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Fatigue and Functional Impairment in Early-Stage Non-Small Cell Lung Cancer Survivors

Robert Hung, MD, MPH[1], **Paul Krebs, PhD**[1], **Elliot J. Coups, PhD**[2], **Marc B. Feinstein, MD**[1], **Bernard J. Park, MD**[1], **Jack Burkhalter, PhD**[1], and **Jamie S. Ostroff, PhD**[1]

[1]Departments of Medicine (R.H., M.B.F), Surgery (B.J.P.), and Psychiatry and Behavioral Sciences (P.K., J.B., J.S.O.), Memorial Sloan-Kettering Cancer Center, New York, New York

[2]Cancer Institute of New Jersey (E.J.C.); and UMDNJ-Robert Wood Johnson Medical School, Department of Medicine (E.J.C.); and UMDNJ-School of Public Health, Department of Health Education and Behavioral Science (E.J.C.)

Abstract

Context—Fatigue is the most common sequela among non-small cell lung cancer (NSCLC) survivors 1–6 years post-treatment and is associated with functional limitations.

Objectives—This study examined the prevalence, severity, and correlates of fatigue among early stage NSCLC survivors.

Methods—Three-hundred fifty individuals diagnosed and surgically treated for Stage IA or IB NSCLC completed a survey that included the Brief Fatigue Inventory (BFI) to assess the prevalence and severity of fatigue. The Self-Reported Karnofsky Performance Scale (SR-KPS) was used as a measure of functional status and was compared with the severity of fatigue though chi-square analyses. Demographic, psychological, and medical correlates of fatigue were examined using logistic regression.

Results—The prevalence of fatigue was 57%. Forty-one percent (n = 142) of participants had mild fatigue and 16.8% (n = 59) had moderate or severe fatigue (BFI ≥ 4). Among the individuals reporting moderate or severe fatigue, 23.7% (n=14) had significant functional impairment (SR-KPS ≤ 70%) compared to 2.8% (n =8) with mild or no fatigue ($\chi^2 = 58.1$, $p < 0.001$). In the multi-variate analysis, NSCLC survivors with pulmonary disease (OR = 2.28), depressive symptoms (OR = 6.99), and anxiety symptoms (OR = 2.31) were more likely to report experiencing clinically significant fatigue, while those who met physical activity guidelines (OR = 0.29) reported less fatigue.

Discussion—Fatigue is highly prevalent among NSCLC survivors and associated with more functional impairment. A comprehensive approach to the treatment of fatigue includes the screening and management of anxious and depressive symptoms, and pulmonary disorders such as chronic obstructive pulmonary disease.

Keywords

Lung cancer survivor; non-small cell lung cancer survivor; fatigue; functional impairment; symptom cluster

Address correspondence to: Robert Hung, MD, MPH, Pulmonary Division, Memorial Sloan-Kettering Cancer, Center, 1275 York Avenue, New York, N.Y. 10065, USA. hungr@mskcc.org.

Introduction

While lung cancer remains the most common fatal malignancy in the United States,[1–2] many patients diagnosed in the early stages (IA and IB) are potentially cured with surgical resection.[3–5] In the United States five-year survival rates for individuals with stage IA and IB non-small cell lung cancer (NSCLC) are 73% and 58%, respectively,[6] resulting in a significant number of individuals diagnosed in the early stages and living with post-treatment sequelae.

Fatigue is the most common acute symptom before and after cancer treatment, affecting up to 90% of lung cancer patients.[7–11] Among NSCLC survivors, the prevalence of fatigue is as high as 75% four months after thoracotomy.[12] Several studies show complete resolution of fatigue by 3–6 months after lung cancer surgery[13–15], whereas other studies show fatigue persisting for months to years after treatment completion.[12, 16–17]

Fatigue can be associated with depressed mood, dyspnea, as well as functional dependency and the inability to perform activities of daily living.[12, 18–20] Therefore, examining the prevalence, severity, and association of fatigue with other health outcomes is important for understanding quality of life among lung cancer survivors.[12, 20] With the exception of one study on NSCLC survivors[12], prior research has used generic quality of life instruments such as the Medical Outcomes Study 36-Item Short Form (SF-36)[14, 16–17, 20–22], which assesses health-related quality of life, but provides little specific data on fatigue. This limitation in measurement precludes a more clinically relevant understanding of the nature and severity of post-treatment fatigue in NSCLC survivors.

The current study reports the prevalence, severity, and selected medical and psychosocial correlates of fatigue among early-stage lung cancer survivors who underwent lung resection with curative intent. Consistent with previous research[23–24], we hypothesized that a moderate to high level of fatigue would be associated with higher levels of depressed mood, dyspnea, and more functional limitations. Identifying the correlates of fatigue may inform rehabilitation programs to improve the quality of life for NSCLC survivors.

Methods

Participants and Procedure

Study participants were identified from institutional clinical and research databases at Memorial Sloan- Kettering Cancer Center (MSKCC). Participants were eligible if they met the following criteria: 1) diagnosis of stage IA or IB NSCLC, 2) surgical resection with curative intent for NSCLC, 3) were between one and six years post-treatment, 4) had no evidence of lung cancer at the time of recruitment, 5) their oncologist granted permission for study participation, 6) had no severe psychiatric or cognitive impairment judged to interfere with participation, and 7) could give informed consent. The study was approved by the Institutional Review Board.

A consent form and letter inviting study participation was mailed to potential participants. Within two weeks of sending the letters, research assistants phoned survivors and interested participants provided verbal consent. Study participants completed a 45–60 minute survey via phone or mail. All participants were offered print educational resources summarizing the availability of psychosocial and rehabilitation services for cancer survivors.

Measures

Fatigue—The Brief Fatigue Inventory (BFI) is a widely used and well-validated 9-item self-report instrument for measuring clinically relevant fatigue.[25] The BFI evaluates fatigue

right now and during the past week (worst and usual), as well as the severity and interference of fatigue with daily functioning during the past week. It has been used extensively with several cancer patient populations[26–31] and evidenced good internal reliability in the current sample (α=0.94). A score of 0 indicates no fatigue, 1–3 is considered mild, 4–6 is moderate, and 7–10 is severe fatigue.[25] For this study, clinically significant fatigue was defined as a score of 4 or above.[25]

Demographic Factors—Participants reported their age, sex, marital/partnered status, race/ethnicity, and level of education.

Medical Variables—The following medical variables were abstracted from clinical chart data and represent status at the time of surgical resection: pathological disease stage; forced expiratory volume in one second (FEV1%), expressed in percent predicted prior to surgery; diffusion capacity (DLCO%) expressed in percent predicted prior to surgery; type of surgery, classified as wedge resection, segmentectomy, lobectomy, bilobectomy, or pneumonectomy; use of video-assisted thoracoscopy alone without thoracotomy (expressed as yes or no); and the presence of cardiac or pulmonary co-morbidities with the latter consisting of chronic obstructive pulmonary disease (COPD), asthma, or tuberculosis. Participants reported their current and previous smoking status and completed a self-report version of the Baseline Dyspnea Index (BDI) to assess current dyspnea (α = 0.91).[32] The BDI is scored such that a lower score represents greater dyspnea. The BDI has been well-validated,[33] and is commonly used to assess dyspnea in patients with emphysema undergoing lung volume reduction surgery.[34]

Functional Status Variable—The Self-Reported Karnofsky Performance Scale (SR-KPS) was used to measure patient-reported functional status at the present time.[35] Participants indicated which of seven statements best described their current functional status. The modified response scale ranges from 100% (able to carry out normal activity with no physical complaints) to 30% (severely disabled with hospital admission required). A score of 70% or lower on the scale was chosen as denoting clinically impaired functional status, consistent with the inability to work or carry on with normal activity without some assistance.

Physical Activity—An adapted version of the Godin Leisure-Time Exercise Questionnaire was used to assess the average frequency and duration of mild, moderate, and strenuous physical activity during a typical seven day period.[36] We categorized individuals according to whether they met national physical activity guidelines, which recommend engaging in at least 150 minutes per week of at least moderate intensity activity.[37]

Psychological Distress—The Hospital Anxiety and Depression Scale (HADS) was used to measure psychological distress during the past week.[38] This measure is commonly used in patient populations and produces subscale scores for both anxiety (α= 0.93) and depressive symptoms (α= 0.90). A score of 8 or above on either the anxiety or depression subscale is indicative of clinically relevant symptoms.[38]

Analytic Plan—Descriptive statistics were calculated to assess demographic and medical variables. Bivariate correlational analyses were conducted to assess the strength of the relationships between clinically significant fatigue (BFI ≥ 4) and demographic, medical, functional, and psychological variables that previous literature suggested might be related to fatigue. These were: age, sex, education (more than high school); FEV1% and DLCO%; use of video-assisted thoracoscopy alone; presence of any cardiac or pulmonary co-morbidity; post-operative dyspnea (BDI ≤ 9); meeting physical activity guidelines; clinically significant

symptoms of depression (HADS depression ≥ 8); and clinically significant symptoms of anxiety (HADS anxiety ≥ 8). To identify risk factors most associated with fatigue, those variables that had significant (*ps* < .05) bivariate correlations with fatigue were entered as independent variables in a logistic regression predicting current significant fatigue (BFI ≥ 4). To examine the association between fatigue and functional status (ability to engage in everyday tasks and self-care), the percent of participants exhibiting both clinically significant fatigue and impaired functional performance (BFI ≥ 4 and SR-KPS ≤ 70%) was assessed using Chi-square analyses. Analyses were conducted using SAS v9.1, and a *p* value of < .05 was used to determine statistical significance.

Results

Participants

A total of 1,017 NSCLC patients were identified as potentially eligible from the institutional database. Of these, 461 did not meet eligibility criteria. The most common reasons for exclusion were current malignancy (*n* = 144 patients), more than six years since surgical resection (*n* = 95), deceased (*n* = 57), pathological stage II–IV disease (*n* = 55), and the inability to speak English (*n* = 47). Of the remaining 556 potentially eligible patients, 359 individuals provided informed consent (65% participation rate) and 350 provided analyzable fatigue data. Primary reasons for study nonparticipation were: passive refusal (*n* = 54), unable to be reached by telephone (*n* = 47), lack of interest (*n* = 23), wishing to avoid discussing cancer (*n* = 20) and feeling too poorly to participate (*n* = 10). For the multivariate analysis, listwise deletion of missing data reduced the analyzable data to 329 participants. Recruitment and data collection were conducted from September 2005 through July 2007. There were no statistically significant ($p < 0.05$) differences between those who completed the survey and those who declined participation with regard to mean age, sex, time since resection, pathological stage, preoperative pulmonary function, type of resection, length of hospital stay, or number of surgical complications.

Descriptive Statistics for the Demographic, Medical, Functional Status, and Psychological Variables

The demographic characteristics of the study participants are shown in Table 1. The sample comprised mostly of females (63.4%) and non-Hispanic whites (92.8%). They were well-educated (48.7% had completed a college or graduate degree) and had a mean age of 68.8 years. Medical, functional, and psychological characteristics are shown in Table 2. The majority were former smokers (78.6%). The mean duration since surgical resection was 3.5 years and most (69.2%) had been diagnosed with stage IA lung cancer. The majority (80.9%) had mildly impaired pre-surgical forced expiratory volumes in one second (FEV1%) and mildly impaired diffusing capacities (72.6%). Most of the sample had undergone lobectomy (75.7%) with an open thoracotomy (81.7%). Almost one-third of the sample had pulmonary co-morbidities such as COPD (24.4%) or asthma (6.0%), and nearly two-thirds had significant dyspnea (59.9%). Just under a quarter (24.0%) of participants met physical activity guidelines. Seven percent reported clinically significant functional impairment (SR-KPS ≤ 70%). One in five participants (19.7%) had clinically relevant symptoms of anxiety and 8.9% had clinically relevant depressive symptoms.

Prevalence and Severity of Fatigue

The majority (57.4%) of participants (201 of 350) reported some level of fatigue, 40.6% (n = 142) had mild fatigue (BFI = 1–3), and 16.8% (n = 59) had moderate or severe fatigue (BFI ≥ 4) (see Table 2). Among the 59 individuals with data on functional impairment who reported moderate or severe fatigue, 23.7% (n = 14) had significant functional impairment (SR-KPS ≤ 70%) compared to 2.8% (n = 8) with mild or no fatigue ($\chi 2 = 58.1$, $p < .001$).

Among the 14 participants with clinically significant (moderate/severe) fatigue and significant functional impairment, 57.1% (n = 8) were able to care for themselves, but were unable to carry on normal activity or do active work, while 42.9% (n = 6) had some signs and symptoms of disease, but were able to perform normal activity with effort.

Correlates of Moderate/Severe Fatigue

As shown in Table 3, variables that were significantly correlated with moderate/severe fatigue were: greater than high school education ($r = -0.13$, $p = 0.01$), pre-surgical FEV1% ($r = -0.15$, $p = 0.01$), presence of pulmonary diseases ($r = 0.15$, $p = 0.01$), current dyspnea ($r = 0.20$, $p < 0.01$), meeting physical activity guidelines ($r = -0.16$, $p < 0.01$), and clinically significant depressive ($r = 0.31$, $p < 0.01$) and anxious ($r = 0.22$, $p < 0.01$) symptoms.

Correlates of moderate/severe fatigue in the multi-variate model are shown in Table 4. These results indicate that those survivors with pulmonary disease ($OR = 2.28$, $p = 0.04$), symptoms of depression ($OR = 6.99$, $p < 0.01$), and symptoms of anxiety ($OR = 2.31$, $p = 0.03$) are more likely to report experiencing clinically significant fatigue, whereas those who are physically active are less likely to this fatigue ($OR = 0.29$, $p = 0.02$).

Discussion

This study evaluated the prevalence and severity of fatigue in a relatively large sample of NSCLC survivors using both a well-validated fatigue scale (BFI) [25] and a commonly used functional status index (SR-KPS).35 The finding that over one-half of participants had some fatigue is consistent with prior studies showing fatigue to be highly prevalent among cancer survivors.7–12, 20 Fatigue may persist for months or years after lung cancer resection despite no evidence of active cancer.[12, 16–17]

These results also demonstrate the association between moderate/severe fatigue and impairment in daily functioning. One in four individuals with moderate/severe fatigue was functionally impaired (SR-KPS ≤ 70%). These participants reported being unable to work or to independently care for their personal needs outside the home. This study underscores the importance of assessing not only the presence, but the severity and functional impact of fatigue.

The significant correlates of fatigue included both psychological symptoms (i.e. depressive and anxious mood) and the presence of pulmonary disease (ie. COPD or asthma). Our research adds to the literature showing that fatigue is associated with distressed mood and pulmonary disease.20, 39–40 Fatigue was also correlated with dyspnea in the univariate analysis, corroborating previous research showing that these symptoms (i.e. fatigue, dyspnea, depressed and anxious mood) may cluster together.41 Individuals with lung cancer often have concomitant diseases such as COPD, which can restrict physical activity and worsen fatigue.42 Anxiety may exacerbate dyspneic symptoms, leading to more anxiety and further dyspnea, creating a positive feedback loop.43 Depression and anxiety may elicit negative cognitions (i.e. catastrophizing) that can lead to behavioral habituation (i.e. avoiding physical activity because it leads to more symptoms) that makes it more difficult to break the cycle of negativity and inactivity.44 Clinically, fatigue is a prevalent symptom that correlates with a cluster of other symptoms associated with limitations in everyday functioning.45

Study Strengths and Limitations

Strengths of this study include a relatively large sample size with a good response rate, and no indication of sample bias as evidenced by the lack of differences in demographic and medical factors between study participants and decliners. This is the first study to evaluate

the severity of fatigue in early-stage lung cancer survivors 1–6 years post lung cancer surgery. It used well-validated fatigue (BFI) and functional status measures (SR-KPS) that are associated with the presence or absence of clinically meaningful symptoms.

From a clinical standpoint, the assessment tools used in the present study can be integrated into clinical practice to evaluate the prevalence and severity of fatigue, as well as the extent of functional impairment. In addition, several of the correlates of moderate/severe fatigue identified in this study are modifiable, suggesting interventional approaches for post-treatment lung cancer survivors.

Several limitations should be noted. The prevalence of fatigue may be underestimated because 35% of the eligible individuals declined to participate and one-fifth of the decliners stated a lack of interest or feeling too poorly to participate. The absence of biological markers of fatigue such as hemoglobin/hematocrit (i.e. anemia), thyroid function studies (i.e. hypothyroidism), and testosterone (i.e. low levels), preclude the study of potential underlying treatable causes of fatigue. In addition to the laboratory data, specific functional measures of activities of daily living (ADL) and independent activities of daily living (IADL) would be useful. A more detailed evaluation of functional status would help to determine the extent of assistance needed. Study participants were all survivors of stage I NSCLC, came from a single cancer institution, and were mostly non-Hispanic whites. Future studies should examine fatigue and functional status among a more heterogenous sample of NSCLC survivors. Lastly, the cross-sectional research design prohibits examination of the causal direction in the associations observed between fatigue and the demographic, medical, and psychological variables.

Conclusions and Clinical Implications

These findings provide useful information for clinicians treating early-stage NSCLC survivors with fatigue. Fatigue is common and found in nearly two-thirds of post-surgical NSCLC patients. Notably, we found that moderate and severe fatigue was associated with more functional impairment, anxious and depressive symptoms, dyspnea, and the presence of COPD or asthma. The strong association of fatigue, dyspnea, and depressed and anxious mood suggests the utility of considering the existence of a common symptom cluster.[41] Further research studying the dynamic interplay of these symptoms is important to understand the best way to identify and effectively treat fatigue among lung cancer survivors.

The relatively high prevalence of fatigue suggests the need for routine screening of all lung cancer survivors for clinically significant post-treatment fatigue.[25] If moderate or severe fatigue is present, patients should also be assessed for depressive and anxious symptoms.[42–44] Once identified, treatment of mood symptoms includes psychotherapy such as cognitive behavioral therapy[45–46] and/or administration of medications such as antidepressants with dual anxiolytic effects.[47] For mild levels of anxiety and depressive symptoms, exercise and relaxation training can help alleviate symptoms.[48–49] Furthermore, it is important to assess for dyspnea and other pulmonary disease such as COPD.[50–51] Treatment of COPD may decrease dyspnea,[52] pulmonary rehabilitation may attenuate deconditioning, dyspnea, and fatigue,[53–55] and occupational therapy can assist patients with activities of daily living and prevent inactivity.[56] A comprehensive approach to the treatment of fatigue should encompass screening and management of depressive and anxious symptoms, dyspnea, and pulmonary disorders to promote optimal functioning throughout survivorship.[57–63]

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Table 1

Demographic characteristics of sample (N=350)

Characteristic	N	%
Age (years) (M = 68.8, SD = 9.8)		
35–54	37	10.6
55–64	71	20.3
65–74	128	36.6
≥75	114	32.5
Sex		
Male	128	36.6
Female	222	63.4
Race/ethnicity		
Non-Hispanic white	324	92.8
Non-Hispanic black	11	3.2
Non-Hispanic Asian/Pacific Islander	4	1.1
Non-Hispanic other	2	0.6
Hispanic	8	2.3
Missing (*n*)	(1)	
Education		
≤High school graduate	112	32.1
Some college	67	19.2
College graduate	87	24.9
Graduate degree	83	23.8
Missing (*n*)	(1)	

Table 2

Medical, Functional, and Psychological Characteristics (N=350)

Characteristic	N	%
BFI[a]		
None (BFI = 0)	149	42.6
Mild (BFI = 1–3)	142	40.6
Moderate/Severe (BFI ≥ 4)	59	16.8
Smoking status		
Current smoker	20	5.7
Former smoker		
Quit prior to surgery	229	65.4
Quit after surgery	46	13.2
Never smoker (< 100 lifetime cigarettes)	55	15.7
Pathological disease stage		
IA	241	69.2
IB	107	30.8
Missing (*n*)	(2)	
Time since surgical resection (M = 3.5 years, SD = 1.2)		
1 – < 2 years	38	10.9
2 – < 3 years	102	29.1
3 – < 4 years	92	26.3
4 – < 5 years	75	21.4
5 – < 6 years	43	12.3
Preoperative FEV1%[b] (M = 88.7, SD = 20.4)		
Severe (< 50%)	12	3.5
Moderate (50–69%)	53	15.6
Mild (≥ 70%)	276	80.9
Missing (*n*)	(9)	
Preoperative diffusing capacity%[c] (M = 83.5, SD = 25.6)		
Severe (< 50%)	18	5.7
Moderate (50–69%)	69	21.7
Mild (≥ 70%+)	231	72.6
Missing (n)	(32)	
Type of surgical resection		
Wedge	41	11.7
Segmentectomy	29	8.3
Lobectomy	265	75.7
Bilobectomy	9	2.6
Pneumonectomy	6	1.7
Video-assisted thoracic surgery only		

Characteristic	N	%
Yes	64	18.3
No	285	81.7
Missing (*n*)	(1)	
Presence of cardiac co-morbidity		
Yes	145	41.5
No	204	58.5
Missing (*n*)	(1)	
Pulmonary co-morbidities		
COPD[f]	85	24.4
Asthma	21	6.0
Tuberculosis	1	0.3
None	242	69.3
Missing (*n*)	(1)	
Current dyspnea (BDI[d] ≤9)		
No	136	40.1
Yes	203	59.9
Missing (*n*)	(11)	
Self-Rated Karnofsky		
Performance Status		
100% (low impairment)	206	61.1
90%	72	21.4
80%	37	11.0
70%	13	3.9
60%	9	2.7
Missing (*n*)	(13)	
Meeting physical activity guidelines[e]		
Yes	84	24.0
No	266	76.0
Psychological distress		
HADS[g] Depression (≥8)	31	8.9
HADS Anxiety (≥8)	69	19.7

[a] BFI = Brief Fatigue Inventory

[b] FEV1% =Forced Expiratory Volume in 1 second expressed as percent predicted

[c] DLCO% = Diffusion Capacity expressed as percent predicted

[d] BDI = Baseline Dyspnea Index

[e] American College of Sports Medicine and American Heart Association (≥150 min/week of moderate/strenuous activity)

[f] Chronic Obstructive Pulmonary Disease

[g] HADS = Hospital Anxiety and Depression Scale

Table 3

Correlations between Moderate/Severe Fatigue and Selected Variables

Characteristic	r^*	*p*-value
Age	−0.01	0.79
Sex (Male)	−0.09	0.10
Greater than High School (HS) education vs. ≤ HS education	−0.13	0.01
History of tobacco use (> 100 lifetime cigarettes)	−0.02	0.77
FEV1%[a]	−0.15	0.01
DLCO%[b]	−0.05	0.35
Video-assisted thoracic surgery only	−0.04	0.50
Presence of cardiac disease	0.04	0.47
Presence of pulmonary disease	0.15	0.01
Current dyspnea (BDI[c] ≤ 9)	0.20	<0.01
Met physical activity guidelines[d]	−0.16	<0.01
Clinically significant symptoms of depressed mood (HADS[e] ≥ 8)	0.31	<0.01
Clinically significant symptoms of anxious mood (HADS ≥8)	0.22	<0.01

*For continuous variables *r* was calculated as point biserial correlation; for categorical variables r was calculated as phi coefficient.

[a]FEV1% = Forced Expiratory Volume in 1 second expressed as percent predicted

[b]DLCO% = Diffusion Capacity expressed as percent predicted

[c]BDI = Baseline Dyspnea Index

[d]American College of Sports Medicine and American Heart Association

[e]HADS = Hospital Anxiety and Depression Scale

Table 4

Multivariate Analysis: Correlates of Moderate/Severe Fatigue (N = 329*)

Characteristic	Odds Ratio (95% CI)	*p*-value
Greater than High School (HS) vs. ≤ HS education	0.52 (0.26–1.04)	0.06
FEV1%[a]	1.00 (0.98–1.02)	0.85
Presence of pulmonary disease	2.28 (1.05–4.94)	0.04
Current dyspnea (BDI[b] ≤ 9)	2.20 (0.96–5.05)	0.06
Met physical activity guidelines[c]	0.29 (0.10–0.83)	0.02
Clinically significant symptoms of depressed mood (HADS[d] ≥ 8)	6.99 (2.64–18.49)	<0.01
Clinically significant symptoms of anxious mood (HADS ≥ 8)	2.31 (1.09–4.90)	0.03

*Following listwise deletion sample size for multivariate analysis was N=329

[a]FEV1% = Forced Expiratory Volume in 1 second expressed as percent predicted

[b]BDI = Baseline Dyspnea Index

[c]American College of Sports Medicine and American Heart Association

[d]HADS = Hospital Anxiety and Depression Scale