Support Care Cancer (2016) 24:4747–4759
DOI 10.1007/s00520-016-3326-8

ORIGINAL ARTICLE

Symptoms and quality of life in patients with brain metastases receiving whole-brain radiation therapy

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Received: 29 January 2016 / Accepted: 20 June 2016 / Published online: 29 June 2016

Abstract
Purpose Patients with multiple brain metastases may be treated with whole-brain radiation therapy (WBRT). For these patients, symptom palliation and improvement of quality of life (QOL) and performance status is of the upmost importance. The objective of the present study was to determine the symptom experience and overall QOL in patients with brain metastases before and after WBRT.
Methods A total of 14 symptom scores and overall QOL were collected prospectively in 217 patients for up to 3 months. Wilcoxon signed rank test was applied to determine significant symptoms and QOL changes. Spearman's correlations were applied to determine the relationship between symptom scores and QOL.
Results Appetite loss, weakness, and nausea significantly increased from baseline, while balance, headache, and anxiety significantly decreased from baseline. At baseline, all symptoms other than coordination were significantly correlated with QOL. At 1-month follow-up (FU), changes in concentration, weakness, coordination, and balance were significantly associated with QOL changes. At 2-month FU, changes in pain, insomnia, concentration, balance, and depression were significantly associated with QOL changes. At 3-month FU, only change in nausea was significantly associated with QOL changes.
Conclusions Following WBRT, certain symptoms may influence overall QOL to a greater extent than others, which may fluctuate with time.

Keywords Brain metastases · Symptoms · Quality of life · Whole-brain radiotherapy

Introduction

Approximately 20–40 % of patients develop brain metastases [1, 2]. With large strides in improving treatment for cancer, increasing survival, incidence of brain metastases is expected to increase [2]. This is mediated by the blood brain barrier, which prevents treatment options from entering the brain and treating brain metastases [3]. Due to limited utility of systemic therapies, brain metastases may be treated with whole-brain radiation therapy (WBRT) and dexamethasone [4]. In patients with solitary or fewer brain metastases, surgical resection and stereotactic radiation are treatment options [5].

Brain metastases are associated with a range of symptoms, such as altered mental status, imbalance, and visual impairments with headaches, fatigue, and focal weakness being the most prevalent symptoms [4, 6–8]. Such symptoms can lead to psychological, emotional, social, and physical debilitations that can negatively affect quality of life (QOL) [9–11]. Symptom assessment tools, inclusive of the Edmonton Symptom Assessment Scale, are tools that can be easily implemented into routine practice to provide attending health care professionals (HCPs) with a more

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comprehensive picture of the patient's current symptom burden. Once symptoms are identified through symptom screens, it can provide a platform for discussion between the patient and HCPs to ensure that treatment is aimed at palliating the patient's symptoms. QOL is an important indicator in patients with brain metastases, as those treated with WBRT have limited median survival, typically ranging from 3 to 6 months [12]. To assess QOL, self-administered questionnaires are typically used, such as the Functional Assessment of Cancer Therapy–Brain (FACT-Br) or European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Brain Module (EORTC QLQ-BN20 or BN20 + 2) [10].

As survival is generally limited in patients with brain metastases treated with WBRT, the objective of treatment is symptom palliation and the improvement and/or maintenance of QOL. However, few studies have focused on evaluating these two particular aspects of patients treated with WBRT [13]. Therefore, the objectives of the present study were to determine what symptoms were particularly distressing to patients treated with WBRT and to assess overall QOL before and after WBRT delivery.

Methods

A retrospective analysis of prospectively collected database from 2005 to 2012 was conducted. Patients included had brain metastases with radiographic evidence from CT or MRI. Patients were prescribed with varying dosages of dexamethasone and WBRT.

Data collection

Baseline demographic information was collected from all patients including age, Karnofsky Performance Status (KPS), gender, primary cancer site, number of brain metastases, systemic treatment, and whether the patient was receiving dexamethasone. Fourteen symptom scores and QOL were obtained from multiple QOL and symptom questionnaire. Six questionnaires were used.

Questionnaires

Edmonton Symptom Assessment Scale

The Edmonton Symptom Assessment Scale (ESAS) is a validated nine-item symptom questionnaire from 0 (no experience of the symptom) to 10 (worse possible degree of the symptom). The following five symptoms were evaluated: nausea, pain anxiety, appetite loss, and depression. The well-being item was used as an overall QOL surrogate with 0 being excellent and 10 being very poor QOL.

Spitzer Quality of Life Index

The Spitzer Quality of Life Index (SQLI) is composed of daily living, health, activity, support, and outlook domain. The health item was scored as 0 (worst) and 2 (best) and was used as a surrogate for overall QOL. A symptom questionnaire was used to record symptom scores on a scale of 1 to 4, with 1 = none, 2 = mild, 3 = moderate, and 4 = severe. The following seven symptoms were evaluated: nausea, concentration, memory loss, vision problem, weakness, balance, and headache. To maintain consistency with other QOL scales, the SQLI health item was rescored into 1, 4, and 7 with the higher score representing better overall QOL.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30 (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. The overall QOL item is recorded on a scale of 1 to 7, with 1 meaning very poor QOL and 7 meaning excellent QOL. The following nine symptoms were assessed: nausea, pain, 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

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Core 15 palliative (EORTC QLQ-C15PAL) is a 15-item shortened QOL assessment for palliative patients. The following six symptoms were assessed using the C15PAL: nausea, pain, insomnia, anxiety, appetite, weakness, and depression. This questionnaire assesses symptoms on a scale of 1 to 4, similar to the C30. The overall QOL item on the C15PAL is recorded on a scale of 1 to 7, with 1 meaning very poor and 7 meaning excellent QOL. Patients who completed the C15PAL also completed the BN20 + 2. Both questionnaires included the weakness item, as such records from the C15PAL were used if available. If not, the BN20 + 2 weakness item was used.

EORTC QLQ-BN20 or BN20 + 2

The BN20 is a 20-item accompanying tool to the C30, while the BN20 + 2 is a 22-item in-development tool to accompany the C15PAL. Both questionnaires assess symptoms on a scale from 1 to 4, similar to the C30 or C15PAL. QOL assessment was taken from the C30 and C15PAL, respectively. The following three symptoms were assessed by both the BN20 and BN20 + 2: vision problem, coordination, and headaches, while the BN20 + 2 assessed the following additional two symptoms: concentration and memory loss.

FACT-Br

The FACT-Br assesses QOL in five domains. It is rated on a scale from 0 to 4, with 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much. The following 11 symptoms were assessed: nausea, pain, vision problem, weakness, coordination, headache, anxiety, depression, insomnia, concentration, and memory loss. Insomnia, concentration, and memory loss were reversed due to the wording of the question. The overall QOL score was rescored from 0 to 4 into 1, 2.5, 4, 5.5, and 7 to maintain consistency with other questionnaires.

Statistical analysis

Questionnaires were grouped for analysis by the different rating scale (0–10 or 1–4) in two groups. Group 1 included all symptoms collected on a 0 to 10 scale; this encompassed all patients who completed the ESAS. Group 2 included all symptoms collected on a scale 1 to 4; this encompassed the Spitzer, EORTC QLQ-C15PAL, QLQ-BN20, QLQ-BN20 + 2, QLQ-C30, and FACT-Br. The symptom scores from the FACT-Br were reweighted by combining the scores of 2 (somewhat) and 3 (quite a bit).

The Wilcoxon signed test was conducted at each follow-up to see whether there was a significant score change from baseline. To compare between patients with and without dexamethasone, the Wilcoxon rank-sum test was conducted at first-month follow-up. The Spearman's correlation (r) was used to examine the correlations between symptoms and overall QOL or between symptoms and baseline KPS, respectively. To search for significant relationship between symptom scores and overall QOL, general linear regression analysis was conducted at baseline and follow-ups at months 1, 2, and 3, respectively. Natural logarithm transformation was applied for symptom score and overall QOL at each visit to normalize the distribution. The similar analysis was also performed to search for significant relationship between symptoms and KPS at baseline. Coefficient, standard error (SE) of coefficient, and mean square error (MSE) were estimated for the independent variable (i.e., overall QOL or KPS).

The general linear mixed model (GLMM), or hierarchical linear model, was used to determine whether there was symptom change over time, to determine whether there was significant association with overall QOL over time, or to determine whether there was significant association with baseline KPS. All analyses were conducted using Statistical Analysis Software (SAS Institute, Cary, NC; version 9.3). The MIXED procedure in SAS was used to conduct the GLMM analyses. P value <0.05 was considered statistically significant.

Results

Of the patients receiving WBRT and completed symptoms and QOL questionnaires, 217 were included in this analysis. Group 1 consisted of 22 patients with at least one follow-up (Appendix Table 7). The mean age was 65 years; 45 % of patients were male; and the median KPS was 70, ranging from 40 to 90. The most common primary cancer sites were lung (64 %) and breast (23 %). At baseline, the most problematic symptom was anxiety (mean 3.8; median 5.0). Using Wilcoxon signed rank test, significant appetite loss was found at month 2 compared to baseline (p = 0.004). The median and mean appetite loss scores were 3.0 and 2.7 at baseline and 7.5 and 6.3 at month 2, respectively.

Pain was significantly correlated with overall QOL at baseline (r = −0.55; p = 0.01) (Appendix Table 8). No other significant correlation was found for other symptoms with overall QOL or for symptoms with baseline KPS. At month 1 (Appendix Table 9), depression was significantly correlated to overall QOL (r = −0.57; p = 0.01). Anxiety (r = 0.56; p = 0.02) and depression (r = 0.52; p = 0.03) change scores were also correlated with baseline KPS. At month 2, nausea (r = −0.67; p = 0.03), anxiety (r = −0.75; p = 0.01), and depression (r = −0.89; p = 0.0006) were significantly correlated with overall QOL. Appetite loss (r = −0.74; p = 0.02) change score was also correlated with baseline KPS. At month 3, anxiety (r = −0.82; p = 0.03) was correlated with overall QOL, and nausea change score (r = −0.82; p = 0.02) was correlated with overall QOL changes.

There was significant association between overall QOL and pain (p = 0.008) and appetite loss

Table 1 At baseline and each follow-up month, relationship between symptoms and overall QOL or between symptoms and baseline KPS using linear regression analysis for group 1

Symptom QOL item (0–10)	Overall QOL			Baseline KPS		
	Coefficient (SE)	*p* value	MSE	Coefficient (SE)	*p* value	MSE
At baseline						
Nausea	−0.425 (0.446)	0.3533	0.326	0.021 (0.009)	0.0345*	0.260
Pain	−1.725 (0.585)	0.0082*	0.560	0.004 (0.017)	0.8307	0.811
Anxiety	−0.139 (0.624)	0.8260	0.638	−0.016 (0.017)	0.3551	0.611
Appetite loss	−1.105 (0.492)	0.0370*	0.397	0.013 (0.015)	0.3984	0.483
Depression	−0.647 (0.705)	0.3702	0.814	−0.024 (0.019)	0.2141	0.782
At month 1						
Nausea	−0.175 (0.287)	0.5490	0.733	−0.011 (0.018)	0.5613	0.733
Pain	−0.590 (0.312)	0.0760	0.867	−0.016 (0.021)	0.4540	1.014
Anxiety	−0.025 (0.338)	0.9416	1.017	0.034 (0.020)	0.1035	0.867
Appetite loss	−0.555 (0.314)	0.0967	0.871	0.008 (0.021)	0.7178	1.032
Depression	−0.535 (0.263)	0.0581	0.616	0.012 (0.018)	0.5116	0.746
At month 2						
Nausea	−1.282 (0.625)	0.0744	0.720	0.013 (0.030)	0.6642	1.071
Pain	0.009 (0.689)	0.9899	0.874	0.013 (0.026)	0.6267	0.847
Anxiety	−1.135 (0.433)	0.0306*	0.345	0.033 (0.020)	0.1320	0.474
Appetite loss	−0.652 (0.484)	0.2146	0.431	0.036 (0.017)	0.0640	0.336
Depression	−1.527 (0.401)	0.0052*	0.296	0.043 (0.021)	0.0766	0.550
At month 3						
Nausea	−1.280 (0.562)	0.0719	0.784	0.043 (0.036)	0.2810	1.235
Pain	−0.724 (0.679)	0.3347	1.141	−0.030 (0.036)	0.4384	1.228
Anxiety	−1.302 (0.278)	0.0054*	0.191	0.003 (0.033)	0.9215	1.029
Appetite loss	−0.395 (0.461)	0.4301	0.527	−0.004 (0.025)	0.8839	0.601
Depression	−1.241 (0.434)	0.0355*	0.467	0.025 (0.034)	0.5002	1.113

SE standard error, *MSE* mean square error

**P* value <0.05 was considered statistically significant

(p = 0.04) at baseline (Table 1). Patients with more pain or appetite loss were more likely to have worse overall QOL. At month 2 or month 3, a significant association was found between anxiety (month 2 p = 0.03, month 3 p = 0.005) and depression (month 2 p = 0.005, month 3 p = 0.04) with overall QOL. Patients with greater symptom experiences were more likely to have worse overall QOL. At baseline, there was only significant association between nausea and baseline KPS (p = 0.03).

Nausea, pain, and depression were significantly increasing over time from baseline to month 3, indicating that patients experienced more symptoms over time (Table 2). Negative coefficient of time-varying covariate (time × overall QOL) indicates that patients with more symptoms (higher score) were more likely to have worsen (lower score) overall QOL over time. Anxiety was not significantly changing over time; however, it was significant negatively related to overall QOL (p = 0.02). Patients with more anxiety were more likely to have worse overall QOL over time. Appetite loss was significantly increasing over time (p = 0.02) but no relationship with overall QOL. For the association with baseline KPS, nausea and appetite loss were significantly increasing over time (p = 0.02).

Group 2 consisted of 195 patients with at least one follow-up (Appendix Table 10). The mean age was 63 years with a median KPS 80, ranging from 30 to 100. There were 135 males (69 %), and the most common primary cancer sites were lung (56 %), breast (24 %), and renal cell (5 %). Most patients had two to three brain metastases (45 %) and had not been on systemic therapy (77 %), hormone therapy (78 %), or chemotherapy (50 %). Eighty percent of patients were taking dexamethasone at baseline with an average of 9.7 mg, ranging from 0.5 to 24 mg.

At baseline, insomnia (mean 2.1) and anxiety (mean 2.0) were most severe for patients. For patients not taking dexamethasone, pain and anxiety (mean 2.6 for both) were most severe, while for patients taking dexamethasone, insomnia and anxiety (mean 2.0 for both) were most problematic. At month 1, appetite loss and weakness (mean 2.1 for both) were most problematic for all patients. For patients not taking dexamethasone

Table 2 Time trend of each symptom with time-varying covariate of overall QOL or baseline KPS for group 1 using general linear mixed model

Symptom	Overall QOL			Baseline KPS		
	Independent variable	Coefficient (SE)	*p* value	Independent variable	Coefficient (SE)	*p* value
Nausea	Intercept	0.261 (0.154)	0.1046	Intercept	−0.713 (0.843)	0.4073
	Time	0.604 (0.205)	0.0058*	Time	0.178 (0.074)	0.0211*
	Time × overall QOL	−0.228 (0.103)	0.0331*	KPS	0.015 (0.012)	0.2473
Pain	Intercept	0.860 (0.182)	0.0001	Intercept	1.266 (0.921)	0.1845
	Time	0.643 (0.279)	0.0275*	Time	0.087 (0.106)	0.4160
	Time × overall QOL	−0.302 (0.139)	0.0372*	KPS	−0.006 (0.014)	0.6398
Anxiety	Intercept	1.262 (0.163)	<0.0001	Intercept	0.337 (0.821)	0.6858
	Time	0.439 (0.264)	0.1049	Time	−0.157 (0.105)	0.1444
	Time × overall QOL	−0.327 (0.131)	0.0175*	KPS	0.014 (0.012)	0.2594
Appetite loss	Intercept	0.992 (0.157)	<0.0001	Intercept	0.158 (0.760)	0.8371
	Time	0.628 (0.264)	0.0236*	Time	0.253 (0.103)	0.0199*
	Time × overall QOL	−0.208 (0.130)	0.1195	KPS	0.012 (0.011)	0.2730
Depression	Intercept	0.822 (0.156)	<0.0001	Intercept	0.301 (0.879)	0.7361
	Time	0.813 (0.258)	0.0034*	Time	0.027 (0.104)	0.7981
	Time × overall QOL	−0.427 (0.128)	0.0021*	KPS	0.008 (0.013)	0.5563

SE standard error

**P* value <0.05 was considered statistically significant

at month 1, depression and pain (mean 2.7 and 3.0) were most severe. For patients taking dexamethasone at month 1, weakness and appetite loss were most severe (mean 2.1 and 2.3). At month 2, pain, weakness, and appetite loss were most severe (mean 2.1, 2.1, and 2.6) in all patients; for patients not taking dexamethasone, appetite loss and insomnia were the most problematic (mean 2.7 and 2.3), while for patients taking

Table 3 At each follow-up month, symptom changes from baseline using Wilcoxon signed rank test for group 2

QOL	Wilcoxon signed rank test comparing follow-up with baseline score		
	Month 1	Month 2	Month 3
Nausea	0.5324	0.0449*	0.2497
Pain	0.2272	0.2612	0.2813
Insomnia	0.1309	0.9009	0.8516
Concentration	0.3033	0.3044	0.5853
Memory loss	0.6375	0.2538	0.8328
Vision problem	0.7122	0.5069	0.4790
Weakness	0.0476*	0.0885	0.1206
Coordination	0.7622	0.9999	0.9999
Balance	0.1667	0.0046*	0.5221
Headache	0.1116	0.0051*	0.2308
Anxious	0.1818	0.0172*	0.0117*
Appetite loss	0.0001*	0.0024*	0.0703
Depression	0.2262	0.4316	0.1563
Overall QOL	<0.0001*	0.0062*	0.0251*

**P* value <0.05 was considered statistically significant

Table 4 Spearman's correlation (r) between symptom and overall QOL or baseline KPS and between symptom change and overall QOL change or baseline KPS at each follow-up month for group 2

At follow-up	Correlation between symptom and overall QOL (r and p value)	Correlation between symptom and baseline KPS (r and p value)	Correlation between symptom change score and overall QOL change score (r and p value)	Correlation between symptom change score and baseline KPS score (r and p value)
At month 1				
Nausea	−0.24376 (0.0008*)	−0.02299 (0.7555)	−0.11416 (0.1228)	0.12055 (0.1031)
Pain	−0.17232 (0.0932)	−0.25828 (0.0111*)	−0.13543 (0.1883)	−0.08588 (0.4054)
Insomnia	−0.26251 (0.0102*)	−0.07880 (0.4503)	−0.06916 (0.5054)	0.01612 (0.8774)
Concentration	−0.30703 (0.0001*)	−0.20875 (0.0096*)	−0.17324 (0.0322*)	−0.06726 (0.4104)
Memory loss	−0.20517 (0.0102*)	−0.21684 (0.0067*)	−0.09692 (0.2303)	−0.01636 (0.8404)
Vision problem	−0.17380 (0.0446*)	−0.08727 (0.3179)	−0.09476 (0.2780)	−0.02375 (0.7869)
Weakness	−0.36945 (<0.0001*)	−0.14070 (0.0568)	−0.25159 (0.0006*)	0.12721 (0.0853)
Coordination	−0.09544 (0.5377)	−0.19025 (0.2217)	−0.36742 (0.0141*)	−0.17851 (0.2521)
Balance	−0.47686 (<0.0001*)	−0.22098 (0.0363*)	−0.28760 (0.0063*)	0.02471 (0.8182)
Headache	−0.03521 (0.6852)	0.06250 (0.4731)	0.00317 (0.9709)	0.12344 (0.1553)
Anxious	−0.28647 (0.0049*)	−0.15913 (0.1235)	−0.09443 (0.3653)	0.01034 (0.9212)
Appetite loss	−0.62051 (<0.0001*)	−0.07858 (0.4801)	−0.17199 (0.1223)	0.06216 (0.5767)
Depression	−0.44867 (<0.0001*)	−0.14593 (0.1582)	−0.20212 (0.0507)	−0.10338 (0.3214)
At month 2				
Nausea	−0.27998 (0.0090*)	0.01156 (0.9159)	−0.20330 (0.0620)	0.12212 (0.2656)
Pain	−0.23696 (0.2883)	−0.26532 (0.2327)	−0.48638 (0.0217*)	0.07917 (0.7262)
Insomnia	0.03890 (0.8635)	−0.00461 (0.9838)	−0.43356 (0.0438*)	0.07601 (0.7367)
Concentration	−0.34635 (0.0044*)	0.04163 (0.7399)	−0.28043 (0.0237*)	0.20903 (0.0947)
Memory loss	−0.28022 (0.0227*)	−0.07503 (0.5494)	−0.05325 (0.6736)	0.20149 (0.1075)
Vision problem	−0.15928 (0.1979)	0.02059 (0.8686)	−0.01451 (0.9080)	0.14164 (0.2566)
Weakness	−0.25407 (0.0183*)	−0.16402 (0.1313)	−0.17791 (0.1012)	0.20446 (0.0590)
Coordination	NA	NA	NA	NA
Balance	−0.24156 (0.0545)	−0.10106 (0.4269)	−0.13520 (0.2907)	0.23079 (0.0688)
Headache	−0.34035 (0.0048*)	0.13193 (0.2872)	−0.19667 (0.1107)	0.12202 (0.3253)
Anxious	−0.40911 (0.0655)	−0.19426 (0.3988)	−0.31452 (0.1650)	−0.02700 (0.9075)
Appetite loss	−0.10991 (0.6263)	−0.04110 (0.8559)	−0.00592 (0.9791)	0.16373 (0.4666)
Depression	−0.40756 (0.0597)	−0.00424 (0.9851)	−0.44761 (0.0367*)	−0.25628 (0.2496)
At month 3				
Nausea	−0.17200 (0.2136)	0.07062 (0.6118)	−0.14419 (0.3078)	0.14117 (0.3182)
Pain	0.10437 (0.7113)	−0.02525 (0.9288)	−0.04785 (0.8655)	0.04755 (0.8664)
Insomnia	−0.10950 (0.6977)	0.57737 (0.0242*)	0.04211 (0.8815)	0.22126 (0.4281)
Concentration	−0.43832 (0.0047)	−0.19573 (0.2261)	−0.06840 (0.6791)	−0.03979 (0.8099)
Memory loss	−0.12024 (0.4659)	−0.40375 (0.0108)	0.05060 (0.7629)	−0.17299 (0.2990)
	−0.26313 (0.1056)	0.00199 (0.9904)	−0.13400 (0.4225)	0.34170 (0.0358*)

Table 4 (continued)

At follow-up	Correlation between symptom and overall QOL (r and p value)	Correlation between symptom and baseline KPS (r and p value)	Correlation between symptom change score and overall QOL change score (r and p value)	Correlation between symptom change score and baseline KPS score (r and p value)
Vision problem				
Weakness	−0.31245 (0.0227)	−0.26081 (0.0593)	−0.09719 (0.4887)	0.16774 (0.2299)
Coordination	NA	NA	NA	NA
Balance	−0.50475 (0.0010)	−0.21055 (0.1983)	0.06566 (0.6953)	0.28036 (0.0882)
Headache	−0.07957 (0.6255)	−0.05674 (0.7280)	−0.01337 (0.9347)	−0.01898 (0.9075)
Anxious	0.10566 (0.7192)	0.31144 (0.2784)	−0.30986 (0.2810)	0.06605 (0.8225)
Appetite loss	−0.27595 (0.3195)	0.21436 (0.4430)	−0.35517 (0.1939)	0.19857 (0.4781)
Depression	0.24553 (0.3975)	0.08041 (0.7846)	−0.21579 (0.4587)	−0.16807 (0.5657)

*P value <0.05 was considered statistically significant

dexamethasone, appetite loss and pain were most severe (mean 2.4 and 2.1). At month 3, weakness and appetite loss were the most severe symptoms for all patients (mean 2.2 and 2.1), and for patients taking dexamethasone (mean 2.2 for both), while weakness only (mean 2.1) was the most severe symptom for patients not taking dexamethasone.

Through the Wilcoxon signed rank test (Table 3), weakness (mean 2.1 vs. 1.9 at baseline) and appetite loss (mean 2.1 vs. 1.6 at baseline) significantly increased in severity at month 1 comparing to baseline. At month 2, the following five symptoms significantly changed from baseline: nausea (mean 1.6 vs. 1.4 at baseline), balance (mean 1.5 vs. 1.9 at baseline), headache (mean 1.5 vs. 1.8 at baseline), anxiety (mean 1.7 vs. 2.0 at baseline), and appetite loss (mean 2.6 vs. 1.6 at baseline). At month 3, only anxiety was significantly changed from baseline (mean 1.1 vs. 2.0 at baseline). Overall QOL was significantly decreased from baseline to each follow-up month (mean 4.6 at baseline, 3.9 at month 1, 4.1 at month 2, and 3.8 at month 3). In comparison between patients with and without dexamethasone treatment, there was no significant difference on all symptom change between patients at any follow-up visits, except for insomnia at month 1.

In the Appendix in Table 11, there were significant correlations at baseline between all symptoms and overall QOL, except for coordination. Significant correlations were also found between baseline KPS and nausea, memory loss, weakness, balance, and anxiety. At month 1 (Table 4), all symptoms were significantly correlated with overall QOL, except for pain, coordination, and headache. Pain, concentration, memory loss, and balance were negatively correlated with baseline KPS. Concentration, weakness, coordination, and balance changed scores were significantly correlated with overall QOL change scores. At month 2, five symptoms were significantly correlated with overall QOL, namely, nausea, concentration, memory loss, weakness, and headache, while pain, insomnia, concentration, and depression changed scores were significantly correlated with overall QOL change scores. At month 3, insomnia and vision problem change scores were significantly correlated with baseline KPS (Table 4).

In Table 5, there were significant associations between overall QOL and all symptoms except for appetite loss at baseline. Patients with greater experience of symptoms were more likely to have worse overall QOL. At month 1, there was significant association between overall QOL and all symptoms except for pain, coordination, and headache. Patients with more severe experience of symptoms were more likely to have worse overall QOL. At month 2, the following six symptoms were significantly related to overall QOL: nausea, concentration, weakness, balance, headache, and anxiety. Patients with greater symptom burden are more likely to have worse overall QOL. At month 3, only concentration and balance were negatively related to overall QOL.

At baseline, significant associations were found between five symptoms (nausea, memory loss, weakness, balance, and anxiety) and baseline KPS. Patients with more symptoms (higher score) were more likely to have lower baseline KPS. At month 1, pain, memory loss, and balance were negatively related to baseline KPS. At month 3, patients with more severe memory loss were more likely to have lower baseline KPS. However, patients with more insomnia were more likely to have higher baseline KPS (Table 5).

For symptom change over time and the association with overall QOL, nausea, concentration, weakness, balance, and appetite loss were significantly increasing in severity over time from baseline to month 3. Anxiety and depression were not significant changing over time, but they were negatively related to overall QOL. Patients with more anxiety or

Table 5 Relationship between symptoms and overall QOL scores or between symptoms and baseline KPS at baseline and each follow-up month for group 2

Symptom QOL item (1–4)	Overall QOL			Baseline KPS		
	Coefficient (SE)	*p* value	MSE	Coefficient (SE)	*p* value	MSE
At baseline						
Nausea	−0.166 (0.047)	0.0005*	0.067	−0.003 (0.001)	0.0153*	0.066
Pain	−0.202 (0.078)	0.0106*	0.084	−0.003 (0.002)	0.1839	0.084
Insomnia	−0.216 (0.086)	0.0134*	0.102	0.000 (0.002)	0.9145	0.110
Concentration	−0.201 (0.055)	0.0003*	0.071	−0.002 (0.001)	0.1360	0.075
Memory loss	−0.117 (0.054)	0.0334*	0.069	−0.003 (0.001)	0.0093*	0.067
Vision problem	−0.151 (0.055)	0.0062*	0.066	−0.000 (0.001)	0.7824	0.068
Weakness	−0.286 (0.056)	<0.0001*	0.096	−0.007 (0.001)	<0.0001*	0.097
Coordination	−0.246 (0.110)	0.0311*	0.068	0.002 (0.003)	0.5356	0.065
Balance	−0.262 (0.078)	0.0012*	0.099	−0.006 (0.002)	0.0042*	0.102
Headache	−0.194 (0.064)	0.0029*	0.091	−0.002 (0.002)	0.1839	0.094
Anxiety	−0.256 (0.082)	0.0024*	0.093	−0.005 (0.002)	0.0178*	0.095
Appetite loss	−0.125 (0.094)	0.1847	0.091	−0.003 (0.002)	0.1418	0.090
Depression	−0.339 (0.078)	<0.0001*	0.084	−0.001 (0.002)	0.7532	0.101
At month 1						
Nausea	−0.126 (0.040)	0.0019*	0.067	−0.000 (0.001)	0.8918	0.071
Pain	−0.154 (0.080)	0.0589	0.106	−0.005 (0.002)	0.0305*	0.102
Insomnia	−0.202 (0.079)	0.0117*	0.100	−0.001 (0.003)	0.7029	0.107
Concentration	−0.178 (0.046)	0.0002*	0.080	−0.003 (0.002)	0.0638	0.084
Memory loss	−0.096 (0.047)	0.0414*	0.080	−0.003 (0.001)	0.0173*	0.080
Vision problem	−0.115 (0.044)	0.0097*	0.069	−0.002 (0.001)	0.1851	0.070
Weakness	−0.245 (0.048)	<0.0001*	0.098	−0.003 (0.002)	0.1052	0.111
Coordination	−0.098 (0.103)	0.3425	0.100	−0.004 (0.004)	0.3103	0.096
Balance	−0.307 (0.053)	<0.0001*	0.072	−0.004 (0.002)	0.0416*	0.095
Headache	0.006 (0.049)	0.8950	0.085	0.001 (0.002)	0.4251	0.082
Anxiety	−0.224 (0.079)	0.0057*	0.103	−0.004 (0.003)	0.0892	0.105
Appetite loss	−0.575 (0.085)	<0.0001*	0.073	−0.002 (0.003)	0.4373	0.114
Depression	−0.349 (0.073)	<0.0001*	0.087	−0.004 (0.003)	0.0980	0.105
At month 2						
Nausea	−0.171 (0.068)	0.0142*	0.087	0.000 (0.002)	0.9200	0.094
Pain	−0.245 (0.178)	0.1835	0.110	−0.006 (0.005)	0.2639	0.113
Insomnia	0.008 (0.196)	0.9682	0.134	−0.000 (0.006)	0.9371	0.134
Concentration	−0.162 (0.062)	0.0109*	0.058	0.001 (0.002)	0.5695	0.064
Memory loss	−0.100 (0.058)	0.0862	0.050	−0.002 (0.002)	0.3120	0.052
Vision problem	−0.038 (0.060)	0.5252	0.056	−0.001 (0.002)	0.4644	0.056
Weakness	−0.183 (0.078)	0.0219*	0.114	−0.004 (0.003)	0.1130	0.118
Coordination	NA	NA	NA	NA	NA	NA
Balance	−0.134 (0.065)	0.0443*	0.064	−0.002 (0.002)	0.4957	0.068
Headache	−0.236 (0.061)	0.0003*	0.058	0.001 (0.002)	0.6884	0.071
Anxiety	−0.462 (0.170)	0.0138*	0.092	−0.007 (0.005)	0.2229	0.118
Appetite loss	−0.091 (0.205)	0.6616	0.146	0.000 (0.006)	0.9633	0.148
Depression	−0.342 (0.169)	0.0562	0.099	−0.002 (0.005)	0.7102	0.118
At month 3						
Nausea	−0.109 (0.080)	0.1815	0.094	0.001 (0.003)	0.6651	0.097
Pain	0.165 (0.222)	0.4713	0.115	−0.001 (0.007)	0.8510	0.119
Insomnia	−0.098 (0.239)	0.6870	0.133	0.017 (0.006)	0.0190*	0.087
Concentration	−0.203 (0.077)	0.0119*	0.072	−0.004 (0.003)	0.2338	0.082
Memory loss	−0.041 (0.074)	0.5823	0.064	−0.007 (0.003)	0.0102*	0.053

Table 5 (continued)

Symptom QOL item (1–4)	Overall QOL			Baseline KPS		
	Coefficient (SE)	*p* value	MSE	Coefficient (SE)	*p* value	MSE
Vision problem	−0.126 (0.084)	0.1439	0.083	−0.000 (0.003)	0.9357	0.088
Weakness	−0.163 (0.084)	0.0569	0.102	−0.006 (0.003)	0.0650	0.103
Coordination	NA	NA	NA	NA	NA	NA
Balance	−0.249 (0.075)	0.0019*	0.068	−0.005 (0.003)	0.1195	0.083
Headache	−0.078 (0.086)	0.3725	0.091	−0.004 (0.003)	0.2487	0.089
Anxiety	0.056 (0.101)	0.5868	0.023	0.003 (0.003)	0.3246	0.022
Appetite loss	−0.172 (0.257)	0.5139	0.153	0.005 (0.009)	0.5583	0.154
Depression	0.125 (0.127)	0.3436	0.036	0.001 (0.004)	0.8517	0.039

SE standard error, *MSE* mean square error

**P* value <0.05 was considered statistically significant

depression were more likely to have worse overall QOL. There were four symptoms significantly related to baseline KPS after adjusting for time effect, namely, memory loss, weakness, balance, and anxiety. Patients with more symptoms were more likely to have lower baseline KPS scores (Table 6).

Discussion

A prospective assessment of patient-rated symptoms following WBRT for brain metastases using the ESAS was conducted [14]. Within 12-week period of follow-ups, fatigue, drowsiness, and appetite, all showed statistically significant deteriorations in mean differences from the baseline. In comparison to our group 1 cohort, the only statistically significant change observed was an increase in appetite loss at month 2.

Bezjak et al. conducted another prospective study to evaluate symptom response following WBRT using the FACT-Br to assess QOL. Responses from the FACT-Br showed a mean deterioration in QOL from baseline to 1 month, although this difference was not statistically significant [4]. Moreover, Gerrard et al. found that at 8 weeks after WBRT, 10 out of 38 patients had a transient improvement in QOL, Barthel, or KPS parameters during the assessment period. However, of the 15 patients for whom data were obtained at 8 weeks, 14 suffered deterioration in QOL, assessed using the QLQ-C30 and the QLQ-BN20. In our group 2 cohort, with patients who completed six questionnaires, including the FACT-Br and the EORTC QLQ-C30, overall QOL was found to have decreased at month 1 as well. In fact, overall QOL decreased from baseline in group 2 was statistically significant at months 1–3. While comparison between these studies is not rigorous and is inappropriate given the differences in patient characteristics, the observation of lower QOL in our study post-WBRT elicits the same question that Bezjak et al. raises in their paper. Specifically, the authors raised the question of whether or not the benefit of RT may be overstated. In addition, they noted the fact that studies evaluating the effect of RT have not generally distinguished between the effects of steroids and the effects of RT [4]. As such, studies should attempt to separate the effects of steroid therapy to determine the true benefit of RT.

On the other hand, Yaneva et al. arrived at contrasting results. Using the EORTC QLQ-C30 as well, Yaneva et al. found significant improvements in functional indicators, symptoms, and QOL after WBRT [15]. However, this may be attributable to the fact that Yaneva et al. selected patients with KPS scores above 70, while Gerrard et al. selected patients with KPS levels below 70 [16]. Our group 2 cohort had a median KPS of 80, ranging from 30 to 100. Nevertheless, our findings indicated deterioration in QOL after WBRT in all three follow-up months, more consistent with findings from the Bezjak et al. study [4].

In a literature review published in 2007, Wong et al. noted two other studies, Addeo et al. [17] and Scott et al. [18] in addition to the one by Yaneva et al. [15], which showed significant improvement in certain parameters of QOL after WBRT for patients with better prognosis [13]. Comparison of literature in this area including this current study seems to point to inconsistent findings on symptoms and changes in quality of life associated with WBRT. This may be for several reasons; firstly, few studies of WBRT include a measure of QOL as a primary endpoint and secondly, collecting data in a population of patients with short life expectancy is difficult [13]. As such, dropout bias may affect studies. In addition, no standardized questionnaires currently exist to assess QOL in patients with brain metastases [13]. Thus, the use of different questionnaires complicates the comparison of QOL across different trials and does not permit for effective meta-analyses [10]. As well, the current study was limited by its retrospective nature so important information regarding dose and fractionation of WBRT was not able to be collected for all patients.

The present study examined the QOL and symptoms experienced by patients with brain metastases treated with WBRT. It is imperative to measure these parameters in patients treated with WBRT, as they tend to have limited survival and poor

Table 6 Time trend of each symptom with time-varying covariate of overall QOL or with baseline KPS for group 2 using general linear mixed model

Symptom	Overall QOL			Baseline KPS		
	Independent variable	Coefficient (SE)	*p* value	Independent variable	Coefficient (SE)	*p* value
Nausea	Intercept	0.846 (0.018)	<0.0001	Intercept	0.934 (0.066)	<0.0001
	Time	0.114 (0.028)	<0.0001*	Time	0.025 (0.012)	0.0400*
	Time × overall QOL	−0.062 (0.017)	0.0004*	KPS	−0.001 (0.001)	0.1483
Pain	Intercept	0.996 (0.029)	<0.0001	Intercept	1.250 (0.135)	<0.0001
	Time	0.064 (0.067)	0.3369	Time	−0.002 (0.021)	0.9223
	Time × overall QOL	−0.041 (0.041)	0.3209	KPS	−0.003 (0.002)	0.0510
Insomnia	Intercept	1.045 (0.030)	<0.0001	Intercept	1.004 (0.150)	<0.0001
	Time	0.079 (0.070)	0.2558	Time	−0.023 (0.022)	0.2829
	Time × overall QOL	−0.066 (0.043)	0.1294	KPS	0.001 (0.002)	0.7366
Concentration	Intercept	0.914 (0.020)	<0.0001	Intercept	1.055 (0.082)	<0.0001
	Time	0.110 (0.029)	0.0002*	Time	0.003 (0.013)	0.8160
	Time × overall QOL	−0.075 (0.018)	<0.0001*	KPS	−0.002 (0.001)	0.0678
Memory loss	Intercept	0.897 (0.020)	<0.0001	Intercept	1.176 (0.080)	<0.0001
	Time	0.033 (0.028)	0.2314	Time	−0.002 (0.011)	0.8672
	Time × overall QOL	−0.026 (0.017)	0.1319	KPS	−0.004 (0.001)	0.0003*
Vision problem	Intercept	0.849 (0.021)	<0.0001	Intercept	0.912 (0.083)	<0.0001
	Time	0.023 (0.024)	0.3235	Time	−0.002 (0.010)	0.8061
	Time × overall QOL	−0.018 (0.015)	0.2169	KPS	−0.001 (0.001)	0.4001
Weakness	Intercept	1.026 (0.021)	<0.0001	Intercept	1.353 (0.079)	<0.0001
	Time	0.161 (0.034)	<0.0001*	Time	0.036 (0.014)	0.0119*
	Time × overall QOL	−0.086 (0.021)	<0.0001*	KPS	−0.004 (0.001)	<0.0001*
Coordination	Intercept	0.892 (0.041)	<0.0001	Intercept	0.960 (0.203)	<0.0001
	Time	0.193 (0.140)	0.1761	Time	0.010 (0.042)	0.8154
	Time × overall QOL	−0.117 (0.083)	0.1655	KPS	−0.001 (0.003)	0.6788
Balance	Intercept	0.988 (0.029)	<0.0001	Intercept	1.286 (0.103)	<0.0001
	Time	0.113 (0.032)	0.0006*	Time	−0.021 (0.015)	0.1592
	Time × overall QOL	−0.095 (0.020)	<0.0001*	KPS	−0.004 (0.001)	0.0028*
Headache	Intercept	0.958 (0.023)	<0.0001	Intercept	1.003 (0.089)	<0.0001
	Time	−0.004 (0.030)	0.8909	Time	−0.033 (0.013)	0.0101*
	Time × overall QOL	−0.021 (0.019)	0.2618	KPS	−0.001 (0.001)	0.5575
Anxiety	Intercept	1.066 (0.029)	<0.0001	Intercept	1.420 (0.141)	<0.0001
	Time	0.051 (0.067)	0.4425	Time	−0.092 (0.020)	<0.0001*
	Time × overall QOL	−0.089 (0.042)	0.0337*	KPS	−0.005 (0.002)	0.0117*
Appetite loss	Intercept	0.933 (0.031)	<0.0001	Intercept	1.057 (0.138)	<0.0001
	Time	0.346 (0.080)	<0.0001*	Time	0.104 (0.025)	<0.0001*
	Time × overall QOL	−0.157 (0.049)	0.0018*	KPS	−0.002 (0.002)	0.3285
Depression	Intercept	1.035 (0.029)	<0.0001	Intercept	1.218 (0.151)	<0.0001
	Time	0.104 (0.060)	0.0881	Time	−0.047 (0.018)	0.0127*
	Time × overall QOL	−0.098 (0.037)	0.0096*	KPS	−0.002 (0.002)	0.2114

SE standard error

*P value <0.05 was considered statistically significant

performance status. We determined that patients who experience greater symptom burden have worse overall QOL. As well, QOL decreased over time after WBRT delivery in certain patient groups. It is important to evaluate QOL and symptoms in palliative patients to ensure that treatment prescribed will meet patient care goals and ameliorate distressing symptoms.

Acknowledgments We thank the generous support of Bratty Family Fund, Michael and Karyn Goldstein Cancer Research Fund, Joey and

Mary Furfari Cancer Research Fund, Pulenzas Cancer Research Fund, Joseph and Silvana Melara Cancer Research Fund, and Ofelia Cancer Research Fund.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

Table 7 Demographics of patients included in group 1

Age (years)	
Number	22
Mean ± SD	65.0 ± 12.7
Median (range)	69 (39–84)
KPS	
Number	22
Mean ± SD	66.4 ± 11.8
Median (range)	70 (40–90)
Gender	
Male	10 (45.45 %)
Female	12 (54.55 %)
Primary cancer site	
Lung	14 (63.64 %)
Breast	5 (22.73 %)
Gastrointestinal	1 (4.55 %)
Unknown	2 (9.09 %)

SD standard deviation

Table 8 Spearman's correlation (*r*) between symptom and overall QOL or KPS at baseline for group 1

At baseline	Correlation between symptom and overall QOL (*r* and *p* value)	Correlation between symptom and baseline KPS (*r* and *p* value)
Nausea	−0.23926 (0.2962)	0.36556 (0.0943)
Pain	−0.55020 (0.0098*)	0.05878 (0.7950)
Anxious	−0.06140 (0.7915)	−0.20800 (0.3656)
Appetite loss	−0.28773 (0.2060)	0.23051 (0.3148)
Depression	−0.09575 (0.6797)	−0.29286 (0.1976)

*P value <0.05 was considered statistically significant

Table 9 Spearman's correlation (*r*) between symptom and overall QOL at follow-up or baseline KPS for group 1

At follow-up	Correlation between symptom and overall QOL (*r* and *p* value)	Correlation between symptom and baseline KPS (*r* and *p* value)	Correlation between symptom change score and overall QOL change score (*r* and *p* value)	Correlation between symptom change score and baseline KPS score (*r* and *p* value)
At month 1				
Nausea	−0.24855 (0.3049)	−0.15945 (0.5144)	−0.26243 (0.2928)	−0.19802 (0.4164)
Pain	−0.42102 (0.0726)	−0.23144 (0.3404)	−0.08855 (0.7268)	−0.25552 (0.2911)
Anxious	−0.03752 (0.8788)	0.38719 (0.1015)	−0.29109 (0.2412)	0.55837 (0.0160*)
Appetite loss	−0.44746 (0.0626)	0.05956 (0.8144)	−0.39254 (0.1191)	−0.13186 (0.6139)
Depression	−0.56869 (0.0111*)	0.12684 (0.6049)	−0.40467 (0.0958)	0.51810 (0.0276*)
At month 2				
Nausea	−0.66966 (0.0342*)	0.25681 (0.4738)	−0.10502 (0.7880)	0.27465 (0.4425)
Pain	0.02548 (0.9443)	0.07869 (0.8289)	−0.07557 (0.8468)	−0.35412 (0.3154)
Anxious	−0.75491 (0.0116*)	0.28854 (0.4188)	0.02703 (0.9450)	0.25698 (0.5044)
Appetite loss	−0.52705 (0.1175)	0.12093 (0.7393)	−0.33934 (0.3716)	−0.74140 (0.0222*)
Depression	−0.88783 (0.0006*)	0.61589 (0.0580)	−0.27683 (0.4708)	0.34568 (0.3622)
At month 3				
Nausea	−0.65608 (0.1095)	0.52174 (0.2297)	−0.81683 (0.0249*)	−0.04915 (0.9167)
Pain	−0.16829 (0.7183)	−0.08179 (0.8616)	0.12127 (0.7956)	−0.29794 (0.5163)
Anxious	−0.81512 (0.0255*)	0.04348 (0.9263)	−0.08575 (0.8550)	−0.24077 (0.6030)
Appetite loss	−0.05505 (0.9067)	0.11035 (0.8138)	−0.47203 (0.2849)	−0.23857 (0.6064)
Depression	−0.73560 (0.0595)	0.08696 (0.8529)	−0.19418 (0.6765)	−0.26580 (0.5645)

*P value <0.05 was considered statistically significant

Table 10 Demographics of patients included in group 2

Age (year)	
Number	195
Mean ± SD	63.3 ± 10.8
Median (range)	64 (22–88)
KPS	
Number	194
Mean ± SD	73.2 ± 15.6
Median (range)	80 (30–100)
Gender	
Male	135 (69.23 %)
Female	60 (30.77 %)
Primary cancer site	
Lung	110 (56.41 %)
Breast	47 (24.10 %)
Kidney/renal cell	10 (5.13 %)
Colon	5 (2.56 %)
Gastrointestinal	2 (1.03 %)
Melanoma	1 (0.51 %)
Other	14 (7.18 %)
Unknown	6 (3.08 %)
Number of brain metastases	
1	9 (29.03 %)
2–3	14 (45.16 %)
>3	8 (25.81 %)
Previous systemic treatment	
No	70 (76.92 %)
Yes	21 (23.08 %)
Previous hormotherapy	
No	29 (78.38 %)
Yes	8 (21.62 %)
Previous chemotherapy	
No	62 (50.41 %)
Yes	61 (49.59 %)
With dexamethasone treatment	
No	29 (19.73 %)
Yes	118 (80.27 %)
Dexamethasone dose (mg) only in those with treatment	
Number	147
Mean ± SD	9.7 ± 6.7
Median (range)	12 (0.5–24)

SD standard deviation

Table 11 Spearman's correlation (*r*) between symptom and overall QOL scores or baseline KPS for group 2

At baseline	Correlation between symptom and overall QOL (*r* and *p* value)	Correlation between symptom and baseline KPS (*r* and *p* value)
Nausea	−0.31129 (<0.0001*)	−0.17891 (0.0130*)
Pain	−0.32051 (0.0009*)	−0.17458 (0.0763)
Insomnia	−0.25127 (0.0101*)	−0.04314 (0.6637)
Concentration	−0.33957 (<0.0001*)	−0.13077 (0.1015)
Memory loss	−0.20282 (0.0103*)	−0.21163 (0.0076*)
Vision problem	−0.25738 (0.0025*)	0.01874 (0.8292)
Weakness	−0.37357 (<0.0001*)	−0.32136 (<0.0001*)
Coordination	−0.20269 (0.1718)	0.07796 (0.6066)
Balance	−0.30319 (0.0039*)	−0.28726 (0.0063*)
Headache	−0.26155 (0.0020*)	−0.07695 (0.3732)
Anxious	−0.34986 (0.0003*)	−0.20027 (0.0425*)
Appetite loss	−0.27889 (0.0078*)	−0.16010 (0.1295)
Depression	−0.37249 (0.0001*)	0.00184 (0.9853)

*P value <0.05 was considered statistically significant

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