

Clinical Significance of 4L Lymph Node Dissection in Left Lung Cancer

Ya-Nan Wang, Shuang Yao, Chang-Li Wang, Mei-Shuang Li, Lei-Na Sun, Qing-Na Yan, Shao-Wen Tang, and Zhen-Fa Zhang

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on August 27, 2018.

Corresponding author: Zhen-Fa Zhang, MD, Tianjin Medical University Cancer Institute and Hospital, Department of Lung Cancer Surgery, Huanhu West Rd, Tianjin, China; e-mail: zhangzhenfa1973@163.com.

© 2018 by American Society of Clinical Oncology

0732-183X/18/3699-1/\$20.00

ABSTRACT

Purpose

To investigate the prognostic impact of 4L lymph node (LN) dissection in left lung cancer and to analyze the relative risk factors for 4L LN metastasis.

Patients and Methods

Patients

Patients who underwent 4L LN dissection (4L^{D+} group); the other 518 patients did not receive 4L LN dissection (4L^{D-} group). Propensity score weighting was applied to reduce the effects of observed confounding between the two groups. Study end points were disease-free survival (DFS) and overall survival (OS).

Results

The metastasis rate of station 4L was 20.9%, which was significantly higher than those of station 7 (14.0%; $P = .048$) and station 9 (9.8%; $P < .001$). Station 4L metastasis was associated with most other LN station metastases in univariate analysis, but only station 10 LN metastasis was an independent risk factor for 4L LN metastasis (odds ratio, 0.253; 95% CI, 0.109 to 0.588; $P = .001$) in multivariate logistic analysis. The 4L^{D+} group had a significantly better survival than the 4L^{D-} group (5-year DFS, 54.8% v 42.7%; $P = .0376$; 5-year OS, 58.9% v 47.2%; $P = .0200$). After allowing potential confounders in multivariate survival analysis, dissection of 4L LN retained its independent favorable effect on DFS (hazard ratio, 1.502; 95% CI, 1.159 to 1.947; $P = .002$) and OS (hazard ratio, 1.585; 95% CI, 1.222 to 2.057; $P = .001$). Propensity score weighting further confirmed that the 4L^{D+} group had a more favorable DFS ($P = .0014$) and OS ($P < .001$) than the 4L^{D-} group.

Conclusion

Station 4L LN involvement is not rare in left lung cancer, and dissection of the 4L LN station seems to be associated with a more favorable prognosis as compared with those who did not undergo this dissection.

J Clin Oncol 36. 2018 by American Society of Clinical Oncology

INTRODUCTION

Lymph node (LN) metastasis is a major and common metastatic pathway in lung cancer, with the metastasis rate of 30% to 40%.¹ Mediastinal LN dissection is a crucial component for accurate LN staging, having important prognostic and therapeutic implications for patients with non-small-cell lung cancer (NSCLC).^{2,3} The standard treatment procedure for resectable NSCLC involves lobectomy with systemic mediastinal LN dissection. However, the degree to which the mediastinal LNs should be exposed and the extent of their excision is still under debate.⁴⁻⁶ Current

surgical practice is partly dependent on the experience of the surgeon. Station 4L LN dissection for left lung cancer is more difficult than that for right lung cancer because of anatomic limitations caused by the aortic arch, left recurrent laryngeal nerve, and thoracic duct. Therefore, superior mediastinal LN metastasis of left lung cancer is rarely studied.⁷ The International Association for the Study of Lung Cancer (IASLC) suggests that systematic nodal dissection involves the minimal excision of at least three mediastinal nodal stations, including the subcarinal node, without requirement for 4L LNs in patients with left-sided tumors.⁸ Thus, we carried out this research to evaluate the clinical significance of 4L LN dissection.

ASSOCIATED CONTENT



See accompanying Editorial
DOI: <https://doi.org/10.1200/JCO.2018.79.3299>



Data Supplement
DOI: <https://doi.org/10.1200/JCO.2018.78.7101>

DOI: <https://doi.org/10.1200/JCO.2018.78.7101>

Table 1. Patients' Baseline Data Before and After Propensity Score Weighting

Characteristic	Entire Cohort		P	Propensity Score Weighting*		P
	4L ^{D-} Group	4L ^{D+} Group		4L ^{D-} Group	4L ^{D+} Group	
Sex			.870			.709
Male	354 (68.3)	96 (69.1)		284 (68.4)	94 (70.1)	
Female	164 (31.7)	43 (30.9)		131 (31.6)	40 (29.9)	
Age, years			.669			.962
< 65	327 (63.1)	85 (61.2)		258 (62.2)	83 (61.9)	
≥ 65	191 (36.9)	54 (38.8)		157 (37.8)	51 (38.1)	
Smoking history			.865			.615
Yes	343 (66.2)	94 (67.6)		272 (65.5)	91 (67.9)	
No	175 (33.8)	45 (32.4)		143 (34.5)	43 (32.1)	
Tumor location			.139			.989
Left upper lobe	288 (55.6)	87 (62.6)		232 (55.9)	75 (56.0)	
Left inferior lobe	230 (44.4)	52 (37.4)		183 (44.1)	59 (44.0)	
Tumor area			.845			.906
Central	158 (30.5)	45 (32.4)		123 (29.6)	39 (29.1)	
Peripheral	360 (69.5)	94 (67.6)		292 (70.4)	95 (70.9)	
Tumor size, cm (mean ± SD)	4.15 ± 2.2	4.62 ± 2.3	.028	4.30 ± 2.3	4.26 ± 2.2	.846
pT stage			.094			.869
T1	210 (40.5)	44 (31.7)		153 (36.9)	53 (39.3)	
T1a	12 (2.3)	2 (1.5)		8 (1.9)	3 (2.2)	
T1b	67 (12.9)	15 (10.8)		49 (11.8)	20 (14.9)	
T1c	131 (25.3)	27 (19.4)		96 (23.2)	30 (22.2)	
T2	206 (39.8)	56 (40.3)		169 (40.7)	52 (38.5)	
T2a	126 (24.3)	30 (21.6)		103 (24.8)	28 (20.7)	
T2b	80 (15.5)	26 (18.7)		66 (15.9)	24 (17.8)	
T3	64 (12.4)	22 (15.8)		59 (14.2)	17 (12.6)	
T4	38 (7.3)	17 (12.2)		34 (8.2)	13 (9.6)	
Histology			.705			.950
ADC	204 (39.4)	49 (35.2)		165 (39.8)	52 (38.8)	
SQ	228 (44.0)	68 (48.9)		178 (42.9)	61 (45.5)	
SCC	16 (3.1)	3 (2.2)		14 (3.4)	4 (3.0)	
Others	70 (13.5)	19 (13.7)		58 (14.0)	17 (12.7)	
Adenocarcinoma subtype			.751			.670
AIS/MIA	12 (2.3)	3 (2.1)		12 (2.9)	3 (2.2)	
Lepidic predominant	43 (8.3)	9 (6.5)		36 (8.7)	9 (6.7)	
Acinar predominant	80 (15.5)	19 (13.6)		63 (15.2)	20 (14.9)	
Papillary predominant	28 (5.4)	4 (2.9)		19 (4.6)	4 (3.0)	
Micropapillary predominant	12 (2.3)	5 (3.6)		10 (2.4)	5 (3.8)	
Solid predominant	29 (5.6)	9 (6.5)		25 (6.0)	11 (8.2)	
pTNM stage			.002			.283
I	194 (37.5)	37 (26.6)		142 (34.2)	51 (38.1)	
IA1	11 (2.1)	2 (1.4)		8 (1.9)	3 (2.2)	
IA2	48 (9.3)	13 (9.4)		36 (8.7)	18 (13.5)	
IA3	68 (13.2)	10 (7.2)		44 (10.6)	14 (10.5)	
IB	67 (12.9)	12 (8.6)		54 (13.0)	16 (11.9)	
II	137 (26.4)	29 (20.9)		112 (27.0)	27 (20.1)	
IIA	46 (8.9)	14 (10.1)		42 (10.1)	13 (9.7)	
IIB	91 (17.5)	15 (10.8)		70 (16.9)	14 (10.4)	
III	187 (36.1)	73 (52.5)		161 (38.8)	56 (41.8)	
IIIA	151 (29.2)	57 (41.0)		128 (30.8)	44 (32.8)	
IIIB	36 (6.9)	16 (11.5)		33 (7.9)	12 (9.0)	
pN stage			.034			.788
N0	291 (56.2)	67 (48.2)		228 (54.9)	77 (57.0)	
N1	72 (13.9)	14 (10.1)		52 (12.5)	14 (10.4)	
N2	155 (29.9)	58 (41.7)		135 (32.5)	44 (32.6)	

NOTE. Data presented as No. (%) unless otherwise noted.

Abbreviations: 4LD⁺ group, patients who underwent 4L lymph node dissection; 4L^{D-} group, patients who did not receive 4L lymph node dissection; AIS, adenocarcinoma in situ; ADC, adenocarcinoma; MIA, minimally invasive adenocarcinoma; SCC, small cell carcinoma; SQ, squamous cell carcinoma.

*Number of valid cases is different from the total count in the cross-tabulation table because the cell counts have been rounded. Patients with a missing value were excluded from inverse probability of treatment weighting analysis.

a different weight, from 0.58 to 2.21. If the weighting coefficient is 1.5, it will be considered as 1.5 people. The IPTW uses the weight to construct a virtual standard population, which often results in the number of valid cases being different from the total count in the cross-tabulation table because the cell counts have been rounded (Table 1). However, there will

not be much difference before and after weighting, and the overall proportion is still 100% of the patients in the propensity score weighting (PSW) analysis. In addition, the patients (108) who were lost to follow-up with a missing value were excluded from IPTW analysis. Propensity scores for all patients were calculated by using a multiple logistic regression¹⁴ with

the following covariates: age, sex, pathological T (pT) stage, smoking history, pathological N (pN) stage, histology, tumor location, tumor area, and pathological tumor-node-metastasis (pTNM) stage.

Statistical Analysis

All statistical analyses were performed using the SAS 9.4 software (SAS Institute, Cary, NC). χ^2 test was used for categorical variables, and *t* test was used for continuous variables. Multivariate analysis was performed using a logistic regression model to evaluate the relation between station 4L metastasis and risk factors. Survival was estimated by the Kaplan-Meier method and compared using the log-rank test. Multivariate Cox proportional hazards regression analysis was used to calculate the hazard ratio (HR) and 95% CI. In all analyses, two-tailed $P < .05$ was considered statistically significant.

RESULT

Baseline Data of All Patients

Table 1 shows the baseline data of all of the patients ($n = 657$) and of the PSW patients. A total of 139 (21.2%) and 518 (78.8%) patients were assigned to the 4L^{D+} group and 4L^{D-} group, respectively. Before weighting, difference were observed in terms of pTNM stage ($P = .002$), pN stage ($P = .034$), and tumor size ($P = .028$); after weighting, the results were similar between the two groups ($P > .05$; Table 1).

Distal LN Involvement

Figure 2 summarizes the frequency of node involvement per station in left lung cancer. Of the 139 patients with 4L LN dissection, 29 (20.9%) had 4L involvement. The metastasis rate of station 4L (20.9%) was significantly higher than those of station 7 (14.0%; $P = .048$) and station 9 LNs (9.8%; $P < .001$), but no

significant difference was observed among other node stations ($P > .05$; Fig 2).

Relation of 4L LN Metastasis

As shown in Table 2, the 4L LN metastasis was significantly correlated with all other stations (station 5, $P < .001$; station 6, $P < .001$; station 7, $P = .005$; station 9, $P = .019$; station 10, $P < .001$; station 11, $P = .006$), except station 8 ($P = 0.660$); sex, age, smoking history, pT stage, tumor size, adenocarcinoma subtype, tumor location, and tumor area were shown to have no significant correlation with station 4L metastasis. Those statistically significant factors were further analyzed by multivariate logistic analysis, and the result revealed that station 10 metastasis was independently associated with 4L LN metastasis (OR, 0.253; 95% CI, 0.109 to 0.588; $P = .001$).

Postoperative Survival

At completion of the study, 335 patients died and 179 patients had recurrence or metastasis at follow-up. Seventy patients died and 34 patients had recurrence or metastasis in the 4L^{D+} group. Two hundred sixty-five patients died and 145 patients had recurrence or metastasis in the 4L^{D-} group. The 5-year DFS rates were 54.8% in the 4L^{D+} group and 42.7% in the 4L^{D-} group (median, 71.6 v 39.4 months). The 5-year OS rates in the two groups were 58.9% and 47.2%, respectively (median, 86.0 v 50.1 months). The log-rank test showed that the 4L^{D+} group had a significantly superior survival compared with the 4L^{D-} group (DFS, $P = .0376$; OS, $P = .0200$; Figs 3A and 3C). After PSW, the DFS and OS were significantly higher in the 4L^{D+} group compared with the 4L^{D-} group ($P = .0014$ and $P < .001$, respectively; Figs 3B and 3D).

Analysis of Survival

Several variables, such as status of 4L LN dissection, tumor location, pT stage, histology, and pN stage, were all significant factors for DFS by univariate analysis ($P = .038$, $P = .038$, $P < .001$, $P < .001$, and $P < .001$, respectively), and status of 4L LN dissection, tumor area, pT stage, histology, and pN stage were all significant factors for OS ($P = .020$, $P = .030$, $P = .002$, $P < .001$, and $P < .001$, respectively) by univariate analysis (Table 3). Additional multivariate analysis showed that status of 4L LN dissection was an independent factor for DFS (HR, 1.502; 95% CI, 1.159 to 1.947; $P = .002$) and OS (HR, 1.585; 95% CI, 1.222 to 2.057; $P = .001$), together with pT stage, histology, and pN stage (Table 3).

DISCUSSION

The presence of tumor cell metastases is one of the most important adverse factors for prognosis in lung cancer. Considering the key role of LNs in lung cancer metastasis, thorough removal of LNs is of great importance.

Table 2. Univariate and Multivariate Analysis of Correlation Between Clinicopathological Factors and Station 4L Metastasis

Variable	Univariate Analysis			P	Multivariate Analysis		
	No.	Station 4L Metastasis			OR	95% CI	P
		Positive	Negative				
No.	139	29	110				
Sex				.069			
Male	96	16 (16.7)	80 (83.3)				
Female	43	13 (30.3)	17 (16)p98	1ysis.999942.338-1.2926Age)14.74 gnyearnalisxiex)Tj43.33790332Tm D)Tj/F8691659.8 05			

removal of at least stations 4L, 5, and 6 LNs for left-sided tumors.¹⁶ The current studies usually focus on multiple stations of LNs and summarize station 4L as the superior mediastinal LNs.^{17,18} To date, there is no study involving the comparison of short- and long-outcomes of 4L nodal dissection. One explanation may be the complex anatomy of station 4L: adjacent to the aortic arch, left recurrent laryngeal nerve, and thoracic duct. These anatomic limitations make 4L dissection more difficult and increase the risk of surgery.¹⁹ Therefore, some thoracic surgeons do not remove 4L LNs during the operation of left-sided tumors, which leads to the lack of a large sample of clinical data about the dissection of station 4L and its impact on prognosis. We therefore retrospectively reviewed the clinical significance of removing 4L LNs.

In our study, from a total of 657 patients with left lung cancer, we observed that the frequent metastatic sites of mediastinal LNs

involved station 4L and 5. This finding was in line with some previous studies.^{20,21} Univariate analysis revealed that 4L LN metastasis was significantly correlated with most other stations, but only station 10 metastasis was an independent risk factor for 4L LN metastasis by multivariate analysis. This may be explained by the fact that there is a transition zone between station 4L and station 10 at the tracheobronchial angle. Shimada et al²² reported that left upper lobe tumors had more of a predilection for involvement of superior mediastinal LNs than lower lobe tumors in patients with NSCLC. In our study, we found that the metastasis of station 4L was more likely to occur in the left upper lobe, but there was no statistical significance. This may be due to the small sample size. Therefore, large prospective studies are still needed for additional research.

The results of our study revealed that the 5-year DFS and OS were significantly higher in the 4L^{D+} group than in the 4L^{D-}

-
-
-
-
-

| | | | |

group. Under multivariate analysis, 4L LN dissection proved to be one of the independent predictors of favorable DFS and OS. The reason may be that 4L LN dissection helps to remove localized LN metastasis and undetected micrometastases and reduce the incidence of local recurrence, which could result in better local tumor control.^{16,23,24} Japanese scholars Sakao et al²⁵ and Kuroda

et al²⁶ also found that dissection of 4L LNs was important for the prognosis of patients with left lung cancer. To eliminate selection bias, our study pioneers the use of the PSW method to compare the prognostic impact of pulmonary resection for left lung cancer between the 4L^{D+} group and the 4L^{D-} group. After weighting, the 4L^{D+} group still had a significantly higher survival rate than the

4L^{D-} group. In addition, Watanabe et al²⁷ pointed out that the 5-year survival rate of patients with left lung cancer with N2 disease was worse than that of patients with right-sided lesions, which may be due to insufficient LN dissection caused by anatomic restrictions. On the basis of these findings, we believe 4L LN dissection may be important. Additional prospective evaluation of the role of dissection is warranted to confirm these findings.

With the development of the technique of video-assisted thoracic surgery, surgical field visualization is also constantly improving. Some anatomic regions, such as the left paratracheal LNs (4L), which are difficult to expose by routine surgery, now can be clearly identified and resected by a thoracoscopic approach because of the magnification of the surgical field. Previous studies have demonstrated that it was feasible to dissect 4L LNs avoiding left recurrent laryngeal nerve injury.²⁸⁻³¹ In addition, it was reported that removal of LNs in station 4L could be achieved in 100% of patients by video-assisted mediastinal lymphadenectomy.³² Today, many types of devices are available to make the complete and extensive dissection of LNs easier.

Our study has several limitations. First, our research is a single-center retrospective study, although PSW was used to balance the variables that may influence the outcomes between the groups. Second, the number of patients with 4L LN dissection is small, which may raise the possibility of selection bias. Third, the number of patients lost to follow-up is large. Although there was no statistically significant difference between the patients who lost contact after surgery (108) and the patients who had complete

follow-up information (549) on the basis of the relevant covariances, there are still differences in loss to follow-up between the 4L^{D+} and 4L^{D-} groups. The patients lost to follow-up in the 4L^{D-} group were more likely to have a smoking history and more comorbidities and were older than those in the 4L^{D+} group. Consequently, long-term effects remain to be fully confirmed and should be studied further with a larger sample size and a multi-center randomized clinical trial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosur

and validation used in the development of proposals for revision of the stage classification of NSCLC in the forthcoming eighth edition of the TNM Classification of Lung Cancer. *J Thorac Oncol* 11: 1433-1446, 2016

11. 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* 6:244-285, 2011

12. Austin PC: The use of propensity score methods with survival or time-to-event outcomes: Reporting measures of effect similar to those used in randomized experiments. *Stat Med* 33:1242-1258, 2014

13. Austin PC, Stuart EA: Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med* 34:3661-3679, 2015

14. Austin PC, Schuster T, Platt RW: Statistical power in parallel group point exposure studies with time-to-event outcomes: An empirical comparison of the performance of randomized controlled trials and the inverse probability of treatment weighting (IPTW) approach. *BMC Med Res Methodol* 15:87, 2015

15. Grupo Cooperativo de Carcinoma Broncogénico de la Sociedad Española de Neumología y Cirugía Torácica: Intraoperative lymph node staging in bronchogenic carcinoma surgery. Consensus report [in Spanish]. *Arch Bronconeumol* 37:495-503, 2001

16. Lardinois D, Suter H, Hakki H, et al: 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* 80:268-274, 2005; discussion 274-275

17. Aokage K, Yoshida J, Ishii G, et al: Subcarinal lymph node in upper lobe non-small cell lung cancer patients: Is selective lymph node dissection valid? *Lung Cancer* 70:163-167, 2010

18. Okada M, Tsubota N, Yoshimura M, et al: Proposal for reasonable mediastinal lymphadenectomy in bronchogenic carcinomas: Role of subcarinal nodes in selective dissection. *J Thorac Cardiovasc Surg* 116:949-953, 1998

19. Witte B, Hürtgen M: Video-assisted mediastinoscopic lymphadenectomy. *Multimed Man Cardiothorac Surg* 2007:mmcts.2006.002576, 2007

20. Shien K, Toyooka S, Soh J, et al: Clinicopathological characteristics and lymph node metastasis pathway of non-small-cell lung cancer located in the left lingular division. *Interact Cardiovasc Thorac Surg* 20:791-796, 2015

21. Hirono T, Yamato Y, Souma T, et al: How extensive should lymph node dissection be done for the surgery of the left lung cancer? [in Japanese]. *Kyobu Geka* 47:20-23, 1994

22. Shimada Y, Saji H, Kakihana M, et al: Retrospective analysis of nodal spread patterns according to tumor location in pathological N2 non-small cell lung cancer. *World J Surg* 36:2865-2871, 2012

23. Coello MC, Luketich JD, Little VR, et al: Prognostic significance of micrometastasis in non-small-cell lung cancer. *Clin Lung Cancer* 5:214-225, 2004

24. Osaki T, Oyama T, Gu CD, et al: Prognostic impact of micrometastatic tumor cells in the lymph nodes and bone marrow of patients with completely

resected stage I non-small-cell lung cancer. *J Clin Oncol* 20:2930-2936, 2002

25. Sakao Y, Miyamoto H, Yamazaki A, et al: The spread of metastatic lymph nodes to the mediastinum from left upper lobe cancer: Results of superior mediastinal nodal dissection through a median sternotomy. *Eur J Cardiothorac Surg* 30:543-547, 2006

26. 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* 10:e0134674, 2015

27. Watanabe Y, Shimizu J, Oda M, et al: Improved survival in left non-small-cell N2 lung cancer after more extensive operative procedure. *Thorac Cardiovasc Surg* 39:89-94, 1991

28. Kim HJ, Kim YH, Choi SH, et al: Video-assisted mediastinoscopic lymphadenectomy combined with minimally invasive pulmonary resection for left-sided lung cancer: Feasibility and clinical impacts on surgical outcomes. *Eur J Cardiothorac Surg* 49:308-313, 2016

29. Nagashima T: Thoracoscopic left mediastinal lymph node dissection. *Ann Transl Med* 4:10, 2016

30. Liu J, Cui F, Li SB: Radical treatment for left upper-lobe cancer via complete VATS. *J Thorac Dis* 5: 868-872, 2013

31. Lee HS, Jang HJ: Thoracoscopic mediastinal lymph node dissection for lung cancer. *Semin Thorac Cardiovasc Surg* 24:131-141, 2012

32. Leschber G, Holinka G, Linder A: Video-assisted mediastinoscopic lymphadenectomy (VAMLA)—a method for systematic mediastinal lymphnode dissection. *Eur J Cardiothorac Surg* 24: 192-195, 2003

A i i i i i

Ya-Nan Wang, Shuang Yao, Chang-Li Wang, Mei-Shuang Li, Lei-Na Sun, Qing-Na Yan, and Zhen-Fa Zhang, Tianjin Medical University Cancer Institute and Hospital, Tianjin; and Shao-Wen Tang, Nanjing Medical University, Nanjing, China.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Significance of 4L Lymph Node Dissection in Left Lung Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Ya-Nan Wang

No relationship to disclose

Shuang Yao

No relationship to disclose

Chang-Li Wang

No relationship to disclose

Mei-Shuang Li

No relationship to disclose

Lei-Na Sun

No relationship to disclose

Qing-Na Yan

No relationship to disclose

Shao-Wen Tang

No relationship to disclose

Zhen-Fa Zhang

No relationship to disclose