

Original Article

Video-assisted thoracoscopic lobectomy versus open lobectomy for clinical stage I non small cell lung cancer: a case-control study

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Abstract: This study aimed to compare outcomes following video-assisted thoracoscopic lobectomy (VATS) versus open lobectomy for clinical stage I non small cell lung cancer at a China center. Eighty-one consecutive patients who underwent video-assisted thoracoscopic lobectomy from January 2007 to December 2013 were compared with 94 patients undergoing open surgery during the same time period. Patients were matched for age, sex, American Society of Anesthesiologists (ASA) class, location of tumor and clinical TNM stage. Endpoints were short- and long-term perioperative outcomes. The VATS approach was associated with longer operative time, less blood loss, similar surgical margin, and decreased duration of narcotic and epidural use, similar complications and decreased length of stay. There was no difference in the number of lymph nodes harvested, 5-year overall survival and 5-year disease-free survival between the VATS group and open group. VATS is safe and effective for clinical stage I non small cell lung cancer.

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

Introduction

Diagnosis of clinical stage I non small cell lung cancer, has been increasing worldwide because of the development of screening methods [1-5]. An aggressive surgical approach of pulmonary resection plus mediastinal lymphadenectomy has long been the standard treatment, even for early stage non small cell lung cancer [6-8]. Non-small cell lung cancer, even at this early stage, tends to metastasize to the mediastinal lymph nodes, and mediastinal lymphadenectomy is often required [9-11]. Recently, video-assisted thoracoscopic lobectomy (VATS) has been introduced to treat patients with clinical stage I non small cell lung cancer. Previous studies demonstrated that VATS is less invasive than open resection, thus leading to faster recovery and better cosmetic outcomes [12-15]. However, the prognosis of patients who underwent VATS for clinical stage I non small cell lung cancer was controversial. The objec-

tive of this study was to compare VATS and open lobectomy for clinical stage I non small cell lung cancer in terms of clinical results and the survival of patients.

Materials and methods

Patient selection

The institutional review board of our institution approved this study. Surgery was performed after all possible alternative procedures or treatments had been explained to the patients and they had given their informed consent.

All patients who underwent VATS for clinical stage I non small cell lung cancer with curative intent from January 2007 to December 2013 were identified using a prospectively-maintained database. Patients undergoing palliative resection extend organ resection, or those with neoadjuvant therapy were excluded. Patients who underwent attempted VATS but who

required conversion to an open procedure were also excluded. The most common reasons for conversion in these patients were the direct invasion of adjacent organs, uncontrolled bleeding, and positive proximal margin on frozen section analysis. A total of 94 patients who met these criteria above mentioned were identified. These 94 patients were matched to 94 patients who underwent open lobectomy for the same indication during the same time period. Matching variables were age, sex, American Society of Anesthesiologists (ASA) class, location of tumor and clinical TNM stage. The TNM stage was based on the 7th edition of the TNM classification of lung cancer, which was proposed by Union for International Cancer Control (UICC) and International Association for the Study of Lung Cancer (IASLC), and the mediastinal lymph node staging was based on the newest lymph node map proposed by IASLC [16, 17]. 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 and IASLC.

Operative technique for VATS

VATS was performed as previously described [14]. Only trocar and endoscopic instruments were used in VATS approach and no rib spreading was applied. All patients underwent one-lung ventilation and were placed in the lateral decubitus position. Mediastinal lymphadenectomy was performed after lobectomy. We perform intra-operative lymph nodes frozen sections. On the left side, lymph node station 5, 6, 7, 8, 9, 10, 11 and 12 were systematic dissected. On the right side, dissection of lymph node station 2R, 4R, 7, 8, 9, 10, 11 and 12 were also performed. Lymph nodes mentioned above were dissected with the integrity of the surrounding structure, the anatomical landmarks clear recognition and with no nodal structures. Lymph node station 10, 11, 12 and the affected lobe were systematic dissected and removed *en bloc*. Briefly, on the right side, when the mediastinal pleura was opened, the dissection of station 2R and 4R was undertaken up to the lowest visible part of the subclavian artery. After the lung was retracted anteriorly, the dissection of station 7 was performed. Regardless of middle lobectomy and lower lobectomy, station 8 and 9 was systematically harvested. On the left side, station 5 and 6 was systematically

harvested. Then, dissection of station 7, 8 and 9 was done.

Clinical and follow-up data

Clinical and follow-up data were obtained from a prospectively maintained database. A complication was defined as any unintended event occurring within 30 days of pulmonary resection. Complications were graded in severity from 1 to 5 based on a modified Clavien-Dindo system. 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. Minor complications were defined as Grades 1-2 and major complications as Grades 3-5 [18]. During the first year after radical resection and/or adjuvant therapy was completed, patients were seen every 3 months at the outpatient department. In the second year, follow-up took place every 6 months, and then follow-up was performed at the end of each year after treatment. During follow-up, diagnostic investigations were performed. All patients received CT scan of chest before discharge and before each follow-up visit. Any post-operative complications and medical conditions requiring hospitalization were reviewed. The follow-up was closed in December 2014.

Statistical analysis

Patients were matched one-to-one by age (within 5 years), sex, ASA score, location of tumor and clinical TNM stage. 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 semi-quantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. The overall survival was assessed from the date of radical lobectomy until the last follow up or death of any cause. The disease-free survival was calculated from the date of radical lobectomy until the date of cancer recurrence or death of any cause. Univariate analyses were performed to identify prognostic vari-

Table 1. Demographic data

	VATS (n = 94)	Open (n = 94)	P value
Age (y)	63 (42-71)	64 (39-70)	0.485
Gender (Male:Female)	58:36	54:40	0.552
Location of tumor			0.857
Right upper lobe	41	38	
Right middle lobe	4	7	
Right lower lobe	13	14	
Left upper lobe	24	21	
Left lower lobe	12	14	
Clinical stage			0.767
IA	37	39	
IB	57	55	
ASA score			0.463
I	69	73	
II	21	19	
III	4	2	

Table 2. Intraoperative and postoperative data

	VATS (n = 94)	thoracotomy (n = 94)	P value
Type of resection			0.857
Right upper lobe	41	38	
Right middle lobe	4	7	
Right lower lobe	13	14	
Left upper lobe	24	21	
Left lower lobe	12	14	
Operative time (min)	210 (160-350)	170 (150-320)	0.001
Blood loss (ml)	210 (180-420)	310 (150-600)	0.005
Intravenous narcotic use (day)	3 (1-5)	5 (2-6)	0.020
Epidural use (day)	2 (1-5)	4 (2-6)	0.001
Hospital stay (d)	10 (7-20)	14 (10-29)	0.002
Overall complications	19	24	0.407
Minor complications	16	19	-
Major complications	3	5	-

ables 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 odds 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

Patient demographics

The VATS and open groups were similar for the matched variables of age, sex, ASA score, loca-

tion of tumor and clinical TNM stage. Demographic variables for all patients are summarized in **Table 1**.

Operative characteristics and complications

The VATS and open groups were similar for type of resection. The VATS approach was associated with longer operative time, less blood loss, less postoperative pain measured by decreased duration of IV narcotic use and decreased duration of epidural use for patients who had epidural anesthesia. Length of stay was shorter in the VATS group. Overall, minor and major complications were similar between the groups (**Table 2**).

Pathologic characteristics

No patients had grossly positive margins. Tumor pathological TNM stage, histological subtype and lymph node retrieval were similar between the two groups. Pathologic variables for all patients are summarized in **Table 3**.

Long-term outcomes

Median follow-up period was 36 months in our series. The calculated 5-year disease-free survival rate for all stages was 66% in the VATS group and 62% in the open group ($P = 0.675$, **Figure 1**).

There were no differences between the groups with regard to pathologic TNM stage (**Table 4**). The calculated 5-year overall survival rates for all stages were 73% in the VATS group and 68% in the open group ($P = 0.806$, **Figure 2**). There were no differences between the groups with regard to pathologic TNM stage (**Table 4**).

Fifty-three patients in the VATS group developed tumor recurrence, 23 from distant or hematogenous recurrence, and 15 from locoregional or lymphatic recurrence; the corresponding findings in the open group were 15, and 11, respectively. The pattern of recurrence was similar in the two groups, and no unexpected

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Table 3. Pathological data

	VATS (n = 94)	thoracotomy (n = 94)	P value
Histological subtype			0.460
Adenocarcinoma	84	87	
Squamous cell carcinoma	9	5	
Others	1	2	
Pathological stage			0.763
IA	31	34	
IB	45	41	
IIA	8	10	
IIB	6	7	
IIIA	4	2	
Residual tumor (R0/R1/R2)	94/0/0	94/0/0	1.000
Number of harvested lymph nodes	23 (19-31)	24 (19-32)	0.587
Mediastinal lymph nodes dissected	16 (15-24)	17 (16-25)	0.354

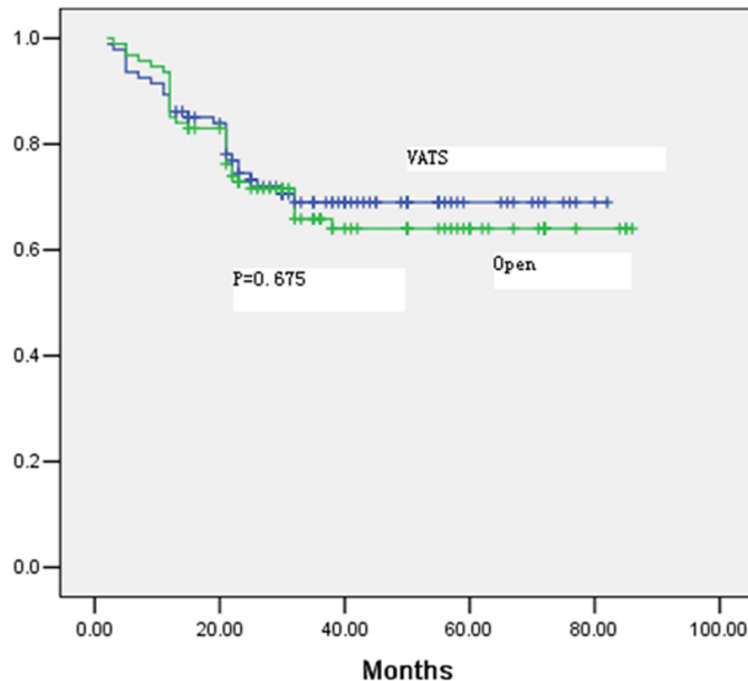


Figure 1. There was no significant difference in disease-free survival between the VATS and open groups (66% vs. 62%) ($P = 0.675$).

tumor dissemination or port-site recurrence was observed.

Multivariate analysis identified pathological N stage and pathological venous invasion as the factors with independent effects on disease-free survival (**Table 5**). The type of operative approach (VATS vs open lobectomy) did not influence the recurrence-free survival. In multivariate analysis, the pathological T stage and

pathological N stage had independent effects on overall survival (**Table 6**). The type of operative approach was not important in the multivariate analysis for overall survival.

Discussion

There is a growing interest in video-assisted thoracoscopic surgeries for many different operative procedures [19]. While video-assisted thoracoscopic surgery has been widely adopted for many benign diseases, the role of video-assisted thoracoscopic surgery for malignant diseases continues to evolve. The long-term oncologic result is very important to the use of laparoscopic gastrectomy. The video-assisted thoracoscopic surgery has been described for the management of certain malignant indications. However, data on feasibility, safety, and long-term results with video-assisted thoracoscopic surgery for lung neoplasm have not been well defined [20-25]. One of the objectives of the current study was to establish the feasibility and safety of VATS for clinical stage I non small cell lung cancer.

In examining short-term outcomes, VATS compared favorably to an open resection. While the median operative time in the VATS group was slightly longer, blood loss was lower in the VATS group. With regard to postoperative complications, several previous groups had noted a

lower risk of postoperative complications following VATS versus open lobectomy [6]. While we did not note any overall differences in the incidence of complications among the two groups, we did find that there was a slightly higher incidence of minor complications following open lobectomy versus VATS. In the current study, we also noted that the median hospital stay following VATS was fewer than the open lobectomy group.

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Table 4. Prognosis according to pathologic TNM stage

	VATS (n = 94)	thoracotomy (n = 94)	P value
Five-year disease-free survival (%)			
I	75	72	0.587
II	54	56	0.580
III	35	32	0.641
Five-year overall survival (%)			
I	87	85	0.871
II	65	67	0.552
III	49	43	0.690

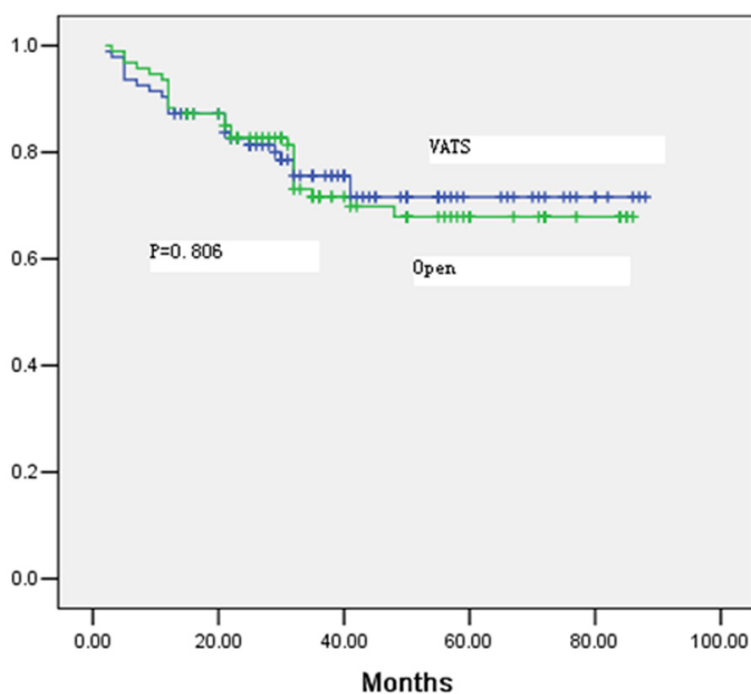


Figure 2. There was no significant difference in overall survival between the VATS and open groups (73% vs. 68%) ($P = 0.806$).

Adequate mediastinal lymphadenectomy is a critical component in radical lobectomy for non small cell lung cancer [24]. Several previous studies have noted no difference in the total number of mediastinal lymph nodes dissected among on small cell lung cancer patients undergoing VATS versus open techniques [20-25]. Early study found that fewer mediastinal lymph nodes were generally retrieved with VATS. In our series, we noted that patients treated with VATS had a comparable number of mediastinal lymph nodes retrieved as with an open approach. These data serve to emphasize that adequate mediastinal lymphadenectomy is feasible with VATS. In addition, consistent with pre-

vious data [20-25], we found that VATS for non small cell lung cancer was very successful in achieving an RO resection. Taken together, these data demonstrate that VATS for non small cell lung cancer can achieve acceptable oncological surgical results.

To the best of our knowledge, there are no multicenter, randomized controlled clinical trials focused on the VATS and open radical pulmonary resection in the treatment of patients with non small cell lung cancer. Thus, before conducting a large multicenter phase III randomized clinical trial comparing VATS with open lobectomy for non small cell lung cancer; it would be good to have the basis of retrospective study on the long-term outcomes. The present comparative study enrolled 188 consecutive patients with clinical stage I non small cell lung cancer that underwent VATS or open lobectomy from a single institute, and long-term results were confirmed in all patients with a 36-month median follow-up period. The long-term results of the present study were acceptable as in other reported studies. Survival of patients who underwent VATS was acceptable and comparable with open radical lobec-

omy. These long-term results of the present data suggest that VATS for clinical stage I non small cell lung cancer is feasible and safe [26-30].

There are several limitations that need to be considered when interpreting our data. Limitations of this study include its retrospective nature and limited follow-up period. Despite efforts to control for baseline factors by matching, this was not a prospective, randomized trial and the two groups of patients were not the same. Furthermore, the median follow-up is not too long, so later cancer recurrence did not observe.

Table 5. Prognostic factors related to disease-free survival

	Hazard ratio	95% CI	P value
Pathological N stage			
NO-1	1.00		
N2	1.78	1.31-3.45	0.008
Pathological venous invasion			
Negative	1.00		
Positive	2.08	1.36-3.30	0.005

Table 6. Prognostic factors related to overall survival

	Hazard ratio	95% CI	P value
Pathological T stage			
T1-2	1.00		
T3	1.88	1.18-2.98	0.023
Pathological N stage			
NO-1	1.00		
N2	3.48	2.01-5.88	0.001

In conclusion, VATS to clinical stage I non small cell lung cancer was associated with adequate mediastinal lymph node dissection, a high incidence of R0 resection, and comparable long-term oncological outcomes versus open radical lobectomy. As such, in appropriately selected patients, VATS should be considered a surgically and oncologically appropriate approach to patients with clinical stage I non small cell lung cancer.

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Disclosure of conflict of interest

None.

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