

Original  
Article

# Lobe-Specific Node Dissection Can Be a Suitable Alternative to Systematic Lymph Node Dissection in Highly Selective Early-Stage Non-Small-Cell Lung Cancer Patients: A Meta-Analysis

Zihuai Wang, MD,<sup>1,2</sup> Zhuoran Qi, MD,<sup>1</sup> Diou Cheng, MD,<sup>1</sup> Xiaohu Hao, MD,<sup>1,2</sup> Qiang Pu, MD,<sup>1,2</sup> and Lunxu Liu, MD, PhD, FRCS<sup>2</sup>

**Purpose:** Whether the lobe-specific lymph node dissection is an alternative to systematic lymph node dissection for early-stage non-small-cell lung cancer remains controversial. An elaborate meta-analysis was conducted to evaluate the effects of lobe-specific lymph node dissection in early-stage patients.

**Methods:** A systematic literature search was conducted up to February 19, 2020 in PubMed, Ovid, Web of Science, and China National Knowledge Infrastructure databases. The outcomes including overall survival (OS), complications, and recurrence rate were extracted and analyzed.

**Results:** Nine studies including one randomized controlled trial (RCT) and eight retrospective cohort studies with 8499 non-small-cell lung cancer patients were included. The results indicated that lobe-specific lymph node had a lower rate of postoperative complication (relative risk [RR]: 0.83, 95% confidence interval [CI]: 0.72–0.95,  $P = 0.006$ ). No significant difference was observed between lobe-specific lymph node and systematic lymph node dissection in OS (hazard rate = 1.12, 95% CI: 0.81–1.54,  $P = 0.501$ ) with high heterogeneity ( $I^2 = 71.9\%$ ).

**Conclusion:** Lobe-specific lymph node can reach a comparable long-term prognosis in some highly selected patients. However, these results should be viewed cautiously with the existence of high heterogeneity. Due to the high heterogeneity, a strict patient selection process by experienced thoracic surgeons was recommended before validating lobe-specific lymph node.

**Keywords:** non-small-cell lung cancer, lobe-specific lymph node dissection

<sup>1</sup>Department of Thoracic Surgery, West China Hospital, Sichuan University, Chengdu, China

<sup>2</sup>West China School of Medicine, Sichuan University, Chengdu, China

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Corresponding author: Lunxu Liu, MD, PhD, FRCS. West China School of Medicine, Sichuan University, No. 37, Guoxue Alley, Chengdu, Sichuan 610041, China

Email: lunxu\_liu@aliyun.com



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## Introduction

Lung cancer ranks the first position in mortality among all malignances in the world.<sup>1)</sup> With the development of radiological techniques for diagnosis, the population of clinical early-stage non-small-cell lung cancer (NSCLC) has dramatically increased. Lymphatic system is one of the most important way to metastasize in NSCLC patients and can be an important prognostic marker.<sup>2)</sup> The National Comprehensive Cancer Network guideline recommends pulmonary lobectomy and systemic lymph node dissection (SND) as standard treatment option for NSCLC surgery.<sup>3)</sup> However, as for early-stage NSCLC,

the method of lymph node dissection is still controversial.<sup>4,5)</sup> The lobe-specific mediastinal node dissection based on lymphatic drainage pathway has been proposed for many years.<sup>6)</sup> Some surgeons believe that the lobe-specific node dissection (LND) leads to a comparable survival outcome compared with SND for early-stage NSCLC patients.<sup>7,8)</sup> More evidence-based information is needed for the effectiveness of LND, especially in early-stage patients. Therefore, we conducted this comprehensive meta-analysis to evaluate the effectiveness of LND for early-stage NSCLC patients.

## Materials and Methods

### Search strategy and selection criteria

Pubmed, Ovid, Web of Science, Cochrane database as well as Chinese databases including CNKI, Wanfang Data were searched using the following terms: (“lung cancer” OR “lung neoplasms” OR “lung carcinoma” OR “malignant lung nodule”) AND (“systematic lymph node dissection” OR “systematic lymph node resection” OR “system lymphadenectomy” OR “mediastinal lymph node dissection” OR “lymphadenectomy”) AND (“lobe-specific nodal dissection” OR “lobe-specific regional lymph node” OR “lobe-specific lymphadenectomy” OR “lobe-specific mediastinal lymphadenectomy”). The reference lists in the retrieved articles were searched for additional relevant studies as well.

The titles, abstracts, and full texts of the studies were independently evaluated by two investigators (Zhuoran Qi and Zihuai Wang) and any discrepancies would be checked by Diou Cheng. Studies were included if they met the following criteria: (1) directly compared NSCLC patients who received SND and LND, (2) included sufficient data for perioperative outcomes and long-term survival, and (3) either randomized controlled trial (RCT) or observational studies. Studies were excluded for the following reasons: (1) no relevant outcomes were included, (2) articles were published in languages other than English and Chinese, (3) articles of case reports, reviews, and conferences, and (4) articles without a comparable group or did not report any outcome of interest.

When evaluating the prognosis of SND and LND, the overall survival (OS), postoperative complications especially postoperative chylothorax and the recurrence rate were collected from the publications. OS was collected with hazard ratio and the associated 95% confidence interval (CI) from the articles. If the relevant data were not provided, the hazard ratios (HRs) would be calculated

by Engauge Digitizer version 4.1 from the Kaplan–Meier curves with Parmar and Tierney methods.<sup>9,10)</sup>

### Assessment of study quality

The information of publications enrolled including following data: first author, year of publication, study design, preoperative clinical stage of NSCLC, detection of station 7 lymph node, whether matched or not, the patient number of each group. The quality of studies was assessed by The Newcastle Ottawa Scale (NOS)<sup>11)</sup> for non-RCT studies, which assessed the selection (0–4 scores), comparability (0–2 scores), and exposure (0–3 scores) for case–control studies. Each study had a NOS score varied from 0 to 9, and the studies with high-quality were defined as with 7 scores at least. Jadad score<sup>12)</sup> was validated when assessing the quality of RCT.

### Statistical analysis

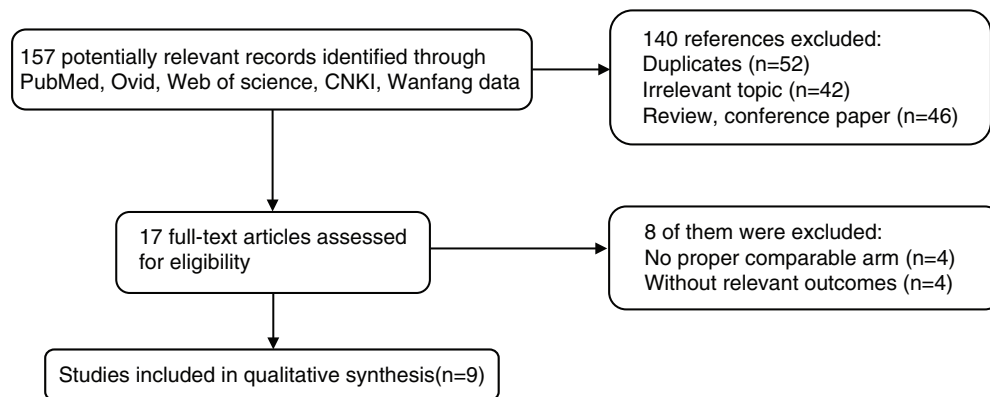
The survival data of OS were evaluated by HR with the upper and lower limit of 95% CI of HR collected. The HR data were obtained using the Engauge Digitizer software if were not provided directly. The dichotomous variables including complications and recurrence rate were evaluated by relative risk (RR) and their corresponding 95% CI. For each result, the heterogeneity between studies was assessed by the  $I^2$  test.  $I^2 > 50\%$  implicated a substantial heterogeneity.

Publication bias was assessed by funnel plot, with a maximum of 10 articles included. And sensitivity analysis was conducted to detect the stability of outcomes by omitting each study sequentially. Statistical significance was defined as  $P < 0.05$ . STATA version 12.0 (StataCorp, College Station, TX, USA) and Review Manager Version 5.3. were conducted for analyses.

## Results

### Result of search

**Figure 1** shows the flow chart of search process. A total of 157 papers were collected from the initial search, 52 articles were excluded for duplication. After evaluation of the titles and abstracts, 17 articles were selected. All of them underwent full-text evaluation, and finally nine papers<sup>8,13–20)</sup> were included in our analyses. The characteristics of the studies included are shown in **Table 1**. A total of 8499 patients were included in our analysis. In all, 2347 (27.6%) of them underwent LND, while 6152 patients (72.4%) underwent SND. All



**Fig. 1** The PRISMA flow diagram of literature retrieval process. PRISMA: preferred reporting items for systematic reviews and meta-analyses

patients included were considered as clinical stage I or II NSCLC and underwent different preoperative evaluations. In SND group, complete mediastinal lymph node dissection was performed according to the proposed definition and at least three stations in the same side of mediastinum were completely resected.<sup>21)</sup> In LND group, selective mediastinal lymph node dissection was performed as follows: For upper lobe tumors, the dissection of lymph node in the upper mediastinum was performed. For tumors located in lower lobe, lymph node dissection was performed in the lower mediastinum (mainly station 7 and 9). Articles reporting one of the following outcomes including OS, pathological up-staging, postoperative complications, postoperative chylothorax, and recurrence rate were included. The outcome is shown in **Table 2**.

### Quality assessment and risk of bias

The quality assessment and risk-of-bias analysis of the cohort studies included were measured by NOS. The only RCT<sup>16)</sup> was evaluated by Jadad scale. However, the RCT did not mention withdrawal of patients or study blinding. Hence, it only received 1 score for randomization, which represented low quality. Among all the included cohort studies, one<sup>18)</sup> was viewed as low quality for the following reasons: a non-neglectable selection bias was reported between the two groups as some patients intended for LND might converted to SND for intraoperative suspicion of nodal involvement. The baseline characteristics in two groups were not comparable, LND group patients had a significantly smaller tumor size and fewer implementation of adjuvant chemotherapy. The NOS assessment for this work was ranked with only 5 scores which showed a low quality. All the other cohort studies were ranked as high quality.

### Overall survival

OS was assessed in all included studies. These studies reported OS of patients with early-stage NSCLC receiving either LND or SND with a total of 8499 patients. The result showed that LND had a comparable OS compared with SND, which is shown in **Fig. 2A** (HR = 1.12, 95% CI: 0.81–1.54, P = 0.501). Since the existence of high heterogeneity in OS ( $I^2 = 71.9\%$ ), a subgroup analysis was conducted in stage I patients only. And the result was stable (HR = 1.21, 95% CI: 0.82–1.78, P = 0.339) with a still considerable heterogeneity ( $I^2 = 52.2\%$ ) (**Fig. 2B**).

### Recurrence rate

To evaluate the relationship between LND and recurrence, we assessed the total recurrence rate among all included articles. As the time interval to recurrence might lower the efficacy of our evaluation, we validated recurrence rate instead of disease-free survival as the outcome. Six studies with 1472 patients were included to compare the recurrence rate between LND and SND. The result showed that LND group patients had lower recurrence rates compared with SND while no heterogeneity was observed (RR = 0.87, 95% CI: 0.79–0.96, P = 0.005,  $I^2 = 0.0\%$ ) (**Fig. 3A**). While the result was not consistent when only assessing stage I patients in recurrence rate (RR = 0.92, 95% CI: 0.75–1.13, P = 0.414,  $I^2 = 50.40\%$ ).

### Complications

Eight studies provided the outcome of postoperative complications. The analysis showed that LND was associated with reduced postoperative complication compared with SND (RR = 0.83, 95% CI: 0.72–0.95, P = 0.006,  $I^2 = 45.7\%$ ) (**Fig. 3B**). Furthermore, we analyzed the postoperative chylothorax between LND and SND. The result showed that LND had a tendency of lower rate of

**Table 1 Characteristics of the studies included**

Study	Year	Study design	Country	Clinical stage <sup>a</sup>	Detection of station 7 LN in LND	Preoperative Staging method	Match or not	Population		Quality assessment
								LND	SND	
Adachi	2017	Retrospective	Japan	Clinical T1a-2b N0-1 M0	Lower-lobe tumor	CT and PET	Matched	49	49	8
Chen	2012	Retrospective	China	Pathological stage T1a-2aN0M0	Both	NA	Unmatched	150	148	7
Hishida	2016	Retrospective	Japan	Clinical stage I/II	Lower-lobe tumor	Contrast-enhanced CT	Matched	1268	4124	6
Ishiguro	2010	Retrospective	Japan	Clinical stage Ia-IIIb	Lower-lobe tumor	NA	Matched	147	625	7
Jiang	2013	Retrospective	China	Clinical stage I	Lower-lobe tumor	CT	Unmatched	94	309	8
Maniwa	2013	Retrospective	Japan	Clinical N0	Lower-lobe tumor	CT and PET	Unmatched	129	206	8
Okada	2006	Prospective	Japan	Clinical stage I	Lower-lobe tumor	Not reported	Unmatched	377	358	7
Shapiro	2013	Retrospective	America	Clinical N0/N1	Lower-lobe tumor	CT and PET	Unmatched	88	282	7
Ma	2013	RCT	China	Clinical stage T1aN0M0	Both	CT	Unmatched	45	51	1 <sup>b</sup>

<sup>a</sup>Based on seventh edition of TNM staging. <sup>b</sup>Jadad score. CT: computed tomography; LND: lobe-specific node dissection; NA: not applicable; PET: positron emission computed tomography; RCT: randomized controlled trial; SND: systematic lymph node dissection

postoperative chylothorax compared with SND (RR = 0.66, 95% CI: 0.40–1.09, P = 0.103, I<sup>2</sup> = 0) (**Fig. 3C**). A lower rate of pulmonary atelectasis was also observed in LND group (RR = 0.44, 95% CI: 0.21–0.92, P = 0.029, I<sup>2</sup> = 0). No significant difference was detected in arrhythmia rate (RR = 0.76, 95% CI: 0.26–2.23, P = 0.621, I<sup>2</sup> = 79.2%), pneumonia rate (RR = 1.07, 95% CI: 0.24–4.86, P = 0.931, I<sup>2</sup> = 89.0%), prolonged air leak rate (RR = 1.81, 95% CI: 0.35–9.55, P = 0.482, I<sup>2</sup> = 79.2%) or recurrent nerve palsy rate (RR = 0.95, 95% CI: 0.09–9.65, P = 0.968, I<sup>2</sup> = 75.5%).

### Pathological up-staging rate

As for pathological up-staging, six studies were included in our analysis. As was shown in the forest plot (**Fig. 3D**), a comparable mediastinal lymph node up-staging rate was reported between LND and SND (RR = 0.95, 95% CI: 0.68–1.35, P = 0.793, I<sup>2</sup> = 0.0%).

### Sensitivity analysis and publication bias

Sensitivity analysis was applied assessing 5-year OS by sequentially removing each study to evaluate the stability of our result, and it showed that the result did not change from the previous analysis (Supplementary Fig. 1). A funnel plot was adopted to test the publication bias of all included articles in OS with Review Manager Version 5.3. No significant publication bias was observed in the funnel plot (Supplementary Fig. 2).

### Discussion

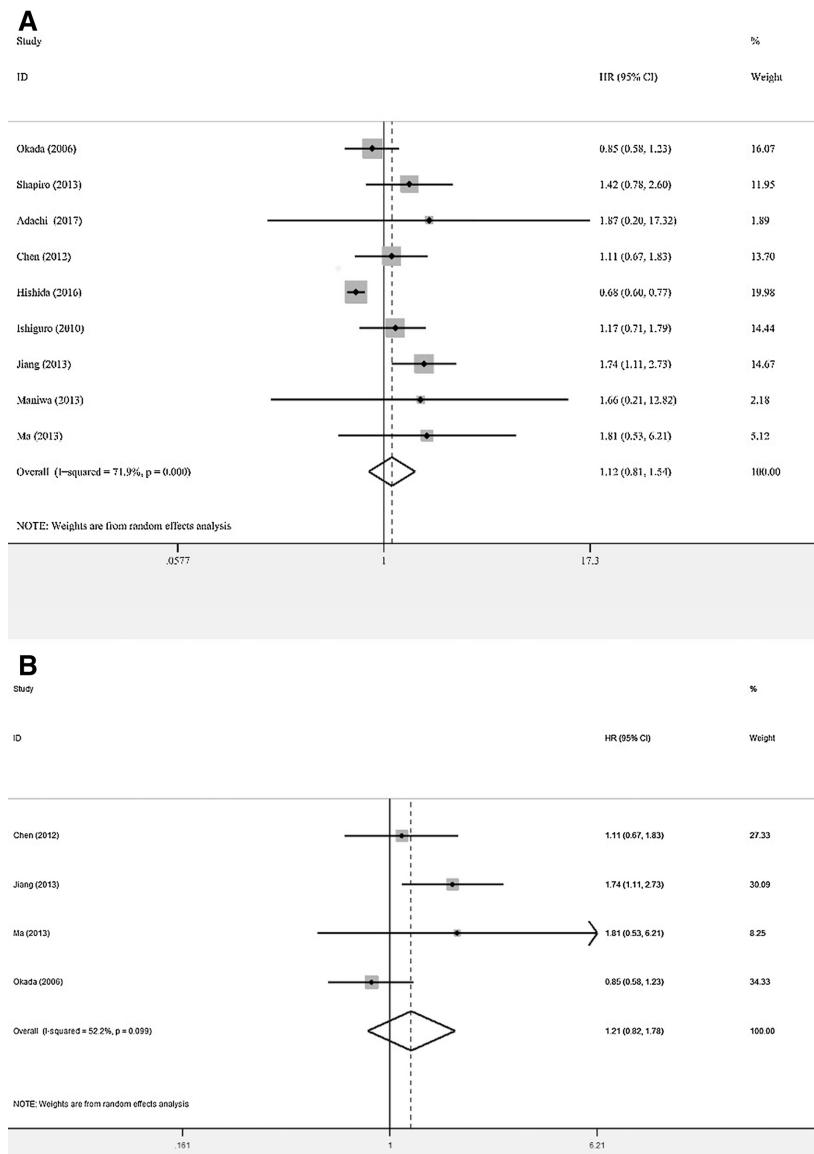
It is widely accepted that the lobectomy with systematic lymph node dissection is the standard surgical option for NSCLC patients.<sup>6)</sup> Recently, some articles reported that the LND had similar OS rate compared with the SND, and can be an alternative in selected patients with clinical stage I NSCLC.<sup>8)</sup> In the revision of N staging for the eighth edition of TNM staging, a subclassification of mediastinal lymph node metastasis has been introduced as single-station metastasis (skip/non-skip) and multi-station metastasis.<sup>22)</sup> Different pattern of mediastinal lymph node metastasis can lead to different prognosis; thus, a thorough examination of mediastinal lymph node according to metastatic risk is important. It would be of prognostic significance to evaluate the effectiveness of LND in selected patients. A previous meta-analysis tried to compare the outcome between SND and LND.<sup>23)</sup> However, the sample size was limited and the selection bias among the included articles were not well discussed,

**Table 2 Main outcomes included in our meta-analysis**

Author (year)	Surgical procedure	Patient number	5-year OS rate	Total complication (%)	Recurrence (%)	Pathological up-staging <sup>a</sup>
Okada et al. (2006)	LND	377	83.6%	38 (10.1%)	95(25.2%)	2 (0.5%)
	SND	358	79.6%	62 (17.3%)	113 (31.6%)	3 (0.8%)
Ishiguro et al. (2010)	LND	147	76.0%	NA†	NA	NA
	SND	625	71.9%	NA	NA	NA
Chen et al (2012)	LND	150	68.7%	7 (4.7%)	NA	NA
	SND	148	73.6%	20 (13.5%)	NA	NA
Jiang et al (2013)	LND	94	68.1%	7 (7.4%)	29 (30.9%)	17 (18.0%)
	SND	309	74.4%	14 (4.5%)	79 (25.6%)	59 (19.0%)
Maniwa et al (2013)	LND	129	89.9%	19 (14.7%)	24 (18.6%)	4 (3.1%)
	SND	206	89.8%	39 (18.9%)	46 (22.3%)	16 (7.8%)
Ma et al (2013)	LND	45	68.9%	5 (11.1%)	NA	5 (11.1%)

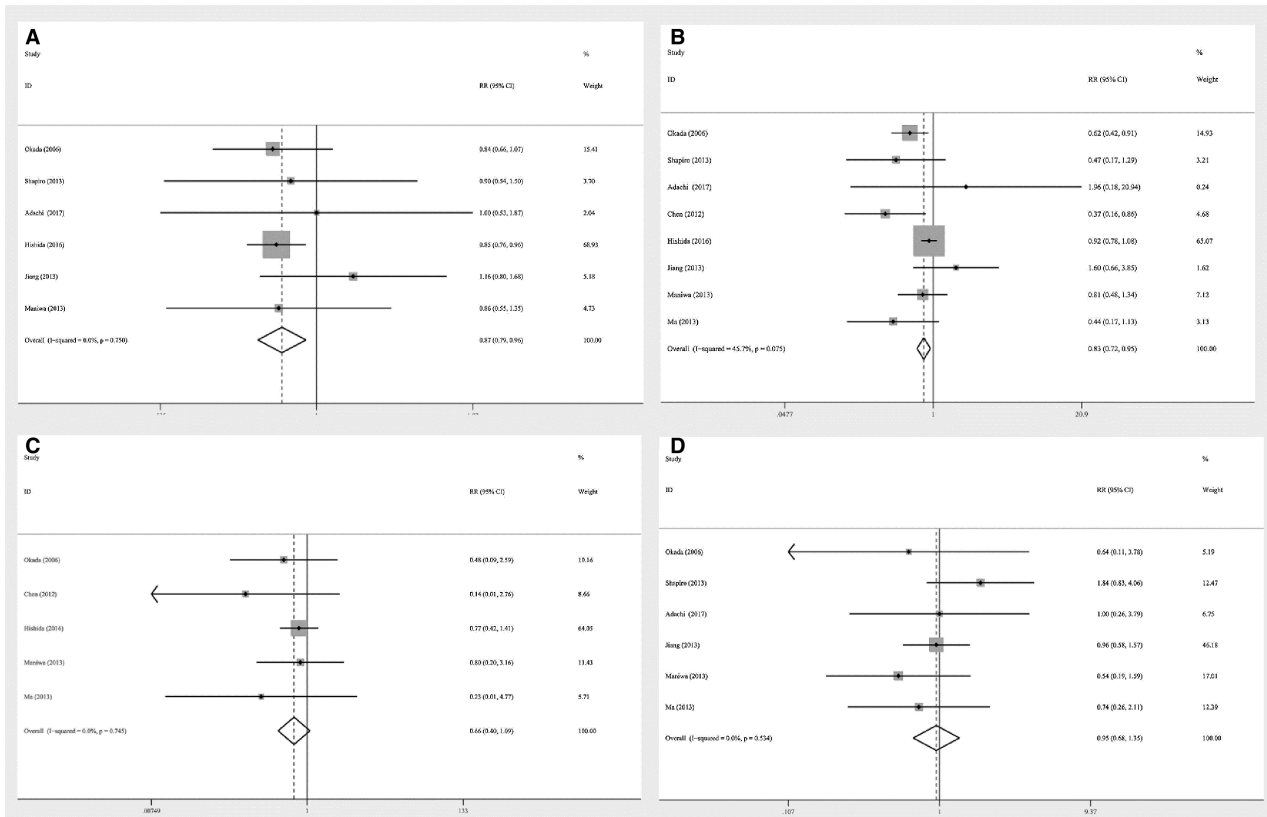
<sup>a</sup>Only mediastinal lymph node up-staging records were included (not N1).

LND: lobe-specific node dissection; NA: not applicable; SND: systemic lymph node dissection



**Fig. 2** Forest plot in OS among all stage patients (A) and clinical stage I patients (B). OS: overall survival





**Fig. 3** Forest plot for recurrence rate (A), complication rate (B), postoperative chylothorax rate (C) and pathological up-staging (D)

which might exaggerate the advantage of LND. In addition, some relevant studies were not included in the article and would add evidence for further analysis.<sup>20)</sup> Thus, an update meta-analysis with a direct comparison between LND and SND was conducted.

Our results showed a high heterogeneity in OS among all included articles in the comparison between LND and SND, which was likely due to the high selection bias. Many reported that the inclusion criteria for LND were based on surgeons' experience. Meanwhile, a small group of patients, planned for LND, converted to SND during surgery and were included in SND group without any detailed explanation for the conversion.<sup>8)</sup> To minimize the influence of underlying selection bias, a subgroup analysis was conducted in clinical stage Ia patients. Four included articles reported outcomes in stage I patients<sup>14,16,17,19)</sup> only. However, a considerable heterogeneity still existed ( $I^2 = 52.2%$ ).

Based on the results above, we assumed that some other factors also played roles in the selection process for LND during which patients with less aggressive tumors were more likely to be selected. Though propensity score was validated to match the baseline characters between groups in few articles, some underlying factors related to

lymph node metastasis and tumor invasiveness were not comparable between the two groups, such as tumor location and ground glass opacity (GGO) component percentage. Lymphatic drainage pattern differs among lobes and segments.<sup>24)</sup> Previous studies have also confirmed the predominance but not exclusiveness of the drainage into the "lobe-specific" mediastinum, which provided the anatomic proof for the association between lymph node metastatic pattern and tumor location.<sup>25)</sup> GGO rate has been taken more consideration when evaluating tumor invasiveness. GGO component >50% has been viewed as an important indicator for segmentectomy.<sup>26)</sup> Previous studies proved the relationship between GGO >50% and mediastinal lymph node metastasis.<sup>27)</sup> The existence of these residual confounding between the two groups is likely to lead to the favorable prognosis in LND group.

Recurrence rate of mediastinal lymph node in LND patients has been widely discussed. Due to the underlying selection bias, patients underwent LND may have less invasive tumors compared to those of SND, which might be the reason for the lower recurrence rate in LND group. In Maniwa's work,<sup>15)</sup> patients underwent LND were divided into two groups according to the reason to underwent LND. The baseline characters between two

groups including the GGO component were comparable. The comparison between patient-related LND group and SND group can minimize the selection bias mentioned above. According to this article, patients who underwent LND due to existing comorbidities showed a higher rate of LN recurrence compared with SND group (6.2% versus 1.5%). Unfortunately, only one article conducted the comparison between patient-related LND and SND and it is hard to conclude the relationship between LND and mediastinal recurrence.

It is important to evaluate the mediastinal lymph node recurrence event when assessing the effectiveness of lobe-specific lymph node dissection. The mediastinal lymph node recurrence was reported in two studies. Maniwa's work showed a significant higher risk of mediastinal node recurrence in LND group with patient-related factors (group B) compared with SND group (group A) ( $p = 0.005$ ). While Adachi and his colleagues reported regional lymph node recurrence rates of 3/49 and 4/49 in LND and SND groups, respectively, after propensity score matching and no significant difference was found.

Last year, an article reported the cumulative incidence of recurrence (CIR) between LND and SND.<sup>28)</sup> And the result showed a significantly higher CIR in LND group. Another study reported that even in clinical stage Ia patients, mediastinal lymph node metastases or beyond lobe-specific zone were sometimes found.<sup>29)</sup> In addition, it is the long-term survival, instead of simply the pathological examination of lymph node, being the most suitable outcome in determining the effectiveness of different lymph node dissection method. Some further studies are warranted to conduct the comparison in prospective randomized trials to answer this question. Thus, further studies might need to focus on predictive factors in MLNM and establish predictive models accordingly before simply validating LND in large scales of patients.

Postoperative outcomes are also important in evaluating LND. Our result showed a better postoperative result in LND than SND group with a significantly lower rate of overall complication. According to the analysis, LND group had a significant lower rate in pulmonary atelectasis and a tendency of lower rate in postoperative chylothorax compared with SND group, which indicated that LND can be a less invasive technique. The perioperative outcome between the two groups demonstrated the potential benefits of validating LND in selected early-stage NSCLC patients.

Our meta-analysis still remained some limitations. It is hard to eliminate or minimize the underlying selection bias among the included articles. And only one randomized trial was included in our analysis. More prospective and well-designed trials are warranted in this field in the future.

## Conclusion

LND may be a proper alternative in highly selective early-stage NSCLC patients, and simply set the inclusion criteria based on tumor diameter is inappropriate. Previous studies have proven that LND can achieve comparable outcome compared with SND in highly selected patients. Further studies are warranted for risk factors identification for mediastinal lymph node metastasis other than tumor diameter before validate LND in large populations.

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## Disclosure Statement

The remaining authors declare no conflict of interest.

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