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의학석사 학위논문

**Comparison of respiratory function
recovery in video-assisted thoracic
surgery and thoracotomy in patients
with lung cancer**

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비디오 흉강경 수술 및 개흉술에
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2014년 2월

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February 2014

**The Department of Medicine
Seoul National University
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Comparison of respiratory function recovery in video-assisted thoracic surgery and thoracotomy in patients with lung cancer

by

Tae Yeon Park

A thesis submitted to the Department of Medicine in partial fulfillment of the requirement of the Degree of Master of Science in Medicine (Internal medicine) at Seoul National University College of Medicine

February 2014

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ABSTRACT

Introduction: Lobectomy is standard treatment for early lung cancer, with lobectomy by thoracotomy and video-assisted thoracic surgery (VATS) as the most common types. Some studies have shown that VATS lobectomy enables faster recovery of respiratory function than does thoracotomy because the former involves making only a small incision in the chest to access the lung. However, these studies featured only short-term follow-up periods. We evaluated and compared the advantages of VATS lobectomy and thoracotomy in terms of recovery of pulmonary function in patients with early lung cancer. We increased the follow-up period and analyzed respiratory recovery rate during the late postoperative phase.

Methods: Data on 649 patients with early lung cancer who underwent VATS lobectomy and thoracotomy at Seoul University Hospital and Bundang Seoul University Hospital from January 2005 to December 2010 were retrospectively reviewed. We classified the patients into the VATS (n = 406) and thoracotomy groups (n = 243) and compared baseline characteristics, pulmonary function data including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak flow rate (PFR) at 3, 6, and 12 months after surgery.

Results: Among the 649 patients, the pulmonary function testing was conducted on 300, 497, and 362 cases at 3, 6, and 12 months after surgery and only 91 patients underwent all 3-, 6-, and 12-month pulmonary function tests. Repeated-measures analysis of covariance was performed on these 91 patients, and the 649 patients with missing data were analyzed by linear mixed effect

model. All confounding factors that may have affected pulmonary function recovery were adjusted. Of the 91 patients, the VATS group exhibited a better FVC than did the thoracotomy group ($p < 0.005$). After analyzing the 649 patients by linear mixed model, the VATS group also showed better FVC than that of the thoracotomy group and this effect had an interaction over time (103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$ at 6 months, 107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$ at 12 months). No significant differences were observed for in FEV_1 or PFR.

Conclusions: VATS lobectomy presented more advantages in terms of recovery of late postoperative FVC than did thoracotomy after surgery, but no significant group differences were observed in FEV_1 and PFR. Long-lasting postoperative pain after thoracotomy is thought to be the cause of this result.

Keywords: lung cancer, lobectomy, surgical method, pulmonary function test

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INTRODUCTION

Lobectomy is standard treatment for resectable nonsmall cell lung cancer (NSCLC), but such procedures typically diminish lung function for a few weeks or months after surgery. Such a decline in lung function is influenced by preoperative pulmonary function, size of the resected lung, and the functional characteristics of the resected lung (1). In addition, few studies have discussed the differences in lung function recovery enabled by various surgical methods.

Video-assisted thoracic surgery (VATS) and thoracotomy are widely used lobectomy procedures, but the former presents less postoperative pain and faster recovery because it entails making only a small incision in the chest to access the lung (2, 3). A number of studies have explored whether VATS patients exhibit superior recovery of lung function to that presented by patients who underwent thoracotomy (4, 5). Nakata et al. revealed that VATS lobectomy has advantageous effects on early postoperative pulmonary function (6). Although much progress has been made in research, previous studies have shown only early postoperative recovery of pulmonary function. We evaluated and compared the benefits that VATS lobectomy and thoracotomy provide in terms of pulmonary function recovery after lung cancer surgery by increasing the follow up period.

METHODS

1. Patients

We reviewed the medical records of 649 patients with clinical stage I or II resectable NSCLC who underwent lobectomy by VATS (n = 406) and thoracotomy (n = 243) at Seoul University Hospital and Bundang Seoul University Hospital from January 2005 to December 2010. The indications for VATS lobectomy were as follows: clinical stage I or II peripheral NSCLC; tumor < 5 cm in diameter. Only patients who satisfied the aforementioned preoperative indications were selected to compare the VATS group with the thoracotomy group. Patients who did not complete a postoperative follow-up pulmonary function test (PFT), had lung cancer with bronchial obstruction, and small cell lung cancer, as well as those who underwent sleeve lobectomy or bronchoplasty, bilobectomy, pneumonectomy, segmentectomy, or wedge resection were excluded. Data on age, sex, comorbidities, smoking history, pre and postoperative PFT, lung cancer stage, histology, and tumor location and size were collected.

2. Operative procedure

The latissimus dorsi and serratus anterior muscles were dissected during posterolateral thoracotomy. The thoracotomy was performed through the fourth or fifth intercostal space, and the two ribs were divided. VATS lobectomy was initiated by three incisions with rib sparing. Two incisions served as thoracoscopic ports and the third was an access thoracotomy incision made anteriorly in the fourth or fifth intercostal space. The latissimus dorsi was spared. Lymph node dissection was carried out in both the VATS and thoracotomy groups. The surgical approach was chosen based on clinical

attributes such as tumor size, patient age, general condition, and pulmonary function. The operative method was decided on by six attending thoracic surgeons who performed the operations.

3. Pulmonary function test

Pulmonary function data, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak flow rate (PFR), were collected at preoperative and postoperative phases (i.e., 3, 6, and 12 months before and after surgery).

4. Statistical analysis

We divided the patients into two groups based on the surgical method for analysis. Baseline characteristics were analyzed with the Student's *t*-test for continuous variables and the chi-square for categorical variables. A linear mixed model approach and repeated-measures analysis of covariance (ANCOVA) were performed to examine the relationship between surgical method and improvement in respiratory function over time. Factors that may have affected pulmonary function such as age, smoking history, history of lung disease, preoperative pulmonary function were included in the model and adjusted. Differences with a *p*-value < 0.05 were considered significant. The SPSS 19.0 statistical program (Chicago, IL, USA) was used for the analysis.

RESULTS

A total of 649 patients were analyzed. The VATS group included 406 cases and the thoracotomy group included 243 cases (Figure 1). Table 1 shows the baseline characteristics of the patients. No significant differences were found between the two groups, except those of sex, underlying lung disease, and PFR (Table 1). The most common histologic type was adenocarcinoma and stage I accounted for the highest percentage of progression. The VATS group included more patients with adenocarcinoma ($p < 0.001$) and stage I disease ($p < 0.001$). This group also exhibited smaller tumor sizes and a smaller number of dissected lymph nodes than those of the thoracotomy group (Table 2). Lung function after surgery at 3-, 6-, and 12-months was analyzed. Because postoperative pulmonary function is affected by which lobe is resected, postoperative FVC and FEV₁ are presented as percentages of predicted postoperative values in accordance with the formula of Nakahara (Figure 2) (7).

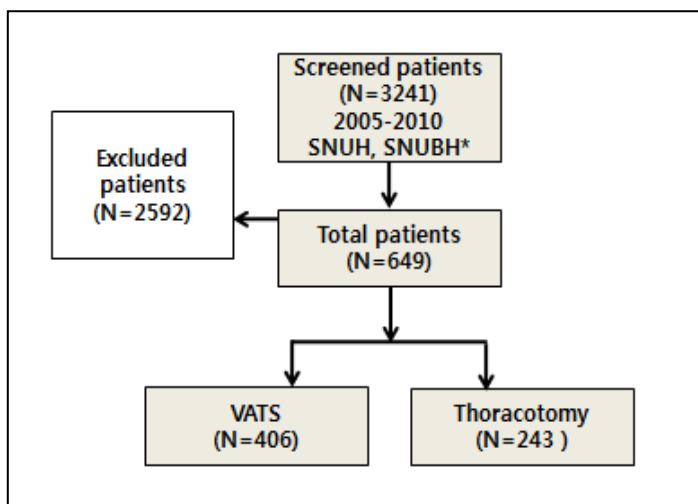


Figure 1. Flow chart for the study design

SNUH, Seoul University Hospital; SNUBH, Bundang Seoul University Hospital

The postoperative changes in PFR were evaluated as percentages of preoperative values. The pulmonary function test data cover 300 (VATS: 197, thoracotomy: 103), 497 (VATS: 320, thoracotomy: 177), and 362 (VATS: 241, thoracotomy: 121) cases for 3, 6, and 12 months after surgery, respectively. Only 91 patients have performed all the 3-, 6-, 12-month pulmonary function tests. Among these 91 patients, the VATS group accounted for 72 patients and the thoracotomy group accounted for 19.

Table 1. Comparison of the baseline characteristics*

	VATS (n= 406)	Thoracotomy (n = 243)	p value
Gender (male), no (%)	217 (53.4)	155 (63.8)	0.010
Age (year)	63.10 ± 9.69	63.65 ± 9.17	0.563
Preoperative pulmonary function			
FEV ₁ (L)	2.46 ± 0.61	2.43 ± 0.63	0.750
FVC (L)	3.44 ± 0.85	3.48 ± 0.85	0.858
FEV ₁ /FVC (%)	71.95 ± 9.72	70.62 ± 10.88	0.182
Peak flow rate (%)	112.18 ± 21.98	107.63 ± 24.08	0.030
Current or ex- smoker, no. (%)	175 (43.1)	121 (49.8)	0.098
Pack year	15.16 ± 23.25	19.07 ± 25.43	0.030
Comorbidities, no. (%)			
DM	45 (11.1)	29 (11.9)	0.741
HTN	115 (28.3)	63 (25.9)	0.507
Lung disease	54 (13.3)	52 (21.4)	0.007
Heart disease	28 (6.9)	11(4.5)	0.219

*Data are mean ± standard deviation or no. (%).

Table 2. Pathology and staging*

	VATS (n = 406)	Thoracotomy (n = 243)	p value
Tumor size (cm)	2.21 ± 0.99	2.72 ± 1.12	0.010
No. of dissected lymph nodes	21.39 ± 10.81	25.38 ± 13.39	0.001
Pathology, no. (%)			<0.001
Adenocarcinoma	329 (81)	148 (60.9)	
Squamous cell carcinoma	52 (12.8)	72 (29.6)	
Others	25(6.2)	23 (9.5)	
Pathological staging, no. (%)			<0.001
Ia	308 (75.9)	135 (55.6)	
Ib	62(15.3)	65 (26.7)	
IIa	36 (8.9)	43 (17.7)	

*Data are mean ± standard deviation or no. (%).

Predicted value (mL)=
preoperative value (mL) x (19 - the number of resected segment)/19

The number of segments in each lobe was defined as follows:
right upper lobe: 3, right middle lobe: 2, right lower lobe: 5,
left upper lobe: 5, left lower lobe: 4

Predicted recovery of lung function
=Post OP value(ml)/ Predicted value (ml) (%)

Figure 2. Formula for respiratory function recovery prediction

Table 3 shows the baseline characteristics of the 91 patients. The repeated-measures ANCOVA analysis showed that the VATS group exhibited a better FVC than did the thoracotomy group. At 3 months, 6 months, and 12 months after surgery, the recovery rate of FVC in the VATS group was $107.99 \pm 14.56\%$, $113.97 \pm 15.98\%$, $117.82 \pm 16.90\%$ for each and in thoracotomy group, the rates were 93.84 ± 20.34 , 98.37 ± 18.91 , 100.66 ± 17.69 for each ($F = 13.527$, $p < 0.005$). No interaction effect was observed between surgical method and time ($F = 1.297$, $p = 0.276$) (Table 4). Except for the FVC, no significant differences were found on the PFTs between the two groups after surgery (Table 4).

Table 3. Baseline characteristics of the 91 patients*

	VATS (n = 72)	Thoracotomy (n = 19)	p value
Gender (male), no (%)	38 (52.8)	13 (68.4)	0.222
Age (year)	63.33 ± 10.06	63.37 ± 11.02	0.564
Preoperative pulmonary function			
FEV ₁ (L)	2.41 ± 0.54	2.21 ± 0.62	0.276
FVC (L)	3.37 ± 0.71	3.28 ± 0.91	0.025
FEV ₁ /FVC (%)	71.74 ± 10.03	68.74 ± 12.97	0.241
Peak flow rate (%)	109.57 ± 21.88	99.58 ± 24.87	0.326
Current or ex-smoker, no. (%)	33 (45.8)	10 (52.6)	0.598
Pack year	16.88 ± 24.49	18.68 ± 20.67	0.630
Comorbidities, no. (%)			
DM	8 (11.1)	1 (5.3)	0.448
HTN	22 (30.6)	8 (42.1)	0.341
Lung disease	13 (18.1)	6 (31.6)	0.197
Heart disease	8 (11.1)	1 (5.3)	0.448

*Data are mean \pm standard deviation or no. (%).

Table 4. Comparison of respiratory function recovery * (n = 91)

Variable	N	3 month M ± SD [†]	6month M ± SD	12 month M ± SD	Group * Time					
					F	P				
VATS	72	108.09 ± 14.87	113.49 ± 106.96	115.40 ± 17.45	Group	3.413	0.068			
								Time	4.017	0.022
VATS	72	107.99 ± 14.56	113.97 ± 15.98	117.82 ± 16.90	Group	13.527	<0.005			
								Time	1.472	0.232
Thoracotomy	19	100.77 ± 17.86	106.96 ± 19.05	108.85 ± 19.50	Group	0.019	0.891			
								Time	1.153	0.318

* Repeated-measures analysis of covariance

† Mean ± standard deviation

All patients with missing data ($n = 649$) were analyzed using a linear mixed effect model (LME). We considered the interaction over the time to evaluate the differences of lung function recovery rate according to surgical method and adjusted for factors that may have affected the pulmonary function recovery, including age, sex, smoking, preoperative FEV₁, and history of lung disease. The results of the LME-based analysis are shown in Tables 5 and 6. No time-dependent effects in FEV₁ or PFR were observed after the LME was conducted. After adjusting for confounding factors, overall recovery of FEV₁ was 2.60% higher in the VATS group than that in the thoracotomy group, but it is not significant ($p = 0.0834$). Similarly, PFR was not significant ($p = 0.5415$). However, a significant group \times time interaction for recovery rate of FVC was observed ($p = 0.0453$), suggesting that the recovery rate in the VATS group improved over time. A post-hoc analysis was performed to compare the difference at the point of time and the adjusted p-value is presented after using Bonferroni method. The recovery rate of FVC in VATS groups was 4.0% higher than that of thoracotomy group 3 months after surgery, but the difference was not significant (98.25 ± 1.32 vs. 94.24 ± 1.60 , $p = 0.0762$). The recovery rate of FVC was 7.29% higher (103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$) and 6.73% higher (107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$) at 6 and 12 months than those in the thoracotomy group (Table 6 and Figure 3).

Table 5. Estimated postoperative recovery rate in forced expiratory volume in 1 sec (FEV₁) and peak flow rate (PFR)

	Surgical method	LSMEANS * ± SE	p-value
FEV₁ (%)	VATS	104.12 ± 1.19	0.0834
	Thoracotomy	101.52 ± 1.37	
PFR (%)	VATS	83.77 ± 0.86	0.5415
	Thoracotomy	83.10 ± 0.99	

* Least squares means, analyzed by linear mixed model effect

Table 6. Estimated postoperative forced vital capacity (FVC) recovery rate over time

Time	Surgical method	LSMEANS * ± SE	p-value†
3 month after lobectomy	VATS	98.25 ± 1.32	0.0762
	Thoracotomy	94.24 ± 1.60	
6 month after lobectomy	VATS	103.66 ± 1.27	<0.0001
	Thoracotomy	96.37 ± 1.49	
12 month after lobectomy	VATS	107.01 ± 1.30	0.0003
	Thoracotomy	100.28 ± 1.54	

* Least square means, analyzed by linear mixed model effect

† Adjusted p-value by Bonferroni method

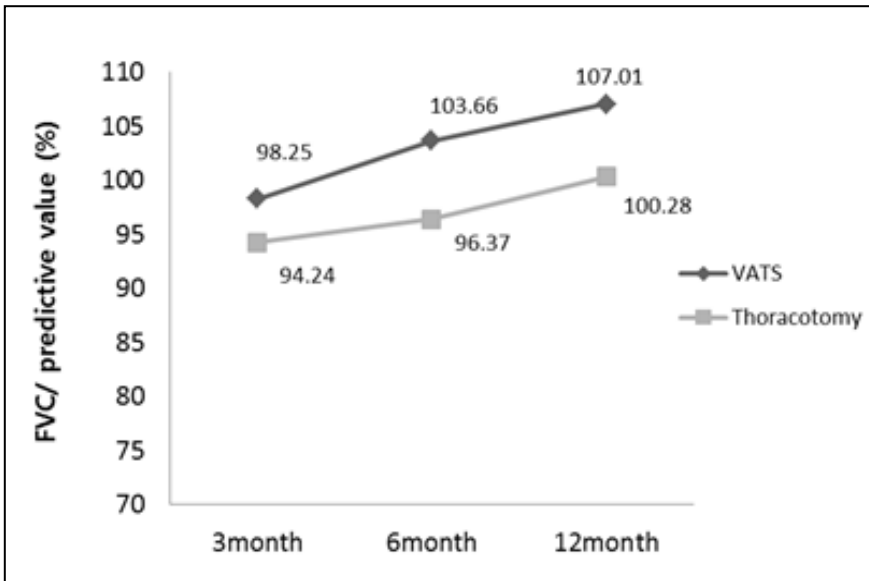


Figure 3. Postoperative changes in forced vital capacity (FVC) over time

DISCUSSION

Lobectomies are frequently applied procedures for patients with lung cancer and thoracotomy is the standard method. However, the frequency of VATS lobectomy has increased, driving researchers to compare the advantages and disadvantages of these two surgical procedures. Thoracotomy enables access through a suitable surgical area, but it requires dissecting the thoracic muscles and ribs (8). VATS lobectomy involves fewer incisions, presents less postoperative pain, and enables faster recovery of respiratory function than does thoracotomy (2-4, 9). Therefore, the recovery of pulmonary function proceeds more quickly in patients who undergo VATS than that in patients who undergo thoracotomy. Nakata et al. compared the oxygenation degree and recovery of FEV₁ and FVC in 21 patients who underwent VATS or thoracotomy, and found that the recovery of pulmonary function and oxygenation in the VATS group was superior to that in the thoracotomy group during the early postoperative period (6). However, no significant differences were found between the two groups 1 year after surgery. Qiang et al. verified pulmonary function in 102 patients with lung cancer at 1, 3, 7, 30, and 90 days after lobectomy (10), and derived similar results. FVC recovery was delayed by up to 3 months after lobectomy in the thoracotomy group. The treatment appeared to have achieved superior FEV₁ recovery, but no significant difference was found between the VATS and thoracotomy groups. The authors also measured pain scores on pre and postoperative days 1, 3, 7, 30, and 90, and revealed that the pain score was significantly lower in the VATS group for up to a 3-month period. However, these previous studies only confirmed respiratory recovery during the early postoperative period. In this study, the recovery of lung function during the late postoperative phase

was analyzed. The FEV₁ was not significantly different according to surgical method over the time by analyzed by the repeated-measures ANCOVA and linear mixed effect model. The FEV₁ recovery rate reached the predicted postoperative value at 3 months in both the VATS and thoracotomy groups. These results are consistent with previous findings, indicating that the remaining lobe may need up to 3 months of adaptation or adjustment (11, 12). PFR reflects the change in a relatively large airway, but it did not reach the previous level and was not different. This result may have been due to removal of the large airway during the lobectomy. FVC recovery rate tended to be better in the VATS group than that in the thoracotomy group and the changes in lung function recovery over time were significant by the linear mixed model. The recovery rate of FVC did not reach the predicted 100% value until 12 months in the thoracotomy group. Although we did not collect pain data, we believe that the pain after thoracotomy lasts much longer after lobectomy compared to that after VATS. One study demonstrated that long-term post-thoracotomy pain may persist for 12 months. The incidence rate of post-thoracotomy pain is 80% at 3 months, 75% at 6 months, and 61% one year (13). Another study suggested a relationship between postoperative pain and FVC recovery (10). Because the quality of life after lobectomy is important for patients with lung cancer, VATS lobectomy can be a more favorable procedure for patients requiring lobectomy. It can be particularly beneficial for elderly patients and patients with poor pulmonary function test results. However, VATS has a limitation for suitable surgical area compared to thoracotomy. Thus, the selection of a surgical method should be based on the advantages and disadvantages of each approach and determined by clinical significance.

This study had some limitations that may be viewed as starting points for future research. Because lung perfusion scans were not performed, the exact

postoperative lung function could not be predicted. Nevertheless, checking perfusion scans would not have generated a huge difference in results because we used a formula suitable for resected lobes. Furthermore, retrospective data were used and propensity score matching was not used due to the large amount of missing data. Thus, the patients in the two groups were not perfectly matched. In addition, pre-operative lung function can affect recovery rate. To overcome these limitations, we chose an appropriate statistical model, and confounding factors were adjusted. Overall, the FVC recovery was better in the VATS group than that in the thoracotomy group, but the number of patients who has all serial PFT data was small ($n = 91$) and a group \times time interaction was not observed. However, the analysis of all 649 patients showed a group \times time interaction. This discrepancy occurred due to the number of patients. Despite these limitations, our study features a greater number of patients and provides confirmed results for long-term lung function according to surgical method.

CONCLUSION

VATS lobectomy presented more advantages for recovery of late postoperative FVC after surgery than does thoracotomy after surgery. We hypothesize that pain after thoracotomy is more severe than that experienced after VATS lobectomy; such pain may persist for quite a long period and may affect the recovery rate of FVC. Further prospective studies will be necessary due to the limitations of this retrospective study.

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국문 초록

서론 폐엽 절제술은 조기 폐암의 기본적인 치료이며, 폐엽 절제술에는 비디오 흉강경 수술 혹은 개흉술이 가장 많이 쓰인다. 몇몇 연구에서는, 수술 시 절개창이 작은 비디오 흉강경 그룹이 호흡 기능의 회복에 있어 흉강경 보다 양호함을 보여 주었다. 그러나 이들 연구는 수술 후 조기 폐기능만을 본 연구가 대부분이었다. 이 연구의 목적은 비디오 흉강경 수술과 개흉술에서 폐기능 회복을 비교하는 것으로, 추적 관찰 기간을 늘려 수술 후 후기 폐기능을 관찰하고 분석하였다.

방법 2005 년 1월부터 2010년 12월 까지 조기폐암으로 서울대병원 및 분당 서울대병원에 입원하여 비디오 흉강경 수술 및 개흉술을 받은 환자 649 명의 데이터를 후향적으로 분석하였다. 이 환자들을 비디오 흉강경 군 (n=406) 과 개흉술 (n=243) 군으로 나누어 기본 특성, 수술 전 및 수술 후 3개월, 6개월, 12개월 째 강제 폐활량 및 1초간 강제 호기량, 최대 호기속도의 차이를 비교하였다.

결과 649 명의 환자 중에서 수술 후 폐기능 검사는 3개월, 6개월 12개월째 각각 300, 497, 362 건이 시행되었고, 91명만이 3개월, 6개월, 12개월 자료를 모두 가지고 있었다. 이 91 명의 환자에는 반복 측정 공분산 분석을, 결측치가 있는 649 명의 환자에게는 선형 혼합 모델을 이용하여 결과를 분석하였다. 폐기능 회복에 영향을 미칠 수 있는, 다른 혼란 변수들은 보정되었다. 91 명의 환자를 반복 측정

공분산 분석으로 분석하였을 때, 비디오 흉강경 그룹은 흉강경 그룹에 비해 강제 폐활량 회복률이 양호함을 보여 주었다 ($p < 0.005$). 649 명의 환자를 선형 혼합 모형으로 분석한 경우에도, 비디오 흉강경 그룹은 흉강경 그룹보다 강제 폐활량 회복률이 양호함을 보여주었고, 각 군에서 이러한 강제 폐활량 회복률의 변화 정도는 시간에 따른 차이가 있었다 (6개월; 103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$, 12개월; 107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$). 그러나, 1초간 강제 호기량 및 최대 호기속도 회복률은 수술 방법에 따른 유의한 차이는 없었다.

결론 비디오 흉강경 수술은 수술 후 후기 강제 폐활량 회복에 있어서 개흉술보다 양호한 회복을 보이지만, 1초간 강제 호기량 및 최대 호기속도 회복률은 수술 방법에 따른 차이는 보이지 않았다. 개흉술 후에 지속되는 수술 후 통증이 이러한 결과의 원인일 것으로 생각된다.

주요어 : 폐암, 폐엽 절제술, 수술 방법, 폐기능

학번 : 2012-21690



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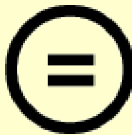
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의학석사 학위논문

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**Comparison of respiratory function
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February 2014

**The Department of Medicine
Seoul National University
College of Medicine
Tae Yeon Park**

Comparison of respiratory function recovery in video-assisted thoracic surgery and thoracotomy in patients with lung cancer

by

Tae Yeon Park

A thesis submitted to the Department of Medicine in partial fulfillment of the requirement of the Degree of Master of Science in Medicine (Internal medicine) at Seoul National University College of Medicine

February 2014

Approved by Thesis Committee:

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Professor _____ Vice chairman

Professor _____

폐암 환자에서
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ABSTRACT

Introduction: Lobectomy is standard treatment for early lung cancer, with lobectomy by thoracotomy and video-assisted thoracic surgery (VATS) as the most common types. Some studies have shown that VATS lobectomy enables faster recovery of respiratory function than does thoracotomy because the former involves making only a small incision in the chest to access the lung. However, these studies featured only short-term follow-up periods. We evaluated and compared the advantages of VATS lobectomy and thoracotomy in terms of recovery of pulmonary function in patients with early lung cancer. We increased the follow-up period and analyzed respiratory recovery rate during the late postoperative phase.

Methods: Data on 649 patients with early lung cancer who underwent VATS lobectomy and thoracotomy at Seoul University Hospital and Bundang Seoul University Hospital from January 2005 to December 2010 were retrospectively reviewed. We classified the patients into the VATS (n = 406) and thoracotomy groups (n = 243) and compared baseline characteristics, pulmonary function data including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak flow rate (PFR) at 3, 6, and 12 months after surgery.

Results: Among the 649 patients, the pulmonary function testing was conducted on 300, 497, and 362 cases at 3, 6, and 12 months after surgery and only 91 patients underwent all 3-, 6-, and 12-month pulmonary function tests. Repeated-measures analysis of covariance was performed on these 91 patients, and the 649 patients with missing data were analyzed by linear mixed effect

model. All confounding factors that may have affected pulmonary function recovery were adjusted. Of the 91 patients, the VATS group exhibited a better FVC than did the thoracotomy group ($p < 0.005$). After analyzing the 649 patients by linear mixed model, the VATS group also showed better FVC than that of the thoracotomy group and this effect had an interaction over time (103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$ at 6 months, 107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$ at 12 months). No significant differences were observed for in FEV_1 or PFR.

Conclusions: VATS lobectomy presented more advantages in terms of recovery of late postoperative FVC than did thoracotomy after surgery, but no significant group differences were observed in FEV_1 and PFR. Long-lasting postoperative pain after thoracotomy is thought to be the cause of this result.

Keywords: lung cancer, lobectomy, surgical method, pulmonary function test

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INTRODUCTION

Lobectomy is standard treatment for resectable nonsmall cell lung cancer (NSCLC), but such procedures typically diminish lung function for a few weeks or months after surgery. Such a decline in lung function is influenced by preoperative pulmonary function, size of the resected lung, and the functional characteristics of the resected lung (1). In addition, few studies have discussed the differences in lung function recovery enabled by various surgical methods.

Video-assisted thoracic surgery (VATS) and thoracotomy are widely used lobectomy procedures, but the former presents less postoperative pain and faster recovery because it entails making only a small incision in the chest to access the lung (2, 3). A number of studies have explored whether VATS patients exhibit superior recovery of lung function to that presented by patients who underwent thoracotomy (4, 5). Nakata et al. revealed that VATS lobectomy has advantageous effects on early postoperative pulmonary function (6). Although much progress has been made in research, previous studies have shown only early postoperative recovery of pulmonary function. We evaluated and compared the benefits that VATS lobectomy and thoracotomy provide in terms of pulmonary function recovery after lung cancer surgery by increasing the follow up period.

METHODS

1. Patients

We reviewed the medical records of 649 patients with clinical stage I or II resectable NSCLC who underwent lobectomy by VATS (n = 406) and thoracotomy (n = 243) at Seoul University Hospital and Bundang Seoul University Hospital from January 2005 to December 2010. The indications for VATS lobectomy were as follows: clinical stage I or II peripheral NSCLC; tumor < 5 cm in diameter. Only patients who satisfied the aforementioned preoperative indications were selected to compare the VATS group with the thoracotomy group. Patients who did not complete a postoperative follow-up pulmonary function test (PFT), had lung cancer with bronchial obstruction, and small cell lung cancer, as well as those who underwent sleeve lobectomy or bronchoplasty, bilobectomy, pneumonectomy, segmentectomy, or wedge resection were excluded. Data on age, sex, comorbidities, smoking history, pre and postoperative PFT, lung cancer stage, histology, and tumor location and size were collected.

2. Operative procedure

The latissimus dorsi and serratus anterior muscles were dissected during posterolateral thoracotomy. The thoracotomy was performed through the fourth or fifth intercostal space, and the two ribs were divided. VATS lobectomy was initiated by three incisions with rib sparing. Two incisions served as thoracoscopic ports and the third was an access thoracotomy incision made anteriorly in the fourth or fifth intercostal space. The latissimus dorsi was spared. Lymph node dissection was carried out in both the VATS and thoracotomy groups. The surgical approach was chosen based on clinical

attributes such as tumor size, patient age, general condition, and pulmonary function. The operative method was decided on by six attending thoracic surgeons who performed the operations.

3. Pulmonary function test

Pulmonary function data, including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak flow rate (PFR), were collected at preoperative and postoperative phases (i.e., 3, 6, and 12 months before and after surgery).

4. Statistical analysis

We divided the patients into two groups based on the surgical method for analysis. Baseline characteristics were analyzed with the Student's *t*-test for continuous variables and the chi-square for categorical variables. A linear mixed model approach and repeated-measures analysis of covariance (ANCOVA) were performed to examine the relationship between surgical method and improvement in respiratory function over time. Factors that may have affected pulmonary function such as age, smoking history, history of lung disease, preoperative pulmonary function were included in the model and adjusted. Differences with a *p*-value < 0.05 were considered significant. The SPSS 19.0 statistical program (Chicago, IL, USA) was used for the analysis.

RESULTS

A total of 649 patients were analyzed. The VATS group included 406 cases and the thoracotomy group included 243 cases (Figure 1). Table 1 shows the baseline characteristics of the patients. No significant differences were found between the two groups, except those of sex, underlying lung disease, and PFR (Table 1). The most common histologic type was adenocarcinoma and stage I accounted for the highest percentage of progression. The VATS group included more patients with adenocarcinoma ($p < 0.001$) and stage I disease ($p < 0.001$). This group also exhibited smaller tumor sizes and a smaller number of dissected lymph nodes than those of the thoracotomy group (Table 2). Lung function after surgery at 3-, 6-, and 12-months was analyzed. Because postoperative pulmonary function is affected by which lobe is resected, postoperative FVC and FEV₁ are presented as percentages of predicted postoperative values in accordance with the formula of Nakahara (Figure 2) (7).

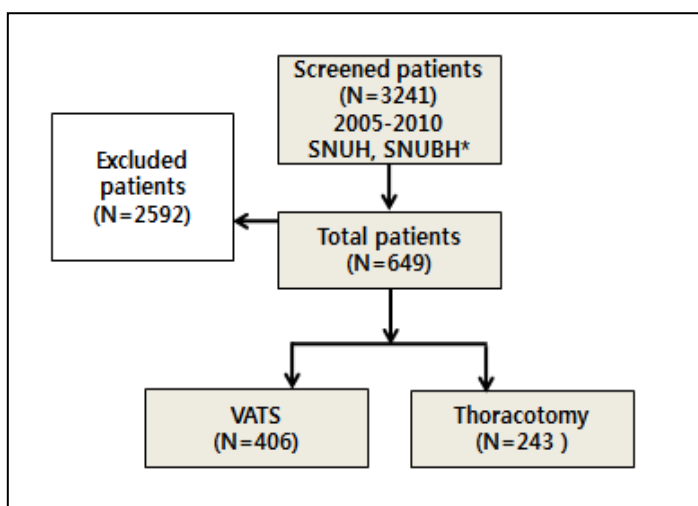


Figure 1. Flow chart for the study design

SNUH, Seoul University Hospital; SNUBH, Bundang Seoul University Hospital

The postoperative changes in PFR were evaluated as percentages of preoperative values. The pulmonary function test data cover 300 (VATS: 197, thoracotomy: 103), 497 (VATS: 320, thoracotomy: 177), and 362 (VATS: 241, thoracotomy: 121) cases for 3, 6, and 12 months after surgery, respectively. Only 91 patients have performed all the 3-, 6-, 12-month pulmonary function tests. Among these 91 patients, the VATS group accounted for 72 patients and the thoracotomy group accounted for 19.

Table 1. Comparison of the baseline characteristics*

	VATS (n= 406)	Thoracotomy (n = 243)	p value
Gender (male), no (%)	217 (53.4)	155 (63.8)	0.010
Age (year)	63.10 ± 9.69	63.65 ± 9.17	0.563
Preoperative pulmonary function			
FEV ₁ (L)	2.46 ± 0.61	2.43 ± 0.63	0.750
FVC (L)	3.44 ± 0.85	3.48 ± 0.85	0.858
FEV ₁ /FVC (%)	71.95 ± 9.72	70.62 ± 10.88	0.182
Peak flow rate (%)	112.18 ± 21.98	107.63 ± 24.08	0.030
Current or ex- smoker, no. (%)	175 (43.1)	121 (49.8)	0.098
Pack year	15.16 ± 23.25	19.07 ± 25.43	0.030
Comorbidities, no. (%)			
DM	45 (11.1)	29 (11.9)	0.741
HTN	115 (28.3)	63 (25.9)	0.507
Lung disease	54 (13.3)	52 (21.4)	0.007
Heart disease	28 (6.9)	11(4.5)	0.219

*Data are mean ± standard deviation or no. (%).

Table 2. Pathology and staging*

	VATS (n = 406)	Thoracotomy (n = 243)	p value
Tumor size (cm)	2.21 ± 0.99	2.72 ± 1.12	0.010
No. of dissected lymph nodes	21.39 ± 10.81	25.38 ± 13.39	0.001
Pathology, no. (%)			<0.001
Adenocarcinoma	329 (81)	148 (60.9)	
Squamous cell carcinoma	52 (12.8)	72 (29.6)	
Others	25(6.2)	23 (9.5)	
Pathological staging, no. (%)			<0.001
Ia	308 (75.9)	135 (55.6)	
Ib	62(15.3)	65 (26.7)	
IIa	36 (8.9)	43 (17.7)	

*Data are mean ± standard deviation or no. (%).

<p>Predicted value (mL)= preoperative value (mL) x (19 - the number of resected segment)/19</p> <p>The number of segments in each lobe was defined as follows: right upper lobe: 3, right middle lobe: 2, right lower lobe: 5, left upper lobe: 5, left lower lobe: 4</p> <p>Predicted recovery of lung function =Post OP value(ml)/ Predicted value (ml) (%)</p>
--

Figure 2. Formula for respiratory function recovery prediction

Table 3 shows the baseline characteristics of the 91 patients. The repeated-measures ANCOVA analysis showed that the VATS group exhibited a better FVC than did the thoracotomy group. At 3 months, 6 months, and 12 months after surgery, the recovery rate of FVC in the VATS group was $107.99 \pm 14.56\%$, $113.97 \pm 15.98\%$, $117.82 \pm 16.90\%$ for each and in thoracotomy group, the rates were 93.84 ± 20.34 , 98.37 ± 18.91 , 100.66 ± 17.69 for each ($F = 13.527$, $p < 0.005$). No interaction effect was observed between surgical method and time ($F = 1.297$, $p = 0.276$) (Table 4). Except for the FVC, no significant differences were found on the PFTs between the two groups after surgery (Table 4).

Table 3. Baseline characteristics of the 91 patients*

	VATS (n = 72)	Thoracotomy (n = 19)	p value
Gender (male), no (%)	38 (52.8)	13 (68.4)	0.222
Age (year)	63.33 ± 10.06	63.37 ± 11.02	0.564
Preoperative pulmonary function			
FEV ₁ (L)	2.41 ± 0.54	2.21 ± 0.62	0.276
FVC (L)	3.37 ± 0.71	3.28 ± 0.91	0.025
FEV ₁ /FVC (%)	71.74 ± 10.03	68.74 ± 12.97	0.241
Peak flow rate (%)	109.57 ± 21.88	99.58 ± 24.87	0.326
Current or ex-smoker, no. (%)	33 (45.8)	10 (52.6)	0.598
Pack year	16.88 ± 24.49	18.68 ± 20.67	0.630
Comorbidities, no. (%)			
DM	8 (11.1)	1 (5.3)	0.448
HTN	22 (30.6)	8 (42.1)	0.341
Lung disease	13 (18.1)	6 (31.6)	0.197
Heart disease	8 (11.1)	1 (5.3)	0.448

*Data are mean \pm standard deviation or no. (%).

Table 4. Comparison of respiratory function recovery * (n = 91)

Variable	N	3 month M ± SD [†]	6month M ± SD	12 month M ± SD	Group * Time					
					F	P				
VATS	72	108.09 ± 14.87	113.49 ± 106.96	115.40 ± 17.45	Group	3.413	0.068			
								Time	4.017	0.022
VATS	72	107.99 ± 14.56	113.97 ± 15.98	117.82 ± 16.90	Group	13.527	<0.005			
								Time	1.472	0.232
Thoracotomy	19	100.77 ± 17.86	106.96 ± 19.05	108.85 ± 19.50	Group	0.019	0.891			
								Time	1.153	0.318

* Repeated-measures analysis of covariance

† Mean ± standard deviation

All patients with missing data ($n = 649$) were analyzed using a linear mixed effect model (LME). We considered the interaction over the time to evaluate the differences of lung function recovery rate according to surgical method and adjusted for factors that may have affected the pulmonary function recovery, including age, sex, smoking, preoperative FEV₁, and history of lung disease. The results of the LME-based analysis are shown in Tables 5 and 6. No time-dependent effects in FEV₁ or PFR were observed after the LME was conducted. After adjusting for confounding factors, overall recovery of FEV₁ was 2.60% higher in the VATS group than that in the thoracotomy group, but it is not significant ($p = 0.0834$). Similarly, PFR was not significant ($p = 0.5415$). However, a significant group \times time interaction for recovery rate of FVC was observed ($p = 0.0453$), suggesting that the recovery rate in the VATS group improved over time. A post-hoc analysis was performed to compare the difference at the point of time and the adjusted p-value is presented after using Bonferroni method. The recovery rate of FVC in VATS groups was 4.0% higher than that of thoracotomy group 3 months after surgery, but the difference was not significant (98.25 ± 1.32 vs. 94.24 ± 1.60 , $p = 0.0762$). The recovery rate of FVC was 7.29% higher (103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$) and 6.73% higher (107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$) at 6 and 12 months than those in the thoracotomy group (Table 6 and Figure 3).

Table 5. Estimated postoperative recovery rate in forced expiratory volume in 1 sec (FEV₁) and peak flow rate (PFR)

	Surgical method	LSMEANS * ± SE	p-value
FEV₁ (%)	VATS	104.12 ± 1.19	0.0834
	Thoracotomy	101.52 ± 1.37	
PFR (%)	VATS	83.77 ± 0.86	0.5415
	Thoracotomy	83.10 ± 0.99	

* Least squares means, analyzed by linear mixed model effect

Table 6. Estimated postoperative forced vital capacity (FVC) recovery rate over time

Time	Surgical method	LSMEANS * ± SE	p-value†
3 month after lobectomy	VATS	98.25 ± 1.32	0.0762
	Thoracotomy	94.24 ± 1.60	
6 month after lobectomy	VATS	103.66 ± 1.27	<0.0001
	Thoracotomy	96.37 ± 1.49	
12 month after lobectomy	VATS	107.01 ± 1.30	0.0003
	Thoracotomy	100.28 ± 1.54	

* Least square means, analyzed by linear mixed model effect

† Adjusted p-value by Bonferroni method

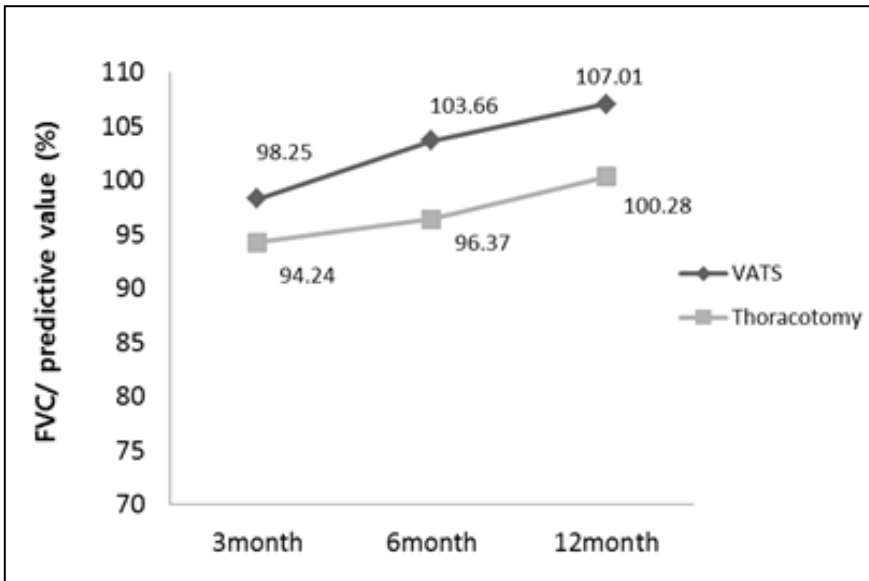


Figure 3. Postoperative changes in forced vital capacity (FVC) over time

DISCUSSION

Lobectomies are frequently applied procedures for patients with lung cancer and thoracotomy is the standard method. However, the frequency of VATS lobectomy has increased, driving researchers to compare the advantages and disadvantages of these two surgical procedures. Thoracotomy enables access through a suitable surgical area, but it requires dissecting the thoracic muscles and ribs (8). VATS lobectomy involves fewer incisions, presents less postoperative pain, and enables faster recovery of respiratory function than does thoracotomy (2-4, 9). Therefore, the recovery of pulmonary function proceeds more quickly in patients who undergo VATS than that in patients who undergo thoracotomy. Nakata et al. compared the oxygenation degree and recovery of FEV₁ and FVC in 21 patients who underwent VATS or thoracotomy, and found that the recovery of pulmonary function and oxygenation in the VATS group was superior to that in the thoracotomy group during the early postoperative period (6). However, no significant differences were found between the two groups 1 year after surgery. Qiang et al. verified pulmonary function in 102 patients with lung cancer at 1, 3, 7, 30, and 90 days after lobectomy (10), and derived similar results. FVC recovery was delayed by up to 3 months after lobectomy in the thoracotomy group. The treatment appeared to have achieved superior FEV₁ recovery, but no significant difference was found between the VATS and thoracotomy groups. The authors also measured pain scores on pre and postoperative days 1, 3, 7, 30, and 90, and revealed that the pain score was significantly lower in the VATS group for up to a 3-month period. However, these previous studies only confirmed respiratory recovery during the early postoperative period. In this study, the recovery of lung function during the late postoperative phase

was analyzed. The FEV₁ was not significantly different according to surgical method over the time by analyzed by the repeated-measures ANCOVA and linear mixed effect model. The FEV₁ recovery rate reached the predicted postoperative value at 3 months in both the VATS and thoracotomy groups. These results are consistent with previous findings, indicating that the remaining lobe may need up to 3 months of adaptation or adjustment (11, 12). PFR reflects the change in a relatively large airway, but it did not reach the previous level and was not different. This result may have been due to removal of the large airway during the lobectomy. FVC recovery rate tended to be better in the VATS group than that in the thoracotomy group and the changes in lung function recovery over time were significant by the linear mixed model. The recovery rate of FVC did not reach the predicted 100% value until 12 months in the thoracotomy group. Although we did not collect pain data, we believe that the pain after thoracotomy lasts much longer after lobectomy compared to that after VATS. One study demonstrated that long-term post-thoracotomy pain may persist for 12 months. The incidence rate of post-thoracotomy pain is 80% at 3 months, 75% at 6 months, and 61% one year (13). Another study suggested a relationship between postoperative pain and FVC recovery (10). Because the quality of life after lobectomy is important for patients with lung cancer, VATS lobectomy can be a more favorable procedure for patients requiring lobectomy. It can be particularly beneficial for elderly patients and patients with poor pulmonary function test results. However, VATS has a limitation for suitable surgical area compared to thoracotomy. Thus, the selection of a surgical method should be based on the advantages and disadvantages of each approach and determined by clinical significance.

This study had some limitations that may be viewed as starting points for future research. Because lung perfusion scans were not performed, the exact

postoperative lung function could not be predicted. Nevertheless, checking perfusion scans would not have generated a huge difference in results because we used a formula suitable for resected lobes. Furthermore, retrospective data were used and propensity score matching was not used due to the large amount of missing data. Thus, the patients in the two groups were not perfectly matched. In addition, pre-operative lung function can affect recovery rate. To overcome these limitations, we chose an appropriate statistical model, and confounding factors were adjusted. Overall, the FVC recovery was better in the VATS group than that in the thoracotomy group, but the number of patients who has all serial PFT data was small ($n = 91$) and a group \times time interaction was not observed. However, the analysis of all 649 patients showed a group \times time interaction. This discrepancy occurred due to the number of patients. Despite these limitations, our study features a greater number of patients and provides confirmed results for long-term lung function according to surgical method.

CONCLUSION

VATS lobectomy presented more advantages for recovery of late postoperative FVC after surgery than does thoracotomy after surgery. We hypothesize that pain after thoracotomy is more severe than that experienced after VATS lobectomy; such pain may persist for quite a long period and may affect the recovery rate of FVC. Further prospective studies will be necessary due to the limitations of this retrospective study.

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국문 초록

서론 폐엽 절제술은 조기 폐암의 기본적인 치료이며, 폐엽 절제술에는 비디오 흉강경 수술 혹은 개흉술이 가장 많이 쓰인다. 몇몇 연구에서는, 수술 시 절개창이 작은 비디오 흉강경 그룹이 호흡 기능의 회복에 있어 흉강경 보다 양호함을 보여 주었다. 그러나 이들 연구는 수술 후 조기 폐기능만을 본 연구가 대부분이었다. 이 연구의 목적은 비디오 흉강경 수술과 개흉술에서 폐기능 회복을 비교하는 것으로, 추적 관찰 기간을 늘려 수술 후 후기 폐기능을 관찰하고 분석하였다.

방법 2005 년 1월부터 2010년 12월 까지 조기폐암으로 서울대병원 및 분당 서울대병원에 입원하여 비디오 흉강경 수술 및 개흉술을 받은 환자 649 명의 데이터를 후향적으로 분석하였다. 이 환자들을 비디오 흉강경 군 (n=406) 과 개흉술 (n=243) 군으로 나누어 기본 특성, 수술 전 및 수술 후 3개월, 6개월, 12개월 째 강제 폐활량 및 1초간 강제 호기량, 최대 호기속도의 차이를 비교하였다.

결과 649 명의 환자 중에서 수술 후 폐기능 검사는 3개월, 6개월, 12개월째 각각 300, 497, 362 건이 시행되었고, 91명만이 3개월, 6개월, 12개월 자료를 모두 가지고 있었다. 이 91 명의 환자에는 반복 측정 공분산 분석을, 결측치가 있는 649 명의 환자에게는 선형 혼합 모델을 이용하여 결과를 분석하였다. 폐기능 회복에 영향을 미칠 수 있는, 다른 혼란 변수들은 보정되었다. 91 명의 환자를 반복 측정

공분산 분석으로 분석하였을 때, 비디오 흉강경 그룹은 흉강경 그룹에 비해 강제 폐활량 회복률이 양호함을 보여 주었다 ($p < 0.005$). 649 명의 환자를 선형 혼합 모형으로 분석한 경우에도, 비디오 흉강경 그룹은 흉강경 그룹보다 강제 폐활량 회복률이 양호함을 보여주었고, 각 군에서 이러한 강제 폐활량 회복률의 변화 정도는 시간에 따른 차이가 있었다 (6개월; 103.66 ± 1.27 vs. 96.37 ± 1.49 , $p < 0.0001$, 12개월; 107.01 ± 1.30 , 100.28 ± 1.54 , $p = 0.0003$). 그러나, 1초간 강제 호기량 및 최대 호기속도 회복률은 수술 방법에 따른 유의한 차이는 없었다.

결론 비디오 흉강경 수술은 수술 후 후기 강제 폐활량 회복에 있어서 개흉술보다 양호한 회복을 보이지만, 1초간 강제 호기량 및 최대 호기속도 회복률은 수술 방법에 따른 차이는 보이지 않았다. 개흉술 후에 지속되는 수술 후 통증이 이러한 결과의 원인일 것으로 생각된다.

주요어 : 폐암, 폐엽 절제술, 수술 방법, 폐기능

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