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Stability of Symptom Clusters in Patients With Lung Cancer Receiving Chemotherapy

by
Jacquelyn Russell

THESIS
Submitted in partial satisfaction of the requirements for degree of
MASTER OF SCIENCE

in

Nursing

in the

GRADUATE DIVISION
of the
UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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Stability of Symptom Clusters in Patients With Lung Cancer Receiving Chemotherapy

Jacquelyn Russell

ABSTRACT

Context: Patients with lung cancer who undergo chemotherapy (CTX) experience multiple concurrent symptoms. An evaluation of how these symptoms cluster together and how these symptom clusters change over time may provide insights into how to treat these multiple co-occurring symptoms.

Objectives: The purposes of this study, in a sample of lung cancer patients (n=145) who were receiving chemotherapy (CTX) were to evaluate for differences in the number and types of symptom clusters at three time points (i.e., before CTX, the week after CTX, and two weeks after CTX) using ratings of symptom occurrence and severity and to evaluate for changes in these symptom clusters over time.

Methods: At each of the three assessments, a modified version of the Memorial Symptom Assessment Scale was used to assess the occurrence and severity of the 38 symptoms. Exploratory factor analyses were used to extract the symptom clusters.

Results: Across the two symptom dimensions (i.e., occurrence and severity) and the three assessments, six distinct symptom clusters were identified. However, only three of these clusters were relatively stable across both dimensions and across time (i.e., lung cancer specific, psychological, nutritional). Two additional clusters varied by time but not by symptom dimension (i.e., epithelial/gastrointestinal, epithelial). A sickness behavior cluster was identified at each assessment with the exception of the week before CTX using the severity dimension.

Conclusion: These findings provide insights into the most common symptom clusters in patients undergoing CTX for lung cancer. The most common symptoms within each cluster appear to be relatively stable across the two dimensions, as well as across time.

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INTRODUCTION

Lung cancer is the most common cancer with 2.1 million cases worldwide (WHO, 2018).

Patients diagnosed with lung cancer have an extremely high symptom burden throughout the

course of their disease that negatively effects their physical and emotional well-being (Morrison,

2017). Given the high rates of multiple co-occurring symptoms associated with lung cancer, an

evaluation of symptom clusters in these patients is highly relevant. A symptom cluster is defined

as a group of three or more interrelated symptoms that have an influence on each other (Dodd,

2001). In addition, symptoms within a cluster may share the same underlying mechanism (Dodd,

2001). An increased understanding of symptom clusters associated with specific cancer, like lung

cancer, will provide individualized direction for the assessment and management of symptoms in

this vulnerable group of patients (Miaskowski et al., 2017).

In one of the earliest studies of symptom clusters in patients with lung cancer (Sarna &

Brecht, 1997), Sarna and Brecht hypothesized that the treatment of symptoms associated with

chemotherapy (CTX) might improve if we understood the relationships among symptoms and

symptom distress. In a sample of 60 women with advanced lung cancer, four groups of related

symptoms were identified using factor analysis (i.e., emotional and physical suffering,

gastrointestinal distress, respiratory distress, malaise).

Since this initial publication in 1997, eight additional studies have evaluated for symptom

clusters in patients with lung cancer. Four of these studies(Gift et al., 2004; Wang et al., 2006;

Wang et al., 2008; Henoch et al., 2009) were summarized, along with Sarna and Brecht's paper,

in a systematic review by Chen and colleagues (Chen et al., 2011), Three additional studies

(Choi, 2016; Wang & Fu, 2014,Wong, 2017) including one from our research team (Wong,

2017), were published following Chen et al.'s systematic review. Across these eight studies the

number of symptom clusters ranged from two to five. No common symptom cluster was found across all of the studies. However, an emotional/psychological symptom cluster was identified in five studies (Sarna & Bretcht, 1997; Henoch, 2009; Choi, 2016; Wang & Fu, 2014; Wong, 2017), with sad being the most common symptom. In addition, a lung-cancer specific symptom cluster was found in four studies (Sarna et al., 1997; Henoch et al., 2009; Choi, 2016; Wong,2017) , with cough being the most common symptom. Finally, a gastrointestinal symptom cluster was identified in four studies (Sarna & Brecht, 1997; Wang et al, 2006; Wang et al, 2008; Wang & Fu, 2014), with nausea being the most common symptom. Comparisons of findings across these eight studies is difficult because different dimensions of the symptom experience were evaluated, different assessment tools were used, and different statistical procedures were utilized to evaluate the symptom clusters. Of note, except for our own study (Wong, 2017), none of the studies cited above evaluated for differences in symptom clusters using different dimensions of the symptom experience or evaluated for changes in symptom clusters over time.

In our previous study of 145 patients receiving CTX for lung cancer, differences in the number and types of symptom clusters were evaluated using the occurrence and severity ratings of 38 symptoms from the Memorial Symptom Assessment Scale (MSAS). Across both dimensions, five relatively similar symptom clusters were identified (i.e., sickness behavior, lung-cancer specific, psychological, nutritional, epithelial). In addition, across the two symptom dimensions, the specific symptoms within each of the symptom clusters were relatively stable (Wong, 2017)

Given that no studies of changes in symptom clusters over time in lung cancer patients were identified, this study expands on our previous research with this sample (Wong, 2017). The purposes of this study, in a sample of patients with lung cancer (n=145) who were receiving

CTX, were; 1) to evaluate for differences in the number and types of symptom clusters at three time points (I.e., T1, T2, T3) using ratings of occurrence and severity and 2) to evaluate for changes in these symptom clusters over time.

MATERIALS AND METHODS

Patients and Settings

This longitudinal analysis is part of a larger study, funded by the National Cancer Institute, that evaluated the symptom experience of oncology outpatients receiving CTX. (26) Details of the methods from the parent study are published elsewhere. (26, 27) In brief, the parent study enrolled adults who were ≥18 years of age with lung, breast, gastrointestinal, or gynecological cancer. Patients were recruited from two Comprehensive Cancer Centers, one Veterans Affairs hospital, and four community-based oncology programs. All patients had received CTX within the preceding four weeks and were scheduled to receive at least two additional cycles. Patients were required to read, write, and understand English and provided written informed consent. In the parent study, a total of 2,234 patients were approached and 1,343 consented to participate (60.1% response rate). The major reason for refusal was being overwhelmed with cancer treatment. In the the current analysis, only patients with lung cancer were evaluated.

Instruments

The demographic questionnaire obtained information on age, gender, ethnicity, marital status, living arrangements, education, employment status, and income. Patients rated their functional status using the Karnofsky Performance Status (KPS) scale that ranged from 30 (severely disabled) to 100 (normal). (28-30) The Self-Administered Comorbidity Questionnaire (SCQ) evaluated 13 common comorbidities. (31) Patients indicated if they had the condition, if

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they received treatment for it, and if it limited their activities. SCQ scores could range from 0 to 39.

A modified version of the MSAS (33) evaluated the occurrence and severity of 38 symptoms commonly associated with cancer and its treatment. The following six symptoms were added to the original 32 MSAS symptoms: chest tightness, difficulty breathing, increased appetite, weight gain, abdominal cramps, and hot flashes. Patients indicated if they experienced each symptom in the past week (i.e., symptom occurrence). If yes, they rated its severity, frequency, and distress. Symptom severity was rated using a 4-point Likert scale (1 = slight, 2 = moderate, 3 = severe, 4 = very severe). Only symptom occurrence and severity were included in the current analysis. The reliability and validity of the MSAS and its subscales are well established in studies of cancer patients. (33, 34)

Study Procedures

The study was approved by the Institutional Review Board at the University of California, San Francisco and at each study site. Patients completed questionnaires in their homes a total of six times over two cycles of CTX. For this analysis, the first, second, and third assessments that obtained data in the week prior to the next cycle of CTX (T1), approximately one week after CTX administration (T2), and approximately two weeks after the administration of CTX (T3), were used to assess for symptom clusters. Medical records were reviewed for clinical information.

Data Analysis

Data were analyzed using Stata/SE version 14.1 (StataCorp, College Station, TX) and Mplus version 7.3 (Muthén & Muthén, Los Angeles, CA). Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics.

Separate exploratory factor analyses (EFAs) were done to identify symptom clusters using dichotomous occurrence items and ordinal severity items. (32, 35) Factor analysis aims to identify whether correlations between a set of observed variables can be explained by latent, unobserved variables (i.e., factors).(36) In this study, we refer to these factors as symptom clusters. (2, 37).

For the EFA, factor loadings (i.e., structure coefficients following rotation) of ≥0.40 were considered meaningful. (35, 38, 39) In addition, factors were considered to be adequately defined if at least two items (i.e., symptoms) had loadings of ≥0.40. (33) While it is common to require that each item load strongly on only one factor, we retained items that loaded on two factors (i.e., cross loaded) if they met our pre-specified criteria of ≥0.40. The cross loading of symptoms on more than one factor may be beneficial in the interpretation of potential causal mechanisms, especially when oblique rotation is employed. (40-43) To have sufficient variation and covariation in the data to perform the EFAs, only symptoms that were present in >20% but <80% of the patients were included in the analyses.

For the EFA using dichotomous occurrence items, tetrachoric correlations were used to create the matrix of associations. For the EFA using ordinal severity items, polychoric correlations were used to create the matrix of associations. (35, 44) The simple structure for the occurrence and severity EFAs were estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation. The geomin rotation method was chosen to create the best fit for the model and improve the interpretability of each factor solution. (35, 37) The unweighted least squares estimator (ulsmv: unweighted least squares parameter estimates with standard errors and a mean and variance adjusted chi-square test using a full weight matrix (35, 42)) was selected in

order to achieve more reliable results because the scales for the MSAS items are dichotomous (i.e., occurrence) and ordinal (i.e., severity).

The EFA for severity was conducted using severity ratings that ranged from 0 (symptom not present) to 4 (very severe). A preliminary analysis was conducted using severity ratings that ranged from 1 (mild) to 4, omitting observations where the symptom was not present. However, the pairwise missingness (i.e., minimum covariance function across all item pairs) was over 90% for many pairs and the estimation failed. Therefore, the EFAs for the severity ratings were estimated including zeros.

Factor solutions were estimated for two through six factors. After examining all of the factor solutions, the factor solution with the greatest interpretability and clinical meaningfulness was selected, given that it met the criteria set for evaluating simple structure (i.e., size of item loadings, number of items on a factor). Then, each symptom cluster was evaluated to determine a clinically appropriate name based on the majority of the symptoms in the cluster. By conducting EFAs at three specific time points, we were able to compare the stability of symptom clusters over time.

Differences in the Number and Types of Symptom Clusters

To evaluate the agreement among the symptoms within the same cluster using occurrence and severity ratings, within and across each assessment, we used the criteria proposed by Kirkova and Walsh (2007). In their article, they suggested that to be in agreement with each other, at least 75% of the symptoms in the clusters should be present including the prominent and important symptom, namely the symptom with the greatest weight from the factor analyses.

RESULTS

Demographic and Clinical Characteristics

As shown in Table 1, the majority of patients were female (56.6%), white (71.8%), and married or partnered (64.6%). The majority of the patients (69.7%) had a current or former smoking history and an average of 3.2 (±1.6) comorbid conditions.

Symptom Clusters Based on Occurrence

As shown on Table 2, a five-factor solution was found for the T1 assessment. Factor 1 contained six symptoms (i.e., feeling drowsy, lack of energy, problems with sexual interest or activity, hair loss, dizziness, pain) and was named the *sickness behavior* symptom cluster. Factor 2 consisted of five symptoms (i.e., cough, difficulty breathing, shortness of breath, dry mouth, swelling of arms or legs) and was named the *lung cancer specific* symptom cluster. Factor 3 consisted of eight symptoms (i.e., difficulty concentrating, difficulty breathing, feeling bloated, feeling irritable, feeling nervous, feeling sad, worrying, weight loss (loaded negatively)) and was named the *psychologica*l symptom cluster. Factor 4 contained nine symptoms (i.e., abdominal cramps, constipation, nausea, sweats, lack of appetite, weight loss, changes in skin, "I do not look like myself", change in the way food tastes) and was named the *epithelial/gastrointestinal* (GI) symptom cluster. Factor 5 contained 3 symptoms (i.e., increased appetite, weight gain, lack of appetite (loaded negatively)) and was named the *nutritional* symptom cluster.

As shown in Table 3, for the T2 assessment, a five-factor solution was found. Factor 1 contained 8 symptoms (i.e., abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting), and was named the *sickness behavior* symptom cluster. Factor 2 contained four symptoms (i.e., chest tightness, cough, difficulty breathing, shortness of breath) and was named the *lung cancer specific* symptom cluster. Factor

3 consisted of seven symptoms (i.e., difficulty concentrating, feeling bloated, feeling irritable, feeling nervous, feeling sad, problems with sexual interest or activity, worrying) and was named the *psychological* symptom cluster. Factor 4 consisted of four symptoms (i.e., increased appetite, lack of appetite, weight gain, weight loss) and was named *nutritional* symptom cluster. Factor 5 contained four symptoms (i.e., changes in the skin, hair loss, "I do not look like myself", mouth sores) and was named the *epithelial* symptom cluster.

As shown in Table 4, a five factor solution was found for the T3 assessment. Factor 1 included four symptoms (i.e., difficulty concentrating, feeling drowsy, lack of energy, cough) and was named the *sickness behavior* symptom cluster. Factor 2 had seven symptoms (i.e., chest tightness, cough, difficulty breathing, shortness of breath, weight loss, pain, dizziness (loaded negatively)) and was named the *lung cancer specific* symptom cluster. Factor 3 consisted of thirteen symptoms (i.e., abdominal cramps, feeling drowsy, sweats, feeling bloated, lack of appetite, weight gain, changes in skin, hair loss, "I do not look like myself", mouth sores, problems with sexual interest or activity, dizziness, change in the way food tastes) and was named the *epithelial/GI* symptom cluster. Factor 4 contained six symptoms (i.e., nausea, vomiting, feeling irritable, feeling nervous, feeling sad, worrying) and was name the *psychological* symptom cluster. Factor 5 had three symptoms (i.e., increased appetite, weight gain, lack of appetite (loaded negatively)) and was named the *nutritional* symptom cluster.

Symptom Clusters Based on Severity Ratings

As presented in Table 5, a four factor solution was found for the T1 assessment. Factor 1 contained eight symptoms (i.e., feeling drowsy, lack of energy, chest tightness, cough, difficulty breathing, shortness of breath, dizziness, pain) and was named the *lung cancer specific* symptom cluster. Factor 2 contained eight symptoms (i.e., constipation, nausea, sweats, lack of appetite,

weight loss, changes in skin, "I do not look like myself", change in the way food tastes) and was named the *epithelial/GI* symptom cluster. Factor 3 consisted of seven symptoms (i.e., feeling bloated, feeling irritable, feeling nervous, feeling sad, worrying, difficulty sleeping, weight loss (loaded negatively)) and was named the *psychological* symptom cluster. Factor 4 contained four symptoms (i.e., sweats, increased appetite, weight gain, lack of appetite (loaded negatively)) and was named the *nutritional* symptom cluster.

As shown in Table 6, a five factor solution was found for the T2 assessment. Factor 1 contained seventeen symptoms (i.e., abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting, feeling bloated, feeling nervous, feeling sad, problems with sexual interest or activity, worrying, dizziness, dry mouth, pain, swelling of legs (loaded negatively)) and was named the *sickness behavior* symptom cluster. Factor 2 consisted of five symptoms (i.e., chest tightness, cough, difficulty breathing, shortness of breath, swelling of arms or legs) and was named the *lung cancer-specific* symptom cluster. Factor 3 contained four symptoms (i.e., lack of appetite, weight loss, increased appetite, weight gain (both loaded negatively)) and was named the *nutritional* cluster. Factor 4 contained four symptoms (i.e., feeling irritable, feeling nervous, feeling sad, worrying) and was named the *psychological* symptom cluster. Factor 5 contained four symptoms (i.e., changes in skin, "I do not look like myself", mouth sores, swelling of arms and legs) and was named the *epithelial* symptom cluster.

As presented in Table 7, a five factor solution was found for the T3 assessment. Factor 1 contained five symptoms (i.e., difficulty concentrating, feeling irritable, feeling nervous, dizziness, chest tightness (loaded negatively)) and was named the *sickness behavior* symptom cluster. Factor 2 consisted of nine symptoms (i.e., difficulty concentrating, feeling drowsy, lack

of energy, chest tightness, cough, difficulty breathing, shortness of breath, dry mouth, pain) and was named the *lung cancer-specific* symptom cluster. Factor 3 contained thirteen symptoms (i.e., abdominal cramps, constipation, sweats, feeling bloated, problems with sexual interest or activity, lack of appetite, weight loss, changes in skin, hair loss, "I do not look like myself", mouth sores, dizziness, change in the way food tastes) and was named the *epithelial/GI* symptom cluster. Factor 4 contained five symptoms (i.e., nausea, vomiting, feeling nervous, feeling sad, worrying) and was named the *psychological* symptom cluster. Factor 5 contained three symptoms (i.e., increased appetite, weight gain, weight loss (loaded negatively)) and was named the *nutritional* symptom cluster.

Similarities and Differences in the Number and Types of Symptom Clusters

As shown in Table 8, for the occurrence dimension, the number of symptom clusters was five for all three time points. Across the three occurrence assessments, four of the symptom clusters were the same, namely; sickness behavior, lung cancer specific, psychological, and nutritional. While an epithelial/GI cluster occurred at T1 and T3, the epithelial symptom cluster was identified at T2.

For the severity dimension, the number of symptom clusters ranged from four to five. Across the three severity assessments, three of the symptom clusters were the same, namely; lung cancer specific, psychological, and nutritional. The sickness behavior cluster was identified for the T2 and T3 assessments. While the epithelial/GI cluster was found at T1 and T3, the epithelial cluster was only identified at T2.

Agreement in the Types of Symptoms Within Each Symptom Cluster

Table 8 presents a summary of the percentage agreement among the symptoms across the occurrence and severity dimensions and across time. For the sickness behavior cluster, the total

number of symptoms ranged from zero to seventeen and the percent agreement from 0.0% to 81.0%. While no symptom was included across all of the EFAs, lack of energy and feeling drowsy loaded on four of the five EFAs. For the lung cancer specific cluster, the total number of symptoms ranged from four to nine, with percent agreement from 33.3% to 75.0%. The three symptoms that were included in all six EFAs were: cough, difficulty breathing, and shortness of breath. For the psychological cluster, the total number of symptoms ranged from four to eight and the percentage agreement ranged from 33.3% and 66.7%. The three symptoms that were included in all six EFAs were: feeling nervous, feeling sad, and worrying. For the nutritional cluster, the total number of symptoms ranged from three to four and the percent agreement ranged from 60.0% to 80.0%. The two symptoms that were found in all of the EFAs were: increased appetite and weight gain. The total number of symptoms in the epithelial/GI cluster ranged from zero to thirteen and the percent agreement ranged from 0.0% to 81.3%. The symptoms that were included in the four EFAs were: sweats, lack of appetite, changes in skin, "I do not look like myself", and change in the way food tastes. For the epithelial cluster, the total number of symptoms ranged from zero to four and the percentage agreement ranged from 0.0% to 80.0%. Across the two EFAs, the symptoms that were common were: "I do not look like myself" and mouth sores.

DISCUSSION

This study is the first to evaluate for changes over time in the number and types of symptom clusters in patients with lung cancer who received CTX, by using occurrence rates and severity ratings. As summarized in Table 8, six clusters were identified across the two dimensions and the three assessments. However, only three of these clusters remained relatively stable across all dimensions and time (i.e., lung cancer specific, psychological, and nutritional).

Two of the remaining clusters varied by time, but not by dimension. For both occurrence and severity, the epithelial/GI cluster was identified one week before the next dose of CTX (T1) and two weeks after receiving CTX (T3). The epithelial cluster was found only at the T2 assessment for both occurrence and severity. Except for severity at T1, the sickness behavior cluster was found across all dimensions at T2 and T3.

Taken together, our findings suggest that the symptom clusters remained relatively stable over time, regardless of the dimensions used to create the clusters. The remainder of the discussion will describe the variability in the specific symptoms within each cluster. Our findings will be compared with previous findings and the clinical implication of each symptom cluster will be explored.

Lung Cancer Specific Symptom Cluster

A lung cancer specific cluster was identified in all six EFAs. The number of symptoms in this cluster ranged from four to nine. Cough, difficulty breathing, and shortness of breath were identified across all dimensions and time points. Of note, chest tightness was identified across all time points for severity and at T2 and T3 for occurrence. In three previous studies of symptom clusters in patients with lung cancer (Sarna & Brecht, 1997; Henoch et al., 2009; Choi, 2016), some type of respiratory cluster was identified. Direct comparisons of the specific symptoms within the lung cancer specific symptom cluster are not possible because of the different symptom measures used (i.e., Symptom Distress Scale (Sarna & Bretcht, 1997; Henoch et al., 2009), M.D. Anderson Symptom Inventory (Choi et al., 2016)).

However, across these four studies, cough, difficulty breathing, and shortness of breath were the common symptoms. This consistent finding highlights the clinical importance of this symptom cluster in patients with lung cancer. Additional support for the clinical significance of

this cluster is the fact that a higher incidence of respiratory symptoms on initial presentation of lung cancer is associated with a poorer prognosis (Ban, et al., 2016). In addition, respiratory symptoms interfere with patients' ability to perform routine activities of daily life while also maintaining their quality of life (Keiko et al., 2002) .

Psychological Symptom Cluster

In our study a psychological cluster was identified across all of the EFAs for occurrence and severity. The total number of symptoms ranged from four to eight. Feeling nervous, feeling sad, and worrying were present in both dimensions and across all time points. In addition, feeling irritable was identified in five of six EFAs.

While none of the previous studies used the MSAS, our findings are consistent with four previous reports in patients with lung cancer (Sarna & Bretcht, 1997; Henoch et al., 2009; Wang & Fu, 2014; Choi et al., 2016). Two of these studies used the Symptom Distress Scale (SDS) (Sarna & Brecht, 1997; Henoch et al., 2009) and two used the MDASI (Wang & Fu, 2014; Choi et al., 2016) While the specific psychological symptoms on these three instruments are rather disparate, sad was the single common symptom across all five studies. This finding is of particular interest because the prevalence rates for depressive symptoms in patients with lung cancer ranges from 9% to 53% (Hung, et al., 2017). In addition, in a study that isolated the incidence of depression in the four most common cancers in the United States (Patel, Wen, & Aggarwal, 2018), lung cancer ranked first. Given this consistent finding, clinicians need to screen for psychological symptoms and recommend efficacious interventions such as cognitive based therapy, mindfulness training, and participation in support groups (Hulbert-Williams, Beatty & Dhillon, 2018).

Nutritional Symptom Cluster

A nutritional cluster that included the common symptoms of increased appetite and weight gain was identified across both dimensions and all EFAs. Of note, lack of appetite was identified in five of the six EFAs and weight loss was included in three of the six EFAs. The fact that none of the previous studies identified a nutritional cluster in lung cancer patients may be related to differences in symptoms assessed. For example, in the two studies (Sarna &Brecht, 1997; Henoch et al., 2009) that used the SDS, which assesses appetite (i.e., I have my normal appetite to I cannot stand the thought of food), these symptoms loaded on a gastrointestinal distress cluster (Sarna & Brecht, 1997) or on a pain cluster (Henoch et al., 2009). In the two studies that used the MDASI which assess for lack of appetite, this symptom loaded on a general symptom cluster (Wang, 2008) and on a cluster named "pattern 3" that included drowsiness, fatigue, dry mouth, sleep disturbance, and distress (Wang, 2006). Lastly, in the study that used the Physical Symptom Experience tool, (Gift et al., 2004) weight loss and loss of appetite were part of a general symptom cluster. Weight loss and malnutrition are prevalent problems in patients with lung cancer and have a negative impact on an individual's ability to tolerate treatment as well as survival (Kiss, 2016). Given this problem, clinicians need to assess for decrease in appetite and weight loss and integrate nutrition counseling.

Epithelial/Gastrointestinal Symptom Cluster

Our epithelial/GI cluster included symptoms associated with changes in skin, hair and oral mucosa that occur as a result of CTX's action on rapidly dividing cells. While not identified at the T2 assessment, the common symptoms that were included in the other four EFAs were sweats, lack of appetite, changes in the skin, I do not look like myself, and change in the way food tastes. While none of the previous studies reported an epithelial/GI cluster, four studies did

report a GI cluster. (Sarna & Brecht, 1997; Wang, 2006; Wang 2008; Wong & Fu, 2014). Across these four studies the two common symptoms were nausea and vomiting. In one of the reviewed studies that used the SDS, (Sarna & Brecht, 1997) the appearance symptom loaded only on the emotional and physical suffering cluster (Sarna & Brecht, 1997). It should be noted that the MDASI does not assess for any symptoms related to changes in appearance, hair loss, or changes in skin. However, two studies that used the MSAS to assess symptom clusters in patients with other cancer diagnosis, a cluster that contained the symptoms I do not look like myself, changes in skin, and change in the way food tastes was identified (Suwisith, 2008; Yates, 2015). The presence of these symptoms across three heterogeneous studies suggests that they warrant evaluation in patients of these cancer diagnoses.

Sickness Behavior Symptom Cluster

We identified a sickness behavior cluster in both dimensions and across all time points, except for severity at T1. This cluster included the largest number of symptoms. The three most common symptoms that were identified were lack of energy, difficulty concentrating, and feeling drowsy. While this cluster was not identified in previous studies of lung cancer patients (Sarna & Brecht, 1997; Gift et al., 2004; Wang et al., 2008; Choi, 2016), it is a common symptom cluster in a number of studies of oncology patients undergoing active treatment (Sullivan et al., 2018). Additional studies are needed to confirm the presence of this symptom cluster in patients with lung cancer, and to assess if the complex treatment has a relationship to it's existence.

Epithelial Symptom Cluster

Our epithelial symptom cluster, was only identified at the T2 timepoint for both dimensions. Similar to the epithelial/GI cluster, changes in skin, "I do not look like myself" and mouth sores, were the three common symptoms across the two EFAs. While it is not exactly

clear why this cluster was identified only at the T2 assessment, in other studies of patients with breast, ovarian, or heterogenous cancer diagnosis that used the MSAS, a body image related symptom cluster was identified that included these three symptoms (Nongluck et al., 2008; Huang et al., 2016; Molassiotis, 2010; Sullivan et al., 2018). Additional research is needed to confirm the presence of this cluster, and how it changes over time and in relation to treatments that are known to effect body image.

Limitations

Several study limitations warrant consideration. Patients were enrolled at various cycles during their treatment course. The number and types of symptom clusters by occurrence and severity may have varied if the patients were enrolled prior to the initiation of CTX. In addition, we were unable to use symptom distress, another important dimension of the symptom experience, to identify symptom clusters and compare our results using occurrence and severity ratings. When we evaluated the symptom distress ratings, not enough patients with each symptom were available to allow for accurate estimation. Lastly, five symptoms with occurrence rates <20% were omitted from the EFAs so their contribution to the various symptom clusters could not be determined.

Conclusions

Despite these limitations, our findings suggest that three symptom clusters (i.e., lung cancer specific, psychological, and nutritional) were relatively stable across both symptom dimensions and time. These findings warrant confirmation in independent samples. The other clusters that were less consistent and stable over time (i.e., sickness-behavior, epithelial/GI, epithelial) warrant additional research to determine their relevance in patients with lung cancer.

Implications for Clinical Practice and Research

Findings from this study confirm that patients with lung cancer experience a high symptom burden and that three symptom clusters occur over the course of one cycle of CTX. Clinicians need to assess for these symptom clusters, the impact of these clusters on patients' functional status, and quality of life, and initiate appropriate interventions and referrals. For example, referrals to mental health professionals and dieticians may be warranted in patients who report a psychological and nutritional symptom cluster.

Future studies of lung cancer patients should be done to confirm the presence of all of these symptoms and to determine whether these clusters persist over the entire course of CTX and after. Additional studies are needed to identify the most effective interventions to treat these symptom clusters as well as identifying mechanisms for these clusters.

Table 1. Demographic and clinical characteristics of lung cancer patients receiving CTX (n = 145)[a]

Characteristic	N (%)
Age in years, mean (SD)	64.0 (11.1)
Gender	
Female	82 (56.6)
Male	63 (43.4)
Race/ethnicity	
White	102 (71.8)
Asian or Pacific Islander	14 (9.9)
Black	14 (9.9)
Hispanic, Mixed, or other	12 (8.5)
Annual household income	
<$30,000	37 (27.6)
$30,000 to $69,999	31 (23.1)
$70,000 to $99,999	21 (15.7)
>$100,000	45 (33.6)
Currently employed	36 (24.8)
Education in years, mean (SD)	16.1 (3.4)
Married or partnered	93 (64.6)
Lives alone	36 (25.0)
Smoking history	
Current or former smoker	99 (69.7)
Never smoker	43 (30.3)
BMI kg/m^2, mean (SD)	25.3 (4.6)
Patient-reported KPS score, mean (SD)	79.1 (14.6)
SCQ score, mean (SD)	7.3 (3.9)
No. of comorbidities, mean (SD)	3.2 (1.6)
Comorbidities	
Lung disease	87 (60.0)
Hypertension	58 (40.0)
Back pain	53 (36.6)
Depression	26 (17.9)
Osteoarthritis	21 (14.5)
Heart disease	20 (13.8)
Diabetes	18 (12.4)
Anemia or other blood disease	12 (8.3)
Liver disease	12 (8.3)
Rheumatoid arthritis	12 (8.3)
Ulcer or stomach disease	9 (6.2)
Kidney disease	1 (0.7)
Type of lung cancer	
Non-small cell lung cancer	126 (88.1)
Small cell lung cancer	17 (11.9)
Months since cancer diagnosis, mean (SD)	15.1 (31.7)
Months since cancer diagnosis, median (IQR)	4.2 (2.5-14.5)
Metastatic disease at time of study	110 (76.9)
Number of prior cancer treatments, mean (SD)	1.4 (1.4)
Prior treatment	
No prior treatment	54 (38.9)
Surgery only	17 (12.2)
CTX only	12 (8.6)
Radiation only	18 (13.0)
Surgery and CTX	5 (3.6)
Surgery and radiation	3 (2.2)
CTX and radiation	13 (9.4)
Surgery, CTX, and radiation	17 (12.2)
CTX regimen at time of study	
Platinum-doublet	113 (77.9)
Single agent CTX	29 (20.0)
Monoclonal antibody alone	3 (2.1)
Mean number of MSAS symptoms (out of 38, SD)	14.3 (7.1)

Abbreviations: BMI, body mass index; CTX, chemotherapy; IQR, interquartile range; kg/m^2, kilogram per meter squared; KPS, Karnofsky Performance Status; MSAS, Memorial Symptom Assessment Scale; SCQ, Self-Administered Comorbidity Questionnaire; SD, standard deviation.
[a]Reprinted with permission from reference 45.

Table 2. Exploratory factory analysis[a] using ratings of symptom occurrence for the week prior to the next cycle of chemotherapy

Symptom[b]	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Sickness Behavior Symptom Cluster	Lung Cancer-Specific Symptom Cluster	Psychological Symptom Cluster	Epithelial/GI Symptom Cluster	Nutritional Symptom Cluster
Abdominal cramps	0.144	0.034	0.222	**0.443**	0.129
Constipation	-0.091	0.154	-0.019	**0.627**	0.021
Difficulty concentrating	0.364	-0.066	**0.517**	-0.045	0.102
Feeling drowsy	**0.564**[c]	0.187	0.298	-0.064	-0.170
Lack of energy	**1.021**	0.081	0.025	0.004	-0.273
Nausea	0.269	0.032	0.108	**0.476**	-0.091
Sweats	0.148	0.013	0.014	**0.430**	0.296
Vomiting	-0.105	0.217	0.179	0.278	0.112
Chest tightness	0.297	0.399	0.042	0.203	0.000
Cough	0.280	**0.504**	0.076	0.023	0.074
Difficulty breathing	0.060	**0.772**	**0.407**	0.006	-0.038
Shortness of breath	0.037	**0.469**	0.368	0.101	0.119
Feeling bloated	-0.167	0.074	**0.548**	0.231	0.138
Feeling irritable	0.086	-0.053	**0.525**	0.372	-0.027
Feeling nervous	0.385	0.017	**0.505**	-0.053	0.243
Feeling sad	0.148	-0.361	**0.601**	0.225	-0.020
Problems with sexual interest or activity	**0.467**	-0.349	0.132	0.031	0.158
Worrying	-0.021	-0.297	**0.925**	0.088	-0.006
Increased appetite	-0.077	-0.116	0.027	0.023	**1.056**
Lack of appetite	-0.003	-0.206	0.049	**0.814**	**-0.470**
Weight gain	0.046	0.037	0.070	-0.148	**0.783**
Weight loss	0.380	-0.058	**-0.620**	**0.717**	0.004
Changes in skin	-0.051	0.122	0.094	**0.714**	-0.029
Hair loss	**0.565**	0.004	-0.314	0.264	0.275
I do not look like myself	0.061	0.042	0.175	**0.543**	0.003
Mouth sores	0.206	0.027	0.310	0.136	0.295
Dizziness	**0.413**	0.174	0.032	0.239	0.132
Dry mouth	0.316	**0.438**	0.049	0.140	0.001
Pain	**0.456**	0.226	-0.075	0.232	-0.061
Swelling of arms or legs	0.033	**0.483**	-0.068	0.302	0.002
Change in the way food tastes	-0.253	0.108	-0.018	**0.852**	0.021
Difficulty sleeping	0.132	-0.134	0.356	0.026	0.041
Numbness/tingling in hands/feet	0.312	0.028	-0.125	0.355	0.166
Total number of symptoms	6	5	8	9	3

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.
[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.
[c]Factor loadings ≥0.40 are in bold.

Table 3. Exploratory factory analysis[a] using ratings of symptom occurrence for one week after the administration of chemotherapy

Symptom[b]	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Sickness Behavior Symptom Cluster	Lung Cancer-Specific Symptom Cluster	Psychological Symptom Cluster	Nutritional Symptom Cluster	Epithelial Symptom Cluster
Abdominal cramps	**0.560**[c]	-0.006	0.241	-0.063	0.307
Constipation	**0.438**	-0.359	-0.060	0.128	0.256
Difficulty concentrating	**0.498**	0.022	**0.445**	-0.147	0.074
Feeling drowsy	**0.768**	0.028	0.003	0.003	-0.146
Lack of energy	**0.766**	0.165	0.154	0.036	0.004
Nausea	**0.869**	-0.319	-0.035	0.095	-0.108
Sweats	**0.416**	0.160	0.071	-0.027	0.328
Vomiting	**0.600**	-0.029	0.032	0.033	-0.040
Chest tightness	0.255	**0.601**	-0.012	0.089	0.098
Cough	0.185	**0.608**	-0.234	-0.025	-0.002
Difficulty breathing	0.011	**0.934**	0.023	0.022	-0.028
Shortness of breath	0.070	**0.900**	0.080	0.140	-0.039
Feeling bloated	0.230	-0.001	**0.433**	0.019	0.246
Feeling irritable	-0.163	0.175	**0.803**	0.036	-0.021
Feeling nervous	0.387	0.177	**0.663**	0.021	-0.064
Feeling sad	0.269	0.059	**0.571**	0.174	0.020
Problems with sexual interest or activity	0.093	-0.022	**0.526**	-0.073	0.029
Worrying	0.323	-0.058	**0.744**	-0.021	0.003
Increased appetite	0.056	0.359	-0.002	**-0.841**	-0.025
Lack of appetite	0.289	0.044	0.056	**0.709**	0.028
Weight gain	-0.033	0.356	-0.021	**-0.867**	0.214
Weight loss	0.020	0.177	-0.128	**0.526**	0.385
Changes in skin	0.030	-0.201	0.311	-0.051	**0.795**
Hair loss	0.136	0.051	-0.216	0.242	**0.428**
"I do not look like myself"	-0.145	-0.063	0.288	0.098	**0.693**
Mouth sores	0.001	0.131	-0.049	0.046	**0.643**
Dizziness	0.224	-0.015	0.266	-0.153	0.226
Dry mouth	0.398	0.202	-0.003	0.099	0.128
Pain	0.386	0.287	-0.067	-0.020	0.125
Swelling of arms or legs	-0.182	0.285	0.041	-0.038	0.344
Change in the way food tastes	-0.079	0.180	0.302	0.205	0.288
Difficulty sleeping	0.392	0.104	0.148	-0.117	0.011
Numbness/tingling in hands/feet	0.274	0.279	0.002	-0.119	0.349
Total number of symptoms	8	4	7	4	4

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.

[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.

[c]Factor loadings ≥ 0.40 are in bold.

Table 4. Exploratory factory analysis[a] using ratings of symptom occurrence for approximately two weeks after the administration of chemotherapy

Symptom[b]	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5
	Sickness Behavior Symptom Cluster	Lung Cancer-Specific Symptom Cluster	Epithelial/GI Symptom Cluster	Psychological Symptom Cluster	Nutritional Symptom Cluster
Abdominal cramps	0.013	0.068	**0.579**	0.338	0.068
Constipation	-0.062	0.102	0.390	0.083	0.237
Difficulty concentrating	**0.641**[c]	0.034	0.009	0.394	0.088
Feeling drowsy	**0.518**	0.069	**0.488**	0.004	-0.206
Lack of energy	**0.729**	-0.039	0.360	0.041	-0.099
Nausea	0.001	0.176	0.220	**0.535**	-0.290
Sweats	0.018	0.266	**0.451**	0.208	0.011
Vomiting	-0.089	0.246	0.078	**0.624**	-0.141
Chest tightness	0.087	**0.827**	0.013	0.200	0.093
Cough	**0.426**	**0.459**	-0.008	0.056	0.018
Difficulty breathing	0.366	**0.794**	-0.057	0.095	-0.057
Shortness of breath	0.367	**0.631**	0.105	-0.016	0.034
Feeling bloated	0.046	-0.189	**0.518**	0.296	0.084
Feeling irritable	0.117	-0.105	0.274	**0.522**	0.080
Feeling nervous	0.260	-0.027	-0.047	**0.735**	0.022
Feeling sad	0.150	0.074	0.023	**0.771**	-0.088
Problems with sexual interest or activity	0.082	-0.344	**0.561**	0.180	0.051
Worrying	-0.013	-0.110	-0.008	**1.001**	-0.054
Increased appetite	-0.065	0.147	0.026	0.063	**0.889**
Lack of appetite	-0.203	-0.017	**0.559**	0.209	**-0.420**
Weight gain	-0.057	-0.022	0.407	-0.021	**0.866**
Weight loss	-0.259	**0.451**	0.285	-0.015	-0.357
Changes in skin	-0.113	0.157	**0.589**	0.085	-0.033
Hair loss	-0.055	-0.010	**0.460**	-0.066	0.049
I do not look like myself	-0.297	0.056	**0.518**	0.304	0.052
Mouth sores	0.078	-0.025	**0.682**	-0.124	0.025
Dizziness	0.333	**-0.468**	**0.889**	0.017	-0.026
Dry mouth	0.395	0.237	0.368	-0.197	-0.109
Pain	0.284	**0.406**	0.294	-0.045	0.123
Swelling of arms or legs	0.107	0.181	0.234	-0.124	0.013
Change in the way food tastes	-0.365	0.078	**0.624**	-0.024	-0.042
Difficulty sleeping	0.182	0.103	0.015	0.183	0.119
Numbness/tingling in hands/feet	-0.014	0.351	0.209	0.250	-0.023
Total number of symptoms	4	7	13	6	3

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.

[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.

[c]Factor loadings ≥0.40 are in bold.

Table 5. Exploratory factory analysis[a] using ratings of symptom severity for the week prior to the next cycle of chemotherapy administration

Symptom[b]	Factor 1	Factor 2	Factor 3	Factor 4
	Lung Cancer-Specific Symptom Cluster	Epithelial/GI Symptom Cluster	Psychological Symptom Cluster	Nutritional Symptom Cluster
Abdominal cramps	0.129	0.384	0.187	0.177
Constipation	0.046	**0.528**	0.072	0.204
Difficulty concentrating	0.281	0.126	0.383	0.122
Feeling drowsy	**0.679**	-0.038	0.238	-0.165
Lack of energy	**0.621**	0.215	0.039	-0.227
Nausea	0.336	**0.453**	0.004	-0.022
Sweats	0.016	**0.447**	-0.014	**0.428**
Vomiting	0.295	0.172	-0.009	0.159
Chest tightness	**0.557**	0.145	-0.066	0.133
Cough	**0.584**	0.043	-0.014	0.056
Difficulty breathing	**0.835**	-0.023	0.038	-0.048
Shortness of breath	**0.730**	0.042	0.040	0.056
Feeling bloated	0.045	0.249	**0.404**	0.238
Feeling irritable	0.098	0.362	**0.453**	0.082
Feeling nervous	0.282	-0.028	**0.491**	0.351
Feeling sad	-0.019	0.141	**0.702**	-0.069
Problems with sexual interest or activity	0.097	-0.021	0.262	0.265
Worrying	-0.047	0.073	**0.911**	-0.006
Increased appetite	-0.347	0.043	0.044	**0.984**
Lack of appetite	-0.012	**0.815**	0.109	**-0.508**
Weight gain	-0.171	-0.075	0.019	**0.879**
Weight loss	0.038	**0.740**	**-0.443**	0.028
Changes in skin	-0.042	**0.790**	0.048	-0.039
Hair loss	0.177	0.340	-0.196	0.263
I do not look like myself	-0.018	**0.597**	0.190	0.017
Mouth sores	0.056	0.224	0.252	0.399
Dizziness	**0.403**	0.261	0.029	0.187
Dry mouth	0.354	0.336	0.052	0.024
Pain	**0.454**	0.280	-0.076	0.036
Swelling of arms or legs	0.281	0.317	-0.228	-0.029
Change in the way food tastes	-0.160	**0.894**	-0.076	-0.064
Difficulty sleeping	0.189	-0.085	**0.470**	-0.011
Numbness/tingling in hands/feet	0.114	0.374	-0.021	0.233
Total number of symptoms	8	8	7	4

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.

[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.

[c]Factor loadings ≥0.40 are in bold.

Table 6. Exploratory factory analysis[a] using ratings of symptom severity for one week after the administration of chemotherapy

Symptom[b]	Factor 1 Sickness Behavior Symptom Cluster	Factor 2 Lung Cancer-Specific Symptom Cluster	Factor 3 Nutritional Symptom Cluster	Factor 4 Psychological Symptom Cluster	Factor 5 Epithelial Symptom Cluster
Abdominal cramps	**0.572**[c]	0.013	-0.102	0.037	0.226
Constipation	**0.441**	-0.230	0.072	-0.049	0.183
Difficulty concentrating	**0.509**	0.010	0.010	0.307	0.125
Feeling drowsy	**0.667**	0.117	0.139	-0.027	-0.081
Lack of energy	**0.775**	0.135	0.197	0.010	0.007
Nausea	**0.709**	-0.189	0.193	-0.059	-0.068
Sweats	**0.629**	0.130	-0.066	-0.135	0.159
Vomiting	**0.543**	0.033	-0.079	-0.044	-0.092
Chest tightness	0.254	**0.643**	-0.018	-0.023	0.032
Cough	0.114	**0.670**	-0.109	-0.017	-0.212
Difficulty breathing	-0.083	**0.948**	0.004	0.203	0.032
Shortness of breath	0.128	**0.806**	0.044	0.217	-0.026
Feeling bloated	**0.430**	-0.110	-0.090	0.069	0.358
Feeling irritable	0.004	0.156	-0.008	**0.674**	0.225
Feeling nervous	**0.429**	0.234	-0.008	**0.469**	-0.036
Feeling sad	**0.408**	0.047	0.141	**0.653**	0.006
Problems with sexual interest or activity	**0.555**	-0.267	-0.169	0.108	0.012
Worrying	**0.482**	-0.079	-0.025	**0.668**	0.069
Increased appetite	0.194	0.088	**-0.845**	0.012	0.000
Lack of appetite	0.323	0.076	**0.723**	0.025	0.119
Weight gain	0.027	0.205	**-0.843**	-0.102	0.211
Weight loss	0.054	0.349	**0.524**	-0.158	0.262
Changes in skin	-0.004	-0.078	0.032	0.026	**0.889**
Hair loss	0.137	0.157	0.197	-0.244	0.238
"I do not look like myself"	-0.046	-0.026	0.107	0.129	**0.752**
Mouth sores	0.079	0.125	-0.032	-0.307	**0.535**
Dizziness	**0.489**	0.038	-0.190	0.039	0.133
Dry mouth	**0.407**	0.227	0.068	-0.031	0.118
Pain	**0.432**	0.219	0.103	0.171	-0.082
Swelling of arms or legs	**-0.453**	**0.438**	-0.003	0.005	**0.448**
Change in the way food tastes	0.190	0.012	0.242	0.104	0.339
Difficulty sleeping	0.313	0.178	-0.065	0.229	0.164
Numbness/tingling in hands/feet	0.071	0.284	-0.137	0.111	0.296
Total number of symptoms	17	5	4	4	4

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.

[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.

[c]Factor loadings ≥0.40 are in bold.

Table 7. Exploratory factory analysis[a] using ratings of symptom severity for approximately two weeks after the administration of chemotherapy

Symptom[b]	Factor 1 Sickness Behavior Symptom Cluster	Factor 2 Lung Cancer-Specific Symptom Cluster	Factor 3 Epithelial/GI Symptom Cluster	Factor 4 Psychological Symptom Cluster	Factor 5 Nutritional Symptom Cluster
Abdominal cramps	0.238	0.138	**0.541**	0.154	0.015
Constipation	0.048	-0.021	**0.543**	0.046	0.236
Difficulty concentrating	**0.629**	**0.418**	-0.091	0.043	0.007
Feeling drowsy	0.223	**0.415**	0.214	0.120	-0.135
Lack of energy	0.292	**0.586**	0.074	-0.056	-0.162
Nausea	0.014	0.234	0.196	**0.525**	-0.120
Sweats	-0.043	0.285	**0.455**	0.212	0.032
Vomiting	0.005	0.155	-0.028	**0.771**	0.027
Chest tightness	**-0.418**	**0.745**	-0.004	0.233	0.136
Cough	-0.126	**0.595**	-0.004	0.134	-0.157
Difficulty breathing	0.078	**0.898**	-0.094	-0.012	-0.042
Shortness of breath	0.055	**0.764**	0.094	-0.107	0.111
Feeling bloated	0.328	0.039	**0.467**	0.096	0.225
Feeling irritable	**0.452**	0.013	0.366	0.173	-0.004
Feeling nervous	**0.425**	0.026	-0.007	**0.566**	0.026
Feeling sad	0.328	0.017	0.077	**0.701**	-0.159
Problems with sexual interest or activity	0.355	-0.104	**0.483**	0.010	0.073
Worrying	0.322	-0.049	0.109	**0.733**	-0.019
Increased appetite	-0.029	0.054	0.032	0.015	**0.855**
Lack of appetite	0.050	0.016	**0.661**	0.046	-0.370
Weight gain	0.013	0.022	0.327	-0.036	**0.854**
Weight loss	-0.333	0.236	**0.617**	-0.007	**-0.446**
Changes in skin	0.001	0.059	**0.662**	0.044	-0.038
Hair loss	0.006	0.089	**0.419**	0.012	-0.050
I do not look like myself	-0.046	-0.125	**0.604**	0.339	0.111
Mouth sores	0.193	-0.024	**0.736**	-0.278	0.008
Dizziness	**0.434**	0.094	**0.562**	-0.097	0.028
Dry mouth	0.052	**0.448**	0.309	-0.149	-0.084
Pain	-0.079	**0.530**	0.175	0.067	0.052
Swelling of arms or legs	-0.056	0.083	0.202	0.052	-0.053
Change in the way food tastes	-0.190	-0.095	**0.831**	0.018	-0.069
Difficulty sleeping	0.279	0.210	-0.038	0.299	0.053
Numbness/tingling in hands/feet	-0.024	0.296	0.245	0.093	0.093
Total number of symptoms	5	9	13	5	3

[a]Extraction method: Unweighted least squares. Rotation method: Geomin (oblique) rotation.

[b]Five symptoms present in <20% of patients did not meet our criteria for inclusion in the EFA: diarrhea, difficulty swallowing, hot flashes, itching, problems with urination.

[c]Factor loadings ≥0.40 are in bold.

Table 8. Summary of symptom clusters over time using occurrence rates and severity ratings

Symptom Cluster	Symptoms Within the Cluster	Occurrence			Severity		
		T1	T2	T3	T1	T2	T3
Sickness Behavior Symptom Cluster	Lack of energy	●	●	●	N O T I D E N T I F I E D	●	
	Problems with sexual interest or activity	●				●	
	Hair loss	●					
	Dizziness	●				●	●
	Dry mouth					●	
	Abdominal cramps		●			●	
	Constipation		●			●	
	Difficult concentrating		●	●		●	●
	Nausea		●			●	
	Sweats		●			●	
	Vomiting		●			●	
	Cough			●			
	Feeling bloated					●	
	Feeling drowsy	●	●	●		●	
	Feeling irritable						●
	Feeling nervous					●	●
	Feeling sad					●	
	Worrying					●	
	Pain	●				●	
	Swelling of arms or legs					●	
	Chest tightness						●
	Percent agreement	28.6%	38.1%	19.0%	0.0%	81.0%	23.8%
Lung Cancer Specific Symptom Cluster	Cough	●	●	●	●	●	●
	Difficulty breathing	●	●	●	●	●	●
	Shortness of breath	●	●	●	●	●	●
	Dry mouth	●				●	●
	Swelling of arms or legs	●					
	Chest tightness		●	●	●	●	●
	Weight loss			●			
	Dizziness		●		●		
	Pain		●		●		●
	Difficulty concentrating						●
	Feeling drowsy				●		●
	Lack of energy				●		●
	Percent agreement	41.6%	33.3%	58.3%	66.7%	41.7%	75.0%
Psychological Symptom Cluster	Difficulty concentrating	●	●				
	Difficulty breathing	●					
	Feeling bloated	●	●		●		
	Feeling irritable	●	●	●	●	●	
	Feeling nervous	●	●	●	●	●	●
	Feeling sad	●	●	●	●	●	●
	Worrying	●	●	●	●	●	●
	Weight loss	●			●		
	Problems with sexual interest or activity		●				

	Vomiting			•			•
	Nausea			•			•
	Difficulty sleeping				•		
	Percent agreement	66.7%	58.3%	50.0%	58.3%	33.3%	41.7%
Nutritional Symptom Cluster	Increased appetite	•	•	•	•	•	•
	Sweats				•		
	Lack of appetite	•	•	•	•	•	
	Weight gain	•	•	•	•	•	•
	Weight loss		•			•	•
	Percent agreement	60.0%	80.0%	60.0%	80.0%	80.0%	60.0%
Epithelial/Gastrointestinal Symptom Cluster	Abdominal cramps	•	NOT IDENTIFIED	•		NOT IDENTIFIED	•
	Constipation	•			•		•
	Nausea	•			•		
	Sweats	•		•	•		•
	Lack of appetite	•		•	•		•
	Weight loss	•			•		•
	Changes in skin	•		•	•		•
	I do not look like myself	•		•	•		•
	Change in the way food tastes	•		•	•		•
	Mouth sores			•			•
	Hair loss			•			•
	Feeling drowsy			•			
	Feeling bloated			•			•
	Weight gain			•			
	Dizziness			•			•
	Problems with sexual interest or activity			•			•
	Percent agreement	56.3%	0.0%	81.3%	50.0%	0.0%	81.3%
Epithelial Symptom Cluster	Changes in skin	NOT IDENTIFIED	•	NOT IDENTIFIED	NOT IDENTIFIED	•	NOT IDENTIFIED
	Hair loss		•				
	"I do not look like myself"		•			•	
	Mouth sores		•			•	
	Swelling of arms and legs					•	
	Percent agreement	0.0%	80.0%	0.0%	0.0%	80.0%	0.0%
Total number of symptom clusters		5	5	5	4	5	5

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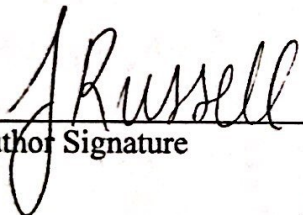
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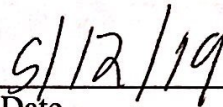
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