



Comparison of oncological outcomes of single-port versus multi-port video-assisted thoracoscopic surgery for non-small-cell lung cancer: a propensity-matched analysis

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ABSTRACT

Purpose: There are few reports about oncological outcomes of single-port (SP) video-assisted thoracoscopic surgery (VATS) lobectomy, represented by overall survival (OS), disease-free survival (DFS), and adequacy of lymph node retrieval. We designed this study to analyze the oncological outcomes of SP versus multi-port (MP) VATS lobectomy for non-small-cell lung cancer (NSCLC).

Methods: From January 2012 to February 2014, 243 consecutive patients undergoing VATS lobectomy for NSCLC were enrolled. Intention-to-treat analysis with propensity score matching was conducted to compare the oncological outcomes between SP and MP VATS lobectomy for NSCLC.

Results: Seventy-three patients underwent SP VATS lobectomy, and 154 patients underwent conventional MP VATS lobectomy. Propensity score matching created 63 patients in each group. The median follow-up was 65.8 and 72.5 months in the SP and MP VATS groups, respectively. No significant differences were observed in the number of resected lymph nodes (14.6 vs. 16.1, $P=0.329$), number of resected mediastinal lymph node stations (2.3 vs. 2.5, $P=0.091$), and postoperative complications. The OS at 5 years was 89.9% and 86.9% in the SP and MP VATS groups, respectively (log-rank test, $P=0.344$). The DFS at 5 years was 75.1% and 75.7% in the SP and MP VATS groups, respectively (log-rank test, $P=0.899$).

Conclusion: There were no significant differences in oncological outcomes of SP VATS lobectomy for NSCLC and those of MP VATS lobectomy.

Keywords: Carcinoma, non-small-cell lung; Survival rate; Thoracic surgery, video-assisted

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INTRODUCTION

Lung cancer is the most common cancers in the world and its prevalence is increasing. In Korea, there are 25,780 annual incident cases of lung cancer [1]. For the intent of cure, anatomical resection remains the gold standard of lung cancer therapy. Video-assisted thoracoscopic surgery (VATS) in selected patients results in improved perioperative outcomes without compromising the cancer outcomes [2-9]. Recently, the existing VATS technique has been further developed, and single-port (SP) VATS lobectomy has been performed with a single incision [10]. SP VATS has resulted in shorter hospital stay [11], less intraoperative blood loss [12], and decreased pain [13,14], although not all studies have shown the same results [15]. However, there are few reports about oncological outcomes of SP VATS lobectomy. Previous studies reported acceptable survival outcomes but showed only 1- or 2-year survival outcomes [16-18]. The objective of this research was to compare the oncological outcomes, including long-term overall survival (OS), disease-free survival (DFS), and adequacy of lymph node retrieval, in two comparable propensity-matched groups of patients undergoing either SP or multi-port (MP) VATS lobectomy for non-small-cell lung cancer (NSCLC).

METHODS

Study design and patient selection

We retrospectively reviewed lung cancer data at the Sam-

sung Medical Center. The following tests were involved in a staging workup: a complete history and physical examination, complete blood counts, chemistry profiles, pulmonary function tests, simple chest X-ray, computed tomography of the chest and upper abdomen, whole-body ^{18}F -fluorodeoxyglucose positron emission tomography, and magnetic resonance imaging of the brain. A curative-intent anatomical resection was recommended to the patients with clinical stage I or II. In cases of stage IIIA patients, we generally recommended definitive concurrent chemoradiotherapy (CCRT) if cancer lesions were unresectable. When tumors were considered resectable, we conducted neoadjuvant CCRT, and performed surgical resection after 4 to 6 weeks from the completion of CCRT.

To be included in this study, patients needed to undergo curative-intent surgical lobectomy for NSCLC. The data of all patients (n=243) undergoing lobectomy performed by an author (YSC) between January 2012 and February 2014 at the Samsung Medical Center in Seoul, Korea, were reviewed. We excluded 16 patients for the following reasons: surgery started with thoracotomy (14 patients), loss to follow-up after surgery (one patient), and no pulmonary function test before surgery (one patient). After exclusion, 227 patients were enrolled in this study.

SP VATS was introduced in June 2012 and was initially only performed in wedge resection of lung cancer or lobectomy for benign lung diseases. After the surgeons have been accustomed to the new surgical approach, SP VATS lobectomy

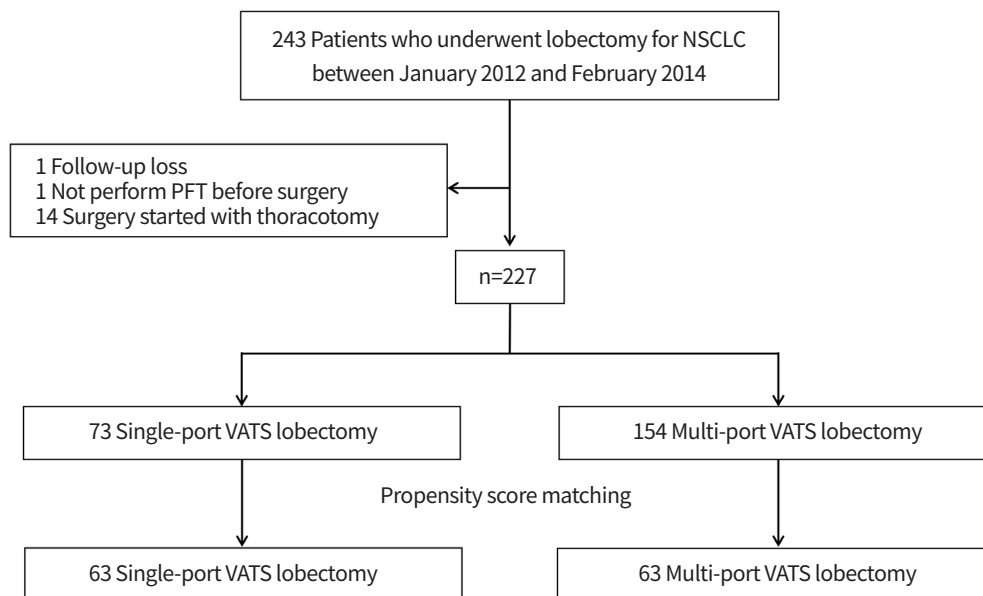


Fig. 1. Flowchart summarizing the patient selection and propensity score matching processes. NSCLC, non-small-cell lung cancer; PFT, pulmonary function test; VATS, video-assisted thoracoscopic surgery.

for NSCLC started in May 2013. From May 2013, we have chosen the SP VATS technique in all lung cancer patients except for central tumor or sizes greater than five centimeters.

To minimize selection bias and evaluate the real impact of SP VATS, we conducted an intention-to-treat analysis. The SP VATS group included patients who initially underwent SP VATS but were converted to MP VATS or open surgery owing to intraoperative circumstances. The SP VATS lobectomy group comprised 73 patients, and the MP VATS lobectomy group consisted of 154 patients. Propensity score matching yielded 63 patients in each group, and we compared the oncological outcomes of SP VATS with those of MP VATS (Fig. 1).

The study was approved by the Institutional Review Board (IRB) of the Samsung Medical Center; the requirement for informed consent was waived (IRB no. SMC 2017-07-055-003).

Surgical technique

All patients received general anesthesia with double-lumen intubation and were placed in the lateral decubitus position. The operator stood on the right side of the patient, and two assistants stood on the left side. The assistant rotated the camera 90° towards the operator, giving the assistants on the left side the same view as during an open thoracotomy. The operator watched another monitor rotated 180° to perform the surgery, also with the same view as during open thoracotomy. And the same surgical instruments were used for the SP and MP VATS.

The same surgical instruments were used for SP VATS and MP VATS. SP VATS was mostly started with a mid-axillary 5-mm incision at the 5th intercostal space (ICS). In case of upper lobe procedure, 4th ICS incision was used in some cases, and 6th ICS in case of lower lobe procedure. After the first checking of the pleural space through this incision with a 5-mm 30° thoracoscope, the 5-mm incision was enlarged to a 3.5 to 5 cm at the mid-axillary line (Supplementary Fig. 1A).

A same size incision at the same location was created in the conventional MP VATS, and used as a utility port. Two 5- and 12-mm incisions at the mid-axillary line at the 4th and 7th ICS were added for ports in the conventional MP VATS lobectomy procedure (Supplementary Fig. 1B).

Radical mediastinal lymph node resection was routinely conducted in the same manner in both groups. When the procedure was finished, a single chest tube was inserted into the anterior part of the incision for SP VATS and into the port at the 7th ICS for conventional MP VATS.

Data acquisition and follow-up

All patients visited the outpatient clinic 1 week after discharge, then every 3 months for the first 2 years and every 6 months thereafter. Survival data were renewed in March 2019 according to the medical records of the Samsung Medical Center or by directly contacting the patients. Recurrence of lung cancer was defined as loco-regional if cancer recurred in the ipsilateral thorax (mediastinum, hilum, and pleura) or at the surgical margin. Distant recurrence was determined when cancer developed in the contralateral thorax (lung, mediastinum, hilum, and pleura), ipsilateral lung, supraclavicular lymph node, or a distant organ. A recurrence simultaneously detected in both a local area and a distant area was defined as a local recurrence. We used the TNM (tumor, node, metastasis) stage of the American Joint Committee on Cancer staging system, 7th edition. After matched analysis, the median follow-up time of the SP and MP VATS patients was 65.8 and 72.5 months, respectively.

Statistical analysis

We used a 1:1 matching analysis between the SP and MP VATS lobectomy groups according to the propensity scores. From this, we can minimize selection bias which can be caused by the nonrandom distribution of patients to the treatment groups. Propensity scores were created by a logistic regression model including the variables: age, sex, Charlson comorbidity index, smoking history, American Society of Anesthesiologists Risk Scale, forced expiratory volume in 1 second (FEV₁), FEV₁/forced vital capacity ratio, histology, clinical tumor (T) and nodal (N) status, and previous chemotherapy or radiotherapy. Each patient undergoing SP VATS lobectomy was matched with a patient undergoing MP VATS lobectomy based on the closest calculated propensity score on the logit scale.

Continuous data were presented as mean \pm SD. Categorical variables were presented as frequency and percentages. Differences among the groups were examined using 2-way analysis of variance for both continuous and categorical variables. Survival data was created using the Kaplan-Meier method.

RESULTS

Patients characteristics

After propensity score matching with 12 variables, 63 patients from each group were paired, and clinical stage I accounted for 87.3% of the SP VATS group and 80.9% of the MP VATS group. Table 1 showed characteristics of all patients.

Table 1. Patients' characteristics

Characteristic	Unmatched data			Matched data		
	SP (n=73)	MP (n=154)	P-value	SP (n=63)	MP (n=63)	P-value
Age (yr)	61.4±9.2	60.9±9.9	0.339	60.5±9.3	61.3±11.7	0.656
Female sex	36 (49.3)	59 (38.3)	0.117	34 (54.0)	28 (44.4)	0.287
Smoking			0.552			0.420
Never smoked	40 (54.8)	72 (46.8)		38 (60.3)	31 (49.2)	
Former smoker	22 (30.1)	67 (43.5)		15 (23.8)	25 (39.7)	
Current smoker	11 (15.1)	15 (9.7)		10 (15.9)	7 (11.1)	
Charlson comorbidity index			0.010			0.713
0	37 (50.7)	103 (66.9)		34 (54.0)	36 (57.1)	
1	16 (21.9)	30 (19.5)		15 (23.8)	14 (22.2)	
2	15 (20.5)	15 (9.7)		10 (15.9)	10 (15.9)	
3	4 (5.5)	4 (2.6)		3 (4.8)	2 (3.2)	
4	1 (1.4)	2 (1.3)		1 (1.6)	1 (1.6)	
ASA class			0.972			0.762
1	17 (23.3)	40 (26.0)		15 (23.8)	15 (23.8)	
2	54 (74.0)	105 (68.2)		47 (74.6)	45 (71.4)	
3	2 (2.7)	9 (5.8)		1 (1.6)	3 (4.8)	
FEV ₁ , %	91.5±15.4	90.3±13.7	0.572	92.3±15.4	91.6±15.2	0.821
FEV ₁ /FVC	74.9±8.0	74.5±9.6	0.347	75.5±7.9	74.3±9.5	0.447
Histology			0.953			0.502
Adenocarcinoma	58 (79.5)	121 (78.6)		52 (82.5)	49 (77.8)	
Squamous	9 (12.3)	29 (18.8)		8 (12.7)	10 (15.9)	
Others	6 (8.2)	4 (2.6)		3 (4.8)	4 (6.3)	
Clinical T stage			0.001			0.710
T1	53 (72.6)	77 (50.0)		45 (71.4)	43 (68.3)	
T2	18 (24.7)	58 (37.7)		16 (25.4)	18 (28.6)	
T3	2 (2.7)	16 (10.4)		2 (3.2)	2 (3.2)	
T4	0	3 (1.9)		0	0	
Clinical N stage			0.093			0.629
N0	65 (89.0)	123 (79.9)		57 (90.5)	55 (87.3)	
N1	4 (5.5)	17 (11.0)		3 (4.8)	7 (11.1)	
N2	4 (5.5)	14 (9.1)		3 (4.8)	1 (1.6)	
Clinical stage			<0.001			0.369
IA	51 (70.8)	70 (45.8)		44 (69.8)	39 (61.9)	
IB	12 (16.7)	37 (24.2)		11 (17.5)	12 (19.0)	
IIA	3 (4.2)	11 (7.2)		2 (3.2)	7 (11.1)	
IIB	3 (4.2)	18 (11.8)		3 (4.8)	4 (6.3)	
III	3 (4.2)	17 (11.1)		3 (4.8)	1 (1.6)	
Previous chemotherapy	2 (2.7)	17 (11.0)	0.035	2 (3.2)	0	0.156
Previous radiotherapy	1 (1.4)	12 (7.8)	0.052	1 (1.6)	0	0.317
Conversion to MP VATS	13 (17.8)			10 (15.9)		
Conversion to thoracotomy	4 (5.5)	25 (16.2)	0.052	3 (4.8)	7 (11.1)	0.346

Values are presented as mean ± standard deviation or number (%).

SP, single-port; MP, multi-port; ASA, American Society of Anesthesiologists; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; VATS, video-assisted thoracoscopic surgery.

PRECISION AND FUTURE MEDICINE

Oncological outcomes of single-port VATS

To examine the representativeness of the selected patients, we compared the difference in variables before and after matching in each group. The details are provided in Supplementary Table 1.

A conversion from SP VATS to MP VATS and thoracotomy was performed in 13 and four patients, respectively. Further,

Table 2. Reasons for conversion

Surgical approach	Reason for conversion	Number
From single-port to multi-port	Anthracofibrosis	3
	Extranodal invasion	2
	Severe adhesion	4
	Anatomical difficulty	4
From single-port to thoracotomy	Severe adhesion	3
	Extranodal invasion	1
From multi-port to thoracotomy	Anthracofibrosis	4
	Severe adhesion	12
	Large tumor size	1
	Incomplete fissure	4
	Rib invasion	1
	Intraoperative bleeding	2
	Miscellaneous	1

a conversion from MP VATS to thoracotomy was conducted in 25 patients. The cause of conversion are listed in Table 2.

Pathological findings

After matched analysis, there are no differences between two groups in the total number of resected lymph nodes (14.6 vs. 16.1, $P=0.329$) and the number of resected mediastinal lymph node stations (2.3 vs. 2.5, $P=0.091$). There were also no differences in pathological stage and pattern of nodal upstaging. The details of pathological findings are shown in Table 3.

Perioperative outcomes

In the MP VATS group, one patient died of acute respiratory distress syndrome at 17 days after surgery. After matched analysis, no in-hospital death or 90-day mortality was observed in either group. There was no difference between the groups in the length of hospital stay (6.4 days vs. 6.6 days, $P=0.121$). The operative time was longer in the MP VATS group (142 minutes vs. 165 minutes, $P=0.020$). Table 4 showed the details of perioperative outcomes.

The SP VATS group had eight cases of complications, and the MP VATS group had 14 cases of complications. In the

Table 3. Pathological findings

Variable	Unmatched data			Matched data		
	SP (n=73)	MP (n=154)	P-value	SP (n=63)	MP (n=63)	P-value
Pathological stage			0.687			0.934
Ia	38 (52.1)	72 (46.7)		34 (54)	33 (52.4)	
Ib	11 (15.1)	33 (21.4)		10 (15.9)	15 (23.8)	
IIa	8 (11.0)	12 (7.8)		8 (12.7)	3 (4.8)	
IIb	2 (2.7)	12 (7.8)		1 (1.6)	4 (6.3)	
IIIa	13 (17.8)	22 (14.3)		10 (15.9)	7 (11.1)	
IV	1 (0.6)	1 (0.6)		0	0	
Complete remission	0	2 (1.3)		0	1 (0.8)	
Resected N1 LNs	7.0±4.6	8.1±5.1	0.116	6.9±4.6	7.8±5.3	0.336
Resected N2 LNs	7.5±4.1	8.6±6.6	0.136	7.7±4.1	8.3±6.5	0.533
Total resected LNs	14.5±6.9	16.6±9.1	0.053	14.6±6.9	16.1±9.4	0.329
Resected N2 stations	2.3±0.8	2.8±1.3	0.001	2.3±0.8	2.5±1.0	0.091
Nodal upstaging	18 (24.7)	19 (12.3)	0.021	15 (23.8)	9 (14.3)	0.206
cN0→pN1	7 (9.6)	7 (4.5)		7 (11.1)	2 (3.2)	
cN0→pN2	8 (11.0)	9 (5.8)		6 (9.5)	4 (6.3)	
cN1→pN2	3 (4.1)	3 (1.9)		2 (3.2)	3 (4.8)	

Values are presented as number (%) or mean±standard deviation.

SP, single-port; MP, multi-port; LN, lymph node.

analysis with respect to the Clavien-Dindo classification [19], the severity of surgical complications did not show any differences between the two groups. Supplementary Table 2 showed the details of postoperative complications.

Overall survival

The 5-year OS was 89.9% in the SP VATS group and 86.9% in the MP VATS group (log-rank test, $P=0.339$) (Fig. 2A). The surgical approach for SP VATS was not a significant predictor of

OS (hazard ratio [HR], 0.61; 95% confidence interval [CI], 0.22 to 1.69; $P=0.344$) in univariate analysis. The 5-year OS for clinical stage I NSCLC was 90.4% in the SP VATS group and 89.9% in the MP VATS group (log-rank test, $P=0.947$) (Fig. 2C).

Disease-free survival and recurrence pattern

After matched analysis, 16 patients (25.4%) in the SP VATS group and 13 patients (20.6%) in the MP VATS group had a recurrence. There was no difference between the groups in the

Table 4. Perioperative findings

Variable	Unmatched data			Matched data		
	SP (n=73)	MP (n=154)	P-value	SP (n=63)	MP (n=63)	P-value
Operative time (min)	146 (123–187)	165 (135–210.8)	0.028	142 (121–177)	165 (135–213)	0.020
Blood loss (mL)	200 (100–200)	150 (100–300)	0.354	200 (100–200)	200 (100–300)	0.108
Length of hospital stay (day)	6.5 (4.6–8.5)	7.00 (5.5–10.5)	0.019	6.4 (4.5–7.6)	6.6 (5.0–10.0)	0.121
In-hospital death	0	1		0	0	
90-Day mortality	0	1		0	0	

Values are presented as median (interquartile range).
SP, single-port; MP, multi-port.

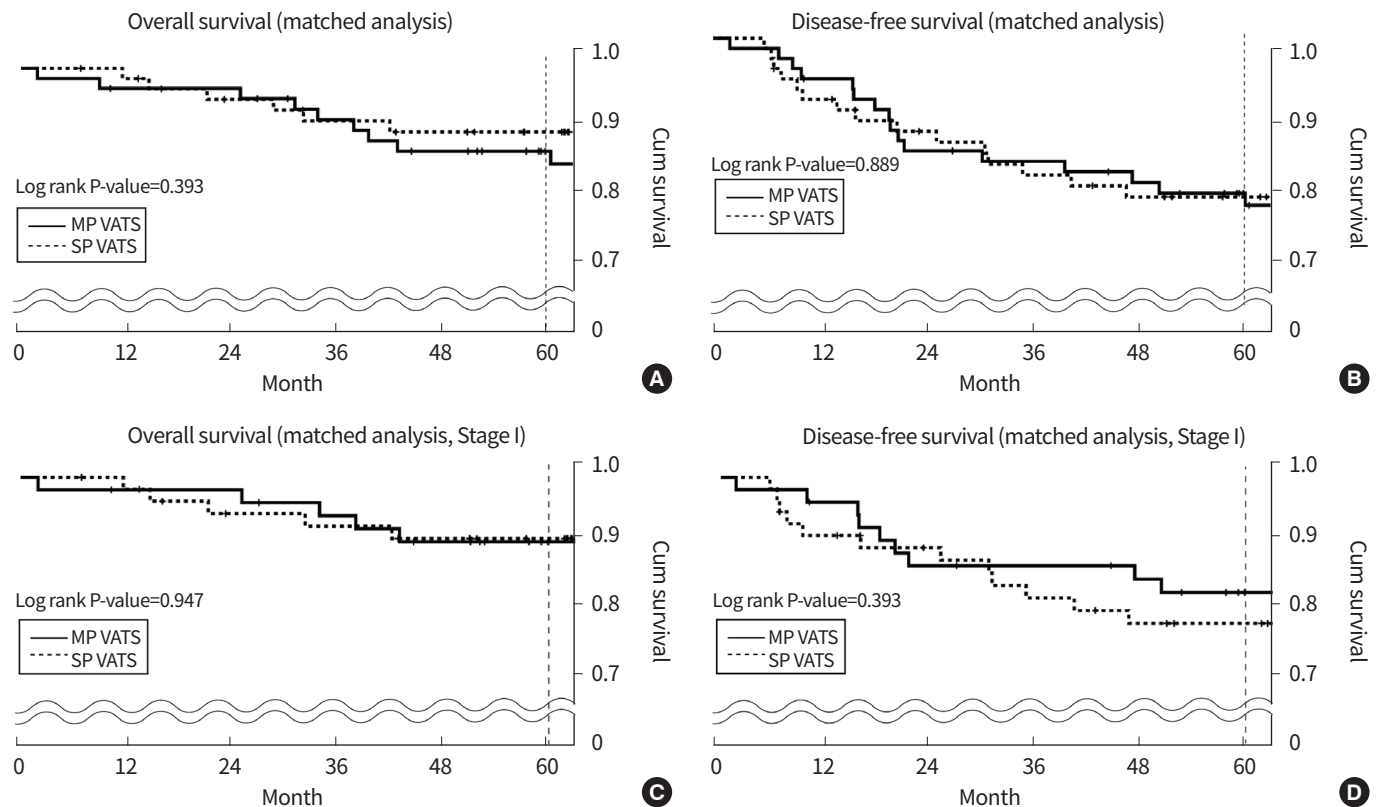


Fig. 2. Survival analysis of single-port (SP) video-assisted thoracic surgery (VATS) versus multi-port (MP) VATS: (A) overall survival of the matched group, (B) disease-free survival of the matched group, (C) overall survival of stage I patients of the matched group, and (D) disease-free survival of stage I patients of the matched group.

Table 5. Recurrence patterns

Variable	Unmatched data			Matched data		
	SP (n=73)	MP (n=154)	P-value	SP (n=63)	MP (n=63)	P-value
Recurrence	19 (26.0)	52 (33.8)	0.241	16 (25.4)	13 (20.6)	0.527
Pattern of recurrence			0.272			0.398
Loco-regional (\pm distant)	8 (11.0)	24 (15.6)		6 (9.5)	9 (14.3)	
Distant only	11 (15.1)	28 (18.2)		10 (15.9)	4 (6.3)	

Values are presented as number (%).

SP, single-port; MP, multi-port.

location of recurrence (Table 5). The 5-year DFS was 75.1% in the SP VATS group and 75.7% in the MP VATS group (log-rank test, $P=0.899$) (Fig. 2B). The surgical approach for SP VATS was not a significant predictor of DFS (HR, 1.05; 95% CI, 0.52 to 2.09; $P=0.899$) in univariate analysis. The 5-year DFS for clinical stage I NSCLC was 77.0% in the SP VATS group and 81.9% in the MP VATS group (log-rank test, $P=0.393$) (Fig. 2D).

DISCUSSION

In recent years, SP VATS has been considered to be an achievable, minimally invasive procedure that is comparable to conventional MP VATS in terms of perioperative outcomes [11-15]. And these studies reported significantly lower pain scores of patients undergoing SP VATS compared to those of MP VATS [13,14]. In the current study, the SP VATS group was found to have similar OS, DFS, recurrence pattern, lymph node retrieval, nodal upstaging, and complications to the MP VATS group.

The primary finding of no difference in OS and DFS between SP VATS and MP VATS for NSCLC is important because the current study is the first to report the 5-year oncological outcomes in patients undergoing SP VATS lobectomy for the treatment of NSCLC. The 5-year OS and DFS in the clinical stage I SP VATS group compared favorably with those in reports of long-term outcomes [5-7,9]. The investigation of the prevalence and distribution of recurrence also did not bring in any difference between the two different operative technique. On the basis of these data, our study demonstrated that the long-term oncological outcomes of the SP VATS technique are at least equivalent to those of conventional MP VATS.

There is a concern that because of technical difficulty, the SP VATS technique compromises the oncological principle of complete surgical lymph node dissection [20]. With this com-

pleteness of lymph node dissection, clinically occult metastases can be found and patients can be treated appropriately. Previous studies demonstrated that fewer resected lymph nodes led to worse survival and that the survival rates were better in patients in whom >11 lymph nodes were resected [21-24]. To evaluate the adequacy of lymph node dissection during SP VATS, we compared the number of resected lymph nodes, number of resected N2 lymph node stations, and nodal upstaging between the two groups. Liu et al. [11] and Wang et al. [12] reported a larger number of resected lymph nodes with SP VATS than with MP VATS. However, in the current study, the number of resected lymph nodes did not differ between the groups, supporting the claim that SP VATS is not inferior to conventional MP VATS in achieving complete lymph node dissection. The number of resected mediastinal lymph node stations was significantly different between the two groups before matched analysis; however, this difference disappeared after the matched analysis. The difference in the pre-matching analysis may be due to the more aggressive lymph node dissections in patients with advanced-stage NSCLC. Reports that question the oncological efficacy of VATS for NSCLC also noted that the rate of nodal upstaging after VATS was lower than after open lobectomy [25-27]. In the same way, we evaluated the nodal upstaging and could not find significant differences between the two groups in all types of nodal upstaging, including upstaging from clinical N0 to pathological N1 or N2. This also suggests that lymph node dissection during SP VATS is not inferior to that during MP VATS.

In our study, conversion to MP VATS was conducted in about 15% of the SP VATS group. When difficult circumstances were encountered during surgery, we added additional ports. Adding a port with a new angle helped with fine dissection in an area that was not easily accessible with SP VATS. When the operation was difficult even after adding

new ports, we converted to thoracotomy. We cannot find significant difference in the conversion rate between the two groups.

With respect to postoperative complications, our results are in line with those of previous studies. Two studies from Taiwan [11,12] reported similar complication rates between the SP and MP VATS groups, and other studies from Japan [14] and China [13,15] also showed the same results. These findings suggested that the SP VATS technique would not increase the complication rate if the surgeons are already accustomed to this technique.

There are several limitations in this study. First, this study was based on retrospective data from medical records. Unobserved confounding factors and selection bias may exist despite the use of propensity score matching. Second, the number of patients in each group was insufficient to discuss the oncological outcomes of a particular surgical approach. Third, selection bias could not be avoided despite performing propensity score matching. Patients with a central tumor or a tumor >5 cm in size underwent MP VATS lobectomy, and the selected patients in the MP VATS group consisted of those who had lower clinical T stage and did not receive previous chemotherapy or radiotherapy compared with the entire MP VATS group. Fourth, all surgeries were conducted by a single surgeon at a single institution, making our patient population homogeneous.

In conclusion, after propensity score matching, there are no significant differences in OS and DFS between SP VATS and MP VATS lobectomy for the treatment of NSCLC. Moreover, we found no difference in the completeness of lymph node dissection, as evidenced by the number of resected nodes, number of resected N2 lymph node stations, and rate of nodal upstaging in the two groups. From these results, we can conclude that SP VATS lobectomy for NSCLC is safe and can achieve oncological outcomes similar to those of conventional MP VATS lobectomy. Therefore, for experienced surgeon, we recommend to conduct SP VATS which has advantage of reduced postoperative pain [13,14]. Further studies comparing the benefits and specific indications of SP VATS lobectomy are warranted.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Conception or design: DWY, YSC, KS, HK.
 Acquisition, analysis, or interpretation of data: DWY, YSC, KS, HK.
 Drafting the work or revising: DWY, YSC.
 Final approval of the manuscript: DWY, YSC, KS, HK.

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