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ORIGINAL REPORT

Longitudinal Study of the Relationship Between Chemoradiation Therapy for Non–Small-Cell Lung Cancer and Patient Symptoms

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ABSTRACT

Purpose
Cancer patients undergoing aggressive therapy suffer from multiple nonspecific treatment-related symptoms. The goal of this prospective study was to establish a profile of the development of different symptoms over the time of therapy and to examine symptom-related functional interference in patients with non–small-cell lung cancer (NSCLC) undergoing concurrent chemoradiation therapy (CXRT).

Patients and Methods
Patients with locally advanced unresectable (stage II-IIIB) NSCLC were recruited for the study (N = 64). The M.D. Anderson Symptom Inventory (MDASI) was used to measure multiple symptoms before and weekly for 12 weeks after the start of CXRT. Mixed-effect growth curve models were used to estimate symptom development during CXRT.

Results
Approximately 63% of patients suffered from moderate to severe levels of multiple symptoms by the end of CXRT. Symptom clusters with four development patterns appeared over the time of CXRT. With some variation between patients, all symptoms had a significant impact on the level of interference (all $P < .001$). Fatigue, distress, and sadness were the single strongest predictors of total symptom interference (each $R^2 \geq 0.49$). Physical symptoms had greater impact on interference with function when they were moderate to severe, whereas affective symptoms had the largest effect on interference when they were mild to moderate.

Conclusion
Longitudinal analysis identified symptom clusters that have different development patterns in NSCLC patients receiving CXRT, providing a base for more accurate symptom management and suggesting the need for further study to identify potential mechanisms that might lead to better symptom control or prevention.

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INTRODUCTION

Patients experience multiple physical and psychological symptoms during and after a substantial insult, such as aggressive cancer treatment. Non–small-cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States,[1] with a 5-year survival rate of only 15%. Symptoms, including those that are disease based or treatment related, are major aspects of morbidity in cancer care.[2] Concurrent chemoradiation therapy (CXRT), a standard curative regimen for patients with stage III NSCLC for whom no surgery is planned,[3-5] is frequently associated with acute radiation and chemotherapy effects, including hematologic suppression, pain, weight loss, esophagitis, and pneumonitis.[6,7] Beyond these specific toxicities, many nonspecific symptoms (including fatigue, sadness, distress, sleep disturbance, drowsiness, and poor appetite) that are the result of treatment may also contribute to the patient's general distress during the course of treatment.[8] Reducing the burden of treatment-related symptoms on a patient's functional status, especially during aggressive curative therapy, should be an important treatment goal.

However, symptom control is dependent on understanding the trajectory of physical and psychological symptom development during treatment and on knowing which symptoms have the greatest impact on a patient's function. Although accurate symptom profiles are critical for establishing effective symptom management, the paucity of empirical

research conducted on multiple-symptom development in patients undergoing aggressive cancer treatment[9] gives rise to unanswered questions. How do clusters of symptoms vary during the course of treatment in a cohort of patients with the same diagnosis receiving the same treatment? What is the mechanism for such variation? Do physical and psychological symptoms interfere with the patient's daily life in similar ways? A study of the process of cancer-related symptom development should provide critical knowledge for developing an understanding of the mechanisms underlying these symptoms and lead to mechanism-based symptom interventions.

In this study, we used a multiple-symptom assessment tool, the M.D. Anderson Symptom Inventory (MDASI), to longitudinally study cancer-related symptoms in patients with NSCLC undergoing CXRT. The MDASI is a patient-reported outcomes tool validated for use in the cancer population.[10] Our primary goals were (a) to determine the levels of prevalence, severity, and longitudinal patterns of dynamic change in both physical and psychological symptoms that were present before, during, and after CXRT, and (b) to assess how each symptom affected the patient's daily activities as a function of the type and severity of the symptom.

PATIENTS AND METHODS

Subjects

Sixty-four patients were recruited from clinic in the Department of Radiation Oncology at The University of Texas M.D. Anderson Cancer Center in Houston, TX, between January 2002 and May 2005. To be eligible for this study, patients had to be scheduled for curative CXRT, be at least 18 years old, and have a pathologic diagnosis of NSCLC with unresectable (stage III) disease. Patients who could not understand the intent of the study, who refused to participate, or who were currently diagnosed with a major psychiatric illness were excluded from the study. The study was approved by the institutional review board of M.D. Anderson Cancer Center, and all participants gave informed consent.

Patients were newly diagnosed at the start of CXRT, and all 64 completed the planned therapy. The total radiation dose was 50 to 70 Gy at 1.8 to 2 Gy per fraction daily over 5 to 7 weeks (mean, 6.5 weeks). The chemotherapy regimen administered concurrently with radiation was carboplatin plus paclitaxel.

Patient-Reported Outcomes Tool: MDASI

Symptoms were assessed via MDASI before the start of CXRT and then weekly for 12 weeks during and after CXRT. The MDASI was designed and validated for use in all cancer populations regardless of specific disease diagnosis or type of therapy.[10] The MDASI includes 13 core symptom items: fatigue, sleep disturbance, pain, drowsiness, poor appetite, nausea, vomiting, shortness of breath, numbness, difficulty remembering, dry mouth, distress, and sadness. The severity of these symptoms during the previous 24 hours is assessed on a 0 to 10 numerical rating scale, with 0 being "not present" and 10 being "as bad as you can imagine." Two additional symptoms (cough and sore throat) were included in the MDASI lung module used in this study.

The MDASI also contains six items that describe how much symptoms have interfered with the patient's life during the last 24 hours: general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life. The interference items also are assessed on a 0 to 10 scale, with 0 being "does not interfere" and 10 being "completely interferes." An interference composite score was computed from the mean of the six individual item scores.

Statistical Analysis

We used SPSS 12.0 statistical software for Windows (SPSS Inc, Chicago, IL) and SAS 8.2. (SAS Institute, Cary, NC). On the basis of previous studies of pain and fatigue in cancer patients, we operationally defined symptom severity as "moderate" if a symptom's worst severity in the last 24 hours was rated as 5 or 6 on the 0-to-10 scale, and as "severe" if the symptom was rated as 7 or greater.[11,12] Proportions represent the percentage of assessments in which patients rated the severity as moderate or severe.

To estimate the change in symptom severity during and after CXRT, we used mixed effect growth-curve models with a random subject effect and linear splines to approximate the change in each symptom item within each of four periods: early (first 2 weeks of CXRT), mid (the weeks between the early and late periods), late (last 2 weeks of CXRT), and after completion of CXRT. The interpretation focuses on the average change in the outcome along the 0-to-10 scale. Observations within 12 weeks of the commencement of CXRT were included in this analysis. The same mixed effect growth-curve models were used to estimate the association of specific symptoms with interference. For this study, we used the symptom interference composite score to present the functional burden of cancer-related symptoms. The proportion of variation in symptom interference between individuals and within each individual was estimated by contrasting a model with and without the time-varying measures of symptom severity. To define the impact of symptom severity level on interference, the prediction of total symptom interference score as a function of level of symptom severity (0 to 3, 3 to 5, 5 to 7, or 7 to 10 on the 0-to-10 scale) of each symptom was calculated.

RESULTS

Patient and Treatment Characteristics

Patient demographics are shown in Table 1. All participants had stage III NSCLC at enrollment; 3% subsequently developed stage IV disease but remained on study. All patients had good Eastern Cooperative Oncology Group (ECOG) performance status (0-1) before the start of CXRT, although ECOG scores of 2 were seen in 18% of patients during therapy and in 26% of patients after therapy. Approximately 10% of eligible patients approached declined to participate.

Table 1. Patient Characteristics

Characteristic	No.	%
Age, years		
% ≥ 60		70
Mean	63.4	
Range	42.5-78.3	
Sex, female	36	56
Race, white non-Hispanic	55	86
Education, beyond high school	30	51
Employment status		
Employed	16	25
Retired	22	35
Not working	26	40
Staging		
III	62	97
IV	2	3
ECOG performance status ≥ 2		
Pre CXRT		0
During CXRT		19
Post CXRT		30
Hemoglobin (sex adjusted)		
Pre CXRT	12.87 ± 1.6 g/dL	
During CXRT	12.12 ± 1.5 g/dL	
White blood count		
Pre CXRT	$8.14 \times 10^3/mm^3$ (± 1.8)	
During CXRT	$4.57 \times 10^3/mm^3$ (± 2.4)	

Abbreviations: CXRT, chemoradiation therapy; ECOG, Eastern Cooperative Oncology Group.

The missing data rate ranged from 8.4% to 8.8% for the MDASI symptom items, stemming primarily from either patient fatigue or administrative error. All of the patients contributed symptom data at baseline and during CXRT, but 10 patients (15% of data) either withdrew from the study or were lost to follow-up after completing CXRT. Of these, two died as a result of pneumonia within 1 to 2 weeks of completing CXRT. Data on toxicities were not used in the analysis because records were not consistent.

Prevalence of Moderate to Severe Symptoms and Symptom Interference

Before commencing CXRT, 25% of the patients in our sample rated their fatigue as 5 or greater on the 0-to-10 scale, and approximately 20% experienced pain, poor sleep, distress, or shortness of breath at moderate to severe levels. During CXRT, approximately 25% of patients reported moderate to severe pain, lack of appetite, and drowsiness, and more than 40% reported fatigue rated 5 or greater. Approximately 63% of patients reported two or more moderate to severe symptoms by the end of CXRT, with fatigue being the most severe symptom throughout the course of CXRT.

On average, the highest levels of symptom interference were seen in general activity and work (including work around the house) during and after therapy (Table 2). With the exception of enjoyment of life, all measures of symptom interference increased significantly during and after the course of treatment.

Longitudinal Patterns of Symptom Development

Four clusters of symptoms demonstrated different development patterns during and after treatment when we estimated the average rate of symptom change across the four therapy periods (early, mid, late, and after therapy). Table 3 shows the rate of weekly change for each symptom over the four periods. Figure 1 presents longitudinal symptom patterns by cluster during and after CXRT.

In pattern 1, we observed that the rates of change for both pain and sore throat steadily and significantly increased in severity over the course of therapy (early, mid, and late periods of CXRT, weeks 1 through 7), and then decreased in the post-CXRT period. Pain increased significantly in the early (0.32 point on a 0-to-10 scale; SE, 0.17), mid (0.49 point), and late (0.46 point) CXRT periods. The two symptoms were correlated, with the severity of sore throat explaining 38% of the variation in reported pain. Sore throat and pain most likely result from radiation-induced inflammation in local tissue. Pattern 2 showed a rapid increase in therapy-related GI toxicities, including nausea and vomiting, in the early and mid CXRT periods. Pattern 3, seen in nonspecific symptoms that included fatigue, lack of appetite, drowsiness, sleep disturbance, dry mouth, and distress, reflected an increase in severity in both the early and late therapy periods. Pattern 4 included affective symptoms (sadness), cognitive issues (difficulty remembering), and other disease- or treatment-related symptoms (shortness of breath, cough, and numbness) for which we observed no major change in severity over the course of therapy.

Impact of Each Symptom on Interference

Interference with daily activities, as rated on the MDASI's 0-to-10 scale, rose 0.26 points per week during CXRT (SE, 0.034; $P < .001$) and declined slowly after the completion of CXRT (-0.09 points per week; SE, 0.56; P = NS). All symptoms had a significant impact on the level of interference (all $P < .001$). By individual symptom, fatigue, distress, and sadness were the strongest single predictors of total interference, with 49% or higher predictive value (Table 4). By symptom cluster (pattern), pattern 3 and its cluster of symptoms (fatigue, lack of appetite, drowsiness, sleep disturbance, dry mouth, and distress) had the highest predictive value for total interference ($R^2 = 0.73$), followed by pattern 4 ($R^2 = 0.59$), pattern 1 ($R^2 = 0.34$), and pattern 2 ($R^2 = 0.25$).

In a cohort of patients with the same disease and treatment background, should we expect only a small variation in symptom interference among all patients, and will they share a similar pattern of symptom development over the time of CXRT? The proportion of variation in symptom interference between patients and within each patient from week to week was estimated by contrasting models with and without the time-varying measures of symptom severity. For most items, the between-subject variation in symptom interference explained more of the overall level of interference than the week-to-week within-subject variation (Table 4; eg, $R^2 = 0.62$ *v* $R^2 = 0.40$ for fatigue, $R^2 = 0.66$ *v* $R^2 = 0.25$ for sadness, $R^2 = 0.63$ *v* $R^2 = 0.29$ for distress, respectively). Fatigue, sadness, distress, and drowsiness explained the greatest proportion of the variation in overall levels of interference between subjects. The symptom that explained the most week-to-week variation in interference within subjects was fatigue ($R^2 = 0.40$).

Does every symptom create its greatest interference in a patient's daily life only when it is severe? When we categorized reported symptoms as mild, moderate, or severe, we found that these three categories had an unequal impact on interference by specific symptom (Table 5). Some symptoms, such as fatigue, drowsiness, nausea, and sore throat, had the greatest impact on interference scores when patients reported them at a severe level. For example, patient-reported ratings of interference increased almost 1 point (0.91) on the 0-to-10 scale for

Table 2. Mean Levels of Symptom Interference for Patients With Non–Small-Cell Lung Cancer Undergoing CXRT

	Before CXRT		Mid CXRT		End CXRT		After CXRT	
Activity	Level	SE	Level	SE	Level	SE	Level	SE
General activity	2.20	0.39	3.58	0.35	5.07	0.39	3.99	0.40
Work	2.36	0.43	3.47	0.39	4.58	0.43	4.23	0.43
Walking	2.02	0.34	2.80	0.29	3.28	0.35	3.49	0.35
Enjoyment of life	1.87	0.39	3.05	0.35	3.44	0.39	3.22	0.39
Mood	1.48	0.36	2.45	0.32	3.22	0.36	2.98	0.37
Relations with others	1.17	0.35	2.08	0.31	2.66	0.35	2.37	0.35
Interference	1.84	0.33	2.90	0.30	3.71	0.33	3.37	0.33

Abbreviation: CXRT, chemoradiation therapy.

Table 3. Weekly Rates of Change in Symptom Severity Over Four Periods of CXRT

Pattern/Symptom	Early CXRT		Mid CXRT		Late CXRT		After CXRT	
	Change	SE	Change	SE	Change	SE	Change	SE
Pattern 1: Steady increase during therapy								
Sore throat	**0.73**	**0.18**	**0.30**	**0.14**	**0.74**	**0.17**	−0.58	0.09
Pain	**0.32**	**0.17**	**0.49**	**0.13**	**0.46**	**0.17**	−0.25	0.08
Pattern 2: Early/mid-therapy increases								
Nausea	**0.66**	**0.19**	**0.23**	**0.15**	0.22	0.19	−0.34	0.10
Vomiting	**0.39**	**0.17**	**0.24**	**0.13**	0.18	0.17	−0.20	0.08
Pattern 3: Early/late-therapy increases								
Lack of appetite	**0.59**	**0.20**	0.04	0.16	**0.85**	**0.20**	−0.27	0.10
Drowsiness	**0.51**	**0.18**	0.12	0.14	**0.44**	**0.17**	−0.30	0.09
Fatigue	**0.45**	**0.16**	0.01	0.13	**0.73**	**0.16**	−0.22	0.08
Sleep disturbance	**0.43**	**0.20**	−0.14	0.16	**0.40**	**0.20**	−0.24	0.10
Dry mouth	**0.38**	**0.13**	−0.10	0.11	**0.22**	**0.13**	−0.11	0.07
Distress	**0.20**	**0.17**	0.13	0.14	**0.23**	**0.17**	−0.05	0.08
Pattern 4: Early decrease or no change								
Difficulty remembering	−0.00	0.13	−0.03	0.10	0.25	0.12	0.00	0.06
Cough	−0.09	0.16	0.28	0.12	0.27	0.16	−0.11	0.08
Numbness	−0.10	0.11	0.15	0.09	−0.10	0.11	0.08	0.06
Sadness	−0.10	0.15	0.27	0.12	0.08	0.15	0.13	0.07
Shortness of breath	−0.15	0.14	0.13	0.11	0.01	0.14	0.14	0.07

NOTE. Boldfacing indicates significant (α = .05) changes.
Abbreviation: CXRT, chemoradiation therapy.

every point increase in fatigue in the severe range (7 to 10) but increased only a half point for every point increase in fatigue in the mild to moderate range (3 to 7). Other symptoms, including pain, lack of appetite, shortness of breath, cough, and drowsiness, had a relatively constant effect on interference over the mild to severe range (3 to 10). In contrast to these physical symptoms, the two affective symptoms (distress and sadness) had a stronger impact at lower severity levels. Sadness significantly affected interference only when it was mild (0 to 5 on the 0-to-10 scale). Finally, a few symptoms (difficulty remembering, dry mouth, vomiting, and numbness) had a constant significant effect on symptom interference over the entire 0-to-10 range of symptom severity (all $P < .001$).

DISCUSSION

This study presents a method of longitudinal symptom data acquisition and analysis that allows for the examination of the temporal

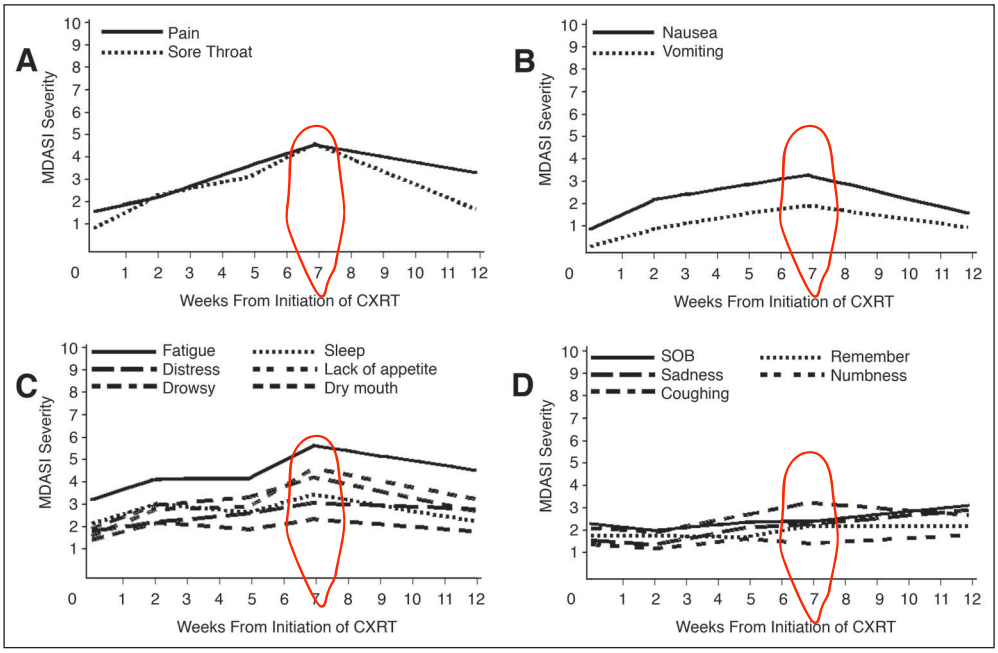

Fig 1. Patterns of multiple symptoms in patients with non–small-cell lung cancer over the course of chemoradiotherapy therapy (CXRT). (A) Pattern 1, steady increase; (B) pattern 2, early increase; (C) pattern 3, early/late increase; (D) pattern 4, minimal change. MDASI, M.D. Anderson Symptom Inventory; SOB, shortness of breath.

Table 4. Proportion of Variation of Symptom Interference (R^2) Explained by Symptom Severity

Symptom	Variance*			R^2		
	Between Subjects	Within Subject	Total	Between Subjects	Within Subject	Total†
None	3.57	2.48	6.05	—	—	—
Fatigue	1.36	1.48	2.84	0.62	0.40	0.53
Sadness	1.21	1.87	3.08	0.66	0.25	0.49
Distress	1.32	1.77	3.09	0.63	0.29	0.49
Drowsiness	1.63	1.87	3.50	0.54	0.25	0.42
Lack of appetite	2.09	1.84	3.94	0.41	0.26	0.35
Pain	2.06	2.17	4.23	0.42	0.13	0.30
Difficulty remembering	2.06	2.19	4.24	0.42	0.12	0.30
Nausea	2.74	1.84	4.58	0.23	0.26	0.24
Dry mouth	2.34	2.25	4.59	0.35	0.09	0.24
Sleep disturbance	2.49	2.10	4.59	0.30	0.15	0.24
Sore throat	2.51	2.20	4.71	0.30	0.11	0.22
Shortness of breath	2.72	2.15	4.87	0.24	0.13	0.19
Vomiting	2.95	1.97	4.92	0.18	0.20	0.19
Numbness	2.79	2.40	5.19	0.22	0.03	0.14
Cough	3.01	2.35	5.36	0.16	0.05	0.11

*Variance of symptom interference by symptom item.
†Larger R^2 values indicate that variation in each symptom is associated with variation in interference. Symptoms in this table are ordered by R^2 values in this column.

pattern of emergence of several symptoms over the course of aggressive cancer therapy. Although most of the patients appeared to tolerate their therapy well, our study showed that by the end of CXRT, the peak of symptom severity, approximately 63% of patients experienced moderate to severe levels of multiple treatment-related symptoms. Further, four clusters of symptoms with unique temporal relationship to the course of CXRT therapy were identified in this homogenous NSCLC patient sample. We also found that specific symptoms and

Table 5. Predicted Change (R^2) in Interference Scores per Unit Change in Symptom Severity

Symptom	Range of Symptom Score on 0 to 10 Scale							
	0-3		3-5		5-7		7-10	
Increasing impact on interference with increasing symptom severity								
Fatigue	0.12		0.50	*	0.50	*	0.91	*
Sleep disturbance	0.18	*	0.18	*	0.18	*	0.70	*
Nausea	0.26	*	0.26	*	0.26	*	0.66	*
Sore throat	0.12	†	0.12	†	0.38	*	0.38	*
Constant impact on interference over symptom severity of 3-10								
Shortness of breath	0.20	‡	0.49	*	0.49	*	0.49	*
Drowsiness	0.15	†	0.49	*	0.49	*	0.49	*
Lack of appetite	0.14	†	0.39	*	0.39	*	0.39	*
Pain	0.05		0.35	*	0.35	*	0.35	*
Coughing	0.08		0.22	*	0.22	*	0.22	*
Decreasing impact on interference with increasing symptom severity								
Sadness	0.61	*	0.61	*	0.15		0.15	
Distress	0.49	*	0.49	*	0.49	*	−0.03	
Constant impact on interference over 0-10								
Difficulty remembering	0.48	*	0.14		0.53	*	0.53	*
Dry mouth	0.31	*	0.31	*	0.31	*	0.31	*
Vomiting	0.32	*	0.32	*	0.32	*	0.32	*
Numbness	0.25	*	0.25	*	0.25	*	0.25	*

NOTE. Larger R^2 values indicate that variation in symptoms is associated with variation in interference.
*$P < .001$.
†$P < .05$.
‡$P < .01$.

specific symptom clusters produced significantly more symptom interference in this patient sample. The evidence from this study suggests that accumulated effects over time from combined radiation and chemotherapy could severely affect a patient's daily functioning, evidencing the need for better and more efficient symptom management.

One symptom cluster (pattern 3) included several nonspecific symptoms (fatigue, lack of appetite, drowsiness, sleep disturbance, dry mouth, and distress) that showed similar development patterns not characterized by a steady linear increase with accumulated dose during CXRT. This symptom cluster had the strongest impact on patients' daily functioning compared with other symptom clusters, yet the effect of these symptoms is often ignored in patient care.

The variation in symptom interference between patients was larger than the week-to-week within-subject variation, indicating that certain patients were at greater risk for symptom development than others throughout their course of treatment. A symptom mechanism study might provide the explanation for such differences in patient response to CXRT.

At a lower severity level, affective symptoms (distress and sadness) contributed more significantly to symptom interference than did physical symptoms. The severity distributions of these symptoms were not skewed, so the reason for this phenomenon is unknown. Nevertheless, this result indicates that symptom intervention for affective symptoms may need to be initiated at a lower symptom-severity threshold.

Given that fatigue is a common disease-induced symptom in lung cancer[11,13] and is a result of CXRT regardless of cancer type,[14-16] it is an especially important symptom to examine when both factors are combined, as in the setting of NSCLC treated by CXRT. This study found that fatigue was the most severe symptom at baseline and over the course of CXRT and did not return to baseline levels even 5 to 6 weeks after the completion of CXRT. Fatigue also had the highest predictive value for interference in the patient's daily life. Accordingly, fatigue is a reasonable target for symptom management.

Worsening pain and sore throat (pattern 1) during CXRT evidences the need for better management for acute esophagitis, a common complication of radiation for NSCLC.[17,18] Because the volume effect from the radiation is needed to control local recurrence of the tumor and its spread to the local lymph nodes, an active plan for routinely using therapeutic agents against radiation-induced esophagitis should be integrated into the CXRT treatment course for NSCLC. For example, topical anesthetics as well as liquid hydrocodone and acetaminophen could be used beginning the second week of therapy. Once symptom reports become severe, a fentanyl transdermal patch could provide better pain control. Hydration and consultation with a dietician are also key in the management of esophagitis.

There are methodologic barriers in symptom research, including inappropriate assessment tools, inappropriate schedules over the course of therapy, or lack of a suitable statistical modeling method. The MDASI, a brief, multiple-symptom assessment tool, can be completed with minimal effort by symptomatic cancer patients, a factor that is especially important for a longitudinal study in which repeated measures are required. The mixed-effects statistical model was used to handle time-varying covariates and other unbalanced designs in this longitudinal study, in preference to examining simple cross-sectional correlations where the various components are mathematically indistinguishable.

Our study had certain limitations. First, inconsistent documentation of treatment-related toxicities did not allow us to compare patient-reported symptoms with items more typically evaluated by clinicians. Second, we did not use additional measures for cognitive testing of anxiety and depression. In future studies, such measures might be helpful for further understanding differences in physical, cognitive, and psychological symptom development over the course of therapy.

The longitudinal symptom profile findings of this study indicate avenues for more accurate methods for patient monitoring that might lead to development of better clinical guidelines, and better information for patients as to when to expect the greatest impact from their symptoms. Although there is increasing literature on symptom clusters in cancer patients,[19,20] many of the studies are cross-sectional. Identification of the developmental time course of symptom clusters and its impact on cancer patients undergoing aggressive therapies such as CXRT will provide greater understanding of the patterns of association and interactions of symptoms. The temporal patterning of these symptom clusters raises the possibility that the clusters might have somewhat different biologic mechanisms. This is worthy of further study, which could lead to mechanism-driven symptom management strategies that provide less distressing and more tolerable treatment.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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