Title Cancer-related symptom clusters for symptom management in outpatients commencing adjuvant chemotherapy, at 6 months, and 12 months

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Running head SYMPTOM CLUSTERS OVER 12 MONTHS

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Abstract

Goals of work The aim of this secondary data analysis was to investigate symptom clusters over time for symptom management of a patient group after commencing adjuvant chemotherapy.

Materials and methods A prospective longitudinal study of 219 cancer outpatients conducted within 1 month of commencing chemotherapy (T1), 6 months (T2), and 12 months (T3) later. Patients' distress levels were assessed for 42 physical symptoms on a clinician-modified Rotterdam Symptom Checklist. Symptom clusters were identified in exploratory factor analyses at each time. Symptom inclusion in clusters was determined from structure coefficients. Symptoms could be associated with multiple clusters. Stability over time was determined from symptom cluster composition and the proportion of symptoms in the initial symptom clusters replicated at later times.

Main results Fatigue and daytime sleepiness were the most prevalent distressing symptoms over time. The median number of concurrent distressing symptoms approximated 7, over time. Five consistent clusters were identified at T1, T2, and T3. An additional two clusters were identified at 12 months, possibly due to less variation in distress levels. Weakness and fatigue were each associated with 2, 4, and 5 symptom clusters at T1, T2, and T3, respectively, potentially suggesting different causal mechanisms.

Conclusion Stability is a necessary attribute of symptom clusters, but definitional clarification is required. We propose a core set of concurrent symptoms identifies each symptom cluster, signifying a common cause. Additional related symptoms may be included over time. Further longitudinal investigation is required to identify symptom clusters and the underlying causes.

Introduction

The cancer symptom experience has been described as dynamic [1], depending on the type and stage of cancer and treatment, although some symptoms are common to most cancers. Fatigue is the most frequently reported cancer-related symptom, irrespective of cancer type [2-4]. Symptom management strategies depend on understanding the complexity of patients' symptom experiences and the underlying causes. A symptom cluster approach to address the multiple symptom experience of cancer patients may lead to new symptom management strategies [5,6].

Symptom clusters have been defined as a stable grouping of at least two related, co-occurring symptoms [7]. Type and strength of relationships [8] and co-occurrence have not been specified. Symptom *relatedness* is generally shown statistically by correlation, but correlated symptoms are not necessarily related physiologically, and there is no sense of causality. Stability of symptom clusters is important clinically to develop intervention strategies, but has not been defined for this context. Conceptually, stability may refer to consistent/replicated symptom clusters for a patient group at a point in time (cross-sectional stability) or over time, or in individuals over time, and for different patient populations (subgroups).

Few studies have investigated symptom clusters using longitudinal data, although symptoms may persist across disease and treatment trajectories [9,10,3]. The purpose of this study was to investigate symptom clusters over time for a patient group, as a basis for symptom management.

Literature Review

For longitudinal data, symptom clusters have been identified for patient groups in separate cross-sectional factor analyses. For example, the structure of two symptom clusters

(Upper-gastrointestinal, Psychoneurological) was identified in a study of 199 breast cancer patients during and after chemotherapy/radiotherapy treatment [11]. Both clusters were replicated after treatment, except *hot flashes* was in the Upper-gastrointestinal cluster during treatment. Using a congruence coefficient to determine similarity across patient subgroups (e.g., treatment type, early/late stage, gender) during treatment and Cronbach's alpha for internal reliability, cross-sectional stability was demonstrated for both clusters. After treatment, only the Upper-gastrointestinal cluster was consistent for all subgroups [11]. Subgroup factor analyses would be a preferred method to identify clusters [12], dependent on sample size.

Typically, stability of symptom clusters identified over time has been determined *qualitatively* by noting similar symptom groupings across clusters. For 66 patients newly-diagnosed with brain tumors, a core set of symptoms was identified consistently in two clusters (Language, Mood), before and after 12 weeks of radiotherapy [13]. Similarly, consistency was evident in three clusters identified for 160 breast and prostate cancer patients at the middle (T1), end (T2), and one month after (T3) radiotherapy [14]. In contrast, symptom clusters varied every week (0-12 weeks) after radiotherapy, in studies of 518 patients with bone metastases [15] and 170 patients with brain metastases [16]. Consistent pairs over time were *fatigue* and *drowsiness*, and *anxiety* and *depression.* In another study of 129 patients with brain metastases, five symptom pairs were consistent, but in different clusters, in three, monthly assessments after whole brain radiotherapy [17].

Stability/consistency of cancer symptom clusters has also been determined by confirmatory factor analysis, but this requires hypotheses of symptom relationships based on prior knowledge. In a validation study, Chen and Lin [18] used confirmatory factor analysis, and replicated three symptom clusters (sickness, gastrointestinal, and emotional) identified previously [19] were replicated [18], despite sample differences in treatments and diagnoses.

A model associating *lack of appetite* with the Gastrointestinal and Sickness clusters was a better-fit model, indicating symptoms may result from more than one cluster. Stability of a symptom cluster (fatigue, weakness, nausea, vomiting, appetite loss, weight loss, altered taste) identified for 112 lung cancer patients at diagnosis was determined three and six months later using Cronbach's alpha [20,21]. Clinical evidence supports the existence of these clusters, but these approaches do not explore the possibility that different symptom clusters may occur over time. Furthermore, Cronbach's alpha represents a limited condition for stability, as correlations do not fully capture the multiple symptom experience assessed by factor analysis.

A limitation of cross-sectional analyses is that each analysis is independent and does not account for the influence of previous symptom experiences. One study investigated longitudinal patterns of rates of change in severity for 64 newly-diagnosed non-small-cell lung cancer patients across 12 weeks of treatment [22]. Using growth curve analysis, four symptom clusters with different developmental trajectories were indicated [22].

This review highlights, not only the variation in symptom cluster membership and symptom experiences over time, but that a core set of concurrent symptoms may occur consistently. Other symptoms may present at different stages of the disease/treatment trajectories. Due to individual variation, symptoms may not occur or be distressing at all assessments. This raises the question of whether a standard number of symptoms must re-occur to constitute stability over time. Kirkova and Walsh [1] proposed symptom cluster stability over time may be established *quantitatively* (numerically) by the presence of at least 75% of symptoms in the initial cluster, identified at subsequent times. This approach has not been investigated.

There is no optimal approach for symptom cluster identification over time. When symptom groupings are unknown, exploratory analyses are appropriate. Latent variable

methods include separate cross-sectional factor analyses for a group and longitudinal analyses of individual rates of change in symptom severity. The strength of a factor analysis model as a basis for symptom management strategies is the theoretical association of common underlying factors with multiple symptoms.

Methods

Participants

Participants were outpatients diagnosed with cancer in the past 6 months, undergoing adjuvant treatment at two major oncology/hematology clinics in Brisbane in 2000-2001 and interviewed within 1 month (T1), at 6 months (T2), and 12 months (T3) after commencing chemotherapy. Ethical approval was obtained from the university and hospitals. All patients signed consent forms prior to participation. Details of the procedures, participants' demographic and medical characteristics at all times, and a comparison of completers and non-completers due to attrition have been reported [23]. Participants not in the analysis at 12 months due to attrition (death, refusal, unwell) and non-response were more likely to have Stage IV tumors and receive palliative treatment.

Measures

Physical symptoms were assessed on a clinician-modified Rotterdam Symptom Checklist (RSCL). Participants self-rated their perceived symptom distress in the past week from 1 (*not at all*) to 4 (*very much*). Current treatment status (*no, new, continuing*) was assessed six-monthly.

Statistical Analysis

This secondary data analysis was conducted using SPSS® version 15.0 (SPSS Inc. Chicago, IL). At each time, prevalence of distressing symptoms, distributions of severity ratings, concurrence, and treatment status were determined. Statistical relationships between symptoms were summarized by Pearson correlations. Data were not missing at random, so to avoid introducing further bias, missing values were not replaced by imputation.

To maximize the use of available data, separate analyses were conducted at each time, in preference to using complete data at all times (n=121). Common factor analysis (CFA) with oblique rotation was implemented as an exploratory factor analysis best practice approach [24] also used by other researchers [11,14,13], although principal components analysis (PCA) with orthogonal rotation has been used [16,15,25,26,17]. To identify and interpret symptom clusters, CFA is appropriate, as *common* variance among symptoms is assessed, and it is assumed correlations between symptoms are due to a common cause. In PCA, *total* variance is assessed, so coefficients and communalities may be overestimated. Furthermore, there is no theoretical foundation to identify underlying factors. Oblique rotation allows correlated clusters, but would identify orthogonal clusters if they exist.

As the data structure was unknown, CFAs were conducted at each time point at T2 and T3 rather than confirmatory analyses at T2 and T3, based on the structure identified at T1. Principal axis factoring (PAF) was the method of extraction requiring no distributional assumptions and suitable for non-normal symptom data [27]. Initial communalities were estimated by squared multiple correlations (SMCs). In each analysis, the number of factors was decided from the scree plot [28] and Minimum Average Partial (MAP) procedure [29] using available syntax [30]. Following oblimin (oblique) rotation, analyses were repeated for varying numbers of factors until a simple structure [31] was evident in the pattern matrix, revealing symptoms more strongly associated with one factor than another. Symptoms were included in a cluster for structure coefficients (correlations between factors and symptoms) ≥

.30, an arbitrarily chosen value indicating the factor explains about 10% of the variance in a symptom [24].

As a basis for management strategies, symptoms could be associated with more than one factor, statistically and clinically. Final communality values indicate the percentage of the variance in each symptom accounted for by the common factors. Communalities from .20 to .40 were classified as low [32], but if meaningful in the cluster, symptoms were retained. Clusters were finalized after clinical plausibility was reviewed, based on the literature and author interpretation. Qualitatively, stability of clusters over time was based on similar cluster composition likely to suggest a common cause. Quantitatively, the proportion of symptoms in clusters at T1 and replicated at T2 and T3 was compared against the proposed 75% replication rate for stability [1].

Results

Participants

Of 219 participants, complete symptom data were reported by 202 at T1, 177 at T2, and 144 at T3. Median age of patients was 52 years (range: 18-79) and the majority were female (64%). Patients received one or more treatments, depending on their primary cancer site, treatment response, and disease progression. At T1, all patients underwent chemotherapy. At T2, new/continuing treatments for patients (77%) were mostly chemotherapy or radiotherapy. At T3, about half (48%) underwent chemotherapy mostly, or hormone therapy. Patient characteristics are summarized in Table 1.

Symptom Distress

The most prevalent distressing symptoms (score>1) at all times (Table 2) were fatigue (62%-65%) and daytime sleepiness (42%-50%). Other distressing symptoms were: hair loss

(41%), nausea (30%) and headache (30%) at T1; weakness (33%), headache (33%), numbness (32%), and dry mouth (31%) at T2; and muscle soreness (34%), dry mouth (31%), and joint pain (31%) at T3. Prevalence rates varied differentially over time; distress rates were consistent (e.g., fatigue), increased (e.g., muscle soreness), and decreased (e.g., loss of taste) over time, or increased at T2 and decreased at T3 (e.g., numbness). The median number of concurrent distressing symptoms was 7 (range: 0-32) at T1, 8 (range: 0-28) at T2, and 7 (range: 0-26) at T3, reflecting a multiple symptom experience over time.

Symptom Clusters at T1, T2, and T3

From the scree plot and MAP, 5, 5, and 7 symptom clusters were suggested at T1, T2, and T3 respectively. Over time, five qualitatively consistent symptom clusters were characterized by a set of core symptoms (Tables 3-5): (1) Vasomotor (sweating, hot/cold spells and night sweats); (2) Oral-discomforts (difficulty swallowing, sore throat, sore mouth/pain swallowing); (3) Upper-gastrointestinal-discomforts/Aerodigestive (indigestion, heartburn and belching); (4) Gastrointestinal-toxicities (poor appetite, vomiting, nausea, shivering, stomach pain and trembling); and (5) Musculoskeletal-discomforts/lethargy (fatigue, sleepiness, muscle soreness and weakness). The Aerodigestive cluster differed from the Upper-gastrointestinal-discomforts clusters at T1 and T2 by the inclusion of *chest pains* and *short of breath*. An additional two clusters identified at T3 were Lethargy and Gastrointestinal/digestive symptoms in Table 6.

Several symptoms were associated with multiple clusters. For example, at T2, poor appetite was associated with Oral-discomforts in Table 3, and Gastrointestinal-toxicities at all times in Table 4, with Lethargy and Gastrointestinal/digestive symptom clusters in Table 6. Weakness and fatigue were the most common symptoms across clusters, each associated with two clusters at T1, four clusters at T2, and five clusters at T3.

Replicating 75% of symptoms in clusters identified at T1 was achieved for the Vasomotor (75%) and Oral-discomforts (86%) clusters at T2, and the Musculoskeletal-discomforts/lethargy (89%) cluster at T3. Otherwise, replication rates ranged from 43% to 69% at T2, and from 38% to 54% at T3. Core symptoms were replicated and other symptoms transitioned in and out of clusters over time.

Overall, clusters comprised from 6 to 14 symptoms and inter-cluster correlations ranged from .05 to .30. Independent symptoms not in clusters, due to coefficients below .30 and communalities below .20, included hair loss (T1), itchiness (T2), and heart pounding (T3). The factors best accounted for sore throat (T1), night sweats (T2) and fatigue (T3).

Discussion

Clinically, recognition of consistent symptom clusters is important to suggest intervention strategies in response to observed patterns in patients' symptom experiences. However, few studies have investigated symptom clusters over time, or the complexity of symptom interrelationships for symptom management. This study assessed more symptoms than similar studies and is the first study to empirically identify symptom clusters for patients commencing chemotherapy, and 6 and 12 months later. Of the 42 symptoms analysed, only nausea, fatigue, pain, and appetite loss were common to other longitudinal studies reviewed.

Compared to other studies, we used pattern coefficients to guide the decision on the number of clusters and structure coefficients to guide symptom inclusion in clusters [33,27]. Interpreting structure coefficients better reflects the clinical reality that symptoms could arise from different causal mechanisms, and as such, may be associated with different symptoms in each cluster. Our clusters comprised 6 to 14 symptoms, compared to clusters of 2 to 4 symptoms in studies assessing fewer symptoms and interpreting pattern coefficients to identify symptoms uniquely associated with one factor.

Overall, the findings support other research that stable symptom clusters may exist, independent of treatment type and primary site [18,19,11]. Core sets of symptoms were identified consistently in five clusters over time; two additional clusters were determined at T3. All patients received chemotherapy at T1, 77% and 50% received treatment (predominantly chemotherapy) at T2 and T3 respectively, so the effects of treatment may be diluted over time. Specific treatment effects could not be determined, as the effects of sequential treatments may overlap (e.g., radiotherapy and chemotherapy). Nevertheless, the possibility remains that the identification of symptom clusters at T3 may be attributed to continuing treatments, particularly chemotherapy, or the effects of disease progression.

Clusters at T3 comprised more symptoms, perhaps due to less variation in symptom distress or a shift in patient response to symptoms experienced over a sustained period (i.e., less bothered). The resolution of some symptoms, as well as the cumulative or long-lasting effect of other symptoms associated with treatments, may account for the different symptom relationships over time, and changing causes.

Alternative management strategies may be suggested for symptoms in multiple clusters. This highlights the advantage of our approach to interpret the complex interrelationships. For example, poor appetite at T2 was associated with Oral-discomforts and Gastrointestinal-toxicities, so appetite may improve if other symptoms (e.g., sore throat or vomiting) are relieved. Further investigation of the symptom clusters identified and their underlying causes is warranted.

The stability of symptoms in clusters over time, such as sleepiness, fatigue, poor appetite, vomiting, and nausea in the Gastrointestinal-toxicities cluster, may suggest an underlying etiology of cytokine production, similar to the Sickness–behavior symptom clusters of pain, fatigue, insomnia, and appetite loss [19], fatigue, drowsiness, and insomnia [14], and nausea, vomiting, and decreased appetite [11]. This finding supports the possibility

that a cluster of Sickness-behavior symptoms may exist independent of treatment type, primary cancer site, and stage of treatment.

The variety of symptoms identified in clusters at different times supports the use of exploratory CFA in this study, as the data structure was unknown. Symptom clusters statistically-derived by CFA are more likely to suggest a common pathophysiology, not theoretically inherent in PCA [24,34]. In contrast, confirmatory factor analyses at T2 and T3, of the clusters identified at T1, would assess stability for that structure only, so were not implemented, although model modifications may be suggested in these analyses. Using Cronbach's alpha for cluster identification also assumes the same cluster exists over time. Such clusters may exist, or the clusters could be a limited set of symptoms. Our Gastrointestinal-toxicities clusters at T1-T3 and our Lethargy cluster at T3 are similar to the cluster of fatigue, weakness, nausea, vomiting, appetite loss, weight loss, and altered taste confirmed over time using Cronbach's alpha[20]. Cronbach's alpha [12] is based on paired correlations, so this approach does not fully capture the multiple symptom experience assessed in CFA. Coefficient alpha represents a necessary, but not sufficient, condition for stability.

Rather than assign cross-loading symptoms only to the most conceptually appropriate cluster [14], we allowed symptoms to indicate more than one cluster, for two reasons. Firstly, there may be no clear choice, conceptually. For example, based on structure coefficients ranging from .37 to .43, *weakness* was associated plausibly with five clusters at T3. Secondly, our intended application of the identified clusters was to consider intervention strategies, not to develop parsimonious symptom scales. Hence, recognizing that symptoms were associated across multiple clusters suggests different etiologies for these symptoms, and increased intervention opportunities based on different clusters. Although there is no correct interpretive approach for all contexts, interpreting structure coefficients reflects the clinical

reality in our study that symptoms could arise from different causal mechanisms, and as such were more likely to be associated with different symptoms across clusters. Pattern coefficients, the basis of cluster identification in other studies, may be useful to decrease cross-loadings and identify distinct factors. This may be important to measure and score symptom clusters to evaluate change in clusters over time.

It is important to identify symptom clusters for a heterogeneous population, as this reflects the clinical setting. The disadvantage is statistical, requiring subgroup factor analyses to address potential confounding, which in this and many studies is not conducted due to the limited sample size. Participants were considered to be representative of outpatients undergoing adjuvant treatment that was predominantly chemotherapy, but the mixed cancer diagnoses and treatments of varying duration may have influenced the aggregations. We assumed the same cluster structure exists for symptoms experienced by patients with different personal and medical characteristics. This may be true: the sample was homogeneous for chemotherapy at T1, chemotherapy was the predominant treatment at T2 and T3, and many of the symptoms associated with radiotherapy and chemotherapy are similar, but differ in their severity [35,36].

In this study, all 42 symptoms were analysed, as exclusion of low prevalence symptoms may ignore symptoms important to the few who experience them. Factor analysis does not require exclusion of variables other than outliers, although exclusion focuses the analysis on the most prevalent symptoms [13,11] and may address lack of variation in response [14]. However, if a symptom (e.g., deafness) is not a stable member over time, it may not belong in the cluster, or more likely, it is correlated with other symptoms not assessed (e.g., neurological). Clearly, deafness should not be ignored.

Determining stability based on 75% replication of T1 symptoms was achieved only for a few clusters. This replication rate may be higher for clusters identified from pattern

coefficients, as typically clusters would have fewer symptoms. Qualitatively, a symptom cluster appears stable if core symptoms are identified consistently over time. The percentage of symptoms replicated (i.e., quantitative determination) may not be important as individuals are unlikely to always experience all symptoms in a cluster.

The present study has several limitations. In this secondary analysis, there was no control over the sample and symptom assessment (i.e., instrument and timing). There was no assessment prior to treatment, so symptom prevalence before treatment is unknown. Only physical symptoms were assessed, although psychological symptoms are known to influence patients' symptom experience [37], and cognitive symptoms (e.g., memory loss, lack of concentration) may follow adjuvant therapy [38]. Patients in poor health were lost to attrition. Hence, the symptom experience assessed in this study may be less variable and less distressing than in the complete cohort. Alternatively, analyses that make the most of longitudinal designs (e.g., linear mixed effects models) may capture this variation.

The advantage of symptom clusters identified by CFA is the assumption of a common cause, but the limitation is the restriction to cross-sectional analyses with no consideration of the correlations between earlier and current experiences, despite the evidence of shift response [39] and symptom burden [40]. Longitudinal analyses are necessary to properly evaluate change in symptom clusters over time. Confirmatory factor analyses may address longitudinal change in symptom clusters, but has not been utilized, due to the exploratory phase of this research. Latent growth curve modeling has the advantage of determining when individuals may expect the greatest impact from each symptom cluster in the course of treatment, and of identifying different patient subgroup experiences, but more time points, fewer symptoms, and large sample size are preferable. Validation of the symptom clusters identified, within patient subgroups and over time, is necessary to confirm their stability and confirm they are really 'clusters' in the clinical sense.

Conclusion

Both consistency and variation over time were evident in the symptom clusters identified at 6-monthly intervals after chemotherapy commenced for outpatients with mixed diagnoses. Stability is a necessary attribute of symptom clusters, but definitional clarification is required. We propose a core set of concurrent symptoms identifies each symptom cluster, signifying a common cause. Additional related symptoms may be included over time. Knowing which symptoms cluster is essential for clinical practice, to identify interventions for improved symptom management and patient outcomes, or if there is change, to tailor treatments to the change expected. Comprehensive symptom checklists are important in this exploratory phase, as shorter instruments result in limited symptom clusters and may not adequately reflect patients' full symptom experience. Further longitudinal investigation is required to identify symptom clusters and the underlying causes (e.g., latent growth curves to identify symptom trajectories and influential factors).

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Table 1 Baseline patient characteristics (N=219)

Characteristic		
Age in years		
Median (Range)	52 (18-79)	
	n	%
Gender		
Male	79	36.1
Female	140	63.9
Primary cancer site		
Breast	63	28.8
Gastrointestinal-colorectal	47	21.5
Hematological malignancies	46	21.0
Genitalia-urinary-reproductive	31	14.2
Respiratory-lung	15	6.8
Head-neck	7	3.2
Soft tissue, skin, brain, CNS[a]	7	3.2
Unknown	3	1.4
Tumor stage		
Stage I	19	9.0
Stage II	62	28.3
Stage III	55	25.1
Stage IV	24	11.0
Unknown/missing	13	5.9

[a]CNS central nervous system

Table 2 Prevalence[a] of patient symptom distress over time

Symptom	< 1 month after commencing chemotherapy (*N*=202)		6 months after commencing chemotherapy (*N*=177)		12 months after commencing chemotherapy (*N*=144)	
	n	%	*n*	%	*n*	%
Fatigue	131	64.9	113	63.9	89	61.8
Sleepy during day	85	42.1	89	50.3	70	48.6
Loss of hair	83	41.1	28	15.8	6	4.2
Nausea	61	30.2	43	24.3	25	17.4
Headache	58	28.7	58	32.8	40	27.8
Dry mouth	56	27.7	55	31.1	44	30.6
Constipation	51	25.2	33	18.6	17	11.8
Belching	40	24.8	31	17.5	23	16.0
Pains in lower back	48	24.8	45	23.4	39	27.1
Sweating	49	24.3	49	27.7	43	29.9
Weakness in body	46	22.8	59	33.3	40	27.8
Hot/cold spells	45	22.3	43	24.3	42	29.2
Muscle soreness	42	20.8	50	28.2	49	34.0
Dizziness	42	20.8	38	21.5	34	23.6
Bad taste in mouth	41	20.3	38	21.5	16	9.7
Loss of taste	41	20.3	19	16.4	11	7.6
Diarrhea	40	19.8	45	25.4	26	18.1
Itchiness	40	19.8	34	19.2	29	20.1
Stomach pain	39	19.7	44	24.9	33	22.9
Cough	37	18.3	51	28.8	34	23.6
Night sweats	36	17.8	40	22.6	29	20.1
Poor Appetite	37	17.3	35	19.8	21	14.6
Indigestion	34	16.8	30	16.9	16	11.1
Weight gain	31	15.3	50	28.2	33	22.9
Numbness/tingling	31	15.3	56	31.6	29	20.1
Sore mouth/pain swallowing	31	15.3	17	9.6	8	5.6
Short of breath	31	15.3	40	24.9	40	27.8
Sore throat	29	14.4	23	13.0	16	11.1
Joint pain	27	13.4	46	26.0	42	29.2
Trembling	27	13.4	11	6.2	13	9.0
Rash	24	11.9	25	14.1	11	7.6
Heartburn	24	11.9	23	13.0	10	6.9
Low abdominal pain	24	11.9	25	14.1	20	13.9
Heavy feelings arms/legs	21	10.4	40	22.6	27	18.7
Muscle cramps	21	10.4	29	16.4	27	18.7
Generalised pain	20	9.9	28	15.8	21	14.6
Chest pains	30	9.9	20	11.3	19	13.2
Shivering	19	9.4	7	4.0	7	4.9
Heart pounding	16	7.9	10	5.6	12	8.3
Vomiting	15	7.4	11	6.2	7	4.9
Difficulty swallowing	13	6.4	12	6.8	7	4.9
Deafness	8	4.0	14	7.9	15	10.4

[a] Percentage of patients with distress score >1 on RSCL

Table 3 Vasomotor and Oral-discomforts symptom clusters identified over time, after participants commenced chemotherapy

Vasomotor symptom clusters					
< 1 month		6 months		12 months	
(α= .73)	SC	(α= .84)	SC	(α= .85)	SC
headache	0.62	headache	0.32		
sweating	0.60	sweating	0.72	sweating	0.87
hot/cold spells	0.58	hot/cold spells	0.72	hot/cold spells	0.77
night sweats	0.53	night sweats	0.75	night sweats	0.72
dizziness	0.52	dizziness	0.41		
numbness/ tingling	0.37	numbness/ tingling	0.42		
chest pains	0.42				
heart pounding /palpitations	0.35				
		muscle soreness	0.60	muscle soreness	0.33
		joint pain	0.52	joint pain	0.33
		generalised pain	0.52	generalised pain	0.34
		weakness	0.44	weakness	0.40
		fatigue	0.42	fatigue	0.43
		lower back pains	0.38		
				heavy feelings arms/legs	0.35
				weight gain	0.34
		dry mouth	0.30		
				sleepy during day	0.31

Table 3 (cont).

Oral-discomforts symptom clusters					
< 1 month		6 months[a]		12 months[b]	
(α= .72)	SC	(α= .80)	SC	(α= .73)	SC
sore throat	0.75	sore throat	0.55	sore throat	0.77
sore mouth /pain swallowing	0.71	sore mouth /pain swallowing	0.46	sore mouth /pain swallowing	0.67
difficulty swallowing	0.63	difficulty swallowing	0.56	difficulty swallowing	0.72
bad taste	0.44	bad taste	0.38		
loss of taste	0.42	loss of taste	0.44		
dry mouth	0.41	dry mouth	0.41		
deafness	0.35				
		cough	0.56	cough	0.57
		weakness in body	0.54	weakness in body	0.37
		short of breath	0.33	short of breath	0.33
		fatigue	0.33	fatigue	0.33
		poor appetite	0.54		
		belching	0.33		

[a]lower back pains excluded (lack of plausibility), [b]rash excluded (lack of plausibility)

Table 4 Gastrointestinal-related symptom clusters identified over time, after commencing chemotherapy

Upper-gastrointestinal-discomforts symptom clusters				Aerodigestive symptom clusters	
< 1 month		6 months		12 months[a]	
(α= .68)	SC	(α= .65)	SC	(α= .71)	SC
indigestion	0.66	indigestion	0.58	indigestion	0.49
heartburn	0.59	heartburn	0.46	heartburn	0.62
belching	0.59	belching	0.49	belching	0.36
stomach pain	0.57				
nausea	0.31			nausea	0.30
low abdominal pain	0.31				
constipation	0.30				
		heart pounding	0.38		
				chest pains	0.43
		shivering	0.37	shivering	0.33
		night sweats	0.34		
				short of breath	0.45
				sleepy in day	0.34
				deafness	0.52
Gastrointestinal-toxicities symptom clusters					
< 1 month		6 months		12 months	
(α= .78)	SC	(α= .79)	SC	(α= .80)	SC
poor appetite	0.54	poor appetite	0.47	poor appetite	0.32
vomiting	0.51	vomiting	0.50	vomiting	0.47

Table 4 (cont).

nausea	0.50	nausea	0.53	nausea	0.44
shivering	0.42	shivering	0.46	shivering	0.60
trembling	0.38	trembling	0.54	trembling	0.52
low abdominal pain	0.38	low abdominal pain	0.47		
stomach pain	0.37	stomach pain	0.64	stomach pain	0.37
diarrhea	0.35	diarrhea	0.40	diarrhea	0.45
belching	0.35				
loss of taste	0.31			loss of taste	0.40
				bad taste	0.66
				dry mouth	0.33
sleepiness	0.67	sleepiness	0.39		
fatigue	0.50	fatigue	0.39		
weakness	0.33	weakness	0.37		
		lower back pains	0.31		
				dizziness	0.38
				heavy feelings arms/legs	0.38

SC = structure coefficient.

[a]Rash, itchiness excluded (lack of plausibility)

Table 5 Musculoskeletal-discomforts/lethargy symptom clusters identified over time, after commencing chemotherapy

Musculoskeletal-discomforts/lethargy symptom clusters					
< 1 month[a]		6 months[a]		12 months	
(α= .73)	SC	(α= .79)	SC	(α= .84)	SC
weakness	0.69	weakness	-0.51	weakness	-.41
muscle soreness	0.66	muscle soreness	-0.34	muscle soreness	-.64
joint pain	0.48			joint pain	-.65
heavy feelings in arms/legs	0.47	heavy feelings in arms/legs	-0.65	heavy feelings in arms/legs	-.65
generalised pain	0.39			generalised pain	-.55
lower back pains	0.34			lower back pains	-.53
fatigue	0.41	fatigue	-0.65	fatigue	-.45
sleepy during day	0.35	sleepy during day	-0.61	sleepy during day	-.35
deafness	0.33				
		dizziness	-0.46	dizziness	-.36
		dry mouth	-0.34		
		short of breath	-0.30		
		shivering	-0.30		
		heart pounding/ palpitations	-0.43	heart pounding/ palpitations	-.30
		muscle cramps	-0.37	muscle cramps	-.56
		headache	-0.36	headache	-.33
				trembling	-.31
				night sweats	-.30

Table 5 (cont).

	weight gain	-.41

SC = structure coefficient

[a]Itchiness excluded (lack of plausibility)

Table 6 Symptom clusters only identified at 12 months after commencing chemotherapy

Lethargy[a] (α = .85)	SC	Gastrointestinal/ digestive symptoms (α = .86)	SC
fatigue	0.58	fatigue	0.41
weakness in body	0.43	weakness in body	0.39
sleepy during day	0.54		
headache	0.45		
dizziness	0.42		
short of breath	0.42		
lower back pains	0.30	lower back pains	0.30
loss of taste	0.56	loss of taste	0.31
poor appetite	0.46	poor appetite	0.60
constipation	0.36	constipation	0.50
nausea	0.37	nausea	0.42
dry mouth	0.33	dry mouth	0.34
		generalised pain	0.58
		low abdominal pain	0.75
		stomach pain	0.78
		indigestion	0.45
		belching	0.43

SC = structure coefficient

[a]Hair loss excluded (lack of plausibility)