ORIGINAL ARTICLE

Clinical Benefits of Lobe-Specific Lymph Node Dissection in Surgery for NSCLC: A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: The impact of lobe-specific lymph node dissection (LS-LND) in surgery for NSCLC remains controversial compared with that of systematic lymph node dissection (S-LND). This study aimed to compare clinical outcomes between the two strategies, including postoperative complications, and to explain the advantages of LS-LND.

Methods: We searched for studies comparing LS-LND and S-LND up to April 14, 2022, using PubMed, EMBASE, and Web of Science. The primary outcomes were overall survival and recurrence-free survival. Secondary outcomes included postoperative complications, such as arrhythmia, chylothorax, and pneumonia. We evaluated the risk of bias and assessed the evidence quality using GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Results: A total of 13 studies, including one randomized controlled trial and 12 retrospective studies with 11,522 patients who underwent curative resections for lung cancer, were included. The results indicated that LS-LND had favorable overall survival (hazard ratio [HR] = 0.80, 95% confidence interval [CI]: 0.73–0.87) but no difference in recurrence-free survival (HR = 0.96, 95% CI: 0.84–1.09) on comparison with S-LND. In terms of postoperative complications, patients undergoing LS-LND had a lower rate of chylothorax (risk ratio [RR] = 0.54, 95% CI: 0.35–0.85) and arrhythmia (RR = 0.74, 95% CI: 0.57–0.97) than patients undergoing S-LND, but the risk of postoperative pneumonia was not different. The overall quality of evidence was low to moderate owing to the risk of bias related to heterogeneous study populations.

Conclusions: Patients undergoing LS-LND had a comparable and favorable long-term prognosis and a lower rate of postoperative complications. Nevertheless, further standardized studies are necessary to improve the quality of evidence.

Keywords: Lymph node dissection; Lung cancer; Non–small cell lung cancer; Surgery

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Introduction

Global cancer statistics 2020 revealed that lung cancer is the second most often diagnosed cancer and the leading cause of cancer death, representing approximately 1 in 5 deaths (18.0%).[1] With the development of lung cancer screening programs, patients with early-stage lung cancers have increased, and their long-term survival rates have shown much progress.[2,3] Lobectomy has for a long period, since the early 1960s, remained the most standard procedure in the management of lung cancers; however, there have been considerable advancements in the surgical management of early-stage lung cancer.[4] One of the recent management considerations was outlined in the JCOG0802/WJOG4607L trial, which exhibited the benefit of segmentectomy over lobectomy in specific patients with clinical stage IA, small-sized peripheral NSCLC.[5]

However, the appropriate method for mediastinal lymph node dissection remains a critical issue among thoracic surgeons. The American College of Surgery Oncology Group (ACSOG Z0030) 101 trial,[6] comparing systematic lymph node dissection (S-LND) and systematic nodal sampling (SS), revealed no significant survival benefit of S-LND over SS; thus, SS was introduced in clinical practices.[7] Other than this, the necessity of S-LND for all locations of the tumor was questioned based on the pattern of N2 metastasis results according to tumor locations.[8] Hence, in 2006, Okada et al.[9] first reported comparative clinical outcome of S-LND and lobe-specific lymph node dissection (LS-LND). Following this study, much discussion has been initiated regarding the definition and standardization of this procedure.

LS-LND means selective mediastinal lymph node dissection according to the location of primary tumor and lobe-specific lymph node metastasis pattern. It assumes a rare possibility of distant skipping N2 metastasis. When the tumor was located in the right upper lobe, the upper mediastinal lymph nodes are selectively dissected. The concept of LS-LND have been improved and well solidified since its first introduction in early 2000, but there is minor variability in the thoroughness of lymph node dissection and difference in domestic and overseas.

Of the studies conducted, one randomized controlled trial (RCT) was performed in 2013, forming a reference point, and currently, a multi-institutional retrospective study by Hishida et al.[10] remains as an important study in this issue. Despite the large-scale nature of this study, it raises several important issues of concern, such as the selection process and ambiguity in patient descriptions. The prospective randomized clinical trial by the Japanese Clinical Oncology Group (JCOG1413) is in progress and we expect it will clearly deliver the clinical evidence of LS-LND in the future; but it would be important to review this topic before have the result from JCOG1413.[11]

This study aimed to comprehensively review and meta-analyze studies on the clinical impact of LS-LND and suggest more reasonable clinical guidelines utilizing the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Materials and Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist (Supplementary Table 1).

Search Strategy and Study Selection

We searched MEDLINE/PubMed, EMBASE, and Web of Science databases up to April 14, 2022. The search terms used are listed in Supplementary Table 2. Two authors (WW and VK) independently reviewed titles and abstracts, and any disagreements were resolved by consulting with a third author (CYL). The full literature search strategy and selection process are shown in Supplementary Figure 1. We included studies that compared LS-LND and S-LND. The exclusion criteria were as follows: (1) studies without hazard ratios (HRs) or Kaplan-Meier survival curves comparing the two surgical strategies and (2) studies describing the clinical outcome of one strategy. All studies were limited to those involving human participants and those in English. Abstracts, case reports, conference presentations, editorials, and reviews were also excluded.

Data Extraction

The primary outcomes of interest were overall survival (OS) and recurrence-free survival (RFS). The secondary outcomes included early mortality and postoperative complications, such as pneumonia, arrhythmia, prolonged air leakage, and chylothorax. Other extracted data included patients' demographics, number of participants, description of surgical procedures, and pathologic reports.

Two authors (WW and VK) extracted data from article texts, tables, figures, and supplementary materials. They independently reviewed and evaluated the quality of each study, and any discrepancies between them were resolved by a thorough discussion with two other authors (CYL and SL).

Statistical Analysis

We evaluated the outcomes of LS-LND and S-LND using HR and 95% confidence interval (CI) for OS and RFS. If the relevant data were not described, the HR and 95% CI were calculated from digitized images of Kaplan-Meier curves using Digitizelt software 2.5. Parmar and

Table 1. Eligibility Criteria for Included Studies

					Number of Participants			Inclusion Criteria		Exclusion Criteria			
Author	Year	Country	Study Design	Study Period	Total	S-LND	LS-LND	Staging (Eighth)[a]	Additional Criteria	Neoadjuvant CTx ± RTx	Sublobar Resection	RML	Others
Kuroda	2021	Japan	Retrospective	2006-2017	799	265	534	cIA-IIIB cT1-4N0-2M0	NSCLC with CEA level	Y	Y		No CEA level Limited MLND[b]
Handa	2021	Japan	Retrospective	2010-2018	375	128	247	cIB-IIIA cT2-3N0-1M0	Hypermetabolic on PET/CT		Y	Y	SUVmax <6.6, No MLND
Hattori	2021	Japan	Retrospective	2008-2016	459	181	278	cIA-IB cT1/2aN0M0	Pure-solid lesion, PET/CT evaluation	Y	Y	Y	Nonpure solid, Limited MLND[b]
Zhao	2021	People's Republic of China	Retrospective	2014-2017	546	446	100	cIA cT1a-cN0M0	Solid dominant lesion	Y	Y	Y	C/T ratio <0.5, multiple lesions
Wang	2019	People's Republic of China	Retrospective	1999-2014	905	328	577	pT1a-2aN0M0		Y	Y		Multiple lesions
Adachi	2017	Japan	Retrospective	2005-2007	335	190	145	cT1-3N0-1M0		Y	Y	Y	
Hishida	2016	Japan	Retrospective	2004-2010	5392	4124	1268	cIA-IIIA cT1-4N0-1M0		Y	Y	Y	No or extended MLND
Shapiro	2013	USA	Retrospective	2004-2011	370	282	88	cIA-IIIA		Y			pN2, multiple lesions
Ma	2013	People's Republic of China	RCT	2004-2008	96	51	45	cIA-IB cT1a-bN0M0		Y			
Maniwa	2013	Japan	Retrospective	2002-2008	335	206	129	cIA-IIIA		Y			Multiple lesions
Jiang	2013	People's Republic of China	Retrospective	2005-2008	403	309	94	cIA-IIA		Y	Y		
Ishiguro	2010	Japan	Retrospective	1995-2003	772	625	147	cIA-IIIC		Y	Y		
Okada	2006	Japan	Retrospective	1997-2002	735	358	377	cIA-IIIA		Y			Surgical N1-2

[a]Re-iterated based on the eighth TNM staging.
[b]Limited MLND: only with hilar dissections.
C/T ratio, consolidation/tumor ratio; CEA, carcinoembryonic antigen; CTx, chemotherapy; LS-LND, lobe-specific lymph node dissection; MLND, mediastinal lymph node dissection; PET-CT, positron emission tomography-computed tomography; pN2, pathologic N2; RCT, randomized controlled trial; RML, right middle lobe; RTx, radiotherapy; S-LND, systematic lymph node dissection; SUVmax, maximum standard unit value; Y, yes.

Table 2. Demographic, Operative, and Pathologic Characteristics of Included Studies

	Male		Smoker		Open Thoracotomy		Lobectomy		Adenocarcinoma		Pathologic N1		Pathologic N2	
Study	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND
Kuroda et al.[21]	157/265 (59.2)	328/534 (61.4)			240/265 (90.6)	407/534 (76.2)	235/265 (88.7)	529/534 (99.1)	183/265 (69.1)	388/534 (72.7)				
Handa et al.[24]	93/128 (72.7)	186/247 (75.3)					128/128 (100.0)	247/247 (100.0)	70/128 (54.7)	113/247 (45.7)				
Hattori et al.[23]	116/181 (64.1)	188/278 (67.6)					181/181 (100.0)	278/278 (100.0)	128/181 (70.7)	191/278 (68.7)	24/181 (13.3)	28/278 (10.1)	41/181 (22.7)	34/278 (12.2)
Zhao et al.[16]	218/456 (47.8)	36/100 (36.0)			75/456 (16.4)	14/100 (14.0)	456/456 (100.0)	100/100 (100.0)	368/456 (80.7)	92/100 (92.0)	30/456 (6.6)	5/100 (5.0)	9/46 (19.6)	2/100 (2.0)
Wang et al.[17]	204/328 (62.2)	359/577 (62.2)	133/328 (40.5)	217/577 (37.6)			308/328 (93.9)	552/577 (95.7)	239/328[a] (72.9)	462/577[a] (80.1)				
Adachi et al.[25]	122/190 (64.2)	97/145 (66.9)	133/190 (70.0)	103/145 (71.0)	135/190 (71.1)	30/145 (20.7)	190/190 (100.0)	145/145 (100.0)	128/190 (67.4)	99/145 (68.2)	21/190 (11.1)	11/145 (7.6)	25/190 (13.2)	13/145 (9.0)
Hishida et al.[10]	2471/4124 (59.9)	780/1268 (61.5)	2225/4124 (54.0)	669/1268 (52.8)			4124/4124 (100.0)	1268/1268 (100.0)	3074/4124 (74.5)	944/1268 (74.4)				
Shapiro et al.[18]	123/282 (43.6)	39/88 (44.3)	220/282 (78.0)	70/88 (79.5)	96/282 (34.0)	44/88 (50.0)	282/282 (100.0)	88/88 (100.0)	211/282 (74.8)	63/88 (71.6)	26/282 (9.2)	10/88 (11.4)	15/282 (5.3)	9/88 (10.2)
Ma et al.[20]											4/51 (7.8)	3/45 (6.7)	8/51 (15.7)	5/45 (11.1)
Maniwa et al.[19]	115/206 (55.8)	55/98 (56.1)							158/206 (76.7)	65/98 (66.3)	17/206 (8.3)	8/98 (8.2)	16/206 (7.8)	4/98 (4.1)
Jiang et al.[15]	173/309 (56.0)	59/94 (62.8)			217/309 (70.2)	55/94 (58.5)			211/309 (68.3)	55/94 (58.5)	29/309 (9.4)	10/94 (10.6)	59/309 (19.1)	17/94 (18.1)
Ishiguro et al.[22]	390/625 (62.4)	84/147 (57.1)					522/625 (83.5)	140/147 (95.2)	436/625 (69.8)	117/147 (79.6)				
Okada[9]	240/358 (67.0)	234/377 (62.1)							233/358 (65.1)	274/377 (72.7)	19/358 (5.3)	21/377 (5.6)	3/358 (0.8)	2/377 (0.5)

Note: Data are presented as n/N (%).
[a]Nonsquamous cell types, which are mostly adenocarcinoma.
LS-LND, lobe-specific lymph node dissection; S-LND, systematic lymph node dissection.

Table 3. Clinical Outcomes of Included Studies According to LS-LND and S-LND														
	5-year overall survival rate			5-Year Recurrence-Free Survival Rate			Early Mortality		Postoperative Pneumonia		Chylothorax		Arrhythmia	
Study	S-LND	LS-LND	*p*-Value	S-LND	LS-LND	*p*-Value	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND	S-LND	LS-LND
Kuroda et al.[21]	60.2	69.0	0.09[a]	35.6	44.0	0.11[a]								
Handa et al.[24]	81.6	75.5	0.17	57.2	58.5	0.53								
Hattori et al.[23]	78.8	79.9	0.665	70.4	66.5	0.669	90 d 1/181	90 d 3/278	4/181	9/278	14/181	4/278	20/181	28/278
Zhao et al.[16]	92.0	96.7	0.411	88.8	95.6	0.130							3/100	1/100
Wang et al.[17]	80.0	77.5	>0.05	75.0	70.5	>0.05								
Adachi et al.[25]	75.3	73.5	0.977[a]											
Hishida et al.[10]	75.9	81.5	<0.001				19/4124 in-hospital	5/1268 in-hospital	78/4124	15/1268	55/4124	13/1268	127/4124	32/1268
Shapiro et al.[18]	82.0	89.0	0.36	68.0	74.0	0.12	2/282	0/88						
Ma et al.[20]	64.9	69.7	0.552	60.8	66.0	0.241			5/51	2/45	2/51	0/45	2/51	1/45
Maniwa et al.[19]	89.7	86.6	0.526	77.7	76.4	0.607	0/206	0/129	3/206	3/129	6/206	3/129	20/206	6/129
Jiang et al.[15]	74.6	68.5	0.216				0/309	0/94	14/309[b]	7/94[b]				
Ishiguro et al.[22]	71.9	76.0	0.29											
Okada et al.[9]	79.7	83.2	0.060	73.4	76.4	0.376			15/358	6/377	4/358	2/377	19/358	12/377

[a]The results of propensity-score matched comparison.
[b]Including all postoperative morbidity.
LS-LND, lobe-specific lymph node dissection; S-LND, systematic lymph node dissection.

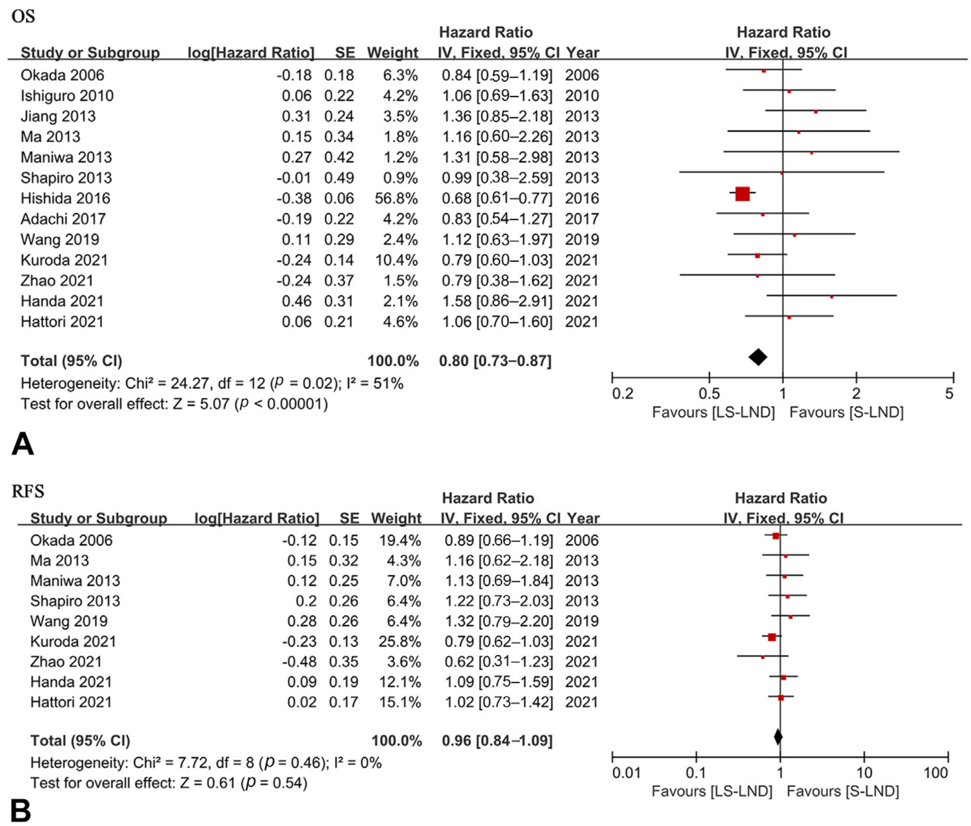

Figure 1. Forest plots for OS and RFS rate. CI, confidence interval; LS-LND, lobe-specific lymph node dissection; OS, overall survival; RFS, recurrence-free survival; S-LND, systematic lymph node dissection.

Tierney methods for HR analysis were implemented.[12,13] Clinical outcomes, which were meta-analyzed, were presented as risk ratio (RR) and 95% CI. I^2 statistics were used to evaluate heterogeneity, and I^2 greater than 50% was considered to represent significant heterogeneity. The fixed and random effects models were used to reveal each comparison between LS-LND and S-LND according to the heterogeneity among studies. In

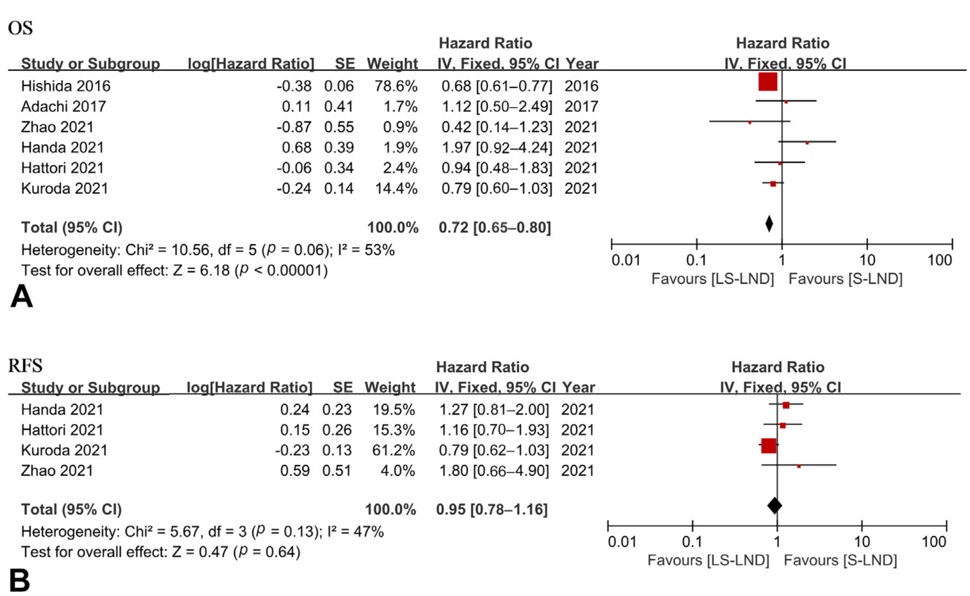

Figure 2. Forest plots for OS and RFS of propensity-score matched studies. CI, confidence interval; LS-LND, lobe-specific lymph node dissection; OS, overall survival; RFS, recurrence-free survival; S-LND, systematic lymph node dissection.

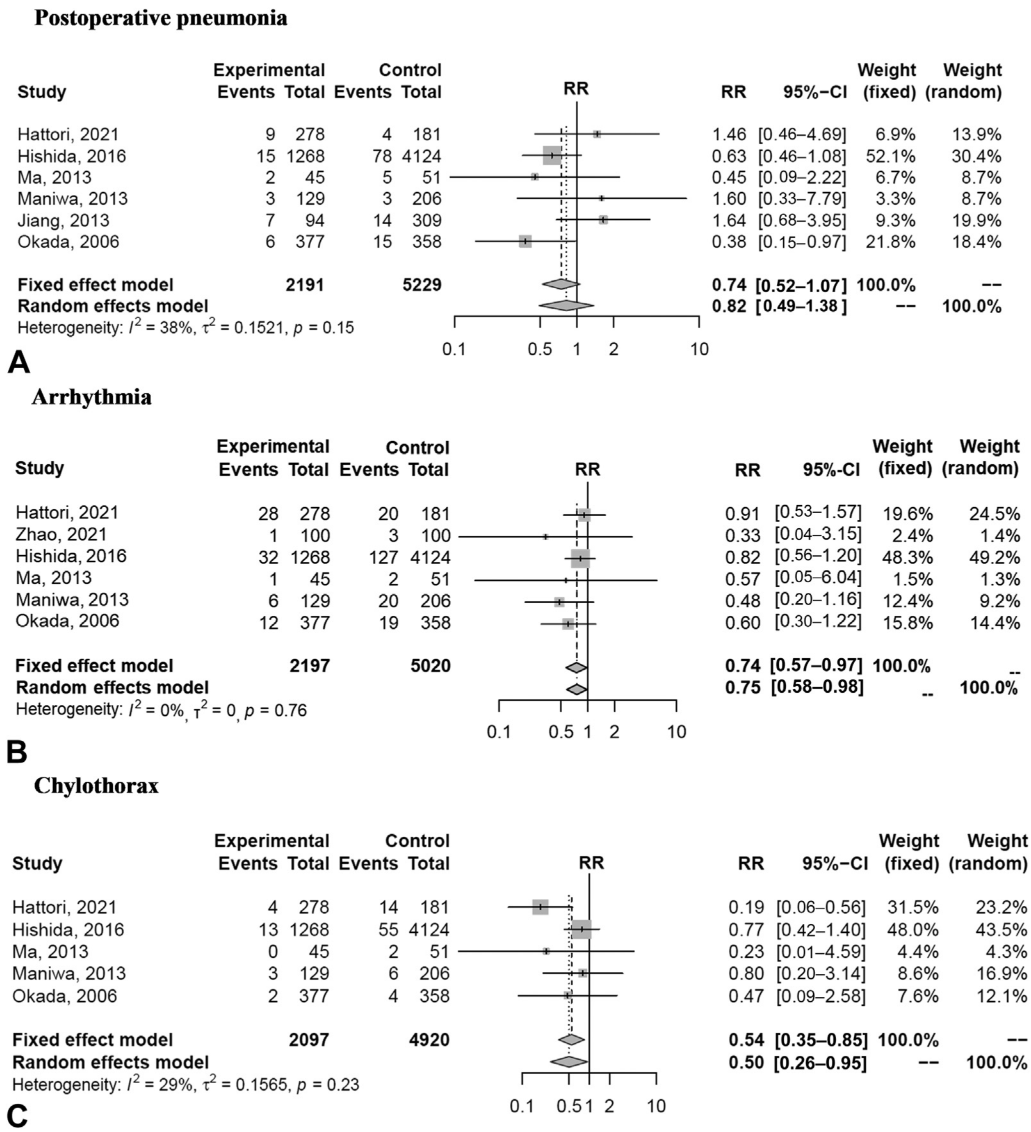

Figure 3. Forest plots for postoperative complications. CI, confidence interval; RR, risk ratio.

addition, funnel plots were used to assess and visualize publication bias and other possible sources of asymmetry.

Statistical significance was defined as a two-sided p value less than 0.05. Statistical analyses were performed using R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and Review Manager (RevMan) software version 5.2.3 (The Nordic Cochrane Centre, Copenhagen, Denmark).

Assessment of Risk of Bias

Because most studies were retrospectively designed, study quality was measured using the Risk of Bias Assessment of Non-randomized Studies (RoBANS) for retrospective studies. Version 2 of the Cochrane risk of bias tool (RoB 2) for randomized studies was used for one RCT included in this study. Moreover, using the GRADEpro program,[14] the list of outcomes was shared among authors, and the evaluation was finalized according to several discussions. Two surgical experts (SL and CYL) and two specialists (JIS and WW) with GRADE training comprised this group. After integrating opinions from others, the evidence table was finalized, and perceived importance was listed.

Results

Systematic Search

From the systematic search, a total of 280 studies were identified. After excluding articles based on titles and abstracts, 107 studies remained for further analyses. Finally, 13 studies were included in the detailed meta-analysis (Supplementary Fig. 1).[9,10,15–25]

Version 2 of the Cochrane risk of bias tool (ROB 2) for RCT comparing LS-LND and S-LND

Study	Risk of bias domains					
	D1	D2	D3	D4	D5	Overall
Ma et al., 2013	!	+	+	+	+	!

A

Risk of Bias assessment tool for Non-randomized Studies (RoBANS) comparing LS-LND and S-LND

STUDY	RISK OF BIAS					
	SELECTION OF PARTICIPANTS	CONFOUNDING VARIABLES	INTERVENTION (EXPOSURE) MEASUREMENT	BLINDING OF OUTCOME ASSESSMENT	INCOMPLETE OUTCOME DATA	SELECTIVE OUTCOME REPORTING
Ishiguro et al., 2010	Low	Low	Low	Low	Low	Low
Hattori et al., 2021	Low	Low	Low	Low	Unclear	Low
Wang et al., 2019	Low	Low	High	Low	Low	Low
Adachi et al., 2016	Low	Low	Low	Low	Low	Low
Zhao et al., 2020	Low	Low	Low	Low	Low	Low
Shapiro et al., 2013	Low	Low	High	Low	Low	Low
Hishida et al., 2016	High	High	High	Low	Unclear	Unclear
Kuroda et al., 2021	Low	Low	Low	Low	Unclear	Low
Maniwa et al., 2013	High	High	Low	Low	Low	Low
Okada et al., 2006	Low	Low	High	Low	Low	Low
Jiang et al., 2013	Low	High	High	Low	Low	Low
Handa et al., 2021	Low	Low	Low	Low	Unclear	Low

B

Figure 4. RoB assessment for included studies. High RoB in selection of participants: lack of detailed description regarding eligibility criteria or possibility of having inadequately selected patients. High RoB in confounding variables: inadequate confirmation and adjustments for confounding variables or lack of propensity-score matching. High RoB in intervention measurement: insufficient description of surgical extent and the presence of right middle lobar lesions. LS-LND, lobe-specific lymph node dissection; RoB, risk of bias; S-LND, systematic lymph node dissection.

Patients and Surgical Characteristics

Table 1 shows the eligibility criteria for the included studies. Four studies had additional inclusion criteria, such as radiologic[16,23,24] or laboratory variables.[21] Most studies excluded patients who underwent neoadjuvant treatment and sublobar resection. Only five studies revealed explicitly precluded main lesions in the right middle lobe. Detailed patient demographics and pathologic results are delineated in Table 2; the proportion of adenocarcinoma was ranged from 45.7% to 92.0% in LS-LND and 54.7% to 80.7% in S-LND.

In terms of surgical procedures, the surgical extent has been modified because LS-LND was firstly suggested by Okada et al.[9] Though there was some variability in the lymph nodes that should be removed, six recent studies[10,16,21,23–25] had the same description, which represented an improved and well-established current practice (Supplementary Table 3).

Survival Outcomes

The primary outcomes were assessed in all included studies, and the 5-year OS and RFS are listed in Table 3. In a pooled analysis, patients undergoing LS-LND had favorable OS compared with those undergoing S-LND, as shown in Figure 1*A* (HR = 0.80, 95% CI: 0.73–0.87, I^2 = 51%, p = 0.02). To minimize the effect of confounding variables, six propensity-score matched studies were integrated, and similar results were observed (HR for LS-LND = 0.72, 95% CI: 0.65–0.80) (Fig. 2*A*). In terms of RFS, LS-LND was comparable to S-LND in all studies (HR = 0.96, 95% CI: 0.84–1.09, I^2 = 0%, p = 0.46), including propensity-score matched ones (HR = 0.95, 95% CI: 0.78–1.16) (Figs. 1*B* and 2*B*). The factors that were adjusted in propensity-score matching are presented in Supplementary Table 4. Though there were some differences in radiological or pathologic variables for propensity-score matching analysis, all studies were well adjusted in age, sex, tumor size, and clinical stages. Therefore, the results could be interpreted as relatively uniformly adjusted analysis.

Postoperative Complications

Early mortality did not differ between LS-LND and S-LND on the basis of a pooled analysis of five studies (RR for LS-LND = 0.95, 95% CI: 0.40–2.23) (Supplementary Fig. 2). Seven studies reported the incidence of postoperative complications (Table 3). Patients undergoing LS-LND had a lower rate of arrhythmia (Fig. 3*B*, RR = 0.74, 95% CI: 0.57-0.97, I^2 = 0%, p = 0.76) and chylothorax (Fig. 3*C*, RR = 0.54, 95% CI: 0.35–0.85, I^2 = 29%, p = 0.23). Others, such as postoperative pneumonia (Fig. 3*A*, RR = 0.74, 95% CI: 0.52–1.07, I^2 = 38%, p = 0.15) and prolonged air leakage (RR = 0.94, 95% CI: 0.74–1.20, I^2 = 0%, p = 0.43), were not significantly different (Fig. 3 and Supplementary Fig. 3)

Quality Assessment and RoB

A summary of the findings from the quality assessment using the RoBANS and RoB 2 tools is shown in Figure 4. One RCT was assessed using the RoB 2 tool

Table 4. GRADE Table Describing the Quality of Evidence and Importance of Recommendations

Certainty Assessment							No of Patients		Effect			
No. of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	LS-LND	S-LND	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Overall survival												
13	Observational studies	Serious[a]	Serious[b]	Not serious	Not serious	None	4029 participants	7493 participants	HR 0.80 (0.73-0.87) [death]		⊕⊕◯◯ Low	CRITICAL
Recurrence-free survival												
9	Observational studies	Serious[a]	Not serious	Not serious	Not serious	None	2375 participants	2245 participants	HR 0.96 (0.84-1.09) [recurrence and death]		⊕⊕⊕◯ Moderate	CRITICAL
Postoperative arrhythmia												
6	Observational studies	Serious[a]	Not serious	Not serious	Not serious	None	80/2197 (3.6%)	191/5020 (3.8%)	RR 0.74 (0.57-0.97)	10 fewer per 1000 (from 16 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	CRITICAL
Postoperative chylothorax												
5	Observational studies	Serious[a]	Not serious	Not serious	Not serious	None	22/2097 (1.0%)	81/4920 (1.6%)	RR 0.54 (0.35-0.85)	8 fewer per 1000 (from 11 fewer to 2 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT
Postoperative pneumonia												
6	Observational studies	Serious[c]	Serious[b]	Not serious	Not serious	None	42/2191 (1.9%)	119/5229 (2.3%)	RR 0.74 (0.52-1.07)	6 fewer per 1000 (from 11 fewer to 2 more)	⊕⊕◯◯ Low	CRITICAL

[a]There was a significant bias in intervention measurement.
[b]Studies revealed different outcomes.
[c]Diagnostic criteria for postoperative pneumonia was obscure.
CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; LS-LND, lobe-specific lymph node dissection; RR, risk ratio; S-LND, systematic lymph node dissection.

(Fig. 4*A*). The RoB judgment for randomization process was rated as "some concerns" owing to the lack of details in the manuscript on whether the allocation sequence was concealed until participants were enrolled and assigned to interventions. Other noted concerns included a lack of mention of whether there was any blinding of the investigators during the outcome assessment. The other domains displayed a low RoB with an overall bias risk rated as "some concerns."

The remaining 12 retrospective studies were assessed using the RoBANS tool (Fig. 4*B*). There was a low RoB in selection of participants. Three studies revealed a high RoB in dealing with confounding variables. There was a significantly high RoB in intervention measurement because the intervention was not described in enough detail for it to be reproduced, or there was the possibility of having different strategies according to the involved institutions.

The quality of evidence comparing RFS and OS between the two methods was moderate and low, respectively. For major postoperative complications, the certainty of the evidence was moderate, except for postoperative pneumonia; the superiority of LS-LND in preventing arrhythmia and chylothorax was observed on the basis of the GRADE approach (Table 4).

Publication Bias

Supplementary Figures 4 and 5, reveal funnel plots for OS and RFS. Regarding OS, the funnel plot revealed asymmetry and the existence of small study effects. This could be owing to the selective outcome reporting and poor methodological design as most studies were conducted retrospectively.

Discussion

Recently published multicenter prospective study by Zhang et al. suggested criteria (consolidation tumor ratio $\leq$0.5, segment location, lipidic-predominant adenocarcinoma, negative hilar nodes, negative visceral pleural invasion) that predict negative node involvement and validated the necessity of selective lymph node assessment in cT1N0 patients.[26] Owing to advancements in surgical techniques for patients with lung cancer, it is important to review the role of LS-LND in comparison with that of S-LND by incorporating recent studies. Moreover, it is critical to identify possible explanations for different clinical outcomes according to each strategy. Although previous analyses comparing the two strategies exist,[27,28] the present study comprehensively included the most recent relevant articles and explained the clinical benefits in detail. Furthermore, the GRADE approach for this review specifically described the quality of evidence so that it could be interpreted with full consideration of possible biases. LS-LND revealed superior results to S-LND in terms of OS; however, RFS did not differ between the two techniques. This superiority could be attributed to the low incidence of postoperative complications among the patients who underwent LS-LND. Furthermore, the present study revealed that the relative risks of chylothorax and arrhythmia were significantly lower in the LS-LND group.

Patients who had postoperative complications revealed a higher rate of non-cancer-related deaths during follow-up,[29] and postoperative arrhythmia in lung cancer surgery was recognized as a poor prognostic factor.[30] Development of supraventricular tachycardia dysrhythmias[31] and atrial fibrillation[32] after pulmonary resection for NSCLC increased hospital stay and morbidity and were associated with a worse long-term outcome. Possible reasons for the increased arrhythmia in S-LND could be the increased extent of resection[33] and manipulation around the vagus nerve branches.[34,35] In this analysis, we could not specifically determine the impact of different arrhythmia types because of the limited information available in each study. Future studies concerning this topic would assist in expanding our understanding of the long-term detrimental effect of postoperative arrhythmia in lung surgery.

The incidence of postoperative chylothorax in lung surgery ranged from 0.26% to 2.4% in previous reports, and higher incidences were observed in patients undergoing S-LND.[36,37] Dissection of lymph nodes IV and VII increased the liability to damage a branch of the thoracic duct.[38] Though most patients with chylothorax after lung surgery recovered with conservative care, some required surgical treatment that lengthened hospitalization and impacted their nutritional status. These late effects can affect the long-term prognosis of patients and increase their vulnerability to other diseases.

Postoperative pulmonary complications were known for their negative long-term clinical impact such as a higher incidence of non-cancer related death.[29,39] The pioneering study by Okada et al.[9] which introduced the concept of LS-LND, suggested a higher incidence of postoperative pneumonia in the S-LND group, indicating possible secondary benefits of LS-LND. However, subsequent studies did not deliver similar results; thus, the meta-analysis results did not indicate the superiority of LS-LND in terms of the incidence of pneumonia. However, the definition of postoperative pulmonary complications could differ, as some studies included atelectasis as a pulmonary complication.[29] The severity of pulmonary complications is also obscure; only two studies[10,16] introduced an objective criteria[40,41] to differentiate the level of adverse events. To evaluate the impact of pulmonary complications precisely, the assessment standards must first be established.

This study had several limitations. First, evolving concepts of LS-LND could pose a RoB as there was minor variability in lymph node station that should be resected for LS-LND among included studies (Supplementary Table 3). In addition, surgical techniques in the thoroughness of lymph node dissection and applicability of frozen-biopsy results may different from institution to institution, and country to country. Enrolled studies in this analysis were mostly from Asian countries even though we approached with systematic search. Lymph node assessments could be different in Western countries and patients characteristics, and there were not many studies comparing two techniques. These issues should be assessed later from collaboration between surgical societies. Second, considering that the study mostly incorporated evidence from retrospective studies, unavoidable selection bias probably exists. Even studies with propensity-score matching had several different factors included for adjustment. Heterogeneities were also observed especially in the intervention measurement. Only five studies explicitly excluded right middle lobe lesions, while some studies included sublobar resection, although the proportion was small. Furthermore, different radiologic features in solid proportion and metabolic activity on positron emission tomography could serve as confounding variables in the interpretation of the results. Though included studies tried to exclude ground-glass opacity dominant lesions, more objective selection criteria especially in radiologic characteristics should be applied as there are accumulating evidence in favor of prognosis with ground-glass opacity accompanying lesions. Although there were biases owing to the study design, the certainty of the evidence was relatively significant in terms of OS, RFS, and postoperative complications. The causes of non-cancer-related deaths also need to be reviewed to assess the clinical benefits of LS-LND. Finally, the Parma and Tierney methods have an inherent limitation because they infer HRs from the survival curves.

In conclusion, LS-LND could be a reasonable surgical strategy compared with S-LND for the treatment of some patients with NSCLC, and its clinical benefits regarding postoperative complications and OS need to be considered. Further RCTs, including a recent study[42] and JCOG 1413,[10] could provide guidance on practicing LS-LND and clarify its impact in more detail.

CRediT Authorship Contribution Statement

Wongi Woo: Conceptualization, Methodology, Data curation, Formal analysis, Investigation, Software, Writing - original draft, Writing – review & editing.

Jae Il Shin: Methodology, Supervision, Writing – review & editing.

Vincent Kipkorir: Methodology, Data curation, Formal analysis, Writing – review & editing.

Young Ho Yang: Writing – review & editing.

Sungsoo Lee: Supervision, Writing – review & editing.

Chang Young Lee: Conceptualization, Methodology, Validation, Supervision, Project administration, Writing – review & editing.

Data Availability Statement

The data underlying this article will be shared by the corresponding author on reasonable request.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100516.

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