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ORIGINAL RESEARCH

Impact of age on functional exercise correlates in patients with advanced lung cancer

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Background: The functional exercise capacity and its correlates in advanced cancer patients in stratified age groups were examined.

Materials and methods: A total of 105 patients with advanced lung cancer were recruited prospectively and stratified into young (≤50 years), middle (51–65 years), and old (>65 years) age groups. Respiratory performances, which included maximal inspiratory and expiratory pressure, forced expiratory volume in 1 second, and forced vital capacity were measured. The distance ambulated in a 6-minute walk test was used as an indicator for functional capacity.

Results: The young age group had lowest baseline pulmonary function and performed worse on the 6-minute walk test among the three age groups. The risk factors for poor functional capacity were female, lower percent predicted maximal expiratory pressure, worse dyspnea, and lower hemoglobin in the young age group; lower percent predicated forced expiratory volume in 1 second and forced vital capacity, and greater weight loss in the middle age group; and only worse dyspnea in the old age group. The above identified risk factors accounted for 73.6%, 58.5%, and 42.1% variance in 6-minute walk distance for the young, middle, and old age group, respectively.

Conclusion: The impacts of these factors on functional exercise capacity should be carefully considered while designing exercise intervention according to age.

Keywords: age, 6-minute walk test, advanced lung cancer, respiratory muscle strength, spirometry

Introduction

Based on GLOBOCAN 2008 statistics, Eastern Asia has one of the highest lung cancer incidence rates in the world, and the mortality rate remains high despite the advances in treatment drugs.[1]

Physical and functional well-being are considered essential dimensions of overall quality of life and foundations for optimal treatment choices. The 6-minute walk test (6MWT), which is a commonly used measurement of functional exercise capacity in patients with pulmonary morbidity, provides a good index of the patient's ability to perform daily activities and correlates better with formal measures of quality of life.[2,3] Recently, the distance covered in 6MWT (6MWD) was found to be an independent unfavorable prognostic factor in patients with newly diagnosed advanced non-small cell lung cancer (NSCLC).[4] Although 6MWD has been investigated in patients with advanced lung cancer,[4] factors other than height, weight, and sex, which are known to affect the 6MWD independently, have not yet been assessed in patients with advanced lung disease.

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In patients with cardiorespiratory disorders, strength of respiratory muscle and pulmonary function have been shown to be independent predictors for 6MWT performance.[5,6] In patients with advanced lung cancer, published research on the evaluation of respiratory muscle strength have focused mainly on its relation to dyspnea,[7,8] and pulmonary function testing (PFT) is often used to screen whether patients are suitable for lung resection. The relations between respiratory muscle strength and PFT to 6MWD is less understood and remains to be determined in this patient population.

Incidence data from the National Cancer Institute's Surveillance Epidemiology and End Results have shown that the risk of developing lung cancer varies with several fold differences between those with an age of less than 50 and those of age 65 or older.[9] Lung cancer impacts a substantial economic burden on individuals and society, and age alone has a great impact on functional exercise capacity and the ability to tolerate systemic anticancer therapy; however, functional exercise capacity has not yet been studied and compared in stratified age groups in this patient population. Therefore, the purpose of this study was to examine the functional exercise capacity and its correlates in patients with advanced lung cancer at diagnosis and prior to receiving any anticancer therapy in three stratified age groups: young (≤50 years), middle (51–65 years), and old (>65 years).

Materials and methods

Participants

Patients with advanced lung cancer were prospectively followed throughout the course of cancer care, in which respiratory performance and functional exercise capacity were examined and compared based on their age groups prior to the designated anticancer treatment delivered. Consecutive patients with advanced lung cancer diagnosed between August 2010 and May 2011 were recruited for the study. Eligible patients were ≥18 years of age, with histologically confirmed lung carcinoma, who had stage IIIb or stage IV disease, and with adequate cognitive function (scored 24 or more on mini mental state examination).[10] Patients were excluded if they had musculoskeletal or lung conditions (eg, recent lung infection) that might compromise functional exercise or PFT prior to the investigation. All patients provided written informed consent before study entry. Approval from the institutional review board of the National Taiwan University Hospital was obtained (No 200912088R).

Respiratory performance tests

Measurement of the maximum static inspiratory pressure (MIP) and maximum expiratory mouth pressure (MEP) were used to assess the global strength of respiratory muscle.[11] The measurements were performed using a manometer (Inspiratory Force Meter, Model 4103; Boehringer, Norristown, PA, USA), with patients in a sitting position and wearing a nose clip. Three acceptable measurements of the maximum static inspiratory pressure and MEP were recorded, and the highest value obtained was utilized for further calculations. Spirometry was performed according to the American Thoracic Society recommendations.[12] Parameters included forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC ratio expressed in absolute and percentage predicted values. Normal predicted values were derived from the equations of Ip et al for an adult Chinese population.[13]

Functional exercise capacity

General functional performance was assessed using Karnofsky Performance Scale and Barthel Index.[14,15] Objective functional exercise capacity was assessed by 6MWT and was performed according to American Thoracic Society/European Respiratory Society criteria.[2] 6MWD were expressed in absolute and percentage predicted values. Normal predicted values were derived from the equations of Troosters et al.[16]

The Modified Borg Scale (categorical scale) was used to measure the average dyspnea experienced in the past week prior to the baseline assessment.[17] Weight loss was defined as a loss of more than 5% of pre-illness body weight over the past 6 months in the absence of simple starvation.[18]

Statistical analyses

Statistical analyses were performed using SPSS version 17.0 (IBM Corporation, Armonk, NY, USA). The Kolmogorov–Smirnov test was used to check for normal distribution of continuous data, and data with a normal distribution was described as mean ± standard deviation (SD). Variable comparisons between age groups were performed using one-way ANOVA with the Bonferroni post hoc test. Differences in categorical variables were compared using the chi-square test. Multicollinearity was tested using Spearman's correlation and eigenvalues of the scaled and uncentered cross-product matrix, condition indexes, variance-decomposition proportions, and the variance inflation factors and tolerances were computed for individual variables. The relations of medical and respiratory performance variables with 6MWD were assessed using single-variable regression analysis in stratified age groups and also for the entire cohort. The potential factors which the single-variable analysis suggested were related to 6MWD were then examined jointly in a multivariable analysis to establish which variable best predicted functional exercise capacity for the entire population. The initial model contained all the variables found to be individually associated with 6MWD. Variables were then dropped in turn from the model, using a backward stepwise selection method, until all remaining variables were significantly associated with 6MWD. A P-value of <0.05 was accepted as indicative of statistical significance.

Results

A total of 105 patients met the inclusion criteria to participate. The characteristics of the study population stratified by age are summarized in Table 1. The mean (±SD) age of the cohort was 62.3 (±11.6) years; and 59 (56.2%) and 46 (43.8%) patients were male and female, respectively. In the entire study cohort, 95 (90.5%) and 10 (9.5%) patients were diagnosed with NSCLC and small cell lung cancer, respectively. All patients in the young age group had NSCLC, and 44 (93.6%) and 32 (82.1%) patients in the middle and old age group had NSCLC, respectively. No significant differences were found in the distribution of sex, cancer stage, educational level, number of metastatic sites, and body mass index among groups. The scores of Karnofsky Performance Scale ($P < 0.001$) and Barthel Index ($P = 0.02$) were significantly lower in the old age group compared to those of the middle age group (Table 1). The percentage of patients being current or former smokers was highest in the old age group (66.7%). The hemoglobin value was significantly lower in the young and old age group compared to that of the middle age group. A total of 46 (43.8%) patients had weight loss status upon diagnosis with no significant distribution difference across the stratified age groups.

The mean absolute but not percent predicted values of FEV_1 (old versus young and middle: $P < 0.001$) and FVC (old versus young: $P = 0.02$; old versus middle: $P < 0.001$) were significantly lower in the old age group than those of the two other age groups. Moreover, patients in the young age group had significantly lower percent predicted FEV_1

Table 1 Demographic and disease characteristics of patients with advanced lung cancer in stratified age groups

	≤50 (n = 19)	51–65 (n = 47)	>65 (n = 39)	*P*-value
Male/female	8/11	26/21	25/14	0.28
Age in years	45.74 ± 4.51[a,b]	59.87 ± 4.39[a,c]	75.36 ± 5.85[b,c]	
Body mass index, kg/m^2	22.28 ± 3.86	22.96 ± 2.78	22.38 ± 3.93	
Cancer stage, n (%)				0.41
Stage IIIb	1 (5.3)	6 (12.8)	7 (17.9)	
Stage IV	18 (94.7)	41 (87.2)	32 (82.1)	
Cancer type, n (%)				0.06
Non-small cell lung cancer	19 (100)	44 (93.6)	32 (82.1)	
Small cell lung cancer	0	3 (6.4)	7 (17.9)	
Smoking, n (%)				0.01*
Current or former smoker	6 (31.6)	18 (38.3)	26 (66.7)	
Never smoked	13 (68.4)	29 (61.7)	13 (33.3)	
Education, n (%)				0.06
Illiterate	0 (0)	2 (4.3)	5 (12.8)	
Elementary school	4 (21.1)	11 (23.4)	18 (46.2)	
Middle school	3 (15.8)	6 (12.8)	4 (10.3)	
Senior high school	3 (15.8)	14 (29.8)	5 (12.8)	
College and above	9 (47.4)	14 (29.8)	7 (17.9)	
Current employment, n (%)				<0.001*
Yes	14 (73.7)	22 (46.8)	4 (10.3)	
No	5 (26.3)	25 (53.2)	35 (89.7)	
Metastatic sites, n (%)				0.10
<2	7 (36.8)	22 (46.8)	25 (64.1)	
≥2	12 (63.2)	25 (53.2)	14 (35.9)	
Karnofsky performance status	86.84 ± 8.20	88.51 ± 5.10	82.89 ± 10.88[c]	
Barthel index	98.68 ± 7.74	98.40 ± 7.16	94.34 ± 10.67[c]	
Hemoglobin, g/dL	12.13 ± 2.01[a]	13.04 ± 1.38	12.39 ± 1.85[c]	
Weight loss, n (%)	6 (31.58)	20 (42.55)	20 (51.28)	0.12

Notes: Data are presented as mean ± standard deviation or number (and percent) as appropriate. *Indicates significant difference among the three groups; [a]≤50 versus 51–65, $P < 0.05$; [b]≤50 versus >65, $P < 0.05$; [c]51–65 versus >65, $P < 0.05$.

(young versus middle: $P = 0.01$; young versus old: $P = 0.04$) and FVC (young versus middle: $P = 0.003$; young versus old: $P = 0.02$) compared to those of patients in the middle age group. The mean absolute value of MEP was significantly lower in the old age group compared to that of the middle age group. However, relative values of maximum static inspiratory pressure and MEP (percent predicted) were not different among the age groups (Table 2).

Compared to the middle age group, the absolute value of 6MWD was significantly lower in the young ($P < 0.001$) and old ($P = 0.02$) age groups. The relative values of 6MWD were found to be significantly lower in the young age group compared to those of the two other age groups. Patients in the young and old age groups both had significantly higher dyspnea scores than that of the middle age group.

In the stratified age groups, univariable regression analysis showed that significant predictors of 6MWD were sex, percent predicted MEP, dyspnea, and hemoglobin ($r = 0.65$, $P = 0.005$) in the young age group; percent predicated FEV_1, FVC, and weight loss in the middle age group; and only dyspnea in the old age group (Table 3).

For the entire study population, the final multivariable regression model is shown in Table 4. Predicted value of FEV_1 and FVC were highly correlated ($r = 0.82$). FEV_1 was a slightly better predictor variable of functional exercise capacity than FVC ($R^2 = 20.8\%$ versus 15.3%), thus only FEV_1 was considered for entering the multivariable regression model. Factors identified for functional exercise capacity were age group, percent predicted FEV_1, dyspnea, hemoglobin, and weight loss. All identified significant factors together explained 47.2% of the total variance of functional exercise capacity measure in patients with advanced lung cancer. All predictors in the final model had a variance inflation factors score <10 and tolerance >0.2, indicating no multicollinearity among these predictors.[19]

Table 2 Respiratory performance and functional exercise capacity of patients with advanced lung cancer in stratified age groups

	≤50 (n = 19)	51–65 (n = 47)	>65 (n = 39)
FEV_1, L	1.90 ± 0.72	1.90 ± 0.63	1.32 ± 0.44[b,c]
FEV_1, % predicted	67.34 ±15.59[a]	81.67 ± 21.02	77.05 ± 23.30
FVC, L	2.36 ± 0.87	2.39 ± 0.74	1.82 ± 0.55[b,c]
FVC, % predicted	70.01 ± 16.86[a]	83.89 ± 18.69	77.91 ± 17.40
MIP, cmH_2O	64.21 ± 23.44	63.47 ± 25.60	55.00 ± 28.83
MIP, % predicted	58.79 ± 19.80	64.33 ± 22.14	61.82 ± 28.88
MEP, cmH_2O	70.21 ± 38.23	84.83 ± 36.12	60.10 ± 29.16[c]
MEP, % predicted	61.44 ± 27.47	68.75 ± 21.07	67.22 ± 27.42
6MWD, m	355.77 ± 123.08[a]	398.77 ± 104.12	305.19 ± 110.14[c]
6MWD, % predicted	56.68 ± 18.69[a,b]	75.72 ± 20.63	68.51 ± 26.33
Modified Borg Dyspnea Scale	3.14 ± 1.32[a]	1.50 ± 0.82	2.25 ± 1.38[b,c]

Notes: Data are presented as mean ± standard deviation. [a]≤50 versus 51–65, $P < 0.05$; [b]≤50 versus >65, $P < 0.05$; [c]51–65 versus >65, $P < 0.05$.

Abbreviations: 6MWD, 6-minute walk distance; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MEP, maximum expiratory pressure; MIP, maximum inspiratory pressure.

Table 3 Univariate predictors of percent predicted 6MWD of patients with advanced lung cancer in stratified age groups

Variables	R^2	Standardized coefficient	*P*-value
Young age			
Female (versus male)	0.303	–0.55	0.01
MEP (% predicted)	0.248	0.50	0.03
Dyspnea	0.218	–0.47	0.04
Hemoglobin	0.421	0.65	0.003
Middle age			
FEV_1	0.336	0.58	<0.0001
FVC	0.311	0.56	<0.0001
Weight loss (versus no weight loss)	0.115	–0.34	0.019
Old age			
Dyspnea	0.22	–0.35	0.03

Abbreviations: 6MWD, 6-minute walk distance; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MEP, maximum expiratory pressure.

Discussion

In previous studies, the 6MWT or 6MWD has been shown to be a reproducible[20,21] and objective functional capacity test for patients with pulmonary morbidity.[2] In patients with lung cancer, the 6MWT has been used most often in the preoperative setting to predict surgery outcome after lung resection.[22,23] For patients with inoperable lung cancer, 6MWD was found to be a useful prognostic factor for survival.[4,24] Various cutoff values for 6MWD have been proposed to predict outcomes in patients with lung cancer under several circumstances, which included surgery resection,[22] radiotherapy,[25] and first two cycles of chemotherapy.[4] The analysis was not yet available to investigate the predictive value of 6MWD and survival outcome in this study; whether the same cutoff values could apply to different stratified age groups remains questionable.

The important finding of this study was that the young age group performed worse on the 6MWT and the average 6MWD was 43.4% below the sex–age predicted distance. Bryant and Cerfolio found that patients younger than 45 years of age with non-small cell lung cancer have a significantly

Table 4 Multivariable predictors of percent predicted 6MWD in patients with advanced lung cancer

Variables	β	SE	95% confidence interval for B	*P*-value	Collinearity statistics	VIF
					Tolerance	
Age group						
Young age (versus middle age)	−10.52	5.89	(−22.50, −1.04)	0.002	0.803	1.25
FEV_1 (% predicted)	3.15	0.12	(1.48, 5.25)	<0.001	0.911	1.10
Dyspnea	−2.56	1.14	(−5.05, −0.52)	0.017	0.881	1.14
Hemoglobin	3.94	1.31	(0.16, 5.34)	0.03	0.873	1.15
Weight loss (versus no weight loss)	−10.64	4.63	(−18.02, −1.84)	0.001	0.931	1.07

Notes: VIF scores <10 and tolerances >0.2 indicate no multicollinearity.
Abbreviations: 6MWD, 6-minute walk distance; B, unstandardized regression coefficients; β, standardized coefficients; FEV_1, forced expiratory volume in 1 second; SE, standard error; VIF, variance inflation factors.

worse prognosis than older patients with similar stages and tumor characteristics.[26] One of the explanations for this phenomenon is that younger patients with lung cancer often present with more extensive disease and have usually waited longer between onset of symptoms and diagnosis.[26,27] In this study, 94.7% (n = 18) of patients in the young age group were confirmed to have a stage IV disease, and most patients presented with symptoms upon diagnosis. Nugent et al found that lung cancer attacks women more frequently in the young age group.[28] In our study, we found 58% (n = 11) patients in the young age group were female, and most of them reported to have a sedentary lifestyle. Although previous studies found no association between physical activity level and 6MWD,[29] in this study, sex was found to be an important factor for 6MWD, with a significantly worse performance in females than in males. All these factors might explain the poor performance on 6MWT in the young age population.

Dyspnea is a relatively common and highly debilitating symptom in patients with advanced lung cancer.[30,31] In this study, dyspnea sensation was found to be higher in patients of young and old age group, which might partly be explained by their worse pulmonary function (ie, percent predicted FEV_1 and FVC) compared to that of the middle age group. Furthermore, we found that dyspnea was negatively associated with 6MWD in the young and old age group, and this finding supports the notion that dyspnea could lead to exercise avoidance and deconditioning in patients with cancer.[32] The dyspnea perception for patients in the young, middle, and old age group was between "moderate to somewhat severe", "very slight to slight", and "slight to moderate", respectively. The average reductions of 6MWD below the age–sex predicted value were 43.4%, 24.4%, and 31.6% for the young, middle, and old age group, respectively. Worse dyspnea paralleled with worse functional exercise capacity implied that in patients with advanced lung cancer, severity of dyspnea and exercise impairment occur in a dose-response manner. Travers et al speculated that respiratory muscle weakness was one possible explanation for the shallow breathing pattern found in outpatients of cancer with unexplained dyspnea.[33] On the contrary, some studies showed no significant correlation between respiratory muscle strength and dyspnea in patients with cancer.[8,34] In this study, for patients with advanced cancer regardless of age, respiratory muscle strength correlated negatively with dyspnea and 6MWD, which implied respiratory muscle strength has potential impact on functional exercise capacity in this population.

Age is another known predictor factor for anticancer treatment planning and prognosis in patients with lung cancer.[35] Advancing age is often associated with having more comorbidity and thus is considered to impart a dismal prognosis for patients with lung cancer. However, in our study, we found younger age (≤50 years) but not old age had an adverse impact on functional exercise capacity. Whether the worse exercise performance at diagnosis would lead to worse survival prognosis warrants further investigation.

The study observed a strong correlation between PFT and 6MWD in the middle age group. This was an interesting and somewhat surprising finding because PFT usually is not the determining factor for exercise performance in persons who have a "within normal range" PFT result. On the other hand, for the entire study population, percent predicted FEV_1 was found to correlate significantly with 6MWD. These results implied that the reduction of exercise capacity in patients with advanced lung cancer might be partly due to the detrimental effect of extensive tumor burden on pulmonary function.

One limitation of this study was that we did not measure the diffusing capacity of the lung for carbon monoxide (DLCO). Since DLCO is a valuable proxy measurement for alveolar oxygen exchange, it is an important factor affecting exercise capacity. For patients with resectable lung cancer, DLCO is usually a recommended test and is an independent predictor of postoperative mortality and morbidity.[36] The main reason for not measuring DLCO in patients of this study was mainly due to the inoperable nature of the disease upon diagnosis.

Weight loss and hemoglobin are important predictive and prognostic factors for treatment response and survival in patients with lung cancer.[35,37] In this study, we found weight loss and hemoglobin correlated significantly with exercise performance in patients with advanced lung cancer prior to any anticancer treatment initiated. Hemoglobin is critical for the transport of oxygen and thus has a well-established role in determining exercise performance. It is interesting to note that in the young age group there was a significant difference in hemoglobin levels between female and male patients (11.4 g/dL versus 13.6 g/dL, $P < 0.001$). The possible explanation for this difference is that low hemoglobin levels are prevalent in premenopausal women due to many potential causes (eg, menstruation).[38] Low hemoglobin in the young age group might also explain the considerably worse 6MWT performance of that group. Op den Kamp et al demonstrated that exercise capacity was reduced in patients with lung cancer, who on average had 3.1% weight loss in the past 6 months and had no experience of any type of anticancer treatment.[39] In our study, 43.8% (n = 46) patients had weight loss within 6 months prior to lung cancer diagnosis with an average weight loss of 6.2%, which was higher than the recent definition of cachexia (weight loss >5%) in a cancer population.[18] Although, weight loss was a risk factor for worse functional exercise performance in the entire study cohort, we found that in the young age group, weight loss was not prominent (average 1%) and thus might not play a part in affecting functional exercise performance in this age group. Whether therapeutic interventions targeting weight loss or low hemoglobin level would provide benefits for exercise performance in patients with advanced lung cancer warrants further exploration.

Conclusion

In conclusion, our data demonstrate that functional exercise performance measured by 6MWT was reduced in patients with advanced lung cancer, and the magnitude of reduction and the factors correlated with the performance were different among stratified age groups. Exercise intervention has an important role in helping patients stay physically strong so they can tolerate anticancer treatment and continue to participate in everyday activities. The results of this study provided additional insight into the various factors that are related to functional exercise capacity in different age groups of patients with advanced lung cancer, and these factors might require attention while designing exercise training protocol for this population.

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Disclosure

The authors report no conflicts of interest in this work.

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