

Impact of health-related quality of life and fatigue on survival of recurrent high-grade glioma patients

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Abstract Quality of life (QoL) impairment and fatigue are frequently experienced during treatment for recurrent high-grade glioma (HGG). Fatigue and QoL impairments can be due to primary neurological dysfunction, cytotoxic treatments, mood disturbances, and supportive medications. We now seek to understand how QoL and fatigue impacts survival in recurrent HGG. Using a prospective observational design, 237 patients with recurrent HGG and

KPS ≥ 70 completed a self-administered questionnaire that evaluated QoL and fatigue. QoL was assessed with Functional Assessment of Cancer Therapy-General (FACT-G) and FACT-Brain (FACT-Br) scales while fatigue was assessed using Functional Assessment of Chronic Illness Therapy (FACIT-F) scale. Cox proportional hazard models were utilized to evaluate the association between QoL and fatigue and survival. Seventy-three (31 %) subjects had recurrent WHO grade III gliomas and 164 (69 %) had recurrent WHO grade IV gliomas. Median follow-up analysis was 27.60 months. In univariate Cox analyses, the FACT-Br specific subscale (HR 0.88; CI 95 %, 0.77–1; $p = 0.048$) and FACIT-F (HR 0.82; CI 95 %, 0.68–0.99; $p = 0.045$) were both significant predictors of survival. Fatigue added prognostic information beyond that provided by KPS, age, sex, tumor grade, and number of prior progressions (HR 0.80; CI 95 %, 0.68–0.9; $p = 0.031$). A greater degree of fatigue was associated with poorer survival in recurrent HGG patients. In multivariable analyses, FACT-G and FACT-Br are not independent predictors of prognosis. Fatigue is a strong independent predictor of survival that provides incremental prognostic value to the traditional markers of prognosis in recurrent HGG. Pharmacological or non-pharmacological strategies to treat fatigue warrant investigation.

Previous patient demographics have been published in Ruden E et al. [20].

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Introduction

High grade gliomas (HGG) represent a heterogeneous but aggressive group of primary brain tumors. Despite multimodal therapy, these cancers can recur with a median progression-free survival after recurrence of only 9 weeks

for WHO grade IV tumors (glioblastoma) and 12 weeks for WHO grade III tumors (anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA)) [1, 2]. There is no standardized method of treatment for recurrent HGG, but most patients continue chemotherapy and may even pursue further surgery and radiotherapy [3, 4]. While direct treatment of the recurrent disease with further chemotherapy, radiation, and/or surgery is paramount, recognition and maintenance of quality of life (QoL) is equally important and is now starting to be utilized as a secondary outcome measure in clinical trials for treatment of recurrent disease [5, 6].

QoL impairment, defined as dysfunction in one's perception of personal well-being in life and community, is evident in both the newly-diagnosed and recurrent HGG population and is measured using patient-reported questionnaires [7–10]. Examples of impairment in brain tumor patients include neurological dysfunction, cognitive dysfunction, fatigue, mood disturbances, physical limitations, and insomnia. Since QoL impairment appears ubiquitous for this population and other cancer types, evaluation of QoL and its significance on prognosis is now being utilized in clinical trials [11]. Meta-analysis from EORTC clinical trials report that baseline QoL is a prognostic factor for survival in patients with many types of cancer [11]; however, for newly diagnosed high grade malignant gliomas, general QoL measures do not add to the prediction of survival beyond traditional measures of prognosis (age, sex, KPS, etc.) [8, 12]. In a study by Brown and colleagues, survival is not impacted by patient-reported outcomes of QoL in newly diagnosed HGG patients [9, 13]. However, fatigue, when measured independently, is a significant independent predictor of survival [9, 13]. Indeed with the dynamic changes seen in recurrence such as worsening neurological, cognitive, and functional decline, QoL could be impacted and fatigue could be more prevalent. Logically, this could potentially impact treatment considerations and ultimately survival.

Meyers and colleagues further have studied HGG patients and QoL with a focus on the recurrent disease population [14]. Per this study of 80 patients, there is no association between measures of QoL and survival, but there is an association between neurocognitive function and survival in recurrent HGG patients [14]. While it has been well-documented that QoL is impaired during treatment for recurrent malignant glioma [10], more evaluation with a larger cohort of patients at different points in the disease trajectory is warranted to understand about how it impacts treatment outcome and survival in patients with recurrent HGG. Moreover, fatigue, as a specific component of QoL impairment in HGG also deserves a particular evaluation and understanding in regards to its association with treatment outcome and survival. First we can

potentially utilize these tools that quantify QoL and fatigue to aid clinicians and prognosis. Next, we can devise interventions to improve QoL and mitigate symptoms such as fatigue that could, in turn, improve overall treatment tolerance and perhaps survival. We now seek to identify whether impaired QoL and fatigue is associated with a poorer prognosis in recurrent HGG patients.

Methods

Patients and setting

Patients with histologically confirmed WHO grades III to IV malignant glioma (e.g. glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma) with recurrent disease on magnetic resonance imaging (MRI), who had received or were receiving salvage therapy, and who were presenting to The Preston Robert Tisch Brain Tumor Center at Duke University Medical Center were eligible. Patients were eligible regardless of treatment (receiving *versus* not receiving treatment) and disease (active *versus* stable disease) status. All eligible patients had to be at least 6 months from original diagnosis and have a documented diagnosis of recurrent HGG per revised assessment in neuro-oncology (RANO) criteria which is standard objective criteria for radiographic assessment of tumor response in HGGs [15]. Additional eligibility criteria included the following: age ≥ 18 years, KPS ≥ 70 , and ability to read and understand English. The Duke University Medical Center institutional review board approved the study, and written informed consent was obtained from all participants before evaluation.

Quality of life and fatigue measures

QoL and fatigue were assessed using patient-reported standardized questionnaires. These included functional assessment of cancer therapy for brain tumors (FACT-Br) and functional assessment of chronic illness therapy-fatigue (FACIT-F). The FACT-Br (version 4) contained the functional assessment of cancer therapy-general (FACT-G), which has subscales for physical well-being (7-items), functional well-being (7-items), emotional well-being (6-items), and social/family well-being (7-items), as well as a 23-item brain cancer subscale (BrCS) that assesses symptoms commonly reported by brain cancer patients [16]. FACT-Br trial outcome index (TOI) was reported as the sum of the physical well-being score from FACT-G, functional well-being score from FACT-G, and BrCS score. FACT-Br total score was based upon all components of the FACT-G plus the BrCS score. FACT-Br total score,

along with BrCS and TOI, were scored separately. Cancer related fatigue was assessed by the 13-item Fatigue Scale using the FACIT-F, version 4 [17]. Score range for FACIT-F was from 0 to 52 with scores less than 30 indicated severe fatigue. Use of questionnaires was registered per the FACT website (www.FACIT.org). Higher scores were associated with better QoL and less symptoms of fatigue for the associated scales.

The questionnaires were administered during a patient visit to the Preston Robert Tisch Brain Tumor Center. They were administered at any stage after a diagnosis of recurrent disease per RANO criteria and as determined by their treating neuro-oncologist. Trained research administrative assistants were responsible for administering the testing and patients completed the questionnaires on paper with pens.

Clinical characteristics and survival data

Data in regards to patient clinical characteristics and survival outcome were obtained from the medical record. Patient characteristics included age, gender, tumor grade, progression number, type of salvage treatment, use of supportive medication (anti-epileptic drugs (AEDs) and corticosteroids), and KPS. Overall survival data was obtained from the medical record through July 2010.

Statistical analysis

Descriptive statistics were reported for clinical parameters and study outcomes. The Cox proportional hazards model was used to examine the effect of QoL (measured by subscales of the FACT-G and FACT-Br) and fatigue on survival. A likelihood ratio (LR) test was used in the context of the Cox model to assess the contribution of QoL and fatigue in predicting survival beyond that provided by KPS (<90 vs. \geq 90) alone as well as the combination of age (<45 vs. \geq 45), gender, grade (III vs. IV), the number of prior disease progressions (<2 vs. \geq 2), and KPS. Of note, we used time from diagnosis as a covariate to control for variable time from diagnosis to death. QoL and fatigue were analyzed as continuous variables. Unadjusted hazard ratios were obtained. Further analysis included hazard ratios adjusted for age, gender, tumor grade, number of prior tumor progressions, and KPS. Fatigue was also categorized using a cut-off score of 35 based on prior work [18, 19]. A fatigue score of 35 corresponded to a score that was approximately one standard deviation (15 points) worse than the general population. Survival time was defined as the time between questionnaire completion and death; for patients remaining alive, survival was censored at the time of last follow-up. A two-sided significance level of 0.05 was used for all statistical tests. All statistical

analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC).

Results

Patient characteristics

Study recruitment was conducted from May 2007 to April 2009. For this study, 244 patients were consented. Full patient characteristics have been published previously [20]. Of the 244 subjects, 237 (95 %) subjects completed the patient-reported outcomes measures for QoL including FACT-Br and FACIT-F and had valid scoring available. Initially 1,528 patients were screened for eligibility with 374 (24 %) meeting inclusion criteria and 237 (65 %) agreeing to participate, consent, and complete questionnaires. Participant characteristics can be seen in Table 1. For this analysis, 73 (31 %) patients had recurrent WHO grade III gliomas and 164 (69 %) had recurrent WHO grade IV glioma. Mean age was 50 years (range 20–77). Most patients were males at 161 patients (68 %). Functional status as measured by KPS ranged from 70 to 100 with a majority at 90. Median scores for the FACT-G total, FACT-Br total, and FACIT-F were 84 (range 34–108), 136 (range 46–182), and 36 (range 10–46), respectively (Table 1).

Association between QoL and survival

The median follow-up was 27.60 months. In follow-up, 145 deaths were recorded (61 % of the patients completing questionnaires). Median overall survival time for the entire sample was 15.76 month (95 % CI 12.70–21.55 months).

The association between QoL and survival can be seen in Table 2. There were no independent associations between survival and the FACT-G physical, emotional, functional, or social well-being subscale scores, the FACT-G total score, the FACT-Br total score, or the trial outcome index (TOI) (Table 2). Though the unadjusted FACT-G and FACT-Br total scores did not achieve a significant association with survival, there was a significant association between the FACT-Br brain cancer subscale and overall survival in recurrent glioma patients in an unadjusted analysis (HR 0.88; CI 95 % 0.77–1.00; $p = 0.048$). In the model where the hazard ratio was adjusted for traditional measures of prognosis including age, gender, number of prior progressions, and KPS, the effect of the FACT-Br brain cancer subscale was not statistically significant ($p = 0.100$). Other adjusted analyses did not show that FACT-G and FACT-BR subscales provided incremental prognostic information beyond the traditional markers of prognosis (Table 2).

Table 1 Demographic and clinical characteristics of participants

Variable	All patients		Grade of disease			
			III		IV	
	No.	%	No.	%	No.	
Total patients	237	100	73	31	164	69
Age, years						
Mean	50		44		52	
SD	12		11		11	
<45	79	33	38	52	41	25
≥45	158	67	35	48	123	75
Male sex	161	68	50	68	111	68
Karnofsky performance status						
70	11	5	4	5	7	4
80	74	31	20	27	54	33
90	121	51	41	56	80	49
100	31	13	8	11	23	14
Status of disease at diagnosis						
Active	42	18	12	16	30	18
Stable	195	82	61	84	134	82
No. of prior treatments						
1	22	9	4	5	18	11
2	74	31	25	34	49	30
3	76	32	19	26	57	35
≥4	65	27	25	34	40	24
No. of prior progressions						
0	17	7	7	10	10	6
1	132	56	37	51	95	58
2	58	24	12	16	46	28
≥3	30	13	17	23	13	8
Receiving salvage therapy at testing						
No	31	13	9	12	22	13
Yes	206	87	64	88	142	87
Receiving bevacizumab						
No	120	51	38	52	82	50
Yes	117	49	35	48	82	50
Receiving dexamethasone						
No	167	70	55	75	112	68
Yes	68	29	16	22	52	32
Unknown	2	1	2	3	0	0
Receiving anti-epileptic medication						
No	57	24	16	22	41	25
Yes	180	76	57	78	123	75
FACT-G: physical well-being (range 0–28)						
Median	23		22		24	
Minimum–Maximum	4–28		5–28		4–28	
FACT-G: functional well-being (range 0–28)						
Median	20		19		20	
Minimum–Maximum	4–28		5–28		4–28	
FACT-G: emotional well-being (range 0–24)						
Median	19		19		19	

Table 1 continued

Variable	All patients		Grade of disease		
			III		IV
	No.	%	No.	%	No.
Minimum – Maximum	4–24		4–24		9–24
FACT-G: social well-being (range 0–28)					
Median	24		23		24
Minimum–Maximum	6–28		6–28		9–28
FACT-G: total score (range 0–108)					
Median	84		83		85
Minimum–Maximum	34–108		34–105		37–108
FACT-Br: Brain Cancer Subscale (range 0–76)					
Median	52		53		52
Minimum–Maximum	12–76		12–76		24–76
FACT-Br: total score (range 0–184)					
Median	136		131		138
Minimum–Maximum	46–182		46–176		72–182
FACT-Br: trial outcome index (range 0–132)					
Median	94		94		95
Minimum–Maximum	25–130		25–128		43–130
FACIT-fatigue subscale (range 0–52)					
Median	36		34		36
Minimum–Maximum	10–46		10–46		11–45

Association between fatigue and survival

The association between fatigue and survival can be seen in Tables 2 and 3. In the univariate model, FACIT-F score was an independent predictor of survival ($p = 0.045$) with an unadjusted hazard ratio of 0.82 (95 % CI, 0.68–0.99) (Table 2). Patients reporting more fatigue symptoms on the FACIT-F scale demonstrated a poorer survival than patients who reported less fatigue. When adjusted for traditional markers of prognosis, the adjusted hazard ratio of 0.80 (95 % CI, 0.65–0.98) remained statistically significant.

A previously described cut point score of 35 on the FACIT-F score was used to categorize patients [19]. In adjusted analyses, the categorized fatigue subscale score (≤ 35 vs. > 35) was a significant predictor of survival (Fig. 1 and Table 3, $p = 0.005$), and it provided incremental prognostic information beyond KPS alone (< 90 vs. ≥ 90) (Table 3, $p = 0.029$). Patients reporting a fatigue score ≤ 35 exhibited significantly poorer survival than those patients reporting a score greater than 35 after adjustment for traditional markers of prognosis (HR 1.66; 95 % CI, 1.18–2.33; $p = 0.003$) (Table 3). Median survival was 12.50 months (95 % CI, 10.62–18.06) for patients reporting a fatigue score ≤ 35 compared with 20.59 months (95 % CI, 14.31– ∞) in those reporting a score greater than 35 (Fig. 1).

Table 2 Association between Quality of Life Measures and Survival

QoL Measure	Unadjusted*		Adjusted [†]	
	Hazard ratio (95 % CI)	Likelihood ratio <i>P</i>	Hazard ratio (95 % CI)	Likelihood ratio <i>P</i>
FACT-G: physical well-being	0.91 (0.66–1.24)	0.541	0.95 (0.67–1.34)	0.758
FACT-G: functional well-being	0.79 (0.60–1.03)	0.086	0.82 (0.62–1.08)	0.148
FACT-G: emotional well-being	0.89 (0.59–1.36)	0.592	0.87 (0.57–1.32)	0.513
FACT-G: social well-being	0.91 (0.65–1.29)	0.612	0.93 (0.63–1.37)	0.702
FACT-G: total score	0.94 (0.84–1.04)	0.242	0.95 (0.84–1.06)	0.329
FACT-Br: brain cancer subscale	0.88 (0.77–1.00)	0.048	0.89 (0.77–1.02)	0.100
FACT-Br: total score	0.95 (0.89–1.01)	0.090	0.95 (0.88–1.02)	0.154
FACT-Br: trial outcome index (TOI)	0.93 (0.86–1.00)	0.062	0.93 (0.85–1.02)	0.124
FACIT-fatigue subscale score	0.82 (0.68–0.99)	0.045	0.80 (0.65–0.98)	0.031

* All hazard ratios are associated with a 10 unit change in each QoL measure

[†]Adjusted for age, sex, grade, number of prior progressions, and KPS

Table 3 Association between FACIT-fatigue (≤ 35 , > 35) and survival

Analysis	FACIT-fatigue score		Likelihood ratio <i>P</i>
	≤ 35	> 35	
No. of events	82	63	
No. at risk	117	120	
Survival, months	12.50	20.59	
Median (95 % CI)	(10.63–18.06)	(14.31– ∞^*)	
Unadjusted HR (95 % CI)	Referent	1.60 (1.15–2.22)	0.005
HR (95 % CI) adjusted for KPS	Referent	1.45 (1.04–2.04)	0.029
Adjusted HR (95 % CI) [†]	Referent	1.66 (1.18–2.33)	0.003

HR hazard ratio, CI confidence interval, KPS Karnofsky performance scale

* Upper value was out of range

[†]Adjusted for age, sex, grade, number of prior progressions, and KPS

Discussion

Patients with HGG are likely to experience recurrent disease and outcomes continue to be poor. Extensive clinical research is being applied to improve these outcomes for this challenging population. While therapeutic clinical interventions are paramount, improvement in prognostication can aid clinicians to provide the best care for recurrent HGG patients. To improve outcomes, researchers have sought to understand the factors associated with survival beyond traditional measures. Traditional characteristics of poor prognosis in the recurrent HGG population have included grade, older age, male gender, KPS <90, and increased number of progressions. Patient-reported measures of QoL have become increasingly used in clinical

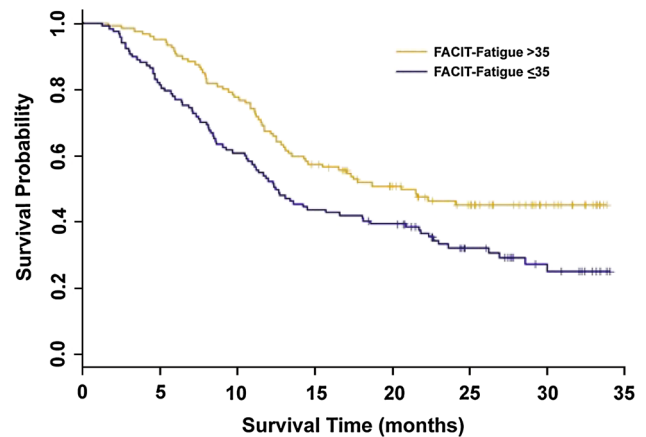


Fig. 1 Association between FACIT-Fatigue and survival

trials not only as a secondary outcome but also as a marker of prognosis in patients with cancer [21]. QoL is routinely impaired in patients with HGG, but associations with survival in this population have not necessarily been supported. In our study, we have evaluated the role of QoL and fatigue in patients with recurrent HGG and our findings include that subjective measures of fatigue, using the FACIT-F, are an independent predictor of survival in this population. This represents the first study to measure specifically fatigue using FACIT-F in the recurrent HGG and associate measures from this questionnaire with survival in recurrent HGG.

One study of 273 newly diagnosed HGG patients have shown that changes in QoL measures have not been found to be associated with survival, but a second study of 194 newly diagnosed HGG patients has shown that fatigue is a significant predictor of survival but other measures of QoL did not add prognostic value. In a study of 80 recurrent high-grade patients, QoL measures (in particular FACT-Br) do not add prognostic value, but presence of cognitive

impairment does have an association with a poorer survival [14]. Our study of 237 recurrent patients shows that the FACT-Br specific subscale does correlate with survival in univariate analysis, but in multivariable analysis does not add to the prognostic value of traditional markers. Furthermore, other measures of QoL (FACT-Br Total Score and Trial Outcome Index) do not provide prognostic information in unadjusted and adjusted models. One concern raised in our analysis is that multiple analyses have been performed on our single data set and that this could increase the odds of yielding a false positive result. In future analyses, this could be controlled for with analysis using the Bonferroni correction [22].

In our study, the key finding is that fatigue, as measured by the FACIT-F, is a strong independent predictor of survival in recurrent HGG patients (Tables 2, 3; Fig. 1). Fatigue has been identified as an significant predictor of survival in other cancers such as metastatic prostate cancer [23], breast cancer [24], and non-small cell lung cancer [25]. Measures used have included FACIT-F, European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), Symptom Distress Scale (SDS). Because this occurs in other cancers, it would suggest that there could be a common etiology to fatigue and a common intervention for the alleviation of fatigue in cancer patients. Our findings and similar findings in other cancers indicate that specific measures of fatigue should be included in studies involving outcomes in health-related QoL.

Fatigue, in the context of QoL, impacts most patients struggling with a cancer diagnosis [26–30]. Diagnostic criteria for cancer-related fatigue are as follows: “diminished energy and mental capacity and increased need to rest that is disproportionate to any recent change in activity level and is evident nearly every day during any 2-week period in the past month [31].” Invariably, it is measured in a subjective fashion using patient-report outcomes. Etiology of cancer-related fatigue is multifactorial and includes comorbid disorders, chemotherapy, radiotherapy, overall frailty, and other medications. Mood disorders such as depression and anxiety often are associated with fatigue [32]. Endocrine dysfunction, in particular adrenal insufficiency, testosterone deficiency, and thyroid hormone deficiency, can occur in the context of cancer, particularly for patients with brain tumors that have received radiotherapy and this can produce fatigue [33–35]. Universally, chemotherapy and radiotherapy, by virtue of affecting bone marrow and blood counts, causes fatigue [12, 19, 36]. For patients with cancer that are receiving chemotherapy actively, fatigue ranks as the most significant symptom in comparison to other symptoms and problems [36]. For brain tumor patients, use of supportive medications such as corticosteroids and anti-epileptics are associated with

fatigue [37]. Recent research in low-grade glioma show that QoL impairment is associated with the presence of seizures and use of anti-epileptics [38]. In brain tumor patients, fatigue severity and risk factors for fatigue have been studied; female sex, poor KPS, disease status, use of opioids and AEDs are predictors of fatigue [39]. Other symptoms associated with fatigue are sleep disturbance, weakness, pain, and psychiatric distress [39]. Fatigue, with its broad associations and causations, remains an important marker of QoL in brain tumor patients and now a predictor of survival in the recurrent HGG population.

In light of its importance, fatigue appears to be an obvious avenue for intervention. Unfortunately, the multifocal nature of this symptom could make identification of one single intervention challenging. Recognition of endocrine dysfunction (e.g. thyroid deficiency and testosterone deficiency) and mitigation of severe bone marrow toxicity must first be undertaken in this population to treat fatigue [37, 40]. Close management of other medications such as anti-epileptics is recommended to help lower side effects such as fatigue [39]. Novel interventions, whether pharmacologic and non-pharmacologic, are now being studied in this population. Psychostimulants, such as methylphenidate and modafinil, have been used to improve cognition and to reduce fatigue in patients with brain tumors [41, 42], but initial results have not shown significant improvements over placebo [43]. Work from our group has focused on the role of exercise behavior and functional capacity outcomes in patients with primary brain tumors. As part of a companion study in the same set of patients, exercise behavior (as measured in MET-h/week) was an independent predictor of survival in recurrent high-grade glioma with median survival of 13.03 months for patients reporting <9 MET-h/week relative to 21.84 months for those patient reporting >9-MET-h/week [20]. Thus, exercise interventions for particular patient populations with cancer could abrogate fatigue and in turn improve survival as these are likely associated. Previous meta-analyses showed the exercise training indeed improves QoL outcomes and fatigue [44]. Exercise in the non-neurological cancer population could, at first glance, appear to be more readily applicable, but further work is needed to evaluate exercise in the cancer population with neurological dysfunction such as cognitive and functional impairments. From our study observations, these pharmacological or non-pharmacological interventions on fatigue, if taken separately or in combination, could potential impact survival and further studies are warranted into this particular aspect.

Primary drawbacks of this current study include the focus on one measurement of self-reported QoL and fatigue rather than a series of assessments as well as the variability of the patient population. Since only one timepoint is evaluated, our conclusions are limited and cannot be

generalized to all recurrent HGG patients. For future therapeutic clinical trials involving recurrent HGG patients, QoL and fatigue should be assessed throughout treatment course. Our study population includes both patients with active progressive and stable disease in the context of recurrent HGG. While this heterogeneity could force a dichotomization, we feel that the presence of this heterogeneity, in fact, reflects the true population of recurrent HGG. Furthermore, it provides large patient numbers to improve the power in this study. Another potential drawback is that QoL can be measured using a variety of different instruments. In this study, we chose to use FACT-Br and FACIT-F, but other studies, such as the study by Meyers and colleagues, have utilized European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire (EORTC QIQ-30) [45]. While it could be concluded that different instruments could lead to different results, we suggest that our use of a specific brain tumor instrument such as the FACT-Br provides our study with increased relevance.

In conclusion, fatigue, as measured by the FACIT-F, is an independent predictor of survival in recurrent HGG. Moreover, the addition of this measure to traditional measures of prognosis improves the prognostic value to a greater degree than with traditional measures alone. Additional studies are warranted to investigate the etiology of fatigue in recurrent HGG patients and to develop interventions to alleviate and/or prevent fatigue.

Conflict of interest The authors have no conflicts of interest to disclose.

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