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Result of the 6-min walk test is an independent prognostic factor of surgically treated non-small-cell lung cancer

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Key question

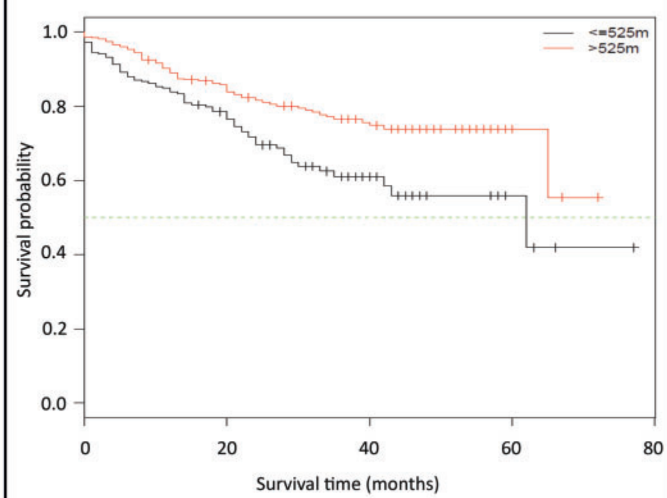
Does the result of the 6-minute walk test (MWT) help to predict survival in patients operated on due to non-small-cell lung cancer (NSCLC)?

Key findings

A distance of 525 metres in the 6-MWT identifies patients with better and worse chances of survival.

Take-home message

The result of the 6-MWT is an independent and convenient prognostic factor for patients with surgically treated NSCLC.



Abstract

OBJECTIVES: Pathological tumour, node and metastasis (TNM) stage remains the most significant prognostic factor of non-small-cell lung cancer (NSCLC). Meanwhile, age, gender, pulmonary function tests, the extent of surgical resection and the presence of concomitant diseases are commonly used to complete the prognostic profile of the patient with early stage of NSCLC. The aim of this study is to assess how the result of a 6-min walk test (6MWT) further assists in predicting the prognosis of NSCLC surgical candidates.

METHODS: Six hundred and twenty-four patients who underwent surgical treatment for NSCLC between April 2009 and October 2011 were enrolled in this study. All patients were accepted for surgery on the basis of a standard evaluation protocol. Additionally, patients completed the 6MWT on the day before the surgery, and threshold values of the test were assessed based on both the Akaike information criterion and the coefficient of determination R^2. Cox proportional hazards regression analysis was used to analyse the effect of important prognostic factors on the overall survival.

RESULTS: Three hundred and ninety men and 234 women with a mean age of 64 years underwent radical surgical treatment for primary lung cancer. Five hundred and twenty-five lobectomies (84%), 77 pneumonectomies (12%) and 24 (4%) lesser resections were performed. Three hundred and thirty-one patients (53%) were treated for stage I NSCLC, 191 patients (31%) for stage II and 102 patients (16%) for stages IIIA–IV. A distance of 525 m in the 6MWT [hazard ratio (HR) = 0.57, 95% confidence interval (CI) 0.41–0.78, $P < 0.001$] was the threshold value differentiating the patients' prognoses ($P < 0.001$). Using the Cox proportional hazards regression analysis, pathological TNM stage (IIA: HR = 1.87, 95% CI 1.95–2.92, $P = 0.006$; IIB: HR = 2.03, 95% CI 1.23–3.37, $P = 0.006$; IIIA–IV: HR = 2.37, 95% CI 1.49–3.75, $P < 0.001$), male gender (HR = 1.88, 95% CI 1.26–2.79, $P = 0.001$), pneumonectomy (HR = 1.78, 95% CI 1.17–2.70, $P < 0.001$) and the results of the 6MWT (HR = 0.50, 95% CI 0.36–0.70, $P < 0.001$) were considered as independent predictive factors of overall survival.

CONCLUSIONS: The result of a 6MWT is an independent and convenient prognostic factor of surgically treated non-small-cell lung cancer.

Keywords: Lung neoplasms • Surgery • Respiratory function tests • Walk test

INTRODUCTION

In the early stages of lung cancer, survival is mainly associated with nodal involvement, anatomical location and size of the tumour (T feature), and pathological grading. The clinical factors negatively influencing survival apart from tumour, node and metastasis (TNM) staging are older age [1, 2], treatment by pneumonectomy or wedge excision [3, 4], male gender [2], concomitant diseases [5], tobacco use [2] and molecular alterations [6, 7]. The poor results of the routinely assessed pulmonary function tests [forced expiratory volume in the first second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO)] also negatively impact long-term survival in operated patients [8]. Similarly, predicted postoperative FEV1 and VO2max values are physiological factors influencing survival [8–10]. The exact correlation of the results of physiological tests with overall survival (OS) still requires validation studies; however, these tests are promising in predicting survival in a homogenous group of patients operated on for NSCLC.

One of the important considerations when deciding whether or not to accept patients for surgery is the perioperative risk of complications and death. In addition to the routine tests performed in perioperative risk assessment, such as spirometry and DLCO [9], as well as the more technologically advanced cardiopulmonary exercise test, which is not administrable on all patients, clinicians should also consider using the more practical physiological tests such as the stair climbing test, the shuttle walk test [8] and, in our opinion, the 6-min walk test (6MWT). Because of its reproducibility and standardization [11], the 6MWT is already being evaluated for its ability to predict perioperative risk [12], and as mentioned above, we hypothesize that it can also be suitable in assessing a patient's long-term survival [13].

The aim of this study was to assess the influence of the 6MWT results on long-term survival in patients who undergo operations for NSCLC.

MATERIALS AND METHODS

Between 1 April 2009 and 30 October 2012, 2281 patients were operated on for various reasons in the Department of Thoracic Surgery, Medical University of Gdansk, Poland. There were six hundred and forty patients operated on for NSCLC who routinely underwent the 6MWT and were prospectively enrolled in the study. Six hundred and twenty-four patients (98%) in whom a complete data set was obtained were included in the final analysis.

All patients were accepted for surgery on the basis of the standard european respiratory society (ERS)/european society of thoracic surgeons (ESTS) physiological protocol [9]. This protocol consists of preoperatively assessed FEV1% and DLCO%. If the initial values are below 80%, then the predicted postoperative FEV1% and DLCO% are calculated. A cardiologist evaluated patients with a history of coronary heart disease or circulatory insufficiency. Additionally, all patients completed the 6MWT performed on the day preceding the surgery. A thoracic surgeon appointed the patients to the preoperative assessment. Meanwhile, the routine preoperative workup consisted of chest computerized tomography, bronchoscopy, abdominal ultrasonography and magnetic resonance of the brain in symptomatic patients. Patients in clinical stage IIB or higher underwent positron emission tomography–computed tomography. The treatment options were decided during multidisciplinary team meetings consisting of thoracic surgeons, medical and radiation oncologists, radiologists and pathologists. The patients were again discussed postoperatively to assess the possibility of delivering adjuvant chemotherapy in pathological stage IIA or higher. The data concerning the postoperative adjuvant treatment were not recorded.

All patients were willing to complete the 6MWT, with no refusals recorded. Previously collected prospective data from the Polish National Lung Cancer Registry (Krajowy Rejestr Raka Pluca) were combined with the results of the 6MWT, a routinely performed test in the department. The data were analysed retrospectively. The walk test was carried out along the hospital corridor with a length of 33 m. Two certified physiotherapists supervised the task, while a responsible physician was available during each test to resuscitate a patient, if necessary. The physiotherapists were trained in providing basic life support as well. The tests were performed following guidelines set by the American Thoracic Society [11]. In this study, we evaluated the impact of the crude result of 6MWT on OS. The other factors recorded during the test such as oxygen saturation, blood pressure, heart rate and dyspnoea scale were not considered in the final analysis.

A follow-up concerning survival was recorded for every patient in the study group in the database of the Ministry of Internal Affairs and Administration. The follow-up data included OS only, and the data on disease-free survival and cancer-specific survival were not collected at follow-up. The last follow-up visit was recorded on January 2017. No patients were lost. The median follow-up time was 54 months, whereas the maximum follow-up time was 92 months. Two hundred and seventy-five patients died during the study period. Meanwhile, the reference value of the 6MWT (%6MWT), influenced by gender, height, weight and age, was determined based on the equation of Enright and Sherrill

[14]. For the purposes of the initial data analysis, unpaired data characterized by normal distribution were compared with the unpaired *t*-test. In the case of non-normal distribution, the Mann–Whitney *U*-test was used for comparing 2 unmatched samples. Categorical variables were assessed by the χ^2 test (Table 1). Additionally, the univariable models were evaluated with the Wilcoxon test and the log-rank test. The accepted level of significance was $P<0.05$, and hazard ratios (HRs) were calculated with 95% confidence interval (CI). In univariable analysis, data were split into 2 groups: alive or deceased at the end of the study. Those 2 groups were then compared.

Because of the nature of this study as a retrospective analysis of prospectively gathered data and the lack of experimental intervention in the study group, the university institutional review board accepted the study and decided to waive informed consent.

The analysis was performed using the R software (version 2.15.2, Vienna, Austria). The patients were divided into groups (with cut-off values for age, result of the 6MWT, %6MWT and the age-adjusted Charlson comorbidity index) to achieve an easily interpretable model. The Akaike information criterion (AIC) was chosen as the primary method for calculating optimal cut-off value, and the results were confirmed by the pseudo R2, Wald and log-rank tests. The multivariable analysis was performed using the SAS software (version 9.3). In the first step, we analysed using multivariable Cox proportional hazards models for the following variables: age (continuous variable), age-adjusted Charlson comorbidity index (continuous variable), gender, pathological TNM (7th edition, indicator variable with reference groups IA and IB), type of resection (indicator variable with reference group lobectomy and lesser resections), result of the 6MWT (as a continuous variable) and a second model using %6MWT (as a continuous variable). Additionally, 2 analyses were performed using univariable Cox proportional hazards models for the following variables: age (categorical and 2-argument variables), age-adjusted Charlson comorbidity index (indicator variable with reference groups 0–3), gender, pathological TNM (7th edition, indicator variable with reference groups IA and IB), type of resection (indicator variable with reference group lobectomy), result of the 6MWT (as a dichotomized variable) and %6MWT (as a dichotomized variable). Factors with $P<0.05$ in the univariable analysis were considered for further assessment via Cox multivariable models of proportional hazards, a multivariable analysis model that makes use of stepwise regression (backwards elimination using the AIC). All variables had $P>0.05$ in Schoenfeld residuals test, meaning that the slope of scaled residuals on time is not statistically different from zero, thus, not violating the proportionality assumption.

Finally, despite the low influence of 6MWT as a continuous variable, 2 approaches were used to check the influence of 6MWT as a dichotomized value. In the first method, percentage values of 6MWT were used together with other variables in stepwise regression. This model consisted of age, TNM, type of resection, %6MWT and age-adjusted Charlson comorbidity index, which significantly influenced survival. The second model used values of 6MWT distance. In this model, survival was affected by gender, TNM, type of resection and 6MWT distance.

Table 1: Characteristics of patients

Features	Patients, *n* (%)
Age (years)	
≤63	310 (50)
>63	314 (50)
Gender	
Female	234 (38)
Male	390 (62)
7th pTNM	
IA–IB	331 (53)
IIA	121 (20)
IIB	70 (11)
IIIA–IV	102 (16)
Type of resection	
Lobectomy	525 (84)
Pneumonectomy	77 (12)
Sublobar resections	22 (4)
Operative access	
VATS	124 (20)
Thoracotomy	500 (80)
6MWT result (m)	
≤525	245 (39)
>525	379 (61)
%6MWT	
≤92	87 (14)
>92	537 (86)
Charlson comorbidity index	
0–3	259 (41)
4–5	256 (41)
6+	109 (17)

The mean age of the patients was 64.03 years and standard deviation 8.47. Mean 6MWT 540 m and standard deviation 88.54. Mean %6MWT 105.97 and standard deviation 15.85.

RESULTS

A total of 624 patients—234 women (38%) and 390 men (62%)—were enrolled in the study. Characteristics of the study population are presented in Table 1, and a histogram of the 6MWT results is shown in Fig. 1.

The AIC method was used to determine values that separated the study population into higher and lower mortality strata. The cut-off value of the 6MWT result in the whole study population was calculated to be 525 m (log-rank $P<0.001$) (Fig. 2A–C). One hundred and two patients in stages pIIIA–pIV had various factors influencing their short-term mortality and long-term mortality, representing a very heterogenous group. Consequently, when we restricted the estimation of the 6MWT result cut-off value to a more homogenous group of patients in stages pIA–pIIB, repeated AIC analysis revealed a cut-off value of 485 m (log-rank $P=0.002$) (Fig. 3A–C). The cut-off values for age that stratified survival (63 years) and the %6MWT result (92%) were also obtained with this method.

These cut-off values stratified the groups of patients and were subsequently used in stepwise regression analyses to assess their probabilities of survival. In the univariable model of analysis, age, gender, TNM, type of resection, the 6MWT result, %6MWT and age-adjusted Charlson comorbidity index were significant variables. Other data discussed to influence the survival in patients operated on for NSCLC were not taken into consideration for the analysis.

The models assessing the influence of 6MWT distance and %6MWT taken as continuous variables proved a minimal effect of %6MWT (HR 0.99, 95% CI 0.97–0.99), whereas 6MWT distance did not affect the survival. The data are presented in Table 2. The

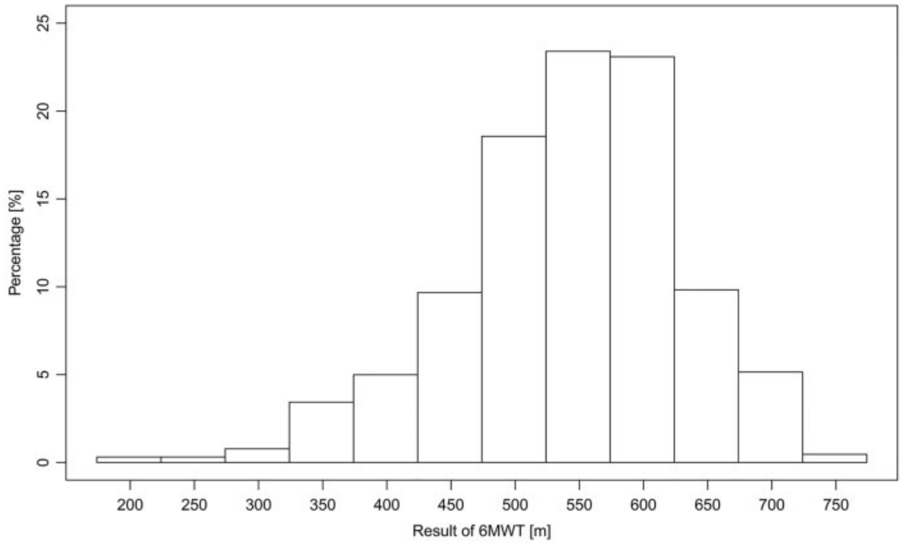


Figure 1: A histogram of the 6MWT result. 6MWT: 6-min walk test.

need for thoroughly evaluating the influence of 6MWT and %6MWT led to the analysis of the data as dichotomized variables. As both models evaluating the influence of 6MWT and %6MWT as dichotomized values indicated their effects, we decided to present the data and elucidate the 6MWT and %6MWT as independent factors influencing long-term survival (Table 3). Every time, we built separate models for 6MWT and %6MWT to avoid placing dependent data into 1 model.

DISCUSSION

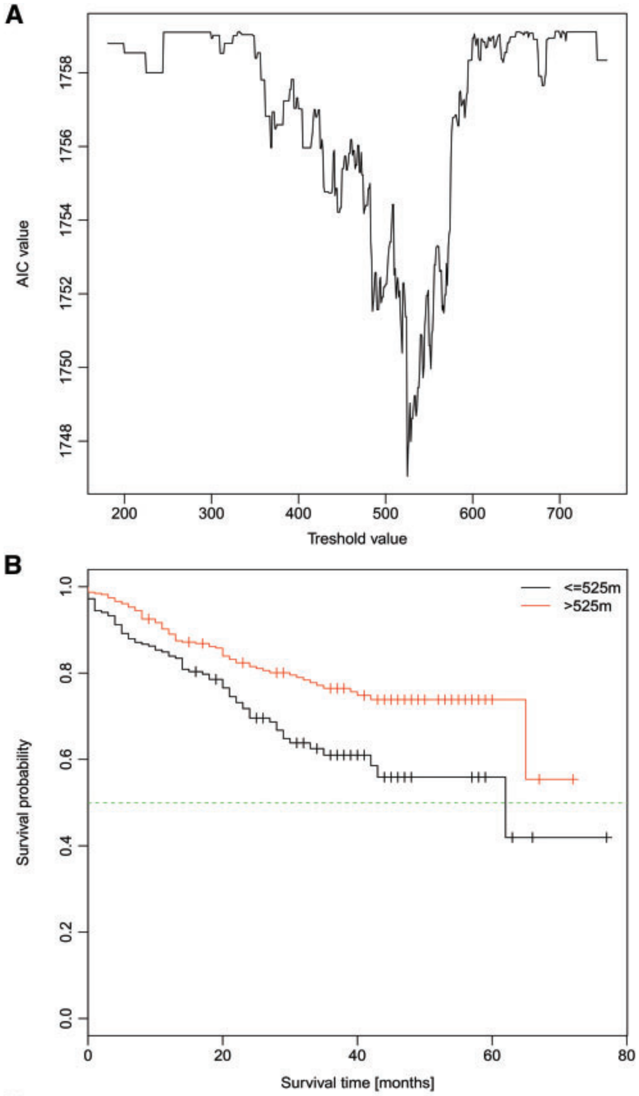
Patients undergoing debilitating surgical treatment for lung cancer require complex assessment from the beginning of treatment [8, 9, 15–17]. The assessment must go beyond the anatomy of their neoplastic disease described by TNM staging. It must be bolded that insufficient preoperative pulmonary efficiency examined by different measures, such as spirometry, is as strong of a predictive factor of OS as the pathological stage of non-small-cell lung cancer, type of performed resection and gender [5, 18–21]. The association of 6MWT with OS in the study group reflects the influence of complex cardiopulmonary diseases, i.e. chronic obstructive pulmonary disease (COPD), circulatory insufficiency and atherosclerosis. The limitation of the outcome of treatment in high-risk patients is a result of not only the oncological advancement of the process but also the concomitant diseases.

The aim of this study was to verify the hypothesis stating that the 6MWT, in correspondence with a patient's cardiovascular efficiency and their general well-being, is an independent factor in long-term survival after curative resections for NSCLC.

The main result of the study showed that a 6MWT distance of 525 m or 92% of a patient's predicted value differentiated the groups into different OS strata. The patients with shorter distance of 6MWT or lower percentage of reference value had worse survival, as proved by 2 different and independent models of stepwise regression analysis. These reflect the impact of this preoperative physiological test on the prediction of OS in lung cancer patients undergoing curative resections. We decided that only the data concerning the distance and percentage of reference value as the results of the 6MWT would be included in the final analysis. The vast amount of data gathered such as oxygen saturation or grade of dyspnoea would generate results that are difficult to interpret in daily clinical practice and would blur the overall message derived from this study. However, it will provide insights for future studies in defining the potential risk factors of lung cancer surgery.

An important clinical implication of our study reveals how the simple physiological 6MWT, which allows for both accurate and easily administered evaluation of respiratory and cardiovascular function, independently plays a role in predicting survival. In fact, a comparison of the HRs reveals that the 6MWT is roughly as significant of a factor of OS as the clinical stage of lung cancer. The simplicity of this method raises interest among physicians treating patients with marginal cardiorespiratory efficiency. Currently, among these tests, only the shuttle walk test and stair climb test have gained attention [8]. Both these tests are used in the american college of chest physycians (ACCP) algorithm in patients with mediocre-predicted postoperative values of FEV1% and DLCO% [8]. The use of these tests is justified by their correlation with VO2max and allows patients with satisfactory pulmonary function test results to be accepted for surgery. Similarly, the 6MWT was documented to excellently correlate with VO2max, as shown in a group of 50 patients aged 63 years with mild-to-severe COPD [22]. This group is very reflective of our patients with NSCLC requiring physiological qualification. Previously published material has also recognized that a 6MWT result of 498 m distinguished patients with different postoperative complications risk [12]. In our current study, a distance of 525 m distinguished the groups of patients with better long-term survival and worse long-term survival. Taken together, these cut-off values could be approximated to 500 m to identify the patients who are at higher risk of postoperative complications and with poorer OS. Thus, the strong correlation of 6MWT with VO2max [22] and the potential of 6MWT to predict complications and prognoses may lead to its implementation in the standard algorithm of physiological qualification for radical therapy in lung cancer [9].

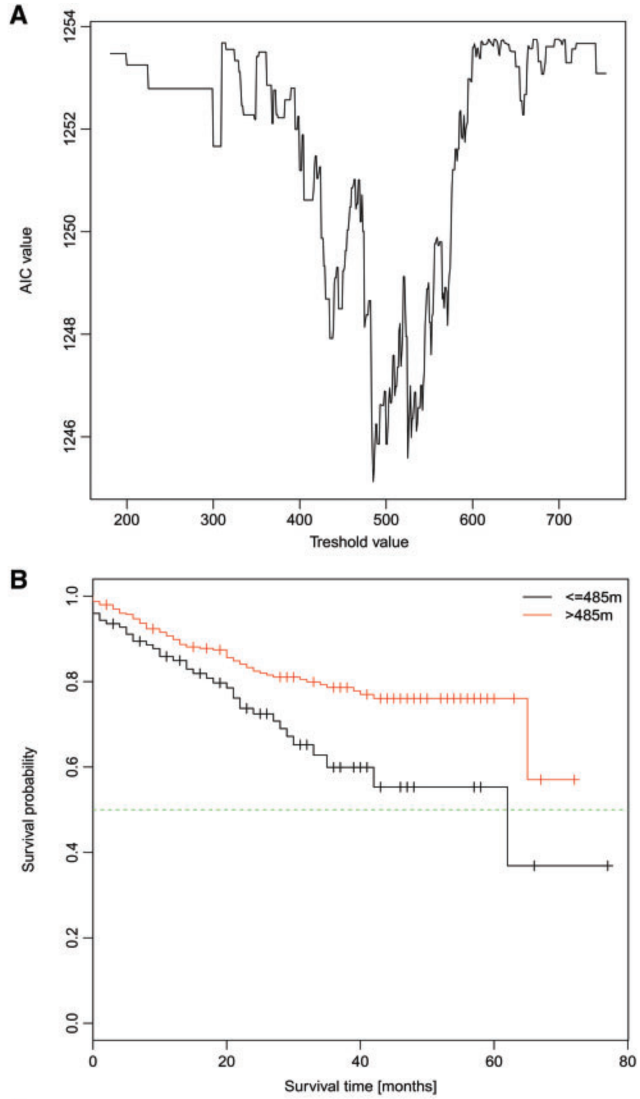
In addition, when taking into account that approximately 50% of NSCLC patients being considered for surgical resection may have contraindications for cardiopulmonary exercise test [10], the 6MWT is suggested as a simple, safe and inexpensive alternative.



C

Number at risk	0 months	12 months	24 months	36 months	48 months	60 months
≤525 metres	252	178	98	39	8	4
>525 meters	389	301	192	108	38	6

Figure 2: (**A**) The AIC value of the cut-off value of the result of 6-min walk test in the group of patients operated on due to stages pIA–pIV non-small-cell lung cancer. (**B**) Probability of survival in groups stratified by the result of the 6-min walk test in the group of patients operated on due to stages pIA–pIV non-small-cell lung cancer. Log-rank $P < 0.001$. (**C**) Number at risk. Probability of survival in groups stratified by the result of the 6-min walk test in the group of patients operated on due to stages pIA–pIV non-small-cell lung cancer. AIC: Akaike information criterion.



C

Number at risk	0 months	12 months	24 months	36 months	48 months	60 months
≤485 metres	124	90	57	21	6	3
>485 meters	400	318	200	114	38	7

Figure 3: (**A**) The AIC value of the cut-off value of the result of the 6-min walk test in the group of patients operated on due to stages pIA–pIIB non-small-cell lung cancer. (**B**) Probability of survival in groups stratified by the result of the 6-min walk test in the group of patients operated on due to stages pIA–pIIB non-small-cell lung cancer. Log-rank $P = 0.002$. (**C**) Number at risk. Probability of survival in groups stratified by the result of the 6-min walk test in the group of patients operated on due to stages pIA–pIIB non-small-cell lung cancer. AIC: Akaike information criterion.

There were no refusals to undergo the 6MWT in our study population; however, groups of patients unable to complete it have inherently higher risks of postoperative complication [12]. Functional tests, due to their simplicity and common applicability, deserve recognition in routine cardiopulmonary assessments. The 6MWT, the shuttle walk test, the stair climbing test and the self-paced walk test have already been thoroughly studied in COPD and heart failure. In fact, these tests may even be a tool to screen for the potential progression of respiratory or circulatory insufficiency in chronic conditions [8].

The analysis of 6MWT and %6MWT as continuous variables revealed the impact of these parameters on survival (Table 2, HR 0.99, 95% CI 0.98–0.99, $P = 0.009$), as well as the analysis of dichotomized data (Table 3, 6MWT: HR 0.50, 95% CI 0.36–0.70, $P < 0.001$ and %6MWT: HR 0.53, 95% CI 0.36–0.78, $P = 0.001$). The lower impact of factors, when analysed as continuous variables, can be

Table 2: Cox proportional hazards regression models of survival probability

	Model 1 (6MWT result)		Model 2 (%6MWT)	
Covariates	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)	1.02 (1.01–1.04)	0.019	1.03 (1.01–1.04)	<0.001
Gender				
Male	Ref.	Ref.	Ref.	Ref.
Female	0.71 (0.53–0.94)	0.017	0.76 (0.57–1.01)	0.066
7th pTNM				
IA–IB	0.47 (0.33–0.68)	<0.001	0.47 (0.33–0.67)	<0.001
IIA	Ref.	Ref.	Ref.	Ref.
IIB	1.06 (0.68–1.64)	0.782	1.06 (0.69–1.64)	0.775
IIIA–IV	1.66 (1.15–2.40)	0.006	1.67 (1.16–2.41)	0.005
Type of resection				
Lobectomy and sublobar resections	Ref.	Ref.	Ref.	Ref.
Pneumonectomy	1.41 (0.99–2.02)	0.055	1.41 (0.99–2.01)	0.058
Age-adjusted Charlson comorbidity index				
0–5	Ref.	Ref.	Ref.	Ref.
6+	1.16 (0.85–1.57)	0.339	1.18 (0.87–1.61)	0.281
6MWT result (m)	0.99 (0.99–1.00)	0.230		
%6MWT			0.99 (0.98–0.99)	0.009

CI: confidence interval; HR: hazard ratio; pTNM: pathological TNM; 6MWT: 6-min walk test.

Table 3: Cox proportional hazards regression models of survival probability

	Univariable model		Cox proportional hazards regression			
			Model 1		Model 2	
Covariates	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (years)						
≤63	Ref.	Ref.	Ref.	Ref.		
>63	1.78 (1.28–2.49)	<0.001	1.69 (1.19–2.38)	0.003		
Gender						
Female	Ref.	Ref.			Ref.	Ref.
Male	2.04 (1.39–2.98)	<0.001			1.88 (1.27–2.79)	0.002
7th pTNM						
IA–IB	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
IIA	2.02 (1.30–3.13)	0.002	1.79 (1.14–2.80)	0.011	1.87 (1.20–2.92)	0.006
IIB	2.52 (1.55–4.11)	<0.001	2.41 (1.46–3.97)	0.001	2.03 (1.23–3.37)	0.006
IIIA–IV	3.26 (2.13–4.98)	<0.001	2.57 (1.63–4.06)	<0.001	2.37 (1.49–3.76)	<0.001
Type of resection						
Lobectomy and sublobar resections	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Pneumonectomy	2.76 (1.88–4.06)	<0.001	1.94 (1.28–2.95)	0.002	1.78 (1.17–2.71)	0.007
6MWT result (m)						
≤525	Ref.	Ref.			Ref.	Ref.
>525	0.57 (0.41–0.79)	0.001			0.50 (0.36–0.70)	<0.001
%6MWT						
≤92	Ref.	Ref.	Ref.	Ref.		
>92	0.5 (0.34–0.73)	<0.001	0.53 (0.36–0.78)	0.001		
Age-adjusted Charlson comorbidity index						
0–5	Ref.	Ref.	Ref.	Ref.		
6+	1.61 (1.11–2.33)	0.012	1.57 (1.07–2.31)	0.022		

CI: confidence interval; HR: hazard ratio; pTNM: pathological TNM; 6MWT: 6-min walk test.

related to a non-linear relation between the predictor and the variable. Despite the lower mathematical impact of the discovered relations, we decided to publicize the data, supporting the implications of 6MWT distance and %6MWT, as we believe that not publishing the results of this study will result in a loss to patients and their surgeons. However, another weakness of the study is the lack of information about the reason for death. In this type of research, OS does not reflect the exact meaning of a discovered relationship between the result of 6MWT and the length of the life after treatment. However, the only reliable and available data derived from the government database are the data concerning the time of event. Furthermore, the data gathered does not distinguish between the groups of patients who underwent preoperative or postoperative radiotherapy or chemotherapy. Nevertheless, 84% of patients underwent surgery due to stages I–IIB, where the effect of adjuvant treatment is restrained. We performed a subgroup analysis in patients who are in early stages of lung cancer, which repeatedly confirmed the major findings of the study.

The clinical meaning of this test is not unequivocal. We clearly state that we do not advocate abandoning surgical treatment on the basis of the 6MWT alone. However, this test may be helpful for decision-making in border-line patients (i.e. senile patients) and in patients in whom the appropriate qualification may be difficult (i.e. tracheostomy patients).

CONCLUSIONS

We conclude that the 6MWT can be a useful tool in differentiating patients with different prognoses concerning survival after curative resections for NSCLC.

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Conflict of interest: none declared.

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