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The effect of symptom clusters on functional status and quality of life in women with breast cancer

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Abstract

Purpose—The purposes of this study of women with breast cancer receiving chemotherapy with/without radiation therapy were to determine whether: 1) subgroups of oncology outpatients can be identified based on a specific symptom cluster (i.e., pain, fatigue, sleep disturbances, depression); 2) these subgroups differ on outcomes (i.e., functional status, quality of life; 3) subgroup membership changes over time.

Methods—A secondary data analysis using data collected from 112 women at initial chemotherapy. Symptom and outcome measures were completed at three time points: baseline (i.e., the week before cycle two - T1); end of cancer treatment (T2), end of the study (approximately one year after the start of chemotherapy - T3). Cluster analysis identified patient subgroups based on symptom severity scores.

Results—At T1 and T2, four patient subgroups were identified: ALL LOW (one or no symptom greater than the cut score), MILD (two symptoms), MODERATE (three or four symptoms), and ALL HIGH (four symptoms). At T3, three subgroups were identified: MILD, MODERATE and ALL HIGH. Subgroups with high severity levels of all four symptoms had poorer functional status and QOL at each time point than other subgroups ($p<.001$). Group membership changed over time.

Conclusions—Subgroups of patients with different symptom experiences were identified. For some patients severity of all four symptoms persisted months after cancer treatment. Initial and ongoing assessment to identify those patients in the ALL HIGH patient subgroup is important so that appropriate interventions to improve functional status and quality of life can be offered.

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Patient Consent: This study was conducted under full compliance to the University of California, San Francisco's Committee on Human Research guidelines, and informed consent was obtained for each subject.

Keywords

symptom experience; symptom cluster; pain; fatigue; sleep disturbance; depression; cluster analysis; functional status; quality of life

INTRODUCTION

A symptom cluster is defined as three or more concurrent symptoms that are related to each other but are not required to share the same etiology (Dodd, Miaskowski et al. 2001). Further, it was proposed by Dodd and associates that symptom clusters have an adverse effect on patient outcomes (Dodd, Miaskowski et al. 2001). Since this concept of a 'symptom cluster' in oncology patients was proposed in 2001, a literature search of the journal database of the National Center for Biotechnology Information (Pub Med) using the keywords, 'symptom cluster' and 'cancer,' yielded over 100 citations in which many researchers have endeavored to understand this complex issue in cancer patients. Kim, McGuire et al. (2005) proposed modifying this definition as follows: "A symptom cluster consists of two or more symptoms that are related to each other that occur together. Symptom clusters are composed of stable groups of symptoms, are relatively independent of other clusters, and may reveal specific underlying dimensions of symptoms. Relationships among symptoms within a cluster should be stronger than relationships among symptoms across different clusters." (p. 278). Though the definition of a symptom cluster is still being refined (Barsevick, Whitmer et al. 2006), many researchers have tried to clarify this concept in their studies of symptoms that manifested during and after cancer treatments in various types of cancer, using various statistical analyses.

Two different conceptual approaches to symptom cluster research have been used (i.e., grouping symptoms to create symptom clusters versus grouping individuals who report similar symptom experiences with a specific symptom cluster) (Miaskowski, Aouizerat et al. 2007). Most studies of symptom clusters have grouped symptoms using symptom inventory types of instruments (e.g., MD Anderson Symptom Inventory) with factor analysis and cluster analysis. (Cleeland, Mendoza et al. 2000; Gift, Stommel et al. 2003; Wang, Tang et al. 2003; Gift, Jablonski et al. 2004; Wang, Wang et al. 2004; Chen and Tseng 2006; Wang, Laudico et al. 2006; Fan, Hadi et al. 2007; Gleason, Case et al. 2007; Chow, Fan et al. 2008; Hadi, Fan et al. 2008; Kim, Barsevick et al. 2008; Tseng, Cleeland et al. 2008; Wang, Tsai et al. 2008; Cheung, Le et al. 2009). A challenge with this approach is that it does not allow one to distinguish among patient subgroups on symptom severity scores or on different patterns of low and high symptom severity across subgroups. The authors of the present study have selected the second conceptual approach.

Grouping individuals based on their symptom experience has occurred in a few studies of oncology patients (Trask and Griffith 2004; Bender, Ergyn et al. 2005; Glaus, Boehme et al. 2006; Miaskowski, Cooper et al. 2006; Ferreira, Kimura et al. 2008; Gwede, Small et al. 2008; Maliski, Kwan et al. 2008; Pud, Ben Ami et al. 2008). Depending on the type of cancer and its treatment, and the symptoms being focused on, the patient subgroups have varied. For example, Bender et al. (2005) identify and describe three disease stages of breast cancer (group 1: early stage; group 2: stage I, II, and III; group 3: metastatic) and found three symptom clusters (i.e., fatigue, perceived cognitive impairment, mood problems) in each group. Trask and Griffith (2004) studied psychosocial variables of symptom clusters in melanoma patients (N=351) and identified four distinct subgroups (i.e., psychologically unhealthy, physically unhealthy, combined psychologically and physically unhealthy, and healthy. Two studies (Miaskowski, Cooper et al. 2006; Pud, Ben Ami et al. 2008) used predetermined symptoms (i.e., pain, fatigue, sleep disturbance, and depression) which were identified as highly prevalent symptoms during active cancer therapy.

Both studies were cross-sectional and included patients with various cancer diagnoses who were receiving cancer treatment. In the study by (Miaskowski, Cooper et al. 2006), based on symptom severity scores the four patient subgroups were: low levels of all four symptoms, high fatigue and low pain; low fatigue and high pain; and high levels of all four symptoms. Patients who reported high levels of all four symptoms reported the worst functional (performance) status and QOL. In a subsequent replication study of 228 oncology outpatients (Pud, Ben Ami et al. 2008), four distinct patient subgroups were identified: low levels of all four symptoms; high fatigue and low pain; moderate fatigue and high pain; and high levels of all four symptoms. Again, patients who reported high levels of all four symptoms had significantly poorer functional status and QOL. The identification of subgroups of patients who have similar symptom experiences may help to identify low, moderate, and high-risk groups of patients who may warrant different types, different doses, or more targeted symptom management interventions which could improve patient outcomes (Miaskowski, Cooper et al. 2006; Gwede, Small et al. 2008; Pud, Ben Ami et al. 2008).

Symptom clusters in breast cancer

Reviewing previous studies that used the ‘clustering of symptoms’ or ‘clustering of patients’ approaches mentioned earlier, we found approximately 13 studies that studied a homogeneous sample of women with breast cancer during and after cancer treatment. The majority of the studies reported two or three symptoms such as fatigue and sleep (Broeckel, Jacobsen et al. 1998; Berger and Farr 1999; Jacobsen, Hann et al. 1999; Berger and Higginbotham 2000); fatigue, pain, and depression (Gaston-Johansson, Fall-Dickson et al. 1999); fatigue, sleep, and depression (Carpenter, Elam et al. 2004; Liu, Fiorentino et al. 2009); fatigue, sleep, pain and other symptoms (Byar, Berger et al. 2006); fatigue, mood changes, and cognitive impairment (Bender, Ergyn et al. 2005); fatigue and menopausal symptoms (Glaus, Boehme et al. 2006); fatigue, pain, depression, insomnia, and menopausal symptoms (Bower, Ganz et al. 2000); upper gastro-intestinal symptoms and psychoneurological symptom clusters (Kim, Barsevick et al. 2008); high-symptom and low-symptom cluster groups (Gwede, Small et al. 2008); and symptom clusters in patients with lymphedema (e.g., alteration in limb sensation, loss of confidence in body) (Ridner 2005).

Research on symptom clusters in oncology patients is still in its infancy (Miaskowski, Dodd et al. 2004). Previous studies focused on two or three symptoms, using cross-sectional design to collect symptom data, or using longitudinal data collection during the treatment phase (during chemotherapy cycles) or after treatment, and had relatively small sample sizes. According to Barsevick (2007), it seems right to begin with the most prevalent and distressing symptoms (i.e., pain, fatigue, insomnia, and depression) because these symptoms show strong evidence for clustering during and after cancer treatment.

No study was found that explored the most prevalent symptoms of pain, fatigue, sleep disturbance and depression in breast cancer patients in a longitudinal design (both during and after cancer treatment). The present study attempted to replicate the Miaskowski, Cooper et al. (2006) and Pud, Ben Ami et al. (2008) studies. Furthermore, the present study followed patients over time to ascertain any changes in subgroup membership.

Theoretical framework for symptom clusters

Various theoretical frameworks are available to guide our understanding of symptom clusters (Barsevick, 2007). In the present study, we used the Symptom Management Model (SMM) (recently renamed Symptom Management Theory (Humphreys, Lee et al. 2008). In this model, symptom experience is the primary reason people seek health care. According to Dodd, Miaskowski et al. (2001), the definition of a symptom is “a subjective experience reflecting changes in the biopsychosocial functioning sensations, or cognition of an individual” (page

669). SMM is based on the premise that effective management of any given symptom or group of symptoms demands that all three dimensions: Symptom Experience, Symptom Management Strategies, and Outcomes related to symptom status need to be considered. The three nursing domains: Person, Health and Illness, and Environment are contextual variables influencing and surrounding all three dimensions of symptoms.

The three dimensions of symptoms (experience, management, and outcomes) are based on the premise that they are dynamically interrelated. In the present study, we focused on the symptom experience dimension. Symptom experience involves perception, evaluation and response. Perception refers to whether the individual notes a change from the way they usually feel or behave through individual conscious or cognitive interpretation of the information in a specific context. Symptom evaluation refers to the judgment of severity, intensity, location, temporal nature, frequency, and treatability of symptoms. Response refers to feeling, thoughts, or behaviors related to the health problem. This response is demonstrated through psychological, physiological and behavioral components.

According to Barsevick (2007), using the SMM in symptom clusters may not address the following issues:which groups of symptoms should be categorized as symptom clusters, which symptom is more or less important, and how to identify which of the multiple symptoms are part of a cluster. Despite the limitations of SMM, it is useful in its ability to provide clear direction and guidance for clinical practice and research. The SMM is a general model that was developed and tested on various clinical populations. To identify specific symptoms across populations is folly – each clinical population will have unique symptoms that are prominent.

Aims

The purposes of this study in a sample of women with breast cancer who received adjuvant chemotherapy (CTX) with/without radiation therapy (RT) were to: 1) determine the number of patient subgroups based on a specific symptom cluster (i.e., pain, fatigue, sleep disturbance, and depression); 2) evaluate the outcomes (i.e., functional status and quality of life) in these subgroups; and, 3) describe subgroup membership changes over time.

METHODS

Design

The present study was a secondary analysis of data collected as part of a longitudinal, randomized controlled trial that tested the effectiveness of a systematic exercise intervention for cancer-related fatigue and associated symptoms: “Exercise: An intervention for fatigue in cancer patients,” which was funded by the NIH/NINR (RO1 CA83316). In the trial, participants were randomized into three arms that were comprised of a group receiving an exercise prescription throughout the study period, a group that received an exercise prescription after having completed their cancer treatment, and a group receiving usual care throughout the study period. The participants completed questionnaires at baseline – T1 (i.e., the week before cycle two) at the end of cancer treatment - T2, and at the end of the study – T3 (approximately one year after the start of chemotherapy). Researchers were blinded as to which arm of the study the participant was assigned when collecting data. Primary outcome of the clinical trial was cancer-related fatigue, and associated symptoms (i.e., pain, sleep disturbance, and depression). The trial failed to show significant effect of an exercise intervention on fatigue (p=.69), pain (p=.55), sleep disturbance (p=.22), or depression (p=.39). Therefore, the three patient groups were collapsed into one and evaluated based on characteristics of their symptom severities.

Sample and Setting

Approval for the study was received from the institutional review boards of the study sites. In the primary study, women with breast, ovarian, and colorectal cancer (N=119) were recruited from six outpatient cancer clinic settings throughout Northern California between 1999 and 2005. For this secondary analysis, only breast cancer women were included (N=112). Patient inclusion criteria were: > 21 years of age; confirmed diagnosis of breast cancer, able to read, write, and understand English; a Karnofsky Performance Status of > 60; mentally able to complete the written informed consent; and expected to survive > 12 months. Patients were excluded if they had: uncontrolled hypertension, diabetes mellitus; AIDS-related malignancies, leukemia; a pain intensity rating >3 on a 0 to 10 NRS; history of major depression, or a sleep disorder.

Procedures

Participants who met the study criteria and were scheduled to begin chemotherapy were told about the study by referring oncologists and nurses at each recruitment site and then approached by the research staff. The participants were given a packet of questionnaires to complete at the clinic or at their homes that were to be returned to the research staff. The present study used four instruments to measure symptoms with different dimensions (i.e., severity and frequency) and time frames (i.e., now, past 24 hours, and past week). As noted by Barsevick, Whitmer et al. (2006) it would be ideal to use the following aspects to measure symptoms: consistent scaling, parallel dimensions, consistent time frame, consistent clinical context, and reasonable response burden; however, as this study is a replication of previous studies (Miaskowski, Cooper et al. 2006) and (Pud, Ben Ami et al. 2008) this ideal cannot be met.

Instruments

Demographic Profile—The Demographic Profile-Baseline Form (30 items) was completed by the subjects at baseline (T1). Data were collected on age, income, ethnicity, gender, menopausal status, perceived Karnofsky Performance Status (KPS) and current symptomatology. It took the subjects approximately 10 minutes to complete the Baseline Form. The Current Demographic Profile Form was completed at T2 and T3 to document any changes that occurred in occupational status, KPS, menstrual status, and symptomatology. It took the subjects approximately 5 minutes to complete the Current Demographic Profile Form.

Worst Pain Scale (Jensen 2003)—The severity of worst pain in the past 24 hours was measured using a numeric rating scale (NRS): 0 (no pain) to 10 (worst pain imaginable). A descriptive numeric rating scale is a valid and reliable measure of pain intensity (Jensen 2003). It has been used in previous studies, e.g., Miaskowski, Cooper et al. (2006; and Pud, Ben Ami et al. (2008)

Piper Fatigue Scale (PFS) (Piper, Dibble et al. 1998)—The PFS uses a NRS of 0 (none) to 10 (severe) with descriptive anchors; it consists of 22 items and four subscales: behavioral/severity, affective meaning, sensory and cognitive/mood. For this analysis, the total fatigue score was used. The PFS records current experience of fatigue severity. It has well-established content and concurrent validity and internal consistency in cancer patients. The average total fatigue score is calculated by summing participants' responses, then dividing by the number of items. In the current study, Cronbach's alpha for the PFS ranged from .92 to .97.

General Sleep Disturbance Scale (GSDS) (Lee 1992)—The GSDS consists of 21 items that evaluate various aspects of sleep disturbance (i.e., quality and quantity of sleep, sleep latency, waking up during sleep, daytime sleepiness, medication use). Each item is rated on a 0 (never) to 7 (every day) scale that describes the frequency of its occurrence during the past

week. The 21 items are summed to yield a total score that could range from 0 (no disturbance) to 147 (extreme disturbance). A score ≥ 43 reflects sleep disturbance in the general population (Lee and Gay 2004). The GSDS has well-established validity and reliability in shift workers, pregnant women, and patients with HIV (Lee 1992; Humphreys, Lee et al. 1999; Lee, Portillo et al. 2001; Dorsey, Lee et al. 2004). In the current study, Cronbach's alpha for the GSDS ranged from .83 to .86.

Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977)— The CES-D consists of 20 items that evaluate for symptoms of depression. Each item is rated on a 0 to 3 scale that describes the frequency of its occurrence during the previous week. Scores can range from 0 to 60, with higher scores reflecting more depressive symptoms. A score of ≥ 16 indicates a need for clinical assessment for depression. The CES-D has well-established concurrent and construct validity (Sheehan, Fifield et al. 1995; Carpenter, Andrykowski et al. 1998). In the current study, Cronbach's alpha for the CES-D ranged from .86 to .92.

Karnofsky Performance Status Scale (KPS) (Karnofsky 1977)—A self-report of the physical abilities of the patient is based on the definitions provided on a 0 to 100 (%) ratings scale, in increments of 10%. Since its development, the scale has been used extensively in oncology to evaluate performance status. A score of 100% indicates that the individual is able to carry on normal activities and that there is no decrease in performance status. A score of 30% indicates that the individual is severely disabled and needs to be hospitalized. The KPS has well-established inter-rater reliability, concurrent validity, and criterion validity (Hyde 1973; Karnofsky 1977). Clinical trial studies have demonstrated that pretreatment performance by Karnofsky rating is a good predictor of response to cancer treatment (Dodd 1988).

Multidimensional Quality of Life Scale-Cancer (MQOLS-CA) (Ferrell, Wisdom et al. 1989)—This 33-item instrument measures five dimensions of QOL (i.e., psychological well-being, physical well-being, nutrition, symptom distress, and interpersonal well-being). Items are rated on an NRS from 0 (not at all) to 10 (extremely positive) on current well-being. The average total QOL score is calculated by summing participants' responses, then dividing by the number of items. Higher scores indicate better quality of life, but there is no cutoff score for better or worse quality of life. The MQOLS-CA has well-established construct validity and test-retest reliability coefficient (Ferrell, Wisdom et al. 1989; Padilla, Ferrell et al. 1990; Padilla 1992; Padilla 2003). In the current study, Cronbach's alpha ranged from .94 to .95.

Statistical Analysis

Data were analyzed using SPSS® 15.0(SPSS 2008) and Stata ® version 10 (StataCorp 2007). Descriptive statistics and frequency distributions were generated on the sample characteristics. Cluster analysis was used to identify subgroups of patients based on their responses to the four symptom inventories (i.e., worst pain, Piper Fatigue Scale, General Sleep Disturbance Scale, and CES-Depression). Scores were standardized on their ranges and then used in the cluster analysis in order to reduce any differential influence variables with different scale lengths might have on the cluster solution (Everitt et al., 2001; Milligan & Cooper, 1985). The standardized symptom scores for the four patient subgroups are shown in Figure 1. To determine the number of subgroups of patients, an agglomerative, hierarchical cluster analysis was performed with squared Euclidean distances used in the proximities matrix and weighted average linkage used as the clustering method (McQuitty 1966; Everitt 2001). For the question at hand, this clustering method is preferable to the commonly used Ward's method because the authors had no reason to expect that the sizes of the patient subgroups would be similar. Ward's method is known to produce spherical clusters, forcing them toward subgroups of similar sizes, and the method is sensitive to outliers (Everitt 2001).

The Calinski and Harabasz *pseudo-F* stopping rule index and the Duda and Hart Je(2)/Je(1) index were used jointly to select the number of clusters for the analysis (Milligan 1985; StataCorp 2003). Milligan and Cooper identified these two stopping rules as the best among 30 stopping rules for recovering from two to five true clusters in a Monte Carlo simulation. A large Calinski and Harabasz *pseudo-F* statistic, combined with two measures from Duda and Hart [i.e., a large Je(2)/Je(1) index and its associated small *pseudo–T-squared* value], results in four as the most appropriate number of clusters for the data (Milligan 1985; Everitt 2001; StataCorp 2003) at T1 and T2, and three clusters at T3. Detailed explanation on hierarchical cluster analysis was reported in previous publications by our research team (Miaskowski, Cooper et al. 2006).

The Kruskal-Wallis H-test (a one-way ANOVA on ranks) was used to test differences in outcomes among the patient subgroups identified at each time point. It was used to determine whether significant differences existed between the patient subgroups in quantitative demographic characteristics, the defining symptom scores, and outcome measures not included in the cluster analysis (i.e., functional status and QOL). If significant differences among subgroups were found, Mann-Whitney U-tests were used to test pairwise differences among the subgroups. Cross tabulation was used to examine patterns of subgroup membership in adjacent times (from T1 to T2 and from T2 to T3).

RESULTS

Demographic and Clinical Characteristics (Participants)

A total of 112 women with breast cancer participated in the study. Patient demographic and clinical characteristics are summarized in Table 1. The participants were middle aged (mean 50 years, SD=9.3), mainly white (73%), married or partnered (69%), employed full- or part-time (46%), postmenopausal (44%), mostly receiving adriamycin and cytoxan chemotherapy (AC CTX) (88%), with stage I or II breast cancer (84.6%). To reduce possible confounding effects of treatment -related symptoms by aggregating the predetermined symptoms for this study, the authors carefully evaluated the cancer treatment regimens and menopausal status. The patients in this study received more than 20 various regimens for treatment of stage I, II and III breast cancer. The major chemotherapy regimens were: adriamycin and cytoxan with or without radiation therapy, taxane derivatives (e.g., paclitaxel, docetaxel), surgery (neo-adjuvant), or hormonal treatments (e.g., tamoxifen). Since there were more than 20 permutations of AC CTX in the sample size of 112, it was not statistically meaningful to compare the regimens to each other. However, we did conduct selected comparisons: AC CTX (88.4%) vs. non-AC CTX; radiation therapy (68.5%) vs. non-radiation therapy (given after CTX), hormonal treatment (27%) vs. non-hormonal treatment (given after CTX) on pain, fatigue, sleep disturbances, and depression at each time point. There were no statistical differences in pain, fatigue, sleep disturbance, or depression between these group comparisons.

Menopausal status changed in this sample over the course of chemotherapy. A self-report question regarding the women's menopausal status was asked at each time point: premenopausal, "still having periods;" perimenopausal, "usual pattern of periods is altered;" and postmenopausal, "no period for a year or more." At T1, approximately 40% of women were premenopausal, 18% perimenopausal, and 44% postmenopausal. At T2, there were some shifts: premenopausal (9.6%), perimenopausal (46%), and postmenopausal (44.7%). At T3, 24.7% of the women were perimenopausal, and 64% of the women were postmenopausal. Using analysis of variance at each time point to test differences for our four symptoms across menopausal status, no statistical significance was found at any time point. Our findings of chemotherapy-induced premature menopause have also been reported by others (Goldhirsch, Gelber et al. 1990; Richards, O'Reilly et al. 1990; Bianco, Del Mastro et al. 1991; Reyno, Levine et al. 1992; Pagani, O'Neill et al. 1998; Castiglione-Gertsch, O'Neill et al. 2003).

Patient subgroup labeling based on symptom cut scores

In order to name the various subgroups identified using cluster analysis at each time point, descriptive symptom cut points were defined for severity pain scores 1–4 (mild), 5–6 (moderate), 7–10 (severe) (Serlin, Mendoza et al. 1995); fatigue scores 1–3 (mild), 4–6 (moderate), 7–10 (severe) (Piper, Dibble et al. 1998); sleep disturbance scores ≥43 (Lee Gay 2004); depression scores ≥16 (Radloff 1977). Since this study was a longitudinal design but the cluster analyses were performed separately at each time point, general but consistent description is important to the understanding of the transitions within and across patient subgroups. Therefore we used simplified, consistent terms to define patient subgroups at all three time points. For the remainder of this paper the patient subgroups will be referred to as ALL LOW, MILD, MODERATE, and ALL HIGH depending on how many symptoms are greater than the cut score of each symptom and the severity of symptoms at each time point. Consequently, ALL LOW is one or no symptom greater than the cut score, MILD is two symptoms greater than the cut scores, MODERATE is three or four symptoms greater than the cut scores, and ALL HIGH is all four symptoms above the cut scores.

As shown in Figure 1, four patient subgroups were identified at T1 and T2 based on their reports for the four symptoms. At T3, only three patient subgroups were identified. Of note, no significant differences in demographic or clinical characteristics were found among the patient subgroups at any of the time points except T2. At T2, more women in the ALL LOW subgroup were employed.

Patient Subgroup Differences in Symptom Severity Scores

The symptom scores for the patient subgroups and differences in symptom scores over time are listed in Table 2. Unfortunately, the sample sizes of a few subgroups were too small to make statistically meaningful comparisons, e.g. at T3 the ALL HIGH subgroup was n=3. Therefore, interpretation of these comparisons should be made with caution.

ALL LOW Subgroup—Patients in the ALL LOW subgroup reported only mild fatigue at T1 and T2. At T1, pain severity in the ALL LOW patient subgroup was significantly lower than the other three subgroups. At T2, fatigue, sleep disturbance, and depression scores were significantly lower in the ALL LOW patient subgroup than the other three subgroups. This subgroup did not appear at T3.

MILD Subgroup—This subgroup had mild levels of two symptoms i.e., pain and fatigue (T1 and T3) or sleep disturbance and fatigue (T2). At T1, pain severity in the MILD subgroup was higher than the ALL LOW and the MODERATE subgroups, but was similar in severity to the ALL HIGH subgroup.

MODERATE Subgroup—The MODERATE subgroup had moderate levels of three or four symptoms at each time point. At T1 and T3, patients who had mild to moderate pain and fatigue, as well as sleep disturbance, and depression were clustered. At T2, patients who had moderate pain and fatigue, as well as sleep disturbance were clustered. At each time point, most patients in the MODERATE subgroup reported higher levels of symptoms than the ALL LOW and MILD subgroups but lower levels than the ALL HIGH subgroup.

ALL HIGH Subgroup—This subgroup reported high severity scores for all four symptoms compared to other subgroups. Despite the small sample size, this subgroup was identified at all three points. The subgroup size increased at the completion of cancer treatment T2 (n=10), and then decreased at T3 (n=3).

Differences in Functional Status and QOL between Subgroups[1]

Functional status—Figure 2 illustrates the changes in KPS scores for each patient subgroup. At T1, KPS scores were significantly different only between the ALL LOW (90.3±7.9) and the MODERATE (81.7±10.5) patient subgroups (p=.002). At T2, significant differences in KPS scores were found among the subgroups (p<.0001). The ALL LOW subgroup had significantly higher KPS scores than the other three subgroups (p<.0001). No significant differences in KPS were found between the remaining three subgroups. At T3, statistically significant differences in KPS scores were found between the subgroups (p<.0001). The MILD (90.4±8.8) subgroup had a significantly higher KPS score than the MODERATE (82±6.8) and ALL HIGH (60±10) subgroups (p<.005).

QOL—Figure 3 illustrates the changes in QOL scores for each patient subgroup. At T1, significant differences in QOL scores were found between patient subgroups (p<.0001). Women in the ALL LOW (8.1±.9) or MILD (8.5±.5) subgroups reported significantly higher QOL scores compared to the MODERATE (6.7±.9) and ALL HIGH (6.3 ± 1.1) subgroups.

At T2, significant differences in QOL scores were found between the patient subgroups (p<.0001). The ALL HIGH subgroup reported significantly lower QOL scores (5.5 ± .7) than patients in the other three subgroups (all $p \leq .001$). The ALL LOW subgroup reported higher QOL scores (8.4±.8) than those in the other three subgroups (p<.001).

At T3, significant differences in QOL scores were found between the patient subgroups (p<.0001). The MILD subgroup reported significantly higher QOL scores (8.1 ±.9) than those in the MODERATE (7.1±.6) and the ALL HIGH subgroups (all $p \leq .008$). The ALL HIGH subgroup (4.0 ± .4) reported the lowest QOL scores compared to the other two subgroups.

Changes in Patient Subgroup Membership over Time[2]

Since the number of patients in each subgroup was small in some cases and not stable, we were unable to use inferential statistical techniques. Figure 4 illustrates the movement of patients from one subgroup to another from T1 to T2, and from T2 to T3. At the beginning of the study (T1), 47 women clustered into the ALL LOW subgroup. Twenty-seven of these women remained in the ALL LOW subgroup at T2, but 18 of the ALL LOW women migrated to the MILD (n=10), and MODERATE (n=8) subgroups at T2. A small number of women migrated from the MODERATE to the ALL LOW (n=4), MILD (n=8), and ALL HIGH (n=6) subgroups. From T2 to T3, a large number of women migrated to the MILD subgroup. Twenty-eight women (97%) moved from the ALL LOW to the MILD subgroup, and one woman moved to the MODERATE subgroup. Fourteen women in the MODERATE subgroup migrated to the MILD subgroup at T3. Approximately 90% of the women in the MILD subgroup remained in this subgroup between T2 and T3. Notably, all of the women still experienced at least mild levels of one or more symptoms six months after the completion of their cancer treatment.

DISCUSSION

To the best of our knowledge, the present study is the first to cluster patients based on a specific symptom cluster (i.e., pain, fatigue, sleep disturbance, and depression) both during and after

[1]Means and standard deviations are reported on the original scales for the symptom scales for ease of interpretive description. However, the tests for differences among the groups were conducted with nonparametric tests on mean ranks, due to the non-normal distributions of the symptoms. The significance levels (*p*-values) are for the rank tests.

[2]Note that traditional categorical significance tests for change cannot be done in this instance. An appropriate test for change in categories is the McNemar test, but the use of this test requires that the number and meaning of the categories be identical at each time. A preferable alternative that would not have this assumption would be latent transition analysis, but the small sample precluded the use of this method of analysis.

cancer treatment in breast cancer. As already mentioned, the cluster analysis identified four relatively distinct patient subgroups at the beginning of the treatment (T1) and at the end of the cancer treatment (T2): ALL LOW, MILD, MODERATE, and ALL HIGH. At T3 (one year after the start of CTX), three clusters of patient subgroups were identified: MILD, MODERATE, and ALL HIGH.

The present study confirmed and extended previous research. First to be discussed are the comparisons of our findings to those of Miaskowski, Cooper et al. (2006) and Pud, Ben Ami et al. (2008), next to be discussed are the unique contributions of our study related to patient subgroups both during and after cancer treatment, and subsequent subgroup membership changes.

First, the identification of subgroups of oncology patients who reported similar experiences with four common symptoms (Miaskowski, Cooper et al. 2006; Pud, Ben Ami et al. 2008) were relatively consistent with the patient subgroups identified in the present study. This was particularly true for those patients who reported low and high severities of all four symptoms.

The previous two studies had very few significant demographic and clinical characteristics related to the patient subgroups in their heterogeneous samples (Miaskowski, Cooper et al. 2006; Pud, Ben Ami et al. 2008). In the Miaskowski et al. (2006) study, patients in the ALL HIGH subgroup were significantly younger than those in the other three subgroups. However, in the study by Pud et al. (2008), no significant differences in any demographic or clinical characteristics were found between the four patient subgroups. Although most demographic and clinical characteristics were similar to the Miaskowski et al. and Pud et al. sample, the present study showed only one significant difference: employment status. Women in the ALL LOW patient subgroup were employed outside the home. Therefore, there has been, as yet, no replication of findings regarding demographic and clinical variables across studies' patient subgroups.

At each time point, the ALL HIGH patient subgroup reported the lowest functional status (ranging from 60–84%) and quality of life (ranging from 4 to 6.3). Patients who belonged to the ALL LOW or MILD subgroups reported high functional status and quality of life. Differences of standard deviation (SD) units between ALL LOW and ALL HIGH on functional status scores were calculated as follows: (d = [mean score for ALL LOW subgroup − mean score for ALL HIGH subgroup]/standard deviation of the total sample). At T1, SD unit was not statistically significant between these two subgroups (ALL LOW and ALL HIGH) (SD unit=0.63, p=.53), but both of these subgroups were significantly different at T2 and T3 (SD units, respectively = 1.93, 2.93, both $p<0.001$).

The ALL HIGH patient subgroup with all four high symptom severities had significantly lower QOL than the ALL LOW subgroup. The differences in SD units between these two subgroups ranged from 1.5 to 3.52 (all $p<0.001$). Minimum criteria of 0.2 to 0.5 SD units have been shown to be not only statistically significant but also clinically meaningful in QOL studies (Osoba, Rodrigues et al. 1998; Guyatt, Osoba et al. 2002; Norman, Sloan et al. 2003). Therefore, the ALL HIGH patient subgroup had clinically important diminished QOL as compared to the other subgroups.

Second, the overall pattern of change in subgroup membership was from milder levels of symptoms at the beginning of cancer treatment to moderate to severe levels of symptoms at the completion of treatment. This overall pattern reversed direction from the time of completion of treatment to the end of the recovery period approximately six months later. A surprising finding was the total absence of anyone in the ALL LOW subgroup at the end of the recovery period. All of women in the ALL LOW subgroup at T2 were in either the MILD or MODERATE subgroups at T3. It is not known whether the symptoms experienced

approximately six months after the completion of cancer treatment were related to treatment. However, this finding is important because it suggests that women with breast cancer need to be assessed for and have symptoms managed after treatment is completed.

One of the eligibility criteria for participation in the study was a pain rating not greater than 3, based on the 1995 American College of Sports Medicine Guidelines regarding contraindications for exercise training and testing (American College of Sports Medicine 1995). When these participants were screened for the study they met that criteria, but when they completed the T1 baseline questionnaires (after their first cycle of chemotherapy, but before their second cycle) some women reported pain >3, but were still included in the sample. The mean score of the total sample was 1.86 (SD 2.6) at T1. Cluster analysis groups patients who have similar characteristics together, therefore we had two patient subgroups that showed a pain score higher than 3 at T1. The etiology of this pain is unknown, as the women were not asked what was causing their pain. All of the women were asked, “Throughout our lives most us have had pain from time to time (such as minor headaches, toothaches). Is the pain you are experiencing today different from this kind of pain?” The five women in the MILD subgroup responded either ‘yes’ (two), or ‘no’(three) to this question, but all of the eight women in the ALL HIGH subgroup responded ‘yes’ and indicated different regions of their body where the pain was being experienced. This pattern of uniform ‘yes’ responses for the ALL HIGH subgroup was repeated again at T2 and T3, although the women who constituted this subgroup may not be the same women who were in this subgroup at T1. Unfortunately, the etiologies of the pain experiences cannot be determined from our data.

The biological basis for differences in individual patients’ experiences with four highly prevalent and deleterious symptoms, and changes in subgroup membership over time remains to be determined. While some preclinical and clinical evidence suggests a role for pro-inflammatory cytokines in the development of cancer-related symptoms (Lee, Dantzer et al. 2004), others suggest that inter-individual differences in symptom experiences may be genetically determined (Miaskowski and Aouizerat 2007). A few researchers have attempted to understand the mechanisms of symptom clusters in animal models (Cleeland, Bennett et al. 2003; Walsh and Rybicki 2006). Cleeland, Bennett, et al. propose cytokine-induced sickness behavior as a possible explanation for concurrent, related symptoms. Some clinical evidence already exists to support the hypothesis that some of the most common symptoms that patients with cancer experience may occur through the release of pro-inflammatory cytokines. However, based on the symptom cluster studies conducted to date, it is not possible to draw definitive conclusions about whether there is a biological basis for symptom clustering (Miaskowski, Aouizerat et al. 2007). Further study is needed to compare the association of biological mechanism and phenotypes of characteristics to low and high severity of symptoms in patient subgroups.

Limitations

Several limitations need to be acknowledged. While the study lasted over 12 months, data were collected at only three time points, which precluded evaluation of variations that occurred between these time points. Due to attrition and some relatively small subgroup sizes, some contrasts between different subgroups were limited and the statistical techniques used for tracking of individuals across subgroups over time were prohibited. Another limitation is that there are various types of treatment regimens due to the evolution of breast cancer treatment. It is impractical to compare all of these regimens. We assumed that different types of treatment regimens could have various symptom profiles and severities. Further study with an adequate sample is needed to test this assumption.

Conclusions

The study fulfilled the proposed aims of identifying subgroups of patients, determining whether these subgroups differed on outcomes, and describing subgroup membership changes. Even though we have identified various subgroups of patients at each time point, it is still premature to provide specially designed interventions for each distinct subgroup of patients. Despite these limitations the findings suggest that the ALL HIGH patient subgroup existed at each time point and reported significantly poorer functional status and quality of life. This finding replicates and confirms previous studies (Miaskowski, Cooper et al. 2006; Pud, Ben Ami et al. 2008). Clinicians need to assess and identify those patients in the ALL HIGH severity subgroups and offer appropriate interventions for all four symptoms.

Implications for future research rest on what is occurring currently, i.e., intervention studies target one primary symptom and observe whether its associated symptoms improve as a result of the intervention. Future intervention studies must be designed and tested that will have an overall benefit on the clustered symptoms. Many more studies are needed to provide guidance in this emerging field.

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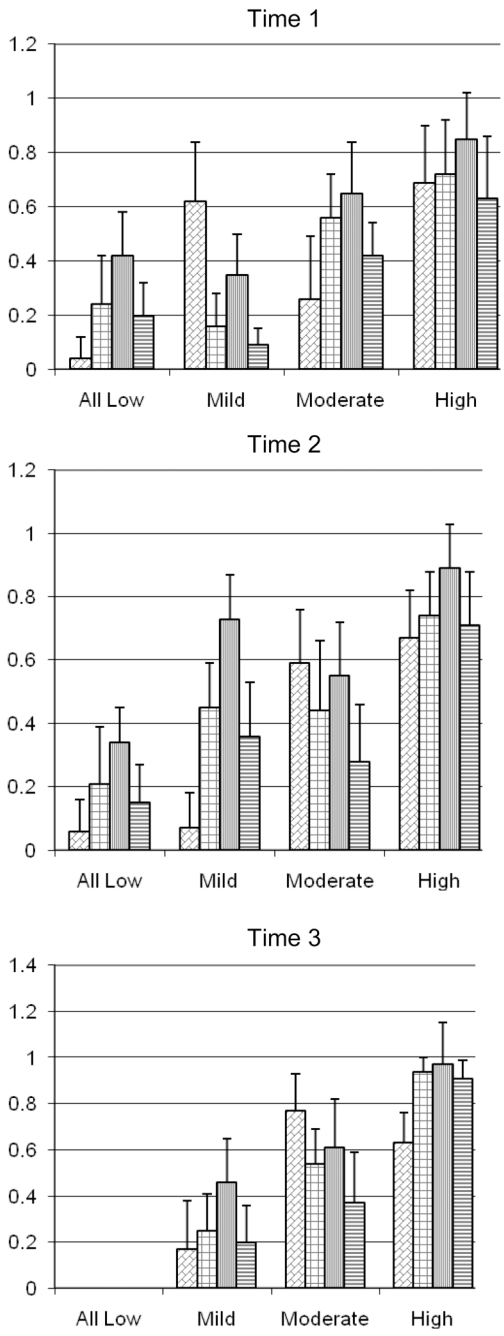


Figure 1.
Standardized scores for the four symptoms at T1, T2, and T3. All values are plotted as standardized mean scores and their standard deviations.

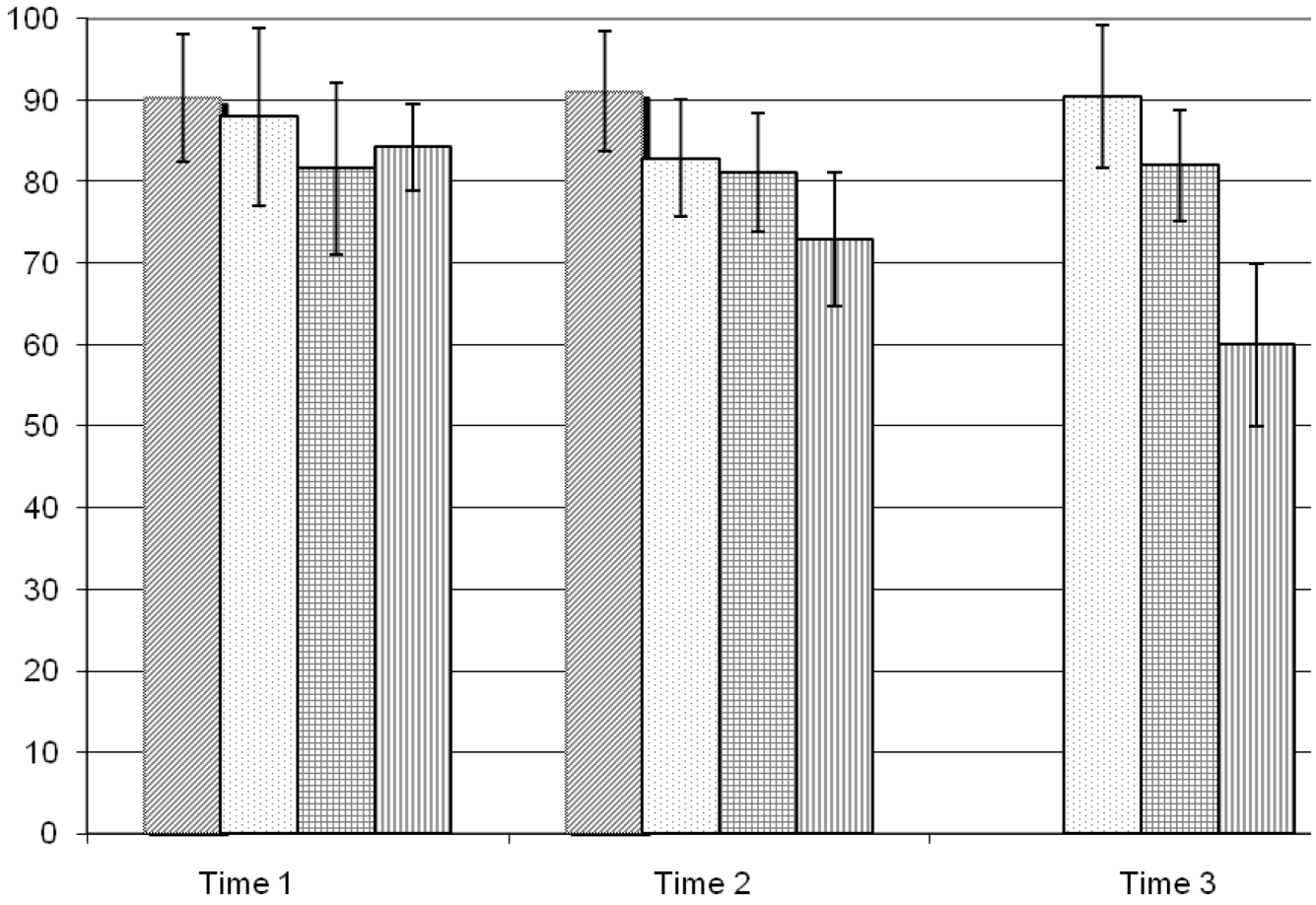


Figure 2.
Changes in functional status scores among patient subgroups at T1, T2, and T3. All values are plotted as mean and standard deviations.

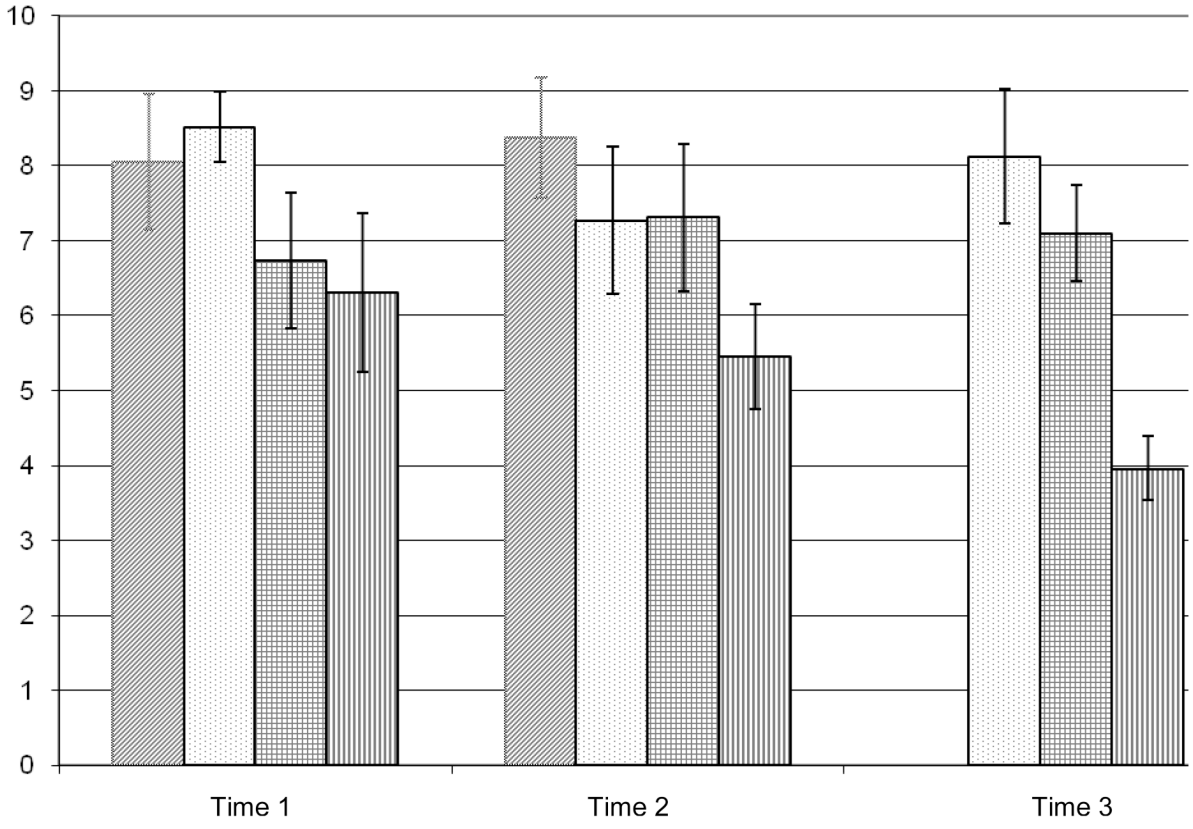
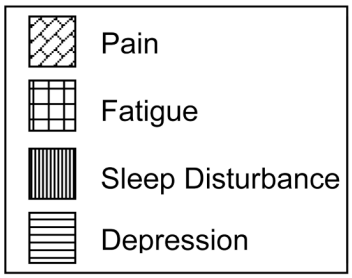


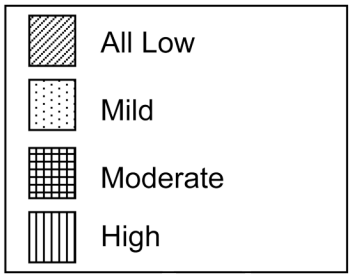
Figure 3.
Changes in quality of life scores among patient subgroups at T1, T2 and T3. All values are plotted as mean and standard deviations.

	Time 1 → Time 2		Time 2 → Time 3	
ALL LOW	◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆ n=47	◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆ ♣♣♣ ♥♥♥♥ n=34	◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ n=29	
MILD	♣♣♣♣ n=4	◆◆◆◆◆◆◆◆◆◆ ♥♥♥♥♥♥♥♥ ♣ n=19	♣♣♣♣♣♣♣♣♣♣ ♣♣♣♣♣♣♣♣♣♣ ♣ n=21	◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆◆◆ ◆◆◆◆◆◆◆◆ ♣♣♣♣♣♣♣♣♣♣ ♣♣♣♣♣♣♣♣♣ ♥♥♥♥♥♥♥♥♥♥ ♥♥♥♥ ♠♠♠♠♠♠ n=67
MODERATE	♥♥♥♥♥♥♥♥♥♥ ♥♥♥♥♥♥♥♥♥♥ ♥♥♥♥♥♥♥ n=27	◆◆◆◆◆◆◆◆◆◆ ♣ ♥♥♥♥♥♥♥♥♥ ♠♠♠♠ n=22	♥♥♥♥♥♥♥♥♥♥ ♥♥♥♥♥♥♥♥♥♥ ♥♥♥ n=23	◆ ♣♣ ♥♥♥♥♥♥♥♥♥♥ ♠♠ n=14
ALL HIGH	♠♠♠♠♠♠♠ n=7	◆◆ ♥♥♥♥♥♥ ♠♠ n=10	♠♠♠♠♠♠♠♠♠♠ n=9	♠ n=1

*Sample size is smaller than cluster subgroups due to missing data from either time point at T1 or T2 or time point at T2 or T3.

Figure 4.
Changes in patient subgroup membership from T1 to T2 and from T2 to T3





♦ Low
♣ Mild
♥ Moderate
♠ High

Table 1

Sample demographic and clinical characteristics (N=112)

	n	%
Age (years)		
Range=28–78 Mean=50.1 Standard Deviation=9.3		
Ethnicity		
White	83	74.11
Black	12	10.71
Asian - Pacific Islander	12	10.71
Hispanic	2	1.79
Other	3	2.68
Marital Status(*n*=110)		
Single	34	30.9
Married	76	69.1
Employment (*n*=100)		
Not employed	53	53.8
Employed	49	46.2
Menopausal Status (*n*=103)		
Premenopausal	40	38.8
Perimenopausal	18	17.5
Postmenopausal	45	43.7
Chemotherapy Types		
Adriamycin + Cytoxan +/− combination of radiation therapy or biological or hormonal therapy	99	88.4
CMF (Cytoxan+Methotrexate+5 flourouracil +/−radiation therapy)	7	6.25
Other	6	5.35
Stage of Disease (*n*=105)		
I	39	37.1
II	50	47.7
III	16	15.2
Mean Days	**Mean**	**SD**
T1 – T2	169.0	64.62
T2 – T3	164.83	60.79

Table 2

Mean symptom severity scores for patient subgroups and differences in pain, fatigue, sleep disturbance, and depression scores at Times 1, 2, and 3.

	Time 1				Time 2				Time 3			
Patient Subgroup	**ALL LOW (1) N=49**	**MILD (2) N=5**	**MODERATE (3) N=32**	**ALL HIGH (4) N=8**	**ALL LOW (1) N=37**	**MILD (2) N=21**	**MODERATE (3) N=26**	**ALL HIGH (4) N=10**	**ALL LOW (1) N=0**	**MILD (2) N=72**	**MODERATE (3) N=15**	**ALL HIGH (4) N=3**
	Pain				**Pain**				**Pain**			
Mean (SD)	0.41 (.81)	6.20 (2.17)	2.56 (2.29)	6.88 (2.10)	0.57 (.93)	0.62 (.97)	5.35 (1.55)	6.00 (1.33)		1.38 (1.66)	6.13 (1.25)	5.00 (1.00)
Statistics*	$\chi2$=46.51, p<.0001 1<2,3 and 4 all p<.005 3<2 and 4, both p<.005 2 vs.4 NS				$\chi2$=70.99, p<.0001 1<3 and 4, both p<.0001 2<3 and 4, both p<.0001 1 vs.2 NS; 3 vs.4 NS				$\chi2$=46.51, p<.0001 2<3 and 4, both p≤.003 3 vs.4 NS			
	Fatigue				**Fatigue**				**Fatigue**			
Mean (SD)	1.97 (1.46)	1.33 (1.00)	4.61 (1.30)	5.91 (1.66)	1.88 (1.58)	4.01 (1.25)	3.95 (1.94)	6.62 (1.26)		2.28 (1.46)	4.86 (1.32)	8.47 (.050)
Statistics*	$\chi2$=49.44, p<.0001 1<3 and 4, both p=.0008; 2<3 and 4, both p<.005 1 vs.2 NS; 3 vs.4 NS				$\chi2$=42.41, p<.0001 1<2,3 and 4, all p<.0001 2<4, p<.0001 3<4, p<.0001 2 vs.3 NS				$\chi2$=30.89, p<.0001 2<3 and 4, both p<.0001 3<4, p<.008			
	Sleep				**Sleep**				**Sleep**			
Mean (SD)	37.80 (14.49)	31.33 (13.50)	57.69 (16.94)	75.95 (15.10)	29.70 (9.77)	64.09 (12.58)	47.79 (14.72)	77.60 (11.91)		41.54 (16.95)	55.80 (18.85)	88.00 (16.52)

	Time 1				Time 2				Time 3			
Patient Subgroup	**ALL LOW (1) N=49**	**MILD (2) N=5**	**MODERATE (3) N=32**	**ALL HIGH (4) N=8**	**ALL LOW (1) N=37**	**MILD (2) N=21**	**MODERATE (3) N=26**	**ALL HIGH (4) N=10**	**ALL LOW (1) N=0**	**MILD (2) N=72**	**MODERATE (3) N=15**	**ALL HIGH (4) N=3**
Statistics*	$\chi2$=37.65, p<.0001 1<3 and 4, both p<.0001 2<3 and 4, both p<.005 1 vs.2 NS; 3 vs.4 NS				$\chi2$=62.85, p<.0001 1<2,3 and 4, all p<.0001 2<4, p=.007; 2>3, p<.0001 3<4, p<.0001				$\chi2$=13.93, p<.001 2 vs.3 NS; 2<4, p<.008 3 vs.4 NS			
	Depression				**Depression**				**Depression**			
Mean	7.90	3.60	16.88	25.25	6.27	14.85	11.49	29.30		9.25	17.00	42.00
(SD)	(4.81)	(2.51)	(4.62)	(9.32)	(4.80)	(6.78)	(7.23)	(7.10)		(7.34)	(9.92)	(346)
Statistics*	$\chi2$=54.40, p<.0001 1<3 and 4, both p<.0001 2<3 and 4, both p<.003 1 vs.2 NS; 3 vs.4 NS				$\chi2$=42.26, p<.0001 1<2,3 and 4, all p<.0001 2 vs.3 NS 2<4, p<.0001 3<4, p<.0001				$\chi2$=15.65, p<.0001 2<3 and 4, both p<.001 3<4, p<.008			

Mann-Whitney U-test Bonferroni Pairwise comparisons, p<.0083

*Statistics, listed in order: Kruskal-WallisTest, Statistical Significance, Post-hoc Contrasts