Short-and long-term outcomes of video-assisted thoracoscopic lobectomy in elderly patients with non-small-cell lung cancer

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Abstract

Objective This study aimed to explore the short-and long-term outcomes of video-assisted thoracoscopic (VATS) lobectomy in older patients with non-small-cell lung cancer (NSCLC).

Methods A total of 218 NSCLC patient data between January 2014 and January 2019, which included pathological, clinical, and follow-up surveys on VATS lobectomy, were retrospectively analyzed. Of the 218-patient data analyzed, a total of 77 patients were 70 years of age and older (elderly group), while a total of 141 patients were below 70 years of age (nonelderly group).

Results Concerning general preoperative data, the simplified comorbidity score (SCS) and the American Society of Anesthesiologists (ASA) scores were higher in the elderly patient group as compared to the nonelderly patient group. Also, elderly patients had poor pulmonary function performance as compared to their counterparts. There were, however, no significant statistical differences found with surgical data between the two groups concerning intraoperative blood loss, operation duration, and conversion to thoracotomy. None of the patients in either of the groups died within thirty days of the operation. Additionally, there were no significant statistical differences in the five-year overall survival rate and the five-year disease-free survival rate between both groups.

Conclusion NSCLC treatment with VATS lobectomy is safe and feasible in elderly patients, and it can provide excellent long-term outcomes. However, it is necessary to strengthen perioperative management and promote early postoperative recovery to reduce complications.

Introduction

Lung cancer is one of the leading causes of cancer-related deaths worldwide and poses a severe threat to human health [1–2]. The global incidence of lung cancer has increased significantly in the past 50 years [3]. Both in developed and developing countries, the prevalence of lung cancer is the highest among all malignant tumors and is related to smoking, occupational carcinogens, air pollution, and ionizing radiation[3]. According to histopathology, lung cancer is classified into non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) [4]. Among them, NSCLC is the most prevalent, which constitutes about 85% of the total cases [4]. Patients diagnosed with NSCLC in developed countries have a median age of sixty-nine and sixty-seven years in both men and women, respectively [5–7]. With the average age of the Chinese population on the rise, the number of elderly NSCLC patients in China is showing an increasing trend [5–7]. At present, the principal methods for treating NSCLC are surgery, radiotherapy, and chemotherapy [8]. For patients the first and second clinical-stage (cI to II) NSCLC, the preferred treatment method is surgery. Lobectomy is the standard surgery for cI to II NCSLC [8].

Elderly patients have considerable concerns regarding open lobectomy as it is highly invasive and has numerous complications [9]. Elderly NSCLC patients treated with thoracic lobectomy have a postoperative mortality rate of 0 to 4.8% and a postoperative complication rate of 20–54% [9, 10]. Since the first video-assisted thoracoscopic (VATS) lobectomy was performed in 1992 [11], the continuous development of

minimally invasive surgical techniques and instruments, accumulation of surgical experience, and continuous reports of good long-term survival in surgical patients [12–27] has prompted the NCCN guidelines to recommend VATS lobectomy as a surgical method for treatment of resectable NSCLC [28]. However, there are few studies on VATS lobectomy in elderly NSCLC patients, and majority of them only report short-term outcomes [29–37]. This study aimed to compare the efficacy of VATS lobectomy in elderly versus non-elderly NSCLC patients in order to explore the short-and long-term outcomes of VATS lobectomy in elderly NSCLC patients.

Patients And Methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by the ethics review board of Yanan University Affiliated Hospital. The need for informed consent from all patients was waived because of retrospective study, not prospective trial.

We carried out a retrospective analysis of VATS lobectomy patients in our institution between the period of January 2014 and January 2019. The inclusion criteria were: (1) patients in whom postoperative pathology confirmed NSCLC; (2) patients who had preoperative clinical stage I to II NSCLC; (3) patients who had not received neoadjuvant therapy, interventional therapy, and other tumor-related treatments before surgery; (4) patients whose data were complete. The exclusion criteria were, however: (1) patients with metastatic cancer, (2) patients with other MTs or with a history of MTs. Of the 218-patient data analyzed, a total of 77 patients were 70 years of age and older (elderly group), while a total of 141 patients were below 70 years of age (nonelderly group).

The patients underwent double-lumen tracheal intubation and were positioned in the lateral decubitus position. They underwent intraoperative unilateral ventilation of the healthy lung. A 2-cm incision was made at the 7th intercostal space in the midaxillary line as a thoracoscopic observation hole. Furthermore, after considering the position of the tumor, a 2-cm incision was made as an operation hole at the sixth, seventh, and eighth intercostal space in the posterior axillary line, and a 3-5-cm operation hole was made at the fourth or fifth intercostal space in the anterior axillary line. Under thoracoscopy, lobectomy and mediastinal lymph node dissection were performed. During the operation, pulmonary veins and bronchi were divided with a disposable linear cutter stapler. Pulmonary artery branches were double ligated with a common silk ligature and divided with an ultrasonic dissector followed by ligation either with Hem-o-Lok clips or with a disposable linear cutter stapler. Excised lymph nodes consisted of the intra-pulmonary, pulmonary hilar, and mediastinal lymph nodes, with the latter comprising mediastinal lymph nodes at stations 4L and 5–9 in the left mediastinum and at stations 2R, 4R, and 7–9 in the right mediastinum [38]. Perioperative management was carried out using the Enhanced Recovery After Surgery (ERAS) principles [39–41].

The Clavien–Dindo classification system was used to classify postoperative complications severity [42–46]. Cause of death, overall survival, local recurrence, disease-free survival, and distant metastasis were recorded during follow-up. Overall survival, disease-free survival, local recurrence, distant metastasis, and

cause of death of the patients were recorded in the follow-up, which was conducted through outpatient visits, telephone interviews, or home visits, or was entrusted to the local hospital physicians. The last follow-up was performed on June 1, 2020. Local recurrence was defined as recurrence of the primary lesion or recurrence in the corresponding drainage area, including recurrence in the pulmonary hilar and mediastinal lymph nodes as well as bronchial stump recurrence, while recurrence at other sites was defined as distant metastasis.

Statistics

All the statistical analyses were performed using SPSS, Version 14.0 (SPSS Inc., Chicago, IL, USA). Normally distributed variables were analyzed by Student *t* tests and presented as means and standard deviations. Non-normally distributed variables were analyzed by Mann–Whitney *U* test and presented as medians and ranges. Differences between semiquantitative results were analyzed by Mann–Whitney *U* tests. Differences between qualitative results were analyzed by chi-square or Fisher exact tests, as appropriate. Survival rates were analyzed by the Kaplan–Meier method, and differences between the two groups were analyzed by log-rank test. Multivariate Cox regression analysis was performed to identify factors predictive of poor disease-free survival and overall survival by using both forward and backward stepwise selection. Explanatory variables with univariate *P* values ≤ 0.100 were included in the multivariate analysis. The results are reported as hazard ratios with 95% confidence intervals. *P* < 0.05 was considered to be statistically significant.

Results

Concerning general preoperative data, the simplified comorbidity score (SCS) and the ASA scores were higher in the elderly group as compared to the nonelderly group. Also, elderly patients had poor pulmonary function performance as compared to their counterparts. There was no statistically significant difference in other general preoperative data (Table 1).

Table 1 Comparison of baseline characteristics of the two groups

<i>Characteristics</i>	<i>Elderly (n=77)</i>	<i>Nonelderly (n=141)</i>	<i>P value</i>
Age (y)	73 (70-77)	61 (45-69)	0.000
Gender (Male: Female)	51: 26	97:44	0.699
SCS			0.008
≥9	21	18	
<9	56	123	
Pulmonary function			
FEV1 (L)	2.3 (1.8-2.7)	2.6 (1.9-2.9)	0.044
MVV (%)	74 (69-97)	80 (71-98)	0.040
Clinical TNM stage			0.949
IA	2	5	
IB	23	41	
IIA	36	67	
IIB	16	29	
ASA score			0.000
I	45	118	
II	26	19	
III	6	4	
Tumor location			
Left upper lobe	12	21	0.842
Left lower lobe	14	25	0.934
Right lower lobe	19	24	0.175
Right upper lobe	23	51	0.348
Right middle lobe	9	20	0.604

SCS: Simplified Comorbidity Score

ASA: American Society of Anesthesiologists

FEV1: Forced Expiratory Volume in the first second

MVV: maximal voluntary ventilation

There were, however, no significant statistical differences found with surgical data between the two groups concerning intraoperative blood loss, operation duration, and significant postoperative complications within thirty days (Table 2), nor pathological outcomes (Table 3).

Table 2 Comparison of surgical outcomes of the two groups

<i>Outcomes</i>	Elderly (<i>n</i> =77)	Nonelderly (<i>n</i> =141)	<i>P value</i>
Conversion to thoracotomy	2	3	1.000
Blood loss (ml)	190 (160-290)	180 (140-270)	0.279
Surgical duration (min)	180 (150-220)	170 (140-230)	0.354
Tube duration (d)	5 (4-9)	5 (3-8)	0.589
postoperative hospital stay (days)	10 (7-20)	9 (6-17)	0.397
Patients with postoperative 30-day complications	10	12	0.294
Pneumonia	4	5	
Atelectasis	2	2	
Prolonged air leak (more than 7 days)	1	2	
Respiratory failure	1	1	
Acute heart failure	1	0	
Arrhythmia	1	2	
Patients with major complications	1	2	1.000
postoperative 30-day mortality	0	0	-

Table 3 Comparison of pathological outcomes of the two groups

<i>Outcomes</i>	Elderly (<i>n</i> =77)	Nonelderly (<i>n</i> =141)	<i>P value</i>
Histological type			0.997
Adenocarcinoma	53	97	
Squamous cell carcinoma	24	44	
Harvested lymph nodes	12 (9-21)	13 (10-25)	0.418
Pathological stage			0.805
IA	1	3	
IB	19	35	
IIA	24	44	
IIB	21	39	
IIIA	12	20	
Residual tumor			1.000
R0	77	141	
R1	0	0	
R2	0	0	

In this study, a total of 22 complications occurred 30 days after surgery, and no patient had more than two complications (Table 2). There were ten and twelve cases of complications in two groups, elderly group and non-elderly group, respectively (Table 2). The complications included pulmonary infection, atelectasis, air leak, and respiratory failure in order of decreasing incidence (Table 2). In terms of complications severity, two patients in both groups had a major 30-day postoperative complication (Table 2). None of the patients in either of the groups died within 30 days of the operation (Table 2).

There were two and three cases of conversion to thoracotomy in the elderly group and non-elderly group, respectively (Table 2). Among the two cases in the elderly group, one presented with calcified lymph nodes, which were adherent to the pulmonary vessels and difficult to separate; the other one presented

with pulmonary vessel injury. Among the three cases in the non-elderly group, two presented with pulmonary vessel injury, two presented with calcified lymph nodes adherent to the pulmonary vessels accompanied by difficulty in separation, and one presented with pulmonary vessel injury.

Concerning long-time outcomes, during the last follow-up, a total of eighteen patients died in the elderly group, while a total of twenty-five patients died in the nonelderly group. There was no remarkable difference concerning mortality between both groups (Table 4). The five-year overall survival rates for the elderly and the nonelderly groups, were 67% and 71%, respectively. There were, however, no significant statistical differences between both groups (Fig. 1, $P = 0.358$). Univariate analysis showed that the T stage, SCS, N stage, and the ASA score significantly affected the five-year OS rate (Table 5). Age, gender, histological type, pathological type, and tumor laterality do not affect the five-year OS rate (Table 5). MCR analysis showed that $SCS \geq 9$, T3-T4 stage, and N2 stage were independent risk factors affecting the five-year OS rate (Table 6).

Table 4 Comparison of follow-up data of the two groups

<i>Outcomes</i>	Elderly (<i>n</i> =77)	Nonelderly (<i>n</i> =141)	<i>P value</i>
Mortality	18	25	0.151
Death from primary cancer	16	24	
Death from other diseases	2	1	
Overall recurrence	20	29	0.361
Local recurrence	6	8	
Distant recurrence	16	18	
Concurrent recurrence	2	3	
Time to first cancer recurrence (median, months)	18 (10-45)	15 (15-47)	0.495

Table 5 Univariate Kaplan–Meier analysis of overall survival

Variable	Five-year overall survival	<i>P</i> value
Age		0.358
<70 years	71	
≥70 years	67	
Gender		0.287
Male	70	
Female	65	
SCS		0.037
≥9	62	
<9	74	
ASA score		0.079
I-II	73	
III	66	
T stage		0.028
T1-T2	78	
T3-T4	63	
N stage		0.034
N0-N1	75	
N2	66	
Histological type		0.574
Adenocarcinoma	73	
Squamous cell carcinoma	68	
Tumor laterality		0.458
Left	73	
Right	67	

SCS: Simplified Comorbidity Score

ASA: American Society of Anesthesiologists

Table 6 Cox proportional hazards model for overall survival

Variables	Hazard ratio (95% CI)	<i>P</i> value
SCS <9 versus ≥9	1.528 (1.215-1.922)	0.044
T stage T1-T2 versus T3-T4	2.358 (1.478-3.762)	0.032
N stage N0-N1 versus N2	2.684 (1.589-4.534)	0.019
ASA score I-II versus III	1.347 (0.678-2.676)	0.120

SCS: Simplified Comorbidity Score

ASA: American Society of Anesthesiologists

The five-year disease-free rates for the elderly and the nonelderly were 59% and 66%, respectively. There were, however, no significant statistical differences between both groups (Fig. 2, *P* = 0.289). Univariate analysis showed that SCS, T stage, and N stage affected 5-year disease-free rate (Table 7). Age, gender, histological type, ASA score, pathological type, and tumor laterality have no effect on 5-year disease-free rate (Table 7). Multivariate analysis showed that SCS ≥ 9, T3-T4 stage, and N2 stage were independent risk factors that affected the 5-year disease-free rate (Table 8).

Table 7 Univariate Kaplan-Meier analysis of disease-free survival

Variable	Five-year overall survival	P value
Age		0.289
<70 years	66	
≥70 years	59	
Gender		0.207
Male	67	
Female	58	
SCS		0.045
≥9	54	
<9	71	
ASA score		0.149
I-II	65	
III	58	
T stage		0.030
T1-T2	71	
T3-T4	54	
N stage		0.027
N0-N1	69	
N2	53	
Histological type		0.578
Adenocarcinoma	67	
Squamous cell carcinoma	61	
Tumor laterality		0.590
Left	68	
Right	62	

SCS: Simplified Comorbidity Score

ASA: American Society of Anesthesiologists

Table 8 Cox proportional hazards model for overall survival

Variables	Hazard ratio (95% CI)	P value
SCS <9 versus ≥9	1.594 (1.114-2.281)	0.031
T stage T1-T2 versus T3-T4	1.974 (1.257-3.099)	0.040
N stage N0-N1 versus N2	3.007 (1.700-5.319)	0.010

SCS: Simplified Comorbidity Score

ASA: American Society of Anesthesiologists

Discussion

Older patients have a poor preoperative pulmonary function, and an increased risk of postoperative pulmonary complications. The risk of pulmonary complications in patients with FEV1 less than 2L and less than 1L is moderate and high, respectively. PF test criteria for lobectomy are a forced expiratory volume in 1 second (FEV1) > 1.0L and maximum voluntary ventilation (MVV) > 40% of predicted [7–9]. In this study, the older patients had poor pulmonary function performance as compared to their counterparts, which indicated that the postoperative risk complications were higher with older patients (≥ 70 years of age) as compared to younger patients (≤ 70 years of age). The ERAS model was first proposed by the Danish surgeon Kehlet in 1997[39–41]. It refers to the comprehensive use of a series of optimization measures supported by evidence-based medicine during the perioperative period, including multidisciplinary collaboration of surgery, anesthesia, nursing, and nutrition, to optimize the clinical

pathway for perioperative management, in order to reduce the perioperative stress response (i.e., physiological and psychological traumatic stress) and postoperative complications in surgical patients with the aim of achieving the best health status and rapid recovery with minimal cost. Since the ERAS model was successfully applied for the first time in gastrointestinal surgery, this concept has now been adopted in neurosurgery, thoracic surgery, and other surgical fields [39–41]. Studies have shown that under the ERAS protocol, it is possible to effectively reduce surgical trauma and postoperative stress response, shorten the length of hospitalization, and promote patient recovery in the perioperative period of VATS lobectomy[39–41]. The results of our study revealed that postoperative complications and severe complications in the elderly group were similar to that of the nonelderly group. This suggests that although the preoperative pulmonary function of elderly NSCLC patients is worse than the non-elderly patients, VATS lobectomy allows elderly NSCLC patients to have similar short-term outcomes as non-elderly patients, thus indicating the safety of VATS lobectomy for the treatment of elderly NSCLC patients.

Postoperative complications after VATS may adversely affect the long-term outcomes [7–9]. The surgery may cause a systemic inflammatory reaction, and the level of inflammatory factors and C-reactive protein will increase [7–9]. Postoperative complications, especially major complications, may exacerbated Inflammation and immunosuppression [7–9]. The perioperative stress response will inhibit the activity of natural killer cells, increase tumor burden, inhibit endogenous mediators, lead to the downregulation of effector lymphocytes and regulatory pathways, and put the body in a state that promotes tumor growth [7–9]. Stress and inflammation caused by major postoperative complications may cause the residual cancer cells to grow and proliferation, which will have an adverse effect on long-term prognosis [7–9]. In this study, the postoperative 30-day complication rate and the rate of serious complications were similar in both groups, which may also be one of the reasons for the similar prognosis of the two groups.

The results of a prospective study showed that the local recurrence rates of early stage NSCLC patients underwent lobectomy are significantly lower than sublobar resection, and the survival rate is significantly higher than sublobar resection. Therefore, the current standard surgical procedure for early stage NSCLC is still anatomical lobectomy. Sublobar resection is currently still in clinical research. Two prospective multicenter randomized controlled trials comparing early lung cancer lobectomy with sublobar resection have been completed, and there are reports of short-term outcomes. Differences in surgical complications or mortality are statistically significant and are currently waiting for long-term follow-up results.

Conversion to thoracotomy is an inevitable phenomenon during VATS lobectomy [47–53]. The overall conversion to thoracotomy rate of the 218 patients included in this study was 1.7%, and the two age groups had similar conversion to thoracotomy rates. A study by Sawada showed that the most important cause of conversion to thoracotomy was the calcification of lymph nodes and their adhesion to pulmonary vessels with subsequent difficult separation [47]. This accounted for 60% of the conversion to thoracotomy rates in our study. In contrast, a study demonstrated that the most common cause of conversion to thoracotomy was vascular injury leading to uncontrollable bleeding, and vascular injury is a common cause of conversion to thoracotomy in minimally invasive surgery such as thoracoscopic esophagectomy and laparoscopic gastrectomy [48]. Although conversion to thoracotomy can cause

prolonged operation duration, increased length of postoperative hospital stay, and increased postoperative pain, it does not cause serious complications or death.

It is common for elderly NSCLC patients to have comorbidities, and the impact of comorbidities on elderly NSCLC patients is getting more and more attention. Charlson Comorbidity Index (CCI) and SCS are the two commonly used methods to assess comorbidities. Compared with CCI, SCS can more accurately assess the impact of comorbidities on the prognosis of NSCLC patients. Through a prospective study of 136 elderly NSCLC patients, Colinet et al. showed that the median survival of patients with a score of ≤ 9 was longer than those with a score of > 9 , suggesting that a SCS of > 9 is an unfavorable prognostic factor in elderly NSCLC patients [54], which is consistent with the results of this study. In the SCS scheme, smoking accounts for a high proportion (weighting = 7) of the total score, as smoking has been confirmed to be closely related to the incidence of common comorbidities in elderly patients such as cardiovascular and respiratory diseases. Therefore, the SCS method provides a more objective and comprehensive assessment of comorbidities in NSCLC patients and is more suitable for studying the impact of comorbidities on the prognosis of NSCLC patients.

VATS lobectomy is mainly performed through multiple incisions, predominantly three incisions, and the three-incision method was also adopted in this study. Minimally invasive surgery is one of the growing developments of surgery. At present, single-incision endoscopic surgeries such as single-incision appendectomy and single-incision cholecystectomy are widely performed [55, 56]. Since Gonzalez's first report of single-incision VATS lobectomy [57], retrospective studies have shown that single-incision VATS lobectomy is safe and feasible [58–62]. In 2016, a randomized controlled trial comparing single-incision versus multi-incision VATS lobectomy revealed that the two groups of patients demonstrated similarities in short-term outcomes such as analgesic medication use, duration of chest tube placement, length of postoperative hospital stay, and incidence of complications [63]. However, there are few reports on long-term outcomes of single-incision VATS lobectomy in the treatment of NSCLC. The key to evaluating a new minimally invasive tumor surgery is the long-term survival rate. Consequently, we should refrain from performing single-incision VATS lobectomy until sufficient research progress has been made.

The present study suffered from numerous limitations since the study was a single-center retrospective analysis with limited sample size; thus, the possibility of selection bias is inevitable.

Conclusion

This study shows that NSCLC treatment with VATS lobectomy is safe and feasible in elderly patients, and it can provide good long-term outcomes. However, it is necessary to strengthen perioperative management and promote early postoperative recovery so as to reduce complications.

Abbreviations

VATS: video-assisted thoracoscopic

NSCLC: non-small-cell lung cancer

SCS: simplified comorbidity score

ASA: American Society of Anesthesiologists

ERAS: Enhanced Recovery After Surgery

CCI: Charlson Comorbidity Index

Declarations

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Contributions

YY and JG contributed to study conception and design, QiR, RX and JG contributed to acquisition of data, Q R, RX and JG contributed to analysis and interpretation of data, YY and JG contributed to drafting of manuscript, YY and JG contributed to critical revision.

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Ethics declarations

Ethics approval and consent to participate

The study was approved by ethics review board of Yanan University Affiliated Hospital. Due to the retrospective study design and the anonymization of data, consent to participate was not necessary.

Consent for publication

All the authors agreed to the publication of this work.

Competing interests

No competing interest by the authors.

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Figures

Figure 1

Comparison of overall survival rates after VATS lobectomy for NSCLC between elderly and middle-aged patients ($P=0.358$).

Figure 2

Comparison of disease-free survival rates after VATS lobectomy for NSCLC between elderly and middle-aged patients (P= 0.289).