

ORIGINAL ARTICLE

Persistence of the Postoperative Change in the Six-minute Walking Distance of Lung Cancer Patients with Chronic Obstructive Pulmonary Disease

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Objectives: The aim of this prospective follow-up study was to investigate the difference before and after surgery in the six-minute walking distance (6MD) of lung cancer patients with chronic obstructive pulmonary disease (COPD) and to examine the long-term effect of the change in 6MD in the early postoperative period. **Methods:** This was a retrospective analysis of 25 COPD patients who underwent lung cancer surgery and perioperative rehabilitation in our department. Assessments of 6WD were carried out preoperatively and at 1, 3, and 6 months postoperatively. The changes in 6MD at 1, 3, and 6 months postoperatively compared with the preoperative value were designated the 1-month Δ 6MD, the 3-month Δ 6MD, and the 6-month Δ 6MD, and the associations between them were investigated. **Results:** The mean 6MD distance was 412.0 ± 27.3 m (95% confidence interval) preoperatively, 369.0 ± 33.8 m at 1 month, 395.6 ± 32.2 m at 3 months, and 400.0 ± 38.2 m at 6 months, with a significant difference between the preoperative and 1-month values ($P < 0.01$). There were strong correlations between 1-month and 3-month Δ 6MDs ($r = 0.74$, $P < 0.0001$) and between 1-month and 6-month Δ 6MDs ($r = 0.88$, $P < 0.0001$). **Conclusions:** In lung cancer patients with COPD, the 1-month Δ 6MD was strongly associated with both the 3-month Δ 6MD and the 6-month Δ 6MD. These findings suggest that the decrease in exercise tolerance of patients whose 6MD is low at 1 month postoperatively may be prolonged, and such patients may therefore be in greater need of postoperative outpatient rehabilitation.

Key Words: non-small cell lung cancer; postoperative rehabilitation; pulmonary resection

INTRODUCTION

Follow-up with post-discharge rehabilitation to maintain and/or improve postoperative physical function and quality of life is becoming increasingly important in patients who undergo lung cancer resection. A meta-analysis of the effectiveness of rehabilitation after lung cancer surgery found that it significantly improved exercise tolerance.¹⁾ Moreover, the dyspnea score was also significantly improved by aerobic exercise in comparatively young patients whose preoperative respiratory condition was maintained.²⁾

Chronic obstructive pulmonary disease (COPD) accounts for 54% of the comorbidities of patients with preoperative lung cancer³⁾ and affects the postoperative prognosis of those who undergo lung cancer resection.⁴⁾ In addition to age ≥ 75 years, obesity, and smoking,⁵⁾ COPD is also a risk factor for postoperative pulmonary complications. The presence of COPD was found to significantly increased the length of hospital stay, the rates of prolonged mechanical ventilation, and postoperative complications after lung cancer resection.⁶⁾ Postoperative complications are also more frequent in

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patients with COPD, irrespective of its severity.⁷⁾

Perioperative rehabilitation for lung cancer resection that starts before surgery has a beneficial effect on postoperative pulmonary complications, the duration of thoracic drain placement, and the length of hospital stay.⁸⁾ Furthermore, studies of perioperative rehabilitation in lung cancer patients with COPD have also found that preoperative interventions help improve preoperative respiratory function and exercise tolerance.⁹⁾ However, the postoperative decrease in the six-minute walking distance (6MD) was found to be significantly greater in lung cancer patients with COPD than in those without COPD. Moreover, postoperative problems such as respiratory discomfort and recurrent pneumonia occurred in lung cancer patients with COPD even with postoperative rehabilitation.^{10,11)} Consequently, patients with COPD require more careful postoperative rehabilitation than do those with lung cancer alone.

After curative surgery in patients with lung cancer, exercise endurance measured by the shuttle walking test was on average restored to the preoperative level within 1 month after curative surgery even without implementation of an exercise program¹²⁾; however, for some patients, exercise endurance was not restored within 1 month. Indeed, exercise capacity measured as maximal oxygen consumption after lobectomy had not improved to preoperative levels even 6 months after surgery in lung cancer patients. Therefore, we hypothesized that for some patients 6MD after surgery could take more than 3 or 6 months after surgery to return to preoperative levels. The objective of the current study was to examine changes in the 6MD before and after surgery in lung cancer patients with COPD and to investigate the persistence of the change in 6MD in the early postoperative period.

METHODS

Patients

Perioperative rehabilitation was implemented for a total of 97 consecutive patients who underwent lung cancer resection in the Department of Respiratory Surgery of Toho University Omori Medical Center between April 2010 and February 2018. These patients were at high risk of postoperative respiratory complications due to age ≥ 70 years or because pulmonary function tests had demonstrated an obstructive pulmonary disorder, of whom 60 had COPD. After the exclusion of 18 patients who failed to attend postoperative outpatient appointments, 7 who were unable to undergo 6MD measurement due to poor health, 4 who declined the assessment, 3 who could not undergo assessment because of

postoperative readmission, 2 who died, 1 who moved house, and 1 who was found not to have lung cancer on intraoperative diagnosis, the remaining 25 patients made up the study subjects and were followed up for 6 months (**Fig. 1**).

Respiratory Rehabilitation Program

In our hospital, patients with suspected lung cancer are examined as outpatients in the Department of Respiratory Surgery and then hospitalized for 2 days for biopsy and definitive diagnosis, after which the date of surgery is determined. Patients are then admitted 7 days preoperatively and ultimately discharged depending on their postoperative course. Respiratory rehabilitation is started after the preoperative outpatient examination or the biopsy.

Preoperative respiratory rehabilitation was conducted on an outpatient basis at least once a week, depending on preoperative tests and observations. Each respiratory rehabilitation session lasted 40 min and was led by a physiotherapist who used a pamphlet to instruct patients on breathing methods, coughing, and respiratory muscle stretching. Patients were instructed to keep a diary of the daily exercise they performed at home and to manage their exercises at home by themselves. In patients with cognitive decline or in whom motivation for exercise was low, the patient's family was asked to get involved with the rehabilitation, and they were instructed to exercise together. If the patient did not opt to take part in preoperative rehabilitation, the patient was contacted directly by telephone by physiotherapists, or the respiratory surgeon was tasked to persuade them to undertake preoperative rehabilitation. Patients were also instructed to perform exercises postoperatively at the bedside. The patients were instructed to continue these exercises at home twice a day (morning and afternoon) for 20–30 min each time. From the standpoint of comprehensive respiratory rehabilitation, patients were also taught how to use inhaled medication for COPD and were instructed about postoperative pain control and drain management.

On preoperative admission, patients continued to carry out rehabilitation as before and also used a cycle ergometer for endurance training. The target heart rate was set at 60% of the maximum heart rate, calculated as their age subtracted from 220. The exercise challenge at 60 rpm was adjusted according to the target heart rate, with an exercise time of 15 min. The exercise load was 26.4 ± 2.9 W before surgery and 14.9 ± 2.8 W after surgery. Postoperatively, starting from the day after surgery, the diaphragmatic respiration practiced from before surgery was performed at the bedside with the patients seated, and the patients started walking exercises

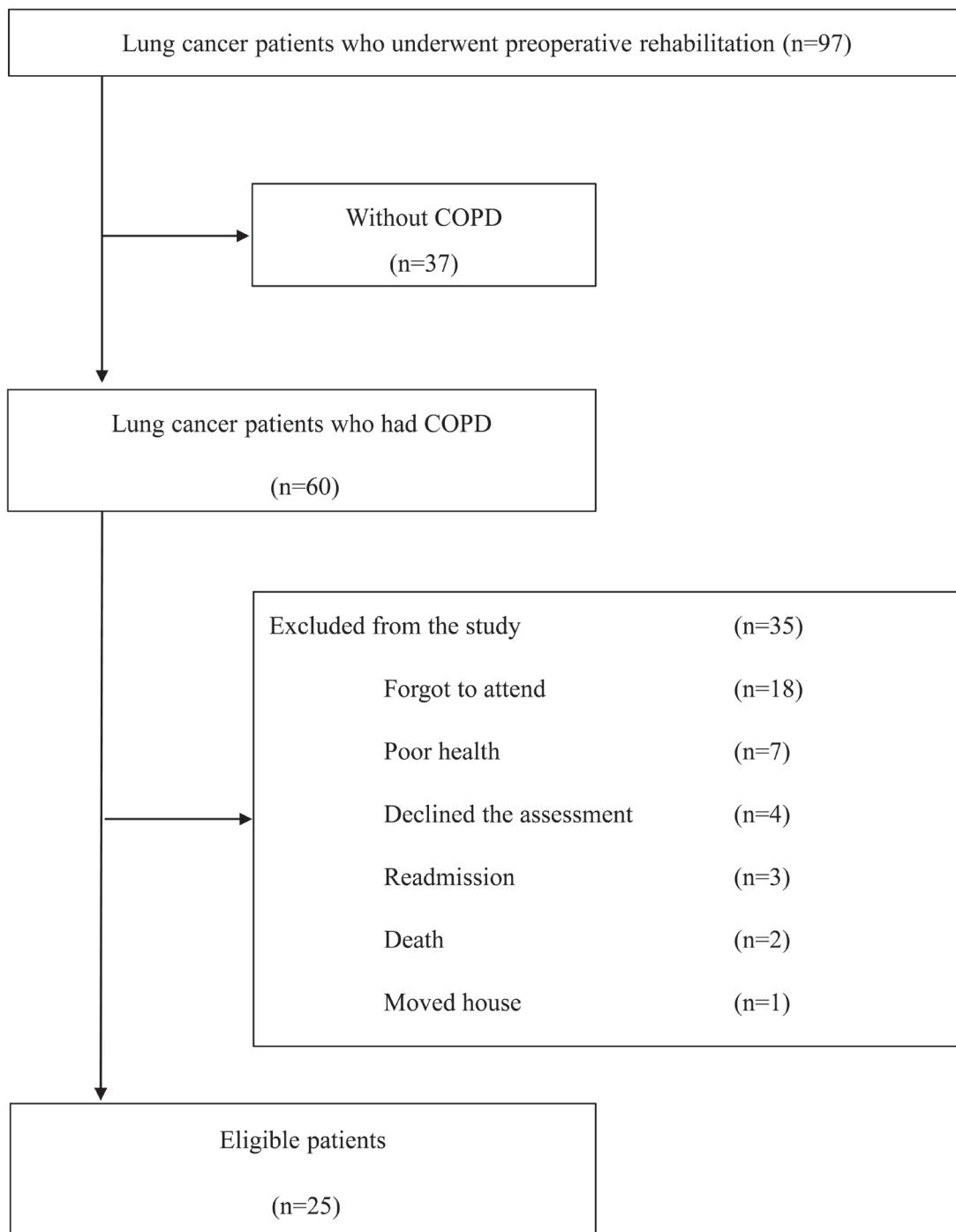


Fig. 1. Flowchart showing patient selection.

around the ward under the supervision of a physiotherapist. Once their chest drains were removed, patients carried out the endurance training they had practiced before preoperative admission in the rehabilitation room. Patients were encouraged to walk outdoors to improve their endurance at discharge. It was also explained that the exercise they

performed at home should be written down on paper and managed by themselves. No outpatient rehabilitation was carried out post-discharge, because, postoperatively, only assessments were performed.

After discharge, patients visited the respiratory surgery department after 1 week and then every month. In addition,

the patients visited for rehabilitation assessment 1, 3, and 6 months after surgery. The patients were instructed to engage in outdoor walking for at least 20 min a day. Target ratings of perceived exertion were based on the “somewhat hard” level to increase postoperative physical activity. The patients were also instructed in physical activities that mobilize the upper body and limbs with great care after permitted by the respiratory surgery department. Home rehabilitation implementation was confirmed by respiratory surgeons checking the records completed by the patients.

Items Investigated

Patients’ background characteristics, preoperative respiratory function, operative factors, and 6MD were collected from the medical records. Preoperative lung function testing was performed using the CHEST AC-8900 spirometer (manufactured by CHEST, Tokyo, Japan), and the residual volume (RV) and total lung capacity (TLC) were calculated by the gas dilution method. The percentage of the predicted values for vital capacity (VC), forced vital capacity (FVC), and the forced expiratory volume in the first second (FEV₁) were calculated using Japanese Respiratory Society reference values (the LMS method). The percentage of the predicted values for diffusing capacity for carbon monoxide were calculated using Burrows’ equation (DLCO) and McGrath’s equation (DLCO’). The percentage of the predicted values for TLC were calculated using Rossier’s equation.

The background characteristics investigated were sex, age, height, weight, body mass index (BMI), Brinkman index, COPD severity evaluated by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage, lung cancer stage, type of cancer, and the modified Medical Research Council (mMRC) Dyspnea Scale score.

The 6MD was measured following the ATS Guidelines,¹³⁾ with patients instructed to walk as far as they could in 6 min while being encouraged verbally once every minute. At the same time, oxygen saturation (SpO₂) and breathlessness, as assessed by the modified Borg scale, were also measured every minute. The 6MD was measured preoperatively and at 1, 3, and 6 months postoperatively, and the change at each time point was calculated with reference to the preoperative distance. The changes were designated the 1-month Δ 6MD, 3-month Δ 6MD, and 6-month Δ 6MD.

The preoperative 6MD was measured at the first rehabilitation session. The number of days between the bronchoscopic biopsy and the preoperative 6MD measurement was 39.0 \pm 18.4 days, and the number of days between the preoperative 6MD measurement and the date of surgery was

15.0 \pm 17.0 days. The number of preoperative rehabilitation sessions done with physiotherapists was 1.7 \pm 1.0; therefore, 6MD measurement could be performed only once before surgery. We understood that the 6MD should be measured just before surgery; however, in the real-world clinical setting, this was difficult to achieve.

Preoperative daily exercise was assessed using the Godin Leisure Time Exercise Questionnaire (GLTEQ). The GLTEQ calculates the weekly leisure activity score, and the scores were used to classify patients into three groups: the active group, 24 units and more; the moderately active group, 14–23 units; and the insufficiently active/sedentary group, less than 14 units.¹⁴⁾ For further analysis, the sedentary group was defined as those with a GLTEQ score of less than 14 points, and the active group was defined as those with 14 points or more. The GLTEQ has been frequently used as an index of physical activity in patients with lung cancer.¹⁵⁾

Statistical Analysis

RESULTS

Table 1 shows the patients’ characteristics. Among the 25 patients, preoperative COPD was Stage I in 6 patients (24%), Stage II in 13 (52%), and Stage III in 6 (24%). Moderate air-flow limitation was evident, with mean %FEV₁ 65.1% \pm 19.3% and mean FEV₁/FVC 56.5% \pm 10.6%. However, vital capacity was maintained, with mean %FVC 88.7% \pm 20.2%. In terms of operative factors, the approach was by thoracotomy in 9 cases (36%) and by video-assisted thoracic surgery (VATS) in 16 (64%); lobectomy was performed in 22 cases (88%) and pneumonectomy in 3 (12%).

Figure 2A shows the mean and 95% confidence interval (CI) of the 6MD at each time point. The mean 6MD was 412.0 \pm 27.3 m preoperatively, 369.0 \pm 33.8 m at 1 month, 395.6 \pm 32.2 m at 3 months, and 400.0 \pm 38.2 m at 6 months, with a significant difference between the preoperative and 1 month postoperative values ($P<0.01$). **Figure 2B** shows the mean and 95% CI of the lowest SpO₂ during the 6MD at each time point. The mean value was 92.9% \pm 0.9% preoperatively, 90.4% \pm 1.6% at 1 month, 91.3% \pm 1.5% at 3 months, and 91.3% \pm 1.4% at 6 months, with significant differences between the preoperative value and those at 1 month ($P<0.01$), 3 months ($P<0.05$), and 6 months ($P<0.05$).

Figure 3A shows the difference in Δ 6MD (mean and 95% CI) between VATS and thoracotomy at 1 month. The values were 29.1 \pm 26.1 m for the VATS group and 67.8 \pm 25.3 m for the thoracotomy group, with no significant difference be-

Table 1. Patient characteristics

	Mean±SD
Preoperative characteristics	
Age (years)	70.5±6.5
Sex (male/female)	20/5
Height (m)	1.6±0.08
Weight (kg)	58.8±8.0
BMI (kg/m ²)	22.2±2.6
Brinkman Index	1084.4±372.1
GOLD Stage (I/II/III/IV)	6/13/6/0
TNM Stage (I/II/III/IV)	17/6/2/0
Histology (squamous/adeno/large)	11/11/3/1
GLTEQ	5.6±9.6
GLTEQ (active/moderately active/insufficiently active)	2/3/20
mMRC scale (0/1/2/3/4)	16/6/3/0/0
6MD (m)	412.0±69.8
%6MD (%)	87.6±14.8
Lung function	
VC (L)	3.1±0.7
%VC (%)	89.7±17.9
IC (L)	2.0±0.4
FVC (L)	2.9±0.8
%FVC (%)	88.7±20.2
FEV ₁ (L)	1.6±0.6
%FEV ₁ (%)	65.1±19.3
FEV ₁ /FVC (%)	56.5±10.6
RV/TLC (%)	43.7±7.1
IC/TLC (%)	35.7±4.7
DLCO (L)	13.1±4.7
%DLCO (%)	81.9±23.7
DLCO' (L)	12.5±5.0
%DLCO' (%)	79.3±24.2
DLCO/VA (ml/min/mmHg/L)	3.1±1.3
DLCO/VA (%)	70.4±28.8
Operation data	
Surgery time (min)	299.6±127.7
Approach (thoracotomy/VATS: cases)	9/16
Procedure (lobectomy/pneumonectomy: cases)	22/3
Postoperative status	
Using home oxygen therapy at discharge (cases)	2
Length of hospital stay (days)	14.5±7.0
Complications (chylothorax/pulmonary fistula/pneumonia)	1/6/3

BMI, body mass index; GOLD stage, Global Initiative for Chronic Obstructive Lung Disease; TNM stage, tumor–lymph node–metastasis stage; mMRC scale, modified Medical Research Council scale; 6MD, 6-minute walk distance; VC, vital capacity; IC, inspiratory capacity; FVC, forced vital capacity; FEV₁, forced expiratory volume at first second; RV/TLC, residual volume/total lung capacity; IC/TLC, inspiratory capacity/total lung capacity; DLCO, diffusing capacity for carbon monoxide using Burrows' equation; DLCO', diffusing capacity for carbon monoxide using McGrath's equation; DLCO/VA, diffusing capacity for carbon monoxide divided by alveolar volume; VATS, video-assisted thoracic surgery; parameters prefixed with “%” show the percentage of the expected values.

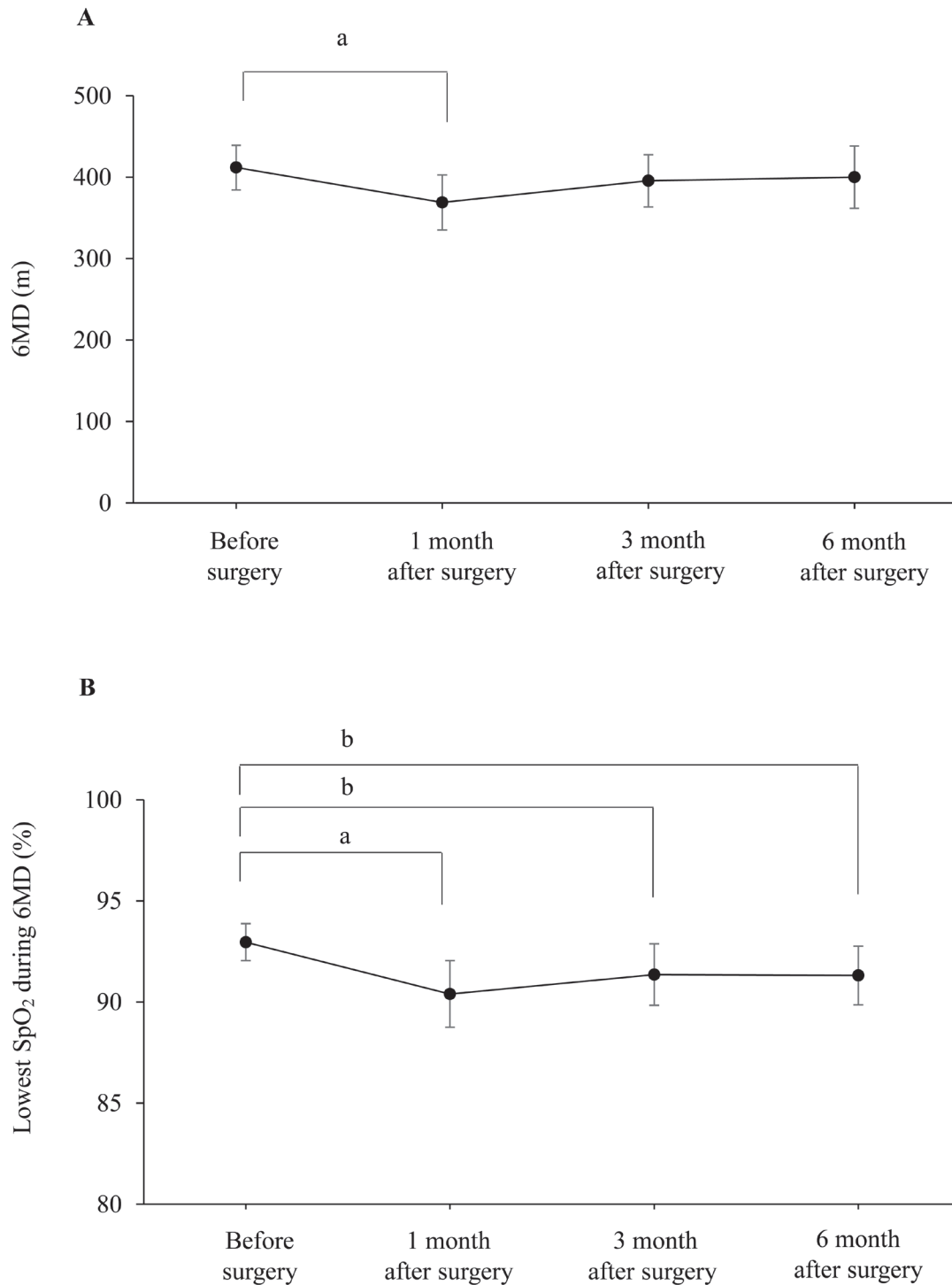


Fig. 2. Values from before surgery to 6 months after surgery of 6MD and the lowest SpO₂ during the 6MD test. (A) 6MD at each measurement time and (B) the lowest SpO₂ at each measurement time. ^aP<0.01 compared with before surgery by ANOVA. ^bP<0.05 compared with before surgery by ANOVA. Error bars represent 95% confidence intervals.

tween the groups. **Figure 3B** shows the difference in Δ 6MD (mean and 95% CI) at 3 months between VATS and thoracotomy. The values were -5.0 ± 23.8 m for the VATS group

and 54.4 ± 29.2 m for the thoracotomy group, with a significant difference between them (P<0.05). **Figure 3C** shows the difference in Δ 6MD (mean and 95% CI) between VATS and

thoracotomy at 6 months. The values were -11.9 ± 27.7 m for the VATS group and 54.4 ± 40.4 m for the thoracotomy group, with no significant difference between them.

Table 2 shows the GLTEQ and $\Delta 6MD$ values at 1, 3, and 6 months for the sedentary group and the active group. There was a significant difference in the GLTEQ between the sedentary group and the active group ($P < 0.0001$), but $\Delta 6MD$ at each time point was not significantly different between the groups.

Figure 4A–C shows the correlations between the values of $\Delta 6MD$ at the different time points. There were strong correlations between 1-month and 3-month $\Delta 6MD$ s ($r = 0.74$, $P < 0.0001$) and between 1-month and 6-month $\Delta 6MD$ s ($r = 0.89$, $P < 0.0001$). There was also a strong correlation between 3-month and 6-month $\Delta 6MD$ s ($r = 0.88$, $P < 0.0001$). This suggests that if patients had severely reduced exercise tolerance at 1 month postoperatively, this decrease in exercise tolerance would likely be prolonged until 6 months postoperatively. Because previous studies have shown a correlation between postoperative 6MD and age,¹⁶ this relation was also investigated; however, no such correlation was found (data not shown).

Correlations between preoperative %FEV₁ and preoperative 6MD and $\Delta 6MD$ at each time point were as follows: preoperative 6MD $r = 0.33$, $P = 0.10$; 1-month $\Delta 6MD$ $r = -0.05$, $P = 0.77$; 3-month $\Delta 6MD$ $r = -0.02$, $P = 0.93$; and 6-month $\Delta 6MD$ $r = -0.05$, $P = 0.78$. No significant correlation was found in this analysis.

Correlations between preoperative IC and preoperative 6MD and $\Delta 6MD$ at each time point were as follows: preoperative 6MD $r = 0.37$, $P = 0.06$; 1-month $\Delta 6MD$ $r = -0.04$, $P = 0.81$; 3-month $\Delta 6MD$ $r = 0.12$, $P = 0.56$; and 6-month $\Delta 6MD$ $r = 0.02$, $P = 0.89$. No significant correlation was found in this analysis.

Correlations between preoperative IC/TLC and preoperative 6MD and $\Delta 6MD$ at each time point were as follows: preoperative 6MD $r = 0.03$, $P = 0.88$; 1-month $\Delta 6MD$ $r = 0.02$, $P = 0.89$; 3-month $\Delta 6MD$ $r = -0.01$, $P = 0.95$; and 1-month $\Delta 6MD$ $r = 0.01$, $P = 0.92$. No significant correlation was found in this analysis.

Correlations between the GLTEQ score and preoperative 6MD and $\Delta 6MD$ at each time point were as follows: preoperative 6MD $r = 0.28$, $P = 0.17$; 1-month $\Delta 6MD$ $r = -0.09$, $P = 0.64$; 3-month $\Delta 6MD$ $r = 0.19$, $P = 0.34$; and 6-month $\Delta 6MD$ $r = 0.17$, $P = 0.41$. No significant correlation was found in this analysis.

In **Table 3**, patients were divided into two groups based on whether the 1-month $\Delta 6MD$ was greater than the minimally

important difference (MID); a MID value of 42 m for lung cancer was adopted.¹⁷ In comparisons between the groups, there were no significant differences in any characteristics (**Table 3**).

DISCUSSION

To the best of our knowledge, this is the first study to report long-term postoperative changes in 6MD in lung cancer patients with COPD and the long-term effect of the change in 6MD at 1 month postoperatively. In the present study, the mean 1-month $\Delta 6MD$ was -43.0 ± 62.7 m; the reported minimal clinically important difference in the 6MD of lung cancer patients is 22.0–42.0 m,¹⁷ and that for COPD is 23.5 m.¹⁸ Therefore, the decrease in the 6MD of lung cancer patients with COPD at 1 month postoperatively was a clinically important reduction. This finding is consistent with those of other studies,¹⁹ but the present study is the first to restrict subjects to lung cancer patients with COPD and to measure changes in 6MD at 3 and 6 months postoperatively, as well as at 1 month.

Respiratory discomfort and chest pain are often prolonged in the early post-lobectomy period.²⁰ Furthermore, COPD is a risk factor for pulmonary complications after pulmonary resection,⁵ and COPD significantly increases the postoperative length of hospital stay compared to that of lung cancer patients without COPD.²¹ The postoperative hospital stay for lung cancer patients is reported to be 4.3 days with preoperative rehabilitation and 9.7–12.2 days without preoperative rehabilitation.⁸ In the present study, the mean postoperative hospital stay was 14.5 ± 7.0 days, suggesting that prolonged hospitalization could make it difficult to maintain activity levels after surgery. Lung cancer resection surgery in patients with COPD usually requires a longer operation time and is a more difficult resection procedure. These factors are related to the postoperative lung function decrease, the postoperative maximal oxygen uptake decrease, respiratory distress, and decreased activity. These multiple combined factors likely contributed to the reduced 6MD at 1 month postoperatively.

Previous studies have shown that FEV₁, VC, and maximum oxygen consumption do not recover to their preoperative levels by 6 months after lobectomy,²² and that, in COPD patients who have undergone lobectomy, this decrease in maximum oxygen consumption persists for more than 6 months.²³ These findings suggest that the decrease in the area of the vascular bed due to pulmonary resection may impede smooth gas exchange following lung cancer surgery,

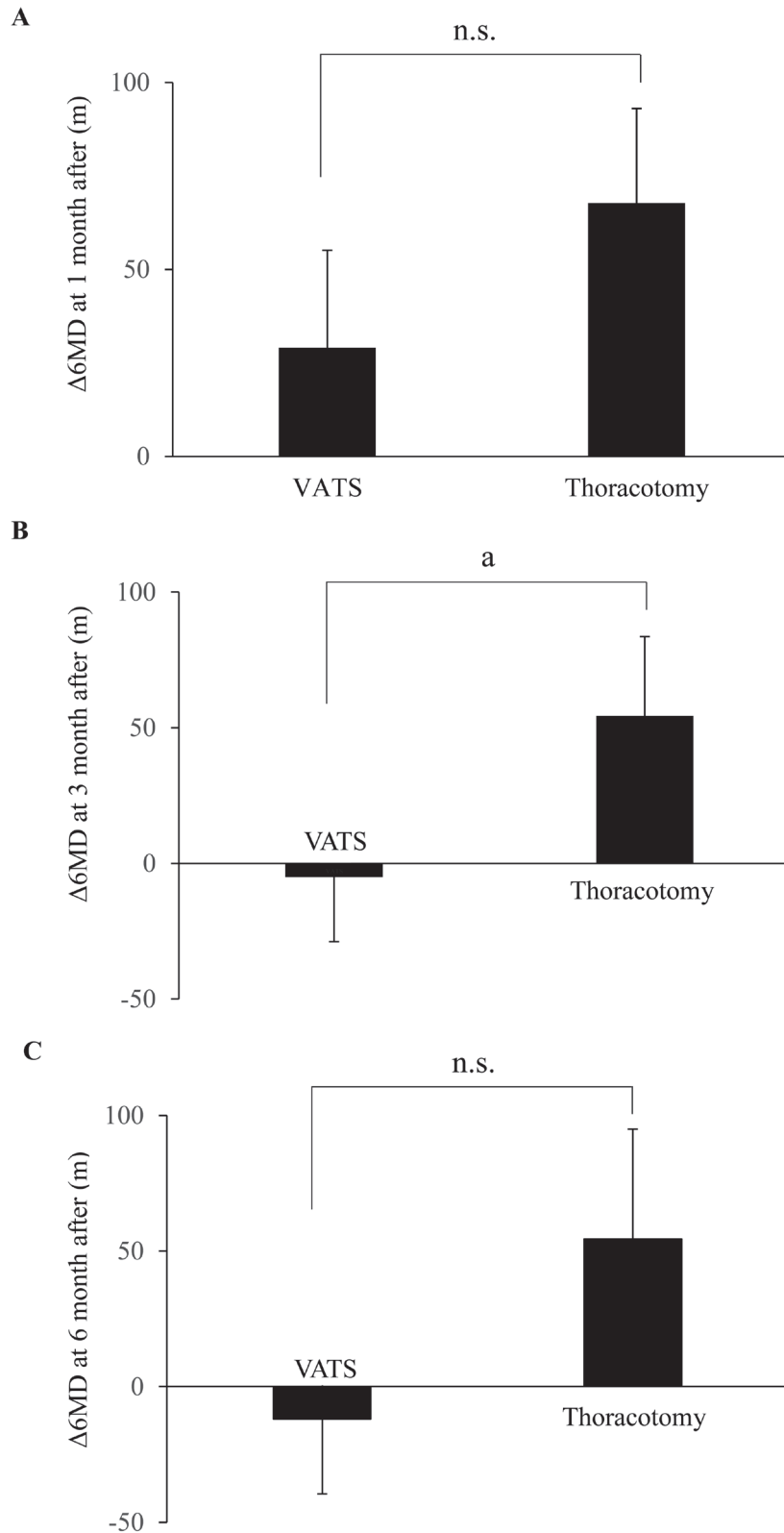


Fig. 3. Differences in $\Delta 6\text{MD}$ between video-assisted thoracic surgery (VATS) and thoracotomy at 1, 3, and 6 months post-operatively. (A) Difference in $\Delta 6\text{MD}$ at 1 month after surgery, (B) difference in $\Delta 6\text{MD}$ at 3 months after surgery, (C) difference in $\Delta 6\text{MD}$ at 6 months after surgery. ^a $P < 0.05$ compared with VATS by the Mann-Whitney U test. Error bars represent 95% confidence intervals.

Table 2. Differences between the sedentary group and the active group

	Sedentary group (n=20)	Active group (n=5)	P-value
GLTEQ	1.3±2.5	23.0±6.8	<0.0001
6MD (m)	403.5±68.1	446.0±58.9	0.29
1-month Δ6MD (m)	40.8±66.3	52.0±44.9	0.54
3-month Δ6MD (m)	9.5±65.3	44.0±61.5	0.22
6-month Δ6MD (m)	3.5±78.4	46.0±89.1	0.41

Sedentary, GLTEQ score less than 14; active, GLTEQ score 14 or over.

GLTEQ, Godin Leisure-Time Exercise Questionnaire; Δ6MD, change in 6MD between preoperative and the indicated number of months after surgery.

and this mechanism may also have contributed to the failure of exercise tolerance to improve to its preoperative level in this study. However, lung volume reduction surgery (LVRS) in COPD patients reportedly causes decreased dynamic hyperinflation of the lung, thereby improving exercise tolerance and percutaneous oxygen saturation.²⁴⁾ The present study of lung cancer patients with COPD therefore included some patients whose 6MD improved presumably due to the LVRS effect of lobectomy.

The present investigation of the change in the 6MD compared with the preoperative value in lung cancer patients with COPD showed that the 1-month Δ6MD was strongly associated with the 3-month and 6-month Δ6MDs. This suggested that if 6MD was reduced at 1 month postoperatively, this effect was likely to last until 3 and 6 months postoperatively. To investigate the reasons for this, we examined whether preoperative COPD severity affected postoperative 6MD. However, there was no correlation between postoperative 6MD and COPD severity as assessed using %FEV₁ or IC/TLC. In contrast, there was a significant difference in 3-month Δ6MD depending on the surgical approach. Therefore, we considered that the surgical approach was one of the reasons. Additionally, postoperative muscle strength and physical activity may have an effect. Furthermore, the effect of LVRS is more likely to be obtained in upper lobe resection than in lower lobe resection.²⁵⁾ In the present study, it was difficult to test the difference between the resection sites and postoperative 6MD because of the small number of subjects, but it is possible that the resection site had an effect. Multivariate analysis of factors such as excision site, physical activity, and lower limb muscle strength will be required in the future.

A previous study found that older patients had greater decreases in 6MD at 6 months postoperatively than younger patients did.¹⁷⁾ In the present study, there was no correlation between age and Δ6MD at 1, 3, and 6 months, but this is

the first study to show that decreased exercise tolerance at 1 month postoperatively was correlated with the exercise tolerance at 3 and 6 months.

The subjects of the present study were patients with stable COPD, and their 6MD was already low preoperatively. In lung cancer patients with COPD, pulmonary resection causes pain, impaired respiratory function, and decreased maximum oxygen consumption in the early postoperative period. All these factors interfere with improving physical activity, and their effects may persist in the long term. However, in the present study, only respiratory function tests were performed, including FEV₁, FVC, and DLCO, which are limiting factors for the 6MD of COPD patients.²⁶⁾ Furthermore, comparisons between the patients based on whether their 1-month Δ6MD was greater than the MID did not show significant differences in any characteristic (**Table 3**); this finding failed to support the pathophysiological mechanism of greater 6MD decline. Further studies are required.

The physical activity of cancer patients is currently a focus of attention, and in breast cancer patients, proactive physical activity after diagnosis has been shown to significantly reduce all-cause mortality.²⁷⁾ Other studies have similarly shown that physical activity levels are associated with survival rates in lung cancer survivors.²⁸⁾ However, few patients engage voluntarily in physical activity after lung cancer treatment.²⁹⁾ More proactive efforts at discharge or during outpatient rehabilitation, such as giving patients accelerometers or other means of self-management, are therefore needed to improve the physical activity levels of lung cancer patients.

This study had some limitations, including the fact that the study was conducted at a single site with a relatively small sample size. Furthermore, because postoperative respiratory function and physical activity were not measured, these are topics for further study. Because the subjects of the present study were selected from among those who participated in

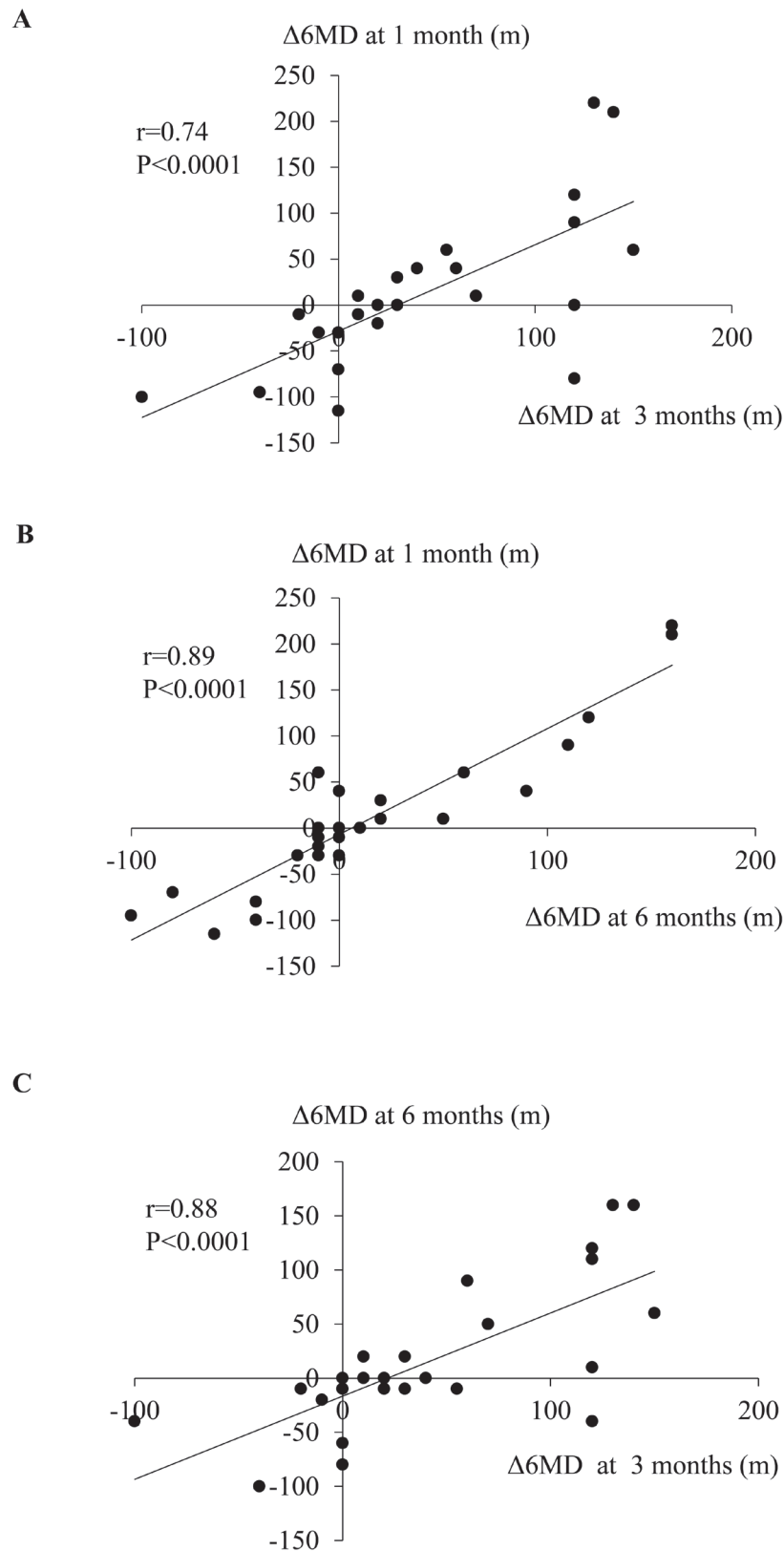


Fig. 4. Correlation of $\Delta 6\text{MD}$ at 1, 3, and 6 months postoperatively. (A) Correlation of $\Delta 6\text{MD}$ at 1 month and $\Delta 6\text{MD}$ at 3 months after surgery. (B) Correlation of $\Delta 6\text{MD}$ at 1 month and 6 months after surgery. (C) Correlation of $\Delta 6\text{MD}$ at 3 months and 6 months after surgery. Spearman's rank correlation test was used.

Table 3. Comparisons of subjects in whom the 1-month Δ 6MD was less than or greater than the minimally important difference (42 m)

	1-month Δ 6MD >42 m (n=10)	1-month Δ 6MD \leq 42 m (n=15)	P-value
Preoperative characteristics			
Age (years)	71.5 \pm 6.9	69.9 \pm 6.7	0.54
Height (m)	162.4 \pm 7.5	162.8 \pm 8.0	0.61
Weight (kg)	58.3 \pm 8.7	59.2 \pm 8.0	0.69
BMI (kg/m ²)	22.0 \pm 2.7	22.3 \pm 2.8	0.61
Brinkman Index	1062.0 \pm 377.2	1099.3 \pm 397.0	0.91
GOLD Stage (I/II/III/IV)	2/3/5/0	4/10/1/0	0.12
TNM Stage (I/II/III/IV)	5/4/1/0	12/2/1/0	0.35
mMRC Scale score (0/1/2/3/4)	5/3/2/0/0	11/3/1/0/0	0.58
GLTEQ	3.4 \pm 7.1	7.3 \pm 11.2	0.71
6MD (m)	434.0 \pm 62.9	397.3 \pm 72.5	0.14
%6MD (%)	95.2 \pm 14.7	82.5 \pm 13.0	0.052
Lung function			
VC (L)	3.1 \pm 0.5	3.0 \pm 0.9	0.57
%VC (%)	88.4 \pm 12.5	90.5 \pm 20.6	0.93
IC (L)	1.9 \pm 0.3	1.9 \pm 0.4	0.71
FVC (L)	2.9 \pm 0.6	2.9 \pm 0.9	0.78
%FVC (%)	87.2 \pm 16.4	89.7 \pm 22.3	0.84
FEV ₁ (L)	1.5 \pm 0.6	1.7 \pm 0.6	0.57
%FEV ₁ (%)	59.6 \pm 19.7	68.6 \pm 18.2	0.31
FEV ₁ /FVC (%)	52.1 \pm 11.5	59.4 \pm 9.6	0.07
RV/TLC (%)	41.8 \pm 6.6	45.0 \pm 7.6	0.20
IC/TLC (%)	35.3 \pm 5.0	35.8 \pm 4.8	0.91
%DLCO (%)	75.2 \pm 20.6	85.8 \pm 25.9	0.49
%DLCO' (%)	73.9 \pm 23.4	82.4 \pm 24.8	0.49
DLCO/VA (ml/min/mmHg/L)	2.7 \pm 0.7	3.2 \pm 1.4	0.49
DLCO/VA (%)	63.3 \pm 17.8	74.6 \pm 33.6	0.53
Operation data			
Surgery time (min)	304.0 \pm 113.8	298.6 \pm 141.3	0.50
Approach: cases (thoracotomy/VATS)	5/5	4/11	0.39
Procedure: cases (lobectomy/pneumonectomy)	9/1	13/2	1.00
Postoperative state			
Using home oxygen therapy at discharge: cases	2	0	0.07
Length of hospital stay (days)	15.4 \pm 5.1	13.9 \pm 8.1	0.27
Complications			
Chylothorax	0	1	0.40
Pulmonary fistula	2	4	0.70
Pneumonia	1	2	0.80

all the evaluations at 1, 3, and 6 months after the operation, the number of subjects was low. Therefore, the data were clearly representative of enthusiastic patients who attended three times in a row. In the future, it will be necessary to

consider a follow-up system to reduce the number of drop-outs. Regarding the study design, it will be necessary to compare patients with normal preoperative respiratory function and those with COPD to clarify the characteristics of

COPD patients. Finally, in this study, univariate analysis was performed with a small number of subjects, and it was not possible to perform multivariate analysis of factors associated with postoperative Δ 6MD.

CONCLUSIONS

It was found that, compared with the preoperative value, 6MD decreased significantly at 1 month postoperatively in lung cancer patients with COPD. Moreover, the 1-month Δ 6MD was strongly correlated with both the 3-month and 6-month Δ 6MDs. This suggests that the decrease in exercise tolerance of lung cancer patients with COPD whose 6MD is low at 1 month postoperatively may be prolonged, and such patients may therefore be in greater need of postoperative rehabilitation. However, exercise is not the only approach for improving postoperative 6MD. We believe that comprehensive pulmonary rehabilitation, such as improving adherence to bronchodilators, patient education to improve physical activity, and nutritional guidance to improve muscle strength, is important.

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CONFLICTS OF INTEREST

All authors declare that there are no conflicts of interest.

REFERENCES

1. Cavalheri V, Burtin C, Formico VR, Nonoyama ML, Jenkins S, Spruit MA, Hill K: Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. *Cochrane Database Syst Rev* 2019;6:CD009955. DOI:10.1002/14651858.CD009955.pub3, PMID:31204439
2. Edvardsen E, Skjønsberg OH, Holme I, Nordsletten L, Borchsenius F, Anderssen SA: High-intensity training following lung cancer surgery: a randomised controlled trial. *Thorax* 2015;70:244–250. DOI:10.1136/thoraxjnl-2014-205944, PMID:25323620
3. Hashimoto N, Matsuzaki A, Okada Y, Imai N, Iwano S, Wakai K, Imaizumi K, Yokoi K, Hasegawa Y: Clinical impact of prevalence and severity of COPD on the decision-making process for therapeutic management of lung cancer patients. *BMC Pulm Med* 2014;14:14. DOI:10.1186/1471-2466-14-14, PMID:24498965
4. Sekine Y, Yamada Y, Chiyo M, Iwata T, Nakajima T, Yasufuku K, Suzuki M, Fujisawa T: Association of chronic obstructive pulmonary disease and tumor recurrence in patients with stage IA lung cancer after complete resection. *Ann Thorac Surg* 2007;84:946–950. DOI:10.1016/j.athoracsur.2007.04.038, PMID:17720404
5. Agostini P, Cieslik H, Rathinam S, Bishay E, Kalkat MS, Rajesh PB, Steyn RS, Singh S, Naidu B: Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? *Thorax* 2010;65:815–818. DOI:10.1136/thx.2009.123083, PMID:20805178
6. Sekine Y, Suzuki H, Yamada Y, Koh E, Yoshino I: Severity of chronic obstructive pulmonary disease and its relationship to lung cancer prognosis after surgical resection. *Thorac Cardiovasc Surg* 2013;61:124–130. PMID:22535670
7. Kim ES, Kim YT, Kang CH, Park IK, Bae W, Choi SM, Lee J, Park YS, Lee CH, Lee SM, Yim JJ, Kim YW, Han SK, Yoo CG: Prevalence of and risk factors for postoperative pulmonary complications after lung cancer surgery in patients with early-stage COPD. *Int J Chron Obstruct Pulmon Dis* 2016;11:1317–1326. DOI:10.2147/COPD.S105206, PMID:27366059
8. Cavalheri V, Granger C: Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev* 2017;6:CD012020. DOI:10.1002/14651858.CD012020.pub2, PMID:28589547
9. Mujovic N, Mujovic N, Subotic D, Marinkovic M, Milovanovic A, Stojsic J, Zugic V, Grajic M, Nikolic D: Preoperative pulmonary rehabilitation in patients with non-small cell lung cancer and chronic obstructive pulmonary disease. *Arch Med Sci* 2014;1:68–75. DOI:10.5114/aoms.2013.32806, PMID:24701217
10. Nomori H, Watanabe K, Ohtsuka T, Naruke T, Sue-masu K: Six-minute walking and pulmonary function test outcomes during the early period after lung cancer surgery with special reference to patients with chronic obstructive pulmonary disease. *Jpn J Thorac Cardiovasc Surg* 2004;52:113–119. DOI:10.1007/s11748-004-0126-8, PMID:15077844

11. Nakajima T, Sekine Y, Yamada Y, Suzuki H, Yasufuku K, Yoshida S, Suzuki M, Shibuya K, Fujisawa T, Yoshino I: Long-term surgical outcome in patients with lung cancer and coexisting severe COPD. *Thorac Cardiovasc Surg* 2009;57:339–342. DOI:10.1055/s-0029-1185571, PMID:19707975
12. Arbane G, Douiri A, Hart N, Hopkinson NS, Singh S, Speed C, Valladares B, Garrod R: Effect of postoperative physical training on activity after curative surgery for non-small cell lung cancer: a multicentre randomised controlled trial. *Physiotherapy* 2014;100:100–107. DOI:10.1016/j.physio.2013.12.002, PMID:24703523
13. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS Statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166:111–117. DOI:10.1164/ajrccm.166.1.at1102, PMID:12091180
14. Godin G, Shephard RJ: A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci* 1985;10:141–146. PMID:4053261
15. Edbrooke L, Denehy L, Parry SM, Astin R, Jack S, Granger CL: How is physical activity measured in lung cancer? A systematic review of outcome measures and their psychometric properties. *Respirology* 2017;22:263–277. DOI:10.1111/resp.12975, PMID:28102971
16. Saito H, Shiraishi A, Nomori H, Matsui H, Yoshida K, Matsue Y, Fujii T, Kawama K: Impact of age on the recovery of six-minute walking distance after lung cancer surgery: a retrospective cohort study. *Gen Thorac Cardiovasc Surg* 2020;68:150–157. DOI:10.1007/s11748-019-01191-7, PMID:31485843
17. Granger CL, Holland AE, Gordon IR, Denehy L: Minimal important difference of the 6-minute walk distance in lung cancer. *Chron Respir Dis* 2015;12:146–154. DOI:10.1177/1479972315575715, PMID:25749346
18. Holland AE, Hill CJ, Rasekaba T, Lee A, Naughton MT, McDonald CF: Updating the minimal important difference for six-minute walk distance in patients with chronic obstructive pulmonary disease. *Arch Phys Med Rehabil* 2010;91:221–225. DOI:10.1016/j.apmr.2009.10.017, PMID:20159125
19. Mujovic N, Mujovic N, Subotic D, Ercegovac M, Milovanovic A, Nikcevic L, Zugic V, Nikolic D: Influence of pulmonary rehabilitation on lung function changes after the lung resection for primary lung cancer in patients with chronic obstructive pulmonary disease. *Aging Dis* 2015;6:466–477. DOI:10.14336/AD.2015.0503, PMID:26618048
20. Balduyck B, Hendriks J, Lauwers P, Van Schil P: Quality of life evolution after lung cancer surgery: a prospective study in 100 patients. *Lung Cancer* 2007;56:423–431. DOI:10.1016/j.lungcan.2007.01.013, PMID:17306905
21. Rodrigues F, Grafino M, Faria I, Pontes da Mata J, Papoila AL, Félix F: Surgical risk evaluation of lung cancer in COPD patients – a cohort observational study. *Rev Port Pneumol Engl Ed* 2016;22:266–272. DOI:10.1016/j.rppnen.2016.02.010, PMID:27174411
22. Nezu K, Kushibe K, Tojo T, Takahama M, Kitamura S: Recovery and limitation of exercise capacity after lung resection for lung cancer. *Chest* 1998;113:1511–1516. DOI:10.1378/chest.113.6.1511, PMID:9631786
23. Kushibe K, Kawaguchi T, Kimura M, Takahama M, Tojo T, Taniguchi S: Exercise capacity after lobectomy in patients with chronic obstructive pulmonary disease. *Interact Cardiovasc Thorac Surg* 2008;7:398–401. DOI:10.1510/icvts.2007.165696, PMID:18270219
24. Lammi MR, Ciccolella D, Marchetti N, Kohler M, Criner GJ: Increased oxygen pulse after lung volume reduction surgery is associated with reduced dynamic hyperinflation. *Eur Respir J* 2012;40:837–843. DOI:10.1183/09031936.00169311, PMID:22267766
25. Kushibe K, Takahama M, Tojo T, Kawaguchi T, Kimura M, Taniguchi S: Assessment of pulmonary function after lobectomy for lung cancer — upper lobectomy might have the same effect as lung volume reduction surgery. *Eur J Cardiothorac Surg* 2006;29:886–890. DOI:10.1016/j.ejcts.2006.02.047, PMID:16675249
26. Singh SJ, Puhan MA, Andrianopoulos V, Hernandez NA, Mitchell KE, Hill CJ, Lee AL, Camillo CA, Troosters T, Spruit MA, Carlin BW, Wanger J, Pepin V, Saey D, Pitta F, Kaminsky DA, McCormack MC, MacIntyre N, Culver BH, Sciurba FC, Revill SM, Delafosse V, Holland AE: An official systematic review of the European Respiratory Society/American Thoracic Society: measurement properties of field walking tests in chronic respiratory disease. *Eur Respir J* 2014;44:1447–1478. DOI:10.1183/09031936.00150414, PMID:25359356

27. Bao PP, Zhao GM, Shu XO, Peng P, Cai H, Lu W, Zheng Y: Modifiable lifestyle factors and triple-negative breast cancer survival: a population-based prospective study. *Epidemiology* 2015;26:909–916. DOI:10.1097/EDE.0000000000000373, PMID:26360370
28. Sloan JA, Cheville AL, Liu H, Novotny PJ, Wampfler JA, Garces YI, Clark MM, Yang P: Impact of self-reported physical activity and health promotion behaviors on lung cancer survivorship. *Health Qual Life Outcomes* 2016;14:66. DOI:10.1186/s12955-016-0461-3, PMID:27129406
29. Coups EJ, Park BJ, Feinstein MB, Steingart RM, Egleston BL, Wilson DJ, Ostroff JS: Physical activity among lung cancer survivors: changes across the cancer trajectory and associations with quality of life. *Cancer Epidemiol Biomarkers Prev* 2009;18:664–672. DOI:10.1158/1055-9965.EPI-08-0589, PMID:19190151