

Factors Influencing Functional Exercise Capacity After Lung Resection for Non–Small Cell Lung Cancer

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Abstract

Purpose: We investigated, in patients who underwent lung resection for non–small cell lung cancer (NSCLC), the magnitude of early limitation in functional exercise capacity and the associations with pre- and postoperative factors. **Methods:** Consecutive patients with preoperative clinical stage I to IIIA NSCLC who underwent lung resection were prospectively enrolled. We measured functional exercise capacity (6-minute walk distance [6MWD]) and skeletal muscle strength (handgrip [HF] and quadriceps force [QF]) within 2 days prior to surgery and on day 7 postoperatively. **Results:** Two hundred eighteen participants were recruited (median age 69 years) of whom 49 developed postoperative complications (POCs). 6MWD was markedly decreased (514 m vs 469 m, $P < .001$); HF and QF were slightly decreased following surgery. Multiple linear regression showed that preoperative vital capacity ($P < .01$), QF ($P < .05$), the duration of chest tube drainage ($P < .001$), and presence of POCs ($P < .05$) were significant predictors. However, intraoperative factors were not significantly associated with the decline in 6MWD. **Conclusions:** These results suggest that patients with preoperative impairments in pulmonary function and muscle strength, and those who require prolonged chest tube drainage or develop POCs are likely to have impaired exercise capacity. Therefore, individual assessment and follow-up of patients with such factors is indicated.

Keywords

6-minute walk distance, exercise capacity, lung resection, non–small cell lung cancer, muscle strength

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Introduction

Complete surgical resection with curative intent is the most effective treatment for localized non–small cell lung cancer (NSCLC).¹ Hospital mortality, in Japan, in patients who undergo lung resection is less than 1%, and most patients have no problems with activities of daily living following hospital discharge.² Regarding exercise capacity after surgery, the maximum oxygen uptake (VO_2 max) declines by 19% to 28% during the 14 days after surgery.^{3,4} However, most patients have a short postoperative stay, and the magnitude of impairment in functional exercise capacity at discharge is unclear.

Functional exercise capacity is important in NSCLC patients, because it is a strong independent predictor of survival that may complement traditional markers of prognosis to improve risk stratification.⁵ Assessment of functional

exercise capacity during the early period after lung resection would permit the detection of significant impairment, and early intervention aimed at ameliorating this impairment. Several studies using the 6-minute walk test (6MWT) showed that 6-minute walk distance (6MWD) decreased

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Table 1. Definition of CONUT.

Parameters	CONUT			
	Normal	Light	Moderate	Severe
Serum albumin (g/dL)	3.5-4.5	3.0-3.4	2.5-2.9	<2.5
Alb score	1	2	3	4
Total lymphocyte (count/mm ³)	≥1600	1200-1599	800-1199	<800
TLC score	0	1	2	3
Total cholesterol (mg/dL)	>180	140-180	100-139	<100
T-cho score	0	1	2	3
CONUT score (total)	0-1	2-4	5-8	9-12
Assessment	Normal	Light	Moderate	Severe

Abbreviations: Alb, serum albumin; CONUT, Controlling Nutritional Status; T-cho, total cholesterol; TLC, total lymphocyte count.

significantly when measured within 14 days after surgery.^{6,7} However, the limitations of these studies include small sample size (n = 28 patients following thoracoscopic surgery)⁶ and heterogeneity (including patient with metastatic tumors and those with nonmalignant tumors).⁷ Furthermore, peripheral muscle force is strongly related to 6MWD in chronic obstructive pulmonary disease (COPD),^{8,9} as well as important in exercise capacity of patients after lung resection in lung cancer,¹⁰ but it has not been evaluated in these studies. Participants in the previous study¹⁰ were stable patients within 1 year following surgery. In the early postoperative period, factors such as preoperative pulmonary function, surgical procedure, and postoperative progress may also affect the magnitude of impairment in exercise capacity; however, such data are lacking.

The aims of this study were to identify the following: (1) the magnitude of decline in 6MWD during the early period after surgery and (2) associations between the changes in 6MWD and factors such as preoperative peripheral muscle force and pulmonary function, surgical procedure, and postoperative progress in patients following surgical resection for NSCLC.

Methods

Study Population

This was a prospective observational study. Consecutive patients with preoperative clinical stage I to IIIA NSCLC who underwent lung resection between April 1, 2011, and March 31, 2015, at Nagasaki University Hospital (Nagasaki, Japan) were enrolled. Patients in whom functional exercise capacity and skeletal muscle strength tests were performed pre- and postoperation as standard assessment were potentially eligible for the study. Exclusion criteria were musculoskeletal and neurological disorders, or cognitive impairment, and severe postoperative complications (POCs, Clavien-Dindo ≥grade 3B)¹¹ affecting the performance of exercise

tests. In addition, patients who underwent a pneumonectomy or had a history of thoracic surgery were excluded from the study, because in our hospital, the postoperative care is different for such patients.

The study was approved by the Human Ethics Review Committee of Nagasaki University Graduate School of Biomedical Sciences (Approval Number 12092420-2). All participants gave written informed consent.

Baseline Characteristics

We collected data on clinical stage of cancer, comorbidity, performance status (Eastern Cooperative Oncology Group Performance Status)¹² and nutrition status; pulmonary function (forced expiratory volume in 1 second [FEV₁], forced vital capacity [FVC], FEV₁/FVC, vital capacity [VC], and diffusing capacity of the lung for carbon monoxide [DL_{CO}]) was measured approximately 1 month prior to surgery.

Pulmonary function tests were performed using a spirometer (CHSTAC-8900; Chest Corporation, Tokyo, Japan) in accordance with international guideline.¹³ The predicted FVC and FEV₁ were calculated from equations developed in healthy nonsmoking Japanese.¹⁴

The preoperative nutritional status was evaluated using the CONUT (Controlling Nutritional Status) score.¹⁵ The score is derived from serum albumin concentration, total blood cholesterol level, and total peripheral lymphocyte count (Table 1).

Measurements

The following tests were carried out within 2 days prior to surgery and on day 7 postoperatively. Four physiotherapists (MO, MH, HN, and RK) were involved in data collection.

Functional Exercise Capacity. The 6MWT was used to assess functional exercise capacity with the main test outcome being 6MWD. The test was performed according to

published guidelines,¹⁶ and the better of 2 attempts was recorded. A 30-m corridor was used with patients instructed to walk as far as possible in the 6 minutes. Standardized encouragement was given at the end of every minute. Oxygen saturation and pulse rate were monitored continuously throughout the test (PULSOX-300; KONICA MINOLTA, Japan). The modified Borg scale¹⁷ was used to quantify the level of dyspnea and leg fatigue immediately after the test.

Skeletal Muscle Strength. Handgrip force (HF) and quadriceps force (QF) were measured as indices of skeletal muscle strength. The HF was assessed using a dynamometer (T.K.K.5401; Takei-Kiki-Kogyo Corporation, Niigata, Japan). Patients were required to squeeze the dynamometer with maximum effort for at least 5 seconds. Following 1 practice attempt, HF was tested twice with a minimum of 60 seconds rest between each attempt. The highest value of 2 attempts was recorded (kg) on both hands. HF was measured on both limbs to account for the potential influence of pain on the operative side following surgery. During the test, patients were standing upright with their feet hip-width apart and with elbow fully extended, and holding the hand dynamometer, with the wrist in neutral position and index finger flexed at 90°.^{18,19}

Quadriceps force was evaluated as the peak force developed by the dominant leg during a maximal isometric knee extension maneuver in the sitting position using a handheld dynamometer with a fixing belt (μ -Tas F-1; Anima Corporation, Tokyo, Japan) in accordance with a standard protocol.²⁰ The highest value of at least 2 maneuvers was recorded and expressed in kilograms force (kgf).

Surgical and Perioperative Management

Patients were selected for thoracoscopic surgery or thoracotomy on the basis of the results of chest radiographic studies, bronchoscopy, the patient's general condition (performance status), and comorbidities (eg, presence of interstitial lung disease). An epidural or continuous intravenous analgesia was used to manage postoperative incisional pain until removal of the chest drain after which oral analgesics were taken. The definition used for thoracotomy in this study was an incision ≥ 6 cm and/or use of a rib retractor. We defined POCs as complications that occurred during the postoperative hospital stay. The POCs were diagnosed by a surgeon and/or a radiologist, and we identified these POCs from the medical records according to the Clavien-Dindo classification.¹¹ The Clavien-Dindo classification categorizes POCs into 5 major groups according to the intervention required for patient care: grade 1, requiring no pharmacological intervention other than antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy; grade 2, requiring pharmacological intervention with medications other than those allowed for grade 1 complications; grade 3, requiring further intervention with

(3B) or without (3A) general anesthesia; grade 4, life-threatening complications and those requiring intensive care unit management; and grade 5, death of the patient.¹¹

Postoperative management included physiotherapy comprising early ambulation and airway clearance techniques (as indicated). Physiotherapy was commenced on the first postoperative day and continued until the day prior to discharge. The schedule of postoperative physiotherapy was as follows: postoperative day 1, sit on the edge of the bed, stand, and walk along the corridor (70-200 m, if possible); day 2 to 3, walk 200 to 400 m; day 3 to 6, climb 1 to 3 floors of stairs plus upper and lower limb resistance training; day 7, measurements of muscle strength and functional exercise capacity, and advice about unsupervised exercise training and activities of daily living for postdischarge. No supervised exercise training was provided after the seventh postoperative day.

Statistical Analysis

The Kolmogorov-Smirnov test was used to examine the distribution of data. Variables were expressed as the median and interquartile range or as mean \pm standard deviation, absolute number and percentage, or 95% confidence intervals.

Comparisons between pre- and postoperative 6MWD and skeletal muscle strength were made using paired *t* tests. Multiple linear regression analysis was used to determine the associations between change in 6MWD following surgery with preoperative skeletal muscle strength and pulmonary function, surgical procedure, and postoperative progress. A multiple linear regression analysis, adjusted for preoperative 6MWD, was first performed to identify any potential predictor variables. Variables with a *P* value $< .2$ and those considered to be clinically relevant were then included in the multivariate analysis to determine any independent predictors. When multicollinearity was present in the model, highly related variables were identified and only the variable showing the highest univariate relationship with the dependent variable was included in the model.

The level of significance was set at .05 for all statistical tests. Analyses were performed using a statistical software package (IBM SPSS Statistics version 23.0, IBM, Chicago, IL).

Results

Patient Characteristics

Four hundred seventy-two consecutive patients were screened for eligibility of whom 297 (63%) patients were recruited to the study (Figure 1). Of these, 56 (19%) patients refused to complete the 6MWT following surgery due to symptoms such as postoperative pain and fatigue, and presence of chest drainage (Supplementary File 1, available online). Data from 218

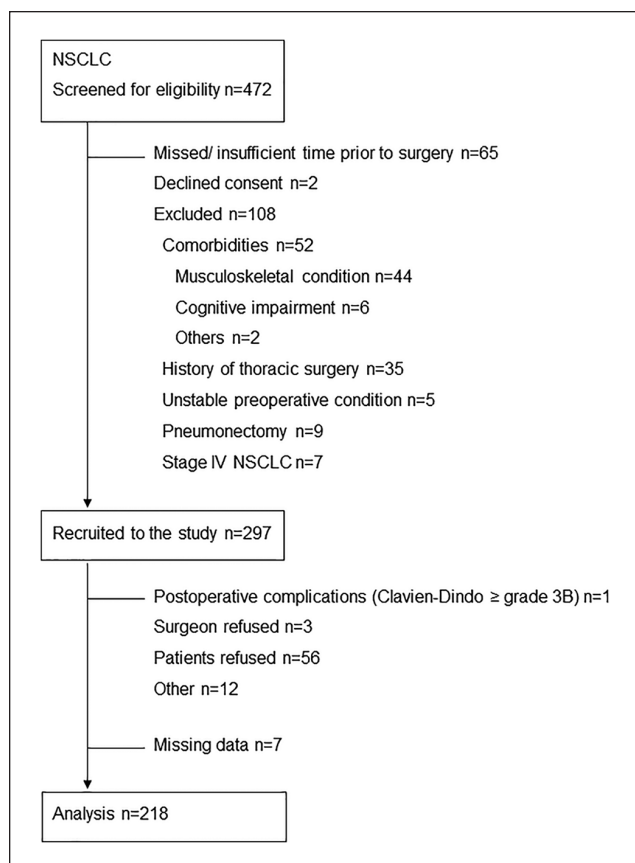


Figure 1. Patient flow diagram.

Abbreviation: NSCLC, non-small cell lung cancer.

(73%) patients were included in the analysis. Table 2 and Supplementary File 2 (available online) show the characteristics of the 218 patients. Forty-nine patients developed POCs: 14 cases of prolonged air leakage for 4 days, 13 cases of atrial fibrillation, 7 cases of chylothorax, 4 of delirium, 3 cases of pneumonia, 3 cases of atelectasis, 2 cases of hemothorax, 2 cases of recurrent nerve paralysis, 1 case of pyothorax, and 1 case of acute exacerbation of COPD. On average, the chest drains and epidural catheters were removed on postoperative day 3. Most patients (65%) ambulated on the first postoperative day (Table 2). Two hundred six patients (95% of the sample) achieved a walking distance of 200 m by postoperative day 4. After surgery, only one patient performed the 6MWT with the chest drain in situ, with the physiotherapist carrying the drainage tube.

Comparison of 6MWD and Skeletal Muscle Strength Before and After Surgery

Pre- and postoperative 6MWD and skeletal muscle strength are shown in Table 3. 6MWD was decreased, and dyspnea in post-6MWT was significantly increased during the early postoperative period. Skeletal muscle strength was decreased.

Table 2. Baseline Characteristics of the Patients (N = 218).

Variable	Median [IQR] or n (%)
Age, years	69 [63-72]
Gender, male	140 (64)
Body mass index, kg/m ²	22.4 [20.5-24.3]
Comorbidities	
Pulmonary	52 (24)
Cardiac	42 (19)
Metabolic	106 (49)
Other	15 (7)
Smoking status	
Never	82 (38)
Ever and current	136 (62)
Pack/years	25 [0-51]
Preoperative lung cancer stage	
Stage I	187 (86)
Stage II	14 (6)
Stage III	17 (8)
Prior adjunct treatment	
No treatment	206 (94)
Chemotherapy only	6 (3)
Chemotherapy and radiotherapy	6 (3)
ECOG-PS	
0	193 (89)
I	25 (11)
≥2	0
CONUT score	
Normal	147 (68)
Light	68 (31)
Moderate	3 (1)
Severe	0
Preoperative pulmonary function	
FEV ₁ , L	2.25 [1.88-2.71]
FEV ₁ , % predicted	106 [92-120]
FVC, L	3.16 [2.58-3.72]
FVC, % predicted	109 [97-119]
FEV ₁ /FVC, %	74 [66-80]
VC, L	3.19 [2.64-3.77]
VC, % predicted	109 [98-120]
DL _{CO} , mL/min/mm Hg	14.0 [10.7-17.1]
DL _{CO} , % predicted	86 [72-101]
Surgical procedure	
Thoracoscopy	103 (47)
Thoracotomy	115 (53)
Resection	
Wedge	21 (10)
Segmentectomy	28 (13)
Lobectomy	169 (77)
Duration of surgery, minutes	224 [186-273]
Blood loss, g	100 [50-230]
Duration of chest tube drainage, days	3 [2-5]
Clavien-Dindo classification	
Grade I	14 (6)
Grade 2	16 (7)
Grade 3A	19 (9)
No grade (no complications)	169 (78)
Day of first ambulation	1 [1-2]

Abbreviations: CONUT, Controlling Nutritional Status; DL_{CO}, diffusing capacity of the lung carbon monoxide; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; VC, vital capacity.

Table 3. Functional Exercise Capacity and Skeletal Muscle Strength.

	Preoperation (Mean ± SD)	Postoperation (Mean ± SD)	Mean Difference (95% CI)	P
6MWT				
6MWD (m)	514 ± 83	469 ± 87	-45 (-52 to -38)	<.001
Dyspnea end test (0-10)	3.7 ± 1.6	5.1 ± 1.9	1.4 (1.2 to 1.6)	
Leg fatigue end test (0-10)	3.4 ± 2.0	3.6 ± 2.0	0.2 (-0.4 to 0.5)	
Baseline SpO ₂ (%)	97 ± 1	97 ± 1	0 (0 to 0)	
Nadir SpO ₂ (%)	95 ± 4	93 ± 4	-2 (-3 to -2)	
Baseline PR (bpm)	75 ± 11	85 ± 13	10 (9 to 11)	
Peak PR (bpm)	110 ± 19	113 ± 21	4 (1 to 6)	
Isometric handgrip force				
Operative side (kg)	29.1 ± 9.4	27.7 ± 9.6	-1.4 (-1.9 to -0.9)	<.001
Contralateral side (kg)	29.0 ± 9.2	28.7 ± 9.3	-0.4 (-0.7 to -0.1)	.024
Isometric quadriceps torque				
Quadriceps force (kgf)	32.9 ± 13.0	31.1 ± 12.5	-1.9 (-3.0 to -0.9)	<.001
Quadriceps force per body mass (kgf/kg)	0.56 ± 0.18	0.53 ± 0.18	-0.03 (-0.05 to -0.01)	<.001

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; CI, confidence interval; PR, pulse rate; SpO₂, percutaneous oxygen saturation.

Table 4. Results of Multiple Linear Regression Analysis.

	B	β	P	95% CI
Preoperative variables				
6MWD at baseline (m)	-0.274	-0.428	<.001	-0.363 to -0.185
QF (kgf)	0.680	0.165	.034	0.052 to 1.309
Preoperative VC (L)	16.859	0.246	.001	6.864 to 26.854
Postoperative variables				
POCs (yes/no)	-21.759	-0.171	.014	-39.101 to -4.416
Duration of chest tube drainage (days)	-4.801	-0.252	<.001	-7.429 to -2.174

Abbreviations: 6MWD, 6-minute walk distance; CI, confidence interval; POCs, postoperative complications; QF, quadriceps force; VC, vital capacity.

Relationships Between Postoperative Deterioration in 6MWD and Pre- and Postoperative Factors

First, we explored potential predictors using multiple linear regression adjusted for preoperative 6MWD. As a result, potential predictor variables were age, gender, FEV₁, FVC, VC, DL_{CO}, HF, QF, surgical procedure, the duration of chest tube drainage, and presence of POCs (Supplementary File 3, available online). For the following variables, preoperative pulmonary function (FEV₁, FVC, VC, DL_{CO}) and muscle strength (HF, QF), we detected the presence of multicollinearity so the variables with the highest prediction accuracy in the multiple linear regression were selected. The duration of chest tube drainage ($P < .001$), presence of POCs ($P = .014$), VC ($P = .001$), and QF ($P = .034$) before surgery were significant predictors. However, age and gender, and variables related to surgery were not significant contributors to the outcome. Details of the result above analyses are given in Table 4.

Discussion

We found that (1) the impairment in functional exercise capacity measured as 6MWD during the early postoperative period significantly declined (45 m, 9%); and (2) the preoperative QF and VC, duration of chest tube drainage, and presence of POCs were independent predictors of the decline in 6MWD. To our knowledge, this is the first study to investigate impairment of functional exercise capacity in the early postoperative period following lung resection for NSCLC in a large sample and to examine predictor variables.

We chose to assess functional exercise capacity using the 6MWT. Previous studies^{3,4} have performed a cardiopulmonary exercise test (CPET) as a postoperative exercise capacity test. Cavalheri et al²¹ reported that a CPET is a more maximal test than the 6MWT in patients with lung cancer; however, the 6MWT is more suitable in the early postoperative period because some patients would not tolerate the CPET due to symptom burden (ie, incisional pain, fatigue, and dyspnea).

Seventy-three percent of our sample were able to perform the 6MWT in the early postoperative period. However, 19% of patients, especially elderly patients, refused to complete the 6MWT because of fatigue and dyspnea, incisional pain related to thoracotomy, and presence of a chest drain.

In our study, 6MWD had declined by 45 m when measured at 7 days after surgery. Arbane et al²² reported that 6MWD decreased about 130 m at 5 postoperative days, and a decline was almost 3-fold greater than we observed. However, our finding is quite consistent with reports of Nomori et al⁶ and Brocki et al,⁷ which assessed in the early postoperative period and reported the magnitude of decline in 6MWD (35 m, 47 m). In Arbane's study, we speculate that their patients' effort during the 6MWT was submaximal (mean Borg's dyspnea rating of only 1.4, peak heart rate 101 bpm). Moreover, Granger et al²³ have reported the minimal important difference for the 6MWD in patients with lung cancer to be 22 to 42 m. Because the participants in Granger's study were lung cancer patients assessed 10 weeks after therapies (chemotherapy, radiotherapy, or surgery), it could not be determined whether these treatments influenced 6MWD. However, we also cannot completely assert that the decline of 45 m in postoperative early period is not a problem, because none of previous studies have reported relationship between the magnitude of impairment of postoperative 6MWD and long-term factors such as exercise capacity, health-related quality of life, and survival. If impairment of postoperative functional capacity and long-term factors are related, it is important to detect the exercise limitation at an early stage following surgery so that training can be initiated, given the evidence for this intervention.^{24,25}

The findings of the multiple linear regression analysis identified 4 variables that were independent predictors for the decline in 6MWD, namely, preoperative QF, VC, duration of chest tube drainage, and development of POCs. Burtin et al¹⁰ recruited patients within 1 year after surgery for lung cancer and, consistent with our findings, reported that QF was a factor determining their exercise capacity. The importance of lower limb muscle strength as a contributor to exercise capacity in patients who undergo lung resection is a consistent finding,¹⁰ and it has also been identified as an important contributor to exercise limitation, in respiratory diseases such as COPD.^{8,9}

We found that the higher the preoperative VC, the lower the magnitude of postoperative impairment in exercise capacity. Several previous studies have shown a relationship between postoperative pulmonary function and exercise capacity.^{3,4,10,26} In our study, preoperative VC was more related to postoperative exercise capacity than FEV₁ or DL_{CO}. Probably, the relationship between pulmonary function and exercise capacity such as postoperative VC, FEV₁, or DL_{CO} differs depending on the timing of evaluation. Although ventilatory limitation is caused by the impairment of chest wall movement in the early postoperative period,

this recovers by approximately 1 month after surgery.²⁷ Therefore, we consider the VC involved in ventilation contributed to the decline in exercise capacity in the early postoperative period.

The longer the duration of chest tube drainage the greater decline in postoperative 6MWD. Prolonged chest tube drainage contributes to dysfunction as a result of physical inactivity arising from the associated pain and discomfort. Early removal of the drainage tube is desirable in order to reduce pain and improve ventilatory function in the early postoperative phase.²⁸

The development of POCs limit physical activity due to factors such as an unstable medical condition leading to enforced rest and the symptoms associated with the POCs. Furthermore, POCs such as pneumonia and atelectasis worsen postoperative pulmonary function and also give rise to catabolism in the peripheral muscle by prolonging inflammation.²⁹

Age, gender, and time to first ambulation are also potential predictors of postoperative 6MWD. Age and gender have been reported as predictors in a previous study³⁰ of thoracic surgery patients. In that study, there was a wide age range (17-90 years), in contrast to our study (63-72 years), and this is likely to explain why age was not a predictor in the present study. Regarding gender, 6MWD in a previous study showed a greater postoperative decline in females,³⁰ although no reason given. Delayed time to first ambulation decreases physical activity and may affect 6MWD. However, the assessment of physical activity was outside the scope of this study.

Interestingly, our results showed that intraoperative factors such as the type of surgery and amount of lung resected were not significantly associated with the decline in 6MWD. Some previous studies have reported the determinants of 6MWD in patients undergoing thoracic surgery.^{30,31} Moreover, Nomori et al reported the surgical procedure, for example, posterolateral or anterolateral thoracotomy, did contribute to the decline in postoperative exercise capacity.⁶ In our sample, half of the patients received complete video-assisted thoracoscopic surgery, or small incisions even if thoracotomy. As a result, the muscle incision during surgery was small and the effects may not have been different. In addition, we excluded those who underwent pneumonectomy or had a history of thoracic surgery, as surgery in such patients is more extensive. Some previous studies have reported the impairment in exercise capacity, as measured by CPET, following lung resection was not related to the amount of lung resected consistent with our finding.^{32,33} Importantly, irrespective of the surgical procedure and extent of lung volume resected, a similar magnitude of dysfunction in exercise capacity occurs immediately after surgery.

The main limitation of this study is that it was carried out in 1 center only. Furthermore, we were only able to recruit 63% of the potential sample because of comorbidities and difficulties in undertaking preoperative assessments given most patients were hospitalized for only 1 day prior to

surgery, and this day was taken up with multiple assessments and interventions. As we excluded those with stage IV, pneumonectomy, and history of thoracic surgery, our results are limited to patients undergoing standard surgery for NSCLC in primary stage.

Second, we did not assess pulmonary function following surgery or levels of physical activity. In particular, daily activity level may affect postoperative 6MWD and should be evaluated in future studies.

The strengths of our study include the sample size, which is larger than previous reports, and the homogeneity of the sample given the participants were managed in accordance with clinical guidelines for surgery in NSCLC.¹ Furthermore, we extend previous studies by identifying factors that are associated with the deterioration in functional exercise capacity following surgery.

Some identified factors include factors to be improved by preoperative rehabilitation. Preoperative exercise training improves preoperative exercise capacity, reduces the risk of POCs, and the duration of chest tube drainage.^{34,35} It may also have a role in minimizing impairment of exercise capacity after surgery.

Conclusion

We found that functional exercise capacity during the early postoperative period significantly declined, and the deterioration was related to preoperative QF, VC, and postoperative progress such as the duration of chest tube drainage and development of POCs. However, intraoperative factors such as the surgical procedure and extent of lung resected were not related to the decline. Based on our findings, we recommend the routine evaluation of 6MWD before and after surgery regardless of type of surgery to detect the initial decline in exercise capacity. Future research should evaluate whether preoperative training has any impact on postoperative exercise capacity, as well as the influence of early postoperative training in those patients with identified impairments in exercise capacity.

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Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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