Original Article

Prognostic factors and recurrence dynamics after multiple-port video-assisted thoracoscopic lobectomy for clinical T1-3N0 non-small cell lung cancer

Junghee Lee^, Sumin Shin, Tae Ho Kim, Jong Ho Cho, Yong Soo Choi, Jhingook Kim, Jae Ill Zo, Young Mog Shim, Hong Kwan Kim^

Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea
Contributions: (I) Conception and design: All authors; (II) Administrative support: HK Kim; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: J Lee; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.
Correspondence to: Hong Kwan Kim, MD, PhD. Department of Thoracic and Cardiovascular Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Republic of Korea. Email: hkkimts@gmail.com.

Background: The objectives of this study were to examine the outcomes, including early postoperative course, pathologic nodal upstaging, and long-term survival in patients who underwent video-assisted thoracoscopic surgery (VATS) lobectomy for clinical T1-3N0M0 non-small cell lung cancer (NSCLC) and to analyze the prognostic factors and recurrence dynamics in this cohort.

Methods: Between January 2010 and December 2014, 1,946 patients who underwent curative-intent VATS lobectomy for clinical T1-3N0M0 disease were recognized and their medical records were retrospectively reviewed to assess clinicopathologic characteristics, early postoperative outcomes, recurrence pattern, and survival.

Results: The study included 987 men and 959 women with a mean age of 61 years. The most common histologic type was adenocarcinoma (87%). Preoperative staging workup revealed that all patients had clinical N0 disease. The mean number of harvested lymph nodes (LNs) was 16 (interquartile range, 11 to 21). Pathologic N1 and N2 diseases were finally confirmed in 123 (6.3%) and 146 patients (7.5%), respectively. On multivariable logistic regression analysis, higher clinical T category and 11 or more than 11 total harvested LNs were significant predictors of detecting unexpected pathologic N1 or N2 diseases. Two in-hospital mortalities (0.1%) and 441 complications (22.7%) occurred during the early postoperative period. The median follow-up time was 45 months. At the end of follow-up, there were 1,728 surviving patients (88.8%). Overall survival at 5 years were 89.6% in pathologic N0, 76.5% in pathologic N1, and 61% in pathologic N2. During follow-up, 364 patients (18.7%) developed recurrence. The pattern of recurrence was loco-regional in 67 patients, distant in 226, and both in 71. Recurrence-free survival at 5 years were 81.7% in pathologic N0, 37.8% in pathologic N1, and 29.2% in pathologic N2.

Conclusions: Our findings suggest that VATS lobectomy could result in acceptable long-term survival outcomes in clinical T1-3N0M0 NSCLC even when unexpected N1 or N2 involvement was detected postoperatively.

Keywords: Non-small cell lung cancer (NSCLC); video-assisted thoracoscopic surgery (VATS); nodal upstaging; long-term survival; recurrence pattern and dynamics; prognostic factors

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^ Junghee Lee, ORCID: 0000-0002-5070-8248; Hong Kwan Kim, ORCID: 0000-0002-7815-3336.

Introduction

Over the past three decades, video-assisted thoracoscopic surgery (VATS) has emerged as a preferred surgical approach when performing lobectomy for patients with early-stage non-small cell lung cancer (NSCLC). Owing to the initial efforts of pioneers in this minimally invasive approach (1-7), thoracic surgeons have been increasingly adopting VATS lobectomy (8,9). This led to the accumulation of clinical evidence based on single- and multi-institutional retrospective studies, reporting that early and late outcomes of VATS were comparable to or even superior to those of open thoracotomy (1-17). Recently, several large-scale analyses from national databases have demonstrated that VATS lobectomy can be performed with improved short-term outcomes (18-25) and with favorable long-term survival compared with thoracotomy lobectomy (26). Therefore, VATS lobectomy is now strongly recommended for patients with no medical and surgical contraindications, as long as oncologic principles of surgery is not compromised.

However, questions still remain about whether VATS lobectomy is oncologically effective (14). Most previous studies demonstrating that VATS was not inferior to thoracotomy in terms of survival outcomes might have been subject to selection bias (12). Additionally, given the conflicting results on the incidence of pathologic nodal upstaging after VATS, there are concerns over the adequacy of intraoperative lymph node (LN) assessment during VATS lobectomy (15,24,26-29). Increasing interests in single-port VATS lobectomy might reinforce doubt on the quality of LN assessment through minimally invasive approach (30-33).

As an early adopter, since we reported our initial experience (13), our institution has been continuously raising the proportion of VATS among curative-intent surgical cases (*Figure 1*). It is worthwhile to contribute a high-volume institution's experience on multi-port VATS lobectomy to the current literature on oncological efficacy of VATS lobectomy. Therefore, the objectives of this study were to report our institutional surgical outcomes, including early postoperative course, pathologic nodal upstaging, and long-term survival in patients who underwent VATS lobectomy for clinical T1-3N0M0 NSCLC and to analyze the prognostic factors and recurrence dynamics in this cohort.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/vats-19-58).

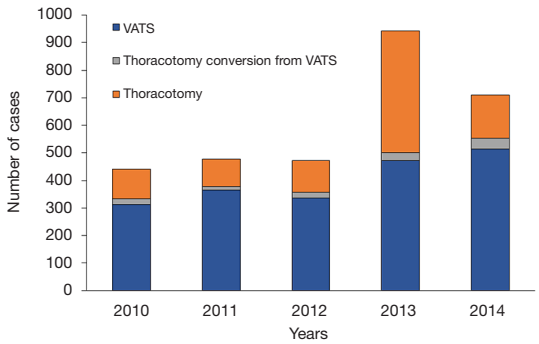

Figure 1 Annual cases of lobectomies for clinical T1-3N0 NSCLC during study period. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery.

Methods

Between January 2010 and December 2014, a total of 4,429 consecutive patients underwent curative-intent surgery for NSCLC at our institution. Among these, 2,074 patients who underwent VATS lobectomy for clinical T1-3N0M0 disease were recognized (*Figure 2*). VATS approach was initially attempted in these patients and of those, we had to convert to open thoracotomy in 128 patients (6.2%). Eventually, the remaining 1,946 patients were focused on this study and their medical records were retrospectively reviewed to assess clinicopathologic characteristics, early postoperative outcomes, recurrence pattern, and survival. The study design of this research is retrospective cohort study and is not related to an experimental study (interventional study) of human being. Therefore, we did not include the Declaration of Helsinki in the manuscript. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2020-08-056). Individual consent for this retrospective analysis was waived.

The routine preoperative workup included a complete history and physical examination, complete blood counts, chemistry profiles, pulmonary function tests (PFTs), simple chest X-ray, computed tomography (CT) of the chest and upper abdomen, bronchoscopy with washing cytology and/or biopsy, integrated whole-body 18F-fluorodeoxyglucose (FDG) positron emission tomography and CT (PET/CT) scans, and brain magnetic resonance imaging (MRI). For patients with suspicious nodal involvement, histopathologic examination through endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) were conducted to rule out nodal metastasis. Candidates for

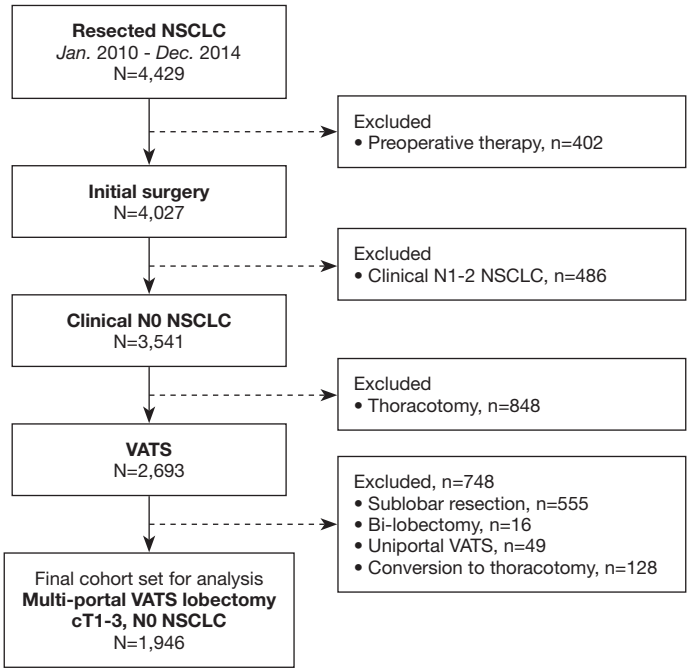

Figure 2 Flow diagram of study cohort. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery.

VATS lobectomy were patients with clinical T1-3N0M0 disease, peripherally located lesions (no endobronchial lesions), and a tumor of 6 cm in diameter or smaller. Patients were required to be able to tolerate single-lung ventilation, as determined by preoperative PFTs.

In general, VATS lobectomy was performed under single-lung anesthesia, using two ports and a utility incision without rib spreading. A 15 mm trocar for the 10 mm, 30-degree thoracoscope was placed through the seventh or eighth intercostal space in the posterior axillary line. A 4 cm utility incision was made through the fourth or fifth intercostal space in the anterior axillary line. An additional 5 mm trocar was placed through the sixth or seventh intercostal space in the posterior scapular line. However, details in surgical techniques of VATS lobectomy varied among surgeons as each surgeon has modified them according to their preferences. Despite these technical variances, oncological principles should be always complied with as follows: (I) the vessels and bronchi of the target lobe were individually dissected, (II) systematic LN dissection was regarded as mandatory, and (III) touching the LN itself and rupturing the capsule of the LN was avoided. Mediastinal LN dissection consisted of en bloc resections of all nodes at stations 2R, 4R, 7, 8, 9, and 10R for right-sided tumors and nodes at stations 4L, 5, 6, 7, 8, 9 and 10L for left-sided tumors. When LN enlargement was observed or LN metastasis was suspected, frozen section biopsies were performed during surgery. All specimens were placed into an impermeable bag and removed through the utility incision.

For patients with pathologic stage II or more advanced disease, adjuvant chemotherapy, radiotherapy or chemoradiation was administered as long as they were able to tolerate additional treatments. Patients were regularly evaluated by CT every 3 to 4 months for the first 2 years following surgery, and then every 6 months thereafter. Patients were evaluated by PET/CT scans when recurrence was suspected. Loco-regional recurrence was defined as that occurring within the ipsilateral hemithorax, including the pleura and mediastinal LNs. Distant recurrence was defined as that developing within the contralateral hemithorax or a distant solid organ. Whenever recurrence was suspected, we tried to obtain histological or unequivocal radiological proof. In cases lost to follow-up, a telephone interview was conducted to determine late outcomes.

Descriptive statistics were used to assess patient demographic characteristics and outcomes. Normally distributed continuous data were expressed as means ± standard deviations (SDs) and were compared using Student's *t*-test. Non-normally distributed continuous data were expressed as median (interquartile range) and

were compared using Mann-Whitney U test. Categorical data were expressed as counts and proportions. Student's *t*-tests and the χ^2 test or Fisher's exact test were used to compare continuous and categorical variables, respectively. Overall survival was defined as the time from the date of surgery until the last date of follow-up for patients who remained alive or until death. Recurrence-free survival was defined as the time from the date of surgery to the confirmed date of non-evidence of recurrence or to the date of recurrence. Survival curves were estimated using the Kaplan-Meier method and were compared using the log-rank test. Monthly hazard rates were estimated at 3-month intervals using a kernel-Epanechnikov smoothing method. The optimal cutoff value of harvested LN for predicting unexpected pN1 or pN2 was estimated using receiver operating characteristics curve analysis. The optimal cutoff count of harvested LNs for predicting overall survival and recurrence-free survival were estimated using maximally selected rank statistics with the R package maxstat and survminer (0.4.4). To determine which factors were associated with unexpected N1 or N2 diseases, a multivariable logistic regression model evaluating age, sex, body mass index (BMI), smoking history, forced expiratory volume in 1 second (FEV1), diffuse capacity of carbon monoxide, Charlson comorbidity index, anatomic location of the tumor, tumor size, clinical T category, histology, number of harvested LNs, optimal cutoff of harvested LNs, and dissected number of N2 stations were performed; nonsignificant variables were excluded in a stepwise fashion to obtain the final model. To determine which factors were significantly associated with survival, a multivariable analysis using Cox proportional hazards model was performed. All statistical tests were two-sided with a significance level set at 0.05 and were performed using R Studio (version 1.138) utilizing R statistical language version 3.4.2.

Results

Clinical and pathologic features

The study included 987 men and 959 women with a mean age of 61 (interquartile range, 54 to 68) years. Details on clinicopathologic features of the study cohort are summarized in *Table 1*. The most common histologic type was adenocarcinoma (1,687 patients, 87%). Preoperative staging workup including EBUS-TBNA revealed that all patients had clinical N0 disease. During surgery, LN metastases were confirmed by frozen section biopsy in 43 patients (2.2%), but none of these patients underwent conversion to open thoracotomy. The mean number of harvested LNs was 16 (interquartile range, 11 to 21). Except for two cases of microscopic residual tumor at the bronchial resection margin, there were no cases of incomplete resection.

Pathologic N1 and N2 diseases were finally confirmed in 123 (6.3%) and 146 patients (7.5%), respectively. The optimal cut-off counts of harvested LNs for predicting nodal upstaging calculated by receiver operating characteristic curve was 11 (sensitivity 87.0%, specificity 27.5%). On a multivariable logistic regression analysis, higher clinical T category and 11 or more total harvested LNs were independent predictors for detecting unexpected pathologic N1 or N2 diseases (*Table 2*). In patients with pathologic N2 disease, 120 patients (82.2%) had single-station involvement and 67 patients (45.9%) had extracapsular invasion. The median diameter of the largest metastatic LNs was 4 (interquartile range, 3 to 8) mm.

Early postoperative outcomes

Two in-hospital mortalities (0.1%) and 441 complications (22.7%) occurred during the early postoperative period. The most common complication was prolonged air leak (109 patients, 5.6%). The median length of hospital stay was 6 (interquartile range, 5 to 7) days. Details of early postoperative outcomes are listed in *Table 3*. Postoperatively, 322 patients (16.7%) underwent adjuvant chemotherapy (n=247), chemoradiation (n=70), or radiotherapy (n=5). Among the remaining 1,621 patients (94.5%), 62 patients (3.2%) were candidates for adjuvant therapy, but they did not undergo adjuvant treatment due to following reasons: Old age or poor performance status (n=25), patient refusal (n=18), comorbidity (n=7), disease progression (n=7), loss of follow-up (n=6), and no social support (n=1). The median time interval between the discharge from surgery and the start of adjuvant treatment was 34 (interquartile range, 28 to 40) days. Of the 247 patients who received chemotherapy, 197 (79.8%) received their full planned dose on schedule without delay. Eighteen patients (7.3%) completed planned schedule, but their regimen was changed during the courses (dose reduction in 13, regimen change in 5) with delay in 1 or more cycles. The remaining 32 patients (12.9%) stopped adjuvant treatment during the courses due to toxicities. Reasons for dose reduction or regimen change were peripheral neuropathy (n=7), neutropenia (n=5), gastrointestinal symptoms (n=3), and unknown cause (n=2).

Table 1 Clinicopathologic characteristics of 1,946 patients with clinical N0 NSCLC who received VATS lobectomy

Characteristics	Total (n=1,946)		pN0 (n=1,677)		pN1–2 (n=269)		P
	N	Values	N	Values	N	Values	
Age (y)	61	[54.0, 68.0]	61	[54.0, 68.0]	59	[53.0, 67.0]	0.216
Sex							0.902
Female	959	(49.3)	825	(49.2)	134	(49.8)	
Male	987	(50.7)	852	(50.8)	135	(50.2)	
BMI	23.9	[22.1, 25.8]	23.9	[22.1, 25.7]	24	[22.0, 25.9]	0.769
Smoking history							0.997
Never smoker	1,040	(53.4)	896	(53.4)	144	(53.5)	
Current smoker	423	(21.7)	365	(21.8)	58	(21.6)	
Ex-smoker	483	(24.8)	416	(24.8)	67	(24.9)	
FEV1 (L)	2.6	[2.2, 3.1]	2.6	[2.2, 3.0]	2.6	[2.3, 3.1]	0.415
FEV1 (% predicted)	97	[87.0, 108.0]	97	[87.0, 108.0]	98	[87.0, 109.5]	0.541
DLCO (% predicted)	94	[83.0, 105.0]	94	[83.0, 105.0]	92	[84.0, 103.0]	0.344
Charlson comorbidity index							0.294
0	204	(10.5)	175	(10.4)	29	(10.8)	0.413
1	531	(27.3)	454	(27.1)	77	(28.6)	0.912
2	505	(26.0)	437	(26.1)	68	(25.3)	0.556
≥3	706	(36.3)	611	(36.4)	95	(35.3)	0.414
Anatomic location of tumor							0.209
RUL	622	(32.0)	539	(32.1)	83	(30.9)	
RML	166	(8.5)	150	(8.9)	16	(5.9)	
RLL	413	(21.2)	356	(21.2)	57	(21.2)	
LUL	416	(21.4)	346	(20.6)	70	(26.0)	
LLL	329	(16.9)	286	(17.1)	43	(16.0)	
Tumor size (cm)	2.3	[1.7, 3.2]	2.2	[1.6, 3.0]	3	[2.3, 3.7]	<0.001
Clinical T category							<0.001
T1a	592	(30.4)	556	(33.2)	36	(13.4)	
T1b	698	(35.9)	606	(36.1)	92	(34.2)	
T2a	552	(28.4)	431	(25.7)	121	(45.0)	
T2b	61	(3.1)	48	(2.9)	13	(4.8)	
T3	43	(2.2)	36	(2.1)	7	(2.6)	
Pathologic T category							<0.001
Tis	3	(0.2)	3	(0.2)	0	(0.0)	
T1a	696	(35.8)	659	(39.3)	37	(13.8)	
T1b	563	(28.9)	496	(29.6)	67	(24.9)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=1,946)		pN0 (n=1,677)		pN1–2 (n=269)		P
	N	Values	N	Values	N	Values	
T2a	575	(29.5)	436	(26.0)	139	(51.7)	
T2b	57	(2.9)	42	(2.5)	15	(5.6)	
T3	50	(2.6)	39	(2.3)	11	(4.1)	
T4	2	(0.1)	2	(0.1)	0	(0.0)	
Pathologic N category							<0.001
pN0	1,677	(86.2)	1,677	(100.0)	0	(0.0)	
pN1	123	(6.3)	0	(0.0)	123	(45.7)	
pN2	146	(7.5)	0	(0.0)	146	(54.3)	
Pathologic M category							0.001
M0	1,940	(99.7)	1,675	(99.9)	265	(98.5)	
M1a	4	(0.2)	1	(0.1)	3	(1.1)	
M1b	2	(0.1)	1	(0.1)	1	(0.4)	
Histology							0.084
Adenocarcinoma	1,687	(86.7)	1,456	(86.8)	231	(85.9)	
Squamous cell carcinoma	187	(9.6)	165	(9.8)	22	(8.2)	
Others	72	(3.7)	56	(3.3)	16	(5.9)	
Differentiation							<0.001
Gx (undetermined)	184	(9.5)	160	(9.6)	24	(8.9)	
G1 (well)	261	(13.5)	254	(15.2)	7	(2.6)	
G2 (moderate)	1,279	(65.9)	1,099	(65.8)	180	(66.9)	
G3 (poor)	216	(11.1)	158	(9.5)	58	(21.6)	
Total positive LN	0	[0.0, 0.0]	0	[0.0, 0.0]	2	[1.0, 3.0]	<0.001
Total harvested LN							
Median [interquartile range]	16	[11.0, 21.0]	16	[11.0, 21.0]	17	[13.0, 24.0]	<0.001
Mean (± SD)	16.8	±8.2	17.2	±8.4	19.5	±9.0	<0.001
Dissected N2 stations							
Median [interquartile range]	4	[3, 4]	4	[3, 4]	4	[3, 4]	0.050
Mean (± SD)	3.6	±1	3.6	±1	3.8	±0.9	0.003
Lymphovascular invasion	514	(26.6)	330	(19.9)	184	(68.4)	<0.001
Pleural invasion							<0.001
PL0	1,707	(87.9)	1,510	(90.3)	197	(73.2)	
PL1	135	(7.0)	94	(5.6)	41	(15.2)	
PL2	90	(4.6)	63	(3.8)	27	(10.0)	
PL3	10	(0.6)	6	(0.4)	4	(1.5)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	Total (n=1,946)		pN0 (n=1,677)		pN1–2 (n=269)		P
	N	Values	N	Values	N	Values	
Bronchial resection margin	3	[2.0, 4.5]	3.5	[2.3, 4.5]	3	[2.0, 4.0]	<0.001
≥5 mm	1,944	(99.9)	1,676	(99.9)	268	(99.6)	0.647
<5 mm	2	(0.1)	1	(0.1)	1	(0.4)	
Bronchial resection margin							0.647
Negative	1,944	(99.9)	1,676	(99.9)	268	(99.6)	
Microscopic positive	2	(0.1)	1	(0.1)	1	(0.4)	
Adjuvant treatment modality							<0.001
No adjuvant therapy	1,621	(94.5)	1,585	(94.5)	36	(13.4)	
Chemotherapy	250	(12.8)	90	(5.4)	160	(59.5)	
Chemoradiotherapy	70	3.6	0	(0.0)	70	(26.0)	
Radiotherapy	5	0.3	2	(0.1)	3	(1.1)	

Values are presented as frequency (percentage), or median [interquartile range]. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracic surgery; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node; SD, standard deviation.

Table 2 Univariable and multivariable analysis of correlation with logistic regression model between clinicopathological factors and nodal upstaging (pN1–2)

Characteristics	Univariable analysis					Multivariable analysis		
	pN0 (n=1,677)		pN1–2 (n=269)		P	OR	95% CI	P
Age <65 (*vs.* ≥65 y)	61	[54.0, 68.0]	59	[53.0, 67.0]	0.787			
Male	852	(50.8)	135	(50.2)	0.850			
BMI	23.9	[22.1, 25.7]	24	[22.0, 25.9]	0.942			
Smoker (*vs*. non-smoker)	781	(46.6)	125	(46.5)	0.975			
FEV1 (% predicted)					0.578			
≤70	63	(3.8)	12	(4.5)				
>70	1,614	(96.2)	257	(95.5)				
DLCO (% predicted)								
≤60	1	(0.1)	0	(0.0)	0.974			
>60	1,534	(91.5)	252	(93.7)	0.233			
Not tested	142	(8.5)	17	(6.3)	Ref.			
Charlson comorbidity index								
0	175	(10.4)	29	(10.8)	0.781			
1	454	(27.1)	77	(28.6)	0.599			
2	437	(26.1)	68	(25.3)	0.996			

Table 2 (*continued*)

Table 2 (*continued*)

Characteristics	Univariable analysis					Multivariable analysis		
	pN0 (n=1,677)		pN1–2 (n=269)		P	OR	95% CI	P
≥3	611	(36.4)	95	(35.3)	Ref.			
Anatomic location of tumor								
RUL	539	(32.1)	83	(30.9)	0.906			
RML	150	(8.9)	16	(5.9)	0.268			
RLL	356	(21.2)	57	(21.2)	0.772			
LUL	346	(20.6)	70	(26.0)	0.157			
LLL	286	(17.1)	43	(16.0)	Ref.			
Tumor size (cm)	2.2	[1.6, 3.0]	3	[2.3, 3.7]	<0.001			
Clinical T category								
T1a	556	(33.2)	36	(13.4)	Ref.	1		Ref.
T1b	606	(36.1)	92	(34.2)	<0.001	2.23	1.49–3.34	<0.001
T2a	431	(25.7)	121	(45.0)	<0.001	4.09	2.75–6.08	<0.001
T2b	48	(2.9)	13	(4.8)	<0.001	3.82	1.88–7.78	<0.001
T3	36	(2.1)	7	(2.6)	0.014	2.72	1.11–6.64	0.028
Histology								
Adenocarcinoma	1,456	(86.8)	231	(85.9)	Ref.	1		Ref.
Squamous cell carcinoma	165	(9.8)	22	(8.2)	0.465	0.68	0.42–1.09	0.108
Other cells	56	(3.3)	16	(5.9)	0.044	1.55	0.85–2.81	0.153
Total harvested LN	16	[11.0, 21.0]	17	[13.0, 24.0]	<0.001	1.08	1.01–1.04	
<11 (counts) (*vs.* ≥11)	361	(21.5)	26	(9.7)	<0.001	0.42	0.28–0.65	<0.001
≥11 (counts)	1,316	(78.5)	243	(90.3)			Ref.	
Dissected N2 stations	4	[3, 4]	4	[3, 4]	0.003	1.08	0.93–1.26	0.294

Values are presented as frequency (percentage), or median [interquartile range]. BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node.

Survival and recurrence pattern

Follow-up was complete for all patients. The median follow-up time was 45 months. At the end of follow-up, there were 1,728 surviving patients (88.8%). Overall survival at 5 years were 89.6% in pathologic N0, 76.5% in pathologic N1, and 61% in pathologic N2 (*Figure 3*). During follow-up, 364 patients (18.7%) developed recurrence. The pattern of recurrence was loco-regional in 67 patients, distant in 226, and both in 71 (*Table 4*). Recurrence dynamics analysis showed that most recurrences occurred within the initial 2 years of postoperative follow-up. The peak incidence of overall recurrence as well as distant metastasis was detected twice (approximately 12 and 24 months after the operation), whereas that of local recurrence was detected one (approximately 12 months after the operation) (*Figure 4*). Recurrence-free survival at 5 years were 81.7% in pathologic N0, 37.8% in pathologic N1, and 29.2% in pathologic N2 (*Figure 3*).

Table 3 Perioperative outcomes after VATS lobectomy (n=1,946) in patients with clinical N2 NSCLC (cT1–3)

Variables	Total (n=1,946)	
	N	Values
Median follow up, month	45	[32.0, 63.0]
Length of hospital stay, days	6	[5.0, 7.0]
Mortality		
In hospital	2	(0.1)
30-day	1	(0.1)
90-day	8	(0.4)
Any morbidity (30-day)	441	(22.7)
Pulmonary	256	(13.2)
Cardiovascular	80	(4.1)
Gastrointestinal	19	(1.0)
Urologic	19	(1.0)
Infectious	7	(0.4)
Neurologic	40	(2.1)
Miscellaneous	99	(5.1)
Morbidities		
Persistent air leak (>5 days)	109	(5.6)
Atrial fibrillation	53	(2.7)
Chylothorax	36	(1.8)
ARDS	30	(1.6)
Pleural effusion	30	(1.5)
Vocal cord palsy	24	(1.2)
Pneumonia	21	(1.1)
Postoperative bleeding	9	(0.5)
Stroke	3	(0.2)
Deep vein thrombosis	1	(0.1)
Myocardial infection	0	(0.0)
Bronchopulmonary fistula	0	(0.0)

Values are presented as frequency (percentage), or median [interquartile range]. VATS, video-assisted thoracic surgery; NSCLC, non-small cell lung cancer; ARDS, acute respiratory distress syndrome.

Prognostic factor analysis

Optimal cut-off counts of total harvested LNs for survival prediction were 16 for both overall survival and recurrence-free survival (*Figure 5*). To better understand the factors associated with improved outcomes, univariable and multivariable analyses were performed and are detailed in *Tables 5,6*. Age (≥65 years), smoking history, higher Charlson comorbidity index, pathologic T category, pathologic N category, tumor differentiation, lymphovascular invasion were significantly associated with both worse overall survival and recurrence-free survival. However, adjuvant therapy was significantly associated with favorable overall survival (HR, 0.59; 95% CI, 0.73–0.94; P=0.025) and recurrence-free survival (HR, 0.60; 95% CI, 0.40–0.91; P=0.015).

Discussion

Previous institutional studies have demonstrated that VATS lobectomy is associated with more favorable short-term results than thoracotomy, including fewer postoperative complication and shorter length of hospital stay (1-17). However, it is doubtful whether the outcomes from such specialized centers can be generalized. Over the past 5 years, several large-scale studies using a national database have been published to resolve the doubts. They demonstrated the short-term safety and feasibility of VATS lobectomy even in real-world practice (18-25). Despite these favorable short-term outcomes, VATS lobectomy has not been widely accepted by thoracic surgeons (34), because questions on its oncologic reliability are unsolved (14). These concerns may be partly due to insufficient evidence on its long-term survival. Recently, Yang *et al*. investigated the long-term survival of VATS versus thoracotomy lobectomy using a national database for the first time. They found that VATS was associated with noninferior long-term survival when compared with thoracotomy lobectomy in real-world data (26). However, since this national study lacks the detailed information such as timing of recurrence or recurrence site, neither disease-free survival nor recurrence pattern analyses are available. In contrast, we have been maintaining strict follow-up plans after curative-intent surgery in our institution. This allowed us to conduct a comprehensive analysis on disease-specific survival as well as recurrence pattern and dynamics. Furthermore, our study

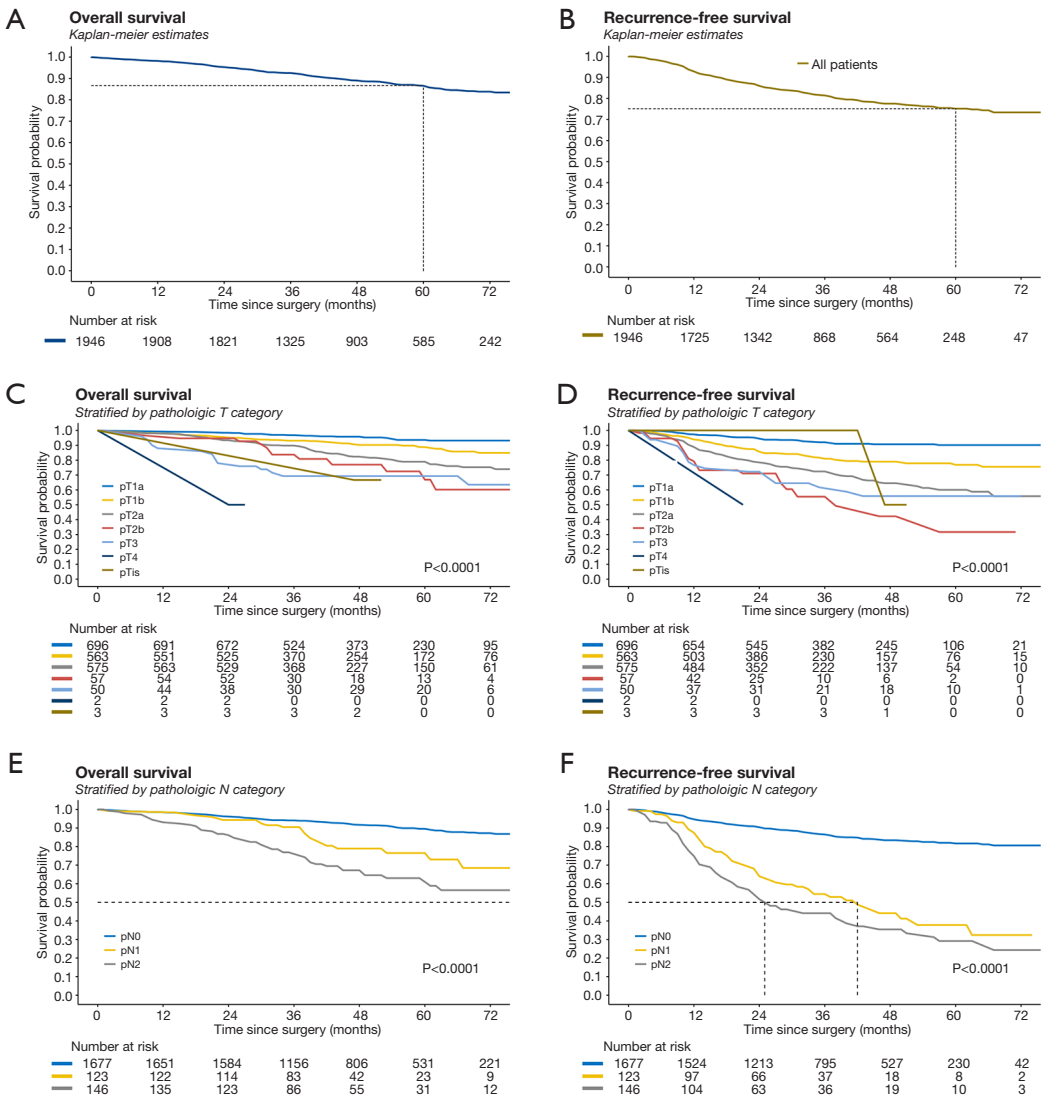

Figure 3 Kaplan-Meier plots for overall survival (A), and recurrence-free survival (B) for entire study cohort. Kaplan-Meier plots of overall survival and recurrence-free survival stratified by pathologic T category (C and D, respectively), and pathologic N category (E and F, respectively).

cohort consists of homogeneous population who received consistent surgical procedure as well as perioperative treatment protocols. Such advantages of data from a high-volume academic institution cannot be addressed by national database analyses.

Although our findings are based on a single institutional series with a single arm alone, long-term overall survival and recurrence-free survival seems to be very promising when compared with historical controls (35). In particular, it should be noted that our favorable survival outcomes are from patients with clinical N0 disease, which eventually included unexpected pathologic N1 or N2 disease. When confined to pathologic N0 disease regardless of pathologic T stage, the 5-year overall survival rate almost reached 90%, which corresponds to overall survival of pathologic stage IA1 according to the eighth edition proposed by the IASLC Staging and Prognostic Factors Committee (35). Our excellent long-term survival can be explained by the fact that VATS was chosen in highly selected patients. We routinely performed integrated PET/CT scans for accurate staging. For suspicious nodal involvement, EBUS-TBNA was also conducted. VATS lobectomy was planned

Table 4 Recurrence patterns of 1,946 patients with clinical N0 NSCLC after VATS lobectomy

Variables	Total (n=1,946)	
	N	Values
Crude recurrence rate	364	(18.7)
Median time to recurrence or non-evidence of disease, months	33	[22.0, 51.0]
Recurrence pattern		
Locoregional	67	(18.4)
Distant	226	(62.1)
Combined	71	(19.5)
Recurrence sites		
Stump or resection margin	16	(0.8)
Pleural seeding (ipsilateral)	79	(4.1)
Regional LNs (ipsilateral)	69	(3.5)
Dissected stations	5	(0.3)
Non-dissected stations	27	(1.4)
Combined dissected and non-dissected stations	37	(1.9)
Lung	134	(6.9)
Bone	72	(3.7)
SCN	56	(2.9)
Liver	22	(1.1)
Regional LNs (bilateral)	21	(1.1)
Regional LNs (contralateral)	19	(1.0)
Distant LNs	14	(0.7)
Adrenal	9	(0.5)
Kidney	4	(0.2)
Soft tissue	4	(0.2)
Pleural seeding (contralateral)	3	(0.2)
Pleural seeding (bilateral)	1	(0.1)
Intestine	1	(0.1)

Values are presented as frequency (percentage), or median [interquartile range]. NSCLC, non-small cell lung cancer; VATS, video-assisted thoracic surgery; SCN, supraclavicular lymph node; LN, lymph node.

only when patients had clinical N0 disease based on such meticulous staging workups. This could have made our study cohort enrich patients with truly early-stage NSCLC. This also suggests that even in patients with pathologic nodal involvement unexpectedly detected at surgery, its extent of nodal metastasis is likely to be minimal and microscopic. This is supported by our findings that N2 disease mostly involved single station and that the median diameter of the largest metastatic LNs was only 4 mm.

Another explanation for our improved long-term survival might be that our VATS cohort may have had more patients physiologically fit for postoperative recovery; for instance, younger age, preserved pulmonary function, good performance status, and fewer comorbidities. These features reflect the fact that our patients were highly selected before we decide to choose VATS. Apart from favorable impact of minimally invasive approach on early postoperative recovery, patients with good cardiopulmonary function might have also led to reduced early morbidities and mortalities, in turn resulting in improved overall survival. Many researchers are currently paying attention to the negative effect of postoperative complications on the long-term survival in various types of malignancies (36,37). In the same context, inflammatory markers or acute phase responses might be substantially favorable after VATS in terms of host immune function (38-41). These findings should be validated in further comparative studies involving VATS versus thoracotomy.

Concerns over the oncologic efficacy of VATS also arise from the risk of inadequate LN assessment through a limited access. Several nation-wide analyses showed that VATS was associated with less frequent nodal upstaging when compared with open thoracotomy (24,27,28). However, intrinsic limitations of exposure and manipulation of VATS can be overcome by the highly magnified view from video-assistance and advances in endoscopic instruments. Also, with experiences in VATS lobectomy accumulating, the quality of LN dissection can be improved. Some researchers have shown no significant differences in nodal upstaging between open and VATS (15,26,29). In this study, although we performed VATS in selected patients with clinical N0 disease based on meticulous staging workups, the rate

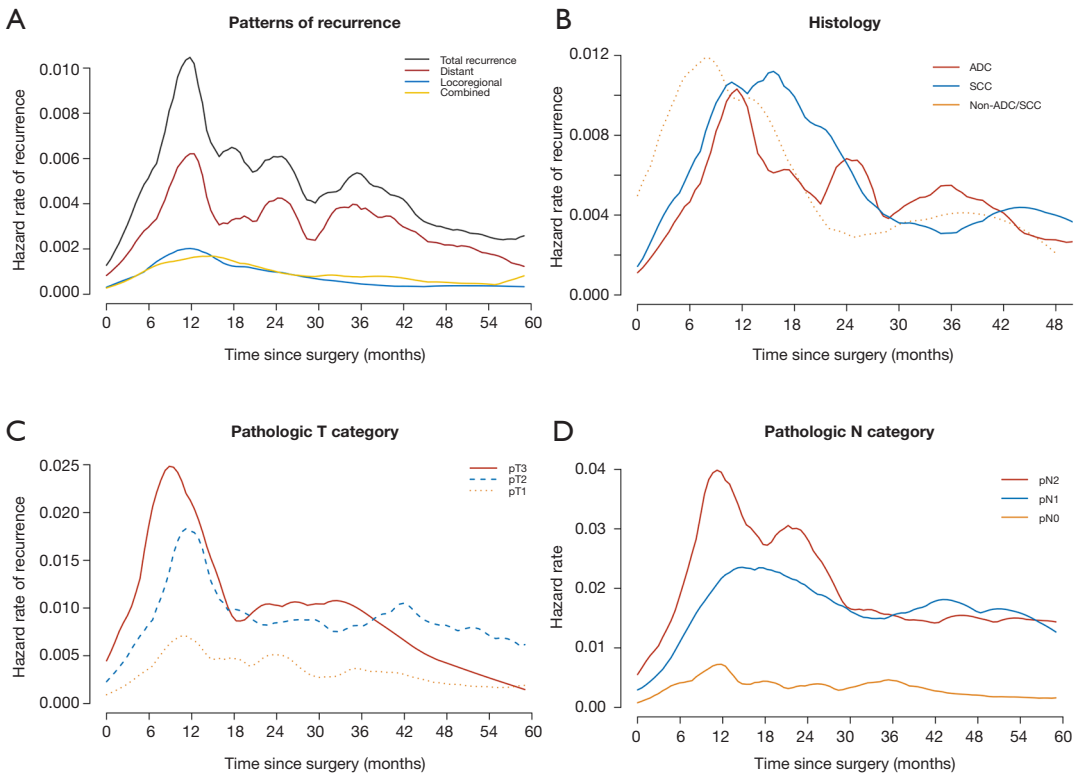

Figure 4 Comparison of the recurrence hazard rate curve stratified by (A) patterns of recurrence, (B) histology, (C) pathologic T category, and (D) pathologic N category in the entire cohort.

of nodal upstaging was not negligible. Among our 1,946 patients with clinical N0 disease, 269 patients (13.8%) turned out to have pathologic N1 or N2 disease. The median number of harvested LNs was 16, which was not inferior to that of the conventional open approach. In our series, the fact that unexpected N1 or N2 diseases were not uncommon despite thorough meticulous preoperative staging suggests that the quality of intraoperative LN assessment through our VATS techniques was reliable. Above all, survival rates of the pathologically upstaged patients were comparable to those of thoracotomy lobectomy from previous reports, which suggests that opening the chest might not have resulted in more favorable long-term outcomes in this subset of patients.

In this study, despite favorable overall survival, a substantial number of patients experienced recurrence. Thanks to prospectively designed elaborate database and strict follow-up plans of our institution, we were able to analyze the details of recurrence pattern and dynamics. Such a detailed analysis might not be available in studies based on national database or registry. As expected, the most common pattern of recurrence was distant metastasis. Recurrence dynamics analysis showed that most recurrences occurred within the initial 2 years of postoperative follow-up. The peak incidence of overall recurrence as well as distant metastasis was detected twice (approximately 12 and 24 months after the operation), whereas that of local recurrence was detected once (approximately 12 months after the operation). Based on these findings, we should be reminded that patients need to be strictly followed up through a meticulous surveillance for the first 2 years.

Since this is a retrospective study, our findings suffer from potential confounding and selection biases. VATS might have been performed in selected patients with favorable prognostic factors. Furthermore, patients who were converted to thoracotomy during VATS lobectomy were not included in this study. Also, since this is a noncomparative study, we are not able to demonstrate the outcomes of VATS in comparison with thoracotomy. To overcome these limitations, prospective randomized trials should be conducted.

In conclusion, in this retrospective study of large-volume

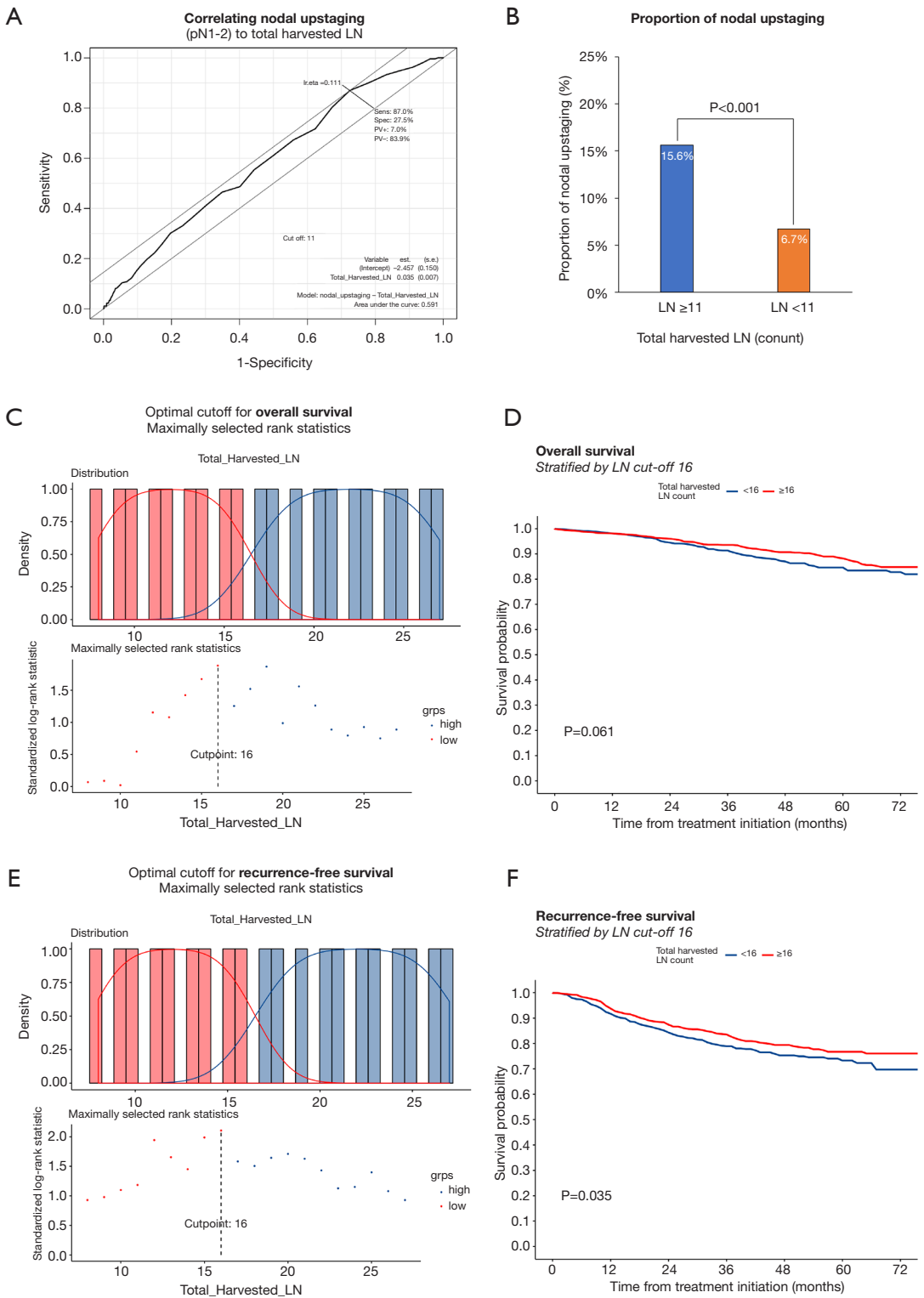

Figure 5 Receiver operating characteristics curve estimated 11 was optimal cut-off LN count for predicting nodal upstaging (A,B). Maximally selective rank statistics estimated that 16 was optimal cut-off of LN count for both overall survival and recurrence-free survival. LN, lymph node.

Table 5 Univariable and multivariable Cox-proportional hazard analysis for overall survival in patients with clinical N0 NSCLC after VATS lobectomy

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Age <65 (*vs.* ≥65 y)	1.1	1.1–1.1	<0.001	0.40	0.27–0.4	<0.001
Male	2.3	1.7–3.1	<0.001	1.17	0.7–1.16	0.551
BMI	0.99	0.95–1	0.810			
Smoker	2.3	1.8–3.1	<0.001	1.72	1.02–2.00	0.041
FEV1 (% predicted) >70	0.77	0.41–1.4	0.410			
DLCO (% predicted) >60	1.03	0.66–1.60	0.800			
Charlson comorbidity index			<0.001			
0	0.181	0.09–0.37		0.41	0.18–0.90	0.027
1	0.242	0.16–0.37		0.57	0.33–0.98	0.040
2	0.436	0.31–0.61		0.68	0.46–0.99	0.045
≥3	Reference			Reference		
Anatomic location of tumor			0.070			
RUL	0.8987	0.59–1.38		1.04	0.67–0.68	0.850
RML	0.9273	0.50–1.70		0.97	0.51–0.57	0.918
RLL	1.48	0.97–2.26		1.57	1.01–0.41	0.045
LUL	1.24	0.80–1.91		1.16	0.74–1.82	0.508
LLL	Reference			Reference		
Tumor size (cm)	1.4	1.3–1.5	<0.001			
Pathologic T category			<0.001			
Tis	4.6	0.64–33.01		6.31	0.82–0.96	0.077
T1	Reference					
T2	2.68	2.03–3.55		1.33	0.94–1.88	0.105
T3	4.67	2.74–7.95		2.99	1.63–5.48	<0.001
T4	15.83	2.19–114.22		5.21	0.36–1.04	0.225
Pathologic N category			<0.001			
pN0	Reference			Reference		
pN1	2.36	1.54–3.72		2.25	1.33–1.59	0.003
pN2	4.51	3.26–6.24		5.40	3.26–8.94	<0.001
Pathologic M category			0.030			
M0	Reference			Reference		
M1a	5.28	1.31–21.29		4.00	0.63–25.42	0.142
M1b	<0.001	0.00–∞		0.00	0.00–∞	0.993
Histology			<0.001			
Adenocarcinoma	Reference					

Table 5 (*continued*)

Table 5 (*continued*)

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Squamous cell carcinoma	2.54	1.81–3.56		1.10	0.75–6.28	0.634
Others	2.27	1.34–3.86		1.40	0.77–2.56	0.269
Differentiation			<0.001			
Gx (undetermined)	8.01	3.52–18.21		5.60	2.38–9.64	<0.001
G1 (well)	Reference			Reference		
G2 (moderate)	5.49	2.56–11.75		3.30	1.51–7.19	0.003
G3 (poor)	10.39	4.66–23.17		4.70	2.03–2.79	<0.001
Total harvested LN	1	1–1	0.065			
Count <16 (≥16)	0.7981	0.61–1.04	0.099	1.08	0.81–1.44	0.587
Dissected N2 stations	1.001	0.87–1.15	0.990			
Lymphovascular invasion	2.7	2.1–3.5	<0.001	1.53	1.12–2.09	0.007
Pleural invasion			<0.001			
PL0	Reference			Reference		
PL1	1.87	1.22–2.84		1.25	1.12–2.09	0.365
PL2	3.69	2.45–5.54		1.59	0.99–2.24	0.055
PL3	4.33	1.38–13.58		1.25	0.35–5.31	0.733
Bronchial resection margin ≥5 mm (*vs.* <5 mm)	1.12	0.28–4.46	0.900			
Adjuvant treatment	2.2	1.6–2.9	<0.001	0.59	0.37–0.94	0.025

NSCLC, non-small cell lung cancer; VATS, video-assisted thoracic surgery; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node.

Table 6 Univariable and multivariable Cox-proportional hazard analysis for recurrence-free survival in patients with clinical N0 NSCLC after VATS lobectomy

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Age (y) <65	0.59	0.48–0.73	<0.001	0.61	0.49–0.76	<0.001
Male	1.3	1.06–1.60	0.010	1.03	0.71–1.51	0.865
BMI	0.99	0.95–1	0.810			
Smoker	2.30	1.8–3.1	<0.001	1.18	0.81–1.72	0.390
FEV1 (% predicted) >70	0.77	0.41–1.4	0.410			
DLCO (% predicted) >60	1.43	0.95–2.15	0.200			
Charlson comorbidity index			0.300			
0	0.90	0.64–1.29				

Table 6 (*continued*)

Table 6 (*continued*)

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
1	0.78	0.60–1.01				
2	0.85	0.66–1.11				
≥3	Reference					
Anatomic location of tumor						
RUL	0.78	0.57–1.09	0.145			
RML	1.13	0.74–1.72	0.582			
RLL	1.17	0.84–1.63	0.344			
LUL	1.16	0.84–1.61	0.370			
LLL	Reference					
Tumor size (cm)	1.40	1.3–1.5	<0.001			
Pathologic T category						
Tis	2.16	0.30–15.40	0.444	1.83	0.25–13.4	0.551
T1	Reference					
T2	2.90	2.35–3.59	<0.001	1.81	1.40–2.34	<0.001
T3	3.61	2.24–5.82	<0.001	3.46	2.02–5.93	<0.001
T4	6.24	0.87–44.68	0.068	5.14	0.49–54.51	0.174
Pathologic N category						
pN0	Reference			Reference		
pN1	4.27	3.17–5.75	<0.001	3.98	2.60–6.08	<0.001
pN2	6.07	4.71–7.82	<0.001	5.81	3.70–9.11	<0.001
Pathologic M category						
M0	Reference			Reference		
M1a	5.89	1.89–18.4	<0.001	0.92	0.23–3.58	0.900
M1b	<0.001	0.00–∞	0.988	0.00	0.00–∞	0.992
Histology						
Adenocarcinoma	Reference					
Squamous cell carcinoma	1.19	0.85–1.68	0.346			
Others	1.27	0.85–1.68	0.313			
Differentiation						
Gx (undetermined)	4.25	2.45–7.37	<0.001	3.55	2.03–6.20	<0.001
G1 (well)	Reference			Reference		
G2 (moderate)	3.59	2.23–5.81	<0.001	2.08	1.27–3.41	0.004
G3 (poor)	4.25	2.45–7.37	<0.001	2.19	1.26–3.81	0.006

Table 6 (*continued*)

Table 6 (*continued*)

Risk factors	Univariable analysis			Multivariable analysis		
	HR	95% CI	P	HR	95% CI	P
Total harvested LN						
Count <16 (≥16)	0.81	0.66–1.00	0.049	1.01	0.82–1.25	0.926
Dissected N2 stations	1.058	0.95–1.18	0.295			
Lymphovascular invasion	2.70	2.1–3.5	<0.001	1.86	1.46–2.36	<0.001
Pleural invasion						
PL0	Reference			Reference		
PL1	1.85	1.33–2.57	<0.001	0.77	0.53–1.10	0.151
PL2	4.51	3.29–6.16	<0.001	1.71	1.20–2.43	0.003
PL3	2.38	0.76–7.41	0.136	0.68	0.20–2.36	0.544
Bronchial resection margin ≥5 mm (*vs.* <5 mm)	0.91	0.34–2.43	0.844			
Adjuvant treatment	2.20	1.6–2.9	<0.001	0.60	0.40–0.91	0.015

NSCLC, non-small cell lung cancer; VATS, video-assisted thoracic surgery; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; LN, lymph node.

academic center, VATS lobectomy can be performed with excellent short-term and long-term outcomes in clinical stage T1-3N0M0 NSCLC. VATS lobectomy is an oncologically sound procedure in terms of acceptable upstaging, reliable LN assessment, and satisfactory long-term survival. Our findings suggest that for patients staged N0 disease through meticulous preoperative workup, there is no need to convert into conventional thoracotomy even if intraoperative frozen section biopsy of the LNs is positive for malignancy during VATS lobectomy. Further comparative studies are needed and long-terms survival outcome from ongoing randomized controlled trials are awaited.

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Footnote

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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 design of this research is retrospective cohort study and is not related to an experimental study (interventional study) of human being. Therefore, we did not include the Declaration of Helsinki in the manuscript. This study was reviewed and approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2020-08-056). Individual consent

for this retrospective analysis was waived.

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