Int J Clin Exp Med 2015;8(8):13604-13609
www.ijcem.com /ISSN:1940-5901/IJCEM0009614

Original Article

Video-assisted thoracoscopic surgery for non-small-cell lung cancer is beneficial to elderly patients

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Received April 26, 2015; Accepted June 21, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: The aim of this study was to explore whether video-assisted thoracoscopic surgery (VATS) has short or long-term benefits in elderly patients with non-small-cell lung cancer compared with open surgery. Between June 2007 and December 2014, 579 patients older than 70 years underwent radical pulmonary resection for non-small-cell lung cancer, including 138 who received VATS and 441 who received open surgery. A retrospective pair-matched study was performed to compare 194 patients (97 pairs) who underwent either VATS or open resection. Patients were matched by age, sex, comorbidity, American Society of Anesthesiologists (ASA) score, tumor location, clinical TNM stage, and extent of pulmonary resection. Short and long-term outcomes were compared between the two groups. The overall incidence of postoperative 30-day complications was significantly lower in the VATS group than in the open surgery group. The major postoperative 30-day complication trended lower in the VATS group but was not significantly different. The length of postoperative hospital stay was significantly shorter. Kaplan–Meier analysis showed that 5-year disease-free survival and overall survival was similar between the two groups. In summary, in surgical management of elderly patients with non-small-cell lung cancer, VATS is associated with lower rates of morbidity as well as comparable disease-free survival and overall survival outcomes.

Keywords: Thoracic surgery, video-assisted, minimally invasive surgical procedures, carcinoma, non-small-cell lung, elderly patients, survival

Introduction

Radical pulmonary resection for operable non-small-cell lung cancer is a surgical procedure associated with high operative risk [1-3]. This operative risk may be more critical in elderly patients (≥70 years) [4-6]. It is imperative to explore a safer approach to minimize operative risk of elderly patients undergoing pulmonary resection for operable non-small-cell lung cancer. The technique of video-assisted thoracoscopic surgery (VATS) for non-small-cell lung cancer has been shown to be associated with better cosmetic results, shorter hospital stay, decreased blood loss, and improved quality of life [7-10]. However, previous studies were mainly focused on the general population [7-11]. Therefore, whether VATS could deliver similar short or long-term benefits to elderly patients of non-small-cell lung cancer remains uncertain. The aim of this study was to analyze short and long-term outcomes in elderly patients who underwent VATS or open surgery for non-small-cell lung cancer.

Methods

This study complied with the Declaration of Helsinki. This retrospective research was approved by our local ethics committees. The need for informed consent from patients was waived because of its retrospective nature.

Between June 2007 and December 2014, there were 579 patients older than 70 years who underwent pulmonary resection with radical intent for non-small-cell lung cancer in our institution, including 138 who received VATS and 441 who received open surgery. Patients who received neoadjuvant therapy or received bilobectomy or received extended resection were excluded. Using the remaining cohort, a retrospective pair-matched study was performed to compare 194 patients (97 pairs) who under-

Table 1. Patient data of the two groups

	VATS (*n*=97)	Open (*n*=97)	*P* value
Age (y)	74 (71-84)	73 (70-80)	0.150
Gender (Male:Female)	58:39	61:36	0.658
Comorbidity			0.947
Heart failure	4	3	
Hypertension	14	11	
Diabetes Mellitus	8	8	
Liver cirrhosis	3	4	
Atrial fibrillation	2	1	
Earlier myocardial infarction	1	2	
Tumor location			0.950
Left upper lobe	23	21	
Left lower lobe	31	29	
Right upper lobe	28	30	
Right lower lobe	15	17	
ASA score			0.623
I	63	66	
II	21	20	
III	13	11	
Clinical stage			0.663
IA	58	55	
IB	39	42	
Extent of pulmonary resection			0.536
Lobectomy	38	41	
Segmentectomy	34	35	
Wedge resection	25	21	

Table 2. The surgical and pathological outcomes of the two groups

	VATS (*n*=97)	Open (*n*=97)	*P* value
Operative time	150 (120-200)	130 (100-170)	0.015
Blood loss	140 (100-350)	190 (150-450)	0.020
Postoperative hospital stay	10 (7-25)	13 (10-31)	0.021
Histological type			0.590
Adenocarcinoma	48	53	
Squamous cell carcinoma	28	24	
Large cell carcinoma	11	14	
Adenosquamous cell carcinoma	10	6	
Pathological stage			0.689
IA	32	31	
IB	31	35	
IIA	11	14	
IIB	17	14	
IIIA	6	3	
Residual tumor			0.651
R0	94	95	
R1	3	2	
R2	0	0	

went either open surgery or VATS. Patients were matched by age, sex, comorbidity, American Society of Anesthesiologists (ASA) score, tumor location, clinical TNM stage, and extent of pulmonary resection. All patients were diagnosed with non-small-cell lung cancer by preoperative biopsy. Preoperative staging was determined mainly by enhanced thoracic and abdominal computerized tomography. Clinical stage I non-small-cell lung cancer patients were selected as candidates for operation. Physical examination, standard laboratory tests, electrocardiograms, and lung function tests were performed in all patients. The tumor TNM stage was based on the 7th edition of the TNM [12] classification of lung cancer, which was proposed by International Association for the Study of Lung Cancer (IASLC), Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC), and the mediastinal lymph node staging was based on the newest lymph node map proposed by IASLC [13]. For those of the patients operated before 2010, their TNM stage was recalculated to match the 7th edition of TNM classification of lung cancer proposed by UICC, AJCC and IASLC.

The operative technique of VATS with radical intent for non-small-cell lung cancer has been described elsewhere [14]. The procedure of open surgery was performed in a manner similar to VATS. Patients were retained overnight in the surgical intensive care unit (ICU) on continuous telemetry before being

Table 3. The post-operative complications of the two groups

	VATS (*n*=97)	Open (*n*=97)	*P* value
Post-operative 30-day complications	18	31	0.032
Pneumonia	4	10	
Pulmonary embolism	1	2	
Respiratory insufficiency	2	4	
Chylothorax	1	2	
Prolonged air leak (more than 5 days)	2	3	
Bronchopleural fistula	1	1	
Acute heart failure	2	2	
Acute coronary syndrome	1	2	
Atrial fibrillation	3	3	
Acute renal failure	1	2	
Severity of complications			0.068
Major (3, 4 and 5)	3	9	
Minor (1 and 2)	15	22	

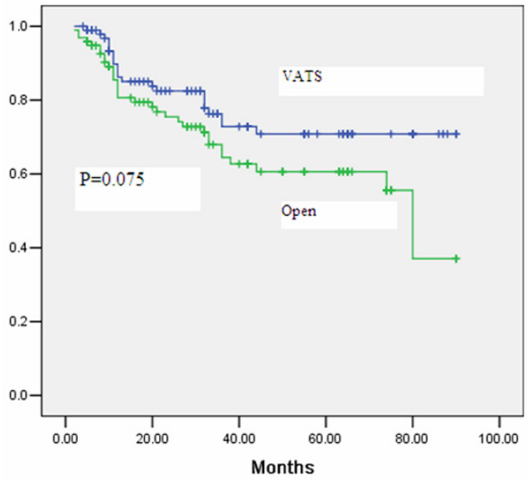

Figure 1. Overall survival time of the pair-matched population.

returned to the dedicated thoracic surgical ward on the first postoperative day. Morbidity, postoperative complications occurring within 30 postoperative days, was classified using Clavien-Dindo classification [15]. The definition of Clavien-Dindo system was as follows: Grade 1: oral medication or bedside medical care required; Grade 2: intravenous medical therapy required; Grade 3: radiologic, endoscopic, or operative intervention required; Grade 4: chronic deficit or disability associated with the event; and Grade 5: death related to surgical complication. Major complications were defined as grades 3, 4 and 5. Minor complications were classified as 1 and 2. Mortality was defined as death of any cause occurring within 30 postoperative days.

Follow-up data were collected from outpatient follow-up database. Adjuvant therapy was delivered to those who had pathological lymph node metastasis or pathological R1 resection with generally good performance. Patients were seen in the outpatient department every 3 months for the first postoperative year, every 4-5 months for the next 2 years, and then annually. The overall survival was calculated from the date of radical resection the last follow up or death of any cause. The disease-free survival was assessed from the date of radical resection until the date of cancer recurrence or death of any cause. The follow-up was closed in January 2015.

Data were presented as mean and standard deviations for variables following normal distribution and were analyzed by *t* test. For data following non-normal distribution, results were expressed as median and range and were compared by nonparametric test. Differences of semiquantitative results were analyzed by Mann-Whitney *U*-test. Differences of qualitative results were analyzed by chi-square tests or Fisher exact test as appropriate. Univariate analyses were performed to identify prognostic variables related to overall survival and disease-free survival. Univariate variables with probability values less than 0.10 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted odds ratios (HR) along with the corresponding 95% confidence intervals (CI) were calculated. $P<0.05$ was considered statistically significant. SPSS 13.0 (SPSS Inc., Chicago, IL, USA) was applied.

Results

After matching for age, sex, comorbidity, ASA score, tumor location, clinical TNM stage, and extent of pulmonary resection, 194 patients were eligible for review (**Table 1**).

The surgical and pathological outcomes were summarized in **Table 2**. There was no conversion to open lobectomy in cases performed

Table 4. Multivariate Cox regression analyses of overall survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Pathological T stage			
T1	1.00		
T2	1.69	0.58-1.22	0.098
T3	2.89	1.35-3.57	0.013
Pathological N stage			
N0	1.00		
N1	1.48	0.55-2.68	0.257
N2	2.78	1.80-4.16	0.032
Differentiation grade			
Good	1.00		
Moderate	1.54	0.47-1.52	0.436
Poor	2.05	1.54-3.00	0.002

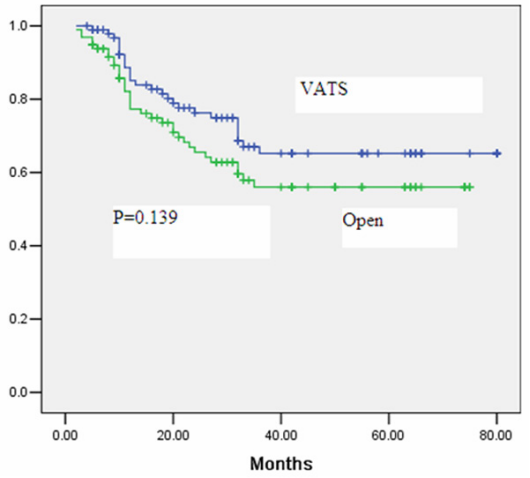

Figure 2. Disease-free survival time of the pair-matched population

VATS. There were no intraoperative or 30-day mortality occurred in our series. There was longer operative time in VATS group than in open group (*P*=0.015). There were no significant differences in pathological stage and residual tumor. Patients in the VATS group enjoyed significantly faster recovery, including less blood loss (*P*=0.020), and earlier hospital discharge (*P*=0.021).

The post-operative complications were reviewed in **Table 3**. Thirty-day morbidity was significantly lower in the VATS group than in the open surgery group (*P*= 0.032). When the severity of 30-day complications was compared, more complications were classified as major in patients underwent open resection, though the difference was not significant (*P*=0.068).

The median follow-up duration was 36 months. The follow-up duration was similar between the two groups. There was no difference in overall survival between VATS group and open group (**Figure 1**, *P*=0.075). Five-year overall survival was 70% in the VATS group compared with 60% in the open group. Multivariate Cox regression analysis of overall survival of all patients in the whole cohort was performed. Significant predictors of worse overall survival were advanced pathologic T3 stage, pathologic N2 disease, and tumors with poor differentiation (**Table 4**).

Five-year disease-free survival was similar between the two groups (**Figure 2**, *P*=0.139). Significant predictors of worse disease-free survival were pathologic N1 or N2 disease and angiolymphatic invasion (**Table 5**) in multivariate Cox regression analysis.

Discussion

Less blood loss, shorter length of hospital stay, fewer 30-day complications, better cosmetic results and comparable long-term survival outcomes were recorded among elderly patients treated with VATS in this pair-matched study.

Previous studies in large series of operable non-small-cell lung cancer patients showed that advanced age is a significant risk factor for surgical mortality [16-20]. However, Dell'Amore A and his colleagues [3] described a series of 319 patients older than 75 years and suggested that radical pulmonary resection could be performed in selected elderly patients with acceptable morbidity (48.6%) and mortality (6.6%). In China, Pei and his colleagues [4] reported that radical pulmonary resection could be carried out safely in patients over 70 years, with an in-hospital mortality of approximately 7.6% in their series of 240 patients older than 70 years vs. 3.3% for patients younger than 70 years.

VATS pulmonary resection is an emerging therapeutic option for non-small-cell lung cancer patients. Multicenter clinical trials have demonstrated VATS pulmonary resection is associated with better less blood loss, shorter length of hospital stay, more rapid postoperative recovery and better cosmetic results, and equally

Table 5. Multivariate Cox regression analyses of disease-free survival

Regression variables	Adjusted hazard ratio	95% CI	*P* value
Angiolymphatic invasion			
No	1.00		
Yes	2.66	1.54-3.18	0.028
Pathological N stage			
N0	1.00		
N1	1.55	0.15-2.68	0.038
N2	2.88	1.54-3.01	0.008

long-term oncologic outcomes compared with open pulmonary resection [7-11, 21-23]. However, these studies were performed in general population, not elderly population. In our series, we found that VATS pulmonary resection could be safely performed in elderly patients with low rate perioperative morbidity. Moreover, VATS approach lead to better short-term outcomes when compared with open surgery, such as better cosmetic results, less blood loss, a shorter postoperative hospital stay, fewer overall postoperative complications.

The analysis of disease-free and overall survival in matched patients found a trend longer in the VATS group but was not significantly different due to small sample size. We considered that there might be multiple reasons accounting for the potential survival advantage among elderly patients by VATS. Chiefly, elderly patients in the VATS group suffered significantly fewer postoperative complications, and even promising better quality of life, which may led to less immunologic suppression, thus increasing the patient's ability to scavenge residual cancer cells shed into the blood or lymphatics at pulmonary resection [24]. What's more, fewer traumas by VATS resection may lead to earlier administration of adjuvant therapy and better compliance of adjuvant therapy [25]. Furthermore, VATS is more costly than open resection. This may lead to patient selection such that the proportion of higher economic classes is greater in patients treated with VATS than that in those treated with open resection. Low economic class might potentially compromise postoperative care, general follow-up, and even adjuvant therapy. However, the detail mechanism needed to be researched in the future.

There are several limitations in our study. First, the decision whether the patient underwent open pulmonary resection or VATS was determined by multiple factors, such as available time and willingness of different surgeons for different patients, and economic and educational background of patients. Since this was a retrospective study, certain defects of this study were uncontrollable. Previously, the common approach for operable non-small-cell lung cancer in our institution was open approach. Since January 2006, we started applying VATS for early stage non-small-cell lung cancer. After slowly accumulating nearly 50 patients of early stage non-small-cell lung cancer, surgeons in our institution have gradually passed their learning curve. Hence, by pair-matching patients, we have attempted to eliminate selection bias as rigorously as possible outside of the setting of a randomized, prospective study. Second, due to the relatively short follow-up period and the acceptable prognosis of early stage non-small-cell lung cancer, later recurrence did not detected in our series.

In summary, compared with traditional open resection, successful utilization of VATS for non-small-cell lung cancer is associated with a reduced incidence of 30-day complications and a comparable survival outcome in elderly patients. In conclusion, a minimally invasive approach to pulmonary resection for non-small-cell lung cancer may be preferred in elderly patients, although further investigations are needed to confirm this conclusion.

Acknowledgements

We sincerely thank the patients, their families and our colleagues who participated in this research.

Disclosure of conflict of interest

None.

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References

[1] Su Q, Sun YP, Liu YH, Li Z, Yang HY, Sun ZG, Cao BW and Jia JH. Prognostic factors in older patients with advanced non-small cell lung cancer in China. Tumori 2014; 100: 69-74.

[2] Rena O, Massera F, Boldorini R, Papalia E, Turello D, Davoli F, Baietto G, Roncon A, Robustellini M and Casadio C. Non-small cell lung cancer in surgically treated women. Tumori 2013; 99: 661-666.
[3] Dell'Amore A, Monteverde M, Sanna S, Caroli G, Stella F, Dell'Amore D and Rocco G. Early and long-term results of pulmonary resection for non-small-cell lung cancer in patients over 75 years of age: a multi-institutional study. Interact Cardiovasc Thorac Surg 2013; 16: 250-256.
[4] Pei G, Zhou S, Han Y, Liu Z and Xu S. Risk factors for postoperative complications after lung resection for non-small cell lung cancer in elderly patients at a single institution in China. J Thorac Dis 2014; 6: 1230-1238.
[5] Qiao D, Wang Z, Lu Y, Wen X, Li H and Zhao H. A retrospective study of risk and prognostic factors in relation to lower respiratory tract infection in elderly lung cancer patients. Am J Cancer Res 2014; 5: 423-432.
[6] Bravo-Iñiguez C and Perez Martinez M, Armstrong KW and Jaklitsch MT. Surgical resection of lung cancer in the elderly. Thorac Surg Clin 2014; 24: 371-381.
[7] Tan Q, Huang J, Ding Z, Lin H, Lu S and Luo Q. Meta-analysis for curative effect of lobectomy and segmentectomy on non-small cell lung cancer. Int J Clin Exp Med 2014; 7: 2599-2604.
[8] Fan X, Zhang Z and Liu Y. Therapeutic efficacy and prognosis in the treatment of lung cancer by video-assisted thoracoscopic surgery. Chin Med J (Engl) 2014; 127: 2096.
[9] Oparka J, Yan TD, Ryan E and Dunning J. Does video-assisted thoracic surgery provide a safe alternative to conventional techniques in patients with limited pulmonary function who are otherwise suitable for lung resection? Interact Cardiovasc Thorac Surg 2013; 17: 159-162.
[10] Fang HY, Hsiao FY, Huang HC, Lin YS, Chen CY, Shieh SH, Chen PR, Chen CK and Chien CR. Cost and effectiveness of video-assisted thoracoscopic surgery for clinical stage I non-small cell lung cancer: a population-based analysis. J Thorac Dis 2014; 6: 1690-1696.
[11] Feng M, Shen Y, Wang H, Tan L, Mao X, Liu Y and Wang Q. Uniportal video assisted thoracoscopic lobectomy: primary experience from an Eastern center. J Thorac Dis 2014; 6: 1751-1756.
[12] Reck M, Heigener DF, Mok T, Soria JC and Rabe KF. Management of non-small-cell lung cancer: recent developments. Lancet 2013; 382: 709-719.
[13] Rusch VW, Asamura H, Watanabe H, Giroux DJ, Rami-Porta R, Goldstraw P; Members of IASLC Staging Committee. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009; 4: 568-577.
[14] Ramos R, Girard P, Masuet C, Validire P and Gossot D. Mediastinal lymph node dissection in early-stage non-small cell lung cancer: totally thoracoscopic vs thoracotomy. Eur J Cardiothorac Surg 2012; 41: 1342-1348; discussion 1348.
[15] Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, de Santibañes E, Pekolj J, Slankamenac K, Bassi C, Graf R, Vonlanthen R, Padbury R, Cameron JL and Makuuchi M. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009; 250: 187-196.
[16] Jaklitsch M and Billmeier S. Preoperative evaluation and risk assessment for elderly thoracic surgery patients. Thorac Surg Clin 2009; 19: 301-312.
[17] Rosen JE, Hancock JG, Kim AW, Detterbeck FC and Boffa DJ. Predictors of mortality after surgical management of lung cancer in the National Cancer Database. Ann Thorac Surg 2014; 98: 1953-1960.
[18] Onder G, D'Arco C, Fusco D and Bernabei R. Preoperative assessment and risk factors in the surgical treatment of lung cancer: the role of age. Rays 2004; 29: 407-411.
[19] Takiguchi Y, Sekine I, Iwasawa S, Kurimoto R and Tatsumi K. Chronic obstructive pulmonary disease as a risk factor for lung cancer. World J Clin Oncol 2014; 5: 660-666.
[20] Saha SP, Bender M, Ferraris VA and Davenport DL. Surgical treatment of lung cancer in octogenarians. South Med J 2013; 106: 356-361.
[21] Kim SJ, Lee YJ, Park JS, Cho YJ, Cho S, Yoon HI, Kim K, Lee JH, Jheon S and Lee CT. Changes in pulmonary function in lung cancer patients after video-assisted thoracic surgery. Ann Thorac Surg 2015; 99: 210-217.
[22] Suda K, Sato K, Mizuuchi H, Kobayashi Y, Shimoji M, Tomizawa K, Takemoto T, Iwasaki T, Sakaguchi M, Mitsudomi T. Recent evidence, advances, and current practices in surgical treatment of lung cancer. Respir Investig 2014; 52: 322-329.
[23] Korc-Grodzicki B, Downey RJ, Shahrokni A, Kingham TP and Patel SG, Audisio RA. Surgical considerations in older adults with cancer. Clin Oncol 2014; 32: 2647-253.
[24] Weiss J and Langer C. Treatment of lung cancer in the elderly patient. Semin Respir Crit Care Med 2013; 34: 802-809.
[25] Caprario LC and Strauss GM. The benefit of chemotherapy in elderly patients with small cell lung cancer. Expert Rev Anticancer Ther 2014; 14: 645-647.