Int J Clin Exp Med 2017;10(6):9432-9439
www.ijcem.com /ISSN:1940-5901/IJCEM0048339

Original Article

Short- and long-term outcomes for patients aged ≥70 years undergoing video-assisted thoracoscopic surgery for non-small cell lung cancer

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Received June 2, 2016; Accepted April 21, 2017; Epub June 15, 2017; Published June 30, 2017

Abstract: We performed a retrospective review including 255 patients with non-small cell lung cancer (NSCLC) who underwent video-assisted thoracoscopic surgery (VATS) between January 2008 and January 2016 at our institution. Short- and long-term outcomes were compared between two groups: elderly (≥70 years old) and nonelderly patients (<70 years). Final pathology results, overall survival (OS), and disease-free survival (DFS) were also compared. Both groups had similar clinical stages at diagnosis, American Society of Anesthesiologists scores, and sex distribution. The overall conversion rate to open procedures was 3% in both groups, and the postoperative 30-day complication rate was not significantly different between elderly and nonelderly patients. Finally, the 5-year OS rates for elderly and nonelderly patients were 62% and 69%, respectively (P = 0.212), while the 5-year DFS rates were 50% and 58%, respectively (P = 0.618). In summary, VATS for NSCLC in elderly patients is not associated with a higher rate of postoperative complications or worse long-term survival outcomes, compared with nonelderly patients, and can be offered as a treatment option in select elderly patients.

Keywords: Non-small cell lung cancer, pulmonary resection, video-assisted thoracoscopic surgery, elderly patients

Introduction

The proportion of aging population has increased globally in recent years. The age of patients with non-small cell lung cancer (NSCLC) has also increased rapidly, increasing the importance of cancer treatment in this population [1]. However, elderly patients generally have cardiac or respiratory comorbidities and often have postoperative morbidity and mortality following thoracotomy [2]. Video-assisted thoracoscopic surgery (VATS) is a minimally invasive treatment for patients with NSCLC that has recently gained popularity throughout Eastern Asian countries [3-5]. Several studies have found that VATS reduces postoperative morbidity and mortality, compared with thoracotomy in the general population [6-8]. However, only a few studies have investigated the safety and efficacy of VATS in elderly patients with NSCLC [9, 10]. These studies mainly focused on short-term surgical outcomes. The purpose of this study was to investigate the short- and long-term outcomes in elderly patients with NSCLC who underwent VATS.

Patients and methods

This retrospective study complied with the Declaration of Helsinki and was approved by the Ethics Committee of our institution. Informed consent from all patients was waived, because of the retrospective design of our study.

We identified 255 patients with NSCLC who underwent VATS at our institution between January 2008 and January 2016. Indications for VATS pulmonary resection were: (1) tumors located in the peripheral area. (2) no neoadjuvant therapy. (3) clinical stage I NSCLC. (4) no extended pulmonary resection (e.g., bilobectomy or chest wall resection). The surgical specimens were reviewed by experienced pathologists. All patients underwent routine preoperative imaging evaluation to determine can-

Table 1. Comparison of clinicopathologic characteristics of the two groups

	Nonelderly (*n* = 176)	Elderly (*n* = 79)	Chi square value	*P* value
Age (y)	61 (38-69)	76 (70-78)	-0.870	0.000
Gender (Male:Female)	99 (56.3%):77 (43.7%)	45 (57.0%):34 (43.0%)	0.011	0.916
Comorbidity				
Cirrhosis	1 (0.6%)	1 (1.3%)	0.000	1.000
Hypertension	5 (2.8%)	14 (17.7%)	16.189	0.000
Type 2 diabetes mellitus	3 (1.7%)	9 (11.4%)	9.354	0.002
Stable angina	2 (1.1%)	3 (3.8%)	0.863	0.353
Chronic atrial fibrillation	1 (0.6%)	4 (5.1%)	3.631	0.057
Chronic heart failure	1 (0.6%)	3 (3.8%)	1.888	0.169
Pulmonary function				
Vital capacity (L)	3.12 (2.97-4.21)	3.01 (2.68-3.88)	-0.458	0.358
FEV_1 (L)	1.87 (0.99-3.42)	1.99 (1.15-3.49)	-0.684	0.300
Two or more comorbidities	1 (0.6%)	5 (6.3%)	5.568	0.018
Clinical stage			0.572	0.450
IA	48 (27.3%)	18 (22.8%)		
IB	128 (72.7%)	61 (77.2%)		
ASA score			-1.829	0.067
I	164 (93.2%)	68 (86.1%)		
II	11 (6.3%)	10 (12.7%)		
III	1 (0.6%)	1 (1.3%)		
Tumor location				
Left upper lobe	61 (34.7%)	25 (31.6%)	0.222	0.638
Left lower lobe	39 (22.2%)	21 (26.6%)	0.593	0.441
Right upper lobe	41 (23.3%)	19 (24.1%)	0.017	0.895
Right lower lobe	35 (19.9%)	14 (17.7%)	0.165	0.685

FEV_1: Forced expiratory volume in one second.

cer staging, including bronchoscopy, endobronchial ultrasound, and computed tomography scans of the brain, chest, and upper abdomen [11]. Mediastinoscopy was not routinely performed except in cases positive for mediastinal or hilar lymph nodes on chest computed tomography imaging [12]. Positron emission tomography-computed tomography [13] and bone scanning [14] were performed when necessary. TNM stage was based on the 7th edition of the TNM classification of NSCLC proposed by the International Association for the Study of Lung Cancer, Union for International Cancer Control, and American Joint Committee on Cancer [15]. TNM stage was recalculated to match the 7th edition of the TNM classification of NSCLC in patients who underwent surgery before 2010. The surgical procedure has been described elsewhere.

Postoperative 30-day complications were defined as complications occurring within 30 days post-VATS. Complications were graded according to the Clavien-Dindo classification system as follows: Grade 1, oral medication or bedside medical care required; Grade 2, intravenous medical therapy required; Grade 3, radiologic, endoscopic, or surgical intervention required; Grade 4, chronic deficit or disability associated with the event; and Grade 5, death related to surgical complications [16]. In this study, minor complications were defined as grades 1-2, and major complications, grades 3-5 [17-20].

Follow-up data were collected from the outpatient follow-up database. Patients were seen every 3 months at the outpatient department the first year after treatment was completed. Follow-up continued every 6 months in the second year and annually thereafter. Diagnostic investigations were performed during the follow-up. All patients received chest computed tomography before discharge and before each follow-up visit. Patients were considered to

Table 2. Comparison of surgical outcomes of the groups

	Nonelderly (*n* = 176)	Elderly (*n* = 79)	Chi square value	*P* value
Conversion	5 (2.8%)	3 (3.8%)	0.000	0.987
Blood loss (ml)	170 (130-480)	150 (110-400)	-0.710	0.201
Surgical duration (min)	190 (140-270)	170 (130-290)	-0.581	0.128
Extent of pulmonary resection				
Lobectomy	136 (77.3%)	64 (81.0%)	0.451	0.502
Segmentectomy	21 (11.9%)	9 (11.4%)	0.015	0.902
Wedge resection	19 (10.8%)	6 (7.6%)	0.632	0.427
Patients with complications	34 (19.3%)	18 (23.7%)	0.404	0.525
Patients with major complications (Clavien-Dindo classification)	8 (4.5%)	5 (6.3%)	0.085	0.771
Complications				
Pneumonia	16 (9.0%)	9 (11.4%)	0.327	0.568
Prolonged air leak (more than 5 days)	9 (5.1%)	5 (6.3%)	0.009	0.923
Chylothorax	7 (4.0%)	4 (5.1%)	0.004	0.951
Respiratory insufficiency	5 (2.8%)	2 (2.6%)	0.000	1.000
Pulmonary embolism	3 (1.7%)	1 (1.3%)	0.000	1.000
Acute coronary syndrome	1 (0.6%)	1 (1.3%)	0.000	1.000
Acute heart failure	1 (0.6%)	1 (1.3%)	0.000	1.000
Atrial fibrillation	1 (0.6%)	2 (2.6%)	0.514	0.474
Postoperative hospital stay (days)	11 (6-49)	13 (7-49)		0.102

Table 3. Comparison of pathological outcomes of the two groups

	Nonelderly (*n* = 176)	Elderly (*n* = 79)	Chi square value	*P* value
Histological type				
Adenocarcinoma	94 (53.4%)	43 (54.4%)	0.023	0.880
Squamous cell carcinoma	61 (34.7%)	28 (35.4%)	0.015	0.903
Large cell carcinoma	21 (11.9%)	8 (10.1%)	0.176	0.675
Pathological stage			-0.081	0.935
IA	21 (11.9%)	10 (12.7%)		
IB	64 (36.3%)	27 (34.2%)		
IIA	48 (27.3%)	22 (27.8%)		
IIB	25 (14.2%)	13 (16.5%)		
IIIA	18 (10.2%)	7 (7.8%)		
Residual tumor			-0.404	0.686
R0	171 (97.2%)	76 (96.2%)		
R1	5 (2.8%)	3 (3.8%)		
R2	0 (0.0%)	0 (0.0%)		

have locoregional recurrence if it occurred in (1) the bronchial stump or cut-end of the lung parenchyma, (2) the ipsilateral pleura and/or chest wall, or (3) the ipsilateral hilar and/or mediastinal lymph nodes. Recurrence was defined as distant if it occurred in a separate lobe of the ipsilateral lung, contralateral thorax, supraclavicular lymph nodes, or in a distant organ. If distant recurrences were uncovered by systemic survey within a month after the detection of locoregional recurrence, these were defined as a concurrent distant and locoregional recurrence [21]. Overall survival (OS) was calculated from the date of surgery to the date of the last follow-up or death from any cause. Disease-free survival (DFS) was assessed from the date of surgery to the date of cancer recurrence or death from any cause. Follow-up was censored in March 2016.

All statistical analyses were performed using SPSS, Version 14.0 (SPSS Inc., Chicago, IL, USA). Normally distributed variables were analyzed by Student's t tests and presented as means and standard deviations. Non-normally distributed variables were analyzed using the Mann-Whitney U test and presented as medians and ranges. Differences between semi-quantitative results were analyzed using the Mann-Whitney U test. Differences between qualitative results were analyzed using chi-

Table 4. Risk factors of postoperative 30-day complications

Variable	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis Adjusted OR (95% CI)	*P* value
Age (≥70 years vs. <70 years)	1.211 (0.509-1.877)	0.157	-	-
Medical comorbidities (>2 vs. ≤2)	1.572 (1.139-2.587)	0.033	1.587 (1.141-2.821)	0.027
Operation time (≥240 min vs. <240 min)	1.844 (1.228-3.259)	0.021	1.229 (1.110-3.228)	0.038
Blood loss (≥300 ml vs. <300 ml)	0.748 (0.521-1.458)	0.099	-	-
Type of resection (lobectomy vs. sublobectomy)	1.160 (0.452-1.820)	0.229	-	-

square or Fisher's exact test, as appropriate. Independent risk factors for postoperative 30-day complications were evaluated using logistic regression analysis. Survival rates were analyzed using the Kaplan-Meier method, and differences between the two groups were analyzed using the log-rank test. Univariate analyses were performed to identify prognostic variables related to OS and DFS. Univariate variables with *P*-values <0.1 were selected for inclusion in the multivariate Cox proportional hazard regression model, and the adjusted odds ratios and their 95% confidence intervals (CI) were calculated. *P*-values <0.05 were considered statistically significant.

Results

The clinical characteristics of the 2 groups are summarized in **Table 1**. The median age of the elderly and nonelderly patients were 76 and 61 years, respectively. Both groups had a similar clinical stage at diagnosis, preoperative pulmonary functions, ASA scores, and sex distribution. However, the elderly group had higher rates of hypertension (*P* = 0.001) and type 2 diabetes mellitus (*P* = 0.014). Moreover, the proportion of patients with ≥2 medical comorbidities was significantly higher in the elderly group than in the nonelderly group (*P* = 0.009).

The overall conversion rate to open procedures was similar in both groups. The reasons for conversion included bleeding (*n* = 4) and massive adhesion (*n* = 4). The surgical variables did not significantly differ between the younger and older patient groups, including median estimated blood loss (*P* = 0.201) and median operating time (*P* = 0.128) (**Table 2**). Both groups had a similar rate and severity of 30-day complications during the postoperative period. The most common complication observed was pneumonia. The median length of hospital stay was significantly longer in the elderly population than in the nonelderly group (*P* = 0.01) (**Table 2**).

The final pathologic outcomes are summarized in **Table 3**. Adenocarcinoma was the most common malignancy observed in both groups; they had similar pathologic outcomes.

Table 4 shows the risk factors for postoperative 30-day complications in the whole cohort. Advanced age was not a statistically significant risk factor. However, multivariate analysis revealed that operation time ay was significantly longer rbidities were independent risk factors for postoperative 30-day complications (**Table 4**).

The follow-up duration was similar between the two groups. Altogether, there were 59 deaths during the follow-up period. No difference in OS was seen between the elderly and nonelderly groups (*P* = 0.212, **Figure 1**). Multivariate Cox regression analysis demonstrated that pathological N2 and T2 disease were significant predictors of poor OS (**Table 5**).

Among those who died, 51 died from lung cancer recurrence and 8 from causes unrelated to lung cancer. Recurrent tumors developed in 31.7% and 26.7% of the patients in the elderly and nonelderly groups, respectively (*P* = 0.186). No significant differences were observed in recurrence sites and times to first recurrence (**Table 6**). Locoregional recurrence was the most common recurrence pattern seen. No cases of port-site metastasis were noted in either group during the follow-up period.

Finally, there was no difference in the DFS rate between the two groups (**Figure 2**, *P* = 0.618). Multivariate analysis demonstrated that advanced T stage, poor cancer differentiation grade, and pathological N2 disease were associated with DFS (**Table 7**).

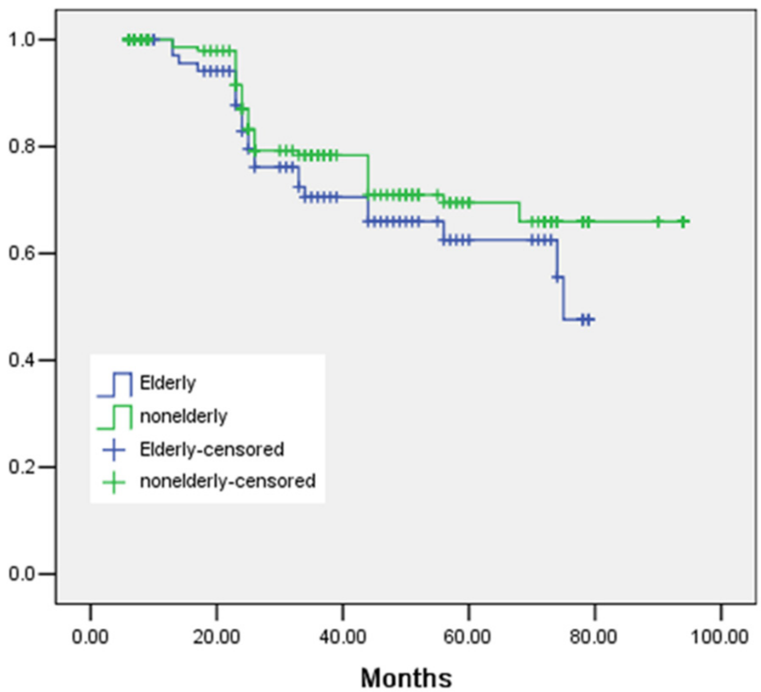

Figure 1. Comparison of overall survival rate between the nonelderly and elderly group (*P* = 0.212).

Table 5. Multivariate Cox regression analysis of overall survival

Regression variables	Adjusted hazard ratio	95% CI	Beta value	*P* value
Age			0.103	0.305
<70 years	1.000			
≥70 year	2.087	0.581-2.690		
Medical comorbidities				0.208
≤2	1.000			
>2	1.584	0.440-1.850	0.658	
Type of resection			0.258	0.695
Lobectomy	1.000			
Sublobectomy	1.289	0.580-1.690		
Operation time			0.540	0.269
<240 min	1.000			
≥240 min	1.360	0.402-1.590		
Blood loss			0.900	0.183
<300 ml	1.000			
≥300 ml	1.158	0.689-1.680		
ASA score				0.197
I-II	1.000			
III	1.109	0.700-1.419	0.615	
Differentiation grade			0.369	0.203
Good-Moderate	1.000			
Poor	1.258	0.690-1.680		
Pathological T stage			2.948	
T1	1.000	1.71-2.588		0.023
T2	2.351			
Pathological N stage			2.698	
N0-N1	1.000			
N2	3.848	1.489-4.892		0.018

Discussion

Radical pulmonary resection is currently the gold standard for treating patients with stage I and II NSCLC. However, it is a major surgical procedure with a reported overall morbidity rate ranging from 10-30% and a mortality rate of up to 8% [9]. Morbidity after radical pulmonary resection has been associated with various patient characteristics [9, 10], including ASA score, particularly if it is 3 or higher; advanced age; and presence of medical comorbidities [9, 10].

However, VATS has been shown to improve postoperative morbidity in selected cases, and, as a result, may be the preferred approach in elderly patients [3-5]. In a previous study, researchers examined outcomes in patients aged >70 years undergoing VATS and found no difference in complications rates, compared with nonelderly patients [22]. In our study, we demonstrated that VATS can be safely performed in elderly patients and that it is associated with a low morbidity rate. This is similar to results reported in open surgery series [3-5]. Furthermore, the elderly patients in our study did not have worse short-term outcomes than nonelderly patients [3-5]. In accordance with these findings, previous studies have reviewed the complications associated with radical pulmonary resection in elderly populations. Although the definition of elderly patients varied widely between the studies (65-80 years), a cut-off age of ≥70 years was used by most of them. These reviews reported that most studies found no relationship

Table 6. Comparison of cancer recurrence of the two groups

	Nonelderly (*n* = 176)	Elderly (*n* = 79)	Chi square value	*P* value
Overall recurrence *n*	47 (26.7%)	25 (31.6%)	0.657	0.418
Locoregional recurrence	29 (16.5%)	17 (21.5%)	0.937	0.333
Distant recurrence	13 (7.4%)	6 (7.6%)	0.003	0.593
Concurrent recurrence	5 (2.8%)	2 (2.6%)	0.000	1.000
Time to first recurrence (median)	18 months	15 months	0.360	0.090

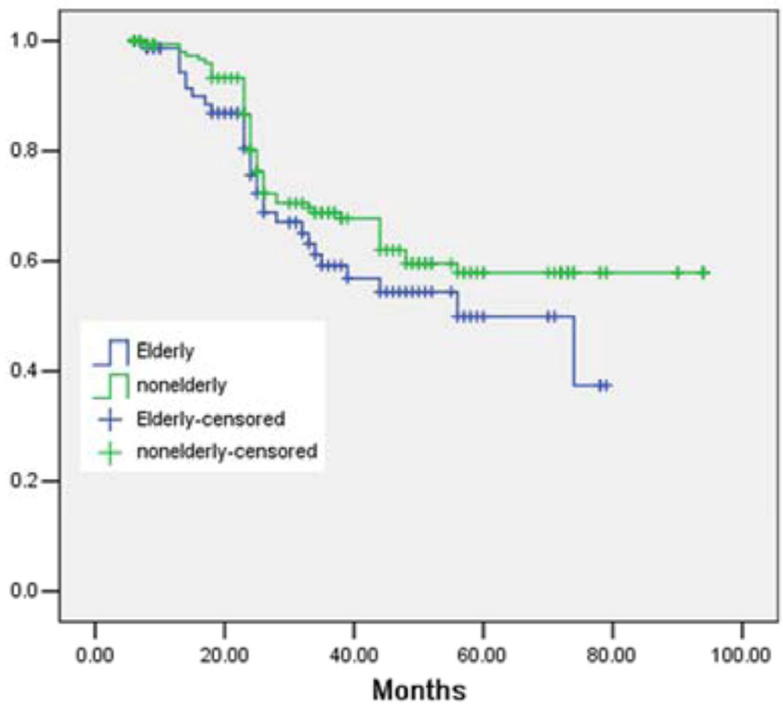

Figure 2. Comparison of disease-free survival rate between the nonelderly and elderly group (*P* = 0.618).

between the age at radical pulmonary resection and complication rates [3-5].

In our study, the postoperative 30-day complication rate was 20.3%, which is similar to data reported in other contemporary series [23-25]. Only 8 patients (3.1%) required conversions. Most complications were minor, such as pneumonia and prolonged air leakage, which is similar to previously reported complications in VATS series [23-27]. Recovery following VATS has been shown to have several benefits, including reduced blood loss, chest drain days, and postoperative opiate use [3-6]. Herein, we also observed a quicker recovery in both groups, compared with patients who underwent open surgery. However, our operative time was longer than that reported in previous studies [23-27]. In these studies, the procedure was generally performed by only one or two surgeons, whereas in our institution, they were performed by several different surgeons, which may explain the longer operative times. In addition, we included the initial "learning curve" surgeries, which had longer operative times.

The median number of hospital stays post-VATS were short in both groups, compared with that reported in previous reports [23-27]; the length of stay was significantly longer in the nonelderly group in our study however. Two patients from this group had major complications that required a 49-day hospital stay. Specifically, these two patients underwent secondary procedures and had significant past medical histories of coronary artery and chronic pulmonary disease requiring a prolonged stay. Furthermore, the hospital length of stay we observed in our study was likely longer because of the difference in the average stay for surgical patients between the Asian and Eastern healthcare systems. This difference depends on cultural and social factors, as well as on the financial aspects of the respective healthcare systems. In addition, we believe that this difference could also be explained by the initial surgeon learning curve for the VATS procedures, which led to higher complication rates. Most major complications that required a second procedure were observed during the early period of our experience (i.e., in the initial 50 cases).

Our long-term outcomes data showed no difference in OS and DFS between the groups. In most previous studies [23-27], the 5-year OS rate in patients aged difference in OS and DFS

Table 7. Multivariate Cox regression analyses of disease-free survival

Regression variables	Adjusted hazard ratio	95% CI	Beta value	*P* value
Age			0.259	0.108
<70 years	1.000			
≥70 years	1.540	0.581-1.897		
Medical comorbidities				0.364
≤2	1.000			
>2	1.258	0.568-1.540	0.198	
Type of resection Lobectomy	1.000		0.150	0.190
Sublobectomy	1.489	0.609-1.991		
Operation time			0.881	0.150
<240 min	1.000			
≥240 min	1.580	0.654-1.901		
Blood loss			0.751	0.201
<300 ml	1.000			
≥300 ml	1.187	0.880-1.521		
ASA score			0.742	0.374
I-II	1.000			
III	1.360	0.549-1.517		
Differentiation grade			0.645	0.190
Good-Moderate	1.000			
Poor	1.364	0.548-1.980		
Pathological T stage			2.410	0.017
T1	1.000	1.45-3.954		
T2	3.012			
Pathological N stage			1.597	0.007
N0-N1	1.000			
N2	2.357	1.577-3.570		

between the groups. In most previog-term survival of elderly patients has been reported to be slightly poorer than that of nonelderly patients, but it is still considerably long and acceptable. The authors of these previous studies suggested that this difference may be due to the more limited survival expectancy and higher prevalence of medical comorbidities in this population [23-30]. The present series supports this finding, even though the limited sample size may explain the absence of statistical differences in OS and DFS.

The major limitations of our study were the retrospective nature of the analysis, despite the prospective recording of the data. Moreover, due to the relatively short follow-up period and the acceptable prognosis of early-stage NSCLC, late recurrences were not detected in our series.

Conclusion

VATS appears feasible in elderly patients with NSCLC. It has acceptable short-term complications and long-term survival outcomes that are similar to those in nonelderly patients. These data suggest that advanced age should not be regarded as a contraindication for VATS in this patient population.

Acknowledgements

We sincerely thank our hospital colleagues who participated in this research.

Discourse of conflict of interest

None.

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