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HEALTH-RELATED QUALITY OF LIFE AMONG EARLY-STAGE, NON-SMALL CELL, LUNG CANCER SURVIVORS

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Abstract

Background—Limited data are available about the physical and mental functioning of individuals diagnosed and treated for early stage lung cancer. To develop post-treatment guidelines and targeted resources for the growing number of lung cancer survivors, clinically relevant information about longer-term health-related quality of life (HQOL) is needed. The current study examines lung cancer survivors' HQOL and identifies associations between HQOL and demographic, disease and psychosocial risk factors.

Methods—A total of 359 individuals diagnosed and surgically treated for Stage IA or IB non-small cell lung cancer completed a post-treatment survey via mail or telephone that included the SF-36v2 as well as demographic, medical, psychological and physical symptom indices. To better understand the impact of lung cancer treatment, we examined age- and gender-adjusted differences in HQOL as compared to a demographically matched sample of older adults, most with a significant smoking history, who participated in a lung cancer screening trial. Risk factors for impairments in HQOL were also identified.

Results—Compared to the screening sample, lung cancer survivors reported lower physical health scores, but did not differ in terms of mental health status. Dyspnea and distressed mood were most associated with HQOL impairments.

Conclusions—Early stage lung cancer survivors are likely to experience mild impairment in physical functioning. They may benefit from management of distressed mood and referral to physical activity and pulmonary rehabilitation programs to promote HQOL outcomes.

Keywords

quality of life; lung cancer; survivorship

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Introduction

In the United States, lung cancer is the second most prevalent cancer with about 219,440 new cases diagnosed annually [1]. Despite the generally poor prognosis, five-year survival rates for individuals diagnosed with early-stage (IA and IB) non-small cell lung cancer (NSCLC) are 73% and 54%, respectively [2]. There are currently an estimated 360,000 survivors of lung cancer in the US, accounting for 4% of the total adult cancer survivor population [3]. Ongoing investigations of early detection and advances in targeted therapies and adjuvant multi-modality treatment hold increased hope for disease-free survival for this growing cohort of relatively understudied individuals diagnosed with early-stage lung malignancies [4].

To guide the long-term care of lung cancer survivors, information is needed regarding their health-related quality of life (HQOL), represented by patient reports of physical symptoms, functional abilities, psychological well-being, and social functioning. Previous studies have noted that post-treatment deficits in HQOL among lung cancer survivors persist throughout survivorship [5–12], yet various methodological shortcomings of prior work limit the conclusions drawn to date. Prior studies have used relatively small samples and typically collected data either only within the first year after treatment or more than five years post-treatment [13]. Most important, few studies have compared lung cancer survivors' HQOL to relevant comparison groups (for an exception, see reference [6]), limiting the ability to control for the confounding effects of smoking history or comorbid conditions (such as chronic lung disease) on HQOL outcomes. Additionally, there is a need to pay greater attention to the clinical importance of HQOL findings [14] and to identify risk factors for impairment in post-treatment HQOL [15] so that supportive care and rehabilitation interventions can be targeted to lung cancer survivors most in need of specialized follow-up care.

This study examines the HQOL of early stage lung cancer survivors (1 to 6 years post resection) who had undergone surgical resection as their primary treatment and remained disease-free. We examined demographic, medical, and psychological correlates of HQOL. In contrast to other cross-sectional studies that compared HQOL to the general population, we compared HQOL (SF-36v2) scores from lung cancer survivors with a comparison sample of older adults who had enrolled in a lung screening trial [16] and who had screened negative for lung cancer. Use of this matched comparison sample allowed us to better control for demographic, tobacco-related, and comorbidity variables that can influence interpretation of HQOL outcomes.

Method

Participants and Procedure

Lung cancer survivors were identified from institutional clinical and research patient databases at Memorial Sloan-Kettering Cancer Center (MSKCC). Eligibility criteria were: diagnosis of primary stage IA or IB NSCLC between one to six years post surgical resection with curative intent, no evidence of disease at time of recruitment, thoracic surgical oncologist's permission to contact the individual for study participation, reachable by phone, no cognitive impairment likely to interfere with study participation (as defined by fewer than four errors on the Brief Six-Item Screener [17]), and able to give informed consent.

After obtaining permission to contact from their attending surgeons, patients were mailed a consent form and letter inviting study participation, which was followed up two weeks later by telephone to confirm eligibility and obtain verbal consent. Participants either completed

the survey via telephone interview or were sent the survey by mail. Following survey completion, all participants received information regarding MSKCC's Post-Treatment Resource Program and a National Cancer Institute brochure entitled, "Facing Forward: Life after Cancer Treatment" [18]. The study procedures were approved by the Institutional Review Board.

Measures

Quality of Life—The SF-36v2 [19] is a 36-item scale that assesses patient-reported quality of life in eight domains: physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health (α 's = 0.75 – 0.94 in the current study). The SF-36v2 also has two higher-order component factors: Physical Health (PCS) and Mental Health (MCS). The SF-36v2 was chosen because this family of measures, including the shorter SF12v2, has been used in prior studies of HQOL in lung cancer survivors [6, 8], permitting cross-study comparisons.

Demographic Variables—Participants reported their age, sex, race/ethnicity, education, and employment status.

Medical Variables—Time since surgical resection and type of surgical resection were extracted from the hospital's thoracic surgery clinical database. Current medical comorbidity was assessed via self-report using a 21-item commonly used checklist of medical conditions [20]. Current dyspnea was measured using the Baseline Dyspnea Index (BDI) [21], which assesses severity of dyspnea along three dimensions: overall functional impairment, task magnitude, and effort magnitude. Total scores on the BDI vary from 0 to 12, with lower scores denoting a higher level of dyspnea. Participants also reported current smoking status. As a potential correlate of HQOL, we used the Hospital Anxiety and Depression Scale (HADS)[22] to assess symptoms of anxiety ($\alpha = 0.93$) and depression ($\alpha = 0.90$) and deemed subscale scores greater than or equal to eight as indicative of clinically significant distress [22].

Analytic Plan

We compared the SF-36v2 data from the lung cancer survivor sample to a cohort of current smokers and former smokers who had completed the SF-12v2 at the time of enrollment in a large, low dose helical computer tomography (CT scan) lung screening trial conducted in the New York metropolitan region [16] equivalent to the geographic catchment area of the comprehensive cancer center treating the lung cancer survivors. We chose this novel comparison group because these individuals were similar to our survivor population in terms of demographic characteristics (older) and smoking history, except for not having been diagnosed and treated for NSCLC. We randomly selected a comparison group ($N = 699$) of screening enrollees with normal CT findings from the available lung cancer screening sample and matched it proportionally to our survivor sample stratified by age, sex, and education using SAS proc survey select [23]. The SF-12v2 completed by the screening sample is highly correlated with ($r > 0.95$) and directly comparable to the SF-36v2 summary scores [19, 24] completed by the survivors using the norm-based T-score approach as recommended by the publisher of the SF scales (QualityMetric). The Physical (PCS) and Mental Health Component (MCS) subscale means from the cancer survivor sample were then adjusted and compared with the lung screening sample. This was accomplished by categorizing the lung cancer survivors and lung screening comparison samples into age and gender groupings that correspond to the SF scoring, then for each of the eight age-gender groupings the mean PCS and MCS scores for the lung cancer survivor sample were subtracted from the screening comparison sample. Using methods employed in meta-

analysis [25], we weighted each grouping by its sample size and computed average standardized (Cohen's *d*) and unstandardized mean differences for both the PCS and MCS scales (see Table 3).

Using multivariate regression analyses, we also examined the extent to which demographic and medical variables were associated with variation in lung cancer survivors' HQOL. The Physical (PCS) and Mental Health (MCS) component scores from the SF-36v2 were selected as dependent variables as they reliably summarize the multiple scale data [19]. We included a set of nine demographic and medical correlates hypothesized to be related to HQOL. These were: age, sex, employment status, years post-surgery, type of lung resection (segmentectomy/wedge resection vs. lobectomy and bilobectomy/pneumonectomy), number of comorbid conditions, presence of significant dyspnea (BDI = 9), and presence of clinically relevant depression and anxiety symptoms (HADS = 8 for each subscale). There were too few current smokers (5.6%) in the lung cancer survivor sample to include smoking status in the regression equation [26]. For all analyses, a cutoff level of $p < 0.05$ was used to determine statistical significance. Examination of residual plots and collinearity reports indicated that statistical assumptions of normality, homoscedasticity, and collinearity were within suggested limits for each analysis [27].

Results

Participants

A total of 510 eligible individuals were identified from the thoracic surgery and institutional databases. Among the 510 potentially eligible patients, 151 declined to participate. The main stated reasons for declining were lack of study interest ($n = 23$), wishing to avoid discussion of lung cancer ($n = 20$) and not feeling well enough to participate ($n = 10$). In total, 359 individuals provided informed consent and analyzable data (65% participation rate). Recruitment and data collection were conducted from September 2005 through July 2007. Those who completed the survey did not differ from those who refused participation by mean age, sex, time since surgical resection, pathological disease stage, pre-operative FEV₁%, or type of surgical resection ($ps > 0.05$). Never and former smokers were more likely to participate as compared to current smokers ($p = .02$).

Demographics and Medical Characteristics

Demographic characteristics of the cancer survivor sample and the comparison lung screening sample are presented in Table 1. As expected, samples were similar in terms of age, ethnicity, sex, and education.

In terms of medical characteristics (Table 2), 69.2% of the lung cancer survivors were diagnosed with stage IA disease and the mean time since surgical resection was 3.5 years. Most (75.9%) of the cancer survivors had undergone lobectomy, with wedge resection being the second most common surgical procedure (11.7%). Lung cancer survivors reported a mean of 2.5 (SD = 1.7) comorbid conditions with cataracts (39.3%), other prior cancers (30.8%), osteoarthritis (26.3%), chronic obstructive pulmonary disease (COPD) (26.0%), and osteoporosis (24.6%) being the most common conditions. While the comparison study employed a slightly different comorbidity measure, we were able to compare rates of several conditions, finding lower prevalence ($ps < .05$) in the screening sample, with 22.9% reporting a history of cancer, 16.1% COPD, and 10.7% a diagnosis of asthma. Sixty percent of the lung cancer survivor sample reported current dyspnea (BDI = 9). Twenty percent reported clinically significant symptoms of anxiety and 9.6% reported symptoms of depression. In terms of smoking status, 5.6% were current smokers, 15.5% smoked fewer than 100 cigarettes in a lifetime (i.e. never smokers), and 78.9% were former smokers with

65.6% reporting having quit prior to surgery and 13.2% reporting having quit since surgery. Lung cancer survivors smoked an average of 53.4 years which was similar in smoking duration to that reported by the lung cancer screening comparison sample (49.2 years). The comparison sample was also similar in terms of the percent of never smokers (15.4%).

HQOL Differences in Lung Cancer Survivors

As shown in Table 3, the mean Physical Health (PCS) T-scores for the lung cancer survivor and screening samples were 46.32 and 48.65 respectively, and the mean Mental Health (MCS) scores were 52.61 and 51.91. After adjustment for age and gender, lung cancer survivors reported lower PCS scores in comparison to the lung screening sample (mean difference = -2.43 , $p < 0.0001$), whereas there were no differences in MCS scores (mean difference = 1.08 , $p = 0.06$). The lowest mean subscale scores reported by lung cancer survivors were found for the Physical Functioning ($M = 45.8$, $SD = 10.5$) and Role Limitations due to Physical Problems ($M = 46.5$, $SD = 11.4$) scales (see Table 4).

Demographic and Medical Correlates of HQOL in Lung Cancer Survivors

Multiple regression results for the PCS and MCS scales are shown in Table 5. The selected correlates explained 40% of the variance in the Physical Health Component (PCS). Being employed was associated with higher PCS, whereas presence of dyspnea (BDI 9), depression symptoms (HADS depression 8), and having a greater number of comorbid conditions were associated with lower PCS scores ($ps < 0.05$). For the Mental Health Component (MCS), the correlates explained 28% of the variance, with significant ($ps < 0.05$) effects revealing that older and male survivors had somewhat better post-treatment mental health, whereas those reporting depression and anxiety symptoms showed more impairment.

To translate results from the multiple regression analysis to a clinically relevant metric, we interpreted parameter estimates for each of the norm-based PCS and MCS summary measures in terms of clinical importance, that is, in terms of a difference that would be noticeable and meaningful for the quality of a patient's life and clinical outcomes. Since the authors of the SF36 suggest that a 3-point difference ($SD = 10$) represents the minimum for identifying a clinically important difference [19], correlates showing a parameter weight of least 3.0 points would have a clinically significant impact on patient HQOL. Thus, for the PCS component, the presence of current dyspnea was associated with a decrement in physical functioning of 8.7 points (95% CI = $6.7 - 10.6$) suggesting that survivors who experience shortness of breath are likely to have a meaningful deficit in physical quality of life. For each comorbid condition PCS was found to be reduced by 1.95 points (95% CI = $1.3 - 2.6$), suggesting that having two or more comorbid conditions was related to decreased physical HQOL. In addition, depression may also be associated with clinically important difficulties in physical functioning with those reporting symptoms of depression showed a deficit in PCS of 4.5 points (95% CI = $1.1 - 8.0$). As would be expected, being employed was also associated with increased physical functioning (4.5 points 95% CI = $2.3 - 6.5$). For the mental health component (MCS), presence of depression ($B = 10.6$, 95% CI = $7.3 - 13.8$) and anxiety ($B = 5.8$, 95% CI = $3.4 - 8.2$) symptoms was also associated with clinically meaningful deficits in HQOL.

Discussion

This study makes several important contributions to clinical care and research focusing on post-treatment lung cancer survivors. In contrast to studies using general population norms, this study compares HQOL in lung cancer survivors with that of closely matched controls, thereby improving the interpretation of the specific impact of disease and treatment

exposure. These analyses also build upon prior research [5–6, 8] by examining correlates of HQOL and by interpreting results in terms of clinical importance, thus enhancing the meaningfulness of these findings for clinical care.

Most encouraging, our results indicate that lung cancer survivors diagnosed with early stage non-small cell disease who underwent resection with curative intent and remain without evidence of disease have, on average, mild physical impairments in quality of life compared to closely matched controls who have not been diagnosed and treated surgically for early-stage lung cancer. The effect size (d -value) approaches a small clinically important difference [28] (see Table 3), indicating that survivors reported relatively mild, but noticeable, disease and treatment related physical sequelae. Our regression analysis also highlights specific subgroups of lung cancer survivors that experience clinically meaningful deficits in HQOL outcomes. Similar to prior findings [5, 8], survivors who experienced dyspnea were more likely to report lower physical HQOL as well as those who reported symptoms of depression and a greater number of comorbid conditions. In contrast with other studies [5, 8], a greater amount of time since diagnosis was not identified as a correlate of physical HQOL suggesting some stability in HQOL following surgical recovery and the early phase of lung cancer survivorship. Symptoms of depressed or anxious mood were associated with lower levels of mental health HQOL, whereas older age and being male were associated with higher levels of mental health HQOL. These are important findings with regard to long-term HQOL outcomes for early stage, completely resected, lung cancer survivors.

The study indicates that a subgroup of lung cancer survivors may have greater need for multi-disciplinary rehabilitation and supportive care focused on improving physical functioning. To date, preliminary studies of pulmonary rehabilitation programs for post-operative lung cancer patients have found positive effects on functional ability, peak exercise capacity, and dyspnea [29–33], supporting the need for further research on the risks and benefits of exercise and pulmonary rehabilitation following lung cancer surgery. In addition, post-treatment screening for anxious and depressed mood would provide a foundation for improved management of mental health impairments in HQOL.

Study Strengths and Limitations

Strengths of the study include a good survey response rate (65%) and use of a well-validated HQOL instrument. The study also examined lung cancer survivors who were 1–6 years post treatment, an understudied yet important timeframe in terms of HQOL outcomes. Moreover, comparison of lung cancer survivors' HQOL with an age-, sex-, and education-matched comparison sample enrolled in a lung cancer screening trial permitted estimation of the specific effects on HQOL of lung resection and cancer treatment while helping to control for the potentially confounding effects of smoking history and associated comorbid medical conditions. In addition, use of clinically-relevant interpretation guidelines focuses the results in terms of clinical importance for physicians providing long-term surveillance and management of lung cancer survivors.

Several limitations to the study should be noted. First, the present findings apply only to longer-term (1–6 year post-treatment) survivors of stage I NSCLC with no current evidence of disease. Second, the cross-sectional research design prohibited examination of the causal direction of associations between selected correlates and HQOL. While study participants and decliners were similar in terms of demographic and medical factors, fewer current smokers participated, a factor that could positively bias HQOL estimates. Future prospective studies should closely examine several HQOL appraisal processes such as response shift [34], level of satisfaction, and evaluation of the importance [35] of other HQOL domains. Similarly, assessment of perceptions of benefits and change of perspective from the cancer

experience may provide a more nuanced picture of the quality of life in lung cancer survivors.

Conclusions

These findings provide clinically useful information for physicians managing post-treatment care of early stage, resected lung cancer survivors. While our finding that lung cancer survivors overall do not experience major deficits in HQOL is encouraging, multi-disciplinary post-treatment follow-up beyond the initial treatment phase is warranted as the presence of either ongoing dyspnea or depression is likely to be associated with clinically meaningful decrements in physical functioning for these survivors. Further research is needed to determine if mood disorder screening and management as well as pulmonary rehabilitation programs that have been shown to improve dyspnea [36], result in improved HQOL outcomes for lung cancer survivors. In addition, while the growing use of minimally invasive surgical procedures is likely to reduce post-surgical sequelae, the rising use of radiation therapy and neoadjuvant and adjuvant chemotherapy warrants examination of the effects of multi-modality treatment regimens on long-term HQOL outcomes among lung cancer survivors. These findings guide the development of clinical guidelines needed for the management of post-treatment care among the growing cohort of lung cancer survivors.

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Summary

This study examines health-related quality of life (HQOL) in early stage, non-small cell lung cancer survivors and identifies the association between demographic, disease and psychosocial risk factors and lung cancer survivors' HQOL. Early stage lung cancer survivors may benefit from screening and referral for management of distressed mood and referral to physical activity and pulmonary rehabilitation programs to promote HQOL outcomes.

Table 1

Demographic Characteristics of Lung Cancer Survivors (N = 359) and Comparison Lung Screening Sample (N = 699)

Characteristic	Lung Cancer Survivors		Comparison Lung Screening Sample	
	N	%	N	%
Age (years) (<i>M</i> , <i>SD</i>)	68.9 (9.8)		67.8 (10.3)	
35–54	37	10.3	72	10.3
55–64	72	20.0	141	20.2
65–74	132	36.8	257	36.8
75+	118	32.9	229	32.8
Missing (<i>n</i>)	(0)		(0)	
Sex				
Male	130	36.2	258	36.9
Female	229	63.8	441	63.1
Missing (<i>n</i>)	(0)		(0)	
Race/ethnicity				
Non-Hispanic white	333	93.0	665	95.1
Non-Hispanic black	11	3.1	8	1.1
Non-Hispanic Asian/Pacific Islander	4	1.1	6	0.9
Non-Hispanic other	2	1.1	10	0.6
Hispanic	8	2.2	10	1.4
Missing (<i>n</i>)	(1)		(0)	
Education				
High school graduate	116	32.4	227	32.5
Some college	68	19.0	134	19.2
College graduate	90	25.1	175	25.0
Graduate degree	84	23.5	163	23.3
Missing (<i>n</i>)	(1)		(0)	

Table 2**Medical Characteristics of Lung Cancer Survivors (*N* = 359)**

Characteristic	N	%
Pathological disease stage		
IA	247	69.2
IB	110	30.8
Missing (<i>n</i>)	(2)	
Time since surgical resection (<i>M</i> = 3.5 years, <i>SD</i> = 1.2)		
1 – < 2 years	38	10.6
2 – < 3 years	105	29.2
3 – < 4 years	95	26.5
4 – < 5 years	76	21.2
5 – < 6 years	45	12.5
Missing (<i>n</i>)	(0)	
Type of surgical resection		
Wedge	42	11.7
Segmentectomy	30	8.4
Lobectomy	272	75.9
Bilobectomy	9	2.3
Pneumonectomy	6	1.7
Missing (<i>n</i>)	(0)	
Most common comorbid conditions		
Cataracts	140	39.3
Other Cancer	110	30.8
Osteoarthritis	94	26.3
Chronic Obstructive Pulmonary Disease (COPD)	93	26.0
Osteoporosis	88	24.6
Bronchitis	64	17.9
Asthma	61	17.1
Second Lung Cancer	44	12.3
Heart Attack	36	10.1
Missing (<i>n</i>)	(2)	
Current dyspnea (BDI = 9)		
No	137	40.0
Yes	205	60.0
Missing (<i>n</i>)	(17)	
Psychological distress		
HADS Depression (= 8)	34	9.6
HADS Anxiety (= 8)	71	20.0
Missing (<i>n</i>)	(4)	
Smoking status		
Current smoker	20	5.6

Characteristic	N	%
Former smoker	280	78.9
Quit prior to surgery	233	65.6
Quit after surgery	47	13.2
Never Smoker (< 100 lifetime cigarettes)	55	15.5
Missing (<i>n</i>)	(4)	
Number of years smoked (<i>M, SD</i>)	53.4 (12.5)	

BDI = Baseline Dyspnea Index; HADS = Hospital

Anxiety and Depression Scale

Table 3

Means, Age- and Gender-Adjusted Mean Differences, 95% Confidence Intervals, and Standardized Difference Scores for SF Scales for Lung cancer Survivors and the Lung Cancer Screening Sample.

SF Summary Scale	Mean (SD)	Adjusted Mean Difference* (95% CI)	p-value	Cohen's <i>d</i>
Physical Health Component (PCS)				
Lung Cancer Survivors	46.32 (10.85)			
Lung Screening Sample	48.65 (9.62)	−2.43 (−3.64 to −1.23)	< 0.0001	−0.34
Mental Health Component (MCS)				
Lung Cancer Survivors	52.61(9.25)			
Lung Screening Sample	51.91(9.39)	1.08 (−0.06 to 2.22)	0.06	0.16

Norm-based scoring method, employing 1998 SF-12v2 and SF-36v2 U.S. population norms.

* Adjusted for age and gender.

Table 4

Means and Standard Deviations of SF-36v2 Subscales* for Lung Cancer Survivors (N = 359)

SF-36v2 Subscale	Mean (SD)
Physical Functioning	45.79 (10.54)
Role Physical	46.54 (11.39)
Bodily Pain	49.92 (11.17)
General Health	48.37 (10.29)
Vitality	52.20 (10.01)
Social Functioning	49.90 (10.92)
Role Emotional	50.41 (9.79)
Mental Health	51.05 (9.37)

* Norm-based scoring method

Table 5

Correlates of Physical (PCS) and Mental Health (MCS) SF-26v2 Component Scores

SF-36v2 Component	Regression Coefficient (B)	SE	p	Beta ⁺
Physical Health Component (PCS)				
Age	0.05	0.05	0.34	0.05
Sex (male)	−1.09	1.02	0.28	−0.05
Employed (vs. retired/disabled)	4.39	1.08	<0.001	0.20
Years since resection	−0.16	0.38	0.67	−0.02
Type of resection [*]				
Lobectomy	−1.21	1.19	0.31	−0.05
Bilobectomy/pneumonectomy	−2.90	2.58	0.26	−0.05
Number of comorbid conditions	−1.95	0.31	<0.001	−0.30
Current dyspnea (BDI 9)	−8.66	0.98	<0.001	−0.39
HADS depression 8	−4.54	1.77	0.01	−0.12
HADS anxiety 8	0.55	1.29	0.66	0.02
Model	F(10) = 23.75, R ² adj = 0.40 p <0.0001,			
Mental Health Component (MCS)				
Age	0.11	0.05	0.03	0.12
Sex (male)	2.23	0.95	0.02	0.12
Employed (vs. retired/disabled)	1.14	1.01	0.26	0.06
Years since resection	0.56	0.36	0.12	0.07
Type of resection [*]				
Lobectomy	−0.31	1.11	0.78	−0.01
Bilobectomy/pneumonectomy	1.67	2.41	0.49	0.03
Number of comorbid conditions	−0.15	0.29	0.61	−0.03
Current dyspnea (BDI 9)	−0.21	0.92	0.81	−0.01
HADS depression 8	−10.56	1.65	<0.001	−0.34
HADS anxiety 8	−5.80	1.21	<0.001	−0.25
Model	F (10) = 14.00, R ² adj = 0.28 p <0.0001,			

⁺Beta = standardized regression coefficient.

* Type of lung resection as compared to segmentectomy/wedge resection. BDI = Baseline Dyspnea Index, HADS = Hospital Anxiety and Depression Scale.