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Original Article

Long-term outcomes of video-assisted thoracoscopic versus open lobectomy for non-small-cell lung cancer with propensity score matching

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Abstract: The aim of this study was to compare the long-term and short-term outcomes of video-assisted thoracoscopic lobectomy (VATS) with those of open lobectomy for non-small-cell lung cancer (NSCLC) between well-matched patient groups. NSCLC patients underwent lobectomy with radical intent between January 2008 and January 2013, were divided into VATS and open groups. A one-to-one propensity case-matched analysis was used with covariates of baseline characteristics. Long-term and short-term outcomes were compared between the matched two groups. The two groups were well balanced by propensity score matching and 69 patients were matched. There were no significant differences in overall survival and disease-free survival between VATS and open groups. The median blood loss was significantly less with VATS, and the median postoperative hospital stay was significantly shorter for VATS. Complication rate was significantly less in VATS. VATS in selected patients with NSCLC showed similar long-term outcomes, associated with less blood loss, shorter hospital stay, and fewer postoperative complications.

Keywords: Non-small-cell lung cancer, prognosis, video-assisted thoracoscopic surgery, lobectomy

Introduction

Since the first video-assisted thoracoscopic lobectomy (VATS) for thoracic disease was reported in 1990s [1], the number of VATS for thoracic disease has increased steadily worldwide and the greatest diffusion of VATS occurred in East Asia, North America, and Europe [2-4]. Moreover, the number of non-small-cell lung cancer (NSCLC) cases to which VATS is applied has increased over the past years, especially in Asia and Europe [5-8]. However, no randomized controlled trials have been published and the available data derive from multiple case series, case-control studies, reviews, and meta-analyses published over the last years.

For new surgical procedures to become widely adopted as standard operations, they should first be compared with established procedures and shown to be superior in at least some respects [9-13]. Despite its lateness to embrace video-assisted thoracoscopic surgery, pulmonary resection is now gaining momentum in this paradigm shift. Following improvements in technology and equipment, VATS should now be considered a safe option, if performed by experienced surgeons. Additionally, dramatic improvements in the safety of pulmonary resection have facilitated this transition [14]. Thus, adoption of the VATS for the surgical treatment of NSCLC is now progressively expanding. However, unfortunately, it is impossible to reach an accurate conclusion regarding benefits and risks of VATS over open lobectomy in the absence of randomized controlled trials.

Propensity score matched analysis has become increasingly used in retrospective cohorts to reduce the impact of treatment-selection bias in the comparison of treatment to a non-randomized control using observational data. This type of evaluation has been proven to decrease selection bias in retrospective studies and allows comparison between different surgical procedures. Several studies have demonstrated that VATS for NSCLC is less invasive com-

Table 1. Comparison of baseline data

	VATS (*n* = 69)	Open (*n* = 69)	*P* value
Age (y)	61 (48-71)	60 (44-69)	0.540
Gender (Male:Female)	45:24	42:27	0.597
Tumor location			0.906
Right upper lobe	29 (42.0%)	31 (44.9%)	
Right lower lobe	10 (14.5%)	8 (11.6%)	
Left upper lobe	13 (18.8%)	15 (21.7%)	
Left lower lobe	17 (24.6%)	15 (21.7%)	
Clinical stage (7th AJCC-UICC)			0.719
IA	22 (31.9%)	24 (34.8%)	
IB	47 (68.1%)	45 (65.2%)	
ASA score			0.404
I	49 (71.0%)	53 (76.8%)	
II	16 (23.2%)	14 (20.3%)	
III	4 (5.8%)	2 (2.9%)	

VATS: video-assisted thoracoscopic lobectomy; ASA: American Society of Anesthesiologists.

pared with open lobectomy. However, most of these studies were based on retrospective analyses of case-matched studies or meta-analyses of non-randomized studies. The aim of the present study was to compare the long-term outcomes and the short-term outcomes of VATS with those of open lobectomy for NSCLC.

Methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by our local ethics committees. The need for informed consent from patients was waived because of its retrospective nature.

We retrospectively reviewed the data of 257 patients who underwent primary lobectomy for NSCLC with radical intent from January 2008 to January 2013. The patients were divided into VATS (*n* = 87, undergoing VTAS) and open (*n* = 170, undergoing open lobectomy) groups based on the surgical approach. All patients underwent bronchoscopy, endobronchial ultrasound, computed tomographic scans of brain, neck, chest, and upper abdomen to determine the clinical stage. Mediastinoscopy was not necessary except positive mediastinal or hilar lymph node on chest thoracic computed tomographic scan. Positron emission tomography-computerized tomography (PET-CT), staging thoracoscopy and bone scanning were performed selectly. The clinical stage was based on the 7th edition of the TNM [15] classification of lung cancer, which was proposed by Union for International Cancer Control (UICC), International Association for the Study of Lung Cancer (IASLC) and American Joint Committee on Cancer (AJCC). For those of the patients operated before 2010, their staging was recalculated to match the 7th edition of TNM classification of lung cancer proposed by UICC, IASLC and IASLC. VATS was performed as previously described [2]. The indications for VATS were as follows: tumor with clinical stage I disease, without neoadjuvant therapy, with no evidence of metastasis or extended resection for other organ(s).

To avoid confounding differences due to baseline varieties between VATS and open approaches, we performed a propensity score-matched analysis. Propensity score analysis was used to build a matched group of patients for comparison of long-term and short-term outcomes between VATS and open groups. The propensity scores were generated with the preoperative characteristics, including sex, age, American Society of Anesthesiologists (ASA) score, location of tumor and clinical TNM stage. Propensity score matching was performed using a 1:1 ratio without replacement by caliper-matching on the estimated propensity score.

The study criteria for comparing the two matched groups were the following: (1) clinicopathologic data of each matched group; (2) intraoperative, surgical and pathological results, and (3) long-term oncologic outcomes in aspects of overall survival and disease-free survival. Morbidity was defined as postoperative complications occurring within 30 postoperative days, which was graded according to the Clavien-Dindo classification. The definition of Clavien-Dindo system was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2 [16].

Table 2. Comparison of surgical data

	VATS (*n* = 69)	Open (*n* = 69)	*P* value
Operative time (min)	190 (160-320)	160 (150-280)	0.008
Blood loss (ml)	230 (200-440)	340 (280-540)	0.010
Intravenous narcotic use (days)	3 (1-4)	4 (2-5)	0.014
Epidural use (days)	2 (1-3)	3 (2-4)	0.020
Hospital stay (days)	9 (6-23)	10 (8-32)	0.003
Overall complications	9 (13.0%)	19 (27.5%)	0.034
Minor complications	7 (10.1%)	14 (20.3%)	0.819
Major complications	2 (2.9%)	5 (7.2%)	

VATS: video-assisted thoracoscopic lobectomy.

Table 3. Comparison of pathological data

	VATS (*n* = 69)	Open (*n* = 69)	*P* value
Histological subtype			0.688
Adenocarcinoma	63 (91.3%)	60 (87.0%)	
Squamous cell carcinoma	5 (7.2%)	7 (10.1%)	
Others	1 (1.4%)	2 (2.9%)	
Pathological stage			0.884
IA	11 (15.9%)	10 (14.5%)	
IB	23 (33.3%)	25 (36.2%)	
IIA	19 (27.5%)	16 (23.2%)	
IIB	10 (14.5%)	11 (15.9%)	
IIIA	6 (8.7%)	7 (10.1%)	
Residual tumor (R0/R1/R2)	69/0/0	69/0/0	1.000
Number of dissected lymph nodes	20 (19-23)	21 (18-25)	0.251
Mediastinal lymph nodes harvested	16 (13-20)	15 (12-22)	0.541

VATS: video-assisted thoracoscopic lobectomy.

The overall survival was calculated from the date of radical resection the last follow up or death of any cause. The disease-free survival was assessed from the date of radical resection until the date of cancer recurrence or death of any cause. Disease recurrence was defined as locoregional or distant metastasis proven by radiology or pathology when available [17-21]. The follow-up was closed in July 2015.

Data were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t* test. For data following non-normal distribution, results were expressed as median and range and were compared by nonparametric test. Differences of semiquantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. Univariate analyses were performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with probability values less than 0.10 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. $P < 0.05$ was considered statistically significant. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was applied.

Results

Table 1 summarizes the baseline characteristics of the patients. Both the two groups were well balanced for all variables, as shown in **Table 1**.

In the VATS group, the median blood loss was significantly less ($P = 0.010$) than in the open group and the median postoperative hospital stay for the VATS patients was significantly shorter ($P = 0.030$) than for the open lobectomy patients, while the operation time in the VATS group was significantly longer than in the open group ($P = 0.008$) (**Table 2**). No patients in the VATS group required conversion to open lobectomy in our cohort. Postoperative 30-day complication rates in the VATS group were significantly lower than in the open group ($P = 0.003$) (**Table 2**). When the severity of 30-day complications was compared using Clavien-Dindo classification, more complications were classified as major in patients underwent open lobectomy, though the difference was not significant ($P = 0.819$) (**Table 2**). Mortality at 30 postoperative days was none in the whole cohort.

The pathological data were almost similar between the two groups (**Table 3**).

The median observation period in the VATS group was 40 months, and one in the open group was 42 months. We performed Kaplan-Meier analyses for overall survival and disease-

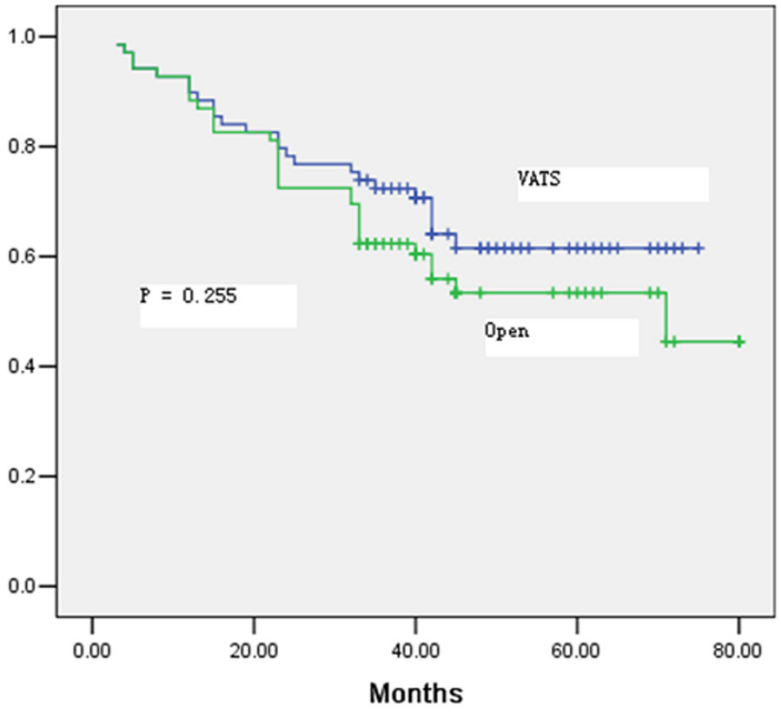

Figure 1. Kaplan-Meier survival curves comparing overall survival in the propensity score matching cohorts.

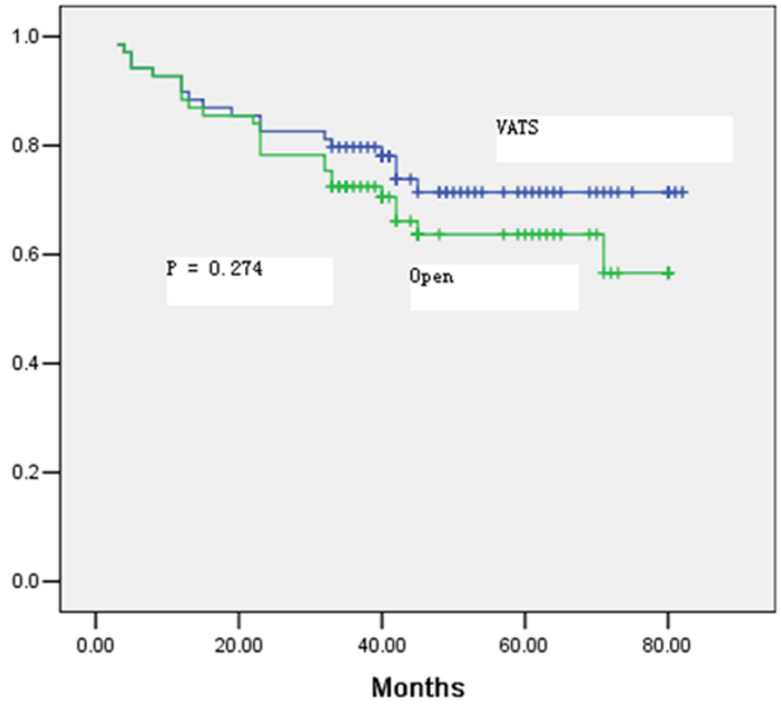

Figure 2. Kaplan-Meier survival curves comparing disease-free survival in the propensity score matching cohorts.

free survival curves, as shown in **Figures 1** and **2**. The cumulative 5-year overall survival rate was 71% in the VATS group and 63% in the open group. The cumulative 5-year disease-free survival rate was 61% in the VATS group and 57% in the open group, respectively. There were no significant differences in overall survival (P = 0.274) and disease-free survival (P = 0.255) between the matched two groups. The pattern of recurrence and median time to cancer recurrence were similar in the two groups, and no port-site recurrence was observed in our series (**Table 4**).

Multivariate analysis identified poor differentiation grade (HR: 2.30, 95% CI: 1.25-3.77, P = 0.020) and pathological N stage (HR: 1.89, 95% CI: 1.25-2.88, P = 0.025) as the factors with independent effects on overall survival (**Table 5**). The type of operative approach did not influence the overall survival. In multivariate analysis, pathological lymphatic invasion (HR: 1.88, 95% CI: 1.25-2.69, P = 0.010) and pathological N stage (HR: 3.21, 95% CI: 1.88-3.68, P = 0.018) had independent effects on disease-free survival (**Table 6**). The type of operative approach was not important in the multivariate analysis for disease-free survival.

Discussion

This was a comparative study analyzing data on patients with NSCLC operated on with VATS or open surgery. At the best of our knowledge, only a few studies conducted in China have explored differences between VATS and conventional open surgery [22, 23]. Our results showed that VATS was associ-

Table 4. Tumor recurrence pattern and site of the two groups

	VATS (*n* = 69)	Open (*n* = 69)	*P* value
Overall recurrence	20 (29.0%)	30 (43.5%)	0.077
Locoregional	12 (17.4%)	18 (26.1%)	0.983
Mediastinal lymph node	5 (7.2%)	7 (10.1%)	
Pleura	3 (4.3%)	5 (7.2%)	
Ipsilateral lung	4 (5.8%)	6 (8.7%)	
Distant	7 (10.1%)	10 (14.5%)	0.845
Brain	2 (2.9%)	3 (4.3%)	
Liver	3 (4.3%)	3 (4.3%)	
Adrenal	1 (1.4%)	2 (2.9%)	
Distant lymph node	1 (1.4%)	1 (1.4%)	
Bone	0 (0.0%)	1 (1.4%)	
Mixed	1 (1.4%)	2 (2.9%)	
Time to recurrence (median)	21 months (5-42)	16 months (4 -42)	0.120

Table 5. Multivariate Cox regression analyses of overall survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Pathological N stage			
N0	1.00		
N1	1.25	0.55-1.87	0.123
N2	1.89	1.25-2.88	0.025
Differentiation grade			
Good	1.00		
Moderate	1.24	0.47-1.38	0.129
Poor	2.30	1.25-3.77	0.020

Table 6. Multivariate Cox regression analyses of disease-free survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Pathological N stage			
N0	1.00		
N1	1.38	1.12-1.99	0.084
N2	3.21	1.88-3.68	0.018
Lymphatic invasion			
No	1.00		
Yes	1.88	1.25-2.69	0.010

ated with better early postoperative outcomes and survival compared with the conventional open procedure.

In our study we found significant improvements in postoperative recovery among VATS-treated patients. The postoperative hospital stay for patients who underwent VATS ranged between about 4 to 7 days in some series which was a shorter time than the 9 days reported in this study [4-7]. Several confounding factors could affect the comparison of hospital stay between the two groups as well as between different studies. For example, disparities according to socioeconomic status are well documented in Eastern countries, thus introducing bias in the results if they are not adjusted for this variable. In China, the healthcare system provides ensuring equity in the availability of care by removing financial barriers for all cancer patients. Therefore, in the China comparison length of hospital stay should not be influenced by socioeconomic status of patients, and China patients tend to leave the hospital slowly because hospital charges are inexpensive and covered by the China healthcare system.

We also assessed any significant advantages in the VATS approach over the open surgical method for pain score and analgesic consumption. As the VATS causes less pain, patients who underwent VATS definitely required smaller doses of analgesic than their counterparts who received open surgery treatment. In the results of most studies reported previously, short-term outcomes after VATS for NSCLC were shown to be better than those of open surgery [4-7].

Further, the VATS patients had less morbidity than the patients undergoing open lobectomy. These results are consistent with other reports [4-8]. However, in the subgroup analysis, major complications failed to show less in the VATS group. This can be attributed to the small sample size.

In our study, short-term oncological outcomes were assessed by examining pathological results, such as the resection margin and the number of exciesed mediastinum lymph nodes. Our results showed that the outcomes of VATS were comparable to those achieved by open lobectomy. In this study, none of the resection margins was found to be positive, as reported

in most previous articles with data on resection margins. The median number of resected lymph nodes was 20 in patients who underwent VATS and 21 in those who underwent open surgery, thus confirming that there were no differences in lymph nodes harvested between the two groups of patients. This finding demonstrated that the short-term oncological safety of VATS was comparable to previous results of other series [4-8].

In this study, the long-term survival outcomes were assessed over a period of 5 years and a median follow-up of 40 months for both groups, including local and distant recurrence rate, overall survival, and disease-free survival. With regard to cancer recurrence rate, patients who underwent VATS were shown to have rates comparable to those who underwent open lobectomy. Our study revealed that the recurrence rate for clinical stage I NSCLC patients were similar to other reports with large sample size [14, 22-30]. Similar overall and disease-free survival in the two groups confirmed the long-term oncologic safety of the VATS compared with open lobectomy. Our results were in line with previous finding.

The present study was limited in that the patients were non-randomized into the two treatment arms. However, as there were no differences in demographic data, we suggest that this bias had a negligible affect on the results. In addition, the median follow-up time was relatively short, which may cause deletions of the long-term follow-up results; thus, we cannot provide a more reliable basis with regard to the long-term outcomes.

In conclusion, compared with open lobectomy, VATS in selected patients with NSCLC showed similar long-term outcomes, associated with less blood loss, shorter hospital stay, and fewer postoperative 30-day complications.

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Disclosure of conflict of interest

None.

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