Thoracic Cancer ISSN 1759-7706

ORIGINAL ARTICLE

Comparison of complete and minimal mediastinal lymph node dissection for non-small cell lung cancer: Results of a prospective randomized trial

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Keywords
Lymph node dissection; non-small cell lung cancer; staging; surgery; survival.

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Received: 24 January 2013; accepted 6 March 2013.

doi: 10.1111/1759-7714.12040

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Abstract

Background: To compare surgical results, pathological staging, and survival between complete and minimal mediastinal lymph node dissection for non-small cell lung cancer (NSCLC).

Methods: A randomized controlled trial was carried out in 202 patients who were assigned to undergo either skeletonized complete mediastinal lymph node dissection (CLD) or minimal mediastinal lymph node dissection (MLD). Clinical and pathological characteristics, surgical results, postoperative staging, and five-year survival were recorded for statistical analysis.

Results: Significantly more stations of lymph nodes were harvested through CLD, than MLD (8.9 vs. 6.2, $P < 0.001$). There was no difference in major complications (CLD 14.7% vs. MLD 14.0%, $P = 0.884$) or postoperative death (CLD 2.1% vs. MLD 1.9%, $P = 0.904$). No significant difference was detected in pathological staging between the two groups. The pN2 rates (27.1% vs. 24.2%), skip-mediastinal metastasis (9.3% vs. 7.4%), and multi-stational mediastinal involvement (15.0% vs. 16.8%) were similar between MLD and CLD. However, CLD had significantly better five-year survival than MLD (55.7% vs. 37.7%, $P = 0.005$), especially in patients with a tumor size >3 cm, pleural invasion, pN1-N2, stage II-III, adenocarcinoma, and low-differentiation carcinoma. Upon multivariate analysis, CLD, along with stage I and high-differentiation, were independent prognostic factors for better overall survival.

Conclusions: Complete and minimal mediastinal dissections have similar surgical risks and mediastinal staging effect in patients with NSCLC. Minimal dissection is enough for early stage high-differentiation tumors. For patients with stage II-III or low-differentiation carcinoma, skeletonized complete mediastinal dissection may improve survival compared with minimal dissection.

Introduction

Lung cancer is one of the most common malignant tumors, with 80% of patients diagnosed with non-small cell lung cancer (NSCLC).[1] Complete surgical resection is the most effective treatment modality for stage I-II and some stage IIIa NSCLC. Systemic lymph node dissection (SND) has been accepted as an important component of intraoperative staging and complete resection for lung cancers.[2,3] Compared with lymph node sampling (LNS), SND carries the potential advantage of accurate staging[4,5] and survival benefit.[5,6] But it may also be associated with increased surgical risks by prolonging operation time, increasing blood loss, and resulting in more complications. So far, there have only been four randomized controlled trials (RCTs) comparing SND and LNS, with conflicting results.[6–11] Furthermore, there is no consensus on the range of dissection in SND. Even in the previous four trials, the extent of mediastinal dissection was disparate and inconclusive. Therefore, we studied the different extents of mediastinal dissection in a prospective trial to compare their safety and effect on staging and prognosis.

Materials and methods

Patients enrollment

A total of 202 patients with primary NSCLC who had undergone curative resection at Shanghai Chest Hospital from January 2006 to December 2007, were enrolled in a prospective clinical trial. The ethical committee of the Shanghai Chest Hospital approved the study, and written informed consent was obtained from all patients prior to enrolment. All candidates were decided as clinical stage I-IIIa upon preoperative evaluation, which included fibrous bronchoscopy, computed tomography (CT) scan of the chest and brain, abdominal ultrasonography, positron emission tomography (PET) or single photon emission computed tomography (SPECT). Mediastinoscopy was not routinely performed and was reserved for patients suspected of multiple, bulky N2 disease or N3 involvement. The patients were then randomized to receive either skeletonized complete mediastinal lymph node dissection (CLD) or minimal mediastinal lymph node dissection (MLD).

Surgical procedure

The extent of mediastinal lymph node dissection was decided according to the European Society of Thoracic Surgeons (ESTS) guideline.[12] In CLD, both the superior and inferior mediastinum was dissected, regardless of the location of the tumor. En-bloc removal of all fatty tissue, including the lymph nodes, was systemically carried out, leaving the landmarks, such as the trachea, bronchus, vagus nerve, superior vena cava, aorta, pulmonary vessels, and pericardium, skeletonized.

In MLD, only the superior mediastinal and subcarinal nodes were removed in the case of upper-lobe resections. Station 4 on the right side or station 5 on the left side, together with subcarinal and inferior pulmonary ligament nodes, were harvested for middle and lower lobe tumors. However, mediastinal structures were not skeletonized.

Follow-up

The patients were under follow-up every four months during the first two years after surgery, and every six months after that, up to five years. Routine check-up included chest CT scan, cervical and abdominal ultrasound, and serum level of tumor markers. Brain CT, bone scan, PET-CT or bronchoscopy was not routinely applied, unless metastasis in a corresponding site was suspected.

Statistical analysis

All statistical analyses were performed using SPSS17.0 software. Overall survival rates were calculated by Kaplan-Meier analysis, and differences among subgroups were compared using the log-rank test. Multivariate analysis of risk factors for survival was performed using a Cox's proportional hazard model. A *P*-value less than 0.05 was considered statistically significant.

Results

Clinical and pathological characteristics of the patients

Of the 202 patients enrolled in the study, 107 were randomly assigned to receive pulmonary resection with MLD and 95 with CLD. Patients' characteristics are shown in Table 1. The mean age of enrolled patients was 59.7 years, ranging from 25 to 81 years of age. No significant differences were detected in clinical or pathological characteristics between the two groups.

Table 1 Clinical and pathological characteristics of 202 patients

	No.(%) of patients		
Characteristic	MLD	CLD	P value
Mean age (years)	59.7	59.7	0.999
Sex			
Male	76 (71.0%)	64 (67.4%)	0.574
Female	31 (29.0%)	31 (32.6%)	
Clinical stage			
I	67 (62.6%)	59 (62.1%)	0.983
II	17 (15.9%)	16 (16.8%)	
IIIa	23 (21.5%)	20 (21.1%)	
Tumor size (cm)			
≤3	41 (38.3%)	39 (41.1%)	0.692
>3	66 (61.7%)	56 (58.9%)	
Pleural invasion			
No	37 (34.6%)	29 (30.5%)	0.540
Yes	70 (65.4%)	66 (69.5%)	
Lymph node metastasis			
N0	54 (50.5%)	50 (52.6%)	0.945
N1	24 (22.4%)	21 (22.1%)	
N2	29 (27.1%)	24 (25.3%)	
Pathological stage			
I	39 (36.4%)	37 (38.9%)	0.200
II	28 (26.2%)	33 (34.7%)	
IIIa	40 (37.4%)	25 (26.3%)	
Histology			
Adenocarcinoma	54 (50.5%)	45 (47.4%)	0.113
Squamous	26 (24.3%)	36 (37.9%)	
Adenosquamous	12 (11.2%)	7 (7.5%)	
Other	15 (14.0%)	7 (7.4%)	
Cell Differentiation			
Low	71 (66.4%)	68 (71.6%)	0.704
High	36 (33.6%)	27 (28.4%)	

CLD, complete mediastinal lymph node dissection; MLD, minimal mediastinal lymph node dissection.

Table 2 Surgical results

Variable	MLD	CLD	P value
Type of resection			
Lobectomy	76 (71.0%)	69 (72.6%)	0.641
Bilobectomy	9 (8.4%)	7 (7.4%)	
Pneumonectomy	12 (11.2%)	13 (13.7%)	
Others†	10 (9.3%)	6 (6.3%)	
Average lymph node stations removed, no.	6.2	8.9	0.001
Average operative time, minute	129	142	0.190
Average estimated blood loss, mL	205	213	0.441
Average chest tube drainage‡, mL	240	242	0.202

†Other types of resection including segmentectomy, sleeve lobectomy, lobectomy + segmentectomy, and lobectomy + carina resection. ‡The average volume of chest tube drainage per day (from 1st to 3rd day after operation). CLD, complete mediastinal lymph node dissection; MLD, minimal mediastinal lymph node dissection.

Surgical results

The same thoracic surgeons performed surgical resections through posterolateral thoracotomy incisions, and the same technique of resection of the primary lung cancer was applied in both groups. Lobectomies were performed in 145 patients, bilobectomies in 16, pneumonectomies in 25, and other types of resections in 16. Significantly more stations of lymph nodes were removed through CLD than MLD (8.9 vs. 6.2, $P < 0.001$) (Table 2). Otherwise there were no differences in the type of resection, operating time, estimated blood loss, and chest tube drainage between the two groups ($P > 0.05$, Table 2).

Surgical complications

The overall morbidity rate was similar between the two groups (Table 3). There was no reoperation for bleeding during the study. Three observations were classified as postoperative complications related to lymph node dissection: air leak, chylothorax, and recurrent laryngeal nerve paralysis. Three patients had temporary recurrent nerve palsy after CLD on the left side; another three developed chylothorax after CLD on the right side. All of these were early cases in the study. Two patients in the MLD group died of systemic infection followed by multiple organ failure on the 8th and 14th days after surgery. In the CLD group, one patient died of acute renal failure on the 6th day after surgery, while another died of acute pulmonary embolism on the 7th day after surgery.

Table 3 Surgical morbidity and mortality

Variable	MLD	CLD	P value
Overall morbidity	13 (14%)	12 (14.7%)	0.884
SND Related complications			
Air leak	5	5	
Chylothorax	0	3	
Recurrent laryngeal nerve paralysis	0	3	
Postoperative death	2 (1.9%)	2 (2.1%)	0.904

CLD, complete mediastinal lymph node dissection; MLD, minimal mediastinal lymph node dissection; SND, systemic lymph node dissection.

Table 4 Postoperative pathological tumor node metastasis (TNM) staging

pTNM		MLD NO. (%)	CLD NO. (%)	P value
pT	T1	4 (3.7)	7 (7.4)	0.126
	T2	80 (74.8)	73 (76.8)	
	T3	21 (22.2)	15 (15.8)	
	T4†	2 (1.9)	0 (0)	
pN	N0	56 (52.3)	51 (53.7)	0.888
	N1	22 (20.6)	21 (22.1)	
	N2	29 (27.1)	23 (24.2)	

†Including 1 patient with carina invasion, and 1 patient with left atrium invasion. CLD, complete mediastinal lymph node dissection; MLD, minimal mediastinal lymph node dissection; TNM, tumor node metastasis.

Staging analysis

No significant difference was detected in histological staging between the two groups (Table 4). The pN2 rates were similar after MLD and CLD (27.1% vs. 24.2%, $P = 0.888$). Upon stratified analysis according to T stages, N stages were still similar between the two groups (Table 5). There was no difference in skip metastasis to mediastinal nodes (MLD 9.3% vs. CLD 7.4%, $P = 0.613$), or multi-stational mediastinal involvement (MLD 15.0% vs. CLD 16.8%, $P = 0.714$).

Survival analysis

The follow-up rate was 90.9%; the loss ratio of follow-up is 9.3% for the MLD group and 8.4% for the CLD. Overall five-year survival was 37.7% for the MLD group and 55.7% for the

Table 5 Stratified analysis of N status on T stage

		Pathological N stage NO. (%)			
T stage	Group	pN0	pN1	pN2	P value
pT1	MLD	4 (100)	0 (0)	0 (0)	0.497
	CLD	5 (71.4)	1 (14.3)	1 (14.3)	
pT2	MLD	41 (51.3)	17 (21.3)	22 (27.5)	0.727
	CLD	37 (50.7)	19 (26.0)	17 (23.3)	
pT3	MLD	8 (44.4)	4 (22.2)	6 (33.3)	0.429
	CLD	9 (60.0)	1 (6.7)	5 (333)	

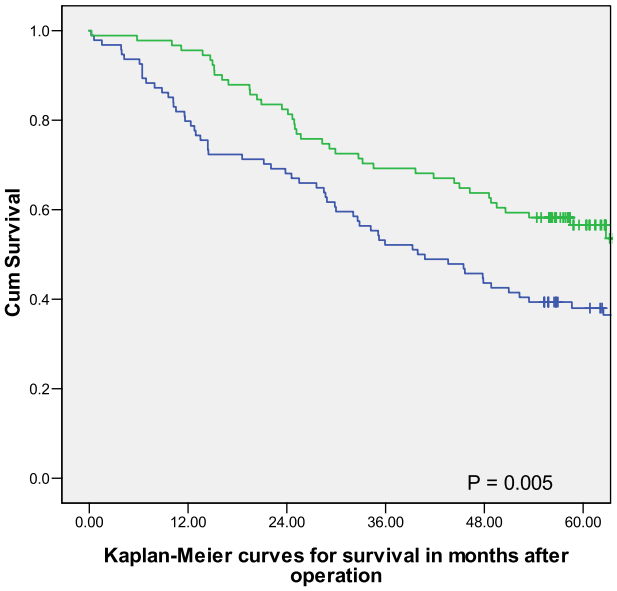

Figure 1 Overall survival curves in patients with non small cell lung cancer (NSCLC) treated by complete mediastinal lymph node dissection (CLD) and minimal mediastinal lymph node dissection (MLD).

CLD group (Fig. 1, P = 0.005). Furthermore, CLD was associated with significantly superior five-year survival than MLD in subgroups of patients with a tumor size >3 cm, pleural invasion, pN1-N2, stage II-III, adenocarcinoma, or low cell differentiation (Table 6).

Prognostic factors

Tumor size, N status, stage, pathological type, cell differentiation, and extent of lymph node dissection were found to be associated with overall survival in univariate analysis. These were entered into a Cox proportional hazards regression multivariate model. Stage I, high cell differentiation, and CLD, were found to be independent prognostic factors for better overall survival (Table 7).

Table 6 Comparison of five-year survival after minimal mediastinal lymph node dissection (MLD) and complete mediastinal lymph node dissection (CLD)

	Survival (five years)		
Characteristic	MLD	CLD	P value
Tumor size (cm)			
≤3	46.57%	63.88	0.085
>3	32.81%	49.96%	0.039
Pleural invasion			
No	40.93%	43.96%	0.644
Yes	36.16%	60.76%	0.001
Lymph node status			
N0	50.30%	67.35%	0.053
N1-N2	22.83%	42.52%	0.024
Pathological stage			
I	60.19%	77.78%	0.061
II–III	23.78%	41.19%	0.030
Histology			
Adenocarcinoma	41.56%	68.67%	0.006
Other	33.84%	41.89%	0.229
Differentiation status			
Low	20.00%	48.27%	0.003
High	46.01%	58.59%	0.180

CLD, complete mediastinal lymph node dissection; MLD, minimal mediastinal lymph node dissection.

Discussion

Lymph node metastasis is of critical importance to the prognosis of NSCLC, with an even closer correlation with prognosis than the extent of local invasion of the tumor. Five-year survival of patients without lymph node involvement (N0) could reach 80%, while rates for those with lymph node metastasis are only 42% (N1) and 15% (N2).[13] Therefore, lymph node status has important clinical value for the accurate staging of lung cancer, as well as for deciding reasonable therapeutic management to improve prognosis. In this study, we explored the surgical complications, staging, and prognosis between two different models of mediastinal dissection through a prospective RCT. Both CLD and MLD in our study

Table 7 Univariate and Multivariate analysis for overall survival

	Univariate analysis			Multivariate analysis		
Variables	OR	95% CI	P value	OR	95% CI	P value
Gender (male)	0.76	0.49–1.17	0.206	Not included		
Tumor size (≤3 cm)	1.61	1.06–2.44	0.025	1.06	0.67–1.69	0.80
Pleura (no invasion)	1.01	0.67–1.54	0.935	Not included		
N status (Stage N0)	1.85	1.25–2.75	0.002	1.14	0.68–1.93	0.614
TNM (Stage I)	2.73	1.73–4.29	0.000	2.68	1.40–5.11	0.003
Histology type (Adenocarcinoma)	1.57	1.06–2.33	0.024	1.19	0.79–1.79	0.404
Differentiation status (High)	1.91	1.28–2.85	0.002	1.65	1.07–2.54	0.023
Lymph node dissection (CLD)	1.75	1.17–2.62	0.005	1.82	1.21–2.75	0.004

CI, confidence interval; CLD, complete mediastinal lymph node dissection; OR, odds ratio; TNM, tumor node metastasis.

could be classified as SND according to the International Association for the Study of Lung Cancer (IASLC) criterion.[3] Our results provided a clue to several questions that remained unanswered by the existing literature.

Does CLD increase the surgical risks in patients with lung cancer? Theoretically, SND may be associated with prolonged operation duration, increased blood loss during surgery, and chest tube drainage post-surgery, and further complications, including increased bleeding, air leak, atrial fibrillation, chylothorax, and recurrent laryngeal nerve paralysis. However, Izbicki *et al.*[14] reported that compared with LNS, SND prolonged the duration of surgery, but did not increase postoperative complications in a prospective RCT in 182 cases of NSCLC. So far, the only multi-center RCT (ACOSOG Z0030),[9] including 1111 cases of early stage NSCLC, indicated that surgical morbidity rates were the same between SND and LNS, with both at a rate of 38%. The overall morbidity rates were also similar after CLD and MLD in our study. Yet we did encounter three chylothorax and three recurrent nerve palsy cases early in our series. All three chylothorax were on the right side, and were attributed to skeletonized dissection in the superior mediastinum near the aortic arch. A harmonic scalpel was used instead of an electrical cautery, a modification of surgical process. The right superior mediastinum was sealed with fibrin glue after dissection. No further chylothorax was detected after this treatment. It is not surprising that all three recurrent nerve palsy cases were on the left side, as the right recurrent nerve is located posterior to the right vagus nerve, and is, thus, beyond the range of the lymph node compartment for lung cancer. Care was taken to expose the left recurrent nerve under the aortic arch and surgical clips were used instead of electrical cautery for hemostasis in this area. No further recurrent nerve palsy occurred in later patients. Thus, from a technical point of view, in experienced hands, good exposure of important surrounding structures may prevent certain complications associated with CLD. No difference in mortality was detected between CLD and MLD, in this study.

The kernel of clinical research on lymph node dissection is to ensure radical dissection in order to increase the accuracy of staging and potential benefit in prognosis. Is CLD superior to MLD in lymph node staging? Compared to LNS, SND may have the advantages of improved pathological stage, and prolonged survival. A prospective RCT by the Eastern Cooperative Oncology Group (ECOG 3590) in patients with completely resected stages II and IIIa NSCLC, showed that multiple levels of N2 disease were documented in 30% of patients who had undergone SND, but only 12% after LNS.[5] The ACSCO Z0030 trial only included patients clinically staged as N0-1 by mediastinoscopy. With more lymph nodes harvested, occult N2 disease was found in 4% (21/525) of patients in the SND group.[10] Although significantly more stations of lymph nodes were removed via CLD in our study, we failed to notice any stage migration. Rates of pN2 were similar between the two different dissection models (24.2% vs. 27.1%, P = 0.888). Even after stratification by T staging in order to exclude any potential confounding bias, there was still no difference in pN2 rates in each T category. We detected no significant difference in the ratio of skip mediastinal nodal involvement (MLD 9.3% vs. CLD 7.4%, P = 0.613) or multistational mediastinal metastasis (MLD 15.0% vs. CLD 16.8%, P = 0.714). Thus, solely from the staging point of view, both of these two SND models had similar effects, and CLD showed no advantage over MLD. Our results are consistent with ESTS guidelines.

Does CLD improve survival in lung cancer patients? Until now, there have been only four RCTs comparing SND and LNS for NSCLC. Izbicki *et al.*[7] reported no significant difference in survival between the patients with clinical stage I–IIIA lung cancer who underwent SND and LNS. However, the number of patients enrolled in each arm (SND 76 vs. LNS 93) might have been insufficient because more than half of the patients turned out to be node-negative. In a subgroup analysis, they detected a borderline effect of SND on overall survival (P = 0.058) in patients with pN1 or pN2 disease. Sugi *et al.*[8] reported no significant difference in survival for SND or LNS. However, the number of enrolled patients (SND 59 vs. LNS 56) was even less than that of the study by Izbicki *et al.*, and the inclusion criteria was peripheral cancer less than 2 cm (namely stage I). The result from the ACOSOG Z0030 study was also negative.[11] But again, only N0 or nonhilar N1, T1, and T2 tumors were included. Wu *et al.*[6] reported the results of a prospective RCT in 532 patients and suggested that SND (n = 268) showed significantly better survival compared with LNS (n = 264). This has been the only randomized study to suggest the survival benefit of nodal dissection. In the meta-analysis of the three RCTs[6–8] comparing SND and LNS, Wright *et al.*[15] reported a significant reduction in the risk of death after SND, with a hazard ratio estimated at 0.78 (95% confidence interval [CI] 0.65–0.93; P = 0.005).

To our knowledge, the current study is the first trial comparing the different extents of mediastinal dissection, rather than comparing lymph node dissection with systemic sampling. While MLD refers to the minimum extent of mediastinal dissection, skeletonized whole mediastinal CLD can be considered as the maximum extent of lymphatic dissection. The results showed that five-year survival was significantly superior after CLD than MLD (55.7% vs. 37.7%, P = 0.005). Under multivariate analysis, CLD proved to be one of the independent prognostic factors for overall survival. Upon stratification, the difference in survival between MLD and CLD appeared to be statistically significant in patients with a tumor size >3 cm or pleural invasion (namely over T2), pN1-N2, stage II-III, adenocarcinoma, or low cell differentiation. Our result is consistent with the trend toward better survival in pN1-2 patients reported by Izbicki *et al.*[7] The ECOG 3590

study, although non-randomized, also showed that SND significantly improved survival in stage II–IIIa NSCLC over LNS. On the other hand, it seemed less likely for patients with stage I or high cell differentiation tumors to benefit from wider and more thorough mediastinal dissection. The result of the current study is consistent with both of the RCTs[8,11] conducted in stage I NSCLC. Therefore, patients most likely to benefit from nodal dissection are those who have resectable metastatic nodes, as pointed out by Watanabe and Asamura.[16] The rationale is that distant metastasis remains the most commonly seen relapse pattern after complete resection of lung cancer. The major merit of lymph node dissection as a local therapy is to achieve a better local control, rather than to reduce distant metastasis.

As to cell differentiation, Kamiyoshihara *et al.*[17] retrospectively reported on 10 patients with low-grade (high differentiation) carcinoma. None of those patients had mediastinum metastasis. The current study was carried out before the publication of the new histological classification of pulmonary adenocarcinoma. Non-invasive adenocarcinomas (previously named bronchio-alveolar adenocarcinoma [BAC]), were also included in this study. It is well known that these low-grade tumors seldom have lymphatic metastasis. Thus, it seems reasonable that patients with high differentiation tumors are less likely to benefit from extensive nodal dissection.

Conclusion

In conclusion, the current study is the first to compare skeletonized whole mediastinal nodal dissection with minimal dissection for NSCLC. Although surgical risks and staging effects were similar, more thorough mediastinal dissection appeared to be associated with better long-term survival, especially in patients with stage II-III and low cell differentiation tumors. For stage I and high differentiation tumors, minimum dissection is warranted, with satisfying effects, both in accurate staging and distant prognosis.

Disclosure

No authors report any conflict of interest.

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