HHS Public Access

Author manuscript

Am J Crit Care. Author manuscript; available in PMC 2019 August 01.

Published in final edited form as:

Am J Crit Care. 2008 September ; 17(5): 455–468.

Symptom severity one to four months post-thoracotomy for lung cancer

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Abstract

Background: Information about the severity of symptoms during recovery from surgery for lung cancer can be useful in planning for and anticipating needs for recovery.

Objectives: To describe symptom severity and changes during the first four-months of recovery from thoracotomy for non-small cell lung cancer; and factors associated with overall symptom severity at one (T1) and four (T3) months post surgery.

Methods: 94 patients (58% female, mean age 63 years, 52% adenocarcinoma, 79% lobectomy) were assessed at one-, two-, and four-months post-thoracotomy using the Lung Cancer Symptom Scale (LCSS), Brief Pain Inventory, Schwartz Fatigue Scale, Dyspnea Index, and Centers for Epidemiology and Depression scale (CES-D). Clinically meaningful changes (LCSS ≥10% improvement), decline in the proportion of patients with severe symptoms (rated >25mm on the LCSS), and relationships among symptoms are reported. Fixed and GEE models were used to evaluate changes in symptom severity over time. Multiple regression models were used to examine correlates of overall symptom burden (LCSS) at T1 and T3.

Results: Average LCSS symptom severity significantly declined over time for most symptoms. However, clinically meaningful improvement was only seen in disrupted appetite and dyspnea. Severe symptoms included fatigue (51%), dyspnea (40%), cough (32%), and pain (19%). The prevalence of depressed mood (CES-D >15) decreased from 33% to 26% at four-months, and co-occurred with other symptoms. Most (77%) had at least one comorbid condition. A model

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including number of comorbidities and CES-D explained 54% of the variance in symptom severity at T1; comorbidity, male sex, treatment with neoadjuvant treatment, and CES-D score explained 50% of the variance in symptom severity at T3.

Conclusions: Severe symptoms, especially fatigue, dyspnea, and cough continued four-months after surgery for some patients, indicating the need for support during recovery, especially for patients with multiple comorbidities and depressed mood.

Keywords

lung cancer; thoracotomy; symptoms; surgery

Introduction

Only a minority of patients diagnosed with non-small cell lung cancer (NSCLC) are surgical candidates for curative resection due to late stage disease at diagnosis. Surgery provides an opportunity for cure for a cancer with a generally poor prognosis.[1] The impact of thoracotomy on quality of life (QOL) among lung cancer survivors, regardless of the length of survival, has been the focus of a growing number of studies.[2–7] To date, the majority of studies of lung cancer-related symptoms such as dyspnea, weight loss, and pain are from patients with advanced stage disease[8] with limited information about symptoms experienced by patients post potentially curative lung cancer surgery.[9] The few available reports of symptoms and QOL of survivors of NSCLC who have received surgical intervention provide limited information about symptom severity, or duration of symptoms, post surgery.[10, 11] The lack of data about severity of symptoms during the first months after surgery, factors associated with increased severity, or patterns of multiple symptoms, make planning appropriate interventions to support patients over the course of recovery challenging.

Symptoms and recovery post-thoracotomy

A focus on symptom severity is important as some reports suggest that both physical and psychological symptoms continue long after thoracotomy. Mangioine et al.[12] reported that even 12 months after thoracotomy physical functioning and health perceptions remained lower than pre-operative levels, and pain continued. However, Zieren et al.[3] reported return to preoperative QOL levels within six-months after thoracotomy. Symptom resolution was not described in this report. Another prospective study of 84 patients supports the 12-month period for recovery to baseline QOL levels.[6]

Common symptoms post-thoracotomy include pain, dyspnea, and fatigue. Pain may persist six-months[13] to a year after surgery.[14, 15] In a review by Rogers and Duffy,[16] the incidence of chronic mild to moderate post-thoractomy pain is described as “under-rated,” and affecting approximately 50% of patients. Due to the extent of resection as well as the presence of comorbid conditions such as chronic obstructive pulmonary disease (COPD), dyspnea may continue or even be exacerbated after curative surgery. In a study of 142 long-term disease-free five-year minimum lung cancer survivors, two-thirds reported at least one respiratory symptom, with 39% reporting dyspnea at rest and 36% reporting multiple symptoms.[17] Other than for cough, disease and treatment characteristics were not associated

with differences in symptoms or pulmonary function. Although fatigue may be an expected part of the de-conditioning after surgery, and is a common symptom associated with cancer, few studies have reported the severity of fatigue after lung cancer surgery.[18]

In addition to physical symptoms, recovery also may be complicated by psychological symptoms. Compared to other cancer diagnoses, emotional distress was been reported as highest among people with lung cancer.[19] Depression may be present at the time of surgery. In a study of 223 patients with NSCLC who had potentially curative surgical treatment, 14.8% met the criteria for clinical depression post-surgery.[20] Prevalence declined monthly over the 3-month assessment period (9.0%, 9.4%, 5.8%, respectively). Patients with poorer social support were at higher risk for depression. There is evidence that depressed mood is an ongoing concern for some lung cancer survivors.[21]

Factors potentially influencing symptom severity during recovery

A variety of factors have been identified as influencing symptom severity in theoretical models depicting symptom experiences.[22, 23] Patient demographic, treatment, and health status characteristics could influence symptom severity of patients with NSCLC post-surgery. The demographic factors of older age and living alone were associated with poorer physical QOL, suggesting increased symptoms, among long-term lung cancer survivors.[21] Living alone may make symptom management during recovery more challenging, and has been associated with lower QOL post lung cancer surgery.[6] Gender may also make a difference in QOL outcomes and severity of symptoms among patients with lung cancer[24, 25], including some studies suggesting more common symptoms among women.[4, 26]

Treatment variables such as the extent of surgery, especially pneumonectomy, may influence the type and severity of a number of symptoms. For example, Nugent et al.[27] reported long-term impaired exercise performance in patients undergoing a pneumonectomy and others have reported diminished QOL.[28] The less invasive video-assisted thoracic surgery (VATS) pulmonary resection has been suggested to decrease morbidity,[29] but current data, including information about the symptom profile, are limited.[30] Post-operative symptom severity and patterns may be quite different among patients who receive this option. For some it may appear to result in fewer symptoms, however for others who receive this procedure when thoracotomy is not feasible due to poor health status may have even more severe symptoms.[31] Additionally, adjuvant chemotherapy or radiation treatment prior to or post-lung cancer surgery, given to improve survival and reduce risk of recurrence, may increase symptom severity. At least one study has reported that it did not influence functional health or QOL six-months post surgery.[13]

Health status factors are important considerations in the evaluation of symptoms as the diagnosis of lung cancer increases with age[32] and comorbid conditions, especially those influenced by longterm smoking, may influence symptom severity during recovery[21]. For example cardiovascular and respiratory diseases, including COPD, are common comorbid conditions in patients with lung cancer[33]. COPD, has been associated with dyspnea post-thoracotomy as well as with increased risk of perioperative mortality.[34] Smoking status also may influence severity of symptoms. Although many diagnosed with lung cancer have

already stopped smoking at the time of diagnosis, former smoking as well as continued smoking may affect morbidity post-surgery.[35] In a cross-sectional survey of 1019 lung cancer survivors, (24% current smokers, 22% with advanced stage disease), statistically and clinically important differences in the symptoms (i.e. worse appetite, fatigue, cough, shortness of breath), were reported by smoking status with current smokers having the most distress. Obesity has been reported among lung cancer survivors[36] and may increase the severity of symptoms such as fatigue and dyspnea.

Symptoms are rarely experienced in isolation and multiple symptoms, groups or clusters of symptoms are the focus on current research in symptom management.[37] The co-occurrence of symptoms, even if they do not share the same etiology, may complicate assessment and intervention post-surgery and has received little attention

The specific aims of this study were to 1) describe severity of symptoms at one-, two-, and four-months post thoracotomy for patients with potentially curative NSCLC; 2) describe changes in symptom severity from one- to four-months post surgery; 3) determine characteristics (demographic, treatment, health status) associated with overall symptom severity at one- and four months post surgery; and 4) identify and describe relationships among co-occurring symptoms during recovery.

Methods

Design

A prospective repeated measures design was used in this exploratory study to capture changes in symptom severity approximately one-month (Time 1, T1), two-months (Time 1, T2), and four-months (Time 3, T3) post-thoracotomy. This time period was selected because it coincided with typical post-operative visits and partial recovery of symptoms was expected at two-months, with resolution of the majority of symptoms expected by four-months post-surgery.[2] Demographic, treatment, and health status factors were evaluated as potential predictors influencing symptom severity over time. It was expected that patients would have multiple related symptoms at each point in time.

Sample and Setting

A convenience sample of patients was recruited from outpatient settings in tertiary care hospitals in four metropolitan areas (Los Angeles, California; Buffalo, New York; Boston, Massachusetts; and Atlanta, Georgia). Integrity of data across sites was maintained by maintaining a standardized protocol with consistent forms, and with frequent communication among the investigators. After approval form the institutional review board (IRB) at each of the participating instructions, patients were invited to participate if they had received surgical treatment (thoracotomy) for early stage (I, II, III) NSCLC, were 18 years of age or older, and were able to read and understand English. Patients who had a second primary lung cancer or a history of a cured non-pulmonary cancer were eligible. Because of the exploratory nature of our study, we used the “rule of thumb” with 10 patients per covariate, targeting 90–100 patients for enrollment in the study. Ninety-seven patients were recruited. Three patients who initially agreed to participate did not meet the study criteria

and were excluded from analysis. Ninety-four patients provided data at T1; 92 at T2; and 86 at Time 3. Reasons given for dropping out of the study included: health limitations (n = 5), left the area (n = 1), lost to follow-up (n = 1), no time to participate (n = 1).

Procedures

All potential participants were recruited via IRB-approved letters sent on the letter-head of the treating surgeon/oncologist or through responses to an IRB-approved flyer. Trained research assistants consented patients and made an appointments to assess their symptoms on the first post-operative visit after surgery (T1, i.e. approximately 3–4 weeks after surgery). Due to IRB constraints, patients were required to approach us, thus we are not able to determine the pool of patients who potentially met the inclusion criteria at each site and who were not interested in participating. Participants received a small stipend for their time and efforts for each of the three interviews.

Data describing symptoms were collected at the first post-operative visit (T1). At this time, patients completed demographic, disease/treatment, and health status information and symptom appraisal. Follow-up assessments of symptoms occurred at two (T2) and four (T3) months after discharge, corresponding to follow-up care. At follow-up, participants were asked if there were changes in their health or personal situation (including smoking cessation, participation in rehabilitation). Height was assessed at T1 and weight was assessed at each time-point in order to calculate body mass index (BMI). Medical record data regarding diagnosis and treatment was abstracted from the clinical records.

Measures

Symptom Severity.—We used five symptom measures to provide us a comprehensive as well as a detailed description of the symptom experience during recovery from thoracotomy.

The *Lung Cancer Symptom Scale* (LCSS)[38–40] provides an overview of symptom severity and was developed specifically for patients with lung cancer. The patient's perception of severity of six symptoms (loss of appetite, fatigue, cough, shortness of breath, hemoptysis, and pain), overall symptom severity, ability to carry out normal activities, and overall QOL, "during the past four weeks", are recorded on 100mm visual analogue scales. Responses to each symptom range from "none" to "as much as it could be". Responses are summed for a mean overall score with higher scores indicating greater symptom severity (possible range 0 – 100). We also used unadjusted cumulative mean scores for a measure of the mean severity of six symptoms (fatigue, appetite, shortness of breath, pain, cough, hemoptysis). The LCSS is suitable for patients with different levels of symptom burden and is sensitive to detecting change over time. One of the advantages of the LCSS is that it has established parameters for detecting clinically meaningful differences in symptom changes.[39, 40] A "clinically meaningful difference" is a concept that has been used in cancer clinical trials and quality of life research to distinguish those difference which are not just statistically significant, but correspond to clinically important outcomes[41]. The LCSS has undergone extensive psychometric testing and has well-established reliability, validity, and normative scores for comparison with other lung cancer populations.[38]

The *American Thoracic Society (ATS) Dyspnea Index*.[42] was used to provide more detail about the symptom of dyspnea. It was used in a prior study of lung cancer survivors.[17] This five-item self-report describes difficulty with breathlessness according to level of activity (scores range from 0 “not troubled with breathlessness except with strenuous exercise” to 4 “too breathless to leave the house or breathless when dressing or undressing”). Higher scores indicate more severe problems. Test-retest reliability >.70 and internal consistency >.75 have been reported.[43]

The *Brief Pain Inventory* (BPI) short-form[44] allowed us to provide more detail about the pain experience. Pain severity and interference with day-to-day activities “during the last 24 hours” were used in this analysis. As recommended, pain severity was calculated using the arithmetic mean of the four severity items (possible score range 0–40). Pain interference was calculated as the arithmetic mean of the seven interference items (possible score range, 0–70). Higher scores indicate more severe pain. Additionally, a single item “worst pain” “right now” was used to categorize pain severity as mild (scores 1 – 4), moderate (scores of 5 – 6), and severe (scores of 7 – 10).

The *Schwartz Cancer Fatigue Scale* (SCFS, version 6)[45, 46] provided greater detail about fatigue. This six-item self-report has been used successfully with patients with a variety of cancer diagnoses and treatments and is sensitive to change over time. The time frame for responses is over “the past two-three days”. Internal consistency and validity have reported.[47] Respondents are requested to score 1 “not at all” to 5 “extremely” to six feelings associated with fatigue (“tired, difficulty thinking, overcome, listless, worn out, and helpless”). Scores for the six-item scale range from 6 – 30.

The *Center for Epidemiological Studies—Depression scale* (CES-D)[48], has been used in multiple studies of patients with cancer[49] to assess depressed mood. This 20-item self-report (possible scores range from 0 to 60) can be used to indicate potential depression (scores >15). Responses are requested for feelings “during the last week”. Acceptable reliability and validity including discrimination between normal and clinical samples have been reported. The Cronbach’s alpha for this study was 0.91.

Potential Predictors of Symptom Severity

Demographic Characteristics.—Data describing the demographic characteristics of the sample, including age, sex, marital status, race/ethnicity, living situation (alone or with others), education, and employment status was collected using a self-report. We also collected information about attendance at support groups after surgery.

Health Status.—Health status information included data on comorbidity, smoking status, and BMI,

The *Charlson Comorbidity Index* self-report[50, 51] with established reliability and validity in a number of patient samples was used to assess comorbidity. In this study, we examined the prevalence of each of eleven conditions individually as well as the extent of comorbidity as a summed score. We collapsed responses to three conditions (heart attack, heart failure, or

operation to unclog arteries) into a single summary for heart disease to allow for comparisons.

Smoking status (never, former, current smoker) at study entry was determined through responses to questions about tobacco history and current smoking status based on questions from the Behavioral Risk Factor Survey;[52] and the Fagerstrom Test for Nicotine Dependence.[53, 54] Change in smoking status was evaluated at T2 and T3. As recommended by the Society for Nicotine and Tobacco Research,[55] biochemical validation of smoking status was performed at the time of the interview using a urine sample and cotinine dipstick (NicAlert™, for urine, Jant Corporation). Participants who described themselves as non-smokers, but scored 3 or higher on the dipstick were reclassified as smokers. We also assessed the use of the concurrent use of nicotine replacement therapy medications in order to prevent “false positive” readings on the dipstick.

Body mass index (BMI) one-month post-op (T1) and changes during the study period were evaluated. Height and weight (with participant fully clothed) were measured at the time of interview using a protocol to assure reliability used in a previous study.[24] BMI (kg/m^2) was calculated at each assessment period and categorized as malnourished (<18.5), healthy weight (18.5 −24.99), overweight (25–29.99), and obese (≥30.0).[56]

Treatment characteristics.—Treatment details, including the extent of surgery (lobectomy, segmental/wedge or sleeve resection, and pneumonectomy) and use of adjuvant treatment were collected using a Medical Record Form. These data and other clinical characteristics (histology, TNM staging), the number of days in the hospital prior to discharge, and any complications during recovery were recorded from the medical record. In some cases, TNM information in the operative reported was translated to stage according to the American Joint Committee on Cancer Staging Manual.[57]

Data Analysis

Descriptive statistics, appropriate to level of measurement, were used to describe sample demographics, health status, treatment characteristics, and symptom outcomes. We determined the severity of symptoms at each time point. We excluded any patient with a symptom item rated a “0” on the LCSS when calculating the mean raw scores for that symptom. Further, we described the presence of *severe* individual symptoms on the LCSS (appetite, fatigue, cough, dyspnea, pain, hempotysis) based on a cut-point of > 25mm on the visual analogue scale to indicate the presence of severe symptoms (present/absent). Because of the small percentage of patients rating any problems with hemoptysis, this symptom was subsequently removed from the analysis. We determined the mean BPI (severity and interference scores), SCFS-6 total score, and CES-D total scores. For the BPI, severity also was calculated using the recommended categorical definitions to denote severe pain. Patients with CES-D scores >15 were defined has having depressed mood (potential depression).

We calculated percent change in average symptom severity scores from T1-T3 in order to describe the magnitude of changes. In a similar fashion, we described percent change in the proportion with severe symptoms (LCSS symptoms rated ≥ 25) from T1 to T3 and for the presence/absence of depressed mood (CES-D >15).

In order to determine statistically significant changes in symptom severity over time (T1 – T3), we used generalized linear models (GEE) for repeated measures analysis with mixed effects for continuous and ordinal outcomes. All repeated measures analyses included time, demographic characteristics (age, sex), health status characteristics (presence of comorbid conditions, smoking status) and treatment factors (adjuvant treatment, type of surgery) as fixed effects and subject as random effect. Significant changes in severe symptoms, including depressed mood, adjusted for covariates, also were computed. We determined differences in the number of symptoms at each time point (defined as > 0 on the LCSS) using logistic regression. In addition to statistically significant changes, we examined *clinically meaningful* differences in symptoms by identifying those symptoms with ≥10mm reductions in symptom scores from T1-T3, as recommended by Hollen et al[58] and used in another study of QOL of lung cancer survivors.[25]

Multivariate regression was used to determine predictors associated with overall symptom severity (LCSS mean total score) at one-month (T1) and four-months (T3) post thoracotomy. For this model, in addition to demographic, health status, and treatment characteristics, we considered mood, total CES-D, as a potential predictor of symptom severity.

Finally, the relationship among co-occurring symptoms from the LCSS (i.e. pain, fatigue, dyspnea, cough, appetite) during recovery was done separately for the presence of each symptom in comparison to all others. For example, for all patients reporting pain at each point in time, we examined other symptoms related to pain using a correlation matrix of individual mean LCSS scores, including the presence of depressed mood (CES-D > 15). Symptoms significantly correlated ($r > .30$) with other symptoms, including depressed mood, were identified. The presence of 3 or more symptoms significantly related to the sentinel symptom were identified as potential symptom clusters.[59]

SAS 9.1 software was used for the analysis. Level of significance was set at $P < 0.05$.

Results

Demographic characteristics are displayed in Table 1. The typical participant was female, aged 63 (range 32–86 years), Caucasian, married/partnered, with a minimum of high school education, and was not currently employed. Eight patients attended a support group during their post-operative recovery (n =1 at three times, n = 2 twice, and 5 once); data not displayed.

Clinical and treatment characteristics, displayed in Table 2, indicate that the majority had a diagnosis of adenocarcinoma, received a lobectomy, had stage I disease, and was in the hospital for 6-days post-surgery. Additionally, twelve (13%) patients received a VATS. A minority (21%) reported post-operative complications, most commonly atelectasis (13%). A minority of patients received neo- (12.2%) or post-adjuvant (11.1%) chemotherapy or radiation therapy.

Health status characteristics are displayed in Table 3. The majority of patients had one comorbid condition (56.4%). The most common condition was emphysema/COPD. Previous cancer diagnoses (excluding in situ skin and cervical cancer) included: breast (n = 4),

bladder/kidney (n = 4), prostate (n = 2), thyroid (n = 2), melanoma (n = 2), second primary lung cancers (n = 2), ovarian (n = 1), and n = 2 not specified. Forty-two percent report smoking at the time of diagnosis, with 17% continuing to smoke at the first post-operative visit (T1). Thirty-two percent of the former smokers had quit within the past six months. The mean BMI at each point in time was in the "overweight" category (BMI ≥25).

Severity of post-thoracotomy symptoms

The unadjusted mean scores for severity of symptoms are displayed in Table 4. Changes in severity of symptoms are indicated by the percent change in scores from one-month (T1) to four-months (T3). Using adjusted repeated measures analyses to examine changes in symptoms, excepting the symptoms of cough and hemoptysis on the LCSS, all symptoms significantly decreased from T1 to T3. Appetite, the second most severe symptom at T1, had the largest percent change in mean score, being reduced by over half (54%) by T3, followed by pain (44% decline). Patient responses to how "bad" are symptoms did not significantly decline from one- to four-months post surgery.

Symptom decline was noted in the BPI. The 37% reduction in reports of pain severity and interference with the BPI were similar to changes in LCSS pain item. Although the shortness of breath item significantly declined in the LCSS ratings, the change in categories of the Dyspnea Index were not significantly different. According to the Dyspnea Index, some patients had serious difficulty ("need to stop walking after breathing for 100 yards"): 19.50% at T1, 17.20% at T2, and 16.28% at T3; and three patients (3.19%) at T1 and one (1.16%) at T3 reported that they were "too breathless to leave the house or were breathless when dressing" (data not displayed). Similar to the LCSS item, the SCFS-6 measure also showed significant decrease in fatigue. Additionally, the number of symptoms (LCSS) significantly decreased from T1 to T3 (OR = .72, CI = .55 −.97, $p < .05$). Also displayed on Table 4 are data for BMI by quartiles. The range of BMI during recovery varied: 14.8 – 38.8 at TI, 11.3 – 41.4 at T2, and 14.8 – 41.7 at T3. From T1 to T3, 50% reported weight gain and 30% reported weight loss (data not displayed).

Severe symptoms

As displayed in Table 5, the frequency of patients with the most severe symptoms (rated ≥ 25mm on the LCSS) declined over time for all symptoms, except for cough. The most common severe symptom at each point in time was fatigue, followed by shortness of breath. The frequency of severe problems in appetite disruption had the greatest reduction, and those with severe cough with the least reduction. Patients with depressed mood (CES-D >15) decreased by a third but continued for 26% of patients at T3. Severe fatigue, shortness of breath, and cough also remained persistent problems. Severe pain (using the categorical definitions for severe pain from the BPI), was reported by 26% at T1, 17%, at T2, and 12% at T3 (data not displayed). Changes in the proportion of patients in the severe BPI categories significantly decreased (OR =.29, CI = .43 - .75, $p < .05$).

Clinically meaningful differences

Similar to the results from the evaluation of symptom severity, when clinically meaningful improvement in symptom severity (LCSS) was examined, using >10 mm as a cut-point, the

majority of patients had improvement in appetite (61.9%), dyspnea (53.0%), and pain (50.0%). However, only a minority had meaningful reductions in fatigue (43.3%) and cough (31.3%).

Predictors of symptom severity

Two separate multivariate regression models were used to examine characteristics associated with overall symptom severity (LCSS) at one-month and four-months post thoracotomy (Table 7). Both models explained a significant amount of the variance in symptom severity (50% at T1 and 47% at T3). The number of cases in the second model was different from the first as some patients had dropped out of the study. Number of comorbidities and the CES-D score were significantly associated with symptom severity at both time points. Younger age was associated with greater severity at T1 only. Being male, and receiving neoadjuvant treatment was associated with overall symptom severity four-months post-surgery.

Relationships and co-occurrence of symptoms

Symptoms on the LCSS (pain, fatigue, shortness of breath, cough, and appetite, excepting hemoptysis), were selected as a sentinel symptoms for comparison with other LCSS symptoms and depressed mood (CES-D > 15) as displayed on Table 7. Depressed mood was significantly associated with severity of symptoms at almost all time points. In several cases, symptom clusters (three or more correlated symptoms) were identified. For example, pain was associated with severity of appetite disruptions, fatigue, cough, dyspnea, and depressed mood at four-months.

Discussion

Symptom Severity Post-Thoracotomy

Patient's reports of symptoms can provide meaningful information about short and longterm clinical outcomes.[60] The findings of this study indicate that although symptom severity declined four-months post-thoracotomy for lung cancer, some patients still experienced multiple severe symptoms. Fatigue continued as the most severe symptom, followed by dyspnea, and cough. These findings are similar to findings of a prospective study of 110 patients with data pre-, three-month, and six-months post-surgery.[7] These investigators also noted the continued problem with cough six-months post surgery.[7] Our finding of continued dyspnea, with a small proportion with extreme difficulty, is different from that reported by Win et al[7] were dyspnea improved at three-months, and returned to preoperative levels at six-months. In that study ongoing support was given to patients during recovery by a respiratory physician and nurse. They were able to demonstrate that fatigue and pain improved to preoperative levels at six-months, but our study only focused on the first four-months post recovery.

Although we demonstrated statistically significant changes in symptom decline, only two symptoms, appetite disruptions dyspnea, and pain met the threshold for clinically meaningful changes from one- to four-months after surgery. Perhaps more clinically meaningful changes would have been seen if the change had been measured from the time of discharge or the period had been extended to six-months. It is challenging to interpreting the

LCSS scores for this sample with population norms as there are no standards for patients recovering from surgery. In comparing data from a report for LCSS (version 2)[38] based on 144 patients with advanced stage disease pre-treatment, our data suggest that on average, after thoracotomy, our patients had more dyspnea (shortness of breath, normative score 35.65) in the acute post-operative month, but have less dyspnea at four-months. Similarly, those with advanced stage disease are more troubled by cough (normative score, 31.67), but have lower levels of fatigue as compared to mean scores of those in the first two-months post-surgery surgery (normative score 40.45). The mean pain scores at four-months post-thoracotomy are lower than the pain scores (normative score 21.28) for those with advanced stage disease. Further research using the LCSS in the post-surgical setting, including evaluation of an adequate sample receiving the newer VATS procedure, will allow for creation of normative symptoms standards for recovery post-surgery.

Our data demonstrate that even with the prospect of potentially curable lung cancer, depressed mood (CES-D >15) was evident for over a third of patients one-month post-surgery and for over a quarter of patients four-months post surgery. These data are only suggestive of depression and further clinical assessment is needed to evaluate clinical depression. Sarna et al[21] report depressed mood as a continuing issue for lung cancer survivors affecting overall emotional well-being.

Predictors of symptom severity

Health status factors were important predictors in severity of symptoms. One might expect comorbidity in an aging sample with a strong tobacco use history. Thus, it was not surprising to see the extent of comorbidity (77%) or the relationship to symptom severity during recovery. However, selection criteria for surgical candidates may vary. For example, a QOL study of patients with lung cancer reports data from healthier samples (e.g. 52% comorbidity).[6] The most frequent comorbidities in our sample, emphysema/COPD and heart disease, are associated with tobacco use.[61] As has been reported by others, for a minority of patients, smoking continues to be a concern during the post-operative course.[62, 63] Although current tobacco use was not associated with increased symptoms severity, our sub-sample of current smokers at one-month post surgery was small (17%). Weight was not included in the regression models as it was not significant in any of the preliminary univariate analyses. Fluctuations in weight or the prevalence of overweight patients has not been reported in QOL studies of patients recovering from surgery. As many of the patients in our sample were overweight, the fear of weight gain, often associated with smoking cessation, may be a concern for those quitting smoking and should be addressed in intervention programs. Overweight might also be result in difficulties with physical activity.

CES-D was a significant predictor in both models of symptom severity one-month and four-months post surgery. As our sample was too small (n = 8), we are unable to determine if attendance at a support group was associated with changes in mood during recovery. Further research is warranted to evaluate the role of mood on symptom recovery.

The use of neoadjuvant treatment was linked with the symptom severity model at four-months post-recovery. Some of the symptoms that patients experienced may have been associated with the side effects of chemotherapy or radiation therapy. However, we only had

a small sample who received treatment prior to surgery. Handy et al[13] did not find that preoperative chemoradiation or adjuvant therapy negatively influenced physical function or overall QOL six-months post surgery. As the use of benefits of adjuvant treatment for early stage patients with NSCLC has been established[64], further research is needed to explore the special needs of this population during recovery.

Younger age was associated with increased severity in the model for severity in the first post-operative month, but not at four months. Our patient population had a wide age span (32 – 86 years), but the mean of 63 years was similar to the typical patient diagnosed with lung cancer. It may be that the younger patients had less experience managing symptoms or rated them as more distressing.

The fact that male sex was associated with increased symptom severity is different from other reports where females identify more symptoms and distressed mood.[25] Males may have been different in other ways, i.e. more comorbidity, that might account for this difference.

Co-occurrence of symptoms

As inter-related symptoms (i.e. clusters) are a focus of interest[22] our data depicted several constellations of multiple inter-related symptoms during recovery. We used a different approach than conventional cluster analysis. We selected to identify sentinel symptoms first and then evaluated related symptoms. Depressed mood (CES-D >15) was associated with severity of other physical symptoms such as pain, fatigue, and dyspnea. These finding suggests the interrelationship of physical and psychological symptoms. Future studies are needed to determine if treatment for one symptom has unintended consequences on other symptoms (e.g. pain relief with narcotics and related anorexia), or if treatment of a sentinel symptom (i.e. dyspnea) results in reduction of overall symptom distress.

Limitations

Our study had several limitations that should be considered in the interpretation of the results. We did not have symptom assessments prior to thoracotomy, thus we are unable to determine the premorbid level of symptomatology and to evaluate recovery in light of these ratings. Some symptoms, especially those due to comorbid diseases such as dyspnea, may have been present prior to surgery. However, although pre-surgery level of symptoms has been used for comparison in other studies, this was not the primary intent of our study which was to identify severe symptoms, regardless or premorbid condition, during the recovery period. Additionally, the timing of measurement for those patients who may have had neoadjuvant treatment and be experiencing treatment-related symptoms must be carefully considered as it may confound evaluation of symptom severity assessment.

In this study, we only evaluated patients who received a thoracotomy. Thus, our sample may have been healthier as some patients may not have been offered or be eligible for this treatment. Only a minority of our sample had received a VATS procedure. Although we did not find statistically significant differences in severity of symptoms, our study was not adequately powered to determine if there was a difference in symptom outcomes. We expected that extent of surgery would make significant differences in recovery, but the small

number of patients in our sample who received pneumonectomy did not allow for meaningful comparisons. Although this study was not focused on the immediate post-operative period, long term recovery may be influenced by type of anesthesia, hours required for surgery, and other surgical factors which deserve further study.

We had a slight over-representation of females in our study, compared to the percentage of those diagnosed with lung cancer. As females have been reported to score higher on symptom and emotional distress surveys,[26] this might have inflated our findings of depressed mood.

Finally, we did not monitor the quality of care or programs in place at the different institutions that might make a difference in symptom management during recovery. Future research is needed to explore the impact of symptom management in the immediate post-operative period to see if this makes a difference in long term recovery.

Clinical Implications

Our study revealed significant fatigue and dyspnea four-months post thoracotomy. The inclusion of ongoing symptom assessment during recovery from lung cancer could provide information useful to patients and clinicians. Some have argued that because of the precarious future for many of these patients, support for QOL and symptom relief for the short term is even more important than for those with higher expectations for longterm survivorship.[6] Currently, there are no recommendations or guidelines for routine rehabilitative support after lung cancer surgery. There are no normative data for which to compare our findings with projected symptom severity during the course of recovery post surgery. In this study, although the average severity of several symptoms decreased from one-month to four-months post-thoracotomy, the changes for cough and fatigue did not meet the threshold of clinically meaningful improvement. A minority of patients continued to experience severe problems with pain and with dyspnea.

Overall symptom severity was related to the extent of comorbidity as well as depressed mood, two conditions which can be identified prior to surgery. These characteristics might identify a sub-population that requires additional support and follow-through post thoracotomy. Some patients, for example, those with continuing fatigue, might benefit from conditioning exercises to promote recovery. Additional studies are needed to examine the influence of adjuvant treatment on changes in symptom severity and speed of post-surgical recovery. These data add to the limited research in this area and suggest many areas where research is needed.

Acknowledgments

Funded by the Oncology Nursing Foundation, #03018863

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Key Points

There is limited study of symptom severity after thoracotomy for lung cancer.

The continued problems of fatigue, dyspnea, and cough four-months after resection, underscore the importance of rehabilitative efforts to support recovery for some patients.

Comorbid conditions and depressed mood are associated with the severity of other symptoms, suggesting the need to address both physical and emotional well-being in recovery efforts.

Table 1.

Demographic characteristics of patients post-thoracotomy*

Characteristic	N = 94
Age, mean (SD),	63.3 (9.9)
Sex	
Female	54 (57.5)
Male	40 (42.5)
Race/Ethnicity	
White	84 (89.4)
African American	9 (9.6)
Asian	1 (1.0)
Years of Education	
< High School	24 (25.5)
High School	35 (37.2)
> High School	35 (37.2)
Marital Status	
Married/partnered	57 (60.6)
Live Alone	21 (22.6)
Currently Employed	28 (29.8)

*Values are No. (%) of patients unless otherwise indicated. All percentages are calculated on the basis of the number of respondents for that characteristic. Percentages may not total 100 because of rounding.

Table 2.

Clinical and treatment characteristics of patients post-thoracotomy

Variable	N = 94
Type of lung cancer	
Adenocarcinoma	49 (52.1)
Bronchioalveolar	6 (6.4)
Squamous Carcinoma	25 (26.6)
Large Cell	3 (3.2)
Other	11 (11.7)
Type of resection	
Lobectomy	74 (78.7)
Segmental/wedge/sleeve	12 (12.2)
Pneumonectomy	8 (8.5)
Stage	
I	64 (68.8)
II	22 (23.7)
III	7 (7.5)
Days in hospital, mean (SD)	5.6 (2.9)
Neoadjuvant treatment	11 (12.2)
Chemotherapy	11 (100.0)
Radiation therapy	7 (63.6)
Post-operative adjuvant treatment	10 (11.1)
Chemotherapy	5 (55.6)
Radiation therapy	3 (33.3)

*Values are No. (%) of patients unless otherwise indicated. All percentages are calculated on the basis of the number of respondents for that characteristic. Percentages may not total 100 because of rounding.

Table 3.

Health Status: comorbid conditions, tobacco use, and body mass index *

Variable	Mean (SD)
Comorbid conditions, mean (SD)	1.45 (1.18)
Patients with comorbid disease	72 (76.6)
1–2 conditions	57 (60.6)
3–4 conditions	15 (16.0)
Type of condition †	
Emphysema/COPD	36 (38.3)
Heart disease	16 (7.0)
Cancers	24 (26.1)
Diabetes	12 (12.8)
Asthma	12 (12.8)
Peptic ulcer	12 (12.8)
Rheumatoid arthritis	11 (11.7)
Stroke/CVA/TIA	8 (8.5)
Tobacco status	
Ever	84 (89.4)
Years smoked, mean (SD)	37.0 (13.0)
Smoking	
at diagnosis	35 (41.7)
Time 1	16 (17.0)
Body Mass Index, mean (SD)	
Time 1	25.8 (4.9)
Time 2	25.6 (5.3)
Time 3	25.5 (5.2)

* Values are No. (%) of patients unless otherwise indicated. All percentages are calculated on the basis of the number of respondents for that characteristic. Percentages may not total 100 because of rounding.

† may have more than one condition

COPD = chronic obstructive pulmonary disease, CVA= cerebral vascular accident, TIA = transient ischemic attack

Time 1 = one-month post-thoracotomy, Time 2 = two-months post-thoracotomy, Time 3 = four-months post-thoracotomy

Table 4.

Symptom severity, body mass index, and changes one to four months post-thoracotomy for lung cancer

	Time 1 (one month)	Time 2 (two-months)	Time 3 (four-months)	% Change from T1 – T3	P-value
Lung Cancer Symptom Scale *	Mean ± SD	Mean ± SD	Mean ± SD		
Overall	274.3 (138.8)	224.7 (141.1)	197.6(153.7)	−28.0	<0.0001
1st six symptoms	184.7 (87.9)	151.8 (90.5)	130.9 (98.2)	−28.8	<0.0001
Fatigue	47.6 (25.9)	42.2 (28.5)	38.4 (28.5)	−19.3	0.009
Appetite	40.1 (30.3)	25.6 (27.4)	18.6 (22.3)	−53.6	<0.0001
Shortness of breath	39.9 (26.9)	33.6 (25.6)	31.1 (26.3)	−22.1	0.002
Pain	30.5 (26.2)	20.9 (24.8)	16.9 (22.1)	−43.5	<0.0001
Cough	24.7 (25.5)	27.3 (27.9)	23.3 (25.6)	−5.7	0.52
Hemoptysis	1.4 (2.2)	1.2 (2.01)	2.8 (11.2)	+1.0	0.22
How bad are symptoms	19.5 (24.1)	18.9 (22.4)	17.0 (22.2)	−12.8	0.20
BPI					
Severity	11.4 (8.5)	7.6 (7.6)	7.2 (7.4)	−36.8	<0.0001
Interference	21.8 (19.6)	13.6 (15.6)	10.5 (15.1)	−51.8	<0.0001
Dyspnea Index	1.5 (1.2)	1.3 (1.0)	1.3 (1.1)	−0.13	0.09
Fatigue (SCFS-6)	12.4 (5.7)	11.1 (5.7)	11.1 (5.7)	−10.5	0.01
CES-D	13.4 (11.5)	11.1 (10.4)	11.1 (10.4)	−17.2	0.008
BMI					
<18.5	7 (7.78)	8 (8.79)	8 (9.52)	+1.7	0.92
18.5–24.9	32 (35.6)	33 (36.3)	30 (35.7)	+0.15	0.91
25–29.9	35 (38.9)	34 (37.4)	31 (36.9)	−1.99	0.26
>30	16 (17.8)	16 (17.6)	15 (17.9)	+0.08	0.36

*All values are mean (SD) of the scores on that measure. Higher scores indicate more severe problems

†P-values calculated using adjusted repeated measures analysis (time, health status, treatment, and demographic characteristics)

BPI = Brief Pain Index, SCFS-6 = Schwartz Cancer Fatigue Scale, CES-D = Center for Epidemiological Studies-Depression, BMI = body mass index

Table 5.

Changes in frequency of patients with severe symptoms (LCSS symptoms rated as ≥ 25mm) one- to four-months post-thoracotomy [*] for lung cancer.

Symptoms	Time 1	Time 2	Time 3	% Change	P-value [†]
Fatigue	70 (75.3)	57 (60.6)	48 (51.2)	−24.1	0.0002
Shortness of breath	60 (63.8)	51 (54.3)	41 (43.6)	−20.2	0.0008
Appetite	56 (59.6)	33 (35.1)	17 (18.1)	−41.5	<0.0001
Pain	47 (50.0)	30 (31.9)	17 (18.1)	−31.9	<0.0001
Cough	36 (38.3)	38 (40.4)	30 (31.9)	−6.4	0.37
Depressed mood category [‡]	30 (35.29)	24(28.92)	20(26.32)	−33.3%	0.01

[*] From Time 1 (one-month) to Time 3 (four-months) post-surgery

[†] P-values calculated using adjusted repeated measures analysis.

[‡] CES-D > 15)

Table 6.

Significant relationships* among individual symptoms (LCSS) and depressed mood category† at one- to four-months post thoracotomy for lung cancer

Symptom Presence	Time 1	Time 2	Time 3
Pain	fatigue cough depressed mood	appetite cough depressed mood	appetite, fatigue, cough, dyspnea depressed mood
Fatigue	appetite dsypnea depressed mood	dyspnea depressed mood	appetite cough dyspnea depressed mood
Dyspnea	depressed mood		appetite cough
Cough	depressed mood	depression	appetite depressed mood
Appetite	depressed mood	depressed mood	depressed mood

* r ≥ .30, P <.05

† CES-D >15

Table 7.

Results of multiple regression analysis of predictors of average overall symptom severity at one-month and four-months post thoracatomy

Outcome	Adjusted R^2	F-test, P value	Covariates	Parameter estimate	SE	P-value
Symptom severity * (one month post-thoracotomy)	0.50	<0.0001	Age	−0.3	0.1	0.04
			Current smoker	−1.4	3.6	0.70
			Comorbidities	4.2	1.1	0.0002
			Male	0.6	2.5	0.83
			Neo-adjuvant	−3.2	4.0	0.43
			Pneumonectomy	4.3	5.0	0.39
			Live alone	0.6	3.0	0.85
			CESD total score	0.8	0.1	<0.0001
Symptom severity * (four months post-thoracotomy)	0.47	<0.0001	Age	−0.3	0.2	0.09
			Current smoker	−2.7	4.5	0.55
			Comorbidities	3.4	1.3	0.01
			Male	7.0	3.4	0.04
			Neo-adjuvant	11.8	5.5	0.03
			Post-adjuvant	0.1	4.8	0.99
			Pneumonectomy	2.7	6.3	0.67
			Live alone	−1.5	3.6	0.68
			CESD total score	1.0	0.2	<0.0001

* Lung Cancer Symptom Scale, overall mean score