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Lymph node dissection and survival in patients with early stage nonsmall cell lung cancer

A 10-year cohort study

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Abstract

It is still debatable whether complete mediastinal lymph node dissection (MLND) is associated with better survival than mediastinal lymph node sampling (MLNS) in surgical treatment of nonsmall cell lung cancer (NSCLC). We aimed to assess the impact of lymph node dissection on long-term survival among stage I NSCLC patients.

In this cohort study, 317 stage I NSCLC Chinese patients in Shanghai Chest Hospital were followed up for at least 10 years to evaluate the impact of different lymph node dissection modes on their survival. Among them, 161 patients were in the MLND group and 156 in the MLNS group. Overall survival and median survival times were calculated for the 2 groups. The association between lymph node dissection and the survival of NSCLC patients was assessed using Cox proportional-hazard models.

Patients in the MLND group presented better survival (median survival time = 154.67 months) than those in the MLNS group (median survival time = 124.67 months). The MLNS had higher mortality than the MLND group, with the crude hazard ratio of the MLNS group relative to the MLND group as 1.32 (95% confidence interval [CI] 0.97, 1.78). After adjusting for age and sex, the association between lymph node dissection and mortality (hazard ratio 1.36, 95% CI 1.00, 1.84) was statistically significant ($P = .047$). Further adjusting for baseline clinical characteristics, the association (hazard ratio 1.40, 95% CI 1.02, 1.92) remained statistically significant ($P = .036$). The association between lymph node dissection mode and mortality was strong among patients with tumor size between 2.0 and 3.0 cm (hazard ratio 2.79, 95% CI 1.45, 5.37).

We found that the MLND was associated with better survival for patients with early-stage NSCLC, compared with the MLNS. The effects of MLND on survival may depend on tumor size. Our findings have important implications in the treatment of early-stage NSCLC. Further prospective studies with a large sample size are needed to confirm our findings.

Abbreviations: CI = confidence interval, ESTS = European Society of Thoracic Surgeons, MLND = mediastinal lymph node dissection, MLNS = mediastinal lymph node sampling, NSCLC = nonsmall cell lung cancer.

Keywords: cohort study, lymph node dissection, mortality, nonsmall cell lung cancer, survival

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YS-T and FM contributed equally to this work.

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1. Introduction

Surgical resection has been proved to be the single curative treatment for patients with early stage nonsmall cell lung cancer (NSCLC).^[1-3] Lobectomy (or pneumonectomy) with lymph node dissection has become a common treatment procedure. However, it is still debatable whether the complete mediastinal lymph node dissection (MLND) is superior to the mediastinal lymph node sampling (MLNS) in the survival of NSCLC patients with surgical treatment. In a randomized trial of systematic lymph node dissection in Chinese patients with resectable NSCLC, Wu et al^[4] reported that lobectomy (pneumonectomy) combined with systematic lymph node dissection improved survival in NSCLC patients. However, their findings are questionable due to the imbalanced distribution of early-stage patients between 2 groups. Globally, about 40% to 50% NSCLC diagnosed are in stage I.^[5] Several studies evaluated the association between lymph node dissection mode and survival in patients with stage I NSCLC who underwent curative-intent surgery, and concluded that the dissection mode did not significantly influence either disease-free survival or overall survival.^[6,7] In a randomized multi-institutional trial, Darling et al^[8] reported that MLND does not improve survival compared to MLNS in patients undergoing resection for N0 or nonhilar N1, T1 or T2 NSCLC. On the contrary, in a recent study of 15,195 patients of stage I to III NSCLC treated with surgical resection, David et al^[9] concluded

that the number of lymph nodes sampled influenced both overall survival and cancer-specific survival, but the optimal number of lymph nodes sampled remains unclear.

China has experienced a rapid economic growth in recent decades. The prevalence of NSCLC has increased over time.^[10] As a large number of patients with early stages of NSCLC are detected in China^[11], it is critically important to understand that which lymph node dissection mode has better survival among early-stage NSCLC patients. The previous research in this area in China mainly focused on 3-year or 5-year survival rates.^[4,12] In this retrospective cohort study, we analyzed the 10-year survival rates according to lymph node dissection modes in Chinese patients with stage I NSCLC.

2. Methods

2.1. Approaches for lymph node dissection

There is no consensus on the approaches for lymph node dissection currently. To standardize and improve preoperative and intraoperative lymph node staging and pathologic evaluation of NSCLC, the European Society of Thoracic Surgeons (ESTS) guidelines suggest that systematic lymph node dissection is recommended in all cases to ensure complete resection.^[13] Two lymph node dissection modes were compared in this study: the MLNS with a predetermined selection of the lymph node stations specified by the surgeon; and MLND with all the lymph nodes dissected and removed systematically within anatomical landmarks.

2.2. Participants

All NSCLC cases in this cohort study were recruited from Shanghai Chest Hospital from January 1998 to January 2005. During this period, 4240 patients with diagnosed lung cancer were operated with either pneumonectomy or lobectomy. Eligible patients for this study met the following criteria: without preoperation chemotherapy; with complete lesion removal via lobectomy; consistent with the ESTS MLND or MLNS; post-operation staging was stage I (T1a-2aN0M0); without post-operation chemotherapy; and with at least 10-year follow-up. A total of 317 patients met the above criteria according to the 2005 international definition of complete resection in lung cancer surgery^[14] and 2009 lung cancer staging.^[15] Among 317 participants, 161 patients were in the MLND group and 156 in the MLNS group.

2.3. Follow-up

All participants were followed up to the date of death or April 30, 2015 if surviving. The data on mortality status during the follow-up period were collected through the death records in the Shanghai Centre for Disease Control and Prevention. The postoperative survival time was calculated as the difference between the surgery date and the date of death. Patients surviving beyond April 30, 2005 were censored on that day and their survival time was determined as the difference between April 30, 2015 and the surgery date.

2.4. Data analysis

The Kaplan–Meier method was used for calculating median survival time. To adjust for potential confounding factors, Cox proportional-hazard models were used to calculate adjusted

hazard ratios (HRs) with the MLND group as the reference. A *P* value of less than .05 was considered significant. All statistical analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL). This project was approved by the Ethics Review Committee of Shanghai Chest Hospital, and the need for individual consent was waived by the ethics committee due to the retrospective nature.

3. Results

3.1. Characteristics of different lymph node dissection groups

Table 1 shows clinical characteristics of the 2 groups. As expected, the MLNS group had a significantly less number of total dissected lymph nodes than in the MLND group (*P* < .001). The 2 groups were also significantly different in histological types (*P* = .038). However, there were no significant differences

Table 1
Clinical characteristics of different lymph node dissection groups.

Variables	MLND, n (%)	MLNS, n (%)	<i>P</i> *
Counts	161	156	
Sex			.207
Male	106 (65.8)	92 (59.0)	
Female	55 (34.2)	64 (41.0)	
Age, y			.377
<70	118 (73.3)	121 (77.6)	
≥70	43 (26.7)	35 (22.4)	
Pathological stage			.836
IA	71 (44.1)	67 (42.9)	
IB	90 (55.9)	89 (57.1)	
Histology			.038
Ad	87 (54.0)	106 (67.9)	
Sq	50 (31.1)	35 (22.4)	
Ad-sq	24 (14.9)	15 (9.6)	
Tumor size, cm			.328
≤2	29 (18.0)	25 (16.0)	
>2 to ≤3	47 (29.2)	36 (23.1)	
>3 to 5	85 (52.8)	95 (60.9)	
Degree of differentiation			.333
Low	24 (14.9)	22 (14.1)	
Moderate	52 (32.3)	43 (27.6)	
High	31 (19.3)	44 (28.2)	
Middle/low	20 (12.4)	22 (14.1)	
Middle/high	34 (21.1)	25 (16.0)	
Tumor location			.263
Left upper lobe	39 (24.2)	41 (26.3)	
Left lower lobe	27 (16.8)	23 (14.7)	
Right upper lobe	59 (36.6)	45 (28.8)	
Right middle lobe	9 (5.6)	18 (11.5)	
Right lower lobe	27 (16.8)	29 (18.6)	
Lymph node dissection number			<.001
<6	80 (49.7)	156 (100)	
≥6	81 (50.3)	0 (0)	
Operative location			.572
Left upper	40 (24.8)	40 (25.6)	
Left lower	27 (16.8)	21 (13.5)	
Right upper	54 (33.5)	44 (28.2)	
Right middle	6 (3.7)	11 (7.1)	
Right lower	24 (14.9)	30 (19.2)	
Right upper middle/right middle lower	10 (6.2)	10 (6.4)	

MLND = mediastinal lymph node dissection, MLNS = mediastinal lymph node sampling.

* Fisher exact test or chi-square test.

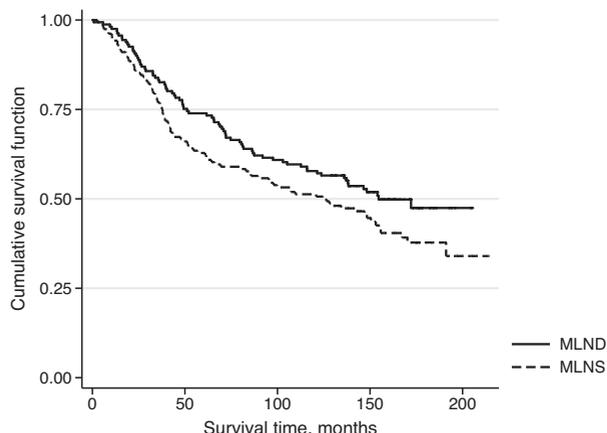


Figure 1. Survival time (month) by lymph node dissection groups: mediastinal lymph node dissection (MLND) and mediastinal lymph node sampling (MLNS) in stage I nonsmall cell lung cancer patients.

between MLND and MLNS groups in other clinical characteristics.

3.2. Survival time and cumulative survival rates of different lymph node dissection groups

Among the 317 patients, the median survival time was 146.47 months. The 3, 5, and 10-year cumulative survival rates were 80.1%, 68.5%, and 54.6%, respectively. The median survival time was 124.67 months for the MLNS group and 154.67 for the MLND groups, as shown in Fig. 1. The MLND group survived longer than the MLNS group. The 3, 5, and 10-year cumulative survival rates were 76.9%, 62.8%, and 51.3% for the MLNS group, and 83.2%, 73.9%, and 57.8% for the MLND group, respectively (Table 2).

3.3. Association between lymph node dissection and mortality after adjusting for baseline characteristics

In univariate analysis, age, sex, pathological staging, operative location, tumor size, tumor location, and differentiation were significantly associated with survival, but pathological types and differentiation were not significantly associated with survival (Table 3). As a result, it is important to adjust for potential confounding effects of those baseline characteristics when assessing the association between different lymph node dissection modes and survival. Table 4 shows the crude and adjusted HRs and their 95% confidence intervals (CIs). The crude HR was 1.32 (95% CI 0.97, 1.78) between lymph node dissection and mortality, indicating that the MLNS group had a higher

Table 2
Survival rates and median survival time of different lymph node dissection groups.

Variables	All patients	MLND	MLNS
n	317	161	156
Survival rates of 3 y(%)	254 (80.2)	134 (83.2)	120 (76.9)
Survival rates of 5 y(%)	217 (68.5)	119 (73.9)	98 (62.8)
Survival rates of 10 y(%)	173 (54.6)	93 (57.8)	80 (51.3)
Median survival time (m)	146.5	154.7	124.7

MLND=mediastinal lymph node dissection, MLNS=mediastinal lymph node sampling.

Table 3
Univariate analysis of postoperative survival in the 317 patients with stage I NSCLC according to baseline characteristics.

Variables	Counts	Percentage (%)	Median survival (mos)	P
Sex				
Male	198	62.46	120.90	.044*
Female	119	37.54	>208	
Age				
<70	239	75.39	167.27	.000†
≥70	78	24.61	82.98	
Pathological staging				
IA	138	43.53	172.17	.010*
IB	179	56.47	109.6	
Operative location				
Left upper	80	25.24	97.87	.002†
Left lower	48	15.14	>208	
Right upper	98	30.91	191.10	
Right middle	17	5.36	>208	
Right lower	54	17.03	82.98	
Right upper middle/ right middle lower	20	63.09	89.60	
Pathological types				
Ad	193	60.88	148.33	.075
Sq	85	26.82	167.27	
Ad-sq	39	12.30	87.40	
Lymph node dissection				
MLND	161	50.79	154.67	.072
MLNS	156	49.21	124.67	
Tumor size, cm				
≤2	54	17.03	>208	.005†
>2 to ≤3	83	26.18	146.97	
>3 to ≤5	180	56.79	107.27	
Degree of differentiation				
Low	46	14.51	69.37	.257
Moderate	95	29.97	115.97	
High	75	23.66	191.1	
Middle/low	42	13.25	126.37	
Middle/high	59	18.61	170.20	
Tumor location				
Left upper lobe	80	25.24	97.87	.003†
Left lower lobe	50	15.77	>208	
Right upper lobe	104	32.81	191.10	
Right middle lobe	27	8.52	136.00	
Right lower lobe	56	17.66	80.47	

MLND=mediastinal lymph node dissection, MLNS=mediastinal lymph node sampling.

* P<.05.

† P<.01.

mortality than the MLND group, although the difference is not significant (P=.073). However, after adjustment for age and sex, the association (HR 1.36, 95% CI 1.00, 1.84) became statistically significant (P=.047). With further adjustment for age, sex, pathological staging, operative location, tumor size, tumor location, and differentiation, the HR (1.40, 95% CI 1.02, 1.92) remained statistically significant (P=.036). Table 5 shows the adjusted HRs stratified by tumor size. The association was only strong and statistically significant for patients with tumor sized 2 to <3 cm (HR 2.79, 95% CI 1.45, 5.37).

4. Discussion

In this retrospective study of 317 NSCLC patients, we found that the MLND was associated with longer survival time and lower mortality compared with the MLNS group. A number of baseline

Table 4**Association between lymph node dissection and survival in 317 stage I NSCLC patients.**

	Hazard ratio	95% CI	P
Crude	1.32	0.97, 1.78	.073
Adjusted for age, sex	1.36	1.00, 1.84	.047
Adjusted for clinical characteristics*	1.40	1.02, 1.92	.036

CI = confidence interval, NSCLC = nonsmall cell lung cancer.

* Adjusted for age, sex, pathological staging, operational location, tumor size, tumor location, and differentiation.

clinical characteristics were also found to be relevant with patients' survival rates. After adjustment for those baseline characteristics, the association between different lymph node dissection modes and survival was statistically significant. The focus of the recent debate is whether the MLND is associated with improved survival rates of early-stage NSCLC. With our long-term follow-up data from China, our findings support the use of complete lymph node dissection for early-stage NSCLC patients. These findings, if further confirmed in more prospective studies, would have important implications in the treatment of Chinese patients with early-stage NSCLC.

With recent improvement in diagnostic techniques such as radiologic imaging, more patients are being detected in early stage of NSCLC in China. It has been considered that tumor cells would rarely metastasize through the pathway of lymph drainage to the regional lymph nodes^[16,17] at this stage. Therefore, is it really necessary to execute complete mediastinal lymph node dissection for stage I NSCLC patients? In our study, we found that MLND was associated with higher survival time and lower mortality in stage I NSCLC Chinese patients. In another study of 526 patients with 268 in the MLND group and 264 in the MLNS, Wu et al^[4] found that the MLND group had a significantly higher survival rate than the MLNS group. These findings support assumption that NSCLC patients who have undergone MLND would have better prognosis. However, some studies reported contradictory results. Okada et al^[6] divided patients with stage I NSCLC into 2 groups: selective mediastinal dissection (n = 377) and systematic lymph node dissection groups (n = 358). They found there was no significant difference in disease-free survival or overall survival, and the rates of distant metastasis and local recurrence were also similar in these 2 groups. They concluded that selective mediastinal dissection and systematic lymph node dissection groups had similar clinical outcomes. A systematic review and meta-analysis by Huang et al^[18] also revealed that results for overall survival, local recurrence rates, and distant metastasis rates were similar between MLND and MLNS groups in early-stage NSCLC patients. In another meta-analysis, Wright et al^[19] suggested that MLND is associated with improved survival compared with MLNS group in patients with stage I to

Table 5**Association between lymph node dissection and survival stratified by tumor size.**

Tumor diameter, cm	Hazard ratio*	95% CI	P
<2	1.41	0.44, 4.49	.56
2 to <3	2.79	1.45, 5.37	.0022
3 to 5	1.14	0.76, 1.69	.53

CI = confidence interval.

* Adjusted for age, sex, pathological staging, operational location, and differentiation.

IIIA NSCLC undergoing resection. In a randomized trial, Darling et al^[8] reported that the MLND did not improve survival compared with the MLNS. However, in their study, the MLND group had a higher survival rate than the MLNS group, although the difference was not statistically significant. Although we do not know the reasons for the inconsistent findings among different studies, 1 possible explanation is the differences in the clinical characteristics such as tumor size.

Generally, the MLND is considered to have the benefit of identifying the metastatic state of lymph nodes for accurate pathological staging. Several studies reported the impact of systematic lymph node dissection on the accuracy of staging, and these findings, nevertheless, are still inconclusive due to the lack of controls or a limited number of controls.^[12,20] Furthermore, some researchers had raised the question that the complete mediastinal lymph node dissection did not have significant advantage in staging, and reported that the 2 dissection groups had similar proportions of N1 and N2.^[21,22] We could not assess this aspect since our study only included patients with N0.

In this study, we found that tumor size was a key factor associated with survival, which is consistent with some other studies.^[9,23,24] Okada et al^[23] found that tumor size was associated with the prognosis in patients receiving complete resection of NSCLC. Christian et al^[24] reported that the risk of death would increase 58% and 118% once the tumor size reached 2 and 5 cm thresholds, respectively. Our study further demonstrated that the association between dissection mode and mortality depended on tumor size, and there appeared to be a stronger association in those with tumor diameter 2 to <3 cm. Ma et al^[12] also reported an obvious association in those with tumor diameter 2 to <3 cm, but there was no association in those with tumor size <2 cm. These findings, if confirmed, suggest that the dissection modes should be determined according to tumor size. Those with tumor diameter 2 to 3 cm would benefit most from the MLND.

Most of the previous studies in China evaluated the impact of lymph node dissection on the survival of patients with NSCLC by comparing 3 or 5-year survival outcomes. The strength of this study was that we followed the participants for 10 years or longer for assessing the impact of nodal dissection on long-term survival. The major limitation of this study was the relatively small sample size. Although we found that systematic dissection might be associated with better survival and lower mortality, the accuracy of this association needed to be further assessed. As shown in Table 4, after adjustment for age and sex, the association (HR 1.36, 95% CI 1.00, 1.84) was statistically significant ($P = .047$). With further adjusted for age, sex, pathological staging, operative location, tumor size, tumor location, and differentiation; the hazard ratio (1.40, 95% CI 1.02, 1.92) remained statistically significant ($P = .036$). Our study suggests that the MLNS group potentially has 2% to 92% higher mortality risk than the MLND group, and prospective research with larger samples would further indicate the impacts of dissection modes on mortality.

5. Conclusions

For stage I NSCLC patients, complete mediastinal lymph node dissection is associated with better survival and lower mortality compared with the mediastinal lymph node sampling. The effects of complete mediastinal lymph node dissection on survival may depend on tumor size. Our findings have important implications in the treatment of early-stage NSCLC, and further prospective studies with large samples to confirm our findings are warranted.

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