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Consistency of symptom clusters among advanced cancer patients seen at an outpatient supportive care clinic in a tertiary cancer center

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ABSTRACT

Objective: Advanced cancer patients often develop severe physical and psychological symptom clusters (SCs), but limited data exist on their consistency or severity after an outpatient interdisciplinary team consultation led by palliative care specialists. The primary aim of the study was to determine the consistency and severity of SCs in advanced cancer patients in this setting.

Method: A total of 1373 patients with advanced cancer who were referred to The University of Texas MD Anderson Cancer Center's Outpatient Supportive Care Center between January 2003 and October 2008 with a complete Edmonton Symptom Assessment Scale (ESAS; 0–10 scale) occurred at initial and first follow-up visit were reviewed (median 14 days, range 1–4 weeks). We used a Wilcoxon signed-rank test to determine whether symptoms changed over time, and a principal components factor analysis with varimax rotation to determine SCs at baseline and at first follow-up. The number of factors calculated was determined based upon the number of eigenvalues.

Results: The patients' ratings of the following symptoms (mean, SD) at the initial and follow-up visits, respectively, were: fatigue 6.2 (2.3) and 5.7 (2.5, $p < 0.0001$), pain 5.4 (2.9) and 4.6 (3, $p < 0.0001$), nausea 2.2 (2.8) and 2.0 (2.6, $p < 0.0001$), depression 3.0 (2.9) and 2.5 (2.7, $p < 0.0001$), anxiety 3.4 (3.0) and 2.8 (2.8, $p < 0.0001$), drowsiness 4.8 (3.1) and 4.4 (3.1, $p < 0.0001$), dyspnea 3.0 (2.9) and 2.7 (2.8), $p < 0.0001$), loss of appetite 4.2 (2.7) and 3.9 (2.7, $p < 0.0001$), sleep disturbances 4.2 (2.6) and 3.8 (2.6, $P < 0.0001$), and well-being 4.3 (2.5) and 3.9 (2.3, $p < 0.0001$). Cluster composition differentiated into physical (fatigue, pain, nausea, drowsiness, dyspnea, and loss of appetite) and psychological (anxiety and depression) components at the initial visit, and these two SCs were consistent upon follow-up.

Significance of results: We conclude that SCs remain constant between baseline and near-term follow-up but that the severity of those symptoms lessened during that interval. This knowledge may allow palliative care teams to provide more targeted and higher-quality care, but further studies are needed.

KEYWORDS: Palliative care, SCs, Advanced cancer, Consistency of symptoms, Severity of symptoms

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INTRODUCTION

Patients with advanced cancer may experience severe physical and psychological symptoms during

the course of the disease. (Dodd et al., 2001; Paice, 2004; Trask & Griffith, 2004) Symptoms reported in advanced cancer patients include: pain (in 41–76% of patients), fatigue (in 90%), nausea (in 24–90%), depression (in 33–40%), anxiety (in 57–68%), sedation/confusion (in 46–60%), anorexia (in 85%), dyspnea (in 12–58%), sleep disturbance (in 50%), and constipation (in 65%) (Walsh et al., 2000; Klinkenberg et al., 2004) Many of these symptoms occurred simultaneously as groups or clusters, (Portenoy et al., 1994; Chang et al., 2000; Cleeland et al., 2000) in particular pain, fatigue, depression, and sleep disturbance (Walsh & Rybicki, 2006).

A symptom cluster (SC) is defined as two or more symptoms that co-occur and are strongly correlated among symptoms within that group (Dodd et al., 2001; Kim et al., 2005; Miaskowski, 2006). The etiology of SCs is not currently known; however, the last decade has seen increased interest in the field of SC research in patients with advanced cancer (Dodd et al., 2001). These symptoms may be the result of patient factors, cancer and/or treatment (e.g., cytotoxic chemotherapy, radiation, or surgery) (Rosenthal et al., 2007; Hadi et al., 2008; Cleeland et al., 2011; Thong et al., 2011; Yang et al., 2012) and can have severe psychosocial impact on patients' quality of life (Kramer et al., 2000; Efficace et al., 2004). Even though studies have been undertaken to understand the frequency and intensity of SCs, few studies focused on identifying SCs in patients receiving outpatient palliative care (Cheung et al., 2009; Tsai et al., 2010). There also are limited data on the consistency and severity of SCs presented following an outpatient interdisciplinary team consultation led by palliative care specialists.

Further knowledge of SCs is needed because patients may receive limited contact with the palliative care team because of late referrals or outpatient status, and these data could be helpful to develop effective management strategies and thus provide quality palliative care to patients with advanced cancer. The aim of this retrospective trial was to determine the consistency and severity of SCs after an outpatient interdisciplinary palliative team consultation.

METHODS

Patient Selection

We reviewed the medical records of consecutive patients with advanced cancer (defined as locally advanced and/or metastatic) seen at the outpatient Supportive Care Center in The University of Texas MD Anderson Cancer Center between January 2003 and October 2008. Advanced cancer patients who had at least one follow-up visit within 7–30 days of initial visits and who completed an Edmonton Symptom Assessment Scale (ESAS) questionnaire at the time of initial and follow-up visits were included in the study. Of the 1378 patients initially enrolled in the trial, 5 were excluded because of missing data from the ESAS at the baseline visit ($n = 4$) or at follow-up ($n = 1$).

We received institutional review board approval for conducting this study.

Process of Palliative Care Service

Palliative care in the outpatient setting is provided by an interdisciplinary team led by board-certified palliative care specialists. The team includes a physician and may involve other specialists such as a registered nurse trained specifically in palliative care, a pharmacist, a nutritionist, a chaplain, a social worker, and a palliative- and psychiatry-trained advanced practice nurse who provides counseling services. The mutual coverage by our team helps to maintain consistent case assessment and management as well as communication with patients and their families. Care providers in wound management, speech therapy, occupational therapy, and physical therapy also are consulted when needed. Each patient's care plan is developed according to a standardized management plan (Bruera & Elsayem, 2008).

Once the registered nurse assesses the patient using the ESAS, the Memorial Delirium Assessment Scale (to screen for delirium) and constipation and family support questionnaires, the team proposes a treatment plan on the basis of the input of patients and their families. This plan follows the guidelines of the National Comprehensive Cancer Network and National Consensus Project (Levy et al., 2006). These guidelines demonstrate the importance of the multidimensional team approach, including the following aspects of care:

- structure and processes of a treatment plan
- physical, psychosocial and psychiatric
- social and cultural
- ethical and legal
- spiritual, religious, and existential
- the unique needs of the imminently dying patient

Assessments

We collected data on each patient's demographic features including age, sex, and race as well as cancer diagnosis.

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ESAS

The ESAS is a self-reported instrument developed and modified to measure symptoms of cancer patients in palliative care (Bruera et al., 1991). It catalogs pain, fatigue, nausea, depression, anxiety, loss of appetite, drowsiness, well-being, dyspnea, and sleep disturbance. ESAS is validated as a simple bedside method for symptom assessment in patients receiving palliative care (Watanabe et al., 2011). The symptom distress score for each defined SC as well as total scores were calculated with a sum of score of each item included in that same SC.

Statistical Analysis

We analyzed demographic variables (age, sex, and race) and clinical characteristics of patients using descriptive statistics (means, medians, frequencies, and percentages) and compared differences between baseline and a follow-up ESAS score using a Wilcoxon signed-rank test. We used the Spearman rank correlation coefficient to measure the association between ESAS symptom scores at baseline and at follow-up. Principal component factor analysis was used to determine SCs at baseline and follow-up by transforming the data to the natural log scale to obtain a normal distribution. The analysis of symptoms was based on a patient's ESAS score at the baseline Supportive Care Center visit and the first subsequent follow-up. Similarity between symptoms was measured using correlations, and average linkage was used to join clusters.

RESULTS

Patient characteristics are shown in Table 1. In the 1373 patients in the study, the median age was 59 years and 53% were male (732/1373). The most common cancer was lung cancer (24%) followed by gastrointestinal cancer (20%). The median time between the initial visit and follow-up was 14 days.

Table 1. *Patients' characteristics* (n = *1373)*

Characteristic		Number of patients (%)
Age (Median Interquartile Range)		59 (51–68)
Sex		
	Male	732 (53.3)
	Female	641 (46.7)
Race		
	White	1007 (73.4)
	Black	154 (11.2)
	Hispanic	142 (10.3)
	Asian	48 (3.5)
	Other	22 (1.6)
Cancer diagnosis		
	Lung	327 (23.8)
	Gastrointestinal	280 (20.4)
	Genitourinary	142 (10.3)
	Head and neck	137 (10)
	Gynecological	118 (8.6)
	Breast	96 (7)
	Sarcoma	86 (6.3)
	Hematological	55 (4)
	Other	132 (9.6)

All ESAS values improved between baseline and follow-up except for appetite (Table 2).

Tables 3 and 4 show that all ESAS items strongly correlated with each other ($p < 0.0001$) except dyspnea and pain ($p = 0.30$) and drowsiness and pain ($p = 0.06$) at baseline. The highest correlation was observed between anxiety and depression, both at baseline and follow-up.

At baseline, the principal component factor analysis identified two SCs that accounted for 42% of the

Table 2. *ESAS scores at baseline and follow-up*

Factor	Baseline		Follow-up		*p* value
	Mean (SD)	Median (Q1, Q3)	Mean (SD)	Median (Q1, Q3)	
Pain	5.4 (2.9)	6 (3, 8)	4.6 (3)	4 (2, 7)	<0.001
Fatigue	6.2 (2.3)	6 (5, 8)	5.7 (2.5)	6 (4, 8)	<0.001
Nausea	2.2 (2.8)	1 (0, 4)	2 (2.6)	1 (0, 3)	<0.001
Depression	3 (2.9)	3 (0, 5)	2.5 (2.7)	2 (0, 4)	<0.001
Anxiety	3.4 (3)	3 (0, 5)	2.8 (2.8)	2 (0, 5)	<0.001
Appetite	3.7 (3.1)	3 (0, 6)	3.5 (3)	3 (1, 6)	0.156
Drowsiness	4.8 (3.1)	5 (2, 7)	4.4 (3.1)	4 (2, 7)	<0.001
Feeling of well-being	4.9 (2.8)	5 (3, 7)	4.3 (2.7)	4 (2, 6)	<0.001
Dyspnea	3 (2.9)	2 (0, 5)	2.7 (2.8)	2 (0, 5)	<0.001
Sleep disturbance	4.6 (2.9)	5 (2, 7)	4.1 (2.9)	4 (2, 6)	<0.001
SDS	36.1 (14.9)	35 (25, 46)	32.3 (15.1)	30.5 (21, 42)	<0.001

ESAS, Edmonton Symptom Assessment Scale; SDS, total symptom distress score; SD, standard deviation; Q1–Q3, endpoints of the interquartile range.

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Table 3. *Spearman's correlation of ESAS scores at baseline*

Score	Pain	Fatigue	Nausea	Depression	Anxiety	Appetite	Drowsiness	Well-being	Dyspnea	Sleep disturbance
Pain	1.000									
Fatigue	0.247*	1.000								
Nausea	0.183*	0.282*	1.000							
Depression	0.180*	0.290*	0.244*	1.000						
Anxiety	0.184*	0.286*	0.217*	**0.659***	1.000					
Appetite	0.147*	0.432*	0.290*	0.278*	0.276*	1.000				
Drowsiness	0.030[a]	0.249*	0.366*	0.197*	0.203*	0.269*	1.000			
Well-being	0.216*	0.356*	0.234*	0.357*	0.379*	0.369*	0.378*	1.000		
Dyspnea	0.059†	0.292*	0.203*	0.224*	0.240*	0.251*	0.196*	0.187*	1.000	
Sleep disturbance	0.209*	0.220*	0.186*	0.232*	0.291*	0.235*	0.224*	0.356*	0.251*	1.000

*$p < 0.0001$ (2-tailed). †$p = 0.0.28$. Correlation is significant at the 0.05 level (2-tailed).
[a]$p = 0.2$.
ESAS, Edmonton Symptom Assessment Scale.

Table 4. *Spearman's correlation of ESAS scores at follow-up*

Score	Pain	Fatigue	Nausea	Depression	Anxiety	Appetite	Drowsiness	Well-being	Dyspnea	Sleep disturbance
Pain	1.000									
Fatigue	0.349*	1.000								
Nausea	0.215*	0.303*	1.000							
Depression	0.213*	0.264*	0.297*	1.000						
Anxiety	0.227*	0.286*	0.262*	**0.668***	1.000					
Appetite	0.224*	0.449*	0.271*	0.278*	0.224*	1.000				
Drowsiness	0.127*	0.315*	0.316*	0.225*	0.207*	0.281*	1.000			
Well-being	0.262*	0.446*	0.280*	0.387*	0.397*	0.399*	0.420*	1.000		
Dyspnea	0.121*	0.317*	0.184*	0.241*	0.317*	0.276*	0.150*	0.243*	1.000	
Sleep disturbance	0.231*	0.286*	0.194*	0.254*	0.312*	0.282*	0.271*	0.421*	0.421*	1.000

*$p < 0.0001$ (2-tailed). ESAS, Edmonton Symptom Assessment Scale.

variance: physical and psychological (Table 5). The physical SC included pain, fatigue, nausea, loss of appetite, drowsiness, well-being, dyspnea, and sleep disturbance; the standardized Cronbach's α score was 0.68. The psychological SC consisted of depression and anxiety; standardized Cronbach's α score was 0.77. At the follow-up visit, we identified two clusters with 44% variance. Components for each cluster were the same as in the baseline SCs and Cronbach's α scores were 0.71 for the physical SC and 0.80 for the psychological SC.

We next compared the mean total symptom distress score and the mean symptom score for each SC between baseline and follow-up (Fig. 1). Physical, psychological, and total distress scores all decreased significantly from the time of baseline to follow-up ($p < 0.001$).

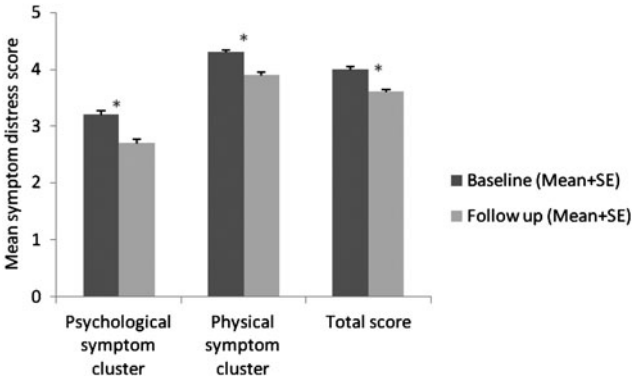

Fig. 1. Mean symptom distress scores at baseline and follow-up for each symptom cluster and the total (*$p < 0.001$, SE: Standard error).

DISCUSSION

Our data lead us to conclude that SC composition in advanced cancer patients presenting to outpatient palliative care can be easily differentiated into physical and psychological components at the initial visit, and that these two SCs are consistent at follow-up. Our data also indicate that advanced cancer patients in outpatient palliative care who experience severe physical and psychological symptoms at presentation can attain significant improvement by the time of the first follow-up visit after an initial palliative care consultation.

Table 5. *Principal component analysis of baseline and follow-up ESAS scores*

Score	Baseline		Follow-up	
	Factor 1	Factor 2	Factor 1	Factor 2
Pain	0.33	0.15	0.45	0.07
Fatigue	0.29	0.54	0.60	0.24
Nausea	0.13	0.65	0.53	0.21
Depression	**0.84***	**0.10***	**0.17***	**0.85***
Anxiety	**0.85***	**0.09***	**0.14***	**0.89***
Appetite	0.26	0.59	0.61	0.19
Drowsiness	0.04	0.66	0.66	0.02
Well-being	0.51	0.34	0.55	0.35
Dyspnea	0.15	0.52	0.23	0.46
Sleep disturbance	0.37	0.37	0.55	0.19
% of Variance	31.1%	10.8%	33.1%	10.9%
Cronbach's α	0.68	0.77	0.71	0.80

*Indicates symptom clustering in each factor. Baseline: On the basis of the eigenvalues, we chose to examine two factors that accounted for 42% of variance. Follow-up: On the basis of the eigenvalues, we chose two factors that explained 44% of the variance. ESAS, Edmonton Symptom Assessment Scale.

To our knowledge, this is the first study to provide information about the consistency of SCs and changes in the severity of both physical and psychological SCs at the first follow-up visit after an initial palliative consultation. Such a consistent outcome measure may help us target a common treatment strategy that would alleviate the severity of physical or psychological symptoms. This consistency also may enable us to more easily monitor changes in symptom severity at follow-up visits.

Prior studies have examined the consistency of symptom SCs longitudinally in patients with advanced cancer. Some of these studies used ESAS items for SC analysis. In a study by Chow et al. (2008) of 170 patients with brain metastases receiving radiation therapy, three SCs were identified: a fatigue, drowsiness, shortness of breath, and pain cluster; an anxiety and depression cluster; and a poor appetite, nausea, and poor sense of well-being cluster. In contrast with our results, however, over time during radiation therapy, the composition of the SCs changed (Chow et al., 2008).

In another study by Chow et al. of 518 patients with bone metastases receiving radiation therapy, three SCs were identified: a fatigue pain, drowsiness, and poor sense of feeling of well-being cluster; an anxiety and depression cluster; and a shortness of breath, nausea, and poor appetite cluster (Chow et al., 2007). As in the previous study, over time during radiation therapy, the composition of the SCs changed. Like us, Chow et al. found depression and anxiety to be a distinct SC at baseline and follow-up in patients receiving radiation therapy for brain metastases and bone metastases.

In a study of 1296 advanced cancer patients, Chen et al. also found depression and anxiety as a distinct category of symptom distress, and they

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supported their data using three statistical methods (principal component analysis, hierarchical cluster analysis, and exploratory factor analysis)(Chen et al., 2012). In a study of 1366 advanced cancer patients, Cheung et al. identified two SCs at an outpatient palliative care clinic. Similar to us, they found a physical cluster that included fatigue, drowsiness, nausea, decreased appetite, and dyspnea and a psychological cluster that included anxiety and depression (Cheung et al., 2009). In that study, anxiety and depression continued to constitute a cluster even when patients with solid tumors were partitioned into subgroups on the basis of the cancer site.

In another study of 1296 patients with advanced cancer who were seen at an outpatient palliative radiation clinic, Fan et al. found two distinct physical SCs (cluster 1 included lack of appetite, nausea, poor sense of well-being, and pain; cluster 2 included fatigue, drowsiness, and shortness of breath) and a psychological cluster (depression and anxiety) (Fan et al., 2007).The authors of that study reported that anxiety and depression had no relationship to the physical symptoms.

Even though the patient populations were different, all studies cited found that depression and anxiety combined to form a distinct SC. These results suggest that all advanced cancer patients receiving outpatient palliative care require supportive counseling in addition to physical symptom management. Future studies using multimodal strategies to determine the optimal use of an interdisciplinary team should be considered.

Prior studies reported interventions using SCs as an outcome measure. The responses to these interventions varied according to the type of intervention (Jarden et al., 2009; Dodd et al., 2010; Husain et al., 2010; Kwekkeboom et al., 2010; Chan et al., 2011) Improvement of SCs after intervention was reported in the trials with multidimensional management (Jarden et al., 2009) or a pathophysiology-based approach (Husain et al., 2010; Chan et al., 2011), whereas a single modality approach did not cause improvement in SCs (Dodd et al., 2010; Kwekkeboom et al., 2010). These data suggest that either a multimodal- or a pathophysiology-based approach to SCs could be reasonable in management of SCs (Cheville et al., 2011). Prior studies have used biological markers (Steel et al., 2010) and the number of SCs (Jiménez et al., 2011) have been suggested as indicators of clinical outcomes in the improvement of quality of life. Our study did not analyze the SC as an indicator of outcomes. However, the consistency during follow-up of the order of severity of each symptom and the stability of the SCs suggest that SCs could be used as effective outcome measures. Further prospective studies are needed to validate these findings.

Limitations

Our study had many limitations. Our study used the 10 item ESAS score to identify symptom candidates for the cluster analysis. Considering that a median of 11 symptoms was reported in cancer patients (Walsh & Rybicki, 2006) other symptoms also may have shown high correlation with symptoms in the ESAS, including altered sexuality (Wilmoth et al., 2004), cognitive impairment (Fox et al., 2007), weight loss (Francoeur, 2005), or some side effects of chemotherapy such as mucositis. Also, although our study was based on prospectively collected ESAS scores, the analysis was performed retrospectively. The absence of a control group in our study could be another limitation; however, the data presented have significance, as the patients with advanced cancer showed improvement rather than worsening of symptoms upon follow-up, in contrast to what is commonly expected in advanced cancer as a result of disease progression. The higher baseline mean intensity of the physical SC score compared with the psychological SC score ($p < 0.0001$) in our study suggests that the physical distress of our patient population was more severe than the psychological distress; however, it also is possible that we were unable to capture the entire dimension and severity of psychological distress using ESAS anxiety and depression items as compared with validated tools such as the Hospital Anxiety and Depression Scale.

Because of the wide use of ESAS among palliative care clinicians, an effort to find SCs in the ESAS and to develop care plans addressing ESAS clusters will have great implications in the clinical world. For example, there is a paucity of studies about managing symptoms of cancer patients according to SCs.

Several biologic markers have been suggested in the pathophysiology of cancer-related symptoms. The C-reactive protein as a marker for systemic inflammation is known to be associated with cancer-related pain (Rokyta et al., 2009; Laird et al., 2011a), SCs (e.g., pain, depression, and fatigue) (Laird et al., 2011b), and anxiety and depression (Brown et al., 2005). Other markers including interleukins such as Interleukin-6 also have been associated with cancer pain (Starkweather et al., 2011). The antitumor necrosis factor alpha (anti-TNF-α) antibody also has been suggested as a biologic marker of the pathophysiology of cancer-related symptoms (Beutler & Cerami, 1988; Argilés & López-Soriano, 1999; Kurzrock, 2001) For example, an anti-TNF-α antibody was tested in cancer-related

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fatigue and conferred marginal benefit, which may lead one to assume that some SCs have a common pathophysiology; future studies to characterize the pathophysiology of SCs in advanced cancer and to manage the patient's symptoms according to the SCs (e.g., use of anti-inflammatory agents such as dexamethasone or thalidomide for management of physical SCs and psychotherapy and anti-inflammatory agents for psychological SCs) are needed.

CONCLUSION

In conclusion, we identified two SCs, physical and psychological, at the initial visit, and found that these SCs were consistent at the first follow-up visit. The intensity of these physical and psychological SCs decreased, however. This knowledge may allow palliative care teams to provide more targeted and higher-quality care, but further studies are needed.

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REFERENCES

Argilés, J.M. & López-Soriano, F.J. (1999). The role of cytokines in cancer cachexia. *Medicinal Research Reviews*, *19*, 223–248.

Beutler, B. & Cerami, A. (1988). Tumor necrosis, cachexia, shock, and inflammation: a common mediator. *Annual Review of Biochemistry*, *57*, 505–518.

Brown, D.J.F., McMillan, D.C. & Milroy, R. (2005). The correlation between fatigue, physical function, the systemic inflammatory response, and psychological distress in patients with advanced lung cancer. *Cancer*, *103*, 377–382.

Bruera, E. & Elsayem, A. (2008). *The MD Anderson Supportive and Palliative Care Handbook*. UT Printing & Media Services. Houston: The University of Texas Health Science Center.

Bruera, E., Kuehn, N., Miller, M.J., et al. (1991). The Edmonton Symptom Assessment System (ESAS): a simple method for the assessment of palliative care patients. *Journal of Palliative Care*, *7*, 6–9.

Chan, C.W.H., Richardson, A. & Richardson, J. (2011). Managing symptoms in patients with advanced lung cancer during radiotherapy: results of a psychoeducational randomized controlled trial. *Journal of Pain and Symptom Management*, *41*, 347–357.

Chang, V.T., Hwang, S.S., Feuerman, M., et al. (2000). Symptom and quality of life survey of medical oncology patients at a veterans affairs medical center: a role for symptom assessment. *Cancer*, *88*, 1175–1183.

Chen, E., Nguyen, J., Cramarossa, G., et al. (2012). Symptom clusters in patients with advanced cancer: Subanalysis of patients reporting exclusively non-zero ESAS scores. *Palliative Medicine*, *26*, 826–833.

Cheung, W.Y., Le, L.W. & Zimmermann, C. (2009). Symptom clusters in patients with advanced cancers. *Supportive Care in Cancer*, *17*, 1223–1230.

Cheville, A.L., Novotny, P.J., Sloan, J.A., et al. (2011). The value of a symptom cluster of fatigue, dyspnea, and cough in predicting clinical outcomes in lung cancer survivors. *Journal of Pain and Symptom Management*, *42*, 213–221.

Chow, E., Fan, G., Hadi, S., et al. (2007). Symptom clusters in cancer patients with bone metastases. *Supportive Care in Cancer*, *15*, 1035–1043.

Chow, E., Fan, G., Hadi, S., et al. (2008). Symptom clusters in cancer patients with brain metastases. *Clinical Oncology (Royal College of Radiologists)*, *20*, 76–82.

Cleeland, C.S., Mendoza, T.R., Wang, X.S., et al. (2000). Assessing symptom distress in cancer patients: The M.D. Anderson Symptom Inventory. *Cancer*, *89*, 1634–1646.

Cleeland, C.S., Mendoza, T.R., Wang, X.S., et al. (2011). Levels of symptom burden during chemotherapy for advanced lung cancer: differences between public hospitals and a tertiary cancer center. *Journal of Clinical Oncology*, *29*, 2859–2865.

Dodd, M.J., Cho, M.H., Miaskowski, C., et al. (2010). A randomized controlled trial of home-based exercise for cancer-related fatigue in women during and after chemotherapy with or without radiation therapy. *Cancer Nursing*, *33*, 245–257.

Dodd, M.J., Miaskowski, C. & Paul, S.M. (2001). Symptom clusters and their effect on the functional status of patients with cancer. *Oncology Nursing Forum*, *28*, 465–470.

Efficace, F., Biganzoli, L., Piccart, M., et al. (2004). Baseline health-related quality-of-life data as prognostic factors in a phase III multicentre study of women with metastatic breast cancer. *European Journal of Cancer*, *40*, 1021–1030.

Fan, G., Hadi, S. & Chow, E. (2007). Symptom clusters in patients with advanced-stage cancer referred for palliative radiation therapy in an outpatient setting. *Supportive Cancer Therapy*, *4*, 157–162.

Fox, S.W., Lyon, D. & Farace, E. (2007). Symptom clusters in patients with high-grade glioma. *Journal of Nursing Scholarship*, *39*, 61–67.

Francoeur, R.B. (2005). The relationship of cancer symptom clusters to depressive affect in the initial phase of palliative radiation. *Journal of Pain and Symptom Management*, *29*, 130–155.

Hadi, S., Fan, G., Hird, A.E., et al. (2008). Symptom clusters in patients with cancer with metastatic bone pain. *Journal of Palliative Medicine*, *11*, 591–600.

Husain, A., Bezjak, A. & Easson, A. (2010). Malignant ascites symptom cluster in patients referred for paracentesis. *Annals of Surgical Oncology*, *17*, 461–469.

Jarden, M., Nelausen, K., Hovgaard, D., et al. (2009). The effect of a multimodal intervention on treatment-related symptoms in patients undergoing hematopoietic stem cell transplantation: a randomized controlled trial. *Journal of Pain and Symptom Management*, *38*, 174–190.

Jiménez, A., Madero, R., Alonso, A., et al. (2011). Symptom clusters in advanced cancer. *Journal of Pain and Symptom Management*, *42*, 24–31.

Kim, H.J., McGuire, D.B., Tulman, L., et al. (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing*, *28*, 270–282.

Klinkenberg, M., Willems, D.L., van der Wal, G., et al. (2004). Symptom burden in the last week of life. *Journal of Pain and Symptom Management*, *27*, 5–13.

Kramer, J.A., Curran, D., Piccart, M., et al. (2000). Identification and interpretation of clinical and quality of life prognostic factors for survival and response to treatment in first-line chemotherapy in advanced breast cancer. *European Journal of Cancer*, *36*, 1498–1506.

Kurzrock, R. (2001). The role of cytokines in cancer-related fatigue. *Cancer*, *92*, 1684–1688.

Kwekkeboom, K.L., Abbott-Anderson, K. & Wanta, B. (2010). Feasibility of a patient-controlled cognitive-behavioral intervention for pain, fatigue, and sleep disturbance in cancer. *Oncology Nursing Forum*, *37*, E151–159.

Laird, B.J.A., Scott, A.C., Colvin, L.A., et al. (2011a). Cancer pain and its relationship to systemic inflammation: an exploratory study. *Pain*, *152*, 460–463.

Laird, B.J.A., Scott, A.C., Colvin, L.A., et al. (2011b). Pain, depression, and fatigue as a symptom cluster in advanced cancer. *Journal of Pain and Symptom Management*, *42*, 1–11.

Levy, M.H., Back, A., Bazargan, S., et al. (2006). Palliative care. Clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *4*, 776–818.

Miaskowski, C. (2006). Symptom clusters: establishing the link between clinical practice and symptom management research. *Supportive Care in Cancer*, *14*, 792–794.

Paice, J.A. (2004). Assessment of symptom clusters in people with cancer. *Journal of the National Cancer Institute. Monographs*, *32*, 98–102.

Portenoy, R.K., Thaler, H.T., Kornblith, A.B., et al. (1994). Symptom prevalence, characteristics and distress in a cancer population. *Quality of Life Research*, *3*, 183–189.

Rokyta, R., Haklova, O. & Yamamotova, A. (2009). Assessment of chronic benign and cancer pain using blood plasma biomarkers. *Neuro Endocrinology Letters*, *30*, 637–642.

Rosenthal, D.I., Mendoza, T.R., Chambers, M.S., et al. (2007). Measuring head and neck cancer symptom burden: The development and validation of the M. D. Anderson symptom inventory, head and neck module. *Head and Neck*, *29*, 923–931.

Starkweather, A.R., Lyon, D.E. & Schubert, C.M. (2011). Pain and inflammation in women with early-stage breast cancer prior to induction of chemotherapy. doi: 10.1177/1099800411425857 .

Steel, J.L., Kim, K.H., Dew, M.A., et al. (2010). Cancer-related symptom clusters, eosinophils, and survival in hepatobiliary cancer: An exploratory study. *Journal of Pain and Symptom Management*, *39*, 859–871.

Thong, M.S., Mols, F., Lemmens, V.E., et al. (2011). Impact of chemotherapy on health status and symptom burden of colon cancer survivors: a population-based study. *European Journal of Cancer*, *47*, 1798–1807.

Trask, P.C. & Griffith, K.A. (2004). The identification of empirically derived cancer patient subgroups using psychosocial variables. *Journal of Psychosomatic Research*, *57*, 287–295.

Tsai, J.S., Wu, C.H., Chiu, T.Y., et al. (2010). Significance of symptom clustering in palliative care of advanced cancer patients. *Journal of Pain and Symptom Management*, *39*, 655–662.

Walsh, D., Donnelly, S. & Rybicki, L. (2000). The symptoms of advanced cancer: Relationship to age, gender, and performance status in 1,000 patients. *Supportive Care in Cancer*, *8*, 175–179.

Walsh, D. & Rybicki, L. (2006). Symptom clustering in advanced cancer. *Supportive Care in Cancer*, *14*, 831–836.

Watanabe, S.M., Nekolaichuk, C.L. & Beaumont, C. (2011). The Edmonton Symptom Assessment System, a proposed tool for distress screening in cancer patients: Development and refinement. *Psycho-oncology*, *21*, 977–85.

Wilmoth, M.C., Coleman, E.A., Smith, S.C., et al. (2004). Fatigue, weight gain, and altered sexuality in patients with breast cancer: exploration of a symptom cluster. *Oncology Nursing Forum*, *31*, 1069–1075.

Yang, P., Cheville, A.L., Wampfler, J.A., et al. (2012). Quality of life and symptom burden among long-term lung cancer survivors. *Journal of Thoracic Oncology*, *7*, 64–70.