Title

Differences in Symptom Clusters Identified Using Ratings of Symptom Occurrence vs. Severity in Lung Cancer Patients Receiving Chemotherapy

Journal

Journal of Pain and Symptom Management, 54(2)

ISSN

0885-3924

Authors

Wong, Melisa L
Cooper, Bruce A
Paul, Steven M
et al.

Publication Date

2017-08-01

DOI

10.1016/j.jpainsymman.2017.04.005

Peer reviewed

HHS Public Access

Author manuscript

J Pain Symptom Manage. Author manuscript; available in PMC 2018 August 01.

Published in final edited form as:

J Pain Symptom Manage. 2017 August ; 54(2): 194–203. doi:10.1016/j.jpainsymman.2017.04.005.

Differences in Symptom Clusters Identified Using Ratings of Symptom Occurrence Versus Severity in Lung Cancer Patients Receiving Chemotherapy

Melisa L. Wong, MD[1], **Bruce A. Cooper, PhD**[2], **Steven M. Paul, PhD**[2], **Jon D. Levine, MD, PhD**[1], **Yvette P. Conley, PhD**[3], **Fay Wright, RN, PhD**[4], **Marilyn Hammer, RN, PhD**[5], and **Christine Miaskowski, RN, PhD**[2]

[1]School of Medicine, University of California, San Francisco, CA

[2]School of Nursing, University of California, San Francisco, CA

[3]School of Nursing, University of Pittsburgh, Pittsburgh, PA, USA

[4]Yale School of Nursing, New Haven, CT, USA

[5]Department of Nursing, Mount Sinai Hospital, New York, NY, USA

Abstract

Context—An important question in symptom clusters research is whether the number and types of symptom clusters vary based on the specific dimension of the symptom experience used to create the clusters.

Objectives—Given that lung cancer patients undergoing chemotherapy (CTX) report an average of 14 co-occurring symptoms and studies of symptom clusters in these patients are limited, the purpose of this study, in lung cancer patients undergoing CTX (n=145), was to identify whether the number and types of symptom clusters differed based on whether symptom occurrence rates or symptom severity ratings were used to create the clusters.

Methods—A modified version of the Memorial Symptom Assessment Scale was used to assess for the occurrence and severity of 38 symptoms, one week after the administration of CTX. Exploratory factor analysis was used to extract the symptom clusters.

Results—Both the number and types of symptom clusters were relatively similar using symptom occurrence rates or symptom severity ratings. Five symptom clusters were identified using both symptom occurrence rates and severity ratings (i.e., sickness behavior, lung cancer-specific, psychological, nutritional, epithelial). Across these two dimensions, the specific symptoms within each of the symptom clusters were relatively similar.

Address correspondence to: Christine Miaskowski, RN, PhD, Department of Physiological Nursing, University of California San Francisco, 2 Koret Way-N631Y, San Francisco, CA 94143-0610, Phone: (415) 476-9407, Fax: (415) 476-8899 chris.miaskowski@ucsf.edu.

Conflicts of interest: The authors have no conflicts of interest to report.

Conclusions—Identification of symptom clusters in patients with lung cancer may assist with the development of more targeted symptom management interventions. Future studies are warranted to determine if symptom clusters change over a cycle of CTX in patients with lung cancer.

Keywords

symptoms; symptom clusters; lung cancer; chemotherapy; exploratory factor analysis; symptom occurrence; symptom severity

INTRODUCTION

Cancer patients commonly experience multiple co-occurring symptoms from both the underlying cancer and its treatment.[1] These symptom clusters, which consist of two or more interrelated symptoms that may or may not share a common etiology,[2] are associated with decrements in physical functioning after a cancer diagnosis[3] and during chemotherapy (CTX) treatment.[4] Several studies found that different symptom clusters are associated with worse quality of life (QOL) outcomes among patients with various types of cancer,[5–8] including lung cancer.[9–11]

Lung cancer, which remains the leading cause of cancer deaths in the United States,[12] is associated with a high symptom burden.[13–14] One of the earliest studies of symptom clusters in lung cancer patients used the dimension of symptom distress to empirically derive four symptom clusters (i.e., emotional and physical suffering, gastrointestinal distress, respiratory distress, malaise) in women with advanced lung cancer receiving various types of treatment.[15] In contrast, the dimension of symptom severity was utilized to identify symptom clusters in four studies of lung cancer patients after diagnosis,[16] during CTX,[17] during chemoradiation,[18] and in a heterogeneous sample of lung cancer patients at various time points during their disease.[19] Across these four studies, one[16] to three[18] clusters were identified. A gastrointestinal symptom cluster, that included nausea and vomiting, was the most common cluster.

In two recent reviews,[20,21] one of the identified gaps in symptom clusters research is whether the number and types of symptom clusters are similar regardless of which dimension of the symptom experience is used to create the clusters. While this type of comparison was performed in studies of breast and prostate cancer patients at the end of radiation therapy (occurrence versus severity),[22] pediatric cancer patients during CTX (occurrence versus severity),[23] and women with breast cancer during CTX (severity versus distress),[24] the findings were inconsistent. However, no studies of lung cancer patients have compared the number and types of symptom clusters identified using different dimensions of the symptom experience.

Therefore, the objective of this study was to compare the number and types of symptom clusters identified using ratings of symptom occurrence versus severity in a homogenous sample of lung cancer patients one week after CTX administration. The uniform timing of the symptom assessment is important since symptoms fluctuate within and across cycles of CTX. To evaluate the agreement among the symptoms within the same cluster identified

using occurrence and severity, we used the criteria proposed by Kirkova and Walsh (i.e., at least 75% of the symptoms in the cluster should be present including the most prominent and important symptom, namely that symptom with the greatest weight from the factor analysis).[25] We hypothesized that while the symptom clusters identified using both dimensions would be similar, the number and specific symptoms within each cluster would vary.

MATERIALS AND METHODS

Patients and Settings

This cross-sectional analysis is part of a longitudinal parent study 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 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. The current analysis evaluated only patients with lung cancer.

Instruments

A 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 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 they received treatment for it, and if it limited their activities, for a maximum of 3 points per condition resulting in an overall score of 0 to 39. The SCQ has well established validity and reliability.[32]

A modified version of the Memorial Symptom Assessment Scale (MSAS)[33] evaluated the occurrence and severity of 38 symptoms commonly associated with cancer and its treatment. In addition to the original 32 MSAS symptoms, the following six symptoms were assessed: chest tightness, difficulty breathing, increased appetite, weight gain, abdominal cramps, and hot flashes. Patients indicated if they experienced each symptom in the past week (symptom occurrence), and if yes, they rated its severity, frequency, and distress. Symptom severity was measured using a 4-point Likert scale (1 = sight, 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 second assessment that obtained data approximately one week after CTX administration was used to assess acute symptoms. 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 conducted 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.

RESULTS

Demographic and Clinical Characteristics

Of the 157 lung cancer patients enrolled, 145 completed the MSAS one week after CTX administration and were included in the analysis. The demographic and clinical characteristics of the sample were described in detail elsewhere.[45] As summarized in Table 1, the mean age was 64.0 years (SD 11.1), 56.6% were female, and 71.8% were white. The mean KPS score was 79.1 (SD 14.6) and the mean SCQ score was 7.3 (SD 3.9) with an average of 3.2 comorbid conditions. The majority of patients had non-small cell lung cancer (88.1%) with a median of 4.2 months since the time of their lung cancer diagnosis and a mean of 1.4 prior cancer treatments. During the study, 77.9% of patient received a platinum-doublet CTX regimen and 76.9% had metastatic disease. On average, patients reported 14.3 symptoms (SD 7.1, range 1–37) on the MSAS.

Symptom Occurrence and Severity

Details of symptom occurrence and severity ratings for this cohort are published elsewhere.[45] Five symptoms present in <20% of patients were not included in the EFAs (i.e., diarrhea, difficulty swallowing, hot flashes, itching, problems with urination).

Symptom Clusters Based on Symptom Occurrence

As shown in Table 2, the EFA for the dichotomous ratings of symptom occurrence indicated that a five-factor solution was the best fit for the data. The number of symptoms within each cluster ranged from four to eight. The eight symptoms in Factor 1 (i.e., abdominal cramps, constipation, difficulty concentrating, feeling drowsy, lack of energy, nausea, sweats, vomiting) were named the “sickness behavior symptom cluster.” The four symptoms in Factor 2 (i.e., chest tightness, cough, difficulty breathing, shortness of breath) were named the “lung cancer-specific symptom cluster.” The seven symptoms in Factor 3 (i.e., difficulty concentrating, feeling bloated, feeling irritable, feeling nervous, feeling sad, problems with sexual interest or activity; worrying) were named the “psychological symptom cluster.” The four symptoms in Factor 4 (i.e., increased appetite, lack of appetite, weight gain, weight loss) were named the “nutritional symptom cluster.” Of note, increased appetite and weight gain loaded negatively on the nutritional symptom cluster, which indicates that lower scores on those symptoms (i.e., equivalent to decreased appetite and weight loss) were more likely to be present among patients with that symptom cluster. The four symptoms in Factor 5 (i.e., changes in skin, hair loss, “I do not look like myself,” mouth sores) were named the “epithelial symptom cluster.” Seven symptoms (i.e., dizziness, dry mouth, pain, swelling of arms or legs, change in the way food tastes, difficulty sleeping, numbness/tingling in the hands/feet) did not load on any factor.

Symptom Clusters Based on Symptom Severity

As shown in Table 3, the EFA for the ordinal ratings of symptom severity indicated that a five-factor solution was the best fit for the data. The number of symptoms within each cluster ranged from four to seventeen. The seventeen symptoms in Factor 1 were named the "sickness behavior symptom cluster." The five symptoms in Factor 2 (i.e., chest tightness, cough, difficulty breathing, shortness of breath, swelling of arms or legs) were named the "lung cancer-specific symptom cluster." The four symptoms in Factor 3 (i.e., increased appetite, lack of appetite, weight gain, weight loss) were named the "nutritional symptom cluster." Of note, increased appetite and weight gain loaded negatively on the nutritional symptom cluster. The four symptoms in Factor 4 (i.e., feeling irritable, feeling nervous, feeling sad, worrying) were named the "psychological symptom cluster." The four symptoms in Factor 5 (i.e., changes in skin, "I do not look like myself," mouth sores, swelling of arms or legs) were named the "epithelial symptom cluster." In this EFA, four symptoms (i.e., hair loss, change in the way food tastes, difficulty sleeping, numbness/tingling in the hands/feet) did not load on any factor.

Comparison of Symptom Clusters Based on Symptom Occurrence Versus Severity

While both of the EFAs identified the same five symptom clusters, the specific symptoms within each cluster varied (Table 4). The sickness behavior symptom cluster using occurrence included eight primarily physical symptoms (i.e., 47.1% agreement) while the cluster using severity included 17 physical and psychological symptoms (i.e., 100.0% agreement). The lung cancer-specific symptom cluster included four respiratory symptoms when occurrence ratings (i.e., 80% agreement) were used but included an additional symptom (i.e., swelling of arms or legs) when severity ratings were used (i.e., 100.0% agreement). In both EFAs, the nutritional symptom cluster included the same four symptoms (i.e., 100.0% agreement for both dimensions). The psychological symptom cluster included seven symptoms when occurrence ratings were used (i.e., 100.0% agreement) but only four of those symptoms when severity ratings were used (57.1% agreement). In both EFAs, the epithelial symptom clusters shared three out of four symptoms in common (i.e., changes in skin, "I do not look like myself," mouth sores) but the fourth symptom differed (i.e., 80.0% agreement on both dimensions). Hair loss was the fourth symptom in the cluster when occurrence ratings were used while swelling of arms or legs was the fourth symptom when severity ratings were used.

DISCUSSION

To our knowledge, this study is the first to evaluate for differences in symptom clusters using both ratings of symptom occurrence and severity in a sample of lung cancer patients receiving CTX. While the specific symptoms within each cluster varied, both approaches identified five similar symptom clusters. Therefore, our results support our hypothesis that the number and types of symptom clusters identified would be relatively similar using the two symptom dimensions of occurrence and severity.

Our results are consistent with prior studies that found similar symptom clusters using ratings of occurrence and severity in heterogeneous samples of cancer patients.[22,23] For

example, three similar symptom clusters (i.e., mood-cognitive, sickness-behavior, and treatment-related) were derived using occurrence and severity in a sample of breast and prostate cancer patients at the end of radiation.[22] Three similar symptom clusters (i.e., CTX sequela, mood disturbance, neuropsychological discomfort) were found using occurrence and severity in a sample of pediatric cancer patients during CTX.[23] In contrast, in a study of breast cancer patients during CTX,[24] while four symptom clusters were found using symptom severity (i.e., emotions related symptoms, GI and fatigue related symptoms, image related cutaneous symptoms, pain related discomfort symptoms), three different clusters were found using symptom distress (i.e., emotions and pain related symptoms, GI symptoms, image related cutaneous symptoms). We hypothesize that symptom occurrence and severity may assess more related dimensions of the symptom experience while severity and distress may assess distinct dimensions.[34] Additional research is needed that compares symptom clusters using severity versus distress and occurrence versus distress to better understand how clusters vary by different symptom dimensions.

In the current study, except for the nutritional symptom cluster, the number of symptoms within each cluster differed when ratings of symptom occurrence and severity were used. However, for three of the five symptom clusters identified (i.e., lung cancer specific, nutritional, epithelial), the 75% agreement criterion proposed by Kirkova and Walsh was met.[25] In addition, an evaluation of the factor loadings for the symptoms that were consistent within the sickness behavior and the psychological symptom clusters found that these symptoms had the highest weights in both EFAs.

Specifically, the EFA using severity ratings identified more than double the number of symptoms for the sickness behavior cluster (i.e., seventeen symptoms with severity compared to eight symptoms with occurrence), which added psychological symptoms such as feeling nervous, sad, and worrying to the symptom cluster. The inclusion of both physical and psychological symptoms within the sickness behavior symptom cluster is consistent with previous descriptions of sickness behavior.[46,47] While it will require confirmation in future studies, one potential explanation for the larger number of symptoms in the sickness behavior cluster that was identified using severity scores is that more subtle associations were found using the 4-point ordinal severity ratings than with the dichotomous occurrence ratings.

However, severity ratings did not consistently identify more symptoms in the other symptom clusters. The EFA using severity ratings identified fewer symptoms for the psychological symptom cluster (four symptoms with severity compared to seven symptoms with occurrence). This difference in the number of symptoms within each cluster depending on the symptom dimension used was seen in a study of symptom clusters in breast and prostate cancer patients at the end of radiation.[22] In that study, the EFA using severity ratings identified more symptoms in the sickness behavior symptom cluster and fewer symptoms in the mood-cognitive symptom cluster compared to the EFA using occurrence ratings. Additional research is warranted to determine which dimensions of the symptom experience should be used to identify symptom clusters.

When the symptom clusters identified in the current study of lung cancer patients receiving CTX are compared to the clusters identified in other studies of lung cancer patients, both similarities and differences are seen.[48] As in our study, a lung-cancer specific or respiratory symptom cluster were identified in studies of lung cancer patients with newly diagnosed[49] and advanced[15] disease. The feasibility of a multicomponent intervention to target a respiratory distress symptom cluster (i.e., breathlessness, cough, fatigue) in lung cancer patients was demonstrated[50] and a larger intervention trial is underway.

While prior studies identified a similar sickness behavior symptom cluster,[15,16,19] their names for this cluster varied (e.g., general symptom cluster). Our sickness behavior symptom cluster included nausea and vomiting, which was identified as a separate gastrointestinal symptom cluster in other lung cancer studies.[15,18,19] In the current study, nausea and vomiting may have loaded on the sickness behavior symptom cluster rather than on a separate cluster because of the timing of the symptom assessment one week after CTX administration when acute toxicity is at its peak.

A psychological or mood symptom cluster is common in studies of lung cancer patients[15,49] and other oncology patients.[51,52] Interestingly, in the current study, several psychological symptoms (i.e., feeling nervous, feeling sad, worrying) loaded on both the psychological and sickness behavior symptom clusters when severity ratings were used in the EFA. As noted above, the addition of these psychological symptoms to the sickness behavior symptom cluster is consistent with animal studies of sickness behavior (for reviews see 46, 53) and highlights the relationship between the severity of physical and psychological symptoms in lung cancer patients receiving CTX.

The nutritional symptom cluster in the current study was not identified as a separate symptom cluster in prior studies of lung cancer patients. In a study of older lung cancer patients after diagnosis that used the Physical Symptom Experience tool, loss of appetite and weight loss were part of a general symptom cluster (comparable to our sickness behavior symptom cluster) with fatigue, weakness, nausea, vomiting, and altered taste.[16] The lack of identification of a symptom cluster that included lack of appetite and weight loss in prior lung cancer studies may be related to the choice of symptom assessment instrument.[15,16,18,19] The MD Anderson Symptom Inventory[54] assesses lack of appetite but not weight loss while the Symptom Distress Inventory[55] does not assess either symptom.

Our epithelial symptom cluster includes CTX toxicities associated with different epithelial tissues including the skin, hair, and mucosa. Similar to the nutritional symptom cluster, the identification of an epithelial symptom cluster in prior lung cancer studies was limited by the choice of symptom instrument. To our knowledge, no other lung cancer study used the MSAS (which assesses multiple skin, hair, mouth, and appearance symptoms) to identify symptom clusters. However, when the MSAS was used in studies of patients with breast cancer,[24] ovarian cancer,[56] and a heterogeneous group of cancer diagnoses,[57] a similar epithelial symptom cluster was found. Further research is needed to confirm the presence of an epithelial cluster in lung cancer patients.

Several study limitations warrant consideration. This cross-sectional analysis only assessed symptoms at one time point during the course of treatment. Therefore, the stability of these five symptom clusters over time needs to be examined. While all patients were uniformly assessed one week after CTX administration, they were enrolled at various cycles during their treatment course. Symptom clusters by occurrence and severity may have varied if all patients were enrolled prior to the receipt of CTX. In addition, we were unable to use symptom distress, another important dimension of the symptom experience, to derive symptom clusters to compare with our results using occurrence and severity. When examining 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 symptom clusters by occurrence or severity could not be studied.

In conclusion, our study provides additional evidence that symptom clusters identified using symptom occurrence and severity are relatively similar in number and type in a sample of lung cancer patients receiving CTX. These symptom clusters highlight the importance of assessing a comprehensive list of symptoms in lung cancer patients. Once confirmed in future studies, these symptom clusters can be used to guide the design of multicomponent interventions to address multiple, related symptoms simultaneously to decrease the high symptom burden of lung cancer patients. For example, the presence of both physical and psychological symptoms in the sickness behavior cluster identified using severity ratings highlights the need to consider interventions that will address this complex group of symptoms. Future studies need to evaluate the stability of these symptom clusters over time.

Acknowledgments

This study was funded by a grant from the National Cancer Institute (R01CA134900). Dr. Miaskowski is an American Cancer Society Clinical Research Professor and is funded by a National Cancer Institute K05 award (K05CA168960). Dr. Wong is funded by the National Institute on Aging (T32AG000212).

References

1. Dodd MJ, Miaskowski C, Lee KA. Occurrence of symptom clusters. J Natl Cancer Inst Monogr. 2004:76–78. [PubMed: 15263044]
2. Kim HJ, McGuire DB, Tulman L, Barsevick AM. Symptom clusters: concept analysis and clinical implications for cancer nursing. Cancer Nurs. 2005; 28:270–282. [PubMed: 16046888]
3. Given B, Given C, Azzouz F, Stommel M. Physical functioning of elderly cancer patients prior to diagnosis and following initial treatment. Nurs Res. 2001; 50:222–232. [PubMed: 11480531]
4. Dodd MJ, Miaskowski C, Paul SM. Symptom clusters and their effect on the functional status of patients with cancer. Oncol Nurs Forum. 2001; 28:465–470. [PubMed: 11338755]
5. Dodd MJ, Cho MH, Cooper BA, Miaskowski C. The effect of symptom clusters on functional status and quality of life in women with breast cancer. Eur J Oncol Nurs. 2010; 14:101–10. [PubMed: 19897417]
6. Hwang KH, Cho OH, Yoo YS. Symptom clusters of ovarian cancer patients undergoing chemotherapy, and their emotional status and quality of life. Eur J Oncol Nurs. 2016; 21:215–222. [PubMed: 26645947]
7. Cheng KK, Lee DT. Effects of pain, fatigue, insomnia, and mood disturbance on functional status and quality of life of elderly patients with cancer. Crit Rev Oncol Hematol. 2011; 78:127–137. [PubMed: 20403706]

8. Dong ST, Costa DS, Butow PN, et al. Symptom clusters in advanced cancer patients: An empirical comparison of statistical methods and the impact on quality of life. J Pain Symptom Manage. 2016; 51:88–98. [PubMed: 26300025]
9. Fox SW, Lyon DE. Symptom clusters and quality of life in survivors of lung cancer. Oncol Nurs Forum. 2006; 33:931–936. [PubMed: 16955121]
10. Henoch I, Lovgren M. The influence of symptom clusters and the most distressing concerns regarding quality of life among patients with inoperable lung cancer. Eur J Oncol Nurs. 2014; 18:236–241. [PubMed: 24485014]
11. Lin S, Chen Y, Yang L, Zhou J. Pain, fatigue, disturbed sleep and distress comprised a symptom cluster that related to quality of life and functional status of lung cancer surgery patients. J Clin Nurs. 2013; 22:1281–1290. [PubMed: 23574291]
12. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016; 66:7–30. [PubMed: 26742998]
13. Silvoniemi M, Vasankari T, Loyttyniemi E, Valtonen M, Salminen E. Symptom assessment for patients with non-small cell lung cancer scheduled for chemotherapy. Anticancer Res. 2016; 36:4123–4128. [PubMed: 27466520]
14. Barbera L, Seow H, Howell D, et al. Symptom burden and performance status in a population-based cohort of ambulatory cancer patients. Cancer. 2010; 116:5767–5776. [PubMed: 21136579]
15. Sarna L, Brecht M-L. Dimensions of symptom distress in women with advanced lung cancer: A factor analysis. Heart & Lung. 1997; 26:23–30. [PubMed: 9013218]
16. Gift AG, Jablonski A, Stommel M, Given CW. Symptom clusters in elderly patients with lung cancer. Oncol Nurs Forum. 2004; 31:202–212. [PubMed: 15017438]
17. Wang D, Fu J. Symptom clusters and quality of life in China patients with lung cancer undergoing chemotherapy. Afr Health Sci. 2014; 14:49–55. [PubMed: 26060457]
18. Wang XS, Fairclough DL, Liao Z, et al. Longitudinal study of the relationship between chemoradiation therapy for non-small-cell lung cancer and patient symptoms. J Clin Oncol. 2006; 24:4485–4491. [PubMed: 16983118]
19. Wang SY, Tsai CM, Chen BC, Lin CH, Lin CC. Symptom clusters and relationships to symptom interference with daily life in Taiwanese lung cancer patients. J Pain Symptom Manage. 2008; 35:258–266. [PubMed: 18201865]
20. Miaskowski C. Future directions in symptom cluster research. Semin Oncol Nurs. 2016; 32:405–415. [PubMed: 27776833]
21. Miaskowski C, Barsevick A, Berger A, et al. Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. J Natl Cancer Inst. 2017; 109 Epub2017/01/06.
22. Kim E, Jahan T, Aouizerat BE, et al. Differences in symptom clusters identified using occurrence rates versus symptom severity ratings in patients at the end of radiation therapy. Cancer Nurs. 2009; 32:429–436. [PubMed: 19816162]
23. Baggott C, Cooper BA, Marina N, Matthay KK, Miaskowski C. Symptom cluster analyses based on symptom occurrence and severity ratings among pediatric oncology patients during myelosuppressive chemotherapy. Cancer Nurs. 2012; 35:19–28. [PubMed: 21921793]
24. Suwisith N, Hanucharurnkul S, Dodd M, et al. Symptom clusters and functional status of women with breast cancer. Thai J Nur Res. 2008; 12:153–165.
25. Kirkova J, Walsh D. Cancer symptom clusters--a dynamic construct. Support Care Cancer. 2007; 15:1011–1013. [PubMed: 17479300]
26. Miaskowski C, Cooper BA, Melisko M, et al. Disease and treatment characteristics do not predict symptom occurrence profiles in oncology outpatients receiving chemotherapy. Cancer. 2014; 120:2371–2378. [PubMed: 24797450]
27. Miaskowski C, Cooper BA, Aouizerat B, et al. The symptom phenotype of oncology outpatients remains relatively stable from prior to through 1 week following chemotherapy. Eur J Cancer Care (Engl). 2016
28. Karnofsky D, Abelmann WH, Craver LV, Burchenal JH. The use of nitrogen mustards in the palliative treatment of carcinoma. Cancer. 1948; 1:634–656.

29. Ando M, Ando Y, Hasegawa Y, et al. Prognostic value of performance status assessed by patients themselves, nurses, and oncologists in advanced non-small cell lung cancer. Br J Cancer. 2001; 85:1634–1639. [PubMed: 11742480]
30. Schnadig ID, Fromme EK, Loprinzi CL, et al. Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. Cancer. 2008; 113:2205–2214. [PubMed: 18780322]
31. Sangha O, Stucki G, Liang MH, Fossel AH, Katz JN. The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. Arthritis Rheum. 2003; 49:156–163. [PubMed: 12687505]
32. Brunner F, Bachmann LM, Weber U, et al. Complex regional pain syndrome 1--the Swiss cohort study. BMC Musculoskelet Disord. 2008; 9:92. [PubMed: 18573212]
33. Portenoy RK, Thaler HT, Kornblith AB, et al. The Memorial Symptom Assessment Scale-an instrument for the evaluation of symptom prevalence, characteristics and distress. Eur J Can. 1994; 30a:1326–1336.
34. Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res. 1994; 3:183–189. [PubMed: 7920492]
35. Muthen, LK., Muthen, BO. Mplus User's Guide (7th ed.). 7. Los Angeles, CA: Muthen & Muthen; 1998–2015.
36. Babor, TF., de la Fuente, JR., Saunders, J., Grant, M. AUDIT: The Alcohol Use Disorders Identification Test: Guidelines for Use in Primary Care. Geneva, Switzerland: World Health Organization; 1992.
37. Miaskowski C, Dodd M, Lee K. Symptom clusters: the new frontier in symptom management research. J Natl Cancer Inst. 2004:17–21.
38. Berner MM, Kriston L, Bentele M, Harter M. The alcohol use disorders identification test for detecting at-risk drinking: a systematic review and meta-analysis. J Stud Alcohol Drugs. 2007; 68:461–473. [PubMed: 17446987]
39. Portenoy RK, Thaler HT, Kornblith AB, et al. Symptom prevalence, characteristics and distress in a cancer population. Qual Life Res. 1994; 3:183–189. [PubMed: 7920492]
40. SPSS. IBM SPSS for Windows (Version 23). Armonk, NY: SPSS, Inc.; 2015.
41. StataCorp. Stata Statistical Software: Release 14, College Station. Texas: Stata Corporation; 2015.
42. Muthen BO. Dichotomous Factor-Analysis of Symptom Data. Sociological Methods & Research. 1989; 18:19–65.
43. Miaskowski C, Aouizerat BE, Dodd M, Cooper B. Conceptual issues in symptom clusters research and their implications for quality-of-life assessment in patients with cancer. J Natl Cancer Inst. 2007; 37:39–46.
44. Brown, TA. The common factor model and exploratory factor analysis. 2. London: The Guilford Press; 2015.
45. Wong ML, Paul SM, Cooper BA, et al. Predictors of the multidimensional symptom experience of lung cancer patients receiving chemotherapy. Support Care Cancer. In press.
46. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci. 2008; 9:46–56. [PubMed: 18073775]
47. McCusker RH, Kelley KW. Immune-neural connections: how the immune system's response to infectious agents influences behavior. J Exp Biol. 2013; 216:84–98. [PubMed: 23225871]
48. Chen E, Nguyen J, Cramarossa G, et al. Symptom clusters in patients with lung cancer: a literature review. Expert Rev Pharmacoecon Outcomes Res. 2011; 11:433–439. [PubMed: 21831024]
49. Henoch I, Ploner A, Tishelman C. Increasing stringency in symptom cluster research: a methodological exploration of symptom clusters in patients with inoperable lung cancer. Oncol Nurs Forum. 2009; 36:E282–292. [PubMed: 19887341]
50. Yorke J, Lloyd-Williams M, Smith J, et al. Management of the respiratory distress symptom cluster in lung cancer: a randomised controlled feasibility trial. Support Care Cancer. 2015; 23:3373–3384. [PubMed: 26111954]

51. Dong ST, Butow PN, Costa DS, Lovell MR, Agar M. Symptom clusters in patients with advanced cancer: a systematic review of observational studies. J Pain Symptom Manage. 2014; 48:411–450. [PubMed: 24703941]

52. Fan G, Filipczak L, Chow E. Symptom clusters in cancer patients: a review of the literature. Curr Oncol. 2007; 14:173–179. [PubMed: 17938700]

53. Dantzer R, Kelley KW. Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun. 2007; 21:153–160. [PubMed: 17088043]

54. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the MD Anderson Symptom Inventory. Cancer. 2000; 89:1634–1646. [PubMed: 11013380]

55. McCorkle R, Young K. Development of a symptom distress scale. Cancer Nurs. 1978; 1:373–378. [PubMed: 250445]

56. Huang J, Gu L, Zhang L, et al. Symptom clusters in ovarian cancer patients with chemotherapy after surgery: A longitudinal survey. Cancer Nurs. 2016; 39:106–116. [PubMed: 25837811]

57. Molassiotis A, Wengstrom Y, Kearney N. Symptom cluster patterns during the first year after diagnosis with cancer. J Pain Symptom Manage. 2010; 39:847–858. [PubMed: 20226621]

Table 1

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

Characteristic	No. (%)
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	

Characteristic	No. (%)
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 **symptom occurrence** ratings one week after chemotherapy administration (N = 145 lung cancer patients).

Symptom[b]	Factor 1 Sickness Behavior Symptom Cluster	Factor 2 Lung Cancer-Specific Symptom Cluster	Factor 3 Psychological Symptom Cluster	Factor 4 Nutritional Symptom Cluster	Factor 5 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**

Symptom[b]	Factor 1 Sickness Behavior Symptom Cluster	Factor 2 Lung Cancer-Specific Symptom Cluster	Factor 3 Psychological Symptom Cluster	Factor 4 Nutritional Symptom Cluster	Factor 5 Epithelial Symptom Cluster
"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 3

Exploratory factory analysis[a] using ratings of **symptom severity** one week after chemotherapy administration (N = 145 lung cancer patients).

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

J Pain Symptom Manage. Author manuscript; available in PMC 2018 August 01.

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
"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.

J Pain Symptom Manage. Author manuscript; available in PMC 2018 August 01.

Table 4

Comparison of symptoms within each cluster by ratings of symptom occurrence versus severity.

Symptom Cluster	Symptom	Occurrence Factor Loadings	Severity Factor Loadings
Sickness Behavior	Abdominal cramps	0.560	0.572
	Constipation	0.438	0.441
	Difficulty concentrating[a]	0.498	0.509
	Feeling drowsy	0.768	0.667
	Lack of energy	0.766	0.775
	Nausea	0.869	0.709
	Sweats	0.416	0.629
	Vomiting	0.600	0.543
	Feeling bloated		0.430
	Feeling nervous[b]		0.429
	Feeling sad[b]		0.408
	Problems with sexual interest or activity		0.555
	Worrying[b]		0.482
	Dizziness		0.489
	Dry mouth		0.407
	Pain		0.432
	Swelling of arms or legs[b]		−0.453
	Percent agreement	47.1%	100.0%
Lung Cancer-Specific	Chest tightness	0.601	0.643
	Cough	0.608	0.670
	Difficulty breathing	0.934	0.948
	Shortness of breath	0.900	0.806
	Swelling of arms or legs[b]		0.438
	Percent agreement	80.0%	100.0%
Nutritional	Increased appetite	−0.841	−0.845
	Lack of appetite	0.709	0.723
	Weight gain	−0.867	−0.843
	Weight loss	0.526	0.524
	Percent agreement	100.0%	100.0%
Psychological	Difficulty concentrating[a]	0.445	
	Feeling bloated	0.433	
	Feeling irritable	0.803	0.674
	Feeling nervous[b]	0.663	0.469
	Feeling sad[b]	0.571	0.653
	Problems with sexual interest or activity	0.526	

Symptom Cluster	Symptom	Occurrence Factor Loadings	Severity Factor Loadings
	Worrying[b]	0.744	0.668
	Percent agreement	100.0%	57.1%
Epithelial	Changes in skin	0.795	0.889
	Hair loss	0.428	
	“I do not look like myself”	0.693	0.752
	Mouth sores	0.643	0.535
	Swelling of arms or legs[b]		0.448
	Percent agreement	80.0%	80.0%

[a]Symptom that loaded on more than one symptom cluster in the EFA using ratings of symptom occurrence.

[b]Symptoms that loaded on more than one symptom cluster in the EFA using ratings of symptom severity.