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Stability of Symptom Clusters in Patients with Gastrointestinal Cancers Receiving Chemotherapy

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Abstract

Context—Limited evidence suggests that patients with gastrointestinal (GI) cancers receiving chemotherapy (CTX) experience an average of thirteen co-occurring symptoms. An alternative to counting symptoms is to evaluate for symptom clusters.

Objectives—In a sample of patients with GI cancers receiving CTX (n=399), we evaluated the occurrence, severity, and distress of 38 symptoms in the week prior to patients' second or third cycle of CTX (Time 1 [T1]), approximately one week after CTX (Time 2 [T2]), and approximately two weeks after CTX (Time 3 [T3]); evaluated for differences in the number and types of symptom clusters at each of these three assessments using ratings of occurrence, severity and distress; and evaluated for changes in symptom clusters over time.

Methods—Modified version of the Memorial Symptom Assessment Scale collected data on 38 common symptoms. Exploratory factor analyses were used to create the symptom clusters.

Results—Five distinct symptom clusters were identified across the three symptom dimensions and the three assessments (i.e., psychological, CTX-related, weight change, GI, and epithelial). Psychological, CTX-related, and weight change clusters were relatively stable across all three symptom dimensions and time. Across all three symptom dimensions, GI cluster was identified only at T1 and epithelial cluster was identified at T2 and T3.

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Conclusion—The number and types of symptom clusters appear to be relatively stable over time and across the symptom dimensions. Ongoing assessment and management of these clusters is warranted across the entire course of CTX. The underlying mechanism for these clusters warrants investigation.

Keywords

symptoms; symptom clusters; gastrointestinal cancer; chemotherapy; occurrence; severity; distress

INTRODUCTION

In the United States, gastrointestinal (GI) cancers have the third highest incidence in both men and women and are the second leading cause of cancer deaths.[1] Most patients with GI cancers receive chemotherapy (CTX) as their primary treatment.[2,3] Both the cancer itself and its treatment lead to multiple co-occurring symptoms[4] and associated decrements in patients' quality of life (QOL).[5]

An alternative to counting the number of co-occurring symptoms is to evaluate for symptom clusters. In a recent review,[5] a determination of the congruence in the number and types of symptom clusters using different symptom dimensions (e.g., occurrence, severity, distress) and an evaluation of the stability of symptom clusters over time were identified as high priority areas for research.

Only six cross-sectional studies focused on symptom clusters in patients with GI cancers.[6–11] Two of them evaluated patients with pancreatic cancer,[6,11] two evaluated patients with hepatocellular carcinoma,[7,8] one evaluated patients with esophageal cancer,[9] and one compared symptom clusters in younger versus older survivors with colorectal cancer.[10] Because the instruments used to create the symptom clusters varied, no common symptom cluster was identified across these six studies. In contrast, in our recent cross-sectional study that evaluated symptom clusters in patients with a variety of GI cancers,[12] four symptom clusters were identified (i.e., psychological, CTX-related, GI, and weight change) and the numbers and types of symptom clusters were relatively similar across the three symptom dimensions used to create the symptom clusters (i.e., occurrence, severity, distress).

While no studies were identified that evaluated for changes in symptom clusters in patients with GI cancers, in patients with breast,[13–15] lung,[16,17] and ovarian[18] cancers, symptom clusters appear to remain relatively stable over time. Therefore, in this analysis, that builds on our previous study of patients with GI cancers receiving CTX (n=399),[12] we evaluated the occurrence, severity, and distress of 38 symptoms in the week prior to patients' second or third cycle of CTX (Time 1 [T1]), approximately one week after CTX (Time 2 [T2]), and approximately two weeks after CTX (Time 3 [T3]); evaluated for differences in the number and types of symptom clusters at each of these assessments using ratings of occurrence, severity and distress; and evaluated for changes in the symptom clusters over time.

METHODS

Patients and Settings

This analysis is part of a larger study, that evaluated the symptom experience of oncology outpatients receiving CTX f.[19] In brief, patients were ≥18 years of age; had a diagnosis of breast, lung, GI, or gynecological cancer; had received CTX within the preceding four weeks; were scheduled to receive at least two additional cycles of CTX; were able to read, write, and understand English; and gave written informed consent. Patients were recruited from two Comprehensive Cancer Centers, one Veteran's Affairs hospital, and four community-based oncology programs. For this analysis, from a total sample of 1,343 patients, 399 patients with GI cancers (e.g., colon, rectal, esophagus, stomach) were evaluated. Patients were recruited from 2010 to 2015.

Procedures

Patients were approached in the infusion unit, during their first and second cycle of CTX, to discuss participation in the study. After written informed consent was obtained, patients completed questionnaires in their home a total of 6 times over two cycles of CTX. The symptom assessment data from the first three assessments (i.e., T1 (i.e., recovery from previous cycle), T2 (i.e., acute symptoms), T3 (i.e., potential nadir)) were used in these analyses. Medical records were reviewed for disease and treatment information. The parent study was approved by the Committee on Human Research at the University of California, San Francisco and by each sites' Institutional Review Board at each of the study sites.

Instruments

Patients completed a demographic questionnaire, Karnofsky Performance Status (KPS) scale,[20] and Self-Administered Comorbidity Questionnaire (SCQ).[21] The total SCQ score ranges from 0 to 39.[22,23]

A modified version of the 32-item Memorial Symptom Assessment Scale (MSAS)[24] was used to evaluate 38 symptoms commonly associated with cancer and its treatment. Six additional symptoms were assessed: hot flashes, chest tightness, difficulty breathing, abdominal cramps, increased appetite, and weight gain. Patients were asked to indicate whether they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its severity and distress. Severity was rated using a 4-point Likert scale (i.e., 1 = slight, 2 = moderate, 3 = severe, 4 = very severe). Distress was rated using a 5-point Likert scale (i.e., 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much). The validity and reliability of the MSAS is well established.[24]

Data Analyses

Data were analyzed using the Statistical Package for the Social Sciences Version 23,[25] STATA Release 15,[26] and MPlus Version 7.3.[27] Descriptive statistics and frequency distributions were calculated for the demographic and clinical characteristics and for symptom occurrence, severity, and distress ratings.

To identify the symptom clusters, exploratory factor analyses (EFAs) were done for the dichotomous (i.e., occurrence) and ordinal (i.e., severity and distress) items using MPlus.[27] For the EFAs, factors were considered to be adequately defined if at least two items (i.e., symptoms) had loadings of ≥0.40.(28) Items that loaded on two factors (i.e., cross loaded) were retained and used to define both factors (i.e., symptom clusters).[28–30]

In order to have sufficient variation and covariation to perform the EFAs, only symptoms that were present in >20% and <80% of the patients at T1, were included in these analyses. Based on these criteria, 29 out of the 38 MSAS symptoms were used. The nine symptoms excluded were: hot flashes, shortness of breath, mouth sores, chest tightness, difficulty breathing, swelling of arms or legs, difficulty swallowing, problems with urination, and vomiting.

For the EFAs using the dichotomous occurrence items, tetrachoric correlations were used to create the matrix of associations.[27] For the EFAs using the ordinal severity and distress ratings, polychoric correlations were used to create the matrix of associations. The simple structure for the occurrence, severity, and distress EFAs was estimated using the method of unweighted least squares with geomin (i.e., oblique) rotation.[27]

The EFAs for severity were done using severity ratings that included a zero (i.e., 0, 1, 2, 3, 4). If the patient indicated that they did not have the symptom (i.e., occurrence), a severity score of zero was assigned. The EFAs for distress were done using distress ratings that included a 0 (did not have the symptom) and the original ratings shifted from 1 (not at all) to 5 (very much). When the initial EFA analyses were done using severity and distress ratings that did not include zero, the pairwise missingness was over 90% and the estimation failed to converge.

Factor solutions were estimated for two through six factors. After examining all of the 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 factor solution was examined to determine a clinically appropriate name for the symptom cluster. The name of the symptom cluster was based on the majority of the symptoms in the cluster.

Differences in number and types of symptom clusters

To evaluate the agreement among the symptoms within the same cluster using occurrence, severity, and distress ratings, within and across each assessment, we used the criteria proposed by Kirkova and Walsh.[31] These authors 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 most important symptom, namely the symptom with the greatest weight from the factor analyses.

RESULTS

Demographic and Clinical Characteristics

Of the total sample (n=399), 54.9% were male, 63.2% were married or partnered, 68.7% were White, and had a mean age of 57.9 (±11.8) years. Patients had an average of 2.3 (±1.3) comorbid condition and a KPS score of 80.7 ((±12.5), Table 1).[12]

Symptom Characteristics

Mean number of symptoms was 13.0 (±7.1) at T1, 12.5 (±6.7) at T2, and 11.1 (±6.1) at T3 (Table 1). The occurrence, severity, and distress ratings for each symptom at each assessment are listed in Table 2. As shown in Supplementary Table 1 (ST1), across the three assessments, lack of energy, numbness/tingling in hands/feet, difficulty sleeping, pain, and feeling drowsy were the five symptoms with the highest occurrence rates. In patients who reported the symptoms, the five most severe symptoms were: problems with sexual interest or activity, change in the way food tastes, lack of energy, difficulty sleeping, and constipation. In terms of symptoms with the highest distress ratings, lack of energy was the only consistent symptom across the three assessments.

Symptom Clusters Based on Occurrence Ratings

For the T1 assessment, four symptom clusters were identified (Table 3, ST2).[12] Factor 1 with eight symptoms was named the psychological cluster. Factor 2 with eight symptoms was named the CTX-related cluster. Factor 3 with three symptoms was named the GI cluster. Factor 4 with two symptoms was named the weight change cluster. For the T2 assessment, four symptom clusters were identified (Table 3, ST3). Factor 1 with eight symptoms was named the psychological cluster. Factor 2 with twelve symptoms was named the CTX-related cluster. Factor 3 with three symptoms was named the weight change cluster. Of note, lack of appetite loaded negatively on the weight change symptom cluster, which indicates that lower scores on this symptom (i.e., increased appetite) were more likely to be present among patients with this symptom cluster. Factor 4 with three symptoms was named the epithelial cluster. For the T3 assessment, four symptom clusters were identified (Table 3, ST4). Factor 1 with eight symptoms was named the psychological cluster. Factor 2 with ten symptoms was named the CTX-related cluster. Factor 3 with two symptoms was named the weight change cluster. Factor 4 with three symptoms was named the epithelial cluster.

Symptom Clusters Based on Symptom Severity

For the T1 assessment, four symptom clusters were identified (Table 3, ST5).[12] Factor 1 with eight symptoms was named the psychological cluster. Factor 2 with eight symptoms was named the CTX-related cluster. Factor 3 with four symptoms was named the GI cluster. Factor 4 with two symptoms was named the weight change cluster. For the T2 assessment, four symptom clusters were identified (Table 3, ST6). Factor 1 with seven symptoms was named the psychological cluster. Factor 2 with thirteen symptoms was named the CTX-related cluster. Factor 3 with four symptoms was named the weight change cluster. Weight loss and lack of appetite loaded negatively on the weight change symptom cluster, which indicates that lower scores on this symptom (i.e., increased appetite and weight gain) were

more likely to be present among patients with this symptom cluster. Factor 4 with four symptoms was named the epithelial cluster. For the T3 assessment, four symptom clusters were identified (Table 3, ST7). Factor 1 with seven symptoms was named the psychological cluster. Factor 2 with twelve symptoms was named the CTX-related cluster. Factor 3 with four symptoms was named the weight change cluster. Factor 4 with three symptoms was named the epithelial cluster.

Symptom Clusters Based on Symptom Distress

For the T1 assessment, four symptom clusters were identified (Table 3, ST8).[12] Factor 1 with ten symptoms was named the psychological cluster. Factor 2 with eight symptoms was named the CTX-related cluster. Factor 3 with two symptoms was named the weight change cluster. Factor 4 with two symptoms was named the GI cluster. For the T2 assessment, four symptom clusters were identified (Table 3, ST9). Factor 1 with eight symptoms was named the psychological cluster. Factor 2 with ten symptoms was named the CTX-related cluster. Factor 3 with two symptoms was named the weight change cluster. Factor 4 with four symptoms was named the epithelial cluster. For the T3 assessment, four symptom clusters were identified (Table 3, ST10). Factor 1 with nine symptoms was named the psychological cluster. Factor 2 with nine symptoms was named the CTX-related cluster. Factor 3 with four symptoms was named the weight change cluster. Factor 4 with three symptoms was named the epithelial cluster.

Similarities and Differences in the Number and Types of Symptom Clusters

Across all three symptom dimensions and assessments, the number of symptom clusters identified was four. As summarized in Table 4, the psychological, CTX-related, and weight change clusters were found across all three symptom dimensions and time points. The GI cluster was identified across all three dimensions but only at T1. The epithelial cluster was found across all three dimensions but only at T2 and T3.

Agreement in the Types of Symptoms Within Each Symptom Cluster

The specific symptoms within each cluster were relatively stable over time (Table 4). For the psychological cluster, the total number of symptoms ranged from 7 to 10 and the percent agreement ranged from 50.0% to 71.4%. The six symptoms that were included in all nine EFAs were: lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, and feeling irritable. For the CTX-related cluster, the total number of symptoms ranged from 8 to 13 and the percent agreement ranged from 44.4% to 72.2%. The three symptoms that were included in all nine EFAs were: lack of appetite, weight loss and change in the way food tastes. For the weight change symptom cluster, the total number of symptoms ranged from 2 to 4 and the percent agreement ranged from 50.0% to 100%. The two symptoms that were included in all nine EFAs were: increased appetite and weight gain. For the epithelial symptom cluster, the total number of symptoms ranged from 0 to 4 and the percent agreement ranged from 0.0% to 80.0%. None of the symptoms were found across all nine EFAs. However, changes in skin was included in the T2 and T3 EFAs for all three symptom dimensions. Itching and “I don’t like myself” were included in two of the severity and distress EFAs (i.e., T2 and T3). For the GI symptom cluster, the total number of symptoms ranged from 0 to 4 and the percent agreement ranged from 0.0% to 80.0%. None of the

symptoms were found across all nine EFAs. At the T1 assessment, the only symptom that was included across all three symptom dimensions was abdominal cramps.

DISCUSSION

This study is the first to provide detailed information on the occurrence, severity, and distress of 38 common symptoms over a cycle of CTX and to evaluate for changes in the number and types of symptom clusters using occurrence, severity, distress ratings in patients with GI cancers. Similar to previous studies that used the MSAS,[15,18] lack of energy, sleep disturbance, and pain were the most common symptoms in our patients. In terms of severity, problems with sexual interest or activity, which was reported by 27.1% of our sample, had the highest severity ratings across all three assessments ranging from 2.39 to 2.49. In addition, at T2 and T3, this symptom had the highest distress ratings. Given the growing evidence on sexual dysfunction in patients with GI cancers,[32–35] clinicians need to assess for this symptom and initiate appropriate referrals.

While across the three symptom dimensions and the three assessments, five distinct symptom clusters were identified, three of them (i.e., psychological, CTX-related, and weight change) were relatively stable across symptom dimensions and across time. The other two clusters (i.e., GI, epithelial) varied by time but not by symptom dimensions. Overall, our findings suggest that the majority of the symptom clusters remain relatively stable over time. The remainder of the discussion describes each of these symptom clusters.

Psychological Symptom Cluster

While the number of symptoms in the psychological cluster ranged from seven to ten, lack of energy, difficulty concentrating, feeling nervous, feeling sad, worrying, and feeling irritable were included in all nine EFAs. This cluster was identified in only three of the six studies of symptom clusters in patients with GI cancers[8,10,11] and anxiety and depression were the only two consistent symptoms. This inconsistent finding may be related to the lack of psychological symptoms on the instruments used in the previous studies.

However, in numerous studies of patients with breast[13,36,37] lung,[17,38,39] and heterogeneous cancer diagnoses,[8,18,40–44] psychological or mood-related clusters were identified. Similar to our study, feeling nervous, worrying, and feeling sad were common symptoms in the psychological cluster in previous studies that used the MSAS (breast,[13,15,36] lung,[17,39] ovarian,[18,41] heterogeneous cancers[40,42,44]). In addition, feeling irritable was included in this cluster in seven studies.[13,15,17,18,36,39,42] Taken together, these findings suggest the relative importance of assessing for psychological symptoms across cancer diagnoses and initiating appropriate interventions.

While lack of energy loaded on all nine EFAs in our study, it did not load on the psychological cluster in any of the aforementioned studies.[13,15,17,18,36,39–42,44,45] However, and consistent with previous reports,[17,39] lack of energy cross-loaded on our CTX-related cluster. Given that lack of energy was the most common, severe, and distressing symptom among our patients, as well as its association with anemia, disease-related digestive

hemorrhage, and poorer nutritional status in patients with colorectal cancer,[46] this symptom warrants ongoing assessment and appropriate management.

CTX-related Symptom Cluster

While not identified in patients with GI cancers,[6–11] the CTX-related cluster was found in previous studies that used the MSAS (i.e., CTX-neuropathy, sickness behaviors, treatment-related, CTX toxicity) in patients with breast,[15] lung,[17,39] and heterogeneous cancer diagnoses.[42] Across these studies,[15,17,39,42] feeling drowsy, pain, dizziness, lack of energy, nausea, and dry mouth were the common symptoms in this cluster. In our study, this cluster included three additional symptoms (i.e., lack of appetite, weight loss, change in the way food tastes) that were present in all nine EFAs. Of note, at the T1 assessment, these three symptoms were reported by 30.1% (weight loss), 44.1% (lack of appetite), and 49.9% (change in the way food tastes) of the patients. The loading of these symptoms on the CTX-related cluster may be partially explained by the fact that patients with GI cancers often receive oxaliplatin, 5-fluouracil, and/or irinotecan containing regimens[47,48] that are associated with significant GI toxicity.[49]

Weight Change Symptom Cluster

While none of the previous studies of patients with GI cancers identified a weight change cluster,[6–11] this cluster was identified in a study of patients with breast cancer receiving CTX.[15] In previous studies that used the mSAS,[13,17,18,36,39,41,42,50] weight loss was included in GI or nutritional clusters. In our weight change cluster, that included weight loss, weight gain, and lack of appetite, weight loss negatively loaded in this cluster. However, lack of appetite and weight loss cross-loaded on the CTX-related cluster. Taken together, these findings suggest that inter-individual variability exists in appetite changes and weight management in patients with GI cancers undergoing CTX. Given that a 10% loss[51,52] or gain[53] in pretreatment weight is associated with increased mortality in cancer patients, clinicians should monitor for these symptoms and refer patients for nutritional counseling.

GI Symptom Cluster

The GI cluster was identified across all three dimensions but only at T1. Abdominal cramps was the only consistent symptom in this cluster. While three studies of patients with GI cancers,[7,8,11] identified this cluster, the specific symptoms in this cluster included: diarrhea, [7,11] nausea,[8] abdominal cramps, and feeling bloated.[7] While a GI cluster is one of the most common symptom clusters identified in other cancer diagnoses (e.g., breast,[13,36,37] lung, [44,54] ovarian,[18,41] heterogeneous cancer diagnoses[40,42,50,55]), the specific symptoms within this cluster are extremely variable.

An interesting finding in our analysis is that all of the symptoms in the GI cluster (i.e., feeling bloated, abdominal cramps, constipation, nausea, diarrhea) loaded on the CTX-related cluster at T2 and T3. This finding suggests that these symptoms may be more strongly associated with CTX-related adverse effects during the two weeks following the administration of CTX (i.e., more acute symptoms). A similar shift in GI symptoms between clusters was observed in a study of patients with breast cancer.[14] Additional research is

warranted to determine why specific symptoms may load on different clusters across the continuum of cancer treatment.

Epithelial Symptom Cluster

The epithelial cluster was found across all three dimensions, but only at T2 and T3. While none of the previous studies of patients with GI cancers identified this specific cluster,[6–11] some of individual symptoms were included in other symptom clusters. For example, change in the way food tastes was included in a gustatory[11] and a pain-appetite[7] cluster. Itching was included in an itching-constipation cluster.[7] In two of our previous studies of patients with breast[15] and lung cancer,[17] this symptom cluster was identified, In other MSAS studies, the common symptoms, namely: "I don't look like myself",[13,18,36,42,50] hair loss,[13,18,36,42,50] and changes in skin[13,36,42,50] loaded on a similar symptom cluster (e.g., body image cluster[18]). Changes in body image associated with the adverse effects of CTX are well documented.[56,57] In addition, patients with GI cancers may face specific body image changes associated with various surgical procedures,[58,59] as well as skin toxicities associated with the administration of targeted therapies.[60,61]

Several limitations need to be considered. Because this study evaluated symptom clusters in patients undergoing CTX, these symptom clusters may not generalize to other types of cancer treatments (e.g., radiation, surgery). The heterogeneity in the GI cancer diagnoses and CTX agents administered may influence the composition of the symptom clusters. Given that we assessed for symptom clusters over only one cycle of CTX, the variability in symptom clusters over additional cycles of CTX warrant investigation.

Our study is the first to provide detailed information on the occurrence, severity, and distress of 38 common symptoms and changes in symptom clusters over time in a relatively large sample of patients with GI cancers. Our findings suggest that four clusters (i.e., psychological distress, CTX-related, weight change) were relatively stable across time and symptom dimensions. While the other two clusters (i.e., GI, and epithelial) were relatively stable across dimensions, they were not present at all three assessments. Additional studies are needed to confirm our findings and evaluate for underlying mechanisms associated with each of these clusters.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographic and Clinical Characteristics of Patients with Gastrointestinal Cancers (n=399)

Characteristic	Mean	(SD)
Age (years)	57.9	(11.8)
Education (years)	16.0	(3.0)
Body mass index (kilograms/metered squared)	25.8	(5.3)
Karnofsky Performance Status score	80.7	(12.5)
Number of comorbidities out of 13	2.3	(1.3)
Self-administered Comorbidity Questionnaire score	5.4	(2.9)
Time since cancer diagnosis (years)	1.4	(2.8)
Time since diagnosis (median)	0.4	
Number of prior cancer treatments (out of 9)	1.4	(1.3)
Number of metastatic sites including lymph node involvement (out of 9)	1.5	(1.1)
Number of metastatic sites excluding lymph node involvement (out of 8)	0.9	(1.0)
Mean number of MSAS symptoms (out of 38)		
Time 1 - Prior to the initiation of the second or third cycle of CTX	13.0	(7.1)
Time 2 – Approximately one week after CTX	12.5	(6.7)
Time 3 – Approximately two weeks after CTX	11.1	(6.2)
	n	%
Gender		
Female	180	(45.1)
Male	219	(54.9)
Ethnicity		
White	274	(68.7)
Black	36	(9.0)
Asian or Pacific Islander	46	(11.5)
Hispanic, Mixed, or Other	43	(10.8)
Married or partnered (% yes)	252	(63.2)
Lives alone (% yes)	74	(18.5)
Child care responsibilities (% yes)	81	(20.3)
Care of adult responsibilities (% yes)	27	(6.8)
Currently employed (% yes)	133	(33.3)
Income		
< $30,000	73	(18.4)
$30,000 to < $70,000	69	(17.4)
$70,000 to < $100,000	61	(15.3)
> $100,000	155	(38.8)
Exercise on a regular basis (% yes)	263	(65.9)
Current or history of smoking (% yes)	122	(30.6)
Receiving neoadjuvant chemotherapy (% yes)	34	(8.5)

Type of prior cancer treatment		
No prior treatment	113	(28.3)
Only surgery, CTX, or RT	149	(37.3)
Surgery & CTX, or surgery & RT, or CTX & RT	85	(21.3)
Surgery & CTX & RT	42	(10.5)
Gastrointestinal cancer diagnoses		
Colon	185	(46.4)
Rectal	80	(20.1)
Pancreatic	74	(18.5)
Esophageal	21	(5.3)
Gastric	19	(4.8)
Gall blander/bile duct	10	(2.5)
Liver	6	(1.5)
Small intestine	6	(1.5)
Anal	5	(1.3)
Other	25	(6.3)

Abbreviations: CTX = chemotherapy; MSAS = Memorial Symptom Assessment Scale, RT = radiation therapy, SD = standard deviation

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Table 2.

Occurrence Rates and Severity and Distress Ratings for Symptoms Over One Cycle of Chemotherapy

Symptoms[a]	Occurrence Rates % (n)			Severity Ratings with zeros[b] Mean (SD)			Severity Ratings without zeros[c] Mean (SD)			Distress Ratings[d] Mean (SD)		
	Time 1*	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
Lack of energy	79.7 (318)	76.2 (304)	67.2 (268)	1.62 (1.0)	1.73 (1.1)	1.48 (1.1)	2.03 (0.7)	2.06 (0.7)	2.05 (0.7)	1.72 (1.1)	1.88 (1.0)	1.71 (1.1)
Numbness/tingling in hands/feet	62.2 (248)	63.4 (253)	54.4 (217)	1.20 (1.1)	1.31 (1.2)	1.11 (1.1)	1.95 (0.8)	1.99 (0.8)	1.90 (0.8)	1.62 (1.1)	1.63 (1.1)	1.47 (1.1)
Difficulty sleeping	60.7 (242)	56.6 (226)	55.1 (220)	1.21 (1.1)	1.17 (1.1)	1.15 (1.1)	1.99 (0.7)	1.98 (0.7)	1.94 (0.7)	1.73 (1.3)	1.70 (1.0)	1.57 (1.0)
Pain	59.4 (237)	52.4 (209)	50.6 (202)	1.12 (1.1)	1.05 (1.1)	1.06 (1.2)	1.90 (0.7)	1.93 (0.7)	1.97 (0.7)	1.72 (1.1)	1.79 (1.0)	1.75 (1.1)
Feeling drowsy	57.1 (228)	56.6 (226)	46.9 (187)	1.01 (1.0)	1.06 (1.0)	0.87 (0.9)	1.78 (0.7)	1.82 (0.6)	1.74 (0.6)	1.14 (1.0)	1.22 (1.0)	1.13 (1.0)
Nausea	50.9 (203)	55.1 (220)	43.1(172)	0.90 (1.1)	1.05 (1.1)	0.78 (0.9)	1.81 (0.7)	1.84(0.8)	1.71 (0.7)	1.68 (1.1)	1.70 (1.0)	1.52 (1.0)
Change in the way food tastes	49.9 (199)	47.1 (188)	39.8 (159)	1.05 (1.2)	1.04 (1.2)	0.80 (1.1) (	2.10 (0.8)	2.12 (0.8)	1.92 (0.8)	1.61 (1.2)	1.77 (1.2)	1.54 (1.2)
Worrying	47.1 (188)	36.6 (146)	35.1(140)	0.85 (1.0)	0.69 (0.9)	0.67 (0.9)	1.82 (0.7)	1.81 (0.6)	1.76 (0.7)	1.52 (0.9)	1.63 (1.0)	1.46 (0.9)
Difficulty concentrating	44.6 (178)	43.9 (175)	39.3 (157)	0.69 (0.9)	0.71 (0.8)	0.66 (0.9)	1.56 (0.6)	1.55 (0.6)	1.59 (0.6)	1.49 (1.0)	1.43 (0.9)	1.33 (0.8)
Dry mouth	44.4 (177)	38.1 (152)	31.8 (127)	0.77 (1.0)	0.70 (0.9)	0.57 (0.9)	1.75 (0.7)	1.79 (0.7)	1.71 (0.7)	1.20 (1.2)	1.14 (1.0)	1.14 (1.1)
Lack of appetite	44.1 (176)	46.4 (185)	36.3 (145)	0.88 (0.8)	0.96 (1.1)	0.78 (1.1)	1.98 (0.8)	2.01 (0.7)	2.01 (0.8)	1.42 (1.0)	1.50 (1.1)	1.22 (0.9)
Constipation	43.9 (175)	39.1 (156)	29.3 (117)	0.87 (1.1)	0.80 (1.1)	0.61 (1.0)	1.99 (0.8)	1.96 (0.7)	1.96 (0.8)	1.67 (1.2)	1.66 (1.1)	1.60 (1.1)
Feeling sad	40.9 (163)	33.3 (133)	29.1 (116)	0.69 (0.9)	0.58 (0.8)	0.53 (0.8)	1.69 (0.6)	1.69 (0.6)	1.71 (0.7)	1.37 (1.0)	1.54 (1.0)	1.48 (0.9)
Hair loss	40.4 (161)	39.8 (159)	38.6 (154)	0.77 (1.1)	0.73 (1.0)	0.78 (1.1)	1.95 (0.9)	1.78 (0.8)	1.89 (0.8)	1.58 (1.1)	1.71 (1.2)	1.69 (1.2)
Diarrhea	38.3 (153)	34.6 (138)	36.1 (144)	0.75 (1.1)	0.73 (1.1)	0.73 (1.0)	1.97 (0.8)	2.03 (0.8)	1.90 (0.7)	1.65 (1.1)	1.71 (1.1)	1.57 (1.1)
Feeling irritable	36.3 (145)	33.8 (135)	31.3 (125)	0.57 (0.9)	0.60 (0.9)	0.57 (0.9)	1.60 (0.7)	1.71 (0.6)	1.69 (0.7)	1.33 (1.2)	1.45 (0.9)	1.37 (1.0)
Changes in skin	32.6 (130)	34.1 (136)	25.8 (103)	0.62 (1.0)	0.68 (1.0)	0.52 (0.9)	1.91 (0.8)	1.90 (0.8)	1.91 (0.8)	1.61 (1.1)	1.60 (1.2)	1.70 (1.2)
Weight loss	30.1 (120)	27.3 (109)	26.3 (105)	0.53 (0.9)	0.47 (0.8)	0.44 (0.8)	1.78 (0.8)	1.67 (0.7)	1.58 (0.7)	1.38 (1.1)	1.40 (1.2)	1.21 (1.1)
Feeling bloated	29.8 (119)	23.8 (95)	22.1 (88)	0.55 (0.9)	0.48 (0.9)	0.45 (0.9)	1.87 (0.8)	1.96 (0.8)	1.93 (0.7)	1.65 (1.3)	1.70 (1.1)	1.60 (1.0)
Abdominal cramps	28.3 (113)	29.1 (1.6)	23.1 (92)	0.54 (0.9)	0.56 (0.9)	0.46 (0.9)	1.94 (0.8)	1.88 (0.7)	1.92 (0.7)	1.63 (1.0)	1.58 (1.0)	1.62 (1.0)
Feeling nervous	28.3 (113)	22.1 (88)	19.0 (76)	0.46 (0.8)	0.37 (0.7)	0.34 (0.7)	1.64 (0.7)	1.64 (0.6)	1.69 (0.6)	1.40 (0.9)	1.52 (1.0)	1.39 (0.9)
Dizziness	27.8 (111)	26.3 (105)	19.0 (76)	0.43 (0.8)	0.41 (0.7)	0.32 (0.6)	1.55 (0.7)	1.49 (0.7)	1.53 (0.6)	1.28 (1.1)	1.31 (0.9)	1.36 (0.7)
Problems with sexual interest or activity	27.1 (108)	21.8 (87)	20.8 (83)	0.63 (1.2)	0.54 (1.1)	0.56 (1.1)	2.39 (1.0)	2.42 (0.9)	2.49 (0.9)	1.64 (1.1)	2.01 (1.2)	1.96 (1.2)

Symptoms[a]	Occurrence Rates % (n)			Severity Ratings with zeros[b] Mean (SD)			Severity Ratings without zeros[c] Mean (SD)			Distress Ratings[d] Mean (SD)		
	Time 1*	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
"I don't look like myself"	25.6 (102)	23.6 (94)	23.8 (95)	0.48 (0.9)	0.48 (0.9)	0.44 (0.8)	1.92 (0.7)	2.00 (0.9)	1.76 (0.7)	1.77 (1.1)	1.81 (1.2)	1.62 (1.0)
Sweats	24.8 (99)	18.5 (74)	14.1 (56)	0.42 (0.8)	0.32 (0.7)	0.25 (0.7)	1.75 (0.8)	1.66 (0.7)	1.77 (0.8)	1.12 (1.2)	1.23 (1.0)	1.22 (1.2)
Increased appetite	24.6 (98)	17.0 (68)	18.2 (72)	0.42 (0.8)	0.30 (0.6)	0.28 (0.6)	1.76 (0.6)	1.72 (0.5)	1.58 (0.6)	0.75 (1.1)	0.69 (0.9)	0.58 (0.9)
Cough	23.6 (94)	22.1 (88)	18.5 (74)	0.32 (0.6)	0.32 (0.6)	0.31 (0.7)	1.38 (0.5)	1.43 (0.5)	1.60 (0.6)	0.83 (1.0)	1.02 (0.9)	1.18 (1.1)
Weight gain	22.8 (91)	15.8 (63)	14.0 (56)	0.35 (0.7)	0.23 (0.5)	0.22 (0.6)	1.56 (0.6)	1.45 (0.6)	1.59 (0.7)	0.87 (1.3)	0.93 (1.3)	0.94 (1.3)
Itching	21.1 (84)	17.3 (69)	13.5 (54)	0.38 (0.8)	0.31 (0.7)	0.24 (0.6)	1.83 (0.8)	1.75 (0.6)	1.69 (0.5)	1.44 (1.0)	1.49 (1.0)	1.22 (0.9)
Mouth sores	19.0 (76)	20.1 (80)	19.8 (79)	0.32 (0.7)	0.36 (0.7)	0.37 (0.7)	1.74 (0.8)	1.74 (0.7)	1.76 (0.7)	1.41 (1.2)	1.45 (1.0)	1.47 (1.0)
Shortness of breath	18.3 (73)	13.8 (55)	11.3 (45)	0.29 (0.7)	0.23 (0.6)	0.21 (0.6)	1.59 (0.6)	1.59 (0.6)	1.77 (0.7)	1.54 (1.1)	1.44 (0.9)	1.44 (1.0)
Hot flashes	17.8 (71)	14.3 (57)	10.0 (40)	0.32 (0.8)	0.26 (0.7)	0.19 (0.6)	1.82 (0.7)	1.80 (0.8)	1.86 (0.9)	1.23 (1.1)	1.34 (1.3)	1.42 (1.3)
Difficulty swallowing	16.8 (67)	18.5 (74)	11.5 (46)	0.30 (0.7)	0.33 (0.7)	0.22 (0.6)	1.81 (0.8)	1.72 (0.8)	1.76 (0.7)	1.77 (1.2)	1.52 (1.0)	1.49 (1.1)
Vomiting	15.3 (61)	15.0 (60)	9.8 (39)	0.28 (0.7)	0.27 (0.6)	0.18 (0.6)	1.82 (0.9)	1.82 (0.8)	1.74 (0.6)	1.73 (1.1)	1.68 (1.1)	1.55 (1.0)
Difficulty breathing	14.8 (59)	10.8 (43)	8.5 (34)	0.24 (0.6)	0.16 (0.5)	0.12 (0.5)	1.67 (0.7)	1.55 (0.6)	1.68 (0.6)	1.56 (1.2)	1.32 (1.0)	1.55 (1.2)
Problems with urination	14.0 (56)	15.3 (61)	12.3 (49)	0.25 (0.7)	0.27 (0.6)	0.20 (0.5)	1.83 (0.6)	1.71 (0.7)	1.64 (0.6)	1.68 (1.2)	1.56 (1.2)	1.40 (1.0)
Chest tightness	12.8 (51)	9.3 (37)	5.0 (20)	0.17 (0.5)	0.14 (0.5)	0.07 (0.3)	1.39 (0.5)	1.54 (0.7)	1.33 (0.5)	1.33 (1.2)	1.27 (1.0)	1.22 (1.1)
Swelling of arms or legs	8.5 (34)	5.0 (20)	5.8 (23)	0.16 (0.6)	0.10 (0.4)	0.10 (0.4)	1.97 (0.8)	2.11 (0.9)	1.76 (0.7)	1.53 (1.1)	1.56 (1.1)	1.24 (1.0)

Abbreviation: SD = standard deviation

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e, recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

[a] Symptoms from the Memorial Symptom Assessment Scale with the addition of the following six symptoms: chest tightness, difficulty breathing, increased appetite, hot flashes, abdominal cramps, weight gain.

[b] Severity ratings with zeros: 0 = did not have the symptoms, 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

[c] Severity ratings without zeros: 1 = slight, 2 = moderate, 3 = severe, 4 = very severe.

[d] Distress ratings: 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much.

* Orientation column in rank order

Table 3.

Comparison of Symptom Clusters Within Each Assessment Using Ratings of Occurrence, Severity, and Distress

Symptom Cluster	Symptoms	Time 1			Time 2			Time 3		
		Occurrence	Severity	Distress	Occurrence	Severity	Distress	Occurrence	Severity	Distress
Psychological symptom cluster	Lack of energy	0.463	0.498	0.552	0.414	0.435	0.514	0.544	0.429	0.524
	Difficulty concentrating	0.712	0.716	0.767	0.653	0.517	0.527	0.510	0.453	0.485
	Feeling nervous	0.822	0.775	0.707	0.656	0.606	0.751	0.787	0.773	0.729
	Feeling drowsy	0.404	0.458	0.488	-	-	-	-	-	-
	Feeling sad	0.863	0.845	0.760	0.814	0.811	0.784	0.943	0.872	0.969
	Worrying	0.895	0.800	0.959	0.926	0.940	0.992	0.951	0.949	0.959
	Feeling irritable	0.642	0.528	0.618	0.654	0.562	0.630	0.585	0.594	0.642
	Changes in skin	0.420	-	-	-	-	-	-	-	0.432
	Problems with sexual interest or activity	-	0.428	-	0.510	0.402	0.467	0.463	-	0.418
	“I don’t look like myself’	-	-	-	0.403	-	-	-	-	-
	Difficulty sleeping	-	-	0.407	-	-	0.404	0.421	-	-
	Constipation	-	-	-	-	-	-	-	0.404	0.422
	Pain	-	-	0.459	-	-	-	-	-	-
	Sweats	-	-	0.502	-	-	-	-	-	-
	Total number of symptoms in this cluster	8/14	8/14	10/14	8/14	7/14	8/14	8/14	7/14	9/14
Chemotherapy- related symptom cluster	Dry mouth	0.451	-	-	0.641	0.676	0.629	0.535	0.518	0.506
	Nausea	0.464	-	-	0.702	0.615	0.564	0.560	0.518	0.479
	Itching	0.489	0.466	0.516	-	-	-	-	-	-
	Lack of appetite	0.844	0.768	0.807	0.688	0.669	0.714	0.690	0.629	0.705
	Weight loss	0.617	0.582	0.602	0.453	0.481	0.536	0.618	0.605	0.645
	Change in the way food tastes	0.466	0.606	0.559	0.439	0.538	0.552	0.505	0.440	0.482
	Changes in skin	0.500	0.586	0.622	-	-	-	-	-	-
	Dizziness	0.504	0.507	0.564	-	-	-	-	0.425	-
	Cough	-	-	-	0.501	0.544	0.571	0.545	0.428	0.528
	Lack of energy	-	-	-	0.486	0.430	-	0.462	0.516	-

Symptom Cluster	Symptoms	Time 1			Time 2			Time 3		
		Occurrence	Severity	Distress	Occurrence	Severity	Distress	Occurrence	Severity	Distress
	Abdominal cramps	-	-	-	0.530	0.571	0.570	0.478	0.423	0.462
	Feeling bloated	-	-	-	0.478	0.443	-	-	-	-
	Diarrhea	-	-	-	0.476	0.541	0.474	0.497	0.557	0.462
	Feeling drowsy	-	-	-	0.447	0.440	0.423	0.535	0.626	0.520
	Numbness/tingling in hands/feet	-	-	-	0.489	0.521	-	-	0.416	-
	Hair loss	-	0.443	0.449	-	-	-	-	-	-
	“I don’t look like myself’	-	0.418	0.537	-	-	-	-	-	-
	Sweats	-	-	-	-	0.486	0.403	-	-	-
	Total number of symptoms in this cluster	8/18	8/18	8/18	12/18	13/18	10/18	10/18	12/18	9/18
Gastrointestinal symptom cluster	Feeling bloated	0.689	0.616	-	-	-	-	-	-	-
	Abdominal cramps	0.734	0.858	0.621	-	-	-	-	-	-
	Constipation	0.431	-	-	-	-	-	-	-	-
	Nausea	-	0.404	-	-	-	-	-	-	-
	Diarrhea	-	0.561	0.620	-	-	-	-	-	-
	Total number of symptoms in this cluster	3/5	4/5	2/5	0/5	0/5	0/5	0/5	0/5	0/5
Weight change symptom cluster	Increased appetite	0.836	0.785	0.779	0.784	0.708	0.726	0.600	0.621	0.652
	Weight gain	0.962	0.871	0.929	0.808	0.781	0.877	1.020	1.094	0.965
	Lack of appetite	-	-	-	-0.419	-0.451	-	-0.467	-0.442	-0.467
	Weight loss	-	-	-	-	-0.430	-	-0.412	-0.411	-0.446
	Total number of symptoms in this cluster	2/4	2/4	2/4	3/4	4/4	2/4	4/4	4/4	4/4
Epithelial symptom cluster	Hair loss	-	-	-	0.420	0.450	0.489	-	-	-
	Change in the way food tastes	-	-	-	0.573	-	-	-	-	-
	Changes in skin	-	-	-	0.610	0.705	0.820	0.666	0.698	0.624
	Itching	-	-	-		0.433	0.469	0.622	0.483	0.526
	“I don’t look like myself’	-	-	-	-	0.459	0.511	0.513	0.632	0.584
	Total number of symptoms in this cluster	0/5	0/5	0/5	3/5	4/5	4/5	3/5	3/5	3/5

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

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e., recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

– = Factor loadings for these symptoms were <0.40.

Table 4.

Summary of Symptom Clusters Across Time Using Different Dimensions of the Symptom Experience

Symptom Cluster	Symptoms within the Cluster	Occurrence			Severity			Distress		
		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
Psychological symptom cluster	Lack of energy	X	X	X	X	X	X	X	X	X
	Difficulty concentrating	X	X	X	X	X	X	X	X	X
	Feeling nervous	X	X	X	X	X	X	X	X	X
	Feeling drowsy	X			X			X		
	Feeling sad	X	X	X	X	X	X	X	X	X
	Worrying	X	X	X	X	X	X	X	X	X
	Feeling irritable	X	X	X	X	X	X	X	X	X
	Changes in skin	X								X
	Problems with sexual interest or activity		X	X	X	X			X	X
	“I don’t look like myself’		X							
	Difficulty sleeping			X				X	X	
	Constipation						X			X
	Pain							X		
	Sweats							X		
	Percent agreement[a] (n = 14)	57.1%	57.1%	57.1%	57.1%	50.0%	50.0%	71.4%	57.1%	64.3%
Chemotherapy -related symptom cluster	Dry mouth	X	X	X		X	X		X	X
	Nausea	X	X	X		X	X		X	X
	Itching	X			X			X		
	Lack of appetite	X	X	X	X	X	X	X	X	X
	Weight loss	X	X	X	X	X	X	X	X	X
	Change in the way food tastes	X	X	X	X	X	X	X	X	X
	Changes in skin	X			X			X		
	Dizziness	X			X		X	X		

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Symptom Cluster	Symptoms within the Cluster	Occurrence			Severity			Distress		
		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
	Cough		X	X		X	X		X	X
	Lack of energy		X	X		X	X			
	Abdominal cramps		X	X		X	X		X	X
	Feeling bloated		X			X				
	Diarrhea		X	X		X	X		X	X
	Feeling drowsy		X	X		X	X		X	X
	Numbness/tingling in hands/feet		X			X	X			
	Hair loss				X			X		
	“I don’t look like myself’				X			X		
	Sweats					X			X	
	Percent agreement[a] (n =18)	44.4%	66.7%	55.6%	44.4%	72.2%	66.7%	44.4%	55.6%	50.0%
Gastrointestinal symptom cluster	Feeling bloated	X	Not identified	Not identified	X	Not identified	Not identified		Not identified	Not identified
	Abdominal cramps	X			X			X		
	Constipation	X								
	Nausea				X					
	Diarrhea				X			X		
	Percent agreement[a] (n = 5)	60.0%	0	0	80.0%	0	0	40.0%	0	0
Weight change symptom cluster	Increased appetite	X	X	X	X	X	X	X	X	X
	Weight gain	X	X	X	X	X	X	X	X	X
	Lack of appetite		X	X		X	X			X
	Weight loss			X		X	X			X
	Percent agreement[a] (n = 4)	50.0%	75.0%	100.0%	50.0%	100.0%	100.0%	50.0%	50.0%	100.0%
Epithelial symptom cluster	Hair loss	Not identified	X		Not identified	X		Not identified	X	
	Change in the way food tastes		X							

Symptom Cluster	Symptoms within the Cluster	Occurrence			Severity			Distress		
		Time 1	Time 2	Time 3	Time 1	Time 2	Time 3	Time 1	Time 2	Time 3
	Changes in skin		X	X		X	X		X	X
	Itching			X		X	X		X	X
	“I don’t look like myself’			X		X	X		X	X
	Percent agreement[a] (n =5)	0	60.0%	60.0%	0	80.0%	60.0%	0	80.0%	60.0%

Timing of symptom assessments: Time 1 = prior to the initiation of next cycle of chemotherapy (i.e., recovery from the second or third cycle of chemotherapy), Time 2 = approximately one week after chemotherapy (i.e., acute symptoms), Time 3 = approximately two weeks after chemotherapy (i.e., potential nadir).

[a]By way of example, percentage agreement for psychological symptom cluster at Time 1 using the results for the occurrence dimension was calculated as follows: (8 [total number of symptoms of occurrence dimension at Time 1] / 14 [total number of possible symptoms in the psychological symptom cluster in all nine exploratory factors analyses across time and across symptom dimensions]) × 100 = 57.1%.