Prognostic value of pre- and post-treatment health-related quality of life in predicting survival of patients with brain metastases

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Summary points

- Quality of life (QOL) assessments are easy to administer and can help predict prognosis and improve palliative management of patients with brain metastases.
- Health-related quality of life (HRQOL) is a multifaceted concept that includes health, social and emotional well-being, among others, and is an important consideration in the treatment of advanced cancer patients.
- Upon univariate analysis, overall QOL, physical functioning and motor dysfunction were significantly related to overall survival.
- Patients with worse HRQOL at baseline were more likely to have higher probabilities of impending death (HR: 0.994; 95% CI: 0.989–0.999).
- Overall, patients with lower QOL, particularly lower physical functioning and motor dysfunction domains, are more likely to have a poorer survival outcome.
- As patients with brain metastases tend to have limited survival, it is important to define significant prognostic factors to ensure proper clinical course is carried out.
- Prognostic factors can be of great value to both patients and physicians alike and can guide appropriate prescription of irradiation treatment, as well as assist in end-of-life planning.
- Our study concluded that demographic factors, such as Karnofsky Performance Status, age and primary cancer site, were of prognostic value. We conclude that baseline HRQOL and its associated domains are of prognostic significance; however, changes in HRQOL are not.

Aim: The present study aimed to determine the prognostic survival value of pretreatment health-related quality of life (HRQOL) and changes in HRQOL following whole-brain radiation treatment in patients with brain metastases. **Methods:** Patients who were treated with whole-brain radiation treatment and completed HRQOL questionnaires were included. Univariate and multivariate Cox proportional hazard models of overall survival (OS) were conducted for overall HRQOL and domain scores. **Results & conclusion:** Patients with lower HRQOL at baseline, especially lower physical functioning and motor dysfunction domains, were more likely to have poorer survival. Changes in overall HRQOL and its domains were not significantly related to OS. Pretreatment HRQOL, especially physical functioning and motor dysfunction, has added prognostic value in patients with brain metastases.

First draft submitted: 1 April 2016; Accepted for publication: 27 October 2016; Published online: 20 April 2017

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KEYWORDS

• brain metastases • overall survival • prognosis • quality of life

Brain metastases are the most common brain neoplasms and occur in 40–60% of advanced cancer patients [1]. Patients with lung, renal, melanoma, colorectal and breast cancer are more likely to develop brain metastases than other primary cancers [1].

Appropriate treatment depends on the characteristics of the patient themselves (i.e., primary cancer site), the brain metastases (i.e., size and number) and the disease as a whole, including prognosis. Chemotherapy is often not the primary method of treatment for brain metastases due to the limitations of the blood–brain barrier [2]. In patients with a single or a limited number of metastases and good performance status, surgical resection and radiosurgery are potential treatment modalities that have been shown to improve survival [3]. For the majority of patients with multiple brain metastases, whom often have poor performance status, median survival is 3–6 months following treatment [4]. As such, treatment goals are focused on symptom management and maintenance of health-related quality of life (HRQOL) [4–6], a multidimensional concept that includes health, social and emotional well-being, cognition, role functioning, sexual functioning, physical functioning and symptoms and spirituality [7].

The standard of care for these palliative patients is whole-brain radiotherapy (WBRT) with or without adjuvant corticosteroids. Following WBRT, it can take approximately a month for patients to receive full benefits, as such, the 20–30% of patients who die prior to this point do not benefit from the treatment [8]. This highlights how crucial a proper prediction of survival is and the treatment that it dictates. Our study aimed to evaluate the survival prognostic value of HRQOL and its domains in determining survival.

Methods

A retrospective analysis was conducted on all prospectively collected databases from the Rapid Response Radiotherapy Program at Sunnybrook Odette Cancer Centre in Toronto, Ontario. The database was collected from 2005 to 2012. Patients with CT-/MRI-verified brain metastases from various primary cancer sites were included. Included patients were treated with WBRT and varying doses of dexamethasone. All patients provided consent for initial data collection and the study was approved by the Research Ethics Board.

• Data collection

Baseline demographic information was collected that included age, Karnofsky Performance Status (KPS), gender and primary cancer site. OS was calculated in months from initial clinic visit to date of death or the last follow-up visit. Any patients that were alive at time of analysis were censored at the last date of follow-up.

• HRQOL questionnaires

Of the 269 patients included in the study, 108 patients completed the Quality of Life Questionnaire – Core 15 Palliative (QLQ-C15-PAL) and Brain Module (BN20+2) questionnaires, 18 patients completed the Quality of Life Questionnaire – Core 30 (QLQ-C30) and BN20, 129 patients completed the Spitzer questionnaire and 14 completed the Functional Assessment of Cancer Therapy – Brain Scale (FACT-Br). Selections of scales were used from the various questionnaires to represent HRQOL domains. The purpose of the investigation was to observe the impact of baseline HRQOL and post-treatment changes in HRQOL, and thus all of the HRQOL domain scales (i.e., future uncertainty, communication deficit, motor dysfunction and visual disorder) were included from the questionnaires while the symptoms scales were excluded. All HRQOL and domain scores (listed below) were converted into 0–100 scales.

• Spitzer quality of life index

The Spitzer Quality of Life Index consists of five domains: support, daily living, outlook, health and activity domain. The health domain score (converted to 0–100) was used as Global Health Status (GHS) score. No other domain scores were taken from this questionnaire.

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

The European Organization for Research & Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) is a 30-question assessment for HRQOL for general cancer populations. This questionnaire assesses HRQOL domains on a scale of 1–4, with 1 = not at all, 2 = a little bit, 3 = quite a bit and 4 = very much and assesses overall HRQOL on a scale of 1 (very poor) to 7 (excellent). Physical functioning, GHS, emotional functioning, social functioning domain scores (0–100) were taken from this questionnaire.

• EORTC Quality of Life Questionnaire – Core 15 Palliative

The EORTC QLQ-C15-PAL is shortened HRQOL assessment for palliative patients, containing 15 questions. This questionnaire assesses HRQOL domains on a scale of 1–4 and overall HRQOL on a scale of 1–7, similar to the QLQ-C30. Patients who completed the QLQ-C15-PAL also completed the BN20+2. Physical functioning, GHS and emotional functioning domain scores (0–100) were taken from the QLQ-C15-PAL.

• EORTC Quality of Life Questionnaire Brain Module

The BN20 is a 20-item questionnaire to accompany the EORTC QLQ-C30, while the BN20+2 is a 22-item in-development tool to accompany the C15-PAL. Both questionnaires assess HRQOL domains on a scale from 1 to 4, similar to the QLQ-C30 or QLQ-C15-PAL. From the BN20 and BN20+2, the domain scores (0–100) of future uncertainty, visual disorder, motor dysfunction and concentration disorders were taken.

• Functional Assessment of Cancer Therapy – Brain Scale

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 trial outcome index, a summary index of physical and functioning subscales, was used as GHS score. Domain scores (0–100) of physical well-being, social well-being, functioning well-being and emotional well-being were used.

• Baseline HRQOL

Patients were accrued to the study at their initial clinic consultation, before treatment was delivered. All demographic information and first HRQOL assessments were completed at this time. Kaplan–Meier OS curve was conducted in all patients, and in patients stratified by age or KPS, respectively. Log-rank test was performed to compare OS curves between age ≥ 65 and < 65 years, or between KPS ≥ 70 and < 70 , as both age and KPS are significant prognostic factors in patients with brain metastases. A KPS of 70 was chosen as the cutoff because KPS < 70 indicates special care is required for that individual. An age cutoff of 65 years was chosen based on the findings of the prognostic factor study conducted by Gaspar *et al.* [9]. Univariate Cox proportional

hazard (PH) model of OS was conducted in all patients with demographic parameters, HRQOL and domain scores (0–100 continuous variables). The time (months) to death or the last follow-up was considered as the outcome variable. Patients alive or withdrew from the study had censored times based on the last follow-up date. To search for the parameters most predictive of time to death, univariate analysis was conducted. All variables with $p < 0.10$ obtained from the univariate analysis (including all potential variables with limited significance) were analyzed in multivariate analysis, using a backward stepwise selection procedure. A p -value < 0.10 was used to include all potential variables with limited/borderline significant p -values from the univariate analysis. All variables with $p < 0.05$ in the multivariate analysis were retained and were the most predictive of prognosis.

• Change of HRQOL

Follow-up HRQOL assessments were scheduled for 1, 2 and 3 months post-treatment. Patients who completed both baseline and at least one follow HRQOL assessment were included in the analysis. Changes in HRQOL were calculated by comparing baseline to each follow-up record (month 1, 2 or 3 when available). Kaplan–Meier OS curves with Log-rank test were performed in patients with month 1, 2 or 3 measurements. We dichotomized the changes as three categories: increase (baseline HRQOL $<$ follow-up HRQOL; worsening of HRQOL), no change (baseline HRQOL = follow-up HRQOL; same HRQOL) and decrease (baseline HRQOL $>$ follow-up HRQOL; improving HRQOL).

Univariate Cox PH model of OS was also conducted in all patients at month 1, 2 and 3, respectively, with demographic parameters and HRQOL/domain 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). A p -value < 0.05 was considered statistically significant.

Results

• Baseline HRQOL

Two hundred and sixty nine patients were included in the baseline HRQOL analysis. The

Table 1. Patient demographics and clinical characteristics of baseline health-related quality of life analysis.

Demographic		
Age (years):		
– n	269	
– Mean ± SD	63.3 ± 11.2	
– Median (range)	64 (22–88)	
KPS:		
– n	267	
– Mean ± SD	71.3 ± 16.2	
– Median (range)	70 (30–100)	
Gender, n (%):		
– Male	186	(69.14)
– Female	83	(30.86)
Primary cancer site, n (%):		
– Breast	66	(24.54)
– GI	13	(4.83)
– GU	14	(5.20)
– Lung	146	(54.28)
– Other	22	(8.18)
– Unknown	8	(2.97)
Vital status, n (%):		
– Alive	10	(3.72)
– Dead	259	(96.28)
WBRT dosage, n (%):		
– 20 Gy/5	115	(42.75)
– 30 Gy/10	7	(2.60)
– Other/none	7	(2.60)
– Unknown	140	(52.04)

GI: Gastrointestinal; GU: Genitourinary; KPS: Karnofsky performance status; WBRT: Whole-brain radiotherapy.

mean age was 63 years with 69% of patients being male. The most common primary cancer sites were lung (54%) and breast (25%). Among 269 patients, 259 (96%) died and 10 patients were alive (censored rate of 4%). **Table 1** contains a summary of patient demographics and clinical characteristics of the study cohort. Duration of follow-up ranged from 0.2 to 51 months. The actuarial median survival time was 3.8 months (95% CI: 3.2–4.6 months). The survival probability at month 1 was 90.6%, at month 2 was 75.0%, at month 3 was 59.1% and at month 4 was 48.5% (**Table 2**). **Figure 1** shows the Kaplan–Meier OS curve with 95% CI in all patients.

All demographic factors were significantly related to OS except for gender. Patients are more likely to have higher risk of death if they were older in age or have lower KPS. Patients with gastrointestinal (GI), genitourinary (GU) or lung cancer were more likely to have higher probabilities of death comparing to patients with breast site. Overall HRQOL, physical

functioning and motor dysfunction were significantly related to OS. Through multivariate analysis (**Table 3**), two demographic factors and GHS domain score were continued to be significant: KPS <70 (HR: 1.56), age ≥65 years (HR: 1.68) and GHS (HR: 0.994). According to the HR, patients with KPS <70 were found to be at 56% increased risk of death than patients with a KPS ≥70. Patients above the age of 65 were found to be at a 68% higher risk of death than patients less than 65 years of age. For GHS domain score, the hazard of death would be reduced by 6% if the GHS score increased (equating to improved QOL) by ten units. In **Figures 2 & 3**, patients with KPS <70 or older than 65 years were more likely to have higher risk of death compared with others. The actuarial median OS was 2.5 months (95% CI: 2.1–3.0) in patients with KPS <70 and 4.8 months (95% CI: 4.0–5.5) in patients with KPS ≥70. For age, the actuarial median OS was 3.1 months (95% CI: 2.5–3.6) in patients with age ≥65 years and 5.1 months (95% CI: 3.8–6.1)

Table 2. Survival probability of all patients included in baseline health-related quality of life analysis.

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)

in patients with age less than 65 years. Patients with worse HRQOL at baseline were more likely to have higher probabilities of impending death.

• Change of HRQOL

One hundred and seventy nine patients were included in the HRQOL change analysis (Table 4). The mean age was 63 years and 70% of patients were male. The most common primary cancer sites were lung (57%) and breast (23%). Among 171 patients with month 1 HRQOL follow-up records, 165 died and 6 were alive (censored rate of 3.5%); among 87 patients

with month 2 HRQOL follow-up records, 86 died and 1 was alive (censored rate of 1.1%); among 54 patients with month 3 HRQOL follow-up records, all of them died and 0% were censored. The actuarial median survival time was 4.8 months (95% CI: 4.0–6.9), 7.1 months (95% CI: 5.1–9.5) and 9.5 months (95% CI: 6.1–11.5) in patients who had month 1, 2 or 3 measurements, respectively. Log-rank test shows significant difference among three OS curves ($p = 0.019$).

At month 1, age, KPS and primary cancer sites were significantly related to OS, except for

Figure 1. Kaplan–Meier overall survival curve with 95% CI in all patients included in baseline health-related quality of life analysis.

Table 3. Univariate and multivariate Cox proportional hazard model of overall survival for baseline health-related quality of life.

Factor	p-value	HR	95% CI of HR [†]	
Univariate analysis				
Age at baseline (years)	0.0018	1.018	1.007	1.030
Age ≥65 years (1 = yes, 0 = no)	0.0004	1.569	1.223	2.013
KPS score	<0.0001	0.984	0.976	0.992
KPS <70 (1 = yes, 0 = no)	<0.0001	1.864	1.429	2.431
Gender (1 = male, 0 = female)	0.7099	0.950	0.727	1.242
Primary cancer site:	0.0038			
– GI vs breast	0.0002	3.252	1.766	5.992
– GU vs breast	0.0310	1.910	1.061	3.437
– Lung vs breast	0.0304	1.402	1.032	1.905
– Other vs breast	0.0408	1.675	1.022	2.744
– Unknown vs breast	0.2142	1.648	0.749	3.627
GHS and domain scores:				
– GHS	0.0010	0.992	0.988	0.997
– Physical functioning	0.0280	0.993	0.988	0.999
– Emotional functioning	0.1906	0.995	0.988	1.002
– Social functioning	0.3931	0.994	0.980	1.008
– Future uncertainty	0.1411	1.008	0.997	1.018
– Visual disorder	0.2229	0.979	0.946	1.013
– Motor dysfunction	0.0097	1.019	1.005	1.034
– Concentration difficulty	0.1810	1.008	0.996	1.020
Multivariate analysis				
Age ≥65 years (1 = yes, 0 = no)	0.0007	1.676	1.243	2.260
KPS <70 (1 = yes, 0 = no)	0.0107	1.558	1.108	2.189
GHS	0.0199	0.994	0.989	0.999

[†]For GHS and domain scores, HR >1 indicates the hazard of death would be increased by (HR - 1) × 100% when the score increased by one unit; HR <1 indicates the hazard of death would be decreased by (1 - HR) × 100% when the score increased by one unit. Higher functioning and QOL scores indicate better functioning and QOL, while higher scores for certain domains (i.e., concentration difficulty, future uncertainty, visual disorder and motor dysfunction) indicate more impairment and worse QOL.

GHS: Global health status; GI: Gastrointestinal; GU: Genitourinary; HR: Hazard ratio; KPS: Karnofsky performance status; QOL: Quality of life

gender (Table 5). Patients were more likely to have higher risk of death if they had with lower KPS (<70) or were older in age. Patients with GI or GU cancer sites were more likely to have higher probabilities of death compared with patients with breast site. The HRQOL and all domain score changes were not significantly related to OS. Two demographic factors were still significant in the multivariate analysis, namely, KPS <70 (HR: 1.48) and age ≥65 years (HR: 1.46). Patients with KPS <70 or older than 65 years were more likely to have higher risk of death compared with others. At month 1, patients with KPS <70 or with age ≥65 years were at 48% higher and 46% higher hazard, respectively, than patients with KPS ≥70 or age <65 years at month 1.

At month 2, only KPS <70 was significantly related to OS (HR: 1.69; 95% CI: 1.02–2.77).

Physical functioning had limited p-value of 0.059. Patients with lower KPS <70 were more likely to have higher risk of impending death. Patient with a KPS <70 were at 69% increased risk of death compared with patients with KPS ≥70 at month 2.

At month 3, all of 54 patients had expired, so no further univariate or multivariate analysis was able to be conducted.

Discussion

Prognostic factors can guide physicians with regard to appropriate prescription of treatment regimens. In particular, patients with brain metastases generally have a limited survival and prognostic factors can be used to ensure adequate symptom palliation and appropriate referral to supportive services. Survival prognosis is also essential for the patient themselves

Figure 2. Kaplan–Meier overall survival curve in patients stratified by Karnofsky performance status (≥ 70 vs < 70).

when contemplating end-of-life care. The present study examined patients with brain metastases receiving WBRT to determine which baseline characteristics and HRQOL domains are associated with survival. Although we found

a significant relationship between baseline demographics, excluding gender, and survival following WBRT, only two prognostic factors (KPS < 70 and age > 65 years) were significantly related to OS at each monthly interval following

Figure 3. Kaplan–Meier overall survival curve in patients stratified by age (≥ 65 vs < 65 years).

Table 4. Patient characteristics of health-related quality of life change analysis.

Characteristic		
Age (years):		
– n	179	
– Mean ± SD	63.0 ± 11.1	
– Median (range)	64 (22–88)	
KPS:		
– n	178	
– Mean ± SD	73.2 ± 16.1	
– Median (range)	80 (30–100)	
Gender:		
– Male	126	(70.39)
– Female	53	(29.61)
Primary cancer site:		
– Breast	41	(22.91)
– GI	5	(2.79)
– GU	11	(6.15)
– Lung	102	(56.98)
– Other	14	(7.82)
– Unknown	6	(3.35)
Vital status:		
– Alive	7	(3.91)
– Dead	172	(96.09)
Available follow-up data:		
– Month 1	171	(95.53)
– Month 2	87	(48.60)
– Month 3	54	(30.16)
GI: Gastrointestinal; GU: Genitourinary; KPS: Karnofsky performance status.		

treatment. Patients of a greater age and lower performance status were at heightened risk of death at all-time points. Baseline HRQOL, physical functioning and motor dysfunction were significantly associated with OS; however, changes in HRQOL following WBRT delivery were not related to survival outcomes.

Several studies have been conducted to establish the relationship between numerous prognostic factors and OS. Gao *et al.* examined 46 patients treated with WBRT and found a median survival time of 11.8 ± 0.46 months and enhanced HRQOL following treatment [10]. Results showed no significant association between survival time and number of brain metastases, primary cancer site, age or larger tumor size [10]. This contrasts our results, as we found that KPS, age and primary cancer site assessed at baseline were significant prognostic factors. Our study found that changes in HRQOL following WBRT delivery were not associated with OS, perhaps due to the benefits WBRT imparts on HRQOL, it may not have

arisen as a significant prognostic factor. Various patient characteristics may have also contributed to these nonsignificant findings, such as receiving adjuvant chemotherapy or palliative care which may have affected QOL measures. Our study did not conclude that worsened overall HRQOL was associated with poorer survival.

Physical functioning was limitedly related to survival (p = 0.059) in our study. Previous studies have found physical functioning to be of prognostic significance and impart survival benefit [11,12]. One study examined non-small-cell lung cancer patients and determined that physical function predicted patient survival and, with 10-point interval improvements in function, a 10% increase in survival was observed [11]. This interval improvement has also been seen in other patient populations, such as gastro-esophageal cancers [12]. One study conducted in patients with breast cancer undergoing chemotherapy showed that physical well-being was predictive of survival [13]. Our study specifically looked at patients with cranial metastasis, which is associated with poorer performance status and overall poorer function. It is imperative that factors of prognostic significance are uncovered to assist physicians when generating survival prediction, as physicians tend to provide inaccurate estimates of survival [14].

Additionally, our study noted that breast cancer patients with brain metastases tend to have better survival when compared with patients with brain metastases from other primary cancer sites. As OS differs by primary cancer site, with certain sites being associated with improved prognosis, it is imperative to consider primary histology for patients with brain metastases [13]. Our study concluded that primary cancer site was of prognostic significance, as certain sites, such as GU, GI and lung cancers, were associated with increased risk of death.

A previous study conducted by Habets *et al.* examined the HRQOL of 97 patients with brain metastases-treated stereotactic radiotherapy (SRT) [15]. The study observed that patients with intracranial progression deteriorated on HRQOL scales, while those with stable disease had less deterioration. Focal radiation treatment is proposed to have less debilitating effects on neurocognitive function and HRQOL compared with WBRT due to less-treatment side effects. The study concluded that SRT had no additional detrimental effects on HRQOL, which are typically seen after WBRT [15]. However,

Table 5. Univariate and multivariate Cox proportional hazard model of overall survival for post-treatment health-related quality of life at month 1.

Factor	p-value	HR	95% CI of HR†	
Univariate analysis				
Age at baseline (years)	0.0052	1.020	1.006	1.035
Age ≥65 years (1 = yes, 0 = no)	0.0098	1.507	1.104	2.057
KPS score	0.0139	0.988	0.978	0.997
KPS <70 (1 = yes, 0 = no)	0.0130	1.560	1.098	2.216
Gender (1 = male, 0 = female)	0.3981	0.860	0.606	1.220
Primary cancer site:	0.0224			
– GI vs breast	0.0102	3.462	1.342	8.928
– GU vs breast	0.0117	2.497	1.226	5.086
– Lung vs breast	0.0637	1.443	0.979	2.128
– Other vs breast	0.0422	1.946	1.024	3.699
– Unknown vs breast	0.0987	2.212	0.862	5.677
QOL changes:				
– GHS:	0.7938	–	–	–
• Decrease vs no change	0.9890	1.003	0.668	1.506
• Increase vs no change	0.5363	0.856	0.524	1.400
– Physical functioning:	0.5284	–	–	–
• Decrease vs no change	0.4434	1.307	0.659	2.592
• Increase vs no change	0.9254	0.964	0.450	2.065
– Emotional functioning:	0.2490	–	–	–
• Decrease vs no change	0.2736	0.701	0.372	1.324
• Increase vs no change	0.1065	0.641	0.374	1.100
– Social functioning:	0.5338	.	.	.
• Decrease vs no change	0.2775	1.939	0.587	6.402
• Increase vs no change	0.8681	1.125	0.280	4.520
– Future uncertainty:	0.9347	–	–	–
• Decrease vs no change	0.8502	1.096	0.425	2.822
• Increase vs no change	0.7233	1.196	0.444	3.219
– Visual disorder:	0.2006	–	–	–
• Decrease vs no change	0.4660	1.367	0.590	3.172
• Increase vs no change	0.1263	0.388	0.115	1.306
– Motor dysfunction:	0.3342	–	–	–
• Decrease vs no change	0.2925	1.506	0.703	3.228
• Increase vs no change	0.1549	1.915	0.782	4.688
– Concentration difficulty:	0.5672	–	–	–
• Decrease vs no change	0.3388	1.432	0.686	2.992
• Increase vs no change	0.4624	1.458	0.533	3.984
Multivariate analysis				
Age ≥65 years (1 = yes, 0 = no)	0.0184	1.460	1.066	2.001
KPS <70 (1 = yes, 0 = no)	0.0301	1.479	1.038	2.107

†For GHS and domain-changed scores (decrease or increase vs no change), HR >1 indicates that the hazard of death in patients with decreased or increased HRQOL scores has (HR - 1) × 100% higher than the hazard of patients with nonchanged scores; HR <1 indicates that the hazard of patients with decreased or increased HRQOL scores has (1 - HR) × 100% lower than the hazard of patients with nonchanged scores.

GHS: Global health status; GI: Gastrointestinal; GU: Genitourinary; HR: Hazard ratio; HRQOL: Health-related quality of life; KPS: Karnofsky performance status; QOL: Quality of life

patients who receive SRT tend to have better performance status and less steroid prescriptions, which may translate into enhanced HRQOL at baseline [11]. Our study only followed patients for

a maximum of 3 months, which may not have captured changes in HRQOL related to chronic adverse effects of WBRT, such as memory loss. Future studies should consider extending the

duration of follow-up in order to observe the impact of long-term side effects on HRQOL.

A recent Phase III randomized study conducted by Mulvenna *et al.* queried the impact of WBRT on QOL and OS in patients with non-small-cell lung cancer and brain metastases [16]. A total of 538 patients were assigned to receive optimal supportive care and dexamethasone $\pm$ WBRT (20 Gy in five fractions). Participants completed the EQ-5D questionnaire weekly and quality-adjusted life years was used as the primary outcome. Improved survival was seen in a subset of patients less than 60 years. Though nonsignificant trends toward WBRT imparting a survival benefit were seen in patients with good performance status and controlled primary non-small cell lung cancer. No significant difference was found between the two groups in regard to QOL at 4, 8 or 12 weeks. However, the QOL tool used, EQ-5D is not specific to patients with brain metastases and future studies should utilize more nuanced scales to better capture qualities and experience unique to brain metastases patients. As well in the trial, 11% of patients in the WBRT arm did not receive treatment and the study could find no factors that would have predicted their rapid decline. The efficacy of WBRT in patients with poor performance status is questionable and QOL should be further investigated as a prognostic tool to help determine appropriate prescription of treatment.

A Phase III study conducted by Soffietti *et al.* evaluated HRQOL of patients with a limited number of brain metastases that received either adjuvant WBRT after surgery/radiosurgery or only observation [17]. The study examined six primary HRQOL scales from the EORTC-QLQ-C30 questionnaire and brain cancer module, inclusive of GHS, and physical, cognitive, role and emotional functioning, which were similar scales used in our study. At 8 weeks, the study observed better mean scores in physical, role and cognitive functioning and fatigue in the observation group. As well better cognitive functioning, less fatigue and better GHS were seen in the observation group at 12, 3 and 9 months, respectively [17]. The study concluded that adjuvant WBRT after surgery/radiosurgery may lead to transient detriments on HRQOL measures. The intent of treatment for patients with brain metastases is usually to palliate symptoms, thus the maintenance of HRQOL is an essential patient outcome that needs to be further evaluated in the context of WBRT to

further characterize its role in the management of brain metastases. Our study evaluated how the HRQOL of patients undergoing WBRT affected prognosis and found significant associations between baseline HRQOL measures and OS, which further highlights the importance of HRQOL for patient outcomes. We propose that the differences in patient cohorts and differential access to supportive services may explain why changes in HRQOL were not associated with survival in our study. Palliative care interventions have the potential to improve QOL scores in advanced cancer patients [18]. Prior studies have shown that palliative care can improve QOL and mood at the end of life [18,19]. The possible heterogeneous access to adequate palliative care and other supportive services in our patient population may explain why we did not find that change in HRQOL was predictive of survival. As well the potential impact of chemotherapy on QOL could not be assessed. We hypothesized that patients who had shorter follow-ups would have poorer prognosis, this was also corroborated with our data by generating Kaplan–Meier OS curves, which found significant survival differences between the follow-up times. However, there may be other reasons for patients being lost to follow-up, such as declining performance status, attrition or death, and thus limits the conclusion that patients with limited follow-up have poorer prognosis. There was also very low compliance rate with the HRQOL evaluations (25.7%, $n = 46$ of 179), which may have been due to various reasons, as previously mentioned. Patients with CT-/MRI-verified brain metastases were eligible for inclusion in the present study; therefore, not all patients included in the study were newly diagnosed with brain metastases. The time of the disease at which patients were enrolled varied, which limits the strength of conclusion that can be made from the change analysis.

Conclusion & future perspective

In conclusion, WBRT is an efficacious treatment modality for the local control and symptom palliation of brain metastases. Patients with brain metastases have limited survival, thus it is essential to define prognostic factors to ensure proper clinical course is carried out. Factors such as KPS, age and primary site of cancer were prognostic of overall survival. Our study concluded that, although baseline HRQOL (specifically GHS scores) may be associated with

survival, changes in HRQOL are not predictive of survival. Current literature discusses the changes of HRQOL after radiotherapy delivery, rather than HRQOL as a predictor of survival in patients with brain metastases. It is of the utmost important to assess baseline HRQOL and observe changes in HRQOL to determine how such changes will affect survival. Previous studies have observed global declines in QOL prior to death; however, further research should be conducted to elucidate, if HRQOL is a prognostic factor consistent across various cohorts of patients with brain metastases to address the lack of literature in this area.

Financial & competing interests disclosure

The authors 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. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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