

# Comparison of robotic-assisted lobectomy with video-assisted thoracic surgery for stage IIB–IIIA non-small cell lung cancer

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**Background:** With the rapid development of surgical technics and instruments, more and more locally advanced non-small cell lung cancer (NSCLC) patients are being treated by minimally invasive surgery (MIS), including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS). The aim of this retrospective study was to compare the perioperative and long-term outcomes of patients who underwent lobectomy by these two surgical approaches.

**Methods:** We performed a retrospective review of the prospectively collected database of our hospital to identify patients with clinical stage IIB–IIIA NSCLC who underwent video-assisted thoracoscopic or robotic lobectomy. Perioperative outcomes, recurrence, and overall survival (OS) were compared.

**Results:** From January 2014 to January 2017, there were at total of 121 patients, including 36 robotic lobectomy patients and 85 VATS lobectomy patients. One patient (2.8%) in the RATS group and 5 patients (5.9%) in the VATS group were converted to thoracotomy (P=0.79). No perioperative death was observed in both groups. The postoperative morbidity was similar between the two groups (13.9% for RATS *vs.* 15.3% for VATS; P=0.84). Robotic lobectomy was associated with a shorter length of postoperative hospital stay (4 *vs.* 5 d, P<0.01) and more counts of lymph nodes harvested (13 *vs.* 10, P<0.01). The median disease-free survival (DFS) for the RATS and VATS group and 47.6% in the VATS group (P=0.74). The 3-year OS was 75.7% in RATS and 77.0% in the VATS group (P=0.75).

**Conclusions:** For selected NSCLC patients with lymph node involvement, robotic lobectomy is safe and effective with a low complication rate and similar long-term outcome compared with VATS lobectomy. Moreover, the robotic approach resulted in shorter postoperative length of stay and greater lymph node assessment.

Keywords: Lung cancer; lobectomy; robotic surgery; minimally invasive surgery (MIS)

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# Introduction

Minimally invasive surgery (MIS), including videoassisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS), has been widely performed for the treatment of early stage non-small cell lung cancer (NSCLC). Compared with conventional thoracotomy, MIS is associated with reduced postoperative pain, faster recovery, and fewer complications (1-3). Generally, minimally invasive lung resection is indicated for early stage NSCLC, and with more clinical experience being

gained in MIS and the rapid development of surgical technics and instruments, such as endoscopic staplers with rotating heads, high-definition 3D cameras, more and more locally advanced NSCLC patients are being treated by the minimally invasive approach. For appropriately selected patients, previous reports have confirmed that both RATS and VATS are feasible and acceptable in morbidity and mortality along with being associated with similar long-term outcomes compared with thoracotomy (4-9).

Robot-assisted surgery has several advantages over VATS, including 3D visibility and mechanical wrists which enable more bend and rotation than the human hand (10,11). Thus, complete lymph node dissection is easier to perform with RATS than with VATS (12), and so RATS is especially suitable for lung cancer cases with lymph node involvement. However, there are no currently published series comparing these two minimally invasive approaches specifically for locally advanced NSCLC. Therefore, we conducted this study to compare both short- and long-term outcomes of patients who underwent RATS or VATS lobectomy for stage IIB–IIIA (N1–2) NSCLC.

#### Methods

## Patient selection

We performed a retrospective review of the prospectively collected database of our hospital between January 2014 and January 2017. The study was approved by institutional ethics committee of Shanghai Chest Hospital (No. KS1735). Eligible criteria were patients who underwent robotic or VATS lobectomy for clinical stage IIB-IIIA (N1-2) NSCLC by the eighth American Joint Committee on Cancer (AJCC 8) staging system (13). Patients with no lymph node involvement or who had undergone wedge resection or segmentectomy were excluded. Patients who had small cell lung cancer or incomplete data were also excluded. In all, 121 patients were included, of whom 36 had a robotic lobectomy and 85 had a VATS lobectomy. All the patients underwent routine serum chemistry, cardiopulmonary function testing, contrast-enhanced thoracic computed tomography (CT), positron emission tomography, brain magnetic resonance imaging or CT. Endobronchial ultrasound-transbronchial needle aspiration or mediastinoscopic biopsy was not mandatory in every patient.

#### Surgical procedures

Under general anesthesia, patients were placed on doublelumen tracheal intubation and contralateral single-lung ventilation. For both VATS and robotic lobectomy, 4 incisions including a 4–5 cm main incision in the 4th intercostal space at the site of the anterior axillary line were created without rib spreading. The surgical procedures for the pulmonary vessels and bronchi were individually performed, as previously reported (14). All patients underwent systematic mediastinal lymph nodal dissection; lymph nodes in groups 2, 4, 7, and N1 were resected for the right-side tumor, and lymph nodes in groups 5, 6, 7, and N1 were resected for the left-side tumor. Conversion was defined as the use of a rib-spreading thoracotomy at any point during the surgery.

#### Statistical analysis

Categorical data are summarized as numbers and percentages. Continuous data are summarized as means with standard deviations (SDs). Differences between the RATS and VATS groups were explored using Pearson's chi-square test for categoric data and Student t test or Mann-Whitney U test for continuous variables. Since the distribution of age, sex, smoking status, tumor size, pulmonary function, clinical stages were comparable between the two groups (Table 1), we did not perform propensity score matching in further analysis. Overall survival (OS) was calculated from the day of surgery to the time of death. Disease-free survival (DFS) was calculated from the day of surgery to the date of cancer recurrence or death from any cause. OS and DFS were evaluated by Kaplan-Meier survival analysis. Logrank tests were used to determine the statistical significance of survival between the two groups. Multivariate Cox regression models were built using factors with P<0.20 in univariate analyses. A two-sided P<0.05 was considered to indicate statistical significance. We used SPSS for Windows version 22 (IBM, Chicago, Il, USA) for statistical analysis.

# Results

# Patient characteristics

In total, 121 patients fit the inclusion criteria in this study, including 36 patients who underwent RATS lobectomy and 85 patients who underwent VATS lobectomy. Patient

Table 1 Patient characteristics

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Variables	RATS (n=36)	VATS (n=85)	P value
Age, y $\pm$ SD	57.2±8.9	59.7±8.8	0.17
Sex, n (%)			0.80
Male	17 (47.2)	38 (44.7)	
Tumor size, cm ± SD	2.72±0.68	2.73±0.87	0.96
FEV1%	89.75	95.81	0.11
Comorbidities, n (%)			
No comorbidities	24 (66.7)	54 (63.5)	0.74
Diabetes mellitus	4 (11.1)	9 (10.6)	1.00
Hypertension	9 (25.0)	20 (23.5)	0.86
COPD	1 (2.8)	3 (3.5)	1.00
History of CVA	0 (0.0)	1 (1.2)	1.00
Neoadjuvant, n (%)	3 (8.3)	1 (1.2)	0.15
Smoking history, n (%)	14 (38.9)	32 (37.6)	0.90
cTNM, n (%)			0.83
IIB	16 (44.4)	36 (42.4)	
IIIA	20 (55.6)	49 (57.6)	
cN stage, n (%)			0.99
N1	17 (47.2)	40 (47.1)	
N2	19 (52.8)	45 (52.9)	
cT stage, n (%)			0.60
T1	19 (52.8)	51 (60.0)	
T2	16 (44.4)	30 (35.3)	
ТЗ	1 (2.8)	4 (4.7)	
Tumor location, n (%)			0.69ª
Right upper	6 (16.7)	28 (32.9)	
Right middle	6 (16.7)	4 (4.7)	
Right lower	11 (30.6)	19 (22.4)	
Left upper	2 (5.6)	25 (29.4)	
Left lower	11 (30.6)	9 (10.6)	

<sup>a</sup>, tumor location was regrouped into left or right lobe. RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery; SD, standard deviation; FEV1, forced expiratory volume in 1 second; COPD, chronic obstructive pulmonary diseases; CVA, cerebrovascular accident.

characteristics are shown in *Table 1*. The distribution of age, sex, smoking status, tumor size, pulmonary function, comorbidities, and clinical stage were comparable between the two groups.

#### Perioperative outcomes

The comparison of perioperative outcomes of the two groups can be seen in *Table 2*. Operative time, blood loss, resection completeness, sampled lymph nodes stations,

Table 2 Comparison of perioperative outcomes between RATS and VATS groups

Variables	RATS (n=36)	VATS (n=85)	P value
Operative time, min, mean ± SD	96.8±23.0	100.1±37.6	0.63
Blood loss ≤100 mL, n (%)	33 (91.7)	75 (88.2)	0.81
Conversion, n (%)	1 (2.8)	5 (5.9)	0.79
Resection completeness, n (%)			1.00
R0	34 (94.4)	81 (95.3)	
R1	2 (5.6)	4 (4.7)	
Sampled LN stations, median [range]	6 [5–8]	6 [4–8]	0.05
Number of LN, median [range]	13 [5–29]	10 [4–26]	<0.01
Complications, n (%)			
Any complication	5 (13.9)	13 (15.3)	0.84
Prolonged air leak	2 (5.6)	6 (7.1)	1.00
Pneumonia	3 (8.3)	6 (7.1)	1.00
Chest tube reinsertion <sup>a</sup>	1 (2.8)	2 (2.4)	1.00
Atrial arrhythmia	0	2 (2.4)	1.00
Wound infection	0	1 (1.2)	1.00
Postoperative LOS, d, median [range]	4 [3–8]	5 [3–14]	<0.01
Chest tube duration, d, median [range]	4 [2–7]	4 [2–13]	0.50
Histology, n (%)			0.96
Adenocarcinoma	33 (91.7)	78 (91.8)	
Squamous carcinoma	2 (5.6)	4 (4.7)	
Others <sup>b</sup>	1 (2.8)	3 (3.5)	
Gene mutation			0.16
EGFR	12 (33.3)	43 (50.6)	
ALK/ROS1	7 (19.4)	12 (14.1)	
None	14 (38.9)	17 (20.0)	
Unknown	3 (8.3)	13 (15.3)	
pStage, n (%)			0.50
IA	1 (2.8)	2 (2.4)	
IB	2 (5.6)	4 (4.7)	
IIB	16 (44.4)	24 (28.2)	
IIIA	14 (38.9)	46 (54.1)	
IIIB	3 (8.3)	9 (10.6)	
Adjuvant therapy			0.11
Chemotherapy	24 (66.7)	58 (68.2)	
Chemoradiotherapy	5 (13.9)	21 (24.7)	
Target therapy	1 (2.8)	0	
None	6 (16.7)	6 (7.1)	

<sup>a</sup>, all patients requiring chest tube reinsertion were because of plural effusion; <sup>b</sup>, RATS group: 1 case of large cell neuroendocrine lung cancer; VATS group: 1 case of pulmonary sarcomatoid carcinoma, 1 case of large cell neuroendocrine lung cancer and 1 case of adenosquamous carcinoma. RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery; SD, standard deviation; LOS, length of hospital stay; LN, lymph node.



**Figure 1** OS between the RATS and VATS group (P=0.75). RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery; OS, overall survival.

complications, chest tube duration, and final pathology stage were not significantly different between the two groups. There was no perioperative death in both groups. One patient (2.8%) in RATS group and 5 patients (5.9%) in the VATS group were converted to thoracotomy with no statistically significant difference. Reasons for conversion were severe adhesion (n=4) and lymph node calcification (n=2). Robotic lobectomy was associated with a shorter length of postoperative hospital stay (4 *vs.* 5 d, P<0.01) and more counts of lymph nodes harvested (13 *vs.* 10, P<0.01). For the majority of these patients who were stage II and stage III disease, adjuvant chemotherapy or chemoradiotherapy were recommended and the distribution of adjuvant therapy was comparable between the two groups.

#### Long-term outcomes

The median follow-up length was 33.9 months (range, 8.3–62.3 months). Two patients (2.4%) were lost to followup in the VATS group. The recurrence rate was 52.8% (n=19) in the RATS group and 54.1% (n=46) in the VATS group. Mortality from any cause was 16.7% (n=6) in the RATS group and 25.9% (n=22) in the VATS group. The median DFS for the RATS and VATS groups were 31.1 and 33.8 months, respectively. The corresponding 3-year DFS was 40.3% in the RATS group and 47.6% in the VATS group. The 3-year OS was 75.7% in the RATS group and 77.0% in the VATS group. There was no significant difference in OS (P=0.75) (*Figure 1*) and DFS (P=0.74) (*Figure 2*) between the two



**Figure 2** DFS between the RATS and VATS group (P=0.74). RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery; DFS, disease-free survival.

groups.

Multivariable Cox regression analysis of OS showed that two independent predictors were pathologic stage and gene mutation status (*Table 3*). Patients with advanced pathologic stage had a higher risk of death [hazard ratio (HR), 3.45; 95% confidence interval (CI), 1.36–8.80; P=0.01], while patients with gene mutation (*EGFR/ALK/ROS1*) had better OS (HR, 0.40; 95% CI, 0.18–0.90; P=0.03). No factors were associated with DFS in univariate or multivariate analysis (*Table 4*).

#### Discussion

MIS for the treatment of early stage NSCLC has rapidly spread during the last decade as a consequence of numerous investigators having proven its safety and effectiveness (15,16). Although the treatment of locally advanced NSCLC via minimal approaches is controversial, more and more studies have demonstrated that MIS, both VATS and RATS, are acceptable for selected patients (6,17,18). A propensity matched comparison of VATS with thoracotomy for locally advanced NSCLC by Chen et al. showed that video-assisted thoracoscopic lobectomy can be performed in the majority of cases without compromising perioperative outcomes and oncologic efficacy (19). In the largest series of patients with pN2 disease treated robotically (9), the conversion rate and complications were low while the survival was similar to that reported for open surgery. Even for bronchial sleeve resection, robotic surgery had similar

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Table 3	Univariable and	multivariable	Cox analysis	for overall survival	

Variables	Univariable analysis		Multivariable an	Multivariable analysis	
variables	HR (95% CI)	Р	HR (95% CI)	Р	
Age	1.04 (0.99–1.09)	0.10	1.02 (0.97–1.07)	0.40	
Sex (male/female)	2.08 (0.97-4.45)	0.06	1.57 (0.70–3.51)	0.28	
Smoking (no/yes)	0.88 (0.60–1.28)	0.50			
Tumor size	1.18 (0.76–1.85)	0.46			
Comorbidity					
No/yes	1.21 (0.80–1.83)	0.36			
Histology					
Adenocarcinoma/others	0.78 (0.43–1.41)	0.41			
FEV1%	1.75 (0.74–2.08)	0.25			
Tumor location					
Left/right lobe	1.07 (0.50–2.28)	0.86			
pStage					
111/1, 11	3.01 (1.22–7.44)	0.02	3.45 (1.36–8.80)	0.01	
Gene mutation					
Yes/no, unknown	0.43 (0.21–0.91)	0.03	0.40 (0.18–0.90)	0.03	
Group					
RATS/VATS	0.86 (0.34–2.15)	0.75			

HR, hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery.

short-term and mid-term outcomes compared with open procedures (20).

Compared with conventional VATS, robotic lung resection has been proposed to improve surgical outcomes by decreasing pain and enhancing recovery. A metaanalysis of 14 studies including 7,438 patients confirmed that RATS is a feasible and safe alternative to VATS with lower 30-day mortality and conversion rate (21). For longterm outcomes, a propensity matched comparison using the Memorial Sloan Kettering Cancer Center (MSKCC) database revealed a statistically significant difference between the robotic and VATS groups (22), but further multivariate analysis found that the surgical approach was not an independent predictor for OS or DFS. However, the majority of these studies focused on earl stage NSCLC, whereas in our study, we specifically compared these two minimally invasive approaches for stage IIB-IIIA (N1-2) patients. Our data showed OS and DFS were comparable between the two groups, and robotic lobectomy resulted in shorter postoperative length of stay and greater lymph node assessment, suggesting that the robotic approach is safe and effective in selected NSCLC patients with lymph node involvement.

In the current study, only 1 patient (2.8%) in the RATS group and 5 patients (5.9%) in the VATS group were converted to open surgery which was not greater than that in previous report (23), and no conversion occurred due to bleeding. The meta-analysis by Liang *et al.* (21) showed the conversion rate to open surgery was significantly lower in patients who underwent RATS compared to those who underwent VATS [10.3% *vs.* 11.9%; odds ratio, 0.57; P<0.001]. However, we did not see any difference between the two groups (2.8% *vs.* 5.9%; P=0.79).

Only a few patients in our series received neoadjuvant therapy, because about half of these patients were N1 disease. However, for the remaining 64 patients with suspected

Variables	Univariable analysis		Multivariable analysis	
variables –	HR (95% CI)	P	HR (95% CI)	Р
Age	1.01 (0.98–1.04)	0.60		
Sex (male/female)	1.22 (0.75–1.98)	0.43		
Smoking (no/yes)	1.02 (0.79–1.31)	0.87		
Tumor size	1.07 (0.80–1.43)	0.65		
Comorbidity				
No/yes	0.90 (0.70–1.16)	0.43		
Histology				
Adenocarcinoma/others	1.19 (0.71–1.96)	0.52		
FEV1%	0.99 (0.97–1.01)	0.41		
Tumor location				
Left/right lobe	0.99 (0.77–1.28)	0.95		
pStage				
III/I, II	1.57 (0.94–2.63)	0.08	1.54 (0.89–2.67)	0.12
Gene mutation				
Yes/no, unknown	1.15 (0.69–1.91)	0.59		
Group				
RATS/VATS	0.92 (0.53–1.57)	0.74		

 Table 4 Univariable and multivariable Cox analysis for disease-free survival

HR, hazard ratio; CI, confidence interval; FEV1, forced expiratory volume in 1 second; RATS, robotic-assisted thoracic surgery; VATS, video-assisted thoracoscopic surgery.

or proven N2 disease, only 4 patients received inductive chemotherapy. The reason for this is that in our center, we tend to choose surgery followed by chemotherapy or chemoradiotherapy for the treatment of stage IIIA NSCLC if the lymph nodes are smaller than 3 cm.

Lymphadenectomy plays an important role in the treatment of lung cancer, not only by clearing metastatic lesions, but also providing the precise stage assessment to decide whether adjuvant therapy is needed. A previous report showed a greater number of examined lymph nodes were associated with more accurate node staging and better long-term survival (24). The comparison of lymphadenectomy between robotic and VATS lobectomy varied from study to study. Toker *et al.* (12) and Yang *et al.* (17) published their study comparing RATS, VATS, and thoracotomy and found that RATS dissected more lymph nodes at the N1 level and harvested a higher number of median stations of lymph nodes. Wilson *et al.* (25) investigated the nodal upstaging rate

of early stage NSCLC patients who underwent robotic and VATS lung resection and reported a rate of nodal upstaging for robotic resection appeared to be superior to VATS and similar to the thoracotomy data. However, another study conducted by Lee *et al.* (26) showed the two approaches were similar in node upstaging for clinical N0 lung cancer. Moreover, Louie *et al.* (27) and Lee *et al.* (28) also compared RATS and VATS and concluded that both approaches were similar to lymph node dissection. In our study, we found robotic lobectomy was associated with more counts of lymph nodes (13 *vs.* 10, P<0.01); however, greater lymph node assessment did not translate into survival benefit.

The treatment for NSCLC has been refined in recent years with treatments allocated according to histology and specific molecular features. Tyrosine kinase inhibitors (TKIs) can significantly prolong OS for patients with advanced NSCLC harboring epidermal growth factor receptor (EGFR)-mutation, anaplastic lymphoma kinase

(ALK)-rearrangement, or c-ros oncogene 1 receptor kinase (ROS1) fusion (29-31). In our series, multivariable Cox regression analysis revealed patients harboring theses three driver mutations had better over survival (HR, 0.40; 95% CI, 0.18–0.90; P=0.03). A comprehensive investigation of oncogenic driver mutations in Chinese NSCLC patients included 1,356 resected lung adenocarcinomas showed the frequency of EGFR, ALK, and ROS1 were 63.1%, 5.2%, and 0.8%, respectively (32). In the current study, the frequency of EGFR was 33.3% in the RATS group and 50.6% in the VATS group; meanwhile, the frequency of ALK/ROS1 was 19.5% in the RATS group and 14.1% in the VATS group which was higher than that in previous reports because of the small sample size.

Our study has several limitations. First, the analysis was performed retrospectively, and selection bias, which might have influenced the outcomes, could not be avoided. Second, the sample size of the two groups were relatively small and can only reflect the experience of a single center. Third, we did not have the detailed data of adjuvant chemotherapy regimens or further treatment after relapse which might have affected conclusions about DFS and OS. A future multicenter randomized clinical trial is warranted to further compare these two minimally invasive approaches.

# Conclusions

To our knowledge, this is the first study specifically comparing robotic surgery with VATS for the treatment of stage IIB–IIIA NSCLC. Our findings suggest that for selected NSCLC patients with lymph node involvement, robotic lobectomy is safe and effective with a low complication rate and similar long-term outcomes compared with VATS lobectomy. Furthermore, the robotic approach resulted in shorter postoperative length of stay and greater lymph node assessment.

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# Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved by Institutional Ethics Committee of Shanghai Chest Hospital (No. KS1735).

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