Multiple Dimensions of the Symptom Experience in Patients with Advanced Cancer and their Impact on Quality of Life

by

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Abstract

Many people with advanced cancer experience multiple severe symptoms as their disease progresses such as pain, sleep problems, fatigue, and depression. These symptoms can be a result of the cancer itself, cancer treatment or an interaction of the two. The studies reported in this dissertation uses the patients' own responses to survey questions to describe the multiple dimensions of the symptom experience; the factors that predict the total number of symptoms; as well as the optimal cutpoint between a low and a high number of symptoms and the between group differences in patient outcomes (i.e., depression, anxiety, quality-of-life).

At this time, very little is known about the cause or impact of multiple symptoms in patients with advanced cancer. The findings from this research have the potential to improve our understanding of the multiple dimensions of the symptom experience in patients with advanced cancer. Specifically, this work may facilitate the identification of symptoms that share a common biological mechanism. In addition, this research has the potential to lead to the identification of patients who are at higher risk for different symptom experiences and who require different symptom management interventions.

Table of Contents

Introduction

By the end of last year, an estimated 1,529,560 new cases of cancer occurred in the United States.[1] More people than ever are living and dying with advanced cancer. The American Cancer Society estimates that in the United States alone 569,490 people died last year from advanced cancer. In fact, cancer is the second leading cause of death in the United States.[2] In addition, with recent improvements in cancer therapies, more patients are *living* with advanced cancer and the sequelae of these therapies.[1] In advanced stages, it is common for people with cancer to have multiple, acute and chronic symptoms which may result from cancer and/or its treatment. These symptoms are frequently rated as moderate to severe.[3]

Historically, the inclusion of symptom status as both a predictor and an outcome variable has taken a "back seat" to tumor burden and life expectancy in both clinical practice and research.[4] More recently, in cancer patients who received primarily palliative treatments, symptom status has become an important clinical end point and a research outcome measure.[5] However, symptom status is theorized to be an antecedent to functional status, health perception, and quality of life (QOL).[6, 7] This idea is consistent with the perspectives of many palliative care specialists who have identified symptom status and QOL as core domains of palliative care.[8, 9] One notable review summarizes the challenges associated with the examination of the theorized causal relationship between symptoms and QOL.[7] To date, the findings are equivocal and suggest that other factors (e.g., symptoms, functional status, general health perceptions), which are not measured consistently, may influence QOL. In addition, the relationships among <u>multiple</u> symptoms and QOL in cancer patients has not been described in sufficient detail.[10, 11] A

growing body of evidence suggests that the co-occurrence of specific symptoms is significantly related to important outcomes such as physical functioning and QOL[12-15] which support the proposed theoretical relationship between symptoms, functional status, and QOL.[6]

The University of California San Francisco Theory of Symptom Management (TSM)[16] provides a flexible theoretical framework for the exploration of the multiple symptom experience of patients with advanced cancer. TSM suggests that symptoms are experienced across multiple dimensions and that a relationship exists between the person (e.g., demographic characteristics) and health (e.g., clinical characteristics) domains and the symptom experience. Evidence from the cancer symptom clusters literature,[3, 17, 18] as well as from studies of patients with advanced cancer who experience multiple co-occurring symptoms[3, 19-23] support many of the relationships described in the TSM. However, additional research is needed to describe the occurrence rates for symptoms as well as the frequency, intensity, and distress associated with symptoms; to identify predictors of total number symptoms; and to determine if a threshold between low and high number of symptoms exists in patients with advanced cancer.

To date, the majority of symptom management research has focused on single symptoms (e.g., pain, fatigue). Although this approach has advanced the management of some symptoms, it has not facilitated the assessment and management of patients who present with multiple, concurrent symptoms. For patients with advanced cancer, the focus of care often turns from cure or control of the cancer to symptom amelioration and maximization of QOL when the side effects of aggressive curative treatment are no longer manageable. Therefore, improved understanding of the multiple dimensions of the

symptom experience is warranted. In response to this identified gap in the literature the papers in this dissertation present: 1) a comprehensive review of the literature on multiple symptoms in patients with advanced cancer; 2) a descriptive study of 32 common symptoms across multiple dimension in patients with advanced cancer as well as a analysis of predictors for total number of symptoms; and 3) a study that determines the optimal cutpoint for low versus high number of symptoms in patients with advanced cancer and the associated between group differences on depression, anxiety, and QOL.

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A Review of the Literature on Multiple Symptoms, Their Predictors, and Associated Outcomes in Patients with Advanced Cancer

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The text of this dissertation manuscript is a reprint of material that appears in Palliative and Supportive Care. The coauthors listed in this publication directed and supervised the research that forms the basis for this dissertation. As per the dissertation advisor, the student conducted the systematic review of the literature, analyzed the data from the systematic review, and developed the initial manuscript.

Abstract

The findings from several studies suggest that palliative care patients with advanced cancer experience multiple symptoms and that these symptoms may be related to demographic and clinical factors as well as patient outcomes. However, no systematic review has summarized the findings from studies that assessed multiple symptoms, predictors, and outcomes in these patients. The purposes of this review, focused on palliative care patients with advanced cancer, are to: 1) describe the relationships among multiple symptoms; 2) describe the predictors of multiple symptoms; and 3) describe the relationships between multiple symptoms and patient outcomes. Twenty-two studies met the inclusion criteria and examined at least one of these purposes. The majority of these studies were descriptive and used one of 4 common symptom assessment scales. Fifty-six different signs and symptoms were evaluated across various dimensions (i.e., prevalence, severity, distress, frequency, control). Pain, dyspnea, and nausea were the only symptoms measured in all 22 studies. Relationships among concurrent symptoms were examined in 9 studies. Relationships among symptoms and predictors (i.e., demographics, cancer type, health care delivery environment) were examined in 7 studies. Relationships among symptoms and outcomes (i.e., functional status, psychological status, quality-of-life, survival time) were examined in 14 studies. Significant methodological variation was found among these studies. It is difficult to draw conclusions about the relationships among multiple symptoms, predictors, and outcomes due to the heterogeneity of these studies. Future research is needed to determine which symptoms and symptom dimensions to assess in order to better understand how multiple symptoms relate to each

other as well as to predictors and outcomes in palliative care patients with advanced cancer.

Introduction

The experience of multiple unrelieved symptoms and associated distress in patients with advanced cancer may contribute to the increased frequency of clinic appointments, emergency department visits, and hospitalizations for "high tech" symptom management interventions (Hearn & Higginson, 1998; National Comprehensive Cancer Network, 2007). A recent review of the prevalence of symptoms in advanced cancer patients noted that multiple symptoms are highly prevalent during the palliative phase of care (Teunissen et al., 2007). However, little is known about the relationships among multiple concurrent symptoms or about the associations between multiple concurrent symptoms and patient outcomes (i.e., functional status, mood, quality-of-life (QOL)). Therefore, the purposes of this review, focused on palliative care patients with advanced cancer, are to: 1) describe the relationships among multiple symptoms; 2) describe the predictors of multiple symptoms; and 3) describe the relationships between multiple symptoms and patient outcomes.

Search Methods

Comprehensive literature searches were completed using the following databases: PubMed, Cumulative Index to Nursing and Allied Health Literature, and PsychInfo. The key words: *cancer* or *advanced cancer* or *neoplasm,* AND *palliative care* or *terminal care* or *hospice* or *end-of-life,* AND *symptoms* or *multiple symptoms* or *symptom clusters* were combined. Studies were included if they met all of the following criteria: 1) the entire sample had a cancer diagnosis and was receiving palliative care for symptom management; 2) at least three or more symptoms were evaluated and reported on in the results; and 3) the relationships among multiple symptoms or between symptoms and

their predictors (e.g., demographic and clinical characteristics) or patient outcomes were described. Studies were excluded if the patients' prognoses were mixed or if the sole intervention was palliative tumor treatments (i.e., palliative radiation, palliative chemotherapy) rather than global palliative care that included symptom management. Twenty-two studies were identified based on these criteria (Bakitas et al., 2009; Cheung, Le, & Zimmermann, 2009; Doorenbos, Given, Given, & Verbitsky, 2006; Francoeur, 2005; Kirkova et al., 2009; McMillan & Small, 2002; Mercadante, Casuccio, & Fulfaro, 2000; Modonesi et al., 2005; Morasso et al., 1999; Nekolaichuk & Bruera, 2004; Peruselli et al., 1993; Peruselli, Paci, Franceschi, Legori, & Mannucci, 1997; Peters & Sellick, 2006; Rodin et al., 2007; Stromgren et al., 2005; Teunissen, de Graeff, de Haes, & Voest, 2006; Tsai, Wu, Chiu, Hu, & Chen, 2006; Vainio & Auvinen, 1996; von Gruenigen et al., 2006; Walsh, Donnelly, & Rybicki, 2000; Walsh & Rybicki, 2006; Walsh, Rybicki, Nelson, & Donnelly, 2002).

Research of multiple symptoms and their impact on patient outcomes has only recently emerged as a unique focus in palliative care. Therefore, in the majority of the studies included in this review, descriptions of relationships among concurrent symptoms and/or descriptions of relationships between concurrent symptoms and patient outcomes were not the main aims of the studies. However, several of the studies reported results that were pertinent to more than one of the reviews' purposes. The findings from these 22 studies are summarized in sections based on the purposes of this review.

Results

Description of the studies

The majority of the studies used descriptive, prospective, repeated-measures designs (Table 1). Symptom data were obtained primarily using patient self-reports or clinician interviews. Twelve of the twenty-two studies used valid and reliable scales to measure multiple symptoms (Bakitas, et al., 2009; Cheung, et al., 2009; Doorenbos, et al., 2006; McMillan & Small, 2002; Modonesi, et al., 2005; Morasso, et al., 1999; Nekolaichuk & Bruera, 2004; Peruselli, et al., 1993; Peruselli, et al., 1997; Peters & Sellick, 2006; Rodin, et al., 2007; Stromgren, et al., 2005). In addition, several studies used multidimensional scales of single symptoms (e.g. pain, depression, fatigue) (Bakitas, et al., 2009; Doorenbos, et al., 2006; Francoeur, 2005; McMillan & Small, 2002; Peters & Sellick, 2006; Rodin, et al., 2007; Stromgren, et al., 2005).

Sample sizes ranged from 39 to 1640. Thirteen of the studies had fewer than 200 participants (Doorenbos, et al., 2006; Kirkova, et al., 2009; McMillan & Small, 2002; Modonesi, et al., 2005; Morasso, et al., 1999; Nekolaichuk & Bruera, 2004; Peruselli, et al., 1993; Peruselli, et al., 1997; Peters & Sellick, 2006; Stromgren, et al., 2005; Teunissen, et al., 2006; Tsai, et al., 2006; von Gruenigen, et al., 2006). Gender distribution was fairly even across the studies. For the 16 studies that reported age, the grand mean age was 64.9 years. The most prevalent cancer sites were lung (11% to 35%), gastrointestinal (GI) (9% to 30.2%), and genitourinary (GU) (6.3% to 32.7%). However, in most of the studies the samples were heterogeneous in terms of cancer diagnosis.

Finally, the study settings were varied (i.e., 5 inpatient, 7 clinic, 4 home care, and 7 in a combination of settings). Eleven of the studies were conducted in the United States, one in Canada, eight in Europe, one in Taiwan, and one was multinational.

Symptom Measurement

Fifty-six unique symptoms were evaluated across the 22 studies (Figure 1). However, 19 of these "symptoms" are more accurately categorized as *signs* because they can be measured objectively (e.g., fever). The 14 symptoms that were evaluated in >50% of the studies, were pain, dyspnea, nausea, depression, constipation, anorexia, sleep disturbance, anxiety, vomiting, fatigue, weight loss, cough, dysphagia, and drowsiness. Only pain, dyspnea, and nausea were measured in all 22 studies. Table 2 summarizes the symptoms that were evaluated within and across the 22 studies.

In terms of prevalence estimates, only 12 studies reported the prevalence of the various symptoms (Cheung, et al., 2009; Doorenbos, et al., 2006; Kirkova, et al., 2009; Mercadante, et al., 2000; Peters & Sellick, 2006; Rodin, et al., 2007; Teunissen, et al., 2006; Tsai, et al., 2006; Vainio & Auvinen, 1996; von Gruenigen, et al., 2006; Walsh, et al., 2000; Walsh & Rybicki, 2006). However, diverse approaches were used to present prevalence data (e.g., presence of the symptom, percentage of patients who rated the symptom as moderate to severe). In addition, the wording of the items that were used to measure symptoms varied across studies (e.g., present or absent, ability to control the symptom, distress associated with the symptom). Given the variability in symptom measurement and reporting across studies, symptom prevalence estimates cannot be summarized or compared across these 22 studies.

A variety of symptom dimensions (e.g., intensity, frequency, distress, controllability) were assessed across these 22 studies. However, given the diversity of symptom scales used summary data on the various dimensions cannot be calculated. For example, the Edmonton Symptom Assessment Scale (ESAS) assesses the *intensity* of symptoms using 0 (no symptom) to 100 (worst possible) visual analogue scales (VAS). In

contrast, in another study (Francoeur, 2005), participants were asked to rate the *difficulty in controlling* symptoms using a 5-point Likert scale (i.e., complete, a lot, some, little, none). In these 22 studies, symptom *intensity* was the most frequently reported dimension (68%). The only study to examine the relationship between two symptom dimensions found that greater symptom severity was associated with symptom distress (Kirkova, et al., 2009).

Relationships among multiple symptoms and between multiple symptoms, their predictors, and patient outcomes

Relationships among multiple symptoms

Only 9 studies examined the relationships among multiple concurrent symptoms (Cheung, et al., 2009; Francoeur, 2005; Mercadante, et al., 2000; Peruselli, et al., 1993; Peruselli, et al., 1997; Tsai, et al., 2006; von Gruenigen, et al., 2006; Walsh & Rybicki, 2006; Walsh, et al., 2002) using the following methods: examination of correlations among symptom severity scores (Peruselli, et al., 1993; von Gruenigen, et al., 2006); identification of key symptoms that predicted other symptoms or outcomes (Walsh, et al., 2002); and description of occurrence patterns among multiple, concurrent symptoms (Mercadante, et al., 2000; Peruselli, et al., 1997; Tsai, et al., 2006). In addition, three studies identified symptom clusters using cluster analysis (Cheung, et al., 2009; Francoeur, 2005; Walsh & Rybicki, 2006).

Examination of correlations among symptom severity scores

In one study of 43 advanced cancer patients (Peruselli, et al., 1993), principal component analysis was used to identify the relationships among 13 symptoms on the Symptom Distress Scale (SDS). A four factor structure accounted for 67.4% of variance

in symptom distress. Factor 1 consisted of six symptoms (i.e., appetite, fatigue, insomnia, concentration, appearance, mood). Four items loaded on the second factor (i.e., pain frequency, pain intensity, bowel pattern, insomnia). Factor 3 (i.e., nausea frequency, nausea intensity) and factor 4 (i.e., respiration, coughing) each contained two items.

In a second correlation study (von Gruenigen, et al., 2006), the relationships between physical symptoms and psychological symptoms were evaluated in 39 gynecologic-oncology patients who received palliative chemotherapy. Higher total physical symptom severity scores were associated with higher depression (r=.57) but not anxiety scores using the Hospital Anxiety Depression Scale (HADS).

Identification of Key Symptoms

In a large heterogeneous sample of patients with advanced cancer (n=1000) (Walsh, et al., 2002), five symptoms (i.e., anorexia, dry mouth, dyspnea, dysphagia, weight loss) previously identified as key predictors of survival in the National Hospice Study (NHS) (Reuben, Mor, & Hiris, 1988), were examined to determine if they were prognostic for overall symptom presentation. Using a step-wise Cox proportional hazards analysis, as the patient's number of the NHS symptoms increased, the median number of other symptoms reported on a 38 item symptom checklist increased significantly as well (i.e., 0 NHS symptoms to 4 symptoms, 1 NHS symptom to 6 symptoms, 2 NHS symptoms to 9 symptoms, 3 NHS symptoms to 11 symptoms, 4 NHS symptoms to 13 symptoms, 5 NHS symptoms to 15 symptoms).

Patterns of multiple symptoms across time

Only 3 studies evaluated the relationships among symptoms over time (Mercadante, et al., 2000; Peruselli, et al., 1997; Tsai, et al., 2006). In a study that

examined the relationships among symptom distress scores at three time points (Peruselli, et al., 1997), patients with advanced cancer (n=73) who reported a SDS total score of <36 were categorized as minimally distressed and those with a score ≥ 36 were categorized as highly distressed at enrollment. Symptom assessments completed 2 weeks after enrollment and during the last week of life were compared across the two symptom distress groups. At both follow-up assessments, no between groups differences were found in the mean SDS scores. Of note, SDS scores of the highly distressed group improved and those of the minimally distressed group remained the same. Patients in this study were receiving palliative care at home, which may explain the study findings.

In another longitudinal study (Mercadante, et al., 2000), the relationships among symptoms and disease progression were evaluated in a sample of patients (n=373) with a variety of advanced cancers. Patient's Karnofsky performance status (KPS) score was used as a surrogate marker for disease progression over time. The prevalence of dyspnea, drowsiness, weakness, and confusion increased as disease progressed. In contrast, the prevalence of nausea, vomiting, dry mouth, gastric pyrosis, and diarrhea increased initially, peaked at a KPS score of 40, and then decreased as the cancer progressed. These results must be interpreted with caution because changes in performance status were used as a surrogate for disease progression.

In a longitudinal study of 77 patients with various cancers admitted to a palliative care unit in Taiwan, symptom patterns over time were examined (Tsai, et al., 2006). Symptoms were reported at the time of admission, one week later, and two days before death. Symptom patterns were identified based on a visual inspection of the graph of changes in each symptom's severity over time. Symptoms were grouped based on the

similarity of their pattern. Patterns were labeled based on the shape of the curve across the 3 points (i.e., "static" signifying no change in intensity, "increase" signifying steady increase in intensity, "decrease" signifying steady decrease in intensity). Six symptom patterns were identified: (1) *Continuous/static* (i.e., restless/heat [a symptom in Eastern Medicine], abdominal fullness, constipation, dizziness, insomnia); (2) *Static/increase* (i.e., fatigue, weakness, nausea/vomiting, taste alteration, dysphagia, diarrhea, dry mouth, night sweats); (3) *Decrease/static* (i.e., pain, depression); (4) *Decrease/increase* (i.e., anorexia, dyspnea); (5) *Static/decrease* (i.e., aggression); and (6) *Decrease* (i.e., anxiety). No statistical analyses were performed to examine the strength of these relationships.

Symptom Clusters

Finally, three studies identified symptom clusters in palliative care patients with advanced cancer (Cheung, et al., 2009; Francoeur, 2005; Walsh & Rybicki, 2006). In a study of 268 patients with various cancers and bone metastases who received radiation therapy and home-based palliative care (Francoeur, 2005), the occurrence of symptom clusters was examined using an author-developed checklist of 9 symptoms. Using regression analysis, significant interaction terms were found for the following symptom clusters: pain and fatigue, pain and weight loss, pain and fever, and sleep and fever. In addition, each of these clusters predicted depressive affect on the Center for Epidemiologic Study-Depression scale. While similar symptoms were found in the four distinct clusters, the author suggested that these clusters may represent distinct biological mechanisms or pathways (Francoeur, 2005).

In the second study (Walsh & Rybicki, 2006), that evaluated 922 patients with various types of advanced cancer, clinician ratings of the presence or absence of 35 signs

and symptoms were used to identify symptom clusters based on a correlation score of ≥0.68. Seven unique clusters were identified and named: (1) *Fatigue, anorexia/cachexia cluster* (i.e., easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, taste changes); (2) *Neuropsychological cluster* (i.e., sleep disturbance, depression, anxiety); (3) *Upper GI cluster* (i.e., dizzy spells, dyspepsia, belching, bloating); (4) *Nausea/vomiting cluster* (i.e., nausea, vomiting); (5) *Aerodigestive cluster* (i.e., dysphagia, dyspnea, cough, hoarseness); (6) *Debility cluster* (i.e., edema, confusion); and (7) *Pain cluster* (i.e., pain, constipation). While 7 clusters were identified, the use of occurrence rather than severity ratings to form the clusters may have influenced the results, in that the symptom only needed to be present (rather than having to reach a severity cut-off) to be included in a cluster. In addition, the clustering of some symptoms (e.g., dizzy spells with upper GI symptoms, or edema with confusion) suggests that the association criteria (i.e., r ≥0.68) was not sufficiently stringent. Finally, no mechanism was offered to explain these clusters.

In a third study (Cheung, et al., 2009), two symptom clusters were identified using the ESAS in a sample of outpatients (n=1366) with a variety of advanced cancers. Cluster 1 consisted of fatigue, drowsiness, nausea, decreased appetite, and dyspnea. Cluster 2 included anxiety and depression.

Predictors for multiple symptoms

Seven studies attempted to determine predictors for multiple symptoms (Bakitas, et al., 2009; Cheung, et al., 2009; Doorenbos, et al., 2006; Kirkova, et al., 2009; Peters & Sellick, 2006; Vainio & Auvinen, 1996; Walsh, et al., 2000). These studies examined the relationships between symptoms and demographics (i.e., age, gender) (Kirkova, et al.,

2009; Walsh, et al., 2000), cancer type (Cheung, et al., 2009; Doorenbos, et al., 2006; Vainio & Auvinen, 1996), and the health care delivery environment (Peters & Sellick, 2006). Only one randomized control trial was identified for this review (Bakitas, et al., 2009).

In a large study of patients with advanced cancer referred for palliative care (n=1000) (Walsh, et al., 2000), demographic variables (i.e., age, gender) were predictive of symptom report using an author-developed 38 symptom checklist. Eleven symptoms (i.e., blackout, vomiting, pain, nausea, headache, sedation, bloating, sleep problems, anxiety, depression, constipation) were more likely to be reported by younger patients after adjusting for gender and performance status. In addition, after adjusting for age and performance status, gender was found to be a predictor of symptom report as well.

In a follow up study in the same palliative care clinic as described above (Kirkova, et al., 2009), the relationships among demographics (i.e., age, gender), primary cancer site, and performance status and symptom severity as well as symptom distress in 181 patients with advanced cancer were examined. In the regression analysis, female gender, age <65 years, and an ECOG score of 3 or 4 was found to be associated with symptom severity as well as symptom distress. After controlling for symptom severity, primary cancer site was not associated with symptom reports.

In a cross sectional, descriptive study of multiple symptoms in patients with various advanced cancers (Cheung, et al., 2009), differences in identified symptom clusters were found based on primary cancer site. Pain and drowsiness clustered for solid tumors of the central nervous system as well as head and neck cancers. A cluster of lack of appetite and poor well-being was identified for gastrointestinal, genitourinary,

gynecological, breast and lung cancers. Anxiety and depression clustered for all solid tumors while anxiety, depression, fatigue, and dyspnea clustered for hematological malignancies.

In a longitudinal study of patients with various cancers (n=174), Hierarchal Linear Modeling (HLM) was used to identify predictors of patients' total number of symptoms during the last year of life (Doorenbos, et al., 2006). After controlling for gender, age, depression, activities of daily living status, and proximity to death, patients with lung cancer experienced more symptoms in their last year of life than patients with other solid tumors ($p = 0.003$). In addition, after controlling for cancer type, neither gender nor age predicted changes over time in the total number of symptoms reported by these patients.

In a large study of symptom prevalence, in patients with various cancers (n=1640) who received hospice care from 7 different centers across 5 countries (Vainio & Auvinen, 1996), 9 symptoms were assessed using an author-developed questionnaire. Statistically significant differences in symptom prevalence rates were found among various cancer diagnoses for pain, nausea, dyspnea, anorexia, weakness, and weight loss but not for constipation, insomnia, and confusion. Nausea was the most prevalent symptom in patients with gynecologic and stomach cancers, but was seldom reported by patients with head and neck and lung cancers. Gastrointestinal symptoms (i.e., nausea, constipation, anorexia) were prevalent in esophageal, stomach, and colorectal cancers. Finally, compared to all other cancer diagnoses, weakness was highly prevalent in hematologic, colorectal, and esophageal cancers, while dyspnea was most prevalent in lung cancer. No

data were reported on age or gender differences in symptom occurrence rates within or across cancer diagnoses.

In a study of 58 patients with advanced cancers (Peters & Sellick, 2006), while no differences were found in the total number of symptoms, significant differences in the prevalence of several symptoms were found between home care and inpatients on a palliative care unit. The 4 most prevalent symptoms in home care patients were fatigue, pain, weakness, and flatulence. In contrast, the five most prevalent symptoms reported by inpatients were weakness, fatigue, dry mouth, sleeping during the day, and pain. The only symptoms with significantly different prevalence rates were lack of appetite, belching, and diarrhea which were more common with inpatients (66%, 53%, and 47%, respectively) than with home care patients (39%, 27%, and 12%, respectively). In addition, inpatients reported significantly higher total mean intensity ($t = 2.03$, $p<0.05$) and distress ($t = 2.37$, $p<0.05$) scores.

The only randomized clinical trial identified in this review, examined the effect of a nurse practitioner led palliative care program on symptom management of 322 outpatients with various advanced cancers (Bakitas, et al., 2009). No difference was found between the intervention group and usual care on symptom intensity using the ESAS. However, patients in the intervention group did report significantly lower depressed mood on the CES-D over 13 months. It is not known if there were between group differences on individual symptoms since only the ESAS total scores were reported.

Relationships between symptoms and patient outcomes

Fourteen studies examined the relationships between symptoms and patient outcomes (i.e., functional status, psychological status, QOL, survival time) (Doorenbos, et al., 2006; McMillan & Small, 2002; Mercadante, et al., 2000; Modonesi, et al., 2005; Morasso, et al., 1999; Nekolaichuk & Bruera, 2004; Peters & Sellick, 2006; Rodin, et al., 2007; Stromgren, et al., 2005; Teunissen, et al., 2006; Vainio & Auvinen, 1996; von Gruenigen, et al., 2006; Walsh, et al., 2000; Walsh, et al., 2002). In addition, two studies described the relationship between symptoms and other outcomes (i.e., patient satisfaction (von Gruenigen, et al., 2006), study participation (Stromgren, et al., 2005)).

Functional status

In a large study of patients with advanced cancer referred for palliative care (n=1000) (Walsh, et al., 2000), the relationship between performance status and symptom prevalence using an author-developed 38 symptom checklist was evaluated. Performance status was associated with 14 symptoms (i.e., confusion, sedation, blackout, hallucination, weakness, mucositis, anorexia, memory problems, dry mouth, constipation, anxiety, wheezing, pain, itching) after adjusting for age and gender.

In a longitudinal study of patients with various cancers (n=174), HLM was used to evaluate the relationship between prevalence of multiple symptoms and functional status (i.e., activities of daily living) during the last year of life (Doorenbos, et al., 2006). In the final HLM model after controlling for gender, age, depression, cancer site, and proximity to death, patients with greater dependence with activities of daily living (as measured by the Katz Index) experienced increased symptom prevalence in the last year of life.

In a longitudinal study of patients receiving palliative care (n=373) (Mercadante, et al., 2000), the relationship between symptom severity and KPS score was evaluated. Pain was measured using a 0 to 10 NRS, and 14 other symptoms were measured using a 0 to 3 categorical scale (i.e., not at all, slight, a lot, awful). Mean symptom severity score for patients with each respective KPS score were reported. In general, as KPS score decreased, symptom severity scores increased. However, the categorization of KPS scores, rather than using it as a continuous variable did not allow for an examination of the correlation among functional status and symptom severity.

The relationship between symptom severity, functional status, and the decision to continue to participate in a research study was evaluated in patients (n=175) with various cancers in Denmark who were referred to a palliative care program (Stromgren, et al., 2005). Change in mean symptom severity scores on the ESAS and mean KPS scores were calculated between four time points (i.e., T1 - T0, T2 - T1, T3 - T2). The likelihood of continued study participation was evaluated by comparing the change scores on the ESAS and the KPS for patients who dropped out and those who continued to participate. Patients with more severe symptoms at baseline were less likely to continue study participation after baseline data collection. For patients who continued to participate in the study, performance status, rather than symptoms, was found to be the only predictor of continued participation in the study over time. As KPS scores decreased, participation rates decreased.

Finally, in a large multicenter study of 1640 patients with various advanced cancers (Vainio & Auvinen, 1996), the prevalence of common cancer symptoms were estimated. The primary cancer sites with the highest prevalence of pain (i.e., gynecologic,

stomach, colorectal, and prostate) were associated with poorer functional status as measured by the Eastern Cooperative Oncology Group (ECOG) score. No other symptoms had a significant relationship with ECOG scores.

Psychological Status

Only three studies examined the relationships between multiple symptoms and psychological variables (i.e., psychological distress, hope, desire to hasten death) in patients with advanced cancer (Morasso, et al., 1999; Nekolaichuk & Bruera, 2004; Rodin, et al., 2007).

In a study that evaluated the needs and factors associated with unmet needs of advanced cancer patients (n=89) (Morasso, et al., 1999), a moderate positive correlation was found between SDS score and psychological distress measured by the Psychological Distress Inventory (r = .46). In addition, content analysis was performed on transcripts of semistructured interviews regarding met and unmet needs. Six unmet needs (i.e., symptom control, occupational functioning, emotional support, nutrition, sleep, communication needs) were significantly associated with higher psychological and symptom distress.

In a study of 96 inpatients and outpatients with advanced cancers (Nekolaichuk & Bruera, 2004), the relationship between hope and symptom intensity was examined. The 10 item ESAS was used to establish the validity of the Hope Differential-Short (HDS) scale. Exploratory factor analysis was used to determine the factor structure of the HDS. Negative correlations were found between both HDS subscales and depression (r = -0.40 for authentic spirit subscale, -0.25 for comfort subscale) and anxiety (-0.42 for authentic spirit, -0.39 for comfort).

In a study of 326 patients with advanced cancer (Rodin, et al., 2007), factors (including symptoms) associated with wishing to hasten death were examined. The 32 symptom MSAS was used along with the Brief Pain Inventory, and the Beck Depression Inventory to measure multiple aspects of the symptom experience. The 20 item Schedule of Attitudes Toward Hastened Death (SAHD) was used to measure desire to hasten death, the will to live, and the anticipated burden of physical and emotional suffering. An association was found between higher scores on the SAHD (indicating an attitude favoring hastening death) and *higher* levels of depression, physical symptoms, symptom distress, pain intensity, pain interference, as well as hopelessness, and global distress. In addition, increased SAHD scores were associated with *lower* levels of functional status, spiritual well-being, social support, and self esteem, as well as living alone. However, regression analysis revealed that only depression and hopelessness along with lower physical functioning predicted 34.4% of the variance in the desire to hasten death. Of note, physical symptoms and symptom distress did not contributed significantly to the model.

Quality of Life

Only two studies were identified that evaluated the relationship between multiple symptoms and QOL in palliative care patients with advanced cancer (McMillan & Small, 2002; Peters & Sellick, 2006). In a cross sectional study of 178 patients with various cancers receiving hospice home care, the MSAS was used to measure their multidimensional symptom experience (McMillan & Small, 2002). The 28 item Hospice Quality of Life Index was used to measure QOL. Univariate analysis revealed that higher levels of total symptom distress ($r = -0.67$), pain intensity ($r = -0.20$), dyspnea intensity (r

= -0.27), and constipation intensity (r = -0.38) were associated with poorer QOL. However, multiple regression analysis revealed that after controlling for age, symptom distress (i.e., MSAS total score) was the only significant predictor of QOL explaining more the 34% of the variance.

The second study examined the relationships between symptoms and QOL in inpatients and outpatients (n=58) with various advanced cancers (Peters & Sellick, 2006). Participants completed the MSAS, the HADS and four subscales of the European Organization of Research and Treatment of Cancer Quality of Life Questionnaire - Cancer 30. While in univariate analyses, symptom distress was associated with QOL, it was not retained in the final regression model. In the final regression model, global physical condition, total control, and depression (as measured by the HADS) predicted 84.4% of the variance in QOL. However, depression explained only 2.1% of the total variance in QOL compared to 73% explained by global physical condition. Relationships between QOL or global physical condition and single symptoms on the MSAS were not reported.

Survival

Only three studies evaluated the relationships between symptoms and survival (Modonesi, et al., 2005; Teunissen, et al., 2006; Walsh, et al., 2002). In a longitudinal study of 162 patients with various cancers admitted to a palliative care unit (Modonesi, et al., 2005), symptoms were assessed using the ESAS for seven days. Patients were then dichotomized into two groups, those who survived > 30 days and those who survived ≤ 30 days. Patients who survived ≤ 30 days reported significantly higher intensity ratings for fatigue, drowsiness, dyspnea, and anorexia. Patients in the > 30 day survival group

reported significantly higher depression scores. Patients in the > 30 day group (37.5 ±16.5) reported significantly higher total ESAS scores than patients in the ≤ 30 day survival group (33.1 ±16.4). While these findings are interesting, it is not clear whether a difference of 4.4 points represents a clinically meaningful difference.

In a study of 181 patients with various advanced cancers who were hospitalized and referred to a palliative care team (Teunissen, et al., 2006), the prognostic value of symptoms to predict survival was examined. The occurrence of eleven symptoms (i.e., head ache, abdominal pain, anorexia, >10% weight loss, nausea, vomiting, dysphagia, dyspnea, drowsiness, confusion, and depressed mood) was significantly correlated with survival. Patients who reported nausea, dysphagia, dyspnea, and confusion, but not depression had a higher relative risk of dying compared to other patients. In addition, as patients experienced a larger number of these symptoms (or absence of depression), the relative risk of dying increased (i.e., 1 symptom, RR=1.47; 2 symptoms, RR=2.7; 3 symptoms, RR=2.1; 4 symptoms, RR=9.0; Confidence Intervals (CI) not reported in original manuscript). Multivariate analyses revealed that after controlling for diagnosis, the recurrence of four symptoms were associated with an increased likelihood of dying (i.e., nausea, RR=1.96 (CI=1.33-2.89); dysphagia, RR=1.81 (CI=1.11-2.96); dyspnea, RR=1.79 (CI=1.27-2.53); confusion, RR=2.35 (CI=1.52-3.63)). In this model, depressed mood decreased the likelihood of dying with a relative risk of .56. In addition, it was noted that the presence of these four symptoms (i.e., nausea, dysphagia, dyspnea, confusion) resulted in an 83% mortality rate at one month and a 100% mortality rate at 6 months compared to 20% at one month and 48% at 6 months for patients with none of these symptoms.

Finally, the relationships between symptoms and survival were examined in a large sample of patients (n=1000) with various advanced cancers referred to a palliative care program (Walsh, et al., 2002). Baseline symptom assessments, using a 38 item author-developed checklist, were analyzed to determine if the occurrence of certain symptoms predicted survival. After controlling for cancer site and time since diagnosis, a step-wise Cox proportional hazards model revealed that *dysphagia* and *early satiety* along with poor performance status and male gender increased the risk of death significantly (the hazard ratios were 1.3 (CI=1.0-1.6), 1.3 (CI=1.1-1.5), 1.4 (CI=1.3-1.6) and 1.3 (CI=1.1-1.6) respectively). In addition, 5 symptoms (i.e., anorexia, dry mouth, dyspnea, dysphagia, weight loss) previously identified to predict survival in the National Hospice Study (NHS) (Reuben, et al., 1988), were examined. As the number of NHS symptoms increased, the mean number of months of survival decreased significantly (i.e., 0 NHS symptoms, 4.2 months survival; 1 NHS symptom, 3.4 months; 2 NHS symptoms, 3.3 months; 3 NHS symptoms, 2.9 months; 4 NHS symptoms, 2.4 months; all 5 NHS symptoms, 1.9 months).

Conclusions

Several important methodological issues need to be considered when interpreting the results from the 22 studies included in this review. The majority of the studies used author-developed tools to assess symptoms for which the reliability and validity of these instruments are not known. In addition, across the studies both signs and symptoms were evaluated. While, the distinction between a subjective experience (symptom) and an objective indicator (sign) is defined (Dodd et al., 2001), many of these studies did not make a differentiation between signs and symptoms. Certain signs such as fever or cough

can be clearly observed by a health care provider or family caregiver, however other symptoms such as pain, fatigue, or sleep disturbance to name a few are most accurately measured when patient self report is used for data collection. Understanding the difference between subjective and objective data is critical given the emerging importance of psychological symptoms such as anxiety and depression (Irving & Lloyd-Williams, 2010) as well as other psychological factors such as hope, distress, and desire to hasten death (Morasso, et al., 1999; Nekolaichuk & Bruera, 2004; Rodin, et al., 2007) and their relationship with QOL.

Significant variation existed in the number of symptoms assessed. Pain, dyspnea, and nausea were measured in every study, however, one cannot draw any conclusions about their prevalence relative to other symptoms that were not included in every study. While 56 signs and symptoms were evaluated across the 22 studies, it is not clear whether this number represents a complete list of symptoms experienced by advanced cancer patients. Additional research is warranted to determine the most prevalent symptoms in advanced cancer patients, particularly those that co-occur or occur in a cluster.

In addition, it is not yet known which symptom dimensions are the most important to assess. Across most of these studies, intensity and distress were not evaluated as distinct dimensions of symptoms. Furthermore, the terms *symptoms*, *physical status*, and *QOL* were used synonymously across many of these studies. Many QOL instruments that incorporate ratings of symptom severity as part of their total score, may need to be revised or exclude these items from analyses that examine the relationship between symptoms and QOL. The findings across these 22 studies suggest that patients with advanced cancer experience a wide range of symptoms and that a

variety of scales that include various symptom dimensions have been used to examine their symptom experience.

Significant variation existed in the classification of the psychological symptoms of anxiety and depression as either mood states or symptoms. Studies that used multiple symptom scales tended to treat depression and anxiety as symptoms. Whereas studies that used multidimensional symptom scales treated depression and anxiety as mood states. This variation may have contributed to differences in the results among studies. Perhaps the question is whether psychological symptoms, like anxiety and depression, function as stable predictors or as outcome variables that are responsive to treatment interventions. Further research is needed to determine how these psychological symptoms relate to other symptoms as well as predictors and outcomes.

In these 22 studies, a variety of statistical approaches were used to examine the relationships among multiple symptoms. The variation in analytical techniques (i.e., factor analysis, intraclass correlations, relative risk modeling, visual graphing of scores over time, t-test of difference scores, regression analysis, cluster analysis) likely contributed to the differences in the findings. Meaningful comparisons among these studies were limited by that fact that no one scale or analytical approach was used in more than one study. The four studies that identified symptom clusters in this population took very different methodological approaches and subsequently reported very different clusters in their results (e.g., number of symptoms in the clusters, composition of the clusters). Additional research is needed to develop a better understanding of the relationships among multiple concurrent symptoms cross-sectionally as well as over time.

While more than half of the 22 were longitudinal studies traditional statistical approaches used (e.g., repeated measures ANOVA, paired t-tests, factor analysis, comparison of mean change scores) were used to analyze changes in symptoms overtime. Only one study (Doorenbos, et al., 2006) used an advanced modeling procedure to examine the relationships between symptoms, covariates, and the outcome variables. These advanced methods for longitudinal data analysis allow for a more detailed evaluation of inter-individual differences as well as predictors of these differences (O'Connell & McCoach, 2004). However, these approaches require relatively large sample sizes and a minimum of five measurements.

In addition to small sample sizes and varying analytical approaches, each predictor and patient outcome discussed in this review was examined in only a limited number of studies. Replication is needed to confirm the relationships between symptoms, predictors, and outcomes reported to date.

In patients with advanced cancer the experience of multiple symptoms is not well characterized both cross-sectional and over time. Little is known about symptom dimensions other than intensity (i.e., distress, frequency, interference, controllability). The literature that examines the relationships between symptoms and functional status as well as QOL is complex and inconclusive. No literature exists on the potential existence of patient subgroups based on experience with specific symptoms. Additional research is needed to identify symptom clusters in patients with advanced cancer; to examine the relationships among symptoms and identify symptom clusters; to describe the relationships between predictors such as personal as well as clinical characteristics and symptoms; to describe the relationship between symptoms and patient outcomes; to

identify the existence of patient subgroups based on their experience with specific symptoms; and to examine the relationships between patient subgroups, predictors, and patient outcomes.

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Appendix

Table 1: Summary of characteristics of studies of multiple symptoms in palliative care patients with advanced cancer

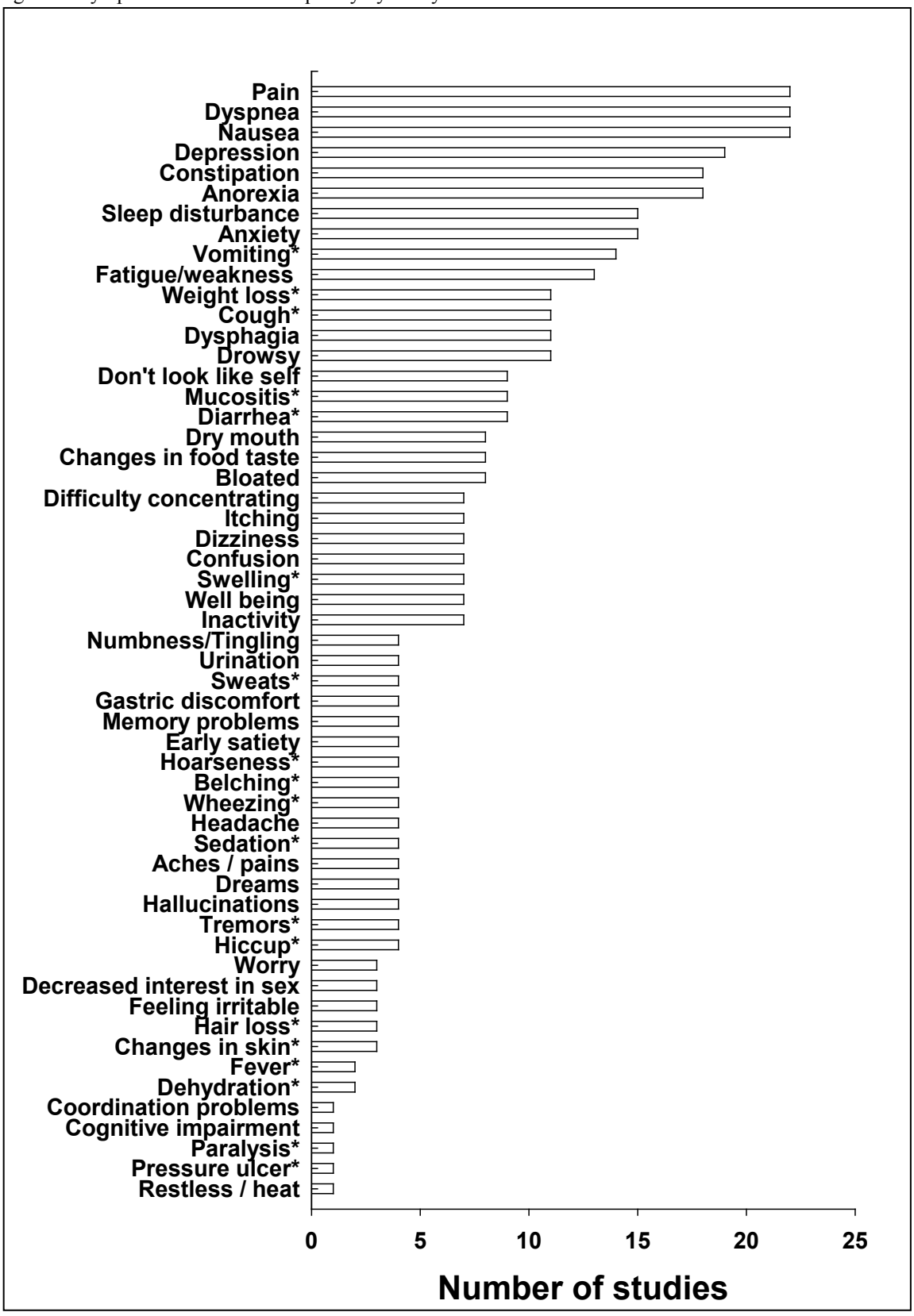
Design • Descriptive - 21 (95%) / Randomized Clinical Trial 1 (5%) • Cross-sectional – 11 (50%) / Longitudinal or Repeated measures - 11 (50%)
Symptom Report • Self-report - 11 (50%) • Clinician interview - 9 (41%) • Mixed (patient report and clinician assessed, proportions not specified) - 2 (9%)
Symptom Scales* Multiple Symptom Scales • Author developed (including author developed 0 to 10 NRS) - 10 (45%) • Edmonton Symptom Assessment Scale - 5 (23%) • Memorial Symptom Assessment Scale - 3 (13%) • Symptom Distress Scale - 3 (13%) • Symptom Experience Tool - 1 (5%) Multidimensional Single Symptom Scales (used in addition to multi-symptom scale) • Hospital Anxiety Depression Scale - 2 (9%) • Center for Epidemiologic Study - Depression Scale - 2 (9%) • Beck Depression Inventory - 1 (5%) • Constipation Assessment Scale - 1 (5%) • Brief Pain Inventory - 1 (5%) • Multidimensional Fatigue Inventory - 1 (5%)
Symptom Dimensions** • Prevalence only - 5 (23%) • Intensity - 15 (68%) • Distress - 7 (32%) • Frequency - 5 (23%) • Control - 1 (5%)
Symptom Relationships*** • Symptom-Symptom - 9 (41%) • Symptom-Predictor - 7 (32%) • Symptom-Outcome -14 (64%)

* Totals may exceed 100% because several studies use more than one scale.

** Totals may exceed 100% because several studies examined more than one dimension.

*** Totals may exceed 100% because several studies examined more than one relationship.

Figure 1: Symptom Assessment Frequency by Study



* Indicates objective "sign"

Table 2. Symptoms Evaluated Within and Across Studies

Symptoms	Symptom Scales[a]										
	MSAS [1,2,3]	ESAS [4-8]	SET [9]	SDS [10-12]	Francoeur (2005)	Mercadante (2000)	von Gruenigen (2006)	Teunissen (2006)	Tsai (2006)	Vainio (1996)	Walsh [13-16]
Pain	X	X	X	X	X	X	X	X	X	X	X
Short of breath **Dyspnea** **Respiration** ***Short of breath / Breathing**	X	X	X	X	X	X	X	X	X	X	X
Nausea ***Nausea / vomiting**	X	X	X	X	X	X	X	X	X	X	X
Vomiting	X	X	X					X			X
Feeling sad **Depression** **Depressive affect** **Depressed mood** **Mood**	X	X		X	X	X		X	X		X
Lack of appetite **Loss of appetite** **Poor appetite** **Anorexia** **Decreased food intake**	X	X	X		X	X		X	X	X	X
Constipation **Bowel pattern change** **Change in bowel habits**	X		X	X	X	X		X	X	X	X
Difficulty Sleeping **Insomnia** **Sleep problems** **Sleeplessness**	X		X	X	X			X	X	X	X
Nervous **Anxiety**	X	X				X		X	X		X
Lack of energy **Fatigue**	X		X	X	X				X		X
Weakness **Asthenia** ***Fatigue / weakness**			X		X	X	X	X	X	X	X
Drowsy	X	X				X	X	X			
Difficulty Concentrating	X		X	X							
Cough	X		X	X							X
Weight Loss ***Weight Loss >10%***	X		X		X			X		X	X
Don't look like self **Appearance**	X			X							
Dry mouth	X		X			X		X			X
Diff. Swallowing **Dysphagia**	X		X			X		X	X		X
Mouth sores **Sore mouth** ***Mucositis***	X		X					X			X

Table 2. Symptoms Evaluated Within and Across Studies (cont.)

Symptoms	Symptom Scales[a]										
	MSAS [1,2,3]	ESAS [4-8]	SET [9]	SDS [10-12]	Francoeur (2005)	Mercadante (2000)	von Gruenigen (2006)	Teunissen (2006)	Tsai (2006)	Vainio (1996)	Walsh [13-16]
Bloated **Abdominal fullness**	X								X		X
Diarrhea	X					X		X			X
Changes in food taste **Taste alteration** **Taste changes**	X								X		X
Numbness/Tingling **Loss of feeling**	X		X								
Urination	X		X								
Sweats ***Night sweats***	X								X		
Itching	X										X
Dizziness	X										X
Well being		X									
Inactivity		X									
Confusion						X		X		X	X
Swelling in arms & legs ***Edema***	X										X
Worry	X										
Decreased interest in sex	X										
Feeling irritable	X										
Hair loss	X										
Changes in skin	X										
Fever			X		X						
Dehydration **Decreased fluid intake**			X			X					
Gastric discomfort **Dyspepsia**						X				X	X
Coordination problems			X								
Cognitive impairment								X			
Paralysis								X			
Pressure ulcer								X			
Restless/heat									X		
Memory problems											X
Early satiety											X
Hoarseness											X
Belching											X
Wheezing											X
Headache											X
Hiccup						X					X
Sedation											X

Table 2. Symptoms Evaluated Within and Across Studies (cont.)

Symptoms	Symptom Scales[a]										
	MSAS [1,2,3]	ESAS [4-8]	SET [9]	SDS [10-12]	Francoeur (2005)	Mercadante (2000)	von Gruenigen (2006)	Teunissen (2006)	Tsai (2006)	Vainio (1996)	Walsh [13-16]
***Aches / pains**											X
Dreams											X
Hallucinations											X
Tremors											X

MSAS – Memorial Symptom Assessment Scale
ESAS – Edmonton Symptom Assessment Scale
SET – Symptom Experience Scale
SDS – Symptom Distress Scale
[a] Author developed symptom scales are listed under the first author's name
*Two symptoms were assessed as a single item
Italics indicates an observable sign (rather than a subjective symptom)

[1]McMillan & Small (2002),
[2]Peruselli, et al. (1993),
[3]Rodin, et al. (2007),
[4]Bakitas, et al. (2009),
[5]Cheung, et al. (2009),
[6]Modonesi, et al. (2005),
[7]Nekolaichuk & Bruera (2004),
[8]Stromgren, et al. (2005),
[9]Doorenbos, et al. (2006), [1]
[0]Morasso, et al. (1999),
[11]Peruselli, et al. (1997),
[12]Peters & Sellick (2006),
[13]Walsh, et al. (2000),
[14]Walsh, et al. (2002),
[15]Walsh & Rybicki (2006),
[16]Kirkova, et al. (2009)

Table 3: Summary of studies of symptom relationships in patients with advanced cancer

First Author (year) **Purpose** **Study design**	**Sample**	**Measurement tool(s)** **Symptom dimensions** **Other variables or scales**	**Symptom Relationships**
Bakitas (2009) Examine the differences between standard care patients and patients exposed to the ENABLE intervention soon after a new diagnosis of an advanced cancer along several dimensions (i.e., participation with care, quality of life (QOL), mood, symptom relief, resource use). Randomized clinical trial	N=322 patients with advanced cancer in a rural comprehensive cancer center in New Hampshire and a VA medical center in Vermont. <u>Intervention</u> Males = 59.6% Mean age 64.7 (±10.8) years <u>Usual care</u> Males = 56.5% Mean age 65.4 (±11.6) years	**Multiple Symptom Scale** Edmonton Symptom Assessment Scale (ESAS) **Symptom dimensions** Intensity **Other variables or scales** Functional Assessment of Chronic Illness Therapy for Palliative Care Center for Epidemiologic Study-Depression Scale (CES-D) Number of hospital days, ICU days, and emergency department visits	**Symptoms**: Not evaluated **Predictors**: No difference between the intervention and usual care on ESAS scores over 13 months. Patients in the invention group reported lower depressed mood over 13 months ($p = .02$). **Outcomes**: Not evaluated
Cheung (2009) Explore symptom clusters among outpatients with different advanced cancers. Cross sectional	N=1366 outpatients with various advanced cancers Males = 50% Median age 64 years	**Multiple Symptom Scale** ESAS **Symptom dimensions** Intensity **Other variables or scales**	**Symptoms**: Two major symptom clusters were identified: fatigue, drowsiness, nausea, decreased appetite, and dyspnea (45% of total variance), AND anxiety and depression (10% of the total variance) **Predictors**: Anxiety and depression clustered for all solid tumors regardless of cancer site. Pain and drowsiness clustered for primary tumors of the central nervous system and head/neck cancers. Lack of appetite and poor well-being clustered for GI, GU, Gyn, breast and lung cancers. Anxiety, drowsiness, fatigue, and dypsnea clustered for hematological cancers. **Outcomes**: Not evaluated
Doorenbos (2006) Examine the symptom	N=174 patients with various cancers	**Multiple Symptom Scale** Symptom Experience Tool (SET), 21	**Symptoms**: Not evaluated **Predictors**: Conditional model revealed that site of cancer (lung

experience trajectory during the last year of life among individuals with cancer and whether it differs by depressive symptomatology, dependence in activities of daily living (ADLs) or instrumental ADLs, sex, site of cancer, or age. Longitudinal (data combined from three different symptom studies)	Males = 64% Mean age 71 years	symptoms (present or absent) **Symptom dimensions** Prevalence **Other variables or scales** CES-D Katz index of ADLs	versus not lung) was related to increased symptom experience. Higher depression scores at baseline was associated with increased symptom experience. After controlling for covariates no difference was found in worsening of symptoms over time. **Outcomes**: Dependence with ADLs at baseline associated with increased symptom experience.
Francouer (2005) Determine if variation in depressive affect could be attributed to symptom clusters in a sample of patients receiving palliative radiation for bone pain. Sickness behavior symptom clusters were explored. Cross sectional	N=268 patients with various cancers and bone metastases receiving palliative radiation Gender not reported Mean age 62.7 (±11.0) years	**Multiple Symptom Scale** Author developed; 9 symptoms Likert scale of "difficulty in controlling symptom" over past month, 5 levels (i.e., complete, a lot, some, little, none) **Symptom dimensions** Controllability **Other variables or scales** CES-D	**Symptoms**: Four distinct symptom clusters were identified: 1) pain, appetite, and weight loss; 2) pain, nausea, and fever; 3) pain, fatigue, and weight loss; 4) pain, breathing problems, and fatigue. Each of these symptom clusters predicted depressive affect. **Predictors**: Not evaluated **Outcomes**: Not evaluated
Kirkova (2009) Determine the relationship of distress with symptom severity in a group of patients with various cancers. In addition, determine whether symptom prevalence or distress was influenced by any demographic characteristics. Cross-sectional, secondary	N=181 patients with various advanced cancers referred for consultation to a palliative medicine program. Gender not reported Mean age 64 (±13) years	**Multiple Symptom Scale** Author developed 48 symptom checklist **Symptom dimensions** Prevalence Intensity Distress **Other variables or scales** ECOG score	**Symptoms:** Symptoms rated as moderate or severe were considered "clinically important". Greater severity was associated with more distress for most symptoms. **Predictors:** Patients <65 years, women, and those with an ECOG score of 3 or 4 had more "clinically important" symptoms and a higher prevalence of distressful symptoms. After controlling for severity, primary cancer site did not influence symptom distress scores. **Outcomes:** Not evaluated

McMillan (2002) Describe and evaluate, in people with advanced cancer who were newly admitted to hospice home care, the relationships between QOL and symptom distress, pain intensity, dyspnea intensity, constipation intensity Cross sectional	N=178 Hospice, home care patients with various advanced cancers Males = 60% Mean age 71 years	**Multiple Symptom Scale** Memorial Symptom Assessment Scale (MSAS) **Symptom dimensions** Prevalence Distress **Other variables or scales** Pain, dyspnea (0-10 NRS, intensity) Constipation Assessment Scale Hospice Quality of Life Index	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: MSAS total score, pain intensity, dyspnea intensity, and constipation intensity were related to QOL. When analyzed as multi-level regression model, only symptom distress remained a significant predictor of QOL with an R^2 of .35 for the model.
Mercadante (2000) Estimate the prevalence and severity of common symptoms in a large population of consecutive patients with advanced cancer who were referred to a home palliative care program and to assess the differences by age, gender, primary site, and performance status. Prospective, repeated measures	N=373 home palliative care patients with various advanced cancer Males = 58% Mean age 66 years	**Multiple Symptom Scale** Pain intensity, 12 other symptoms associated with opioids or cancer Patient report obtained by clinician interview. For patients who were unable to provide self report, symptoms were assessed using a surrogate reporter. **Symptom dimensions** Intensity Prevalence **Other variables or scales** KPS Opioid starting dose Opioid maximum dose	**Symptoms**: Not evaluated **Predictors**: Description of symptom intensity difference between groups (i.e., gender, primary cancer site, age) by KPS score is provided. However, the between group differences were not analyzed using regression to determine if the relationship existed consistently across KPS score. **Outcomes**: When analyzed by KPS group, nausea/vomiting, dry mouth, and dysphagia started low and increased in intensity with decreasing KPS score, reached peak intensity then decreased. Drowsiness, weakness, and confusion showed a large increase in intensity as KPS level decreased. Pain intensity mean score at all KPS levels ranged from 1.4 to 3.9. KPS 40 had the highest mean pain score (3.9). Pain levels for groups KPS 30, 20, and 10 were significantly reduced compared to higher KPS level groups.
Modonesi (2005) Evaluate the impact of palliative care on patients' symptoms from the time of	N=162 patients with various cancers admitted to Palliative Care unit in Italian hospital Males = 56.2%	**Multiple Symptom Scale** ESAS **Symptom dimensions** Intensity **Other variables or**	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: After dichotomizing survival into >30 days and ≤ 30 days, symptom distress (i.e., ESAS to score) at baseline was

admission until one week later Prospective, repeated measures	Median age 67 years	**scales** Demographics	highest for patients in the shorter survival group.
Morasso (1999) Identify terminal cancer patients' needs and the factors associated with unmet needs. The association of both psychological and symptom distress with unsolved needs was evaluated. Cross-sectional, secondary	N=94 patients with various cancers receiving palliative care in Italian hospitals. Males = 57.3% Mean age 61.0 (±11.1)	**Multiple Symptom Scale** Symptom Distress Scale (SDS) **Symptom dimensions** Intensity Frequency Distress **Other variables or scales** Demographics KPS Index of ADLs Unmet needs (open ended questions) Psychological Distress Inventory	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: Individual symptoms were correlated with the PDI total score. Mood was most highly correlated with psychological distress (r = .53), followed by appearance (r = .37). The overall correlation between these two scales was 0.46. Patients with certain unmet needs showed significantly higher psychological distress. Patients who identified symptom control, occupation functioning, emotional support sleep, communication, personal care, and financial support as unmet needs showed significantly higher symptom distress scores.
Nekolaichuk (2004) Gather validity evidence for the Hope Differential Short (HDS) within the context of advanced cancer Prospective, cross sectional	N=96 patients with various advanced cancers (n=42 in an inpatient palliative care unit; n=54 in home hospice) Males = 44.8% Mean age 64.6 (±14.4)	**Multiple Symptom Scale** ESAS (rated 0 "no symptom" to 100 "worst possible") **Symptom dimensions** Intensity **Other variables or scales** Demographics Herth Hope Index Hope –Visual Analogue Scale HDS	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: Both subscales (*authentic spirit* and *comfort*) of the HDS positively correlated with well-being (r =.38 & .41) and were negatively correlated with depression (r = -.40 & -.25) and anxiety (r = -.42 & -.39).
Peruselli (1993) Use the Italian version of the SDS to consider the variations over time in the degree of symptom distress during home care and identify those symptoms that are most responsive to home care.	N=43 patients with advanced cancer who were receiving home care from Pain Therapy and Palliative Care Division. Data was collected during the first, second, and last week of home care.	**Multiple Symptom Scale** SDS **Symptom dimensions** Intensity Frequency Distress **Other variables or scales** Demographics	**Symptoms**: A four factor structure was found that accounted for 67.4% of variance in the symptom findings. Factor 1 loaded six items: appetite (r =.74), fatigue (r =.68), insomnia (r =.29), concentration (r =.75), appearance (r =.84), and mood (r =.78). Factor 2 loaded four items: pain frequency (r =.93), pain intensity (r =.94), bowel pattern (r =.45) and insomnia (r =.34). Factors 3 and 4 each loaded just two items: nausea frequency (r

Prospective, repeated measures	Gender not reported Mean age 67 years		=.95) and nausea intensity (r =.96); respiration (r =.79) and coughing (r =.79) respectively. **Predictors**: Not evaluated **Outcomes**: Not evaluated
Peruselli (1997) Describe the patient's QOL at the outset and during palliative care at home and to define some potential indicators of palliative care outcomes with the aim of assessing the quality of home care as provided by the palliative care unit. Prospective, repeated measures	N=73 patients with advanced cancer who were receiving home care from Pain Therapy and Palliative Care Division. Data was collected upon admission to the Palliative Care Division and every week until death. Males = 52.1% Median age 65 (range 30-85) years	**Multiple Symptom Scale** SDS **Symptom dimensions** Intensity Frequency Distress **Other variables or scales** Demographics Katz Index of ADLs	**Symptoms**: The sample was dichotomized based on baseline symptom distress, those with an SDS total score of <36 and those with a score ≥ 36. Patients in the high distress group (SDS score ≥ 36) had significantly higher distress than patients in the low distress group (SDS score <36). At two weeks there was no longer a difference in mean scores between the high distress group and the low distress group. The highly distressed group improved and the less distressed group maintained. **Predictors**: Not evaluated **Outcomes**: Not evaluated
Peters (2006) Compare the symptom experience, physical, and psychological health status of personal control over the illness and QOL of patients receiving inpatient and home-based palliative care; Identify factors that predict the QOL of terminally ill cancer patients. Prospective, cross sectional	N=58 patients with various terminal cancer in either home based palliative care or a in-patient palliative care unit Males = 38% Mean age 67.8 years	**Multiple Symptom Scale** MSAS **Symptom dimensions** Prevalence Frequency Intensity Distress **Other Variables or scales** Hospital Anxiety and Depression Scale (HADS) Palliative Performance Scale EORTC QLQ-C30 Personal control	**Symptoms**: Not evaluated **Predictors**: Symptom prevalence varied between settings for 3 symptoms. A statistically significant higher proportion of inpatients experienced diarrhea, lack of appetite, and belching. Statistically significant differences for symptoms severity and symptom distress was found between groups with inpatients having higher mean scores. No difference in the total number of symptoms or the frequency of symptoms was found between groups. **Outcomes**: A model of global physical condition, total control, and depression (HADS) significantly predicated QOL. Higher global physical health and personal control and lower depression predicted higher QOL.
Rodin (2007) Determine to what	N= 326 patients with advanced lung or GI cancer	**Multiple Symptom Scale** MSAS	**Symptoms**: Not evaluated **Predictors**: Not evaluated

extent the Desire to Hasten Death (DHD) is present in association with physical suffering and psychological distress in a large sample of ambulatory cancer patients with metastatic disease, the majority of whom had an expected prognosis of >6 months to live. Prospective, cross sectional	Males 186 (57.1%) Mean age 61.8 (±10.7) years	**Symptom dimensions** Prevalence Frequency Intensity Distress **Other variables or scales** Brief Pain Inventory Beck Depression Inventory-II (BDI) FACIT-Spiritual Well-being scale Rosenberg self-esteem scale KPS Medical Outcome Study - Scale of Social Support (MOS-SSS) DHD using the Schedule of Attitudes Toward Hastened Death (SAHD)	**Outcomes**: DHD correlated with: *higher* depression (r =.45) , hopelessness (r =.56), physical symptoms (r =.15), global distress (r =.20), symptom distress (r =.15), pain intensity (r =.15), pain interference (r =.19); and *lower* functional status (r = -.22), spiritual well being (r =.35), social support (r = -.24), self esteem (r = -.26), & living alone (r =.13).
Stromgren (2005) Evaluate the course of patient-reported symptomatology after referral to specialized palliative care. Prospective, repeated measures	N=175 patients with various cancers referred for palliative care in Denmark Males = 44% Mean age 62.8 years	**Multiple SymptomsScale** ESAS **Symptom dimensions** Intensity **Other variables or scales** HADS Multidimensional fatigue inventory, KPS EORTC QLQ-C30 Mini-mental status	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: As KPS score decreased, participation rate decreased. Patients with more severe initial symptoms were less likely to continue with study participation after baseline data collection.
Teunissen (2006) Assess the prognostic value of symptoms in hospitalized advanced cancer patients. Prospective, repeated-measures	N=181 patients with advanced cancer who were hospitalized and referred to a Palliative Care Team in The Netherlands. Males = 44% Median age in years 58 (range 18-91)	**Multiple Symptom Scale** Author developed symptom checklist of 49 symptoms assessed as present or absent Semi-structured interview by a clinical nurse specialist **Symptom dimensions** Prevalence **Other variables and Scales** Demographics KPS	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: Eleven out of 49 symptoms were correlated with survival (headache, abdominal pain, anorexia, weight loss >10%, nausea, vomiting, dysphagia, dyspnea, drowsiness, confusion, and depressed mood). After controlling for diagnosis, multivariate analysis with step-wise selection found that nausea, dysphagia, dyspnea, confusion, and depressed mood were independent variables prognostic for survival. Using multivariate

		Other medical diagnoses Prognostication of death	regression modeling to fit the logarithms of survival, the survival time drastically decreases with the co-occurrence of each identified prognostic symptom.
Tsai (2006) Conduct longitudinal evaluations of symptom management and define the symptom patterns of advanced cancer patients in the Palliative Care Unit of the National Taiwan University Hospital. Prospective, longitudinal	N=77 patients with various cancers admitted to palliative care unit in Taiwan Males = 39% Mean age 62 (range 16 - 86) years	**Multiple Symptom Scale** 16 symptoms from symptom forms and medical records **Symptom dimensions** Prevalence Intensity **Other variables or scales** Demographics Consciousness (alertness, lethargy, obtundation, delirium, stupor, coma)	**Symptoms**: Six different visually determined symptom intensity patterns emerged over time: 1) Continuous/static: restless/heat, abdominal fullness, constipation, dizziness, insomnia; 2) Static/increase: fatigue, weakness, nausea/vomiting, taste alteration, dysphagia, diarrhea, dry mouth, night sweat; 3) Decrease/static: pain, depression; 4) Decrease/increase: anorexia; 5) Static/decrease: aggression; and 6) Decrease: anxiety **Predictors**: Not evaluated **Outcomes**: Not evaluated
Vainio (1996) Estimate the prevalence of pain and eight other common symptoms in a large population of patients with advanced cancer from different palliative care centers and to assess the differences in prevalence of the symptoms by primary cancer site. Prospective, cross sectional	N=1640 patients with various cancers admitted to one of 7 hospice programs in 5 countries Gender and age statistics not reported	**Multiple Symptom Scale** Author developed instrument of 9 symptoms Assessed by clinician with a structured questionnaire **Symptom dimensions** Prevalence Intensity **Other variables or scales** KPS converted to ECOG stage	**Symptoms**: Not evaluated **Predictors**: Statistically significant differences in symptom prevalence rates were found among various cancer diagnoses for all symptoms except constipation, insomnia, and confusion. Nausea was most prevalent in gynecologic and stomach cancers, but rarely found in head and neck and lung cancers. Gastrointestinal symptoms (i.e., nausea, constipation, anorexia) were prevalent in esophageal, stomach, and colorectal cancers. Weakness was highly prevalent in hematological, colorectal, and esophageal cancers. Dyspnea was prevalent in lung cancer. **Outcomes**: Not evaluated
von Gruenigen (2006) Examine the relationship between patients' perception of quality and	N=39 Gynecology-oncology during palliative chemotherapy Females = 100% Mean age 60.33	**Multiple Symptom Scale** *Adapted from Mercadante*: 5 symptoms - pain, SOB, N/V, weakness, drowsiness; (rated as none, mild,	**Symptoms**: Not evaluated **Predictors**: Not evaluated **Outcomes**: No significant correlations between quality of care and satisfaction with care and symptom severity. No

satisfaction with care and symptom severity during palliative chemotherapy for recurrent gynecological malignancies. Prospective, repeated measures	(±10.1) years	moderate, severe) **Symptom dimensions** Prevalence Intensity **Other variables or scales** Patient perception of quality of care and satisfaction with care (QUEST survey)	association between symptom severity and length of survival.
Walsh (2000) Identify common symptoms and see whether symptoms were related to age, gender, or performance status. Prospective, cross sectional	N=1000 patients with various advanced cancers from inpatient and outpatient setting who were referred to a palliative care program. Males = 55% Median age 65 years	**Multiple Symptom Scale** Author developed; 8-page empirically derived clinical assessment form covering pain and 37 other symptoms that affect major organ systems Symptom data were collected through clinician interview. Each was determined to be present or absent and graded as mild, moderate, or severe. It was not specified if the patient or the clinician graded symptom severity. **Symptom dimensions** Prevalence **Other variables or scales** Demographics ECOG score	**Symptoms**: Not evaluated **Predictors**: Adjusting for gender and performance status, 11 symptoms (i.e., blackout, vomiting, pain, nausea, headache, sedation, bloating, sleep problems, anxiety, depression, constipation) were more likely to occur in younger patients. Adjusting for age and performance status, gender was associated with 8 symptoms (i.e., dysphagia, hoarseness, >10% weight loss, sleep problems, early satiety, nausea, vomiting, anxiety). Males were more likely to have dysphagia, hoarseness, >10% weight loss, and sleep problems. Females were more likely to have early satiety, nausea, vomiting, and anxiety. Adjusting for age and gender, performance status was associated with 14 symptoms (i.e., confusion, sedation, blackout, hallucination, weakness, mucositis, anorexia, memory problems, dry mouth, constipation, anxiety, wheezing, pain, itching). **Outcomes**: Not evaluated
Walsh (2002) same data set as above Determine whether any symptoms or patient demographic characteristics were associated	N=1000 patients with various advanced cancers from inpatient and outpatient setting who were referred to a palliative care program. Gender and age statistics not	**Multiple Symptom Scale** Author developed; 8-page empirically derived clinical assessment form covering pain and 37 other symptoms that affect major organ systems Symptom data were	**Symptoms**: Not evaluated **Predictors**: Four correlates for reduced survival were found after adjusting for cancer site and time since diagnosis: poor performance status, male gender, dysphagia, and early satiety. **Outcomes**: Length of survival decreased as the number of

with shorter survival following referral to a palliative medicine program. Prospective, cross sectional	reported	collected through clinician interview. Each was determined to be present or absent and graded as mild, moderate, or severe. It was not specified if the patient or the clinician graded symptom severity. **Symptom dimensions** Prevalence **Other variables or scales** ECOG score Time to death	symptoms (as identified by the National Hospice Study) increased. The symptoms include: anorexia, dry mouth, dyspnea, dysphagia, and weight loss. Patients who had more of these NHS symptoms at the time of enrollment had more symptoms in total. Patients that had all 5 of the NHS symptoms had a median of 16 other symptoms (range 8-26), in contrast to those who had none of the 5 NHS symptoms who had a median of 4 (range 0-13).
Walsh (2006) same data set as above Identify the presence and composition of any symptom clusters. Cross sectional, secondary	N=922 patients with various advanced cancers from inpatient and outpatient setting who were referred to a palliative care program. Males = 56% Median age 65 years	**Multiple Symptoms Scale** Author developed; 8-page empirically derived clinical assessment form covering pain and 37 other symptoms affect-ing major organ systems. Symptom data were collected through clinician interview. Each was determined to be present or absent and graded as mild, moderate, or severe. It was not specified if the patient or the clinician graded symptom severity. **Symptom dimensions** Prevalence Intensity **Other variables or scales** ECOG	**Symptoms**: Seven unique clusters were identified. 1) Fatigue / anorexia / cachexia (easy fatigue, weakness, anorexia, lack of energy, dry mouth, early satiety, weight loss, taste changes) 2) Neuropsychological (sleep disturbance, depression, anxiety) 3) Upper GI (dizzy spells, dyspepsia, belching, bloating) 4) Nausea / vomiting (nausea, vomiting) 5) Aerodigestive (dysphagia, dyspnea, cough, hoarseness) 6) Debility (edema, confusion) 7) Pain (pain, constipation) **Predictors**: Not evaluated **Outcomes**: Not evaluated

Dimensions and Predictors of Multiple Symptoms in Patients with Advanced Cancer

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Abstract

CONTEXT: Multiple symptoms are common in patients with advanced cancer. However, little is known about specific dimensions of the symptom experience.

OBJECTIVES: An evaluation was done to determine: the occurrence rates for and average frequency, severity, and distress ratings for 32 common symptoms, and predictors of total number of symptoms in patients with advanced cancer.

METHODS: Patients with advanced cancer (N=100) completed the Memorial Symptom Assessment Scale. A multiple regression analysis was used to determine the predictors of the total number of symptoms.

RESULTS: Differences in the rankings of specific symptoms were found across the symptom dimensions. Seven symptoms (i.e., pain, sleep disturbance, problems with sexual interest or activity, lack of energy, constipation, numbness/tingling in arms or legs, changes in the way food tastes) were in the top ten symptoms across all dimensions except occurrence. Over 14% of the variance in total number of symptoms was explained by age, gender, race, performance status, and comorbidities. Comorbidity score uniquely explained 4.5% of the variance in total number of symptoms ($p = .036$).

CONCLUSIONS: Multiple symptoms are highly prevalent in patients with advanced cancer. Differences exist in the rankings of symptoms across specific symptom dimensions. Pain, sleep disturbance, problems with sexual interest or activity, lack of energy, constipation, numbness/tingling in arms or legs, and changes in the way food tastes were found to be highly prevalent symptoms across the various dimensions. Worse comorbidity was significantly associated with higher total number of symptoms and when taken together with demographic and other clinical characteristics.

Introduction

Findings from a recent review[1] suggest that multiple symptoms are highly prevalent in patients with advanced cancer. While the negative experience of multiple unrelieved symptoms may contribute to the increased frequency of clinic appointments, emergency department visits, and hospitalizations for "high tech" symptom management interventions,[2, 3] only 22 studies have evaluated multiple symptoms in patients with advanced cancer receiving palliative care.[4] Across these 22 studies, several methodological limitations were noted. First, the majority of these studies did not use valid or reliable symptom assessment scales. Second, the total number of symptoms assessed across these studies varied widely (i.e. 5 to 38 symptoms). Of the 56 different symptoms assessed, 14 symptoms were evaluated in about half of the studies and only 3 symptoms (i.e., pain, dyspnea, nausea) were measured in every study. In the 12 studies that reported symptom prevalence rates, diverse approaches were used to measure symptoms, which makes comparison across studies difficult.[5-16] In addition, very few studies have used comprehensive symptom lists to evaluate the experience of patients with advanced cancer.[17] Therefore, the true prevalence rates for a large array of symptoms in patients with advanced cancer are not known.

While the symptom experience is multidimensional,[18] most instruments that assess multiple dimensions of a symptom (e.g., frequency, severity, distress) do so for only a single symptom. In contrast, most scales that evaluate multiple symptoms assess only a single dimension of the symptom experience. Intensity (or severity) is the symptom dimension most frequently assessed. Only six studies of patients with advanced cancer used the same multidimensional scale (i.e., Memorial Symptom Assessment Scale

(MSAS)) to assess multiple symptoms.[7, 19-23] Five additional studies used author developed scales[9, 10, 16, 24, 25] to evaluate multiple dimensions of the symptom experience in these patients. Only two studies[20, 22] that used the MSAS reported results from one of the three symptom dimensions that the MSAS measures and three studies[10, 24, 25] that used author developed scales evaluated one or more symptom dimension. Finally, just one study of patients with advanced cancer[22] reported results on all four of these dimensions (i.e., occurrence, frequency, severity, and distress).

In order to identify patients who are at greatest risk for multiple symptoms, an evaluation of demographic and clinical characteristics that predict a higher symptom burden is warranted. Only seven studies in the previously cited review[4] reported on the relationships between a variety of predictors (e.g., demographics, cancer type, health care delivery environment) and multiple symptoms.[5, 7, 11, 14-16, 26] However, only two of these studies examined the relationship between predictors and total number of symptoms reported.[5, 7] In a longitudinal study of patients with various cancers, hierarchical linear modeling was used to identify predictors of patients' total number of symptoms during the last year of life. After controlling for gender, age, depression, functional status, and proximity to death, patients with lung cancer experienced more symptoms in their last year of life than patients with other solid tumors.[5] In a study of palliative care inpatients and home care patients,[7] no differences in the total number of symptoms were found between care settings.

In patients with advanced cancer, the experience of multiple symptoms across various symptom dimensions remains poorly understood. In addition, little is known about the predictors of total number of these symptoms in these patients. The Theory of Symptom

Management[18] suggests that symptoms are experienced across multiple dimensions and that a relationship exists between the person (e.g., demographic characteristics) and health (e.g., clinical characteristics) domains and the symptom experience. Increased knowledge of the occurrence, frequency, severity, and distress of symptoms as well as the predictors of the total number of symptoms in patients with advanced cancer is warranted. Research on the multiple dimensions of symptoms in these patients may shed light on the nature of which part of the symptom experience is most difficult for patients to manage. Therefore, the purposes of this study, in a sample of advanced cancer patients with somatic or visceral pain, were to determine the occurrence rates, as well as the frequency, severity, and distress ratings, for 32 common cancer symptoms and determine whether select demographic and clinical characteristics predict the total number of symptoms.

Methods

Design and Sample – This descriptive, cross-sectional study is part of an ongoing randomized clinical trial that will determine the efficacy of two different doses of a psychoeducational intervention to improve cancer pain management. The first 100 patients enrolled in the parent study are included in this analysis. Patients were included if they: were adult oncology outpatients ($\geq$ 18 years of age) experiencing cancer pain; were able to read, write, and understand English; agreed to participate and provided written informed consent; had a Karnofsky Performance Status (KPS) Score of $\geq$ 50; had an average pain intensity score of $\geq$ 3.0 on a 0 to 10 numeric rating scale (NRS); had a life expectancy of at least 6 months; were receiving outpatient treatment for cancer (not AIDS-related) with any single or combination therapy, and had a telephone line.

Patients were excluded if they had a documented previous or current psychiatric disorder or if at the time of recruitment they were receiving hospice care in order not to interfere with the pain management program provided by hospice. However, if patients were referred to hospice care during the course of the study, they were not dropped from the study.

Settings – Patients were recruited from 7 sites in Northern California (i.e., a Comprehensive Cancer Center at an academic medical center, two Veterans' Affairs Hospitals, four community-based oncology clinics). Patients who met the study's inclusion criteria were asked by a staff member at the site whether they would be interested in participating in the study. If the patient was interested, the staff member informed the recruitment nurse who discussed the study and obtained written informed consent. Study instruments were completed in the patients' homes.

Study Instruments – For this study, information from the demographic questionnaire and the MSAS are reported. The Patient Information Questionnaire obtained demographic information (e.g., age, gender, educational level, ethnicity, income) about the patient.

Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.[27, 28] Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).

Self-Administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health

service research settings.[29] The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical knowledge. Patients were asked to indicate if they had the condition using a "yes/no" format. If they indicated that they had a condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and did it limit their activities (yes/no; indication of functional limitations). Patients were given the option to add three additional conditions not listed on the instrument. For each condition, a patient can receive a maximum of 3 points. Because there are 13 defined medical conditions and 2 optional conditions, the maximum score totals 45 points if the open-ended items are used and 39 points if only the closed-ended items are used. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[29-33]

The MSAS is a self-report questionnaire designed to measure the multi-dimensional experience of symptoms.[34] The MSAS contains a list of 32 physical and psychological symptoms that occur as a result of cancer or its treatment. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its frequency of occurrence, severity, and distress. Each symptom dimension was measured using a Likert scale: frequency (i.e., 1=rarely, 2=occasionally, 3=frequently, 4= almost constantly); severity (i.e., 1=mild, 2=moderate, 3=severe, 4=very severe); and distress (i.e., 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much). The MSAS was developed for use in studies of patients with cancer[23, 35] and has established reliability in studies of palliative care patients.[34, 36, 37]

Medical records were reviewed to obtain information on the site of the primary cancer, number of metastatic sites, extent of metastatic disease, current therapy, and reason for therapy.

Data Analysis – Data were analyzed using SPSS version 18. Descriptive statistics were used to characterize the sample and the study variables. Symptom occurrence rates and mean (SD) ratings of frequency (1-4), severity (1-4), and distress (0-4) were generated for those patients who reported the symptom. Multiple linear regression analysis was used to evaluate the effects of predictor variables on the continuous dependent variable of total number of symptoms. The total number of symptoms was calculated by summing the number of symptoms that each patient reported based on a response on any one of the four dimensions (i.e., occurrence, frequency, severity, distress). Predictor variables selected for univariate analysis were drawn from the Theory of Symptom Management[18] and supported by the literature.[4] Independent predictors that reached a significance of $p<.15$ at the univariate level were included in the regression model. Select demographic and clinical characteristics were included in the final model to create the most parsimonious model. Information on the performance of the multiple regression model was assessed by the percentage of variance in the dependent variable that was explained (R^2). Unique contributions of independent variables to the model were measured by the percentage of variance explained by that variable ($R^2\Delta$). All calculations used actual values. A p-value of < 0.05 was considered statistically significant.

Results

Patient Characteristics

A total of 100 patients with advanced cancer who reported pain associated with cancer or its treatment were enrolled. Fifty percent of the sample was male with a mean age of 60.7 (±11.7) years. The sample was primarily white (75%), married/partnered (67%), living with someone (80%), and had 15.5 (±2.8) years of education (Table 1).

The most common cancer diagnoses were breast cancer (38%) and prostate cancer (28%). The majority of the patients (84%) had bone metastases and 54% had metastases to more than one site. The majority of the patients were receiving treatment for control (74%) or palliation (24%) of their disease. Patients had a mean KPS score of 69.9 (±12.4) and a mean SCQ score of 8.6 (±3.6).

Symptom Occurrence, Frequency, Severity, and Distress

The occurrence rates and frequency, severity, and distress scores for the 32 MSAS symptoms are summarized in Table 2. Significant variation in the ranking of symptoms was found across the four symptom dimensions. The five symptoms with the highest occurrence rates were pain, lack of energy, feeling drowsy, difficulty sleeping, and feeling sad. The five symptoms with the highest reported frequency ratings were numbness/tingling in arms or legs, pain, problems with sexual interest or activity, difficulty sleeping, and hair loss. The five most severe symptoms were problems with sexual interest of activity, constipation, numbness/tingling in arms or legs, pain, and feeling sad. The five most distressing symptoms were vomiting, feeling sad, pain, problems with sexual interest or activity, and constipation.

Pain, sleep disturbance, and lack of energy were the three symptoms that ranked in the top five across all four symptom dimensions. Along with pain, sleep disturbance, and lack of energy, four additional symptoms (i.e., problems with sexual interest or

activity, constipation, numbness/tingling in arms or legs, changes in the way food tastes) were consistently ranked among the top ten symptoms across all symptom dimensions with the exception of occurrence. Vomiting was reported to be the most distressing symptom but was not ranked in the top ten for any other symptom dimension. In contrast, numbness/tingling in arms or legs and problems with sexual interest or activity (the most frequent and most severe symptoms, respectively) were included in the top ten rankings for the other symptom dimensions.

Predictors of Total Number of Symptoms

The mean total number of symptoms was 15.5 (±6.0). In the univariate analysis, a statistically significant correlation was found between total number of symptoms and race (Caucasian versus all other races, $p = .027$) as well as SCQ total score ($p = .008$). No statistically significant correlations were found between total number of symptoms and the following predictors: age, gender, living alone, marital status, level of education, employment status, KPS score, number of metastatic sites, and number of cancer treatments.

As shown in Table 3, 14.5% of the variance in total number of symptoms was explained by age, gender, race, KPS score, and SCQ total score. The SCQ total score uniquely explained 4.5% of the variance in total number of symptoms ($p = .036$). While race was significant in the univariate analysis, it did not reach statistical significance in the regression model ($p = .065$).

Discussion

This study is the one of the first to report data on occurrence rates, as well as ratings of multiple dimensions of symptoms using a comprehensive list of symptoms in a representative

sample of patients with advanced cancer. Pain, lack of energy, feeling drowsy, difficulty sleeping, and feeling sad occurred in over 70% of these patients. This finding is consistent with a systematic review of symptom prevalence in patients with incurable cancer,[1] that found that fatigue, pain, lack of energy, and weakness were the most common symptoms. Similarly, physical symptoms (e.g., pain,[7, 9, 10, 16, 19-25] fatigue,[7, 10, 16, 24, 25] lack of energy,[19-23] and drowsiness[19, 22, 23]) were found to be highly prevalent in several recent studies of advanced cancer patients. While lack of appetite and dry mouth were not among the most common symptoms in this study, they did occur in a large portion of the patients (68% and 55%, respectively). These rates are similar to the occurrence rates of 56% to 96% found for lack of appetite[9, 10, 16, 19, 20, 23-25] and the occurrence rates of 58% to 82% for dry mouth[7, 19-23, 25] found in previous studies. While the rankings for the occurrence rates of the most common symptoms differed across studies, these findings suggest that the occurrence rates for the most common symptoms are relatively similar across studies. Interestingly, difficulty sleeping that occurred in 73% of this sample, was not reported as a common symptom in previous studies of patients with advanced cancer. As for the psychological symptoms, feeling sad, worrying, and feeling irritable were very common in this sample. Only four studies found similar psychological symptoms such as worrying,[21, 22] depression,[10] or anxiety[9] to be among the most commonly occurring symptoms in patients with advanced cancer.

In terms of the frequency dimension of the symptom experience, numbness or tingling, pain, problems with sexual interest or activity, difficulty sleeping, and hair loss had the highest frequency scores that ranged from 2.25 (±0.98) for numbness or tingling to 2.19 (±1.03) for

hair loss. This finding is consistent with a similar study of advanced cancer patients[22] that reported that pain and difficulty sleeping had the highest frequency scores.

In this study, problems with sexual interest or activity, constipation, numbness or tingling, pain, and difficulty sleeping were the most severe symptoms. All of these symptoms had mean severity scores that were in the moderate to severe range. While other studies have reported similar severity scores for pain,[10, 22, 24] only two studies reported similar ratings for difficulty sleeping[22] and constipation[24] in similar samples. Since, no other studies found problems with sexual interest or activity or numbness or tingling to be among the most severe symptoms in patients with advanced cancer, this finding warrants confirmation in future studies.

In this study, vomiting, difficulty sleeping, pain, problems with sexual interest or activity, and constipation were the most distressing symptoms with scores that ranged from 2.32 (±1.11) for vomiting to 2.07 (±1.23) for constipation. Similar results were reported for distress from pain[20, 22, 25] and difficulty sleeping.[20] While no studies reported distress from vomiting or constipation, other studies that used the MSAS reported high levels of distress from other gastrointestinal symptoms (e.g., feeling bloated,[20, 22] dry mouth[20]). In a study of patients with advanced cancer that evaluated symptoms as either distressing or not distressing,[25] anorexia, nausea, and sore mouth were among the most distressing symptoms. The consistent finding, across multiple studies, of high levels of distress associated with a variety of gastrointestinal symptoms suggests that future studies need to evaluate the exact etiologies for these symptoms. While these symptoms may be related to decreased intake of food and fluids as well as increased intake of opioid analgesics, the exact etiologies for these symptoms need to be determined in order to plan effective symptom management interventions. It is not entirely

clear why distress ratings for lack of energy (i.e., 2.00 (±0.91)) were lower than reported in previous studies (i.e., 2.60 to 2.71)[20, 22, 25] One possible explanation for this difference is that the previous studies included patients who were hospitalized[22] or enrolled in palliative care[25] or hospice[20] programs. These patients may have reported decreased levels of energy associated with a shorter life expectancy. Similar to our findings for severity, additional research is warranted to determine the reasons why problems with sexual interest or activity and numbness or tingling were among the most distressing symptoms in this sample.

While previous research[16] has evaluated the relationship between age, gender, performance status, and individual symptoms, this study is the first to attempt to determine which demographic and clinical characteristics predicted total number of symptoms in patients with advanced cancer. Taken together older age, being female, being non-white, having a lower KPS score, and having a higher comorbidity score were associated with a higher number of symptoms. While cancer diagnosis was found to predict symptom burden in another study,[5] it was not a predictor in this study. This inconsistent finding may be due to the relatively small number of patients in each diagnostic group in this study. While no studies have examined whether age and functional status predicted the total number of symptoms in this population, these characteristics were associated with higher symptom severity for individual symptoms.[15]

Several study limitations need to be acknowledged. The sample size was relatively small which may have limited our ability to identify predictors of total number of symptoms. While these patients were all advanced cancer patients, they were at various stages of their disease trajectory, which makes it difficult to determine if patients are experiencing symptoms as a result of their treatments, disease progression, or some other mechanism(s). Finally, the

fairly homogeneous sample of primarily white, well-educated, older adults limits the generalizability of the study findings.

Findings from this study suggest that multiple symptoms are highly prevalent in patients with advanced cancer. Significant differences exist in ratings of symptom occurrence, frequency, severity, and distress.[6] While greater symptom severity was associated with more symptom distress[15] these dimensions should not be used interchangeably. In this study, seven symptoms (i.e. pain, sleep disturbance, problems with sexual interest or activity, lack of energy, constipation, numbness/tingling in arms or legs, changes in the way food tastes) were in the top ten symptoms across all dimensions with the exception of occurrence. Further research is needed to determine if this group of symptoms forms a symptom cluster. In addition, the mechanism(s) that underlie multiple symptoms in this vulnerable population warrants investigation.

An interesting and perhaps surprising finding from this study is the high occurrence, frequency, severity, and distress ratings associated with problems with sexual interest or activity. One possible explanation is that researchers and clinicians may not consider sex and sexuality a relevant symptom to assess in patients with advanced cancer. Another possibility is the relatively high proportion of patients with prostate cancer may have influenced these results. Additional research is warranted to examine the significance of this symptom in patients with advanced cancer.

Additional research is needed to determine other predictors of total number of symptoms as well as the impact of increasing number of symptoms on patient outcomes such as QOL and survival. While patients' reports of multiple symptoms across several dimensions were described in this study, it is not known whether the symptom occurrence rates or any of

the other dimensions (i.e., frequency, severity, distress) are related to the total number of symptoms. In addition, an examination of symptom clusters and an identification of patient subgroups based on their experience with multiple symptoms may reveal the underlying mechanisms of multiple symptoms. These findings can be used to develop and test interventions to improve symptom management in this vulnerable population.

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Appendix

Table 1. Demographic and clinical characteristics of the patients (n=100)

Characteristic	**Mean (SD)**	**Range**
Age (years)	60.7 (11.7)	28-89
Education (years)	15.5 (2.8)	8-23
Karnofsky Performance Status	69.9 (12.4)	40-100
Total number of symptoms	15.5 (6.0)	5-32
Self-Administered Comorbidity Questionnaire	8.6 (3.6)	2-20
Number of metastatic sites	1.9 (1.2)	1-5
	%	**n**
Male gender	50%	50
Lives alone	20%	20
Caucasian	75%	73
Married/partnered or living together	67%	65
Not currently working	79%	77
Type of cancer		
Breast	38%	38
Colon	2%	2
Lung	10%	10
Melanoma	1%	1
Prostate	28%	28
Leukemia	1%	1
Non-Hodgkin's lymphoma	1%	1
Other	25%	25
Two primary cancers	6%	7
Type of treatment		
Radiation therapy	10%	10
Chemotherapy	59%	59
Biotherapy	9%	9
Hormonal therapy	31%	31
Number of therapies		
0 therapies	15%	15
1 therapy	62%	62
2 therapies	22%	22
3 therapies	1%	1
Metastastic sites		
0	7%	7
1	39%	39
2	29%	29
3	13%	13
4	8%	8
5	4%	4
Reason for treatment		
Cure	2%	2
Control	74%	64
Palliation	24%	21

* Percentage total exceeds 100% because patients may have more than one type of cancer

Table 2. Ratings of occurrence, frequency, severity and distress of the symptoms on the Memorial Symptom Assessment Scale

Symptom	Occurrence		Frequency[a]		Severity[b]		Distress[c]	
	%	N	Mean (SD)	Rank	Mean (SD)	Rank	Mean (SD)	Rank
Pain	96%	99	3.00 (.91)	2	2.25 (.79)	4	2.24 (.91)	3
Lack of energy	94%	99	2.67 (.96)	6	2.18 (.80)	7	2.00 (1.16)	7
Feeling drowsy	84%	99	2.21 (.78)		1.84 (.76)		1.47 (1.09)	
Difficulty sleeping	73%	99	2.71 (.93)	4	2.23 (.81)	5	2.26 (1.11)	2
Feeling sad	71%	100	1.99 (.79)		1.83 (.73)		1.64 (1.05)	
Lack of appetite	68%	100	2.35 (.94)		2.03 (.93)		1.32 (1.08)	
Worrying	67%	100	2.13 (.91)		1.86 (.74)		1.72 (1.01)	
Constipation	64%	100	2.64 (.91)	7	2.32 (.90)	2	2.07 (1.23)	5
Difficulty concentrating	64%	99	2.17 (.70)		1.89 (.63)		1.67 (1.01)	
Feeling irritable	57%	100	1.98 (.91)		1.84 (.83)		1.71 (1.12)	
Numbness or tingling	56%	99	3.04 (.95)	1	2.25 (.98)	3	1.92 (1.37)	9
Dry mouth	55%	99	2.30 (.81)		1.91 (.56)		1.15 (.93)	
Feeling nervous	54%	99	1.89 (.85)		1.67 (.71)		1.40 (1.01)	
Nausea	53%	99	2.09 (.84)		1.88 (.79)		1.80 (1.12)	
Problems with sexual interest or activity	52%	97	2.95 (1.12)	3	2.58 (1.18)	1	2.17 (1.32)	4
Sweats	46%	100	2.25 (.87)		2.08 (.83)	9	1.83 (1.17)	
Change in the way food tastes	45%	100	2.56 (1.00)	8	2.17 (.98)	8	1.90 (1.24)	10
Itching	44%	100	2.05 (.97)		1.78 (.89)		1.46 (1.22)	
Dizziness	37%	100	1.69 (.87)		1.50 (.66)		1.50 (1.14)	
Cough	36%	99	1.83 (.87)		1.44 (.58)		.89 (.89)	
Feeling bloated	36%	100	2.09 (.82)		1.93 (.74)		1.93 (1.11)	8
Shortness of breath	36%	99	2.00 (.63)		1.72 (.59)		1.63 (.93)	
Weight loss	35%	100	2.13 (.97)		1.90 (.91)		1.50 (1.28)	
I do not look like myself	34%	100	2.41 (1.09)	10	1.90 (.77)		1.72 (1.25)	
Changes in skin	33%	100	2.32 (1.02)		2.07 (.90)	10	1.72 (1.31)	
Swelling	30%	100	2.41 (1.11)		1.89 (.89)		2.00 (1.25)	6
Hair loss	27%	100	2.70 (.923)	5	2.19 (1.03)	6	1.78 (1.35)	
Diarrhea	26%	100	2.00 (.71)		2.05 (.87)		1.65 (1.04)	
Vomiting	26%	100	1.73 (.70)		2.05 (.71)		2.32 (1.11)	1
Problems with urination	24%	100	2.48 (.98)	9	1.85 (.81)		1.90 (1.02)	
Difficulty swallowing	22%	100	1.78 (.88)		1.59 (.80)		1.13 (.81)	
Mouth sores	18%	100	1.93 (1.10)		1.60 (.63)		1.60 (.99)	

[a]Frequency ratings (1=rarely, 2=occasionally, 3=frequently, 4= almost constantly)
[b]Severity ratings (1=mild, 2=moderate, 3=severe, 4=very severe)
[c]Distress ratings (0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, 4=very much)

Table 3. Multiple regression analysis of predictors of total number of symptoms (n=92)

Source	R^2	beta	$R^2\Delta$	df	F	p
Overall	.145			5,86	2.91	.018
Age		0.040	.001	1,86	0.144	.705
Female		-0.093	.007	1,86	0.736	.394
Non-white		-0.196	.035	1,86	3.482	.065
Karnofsky Performance Status score		-0.124	.014	1,86	1.414	.238
Self Administered Comorbidity Questionnaire score		0.228	.045	1,86	4.537	.036

Determination of Cutpoints for Low and High Numbers of Symptoms in Patients with Advanced Cancer

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Abstract

CONTEXT: While the range in number of symptoms experienced by patients with advanced cancer is known to be quite wide, no work has been done to determine if an optimal cutpoint for low/high number of symptoms exists. The analytic approaches that established clinically meaningful cutpoints for the severity of cancer pain and fatigue provided the foundation for this study.

OBJECTIVES: An analysis of various cutpoints was performed to determine the optimal cutpoint for low and high number of symptoms using a range of potential cutpoints and to determine if those cutpoints distinguished between the two symptom groups in any demographic and clinical characteristics as well as in depression, anxiety, and quality of life (QOL).

METHODS: Patients with advanced cancer (N=111) completed a 32 symptom assessment scale, a depression scale, an anxiety inventory, and two QOL scales. Various combinations of cutpoints were tested to yield two cutpoint as well as one cutpoint solutions. Using analysis of variance for QOL total score and multivariate analysis of variance for QOL subscale scores, the F-ratio that yielded the highest between group difference was determined to be the optimal cutpoint between low and high number of symptoms.

RESULTS: A cutpoint of ≤12 symptoms (i.e., 0-12 symptoms is low and 13-32 symptoms is high) was found to be the optimal cutpoint for total number of symptoms in patients with advanced cancer. After controlling for age and comorbidities, significant differences on depression, anxiety, and QOL scores validated that a cutpoint between 12 and 13 symptoms differentiated between two groups of patients with advanced cancer.

Psychological symptoms (i.e., feeling sad, worrying, feeling irritable, and feeling nervous) were ranked higher in occurrence in the high number of symptoms group of patients.

CONCLUSIONS: Findings from this study suggest that a threshold between low and high total number of symptoms exists for patients with advanced cancer. Psychological symptoms are significantly different between patients in the low versus high number of symptoms groups and may play an important role in QOL outcomes in patients with advanced cancer.

Introduction

In a landmark paper published in 1995, Serlin and colleagues provided evidence to support the establishment of clinically meaningful cutpoints for mild, moderate, and severe pain in a heterogenous sample of oncology patients.[1] Since that time, a number of studies have refined these cutpoints for acute,[2, 3] chronic,[4] and cancer[5] pain. In addition, cutpoints were established for fatigue associated with cancer and its treatment.[6] The approach taken to create these cutpoints was based on the idea that within the entire symptom experience, severity comprised the internal sensory dimension and interference comprised the external reactive dimension.[1] The non-linear relationship between severity of pain or fatigue and interference with function was demonstrated by a statistically significant "jump" in interference scores as the symptom severity went from mild to moderate or moderate to severe.[1-5]

The establishment of clinically meaningful cutpoints is important for several reasons. First, they have served as the foundation of treatment guidelines. For example, the National Comprehesive Cancer Network used these pain and fatigue severity cutpoints to establish treatment algorithms for cancer pain[7] and fatigue management.[8] Second, clinicians can use these cutpoints to determine if management strategies are effective. Based on the determination of cutpoints for pain severity and their association with significant decrements in function, the goal of pain management interventions, namely to reduce worst pain scores to below 4 on a 0 to 10 numeric rating scale (NRS) has become a clinical practice standard.[9]

Findings from recent reviews suggest that patients with advanced cancer experience numerous concurrent symptoms.[10, 11] In fact, across 46 studies, 24 different symptoms occurred in ≥20% of the pooled samples (N=25,074). While total number of symptoms has not been examined as a factor that contributes to significant decrements in quality of life (QOL), various

components of this concept of symptom burden[12, 13] (i.e., symptom severity[14, 15] and symptom distress[16, 17]) have been associated with significant decrements in functional status and decreases in QOL. Based on these associations, Cleeland and colleagues recommended that symptom assessment be included in all clinical trials in oncology as a proxy for other QOL domains.[12]

Given the strong association between other aspects of symptom burden and QOL, it is reasonable to suggest that QOL could be used as an outcome measure to evaluate clinically meaningful cutpoints for low and high numbers of symptoms in patients with advanced cancer. In addition, given that patients with advanced cancer report more symptoms than patients with earlier stage cancer[10, 18, 19] and comprehensive, multidimensional symptom assessment tools may be burdensome for patients and clinicians, the determination of this type of cutpoint might have some clinical utility. Clinicians could use a low/high cutpoint to determine when to perform a more in-depth assessment of patients' symptoms. In addition, these cutpoints could assist clinicians to identify high risk patients who warrant more aggressive symptom management interventions.

Expanding on the idea put forward by Serlin and colleagues,[1] in this study the *total number of symptoms* reported by patients with advanced cancer is viewed as the sensory dimension of the symptom experience and *QOL* is viewed as the reactive dimension. If total number of symptoms has a non-linear relationship with QOL (as pain severity and interference does) then a significant "jump" in QOL scores would occur as the total number of symptoms goes from low to high. This idea supports the clinical observations that patients with advanced cancer can go about their lives relatively

effectively with a "low" number of symptoms but when the total number of symptoms crosses some threshold between low and high, various domains of QOL become impaired and patients can no longer manage their symptoms. Clinically meaningful differences in the number of symptoms are expected to be associated with significant differences in QOL. Therefore, the purposes of this study, in a sample of patients with advanced cancer, were to determine the optimal cutpoint for low and high number of symptoms using a range of potential cutpoints and to determine if those cutpoints distinguished between the two symptom groups in any demographic and clinical characteristics as well as in depression, anxiety, and QOL.

Methods

Design and Sample – This descriptive, cross-sectional study is part of an ongoing randomized clinical trial that will determine the efficacy of two different doses of a psychoeducational intervention to improve cancer pain management. The first 111 patients enrolled in the parent study are included in this analysis. Patients were included if they: were adult oncology outpatients ($\geq$ 18 years of age) experiencing cancer pain; were able to read, write, and understand English; agreed to participate and provided written informed consent; had a Karnofsky Performance Status (KPS) Score of $\geq$ 50; had an average pain intensity score of $\geq$ 3.0 on a 0 to 10 NRS; had a life expectancy of at least 6 months; were receiving outpatient treatment for cancer (not AIDS-related) with any single or combination therapy, and had a telephone line.

Patients were excluded if they had a documented previous or current psychiatric disorder or if at the time of recruitment they were receiving hospice care in order not to interfere with the pain management program provided by hospice. However, if patients

were referred to hospice care during the course of the study, they were not dropped from the study.

Settings – Patients were recruited from 7 sites in Northern California (i.e., a Comprehensive Cancer Center at an academic medical center, two Veterans' Affairs Hospitals, four community-based oncology clinics). Patients who met the study's inclusion criteria were asked by a staff member at the site whether they would be interested in participating in the study. If the patient was interested, the staff member informed the recruitment nurse who discussed the study and obtained written informed consent. Study instruments were completed in the patients' homes.

Study Instruments – The Patient Information Questionnaire obtained demographic information (e.g., age, gender, educational level, ethnicity, income) about the patient.

Medical records were reviewed to obtain information on the site of primary cancer, number of metastatic sites, extent of metastatic disease, current therapy, and reason for therapy.

Karnofsky Performance Status (KPS) scale is widely used to evaluate functional status in patients with cancer and has well established validity and reliability.[20, 21] Patients rated their functional status using the KPS scale that ranged from 30 (I feel severely disabled and need to be hospitalized) to 100 (I feel normal; I have no complaints or symptoms).

Self-Administered Comorbidity Questionnaire (SCQ) is a short and easily understood instrument that was developed to measure comorbidity in clinical and health service research settings.[22] The questionnaire consists of 13 common medical conditions that were simplified into language that could be understood without any prior medical

knowledge. Patients were asked to indicate if they had the condition using a "yes/no" format. If they indicated that they had a condition, they were asked if they received treatment for it (yes/no; proxy for disease severity) and did it limit their activities (yes/no; indication of functional limitations). Patients were given the option to add three additional conditions not listed on the instrument. For each condition, a patient can receive a maximum of 3 points. Because there are 13 defined medical conditions and 2 optional conditions, the maximum score totals 45 points if the open-ended items are used and 39 points if only the closed-ended items are used. The SCQ has well-established validity and reliability and has been used in studies of patients with a variety of chronic conditions.[22-26]

The Memorial Symptom Assessment Scale (MSAS) is a self-report questionnaire designed to measure the multidimensional experience of symptoms.[27] The MSAS contains a list of 32 physical and psychological symptoms that occur as a result of cancer or its treatment. Using the MSAS, patients were asked to indicate whether or not they had experienced each symptom in the past week (i.e., symptom occurrence). If they had experienced the symptom, they were asked to rate its frequency of occurrence, severity, and distress. Each symptom dimension was measured using a Likert scale. The MSAS was developed for use in studies of patients with cancer[28, 29] and has established reliability in studies of palliative care patients.[27, 30, 31]

The Multidimensional Quality of Life Scale-Cancer Version 2 (MQOLS-CA2) is a 33-item instrument that measures five dimensions of QOL in cancer patients (i.e., psychological well-being, general physical well-being, nutrition, symptom distress, and interpersonal well-being).[32] The patient responds to each item on the QOL

inventory by circling a number from 0 (not at all positive) to 10 (extremely positive). Subscale scores and a total QOL score are calculated. Higher scores indicate a better QOL. The reliability of this tool was determined to be 0.94 in a sample of 435 patients undergoing treatment for cancer.[33] Content validity of the MQOLS-CA2 was established using a panel of experts in oncology and pain management. Construct and concurrent validity were reported.[32]

The following measures were used to validate the cutpoint identified in this study.

The Center for Epidemiologic Studies-Depression (CES-D) scale consists of 20 items selected to represent the major symptoms in the clinical syndrome of depression. Scores can range from 0 to 60. A higher score indicates higher levels of depression. Scores of $\geq$ 16 indicate the need for individuals to seek clinical evaluation for major depression. The CES-D has well established concurrent and construct validity.[34-36]

The Spielberger State-Trait Anxiety Inventories (STAI-T and STAI-S) consist of 20 items each that were rated from 1 to 4. The scores for each scale are summed and can range from 20 to 80. A higher score indicates greater anxiety. The STAI-T measures an individual's predisposition to anxiety determined by his/her personality and estimates how a person generally feels. The STAI-S measures an individual's transitory emotional response to a stressful situation. It evaluates the emotional responses of worry, nervousness, tension, and feelings of apprehension related to how a person feels "right now" in a stressful situation. Cutoff scores of $\geq$ 31.8 and $\geq$ 32.2 indicate high levels of trait and state anxiety, respectively. The STAI-S and STAI-T inventories have well

established criterion and construct validity and internal consistency reliability coefficients.[37-39]

The Medical Outcomes Study-Short Form (MOS-SF36), a 36 item instrument, is a product of the Medical Outcomes study and is referred to as a generic measure of QOL because it assesses health concepts that represent basic human values that are relevant to everyone's functional status and well-being. The MOS-SF36 consists of 8 subscales that evaluate important health concepts. Higher scores indicate higher QOL. MOS-SF36 scoring guidelines are provided in the published manual. The MOS-SF36 has undergone extensive validity and reliability testing in thousands of healthy individuals and patients with a variety of medical conditions.[40-42]

Data Analysis – Data were analyzed using SPSS version 18. Descriptive statistics were used to characterize the sample and the study variables. Symptom occurrence rates were generated for each of the symptoms evaluated on the MSAS. The total number of symptoms was calculated by summing the number of symptoms that each patient reported based on a response on any one of the four dimensions (i.e. occurrence, frequency, severity, distress).

A cutpoint that divided the sample into low and high number of symptoms was created using the analytic strategy described by Serlin et al.[1] Five categorical variables, that represented dichotomizing the number of symptoms into low and high using the five possible cutpoints between 10 and 14 were created (e.g. 0 to 10 = low, 11 to 32 = high, 0 to 11 = low, 12 to 32 = high, etc.) and related to the five MQOLS-CA2 subscales using multivariate analysis of variance (MANOVA) and to the MQOLS-CA2 total score using analysis of variance (ANOVA).[5] Various combinations of cutpoints were tested to yield

two cutpoints (three groups) as well as one cutpoint (two groups) solutions. The criterion used to determine the optimal cutpoint groups was the F-ratio for the between group effect for both the MANOVA and the ANOVA (Table 1). While several attempts were made to establish cutpoints for low, medium, and high total number of symptoms, a clear cutpoint between medium and high using the established criterion was not identified. Therefore, the analysis proceeded to determine a single cutpoint solution.

In order to determine if the optimal cutpoint for the total number of symptoms distinguished between the low and high symptom groups on demographic and clinical characteristics, independent sample t-tests and Chi-square analyses were used. Based on these preliminary analyses, significant between groups differences were found in age and SCQ scores. Because age and comorbidity are associated with depression,[43-47] anxiety,[46-48] and/or QOL[49-52] analyses of covariance (ANCOVA) were used to evaluate for differences in CES-D subscale and total scores, STAI-S and STAI-T scores, and MQOL-CA2 and MOS-SF36 subscale and total scores. All calculations used actual values. Adjustments were not made for missing data. Therefore, the cohort for each analysis was dependent of the largest set of complete data between the groups. For all tests, a p-value of < 0.05 was considered statistically significant.

Results

Cutpoint Calculations

As shown in Table 1, for total number of symptoms, a cutpoint of ≤12 symptoms (i.e., 0-12 symptoms is low and 13-32 symptoms is high) was the optimal cutpoint, in that it had the largest between group F-ratios on both the MANOVA for the MQOLS-CA2 subscales scores and on the ANOVA for the MQOLS-CA2 total score. Using ≤12

symptoms as the cutpoint, 34% of the sample (n=38) was classified as having a low number of symptoms.

Patient Characteristics

A total of 111 patients with advanced cancer who reported pain associated with cancer or its treatments were enrolled. Forty-six percent of the sample was male with a mean age of 59.8 (±12.3) years. The sample was primarily white (76%), married/partnered (66%), living with someone (79%), and had 15.5 (±2.8) years of education (Table 2).

The most common cancer diagnoses were breast cancer (37%) and prostate cancer (24%). The majority of the patients (84%) had bone metastases and 51% had metastases to more than one site. The majority of the patients were receiving treatment for control (78%) or palliation (19%) of their disease. Patients had a mean KPS score of 70.0 (±12.1) and a mean SCQ score of 8.5 (±3.7).

Differences in demographic and clinical characteristics

As shown in Table 2, no differences were found between the low and high symptom groups in any demographic or clinical characteristics except age, SCQ total score, and living alone. Patients in the high symptom group were significantly younger (p=.034) and had a higher comorbidity score (p=.036).

Differences in symptom occurrence rates

The occurrence rates for the 32 MSAS symptoms for the two groups are reported in Table 3. Differences were found in the ranking of the symptoms as well as in the occurrence rates for the various symptoms. Nine symptoms (i.e., pain, lack of energy, feeling drowsy, difficulty sleeping, constipation, lack of appetite, worrying, feeling sad,

and difficulty concentrating) ranked within the top 12 for both the low and high number of symptom groups. Numbness and tingling, changes in the way food tastes, and dry mouth were among the top 12 symptoms for the low number of symptoms group but not for the high number of symptoms group. In contrast feeling nervous, feeling irritable, and nausea were in the top 12 for the high number of symptoms group but not for the low number of symptoms group. Of note, all four of the psychological symptoms (i.e., feeling sad, worrying, feeling nervous, feeling irritable) were among the top 12 symptoms in the high number of symptoms group.

With regard to occurrence rates, pain and lack of energy has similar occurrence rates in both the low and high number of symptoms groups (i.e., pain 97% and 96%, lack of energy 92% and 96%, respectively). For the low number of symptoms group, after pain and lack of energy, the occurrence rates for the next ten symptoms ranged from as high as 74% for feeling drowsy to 34% for dry mouth. However, for the high number of symptoms group, the next 10 highest ranked symptoms had much higher occurrence rates (i.e., 90% for feeling sad to 65% for nausea).

Differences in depression and anxiety scores

As illustrated in Figure 1, after controlling for the effects of age and comorbidities, significant between group differences were found in three of the four CES-D subscales (i.e., somatic, depressed affect, positive affect) as well as in the total CES-D score. The high symptom group reported lower scores on the positive affect subscale and higher somatic and depressed affect subscale scores as well as total CES-D score.

After controlling for age and comorbidities, significant between group differences in anxiety scores (i.e., STAI-T and STAI-S) were found (Figure 2). Patients in the high symptom group reported significantly higher state and trait anxiety scores.

Differences in QOL scores

As expected, after controlling for the effects of age and comorbidities, significant between group differences were found in the total MQOLS-CA2 score as well as in four of the five MQOLS-CA2 subscale (i.e., physical, psychological, nutrition, symptom distress) scores (Figure 3). Patients in the high symptom group had lower subscale and total MQOLS-CA2 scores.

After controlling for the effect of age and comorbities, significant between group differences were found for 7 of the 8 MOS-SF36 subscale scores (i.e., physical functioning, bodily pain, general health, vitality, social functioning, role limitations – emotional, and mental health), as well as in the mental component score (Figure 4). No between group differences were found for the role limitations – physical subscale or the physical component scores. Patients in the high number of symptoms group reported significantly lower MOS-SF36 scores.

Discussion

This study is the first to determine the optimal cutpoint for total number of symptoms in patients with advanced cancer. Findings from this study suggest that the concept of a clinically meaningful cutpoint for symptom severity scores is transferable to total number of symptoms. In a heterogenous sample of patients with advanced cancer, the cutpoint of 12 symptoms (i.e., 0 to 12 symptoms and 13 to 32 symptoms) successfully

differentiated between patients based on a significant "jump" in both MQOL-CA2 subscale and total scores.

Validation of 12 symptoms as the optimal cutpoint was supported by significant between group differences in depressive symptoms and anxiety scores as well as between group differences in a generic measure of QOL. As shown in Table 4, the medium to large effect sizes[53] suggest that these are clinically meaningful differences in QOL. A *Clinically meaningful* difference in QOL measures was defined as a difference in scores that is large enough to have an implication for the patient's treatment or care.[54] This difference may correspond to what the patient recognizes as a *minimally important difference* in QOL scores. Previous research suggests that an effect size of 0.2 to 0.5 is considered a minimally important difference and a clinically meaningful difference in QOL measures.[55-57] For individual patients as well as groups, clinical significance goes beyond statistical significance to identify whether the statistical difference is large enough to be noticed by the patient and may effect treatment decisions.[58-62] Findings from this study suggest that when a patient crosses the threshold from 12 to 13 symptoms s/he may notice a decrease in certain QOL domains that might not be perceived to the same degree if the number of symptoms increases from 6 to 7.

The assessment of total number of symptoms may be a useful approach for clinicians to use to identify high risk patients. Significantly worse QOL scores were found as the number of symptoms passed the threshold from low to high. This differentiation of patients based on the total number of symptoms is supported by previous research on the association between higher symptom distress scores and worse QOL outcomes in patients with advanced cancer.[14, 16, 17]

The mean total MQOLS-CA2 scores in this study were 5.6 (±1.2) for the total sample and 6.2 (±0.2) and 5.3 (±0.1) for patients in the low and high symptom groups respectively. Only two studies[63, 64] were found that reported total MQOLS-CA2 scores in patients at various stages of the cancer trajectory. In both of these studies, total MQOLS-CA2 scores (i.e., approximately 5.3[63] and 5.8 (±1.4)[64]) were similar to those reported by patients in this study. These results suggest that patients with advanced cancer have moderate decrements in QOL scores. However, further research is needed to determine the generalizability of these QOL scores or whether response shifts occur in evaluations of QOL in patients with advanced cancer.[65, 66]

In addition to clinically meaningful differences on a cancer specific QOL instrument, the cutpoint that differentiated between low and high number of symptoms was validated by between group differences in the rank order of the psychological symptoms on the MSAS. All four psychological symptoms (i.e., worrying, feeling sad, feeling nervous, and feeling irritable) were found in the top 12 symptoms for the high number of symptoms group. Whereas, in the low number of symptoms group, each psychological symptom had a lower overall rank and occurrence rate and only 2 psychological symptoms (i.e., worrying and feeling sad) were in the top 12 symptoms.

The mean total CES-D score of 13.4 (±6.5) for the total sample (10.5 (±1.0) and 14.9 (±0.7) for the low and high symptom groups, respectively) in this study was similar to two descriptive studies[67, 68] of patients with advanced head and neck cancer and a study of patients with pain from bone metastases.[64] In contrast, higher total CES-D scores were reported by patients recruited from a palliative care program[69] and patients with advanced states of ovarian[70] and prostate[71] cancer. In these studies, mean CES-D scores ranged

from 17.2 (±10) to 33.2 (±1.1). Possible reasons for these inconsistent findings may be attributed to heterogeneity in terms of cancer diagnosis, differences in treatment regimens, and timing of assessments.

The mean state and trait anxiety scores in this study are similar to previous reports of patients with advanced cancer.[70, 72-74] Previous reports suggest that state anxiety increases in response to physical danger and psychological stress, whereas, higher scores on the trait anxiety scale are associated with diagnoses of psycho-neuroticism and/or depression.[37-39] The consistent ratings of anxiety across studies suggests that patients with advanced cancer may experience acute anxiety from a variety of physical and emotional stressors as well as chronic anxiety associated with depressive symptoms.

This study found MOS-SF36 mean subscale and component scores that ranged from 32.1 (±8.8) for the physical component score to 64.8 (±19.8) for the mental health subscale. These scores are similar to those reported in one study,[75] lower than MOS-SF36 scores reported in three studies of patients with advanced cancer[76-78] and higher than those reported in one study[79] of patients with advanced cancer. Reasons for these differences may include differences in the studies definition of advanced cancer, its inclusion and exclusion criteria, and timing of the patients' assessment in relationship to death.

Differences in patients' reports of symptom occurrence and the rank order of the most common symptoms support the between group differences found for the depression, anxiety, and psychological/mental health domains of the MOS-SF36. Specifically, the largest effect sizes were found for the MOS-SF36 mental component score and MOS-SF36 subscale scores related to psychological status (i.e., social functioning, vitality, role

limitations – emotional, mental health). Evidence is emerging that supports the fact that psychological symptoms such as anxiety and depression contribute to decrements in QOL in patients with advanced cancer.[80-84] In the symptom cluster literature, depression and anxiety were identified as part of a psychological cluster[80, 81] and may represent a unique biological pathway[82] in patients with advanced cancer. In addition, higher total physical symptom severity scores were found to be associated with higher depression but not anxiety scores.[84] In a longitudinal study of cancer patients in their last year of life,[83] higher depressive symptoms at baseline were associated with a worse symptom experience over time. It is not clear if psychological symptoms result in more total symptoms or if length of time since diagnosis produces psychological "wear and tear" on patients with advanced cancer that results in more psychological symptoms. Furthermore, it is not known if mental disorders and existential distress increase in patients with advanced cancer as they approach the end of life.[85]

Several limitations of this study need to be acknowledged. In this relatively small sample, only one optimal cutpoint for total number of symptoms was found. With a larger sample, two or more cutpoints may be identified and this hypothesis warrants investigation in future studies. As noted previously, a cross-sectional analysis did not allow for control of how the effect of time since diagnosis may have contributed to differences in depression, anxiety, and QOL. Finally, the fairly homogeneous sample of primarily white, well-educated, and older adults limits the generalizability of the study findings.

Findings from this study suggest that a threshold exists between low and high total number of symptoms for patients with advanced cancer. Further research is needed to confirm the results of this study and explore whether additional cutpoints exist in a larger sample. In

addition, research is needed to better understand the relationship between psychological symptoms and total number of symptoms in patients with advanced cancer. Elucidation of the underlying mechanism(s) of the "cluster" of psychological symptoms may facilitate identification of high risk patients and lead to improved symptom management interventions. Further research on cutpoints for total number of symptoms in patients with advanced cancer could lead to improved prognostication resulting in improved clinical assessments and more tailored interventions for this vulnerable population.

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Appendix

Figure Legends

Figure 1. Center for Epidemiologic Studies-Depression (CES-D) subscale and total scores for the total sample (n=111) and differences in CES-D subscale and total scores between patients in the low (n=38) and high (n=73) symptom groups. All values are plotted as means ± standard error of the means after controlling for age and comorbidities.

Figure 2. Spielberger State-Trait Anxiety Inventories (STAI) scores for the total sample (n=111) and differences in STAI state and trait scores between patients in the low (n=38) and high (n=73) symptom groups. All values are plotted as means ± standard error of the means after controlling for age and comorbidities.

Figure 3. Multidimensional Quality of Life Scale-Cancer 2 (MQOLS-CA2) subscale and total quality of life (QOL) scores for the total sample (n=111) and differences in MQOLS-CA2 subscale and total scores between patients in the low (n=38) and high (n=73) symptom groups. All values are plotted as means ± standard error of the means after controlling for age and comorbidities.

Figure 4. Medical Outcomes Study-Short Form 36 (MOS-SF36) subscale and component scores for the total sample (n=111) and differences in MOS-SF36 subscale and component scores between patients in the low (n=38) and high (n=73) symptom groups. All values are plotted as means ± standard error of the means after controlling for age and comorbidities.

Abbreviations:
PF = Physical Functioning
RP = Role Limitations - Physical
BP = Bodily Pain
GH = General Health
V = Vitality
SF = Social Functioning
RE = Role Limitations - Emotional
MH = Mental Health
PCS = Physical Component Score
MCS = Mental Component Score

Table 1. Results of the cutpoint analysis for total number of symptoms using the MQOL total scores (ANOVA) and the subscales (MANOVA) from the Multidimensional Quality of Life-Cancer 2

Cutpoints (Number of symptoms per groups)	ANOVA		MANOVA	
	Rank	F	Rank	F
Low 0-10 High 11-32	2	11.937	2	4.218
Low 0-11 High 12-32	5	6.213	4	3.408
Low 0-12 **High 13-32**	**1**	**13.610**	**1**	**5.363**
Low 0-13 High 14-32	3	11.110	3	3.724
Low 0-14 High15-32	4	10.998	5	3.136

ANOVA = analysis of variance
MANOVA = multiple analyses of variance

Table 2. Demographic and clinical characteristics for low and high total number of symptoms groups and total sample

Characteristic	Total N=111 Mean (SD)	Low Symptoms Group N=38 Mean (SD)	High Symptoms Group N=73 Mean (SD)	Statistics t-test (p-value)
Age (years)	59.8 (12.3)	63.2 (9.8)	58.0 (13.1)	t = 2.15 (**p = .034**)
Education (years)	15.5 (2.8)	15.3 (3.1)	15.6 (2.6)	t = -0.60 (p = .548)
Karnofsky Performance Status score	70.0 (12.1)	73.3 (13.4)	68.4 (11.2)	t = 1.95 (p = .054)
Total number of symptoms	15.6 (6.0)	9.8 (1.9)	18.6 (5.0)	t = -13.39 (**p < .000**)
Number of metastatic sites	1.8 (1.2)	1.7 (1.3)	1.8 (1.2)	t = -0.39 (p = .696)
Self-Administered Comorbidity Questionnaire	8.5 (3.7)	7.5 (3.5)	9.1 (3.6)	t = -2.13 (**p = .036**)

Table 2. (cont.) Demographic and clinical characteristics for low and high total number of symptoms groups and total sample

Characteristic	Total N=111 %	Low Symptoms Group N=38 %	High Symptoms Group N=73 %	Statistics Fisher's exact
Male gender	46%	53%	43%	p =. 324
Lives alone	21%	34%	14%	**p = .025**
Caucasian	76%	84%	71%	p = .163
Married/partnered or living together	66%	63%	67%	p = .678
Not currently working	77%	76%	78%	p = 1.00
Type of cancer				
Breast	37%	37%	37%	p = 1.00
Colon	2%	0%	2%	p = .546
Lung	9%	8%	10%	p = 1.00
Melanoma	2%	3%	1%	p = 1.00
Prostate	24%	24%	25%	p = 1.00
Leukemia	1%	0%	1%	p = 1.00
Non-Hodgkin's lymphoma	1%	0%	1%	p = 1.00
Ovarian	2%	0%	2%	p = .546
Other	29%	32%	27%	p = .664
Two primary cancers	6%	8%	3%	p = .238
Type of treatment				
Radiation therapy	9%	11%	8%	p = .733
Chemotherapy	56%	63%	52%	p = .310
Biotherapy	9%	5%	11%	p = .490
Hormonal therapy	33%	34%	33%	p = 1.00
Number of therapies				
0 therapies	17%	13%	19%	χ = 1.43 (p = .699)
1 therapy	59%	61%	59%	
2 therapies	23%	26%	21%	
3 therapies	1%	0%	1%	
Metastastic sites				
0	12%	13%	11%	χ = 2.31 (p = .805)
1	37%	40%	36%	
2	28%	26%	29%	
3	13%	8%	15%	
4	7%	11%	6%	
5	4%	3%	4%	
Reason for treatment				
Cure	2%	0%	3%	χ = 2.22 (p = .527)
Control	78%	77%	79%	
Palliation	19%	23%	16%	
No treatment	1%	0%	2%	

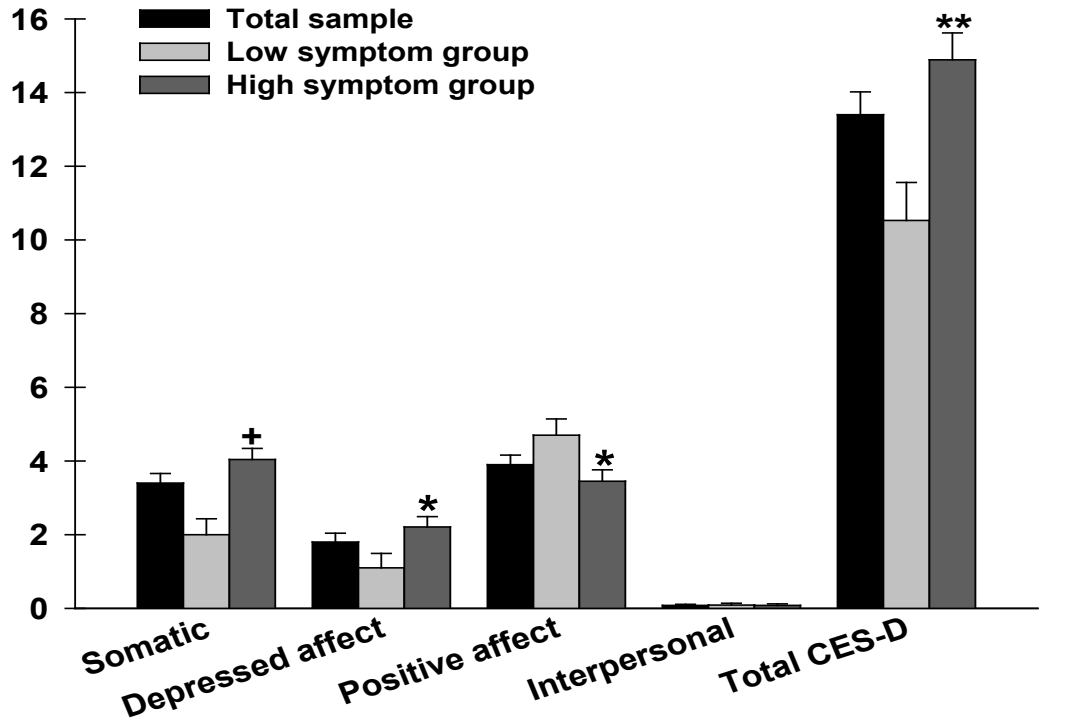
Table 3. Rank order of symptom occurrence in the low and high symptom groups

Low Symptom Group (N=38)	%	High Symptom Group (N=73)	%
Pain	97%	Lack of energy	96%
Lack of energy	92%	Pain	96%
Feeling drowsy	74%	**Feeling sad**	**90%**
Difficulty sleeping	55%	Feeling drowsy	89%
Constipation	47%	**Worrying**	83%
Numbness / tingling	47%	Difficulty sleeping	83%
Lack of appetite	45%	Difficulty concentrating	82%
Worrying	**42%**	Lack of appetite	77%
Feeling sad	**39%**	**Feeling nervous**	**75%**
Difficulty concentrating	37%	**Feeling irritable**	**73%**
Change in the way food tastes	34%	Constipation	70%
Dry mouth	34%	Nausea	65%
Problems with sexual interest or activity	32%	Dry mouth	65%
Feeling irritable	**32%**	Numbness and tingling	65%
Nausea	26%	Problems with sexual interest or activity	61%
Itching	21%	Itching	60%
Dizziness	21%	Sweats	60%
Cough	21%	Feeling bloated	51%
Sweats	18%	Do not look like myself	51%
Diarrhea	18%	Change in the way food tastes	48%
Shortness of breath	18%	Changes in skin	47%
Problems with urination	18%	Dizziness	45%
Feeling bloated	18%	Shortness of breath	44%
Weight loss	16%	Cough	43%
Vomiting	16%	Weight loss	41%
Feeling nervous	**16%**	Swelling	38%
Swelling	11%	Hair loss	36%
Hair loss	11%	Vomiting	30%
Do not look like myself	5%	Difficulty swallowing	30%
Changes in skin	5%	Problems with urination	29%
Difficulty swallowing	5%	Diarrhea	27%
Mouth sores	3%	Mouth sores	26%

Table 4. Effect sizes for between group differences in subscale and total scores for validation scales for depression, anxiety, and quality of life

Instrument	Effect Size
Center for Epidemiologic Study – Depression Scale	
Somatic	.78
Depressed Affect	.53
Positive Affect	-. 50
Interpersonal	.01
Total CES-D	.72
Spielberger State-Trait Anxiety Inventories	
State	.79
Trait	.81
Medical Outcomes Study – Short Form 36	
Physical Functioning	.41
Role Limitations - Physical	.20
Bodily Pain	.59
General Health	.55
Vitality	.74
Social Functioning	.67
Role Limitations - Emotional	.68
Mental Health	.86
Physical Component Score	.17
Mental Component Score	.88

Figure 1.



*p<.03, **p=.001, +p<0.0001

Figure 2.

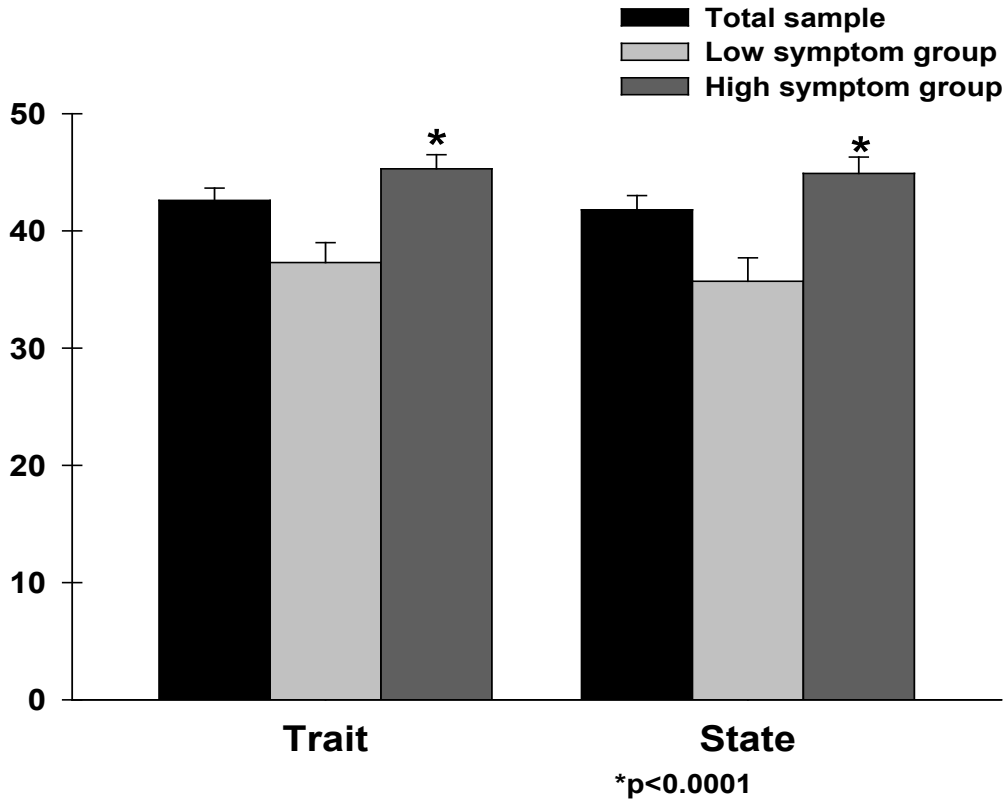
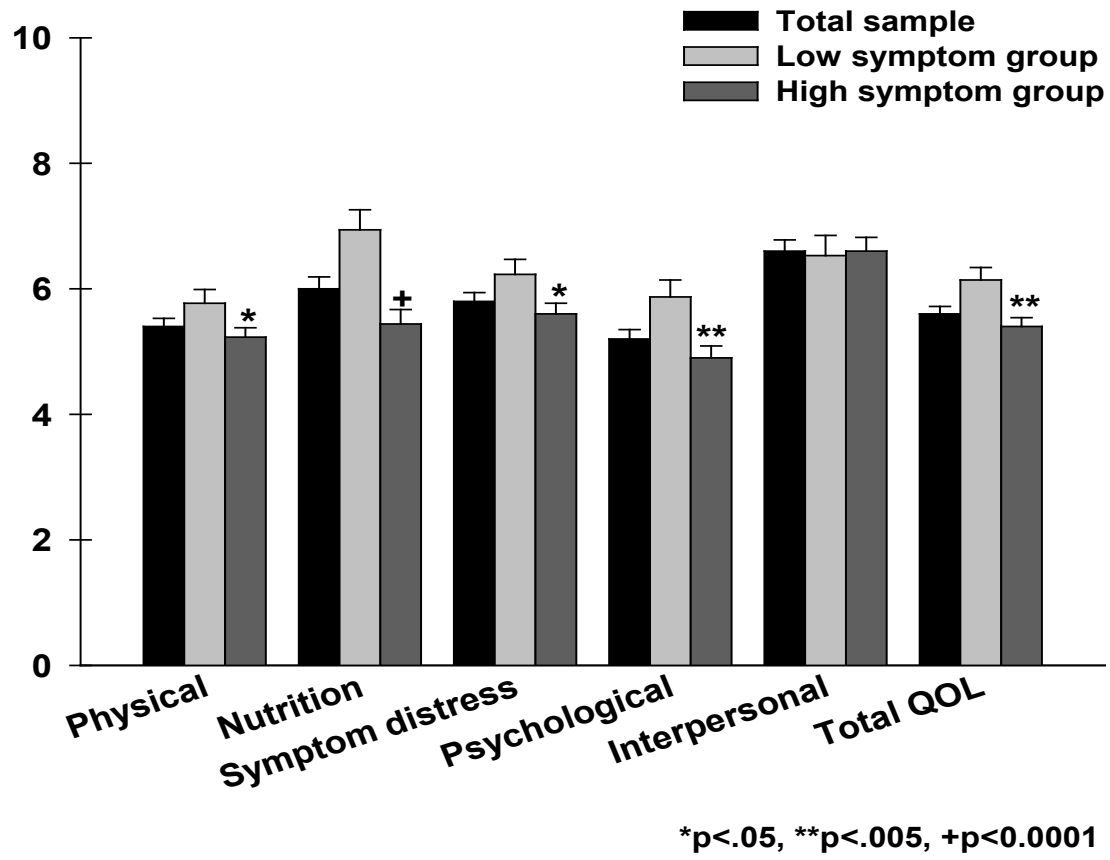
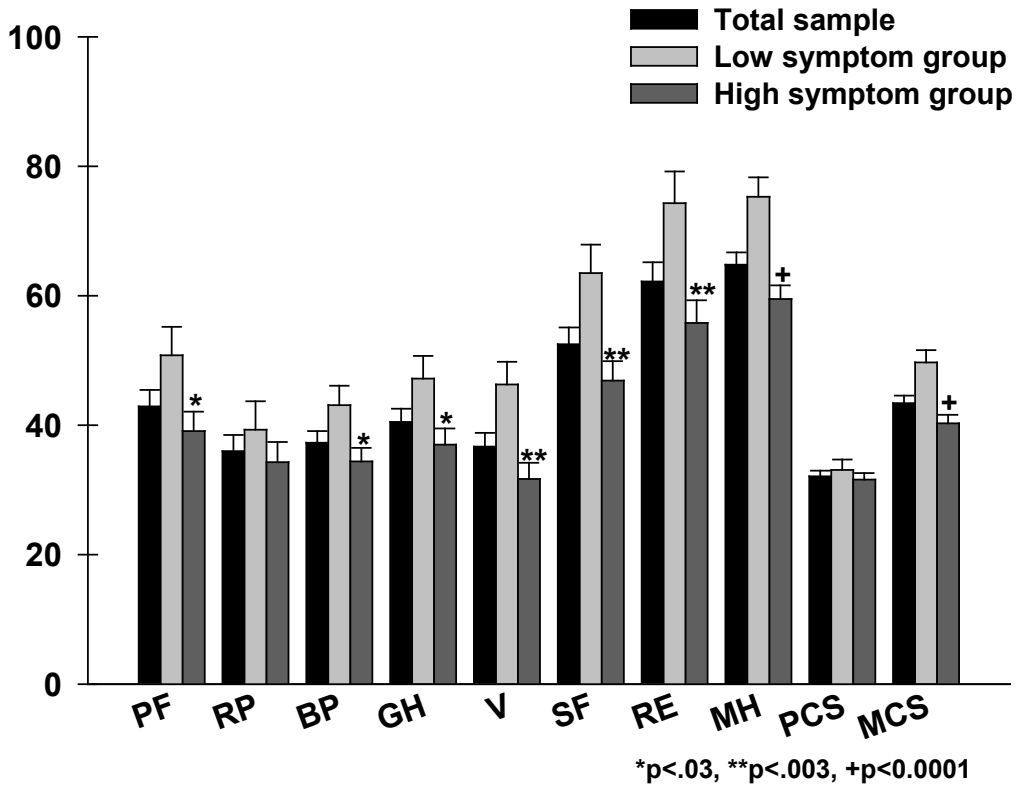

Total sample
Low symptom group
High symptom group
50
40
30
20
10
0
*
*
Trait
State
*p<0.0001

Figure 3.



*p<.05, **p<.005, +p<0.0001

Figure 4.


Total sample
Low symptom group
High symptom group
100
80
60
40
20
0
PF
RP
BP
GH
V
SF
RE
MH
PCS
MCS
*p<.03, **p<.003, +p<0.0001

Conclusions

While the experience of multiple co-occurring symptoms in patients with advanced cancer is not well characterized, findings presented in this dissertation suggest that a thorough symptom assessment across multiple dimensions using a comprehensive symptom list can be a source of significant information regarding the relationship between multiple symptoms, predictors, and outcomes. In addition, the identification of the threshold where number of symptoms goes from low to high may provide a clinically useful approach to assessing "symptom burden" and screening for patients at higher risk of depression, anxiety, and poorer quality of life (QOL).

Findings from the first study suggest that multiple symptoms are highly prevalent in patients with advanced cancer. Significant differences in ratings of symptom occurrence, frequency, severity, and distress existed. Seven symptoms (i.e., pain, sleep disturbance, problems with sexual interest or activity, lack of energy, constipation, numbness/tingling in arms or legs, changes in the way food tastes) were in the ten symptoms with the highest ratings across all dimensions with the exception of occurrence. Further research is needed to determine if this group of symptoms forms a symptom cluster. In addition, this study found high occurrence, frequency, severity, and distress ratings associated with problems with sexual interest or activity. Additional research is warranted to examine the significance of this symptom in patients with advanced cancer.

Further research is needed to determine other predictors of total number of symptoms. While patients' reports of multiple symptoms across several dimensions were described in this study, it is not known whether symptom occurrence rates or any of the dimensions (i.e., frequency, severity, distress) for individual symptoms are related to the

total number of symptoms. Cancer type, length of time since diagnosis, treatment modalities, and medications are possible predictors that merit further examination.

Findings from the second study suggest that a threshold between low and high total number of symptoms exists for patients with advanced cancer. A stable solution for two cutpoints (i.e., low, medium, and high number of symptoms) was not found. Further research is needed to confirm the results of this study and explore whether a two cutpoint solution could be derived if a larger sample were available.

In addition, research is needed to better understand the relationship between psychological symptoms and total number of symptoms in patients with advanced cancer. Patients in the high number of symptoms group were found to have higher occurrence rates for psychological symptoms among the 12 most frequently occurring symptoms. The validation testing of the cutpoint grouping showed that patients in the high number of symptoms group reported higher levels of anxiety and depression, as well as and worse scores on the psychological and mental health domains of two QOL questionnaires. Elucidation of the underlying mechanism(s) for the "cluster" of psychological symptoms may facilitate identification of high risk patients and lead to improved symptom management interventions. Further research on cutpoints for total number of symptoms in patients with advanced cancer could lead to improved prognostication and more tailored interventions for this vulnerable population.

Implications for Clinical Practice

Until the experience of multiple co-occurring symptoms is better understood, clinicians need to include a comprehensive list of symptoms in their assessments of patients with advanced cancer. In addition, the assessment of the multiple dimensions

(i.e., frequency, severity, distress) of various symptoms may provide important information for planning symptom management interventions. Clinicians should keep in mind that younger patients and patients with more co-morbidities are at greater risk for experiencing more symptoms. Other important clinical implications include the importance of further screening patients with 13 or more symptoms for depression, anxiety, and impaired QOL as well as possible difficulties in managing multiple symptoms.

Implications for Research

Several areas of exploratory research on the experience of multiple co-occurring symptoms in patients with advanced cancer remains to be addressed. Research is needed on the relationships between multiple, concurrent symptoms (i.e., symptom clusters) as well as the existence of patient subgroups based on their experience with specific symptoms and their relationship to important clinical outcomes (e.g., functional status, QOL, and survival). Research on the role of genetic variability and its effect on symptom phenotypes may provide insight into the mechanism(s) that underlie the experience of multiple co-occurring symptoms in patients with advanced cancer. Findings from this dissertation and subsequent research ultimately will lead to the development and testing of interventions to improve symptom management in patients with advanced cancer.

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