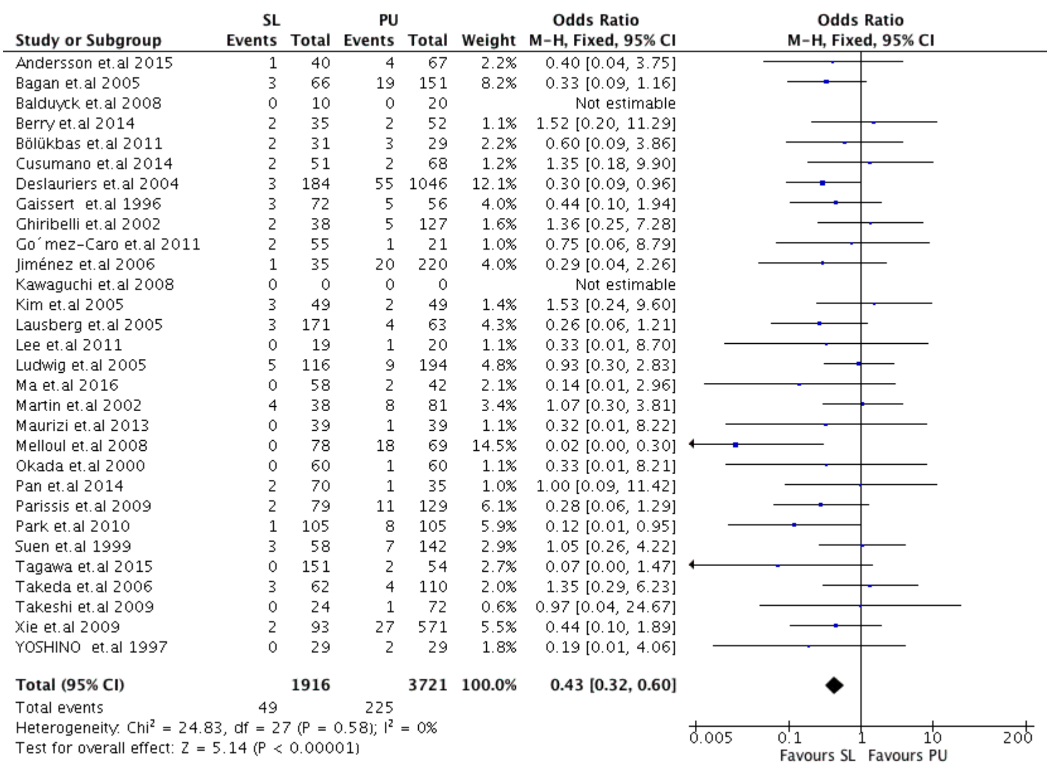

Figure 2. The meta-analysis of perioperative mortality rate between SL and PN group.

3.2. Assessment of locoregional recurrences

Eighteen studies reported the incidence of locoregional recurrences [2,3,5,6,8,11–23]. The meta-analysis showed the locoregional recurrence in SL was 12.2% compared with 8.98% in PN and demonstrated that there was no significant statistical difference in locoregional recurrences (OR = 1.25; 95% CI, 0.92 to 1.69; $P = 0.16$) between the two groups (**Figure 3**) or heterogeneity ($I^2 = 0\%$) among the studies. The cumulative meta-analysis accumulated the studies according to publication year and showed no evidence of increased recurrence rates.

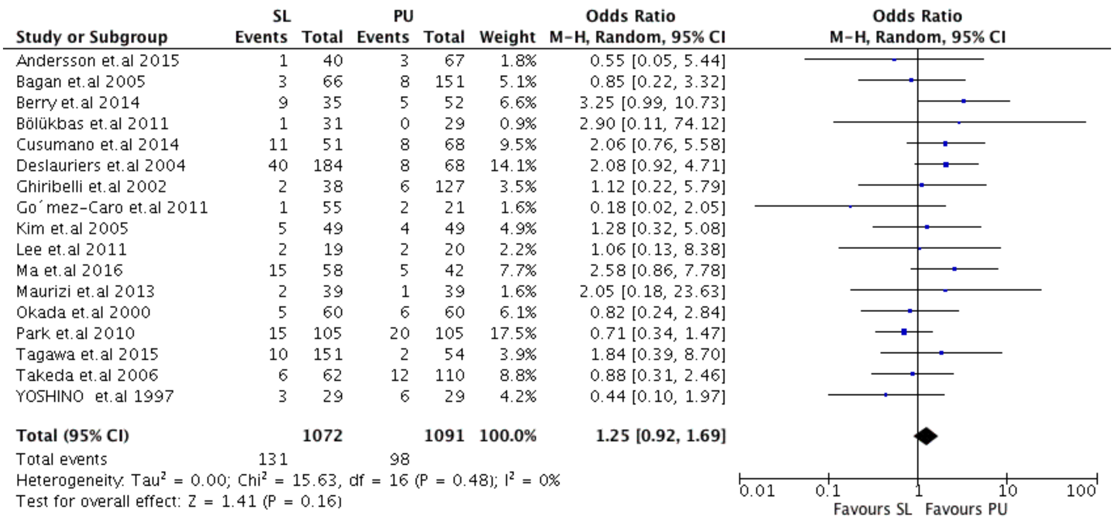

Figure 3. The meta-analysis of locoregional recurrences between SL and PN group.

3.3. Overall survival at 1 and 5 years

The survival difference at one year was derived from a total of 23 studies for examination. For the five-year survival difference, data were gathered from 22 studies. The odds ratios (ORs) consistently favored the SL group, showing significant results at both one year (0.14, 95% CI: 0.12 to 0.17, $p < 0.0001$, **Figure 4**) and five years (2.15, 95% CI: 1.77 to 2.61, $p < 0.0001$, **Figure 5**) regarding overall survival. The analysis revealed that the survival rates at one and five years were greater for the SL group compared to the PN group. Furthermore, there was no evidence of statistical heterogeneity among the included studies (one year: $I^2 = 17\%$, five years: $I^2 = 38\%$). For the cumulative meta-analysis, studies were organized chronologically according to their publication year. This analysis confirmed a significant difference in survival rates at both one and five years between the SL and PN groups.

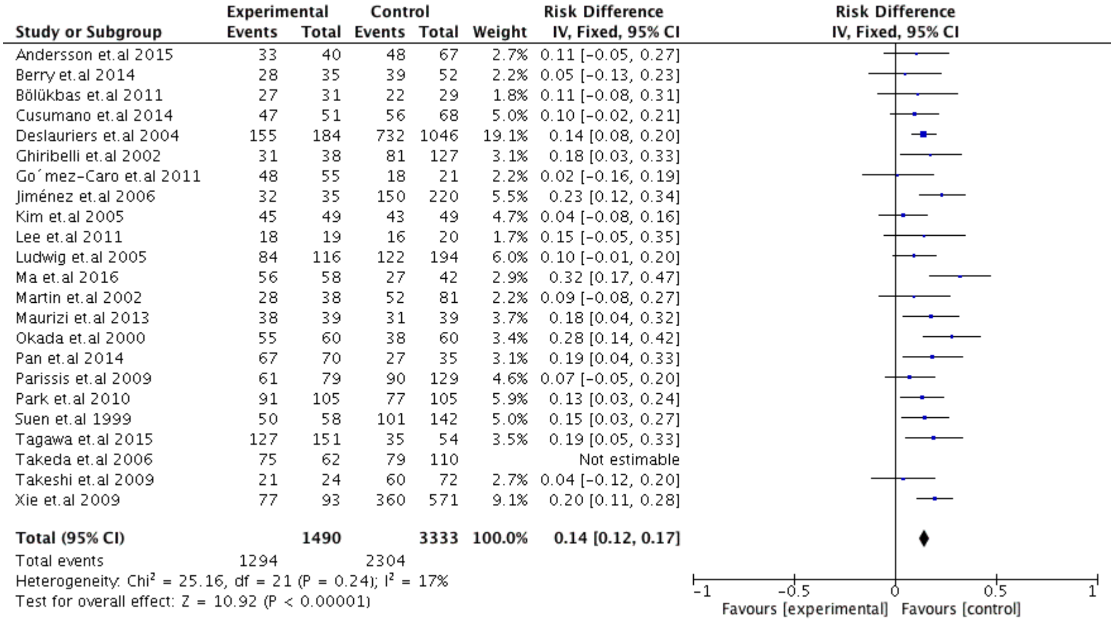

Figure 4. The meta-analysis of overall survival at 1 years between SL and PN group.

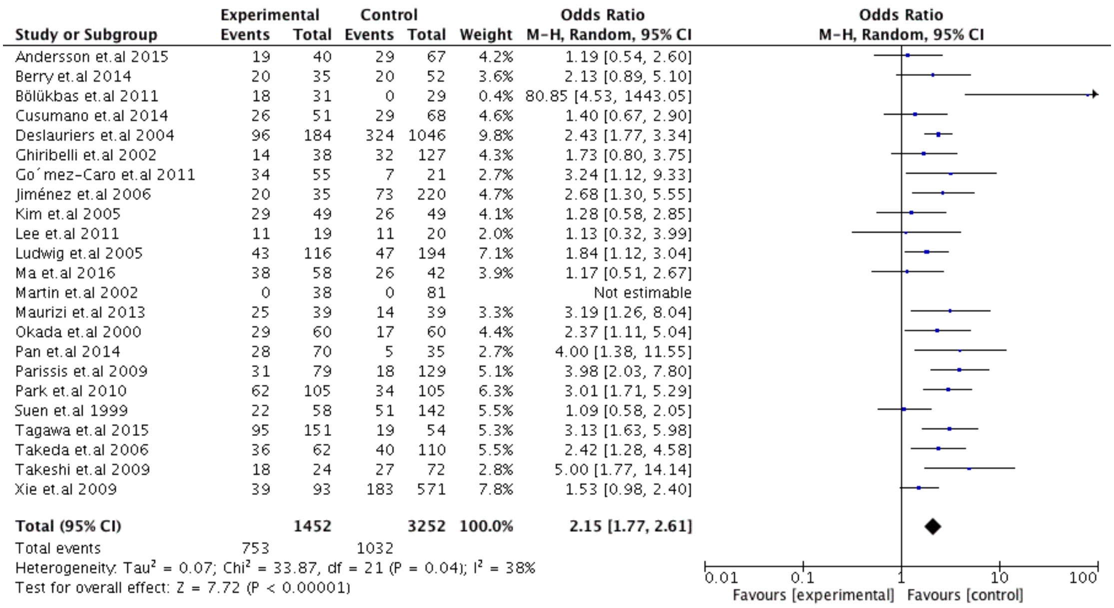

Figure 5. The meta-analysis of overall survival at 5 years between SL and PN group.

3.4. Differences of survival in patients with pN0 or pN1 and pN2 at 1 and 5 years

A total of five studies have reported on the survival rates of patients categorized as pN0 or pN1 over 1 and 5 years [5,12,15,17,24], illustrated in **Figure 6** and **Figure 7**. The meta-analysis revealed a notable survival advantage for patients with pN0 or pN1 at the 5-year mark (odds ratio = 0.13, 95% confidence interval 0.04 to 0.22; *P* = 0.006) when comparing SL to PN, showing no heterogeneity (I^2 = 17%) among the analyzed studies. Additionally, the survival difference at 1 year for patients with pN0 or pN1 between both groups was also significant (odds ratio = 0.13, 95% confidence interval 0.04 to 0.22; *P* = 0.003), although significant heterogeneity was present across studies (I^2 = 79%).

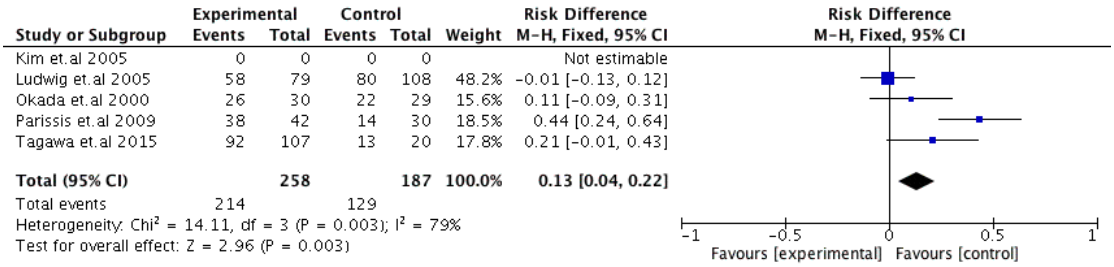

Figure 6. The meta-analysis of in patients with pN0 or pN1 at 1 years between SL and PN group.

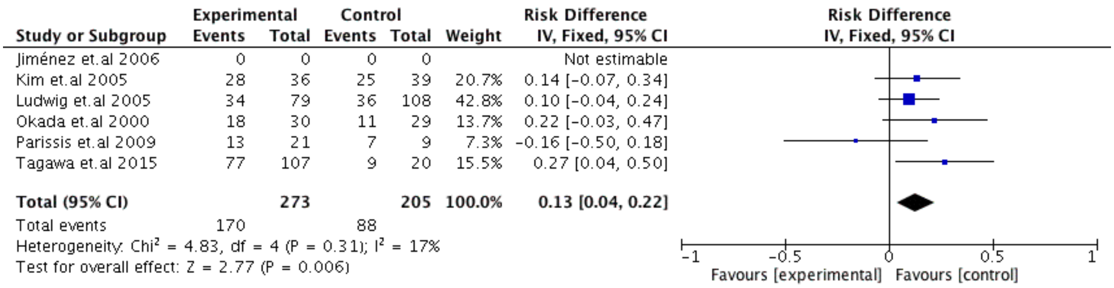

Figure 7. The meta-analysis of in patients with pN0 or pN1 at 5 years between SL and PN group.

Four studies compared the difference of survival in patients with pN2 at 1 and 5 years, respectively (1-year: OR = 1.90, 95% CI: 1.05 to 3.43, *P* = 0.03; 5-year: OR = 0.07, 95% CI: -0.05 to 0.19, *P* = 0.24; **Figure 8** and **Figure 9**).

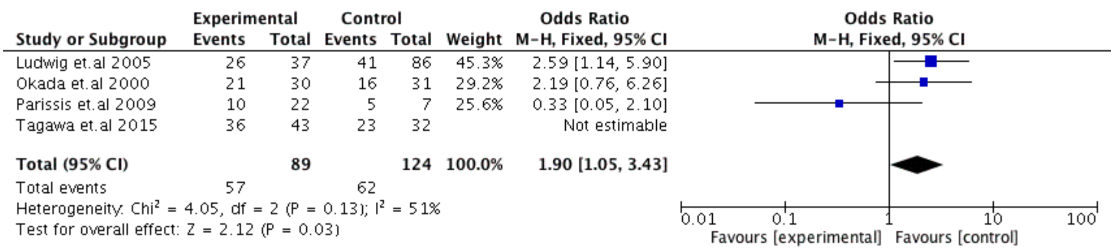

Figure 8. The meta-analysis of in patients with pN2 at 1 years between SL and PN group.

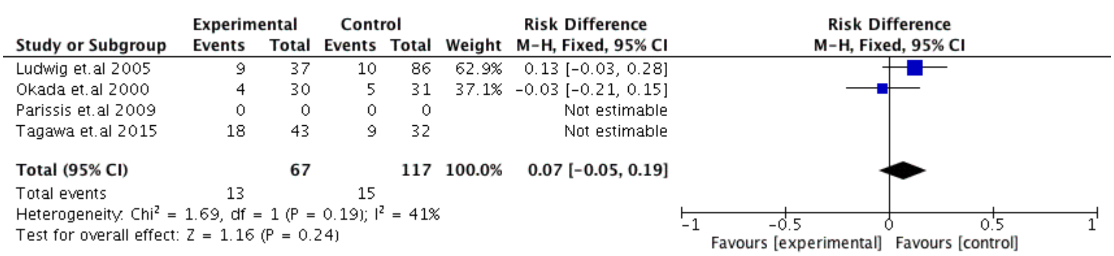

Figure 9. The meta-analysis of in patients with pN2 at 5 years between the SL and PN group.

3.5. Publication bias

The evaluation of publication bias utilized Begg's funnel plot and Egger's test across all findings. The funnel plots depicting the HR after SL and PN in the treatment of NSCLC exhibited signs of asymmetry, indicating potential publication bias. Additionally, Egger's test was conducted to offer statistical support for the symmetry of the funnel plots. However, the outcomes did not indicate any substantial evidence of publication bias.

4. Discussion

SL was initially introduced for NSCLC patients who were unable to tolerate a PN due to compromised lung function. The complexity of SL has been suggested to be associated with a high prevalence of bronchial anastomotic complications or high operative mortality and the incidence of local failure, compared with PN [25,26]. With increased experience in SL, this was progressively employed by most thoracic surgeons. It has been reported that SL offers a better quality of life than PN [27]. However, it is still important to answer the fundamental question of the adequacy of SL in satisfying surgical oncologic principles, as manifested by similar recurrence and survival results compared with PN. Numerous studies on SL were published, but no randomized controlled trials have compared SL and PN groups with respect to short-term outcomes or oncologic impact. In addition, many of these studies had limited sample sizes, making it difficult to draw definitive conclusions. Therefore, a cumulative meta-analysis provides an ideal statistical tool to increase the power of the comparisons and provide the best evidence currently available. Our data suggest that SL represents a valuable alternative surgical technique, with an acceptable risk of perioperative mortality and encouraging long-term outcomes, compared with PN. The use of the SL in NSCLC has expanded slowly. The main reason for the hesitation in performing SL is the uncertain oncologic efficacy, particularly regarding its potential for recurrence, when compared with PN. Tumor postoperative recurrence is the leading cause of late death in NSCLC patients. Concerns over the greater possibility of recurrence in SL might be related to technical reasons in the surgical management, or the risk of leaving residual tumor at the surgical margin [3,20,28].

Numerous investigations that compare segmental lobectomy (SL) and pneumonectomy (PN) suggest that survival rates following SL are generally similar to or may even exceed those after PN, contingent upon achieving a complete tumor resection. In the current meta-analysis, individuals who underwent SL displayed superior overall survival (OS) rates and enhanced 1- and 5-year survival compared to those who received PN. These results imply that SL effectively manages central or locally advanced lung cancer, allowing preservation of unaffected lung lobes, and indicate that SL could serve as a viable alternative to PN for non-small cell lung cancer (NSCLC). Nonetheless, one might contend that the apparent survival advantage associated with the SL technique could largely stem from the notable variation in cancer stage distributions between the SL and PN cohorts. A substantial portion of patients undergoing PN presented with more advanced tumor stages, particularly stage III. The connection between lymph node involvement and survival remains a topic of debate. In various studies, lymph node engagement by the tumor is often cited as a significantly adverse prognostic indicator concerning survival. Given the prevalent use of the SL technique, examining the outcomes related to survival and lymph node involvement among patients treated with either SL or PN is particularly pertinent. It is widely acknowledged that SL generally yields similar or improved outcomes compared to PN for patients with N0 or N1 disease; however, for those with N2 disease, PN tends to be the preferable option. A statistical evaluation conducted by Okada et al. revealed a notable difference that favored SL for patients with N0 or N1 disease. Conversely, a study by Kim et al. reported that the 3-year and 5-year survival rates in patients with N0 or N1 disease did not reach statistical significance.

Furthermore, Okada et al. observed that there were no significant variations in survival outcomes for patients with N2 disease, even though the findings tended to favor SL. Our meta-analysis identified a noteworthy difference in 5-year survival rates between patients with pN0 or N1 who underwent SL and those who received PN, while the survival rate for those with pN2 disease did not show any significant difference. Additionally, at 1 year, the survival rates between SL and PN for patients categorized as either pN0-pN1 or pN2 did not reach statistical significance. These results indicate that SL continues to provide survival rates comparable to those for individuals with N2 disease. In light of the association analysis, these outcomes imply that even for advanced-stage tumors, a more extensive procedure like PN may not be the optimal option and does not inherently lead to better survival rates. Therefore, it can be concluded that nodal status ought not to be regarded as a strong justification against the adoption of SL.

Limitations inherent to this type of analysis must be taken into account when evaluating its significance for informing clinical practice. To begin with, our search was restricted to a few specific databases, and we only considered literature published in English, potentially introducing bias that could affect the findings. Additionally, due to the lung-conserving benefits of sleeve resection, conducting a randomized controlled trial presents challenges; consequently, further prospective studies are recommended. Moreover, the majority of comparative studies included in our review were nonrandomized and retrospective, which could influence the outcomes of our analysis. Furthermore, there was a notable disparity in stage distribution between the SL and PN groups, which could yield unreliable results favoring SL. The influence of a learning curve is a recognized phenomenon that occurs with the introduction of new complex procedures; however, we could not evaluate how this factor impacted our procedure. Lastly, some hazard ratio estimates were derived from the available data or Kaplan-Meier survival curves, relying on extrapolation and assumptions regarding censoring patterns. Lastly, inconsistencies were observed in the follow-up durations across the selected studies.

5. Conclusion

In conclusion, existing research indicates that surgical lobectomy (SL) is both viable and safe for certain patients, without raising mortality rates when compared to partial nephrectomy (PN). It may represent a legitimate alternative if conducted in accredited centers for non-small cell lung cancer (NSCLC) treatment. The SL and PN approaches for NSCLC showed similar outcomes in terms of local regional recurrence, although SL appeared to yield lower survival rates than those associated with PN. Nevertheless, in light of the variability among the studies and the intrinsic limitations of data derived from retrospective analyses, the findings of this meta-analysis must be approached with caution. Additional research is necessary to further clarify the role of SL in managing NSCLC.

Disclosure statement

The authors declare no conflict of interest.

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