Original Article

Perioperative and long-term outcomes of spontaneous ventilation video-assisted thoracoscopic surgery for non-small cell lung cancer

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Background: Spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS) exhibits dual intraoperative and postoperative advantages for patients with non-small cell lung cancer (NSCLC). However, there is a lack of data regarding its long-term survival superiority over the double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery (MV-VATS) or thoracotomy.

Methods: A retrospective study was conducted from 2011 to 2018 in the First Affiliated Hospital of Guangzhou Medical University among patients with NSCLC who underwent the SV-VATS or the MV-VATS. Patients receiving the SV-VATS were the study group, and patients receiving the MV-VATS were the control group. Propensity score matching (PSM) was performed to establish 1:1 SV-VATS versus MV-VATS group matching to balance potential baseline confounding factors. Primary endpoints were overall survival (OS) and disease-free survival (DFS). Secondary endpoints were perioperative outcomes. The baseline information of these patients was recorded. The perioperative data and survival data were collected using a combination of electronic data record system and telephone interview. A 1:1:1 SPM was also used to compare the OS in the SV-VATS, the MV-VATS and thoracotomy group by using another database, including patients undergoing thoracotomy and the MV-VATS.

Results: For the two-group comparison, after 1:1 PSM, a matched cohort with 400 (200:200) patients was generated. The median follow-up time in this cohort was 4.78 years (IQR, 3.78–6.62 years). The OS (HR =0.567, 95% CI, 0.330 to 0.974, P=0.0498) and the DFS (HR =0.546, 95% CI, 0.346 to 0.863, P=0.013) of the SV-VATS group were significantly better than the MV-VATS group. There were no statistically differences between the SV-VATS and the MV-VATS group on the operative time (158.56±40.09 *vs.* 172.06±61.75, P=0.200) anesthesia time (247.4±62.49 *vs.* 256.7±58.52, P=0.528), and intraoperative bleeding volume (78.88±80.25 *vs.* 109.932±180.86, P=0.092). For the three-group comparison, after 1:1:1 PSM, 582 (194:194:194) patients were included for the comparison of SV-VATS, MV-VATS and thoracotomy. The OS of the SV-VATS group was significantly better than the thoracotomy group (HR =0.379, 95% CI, 0.233 to 0.617, P<0.001).

Conclusions: Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

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Keywords: Spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS); long-term survival; non-small cell lung cancer (NSCLC); mechanical ventilation video-assisted thoracoscopic surgery (MV-VATS); lobectomy

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Introduction

Since 1960, lobectomy and systematic mediastinal lymph node dissection was the gold standard for early stage lung cancer (1). Before the widely use of video-assisted thoracoscopic surgery (VATS) in 1990s, thoracotomy was the only option in thoracic surgery (2,3). The past decades have witnessed the gradual replacement of thoracotomy by double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery (MV-VATS) for its better short-term postoperative outcomes, including less incidence of complications (4,5). The long-term survival outcomes of patients underwent lobectomy by MV-VATS were no inferior to thoracotomy (6). With the growing concerns on the perioperative adverse effects caused by anesthesia, such as intubation-related airway trauma, pulmonary barotrauma, muscle relaxants related postoperative myasthenia, and postoperative nausea and vomiting, non-intubated spontaneous ventilation video-assisted thoracoscopic surgery (SV-VATS) emerged (7-9).

In 2004, Pompeo *et al.* (10) described a series of thoracic operations under the SV-VATS, including pulmonary wedge resection and lung volume reduction. In 2011, the first lobectomy by the SV-VATS was reported by Chen *et al.* (11), demonstrating its feasibility and safety. At present, there are many studies on the perioperative outcomes of the SV-VATS compared to the MV-VATS, revealing that the SV-VATS exhibits a shorter postoperative hospital stay and a faster postoperative recovery (12,13). Our team also demonstrated the application of the SV-VATS for lobectomy and even carinal reconstruction in our previous studies (14-17).

Though the intraoperative and postoperative advantages of SV-VATS over MV-VATS have been indicated, there is a lack of study reported its long-term benefit for patients with non-small cell lung cancer (NSCLC). Because of the relatively unstable operation field and moving of mediastinal structures, some researchers may question whether the systematic lymph node dissection under the SV-VATS is eligible and long-term outcomes compared to MV-VATS (11). It was hypothesized that the long-term outcomes of the SV-VATS was not inferior to or even better than the MV-VATS according to the better perioperative outcomes, with less opioid use and less inflammatory response (18,19).

Therefore, we attempted to explore the superiority of the SV-VATS over the MV-VATS in the long-term survival among patients with NSCLC. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/tlcr-21-629).

Methods

Study design and patients inclusion

This is a retrospectively prognosis study. All patients with NSCLC who went through pulmonary surgery between 2011 and 2018 in the First Affiliated Hospital of Guangzhou Medical University were consecutively recruited in the retrospective database (database 1), which included 6,821 patients (6,133 MV-VATS and 688 SV-VATS). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol and methods were reviewed by the institutional ethics committee of the First Affiliated Hospital of Guangzhou Medical University (2020-69). Informed consent was obtained from each patient before inclusion.

Patients were included for recruitment into the database, if they met the following criteria: (I) agreed to participate; (II) underwent thoracoscopic lobectomy as well as lymphadenectomy; (III) postoperative pathology was invasive NSCLC. The following patients were excluded: (I) surgery not for lung cancer or cases with incomplete information; (II) underwent pulmonary surgery more than once; (III) underwent intraoperative radiotherapy (IORT) or thoracic hyperthermia chemotherapy; (IV) with a history of other cancer; (V) underwent thoracotomy or VATS assisted thoracotomy; (VI) underwent pneumonectomy or bilateral operation; (VII) underwent partial resection,

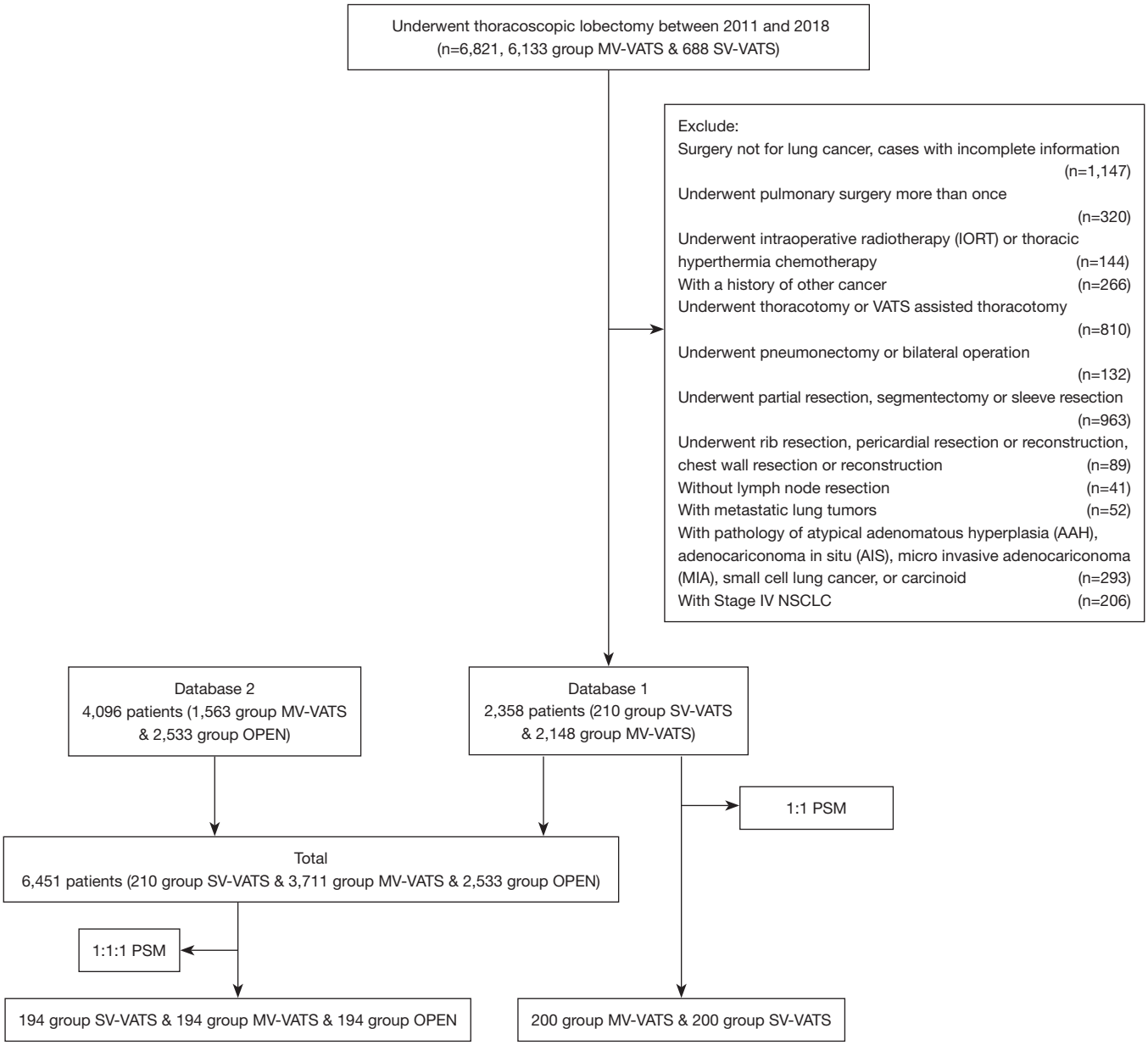

Figure 1 Flow chart of study population. MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; OPEN, thoracotomy; VATS, video-assisted thoracoscopic surgery; NSCLC, non-small cell lung cancer; PSM, propensity score matching.

segmentectomy or sleeve resection; (VIII) underwent rib resection, pericardial resection or reconstruction, chest wall resection or reconstruction; (IX) without lymph node resection; (X) with metastatic lung tumors; (XI) with the pathology of AAH (atypical adenomatous hyperplasia), AIS (adenocarcinoma *in situ*), etc.; (XII) with Stage IV NSCLC (*Figure 1*).

An informed consent for the SV-VATS or the MV-VATS group was obtained from all the patients including explanation of the reason, modalities, risks and benefits. The decision of the surgical type was made by thoracic surgeons, anesthetists and patients together before operation. Patients receiving the SV-VATS were the study group, and patients receiving the MV-VATS were the control group.

The criteria of recruiting patients under the SV-VATS were as follows: ASA score (American Society of Anesthesiologists status) less than 3, without cardiovascular and pulmonary dysfunction, body mass index (BMI) less than 28, and the diameter of tumor less than 10 cm.

Anesthesia and surgical management

All procedures and consumption of anesthesia were described in the previous study (18,20,21). Briefly, tracheal intubation ventilation was not administered throughout the operation under the SV-VATS. The double-lumen tracheal intubation was substituted as a double lumen laryngeal disposable mask airway. Also, a nasal cannula or facial mask could sometimes be a substitute for LMA (laryngeal mask airway), depending on different situations of patients. Muscle relaxant was not administered, while intravenous sedative (propofol) was sufficiently administered. Intravenous analgesics, which was mostly opioid, including remifentanil and sufentanil, was significantly reduced. Moreover, regional block anesthesia, including local anesthesia at the incision, thoracic vagus nerve block, pleural surface block, and intercostal nerve block, were applied (20). Anesthesia was conventionally administered in the MV-VATS.

Perioperatively, end-tidal carbon dioxide partial pressure, pulse oxygen saturation (SpO2), heart rate (HR), electrocardiogram (ECG), and noninvasive blood pressure were routinely measured and continuously monitored both in the SV-VATS group and the MV-VATS. To ensure that patients were at a sufficient depth of anesthesia and to avoid intraoperative awareness and excessive sedation, the Bispectral Index (BIS) was monitored and maintained at 40–60 under the SV-VATS.

The standard NSCLC radical surgery procedure, including lobectomy and lymph node dissection, was the same in both anesthesia methods. Uniportal or biportal VATS was adopted. Stryker 1288 HD 3-Chip Camera was administered in the MV-VATS and the SV-VATS. The surgical procedure and methods of lobectomy and dissection of N1 as well as N2 were the same as in the previous study in our center (22), and studies reported by Swanson *et al.* (4) and Shigemura *et al.* (23).

Postoperative care and follow-up

After surgery, patient at stage IIB to IV would receive adjuvant therapy, including chemotherapy and radiotherapy. Patients with EGFR mutation would receive TKI. If enlarged lymph nodes were found during the follow-up period, patients would receive adjuvant radiotherapy.

Follow-up assessment for patients occurred at a 3- or 6-month interval during the first 2 year after the surgery, and then once a year afterwards, which included chest computed tomography (CT) scans, brain magnetic resonance imaging (MRI) scans. Telephone follow-up was conducted every year until death or July 2021. For patients who lost to follow-up, they were evaluated by the latest medical record or telephone interview.

Data collection and outcomes assessment

The baseline information of these patients was recorded. The perioperative and survival data were collected using a combination of electronic data record system and telephone interview.

The primary outcomes included the 3- and 5-year OS rate and DFS rate of the SV-VATS and the MV-VATS group. The secondary outcomes were perioperative results, including N1 and N2 lymph node resection, days of chest tube use, operative time, anesthesia time, and intraoperative bleeding volume. The definition of N1 and N2 was according to Mountain-Dresler modification of the American Thoracic Society (MDATS) map (24,25). TNM stage classification complied with the 7th edition of TNM classification of the International Association for the Study of Lung Cancer (26).

Statistical analysis

PSM (propensity score matching) was used to control the effects of confounding factors based on the collected baseline information. A propensity score was calculated by multiple logistic regression with the following variables: age, BMI, gender, TNM stage, smoking status, and personal history, including chronic obstructive pulmonary disease (COPD), coronary disease, hypertension, cerebrovascular accident (CVA), arrhythmia, diabetes, asthma, and angina. Patients were matched at a ratio of 1:1 using a nearest-neighbor approach on the logit scale with caliper restrictions of 0.05. PSM was performed using R version 4.0.4 (R Foundation for Statistical Computing, Vienna, Austria; https://www.rproject.org/). After PSM, baseline information of two groups were tested by Chi-2 test or Fisher's exact tests to examine the difference.

Continuous data were shown as mean ± standard deviation

(SD), and categoric data were displayed as a count and percentage of patients. Chi-square test or Fisher's exact test was applied to compare the difference of continuous data, while the Student's *t*-test was used in categorize variables. Survival analysis was performed with the Kaplan-Meier method and the log-rank test. Univariate and multivariate Cox regression analysis was conducted to assess the potential factors affecting survival. All statistical analyses were completed by IBM SPSS Statistics for Windows (Armonk, NY: IBM Corp.) and GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California USA, www.graphpad.com). P value <0.05 is considered statistically significant in all analyses. All statistical tests would be performed two-sided with a level of significance of 5%.

Comparison among three group (SV-VATS, MV-VATS, thoracotomy)

In order to further explore the long-term benefit of the SV-VATS, we compared the OS of patients with NSCLC who underwent SV-VATS, MV-VATS and thoracotomy. A database (database 2) including patients undergoing thoracotomy and MV-VATS from multi-institutions in China between 2001 and 2008 was used in this study (6). Ethics approval was obtained from eight institutions. Patients with invasive lung adenocarcinoma confirmed by postoperative pathology were also recruited. PSM was used to match patients who experienced thoracotomy with those who experienced SV-VATS and MV-VATS, and the survival information was compared by Kaplan-Meier and log-rank test.

Results

Patients characteristics

For the two-group comparison, according to the inclusion and exclusion criteria, there were 2,358 patients enrolled in the study, with 210 patients undergoing the SV-VATS and 2,148 undergoing the MV-VATS (*Figure 1*). Four hundred (200:200) patients remained after the PSM. Features and baseline information of all patients before and after 1:1 PSM are displayed in *Table 1*.

Perioperative outcomes

No surgery-related death occurred. None of the patients in the SV-VATS group required conversion to the MV-VATS methods.

There were no statistically differences between two groups (SV-VATS versus MV-VATS) in the operative time (158.56±40.09 *vs.* 172.06±61.75, P=0.200) anesthesia time (247.4±62.49 *vs.* 256.7±58.52, P=0.528), and intraoperative bleeding volume (78.88±80.25 *vs.* 109.932±180.86, P=0.092).

The group numbers of N2 station lymph nodes (2.63±1.11 *vs.* 3.03±1.18, P=0.001) in the SV-VATS group are less than the MV-VATS group. Lymph node number (4.64±3.9 *vs.* 4.78±3.49, P=0.716), as well as the group number (1.46±1.12 *vs.* 1.47±0.99, P=0.925) of N1 station and number of N2 station (10.91±8.35 *vs.* 12.04±7.83, P=0.162), were the same between the SV-VATS and the MV-VATS group. Other preoperative, intraoperative, and postoperative outcomes were similar in two groups (*Table 2*).

Long-term survival outcomes

The median follow-up time in the whole cohort was 4.78 years (IQR, 3.78–6.62 years). The loss rate during follow-up was 10.25% in total. The median survival time of the SV-VATS or the MV-VATS group cannot be calculated.

In the SV-VATS group, 3-year and 5-year OS rates were 95.0% (91.9–98.1%) and 90.8% (86.1–95.5%), and 3-year, 5-year DFS rates were 90.5% (86.2–94.8%) and 85.5% (79.4–91.6%), respectively. In the MV-VATS group, 3-year, and 5-year OS rate were 87.3% (82.6–92.0%) and 82.7% (77.2–88.2%), and 3-year, 5-year DFS rate were 80.8% (75.3–86.3%) and 76.3% (70.2–82.4%) for NSCLC patients. The SV-VATS group was associated better OS (HR=0.567, 95% CI, 0.330 to 0.974, P=0.0498) and DFS (HR=0.546, 95% CI, 0.346 to 0.863, P=0.013) than the MV-VATS group (*Figure 2*).

Subgroup analyses according to TNM stage indicated that patients with stage III undergoing SV-VATS experienced higher OS and DFS than those undergoing MV-VATS. These results were not observed in patients with stage I and II (*Figure 3*).

Variables, including the mode of anesthesia methods (P=0.015), T stage (P<0.001), N stage (P<0.001), and TNM stage (P<0.001) were significant prognostic factors for DFS by univariate Cox analysis, and T stage (P<0.001), N stage (P<0.001), and TNM stage (P<0.001) were significant prognostic factors for OS. Additional multivariate analysis indicated that mode of anesthesia methods (P=0.001), and T stage (P=0.015) were independent factors for DFS,

Table 1 Baseline demographic and clinical characteristics of patients before and after 1:1 PSM

	Patients number before PSM			Patients number after PSM		
	SV-VATS, 210 (%)	MV-VATS, 2,148 (%)	P value	SV-VATS, 200 (%)	MV-VATS, 200 (%)	P value
Age, year			<0.001			0.759
≤45	31 (14.8)	185 (8.6)		31 (15.5)	29 (14.5)	
45–65	149 (71.0)	1,323 (61.6)		144 (72.0)	141 (70.5)	
>65	30 (14.3)	640 (29.8)		25 (12.5)	30 (15.0)	
BMI, kg/m^2			0.001			0.086
≤18.5	11 (5.2)	139 (6.5)		11 (5.5)	22 (11.0)	
18.5–20	29 (13.8)	192 (8.9)		29 (14.5)	22 (11.0)	
20–25	137 (65.2)	1,221 (56.8)		136 (68.0)	120 (60.0)	
25–28	19 (9.0)	382 (17.8)		19 (9.5)	27 (13.5)	
>28	14 (6.7)	214 (10.0)		5 (2.5)	9 (4.5)	
Gender			0.027			0.841
Male	107 (51.0)	1,264 (58.8)		107 (53.5)	105 (52.5)	
Female	103 (49.0)	884 (41.2)		93 (46.5)	95 (47.5)	
Current or former smoking			0.49			0.848
Unknown	30 (14.3)	361 (16.8)		30 (15.0)	27 (13.5)	
Yes	24 (11.4)	275 (12.8)		24 (12.0)	22 (11.0)	
No	156 (74.3)	1,512 (70.4)		146 (73.0)	151 (75.5)	
Comorbidity			0.004			0.874
No	186 (88.6)	1,728 (80.4)		177 (88.5)	178 (89.0)	
Yes	24 (11.4)	429 (19.6)		23 (11.5)	22 (11.0)	
Pathology			0.005			0.088
Adenocarcinoma	186 (88.6)	1,703 (79.3)		176 (88.0)	188 (94.0)	
Squamous carcinoma	15 (7.1)	311 (14.5)		15 (7.5)	6 (3.0)	
Others	9 (4.3)	134 (6.2)		9 (4.5)	6 (3.0)	
T Stage			<0.001			0.755
T1	132 (62.9)	1,061 (49.4)		124 (62.0)	128 (64.0)	
T2	70 (33.3)	855 (39.8)		68 (34.0)	62 (31.0)	
T3+T4	8 (3.8)	232 (10.8)		8 (4.0)	10 (5.0)	
N Stage			0.006			0.177
N0	163 (77.6)	1,474 (68.6)		154 (77.0)	167 (83.5)	
N1	17 (8.1)	157 (7.3)		17 (8.5)	9 (4.5)	
N2	30 (14.3)	517 (24.1)		29 (14.5)	24 (12.0)	
TNM Stage			0.001			0.422
I	159 (75.7)	1,351 (62.9)		150 (75.0)	160 (80)	
II	19 (9.0)	221 (10.3)		19 (9.5)	13 (6.5)	
III	32 (15.2)	576 (26.8)		31 (15.5)	27 (13.5)	

PSM, propensity score matching; SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery.

Table 2 Perioperative outcomes

	MV-VATS		SV-VATS		P value
	Mean	SD	Mean	SD	
N1 lymph node dissection					
Number	4.78	3.49	4.64	3.9	0.716
Group number	1.47	0.99	1.46	1.12	0.925
Positive number	0.3	0.99	0.27	0.88	0.762
Positive group number	0.18	0.58	0.17	0.48	0.723
N2 lymph node dissection					
Number	12.04	7.83	10.91	8.35	0.162
Group number	3.03	1.18	2.63	1.11	0.001
Positive number	0.52	2.10	0.47	1.74	0.815
Positive group number	0.27	0.76	0.23	0.63	0.544
Days of chest tube use, day	4.29	3.02	4.03	2.19	0.517
Operative time, min	172.06	61.75	158.56	40.09	0.200
Anesthesia time, min	256.70	58.52	247.40	62.49	0.528
Intraoperative bleeding volume, mL	109.93	180.86	78.88	80.25	0.092

SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery.

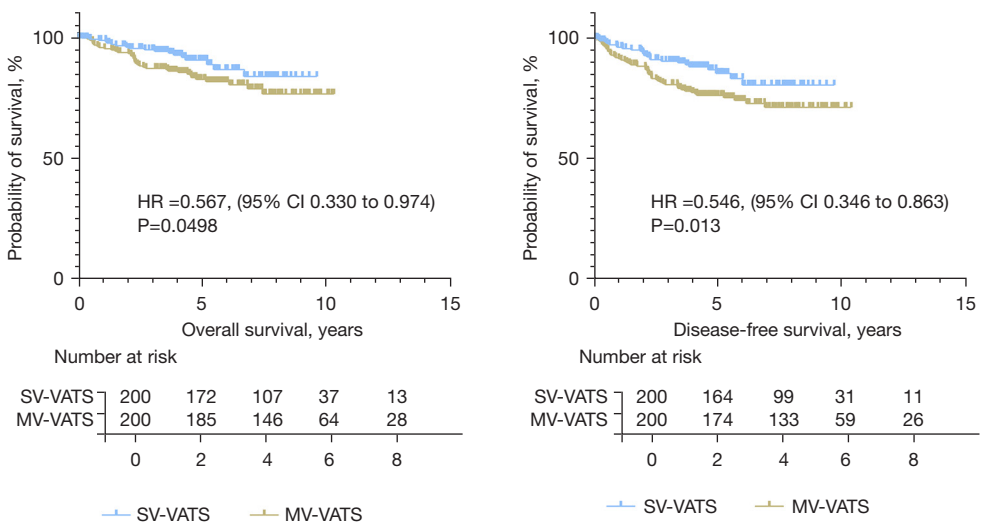

Figure 2 The long-term survival outcomes between SV-VATS and MV-VATS. MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; HR, hazard ratio; CI, confidence interval.

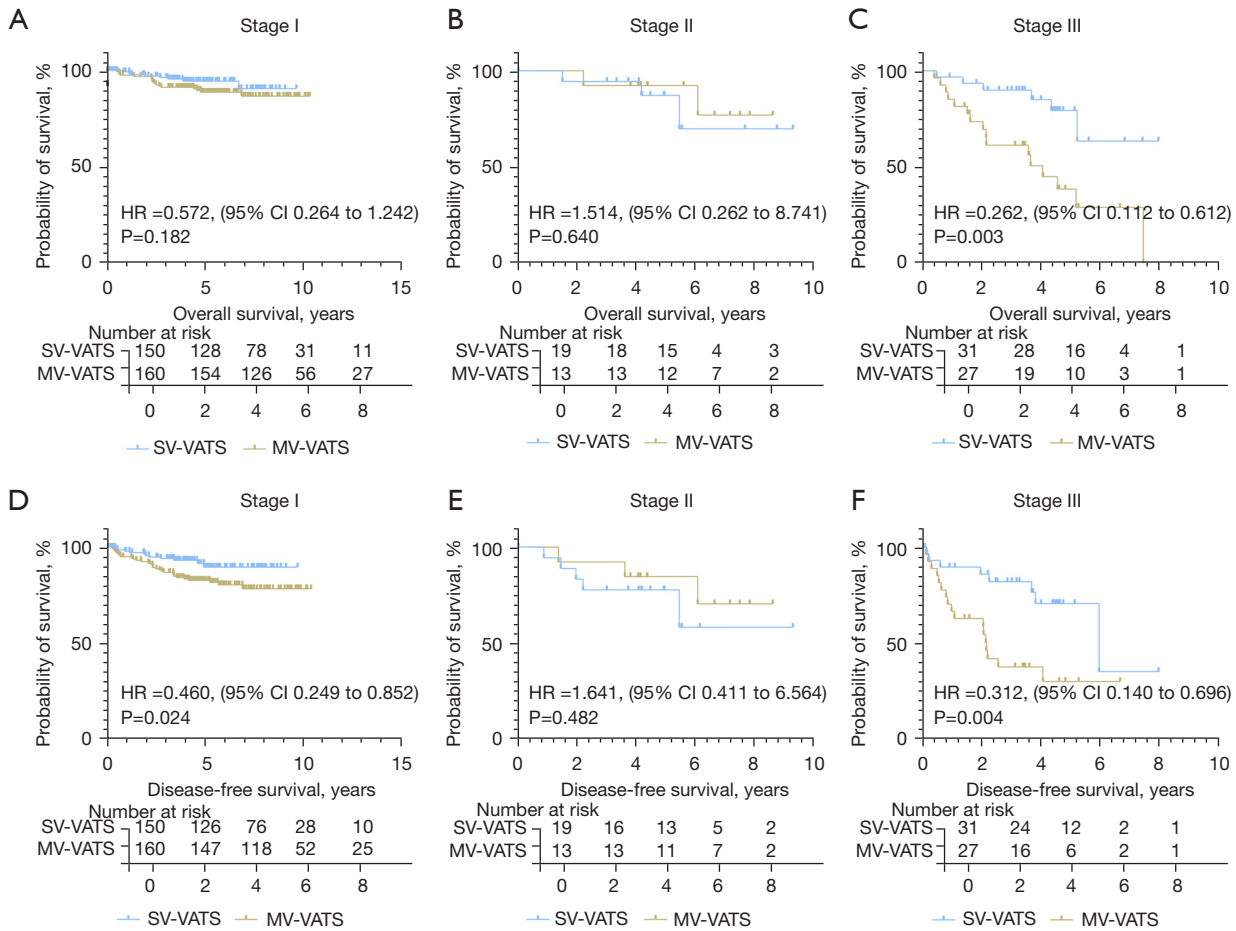

Figure 3 Subgroup analyses according to TNM stage between SV-VATS and MV-VATS. MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery.

and mode of anesthesia methods (P=0.004), and T stage (P=0.037), were independent factors for OS (*Table 3*).

Comparison among three groups (SV-VATS, MV-VATS, thoracotomy)

For three-group comparison, according to the inclusion and exclusion criteria, there were 6,451 patients enrolled in our study, including 2,533 patients undergoing thoracotomy in database 2, 3,711 patients undergoing the MV-VATS in both databases, and 210 patients who underwent the SV-VATS in database 1 (*Figure 1*). After a 1:1:1 PSM, 582 (194:194:194) patients remained. Features and baseline information of all patients before and after 1:1:1 PSM were displayed in *Table 4*. The median survival of the SV-VATS and the MV-VATS was not reached. In SV-VATS, the 3-year OS rate was 93.8% (95% CI, 90.3–97.3%) and 5-year OS rate was 89.4% (95% CI, 84.3–94.5%). In MV-VATS, the 3-year OS rate and 5-year OS rate was 87.8% (95% CI, 81.1–94.5%) and 81.9% (95% CI, 75.2–88.6%), respectively. As for thoracotomy, OS rates at 3-year was 83.5% (95% CI, 78.1–89.0%) and 72.5% (95% CI, 56.2–88.8%) at 5 years. The OS of the SV-VATS group was better than the OPEN group (HR=0.379, 95% CI, 0.233 to 0.617, P<0.001), shown in *Figure 4* and *Table 5*.

Discussion

This is a study that retrospectively proves the survival superiority of patients underwent the SV-VATS lobectomy and lymph node dissection over the MV-VATS. Our results reveal that the OS and DFS of patients undergoing the SV-VATS lobectomy were significantly better than patients who undergoing the MV-VATS lobectomy and thoracotomy.

Table 3 Univariate and multivariate cox regression analysis of prognostic factors in lung cancer

	Univariate analysis				Multivariate analysis			
	DFS		OS		DFS		OS	
	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)
Anesthesia methods	0.015	1.838 (1.128 to 2.996)	0.053	1.772 (0.993 to 3.161)	0.001	2.375 (1.421 to 3.971)	0.004	2.479 (1.335 to 4.606)
Age	0.747	1.004 (0.981 to 1.027)	0.445	1.011 (0.983 to 1.039)	0.625	1.006 (0.983 to 1.029)	0.334	1.015 (0.985to 1.045)
BMI	0.253	0.960 (0.896 to 1.029)	0.091	0.919 (0.832 to 1.014)	0.245	0.958 (0.892 to 1.030)	0.079	0.912 (0.824 to 1.011)
Gender	0.110	0.683 (0.428 to 1.091)	0.157	0.672 (0.387 to 1.166)	0.262	0.759 (0.469 to 1.228)	0.195	0.685 (0.386 to 1.214)
Smoking history	0.907	1.019 (0.739 to 1.405)	0.726	0.937 (0.651 to 1.349)	0.613	1.090 (0.781 to 1.522)	0.620	1.105 (0.745 to 1.638)
Pathology	0.722	1.096 (0.662 to 1.813)	0.754	1.100 (0.605 to 1.999)	0.652	1.131 (0.663 to 1.929)	0.531	1.224 (0.650 to 2.304)
T stage	<0.001	2.153 (1.517 to 3.057)	<0.001	2.464 (1.666 to 3.643)	0.015	1.741 (1.116 to 2.715)	0.037	1.668 (1.031 to 2.697)
N stage	<0.001	1.773 (1.359 to 2.313)	<0.001	2.095 (1.557 to 2.818)	0.826	1.101 (0.468 to 2.587)	0.832	1.092 (0.482 to 2.477)
TNM stage	<0.001	1.939 (1.499 to 2.508)	<0.001	2.319 (1.733 to 3.103)	0.207	1.752 (0.734 to 4.184)	0.087	2.125 (0.897 to 5.033)

OS, overall survival; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval.

Previously, the characters of the non-intubated SV-VATS, included absence of endotracheal intubation and muscle relaxants during anesthesia induction, intravenous sedative, and less intravenous analgesics and opioids (20,21). The SV-VATS was associated with a faster postoperative recovery, decreased complications, and reduced length of hospital stay. The advantages of SV-VATS for thoracic surgery have been confirmed in our previous studies (27). Chen *et al.* published the first study in terms of the long-term survival result of nonintubated thoracoscopic lobectomy earlier this year. It was demonstrated that no differences were observed in recurrence rates and overall survival between nonintubated thoracoscopic lobectomy and intubated procedure (28).

One of the most essential characteristics of the SV-VATS compared to the MV-VATS was the sharp reduction of opioid analgesics, which might accelerate recurrence of cancer. *In vitro* studies, it have been proved that opioids possess the pro-tumor activity and leads to tumor progression through immunosuppression, angiogenesis, and migration of tumor cells (29). Mu opioid receptors (MOR), one of the opioid receptors, is expressed highly in various cancers, which is associated with the direct relations with cancer or opioid immunosuppression (30-32). In a clinical study, high dose of opioid analgesics was associated with the recurrence of esophageal squamous cell carcinoma and oral cancer (33,34). Nelson *et al.* (35) found that the consistent use of opioids for 3 to 6 months after surgery was related to worse survival outcomes of NSCLC. The regional anesthesia in SV-VATS might contribute to the reduction in the prescription of postoperative opioids, which could explain the survival advantage of the SV-VATS (20).

Another characteristic of the SV-VATS compared to the MV-VATS was full utilization of regional anesthesia (20,21). A meta-analysis indicated that epidural anesthesia and analgesia might be related to the increased OS for operable oncological patients (36). Another retrospective study discovered that regional anesthesia was associated with a higher five-year survival after the bladder cancer operation (37). The regional anesthesia may influence the survival outcome of oncological patients by suppressing immune defense mechanisms in the perioperative period (38). However, there are no consensus on the association between regional anesthesia and survival outcome in oncological patients. The analysis of a randomized controlled trial (RCT) demonstrated that regional anesthesia did not associate with lower recurrence of breast cancer after surgery (39). Another RCT by Myles *et al.* (40), showed the negative result of the relationship between epidural analgesia and the intravenous analgesia in surgery for patients with abdominal cancers. The full utilization of regional anesthesia might contribute to the survival advantage in the SV-VATS group.

Propofol-TIVA (total intravenous anesthesia) was suggested to a higher OS in patients having cancer removal surgery (41). There were several in-vitro studies showed

Table 4 Baseline demographic and clinical characteristics of patients before and after 1:1:1 PSM

	Patients number after PSM			
	SV-VATS, 197 (%)	MV-VATS, 197 (%)	OPEN, 197 (%)	P value
Age, year				0.139
≤45	27 (13.7)	27 (13.7)	30 (15.2)	
45–65	140 (71.1)	121 (61.4)	133 (67.5)	
>65	30 (15.2)	49 (24.9)	34 (17.3)	
Gender				0.841
Male	102 (51.8)	95 (48.2)	102 (51.8)	
Female	95 (48.2)	102 (51.8)	95 (48.2)	
Pathology				0.661
Adenocarcinoma	173 (87.8)	170 (86.3)	173 (87.8)	
Squamous carcinoma	15 (7.6)	15 (7.6)	18 (9.1)	
Others	9 (4.6)	12 (6.1)	6 (3.0)	
T stage				0.397
T1	119 (60.4)	100 (50.8)	112 (56.9)	
T2	70 (35.5)	89 (45.2)	78 (39.6)	
T3+T4	8 (4.1)	8 (4.1)	7 (3.6)	
N stage				0.281
N0	151 (76.6)	156 (79.2)	147 (74.6)	
N1	16 (8.1)	13 (6.6)	25 (12.7)	
N2	30 (15.2)	28 (14.2)	25 (12.7)	
TNM stage				0.456
I	147 (74.6)	142 (72.1)	140 (71.1)	
II	18 (9.1)	24 (12.2)	30 (15.2)	
III	32 (16.2)	31 (15.7)	27 (13.7)	

SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; OPEN, thoracotomy.

a pro-metastatic impact of volatile anesthesia and an antimetastatic impact of intravenous anesthesia (42,43). Iwasaki *et al.* (44) pointed that volatile anesthesia changed tumors environments and influenced the apoptosis of tumor cells. Zhang *et al.* (45) found that apoptosis of tumor cells existed, and cell proliferation was reduced when tumor cells were exposed to propofol. A meta-analysis assumed that the usage of TIVA in operation is related to improved RFS and OS in NSCLC and breast cancer compared with volatile anesthesia (41). In patients with digestive tract surgery, an observational study demonstrated a contrary result that there was no difference in OS and RFS between volatile and intravenous anesthesia (46). A retrospective cohort study showed that the relationship between different anesthesia use and long-term survival outcome of breast cancer was weak (47). In our study, TIVA was administered in the SV-VATS group. We hypothesized TIVA may contribute to the positive long-term outcome in the SV-VATS compared to the MV-VATS, which warrants future studies to add clarity in contradictory findings from the current studies.

There are some limitations in our study. First, there may have been selection bias despite the use of 1:1 or 1:1:1 PSM,

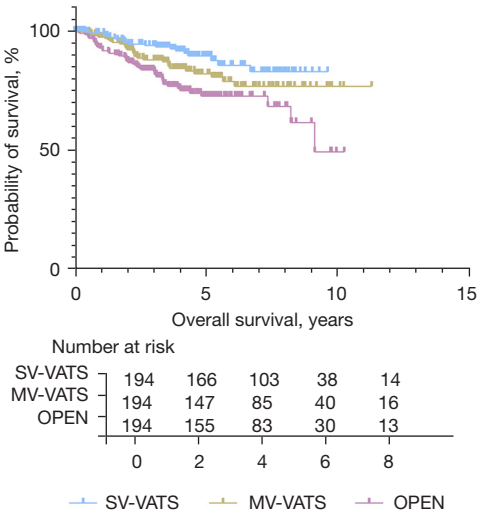

Figure 4 The long-term survival outcomes between SV-VATS, MV-VATS and OPEN group. MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; OPEN, thoracotomy; HR, hazard ratio; CI, confidence interval.

Table 5 Survival information of group SV-VATS, MV-VATS and OPEN

	HR	95% CI	P value
SV-VATS *vs.* MV-VATS	0.606	0.344 to 1.068	0.086
SV-VATS *vs.* OPEN	0.379	0.233 to 0.617	<0.001
MV-VATS *vs.* OPEN	0.625	0.397 to 0.982	0.045

SV-VATS, spontaneous ventilation video-assisted thoracoscopic surgery; MV-VATS, double-lumen intubated mechanical ventilation video-assisted thoracoscopic surgery; OPEN, thoracotomy; OS, overall survival; HR, hazard ratio; CI, confidence interval.

as patients were not randomized before the surgery and the majority of patients undergoing MV-VATS or thoracotomy were excluded after PSM in our analysis. Second, as the technique of the SV-VATS was not mature at the beginning of application, the difference in experience of surgeons may bring potential bias. Third, the sample size was not large enough. There were 400 patients included after PSM in this retrospective analysis. Besides, the follow-up time was not long enough. Though we followed up two groups of patients for more than 4 years on average, the follow-up time was not long enough to calculate the median survival time of SV-VATS. Further RCT studies and multicenter prospective observational studies need to be developed to confirm the survival advantages in the SV-VATS.

Conclusions

Invasive NSCLC patients undergoing SV-VATS lobectomy demonstrated better long-term outcomes compared with MV-VATS.

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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 was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol and methods were reviewed by the institutional ethics committee of the First Affiliated Hospital of Guangzhou Medical University (2020-69). Informed consent was obtained from each patient before inclusion.

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