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Prognostic value of preoperative exercise capacity in patients undergoing thoracoscopic lobectomy for non-small cell lung cancer

Kazumi Hamada[a], Masataka Irie[a,*], Yoshihisa Fujino[b], Masahiro Hyodo[a], Takeshi Hanagiri[c]

[a] Department of Rehabilitation Medicine, Shin-Kokura Hospital, Federation of National Public Service Personnel Mutual Aid Associations, 1-3-1 Kanada, Kokurakita-ku, Kitakyushu, Fukuoka, 803-8505, Japan
[b] Department of Environmental Epidemiology, Institute of Industrial Ecological Sciences, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka, 807-8555, Japan
[c] Department of Thoracic Surgery, Shin-Kokura Hospital, Federation of National Public Service Personnel Mutual Aid Associations, 1-3-1 Kanada, Kokurakita-ku, Kitakyushu, Fukuoka, 803-8505, Japan

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ABSTRACT

Objectives: Whether or not the preoperative exercise capacity, as assessed by 6-min walk test, influences the survival of patients undergoing thoracoscopic lobectomy for lung cancer is unclear. We therefore investigated the prognostic value of the 6-min walk distance in this population.

Materials and methods: This prospective cohort study was conducted between 2005 and 2013. We studied 224 consecutive subjects with stage I-II non-small cell lung cancer who underwent thoracoscopic lobectomy. Survival was calculated by the Kaplan-Meier method. The log-rank test was used to assess the survival rate. Cox proportional hazards models were used to estimate the risk of 5-year all-cause mortality based on the preoperative 6-min walk distance with adjustment for other prognostic factors, including the age, performance status, postoperative cardiopulmonary complication, and pathological stage.

Results: The median follow-up period was 60.8 months. During this period, 38 deaths were recorded. The 5-year overall survival rate of the subjects with a preoperative 6-min walk distance of < 400 m were significantly lower than those with a 6-min walk distance of ≥ 400 m (65.3% vs. 88.0%; $p < 0.001$). A multivariate analysis showed that the 6-min walk distance was significantly associated with the overall survival after adjusting for the age and pathologic stage (hazard ratio, 2.40; 95% confidence interval, 1.20–4.79), but it did not provide additional prognostic value beyond the performance status.

Conclusion: The preoperative 6-min walk distance may be useful as an additional prognostic factor for patients at an increased risk of mortality after thoracoscopic lobectomy for stage I-II non-small cell lung cancer.

1. Introduction

Despite significant advances in various treatment modalities, including surgical procedures, chemotherapy, radiotherapy, targeted therapy, and/or immunotherapy, lung cancer continues to be the leading cause of cancer-related mortality in Japan [1] and worldwide [2]. For patients with clinical stage I and II non-small cell lung cancer (NSCLC), surgical resection remains the optimal treatment. Based on data from a retrospective surgical series, the 5-year survival rates ranged from 60% to 80% for stage I and 30% to 50% for stage II NSCLC [3–5]. Such substantial variability in the survival within the same stage of the disease is probably due to the clinical heterogeneity of patients, including the individual pretreatment exercise capacity.

A number of studies have shown that the exercise capacity is a strong predictor of the survival in patients undergoing various treatments for different stages of NSCLC [6–11]. In patients undergoing lung resection surgery, the preoperative exercise capacity has been shown to be associated with the risk of perioperative morbidity [12–16] and mortality [10,11]. Thus, preoperative exercise tests have been used for the risk stratification of lung resection candidates [6,17].

Although increasing evidence seems to prove a relationship between the preoperative exercise capacity and long-term survival in lung cancer patients undergoing lung resection [10,11], no evidence has been reported on patients with early-stage NSCLC undergoing

* Corresponding author at: Department of Rehabilitation Medicine, Shin-Kokura Hospital, Federation of National Public Service Personnel Mutual Aid Associations, 1-3-1 Kanada, Kokurakita-ku, Kitakyushu, 803-8505, Japan.
E-mail addresses: kazumi55hm@yahoo.co.jp (K. Hamada), DQL02511@nifty.com (M. Irie), zenq@med.uoeh-u.ac.jp (Y. Fujino), hyouhyou6@gmail.com (M. Hyodo), t-hanagiri@shin-kokura.gr.jp (T. Hanagiri).

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lobectomy via a thoracoscopic approach. Furthermore, thus far, no studies have specifically examined the prognostic value of the 6-min walk test (6MWT) in a preoperative evaluation setting.

We therefore investigated the relationship between the exercise capacity, as measured by the 6MWT, and the long-term survival in patients undergoing thoracoscopic lobectomy for early-stage NSCLC.

2. Material and methods

2.1. Study design and subjects

This prospective cohort study included consecutive patients who underwent thoracoscopic lobectomy for pathological stage I and II NSCLC at Shin-Kokura Hospital between June 2005 and July 2013. The indications for thoracoscopic lobectomy were based on the standard criteria for open thoracotomy, including a tumor of ≤6 cm in diameter [18] and a predicted postoperative forced vital capacity of > 800 $mL{\cdot}m^{-2}$ or a forced expiratory volume in 1 s of > 600 $mL{\cdot}m^{-2}$ [19]. Patients were staged according to the 7th edition of the American Joint Committee on Cancer on Cancer tumor, node, metastasis classification system [20]. Patients were excluded if they were not able to walk independently at the time of admission. Details of the surgical and perioperative management, including extubation of the chest tube, and the structured postoperative rehabilitation program have been reported previously [12]. The present study received ethical approval from our hospital's Institutional Review Board of Clinical Research, and informed consent was obtained from all subjects (approval number 2015-0005).

2.2. Data acquisition and follow-up

All enrolled subjects were followed for 5 years. Follow-up survival data were obtained from the medical records of the post discharge visits and regular radiographic follow-up examinations. The vital status of subjects who did not visit a hospital were determined by a telephone interview with the subject or his or her relatives. The patient data from hospitalization, which included demographics, preoperative characteristics, exercise capacity, oncologic data, and postoperative complications, were collected prospectively. The performance status (PS) was assessed by the attending physician at the time of admission using the Eastern Cooperative Oncology Group scale. Postoperative cardiopulmonary complications were defined according to criteria reported previously [12].

2.3. 6MWT

Measurements of the preoperative exercise capacity, as assessed by the 6MWT according to the American Thoracic Society guidelines [21] using a straight indoor corridor 30 m in distance, were performed by certified physical therapists (M.I. and K.H.) without a preliminary test the day before surgery. The subjects were informed of the purpose and method of this test and were instructed to walk at their fastest pace and cover the longest possible distance over 6 min. Subjects were allowed to stop during the test, depending on fatigue or other symptoms. Based on the guideline, they were given encouragement and informed of the amount time remaining every minute during this test. To ensure their safety, subjects were continuously monitored during the 6MWT using electrocardiogram telemetry (WEP-4204, Nihon Kohden Co., Ltd, Tokyo, Japan) and finger pulse oximetry (PULSOX-300, Konica Minolta Co., Ltd, Tokyo, Japan). The distance walked in meters was recorded, and the percentage of predicted value of the 6-min walk distance (6MWD) was calculated using the reference equation developed by Enright et al. [22].

2.4. Statistical analyses

Data obtained prior to July 31, 2018, were included in the analyses. The primary outcomes of the study were the overall survival at 5 years (OS) among the study subjects. The survival time was calculated for each subject from the date of surgery to the date of death from any cause or the end of the follow-up period. To evaluate the association between the exercise capacity and the long-term outcome, Kaplan-Meier curves were initially constructed to display the differences in the survival according to a 6MWD of 400 m, which was used as a cut-off value in the literature [6,9,12]. The log-rank test was performed to compare those survival curves. The hazard ratios (HRs) and 95% confidence intervals (CIs) of the 6MWD for the survival were estimated using a Cox proportional hazards model. The model included the age, pathological stage, development of postoperative complications, and PS, which are considered to have potential effects on the survival in surgically treated patients for lung cancer [23–30]. These variables were therefore included in the models as confounding factors. Continuous variables are presented as the median and interquartile range, as noted. Categorical variables are presented as the number and percentage. P values of ≤0.05 were considered to indicate statistical significance.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Japan), which is a graphical user interface for the R software program (The R Foundation for Statistical Computing, Vienna, Austria, version 2.13.0). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics [31].

3. Results

3.1. Subjects characteristics

A cohort of 523 patients was diagnosed with NSCLC during the study period. Among these, 450 patients underwent curative surgery for lung cancer. In brief, 226 patients were excluded from our analysis because they underwent a surgical procedure other than thoracoscopic lobectomy (n = 159), because they were diagnosed with pathological stage III or IV NSCLC (n = 59), or because they were unable to perform the 6MWT at the time of admission (n = 8). The remaining 224 subjects were enrolled in the current study. The baseline characteristics of the subjects are listed in Table 1. Seventy-five subjects (33.5%) met the criteria for chronic obstructive pulmonary disease (COPD) based on the definition established by the Global Initiative for Obstructive Lung Disease [32]. One hundred and eighty-three subjects (81.7%) were staged with pathological stage I disease. The incidence of adenocarcinoma (72.3%) was higher than the incidence of squamous cell carcinoma (25.9%). For the overall subjects, the median 6MWD was 461 m (interquartile range, 389–525 m), and the median percentage of the predicted value was 108%. There were 62 subjects (27.7%) who did not reach a distance of 400 m during the 6MWT. None of the subjects underwent conversion from thoracoscopic surgery to open thoracotomy.

Postoperative cardiopulmonary complications occurred in 48 subjects. Although some subjects experienced more than one complication, the major complications were prolonged air leakage for more than 7 days (n = 22, 9.8%), arterial fibrillation (n = 17, 7.6%), pneumonia (n = 6, 2.7%), and others (n = 11, 4.8%). There was only one in-hospital death. The case involved a patient who underwent reoperation for a refractory air leak and developed respiratory failure requiring mechanical ventilation before ultimately dying from multiple organ failure on postoperative day 25.

3.2. The overall survival

The median follow-up period was 60.8 months (interquartile range, 52.4–60.8). During this period, 38 deaths were recorded (17.0% of all the subjects). Of the subjects who remained alive, 25 cases (11.2%) were censored because they were lost to follow-up. The 5-year survival rate of those covering a 6MWD of < 400 m was significantly lower than

Table 1
Baseline characteristics of the patients (n = 224).

Variables	
Age, years	71(64 –78)
Males	135 (60.3)
Body mass index, kg·m^2	22.5 (20.5–24.9)
Smoking history	
Never	79 (35.3)
Former or current	145 (64.7)
Presence of comorbidity	115 (51.3)
Charlson Comorbidity Index score	
0	109 (48.7)
1	49 (21.9)
2	39 (17.4)
3	16 (7.1)
4	8 (3.6)
≥ 5	3 (1.3)
ECOG PS	
0	170(75.9)
1	48 (21.4)
2	6 (2.7)
Pulmonary function	
FEV_1, % predicted	97 (82–108)
DLCO, % predicted	94 (78–112)
Pathological stage	
I A	118 (52.7)
I B	65 (29.0)
II A	21 (9.4)
II B	20 (8.9)
Histology	
Adenocarcinoma	162 (72.3)
Squamous cell	58 (25.9)
Others	4 (1.8)
Exercise capacity	
6-min walk distance, m	461 (389–525)
6-min walk distance, % predicted	108 (92–117)
Cardiopulmonary complication	48 (21.4)

Data are shown as No. (%) for categorical variables or median (interquartile range) for continuous variables, unless otherwise stated. ECOG PS, Eastern Cooperative Oncology Group Performance status; FEV_1, forced expiratory volume in 1 s; DLCO, diffusion capacity of the lung for carbon monoxide.

that of those covering a 6MWD of ≥400 m (65.3% vs. 88.0%, $p < 0.001$ [log-rank test]; Fig. 1). The HRs and 95% CIs for the overall survival, as obtained from the Cox proportional hazards model are shown in Table 2. After adjusting for age and pathological stage, the HR for the overall survival among patients with a 6MWD of < 400 m was significant (HR, 2.40; 95% CI, 1.20–4.79; Model 1). We found that a 6MWD of < 400 m remained significant after adjusting for postoperative cardiopulmonary complications (HR, 2.12; 95% CI, 1.03–4.35; Model 2). However, a 6MWD of < 400 m did not provide additional prognostic value beyond the PS, with was included as an additional confounder in Model 1 (HR, 1.78; 95% CI, 0.82–3.84; Model 3).

4. Discussion

The object of the present study was to verify whether or not there is a relationship between the preoperative exercise capacity, as measured by the 6MWT, and the prognosis of patients undergoing thoracoscopic lobectomy for stage I and II NSCLC. Our findings demonstrated that the 6MWD was associated with long-term mortality.

Underlying exercise intolerance is a significant risk factor for poor postoperative outcomes in patients being considered for resection [10–16]. Basically, the reduced exercise capacity of lung cancer patients is directly affected by the pathophysiological effect of the cancer and/or its treatment [33], leading to a worse long-term prognosis. A significant inverse relationship between the exercise capacity measured with a cardiopulmonary exercise test (CPET) and the long-term survival has been demonstrated in patients with suspected stage I to IIIA NSCLC [8], as well as in patients who underwent surgery for early-stage NSCLC [10]. Regarding exercise testing other than via a CPET, Brunelli et al. [11] performed an observational study and reported that an impaired exercise capacity as assessed by a preoperative stair-climbing test was inversely associated with the long-term survival in patients with radical resection for stage I NSCLC. Jones et al. [7] showed that the 6MWD is a strong independent predictor of the prognosis that aids in the prediction of the survival (beyond traditional risk factors) in patients with metastatic NSCLC. Another study by Kasymjanova et al. [9] showed that patients with a 6MWD of ≥400 m before chemotherapy had a greater survival time than those with a 6MWD of < 400 m. To our knowledge, however, no studies have shown an association between the 6MWT and the long-term survival of operable NSCLC patients. This may therefore be the first study to examine the independent influence of the 6MWD on mortality in this patient population.

Although several methods can be used to assess the physical function of lung cancer patients, each exercise test has its own limitations in relation to availability, feasibility, standardization, and interpretation [6]. For this reason, the optimal method of evaluating an individual's exercise capacity remains controversial. Traditionally, the CPET has been considered the gold-standard test for assessing the exercise capacity of lung cancer patients in clinical practice and research because it provides the most accurate determination of their oxygen consumption [34,35]. However, the CPET is not always available due to its expense and the need for trained personnel, specialized equipment, and medical supervision. Due to these limitations, a survey report found that the rate of CPET implementation was relatively low [34]. In contrast, simple non-laboratory tests, such as the 6MWT, the shuttle walk test, or the stair climbing test, do not require advanced technical equipment; thus, these tests are widely implemented. The 6MWT, according to a recent systematic review by Granger, is most commonly used for individuals with various clinical stages of NSCLC [36]. Despite a small number of studies, the 6MWD was found to be a significant predictor of postoperative complications and the length of hospital stay [12,13]. Thus, the addition of the 6MWT to the physiological evaluation of lung cancer patients was proposed based on a recent concise review as a means of predicting a lower risk of perioperative complications [6]. The present study suggested that, in addition to the preoperative evaluation setting, the performance of the 6MWT can provide additional prognostic information for lung resection candidates.

Previous studies have reported that the pathological stage and age were significant independent predictors of the survival in patients with NSCLC [20,23–25]. Independent of these confounders, our analysis showed that there was a significant association between the overall survival and exercise capacity after adjustment in a multivariable analysis. The prognostic value of postoperative complications has also been confirmed by previous studies of morbidity in resected NSCLC patients [28–30]. We previously reported that a reduced preoperative 6MWD was an independent risk factor for postoperative complications [12]. In the present study, however, we found that postoperative complications were not an independent predictor of mortality after thoracoscopic lobectomy. This interesting finding may be due to an impaired 6MWD possibly having a direct influence on the long-term mortality, regardless of the development of the postoperative complications.

On the other hand, the 6MWT was unable to provide additional prognostic information beyond the PS in our subjects. Nevertheless, the 6MWD was a strong independent predictor of the survival (beyond the PS) in patients with metastatic NSCLC [7]. In addition, the VO_2peak (determined by the CPET) was reported to be a prognostic marker for mortality beyond the PS in patients with stage I to IIIA NSCLC [8]. The discrepancy between the present and previous findings may be related

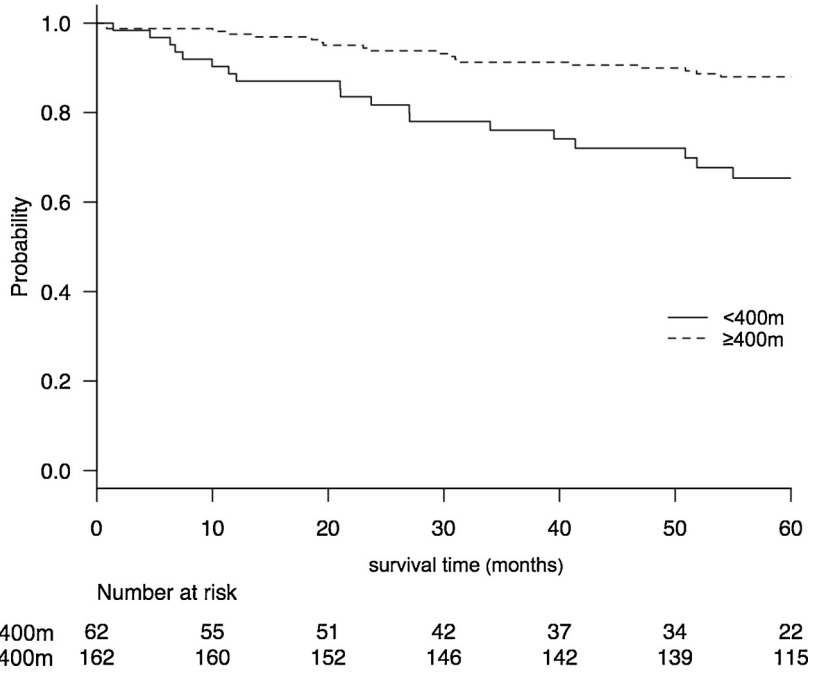

Fig. 1. Kaplan-Meier survival curves for the overall survival after thoracoscopic lobectomy in patients with non-small cell lung cancer, according to the preoperative 6-min walk distance.

Table 2
Multivariate analysis of the overall survival.

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	P Value	HR (95%CI)	P Value	HR (95%CI)	P Value
Age						
< 70years	Reference	0.016	Reference	0.016	Reference	0.027
≥ 70years	2.96 (1.22– 7.18)		2.98 (1.23– 7.24)		2.72 (1.12– 6.63)	
6MWD						
≥ 400 m	Reference	0.013	Reference	0.041	Reference	0.145
< 400 m	2.40 (1.20– 4.79)		2.12 (1.03– 4.35)		1.78 (0.82 – 3.84)	
Pathologic stage						
I	Reference	< 0.001	Reference	< 0.001	Reference	< 0.001
II	3.65 (1.86– 7.13)		3.47 (1.76– 6.81)		3.49 (1.78–6.84)	
Cardiopulmonary complication						
No			Reference	0.161		
Yes			1.66 (0.82– 3.36)			
ECOG PS						
0					Reference	0.078
1-2					1.96 (0.93– 4.16)	

HR: Hazard ratio; CI: confidence interval; 6MWD, 6-min walk distance; ECOG PS, Eastern Cooperative Oncology Group Performance status.

to differences in the patient population (advanced-stage vs. operable early-stage patients). In addition, the 6MWT evaluates each individual's sub-maximal exercise response, whereas the VO_2peak derived from CPET shows their maximal cardiopulmonary fitness [37]. Granger et al. reported that relationships between CPET and the 6MWD were poor in patients with lung cancer [38], despite a moderate relationship in patients COPD [39]. These results indicate that submaximal exercise tests, such as the 6MWT, might not be sensitive enough to sufficiently stress patients with early-stage disease and a good PS compared with the CPET [35], and it should not be used as a surrogate measure in this patient population. Furthermore, the 6MWT represents the functional exercise capacity of the subjects, which may better reflect their PS than the CPET. Thus, neither the 6MWD nor the PS was found to be a significant independent variable, when included in the same model (Model 3, Table 2). Nevertheless, it is noteworthy that the 6MWT, despite being a submaximal test, was a potential prognostic indicator and able to provide important complementary information for the PS, even in our subjects with a relatively well-preserved cardiopulmonary and physical performance.

The present study was associated with several limitations that should be considered when interpreting the findings of this analysis. First, the study was observational in nature, and the study population was limited to those who underwent surgery at a single institution. Thus, the inherent biases in patient selection and the experience of the surgeons should be taken into account. However, the impact of treatment bias from surgical procedures, including the extent of lymph node dissection, which might have influenced the prognosis, might have been lessened because of the high hospital and surgeon volume of our institution (defined as > 20 cases per year [40]). Second, several confounding variables (other than the variables we examined) that contribute additional prognostic information have been reported previously, including the sex, weight loss, smoking history, respiratory

comorbidity, histology, and mutation status [41]. However, based on the report by Peduzzi P et al., we were unable to include these variables in the multivariate analyses due to the small number of deaths [42]. Third, our analyses need to be interpreted with caution given the lack of a preliminary test before the 6MWT. The official technical standard for field walking tests in chronic respiratory disease recommends that two tests be performed, since there is a learning effect for the 6MWD [43]. Furthermore, there is a significant effect of test repetition on the 6MWD not only in people with COPD [44] but also in those who have undergone curative intent treatment for NSCLC [37]. However, when the 6MWT is used to assess risk, the magnitude of its learning effect is probably less important than when it is used to evaluate the response to treatments, and one test may be sufficient [43]. Finally, no information was available regarding recurrence or progression of disease or anticancer therapy, such as adjuvant chemotherapy, which might have influenced the long-term outcomes.

5. Conclusions

The present study showed that the preoperative exercise capacity, as measured by the 6MWT, was associated with the long-term prognosis in patients undergoing thoracoscopic lobectomy for stage I and II NSCLC. The 6MWT before surgery was useful not only in the preoperative evaluation setting but also for providing additional prognostic information for lung resection candidates. Further studies are needed to confirm the results of the present study.

Conflict of interest statements

All authors indicated no potential conflict of interest.

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Transparency document

The Transparency document associated with this article can be found in the online version.

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