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FOCTORS ASSOCIATED WITH TIME TO RESOLUTION OF PAIN AND FATIGUE AMONG CANCER PATIENTS UNDERGOING CHEMOTHERAPY IN A COGNITIVE BEHAVIORAL INTERVENTION GROUP

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Sangchoon Jeon

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By

Sangchoon Jeon

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Submitted to
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ABSTRACT

FACTORS ASSOCIATED WITH TIME TO RESOLUTION OF PAIN AND FATIGUE AMONG CANCER PATIENTS UNDERGOING CHEMOTHERAPY IN A COGNITIVE BEHAVIORAL INTERVENTION GROUP

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To identify factors associated with resolution of pain and fatigue, we investigated time to resolution of these symptoms among cancer patients receiving a cognitive behavioral intervention (CBI). Randomly assigned cancer patients undergoing a first course of chemotherapy received a 10 contact CBI intervention delivered by trained nurses. Patients reported onset and resolution of symptoms at every contact, and survival analysis techniques were employed to test difference in time to resolution by patients' characteristics including age, sex, cancer site, stage of cancer, depression, and co-morbid conditions. The study found that patients with a late stage of cancer were more likely to require longer time to resolve pain. Male patients had significantly longer fatigue resolution times than female patients. High co-morbidity and depression were significantly associated with increased time to resolution of fatigue. We conclude that the duration of pain is more likely to depend on the stage of disease, while the duration of fatigue is more associated with patients' health conditions.

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This research was financially supported by the Data Coordinating Center (DCC) and the Family Home Care Study in Colleges of Human Medicine and Nursing at Michigan State University. The Institutional Review Board (IRB) of Michigan State University has approved (IRB # 06-150) this secondary analysis using collected data from Family Home Care for Cancer in collaboration with the Walther Cancer Institute. Drs Barbara and Charles Given were principal investigator and co-investigator, respectively, for this clinical intervention trial. The project was funded by the National Cancer Institute and the National Institute of Nursing Research (CA79280), 1999 to 2002.

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INTRODUCTION

According to a report from National Cancer Institute (NCI) on January 2001 approximately 9.8 million persons had a history of invasive cancer in the United States. The National Institutes of Health (NIH) reported the overall annual cost of cancer would be about $189.8 billion in 2004. Symptom management, which provides appropriate methods of treatment, is a very important issue in nursing care for cancer patients(1). Patients who are diagnosed with solid tumors and undergoing chemotherapy treatment may experience a variety of side effects such as pain, fatigue, nausea, insomnia, vomiting, and anxiety. These symptoms could be originated from disease itself or the side effects of treatments, and they are a serious burden for oncologists, primary care providers, as well as patients. Due to improvement in early detection and treatment of cancer, more patients have been cured or have survived longer. However, concerns about health related quality of life or costs of cancer care are still important issues for cancer patients and caregivers. The development of symptom management may provide improved quality of life among cancer patients and relieve the burdens of family members and care providers. The impact of cancer-related pain and fatigue is considerable in terms of economic issues. For instance, Curt and his colleagues reported that 75% of patients

and 40% of caregivers changed their employment status due to fatigue in their study(2, 3).

In this study patients who received a cognitive behavioral intervention were given strategies to resolve or moderate their symptoms. Specific strategies delivered to patients with specific symptoms, and the intervention for symptom management across 10 contact times was scheduled. Not only the efficacy of symptom managements but also the characteristics of patients such as age, site of cancer, stage of cancer and chronic health condition may influence symptom improvement or resolution. The identified patients' characteristics related to time to resolution of the symptoms would be important considerations when symptom management strategies are designed.

Pain and fatigue in chemotherapy

Pain and fatigue are frequently reported symptoms in cancer patients, and impact dimensions of quality of life such as physical function and depression(2). The symptoms usually co-occur with other symptoms and are related to the underlying cancer or therapy. Approaches to the assessment of pain and fatigue remain an issue in nursing care for cancer patients. Given and colleagues investigated the impact of personal characteristics on the presentation of pain and fatigue in cancer patients. They found that a late stage of cancer, high number of co-morbid conditions, and lung cancer were

strongly associated with the presence of pain and fatigue. Surgery, radiation, and chemotherapy were significantly associated with pain, fatigue, or their combination within 40 days of ending treatment(4).

The prevalence of pain in cancer patients varies from 36% to 75%, and patients with advanced cancer experience substantial pain(5). Patients have severer pain as they approach death. Cancer-related pain can be effectively managed in most patients even if it cannot always be completely resolved. Pain usually occurs with other symptoms in patients with advanced cancer. According to a study of 110 patients with advanced cancer, patients may have a greater interference with activities of daily living when they believe their pain to be caused by cancer rather than other etiologies(6). The NCI recommends that the management for pain can be flexible and individualized by stage of disease, personal preferences, and responses to pain and intervention. Cognitive-behavioral interventions are an important management tool for pain. Some recent studies have suggested that behavioral interventions for specific symptoms like pain and fatigue are effective in reducing symptom burden and improving the quality of life(7).

Fatigue is a common symptom among individuals with cancer who have undergone chemotherapy. The National Comprehensive Cancer Network (NCCN) defined cancer-related fatigue as "a persistent, subjective, sense of tiredness related to

cancer or cancer treatment that interferes with usual functioning". A recent report from the NCCN highlights that fatigue affects 70-100% of cancer patients(8). In a study conducted by Greene et al, 82% of breast cancer patients who received regimens including cyclophosphamide, methotrexate, and fluorouracil (CMF) reported fatigue after the first course of chemotherapy(9). Other studies on perceptions of cancer-related fatigue report a 75% agreement between patients and oncologists regarding the presence of significant fatigue(10). A prospective cohort study with 157 breast cancer patients receiving CMF reported that fatigue was highly prevalent during as well as after chemotherapy treatment, and the proportion of patients suffering from fatigue started decreasing 4 weeks after the last cycle of treatments(11). Compared to fatigue caused by other diseases, cancer-related fatigue can be very rapid in onset and intense in severity. Fatigue may be more distressing and interrupting to patients' performances of daily activities, relationships with people, and compliance with treatment than the pain. Curt et. al. found that fatigue was ranked first (60%) as the symptom most affecting quality of life among cancer patients(2).

Despite the prevalence of fatigue among cancer patients, it has been difficult to consistently identify factors associated with fatigue due to poor understanding of the biochemical, physiological, and behavioral mechanisms of this complex symptom.

However, several risk factors associated with cancer-related fatigue have been suggested. There are evidences that anemia, which is a common side effect of chemotherapy or radiation therapy in cancer patients, is a major factor causing fatigue(10, 12). The impact of anemia on fatigue may be different depending on onset time, patient age, and comorbidity. Psychological factors such as depression and anxiety may contribute to the development of chronic fatigue among patients with cancer before and after chemotherapy(13). Distress after diagnosis of cancer may cause initial fatigue and other side effects of distress like insomnia may also increase levels of fatigue in patients undergoing chemotherapy. As the result of distress, less daytime activity or more night-time awakenings may contribute to cancer-related fatigue. Although several factors contribute to the increased risk of cancer-related fatigue, the assessment of the effect of each factor remains complex due to the multiple symptoms, the multiple etiologies, varying severity, duration, and co-occurrence of symptoms.

Assessments of symptom resolution after chemotherapy

The cognitive behavioral intervention was developed to solve multi-component problems including pain and fatigue among cancer patients undergoing chemotherapy treatment. We tried to investigate which characteristics or health conditions helped or

impeded resolution of cancer-related pain and fatigue among cancer patients who received the cognitive behavioral interventions.

Unlike symptoms from other diseases, symptoms experienced by cancer patients undergoing chemotherapy have complex properties. First, symptoms are temporal; the onsets and duration of symptoms may vary depending on patients' chronic conditions or the presence of other symptoms. Given the temporality of symptoms and variation in their duration, follow-up time will differ depending on the time of onset for each symptom. Second, many cancer patients undergoing chemotherapy may have multiple-problems which have complex associations with other symptoms. Since the presence of other symptoms may seriously affect the resolution or deterioration of pain or fatigue, it is necessary to consider how other symptoms are associated with resolution of pain and fatigue. Third, unlike symptoms in a normal population, symptoms in cancer patients may have different origins. For example, pain can occur from tumor progression, physical activity, or cancer treatment. Thus, the durations of symptoms may differ according to their causes and sites of cancer.

Proportion of patients with symptom resolved

Many studies have examined the effect of treatments on managing symptoms or

identified the factors associated with symptom resolution. Different analytical methodologies have been utilized in several studies to investigate the efficacy of treatments or drugs in relieving or resolving symptoms. One approach is to compare proportions of patients resolving a symptom among those who have a symptom at specific time points or the end of the follow-up period(14-19). Proportion of symptom resolution is an expression of the number of patients who resolve their symptoms among patients experiencing the symptom in a follow-up time. In many conventional clinical trial studies, the investigators monitored the improvement of symptoms until the end of the research period and compared the proportions of patients who resolved or improved symptoms between treatments or specific groups during follow-up. This method is acceptable among studies for symptoms that are easily resolvable and have short symptom durations, but not for cancer symptoms.

Nevertheless, in practical clinical trials there are a lot of limitations to measuring the actual count of symptom resolutions within varying time intervals. Some symptoms such as the side effects of diseases or treatments may be diagnosed not only in the initial time of the follow-up but also in the middle, later in the follow-up, or around the end of the follow-up interval. Since the proportion of patients with symptoms resolved is observed at a fixed time point, there may be patients who do not have sufficient exposure

to the intervention due to late onset of the symptom. For example, patients who had a symptom at the beginning of the follow-up have more chance to resolve symptom, while patients who had a symptom around the end of the follow-up could not have enough time to resolve the symptom. Rao and Cunningham conducted a similar study on symptoms including; pain, anorexia, weight loss, nausea, and lethargy among patients with advanced biliary cancer(14). The researchers compared the proportions of resolved symptoms between two treatment groups. Due to the nature of symptoms monitored in the study, several patients might have had different onset times during the follow-up period. Therefore, the proportions at the end of the follow-up could be influenced by the onset time as well as the duration of symptoms.

Another limitation of using proportion of patients with resolved symptoms is that the proportions may be different by timing of observations of symptom states. If symptom resolutions are measured too early or late in the follow-up, the proportions of symptom resolution may not capture the actual association between patients' factors and symptom resolution. In most cases, symptoms may not be resolved at an early follow-up but may take more time to be resolved. Timing of capturing the proportion of symptom resolution should be carefully decided based on the average duration of symptoms. In some studies, the proportions of symptoms resolved were measured at

repeated times until the end of the follow-up. The prospective observational study conducted by Curran and Kaefer presented proportions of symptom resolution rates at every year during 5 years(15). They described the proportion of symptoms resolved for each age group every year, but statistical tests were not employed to examine whether there was a significant difference in the proportions of symptoms resolved between two age groups across times. In general, the Chi-square test is used to examine the difference in symptoms resolution rates of each group at each time. However, the Chi-square test is not able to examine overall change of the symptom resolution rates across time controlling for other covariates.

In many clinical trials or longitudinal studies, significant numbers of participants are lost to follow-up. If participants are lost to follow-up due to death, severe deterioration of symptoms, refusal to further participate, or other reasons, the final symptom resolution of those attrited participants are not available to estimate the proportion of symptoms resolved during the follow-up. The proportion of participants with symptoms resolved can be overestimated if large numbers are lost to follow-up or are not included in analyses. The loss of large numbers of participants could lead to a smaller denominator of the proportion. In a randomized clinical trial to study symptoms of gastro-esophageal reflux disease (GERD) which was conducted by Talley and Moore

had approximately 40% of patients lost to follow-up(18). The proportion of patients with resolved symptoms was possibly overestimated due to the patients who dropped out without knowing whether their symptom resolved.

Time to symptom resolution

Another approach to assessing symptom resolution is to measure time to symptom resolution instead of proportion of patients with symptom resolved. Time to symptom resolution, which is the length of time from symptom onset to symptom resolution, is more informative than a binary outcome for proportion of symptom resolution. Multiple linear regression model or the t-test are often employed in many clinical trial studies to analyze time to resolution of a symptom(20-22). However, these models assume that duration of symptom resolution has a normal distribution. Therefore, the distribution of duration of a symptom resolution should be tested for normality test before performing the analysis with the regression model or the t-test. Among three identified studies using linear regression models or t-tests for analyses of time to resolution, only one study used the Shapiro-Wilk W test to check whether time to resolution was normally distributed(22). When time to resolution doesn't have a normal distribution, nonparametric methods such as the Wilcoxon Signed-rank test and Rank

sum test are available to compare differences in the distribution of time to resolution between two groups.

When symptom resolution is not achieved for a given patient by the end of the follow-up, the linear regression model and the t-test cannot use time to resolution in these patients for analysis. The linear regression model and the t-test use only participants who complete the follow-up study and where the symptom is resolved by the end of the follow-up period. A prospective observational study with patients who had hemifacial spasm conducted by Shin and Chung had 17% of participants who were lost to follow-up or had incomplete resolution at the end of the follow-up period(21). Shin and Chung used a linear regression model to identify factors associated with time to resolution of hemifacial spasm symptom. In this study, 39 (17%) patients did not resolve symptoms during the follow-up period or were lost to follow-up. Unfortunately, 39 patients without complete time to resolution of symptom were not involved in the final model, and the result of the treatment effect on resolution of hemifacial spasm symptoms could be biased. Furthermore, in clinical trials when a treatment has significantly higher proportions of lost to follow-up or incompletion of measuring time to resolution compared with a placebo group, the linear regression model is likely to overestimate the efficacy of treatment compared to the effect of placebo. The difference in the

distributions of patients with incomplete time to resolution, as well as the proportions of the lost to follow-up between the two groups could lead biased results when linear regression models or t-tests are used to evaluate the effect of treatment on time to resolution of symptoms.

Survival analysis for assessment of time to resolution of symptoms

Incomplete measurement due to lost to follow-up or no resolution of a symptom by the end of follow-up is known as a right-censored data. The main advantage of survival analysis compared to the other methods is that survival analysis incorporates a censored data. When right-censored data are observed due to lost to follow-up or incomplete resolution by the end of the follow-up period, estimating proportions or use of ordinary linear regression methods would not be appropriate. However, survival analysis incorporates censored observations thereby reducing errors in evaluating the distribution of time to symptom resolution. In most longitudinal clinical trials, there are several participants who fail to complete the follow-up due to death, sickness, severe symptoms, or loss of interest in the study. These issues impede complete assessment of time to a symptom resolution, and increase right-censored data.

To examine time-to-event with censored data, several survival analysis

techniques have been developed. Kaplan and Meier (1958) introduced nonparametric technique with survival curves. The product-limit estimator, which is called Kaplan Meier estimator, uses both censored and non-censored observations to estimate survival curve. Mantel (1966) developed the log-rank statistics to compare survival distributions between two groups. Cox proportional hazard method (1972) was proposed for semi-parametric method. This method does not require some particular probability distribution, but assumes the same proportional hazard between groups over time. Greenhouse and his colleagues addressed to use survival analysis method for evaluating efficacy of a new treatment in clinical trials(23). Survival analysis method has been widely used to analyze data with censoring, and enormous demands of statistical methodology in clinical trials gives motivation to development of new survival analysis techniques.

Time to symptom resolution assessed by survival analysis techniques such as Kaplan Meier estimators or Cox proportional hazard models have the advantage of incorporating right-censored data such as participants who fail to complete the follow-up or to resolve their symptoms during the period. Even though these methods are considered as nonparametric or semi-parametric, there are considered more suitable in the presence of randomly right-censored data as compared to parametric methods. Some

recent studies used survival analysis techniques for assessing time to resolution of symptoms to decrease bias from right censoring(24-27).

Product Limit estimator (Kaplan and Meier 1958) is a popular survival analysis method for estimating the distribution of time to an event based on randomly right-censored data. This function provides an estimator for the cumulative survival distribution, which in our study represents the proportion of participants who have not resolve their symptom up to time t. This estimate is a step function, which jumps only at a time when a participant resolves his/her symptom. At the censored observations there are no jumps except a situation where the last observation is censored in which case the estimator drops to zero. It is important to note that the Kaplan Meier method assumes independence between the time to an event and the time to censoring.

The Cox proportional hazard models are widely used when investigating association between time to event such as time to symptom resolution and several other independent variables simultaneously. The Cox-proportional hazard model provides the estimates for the hazard ratio, which is the ratio of the hazard rates of symptom resolution in a group compared to a referent group. In the context of symptom resolution, the hazard rate at a particular time point, t, is the conditional probability that a participant will resolve symptom in a short period of time after time, t, given that the symptom was

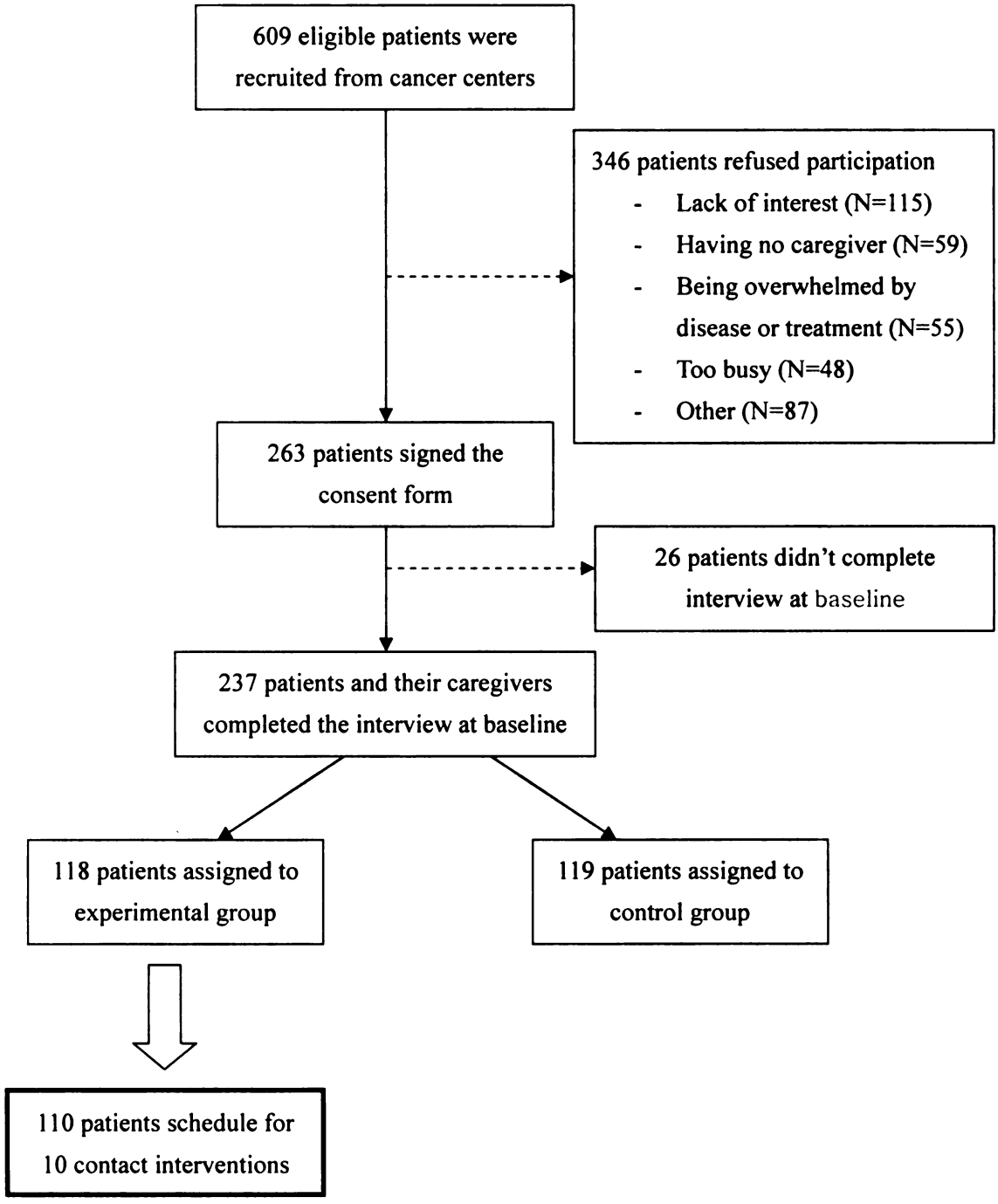
not resolved until time, t. The Cox proportional hazard model can control for the effects of multiple covariates. In order to assess time to resolution of pain or fatigue, many factors such as depression, comorbidity, and patient's age would be considered in the model. In this study, we will use Kaplan Meier and Cox Proportional hazard techniques to identify significant predictors of time to resolution for pain and fatigue among patients undergoing chemotherapy in a cognitive behavioral intervention delivered by specially trained nurses.

METHODS

Study design and subjects

This study is part of a larger clinical intervention trial of Family Home Care for cancer, which was funded by the National Cancer Institute (NCI) and the National Institute of Nursing Research (CA79280), 1999 to 2002. This sub-study focused on only symptom resolution among patients randomized at the beginning of the trial to the intervention group, since no data were available for the control group that received conventional care alone. Patients were accrued from two comprehensive cancer centers and four community-oncology settings nurse. Recruiters were trained according to the study protocol, and recruited 609 eligible patients who satisfied enrollment criteria for entry (A first course of chemotherapy, greater than 20 years old, and being able to read and speak English and cognitively able to respond to interviews). Also, patients should not have experienced previous chemotherapy or radiation prior to the time of entry. Consent from both patient and caregiver to participate in the study was required, and both patients and caregivers had to be able to speak and read English, and both had to be cognitively intact.

Figure 1. Flow chart of recruitment and assignment to intervention



Two hundred and sixty three patients agreed to sign the consent forms, and 346 patients refused to participate due to lack of interest (N=155), having no caregivers

(N=59), being overwhelmed by disease and treatment (N=55), and being too busy (N=48). In addition, 26 patients did not complete the intake interview due to inability to contact, being too ill, or discontinuation of chemotherapy. This left 237 patients and their family caregivers who completed the intake interview. They were randomized into either the 10-contact experimental intervention or conventional care. One hundred eighteen patients and family caregivers were assigned to the experimental and 119 to the control group(1). Among 118 patients in the experimental group, 8 patients were excluded from analyses due to missing information.

Among 118 patients assigned to the experimental intervention, 110 patients were scheduled for the 10-contact intervention to address their symptoms. Specially trained nurses provided intervention strategies to the patients for the management of their symptoms. In this study, subgroup analysis was performed for patients who reported pain or fatigue during the follow-up period. Fifty of the 110 participants reported experiencing pain and 91 reported experiencing fatigue during the follow-up period.

Intervention

The purpose of cognitive-behavioral intervention was to help patients to develop self-management knowledge, skills, and behaviors that would enable them to manage

their symptoms. The intervention was based on cognitive-behavioral theory describing adaptive strategies for patient's addressing problems(1). After the intervention was introduced the nurse evaluated each patient's ability to the undertake requisite cognitive-behavioral strategies designed to reduce the symptom severity, the impact on emotional distress, and physical functioning(28, 29). The nurse provided specific strategies to patients who were assigned to the experimental arm in order to assist them to manage 11 symptoms as well as their role and physical functioning problems, and emotional distress.

The nurses contacted patients in the intervention group to schedule the date and times for up to 10-contacts and assessed the severity of patient's symptoms among 11 master problems (fatigue, alopecia, Gastrointestinal tract problem, anxiety, constipation, pain, insomnia, diarrhea, skin problem, respiratory problem, Mucositis). If the severity of the symptom rated by patients on an 11point scale ranging from zero (not noticeable), to a ten (worst possible) was a five or higher, then the symptom was transferred to the plan of care. Up to four intervention strategies could be delivered to patients for each symptom at each contact. The strategies comprising the intervention content were summarized using the following terms; assessment, counseling, prescribing, teaching, skill, referring, evaluation, and consulting. At each contact patients reported the onset and severity of each symptom and rated development of the symptoms in response to

interventions such as resolved, improved, no change, or deteriorated.

Outcome Measures

The primary outcome measure considered in this study is time to resolution of pain and fatigue. In each contact scheduled, on average 2 weeks apart, the trained nurses asked patients if they had each symptom during the past 2 weeks and how severe the symptoms were at the time of visit. Although the interventions were scheduled for 2 weeks apart on average at the beginning of intervention, in most cases patient had next contact later than 2 weeks. We found that significant number of patients completed their 10-contact intervention longer than even 30 weeks. The status of a symptom with respect to the interventions employed for its managements were rated in four categories resolved, improved, no change, and deteriorated.

Since patients were asked if they experienced each symptom during the past two weeks, symptom onset was considered to be two weeks prior to the contact time when the symptom was first reported. At subsequent contacts, patients reported the impact of the intervention strategies on each symptom by rating it as having deteriorated, no change, improved, and resolved. A symptom was considered resolved if a patient reported that his/her symptom was resolved at the last contact reporting the symptom status. Time to

resolution was measured as the length of time from reporting symptom onset to reporting symptom resolution. However, some patients withdrew or completed the last contact without resolution of a symptom due to having individual health problems or reporting onset of symptoms in the late period of study. These situations created censored information. The length of time from onset of symptom to the last contact reporting the symptom without resolution is considered as censoring time. Patient characteristics such as depression and co-morbidity were measured at the baseline observation prior to randomization. Patient's depression level was measured using the CES-D scale developed by the Center for Epidemiologic Studies (Radloff, 1977). The CES-D score is a widely used reliable measure with established cutoff of 16 or greater indicating potential for clinical depression(30). The CES-D score is measured based on 20-items with 4-point Liert-type scale (almost all of the time, most of the time, some of the time, and rarely/none of the time). Co-morbidity was measured by the total number of chronic conditions including high blood pressure, diabetes, other cancer, chronic bronchitis emphysema, heart problem, stroke, emotional problems, arthritis/Rheumatism, fractured hip, liver disease, incontinence, and other major health problems at the first interview. Site of cancer was collected from an audit of patient's medical records and categorized as breast, lung, and a number of other cancer sites. Stage of cancer was

categorized according to the tumor-node-metastasis staging criteria of the American Joint Committee on Cancer. Based on this scale, stage of cancer was collapsed into early stage (in situ or zero, and stage I and II) and late stage (stages III and IV)(1). Information on patients' age and sex were obtained from their first interviews.

Statistical Analysis

In this study, patients reported onset of symptom at different contact time during the follow-up period. Patients reported resolution of symptoms within the follow-up period, but some patients were lost to follow-up or did not resolve their symptom by the last contact (Figure 2). Time to resolution, $X_1, X_2, \cdots, X_k$ for k patients, is defined as the duration in weeks from symptom onset to symptom resolution. The censoring variable, $Y_1, Y_2, \cdots, Y_k$ for k patients, is defined as the duration in weeks from symptom onset to last contact time reporting symptom status when the symptom is not resolved.

Censored data the form (Z_i, δ_i) where $Z_i = \min(X_i, Y_i)$, the minimum time between time to resolution and the censoring time, and δ_i is an indicator function taking a value equal to one if a patient reported resolution of symptom within the follow-up period, and zero otherwise. In other words, if a patient reported resolution of symptom within the follow-up period, the minimum time between time to resolution and the

censoring time $Z_i = X_i$ and $\delta_i = 1$. Otherwise, $Z_i = Y_i$ and $\delta_i = 0$ (Figure 3).

Survival function of Z, is defined as $S(t) = p\{X > t\}$, $t > 0$, which represents the probability that time to resolution of symptom is more than t. At the time of onset of symptom, i.e., when $t = 0$, the survival function $S(0) = 1$ indicates that none of the participants who reported the presence of symptoms have resolved it at $t = 0$. The hazard function defined as $h(t) = \lim_{\Delta t \to \infty} p\{X \le t + \Delta t \mid X \ge t\} / \Delta t$ represents the conditional probability of resolving a symptom during a small time interval, $t + \Delta t$, given that the symptom was not resolved before time t. The cumulative hazard function is defined by, $H(t) = \int_0^t h(u)\,du$.

In order to identify factors associated with time to resolution of pain and fatigue, we used the Cox proportional hazard model (Cox 1972), which is a semi-nonparametric method for survival analysis. Considering p covariates $Z = (Z_1, Z_2, \cdots, Z_p)$, the Cox proportional hazard model is defined as the following equation;

$h(t \mid Z) = h_0(t)\exp(\beta_1 Z_1 + \beta_2 Z_3 + \cdots + \beta_p Z_p)$, where $h_0(t)$ is a baseline hazard function corresponding to no covariates, when all $Z_i = 0$. The hazard ratio for a binary factor Z_1 is defined by, $h(t \mid z_1 = 1) / h(t \mid z_1 = 0) = \exp(\beta_1)$, which compares the rate of symptom resolution among the patients who have factor $Z_1 = 1$ with that of the patients with $Z_1 = 0$.

In our analysis, we investigated associations between patients' characteristics

including sex, age, site and stage of cancer, co-morbidity, and CES-D at baseline and our main outcome variables time to resolution of pain and fatigue separately. We estimated median time to resolution of symptom instead of mean time. Median time to resolution represents time that half of patients still have not resolved their symptom. Median time was preferred over the mean in this study because the distribution of time to resolution of symptoms is skewed to the right, with a long tail. Since a significant proportion of patients still had not resolved their pain or fatigue at the end of the follow-up in this study, we believe mean resolution time might provide biased estimates as compared to the median resolution time which is less influenced by the outliers. However, the estimated median time could have larger variability. Another limitation of the median time to resolution is that when less than 50% of patients have resolved their symptoms within the follow-up period, then the estimate for median resolution time is not available.

In our univariate analysis for assessing associations between time to resolution of symptoms and each of patients' characteristics, we used the log rank test. For multivariate analysis, the Cox proportional hazard model was used to test associations between patient's factors and time to resolution after adjusting for other covariates. All statistical tests were performed at 5% level of significance and 95% confidence intervals were estimated based on the final model.

Figure 2. Graphical demonstration of onsets and resolution time of symptoms

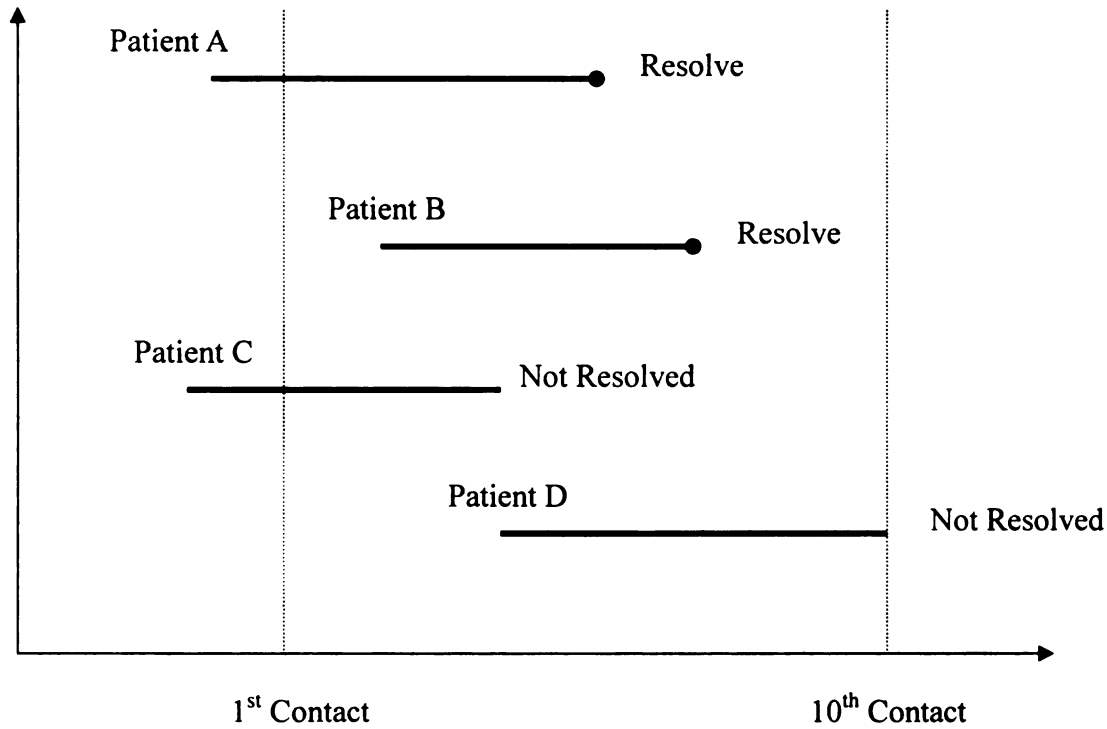
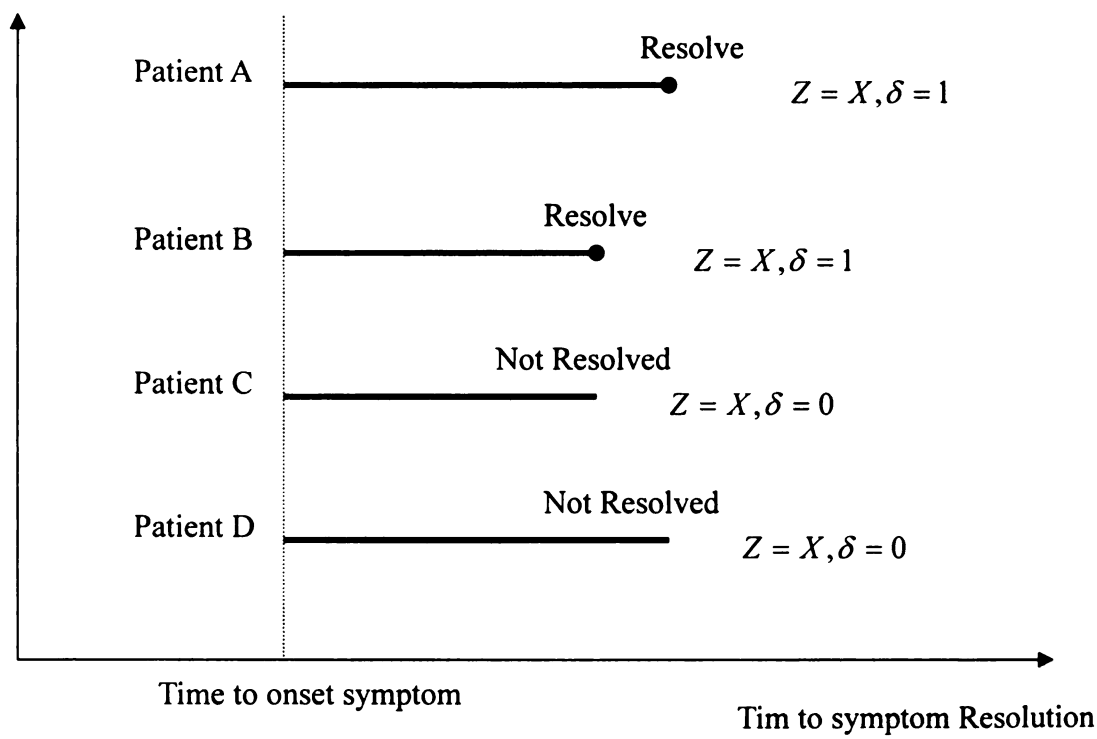


Figure 3. Graphical presentation of censored data for onset and resolution time



RESULTS

Burdens of multiple symptoms among cancer patients

Patients in the cognitive behavioral intervention group were asked to report the status of eleven symptoms at each contact time such as pain, fatigue, alopecia, gastrointestinal problem, insomnia, mucositis, anxiety, constipation, diarrhea, respiratory problem, and skin problem. Seventy-five percent of patients reported at least one symptom within the first four visits. On average, patients reported 4.5 symptoms during the follow-up. Fatigue, gastrointestinal problems, anxiety, pain, and alopecia had a relatively higher prevalence than the other symptoms, and median times to resolution of these five symptoms were between 15 and 20 weeks. Fatigue was the most prevalent symptom reported (82.7%) among patients undergoing chemotherapy and median time to resolution of fatigue was 20 weeks. Pain was reported by 45.5 % of patients, and median time to resolution of pain was also about 20 weeks (Table 1).

Respiratory problems, diarrhea, skin problems, and mucositis had relatively lower prevalence of reported symptoms, all less than 20%. Furthermore, the median time to resolution of diarrhea and mucositis were 6 and 8 weeks respectively. Prevalence and resolution of 11 major reported symptoms within 10 contacts along with

the median time to resolution of these symptoms are presented in Table 1.

Table 1. Prevalence and resolution of 11 major symptoms during 10 contacts

Symptoms	Symptoms reported within the follow-up period		Median Time to resolution (in weeks)	
	N	%	Median	95% CI
Fatigue	91	82.7	20	(16, 13)
Gastrointestinal problem	63	57.3	15	(13, 20)
Anxiety	62	56.4	20	(14, *)
Pain	50	45.5	20	(17, 28)
Alopecia	66	60.0	17	(11, 21)
Insomnia	48	43.6	15	(9, 19)
Respiratory problem	15	13.6	*	(*, *)
Constipation	51	46.4	10	(9, 19)
Diarrhea	21	19.1	6	(2, 7)
Skin problem	20	18.2	8	(6, 23)
Mucositis	14	12.7	5	(4, 12)

*: cannot be reliably estimated due to availability of limited data

Characteristics of patients in the intervention group

Among the patients assigned to the intervention group, eighty-two patients (74%) had completed 10 contacts while 26% of patients left the study before the tenth contact. Seventy-four percent of patients were female and 55% were older than 60 years of age. Thirty-eight percent of patients had breast cancer, 38.2 % had lung cancer, and 27% had other types of cancer. Overall, 67% had late stage cancer. About 25% of patients had CES-D score greater or equal to 16, suggesting clinical depression. Forty four percent

of patients reported at least 3 co-morbid conditions.

Prevalence (%) of reported pain by patients' characteristics is presented in Table 2. Overall, 45.5% of patients reported pain. Prevalence of reported pain among patients with CES-D of at least 16 was 57%, the highest among other subgroups defined in Table 2. Prevalence of reported pain among male patients was 55%. Prevalence of reported pain among early stage cancer patients was the lowest, 36%.

Table 2. Proportion of patients who reported pain during 10 contacts by patients' characteristics

Factor		N	No. of patients reported pain	Prevalence (%) of reported pain
Patient's Sex	Male	29	16	55.2
	Female	81	34	42.0
Patient's Age	< 60 years old	49	25	51.0
	≥ 60 years old	60	25	41.7
Site of Cancer	Breast Cancer	42	20	47.6
	Lung Cancer	38	19	50.0
	Other Cancers	30	11	36.7
Stage of Cancer	Early Stage	36	13	36.1
	Late Stage	74	37	50.0
Patient's CES-D	< 16	70	29	41.4
	≥ 16	28	16	57.1
Co-morbidity	0 – 2	60	28	46.7
	3 +	48	21	43.8
Overall		110	50	45.5

Prevalence of reported fatigue by patients' characteristics is presented in Table 3. Overall, 82.7% of the patients reported fatigue. Prevalence of reported fatigue among breast cancer patients was 90.5%, the highest among other subgroups defined in Table 3. Prevalence of reported fatigue among patients with CES-D of at least 16 was 89.3%. Prevalence of reported fatigue among patients with other types of cancer was the lowest, 70%.

Table 3. Proportion of patients who reported fatigue during 10 contacts by patients' characteristics

Factor		N	No. of patients reported fatigue	Prevalence (%) of reported fatigue
Patient's Sex	Male	29	21	72.4
	Female	81	70	86.4
Patient's Age	< 60 years old	49	43	87.8
	≥ 60 years old	60	47	78.3
Site of Cancer	Breast Cancer	42	38	90.5
	Lung Cancer	38	32	84.2
	Other Cancer	30	21	70.0
Stage of Cancer	Early Stage	36	32	88.9
	Late Stage	74	59	79.7
Patient's CES-D	< 16	70	58	82.9
	≥ 16	28	25	89.3
Co-morbidity	0 – 2	60	47	78.3
	3 +	48	42	87.5
Overall		110	91	82.7

Patients assigned to the intervention group reported multiple symptoms at each contact and the total number of symptoms that patients experienced could affect the resolution of any given symptom. We compared the mean number of symptoms by patients' characteristics using t-test or ANOVA. Patient characteristics such as sex, age, site of cancer, stage of cancer, and co-morbidity were not significantly associated with the numbers of symptoms reported. However, patients with CES-D scores of at least 16 had a mean of 5.4 symptoms while patients with CES-D less than 16 had a mean of 4.4 symptoms. This difference is considered marginally significant, p-value=0.0867. Table 4 provides the mean number of reported symptoms during 10 contacts by patients' characteristics along with the corresponding p-values

Table 4. Comparison of mean number of reported symptoms during 10 contacts by patients' characteristics

Factor		N	Total number of reported symptoms		P-value
			Mean	Std	
Patient's Sex	Male	29	4.10	2.23	0.1889
	Female	81	4.72	2.11	
Patient's Age	< 60 years old	49	4.63	2.26	0.7511
	≥ 60 years old	60	4.50	2.09	
Site of Cancer	Breast Cancer	42	4.90	2.07	0.3662
	Lung Cancer	38	4.45	2.18	
	Other Cancer	30	4.20	2.22	

Continues Table 4.					
Factor		N	Total number of reported symptoms		P-value
			Mean	Std	
Stage of Cancer	Early Stage	36	4.47	2.17	0.7807
	Late Stage	74	4.59	2.15	
Patient's CES-D	Low: < 16	70	4.43	1.84	0.0867
	High: ≥ 16	28	5.39	2.66	
Co-morbidity	0 – 2	60	4.40	2.11	0.6773
	3 +	48	4.79	2.23	
Overall		110	4.52	2.17	

Factors associated with time to resolution of pain

Median time to resolution of pain was estimated by Kaplan Meier method, and the log-rank test was employed to test association between time to resolution of pain and patients' characteristics as shown in Table 5. Patients with early stage cancer had a median pain resolution time of 10 weeks as compared with that of late stage cancer patients who had a median pain resolution time of 23 weeks. This difference indicates a significant association between stage of cancer and time to resolution of pain, p-value=0.0113. We did not find any significant associations between time to resolution of pain and other patient characteristics shown in Table 5. Figure 4 provides a graphical presentation of significant association between time to resolution of pain and stage of cancer.

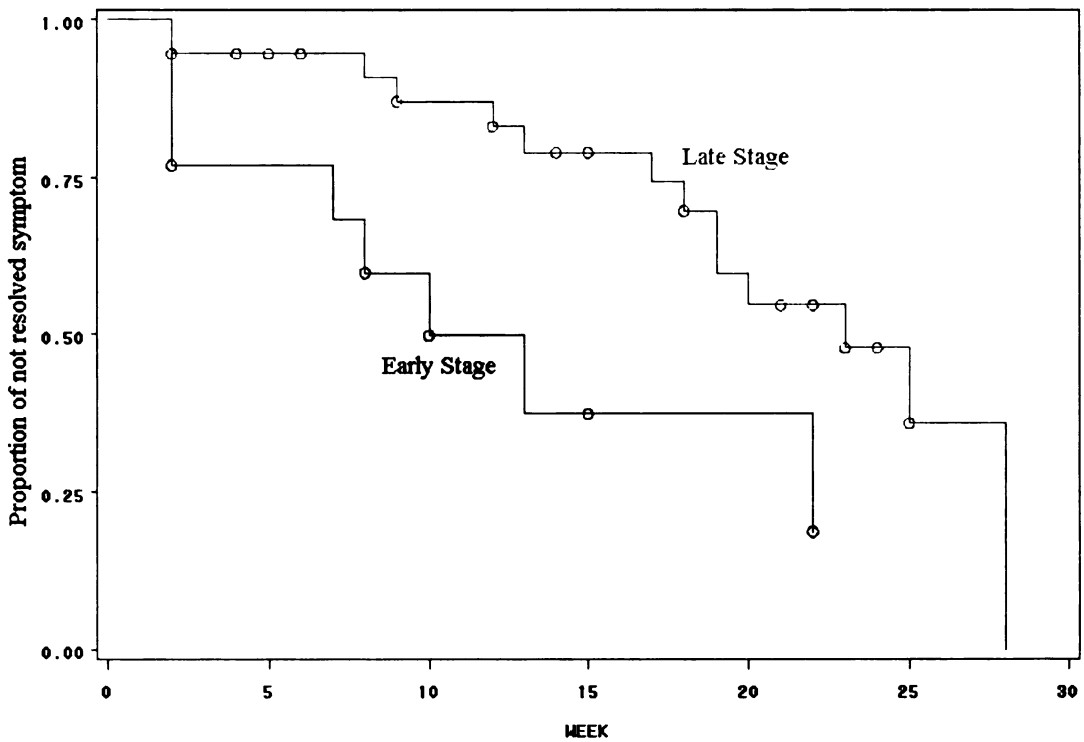
Table 5. Comparison of time to resolution of pain by patients' characteristics

Factor		N	Time to resolution of pain in weeks		P-value [a]
			Median	95% CI	
Patient's Sex	Male	16	19	(9, *)	0.9981
	Female	34	20	(17, 28)	
Patient's Age	< 60 years old	25	19	(13, 25)	0.5449
	≥ 60 years old	25	23	(13, 28)	
Site of Cancer	Lung Cancer	19	19	(13, 28)	0.6497
	Other Cancers	31	22	(13, 15)	
Stage of cancer	Early Stage	13	10	(7, 22)	0.0113
	Late Stage	37	23	(19, 28)	
Patient's CES-D	Low: < 16	29	20	(10, 23)	0.3115
	High: ≥ 16	16	25	(13, 28)	
Co-morbidity	0 – 2	28	22	(13, 25)	0.9434
	3 +	21	19	(13, 28)	
Overall		50	20	(17, 28)	

*: cannot be reliably estimated due to limited data

a: p-value for testing the equality of time to resolution of pain by patients' characteristics using log-rank test

Figure 4. Survival curves for time to resolution of pain by stage of cancer



Factors associated with time to resolution of fatigue

Comparison of median time to resolution of fatigue by patient's sex, site of cancer, CES-D status, and co-morbidity revealed several interesting associations. Patients with high co-morbidity (at least 3) had a median fatigue resolution time of 23 weeks as compared with that of low co-morbidity who had a median fatigue resolution time of 14 weeks. This difference indicates a significant association between co-morbidity status and time to resolution of fatigue (p-value=0.0088). Patients with lung cancer had a median fatigue resolution time of 29 weeks as compared with that of the

patients with other types of cancer who had a median fatigue resolution time of 19 weeks. This difference suggests a significant association between site of cancer and time to resolution of fatigue (p-value=0.0194). Patients with high CES-D (at least 16) had a median fatigue resolution time of 23 weeks as compared with that of low CES-D who had a median fatigue resolution time of 16 weeks. This difference was also statistically significant with a p-value of 0.0290. We also found a statistically significant association between the sex of the patient and time to resolution of fatigue, p-value=0.0143. Female patients had a median fatigue resolution time of 19 weeks which was lower than the median time to resolution for male patients. Since the survival curve for time to resolution of fatigue for male patients remained above 0.5, as shown in Figure 5, we could not reliably estimate the exact median time to resolution of fatigue for male patients.

Median times to resolution of fatigue by other patients' characteristics are shown in Table 6. Figures 5-8 provide graphical presentations of significant associations between time to resolution of fatigue and patients' characteristics, sex, cancer site, CES-D and co-morbidity status.

Table 6. Comparison of time to resolution of fatigue by patients' characteristics

Factor		N	Time to resolution of fatigue in weeks		P-value [a]
			Median	95% CI	
Patient's Sex	Male	21	*	(*, *)	.0143
	Female	69	19	(14, 21)	
Patient's Age	< 60 years old	43	18	(12, 23)	.2546
	≥ 60 years old	46	21	(16, 30)	
Site of Cancer	Lung Cancer	32	29	(18, *)	.0194
	Other Cancers	58	19	(12, 21)	
Stage of Cancer	Early Stage	32	20	(14, 22)	.6400
	Late Stage	58	20	(16, 29)	
Patient's CES-D	Low: < 16	24	16	(14, 21)	.0290
	High: ≥ 16	58	23	(20, 30)	
Co-morbidity	0 – 2	47	14	(10, 20)	.0088
	3 +	41	23	(19, 30)	
Overall		90	20	(16, 23)	

*: cannot be reliably estimated due to limited data

a: p-value for testing the equality of time to resolution of fatigue by patients' characteristics using log-rank test

Figure 5. Survival curves for time to resolution of fatigue by patient's sex

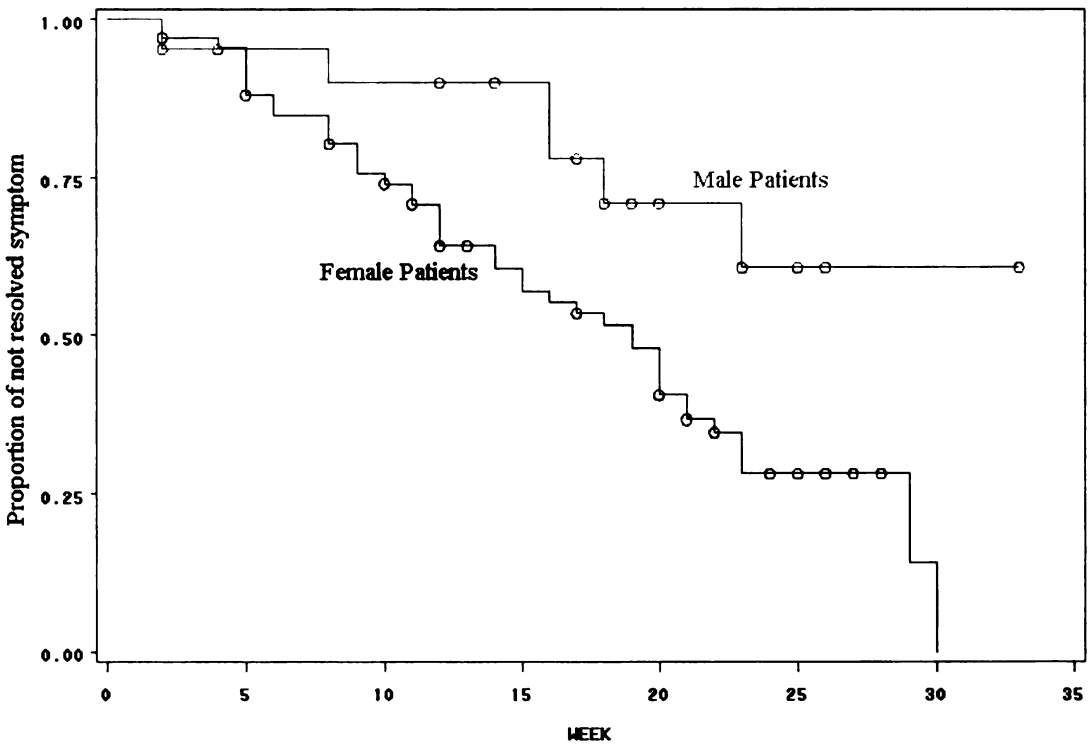


Figure 6. Survival curves for time to resolution of fatigue by site of cancer

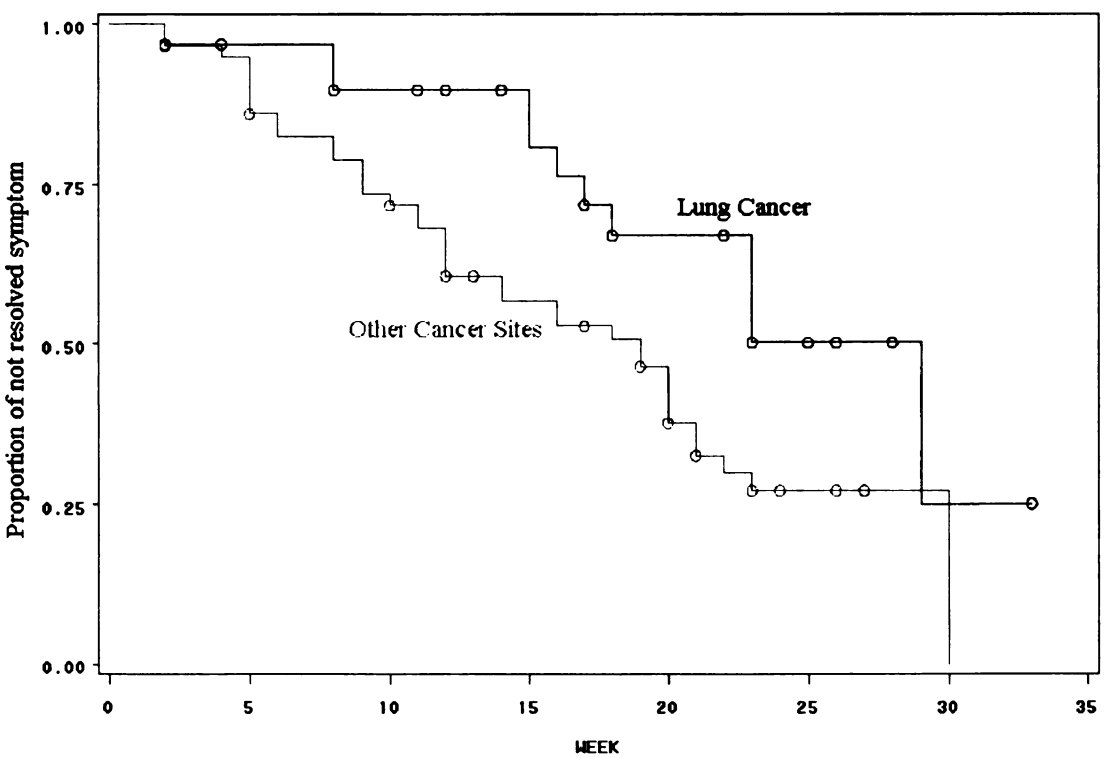


Figure 7. Survival curves for time to resolution of fatigue by CES-D status

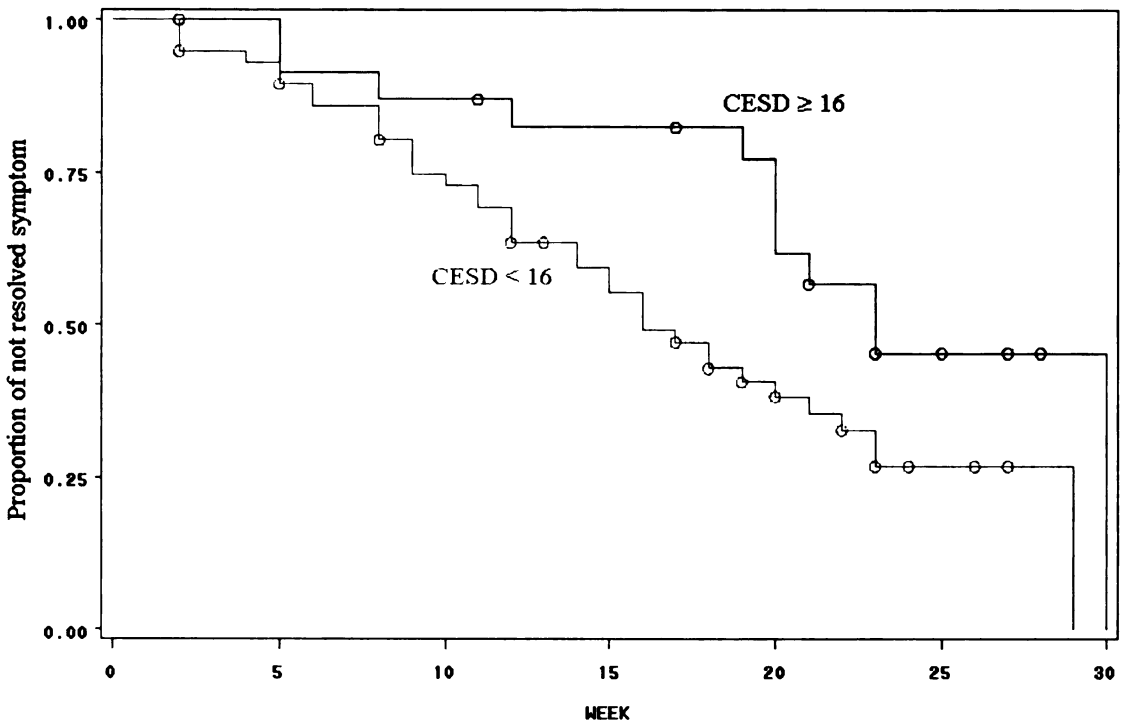
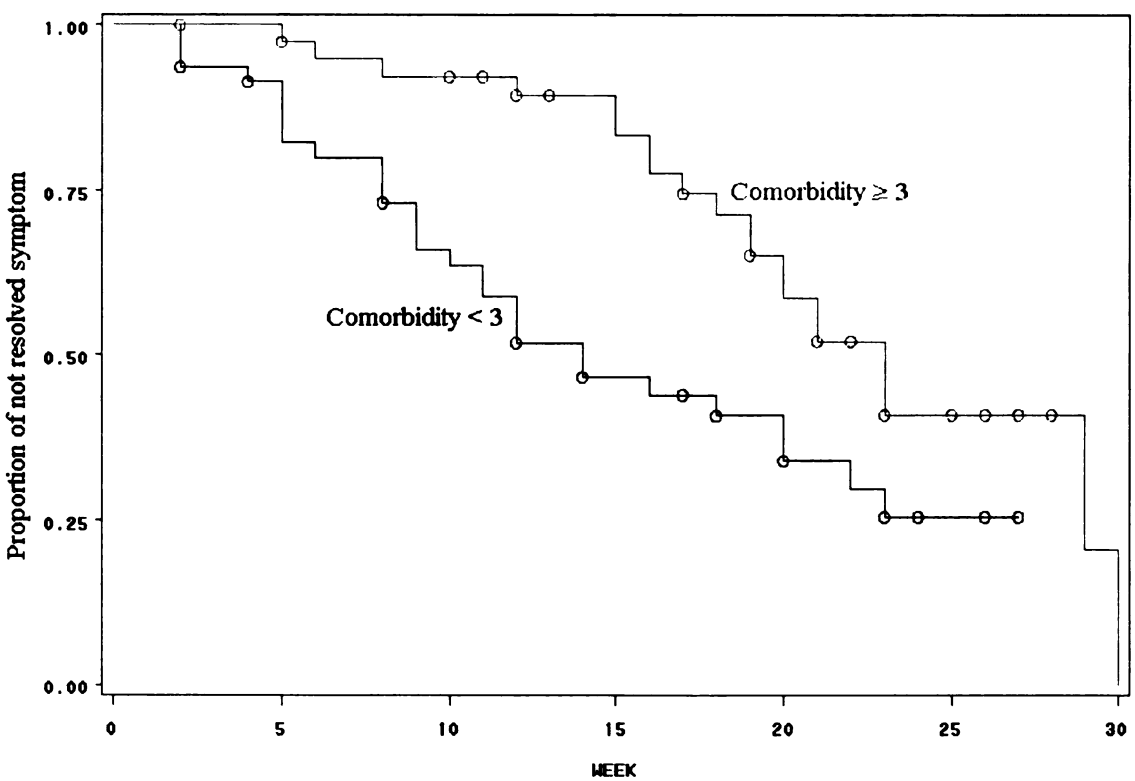


Figure 8. Survival curves for time to resolution of fatigue by co-morbidity status



Cox proportional hazard model for time to resolution of pain and fatigue

The Cox proportional hazard models were employed to examine the association between patients' characteristics and time to resolution of pain and fatigue after controlling for patients' characteristics such as co-morbidity, depression level, age, sex, and stage of cancer.

After controlling for the covariates, only stage of cancer maintained its significant association with time to resolution of pain. Patients with early stage cancer had the shorter time to resolution of pain than that of late stage cancer patients. The ratio of the rates of resolving pain over time (Hazard Ratio: HR) for patients with early stage of cancer compared to those with late stage of cancer is 3.06 (95% confidence interval = [1.21, 7.73]). Patients with early stage cancer had an estimated median pain resolution time of 13 weeks as compared with that of late stage cancer patients who had an estimated median pain resolution time of 23 weeks. This ratio indicates a significant association between stage of cancer and time to resolution of pain, p-value=0.0180. We did not find any other significant associations between time to resolution of pain and other patient characteristics. Also various interaction terms between covariates were tested but these did not have any significant effect on time to resolution of pain.

While only stage of cancer was associated with time to resolution of pain, co-

morbidity, CES-D score, and patient's sex had significant associations with time to resolution of fatigue after controlling for other covariates. Patients with high co-morbidity had the longer median time to resolution of fatigue compared with that of low co-morbidity. The ratio of the rate of resolving fatigue for patients with the larger number of co-morbid conditions ($\geq$ 3) compared to those with less that 3 ($<$ 3) co-morbid conditions is 0.54 (95% confidence interval = [0.30, 0.96]). Patients with high co-morbidity ($\geq$ 3) had an estimated median fatigue resolution time of 29 weeks as compared with that of low co-morbidity who had an estimated median fatigue resolution time of 22 weeks. This ratio indicates a significant association between co-morbidity and time to resolution of fatigue, p-value=0.0374.

Patients with high CES-D had the longer time to resolution of fatigue compared with those with low CES-D. The ratio of the rate of resolving fatigue for patients with high CES-D ($\geq$ 16) compared to those with low CES-D ($<$ 16) is 0.53 (95% confidence interval = [0.53, 1.03]). Patients with high CES-D ($\geq$ 16) had an estimated median fatigue resolution time of 29 weeks as compared with that of low CES-D who had a median fatigue resolution time of 22 weeks. This ratio indicates a marginally significant association between CES-D score and time to resolution of fatigue, p-value=0.0628.

Female patients had shorter times to resolution of fatigue compared with male

patients. The ratio of resolving fatigue over time for female patients compared with male patients is 3.73 (95% confidence interval = [1.53, 9.10]). Female patients had an estimated median fatigue resolution time of 19 weeks as compared with male patients who had an estimated median time to resolution of 30 weeks. This ratio indicates a significant association between patient's sex and time to resolution of fatigue, p-value=0.0038.

The other patients' characteristics were not significantly associated with time to resolution of fatigue after controlling for covariates. Although lung cancer patients had longer time to resolution of fatigue compared to those with other cancer sites in univariate analysis, the effect of cancer sites was disappeared after controlling for patient's sex.

Table 7. Estimated mean time to resolution and hazard ratios of resolving pain and fatigue after adjusting for other covariates

Symptom	Variables		Median Time (week)	Hazard Ratio	95% Hazard Ratio Confidence Limits	
Pain	Stage of Cancer	Late Stage	23	3.06	1.21	7.73
		Early Stage	13			
Fatigue	CES-D score	< 16	22	0.53	0.27	1.03
		≥ 16	29			
	Co-morbidity	0 – 2	22	0.54	0.30	0.96
		3 +	29			
	Patient's Sex	Male	30	3.73	1.53	9.10
		Female	19			

DISCUSSION

We proposed to use survival analysis techniques for assessing symptom resolution in clinical trials. The survival methods allowed using the information of patients who were lost to follow-up or didn't have enough chance to resolve symptoms until the end of the follow-up.

Only stage of cancer was significantly associated with time to resolution of pain. Generally cancer patients at the end of life suffer serious pain, and these patients are more likely to have late stage cancer. The late stage cancer related with the end of life may contribute to the association between the late stage of cancer and longer time to resolution of pain. However, resolution of pain was not significantly influenced by other patient's baseline medical conditions such as CES-D and co-morbidity at baseline.

Stage of cancer, patient's sex, depression, and co-morbid conditions were identified as significant factors related to time to resolution of fatigue in both the log-rank test and the Cox proportional hazard model. Unlike pain, time to resolution of fatigue was longer in patients with higher CES-D and co-morbidity at baseline. The presence of high CES-D or multiple co-morbid conditions can make patients more tired and it will be burdens to resolve fatigue. Male patients required longer time to resolve fatigue than

female patients.

The identified associations in this study will help to develop a strategy of symptom management in several ways. For example, it will help to anticipate which patients are potentially vulnerable to pain or fatigue and predict how long patients need to receive interventions to resolve the symptoms.

Association with demographic characteristics

Patient's sex: The experiences of pain and fatigue were reported differently between male and female patients. Pain was more commonly reported in male patients, while fatigue was more common in female patients in this study. However, the difference in prevalence of reported pain and fatigue by patient's sex was not statistically significant. Patient's sex is significantly associated with time to resolution of fatigue in both univariate and multivariate survival analysis. Female patients resolved their fatigue in a relatively shorter period of time as compared with male patients. More than half of male patients reported that their fatigue was not resolved until 30 weeks. A longitudinal study with lung cancer patients undergoing radiotherapy(31) and a cross-sectional study for symptoms in advanced cancer(32) didn't find gender difference in prevalence of fatigue among cancer patients. Based on the result of her two studies

(RCT and cross sectional study) Miaskowski found no gender differences in severity of pain among cancer patients. This was confirmed by Turk and Okifuji in a retrospective study(33). Miaskowski also reviewed the relevant studies for gender difference in cancer-related fatigue. In her review paper, four studies indicated that female patients had higher fatigue severity than male patients while another four studies found no significant gender differences in the severity or intensity of fatigue. Higher severity of fatigue among female patients does not support the result of shorter time to resolution of fatigue in female patients as discovered in our analysis. Along with the lack of supportive evidence suggesting longer time to resolution of fatigue among male patients, there are several limitations regarding gender effect on time to resolution of fatigue. These include; unequal censoring of data between groups and correlations with site of cancer. These issues will be discussed in the limitations section. Therefore, although the model suggests that female patients are more likely to resolve fatigue earlier than male patients, the gender differences are not conclusive.

Patient's age: Age of patients is a potential factor associated with pain in terms of prevalence, severity, and duration of symptom. Patients who were older than 59 year of age reported less pain compared to younger patients. Traditionally, elderly patients tend to underreport their pain, because they may consider pain as a normal part of aging

and they may believe that their complaint of pain will disturb physician's treatments of their cancer(34). A cohort study conducted with cancer patients in Michigan observed that patients older than 64 years more frequently reported both pain and fatigue(4). The underreporting of pain among elderly patients may be associated with higher levels of severity or intensity of pain. If elderly patients report relatively severe pain, compared to younger patients, then underreporting among elder patients may adversely affect their time to resolution of pain. According to the result from univariate analysis with the log-rank test, there was no significant age effect on time to resolution of pain even if median time to resolution among elder patients (23 weeks) was longer than among younger patients (19 weeks). The age effect was not significant after controlling for co-morbidity, CES-D, patient's sex, stage of cancer. The association between age and anxiety, which contributes to chronic fatigue in cancer patients(35), possibly has responsible to an insignificant aging effect. Among patients reporting pain, the mean age of patients with anxiety was 57 years old and the mean age of those without anxiety was 61 years old. In a longitudinal study conducted with hospitalized cancer patients in Tokyo, younger patients are more distressed and reported more anxiety than elderly patients(36). It will be meaningful test to assess the age effect on time to resolution of pain in patients with and without anxiety separately in future study.

Associations with medical conditions

Stage of cancer: Stage of cancer is an important potential factor associated with cancer-related pain. Unlike fatigue, pain was reported more frequently among late stage cancer patients than those diagnosed at early stages. It was observed in previous studies that advanced cancer was more likely to be related to occurrence of pain(4, 37). However, fatigue was not significantly more prevalent among patients with late stage. Late stage became a risk factor for pain and also disrupted the resolution of pain. According to the result of both univariate and multivariate analyses in this study, stage of cancer was identified as an important factor associated with time to resolution of pain. Patients having late stage cancer needed longer times to resolve pain than those having early stage cancer. By comparison, the median time to resolution of pain in late stage cancer patients was more than two times the median time in early stage of cancer. After adjusting for other covariates, the probability of resolving pain among early stage cancer patients was more than three times the probability in late stage cancer patients. In an earlier survey of cancer-related pain with the Brief Pain Inventory (BPI), 86% of patients with advanced cancer believe that their pain caused by cancer itself(6). When patients believe their pain is caused by cancer, they have a greater interference with activities of

daily living(5). Patients with late stage of cancer may experience more intensive and severe pain, and their pain will be relatively more difficult to resolve compared to pain among those with early stage cancer. Those burdens among patients with later stages of cancer may lead to longer times to resolution of pain.

Co-morbidity: Patients' co-morbidities at their baseline observation have shown to be an important causal factor for cancer-related fatigue(8). In this analysis, patients with higher numbers of co-morbid conditions were more likely to experience fatigue compared to those with low numbers of co-morbid conditions. However, it was observed that co-morbidity was not associated with the prevalence of pain.

In contrast, according to NCCN practice guidelines for cancer-related fatigue, patients' co-morbidity and depression are known to be associated with fatigue. The guideline recommends that more attention should be paid to co-morbidity in conjunction with the treatment of cancer-related fatigue(8). High co-morbidity at baseline was significantly associated with longer time to resolution of fatigue. Patients reporting co-morbid conditions more than 2 at baseline had 23 weeks of median time to resolution while those who had lower co-morbid conditions had less than 14 weeks median time to resolution. According to a cohort study among cancer patients who were older than 64 years of age, high co-morbidity, late stage of cancer, and lung cancer were related to both

pain and fatigue(4). They suggested that co-morbid conditions had an effect on pain and fatigue through the way that cancer interacts with these conditions. We found that co-morbidity was associated with fatigue in terms of prevalence and time to resolution. Co-morbidity can be an important factor to provide appropriate management for relieving cancer-related fatigue.

Depression: Depression at baseline is positively associated with occurrence of pain and fatigue reported by cancer patients. In this study, patients with high CES-D scores ($\geq$ 16) reported pain and fatigue more commonly than those with lower CES-D scores. Further, depression accompanying a diagnosis of cancer may be associated with greater fatigue. In general, a measures of fatigue administered to cancer patients have a high positive correlation with a measure of depression(38). Cancer patients may experience depressive disorders from medical factors, psychological factors, and social factors, and their depression also may be complicated by their fatigue. Fatigue can be the result of depression and it can be also a cause of depression. Fatigue and depression may co-occur without any evidence of a causal relationship, because depression can have the same pathology as fatigue(39). Depression at baseline is associated with time to resolution of fatigue as well as prevalence of fatigue. High CES-D was significantly associated with longer time to resolution of fatigue in both univariate and multivariate

analyses. Correlations between fatigue and depression have been documented in cancer patients(40, 41). A study with Hodgkin's disease conducted by Loge and colleagues found that 26% of the patients had fatigue for 6 months or longer and their fatigue was correlated with higher levels of depression(42). In a longitudinal study performed with cancer patients undergoing radiotherapy at a medical center in Amsterdam, the correlation between fatigue measured by the Multidimensional Fatigue Inventory (MFI-20) and the mood component of the CES-D was assessed at the start of treatment, 2 weeks after completion of treatment, and 9 months later(39). The correlations were significant over time, and especially the correlation with both general fatigue and physical fatigue was higher after treatment than at the start of treatment. Therefore, patient's CES-D score at baseline may be a good predictor of time to resolution of fatigue. Although it was not observed that depression at baseline was significantly associated with time to resolution of pain, there was the pattern of increasing time to resolution of pain as increasing CES-D at baseline. The lack of significance between depression and time to resolution of pain may be due to the small sample size. We had only 50 patients reporting pain while 91 patients reported fatigue. This could be a reason for identifying a fewer significant factors associated with time to resolution of pain as compared with several significant factors associated with time to resolution of fatigue.

Suggestions for further study

Several factors significantly prolonged the time to symptom resolutions and they included; late stage of cancer, high number of co-morbidity conditions, and high CES-D, which are associated with intense symptom severity. Symptom severity could play an important role between patient factors and time to resolution of pain and fatigue. It will be necessary to investigate how overall symptom severity contributes to the time to resolution of pain and fatigue.

We also suggest that it will be necessary to distinguish fatigue by self-reported mental fatigue (lack of motivation and mental exhaustion) and physical fatigue (limitations on activity) in future research. Physical fatigue factors were more pronounced than mental fatigue factors(43). These two kinds of fatigue may differ in cause, intensity, duration, and factors associated with resolution. Cognitive behavioral interventions may differentially influence time to resolution between mental and physical fatigue. Future research will be able to examine how differently patient factors and intervention strategies influence the relief of mental and physical fatigue. Patients with mental fatigue may require different strategies than those needed to resolve physical fatigue.

Limitations

This is a secondary analysis of data from a cognitive behavioral intervention trial. The original study did not intend to use survival analysis techniques for identifying factors associated with time to resolution of symptoms. Therefore, the actual dates of symptom onset and resolution were not collected, rather we estimated the time to resolution of symptom based on the dates of contacts when patient reported symptom onset or resolution.

While patients were scheduled to contact the trained nurses every 2 weeks, the actual time intervals varied. Although the interval between contacts was scheduled to be on average 2 weeks, some patients had longer intervals between contacts due to the fact that they could not be contacted at the designated times. Unequal time intervals between contacts may lead to an unequal chance to report symptom status among patients. For instance, a patient could have had a 2-week time interval between the first and second contact while another patient could have had 3-week interval. Even though both patients might have resolved their pain within 2 weeks, the time to resolution of pain for these two patients could be recorded differently. Therefore, estimation of time to resolution could be influenced by the different time intervals.

Consistency of self-reports of pain and fatigue is a considerable issue. Due to

a lack of uniformity in measurement and methodology in symptom research, the occurrence of pain and fatigue had been estimated in large range of intervals across studies. Reasons for the lack of consistency in terms of measurement issues include individual difference in conceptualization of pain and fatigue and lack of consensus on the criteria to define the resolution of symptoms(44). Since measuring symptom resolution depends on self-reporting by patients, individual characteristic may influence the variation of time to resolution of symptoms. The gender effects on time to resolution of pain and fatigue were possibly biased by individual difference in definitions of symptom resolution.

In this study, some characteristics such as patient's sex and stage of cancer have unequal proportions of censored data. Among patients reporting fatigue, 71% of male patients and 36% of female patients were censored, and among patients reporting pain 38% of patients with early stage of cancer and 62% of those with late stage cancers were censored. If unequal censoring occurs due to beneficial or adverse effect of gender or stage of cancer, then the comparisons may be biased.

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