Video-assisted thoracoscopic surgery for patients with non-small cell lung cancer larger than 5 cm

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Background: Video-assisted thoracic surgery (VATS) has been widely accepted for the treatment of early-stage non-small cell lung cancer (NSCLC). However, the feasibility and safety for VATS was not well-clarified for NSCLC larger than 5 cm.

Methods: Patients with NSCLC larger than 5 cm receiving upfront surgery at Shanghai Chest Hospital from January 2013 to December 2017 were retrospectively collected. Candidates were divided into VATS and thoracotomy groups. After a 1:1 propensity score matching, we assessed the perioperative outcomes and the oncological prognosis between these two groups. Perioperative outcomes of conversion cases to open thoracotomy were also assessed. Further, subgroup analysis was conducted for evaluating the survival benefit for different surgical approaches receiving adjuvant chemotherapy (ACT).

Results: Of 689 patients included, 570 (82.7%) received thoracotomy and 119 (17.3%) received VATS resection. Although with statistically longer operation time, VATS was associated with less intraoperative blood loss (P=0.016) after matching. Numbers of harvested lymph nodes, intra- and postoperative complications, length of stay after surgery, chest drainage duration, and in-hospital mortality showed no significant difference between the two groups. The rate of conversion to open thoracotomy was 6.7% (8/119). The conversion group had comparable perioperative outcomes as those who completed VATS resections. In multivariable analysis, VATS showed comparable progression-free survival (PFS) and overall survival (OS) compared with thoracotomy. In the subgroup of patients receiving ACT, VATS patients presented better OS (P=0.018) and similar PFS (P=0.631) compared to thoracotomy patients.

Conclusions: For patients with NSCLC larger than 5 cm, VATS is safe and feasible. For patients receiving ACT, VATS benefited patients with better OS. VATS could be considered as an alternative approach for surgical treatment of well-selected patients with NSCLC larger than 5 cm.

Keywords: Video-assisted thoracic surgery (VATS); thoracotomy; non-small cell lung cancer larger than 5 cm (NSCLC larger than 5 cm)

Introduction

Non-small cell lung cancer (NSCLC) accounts for almost 70% of lung cancers and contributes to the leading cause of cancer-related mortality around the world (1). According to the 8th tumor node metastasis (TNM) classification, lung cancer is classified into T3 or T4 when tumor diameter is large than 5 cm, and tumor size is a prognostic factor for NSCLC (2). For locally advanced NSCLC (LA-NSCLC), including those larger than 5 cm, effectiveness of treatment is not satisfactory (3,4). For LA-NSCLC, especially T3 and resectable T4 tumors, radical surgical resection is still considered as a recommended treatment (5). As an important part of minimally invasive surgery, video-assisted thoracic surgery (VATS) has been strongly recommended for the resection of early-stage NSCLC, owing to better perioperative results and less postoperative complications compared with open thoracotomy (6-8). Tumor size larger than 5 cm is considered as a locally advanced disease and the indication of VATS approach is in suspense for the current clinical decision (9). According to the 2nd european society for medical oncology (ESMO) consensus on lung cancer in 2013, tumor size larger than 5 cm was regarded as a factor that made minimally invasive surgery inaccessible (10). In recent years, VATS has been gradually adopted not only for early-stage but also for LA-NSCLC of complicated resections, especially performed by experienced surgeons and medical centers (10,11). But the safety and feasibility as well as oncological prognosis of VATS resection for those NSCLC patients with tumor size larger than 5 cm still remain unclear.

Therefore, we aimed to study the safety and feasibility of VATS approach possessed acceptable and if it had any survival benefit for patients with NSCLC larger than 5 cm compared with open thoracotomy. We present this article in accordance with the STROBE reporting checklist (available at https://shc.amegroups.com/article/view/10.21037/shc-23-39/rc).

Methods

Inclusion and exclusion criteria

Patients with NSCLC larger than 5 cm in diameter receiving surgical resection at Shanghai Chest Hospital from January 2013 to December 2017 were retrospectively collected and enrolled in this study. The inclusion and exclusion criteria were plotted in *Figure 1*. Patients would be excluded if they had small cell lung cancer, metastatic lesions, undefined pathology, or multiple primary NSCLCs confirmed by final pathology. Multiple positive N2 lymph node stations and N3 lymph node stations confirmed by preoperative positron emission tomography/computed tomography (PET/CT), endobronchial ultrasound (EBUS) biopsy or mediastinoscopy biopsy were excluded. Those patients with unresectable T4 or stage IV NSCLCs diagnosed by preoperative examination or intraoperative operation as well as patients receiving induction therapy were also excluded.

Patients who met the above inclusion and exclusion criteria were divided into two groups, the VATS group and the thoracotomy group. VATS group was defined as patients received complete VATS resection including those converted to open thoracotomy during operation according to the intention-to-treat analysis. Thoracotomy group was defined as patients receiving open thoracotomy for surgical resection. As for resection extent, lobectomy as well as other operations including bi-lobectomy, sleeve resection and pneumonectomy were all counted.

Research endpoints

The primary endpoint of this study was perioperative safety and feasibility. R0 resection is defined according to International Association for the Study of Lung Cancer (IASLC) recommendations. Intraoperative data including the average operation time, volume of blood loss, lymph node dissection (harvested lymph nodes, as well as

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Highlight box

Key findings
- Video-assisted thoracic surgery (VATS) could be considered as a safe and feasible choice for those well-selected patients with non-small cell lung cancer (NSCLC) larger than 5 cm.

What is known and what is new?
- The size of NSCLC larger than 5 cm, which is classified into T3 and T4 stage tumors, is considered as locally advanced diseases. Surgical resection plays a role in the treatment of those T3 and resectable T4 NSCLCs, though radical resection is complicated
- For patients with NSCLC larger than 5 cm
- VATS not only showed comparable progression-free survival and overall survival (OS) in total in accordance with thoracotomy, but significantly benefited patients receiving adjuvant chemotherapy with better OS outcomes

What is the implication, and what should change now?
- For patients with NSCLC larger than 5 cm, VATS procedure is a preferable option.

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┌─────────────────────────────────────────────┐
│ Patients with lung cancer >5 cm underwent      │
│ surgical resection at Shanghai Chest Hospital   │
│ from Jan 2013 to Dec 2017                       │
│ (n=923)                                         │
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Excluded
- Small cell lung cancer   (n=32)
- Metastatic lesions   (n=25)
- Multiple lesions   (n=20)
- Multiple positive N2 stations   (n=47)
- Unresectable T4 stage   (n=30)
- Stage IV or N3 station   (n=41)
- Receiving induction therapy   (n=36)
- Undefined pathological types   (n=3)

(n=689)

Thoracotomy (n=570)

VATS (n=119)

Conversion to thoracotomy (n=8)
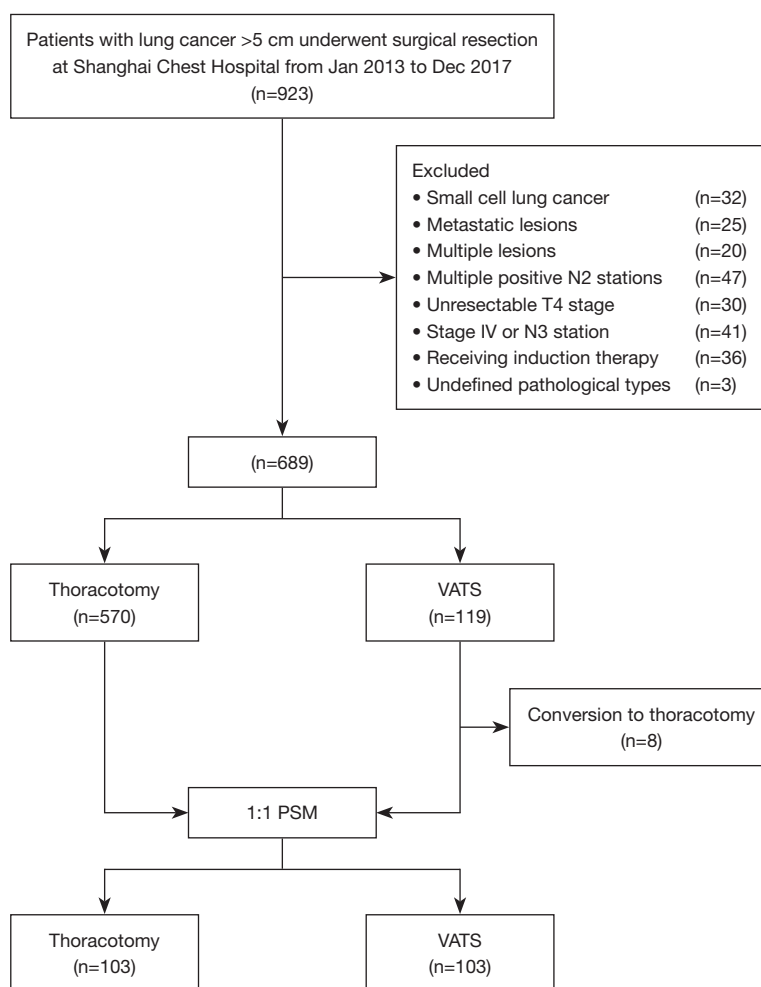
1:1 PSM

Thoracotomy (n=103)

VATS (n=103)

Figure 1 Study flowchart of patients with resected non-small cell lung cancer larger than 5 cm. VATS, video-assisted thoracic surgery; PSM, propensity score matching.

positive lymph nodes), intraoperative complications were retrospectively counted from our lung cancer database. Postoperative data were as following, length of hospital stay (LOS) after surgery, chest drainage duration, rate of postoperative complications as well as rate of in-hospital mortality. Postoperative complications were described and counted according to the Common Terminology Criteria for Adverse Events Version (CTCAE) 5.0, including prolonged air leakage, arrhythmia, postoperative bleeding, bronchopleural fistula (BPF), chylothorax, pulmonary infection or pyothorax, pleural effusion, reoperation, readmission and others. Specifically, prolonged air leakage was defined as air leakage more than 5 days.

Secondary endpoints were cancer recurrence and survivals, including progression-free survival (PFS) and overall survival (OS) (1). PFS was calculated from the date of surgery to the date of cancer recurrence or patient death or last follow-up. OS was defined as the interval between the date of surgery and the date of patient death or last follow-up. For postoperative follow-up, patients were recommended to take routine postoperative examinations including serum tumor markers, chest CT and cervical and abdominal ultrasound every 3 months, as well as brain magnetic resonance imaging (MRI) and bone scan every 6 months during the first year and then repeated every year. PET/CT was required if necessary.

Statistical analysis

Continuous and categorical variables were presented

as mean ± standard deviation (SD) and frequencies (percentages, %), respectively. Differences were tested by Student's *t*-test for continuous variables and Pearson χ^2 or Fisher's exact test for categorical ones. Intraoperative and postoperative outcomes were compared between those two groups before and after propensity score matching (PSM) analysis. The VATS and thoracotomy groups were matched by gender, age, smoking history, body mass index (BMI), forced expiratory volume in 1 second (FEV1), diffusing capacity of the lung for carbon monoxide (DLCO), comorbidity, central location, tumor location, resection extent, tumor size, histology types, pathological T stage and pathological N stage. PSM was carried out with a Caliper value set at 0.1 of the standard deviation. Intraoperative and postoperative outcomes were compared between those two groups before and after PSM analysis. Survival curves were plotted by Kaplan-Meier analysis and verified by Log-rank test. Univariable and multivariable cox proportional hazard regressions were analyzed after PSM to identify independently risk factors for those patients with resected NSCLC large than 5 cm. In addition, subgroup analysis was also conducted according to patients receiving adjuvant chemotherapy (ACT) or not as well as those VATS patients who suffered conversion to open thoracotomy. Statistical difference was set as P<0.05 with two sides. All analyses were performed by SPSS (version 20.0), R (version 3.2.2) and GraphPad (Prism 5).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Shanghai Chest Hospital (No: IS21113) and individual consent for this retrospective analysis was waived.

Results

Clinicopathological characteristics of patients before PSM

A total of 689 patients with resected NSCLC large than 5 cm were enrolled. Among them 119 (17.3%) patients received VATS resection and 570 (82.7%) patients received thoracotomy. VATS was increasingly used over time, from 10.6% (18/170) in 2013 to 32.1% (43/134) in 2017 (Figure S1). In the VATS group, eight cases were converted to open thoracotomy, with a conversion rate of 6.7% (8/119). Clinical and pathological characteristics of patients

before and after PSM are listed in *Table 1*. We found out that the VATS group contained relatively older patients with relatively better FEV1%, less central location, less squamous cell carcinoma (SCC), more pN0 stage and more lobectomy were found in the VATS group. After PSM, 103 VATS patients were well matched with 103 thoracotomy patients (*Table 1*). Rate of R0 resection, grade of tumor differentiation, pleural invasion (PI), lymphovascular invasion, and rate of ACT and radiotherapy were similar between VATS and open groups before and after PSM.

Intraoperative and postoperative outcomes between VATS and thoracotomy

After PSM, significantly less intraoperative blood loss was observed in the VATS group than in the thoracotomy group (111.2±83.1 *vs.* 206.8±390.8 mL, P=0.016). VATS approach demonstrated statistically longer operative time than thoracotomy (140.5±52.7 *vs.* 123.0±41.4 minutes, P=0.008). Median operation time of VATS shortened over time, from 150.8 minutes in 2013 to 130.5 minutes in 2017, while median operative time of thoracotomy remained similar, being 129.5 minutes in 2013 and 125.7 minutes in 2017 (Figure S1). VATS approach did not compromise the yield of lymph node dissection. Neither the total number of harvested lymph nodes nor the number of positive lymph nodes showed no statistical difference between the two groups. In addition, VATS resection did not increase the rate of intraoperative complications [3 (2.9%) *vs.* 1 (1.0%), P=0.313] in comparison with open thoracotomy (*Table 2*).

As for postoperative outcomes, VATS did not compromise the postoperative safety and feasibility in comparison with open thoracotomy before or after PSM. There was no significant difference between the VATS and thoracotomy groups in LOS, chest tube duration, rate of postoperative complications, or in-hospital mortality (*Table 2*).

For detailed postoperative complications, VATS presented similar outcomes including prolonged air leakage, arrhythmia, postoperative bleeding, BPF, chylothorax, pulmonary infection or pyothorax, pleural effusion, reoperation, readmission and other complications in accordance with traditional thoracotomy either before or after PSM (Table S1).

Oncological outcomes

The median follow-up was 42.1 months (0 to 73.9 months).

Table 1 Baseline characteristics of primary cohort

Variables	Before PSM			After PSM		
	Thoracotomy (n=570)	VATS (n=119)	P	Thoracotomy (n=103)	VATS (n=103)	P
Gender			0.499			0.133
Male	479 (84.0)	97 (81.5)		90 (87.4)	82 (79.6)	
Female	91 (16.0)	22 (18.5)		13 (12.6)	21 (20.4)	
Age (years)	61.5±8.8	64.3±9.2	0.002	63.4±8.0	63.6±9.2	0.865
Smoking history			0.928			0.640
No	419 (73.5)	87 (73.1)		73 (70.9)	76 (73.8)	
Yes	151 (26.5)	32 (26.9)		30 (29.1)	27 (26.2)	
BMI (kg/m^2)	22.8±3.2	23.4±3.4	0.060	23.0±3.3	23.1±2.8	0.813
FEV1 (%)	82.2±14.8	93.6±69.7	<0.001	86.2±15.4	86.9±17.4	0.734
DLCO (%)	83.9±19.0	83.8±18.7	0.938	83.5±19.5	84.6±18.8	0.680
Comorbidity			0.175			0.774
No	514 (90.2)	112 (94.1)		97 (94.2)	96 (93.2)	
Yes	56 (9.8)	7 (5.9)		6 (5.8)	7 (6.8)	
Central location			<0.001			>0.99
No	403 (70.7)	109 (91.6)		96 (93.2)	96 (93.2)	
Yes	167 (29.3)	10 (8.4)		7 (6.8)	7 (6.8)	
Tumor location			0.452			0.331
RUL	148 (26.0)	29 (24.4)		29 (28.2)	26 (25.2)	
RML	26 (4.6)	5 (4.2)		1 (1.0)	5 (4.9)	
RLL	122 (21.4)	33 (27.7)		23 (22.3)	30 (29.1)	
LUL	162 (28.4)	26 (21.8)		27 (26.2)	21 (20.4)	
LLL	112 (19.6)	26 (21.8)		23 (22.3)	21 (20.4)	
Surgical procedure			<0.001			>0.99
Lob	400 (70.2)	109 (91.6)		94 (91.3)	94 (91.3)	
Others	170 (29.8)	10 (8.4)		9 (8.7)	9 (8.7)	
Tumor size (mm)	6.7±1.5	6.4±1.3	0.059	6.4±1.2	6.4±1.3	0.825
Pathology			0.001			0.885
SCC	300 (52.6)	43 (36.1)		37 (35.9)	38 (36.9)	
Non-SCC	270 (47.4)	76 (63.9)		66 (64.1)	65 (63.1)	
Pathological T stage			0.104			0.503
pT3	388 (68.1)	90 (75.6)		82 (79.6)	78 (75.7)	
pT4	182 (31.9)	29 (24.4)		21 (20.4)	25 (24.3)	

Table 1 (*continued*)

Table 1 (*continued*)

Variables	Before PSM			After PSM		
	Thoracotomy (n=570)	VATS (n=119)	P	Thoracotomy (n=103)	VATS (n=103)	P
Pathological N stage			0.004			0.347
pN0	260 (45.6)	74 (62.2)		62 (60.2)	61 (59.2)	
pN1	153 (26.8)	21 (17.6)		26 (25.2)	20 (19.4)	
pN2	157 (27.6)	24 (20.2)		15 (14.6)	22 (21.4)	
Surgical margin			0.111			0.517
R0	528 (92.6)	115 (96.6)		97 (94.2)	99 (96.1)	
R1	42 (7.4)	4 (3.4)		6 (5.8)	4 (3.9)	
Grade			0.896			0.664
Well/moderate	346 (60.7)	73 (61.3)		67 (65.0)	64 (62.1)	
Poor	224 (39.3)	46 (38.7)		36 (35.0)	39 (37.9)	
PI			0.086			0.662
No	240 (42.1)	40 (33.6)		38 (36.9)	35 (34.0)	
Yes	330 (57.9)	79 (66.4)		65 (63.1)	68 (66.0)	
LVI			0.462			0.622
No	537 (94.2)	110 (92.4)		93 (90.3)	95 (92.2)	
Yes	33 (5.8)	9 (7.6)		10 (9.7)	8 (7.8)	
ACT			0.108			0.674
No	300 (52.6)	53 (44.5)		48 (46.6)	45 (43.7)	
Yes	270 (47.4)	66 (55.5)		55 (53.4)	58 (56.3)	
ART			0.072			>0.99
No	538 (94.4)	117 (98.3)		101 (98.1)	101 (98.1)	
Yes	32 (5.6)	2 (1.7)		2 (1.9)	2 (1.9)	

Data are presented as n (%) or mean ± SD. PSM, propensity score matching; VATS, video-assisted thoracic surgery; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; Lob, lobectomy; SCC, squamous cell carcinoma; PI, pleural invasion; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy; ART, adjuvant radiotherapy; SD, standard deviation; n, number.

A total of 264 patients (38.3%) experienced cancer recurrence included local relapse or distant metastasis, and 169 patients (24.5%) died within the follow-up interval. Five-year PFS was similar after VATS (42.6%) and thoracotomy (33.0%, P=0.505) and the 5-year OS was similar after VATS (66.1%) and thoracotomy (49.3%, P=0.114), respectively (*Figure 2A,2B*). After PSM, Five-year PFS was similar after VATS (43.4%) and thoracotomy (36.5%, P=0.956) and the 5-year OS was similar after VATS (68.7%) and thoracotomy (49.1%, P=0.274), respectively (*Figure 2C,2D*).

In univariable analysis, VATS approach was not associated with either PFS or OS. Pathological N stage, cancer differentiation grade and PI were found to be associated with recurrence. Further, patient age and cancer differentiation grade were also associated with OS (*Table 3*). In multivariable analysis, pathological N2 stage [hazard ratio (HR) =2.093, 95% confidence interval (CI): 1.263–3.469, P=0.004] and PI (HR =1.808, 95% CI: 1.132–2.886, P=0.013) were independently correlated with shorter PFS. Older age (HR =1.065, 95% CI: 1.026–1.106, P=0.001) and poor differentiation (HR =2.313, 95% CI: 1.353–3.952,

Table 2 Intraoperative and postoperative outcomes before and after PSM

Variables	Before PSM			After PSM		
	Thoracotomy (n=570)	VATS (n=119)	P	Thoracotomy (n=103)	VATS (n=103)	P
Intraoperative outcomes						
Operative time (minutes)	126.1±57.8	143.0±53.9	0.003	123.0±41.4	140.5±52.7	0.008
Harvested LNs	14.6±6.7	13.3±6.4	0.049	14.5±7.4	13.2±6.5	0.177
Harvested positive LNs	1.6±2.4	1.1±2.4	0.042	0.9±1.9	1.2±2.4	0.410
Blood loss (mL)	209.2±277.0	127.7±115.7	0.002	206.8±390.8	111.2±83.1	0.016
Intraoperative complication	19 (3.3)	9 (7.6)	0.034	3 (2.9)	1 (1.0)	0.313
Postoperative outcomes						
LOS (days)	9.4±12.5	7.3±5.4	0.085	8.0±3.8	7.2±5.4	0.197
Chest drainage duration (days)	6.5±12.4	5.3±5.1	0.290	5.2±3.9	5.1±5.1	0.830
Postoperative complications	73 (12.8)	16 (13.4)	0.180	10 (9.7)	12 (11.7)	0.652
In-hospital mortality	4 (0.7)	1 (0.8)	0.877	0	1 (1.0)	0.316

Data are presented as n (%) or mean ± SD. PSM, propensity score matching; VATS, video-assisted thoracic surgery; LN, lymph node; LOS, length of hospital stay; SD, standard deviation; n, number.

P=0.002) were independently correlated with worse OS (*Table 3*).

Further, we performed the subgroup analysis according to the status of postoperative chemotherapy. In the subgroup of patients without receiving ACT, we found that the VATS group demonstrated comparable 5-year PFS and OS in comparison with the thoracotomy group (*Figure 3A,3B*). VATS approach showed better 5-year OS rate than thoracotomy (78.1% *vs.* 50.8%, P=0.018) and similar PFS rate among those patients receiving ACT when against open thoracotomy (*Figure 3C,3D*).

Subgroup analysis of conversion to thoracotomy

There were eight cases converted to thoracotomy during VATS resections, four because of intraoperative massive hemorrhage, two of extensive tumor invasion and two of dense adhesion. The conversion cases had older age (71.8±8.4 *vs.* 63.8±9.1 years, P=0.017) and more central lesions (37.5% *vs.* 6.3%, P=0.002) than VATS (Table S2). Operative time (187.8±37.8 *vs.* 139.7±53.5 minutes, P=0.014) was significantly longer and intraoperative blood loss significantly more (362.5±231.1 *vs.* 110.9±81.6 mL, P<0.001) than those of the VATS group. Conversion to thoracotomy had statistically longer chest drainage duration (8.8±5.6 *vs.* 5.0±5.0 days, P=0.047) and longer LOS

(10.5±6.0 *vs.* 7.1±5.3 days, P=0.085) than VATS approach. But ability of lymph node dissection, rate of postoperative complications, or in-hospital mortality were similar between the conversion and VATS groups (Tables S3,S4). In univariable and multivariable logistic analyses, older age [odds ratio (OR) =5.934, 95% CI: 1.029–34.207, P=0.046] and centrally located lesion (OR =1.117, 95% CI: 1.001–1.248, P=0.049) were independently correlated with higher risk of conversion to open thoracotomy (Table S5).

Discussion

The size of NSCLC larger than 5 cm, which is classified into T3 and T4 stage tumors, is considered as locally advanced diseases. Surgical resection plays a role in the treatment of those T3 and resectable T4 NSCLCs, though radical resection is complicated (2,12). VATS resection has been tried to broaden from the early-stage NSCLC to primary NSCLC which was large than 5 cm in diameter according to previous study (13). The short-term clinical outcomes of VATS have been well-clarified among early-stage NSCLCs, but the safety and feasibility of VATS in NSCLC larger than 5 cm remained unclear (10,14-18). In 2016, Dr. Chen and his teammates pointed out that VATS lobectomy could be of safety with acceptable clinical outcomes for those LA-NSCLC (19). However, this study
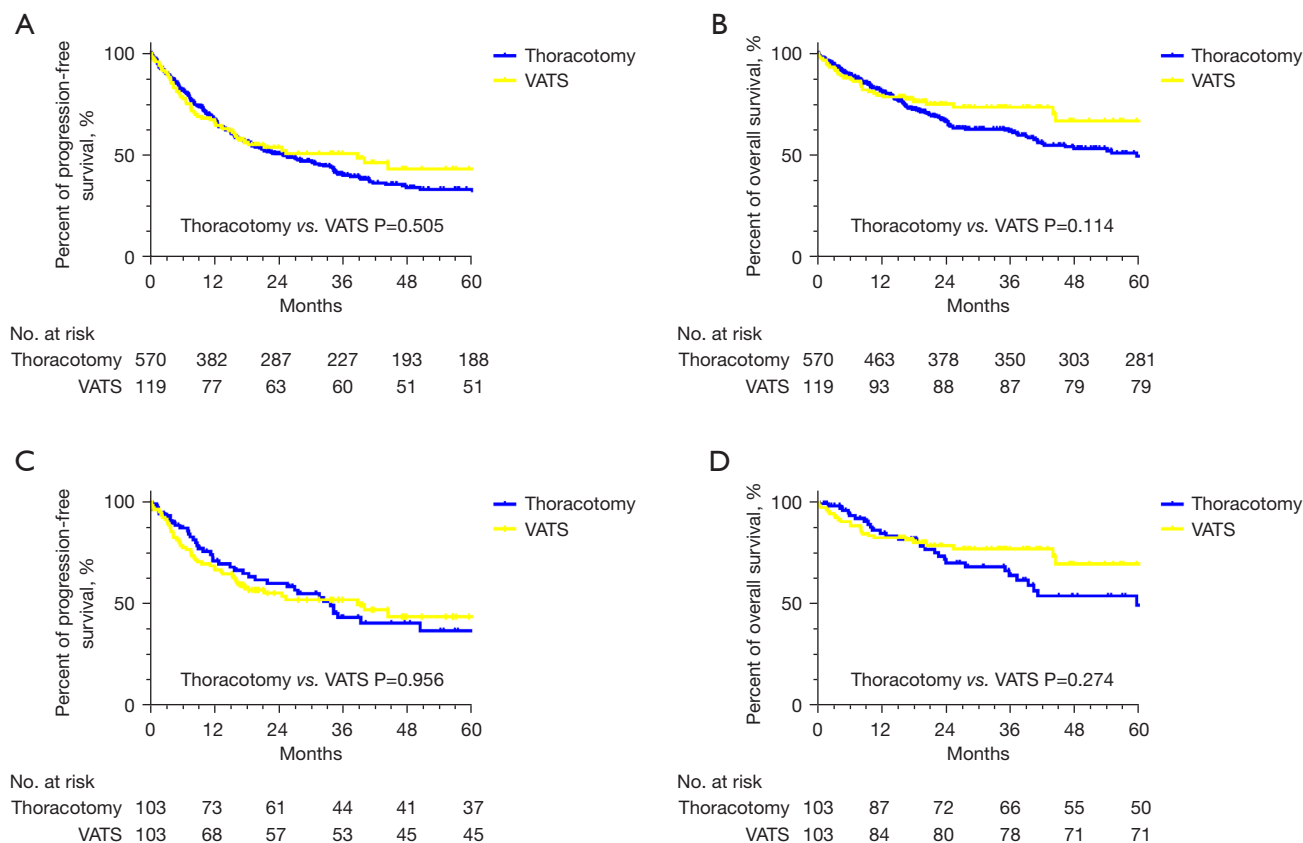
Figure 2 The comparison of recurrence and survival outcomes between VATS and thoracotomy by the Kaplan-Meier curves. (A) PFS curves of VATS and thoracotomy groups before PSM; (B) OS of VATS and thoracotomy groups before PSM; (C) PFS of VATS and thoracotomy groups after PSM; (D) OS of VATS and thoracotomy groups after PSM. VATS, video-assisted thoracic surgery; PFS, progression-free survival; OS, overall survival; PSM, propensity score matching.

enrolled clinical T1 NSCLC into statistical analysis and it might not be convincing for the application of VATS resection to those NSCLC larger than 5 cm according to the 7th TNM classification of lung cancer. In addition, tumor size larger than 5 cm is reclassified into T3 and T4 stage in accordance with the 8th TNM classification and the related researches are still limited.

In this study, we enrolled 689 patients, the largest cohort to now specifically focused on NSCLC larger than 5 cm receiving upfront VATS and open thoracotomy. After 1:1 PSM, we found that VATS was an alternative surgical approach worthy attempted. VATS was safe and feasible in NSCLC larger than 5 cm, with less blood loss, low conversion rate, similar intraoperative and postoperative complication rate, and similar complete resection rate compared to thoracotomy. Though operative time was longer in the VATS group, the gap got shorter as time went on. And VATS improved OS of patients with NSCLC larger than 5 cm receiving ACT, but had no association with PFS or OS in those without ACT.

Surgery for NSCLC larger than 5 cm is more complicated. Large tumor size leads to limited operative space, and is more likely to be companied with invasion of bronchus, vessels and lymph nodes as LA-NSCLC. In our study, only 17.3% (119/689) cases were performed by VATS. The operative time was long, with 123.0±41.4 minutes in the thoracotomy group and 140.5±52.7 minutes in the VATS group (P=0.008). However, rate of VATS got higher and time of operation got shorter over time, especially for VATS (Figure S1). In 2013, the median operative time was 129.5 and 150.8 minutes in the thoracotomy and VATS groups respectively. In 2017, it was 125.7 and 130.5 minutes in the thoracotomy and VATS groups.

Apart from operative time, perioperative clinical results

Table 3 Univariable and multivariable Cox regression analysis after PSM

Variables	Progression-free survival			Overall survival		
	Univariable	Multivariable		Univariable	Multivariable	
	P	HR (95% CI)	P	P	HR (95% CI)	P
Gender (female *vs.* male)	0.605	–	–	0.957	–	–
Age (per years)	0.081	–	–	0.001	1.065 (1.026–1.106)	0.001
Smoking history (yes *vs.* no)	0.503	–	–	0.654	–	–
BMI (per kg/m^2)	0.595	–	–	0.857	–	–
FEV1% (per %)	0.126	–	–	0.066	–	–
DLCO% (per %)	0.306	–	–	0.256	–	–
Comorbidity (yes *vs.* no)	0.782	–	–	0.710	–	–
Central location (yes *vs.* no)	0.388	–	–	0.985	–	–
Tumor location (*vs.* RUL)						
RML	0.130	–	–	0.150	–	–
RLL		–	–		–	–
LUL		–	–		–	–
LLL		–	–		–	–
Surgical procedure (others *vs.* Lob)	0.470	–	–	0.741	–	–
Tumor size (per mm)	0.906	–	–	0.193	–	–
Pathology (non-SCC *vs.* SCC)	0.240	–	–	0.748	–	–
Pathological T stage (pT4 *vs.* pT3)	0.464	–	–	0.830	–	–
Pathological N stage (*vs.* pN0)						
pN1	0.003	1.197 (0.706–2.030)	0.504	0.443	–	–
pN2		2.093 (1.263–3.469)	0.004		–	–
Surgical margin (R1 *vs.* R0)	0.722	–	–	0.891	–	–
Grade (poor *vs.* well/moderate)	0.026	1.311 (0.853–2.016)	0.217	0.002	2.313 (1.353–3.952)	0.002
PI (yes *vs.* no)	0.008	1.808 (1.132–2.886)	0.013	0.055	–	–
LVI (yes *vs.* no)	0.542	–	–	0.569	–	–
ACT (yes *vs.* no)	0.731	–	–	0.100	–	–
ART (yes *vs.* no)	0.556	–	–	0.477	–	–
Surgical approach (VATS *vs.* open)	0.956	–	–	0.276	–	–

PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; Lob, lobectomy; SCC, squamous cell carcinoma; PI, pleural invasion; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy; ART, adjuvant radiotherapy; VATS, video-assisted thoracic surgery.
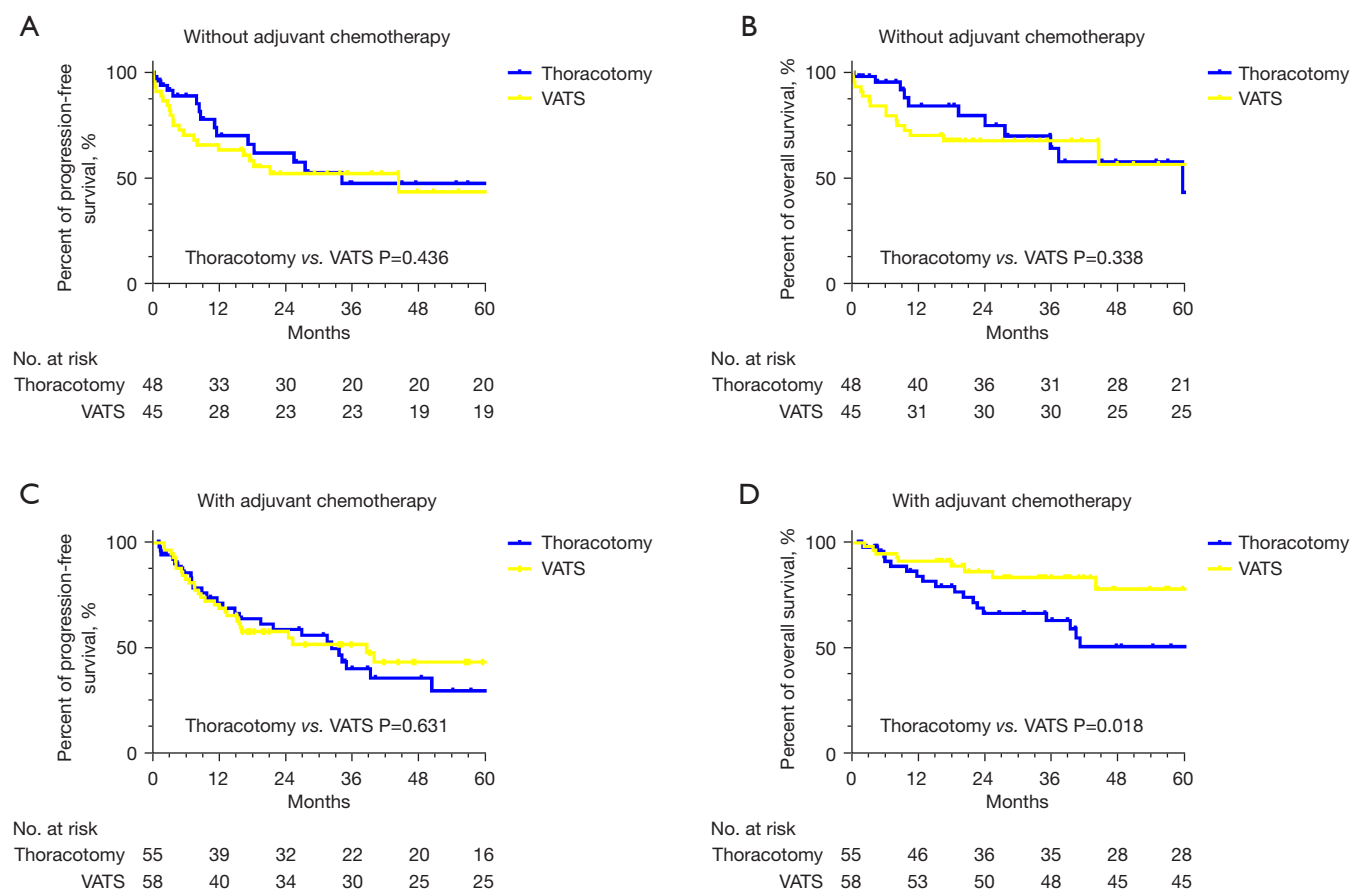
Figure 3 The comparison of recurrence and survival outcomes between VATS and thoracotomy stratified according to whether receive postoperative chemotherapy after PSM by Kaplan-Meier curves. (A) PFS curves of VATS and thoracotomy groups without receiving ACT; (B) OS of VATS and thoracotomy groups without receiving ACT; (C) PFS of VATS and thoracotomy groups receiving ACT; (D) OS of VATS and thoracotomy groups receiving ACT. VATS, video-assisted thoracic surgery; PFS, progression-free survival; OS, overall survival; PSM, propensity score matching; ACT, adjuvant chemotherapy.

of the VATS group were no worse than thoracotomy. For intraoperative outcomes, VATS presented much less volume of blood loss, similar intraoperative complications and comparable ability of lymph node dissection over the thoracotomy, owing to the precise anatomy and operation that VATS given to us thoracic surgeons. For postoperative feasibility and safety, length of stay was shorter in the VATS group than the thoracotomy group (7.3±5.4 vs. 9.4±12.5 days, P=0.085) with borderline P value. Chest tube duration, postoperative complication rate and the rate of in-hospital mortality were similar between the VATS and thoracotomy groups. In detail, the VATS group had similar rate of prolonged air leakage and bleeding, along with comparable arrhythmia and pulmonary infection rate against thoracotomy. More importantly, there was no

case of BPF, chylothorax, large volume of pleural effusion, reoperation, readmission or other complications in the VATS group. Those perioperative results mentioned above were just in same with Dr. Nakano's research and previous results (13,20).

Second is the low conversion rate and acceptable clinical outcomes of the conversion subgroup. The conversion rate (7.8%, 8/103) is totally comparable against that of early-stage NSCLC, which was 5.7% (14/246) (21). Conversion cases were much older patients with relatively aggressive tumor status compared with those of the VATS group. Therefore, longer operative time as well as worse survival outcome was foreseeable under this selection bias. Apart from operative time and blood loss, conversion cases still demonstrated no difference on other perioperative data with

the VATS group, which was in accordance with previous research (22). All these results also reflected the significant safety and feasibility of VATS approach from another aspect.

Third, the rate of R0 resection in the VATS group was similar to those in the thoracotomy group, which strongly indicated that the surgical approaches did not influence the surgically complete resection outcomes. Hence, with the preferable short-term outcomes, low conversion rate and comparable rate of R0 resection against the open group, though with difficulty, VATS could be accepted as a safe and feasible surgery a1pproach for LA-NSCLC.

It has been well-documented that VATS resection benefits patients with better long-term survival outcomes for early-stage NSCLCs than thoracotomy, probably owing to more precise surgical resection, less postoperative pain, earlier recovery (23,24). However, the survival benefit of VATS for NSCLCs larger than 5 cm is still limited. Dr. Bu indicated that complete VATS was similar to open approach in safety, completeness and efficacy, and had a shorter operative time and reduced bleeding among NSCLC with tumor size >5 cm. Nevertheless, long-term survival outcomes were not thoroughly mentioned (9). Dr. Nakano had pointed out the similar survival outcomes for both VATS and thoracotomy among patients with lung cancer >5 cm. However, only 68 patients were enrolled in statistical analysis (13).

In our analysis, we totally enrolled 689 qualified patients. It was found that VATS resection presented obviously improved OS and similar PFS in subgroup of patients receiving ACT compared with thoracotomy after adjustment. In subgroup of patients without ACT, VATS approach presented similar PFS and OS compared with thoracotomy either before or after variable matching. VATS had no impact on oncological results as this surgical approach did not influence R0 rate. But VATS brought less trauma to the whole body. Thoracotomy together with followed ACT might influence OS as thoracotomy and chemotherapy both brought trauma to patients to a certain extent. When we replaced thoracotomy by a less invasive approach, like VATS, less trauma might lead to OS benefits. VATS could be an alternative surgical approach for those LA-NSCLCs larger than 5 cm, with potentially survival benefit for patients receiving ACT.

However, there were still several limitations in this research. First, it was a retrospective analysis, the data were all collected from one single institution. Although variables were adjusted through the PSM, selection biases were still naturally unavoidable. Multicentric randomized clinical trial are required to validate the conclusion. Second, the follow-up time of our study was not adequate. It still needed much more time to follow up oncological prognosis and enhance the power of evidence. Third, patients with induction therapy were excluded to our study. Actually, large amounts of LA-NSCLC patients have been receiving neoadjuvant therapy, such as preoperative chemotherapy, targeted therapy or immunotherapy in recent years. Therefore, investigating the safety and feasibility for VATS resection among LA-NSCLC patients after induction therapy should become our priority in the next step. Moreover, it is truly a challenge for thoracic surgeon to complete a LA-NSCLC surgery under the VATS approach and the learning curves are relatively longer.

Conclusions

In conclusions, upfront surgery of VATS approach presented reliable safety and feasibility for patients with NSCLC larger than 5 cm compared with thoracotomy. Perioperative benefits were likely to be gained over time. VATS not only showed comparable PFS and OS in total in accordance with thoracotomy, but significantly benefited patients receiving ACT with better OS outcomes. Therefore, VATS could be considered as a safe and feasible choice for those well-selected patients with NSCLC larger than 5 cm.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://shc.amegroups.com/article/view/10.21037/shc-23-39/rc

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Conflicts of Interest: All authors have completed the ICMJE

uniform disclosure form (available at https://shc.amegroups.com/article/view/10.21037/shc-23-39/coif). W.F. serves as the unpaid Executive Editor-in-Chief of *Shanghai Chest*. The other authors have no 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 the Institutional Review Board of Shanghai Chest Hospital (No. IS21113) and individual consent for this retrospective analysis was waived.

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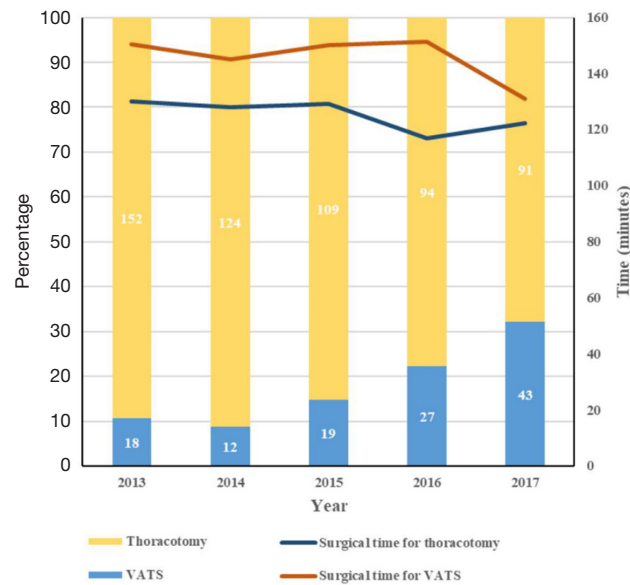
Figure S1 Rate of VATS surgery and surgical time for VATS and thoracotomy from 2013 to 2017 over time. VATS, video-assisted thoracic surgery.

Table S1 Postoperative complications before and after PSM

Variables	Before PSM, n (%)			After PSM, n (%)		
	Thoracotomy (n=570)	VATS (n=119)	P	Thoracotomy (n=103)	VATS (n=103)	P
Any complications	73 (12.8)	16 (13.4)	0.180	10 (9.7)	12 (11.7)	0.652
Air leakage	52 (9.1)	13 (10.9)	0.541	8 (7.8)	10 (9.7)	0.622
Arrhythmia	3 (0.5)	2 (1.7)	0.177	1 (1.0)	2 (1.9)	0.561
Bleeding	6 (1.1)	1 (0.8)	0.834	0	1 (1.0)	0.316
BPF	6 (1.1)	0	0.261	0	0	>0.99
Chylothorax	3 (0.5)	0	0.428	1 (1.0)	0	0.316
Pulmonary infection or pyothorax	3 (0.5)	1 (0.8)	0.682	1 (1.0)	1 (1.0)	>0.99
Pleural effusion	5 (0.9)	0	0.305	1 (1.0)	0	0. 316
Others	2 (0.4)	0	0.518	0	0	>0.99
Reoperation	2 (0.4)	0	0.518	0	0	>0.99
Readmission	2 (0.4)	0	0.518	0	0	>0.99

PSM, propensity score matching; VATS, video-assisted thoracic surgery; n, number; BPF, bronchopleural fistula.

Table S2 Baseline characteristics of primary cohort between conversion to thoracotomy and VATS

Variables	VATS (n=111)	Conversion to thoracotomy (n=8)	P
Gender			0.651
Male	90 (81.1)	7 (87.5)	
Female	21 (18.9)	1 (12.5)	
Age (years)	63.8±9.1	71.8±8.4	0.017
Smoking history			0.342
No	80 (72.1)	7 (87.5)	
Yes	31 (27.9)	1 (12.5)	
BMI (kg/m^2)	23.3±3.4	24.9±2.3	0.196
FEV1 (%)	94.7±71.9	77.5±20.6	0.502
DLCO (%)	84.6±18.7	71.9±15.8	0.062
Comorbidity			0.464
No	104 (93.7)	8 (100.0)	
Yes	7 (6.3)	0	
Central location			0.002
No	104 (93.7)	5 (62.5)	
Yes	7 (6.3)	3 (37.5)	
Tumor location			0.779
RUL	26 (23.4)	3 (37.5)	
RML	5 (4.5)	0	
RLL	32 (28.9)	1 (12.5)	
LUL	24 (21.6)	2 (25.0)	
LLL	24 (21.6)	2 (25.0)	
Tumor size (mm)	6.4±1.3	6.6±1.5	0.669
Surgical procedure			0.665
Lob	102 (91.9)	7 (87.5)	
Others	9 (8.1)	1 (12.5)	
Pathology			0.398
SCC	39 (35.1)	4 (50.0)	
Non-SCC	72 (64.9)	4 (50.0)	

Table S2 (*continued*)

Table S2 (*continued*)

Variables	VATS (n=111)	Conversion to thoracotomy (n=8)	P
Pathological T stage			0.370
pT3	85 (76.6)	5 (62.5)	
pT4	26 (23.4)	3 (37.5)	
Pathological N stage			0.892
pN0	69 (62.2)	5 (62.5)	
pN1	20 (18.0)	1 (12.5)	
pN2	22 (19.8)	2 (25.0)	
Surgical margin			0.585
R0	107 (96.4)	8 (100.0)	
R1	4 (3.6)	0	
Grade			0.183
Well/moderate	70 (63.1)	3 (37.5)	
Poor	41 (36.9)	5 (62.5)	
PI			0.593
No	38 (34.2)	2 (25.0)	
Yes	73 (65.8)	6 (75.0)	
LVI			0.584
No	103 (92.8)	7 (87.5)	
Yes	8 (7.2)	1 (12.5)	
ACT			0.011
No	46 (41.4)	7 (87.5)	
Yes	65 (58.6)	1 (12.5)	
ART			0.702
No	109 (98.2)	8 (100.0)	
Yes	2 (1.8)	0	

Data are presented as n (%) or mean ± SD. VATS, video-assisted thoracic surgery; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; Lob, lobectomy; SCC, squamous cell carcinoma; PI, pleural invasion; LVI, lymphovascular invasion; ACT, adjuvant chemotherapy; ART, adjuvant radiotherapy; SD, standard deviation.

Table S3 Intraoperative and postoperative outcomes between conversion to thoracotomy and VATS

Variables	VATS (n=111)	Conversion to thoracotomy (n=8)	P
Intraoperative outcomes			
Operative time (minutes)	139.7±53.5	187.8±37.8	0.014
Harvested LNs	13.3±6.4	13.0±6.9	0.906
Harvested positive LNs	1.1±2.3	1.8±3.0	0.439
Blood loss (mL)	110.9±81.6	362.5±231.1	<0.001
Postoperative outcomes			
LOS (days)	7.1±5.3	10.5±6.0	0.085
Chest drainage duration (days)	5.0±5.0	8.8±5.6	0.047
Postoperative complications	14 (12.6)	2 (25.0)	0.321
In-hospital mortality	1 (0.9)	0	0.787

Data are presented as n (%) or mean ± SD. VATS, video-assisted thoracic surgery; LN, lymph node; LOS, length of hospital stay; SD, standard deviation.

Table S4 Postoperative complications between conversion to thoracotomy and VATS

Variables	VATS (n=111), n (%)	Conversion to thoracotomy (n=8), n (%)	P
Any complications	14 (12.6)	2 (25.0)	0.321
Air leakage	12 (10.8)	1 (12.5)	0.882
Arrhythmia	2 (1.8)	0	0.702
Bleeding	1 (0.9)	0	0.787
BPF	0	0	>0.99
Chylothorax	0	0	>0.99
Pulmonary infection or pyothorax	2 (1.8)	1 (25.0)	0.062
Pleural effusion	0	0	>0.99
Others	0	0	>0.99
Reoperation	0	0	>0.99
Readmission	0	0	>0.99

VATS, video-assisted thoracic surgery; n, number; BPF, bronchopleural fistula.

Table S5 Univariable and multivariable logistic analysis for the risk factors of conversion to open thoracotomy

Variables	Univariable	Multivariable		
	P	OR	95% CI	P
Gender (female *vs.* male)	0.651	–	–	–
Age (per years)	0.018	5.934	1.029–34.207	0.046
Smoking history (yes *vs.* no)	0.342	–	–	–
BMI (per kg/m^2)	0.193	–	–	–
FEV1% (per %)	0.498	–	–	–
DLCO% (per %)	0.061	–	–	–
Comorbidity (yes *vs.* no)	0.464	–	–	–
Central location (yes *vs.* no)	0.008	1.117	1.001–1.248	0.049
Tumor location (*vs.* RUL)				
RML	0.799	–	–	–
RLL		–	–	–
LUL		–	–	–
LLL		–	–	–
Surgical procedure (others *vs.* Lob)	0.665	–	–	–
Tumor size (per mm)	0.666	–	–	–
Pathology (non-SCC *vs.* SCC)	0.746	–	–	–
Pathological T stage (pT4 *vs.* pT3)	0.370	–	–	–
Pathological N stage (*vs.* pN0)				
pN1	0.869	–	–	–
pN2		–	–	–
Surgical margin (R1 *vs.* R0)	0.999	–	–	–
Grade (poor *vs.* well/moderate)	0.152	–	–	–
PI (yes *vs.* no)	0.593	–	–	–
LVI (yes *vs.* no)	0.584	–	–	–

OR, odds ratio; CI, confidence interval; BMI, body mass index; FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe; SCC, squamous cell carcinoma; PI, pleural invasion; LVI, lymphovascular invasion.