Original Article

Correlating symptoms and their changes with survival in patients with brain metastases

Erin Wong, Leigha Rowbottom, May Tsao, Liying Zhang, Rachel McDonald, Cyril Danjoux, Elizabeth Barnes, Stephanie Chan, Edward Chow

Rapid Response Radiotherapy Program, Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada

Contributions: (I) Conception and design: E Wong, E Chow; (II) Administrative support: L Rowbottom, S Chan; (III) Provision of study materials or patients: L Zhang, C Danjoux, E Barnes, M Tsao, E Chow; (IV) Collection and assembly of data: E Wong, E Chow, L Zhang; (V) Data analysis and interpretation: E Wong, L Zhang, E Chow, L Rowbottom; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Edward Chow, MBBS, MSc, PhD, FRCPC. Department of Radiation Oncology, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada. Email: edward.chow@sunnybrook.ca.

Background: Having a clear prognosis for patients with brain metastases allows health care practitioners (HCPs) to determine appropriate palliative management and assist patients when making informed treatment decisions. The objective of this study was to determine the prognostic significance of commonly experienced symptoms as well as their changes.

Methods: Overall survival (OS) was calculated from the date of consultation for palliative radiotherapy to date of death or censored at last follow-up date. Symptom changes at follow up were defined as worsened, improved, or no change. Univariate and multivariate cox proportional hazard (PH) model of OS was conducted on 14 symptoms at baseline and on changes in those symptoms at 1-, 2-, and 3-month follow-ups.

Results: From 1999 to 2013, 1,660 patients were included for baseline symptom analysis. Through univariate analysis, fatigue, nausea, appetite loss, coordination, concentration, balance and depression were significantly related to OS. Upon multivariate analysis, fatigue and appetite loss were most predictive of short survival. For symptom change, 201 patients were included. The actuarial median OS was 5.0 months [95% confidence interval (CI): 4.3–7.0], 7.1 months (95% CI: 5.2–9.5) and 8.8 months (95% CI: 5.8–11.5) for patients with month 1, 2, and 3 follow-ups, respectively. The most common symptom changes following whole brain radiotherapy (WBRT) were: worsened fatigue, appetite loss, and weakness. Worsened difficulty concentrating, fatigue, nausea and headaches were most predictive of a poorer survival outcome.

Conclusions: HCPs should be aware of the shorter prognosis associated with patients exhibiting one or more of these symptoms and tailor care accordingly to maximize patients' remaining quality of life (QOL).

Keywords: Brain metastases; survival; symptoms; survival

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Introduction

Approximately 40–60% of advanced cancer patients develop brain metastases, the most common brain neoplasms (1). Certain primary cancer sites are more likely to lead to brain metastases such as breast, colorectal, lung, melanoma, and kidney (1). Fatigue, headaches, and focal weakness are the most prevalent symptoms, although other symptoms can include seizures and visual impairments (2). Symptoms experienced by patients with brain metastases may be due to the cancer itself or as a side effect of treatment (3).

Treatment for brain metastases aims to improve health-related quality of life (HRQOL) by palliating symptoms (4,5). The presence of the blood brain barrier

commonly limits the entry of systemic therapies, including chemotherapy; as a result such treatment options are usually not appropriate for these patients (6). For individuals with multiple brain metastases and poor performance status (PS), palliative care with or without whole brain radiotherapy (WBRT) is the standard of care (7,8). However, the full effects of WBRT may take up one month to be experienced, by which point approximately 20–30% of patients will have died (5). Therefore, individuals may never benefit from the prescribed treatment (9). As such, supportive care including symptom management with medication only may be offered for patients with poor PS (7,8). Corticosteroids may palliate symptoms of brain metastases, such as edema and neurological symptoms, in upwards of 70% of patients; however, treatment with corticosteroids alone is indicative of poor survival with a median survival of 2 months (10).

Due to the limited survival of patients with brain metastases, accurate survival prognoses are of the utmost importance to ensure proper prescription of treatment and appropriate care plans. The objective of the study was to determine survival prognosis in patients with multiple brain metastases by using changes in symptoms that patients experienced.

Methods

A retrospective analysis was conducted on prospectively collected databases that were collected from 1999 to 2013. Patients with radiographic evidence of brain metastases verified with CT or MRI were included in the analysis. All patients were treated with WBRT and prescribed varying doses of dexamethasone.

Data collection

Baseline demographic information such as age, gender, Karnofsky performance status (KPS), primary cancer site, number of brain metastases, systemic treatment and dose of dexamethasone (when applicable) were collected for all patients. A total of 14 symptom scores were obtained from six quality of life (QOL) and symptoms questionnaires, which included nausea, pain, anxiety, fatigue, appetite loss, depression, concentration, memory loss, vision changes, weakness, balance, headache, insomnia, concentration. All individuals consented to original data collection and the current study was approved by our institutions Research Ethics Board.

Questionnaires

Edmonton Symptom Assessment Scale (ESAS)

The ESAS is a validated 9-item symptom questionnaire rated on a scale from 0 (no experience of the symptom) to 10 (worse possible degree of the symptom). Six symptoms were evaluated: nausea, pain, fatigue, anxiety, appetite loss and depression.

Spitzer Quality Of Life Index (SQLI)

The SQLI consists of five domains: daily living, health, activity, support, and outlook. An additional symptom questionnaire was also administered rated on a Likert scale from 1 to 4 with 1= none, 2= mild, 3= moderate, and 4= severe. Eight symptoms were evaluated: nausea, concentration, fatigue, memory loss, vision problem, weakness, balance and headache.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

The EORTC QLQ-C30 is a 30-question QOL assessment for general cancer population. This questionnaire assess symptoms on a scale of 1 to 4, with 1= not at all, 2= a little bit, 3= quite a bit, and 4= very much. Ten symptoms were assessed: nausea, pain, fatigue, insomnia, concentration, memory loss, weakness, anxiety, appetite loss and depression.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 15 Palliative (EORTC QLQ-C15-PAL)

The EORTC QLQ-C15-PAL is a QOL assessment for palliative cancer patients consisting of 15 questions. Eight symptoms were assessed: nausea, pain, fatigue, insomnia, anxiety, appetite, weakness and depression. This questionnaire assessed symptoms on a Likert scale of 1 to 4, similar to the C30. Patients who completed the QLQ-C15-PAL also completed the BN20+2. Both questionnaires included the weakness item; as such records from the QLQ-C15-PAL were used if available. If not, the BN20+2 weakness item was used.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Brain Module (EORTC QLQ-BN20 or BN20+2)

The BN20 is a 20-item questionnaire to supplement the QLQ-C30, while the BN20+2 is a 22-item in-development tool to accompany the QLQ-C15-PAL. Both questionnaires

assess symptoms on a Likert scale from 1 to 4, similar to the QLQ-C30 or QLQ-C15-PAL. Four symptoms were assessed by both questionnaires: fatigue, vision problem, coordination, and headache, while the BN20+2 assess two additional symptoms: concentration, memory loss.

Functional Assessment of Cancer Therapy-Brain Scale (FACT-Br)

The FACT-Br assesses QOL in five domains: physical well-being, social/family well-being, emotional well-being, functional well-being, and additional concerns related to the brain. It is rated on a Likert scale from 0 to 4, with 0= not at all, 1= a little bit, 2= somewhat, 3= quite a bit, and 4= very much. Twelve symptoms were assessed: nausea, pain, fatigue, vision problems, weakness, coordination, headache, anxiety, depression, insomnia, concentration and memory loss. Insomnia, concentration and memory loss were reversed due to wording of the question.

Statistical analysis

Overall survival (OS) was calculated from consultation date to the death/last follow-up in months. Survival was defined from date of consult to date of death as baseline assessments were conducted at initial clinic consultation. All patients included in this study were assessed in a rapid referral radiotherapy clinic where the majority of patients receive treatment within 1 week of initial consultation. Patients who were still alive at time of analysis were censored at their last follow-up date.

Baseline symptoms

Univariate Cox proportional hazard (PH) model of OS was conducted in patients with symptom items. The time (months) to death or last follow-up was considered as the outcome variable. Analysis was separated into two groups: group 1 included all patients who completed the ESAS on a scale of 0 to 10; group 2 included all patients who completed one or more of the following questionnaires the EORTC QLQ-C30, SQLI, EORTC QLQ-BN20 or BN20+2, EORTC QLQ-C15 and Fact-Br. To search for the parameters most predictive of time to death, all variables with P<0.10 obtained from the univariate analysis were selected to the backward stepwise selection procedure in the multivariate analysis. Kaplan-Meier OS curve with 95% confidence interval (CI) was conducted in group 1 or group 2 patients. For those significant symptoms obtained from the multivariate analysis, Kaplan-Meier OS curves and Log-rank test were performed.

Symptom change

Only subjects who completed baseline assessment and at least one follow-up QOL questionnaire were included in the analysis. For the symptom change analysis, all patients from both group 1 and group 2 were analyzed together. Symptom changes were calculated between baseline and each follow-up record (month 1, 2, or 3). Kaplan-Meier OS curves with Log-rank test were performed in patients with month 1, 2, or 3 measurements. Symptom changes were sorted into three categories: increase (baseline score was less than follow-up score; severity of symptoms increased or worse QOL), no change (baseline score was equal to follow-up score; same severity), and decrease (baseline score was greater than follow-up score; severity of symptoms decreased or better QOL).

Univariate Cox PH model of OS was also conducted in all patients at month 1, 2, and 3, respectively, with demographic parameters and symptom changes (increase, no change, or decrease). Backward stepwise selection procedure in the multivariate analysis was also performed, using all variables with P<0.10 obtained from univariate analysis. In the final multivariate Cox PH model, we only kept the most significant predictors (P<0.05). All analyses were performed using Statistical Analysis Software (SAS version 9.4 for Windows). P value <0.05 was considered statistically significant.

Results

Baseline symptoms

Group 1 consisted of 1,391 patients who completed the ESAS symptom questionnaire at baseline rated on an 11 point Likert scale from 0 to 10. The mean age was 68 years, with 53% being male. The most common primary cancer sites were lung (36%), genitourinary (26%), and breast (20%). Median KPS was 60, ranging from 10 to 100 (*Table S1*). Among these 1391 patients, 925 (66%) patients were dead and 466 (34%) patients were alive and censored. Duration of follow-up was ranged between 0.1 and 104 months and the actuarial median survival time was 5.8 months (95% CI of 4.9–6.5 months). *Figure 1A* shows the Kaplan-Meier OS curve with 95% CI in all patients (group 1). In *Table S2*, the survival probabilities at 1-, 2-, and 3-month were 89.5%, 77.2%, and 66.8% respectively.

Fatigue, nausea (only categorical), appetite loss, and depression were significantly related to OS (*Table 1*). Through multivariate analysis, patients with moderate (HR =1.31) or severe (HR =1.42) fatigue were more likely to have shorter duration of survivals comparing to those without any fatigue symptoms. As well, patients with mild (HR =1.27) or severe (HR =1.45) appetite loss were more likely to have higher risk of death or shorter survival, as compared to those without such symptoms (*Table 2*, *Figure 1B*,*C*).

In group 2, 269 patients completed a symptom questionnaire (EORTC QLQ-C30, SQLI, EORTC QLQ-BN20 or BN20+2, EORTC QLQ-C15 and Fact-Br) at baseline. The mean age was 63 years, with 69% male. The most common primary cancer sites were lung (54%) and breast (25%). Median KPS was 70 ranging from 30 to 100 (*Table S1*). Among 269 patients, 259 (96%) patients died and 10 (4%) patients alive. Duration of follow-up was ranged from 0.2 to 51 months. *Figure S1* shows the Kaplan-Meier OS curve with 95% CI in patients from group 2. The actuarial median survival time was 3.8 months with 95% CI of 3.2–4.6 months. In *Table S3*, the survival probabilities at 1-, 2-, and 3-month were 90.6%, 75.0%, and 59.1%, respectively. In the univariate analysis, coordination, balance, and concentration (only categorical) were significantly related to OS (*Table 3*). All symptoms items were not significant in the multivariate analysis for group 2 patients.

Symptom change

Two hundred and one patients were included in the symptom change analysis if they had at least one follow-up. The mean age was 63 years, with 68% of the patients being male. The most common primary cancer sites were lung (58%) and breast (23%). Median KPS was 70 ranging from 30 to 100 (*Table S1*). Among 190 patients with month 1 follow-up, 183 died and 7 alive with a censored rate of 3.7%; among 97 patients with month 2 follow-up, 96 died and 1 alive with a censored rate of 1.0%; among 62 patients with month 3 symptoms records, all of them died and 0% censored. The actuarial median survival time was 5.0 months (95% CI: 4.3–7.0), 7.1 (95% CI: 5.2–9.5), and 8.8 (95% CI: 5.8–11.5) in patients who had month 1, 2, or 3 measurements. Log-rank test shows significant difference among three curves (P=0.029; *Figure S2*).

At month 1, the symptom changes of appetite loss, headache, concentration and balance were significantly related to OS (*Table 4*). Symptom changes of concentration and headache remained significant in the multivariate analysis. Patients with increased concentration difficulty (*Figure 2A*) had higher risk of impending death compared to patients with no change (HR =4.74) or with decreased scores (HR =3.19). While for headache (*Figure 2B*), patients with decreased symptom experience were more likely to have shorter survival, compared to patients with no change (HR =1.85) or with increased symptoms experience (HR =1.79) (*Table S4*). For month 2, symptom change of fatigue was significantly related to OS (*Table 4*). Patients with increased experience of fatigue (*Figure 3*) had shorter survival compared to patients with decreased score (HR =2.06) (*Table S4*). For month 3, three symptom changes were significantly related to OS: nausea, appetite loss, and concentration difficulty (*Table 4*). Patients with increased nausea (*Figure 4*) had higher risk of impending death comparing to patients with decreased score (HR =2.06) (*Table S4*).

Discussion

Brain metastases are a common neurological consequence of advanced cancer and are associated with significant morbidity and mortality. Clinical presentation of certain symptoms can act as prognostic factors to help physicians formulate survival estimates. Presenting symptoms and symptom changes can help inform the physician of the patient's PS and necessary action, such as referral to supportive care or further case management.

Several studies have shown that global reductions in QOL and increased severity of other symptom scores are associated with shorter survival (8-10). In one study, higher symptom burden in dyspnea, drowsiness, appetite, and nausea predicated death; however, upon multivariate analysis only dyspnea and drowsiness were significantly correlated with shorter survival (11). One study examined total symptom burden in palliative cancer patients and found it was significantly associated with time to death (12). Interestingly, this study saw no association between psychological symptom burden, such as depression and anxiety, and time of death (12). Another study found that all ESAS items significantly deteriorated in the last month of life (13). It appears that certain symptoms intensify at the end of life with the most symptom burden contributed by worsening fatigue, appetite, and wellbeing (11,13).

Our study found that baseline symptoms of fatigue, nausea, and appetite loss, as measured by the ESAS, were significantly related to OS. In particular, individuals

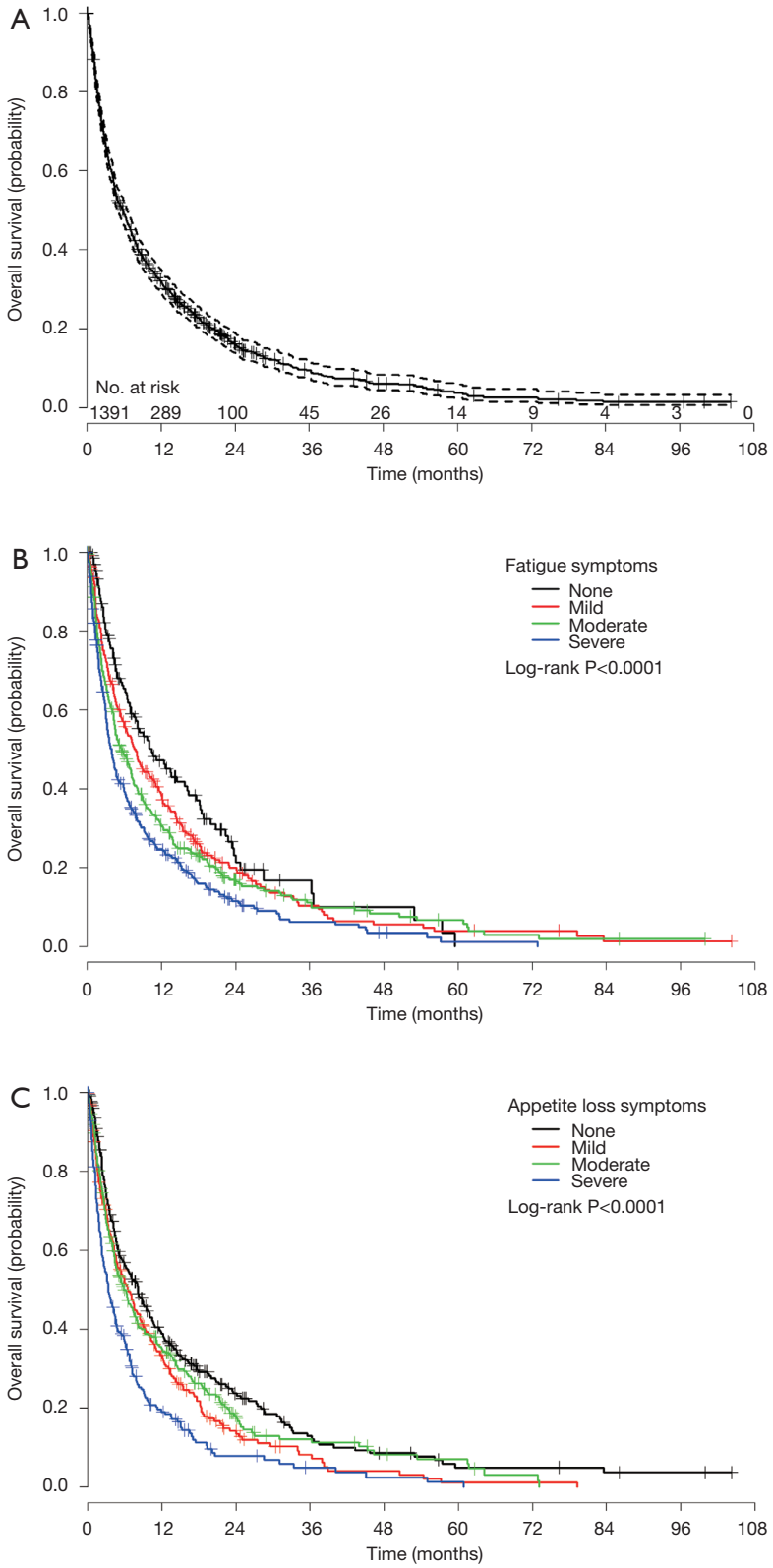

Figure 1 Kaplan-Meier OS curve. (A) With 95% CI for group 1 patients; (B) in group 1 patients based on symptom of fatigue; (C) in group 1 patients based on symptoms of appetite loss. OS, overall survival; CI, confidence interval.

Table 1 Univariate Cox proportional hazard model of OS on symptoms for patients in group 1

Symptom category	P value	HR	95% CI of HR
Symptom items (0–10 continuous variable)			
Nausea	0.1409	1.023	0.993–1.053
Fatigue	<0.0001	1.067	1.042–1.091
Pain	0.5078	0.993	0.974–1.013
Anxious	0.1652	1.016	0.994–1.038
Appetite loss	<0.0001	1.061	1.039–1.083
Depression	<0.0001	1.049	1.024–1.075
Symptom items categories			
Nausea	0.0249		
Mild *vs.* none	0.0036	1.259	1.078–1.470
Moderate *vs.* none	0.7726	1.038	0.806–1.336
Severe *vs.* none	0.1933	1.224	0.903–1.660
Fatigue	<0.0001		
Mild *vs.* none	0.0893	1.241	0.967–1.592
Moderate *vs.* none	0.0049	1.406	1.109–1.784
Severe *vs.* none	<0.0001	1.808	1.427–2.292
Pain	0.1324		
Mild *vs.* none	0.0295	0.798	0.652–0.978
Moderate *vs.* none	0.0937	0.857	0.716–1.026
Severe *vs.* none	0.0849	0.858	0.721–1.021
Anxious	0.2385		
Mild *vs.* none	0.1515	1.134	0.955–1.348
Moderate *vs.* none	0.1268	1.156	0.960–1.392
Severe *vs.* none	0.0733	1.206	0.983–1.480
Appetite loss	<0.0001		
Mild *vs.* none	0.0073	1.292	1.071–1.558
Moderate *vs.* none	0.0731	1.179	0.985–1.411
Severe *vs.* none	<0.0001	1.869	1.543–2.265
Depression	0.0001		
Mild *vs.* none	0.0082	1.244	1.058–1.462
Moderate *vs.* none	0.0012	1.357	1.128–1.633
Severe *vs.* none	0.0002	1.572	1.244–1.988

OS, overall survival; HR, hazard ratio; CI, confidence interval.

Table 2 Multivariate Cox proportional hazard model of OS on symptoms for patients in group 1

Symptom	P value	HR	95% CI of HR
Fatigue	0.0365		
Mild *vs.* none	0.1556	1.201	0.933–1.547
Moderate *vs.* none	0.0290	1.312	1.028–1.674
Severe *vs.* none	0.0055	1.424	1.109–1.828
Appetite loss	0.0002		
Mild *vs.* none	0.0143	1.271	1.049–1.540
Moderate *vs.* none	0.9958	0.999	0.829–1.206
Severe *vs.* none	0.0004	1.454	1.180–1.791

OS, overall survival; HR, hazard ratio; CI, confidence interval.

scoring with moderate to severe fatigue and appetite loss had shorter survival than those presenting with mild or no symptoms. These findings were similar to previous studies (9,10). However, in contrast to Cheung *et al.*, our study found that depression, as measured by the ESAS, was also significantly related to OS. For individuals assessed by the QLQ-C30, QLQ-C15-PAL, BN20, BN20+22, SQLI and Fact-Br, co-ordination, balance and concentration difficulty were significantly related to OS. Greater burden of appetite loss, headache, and difficulty concentrating were also correlated with shorter OS. As time progressed, increased concentration difficulties, issues with balance, and fatigue intensity were associated with higher risk of death. A previous study found that neurocognitive function (NCF) and QOL were correlated and that declines in NCF predicated deteriorations of QOL (14). Our findings regarding concentration difficulties further corroborate this study suggesting that NCF may be an important component of the prognosis estimate.

Several other studies have examined the prognostic significance of symptoms amongst other entities such as characteristics of the brain metastases and patients themselves, and the prescribed treatment. Caballero *et al.* examined prognostic factors for patients with recurrent brain metastases who underwent SRS after previous WBRT (15) and concluded that prognostic factors were dependent on primary site. Another study examined patients with brain metastases where the majority of patients were treated

Table 3 Univariate Cox proportional hazard model of OS on symptoms in group 2 patients

Symptom category	P value	HR	95% CI of HR
Symptom items (0–4 continuous variable)			
Nausea	0.1314	1.126	0.965–1.313
Fatigue	0.3001	1.068	0.943–1.211
Pain	0.5099	1.060	0.891–1.262
Anxious	0.4540	1.069	0.898–1.272
Appetite loss	0.0574	1.194	0.994–1.434
Depression	0.1224	1.148	0.963–1.369
Vision problem	0.5928	1.053	0.870–1.275
Weakness	0.2155	1.081	0.956–1.222
Coordination	0.0468	1.412	1.005–1.983
Headache	0.2040	1.108	0.946–1.297
Sleeping problem	0.8535	1.017	0.853–1.212
Concentration problem	0.0796	1.175	0.981–1.408
Balance problem	0.0005	1.369	1.146–1.635
Memory problem	0.1143	1.159	0.965–1.391
Symptom items categories			
Nausea	0.0841		
A little bit *vs.* not at all (2 *vs.* 1)	0.4623	1.154	0.788–1.690
Quite a bit *vs.* not at all (3 *vs.* 1)	0.0114	1.864	1.151–3.020
Very much *vs.* not at all (4 *vs.* 1)	0.9873	0.995	0.508–1.948
Fatigue	0.6881		
A little bit *vs.* not at all (2 *vs.* 1)	0.9321	0.986	0.714–1.362
Quite a bit *vs.* not at all (3 *vs.* 1)	0.4141	1.154	0.819–1.626
Very much *vs.* not at all (4 *vs.* 1)	0.4606	1.169	0.773–1.768
Pain	0.7496		
A little bit *vs.* not at all (2 *vs.* 1)	0.6282	1.112	0.724–1.708
Quite a bit *vs.* not at all (3 *vs.* 1)	0.9956	0.999	0.628–1.587
Very much *vs.* not at all (4 *vs.* 1)	0.3064	1.385	0.742–2.586
Anxious	0.5481		
A little bit *vs.* not at all (2 *vs.* 1)	0.4723	0.846	0.536–1.335
Quite a bit *vs.* not at all (3 *vs.* 1)	0.3754	1.223	0.784–1.907
Very much *vs.* not at all (4 *vs.* 1)	0.7514	1.108	0.587–2.091

Table 3 (*continued*)

Table 3 (*continued*)

Symptom category	P value	HR	95% CI of HR
Appetite loss	0.2940		
A little bit *vs.* not at all (2 *vs.* 1)	0.6928	1.121	0.635–1.980
Quite a bit *vs.* not at all (3 *vs.* 1)	0.1740	1.484	0.840–2.623
Very much *vs.* not at all (4 *vs.* 1)	0.1263	1.675	0.865–3.245
Depression	0.0795		
A little bit *vs.* not at all (2 *vs.* 1)	0.0315	1.554	1.040–2.323
Quite a bit *vs.* not at all (3 *vs.* 1)	0.9780	1.008	0.559–1.818
Very much *vs.* not at all (4 *vs.* 1)	0.0725	1.742	0.951–3.194
Vision problem	0.6805		
A little bit *vs.* not at all (2 *vs.* 1)	0.6667	0.916	0.614–1.366
Quite a bit *vs.* not at all (3 *vs.* 1)	0.2878	1.381	0.762–2.504
Very much *vs.* not at all (4 *vs.* 1)	0.8040	1.101	0.514–2.362
Weakness	0.3424		
A little bit *vs.* not at all (2 *vs.* 1)	0.5958	1.085	0.802–1.470
Quite a bit *vs.* not at all (3 *vs.* 1)	0.9334	1.014	0.725–1.419
Very much *vs.* not at all (4 *vs.* 1)	0.0751	1.465	0.962–2.230
Coordination problem	0.0108		
A little bit *vs.* not at all (2 *vs.* 1)	0.5603	0.817	0.414–1.613
Quite a bit *vs.* not at all (3 *vs.* 1)	0.2601	1.667	0.685–4.054
Very much *vs.* not at all (4 *vs.* 1)	0.0023	5.704	1.862–17.470
Headache	0.2341		
A little bit *vs.* not at all (2 *vs.* 1)	0.9738	1.006	0.715–1.416
Quite a bit *vs.* not at all (3 *vs.* 1)	0.9176	0.975	0.604–1.575
Very much *vs.* not at all (4 *vs.* 1)	0.0474	1.702	1.006–2.880
Sleeping problem	0.1670		
A little bit *vs.* not at all (2 *vs.* 1)	0.0635	0.661	0.427–1.023
Quite a bit *vs.* not at all (3 *vs.* 1)	0.5333	1.162	0.724–1.864
Very much *vs.* not at all (4 *vs.* 1)	0.9342	0.976	0.542–1.756
Concentration problem	0.0007		
A little bit *vs.* not at all (2 *vs.* 1)	0.3954	1.161	0.822–1.640
Quite a bit *vs.* not at all (3 *vs.* 1)	0.4526	1.170	0.777–1.760
Very much *vs.* not at all (4 *vs.* 1)	<0.0001	8.507	3.041–23.798

Table 3 (*continued*)

Table 3 (*continued*)

Symptom category	P value	HR	95% CI of HR
Balance problem	0.0066		
A little bit *vs.* not at all (2 *vs.* 1)	0.1938	1.334	0.864–2.059
Quite a bit *vs.* not at all (3 *vs.* 1)	0.0039	2.102	1.269–3.481
Very much *vs.* not at all (4 *vs.* 1)	0.0067	2.354	1.268–4.371
Memory problem	0.2761		
A little bit *vs.* not at all (2 *vs.* 1)	0.1295	1.287	0.929–1.784
Quite a bit *vs.* not at all (3 *vs.* 1)	0.1291	1.448	0.898–2.335
Very much *vs.* not at all (4 *vs.* 1)	0.9410	0.958	0.304–3.019

OS, overall survival; HR, hazard ratio; CI, confidence interval.

with WBRT (84%) (16). Survival differed depending on prescribed treatment, with corticosteroids alone having the lowest median survival (1.3 months). Other prognostic factors were identified, which included PS, corticosteroid response, systemic tumor activity, and serum lactate dehydrogenase levels. Lesser prognostic factors included age, primary tumour site, and number of BM. Lagerwaard *et al.* also found variable prognostic factors between primary cancer sites (16). For instance in lung cancer patients, sex had a significant impact on survival and for breast cancer patient length of the period between primary tumour occurrence and development of BM were of prognostic significance. Future studies should be conducted to address the lack of consistency in the literature to determine what symptoms are of prognostic significance.

In addition to symptoms caused by the disease itself, WBRT is associated with certain side effects that may also contribute to QOL debilitations, such as increased fatigue. One study found that patients experienced no difference in fatigue following WBRT if prescribed dexamethasone (2). As fatigue is associated with worsened QOL, it is imperative to monitor and address such debilitating symptoms to prevent further functional declines. In patients presenting with multiple lesions and poor PS, adequate symptom control can be managed through corticosteroid prescription alone without added side effects from WBRT, which may be more appropriate in palliative circumstances (7). For patients where benefits from WBRT and other radiotherapy techniques are indicated, concurrent corticosteroid prescription should be considered to manage side effects of radiation, such as fatigue to prevent functional debilitations and preserve QOL at the end of life.

Recently, Jones *et al.* provided commentary on the interim results of the Quality of Life after Treatment for Brain Metastases (QUARTZ) study (17). The non-inferiority study aimed to elucidate the impact of WBRT on OS and QOL between individuals who received dexamethasone and optimal supportive care with or without WBRT. The interim results of the study showed no differences between the two groups in regards to survival, average QOL, and symptom scores. Interestingly, the QUARTZ cohort had shorter survival than previous studies had observed which highlights the appropriateness of WBRT in certain circumstances. As previously set forth by Tsao *et al.*, patients with poor prognosis with single or multiple fractions can be managed solely by palliative care with optional WBRT (8). The utility of WBRT is particularly important in certain circumstances when the intent of treatment is improved brain control, multiple brain metastases are present, or the chance of brain recurrence in other areas is high (8).

Treatment for brain metastases may not be curative in nature, but survival estimates are essential in providing the patient with information regarding their condition allowing them to prepare for end of life circumstances. Utilizing both presenting symptoms and symptom changes can allow accurate survival predictions to be made. Such predictions can inform proper treatment prescription, ensure that appropriate care goals are formed by the patient and physician, and allow patients to deal with end-of-life matters. Updating prognosis information throughout the treatment process is additionally important so that treatment and goals of care can be adapted accordingly. Furthermore, symptoms and symptom changes associated with poorer

Table 4 Univariate Cox proportional hazard model of OS on symptom changes at month 1, 2, or 3, respectively

Symptom changes	Month 1			Month 2			Month 3		
	P value	HR	95% CI of HR	P value	HR	95% CI of HR	P value	HR	95% CI of HR
Nausea	0.3790			0.6212			0.0160		
Decrease *vs.* no change	0.2073	1.307	0.862–1.983	0.6165	0.855	0.462–1.581	0.5044	1.285	0.615–2.683
Increase *vs.* no change	0.7763	0.949	0.662–1.361	0.3443	0.801	0.506–1.268	0.0088	0.402	0.203–0.795
Fatigue	0.2757			0.0383			0.2259		
Decrease *vs.* no change	0.3905	0.820	0.521–1.290	0.1857	0.651	0.345–1.229	0.6117	0.827	0.398–1.720
Increase *vs.* no change	0.4192	1.156	0.814–1.642	0.2863	1.340	0.783–2.294	0.3113	1.431	0.715–2.865
Pain	0.4310			0.9915			0.4055		
Decrease *vs.* no change	0.8002	1.070	0.633–1.809	0.9376	0.960	0.350–2.639	0.2532	0.532	0.180–1.572
Increase *vs.* no change	0.2012	1.368	0.846–2.210	0.9508	1.026	0.456–2.307	0.7759	1.165	0.407–3.339
Anxious	0.5454			0.1772			0.3577		
Decrease *vs.* no change	0.2709	0.766	0.477–1.231	0.6100	0.796	0.332–1.910	0.1555	0.450	0.150–1.354
Increase *vs.* no change	0.6798	0.884	0.492–1.588	0.1893	2.064	0.700–6.092	0.4278	0.513	0.098–2.671
Appetite loss	0.0381			0.2928			0.0370		
Decrease *vs.* no change	0.8290	0.930	0.482–1.796	0.2892	2.388	0.477–11.945	0.0333	5.236	1.140–24.049
Increase *vs.* no change	0.0258	1.738	1.069–2.825	0.5112	0.746	0.311–1.790	0.4481	0.693	0.268–1.789
Depression	0.4894			0.7354			0.7120		
Decrease *vs.* no change	0.3264	0.787	0.489–1.269	0.8380	1.099	0.443–2.727	0.4185	1.504	0.559–4.045
Increase *vs.* no change	0.3253	0.760	0.441–1.312	0.5408	0.761	0.317–1.825	0.9134	1.091	0.228–5.206
Vision problem	0.3587			0.9428			0.8367		
Decrease *vs.* no change	0.2935	1.301	0.796–2.124	0.7915	1.094	0.562–2.131	0.5509	0.771	0.328–1.813
Increase *vs.* no change	0.4387	0.823	0.503–1.348	0.8591	0.926	0.394–2.173	0.9139	0.950	0.373–2.418

Table 4 (*continued*)

Table 4 (*continued*)

Symptom changes	Month 1			Month 2			Month 3		
	P value	HR	95% CI of HR	P value	HR	95% CI of HR	P value	HR	95% CI of HR
Decrease *vs.* no change	0.1784	1.315	0.882–1.961	0.2718	0.729	0.414–1.281	0.1168	0.547	0.257–1.163
Increase *vs.* no change	0.0434	1.452	1.011–2.084	0.1241	1.482	0.898–2.446	0.5179	0.812	0.431–1.528
Coordination problem	0.1966			NA			NA		
Decrease *vs.* no change	0.2640	1.591	0.704–3.595	NA			NA		
Increase *vs.* no change	0.0920	2.439	0.864–6.883	NA			NA		
Headache	0.0050			0.0919			0.8835		
Decrease *vs.* no change	0.0032	1.864	1.232–2.820	0.2234	1.404	0.813–2.423	0.9154	1.039	0.514–2.101
Increase *vs.* no change	0.6341	0.892	0.558–1.427	0.1714	0.608	0.298–1.240	0.6648	0.816	0.324–2.051
Sleeping problem	0.5218			0.6044			0.0877		
Decrease *vs.* no change	0.7354	1.092	0.656–1.816	0.3344	1.681	0.585–4.827	0.4188	0.599	0.172–2.077
Increase *vs.* no change	0.2548	1.494	0.749–2.980	0.4879	1.484	0.486–4.532	0.0782	3.873	0.858–17.480
Concentration problem	<0.0001			0.0787			0.0320		
Decrease *vs.* no change	0.0172	1.654	1.093–2.504	0.0250	1.992	1.091–3.640	0.8158	0.911	0.414–2.003
Increase *vs.* no change	<0.0001	4.314	2.551–7.295	0.5296	1.231	0.644–2.351	0.0167	2.716	1.198–6.154
Balance problem	0.0196			0.3735			0.6673		
Decrease *vs.* no change	0.1818	1.403	0.853–2.308	0.3600	1.294	0.745–2.245	0.5436	1.259	0.599–2.647
Increase *vs.* no change	0.0059	2.209	1.256–3.883	0.4323	0.731	0.334–1.599	0.6984	0.842	0.352–2.012
Memory problem	0.3588			0.0757			0.3890		
Decrease *vs.* no change	0.1524	1.383	0.887–2.156	0.3792	1.316	0.714–2.424	0.3434	1.608	0.602–4.299
Increase *vs.* no change	0.7791	1.068	0.675–1.689	0.0581	0.492	0.236–1.025	0.4124	0.702	0.301–1.636

OS, overall survival; HR, hazard ratio; CI, confidence interval.

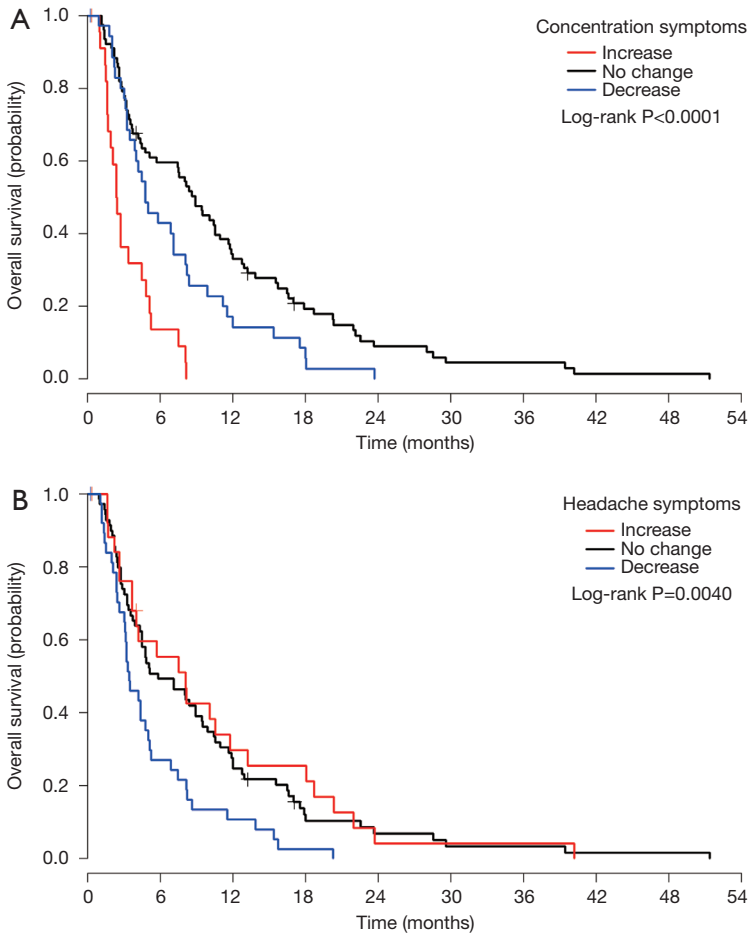

Figure 2 Kaplan-Meier OS curve. (A) In patients based on symptom change of concentration difficulty in month 1. Concentration difficulty: actuarial median OS time was 8.9 months (95% CI: 5.2–10.9) in patients with no change, 2.4 (1.6–4.5) in increase, and 4.8 (3.5–7.1) in decrease; (B) in patients based on symptom change of headache in month 1. Headache: actuarial median OS time was 5.8 months (95% CI: 4.3–9.5) in patients with no change, 8.1 (3.6–11.8) in increase, and 3.4 (3.0–5.0) in decrease. OS, overall survival; CI, confidence interval.

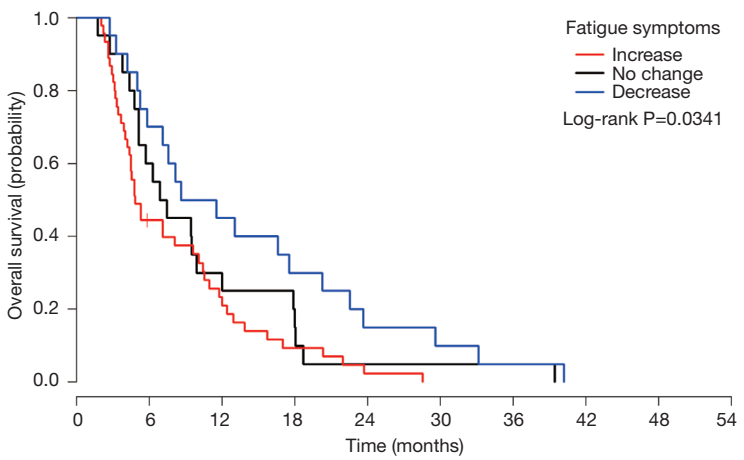

Figure 3 Kaplan-Meier OS curve in patients based on symptom change of fatigue in month 2. Fatigue: actuarial median OS time was 7.2 months (95% CI: 4.8–12.0) in patients with no change, 4.8 (4.2–9.6) in increase, and 10.0 (5.2–20.3) in decrease. OS, overall survival; CI, confidence interval.

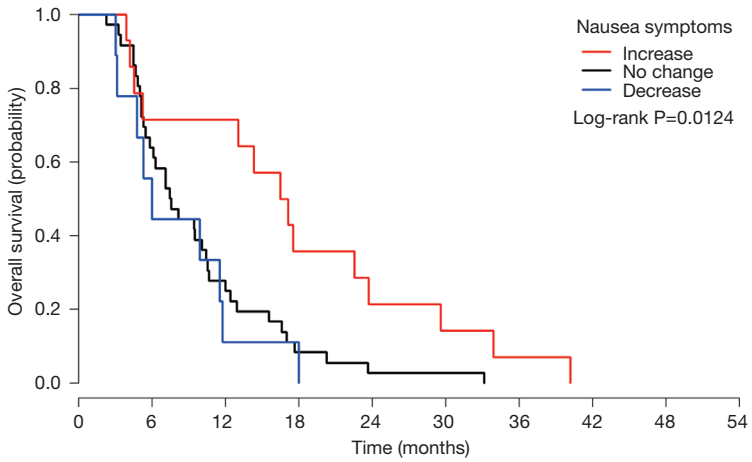

Figure 4 Kaplan-Meier OS curve in patients based on symptom change of nausea in month 3. Nausea: actuarial median OS time was 7.5 months (95% CI: 5.5–10.4) in patients with no change, 16.8 (4.6–23.7) in increase, and 6.0 (3.0–11.8) in decrease. OS, overall survival; CI, confidence interval.

survival may act as a powerful indicator for the involvement of palliative care. Palliative care should be incorporated into a patient's care plan, if not at initial diagnosis, then at least at the first presentation of symptoms that are correlated with poorer survival. However, it remains a challenge for healthcare professionals to provide accurate predictions to their patients; therefore, it is necessary to determine what symptoms should be assessed and monitored to help form accurate prognosis estimates. The current literature on this topic is limited and inconsistent, and future studies should be conducted on the prognostic significance of symptoms experienced by the patients themselves.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by our institutions Research Ethics Board and written informed consent was obtained from all patients.

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Supplementary

Table S1 Patient demographic of group 1 for baseline symptoms

Demographics	Baseline symptom group 1	Baseline symptom group 2	Symptom change
Age (years)			
n	1,391	269	201
Mean ± SD	67.9±12.2	63.3±11.2	63.3±11.3
Median [range]	69 [21–95]	64 [22–88]	64 [22–88]
KPS			
n	1,360	267	200
Mean ± SD	61.6±15.8	71.3±16.2	72.5±15.8
Median [range]	60 [10–100]	70 [30–100]	70 [30–100]
Gender (n, %)			
Male	743 (53.41)	186 (69.14)	136 (67.66)
Female	648 (46.59)	83 (30.86)	65 (32.34)
Primary cancer site (n, %)			
Breast	284 (20.42)	66 (24.54)	46 (22.89)
Gastrointestinal	115 (8.27)	13 (4.83)	6 (2.99)
Genitourinary	365 (26.24)	14 (5.20)	11 (5.47)
Lung	500 (35.95)	146 (54.28)	116 (57.71)
Other	60 (4.31)	22 (8.18)	14 (6.97)
Unknown	67 (4.82)	8 (2.97)	8 (3.98)
Vital status (n, %)			
Alive	466 (33.50)	10 (3.72)	8 (3.98)
Dead	925 (66.50)	259 (96.28)	193 (96.02)

Table S2 Survival probabilities for patients in group 1

Time	All patients survival probability (95% CI)
1 month	89.5% (87.8–91.3)
2 months	77.2% (74.8–79.6)
3 months	66.8% (64.1–69.6)
4 months	59.9% (57.1–62.9)
5 months	52.5% (49.6–55.5)
6 months	49.5% (46.6–52.5)
12 months (1 year)	31.8% (29.1–34.8)
24 months (2 years)	16.3% (13.9–19.0)
60 months (5 years)	3.7% (2.4–5.9)

CI, confidence interval.

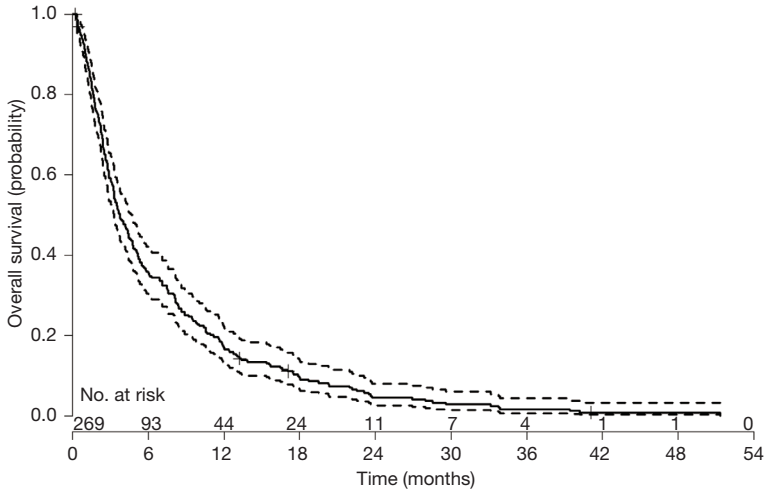

Figure S1 Kaplan-Meier OS curve with 95% CI for group 2 patients. OS, overall survival.

Table S3 Survival probabilities in group 2 patients

Time	All patients survival probability (95% CI)
1 month	90.6% (87.1–94.2)
2 months	75.0% (70.0–80.4)
3 months	59.1% (53.5–65.4)
4 months	48.5% (42.8–54.9)
5 months	41.2% (35.7–47.6)
6 months	35.9% (30.5–42.2)
12 months (1 year)	17.0% (13.0–22.2)
24 months (2 years)	4.5% (2.6–8.0)
36 months (3 years)	1.6% (0.6–4.3)

CI, confidence interval.

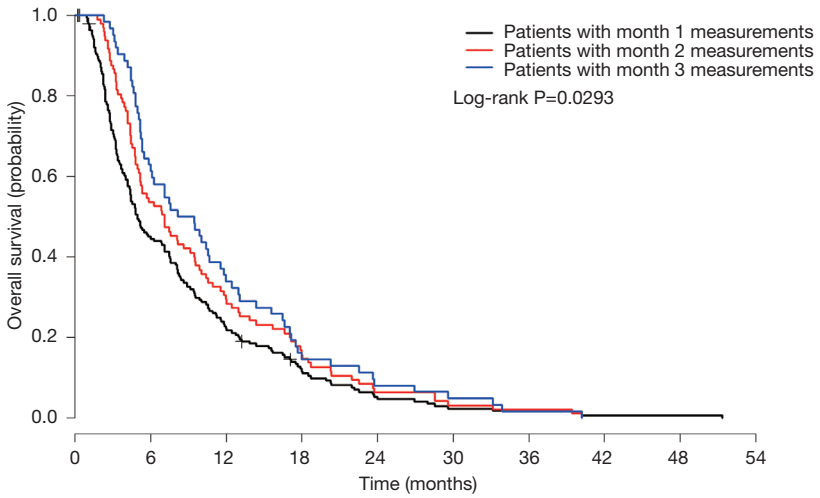

Figure S2 Kaplan-Meier OS curve for all patients included in symptom change analysis. OS, overall survival.

Table S4 Multivariate Cox proportional hazard model of OS on symptom change

Symptom	P value	HR	95% CI of HR
Month 1: concentration problem	<0.0001		
Decrease *vs.* no change	0.1017	1.487	0.925–2.392
Increase *vs.* no change	<0.0001	4.739	2.714–8.274
Increase *vs.* decrease	0.0001	3.187	1.752–5.796
Month 1: headache	0.0183		
Decrease *vs.* no change	0.0062	1.845	1.190–2.860
Increase *vs.* no change	0.9068	1.030	0.632–1.678
Decrease *vs.* increase	0.0389	1.792	1.030–3.117
Month 2: fatigue	0.0383		
Decrease *vs.* no change	0.1857	0.651	0.345–1.229
Increase *vs.* no change	0.2863	1.340	0.783–2.294
Increase *vs.* decrease	0.0110	2.058	1.180–3.591
Month 3: nausea	0.0160		
Decrease *vs.* no change	0.5044	1.285	0.615–2.683
Increase *vs.* no change	0.0088	0.402	0.203–0.795
Decrease *vs.* increase	0.0118	3.195	1.294–7.889

OS, overall survival; HR, hazard ratio; CI, confidence interval.