Original Article

Impact of lymph node management on resectable non-small cell lung cancer patients

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Background: A surgical lung resection with systematic mediastinal lymph node (LN) dissection is recommended by the National Comprehensive Cancer Network guideline. However, the effective number of dissected LNs, stations and positivity is still controversial. The aim of this study is to identify the impact of total numbers, LN stations and positivity of dissected LNs on tumor recurrence and overall death in resectable non-small cell lung cancer (NSCLC).

Methods: This prognostic study used a retrospective data collection design. Adult patients with clinical resectable NSCLC who underwent pulmonary resection and mediastinal lymphadenectomy at Chiang Mai University between June 2000 and June 2012 were enrolled in this study. A multilevel mixed-effects parametric survival model was used to identify the effect of numbers, LN stations and positivity of dissected LNs to tumor recurrence and mortality.

Results: The average number of dissected LNs was 22.7±12.8. Tumor recurrence was found in 51.3% and overall mortality was 43.3%. The number of dissected LNs was a prognostic factor for tumor recurrence [HR 0.98, 95% confidence interval (CI): 0.96–0.99]. There was a significant difference at the cut-pointed value of 11 dissected LNs for tumor recurrence (HR 2.22, 95% CI: 1.26–3.92). Dissection less than 11 nodes and less than 5 stations indicated a poor prognostic factor for tumor recurrence: for 3–4 stations (HR 3.01, 95% CI: 1.22–7.42) and for 1–2 stations (HR 1.96, 95% CI: 1.04–3.72). The positivity of dissected LNs was also a prognostic factor for tumor recurrence and overall mortality (HR 1.01, 95% CI: 1.01–1.02 and HR 1.01, 95% CI: 1.01–1.03, respectively).

Conclusions: Eleven or more LN dissection with at least 5 stations influenced recurrent-free survival. Systematic LN dissection (SLND) should be performed not only to identify the positivity of dissected LNs but also to determine an accurate tumor nodal stage. A larger cohort should be further conducted to support these findings.

Keywords: Mediastinal lymphadenectomy; lung cancer; pulmonary resection; mediastinal node dissection; positivity

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Introduction

Surgical lung resection with systematic mediastinal lymph node (LN) dissection or sampling is recommended by the National Comprehensive Cancer Network guidelines for stages I–II and resectable stage IIIA non-small cell lung cancer (NSCLC) (1). Previous studies have shown that systematic LN dissection (SLND) could improve staging (2-5) and overall survival compared to LN sampling (6-8). Variations in lung cancer lymphatic drainage may be partly responsible for the need of an extensive mediastinal dissection (9,10). A recent systematic review and meta-analysis showed that SLND was associated with a statistically significant improvement in overall survival and recurrence-free survival (11). However, the effect of the number of dissected LNs on tumor recurrence or overall survival is still controversial. Some studies reported that the number of LNs removed in early stage NSCLC patients who underwent lobectomy was an independent positive prognostic factor for overall and lung overall survival (6,12,13). Other studies suggest that the number of dissected LNs has no significant impact on overall survival, whereas the number of positive LNs does (14,15).

We retrospectively investigated the association between the number of LNs and stations resected, and positivity of dissected LNs to tumor recurrence and overall mortality in clinical early stage NSCLC patients who underwent complete resection at Chiang Mai University Hospital.

Methods

Patient selection

From June 2000 to June 2012, medical records of 240 patients who underwent pulmonary resection for primary lung cancer at the Department of Surgery, Faculty of Medicine, Chiang Mai University Hospital, Chiang Mai, Thailand were retrospectively reviewed. All patients received preoperative cancer staging including computed tomography (CT) with contrast, bronchoscopy with biopsy, bronchial washing, brushing or bronchial lavage cytology. If mediastinal lymph nodes were larger than 1 cm, endobronchial ultrasound-guided (EBUS) fine needle aspiration, or mediastinoscope biopsy were performed. Patients with mediastinal lymph nodes involvement were classified as N2 disease, and induction chemotherapy was performed. Positron emission tomography-computed tomography (PET-CT) was not available. CT-brain and bone scans were performed if clinically relevant. These patients represent all clinical early stage NSCLC who underwent curative intent-complete pulmonary resection with SLND or sampling of the hilum and mediastinum according to the international LN map for TNM classification of lung cancer (16). Exclusion criteria were patients who received any induction therapy (radiation or chemotherapy). NSCLC staging was determined according to the 7th edition of the TNM classification of malignant tumors (17). The World Health Organization classification, 3rd edition was used for histological tumor types. All dissected LNs were examined pathologically by expert pulmonary pathologists (Nirush Lertprasertsuke, Sarawut Kongkarnka) who were blinded to the clinical outcomes. To confirm the clinical early status, all patients went through a preoperative evaluation, including medical history, physical examination, plain chest radiography, chest CT, and bone scan or PET-CT if necessary.

Surgical procedures included sublobar resection [3 patients (1.3%) with clinical stage Ia and age 74, 75 and 78 years], lobectomy (232 patients, 96.7%) and pneumonectomy (5 patients, 2.1%) depending on tumor size and location. Mediastinal LN dissection was routinely performed; in some patients, for example T1 tumor in patients age >70 years, A LN sampling was done. LN stations were defined according to the IASLC classification (18). The N2 level included ipsilateral station 2–station 9, N1 level included ipsilateral station 10–station 14, N3 level included station 1, contralateral mediastinal LN, and hilar nodes. Mediastinal LN dissection or sampling was routinely performed after complete pulmonary resection. All dissected LNs were collected in separate labeled-containers according to the dissected stations. Tissues and LNs were sent for routine pathologic analysis and preserved in paraffin blocks. All patients were followed and evaluated for clinical symptoms and a chest X-ray at the thoracic surgery clinic at 2 weeks and at 3 months after surgery; then every 6 months for CT of the chest within the first 2 years after surgery, and then every year after that.

The primary outcomes of this study were tumor recurrence and overall mortality.

Tumor recurrence was defined as the first diagnosis of either local recurrence or distant metastasis after complete surgical resection. This study was reviewed and approved by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand with Study Code: SUR-2556-01811/Research ID: 1811, and ID of the approval 276/2013.

Table 1 Patient characteristics (n=240)

Characteristics	n (%) or mean ± SD
Age (years), range (min–max)	62.6±10.3 [24–84]
Gender	
Female/male	100 (41.7)/140 (58.3)
Smoking	
Never smoker	54 (22.5)
Ex-smoker	170 (70.8)
Current smoker	12 (5.0)
Passive smoker	4 (1.7)
Mean pack-year (among smokers)	27.5±13.5
Comorbidities	
Chronic lung disease	42 (17.5)
Diabetes mellitus	28 (11.7)
Essential hypertension	87 (36.3)
Dyslipidemia	34 (14.2)
Symptoms at diagnosis*	
Hemoptysis	88 (36.7)
Chronic cough	104 (43.3)
Poor appetite	26 (10.8)
Significant weight loss	61 (25.4)
Chest pain	20 (8.3)
Dyspnea	40 (16.7)

*, each patient may have more than one symptom.

Statistical analysis

Categorical variables were presented as frequencies and percentages. Continuous variables were presented as means and standard deviation (SD) or median and interquartile range (IQR) as appropriate, and compared by the Student *t*-test or Wilcoxon Rank Sum test. The impact of the number of LNs resected and positivity of dissected LNs on tumor recurrence and overall death was performed using multilevel parametric survival models adjusting for age, gender, comorbidities, surgical procedures, pathologic findings (histologic cell types, tumor grading, intratumoral lymphatic invasion, intratumoral vessel invasion, visceral pleural invasion, tumor necrosis, and stage of disease), and type of LN dissection (analyzed under stratification of identical number of dissected LNs or positivity of dissected LNs). Dependent variables were number of dissected LNs and positivity of dissected LNs. The positivity of dissected LNs was calculated as the number of tumor positive LNs divided by total number of dissected LNs multiplied by 100. Time to recurrence was calculated from the date of surgery to the time of a diagnosis of tumor recurrence. The overall death was calculated from the time of surgery to the time of death. Recurrent-free parametric survival curves according to the optimal cut-point number of dissected LNs overall and for each NSCLC stage was analyzed by mixed-effects Weibull regression. All tests were two sided. A P value less than 0.05 was considered statistically significant. STATA program version 14.0 (StataCorp, CS, TX, USA) was used for statistical analysis.

Results

Patient characteristics, treatments and pathologic findings

Most of the patients included in the study were ex-smokers (*Table 1*); male to female ratio was 1.4:1. The most common presenting symptoms were chronic cough and non-massive hemoptysis. Asymptomatic patients were approximately 37%. Lung mass or nodule was found by incidental finding from chest X-ray.

The surgical procedures and pathologic findings were shown in *Table 2*. Lobectomy was performed in most cases (96.7%). Sublobar resection included wedge resection (1 patient) and segmentectomy (2 patients). Pneumonectomy was performed in five cases due to intraoperative findings of progressive hilar tumor. The two most common histologic types were adenocarcinoma (61.3%) and squamous cell carcinoma (27.5 %). Pathological stages were 33.8% for stage I, 49.1% for stage II, and 32.9 % for stage III. SLND was performed in most cases (87.1%). The mean number of dissected LNs was 4.3 nodes for sampling and 25.5 nodes for SLND. In most cases (73.8%), LN dissection was performed in more than 5 stations. The mean of positivity of dissected LNs was 10.4±18.4. There was no difference in number of dissected LNs between right and left side [23.1±12.6 and 22.0±13.2 (P value 0.519) respectively]. Tumor recurrence occurred in 51.3% of patients, with median (IQR) recurrent time of 9.5 (6.0–17.9) months. Overall death occurred in 43.3% of patients, with median (IQR) follow-up time of 23.9 (12.5–47.6) months.

Association between LN resection and tumor recurrence

The number and positivity of dissected LNs were statistically significant prognostic factors for tumor recurrence (*Table 3*) at univariable analysis [hazard ratios (HR) and 95% confidence interval (CI) of 0.98 (0.97–0.99) and 1.01 (1.01–1.02), respectively]. At multivariable analysis, the number and

Table 2 Treatments and pathologic reports (n=240)

Parameters	n (%) or mean ± SD
Surgical procedures	
Sublobar resection	3 (1.3)
Lobectomy	232 (96.7)
Pneumonectomy	5 (2.1)
Histologic types	
Adenocarcinoma	147 (61.3)
Squamous cell carcinoma	66 (27.5)
Others	27 (11.3)
Tumor grading	
Well differentiated	88 (36.7)
Moderately differentiated	104 (43.3)
Poorly differentiated	38 (15.8)
Undifferentiated	10 (4.2)
Intratumoral lymphatic invasion	201 (83.8)
Intratumoral blood vessel invasion	97 (40.4)
Perineural invasion	10 (4.2)
Visceral pleural invasion	47 (19.6)
Tumor necrosis	101 (42.1)
Pathological staging	
IA	35 (14.6)
IB	46 (19.2)
IIA	44 (18.3)
IIB	36 (15.0)
IIIA	74 (30.8)
IIIB	5 (2.1)
Tumor diameter (cm), mean ± SD	5.5±2.6
Type of LN dissection	
Sampling	31 (12.9)
Dissection (SLND)	209 (87.1)
Number of LN sampling/dissection	
Sampling, mean ± SD (min–max)	4.3±1.7 [1–7]
Dissection, mean ± SD (min–max)	25.5±11.4 [6–68]
Station of LN dissection	
1–2 stations	44 (18.3)
3–4 stations	19 (7.9)
≥5 stations	177 (73.8)
Positivity of dissected lymph nodes (%), median (IQR)	0 (0–13.1)
Tumor recurrence	123 (51.3)
Overall mortality	104 (43.3)
Follow-up time (months), median (IQR)	23.9 (12.5–47.6)

SD, standard deviation; SLND, systematic LN dissection; LN, lymph node; IQR, interquartile range.

positivity of dissected LNs were independent prognostic factors for tumor recurrence (*Table 4*). When the analysis was stratified according to the stage of disease, the association between number of dissected LNs and tumor recurrence was restricted to stage I. There was an inverse correlation between positivity of dissected LNs and recurrent rate and overall mortality (*Figure 1*).

The optimal cut-off point for total number of dissected LNs was 11 (HR for recurrence 2.22, 95% CI: 1.26–3.92; *Table S1*). The strongest association was observed in stage I and stage II NSCLC as shown by adjusted parametric survival curve analyzed by mixed-effects Weibull regression (*Figure 2*). The unadjusted Kaplan-Meier survival curves and the number of at risk patient were shown in *Figure S1*.

The location of the dissected LNs was not an independent prognostic factor for tumor recurrence (*Table 4*). However, if less than 11 LNs were resected, with ≤5 stations dissected, a significant worse recurrence prognosis was observed (*Table S2*, the interested reader can find a supplementary appendix in online).

The number of metastasized LNs was not an independent prognostic factor for tumor recurrence at multivariable analysis (*Table 4*).

Association between LN resection and overall mortality

The association between number of dissected LNs, the number of N2 stations, the positivity of dissected LNs, and the number of metastasized LNs and overall mortality is shown in *Table 3*. The total number and locations (stations) of dissected LNs were not an independent prognostic factor for overall mortality (HR 0.99, 95% CI: 0.97–1.01), whereas the positivity of dissected LNs was (HR 1.02, 95% CI: 1.01–1.02) for each increasing percentage of positive LN. At multivariable analysis, the positivity of dissected LNs was an independent prognostic factor for overall mortality, whereas the total number and number of stations of dissected LNs did not affect overall mortality (*Table 4*). There was an inverse correlation between positivity of dissected LNs and overall mortality (*Figure 1B*). The number of metastasized LNs was significantly different with survival status at univariable analysis (*Table 3*), but not at multivariable analysis (*Table 4*).

Discussion

LN status is a major prognostic factor for tumor recurrence and survival in lung cancer patients. However, mediastinal

Table 3 Parameters of LN dissection according to recurrence and mortality

Parameters	Recurrence (n=123)	No recurrence (n=117)	P value	Death (n=104)	Survived (n=136)	P value
Number of dissected LNs (mean ± SD)	20.9±12.5	24.6±13.0	0.028	21.3±13.4	23.8±12.3	0.133
Number of N2 station dissection, n (%)			0.035			0.110
1–2 stations	28 (63.6)	16 (36.4)		25 (56.8)	19 (43.2)	
3–4 stations	13 (68.4)	6 (31.6)		9 (47.4)	10 (52.6)	
≥5 stations	82 (46.3)	95 (53.7)		70 (39.6)	107 (60.4)	
Positivity of dissected LNs [median (IQR)]	5.6 (0–17.7)	0 (0–5.3)	<0.001	6.9 (0–24.6)	0 (0–5.6)	<0.001
Number of metastasized LNs [median (IQR)]	1 (0–3.0)	0 (0–1.0)	<0.001	1 (0–3.5)	0 (0–1)	<0.001
0	57 (41.3)	81 (58.7)	0.010	46 (33.3)	92 (66.7)	0.001
1 node	13 (61.9)	8 (38.1)		10 (47.2)	11 (52.4)	
2–3 nodes	28 (63.6)	16 (36.4)		22 (50.0)	22 (50.0)	
4–8 nodes	20 (69.0)	9 (31.0)		21 (72.4)	8 (27.6)	
>8 nodes	5 (62.5)	3 (37.5)		5 (62.5)	3 (37.5)	

LNs; lymph nodes, SD, standard deviation; IQR; interquartile range.

Table 4 Association between various parameters of LN dissection and tumor recurrence and overall mortality

Parameters	Tumor recurrence		Overall mortality	
	HR*	95% CI	HR*	95% CI
Number of dissected LNs				
Overall	0.98	0.96–0.99	0.98	0.96–1.01
Stage I	0.92	0.88–0.97	0.98	0.95–1.02
Stage II	0.99	0.96–1.01	1.00	0.97–1.02
Stage III	0.99	0.97–1.02	0.98	0.95–1.02
Number of N2 station dissection				
≥5 stations	1.00	Reference	1.00	Reference
3–4 stations	1.62	0.86–3.05	1.22	0.52–2.84
1–2 stations	1.04	0.57–1.88	1.47	0.71–3.04
Positivity of dissected LNs#	1.01	1.01–1.02	1.01	1.01–1.03
Number of metastasized LNs	1.06	0.99–1.13	1.07	0.99–1.15
0	1.00	Reference	1.00	Reference
1 node	0.98	0.38–2.52	0.76	0.28–2.11
2–3 nodes	1.11	0.54–2.29	0.93	0.44–1.96
4–8 nodes	1.94	0.76–4.93	2.13	0.79–5.72
>8 nodes	1.96	0.56–6.83	2.69	0.74–9.75

*, adjusted for age, gender, comorbid disease, surgical procedures, pathologic findings, and type of lymph node dissection (analyzed under stratification of identical number of dissected LNs or positivity of dissected LNs by multilevel parametric survival model); #, positivity of dissected LNs calculated as (number of positive LNs/total number of dissected LNs) ×100. LNs, lymph nodes.

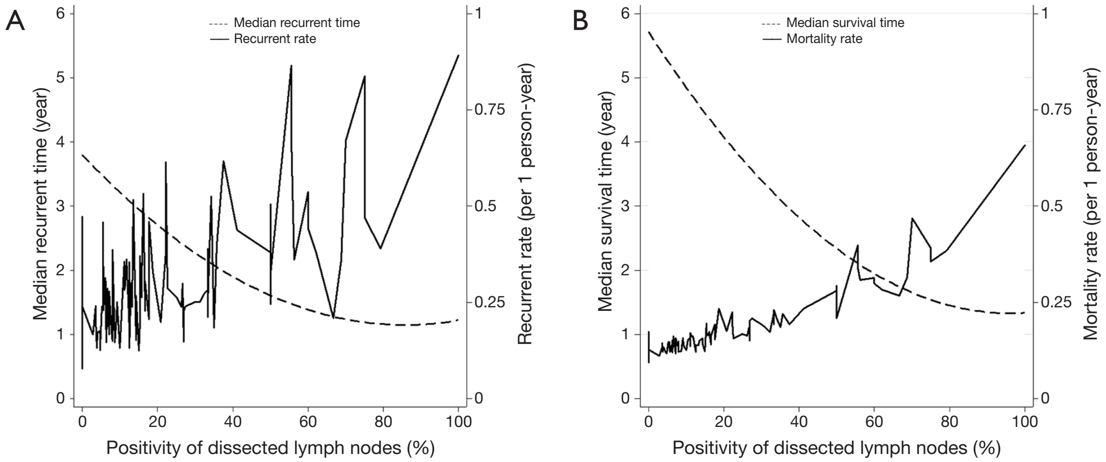

Figure 1 Correlation between positivity of dissected lymph nodes and recurrent rate and recurrent time (A), and mortality rate and survival time (B).

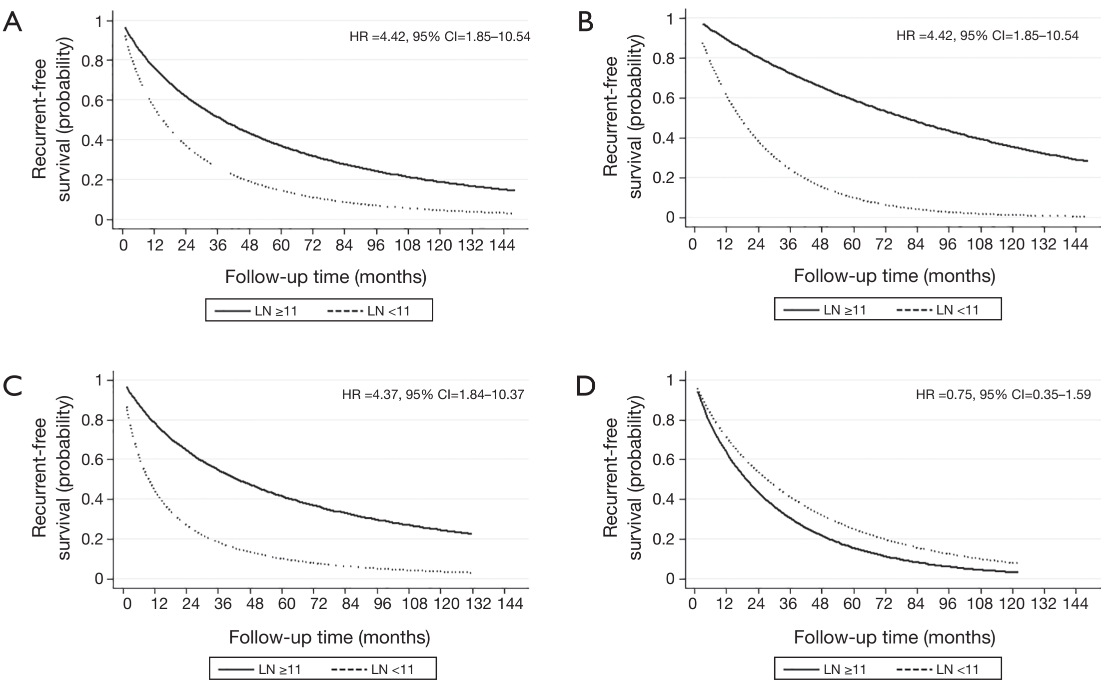

Figure 2 Recurrent-free survival curves according to the cut-point of dissected LNs of 11 LNs. (A) overall; (B) stage I; (C) stage II; (D) stage III, analyzed by mixed-effects Weibull regression.

LN dissection as part of NSCLC treatment is still controversial. The present results indicate that tumor recurrence and overall mortality after complete pulmonary resection and LN dissection are associated with the presence of positive LNs among those dissected. However, the number of LNs dissected is associated with tumor recurrence, but not with overall mortality. The cut-off point for recurrence was 11 LN in this study. Patients having had less than 11 LNs dissected had significantly less recurrent-free survival, but no effect on overall mortality. Previous studies have shown different results, with number of LNs dissected affecting both overall survival and lung overall survival (2,6,7,12). Possible reasons for the discrepancy could be the small sample size of this present study which carries less statistical power, the shorter follow-up time, or different techniques of data analysis. Some previous studies reported on the association between recurrence and number of dissected LNs (13,19). In this study the number of dissected LNs was an independent prognostic factor for tumor recurrence. Previous studies found that the optimal cut-point numbers of dissected LNs was varied, in the range of more than 6 to 15 LNs (2,13,19-21). In the present study, 10 or more LNs should be dissected in order to obtain a significant decrease in tumor recurrence, and this is especially true in pathologic stage I and II NSCLC.

The stations dissected are an important factor when performing LN dissection. Currently, the number of LN stations to be dissected is still under debate. Wang *et al.* suggested dissection of only 3 stations of N2 (7). Gajra *et al.* found that patients with a larger number of mediastinal stations dissected had an improvement in disease-free and overall survival compared to those with fewer mediastinal stations dissected, and suggested a dissection of more than 4 stations (13), similar to what was performed in this study. However, in the present study the number of N2 stations dissected was not an independent prognostic factor for tumor recurrence and overall mortality. The dissection of less than 5 stations and less than 11 LNs suggested significant adverse outcomes in terms of tumor recurrence. Recently, Liang *et al.* reported data from a Chinese multi-institutional registry and the US SEER database on stage I to IIIA resected NSCLC [2001–2008]; in this paper, a larger number of examined LNs was associated with more-accurate node staging and better long-term survival. The authors recommended 16 LNs as the cut point for evaluating the quality of LN examination and declaring a node-negative disease (22). However, the data of the stations of dissected LNs was not available in that publication.

Nwogu *et al.* used the SEER database to explore the prognostic value of the number of LNs examined and the ratio of metastatic LNs to total number of dissected LNs (positivity); and found that the more LNs are resected and the lower the ratio of positive LNs to total examined LNs, indicated better survival (23). The present study also indicated that the positivity of dissected LNs was a significant prognostic factor for tumor recurrence and overall mortality. Therefore, the number of metastatic LNs may be more important than the total number of dissected LNs. Previous studies reported that the number of metastatic LNs can predict the outcome after NSCLC complete resection, and that this is a strong independent prognostic factor (15,24,25). It was suggested that this approach provides more accurate pathologic nodal staging then the method of considering the anatomical location of involved LNs (26). Saji *et al.* found that four or more affected LNs were a good indicator of outcome after surgery (25). Jonnalagadda *et al.* also reported that the number of affected LNs was an independent prognostic factor for overall survival in patients with N1 NSCLC (15). However, all previous studies analyzed the data with the Cox proportional hazards model, with adjustment for other potential prognostic factors. In this study, we analyzed both the positivity of dissected LNs and the total number of dissected nodes using a multilevel parametric survival model under the assumption of an identical number of dissected LNs and adjusting for other potential prognostic factors. Since there was statistical evidence that both the number of total LNs dissected and LN positivity were associated with tumor recurrence and mortality, it is important to quantify the effect of the number of LNs dissected on the two outcomes conditional on LNs positivity, and vice-versa. This analysis was performed under the multilevel (or conditional) parametric model which is statistically more efficient than the traditional Cox's model given the relatively small sample size.

This specific statistical analysis is one of the strengths of this study. There are some limitations in this study because of its retrospective nature. First, clinical stage was not available in the database; therefore it was not possible to compare stage before and after surgery (up-stage). However, all patients in this cohort were clinically resectable, thus the maximum nodal diameter of mediastinal LNs at CT scan was less than 1 cm, and were classified as clinical N0 patients. Second, the small sample size of this study may carry a lower statistical power than previous studies. Further large cohort studies, more complete data collection, and/or multi-center studies are warranted. Third, in 13% of patients LN sampling was performed, following ACCP guidelines (3) that recommend either SLND or sampling in early clinical stage, especially in stage I disease. SLND was routinely performed in all cases; in patients age >70 years with small tumor size (less than 1 cm) in the upper lobe, we performed sublobar resection or lobectomy with LN sampling. In order to address this possible bias which may be associated with patient survival or tumor recurrence, we adjusted the multivariable analyses for type of LN dissection (among other covariates. Finally, some important pre-treatment clinical features including the Charlson comorbidity index, pulmonary function test or other cardiopulmonary test, and patient's socioeconomic status that may be associated with overall mortality are not available for adjusted in multivariable model.

Conclusions

This present study indicates that a dissection of less than 11 LNs, with less than 5 LN stations harvested is inversely associated with tumor recurrence after complete resection in clinical early stage NSCLC patients. Moreover, the positivity of dissected LN is an independent prognostic factor for tumor recurrence and overall mortality. SLND should be performed not only for identifying the exact positivity of dissected LN, but also for determining accurate nodal staging for NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was designed as retrospective and approved by the Institutional Review Board of Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand with study code: SUR-2556-01811/Research ID: 1811, and ID of the approval 276/2013. Because this study is retrospective in nature and all procedures were routinely performed as part of the patients' standard of care, the participants did not sign a specific research informed consent. However, all patients released their fully-informed written consent to perform all surgical procedures.

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Supplementary

Table S1 Correlations between tumor recurrence (HR) and cut-point values of total number of dissected LNs

Cut-point values	HR*	95% CI	P value
<5 *vs.* ≥5	0.99	0.51–1.95	0.989
<6 *vs.* ≥6	1.15	0.64–2.06	0.636
<7 *vs.* ≥7	1.26	0.77–1.02	0.361
<8 *vs.* ≥8	1.42	0.89–2.28	0.139
<9 *vs.* ≥9	2.15	1.13–4.07	0.019
<10 *vs.* ≥10	1.82	1.19–2.81	0.006
<11 *vs.* ≥11	2.22	1.26–3.92	0.006
<12 *vs.* ≥12	1.53	1.01–2.31	0.047
<13 *vs.* ≥13	1.48	0.97–2.25	0.064
<14 *vs.* ≥14	1.55	1.03–2.32	0.033
<15 *vs.* ≥15	1.55	1.04–2.30	0.030
<16 *vs.* ≥16	1.63	1.11–2.38	0.012
<17 *vs.* ≥17	1.49	1.01–2.17	0.040
<18 *vs.* ≥18	1.60	1.10–2.31	0.014
<19 *vs.* ≥19	1.85	1.28–2.68	0.001
<20 *vs.* ≥20	1.87	1.30–2.69	0.001

*, adjusting for age, gender, intratumoral blood vessel invasion, tumor necrosis, and histologic stage (analyzed under stratification of positivity of dissected LNs by multilevel parametric survival model). HR, hazard ratio; LNs, lymph nodes; CI, confidence interval.

Table S2 Correlation between cut-point of LN dissection and number of N2 station dissection, and tumor recurrence

Cut-point & number of station	HR*	95% CI	P value
≥11 LNs and ≥5 stations	1.00	Reference	–
≥11 LNs and 3–4 stations	1.65	0.65–4.17	0.293
≥11 LNs and 1–2 stations	0.47	0.14–1.55	0.218
<11 LNs and ≥5 stations	2.68	0.54–13.28	0.228
<11 LNs and 3–4 stations	3.01	1.22–7.42	0.016
<11 LNs and 1–2 stations	1.96	1.04–3.72	0.039

*, adjusting for age, gender, intratumoral blood vessel invasion, tumor necrosis, and histologic stage (analyzed under stratification of positivity of dissected LNs by multilevel parametric survival model). LN, lymph node; HR, hazard ratio; CI, confidence interval.

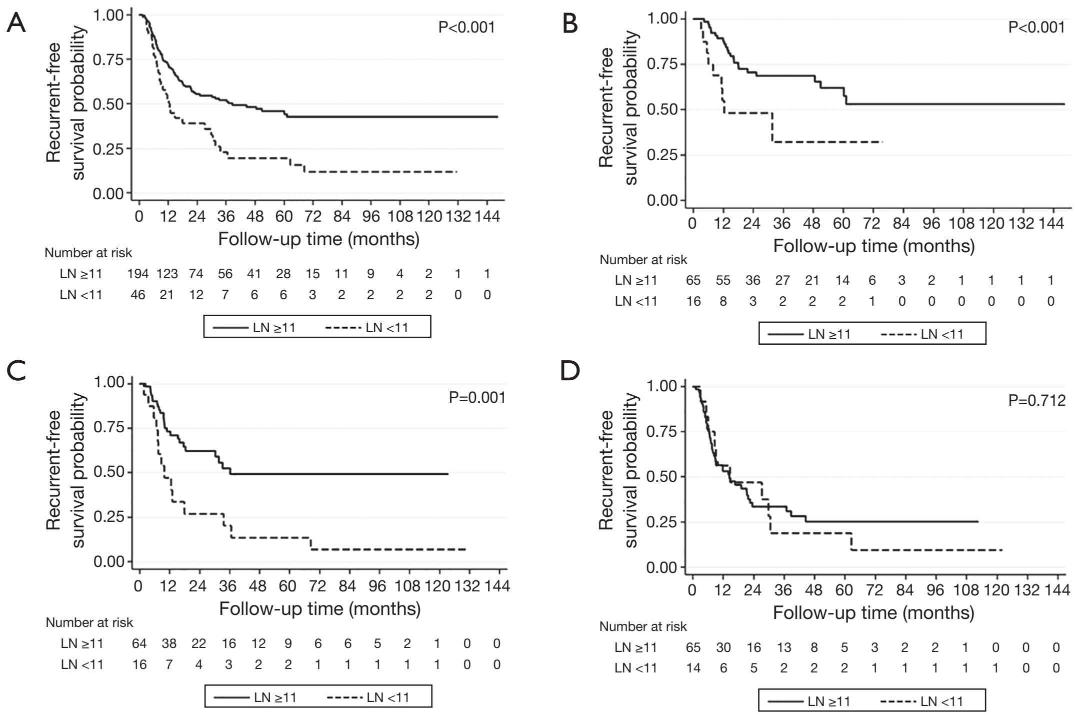

Figure S1 Unadjusted Kaplan-Meier curve demonstrated recurrent-free survival curves according to the cut-point of dissected LNs of 11 LNs. (A) Overall stage; (B) stage I; (C) stage II; (D) stage III.