Ann Surg Oncol (2019) 26:2044–2052
https://doi.org/10.1245/s10434-019-07368-x

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – THORACIC ONCOLOGY

Survival Benefit of Left Lower Paratracheal (4L) Lymph Node Dissection for Patients with Left-Sided Non-small Cell Lung Cancer: Once Neglected But of Great Importance

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ABSTRACT

Objective. The aim of this study was to compare survival outcomes between non-small cell lung cancer (NSCLC) patients with or without 4L node dissection (4LND) and to evaluate the potential patient population who will particularly benefit from 4LND.

Methods. Between January 2009 and December 2015, a total of 2063 patients with primary left-sided NSCLC in the Western China Lung Cancer Database were initially reviewed. After exclusion, 1064 patients were enrolled in this study. A total of 460 patients with 4LND ($4LND^+$ group) were matched with 460 patients without 4LND ($4LND^-$ group) using propensity-matched analysis. Disease-free survival (DFS) and overall survival (OS) were analyzed.

Results. The metastasis rate of station 4L was 14.6%. Patients with 4LND showed higher DFS (5-year DFS 52.6% vs. 46.7%; hazard ratio [HR] 1.25, 95% confidence interval [CI] 1.03–1.50; $p = 0.022$) and OS (5-year OS 65.8% vs. 56.3%; HR 1.36, 95% CI 1.10–1.69; $p = 0.006$) than patients without 4LND. In the multivariate analysis, patients without 4LND (HR 1.33, 95% CI 1.07–1.66; $p = 0.011$), tumor size > 3 cm, lymph node metastasis, and pathologic stage higher than stage I were independent prognostic factors for poor OS. Subgroup analysis according to pathologic TNM stage and N stage showed that stage II, IIIA, and N2 disease indicated better survival outcomes in the $4LND^+$ group ($p = 0.050$, $p = 0.016$, and $p = 0.008$, respectively).

Conclusions. Performing 4LND may bring survival benefits to patients with left-sided NSCLC. We suggest 4LND as a standard procedure for left-sided NSCLC patients with stage II or advanced stage disease.

Lung cancer is the leading cause of cancer-related deaths worldwide, with non-small cell lung cancer (NSCLC) being the predominant type.[1] The cornerstone of treatment for operable patients with NSCLC remains lobectomy with systematic nodal dissection (SND).[2] Since the involvement of lymph nodes (LNs) is one of the main determinants of stage and survival outcome, SND is extremely important for accurate evaluation of pathologic N stage and better postoperative survival. However, no consensus has been reached as to the optimal extent of mediastinal LN dissection (MLND).[3–8] The National Comprehensive Cancer Network (NCCN) guidelines recommend that MLND be conducted by a complete LN dissection or a minimum of three N2 stations sampled.[9] In comparison, the European Society of Thoracic Surgeons (ESTS) recommend that MLND should involve a minimal excision of at least three mediastinal nodal stations, with the subcarinal node always included.[10] Therefore, rigid specifications on the dissection of mediastinal stations is currently lacking.

Electronic supplementary material The online version of this article (https://doi.org/10.1245/s10434-019-07368-x) contains supplementary material, which is available to authorized users.

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First Received: 8 October 2018;
Published Online: 22 April 2019

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A study of pulmonary lymphatic drainage showed that the left lower paratracheal (4L) nodes played an essential role in the left bronchial–recurrent LN chain, an important lymphatic pathway of the left lung [11] (bounded by the aortic arch superiorly, the trachea and esophagus medially, the superior border of the main left bronchus inferiorly, and the pulmonary artery and arterial ligament anteriorly and laterally).[12] In addition, 4L nodes are close to the left recurrent laryngeal nerve, increasing the possibility of nerve damage during dissection.[13] For these reasons, surgeons do not typically dissect 4L nodes during MLND.

Recent research conducted by Wang et al. found patients undergoing 4L node dissection (4LND) had a more favorable prognosis.[14] Our large database provided an opportunity for us to follow-up on this research finding. Thus, we analyzed 1064 left-sided NSCLC patients in a prospective database to evaluate the characteristics of patients who benefited from 4LND.

METHODS

Patients

We conducted a retrospective analysis of 2063 primary left-sided NSCLC patients who underwent pulmonary surgery with lymphadenectomy in the Western China Lung Cancer Database, a large prospective database led by the West China Hospital, between January 2009 and December 2015. Exclusion criteria were age < 18 years or > 80 years, multiple primary NSCLC, wedge or segment resection, MLND did not meet the ESTS criteria,[10] R1 or R2 resections, patients with preoperative treatment (chemotherapy, radiotherapy, surgery), or TNM stage 0, IIIB or IV (Fig. 1). This study was approved by the Institutional Review Board (IRB) of West China Hospital (no. 2016-98). Informed consent was waived for this research.

Propensity Score Matching

To minimize the effects of potential confounding factors between the 4LND$^+$ group and 4LND$^-$ group, we performed propensity score-matching (PSM).[15] We conducted the analysis based on the following variables: age, sex, smoking history, tumor location, tumor size, histologic type, pathologic N (pN) stage, and surgical approach. Patients who underwent surgical resection with or without 4LND were matched 1:1 on propensity scores, without replacement. Matching was performed using a greedy nearest neighbor matching algorithm with caliper restrictions.

Surgical Technique

Pulmonary resection was conducted via a 'single-direction' lobectomy,[16] one of the most widely used lobectomy approaches in China. LN stations were defined according to the LN map proposed in 2009 by the International Association for the Study of Lung Cancer (IASLC).[17] MLND implied removal of at least three mediastinal node stations, with the subcarinal station always included, as per the ESTS guidelines.[10] 'Non-grasping en bloc MLND' was used in our center and 4LND was performed as follows. We opened the pleural area between the ligamentum arteriosum, left main pulmonary artery, vagus nerve, and left main-stem bronchus using an electrocautery hook. Next, we pressed downward 4L block by suction, and dissociated it from the inferior border of the aortic arch. We then dissected the block off the left main pulmonary artery and along the left main-stem bronchus to the trachea using an ultrasonic scalpel. Finally, we hollowed the block out from the interspace between the aortic arch, left main pulmonary artery, and left main-stem bronchus. The left recurrent laryngeal nerve was identified, but there was no need to anatomize it.[18]

Follow-Up

All patients received a standard follow-up schedule, i.e. chest x-ray 1 month postoperatively, then outpatient follow-up at 3- to 6-month intervals for the first 2 years and at 6-month intervals for the subsequent 3 years, and annually thereafter until death or the end of the study on May 2018. During routine follow-up, physical examinations, laboratory tests, computed tomography (CT) scans of the chest and abdomen, CT scan or magnetic resonance imaging (MRI) of the head, bone scintigraphy, and/or positron emission tomography (PET)-CT were performed.

Data Collection and Definition

Baseline data consisted of age, sex, smoking history, tumor location, tumor size, histologic types, lymphatic or vascular invasion, adjuvant chemotherapy, adjuvant radiotherapy, and pathologic stage. Postoperative complications included hoarseness, chest drainage for more than 7 days, pulmonary infection, bronchopleural fistula, chylothorax, deep venous thrombosis, and pulmonary embolism. Histologic typing was based on the 2011 classification of the IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS).[19] Pathologic stage was determined according to the 7th edition of the American Joint Committee on Cancer (AJCC) lung cancer staging system.[20] Disease-free survival (DFS) was measured from the date of surgery to the date of recurrence or

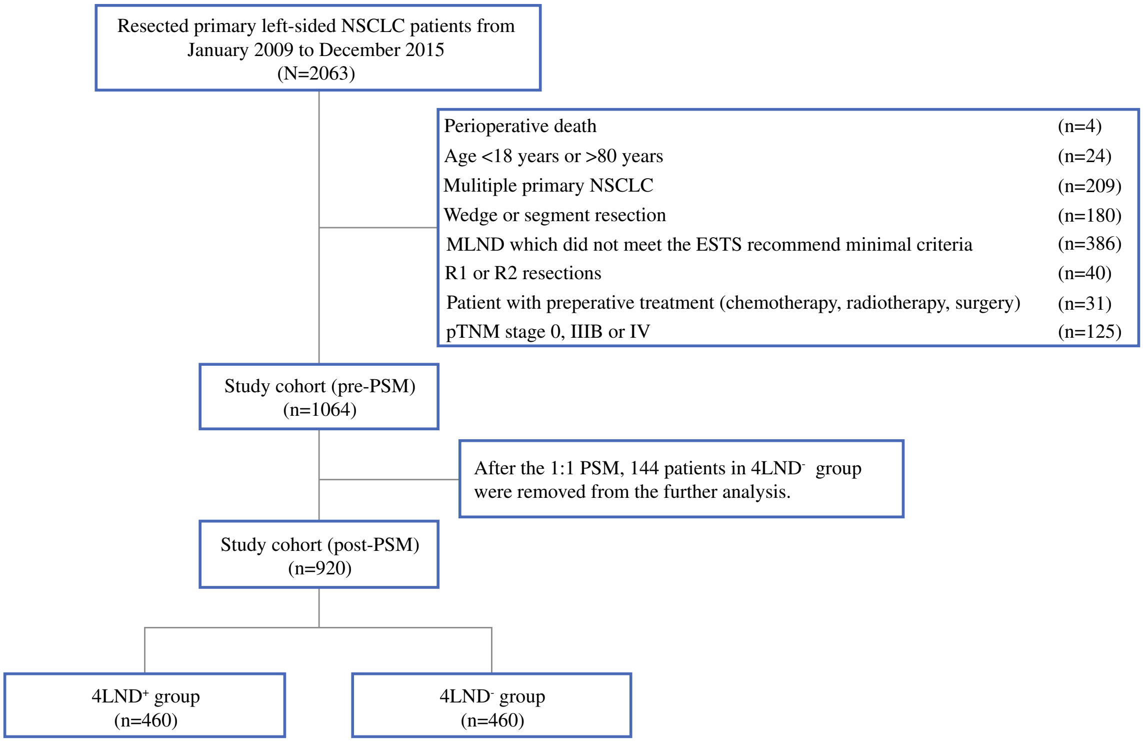

FIG. 1 Patient selection process. *NSCLC* non-small cell lung cancer, *MLND* mediastinal lymph node dissection, *ESTS* European Society of Thoracic Surgeons, *pTNM* pathologic TNM, *PSM* propensity score-matching, *4LND* 4L node dissection

metastasis, and overall survival (OS) was measured from the date of surgery to the date of death or last contact. We defined single-station 4L metastasis as the state where 4L was the only metastasis site among all mediastinal LNs (with or without N1 involvement).

Statistical Analysis

Categorical variables were presented as number (%) and analyzed using Fisher's exact test or Chi square analyses, while continuous variables (age and tumor size) were compared between groups using the independent sample *t* test and expressed as the mean ± standard deviation (SD). DFS and OS were estimated using the Kaplan–Meier method in the matched pairs, and survival curves were compared using the log-rank test. We further conducted univariate analyses to identify the significant factors affecting OS, followed by a forward multivariate Cox hazard regression analysis for variables with statistical significance in univariate analyses. Corresponding hazard ratios (HR), 95% confidence intervals (CIs), and *p*-values were calculated. Subgroup analyses of OS were also performed by the Kaplan–Meier method using the log-rank test. All tests were two-sided, and a p value$<$ 0.05 was considered statistically significant. The propensity-matched procedure was carried out using the psmatch2 routine in STATA SE 12.0 (StataCorp LP, College Station, TX, USA). Other analyses were performed using SPSS statistical software version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

Baseline Characteristics

A total of 1064 patients (460 in the $4LND^+$ group and 604 in the $4LND^-$ group) met the eligibility criteria in the pre-PSM study cohort. After calculating the propensity scores, 460 pairs were matched (Fig. 1). The average age was 58.4 years, and the female to male ratio was 1:2. Four hundred and ninety-three (53.6%) patients were current or former smokers. The mean tumor size was 3.75 cm. Histologic types consisted of 588 adenocarcinomas and 332 non-adenocarcinomas of NSCLC. The pathologic stage distribution was stage I in 405 cases, stage II in 196 cases, and stage IIIA in 319 cases. Patient demographics and tumor characteristics such as age, sex, smoking history, tumor location, tumor size, histologic types, lymphatic or vascular invasion, adjuvant chemotherapy, adjuvant radiotherapy, and pathologic stage were equivalent between the matched groups (Table 1).

TABLE 1 Patient demographics and baseline characteristics in the matched groups

Characteristics	4LND group [n = 460 (%)]	Non-4LND group [n = 460 (%)]	p value
Age (years)			0.644
< 60	232 (50.4)	239 (52.0)	
≥ 60	228 (49.6)	221 (48.0)	
Sex			0.780
Male	309 (67.2)	305 (66.3)	
Female	151 (32.8)	155 (33.7)	
Smoking history			0.947
Yes	247 (53.7)	246 (53.5)	
No	213 (46.3)	214 (46.5)	
Tumor location			0.086
Upper lobe	259 (56.3)	233 (50.7)	
Lower lobe	201 (43.7)	227 (49.3)	
Tumor size (cm)			0.895
≤ 3	213 (46.3)	211 (45.9)	
> 3	247 (53.7)	249 (54.1)	
Surgical technique			0.177
VATS	289 (62.8)	269 (58.5)	
Thoracotomy	171 (37.2)	191 (41.5)	
Histological type			0.410
Adenocarcinoma	288 (62.6)	300 (65.2)	
Non-adenocarcinoma	172 (37.4)	160 (34.8)	
Lymphatic or vascular invasion			0.308
No	445 (96.7)	439 (95.4)	
Yes	15 (3.3)	21 (4.6)	
Lymph node status			0.364
N0	257 (55.9)	247 (53.7)	
N1	68 (14.8)	84 (18.3)	
N2	135 (29.3)	129 (28.0)	
Pathological stage			0.550
Stage I	207 (45.0)	198 (43.0)	
Higher than stage I	253 (55.0)	262 (57.0)	
Adjuvant chemotherapy			0.947
No	231 (50.2)	231 (50.2)	1.000
Yes	229 (49.8)	229 (49.8)	
Adjuvant radiotherapy			0.691
No	404 (87.8)	400 (87.0)	
Yes	56 (12.2)	60 (13.0)	

4LND 4L node dissection, *VATS* video-assisted thoracoscopic surgery

Metastasis Rate of Mediastinal Lymph Nodes

A total of 283 (26.6%, 283/1064) patients were diagnosed as pathologic N2. Among these patients, station 5 LN metastasis ranks first (15.2%, 148/976), followed by station 4L (14.6%, 67/460); metastasis rates of stations 6, 7, 8, and 9 were 11.3, 11.5, 4.5, and 6.1%, respectively (electronic supplementary Fig. 1). The incidence of single-station 4L metastasis was 3.7% (17/460). The rate of an underestimated pN2 frequency was 19.8% (91/460) and 16.3% (75/460) in the 4LND^{+} group and 4LND^{-} groups, respectively.

Survival Outcomes

The median follow-up period was 40 months. The OS for patients with 4LND was significantly higher than those without 4LND (5-year OS 65.8% vs. 56.3%; HR 1.36, 95%

CI 1.10–1.69; $p = 0.006$) [Fig. 2a], and the DFS for patients with 4LND was also significantly higher than those without 4LND (5-year DFS 52.6% vs, 46.7%; HR 1.25, 95% CI 1.03–1.50; $p = 0.022$) [Fig. 2b]. Univariate survival analysis identified patients without 4LND, tumor size > 3 cm, LN metastasis, pathologic stage higher than stage I, and thoracotomy as risk factors for poor OS (Table 2). In the multivariate analysis, patients without 4LND (HR 1.33, 95% CI 1.07–1.66; $p = 0.011$), tumor size > 3 cm (HR 2.16, 95% CI 1.64–2.83; $p < 0.001$), LN metastasis (HR 1.63, 95% CI 1.16–2.29; $p = 0.005$), and pathologic stage higher than stage I (HR 1.96, 95% CI 1.30–2.96; $p = 0.001$) were independent prognostic factors for poor OS (Table 2).

Subgroup analysis for patients with stage II and IIIA cancer showed that $4LND^{+}$ was associated with a better prognosis (HR 1.61, 95% CI 1.00–2.58; $p = 0.050$; and HR 1.43, 95% CI 1.07–1.91; $p = 0.016$; respectively) [Fig. 3a]. Subgroup analysis according to N stage revealed that the $4LND^{+}$ group had better OS in patients with N2 disease compared with the $4LND^{-}$ group (HR 1.53, 95% CI 1.12–2.11; $p = 0.008$) [Fig. 3b].

Postoperative Complications

Postoperative complications of patients in the two matched groups are summarized in electronic supplementary Table 1. The incidence of chest drainage for more than 7 days was higher in the $4LND^{+}$ group than in the $4LND^{-}$ group, but with no statistical significance (13.7% vs. 9.6%; $p = 0.064$). The incidence of hoarseness, pulmonary infection, bronchopleural fistula, chylothorax, deep venous thrombosis, and pulmonary embolism was low and was comparable in the two groups.

DISCUSSION

The lymphatic system is an important facilitator of cancer metastasis. Station 4L was introduced as an important component of the left mediastinal LN drainage system,[11] implying that station 4L may play a vital role in left mediastinal LN metastasis. However, in both the NCCN and ESTS guidelines, 4LND was not recommended as a routine dissection in left-sided NSCLC.[9,10] Considering this, we designed our study to evaluate the necessity of 4LND from the perspective of accurate staging and therapeutic benefit, and to further select the appropriate patients who would benefit from 4LND.

Metastasis Rate

In the current study, we confirmed the high metastasis rate of station 4L, i.e. approximately 14.6%, second to the rate of 15.2% for station 5 among all mediastinal LNs. This result is in line with that of the study performed by Wang et al.,[14] in which the metastasis rate of stations 4L and 5 was 20.9%, the highest among all mediastinal LNs. In addition, both Kuroda et al.,[21] and Sun et al.[22] highlighted the high metastasis rate of 4L nodes when assessing the effect of other node stations, indicating that the metastasis of station 4L is common in left-sided NSCLC.

Survival Outcomes

Recently, Wang et al. performed a retrospective study of 657 left-sided lung cancer patients who underwent surgical pulmonary resection, to investigate the prognostic impact of 4LND.[14] Their study showed that the $4LND^{+}$ group had a significantly better survival than the $4LND^{-}$ group. However, as stated, there were still some limitations, such

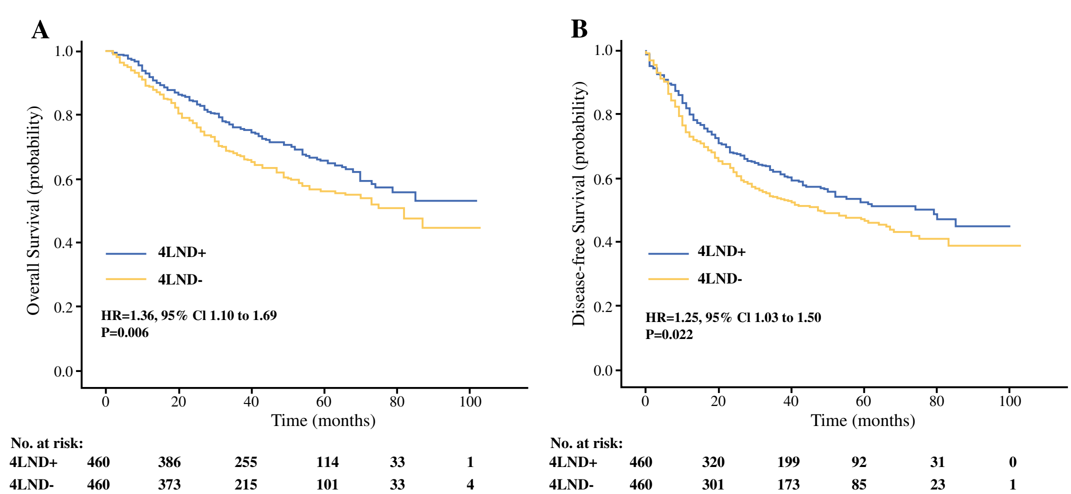

FIG. 2 (**a**) Overall survival and (**b**) disease-free survival for patients with or without 4LND. *4LND* 4L node dissection, *HR* hazard ratio, *CI* confidence interval

TABLE 2 Univariate and multivariate Cox regression analyses for predictors of overall survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	*p* value	HR	95% CI	*p* value
Age (years)						
< 60	Ref					
≥ 60	1.20	0.96–1.48	0.108			
Sex						
Female	Ref					
Male	1.22	0.98–1.55	0.093			
Smoking history						
No	Ref					
Yes	1.22	0.98–1.52	0.075			
Tumor location						
Upper lobe	Ref					
Lower lobe	1.23	0.99–1.52	0.064			
Tumor size (cm)						
≤ 3	Ref					
> 3	3.01	2.34–3.86	< 0.001	2.16	1.64–2.83	< 0.001
Surgical technique						
VATS	Ref			Ref		
Thoracotomy	1.79	1.44–2.22	< 0.001	1.03	0.81–1.29	0.832
4L station dissection						
$4LND^+$	Ref			Ref		
$4LND^-$	1.36	1.10–1.69	0.006	1.33	1.07–1.66	0.011
Histological type						
Adenocarcinoma	Ref					
Non-adenocarcinoma	1.24	0.99–1.55	0.055			
Lymph node status						
N0	Ref			Ref		
N1-2	3.13	2.49–3.94	< 0.001	1.63	1.16–2.29	0.005
Lymphatic or vascular invasion						
No	Ref					
Yes	1.54	0.96–2.48	0.073			
Adjuvant chemotherapy						
No	Ref					
Yes	0.98	0.79–1.23	0.891			
Adjuvant radiotherapy						
No	Ref					
Yes	1.26	0.93–1.72	0.134			
Pathological stage						
Stage I	Ref			Ref		
Higher than stage I	3.91	3.00–5.10	< 0.001	1.96	1.30–2.96	0.001

Ref reference, *HR* hazard ratio, *CI* confidence interval, *VATS* video-assisted thoracoscopic surgery, *4LND* 4L node dissection

as the small sample size, small proportion of patients who underwent 4LND, and the large number lost to follow-up. Considering these factors, we initially reviewed 2063 patients and finally enrolled 1064 patients. Overall, 460 patients who underwent 4LND were matched to 460 patients who did not undergo 4LND after PSM. The rate of loss to follow-up was 6.5% (60/920). Consistent with the results of the study by Wang et al.,[14] the $4LND^+$ group showed an improved OS and DFS compared with the $4LND^-$ group in both univariate and multivariate analyses in our study, which further confirmed the survival benefit of 4LND in left-sided NSCLC patients.

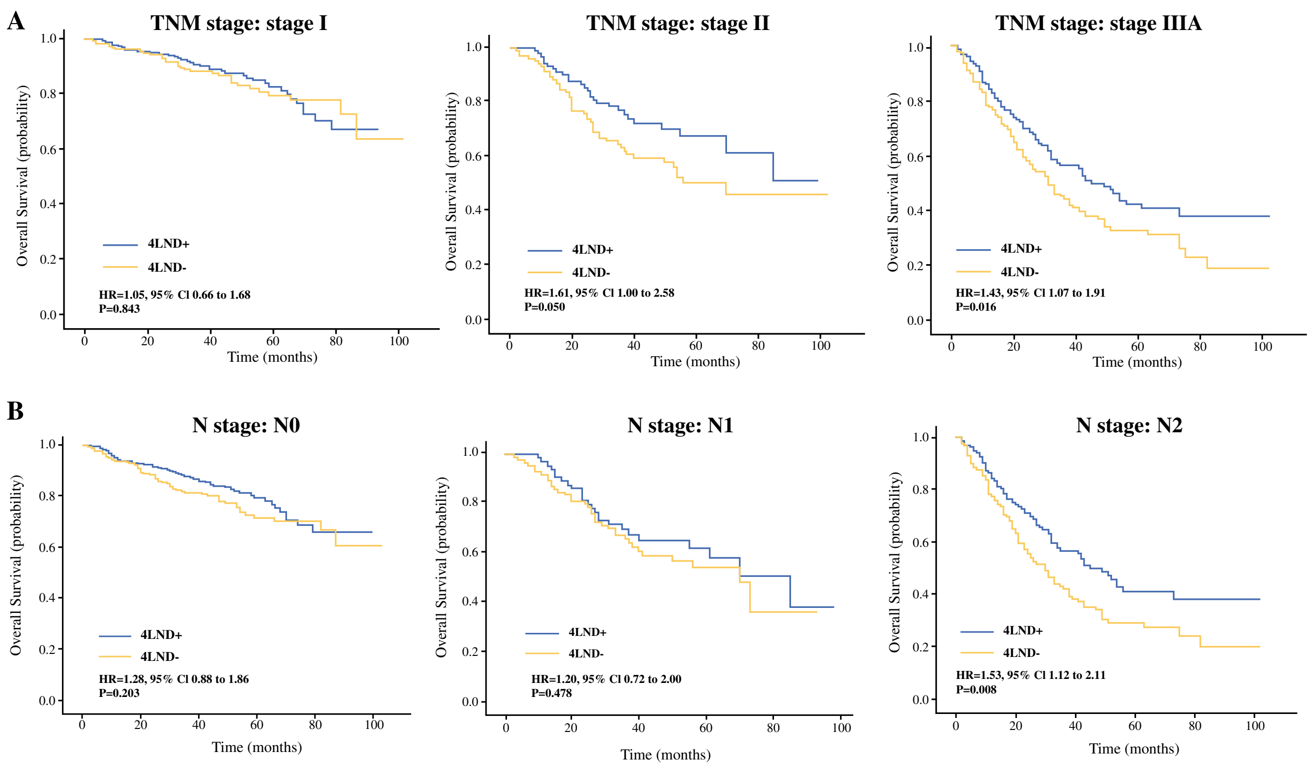

FIG. 3 Subgroup analyses of Kaplan–Meier estimated survival curves for patients with or without 4LND according to (**a**) pathologic TNM stage and (**b**) pathologic N stage. *4LND* 4L node dissection, *HR* hazard ratio, *CI* confidence interval

The benefit of 4LND for survival could be explained by two possible aspects. First, it may be a precise staging effect that the more LNs that are cleaned, the more accurate the postoperative stage of patients is. Furthermore, accurate staging could be translated into survival benefits because whether or not patients received appropriate adjuvant treatments, which were decided by their pTNM stage, would have a key role in their prognosis.[23–25] Second might be its therapeutic effect, i.e. removing localized LN metastasis and undetected micrometastases, which has already been proven in several studies.[26,27] In our study, 3.7% of patients had single-station 4L metastasis, i.e. 3.7% of patients with N2 disease could possibly be underestimated due to the inability to examine 4L nodes. Therefore, our study proved that 4LND indeed had an accurate staging effect. However, several other measures could also help patients achieve an accurate stage, i.e. PET-CT and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA).[28,29] Therefore, we were more interested in whether 4LND had therapeutic effects, and hence performed a subgroup analysis to confirm whether 4LND had a direct therapeutic effect and to identify the characteristics of patients who benefited from this procedure.

We found that patients at stage II, IIIA, and N2 disease in the $4LND^{+}$ group had a statistically significant longer OS compared with those in the $4LND^{-}$ group. In the subset of N2 disease, in which all patients presented with stage IIIA disease, the results indicated that 4LND can provide therapeutic benefit to NSCLC patients with N2 disease since patients in both groups were at the same stage. We therefore concluded that 4LND is important and necessary because both accurate staging and therapeutic benefits were achieved when performing 4LND in NSCLC patients. Patients at stage II, IIIA, and N2 disease might be appropriate candidates who can benefit from 4LND. However, we did not detect statistical significance in patients with stage I disease since stage I is correlated with N0 status. Additionally, the $4LND^{-}$ group also met the minimal criteria of SND.

Challenges for Implementing 4LND

In our experience, SND, including 4LND, is recommended for patients with a tumor diameter > 3 cm or with suspected LN involvement in preoperative CT assessment. In addition, patients who identified LN metastasis by intraoperative frozen section may also need to perform this procedure. However, several challenges impede the implement of 4LND by thoracic surgeons. The lack of consensus on guidelines for the extent of MLND is a primary factor, and therefore the choice of node station to be dissected is partly based on the experience and preference of different surgeons. Based on our results, we suggest that with the exception of early-stage I NSCLC, 4LND may be routinely performed on all left-sided NSCLC patients. Second, station 4L is located deep in the aortopulmonary window and in proximity to the left recurrent laryngeal nerve, which increases the difficulty of dissection. Nevertheless, the methods of 4LND in both thoracotomy and video-assisted thoracoscopic surgery (VATS) have already been reported in many studies.[18,30,31] Additionally, 'non-grasping en bloc MLND' used in this study allowed us to perform 4LND much more conveniently.[18] Third, some experts worry that complete resection of station 4L may result in more frequent operative complications, especially the hoarseness caused by left recurrent laryngeal nerve injury; however, in our study, the incidence of hoarseness was not significantly different in both groups. Together, we believe that 4LND is a much-needed approach that can be performed in a safe and feasible manner.

Study Limitations

This study has several limitations. First, this was a retrospective study of a prospective database, which allowed the possibility of unobserved, and therefore uncontrolled, confounding or selection bias. We used PSM to minimize this bias, but multicenter randomized clinical trials are still needed to confirm these findings. Second, the suggestion that 4LND may be a standard procedure for stage II or advanced stage left-sided NSCLC patients was based on postoperative pathologic TNM stage, which increased the accuracy and credibility of the results while reducing the significance of preoperative guidance. Thus, more accurate preoperative assessments, such as PET-CT, EBUS, or mediastinoscopy, as well as intraoperative frozen section of LNs, may be applied to assess LN status.

CONCLUSIONS

Our study found that station 4L involvement was commonly seen in left-sided NSCLC. 4LND has both precise staging effects and therapeutic effects, which are safe and feasible with survival benefits. Thus, we recommend 4LND as a standard procedure for patients with stage II or advanced-staged left-sided NSCLC.

DISCLOSURE Kejia Zhao, Shiyou Wei, Jiandong Mei, Chenglin Guo, Yang Hai, Nan Chen, and Lunxu Liu have declared no conflicts of interest.

REFERENCES

1. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108.
2. Vansteenkiste J, De Ruysscher D, Eberhardt WE, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2013;24 Suppl 6:vi89–98.
3. Izbicki JR, Passlick B, Pantel K, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg*. 1998;227(1):138-144.
4. Sugi K, Nawata K, Fujita N, et al. Systematic lymph node dissection for clinically diagnosed peripheral non-small-cell lung cancer less than 2 cm in diameter. *World J Surg*. 1998;22(3):290–4 (**discussion 294–5**)
5. Keller SM, Adak S, Wagner H, Johnson DH, Eastern Cooperative Oncology Group. Mediastinal lymph node dissection improves survival in patients with stages II and IIIa non-small cell lung cancer. *Ann Thorac Surg*. 2000;70(2):358–65 (**discussion 356–65**)
6. Wu Y, Huang ZF, Wang SY, Yang XN, Ou W. A randomized trial of systematic nodal dissection in resectable non-small cell lung cancer. *Lung Cancer*. 2002;36(1):1–6.
7. Lardinois D, Suter H, Hakki H, Rousson V, Betticher D, Ris HB. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. *Ann Thorac Surg*. 2005;80(1):268–74 (**discussion 274–65**)
8. 8. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg*. 2011;141(3):662-670.
9. National Comprehensive Cancer Network. NCCN guideline for non-small cell lung cancer. Version 3. NCCN; 2018.
10. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. *Eur J Cardio-thorac Surg*. 2006;30(5):787–92.
11. Riquet M. Bronchial arteries and lymphatics of the lung. *Thorac Surg Clin*. 2007;17(4):619–38
12. Riquet M, Arame A, Foucault C, Le Pimpec BF. Prognostic classifications of lymph node involvement in lung cancer and current International Association for the Study of Lung Cancer descriptive classification in zones. *Interact Cardiovasc Thorac Surg*. 2010;11(3):260–4.
13. Kuzdzal J, Zielinski M, Papla B, et al. Transcervical extended mediastinal lymphadenectomy: the new operative technique and early results in lung cancer staging. Eur J Cardio-thorac Surg. 2005;27(3):384–90 (**discussion 390**)
14. Wang YN, Yao S, Wang CL, et al. Clinical significance of 4L lymph node dissection in left lung cancer. *J Clin Oncol*. 2018;36(29):2935–42.
15. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265–81.
16. Liu L, Che G, Pu Q, et al. A new concept of endoscopic lung cancer resection: Single-direction thoracoscopic lobectomy. *Surg Oncol*. 2010;19(2):e71–7.
17. Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming

seventh edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009;4(5):568–77.
18. Liu C, Pu Q, Guo C, et al. Non-grasping en bloc mediastinal lymph node dissection for video-assisted thoracoscopic lung cancer surgery. BMC surgery. 2015;15(38).
19. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol*. 2011;6(2):244–85.
20. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007;2(8):706–14.
21. Kuroda H, Sakao Y, Mun M, et al. Lymph node metastases and prognosis in left upper division non-small cell lung cancers: the impact of interlobar lymph node metastasis. *PLoS One*. 2015;10(8):e0134674.
22. Sun F, Zhan C, Shi M, et al. Is routine dissection of the station 9 lymph nodes really necessary for primary lung cancer? *Int J Surg*. 2016;34:53–7.
23. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon J, Vansteenkiste J. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med*. 2004;350(4):351–60.
24. 24. Douillard J, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. *Lancet Oncol*. 2006;7(9):719–27.
25. Pignon J, Tribodet H, Scagliotti G, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26(21):3552–9.
26. Lardinois D, Suter H, Hakki H, Rousson V, Betticher D, Ris H. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. *Ann Thorac Surg*. 2005;80(1):268–74 (**discussion 274–65**)
27. Coello M, Luketich J, Litle V, Godfrey T. Prognostic significance of micrometastasis in non-small-cell lung cancer. *Clin Lung Cancer*. 2004;5(4):214–25.
28. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013;143(5 Suppl):e211S–50S.
29. Leong T, Loveland P, Gorelik A, Irving L, Steinfort D. Preoperative staging by EBUS in cN0/N1 lung cancer: systematic review and meta-analysis. *J Bronchology Interv Pulmonol*. Epub 22 Aug 2018. https://doi.org/10.1097/lbr.0000000000000545
30. Nagashima T. Thoracoscopic left mediastinal lymph node dissection. *Ann Transl Med*. 2016;4(1):10.
31. 31. Watanabe A, Nakazawa J, Miyajima M, et al. Thoracoscopic mediastinal lymph node dissection for lung cancer. *Semin Thorac Cardiovasc Surg*. 2012;24(1):68–73.

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