IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Medical Sciences

2014; 11(9): 863-869. doi: 10.7150/ijms.8912

Research Paper

Risk Factors for Major Adverse Events of Video-Assisted Thoracic Surgery Lobectomy for Lung Cancer

Jie Yang*, Yan Xia*, Yang Yang, Zheng-zheng Ni, Wen-xin He, Hai-feng Wang, Xiao-xiong Xu, Yu-ling Yang, Ke Fei✉, Ge-ning Jiang ✉

Department of Thoracic Surgery, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, 200433, China

* Dr. Jie Yang and Yan Xia contribute equally to this work.

✉ Corresponding authors: Dr. Jiang, 507 Zhengmin Road, Shanghai 200433, China. E-mail: jgnwp@aliyun.com. Ke Fei, Lung Cancer Institute, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai 20043, China; ffeik@126.com

Received: 2014.02.24; Accepted: 2014.05.29; Published: 2014.06.11

Abstract

Aims: The purpose of this study was to identify the risk factors for major adverse events of VATS (Video-Assisted Thoracic Surgery) lobectomy for primary lung cancer.

Methods: 1806 Patients (1032 males, 57.1%) planned to undergo VATS lobectomy for stage IA-IIIA lung cancer from July 2007 to June 2012. The Thoracic Morbidity and Mortality Classification TM&M system was used to evaluate the presence and severity of complications. Postoperative complications were observed during a 30-day follow up. Univariate and multivariate analysis were used to analyze the independent risk factors for major adverse events.

Results: Successful rate of VATS lobectomy was 97.6% (1763/1806). Major complications occurred in 129 patients (7.3%), with a mortality of 0.3% (5/1763). Pulmonary complications contribute up to 90.7% of the major complications and 80% of mortality. Logistic regression indicated that comorbidities, elder age ≥70y, operative time ≥240min and hybrid VATS were predictors for major adverse events (P<0.05). Hybrid and converted VATS lobectomy result in higher major adverse events compared with complete VATS, 15.1%, 20.9% and 7.4% respectively (P=0.013).

Conclusions: The overall complication rate and mortality of VATS lobectomy are low, while major complications sometimes occur. Pulmonary complications are the most common major complications and cause of mortality. Age ≥70y, comorbidities, operative time ≥240min and Hybrid VATS are predictors of major adverse events.

Key words: Non-small cell lung cancer, VATS, Lobectomy, Major Adverse Events, Risk factor

Introduction

With the widespread use of early screening tools such as multi-slice spiral computed tomography (CT) and positron emission tomography (PET), more and more early staged lung cancers have been detected and treated with surgery. As a minimal invasive operation, video-assisted thoracic surgery (VATS) has been more and more widely used for the treatment of lung cancer. But indications for the VATS lobectomy vary for different surgeons. How to choose surgical approach still remains a problem for marginal cases.

Although complications of VATS lobectomy are at a low level, there is still certain degree of complications and mortality for the procedure[1-5]. Besides, currently, most of published studies have only taken the presence of complications into account, without concern of the severity, making the conclusion less objective. It is of great importance to make an objective and accurate evaluation and identify the risk factors of

complications. In this retrospective analysis, we use the TM&M system to grade complications and investigated predictors for major complications and mortality after VATS lobectomy for primary lung cancer[6,7].

Patients and Methods

Patients

The study was approved by the ethics committee of Shanghai Pulmonary Hospital. A total of 1806 consecutive patients underwent VATS lobectomy for stage IA-IIIA primary lung cancer between July 2007 and June 2012 in our department. All patients received thorough examinations including abdominal ultrasonography or CT scan, whole-body radionuclide bone scanning, PET-CT and head CT or magnetic resonance imaging (MRI) to exclude distant metastasis. Mediastinoscope or endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) was performed when chest CT scan indicated N3 diseases.

Indications for VATS lobectomy included: no ipsilateral thoracotomy history; no evidence of severe pleural adhesions; resectable lesions ≤5cm; no clinical sign of multiple N2 metastases. Surgeon experience and preference were also relative indications. Preoperative discussion of each case was mandatory. All patients' clinical data were presented to evaluate the safety and efficiency at the routine meetings every Tuesday and Friday morning. The leading group made up of 4 most experienced surgeons in our department would authority the surgery and applicable approach.

This series included consecutive patients whom preoperative intention was to resect with VATS procedure. Exclusion criteria included: Patients with a history of neoadjuvant chemotherapy or radiotherapy, procedures other than lobectomy, such as wedge, segmentectomy, bilobectomy, pneumonectomy, or chest wall resection. All patients were restaged according to the 7th edition of TNM classification.

VATS Technique

Under general anesthesia, double-lumen endotracheal intubation with selective contralateral lung ventilation was achieved. A 30 degree high definition thoracoscope was recommended. 3 ports were used for most of the operations. Complete VATS lobectomy was defined as finishing the whole procedure using only the vision of a monitor and without rib spreading. Surgery employing direct version or rib distractor was defined as Hybrid VATS. Complete VATS was applied in most cases, hybrid VATS or conversion to thoracotomy were performed whenever the performance of complete VATS was considered to be challenging.

Aspirator, electrocautery, electrotome or long scissor was used to separate lung tissue up to surgeon's preference. Staples were used to divide vein, fissures and bronchus. Staples or silk ligature were used to divide artery. After completion of lobectomy, specimen retrieval was performed using an endoscopic retrieval bag. The patients would undergo systematic mediastinal lymph node dissection if the frozen section indicated malignant.

Complication and Classification

A complication was defined as any deviation from normal postoperative course. Perioperative mortality was defined as death during the same hospitalization as surgery or within 30 days after the procedure. All the complications were graded according to TM&M system (Table 1), in which the complication grade of individuals was evaluated according to the most severe complication of each patient. Grade I and II complications were defined as minor complications, grade III and IV were defined as major complications, and grade V was mortality. Major complications and mortality were described as major adverse events. The Common Terminology Criteria for Adverse Events (version 4.03) published by National Institute of Health was also used to refine a number of definitions[8].

Table 1. TM&M Classification of Complications for Thoracic Surgery

Grade	Definition
Complication	Any deviation from the normal postoperative course
Minor	
Grade I	Any complication without need for pharmacologic treatment or other intervention
Grade II	Any complication that requires pharmacologic treatment or minor intervention only
Major	
Grade III	Any complication that requires surgical, radiologic, endoscopic intervention, or multitherapy
IIIa	Intervention does not require general anesthesia
IIIb	Intervention requires general anesthesia
Grade IV	Any complication requiring intensive care unit management and life support
IVa	Single organ dysfunction
IVb	Multiorgan dysfunction
Mortality	
Grade V	Any complication leading to the death of the patient

Data Collection

Preoperative protocols were obtained from the medical history. Operation database was reviewed and all relevant information was collected in detail.

Patient's general information, findings on auxiliary examinations, comorbidities, and pathological diagnosis were collected.

Variables recorded included age, sex, smoking, body mass index (BMI), comorbidities, predicted FEV1% (forced expiratory volume in 1 second, FEV1), tumor size, nodal status, and histologic characteristics. Comorbidities included coronary artery disease, hypertension, cerebral vascular event, chronic obstructive pulmonary disease, chronic renal insufficiency, and diabetes mellitus. One pack year of smoking would mean that someone had smoked one package of cigarettes (20 cigarettes) daily for one year.

Statistical Analysis

SPSS 18.0 software (SPSS Inc, Chicago, IL) was used for the data analysis. χ^2 test was used to compare categorical variables; t test and non-parametric test were used to compare continuous variables. For predictors of complications, univariate analysis was applied for possible variables that may influence complications. A multivariable logistic analysis was then performed using variables with a univariate *P* value less than 0.1. And a *P* value of less than 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

Among 1806 patients, 1763 patients with a mean age of (59.1±10.5) years (range from 19 to 89) underwent VATS lobectomy successfully. The mean operative time was (181±57)min, with an estimated blood loss of (206±352) ml. Nearly 90% of procedures could be finished in less than 240 min with less than 600 ml blood loss. Patient characteristics are shown in table 2. These patients were eligible for analysis of risk factors for major adverse events. Conversion cases were not included when analyzing risk factors of VATS lobectomy.

Complications and Risk Factors

A total of 451 complications occurred in 316 patients (17.9%). Major and mortality accounted for 34.6% of all complications. Grade II complications made up the majority of complications with a proportion of 61.2%. The most common complications included prolonged air leak, arrhythmia, pulmonary atelectasis, and pleural effusion. Pulmonary complications accounted for 59.6% of all complications, 43.4% of minor, 90.7% of major and 80% of mortality respectively. Minor-only complications occurred in 182 patients (10.3%) and major complications occurred in 129 patients (7.3%). No intraoperative deaths occurred. There were 5 postoperative deaths (0.3%). Details of the complications are shown in table 3.

Table 2. Patient Characteristics

Variable	N	%
Age (y)		
≥70	322	18.3
<70	1441	81.7
Gender		
Male	1007	57.1
Female	756	42.9
Pack year of Smoking		
≥20	507	28.8
<20	1256	71.2
BMI (kg/m²)		
>28	129	7.3
18-28	1587	90.0
<18	47	2.7
Location of tumor		
Left Upper Lobe	427	24.2
Left Lower Lobe	306	17.4
Right Upper Lobe	520	29.5
Right Middle Lobe	154	8.7
Right Lower Lobe	356	20.2
Comorbidities		
Yes	393	22.3
No	1370	77.7
FEV1%		
≥50	1716	97.3
<50	47	2.7
TNM staging		
IA	611	34.7
IB	752	42.7
IIA	118	6.7
IIB	28	1.6
IIIA	254	14.4
Tumor size (cm)		
≥3	1062	60.2
<3	701	39.8
N status		
N0	1395	79.1
N1	134	7.6
N2	234	13.3
Histology		
Adenocarcinoma	857	48.6
Squamous carcinoma	170	9.6
Others	420	23.8
Type of VATS		
Complete	1710	97.0
Hybrid	53	3.0
Number of ports		
3	1423	80.7
4	340	19.3
Operative time (min)		
≥240	189	10.7
<240	1574	89.3
Blood loss (ml)		
≥600	225	12.8
<600	1538	87.2

Table 3. Complications of Patients after VATS Lobectomy

Complication Grade	N	%
Grade I	19	4.2
Pulmonary	8	1.8
Pneumothorax (cured without intervention)	8	1.8
Other	11	2.4
Urine tract infection (only need to remove urine tube)	8	1.8
Delirium	3	0.7
Grade II	276	61.2
Pulmonary	120	26.6
Prolonged air leak	68	15.1
Pneumonia	22	4.9
Atelectasis	14	3.1
Chylothorax (≤200ml/24h, need fat free diet)	8	1.8
Subcutaneous emphysema (modification of chest tube position)	8	1.8
Other	156	34.6
Arrhythmia (AF, PVC etc.)	85	18.8
Hypertension (need intravenously drip antihypertensive drugs)	27	6.0
Anemia (need transfusion)	23	5.1
Coagulation disorders	7	1.6
Peptic ulcer	5	1.1
Urine tract infection	4	0.9
Abdominal pain	3	0.7
Delirium (need sedative)	2	0.4
Grade IIIa	99	22.0
Pulmonary	93	20.6
Atelectasis (need sputum suction)	42	9.3
Pleural effusion (need thoracentesis)	43	9.5
Subcutaneous emphysema (need chest tube reinsertion)	4	0.9
Chylothorax (need fasting and TPN)	4	0.9
Other	6	1.3
Heart failure	6	1.3
Grade IIIb	13	2.9
Pulmonary	13	2.9
Pleural bleeding	4	0.9
Lung torsion	2	0.4
Bronchopleural fistula	5	1.1
Chylothorax (need operation)	2	0.4
Other	0	0.0
Grade IVa	37	8.2
Pulmonary	29	6.4
ARDS	12	2.7
Severe pneumonia	7	1.6
Pulmonary embolism	10	2.2
Other	8	1.8
Cerebrovascular events	3	0.7
Heart failure (need ICU management)	5	1.1
Grade IVb	2	0.4
Pulmonary	2	0.4
ARDS combined with heart failure	2	0.4
Other	0	0.0
Grade V	5	1.1
Pulmonary	4	0.9
Pulmonary embolism	2	0.4
Severe pneumonia combined with ARDS	2	0.4
Other	1	0.2
Sepsis, septic shock, multiple organ failure	1	0.2
Total complications	451	100
Total patients with complications	316	17.9

AF = atrial fibrillation, PVC = premature ventricular contraction, TPN = Total Parenteral Nutrition, ARDS = Acute Respiratory Distress Syndrome, ICU = intensive care unit.

Variables with a *P* value <0.1 in univariate analysis were selected for multivariate logistic regression, in terms of age, gender, pack year of smoking, comorbidities, FEV1%, TNM stage, tumor size, operative time, blood loss, histology and types of VATS. Multivariate logistic regression analysis showed that comorbidities (OR=1.764, 95%CI: 1.164-2.673, *P*=0.007), elder age ≥70y (OR=2.919, 95%CI: 1.932-4.409 *P*<0.001), and long operative time ≥240min (OR=2.440, 95%CI: 1.467-4.057, *P*=0.001) and hybrid VATS (OR=2.868, 95%CI: 1.278-6.437, *P*=0.011) were independent risk factors for major adverse events. The results are summarized in table 4.

Table 4. Predictors for Major Adverse Events after VATS lobectomy

		Univariate	Multivariate	
Variable	**N**	***P* Value**	**OR (95%CI)**	***P* Value**
Age, y		<0.001	2.919 (1.932-4.409)	<0.001
≥70	48			
<70	86			
Gender		0.014	1.183 (0.741-1.888)	0.482
Male	90			
Female	44			
Pack year of Smoking		0.002	1.399 (0.900-2.713)	0.136
≥20	54			
<20	80			
BMI (kg/m²)		0.062	1.408 (0.822-2.413)	0.213
>28	18			
18-28	105			
<18	11			
Location of Tumor		0.326		
Left Upper Lobe	25			
Left Lower Lobe	26			
Right Upper Lobe	42			
Right Middle Lobe	14			
Right Lower Lobe	27			
Comorbidities		<0.001	1.764 (1.164-2.673)	0.007
Yes	49			
No	85			
FEV1%		0.001	1.899 (0.841-4.290)	0.123
≥50	124			
<50	10			
TNM stage		0.006	1.085 (0.934-1.262)	0.286
IA	32			
IB	65			
IIA	7			
IIB	2			
IIIA	28			
Tumor size (cm)		0.038	1.395 (0.890-2.186)	0.147
≥3	92			
<3	42			
Nodal status		0.252		
N0	101			
N1	9			
N2	24			
Histology		0.089	0.952(0.739-1.227)	0.705
Adenocarcinoma	84			
Squamous carcinoma	31			
Others	19			
Type of VATS		0.023	2.868 (1.278-6.437)	0.011
Complete	126			
Hybrid	8			
Number of ports		0.209		
3				
4				
Operative time (min)		<0.001	2.440 (1.467-4.057)	0.001
≥240	27			
<240	107			
Blood loss (ml)		0.072	0.987 (0.588-1.654)	0.959
≥600	25			
<600	109			

Conversion Patients

43(2.4%) cases were converted to thoracotomy for the following reasons: uncontrolled bleeding in 7, severe adhesions in 24, sleeve resection in 5, chest wall invasion in 3, vascular invasion in 4 cases. Severe adhesion was the main cause of conversion. The overall postoperative complication rate was 39.5%, and major adverse events occurred in 16.3% in conversion patients.

Comparison of complete, hybrid VATS and converted lobectomy groups showed that elder age ≥70y and comorbidities were similar, but the operative time of 240min and major adverse events were significantly higher in hybrid and converted group (P<0.001 and P=0.013 respectively). (Table 5)

Table 5. Compare of Hybrid, Complete VATS and Conversion Lobectomy

	Hybrid	Conversion	Complete	
Variable	**(N=53)**	**(N=43)**	**(N=1710)**	**P value**
Age y≥70	11(20.8%)	8(18.6%)	311(18.2%)	0.893
Comorbidities	14(26.4%)	11(25.6%)	379(22.2%)	0.739
Operative time ≥240min	8(15.1%)	14(35.0%)	181(10.6)	<0.001
Complications	20(37.7%)	19(44.2%)	297(17.4)	<0.001
Major adverse events	8(15.1%)	9(20.9%)	126(7.4%)	0.013

Discussion

Since first described in 1990s, VATS lobectomy has been gradually adopted in general thoracic surgery. The Society of Thoracic Surgeons database demonstrates 44.7% of pulmonary resections were performed by VATS in 2010 [9]. In the latest 2013 guidelines of the NCCN, VATS lobectomy has been considered as a reasonable and acceptable approach for NSCLC, with no compromise of standard oncologic or dissection principles of thoracic surgery[10].

Many studies have suggested that VATS lobectomy is superior to thoracotomy with less intraoperative blood loss, reduced hospital length of stay, decreased postoperative pain, better treatment compliance, low postoperative complications, better postoperative pulmonary function, similar operative time, and equal long-term outcomes, and VATS lobectomy had a complication rate of 6-34.2% and mortality of 0.6-1.3% [1-5,11-15]. But grading of complications was not mentioned in most studies. Common Terminology Criteria for Adverse Events (CTCAE) was used in some studies, but it was not specific for thoracic surgery. In our study, according to the TM&M system, major adverse events were in acceptable level and the majority of them were pulmonary complications.

There were 5(0.3%) operative mortalities in our series, and complications of any kind occurred in 17.9% of patients in this study, which is much lower than the 32% complication rate (2.5% mortality) among 9033 pulmonary resections for primary lung cancer reported in a STS database study[16]. The favorable results in this group may be related to high selection of patients and rich experience of postoperative care. On the other hand, the major complication rate was 7.6% compared with a Composite major morbidity rate of 7.9% among 18,800 lung cancer resections(65.5% lobectomy) performed at 111 participating centers[17]. These results indicate that minimally invasive approaches reduce overall perioperative complications, but have less effect on major complication. A reasonable explanation is that extent of resection is the most important determinant of major complication.

Operative time is a very important element impacting complications. Haraguchi used receiver-operator characteristics curves to analyze the risk factors of VATS. Results showed that surgery lasting more than 297 min offset the advantages of VATS and if the duration of surgery would be more than five hours for any reason, conversion to limited thoracotomy or muscle-sparing methods was recommended18. Our study showed most VATS lobectomy could be finished in 240 min, and long operative time ≥240min was independent risk factor for major adverse events. The result suggested that duration of operation has a significant influence on postoperative complications. 240 min could be a potential reference for the time to convert. Surgeons could estimate the time needed to complete the operation according to their experience. If the estimated time exceeds 240 min, the surgeon should consider conversion earlier. Meanwhile, we found the same result (i.e., the incidence of major complications in patients with duration of operation over 240 min is significantly higher than that of those with duration of operation under 240 min) in patients who have higher operation difficulty and need to convert to Hybrid VATS. The result suggested that it is beneficial for the patients to convert to Hybrid VATS earlier if the operation can hard to complete VATS. Additionally, duration of operation over 240 min could be served as a predictive factor for postoperative major complications. Such Patients may need more intensive care and early intervention. So surgeons should be more careful when selecting patients for the procedure, especially during learning curve. Conversion should be considered if operative time is too long.

It is reported that VATS lobectomy for clinical stage I non-small cell lung cancer in the elderly (age ≥70y) was associated with fewer (28% vs. 45%; $P < 0.05$) and overall reduced severity of complications compared with thoracotomy [19]. In another study, oc-

togenarians undergoing video assisted major pulmonary resection had a higher incidence of atrial fibrillation and admission to the intensive care unit for cardiopulmonary support but otherwise were not different from younger age groups in the conversion rate, morbidity or mortality [20]. This might be associated with the fact that the institute was at the beginning of VATS program and the complications of both groups were at high levels. Our study showed that elder age was independent risk factors for major complications.

VATS lobectomy was considered to be a feasible and safe procedure for selected patients even with comorbidities [21,22]. But our study showed that comorbidities were also independent risk factor for major adverse events. So we should always be aware of patients with comorbidities and a prolonged postoperative care is recommended.

Poor preoperative pulmonary function has been a well-recognized predictor for morbidity and mortality after lung cancer surgery, and a preoperative FEV1% of greater than 50% has been recommended for patients receiving lung resection[23]. Video-assisted thoracic surgery pulmonary resection for cancer in patients with poor lung function could achieve acceptable functional and oncologic outcome[24]. A STS database analysis concluded that poor pulmonary function predicted respiratory complications regardless of approach and respiratory complications increased at a significantly greater rate in patients with poor pulmonary function after thoracotomy lobectomy compared with VATS[9]. In our study, poor preoperative pulmonary function was not the predictor for major adverse events. It might result from our high selection of patients.

Complete VATS were feasible in most patients. According to our results, hybrid VATS was an independent risk factor for major adverse events. It might be due to the fact that hybrid VATS was performed during the procedure that the surgery would be too difficult without such extension, which resulted in increasing operative time and major adverse events. Conversion to thoracotomy was applied in even more difficult cases. Conversion was reported to occur in 1.6-23% of patients [4,25-28]. Converted VATS caused increased length of surgery, chest tube duration and estimated blood loss when compared with planned thoracotomy [29]. Tumor and pleural conditions are main cause for conversion. Preoperative thorough evaluation to choose the proper approach and conversion to thoracotomy immediately when necessary are recommended. Severe intraoperative complications are other reasons for conversion. Liang et al reported that severe intraoperative complications during VATS lobectomy were manageable, and at a low incidence similar to open lobectomy [30]. Surgeons need to take proper caution in performing VATS lobectomy.

In conclusion, we find that the overall complication rate and mortality of VATS lobectomy are low, while there is still significant incidence of major complications. Pulmonary complications are most common major complications and main cause of mortality. Elder age ≥70y, comorbidities, operative time ≥240min and hybrid VATS are predictors for major adverse events. Hybrid VATS and converted lobectomy result in significant higher major adverse events, so we need to be more careful when selecting patients. If inevitable, an early conversion to Hybrid VATS or thoracotomy is recommended.

The main limitations of this study are the retrospective nature of the study and lack of randomization. There is certainly a degree of bias in patient selection and surgeon experience. The lack of patients in subgroup may cause the failure of finding of effect of pulmonary function on major complications. How some variables such as severity of comorbidities affect complication rate was not discussed because of lack of data. Further prospective randomized controlled trials are needed to confirm these findings.

Acknowledgement

The authors would like to thank Shanghai Hospital Development Center Grant for the support of this study (Grant No.shdc12012111).

Competing Interests

The authors have declared that no competing interest exists.

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