Original Article

Impact of the number of resected lymph nodes during multi-portal VATS lobectomy for clinical N0 non-small cell lung cancer

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Background: The adequacy of lymphadenectomy based on the number of resected lymph nodes in video-assisted thoracoscopic surgery (VATS) for patients with non-small cell lung cancer (NSCLC) has been questioned. Therefore, this study aimed to identify the role of lymph node dissection during VATS lobectomy for NSCLC, and reveal the relationship between the number of lymph node retrieved and overall and recurrence-free survival.

Methods: To adjust different levels of lymphadenectomy proficiency and heterogeneous lymphadenectomy policy, we included all surgical cases from April 2005 to June 2013, irrespective of the surgeon's experience, lymph node sampling or dissection, and solid or subsolid nodule. The relationship between the long-term survival and the number of lymph nodes removed was analyzed using the Cox-regression proportional model. The median follow up duration was 73 months.

Results: A total of 974 patients underwent multi-portal VATS lobectomy. Mean number of resected lymph nodes were 24. The 5-year overall and recurrence-free survival rates were 86.3% and 80.4%, respectively. Recurrences developed in 196 patients (20.1%) and the most common pattern was distant metastasis (n=125, 12.8%). A multivariable Cox-regression analysis revealed that the number of removed lymph nodes, age, tumor size, pathologic stage, histology, and radiologic features were significant prognostic factors for recurrence-free survival. The removal of more than 10 up to 40 lymph nodes was associated with improved recurrence-free survival. However, the number of removed lymph nodes was not a significant risk factor for the overall survival.

Conclusions: The number of removed lymph nodes was closely related to the recurrence-free survival after VATS lobectomy. Therefore, proper lymph node dissection, in terms of number and station, should be performed in VATS lobectomy despite its difficulties.

Keywords: Non-small cell lung cancer (NSCLC); video-assisted thoracoscopic surgery (VATS); lymph node dissection

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Introduction

Video-assisted thoracoscopic surgery (VATS) lobectomy with systematic mediastinal lymph node evaluation has been adopted worldwide for lung cancer surgery due to improved early outcomes—lesser pain, a shorter hospital stay, fewer complications, and a higher compliance to adjuvant chemotherapy compared to thoracotomy—without compromising oncologic outcomes (1-6). Meanwhile, accurate mediastinal lymph nodes evaluation plays a pivotal role by providing precise staging and a therapeutic purpose of loco-regional control, which contribute to improved long-term survival after surgery. Current guideline recommends that N1 and N2 node resection should be a routine component of lung cancer resections—a minimum of three N1 and three N2 stations should be sampled or completely dissected based on the International Association for the Study of Lung Cancer nodal map (7,8). There have been some studies suggesting the removal of a minimum of 10 lymph nodes, however, this number ranges up to 16 lymph nodes depending on the study (9-11). Despite of the guideline which suggests to evaluate and remove lymph nodes, the adherence to the guideline is quite poor (12,13).

The number of resected lymph nodes can be a surrogate for the quality of VATS lobectomy in lung cancer surgery. However, the number of resected lymph nodes is influenced by the patient, surgeon's preference, and tumor factors. Therefore, the efficacy of lymph node evaluation in VATS varies. Several studies based on a large national cohort showed that VATS was associated with a lower detection rate for unsuspected nodal metastasis compared to thoracotomy (14,15). On the contrary, some articles showed that there were no differences in the efficacy of lymph node dissection and related long-term survival according to the surgical approach (16,17). In particular, the type of facility and penetration of surgical approaches were associated with the number of resected lymph node and station, which may have contributed to the difference in proficiency of VATS surgery for lung cancer (9,14). Furthermore, inadequate lymph node evaluation during surgical resection is still quite common, irrespective of surgical approaches (13). With the given heterogeneous results from previous literature, the adequacy of lymphadenectomy based on the number of resected lymph nodes in VATS for patients with non-small cell lung cancer (NSCLC) has been questioned.

Hence, we aimed to reveal oncological long-term results following VATS lobectomy and mediastinal lymph dissection for clinical N0 NSCLC, focusing on the quality of lymph node dissection.

Methods

Study population

From April of 2005 to June of 2013, a total of 2,502 patients underwent curative surgical resection of NSCLC at Seoul National University Hospital. Among them, multi-portal VATS lobectomy was performed in 1,055 patients (42.2%). We identified 974 eligible patients during the study period following the inclusion criteria: (I) who underwent VATS lobectomy for lung cancer with clinical N0 disease, (II) pathologically confirmed as NSCLC. We excluded 81patients based on the following criteria: (I) small cell histology, (II) wedge resection, segmentectomy and pneumonectomy, (III) intentional thoracotomy, and (IV) who were treated with neoadjuvant chemo or radiotherapy. VATS has been adopted for lung cancer since April 2005 in our institute. Currently, we predominantly perform VATS in over 80% of all lung cancer surgeries. All surgical candidates for lung cancer were evaluated with a chest CT scan and whole body FDG PET. In our institution, at least three N2 stations (2R, 4R, 7, 9 for right side and 4L, 5, 6, 7, 9 for left side), hilar, interlobar and peribronchial lymph nodes were completely dissected during the surgical resection except for anthracofibrosis of lymph nodes were technically impossible to be resected completely and mediastinal lymph node dissection was intentionally avoided. In addition, we preferred an *en-bloc* resection of N1 lymph nodes during lobectomy to avoid fragmentation. Complete mediastinal lymph node dissection was defined when at least three N2 stations were examined. This study was approved and an informed consent was waived by the Institutional Review Board in our institute.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (IBM, Inc., Armonk, NY, USA). In the univariable analysis, categorical variables were compared using a χ^2 test. Continuous variables were compared using the Student's *t*-test. Log-rank test was used in analyzing the survival rate. The relationship between the long-term survival and the number of removed lymph nodes was analyzed using Cox-regression proportional model. A P value of <0.05 was

considered statistically significant.

Results

Clinical characteristics

Patients and operative details

A total of 974 patients were enrolled (*Table 1*). The median follow up duration was 73 months. The mean age was 62.7 years. The majority of the patients were clinical stage I (n=911, 93.5%) and adenocarcinoma (n=807, 82.9%) was the dominant histology. The postoperative morbidity rate was 17.8% and the 30-day mortality was 0.3%. The median hospital stay was 5 days. Conversion to thoracotomy were identified in 21 patients (2.2%).

Pathologic outcomes

The mean tumor sized was 2.4 cm. R0 resection was achieved in 970 patients (99.6%). Mean number of resected lymph nodes were 24. Three or more mediastinal lymph nodal stations were evaluated in 947 patients (97.2%). More than 10 lymph nodes in 919 patients (94.4%). Nodal upstaging was found in 124 patients (12.7%). Unsuspected N1 and N2 were identified in 57 patients (5.9%) and 67 patients (6.9%), respectively. Adjuvant treatment was employed in 159 patients (93.0%) among pathologic stage II-IV.

Long-term prognosis and the number of resected lymph nodes

The 5-year overall and recurrence-free survival rates were 86.3% and 80.4%, respectively. The 10-year overall and recurrence-free survival rates were 78.3% and 77.9%, respectively. Recurrences developed in 196 patients (20.1%) and the most common pattern was distant metastasis (n=125, 12.8%). Loco-regional recurrences were found in 71 (7.3%) patients including 20 (2.1%) cases of dissected area, 27 (2.8%) cases of non-dissected area, 24 (2.5%) cases who had isolated pleural seeding. Post-recurrence survival duration was 33 months. There were clear differences in the overall survival (P<0.001) and recurrence-free survival (P<0.001) according to pathologic stages (*Figure 1*). Pathologic N2 showed the worst prognosis. Interestingly, pathologic N1 group had a similar overall and recurrence-free survival rate with those of pathologic N0 group (*Figure 2*). There was a significant difference in the recurrence-free survival according to the number lymph nodes harvested by 10-increment (P=0.033). Kaplan-Meier curves according to the number of resected lymph node by 11–20, 21–30, and 31–40 groups were similar; however, 0–10 and 40+ group tended to show the worse prognosis compared to the other groups (*Figure 3*). A multivariable Cox-regression analysis revealed that the number of removed lymph nodes by 10-increment was a significant prognostic factor for the recurrence-free survival after adjusting for year, age, tumor size, pathologic stage, histology, and radiologic features (*Table 2*). For the number of resected lymph nodes, the number of resected lymph nodes 11–20, 21–30, 31–40 groups were associated with improved recurrence-free survival unlike the group in which only 0–10 lymph nodes were removed. However, a significant survival benefit was no longer observed when more than 40 lymph nodes were removed. The number of resected lymph nodes was not a significant prognostic factor for overall survival (*Table 3*).

Discussion

We demonstrated long-term oncological outcomes of VATS lobectomy and mediastinal lymph node dissection for clinical N0 NSCLC based on a single institution's initial experience. Therefore, we were able to provide long-term survival rates and detailed recurrence patterns in depth with the sufficient follow up duration. In our institution, over 90% of the patient underwent complete mediastinal lymph node dissection and satisfactory overall and recurrence-free survival were achieved. The present study revealed a significant association between the number of resected lymph nodes and long-term survival. Furthermore, harvesting lymph nodes ranging 11 to 40 was associated with improved recurrence-free survival. There was no incremental improvement in the prognostic value after 40+ lymph nodes resection.

Systematic lymph node dissection allows accurate staging and subsequent improved survival. The AJCC TNM staging system for lung cancer uses the nodal stations based on IASLC nodal map, rather than the number of lymph nodes unlike gastrointestinal, breast, and bladder cancers (18). Therefore, there is no definite guideline for the number of examined lymph nodes during operation. The current guideline recommends at least six nodal stations to be examined three from N1 and three from N2 stations (7,8,19). Several studies suggest that at least 10 to 16 lymph nodes should be removed to improve long-term outcomes (9-11,20). Meanwhile, nodal upstaging is a frequently used surrogate for the completeness of node evaluation in the field of cancer surgeries. A recent large scale cohort study

Table 1 Baseline characteristics

Variable	Number (n=974)
Patients characteristics	
Year	
2005–2009	205 (21.0%)
2010–2013	769 (79.0%)
Age, years	62.7±10.0
Sex, male	494 (50.7%)
Pulmonary function	
FVC (pred %)	104.5±14.3
FEV1 (pred %)	107.6±18.5
FEV1/FVC (%)	73.6±9.2
Radiologic feature	
Subsolid nodule	318 (32.6%)
Solid nodule	656 (67.4%)
Clinical TNM stage (7th edition)	
I	911 (93.5%)
II	51 (5.2%)
III	1 (0.1%)
IV	11 (1.1%)
Clinical T category	
1	695 (71.4%)
2	251 (25.8%)
3	27 (2.8%)
4	1 (0.1%)
Operative outcomes	
Morbidity	173 (17.8%)
30-day mortality	3 (0.3%)
90-day mortality	9 (0.9%)
Hospital stay (median, range)	5 [4–7]
Conversion to thoracotomy	21 (2.2%)
Lobe	
RUL	320 (32.9%)
RML	81 (8.3%)
RLL	218 (22.4%)
RUL/RML	6 (0.6%)
RML/RLL	9 (0.9%)
LUL	197 (20.2%)
LLL	143 (14.7%)
Pathologic details	
Tumor size (cm)	2.4±1.3
R0 resection	970 (99.6%)
Complete mediastinal lymph node evaluation	947 (97.2%)
Number of resected lymph nodes	24.3±9.9
0–10	55 (5.6%)
11–20	308 (31.6%)
21–30	365 (37.5%)
31–40	189 (19.4%)
40+	57 (5.9%)
Nodal upstaging	124 (12.7%)
cN0/pN1	57 (5.9%)
cN0/pN2	67 (6.9%)
Pathologic stage (7th edition)	
I	803 (82.4%)
II	93 (9.5%)
III	66 (6.8%)
IV	12 (1.2%)
Adjuvant chemotherapy among pathologic Stage II-IV (n=171)	159 (93.0%)

Continuous variables are presented as means with standard deviation. LLL, left lower lobe; LUL, left upper lobe; RLL, right lower lobe; RML, right middle lobe; RUL, right upper lobe.

based on the National Cancer Database reported that incidence of unsuspected pN1 and pN2 in cN0 disease after lobectomy were 6.7% (8,915/132,604) and 3.9% (5,192/132,604), respectively (21). Our study showed similar nodal upstaging rates with previous literature, irrespective of surgical approach (14,15,21,22). Association between nodal upstaging and the survival advantage has been contradictory so far. Interestingly, although our data showed a good separation according to pathologic stages,

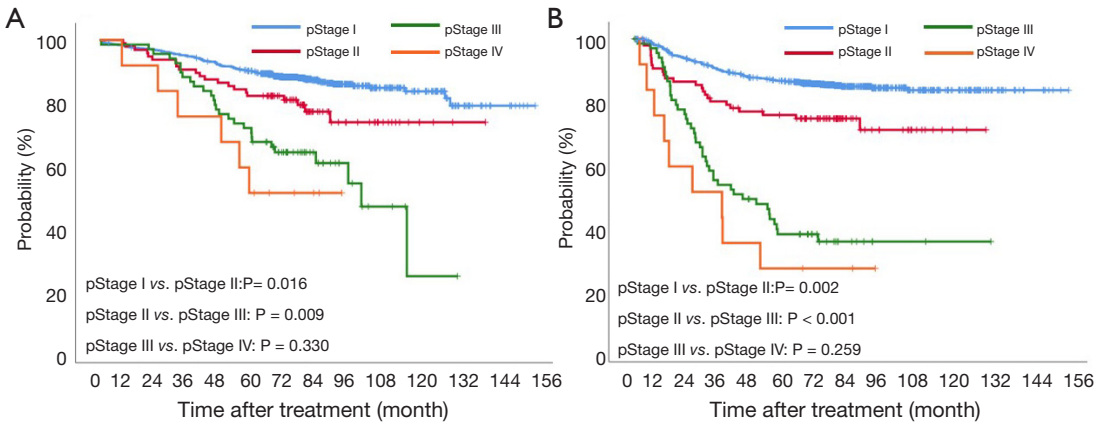

Figure 1 Overall survival (A) and recurrence-free survival (B) according to pathologic TNM stages.

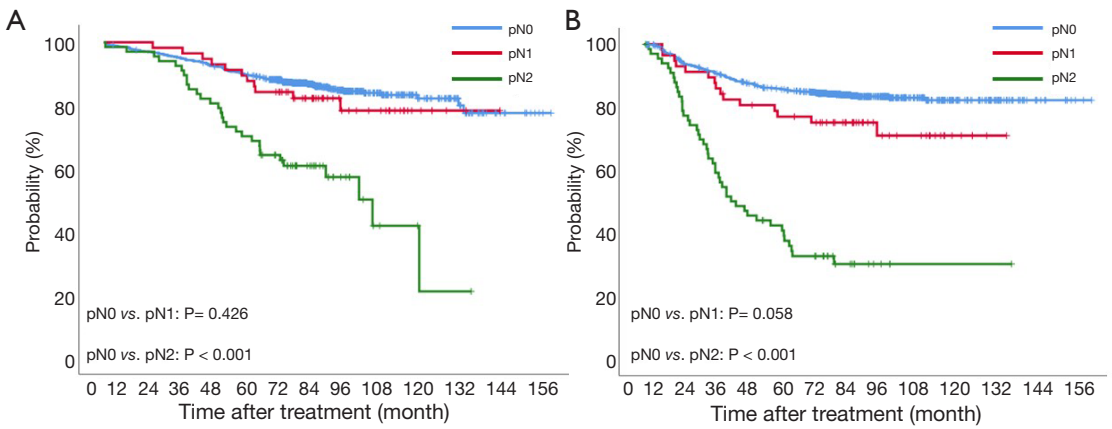

Figure 2 Overall survival (A) and recurrence-free survival (B) according to pathologic N status.

the unsuspected pathologic N1 group showed a comparable long-term survival rate with those of pathologic N0 group. These results may imply that complete dissection of metastatic hilar and peribronchial lymph nodes may have been performed during surgical resection and may also have led to a therapeutic effect.

The quality of lymph node dissection is different according to the facility and surgical approach (9,13-15). The reason for a low incidence of nodal upstaging of VATS is associated with the preferential use of VATS or thoracotomy. In addition, peripheral tumors tend to have lower nodal metastasis than central tumors. This may have influenced the selection for VATS for its surgical approach which may have results showing a discrepancy (23,24). Some surgeons argue that a fissureless technique to avoid air leakage may be related to low number of lymph nodes retrieved (25). The impact of the advanced surgical approach on the efficacy of lymph node assessment is not clear. The development of instrumentation such as robotic and 3D videoscope may allow delicate dissection and substantial high yield of lymph node (22,25). Wilson *et al.* reported that robotic lobectomy achieved similar nodal upstaging with that of thoracotomy, which was significantly higher than that of VATS (22). On the contrary, a large retrospective study showed no association between robotic and VATS for nodal upstaging and long-term survival (17). However, the overall number of harvested lymph nodes, around 10, from each surgical approach is quite low compared to our data. Moreover, the difference according to surgical approach disappeared in the academic/research facility (14,15). Therefore, we should interpret with caution due to the heterogeneity of studies regarding lymph node dissection.

A precise counting of resected lymph nodes is obscured

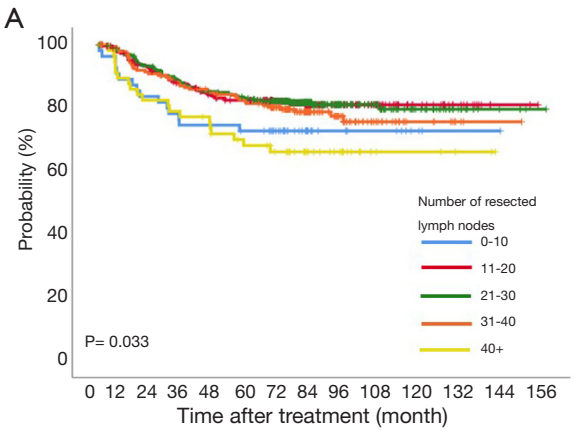

Figure 3 Recurrence-free survival according to the number of resected lymph nodes.

Table 2 Prognostic factor for recurrence-free survival

Variables	HR	95% CI	P value
Year	0.895	(0.831–0.963)	0.003
Male (ref. female)	1.309	(0.954–1.797)	0.095
Age (year)	1.021	(1.006–1.036)	0.006
Tumor size (cm)	1.317	(1.178–1.473)	<0.001
Pathologic stage (ref. I)			<0.001
II	1.028	(0.628–1.684)	0.913
III	4.979	(3.358–7.383)	<0.001
IV	8.771	(4.360–17.648)	<0.001
Histology (ref. adenocarcinoma)			0.145
Squamous cell carcinoma	1.080	(0.713–1.638)	0.716
Others	1.745	(1.002–3.041)	0.049
Subsolid nodule (ref. solid)	0.474	(0.306–0.737)	0.001
Number of lymph nodes (ref. 0–10)			0.038
11–20	0.550	(0.305–0.992)	0.047
21–30	0.511	(0.285–0.916)	0.024
31–40	0.448	(0.240–0.837)	0.012
40+	0.878	(0.441–1.747)	0.710

by fragmentation during the operation, especially in VATS. Different institutions, surgeons, and pathologists affect the assessment of the number and completeness of lymph nodes examined. Although four surgeons performed

Table 3 Prognostic factor for overall survival

Variables	HR	95% CI	P value
Year	0.845	(0.782–0.912)	<0.001
Male (ref. female)	2.048	(1.409–2.976)	<0.001
Age (year)	1.049	(1.030–1.067)	<0.001
Tumor size (cm)	1.293	(1.145–1.461)	<0.001
Pathologic stage (ref. I)			<0.001
II	0.996	(0.591–1.679)	0.989
III	3.676	(2.300–5.875)	<0.001
IV	7.129	(3.044–16.697)	<0.001
Histology (ref. adenocarcinoma)			0.009
Squamous cell carcinoma	1.673	(1.109–2.525)	0.014
Others	2.044	(1.141–3.659)	0.016
Subsolid nodule (ref. solid)	0.586	(0.363–0.947)	0.029
Number of lymph nodes (ref. 0–10)			0.734
11–20	0.826	(0.438–1.555)	0.553
21–30	0.709	(0.380–1.321)	0.279
31–40	0.699	(0.360–1.357)	0.290
40+	0.645	(0.285–1.456)	0.291

VATS lobectomy for lung cancer during the study period, institutional policy with regards to preoperative evaluation for lung cancer and preferential use of mediastinal lymph node dissection rather than sampling were not quite different among the surgeons. Upstaging following surgical resection depends on the accuracy of clinical staging as well. During the study period, preoperative evaluation modality and technology had evolved, particularly, the routine use of PET-CT and EBUS-TBNA (26,27). Therefore, we included the year of surgery as a covariate to adjust those temporal changes.

Despite several limitations related to a retrospective study in a single center, we demonstrated satisfactory long-term survival after VATS lobectomy for N0 NSCLC and the oncologic clearance by VATS lobectomy focused on the number of resected lymph nodes. We concluded that the number of removed lymph nodes was closely related with recurrence-free survival after VATS lobectomy. Therefore, we claim that proper lymph node dissection should be

performed in VATS lobectomy despite its difficulties.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/vats.2020.02.03). The series "Oncological Clearance of VATS Lobectomy for Clinical N0 Non-small Cell Lung Cancer" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Seoul National University Hospital Clinical Research Institute with informed consent not required (IRB No. 1911-139-1080).

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