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ORIGINAL ARTICLE

Exercise capacity and cancer-specific quality of life following curative intent treatment of stage I–IIIA lung cancer

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Abstract

Purpose Lung cancer survivors are at risk for health impairments resulting from the effects and/or treatment of lung cancer and comorbidities. Practical exercise capacity (EC) assessments can help identify impairments that would otherwise remain undetected. In this study, we characterized and analyzed the association between functional EC and cancer-specific quality of life (QoL) in lung cancer survivors who previously completed curative intent treatment.

Methods In a cross-sectional study of 62 lung cancer survivors who completed treatment ≥ 1 month previously, we assessed functional EC with the 6-min walk distance (6MWD) and cancer-specific QoL with the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC-QLQ-C30). Cancer-specific QoL was defined using a validated composite EORTC-QLQ-C30 summary score. Univariable (UVA) and multivariable linear regression analyses (MVA) were performed to assess the relationship between functional EC and cancer-specific QoL.

Results Lung cancer survivors had reduced functional EC (mean 6MWD = 335 m, 65% predicted) and QoL (mean EORTC-QLQ-C30 summary score = 77, scale range 0–100). In UVA, 6MWD was significantly associated with cancer-specific QoL ($R^2 = 0.16$, $p = 0.001$). In MVA, in a final model that also included heart failure, obstructive sleep apnea, and psychiatric illness, 6MWD was independently associated with cancer-specific QoL (partial $R^2 = 0.20$, $p = 0.001$).

Conclusions Functional EC was independently associated with cancer-specific QoL in lung cancer patients postcurative intent treatment. Exercise-based interventions aimed at improving EC may improve cancer-specific QoL in these patients.

Keywords Six-minute walk test · Quality of life · Patient-reported outcome · Lung cancer · Survivorship

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Abbreviations

6MWD	Six-minute walk distance
6MWT	Six-minute walk test
ATS	American Thoracic Society
BFI	Brief Fatigue Inventory
CI	Confidence interval
CPET	Cardiopulmonary exercise test
COPD	Chronic obstructive pulmonary disease
DL_{CO}	Diffusion capacity of the lung for carbon monoxide
EC	Exercise capacity
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30

EORTC-QLQ-LC13	European Organization for Research and Treatment of Cancer QoL Questionnaire Lung Cancer Module 13
EQ-5D/VAS	EuroQoL-5 Dimensions/visual analogue scale
FEV_1	Forced expiratory volume in 1 s
HADS	Hospital Anxiety and Depression Scale
HF	Heart failure
LDCT	Low-dose computed tomography
LLN	Lower limit of normal
MVA	Multivariable linear regression analysis
NSCLC	Nonsmall cell lung cancer
OSA	Obstructive sleep apnea
PRO	Patient-reported outcome
PSQI	Pittsburgh Sleep Quality Index
QoL	Quality of life
TLC	Total lung capacity
SBRT	Stereotactic body radiotherapy
TNM	Tumor node metastasis
UCSD	University of California San Diego
UCSD SOBQ	University California San Diego Shortness of Breath Questionnaire
US	United States
UVA	Univariable linear regression analysis
VASDHS	VA San Diego Healthcare System
VO_{2peak}	Peak oxygen consumption

Introduction

Up to 50% of nonsmall cell lung cancer (NSCLC) cases present at stage I–IIIA [1], the treatment of which involves a combination of modalities including surgical resection, ablative therapy, and chemoradiotherapy aimed at achieving a cure. As of 2016, there were more than 526,000 lung cancer survivors in the US [2].

Lung cancer survivors are at risk for cardiopulmonary impairments resulting from the effects and/or treatment of lung cancer and comorbidities. Perioperative pulmonary [3] and cardiopulmonary [4] complications have been reported in 15 and 35%, respectively, of patients undergoing lung cancer resection surgery and can result in negative health consequences well beyond the perioperative period (e.g., atrial arrhythmias, prolonged respiratory failure/intensive care unit stay). At 6 months following surgery, a loss of forced expiratory volume in 1 s (FEV_1) of 10–15% for lobectomy and 30–35% for pneumonectomy [5] is expected. Chemotherapy and radiotherapy, often part of the treatment for stage IB–IIIA lung cancer, can also lead to long-term cardiopulmonary impairments (e.g., cardiomyopathy, cardiac conduction disturbances, coronary artery disease, valvular disease, pneumonitis, pulmonary fibrosis) [6]. In those undergoing definitive external-beam radiation, it is common to develop some degree of focal pulmonary fibrosis, and a minority will subsequently develop progressive pulmonary fibrosis, cor pulmonale, and respiratory failure [6]. In the peripheral vascular and musculoskeletal systems, altered blood flow response to exercise [7], and decreased skeletal microvascular function [8] have been recently described in cancer survivors treated with adjuvant therapy.

Lung cancer patients can also have major comorbidities that limit health. In a large cohort study of 5683 lung cancer patients, the most common comorbidities included chronic obstructive pulmonary disease (COPD, in 53% of patients), diabetes (16%), and congestive heart failure (13%) [9]. In time, partly due to the long-term effects of lung cancer treatment and comorbidities, patients experience disabling symptoms, which in turn can lead to a downward spiral of health. Dyspnea and fatigue were reported to be worse compared to baseline in 40–50% of lung cancer survivors at 2 years postresection surgery [10]. Long-term respiratory symptoms are highly prevalent and can be present in up to 60–70% of patients at ≥ 5 years [11]. These symptoms have been shown to limit generic quality of life (QoL) [11], which can be more important than the duration of survival for some patients. According to a survey of 660 lung cancer patients, health issues that are deemed important or very important include QoL, maintaining independence, ability to perform normal activities, ability to sleep, and not being fatigued [12].

It is important to characterize health limitations and to identify potential therapeutic options in lung cancer survivors. Practical clinical tools to assess and identify these health limitations are currently lacking. Functional exercise testing offers an opportunity to measure objectively patients' exercise capacities and identify exercise limitations that would otherwise remain undetected. In lung cancer, exercise testing is used most often to risk-stratify patients undergoing evaluation for lung cancer resection [13–15]. In recent years, its use outside this context has been described, including in nonsurgical candidates [16, 17] and lung cancer survivors [18]. In this study, we characterized functional exercise capacity (EC) in lung cancer survivors who have received curative-intent treatment and analyzed the relationship between functional EC and cancer-specific QoL. We hypothesize that functional EC is an important, independent predictor of cancer-specific QoL.

Methods

Study overview We performed a cross-sectional study of patients who completed curative-intent treatment of stage I–IIIA lung cancer (i.e., anatomic lung cancer resection surgery, ablative therapy, or concurrent chemoradiation) ≥ 1 month previously. Eligible participants were identified from a database of consecutive lung cancer patients diagnosed and managed at the VA San Diego Healthcare System (VASDHS), maintained since 2010 to shorten time to diagnosis and improve the quality of care. We allowed at least a 1-month period for recovery following any acute health decrements associated with treatment [19]. Between July 2016 and July 2017, we mailed informational letters to potential candidates identified from October 2010 to July 2017 and followed-up with a telephone call approximately 1 week later to gauge their interest. All exercise testing and patient-reported outcome (PRO) assessments were conducted in person by one observer (DH). We obtained written informed consent from each participant. The protocol was approved by the VASDHS Institutional Review Board (no. H150158). We followed standard guidelines [20] to report the findings of our study.

Participants We included participants (Fig. 1) over 18 years of age and collected available baseline clinical characteristics and potential confounders related to cardiopulmonary/physical health and QoL through electronic chart review including age, gender, body mass index, tobacco exposure, comorbidities [e.g., COPD, heart failure (HF), psychiatric illnesses (anxiety, depression, posttraumatic stress disorder)], lung function [FEV_1, total lung capacity (TLC), diffusion capacity of the lung for carbon monoxide (DL_{CO})], and echocardiography (ejection fraction, diastolic dysfunction, valvular disease). We confirmed the accuracy of data collected using available documentation from clinical specialists where applicable. Lung cancer-related information included clinical stage as defined by the American Joint Committee on Cancer TNM staging system (7th and 8th editions) and the primary curative-intent mode of treatment (surgical resection, ablative therapy, chemoradiotherapy).

Exercise testing Based on our previous review of the utility of exercise testing in patients with lung cancer [18], we chose the 6MWT based on practical considerations (availability and ease of performance), the likelihood that daily activities are performed at submaximal exercise levels, and previous validation in cancer [21], including lung cancer [22] clinical populations. We performed the 6MWT according to the standard protocol at the VASDHS following the American Thoracic Society (ATS) Pulmonary Function Standards Committee recommendations [23] using a ~ 130-ft (~ 40-m) hallway with a flat and hard surface marked with alternating-colored tiles; a finger-probe pulse oximeter was used to obtain oxygen saturation and heart rate before and at the end of the 6MWT. Patients requiring oxygen supplementation used their own equipment at the same flow rate as their regular prescription. No practice test was conducted, as per ATS recommendations in most clinical settings [23].

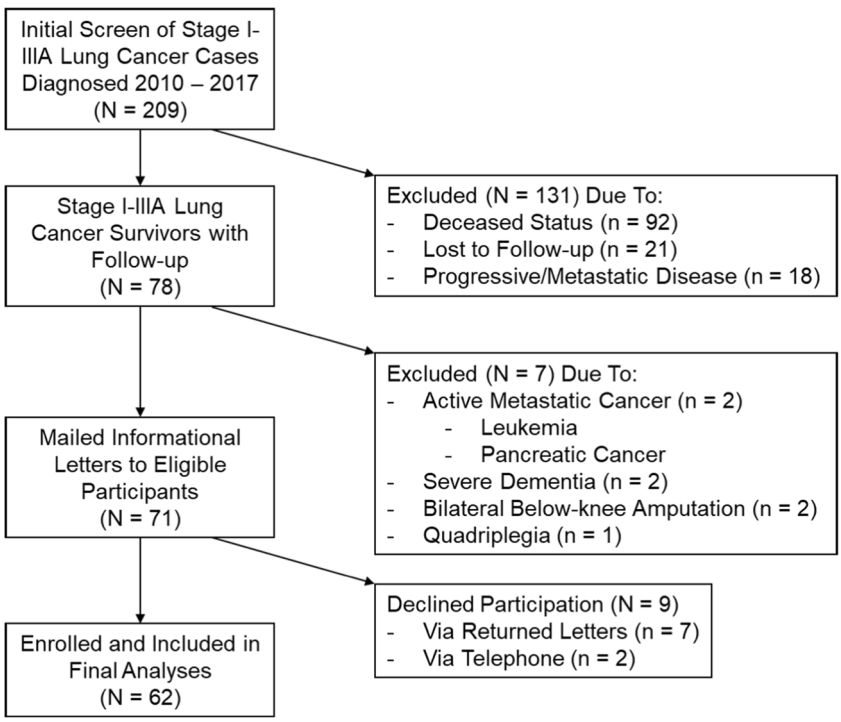

Fig. 1 Flow diagram of enrolled participants

Patient-reported outcome assessments We chose the European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC-QLQ-C30) [24] instrument based on its availability and inclusion of core domains of QoL and other subdomains of health relevant to lung cancer survivors (e.g., dyspnea, fatigue, insomnia). Our primary endpoint was a validated composite score of cancer-specific QoL as defined by the EORTC-QLQ-C30 summary score [25]. We also performed exploratory PRO assessments for lung cancer-specific symptoms, generic health, sleep quality, dyspnea, fatigue, and anxiety/depression using the EORTC-QLQ-Lung Cancer Module 13 (LC13) [26], EuroQoL-5 Dimensions/visual analogue scale (EQ-5D/VAS) [27], Pittsburgh Sleep Quality Index (PSQI) [28], University California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) [29], Brief Fatigue Inventory (BFI) [30], and Hospital Anxiety and Depression Scale (HADS) [31] questionnaires, respectively. All questionnaires were self-administered on printed forms without modifications, scored per their respective instruction manuals, and analyzed as continuous variables.

Statistical analyses Descriptive statistics were summarized as means and standard deviations or medians and ranges for all continuous variables and as counts and percentages for all categorical variables. The 6MWD was recorded and analyzed as a continuous variable, and interpreted using the reference equations for the 6MWT in healthy adults [32]. Correlation coefficients were obtained using Pearson's r and Spearman's ρ for variables with parametric and nonparametric distributions, respectively. Univariable linear regression analyses (UVAs) were performed to assess the relationship between baseline characteristics including functional EC as reflected by the 6MWD and cancer-specific QoL as reflected by the EORTC-QLQ-C30 summary score. Multivariable linear regression analyses (MVAs) were performed using stepwise backward selection modeling of all baseline characteristics with $p < 0.15$. Regression coefficients, 95% confidence intervals (CIs), and coefficients of determination (R^2 and partial R^2) were used to interpret the association between dependent and independent variables. Additional analyses were performed to assess the relationship between the 6MWD and the functional subscales of the EORTC-QLQ-C30 questionnaire (using p value cutoff < 0.01 to account for multiple comparison), as well as baseline clinical characteristics associated with the 6MWD. One-way analyses of variance (ANOVA) with Bonferroni post hoc analyses were performed to assess the differences in 6MWD and cancer-specific QoL between the three most common curative-intent treatment modalities. Exploratory UVAs were performed to assess the relationship between functional EC and other PROs, corrected for multiple comparisons by multiplying the p values for each comparison by the total number of comparisons. All tests were two-tailed. Statistical significance was defined as $p < 0.05$. All data were entered and managed using REDCap electronic data capture tools hosted at the University of California San Diego (UCSD) Clinical and Translational Research Institute [33]. IBM® SPSS® Statistics software version 23.0 was used for all analyses.

Results

We mailed informational letters to 71 eligible patients, 9 of whom declined participation (Fig. 1). There was no significant difference in baseline characteristics between those who participated and those who declined (E-Table 1). Most of the 62 participants had a history of tobacco exposure (58 patients,

Table 1 Participant characteristics

Participant characteristics	Value
Age, mean (SD)	71.6 (8.3)
Race, *n* (%)	
Asian	3 (5)
Black	1 (2)
Hispanic	1 (2)
White	57 (92)
Male sex, *n* (%)	59 (95)
BMI, mean (SD)	26.8 (4.9)
Smoking history, *n* (%)	
Current	20 (32)
Former	38 (61)
Never	4 (7)
Pack years, mean (SD)	56.1 (31.5)
Comorbidities, *n* (%)	
Hypertension	51 (82)
Hyperlipidemia	51 (82)
Diabetes	15 (24)
Atrial arrhythmia	15 (24)
CAD	24 (39)
HF[a]	16 (26)
Diastolic dysfunction	32 (52)[c]
Valvular disease	8 (13)[c]
COPD[b]/asthma	48 (77)
OSA	15 (24)
Anxiety/depression/PTSD	19 (31)
Other cancers	28 (45)
Pulmonary function[d], mean (SD)	
FEV_1/FVC, %	58.5 (14.8)
FEV_1, % predicted	68.9 (25.3)
TLC, % predicted	110.2 (22.8)
DL_{CO}, % predicted	75.9 (24.4)
Ventilatory defects, *n* (%)	
Obstructive defect[b]	48 (77)
Restrictive defect	3 (5)
DL_{CO} limitation	36 (58)

Table 1 (continued)

Participant characteristics	Value
Lung cancer characteristics	
Lesion size (cm), mean (SD)	2.3 (1.4)
Lesion location, *n* (%)	
RUL	27 (44)
RML	4 (7)
RLL	7 (11)
LUL	16 (26)
Lingula	1 (2)
LLL	7 (11)
Clinical stage, *n* (%)	
IA1	9 (15)
IA2	19 (31)
IA3	13 (21)
IB	6 (10)
IIA	2 (3)
IIB	2 (3)
IIIA	9 (15)
Not available	2 (3)
Histologic subtype, *n* (%)	
Adenocarcinoma	27 (44)
Squamous cell carcinoma	16 (26)
Small cell carcinoma	2 (3)
NSCLC, NOS	1 (2)
Carcinoid	2 (3)
Presumed	14 (23)
Curative-intent treatment, *n* (%)	
Lobectomy	27 (44)
Pneumonectomy	1 (2)
SBRT	23 (37)
XRT	2 (3)
Chemoradiation	9 (15)
Months since treatment	
Median (IQR)	18.7 (3.9–44.3)

BMI body mass index, *CAD* coronary artery disease, *COPD* chronic obstructive pulmonary disease, DL_{CO} diffusion capacity of the lung for carbon monoxide, FEV_1 forced expiratory volume in 1 s, *FVC* forced vital capacity, *HF* heart failure, *IQR* interquartile range, *LLL* left lower lobe, *LUL* left upper lobe, *NSCLC* nonsmall cell lung cancer, *NOS* not otherwise specified, *OSA* obstructive sleep apnea, *PTSD* posttraumatic stress disorder, *RLL* right lower lobe, *RML* right middle lobe, *RUL* right upper lobe, *SBRT* stereotactic body radiotherapy, *SD* standard deviation, *SUV* standardized uptake value, *TLC* total lung capacity, *XRT* radiotherapy

[a] Defined as ejection fraction ≤ 50% or clinical documentation of systolic heart failure

[b] Defined as $FEV_1/FVC < 0.7$

[c] Data available in 41 participants

[d] Data available at the time of assessment: 23 pretreatment, 39 posttreatment

94%), clinical stage I–II disease (51 patients, 82%), and lobectomy or stereotactic body radiotherapy as the primary modality for curative-intent treatment (50 patients, 81%). The median time from completion of treatment was 19 months (interquartile range 4–44) (Table 1).

All participants completed the 6MWT and PRO assessments. The overall mean 6MWD was low (335 m, 65% predicted) and most patients (35, 57%) had impaired functional EC (Table 2). Sixteen patients (26%) stopped or paused during the 6MWT due to symptom limitation (7 due to pain, 6 dyspnea, 2 fatigue, and 1 imbalance). The cancer-specific QoL as assessed by the mean EORTC-QLQ-C30 summary score was 77 (range 26 to 99 on a scale of 0 to 100). The most common abnormal subscales, defined as raw symptom score > mean reference value [34], was pain (33 patients, 53%) and the least common was nausea/vomiting (13 patients, 21%). More than half of patients had abnormal dyspnea (36, 58%), pain in arms or shoulders (33, 53%), and pain in other parts (36, 58%) as assessed by the EORTC-QLQ-LC13 (Table 3), and sleep quality (Table 4).

The 6MWD m correlated moderately well with the cancer-specific QoL summary score (correlation coefficient = 0.45, $p < 0.001$). In UVAs (Table 5), in addition to functional EC (Fig. 2a), HF, obstructive sleep apnea (OSA), psychiatric illness, DL_{CO} % predicted, and surgical treatment were also significantly associated with cancer-specific QoL. In MVAs (Table 6) starting with all baseline clinical characteristics with

Table 2 Functional exercise capacity assessment

6MWT-associated measures	Values
Pre-6MWT vital signs	
HR (beats/min)	73.8 (13.8)
SBP (mmHg)	130.1 (18.3)
DBP (mmHg)	77.8 (11.7)
O_2 saturation (%)	96.5 (2.0)
Physiological change, mean (SD)	
HR (beats/min)	+ 20.6 (10.7)
SBP (mmHg)	+ 14.2 (17.5)
DBP (mmHg)	+ 1.9 (6.9)
O_2 saturation (%)	− 3.4 (4.6)
Borg dyspnea score, mean (SD)	
Pre-6MWT	0.81 (1.4)
Post-6MWT	3.7 (2.7)
Change	+ 2.9 (2.4)
Functional EC	
6MWD (m), mean (SD)	334.7 (125.6)
6MWD, % predicted, mean (SD)	65.2 (25.3)
Impaired EC (6MWD < LLN), *n* (%)	35 (57)

6MWD 6-min walk distance, *6MWT* 6-min walk test, *DBP* diastolic blood pressure, *EC* exercise capacity, *HR* heart rate, *LLN* lower limit of normal, O_2 oxygen, *SBP* systolic blood pressure, *SD* standard deviation

Table 3 Cancer and lung cancer-specific quality of life assessments

EORTC-QLQ-C30	Raw score Mean (SD)	Abnormala scores *N* (%)
Functional scales		
Physical function**	66.9 (21.5)	30 (48)
Role function*	71.0 (31.1)	18 (29)
Emotional function	82.9 (22.4)	13 (21)
Cognitive function*	82.3 (23.7)	20 (32)
Social function**	76.1 (32.3)	24 (39)
Symptom scales		
Fatigue**	35.8 (26.1)	19 (31)
Nausea and vomiting	5.1 (11.1)	13 (21)
Pain	30.4 (29.8)	33 (53)
Dyspnea*	34.4 (30.8)	15 (24)
Insomnia	28.4 (33.2)	32 (52)
Appetite loss	18.6 (28.2	23 (37)
Constipation	18.3 (28.7)	22 (36)
Diarrhea	9.7 (19.5)	15 (24)
Financial difficulties	18.8 (29.3)	23 (37)
Global health/QoL*	63.8 (23.7)	19 (31)
Summary score**		
Mean (SD)	76.8 (17.9)	N/A
Range	26.2 – 98.7	N/A
EORTC-QLQ-LC13		
Dyspnea**	34.8 (26.6)	36 (58)
Coughing	38.2 (27.6)	16 (26)
Hemoptysis	3.8 (16.1)	4 (7)
Sore mouth	3.8 (12.2)	6 (10)
Dysphagia	9.8 (21.4)	13 (31)
Peripheral neuropathy	16.7 (28.1)	20 (32)
Alopecia	5.4 (13.8)	9 (15)
Pain in chest	14.5 (23.1)	21 (34)
Pain in arm or shoulder	27.4 (31.1)	33 (53)
Pain in other parts*	32.2 (31.5)	36 (58)

*Significant correlation with the 6MWD at the 0.05 level (two-tailed); **significant correlation with the 6MWD at the 0.01 level (two-tailed)

[a] Defined as raw score < mean reference value [34] for functional scales and global health/QoL, and raw score > mean reference value for symptom scales

Table 4 Exploratory patient-reported outcome assessments

PRO Questionnaire	Raw score Mean (SD)	Abnormal[a] score *N* (%)
EQ-5D US index score**	0.79 (0.17)	25 (40)
EQ-VAS**	70.3 (21.0)	43 (69)
PSQI	7.9 (4.4)	45 (73)
UCSD SOBQ**	33.9 (26.3)	16 (26)
BFI**	24.9 (23.9)	15 (24)
HADS–Anxiety	4.4 (4.2)	12 (19)
HADS–Depression*	5.6 (4.4)	19 (31)

6MWD 6-min walk distance, *BFI* Brief Fatigue Inventory, *EORTC-QLQ-C30/LC13* European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30/Lung Cancer Module 13, *EQ-5D/VAS* EuroQoL-5 Dimensions/visual analogue scale, *HADS* Hospital Anxiety and Depression Scale, *PSQI* Pittsburg Sleep Quality Index, *PRO* patient-reported outcome, *QoL* quality of life, *SD* standard deviation, *UCSD SOBQ* University of California San Diego Shortness of Breath Questionnaire, *US* United States

*Significant correlation with the 6MWD at the 0.05 level (two-tailed); **significant correlation with the 6MWD at the 0.01 level (two-tailed)

[a] For the respective instrument, defined as EQ-5D index score < reference value [27], EQ-VAS < reference value [27], PSQI ≥ 5 [28], UCSD SOBQ > 50 [35], BFI > 40 [30], HADS Anxiety/Depression > 7 [31]

$p < 0.15$ from UVAs, the 6MWD was independently associated with cancer-specific QoL (partial $R^2 = 0.20$, $p = 0.001$).

Additional analyses of the functional subscales showed that in UVAs the 6MWD was associated with the physical function ($R^2 = 0.44$, $p < 0.001$) and social function ($R^2 = 0.18$, $p = 0.001$) domains of cancer-specific QoL (Fig. 2b, c). In MVAs, the 6MWD was an independent predictor of the physical function (partial $R^2 = 0.45$, $p < 0.001$) and social function (partial $R^2 = 0.17$, $p = 0.001$) domains of cancer-specific QoL (Tables 7 and 8). Psychiatric illness was also found in MVAs to be independently associated with cancer-specific QoL and the physical and social function domains of cancer-specific QoL (Tables 6, 7, and 8).

Baseline clinical characteristics significantly associated with the 6MWD in UVAs included age ($R^2 = 0.09$, $p = 0.02$), hyperlipidemia ($R^2 = 0.08$, $p = 0.03$), DL_{CO} % predicted ($R^2 = 0.15$, $p = 0.002$), and surgical treatment ($R^2 = 0.16$, $p = 0.001$). In MVAs, in a model (overall $R^2 = 0.38$, $p < 0.001$) that also contained surgical treatment, age (partial $R^2 = 0.12$, $p = 0.007$), hyperlipidemia (partial $R^2 = 0.07$, $p = 0.04$), and DL_{CO} % predicted (partial $R^2 = 0.16$, $p = 0.002$) were significantly associated with the 6MWD. In one-way ANOVAs, there were significant differences in the 6MWD ($p = 0.003$) and cancer-specific QoL ($p = 0.02$) between the three most common curative-intent treatment modalities (lobectomy, SBRT, chemoradiation). In post hoc analyses, there was a significant difference in 6MWD and cancer-specific QoL in the lobectomy compared to SBRT groups (+ 118 m, $p = 0.002$ and + 14, $p = 0.02$, respectively), but not between lobectomy compared to chemoradiation (+ 85 m, $p = 0.19$, and + 3.4, $p = 1.0$) or SBRT compared to chemoradiation (− 33 m, $p = 1.0$, and − 10, $p = 0.39$).

In exploratory assessments using other PROs, more than half of patients had abnormal scores on the EQ-VAS (43 patients, 69%) and PSQI (45, 73%) (Table 4). Exploratory UVAs showed significant associations (with correction for seven comparisons) between the 6MWD and the EQ-5D index ($R^2 = 0.12$, $p = 0.04$), EQ-VAS ($R^2 = 0.15$, $p = 0.01$), and UCSD SOBQ ($R^2 = 0.14$, $p = 0.02$), but not PSQI, BFI, or HADS.

Table 5 UVA—predictors of cancer-specific QoL summary score

Variable	Regression coefficient	R^2	*p* value
Age	0.32	0.02	0.25
White race	7.88	0.02	0.35
Male sex	4.91	0.004	0.65
BMI	− 0.18	0.002	0.70
Smoking history	N/A (*F*-statistics)	0.03	0.46
Pack-year	0.07	0.01	0.36
Hypertension	3.42	0.005	0.57
Hyperlipidemia	3.82	0.007	0.53
Diabetes	− 1.25	0.001	0.82
Atrial arrhythmia	− 3.04	0.005	0.57
CAD	− 1.99	0.003	0.67
HF	− 12.29	0.09	0.02[a]
PVD	0.33	< 0.001	0.96
COPD/asthma	− 1.68	0.002	0.76
OSA	− 10.69	0.07	0.04[a]
Anxiety/depression/PTSD	− 16.61	0.19	< 0.001[a]
Other cancer	1.00	0.001	0.83
FEV_1% predicted	0.13	0.03	0.16
TLC % predicted	− 0.08	0.009	0.50
DL_{CO} % predicted	0.24	0.10	0.01[a]
Diastolic dysfunction	2.90	0.004	0.71
Valvular disease	− 1.65	0.001	0.84
Surgical treatment	9.98	0.08	0.03[a]
Months since treatment	0.02	0.002	0.76
6MWD (m)	0.06	0.16	0.001[a]

[a] Included in multivariable linear regression analysis

Discussion

In a cross-sectional study of lung cancer survivors who previously completed curative-intent treatment, approximately 60% had functional exercise limitation. Overall, functional EC accounted for 20% of the variance in cancer-specific QoL.

Exercise capacity evaluation in lung cancer is most commonly performed to risk-stratify patients being considered for anatomic lung cancer resection surgery [13, 14]. We previously reviewed the utility of exercise testing outside of the preoperative evaluation context, including in postresection lung cancer survivors [18], and identified that the 6MWT,

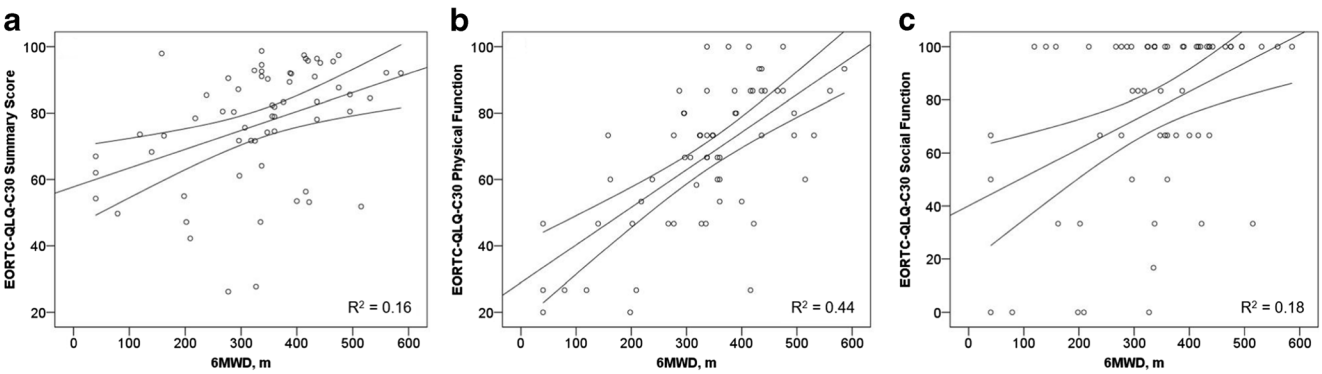

Fig. 2 Scatter plots of functional EC and cancer-specific QoL and selected functional subscales. Legend: scatter plots showing correlations between functional EC (6MWD) with **a** cancer-specific QoL (EORTC-QLQ-C30 Summary Score), **b** physical function (EORTC-QLQ-C30 Physical Function), and **c** social function (EORTC-QLQ-C30 Social Function) subscales. 6MWD 6-min walk distance, EC exercise capacity, EORTC-QLQ-C30 European Organization for Research and Treatment of Cancer QoL Questionnaire Core 30, QoL quality of life

Table 6 MVA—significant independent predictors of cancer-specific QoL summary score

Variable	Regression Coefficient (95% CI)	Partial R^2	p value
HF (no/yes)	8.89 (0.76, 17.03)	0.08	0.03
OSA (no/yes)	11.41 (3.11, 19.71)	0.12	< 0.01
Anxiety/depression/PTSD (no/yes)	17.96 (10.53, 25.40)	0.29	< 0.001
6MWD (m) (for each 1 m)	0.05 (0.02, 0.08)	0.20	< 0.001

Overall model $R^2 = 0.48$ ($p < 0.001$)

6MWD 6-min walk distance, *BMI* body mass index, *CAD* coronary artery disease, *CI* confidence interval, *COPD* chronic obstructive pulmonary disease, DL_{CO} diffusion capacity of the lung for carbon monoxide, FEV_1 forced expiratory volume in 1 s, *HF* heart failure, *MVA* multivariable linear regression analysis, *OSA* obstructive sleep apnea, *PTSD* posttraumatic stress disorder, *PVD* peripheral vascular disease, *QoL* quality of life, *TLC* total lung capacity, *UVA* univariable linear regression analysis

cardiopulmonary exercise test (CPET), and stair-climb test have been used in this group of patients. In the largest study involving the 6MWT, Deslauriers and coworkers [36] assessed functional EC in 100 lung cancer patients at least 5 years postpneumonectomy and found that the 6MWD was 83% of the predicted values in these patients; only 19 of 91 patients (10%) had lower than expected 6MWD. Since our review, Cavalheri and coworkers [37] assessed EC using the 6MWT and CPET in a cross-sectional study of lung cancer survivors who completed curative-intent treatment 4–10 weeks previously and found that, compared to age-and gender-matched healthy controls, there were statistically significant differences in ECs as reflected by the 6MWD and VO_{2peak}. Ten of 22 patients (45%) had 6MWD below the lower limit of normal (LLN) and 15 of 21 patients (71%) had VO_{2peak} below the LLN.

In contrast to most studies to date involving EC evaluation in postcurative intent treated lung cancer patients, where the primary interest lies in characterizing the differences in EC associated with treatment, our study is a cross-sectional study highlighting the prevalence of exercise limitation in these patients. Similar to the study by Cavalheri and coworkers [37], our study reports a prevalence of exercise limitation of at least 50% in a sample size that contains almost three times the number of patients. In the study by Deslauriers and coworkers [36], only 10% of postpneumonectomy patients had impaired functional EC as reflected by the 6MWD. However, one must be cautious in comparing results from these previous studies with ours due to differences in patient selection (postcombined modality vs. postpneumonectomy) and time elapsed since treatment (weeks/months vs. years). In our study, time since completion of treatment was not significantly associated with functional EC or cancer-specific QoL, possibly due to a small sample size or adequate health recovery after a minimum of one month following completion of treatment. In MVAs, the primary curative-intent mode of treatment was not significantly associated with functional EC or cancer-specific QoL, possibly due to nonrandom treatment selection or small sample size.

Similar to that reported in the systematic review by the European Respiratory Society/ATS [38] on the measurement properties of field walking tests in chronic respiratory disease, the 6MWD was moderately correlated (correlation coefficient 0.31 to 0.70) with the PROs included in our study. To the best of our knowledge, our study is the first to analyze the relationship between the 6MWD and cancer-specific QoL using the novel and validated composite EORTC-QLQ-C30 summary score [25]. Additional analyses demonstrate that similar to a previous study involving 56 patients with stage I–IV lung cancer [39], the 6MWD was significantly associated with the physical function domain of the EORTC-QLQ-C30. These results contrast with another study involving 20 patients with stage I-IIIB NSCLC [40] which showed no significant association between the 6MWD and the physical function domain of the EORTC-QLQ-C30. This difference in results may well be due to the small sample size (20 patients) included in that study.

Many of the patients included in our study had comorbidities including COPD and HF that also could limit cardiopulmonary health and EC. Our additional analyses did not demonstrate significant associations between these comorbidities and the 6MWD, suggesting that untreated/unoptimized

Table 7 MVA—significant independent predictors of physical function

Variable	Regression coefficient (95% CI)	Partial R^2	p value
HF (no/yes)	12.07 (3.32, 20.83)	0.12	< 0.01
Anxiety/depression/PTSD (no/yes)	10.91 (2.65, 19.17)	0.11	0.01
6MWD (m) (for each 1 m)	0.11 (0.08, 0.14)	0.45	< 0.001

Overall model $R^2 = 0.54$ ($p < 0.001$)

Table 8 MVA—significant independent predictors of social function

Variable	Regression coefficient (95% CI)	Partial R^2	p value
Anxiety/depression/PTSD (no/yes)	22.05 (6.65–37.45)	0.12	< 0.01
6MWD (m) (for each 1 m)	0.10 (0.04–0.16)	0.17	0.001

Overall model $R^2 = 0.30$ ($p < 0.001$) and also contained HF

6MWD 6-min walk distance, *CI* confidence interval, *HF* heart failure, *MVA* multivariable linear regression analysis, *PTSD* posttraumatic stress disorder

cardiopulmonary disease was not prevalent in these patients. Interventions to improve functional EC in these patients, therefore, could possibly improve cancer-specific QoL without titration of medications (e.g., inhalers, diuretics) to optimize cardiopulmonary health. These findings should not lessen the importance of medically optimizing these comorbidities in the clinical setting. The lack of association between comorbidities and the 6MWD may also be due to a small sample size. The significant associations between psychiatric illness and cancer-specific QoL and physical function highlight the importance of the management of concomitant psychiatric disorders in lung cancer patients. Our exploratory analyses also highlight the important associations between dyspnea and fatigue with functional EC and could serve as secondary endpoints in future studies aimed at improving EC in lung cancer survivors.

Lung cancer is the second-most commonly diagnosed cancer in the US [41]. Historically, the majority of lung cancer cases are diagnosed at an advanced stage when curative-intent treatment is not possible. However, there is an expected increase in the number of cases of lung cancer diagnosed at an earlier stage due to the findings of the National Lung Screening Trial [42] and practice guideline recommendations supporting the role of low-dose computed tomography (LDCT) screening for lung cancer in high-risk patients. A recent analysis shows that LDCT can lead to more early-stage lung cancers being detected [43]. The American Cancer Society projects that by 2026, more than 673,000 lung cancer survivors will be living in the US [2]. Current evidence supports the utility of physical activity and exercise in improving health in posttreatment cancer survivors [44], though the evidence is not as consistent in the lung cancer population [45]. This may be due to factors such as differences in comorbidities and treatment-related effects in lung cancer compared with other cancer populations, variations in study design (e.g., patient selection, type of physical activity, intensity, duration), measured outcomes, and sample sizes. Our study describes exercise limitations and highlights the importance of EC evaluation for curative-intent treated lung cancer survivors. The mean 6MWD of the patients enrolled in our study is similar to a cohort [46] of patients undergoing pulmonary rehabilitation. These findings may present an opportunity for healthcare providers and systems to intervene to improve health and QoL through exercise-based interventions in these patients.

Our study has several strengths. First, all exercise testing and PRO assessments were conducted in person by one observer which optimized the quality and consistency of the data obtained. Second, we analyzed data using a prespecified validated exposure (functional EC) [21, 22] and outcome (cancer-specific QoL) [25] to minimize chance bias. Third, a comprehensive list of baseline characteristics was included in the data collected, much of which (e.g., COPD, HF, OSA, and psychiatric illness) was confirmed for accuracy using available lung function test results, echocardiography reports, and clinical documentation from sleep and psychiatric specialists. Finally, a combination of prespecified, additional, and exploratory UVAs and MVAs enabled us to interpret results which can facilitate future studies and/or clinical practice.

Our study also has some limitations. First, we did not assess other components of cardiopulmonary/physical fitness such as VO_{2peak} and muscle strength which may also be improved with exercise training and contribute significantly to cancer-specific QoL. Second, the cross-sectional design limits our ability to draw conclusions about temporal relationships; it is possible that poor cancer-QoL led to functional EC limitations in some patients and not vice versa. In addition, it is not possible to determine whether the functional EC and cancer-specific QoL limitations were preexisting or related to lung cancer or its treatment. Third, the small sample size may limit our study's power to detect associations between important predictors of functional EC and cancer-specific QoL. Finally, the findings may not be generalizable due to selection bias towards survivors and the high prevalence of comorbidities in a predominantly male veteran patient population with early stage lung cancer recruited from a single VA Health System center.

Important future work on the role of physical activity/exercise in lung cancer survivors may include assessment of barriers and facilitators of exercise, development, and implementation of effective exercise programs to improve physical activity and exercise capacity, patient-reported outcomes and clinical outcomes, and their cost-effectiveness analyses. Investigations of the physiobiological changes associated with exercise in these patients may be equally important. In newly diagnosed lung cancer patients undergoing curative-intent therapy, exercise may also have role in cancer rehabilitation to decrease treatment related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes [47].

We conclude that in a cross-sectional study of lung cancer patients postcurative intent treatment, impaired functional EC was prevalent in > 50% of patients, and functional EC was independently associated with cancer-specific QoL. Exercise-based interventions aimed at improving functional EC may improve cancer-specific QoL in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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