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Clinical Study

Prospective study of quality of life in adults with newly diagnosed high-grade gliomas

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Summary

Objective: To assess baseline quality of life (QOL) and its prognostic importance for adults with newly diagnosed high-grade gliomas, we analyzed QOL and outcome data prospectively collected in three phase II high-grade glioma protocols.

Methods: At study entry, patients completed five self-administered forms to assess overall QOL (linear analogue scale assessment [LASA] and Functional Assessment of Cancer Therapy-Brain [FACT-Br]); fatigue (Symptom Distress Scale [SDS]); excessive daytime somnolence (Epworth Sleepiness Scale [ESS]); and depression (POMS-SF). Folstein Mini-Mental State Examination (MMSE) and Eastern Cooperative Oncology Group (ECOG) performance scores (PS) were obtained by the health care provider.

Results: Baseline QOL data were available for 194 of 220 patients (88%) enrolled in the three protocols. Differences in baseline QOL among the three studies were not statistically significant. One-third of patients had clinically significant fatigue at baseline. Increased fatigue ($P = 0.003$), excessive daytime somnolence ($P = 0.01$), and lower overall QOL scores (LASA, $P = 0.001$; FACT-Br, $P = 0.0001$) correlated with worse ECOG PS. No relation was found between QOL and corticosteroid or anticonvulsant therapy, extent of resection, tumor grade, or sex. Multivariate analyses found worse ECOG PS (PS 2, $P = 0.007$) associated with increased fatigue. Worse ECOG PS (PS 2, $P = 0.002$) was also associated with worse overall QOL (LASA). On multivariate analyses of survival, increased fatigue ($P = 0.003$) predicted poorer overall survival.

Conclusions: Performance status is related to QOL in patients with newly diagnosed high-grade brain tumors. Increased fatigue is an independent predictor of overall survival. Interventional studies directed at improving QOL, especially fatigue, may have important benefits for these patients.

Abbreviations: CART – classification and regression tree; ECOG – Eastern Cooperative Oncology Group; ESS – Epworth Sleepiness Scale; FACT-Br – Functional Assessment of Cancer Therapy-Brain; GTR – Gross Total Resection; KPS – Karnofsky performance scale; LASA – linear analogue scale assessment; MMSE – Folstein Mini-Mental State Examination; NCCTG – North Central Cancer Treatment Group; POMS-SF – Profiles of Mood States Short Form; PS – performance scores; QOL – quality of life; SD – standard deviation; SDS – Symptom Distress Scale

Introduction

High-grade gliomas are extremely aggressive tumors. Despite intensive treatment with surgery, radiotherapy, and chemotherapy, most patients invariably have tumor recurrence, with the median survival time ranging from 1 to 3 years after initial diagnosis [1]. Because life expectancy is brief, issues related to quality of life (QOL) are immensely important to patients and their caregivers. QOL is a multidimensional construct and is best measured with several different instruments [2,3]. Fatigue, depression, cognitive impairment, and excessive daytime somnolence can seriously impair the QOL of patients with high-grade brain tumors. However, because all these are potentially amenable to treatment, it is important to establish pre-treatment QOL baselines for comparison of future therapeutic trials. The primary objective of our study was to prospectively determine the QOL of patients with newly diagnosed high-grade gliomas and to examine the relation between baseline QOL and outcome.

Methods and materials

Subjects

The Glioma QOL study was a companion protocol for three Institutional Review Board-approved high-grade

glioma (newly diagnosed) treatment protocols (98-72-51, 98-72-52, N0074). North Central Cancer Treatment Group (NCCTG) 98-72-51 was a phase II trial in which patients with grade 3 astrocytomas (anaplastic astrocytomas) received two cycles of pre-irradiation chemotherapy [carmustine (40 mg/m^2 daily on days 1 through 3), cisplatin (20 mg/m^2 daily on days 1 through 3 and days 29 through 31), and oral etoposide (50 mg/m^2 daily on days 1 through 21 and days 29 through 49)], followed by one cycle of the same chemotherapy delivered concurrently with radiotherapy [4]. The initial radiotherapy target volume included the tumor plus edema based on the T_2-weighted post-operative magnetic resonance imaging scan plus a 2-cm margin; this target volume received a dose of 5000 cGy in 25 fractions. The enhancing tumor based on the T_1-weighted image with contrast plus a 2-cm margin was the target volume for the boost and was treated to a dose of 1000 cGy in five fractions, for a total dose of 6000 cGy. Twenty-nine patients were enrolled between February 1999 and April 2001.

In NCCTG 98-72-52, patients with glioblastomas received one cycle of pre-irradiation chemotherapy [carmustine (40 mg/m^2 daily on days 1 through 3), cisplatin (20 mg/m^2 daily on days 1 through 3 and days 29 through 31), and oral etoposide (50 mg/m^2 daily on days 1 through 21 and days 29 through 49)], followed by one cycle of the same chemotherapy delivered concurrently with radiotherapy [5]. The radiation was delivered in the same fashion as in NCCTG 98-72-51 to a total dose of 6000 cGy. Radiotherapy was followed by four cycles of carmustine (200 mg/m^2 every 8 weeks). Ninety-three patients were enrolled between May 1999 and August 2000.

NCCTG N0074 was a phase II study of the epidermal growth factor receptor inhibitor ZD1839 (500 mg daily for patients not receiving enzyme-inducing anticonvulsants and escalation up to 1000 mg for those receiving these agents) starting 2–5 weeks after radiotherapy was completed for patients with glioblastomas. ZD1839 was continued for up to 2 years or until tumor progression. Ninety-eight patients were enrolled between May 2001 and August 2002.

Assessment

For the Glioma QOL study, five self-administered forms were completed by the patient (after receiving instructions on how to complete the forms) within 72 h after study entry. Patients also underwent testing with the Folstein Mini-Mental State Examination (MMSE) [6]. The Eastern Cooperative Oncology Group (ECOG) performance score (PS), a simple, widely administered measure of physical function, was also graded by the health-care provider. These tests were completed to assess overall QOL, fatigue, excessive daytime somnolence, depression, and cognitive functioning.

At each protocol-defined evaluation, patients underwent a physical examination that included a neurologic examination and computed tomography or magnetic resonance imaging. The median follow-up for the 60 patients still alive is 7.9 months.

In this manuscript, the following QOL measures (listed below) used to assess certain aspects of QOL (i.e., overall QOL, fatigue, depression, excessive daytime somnolence) are only reported as *pre-defined in the protocol*. Exploratory QOL analyses not pre-defined in the protocol (i.e., subscales of Profiles of Mood States Short Form [POMS-SF]) will be deferred for future reports.

Overall QOL

A simple, five-item linear analogue scale assessment (LASA) and the Functional Assessment of Cancer Therapy-Brain (FACT-Br version 4) were used. LASA has been shown to be effective for obtaining valid and reliable measures of several QOL variables [7,8]. The five aspects measured were overall QOL, physical, emotional, spiritual, and intellectual well-being. FACT-Br [9] was designed to supplement the generic FACT scale, a self-administered questionnaire designed to provide information about the health status of cancer patients in general [7]. FACT-Br is a 46-item measure with 27 general items to assess physical, social/family, emotional, and functional well-being and an additional 19 brain-specific items. In this report, only the total score was analyzed; the subscale scores will be analyzed in future reports.

Fatigue

The Symptom Distress Scale (SDS) was used to measure fatigue. SDS is a 13-item self-administered questionnaire developed to measure common physical concerns of cancer patients [10]. Only the fatigue question from the SDS was used to evaluate fatigue.

Excessive daytime somnolence

The Epworth Sleepiness Scale (ESS) is a simple eight-question self-administered questionnaire that provides sleep propensity results comparable to the multiple sleep latency test [11,12]. This scale has proven reliability [13,14] and clinical utility [15] in assessing excessive daytime somnolence and its response to therapy.

Depression

The depression scale of the Profiles of Mood States Short Form (POMS-SF) was used to assess self-reported items related to depression. POMS-SF is a shortened version of POMS, a questionnaire that has been well validated in cancer populations [16–18]. POMS-SF is a 30-item (6 subscales) self-administered questionnaire that has been used in many patient populations [19,20], including those with cancer [21,22].

Cognitive functioning

MMSE [6], a 30-item test administered by a health-care provider, is a well-validated screening test for dementia and cognitive impairment [23–26]. Although a high

correlation has been reported with other, more comprehensive standardized neurocognitive instruments, such as the Wechsler Memory Scale [27] and the Modified Blessed Test [28,29], there is some concern about the sensitivity of the MMSE in brain tumor patients [30]. However, because of concerns of overburdening high-grade glioma patients with an already lengthy QOL battery, the rather brief MMSE was used instead of more extensive neurocognitive testing.

Collectively, patients completed these QOL tools and the MMSE in approximately 30 min.

Statistical analysis

The raw summative scores from each QOL measure were transformed for analysis. For a given raw score, the transformed score was a value between 0 and 100 inclusive; this represented the relative position of the raw score along the theoretical dimension for the score [31,32]. In all cases, 0 reflected the worst QOL and 100, the best. By using the transformed scores, we were able to compare scores designed to evaluate the same construct as well as compare relative scores designed for different QOL domains. All analyses used the transformed scores.

Transformed QOL scores were viewed as a continuous measure. Continuous baseline, disease, and QOL variables were summarized as the mean ± 1 standard deviation (SD) or the median (25th percentile score, 75th percentile score) or both. Categorical baseline and disease variables were summarized as frequency (percent). Because some of the variables had skewed distributions, comparisons of continuous variables among the three groups were made with the Kruskal-Wallis test. The Wilcoxon rank sum test was used to analyze differences between two groups. Categorical variables were compared among and between groups with the Fisher exact test. Univariate associations between the QOL measures and continuous baseline patient and disease variables were measured with the Spearman rank correlation coefficient denoted as r. The Wilcoxon rank sum test or Kruskal–Wallis test was used to identify univariate associations between the QOL variables and categorical baseline patient and disease variables. Of interest were patient and disease characteristics associated with clinically impaired QOL. This was defined as a score of 50 or less for each QOL measure [33,34]. Time-to-event distributions (e.g., survival, time to progression) were estimated with Kaplan–Meier curves [35] and compared with log-rank tests [36]. Time was measured from the date of surgical procedure or biopsy to the date of the event or last follow-up. Progression was declared if the neurologic examination results worsened or tumor size increased at least 25%, as based on measurement of perpendicular diameters or a clear increase in the size of the tumor on imaging compared with baseline. Classification and regression tree (CART) models [37] and Cox proportional hazards models [38] were used to assess the strength of associations of progression-free or overall survival with various baseline patient, disease, and QOL variables. A bootstrap model selection procedure combining bootstrap methodology [39] and Cox model backward-selection procedures [40] was used to validate the Cox model variable selection. Variables identified as significant ($P < 0.05$) in two-thirds or more of the 1000 bootstrap samples generated were considered valid prognostic indicators.

All statistical tests were two-sided, and to protect against spurious findings due to multiple analyses, $P \leq 0.01$ was considered statistically significant for non-bootstrapped analyses. The statistical analyses were performed with SAS version 8 (SAS Institute Inc, Cary, North Carolina).

Results

QOL responses

There were 220 patients accrued to the 3 trials. Of the 220 patients, 173 (79%) completed all 5 QOL forms, 26 (12%) did not complete any of the 5 QOL forms, and 194 (88%) completed at least 1 of the QOL forms. There were no significant differences in the completion rates of the QOL forms among the three studies ($P = 0.79$).

There were no differences in any of the measured baseline variables between patients who completed at least 1 of the QOL forms and those who did not complete any of the QOL forms (all $P > 0.10$).

Baseline characteristics

The baseline characteristics of patients who completed at least one QOL form were compared across the three studies (Table 1). Patients in 98-72-51 (grade 3 astrocytomas) tended to be younger and to have gross total resection (GTR) of the tumor less often than patients in 98-72-52 and N0074 (glioblastomas in both studies). Patients in N0074 were required to undergo standard radiotherapy before being able to enroll in the study, which was not the case for 98-72-51 and 98-72-52. The latter two protocols had radiotherapy as part of the study treatment regimen. Of note, the baseline MMSE and performance scores were similar among the three studies.

Comparison of QOL scores across studies

Baseline scores for the QOL forms were summarized and compared across studies. Overall, all measures appeared to be similar across the studies. Because there were no statistically significant differences on the QOL scores across the three studies, the patients were pooled for the analysis of QOL at baseline (Table 2). However, previous radiation (yes vs. no) was used as a covariate in the multivariate models as an adjusting variable.

The average score for a healthy population of persons is 70 to 80 for each of the QOL measures [33,34,41]. Furthermore, a 10-point difference in a given QOL score is considered clinically significant [31,32,42,43]. Therefore, the baseline QOL scores of these patients with high-grade gliomas do not appear on average to differ considerably from those of a healthy population.

Table 1. Summary of baseline characteristics by study for patients with some QOL data

Variable	Study			*P*-value
	98-72-51 (n = 26)	98-72-52 (n = 83)	N0074 (n = 85)	
Age (years)				
Median (min, max)	51 (30, 68)	57 (19, 79)	57 (19, 79)	
Mean ± SD	50 ± 12	55 ± 12	57 ± 11	0.03
MMSE				
Median (min, max)	29 (8, 30)	28 (9, 30)	29 (19, 30)	
Mean ± SD	28 ± 5	27 ± 4	28 ± 2	0.67
Sex, no. of patients (%)				
Female	10 (38)	31 (37)	26 (31)	
Male	16 (62)	52 (63)	59 (69)	0.58
Performance score, no. of patients (%)				
0	15 (58)	39 (47)	31 (36)	
1	9 (35)	36 (43)	43 (51)	
2	2 (8)	8 (10)	11 (13)	0.39
Extent of resection, no. of patients (%)				
Biopsy	13 (50)	12 (14)	7 (8)	
Subtotal resection	8 (31)	43 (52)	38 (45)	
Gross total resection	5 (19)	28 (34)	40 (47)	< 0.001
Tumor grade, no. of patients (%)				
3	26 (100)	0	0	
4	0	83 (100)	85 (100)	< 0.001
Tumor location, no. of patients (%)				
Temporal	6 (23)	17 (20)	21 (25)	
Frontal	8 (31)	21 (25)	18 (21)	
Parietal	1 (4)	11 (13)	14 (16)	0.97
Occipital	0	5 (6)	1 (1)	
Other/mixed	11 (42)	29 (35)	31 (36)	
Side, no. of patients (%)				
Right	17 (65)	42 (51)	48 (56)	
Left	8 (31)	36 (43)	36 (42)	
Bilateral/midline	1 (4)	5 (6)	1 (1)	0.32
Anticonvulsant therapy, no. of patients (%)				
Yes	22 (85)	61 (73)	60 (71)	
No	4 (15)	22 (27)	25 (29)	0.39
Corticosteroid therapy, no. of patients (%)				
Yes	15 (58)	54 (65)	51 (60)	
No	11 (42)	29 (35)	34 (40)	0.69

MMSE, Folstein Mini-Mental State Examination; QOL, quality of life.

Association between QOL measures and baseline characteristics

The data were analyzed to determine whether there was an association between the QOL measures and continuous baseline patient characteristics (age, MMSE).

Table 2. Summary of QOL Data

Variable	*N*	Median	25th, 75th percentile	Min, max	Score ≤ 50, no. of patients (%)
SDS-fatigue	189	75	50, 75	0, 100	64 (33.9)
POMS-depression	185	85	70, 95	20, 100	18 (9.7)
ESS	185	67	54, 83	0, 100	39 (21.1)
LASA overall	191	75	50, 88	13, 100	58 (30.4)
FACT-Br	190	74	64, 82	24, 98	7 (3.7)

ESS, Epworth Sleepiness Scale; FACT-Br, Functional Assessment of Cancer Therapy-Brain; LASA, linear analogue scale assessment; POMS, Profiles of Mood State; QOL, quality of life; SDS, Symptom Distress Scale.

LASA overall (r = 0.2, P = 0.01) and FACT-Br (r = 0.25, P = 0.001) were found to have a significant positive association with the MMSE score, but the strength of the associations was relatively weak.

There did not appear to be a univariate association between QOL measures and many of the categorical baseline patient characteristics (gender, performance score, tumor grade, tumor location, tumor laterality, extent of resection, anticonvulsant therapy, corticosteroid therapy, previous radiotherapy; all $P > 0.05$). In particular, tumor characteristics such as type, grade, and location did not appear to be associated with any QOL measure. However, patients with a tumor on the right side of the brain were more fatigued clinically than those with a tumor on the left side (60 ± 30 vs. 72 ± 21, P = 0.01). Performance score was significantly associated with most of the QOL measures, with a performance score of two associated with worse scores on the QOL measures than a performance score of 0: SDS-fatigue (50 ± 35 vs. 73 ± 22, P = 0.003), ESS (54 ± 24 vs. 70 ± 17, P = 0.01), LASA overall

(54 ± 23 vs. 75 ± 19, $P = 0.001$), and FACT-Br (62 ± 15 vs. 76 ± 12, $P = 0.0001$). Patients who had radiotherapy before the baseline QOL assessment tended to be clinically more fatigued (SDS) on average than those who did not have previous radiotherapy (60 ± 29 vs. 70 ± 25, $P = 0.02$).

A multivariate analysis was performed to determine baseline patient and disease characteristics that were independently associated with a clinically impaired QOL measure, defined as a score of 50 or less [33,34]. CART analysis was performed to identify potential interactions among variables. A multivariate backward logistic regression model was used to determine variables or interactions (or both) that were independently associated with impaired QOL (yes/no) for each measure. For most QOL measures, no variable was found to be independently associated with impaired QOL (Table 3). Notably, previous radiotherapy was not associated with any impaired QOL measure. A higher (worse) performance score was associated with impaired overall QOL, as measured by LASA ($P = 0.002$ for a performance score of 2). Worse performance status ($P = 0.007$ for a performance score of 2) was associated with debilitating fatigue as measured by SDS-fatigue, whereas tumor laterality lost its statistical significance ($P = 0.05$).

Association of baseline patient characteristics and QOL measures with progression-free survival

The univariate association of progression-free survival with each patient, disease, and QOL baseline measure was determined. Consistent with other NCCTG studies, younger age ($P = 0.0007$) predicted a better progression-free survival [44]. No QOL measure, including the standard MMSE and performance score measures, had a statistically significant association with progression-free survival.

Kaplan–Meier estimates of progression-free survival were compared between patients who had clinically impaired QOL (score ≤ 50) and those who did not (score > 50) for each of the five QOL measures. No difference in progression-free survival was found between these two groups for each of the five QOL measures (all $P > 0.10$).

A CART analysis was used to identify potential interactions between patient, disease, and QOL measures and progression-free survival. No QOL measure was independently associated with progression-free survival after adjusting for previous radiotherapy. The only variable independently associated with progression-free survival after adjusting for previous radiotherapy was age ($P = 0.002$).

Table 3. Final logistic regression models for determining variables independently associated with impaired QOL[a]

QOL measure	Variable	OR (95% CI)	*P*-value
SDS-fatigue ($n = 169$)	PS		
	0	1.00	
	1	2.1 (1.0–4.1)	0.04
	2	4.0 (1.5–11.2)	0.007
	Tumor side		
	Left	1.00	
	Right	1.9 (1.0–3.6)	0.05
POMS-depression ($n = 166$)		No significant variables	
ESS ($n = 185$)		No significant variables	
LASA overall ($n = 172$)	PS		
	0	1.00	
	1	2.3 (1.1–4.6)	0.02
	2	5.1 (1.8–14.4)	0.002
FACT-Br ($n = 171$)		No significant variables	

CI, confidence interval; ESS, Epworth Sleepiness Scale; FACT-Br, Functional Assessment of Cancer Therapy-Brain; LASA, linear analogue scale assessment; OR, odds ratio; POMS, Profiles of Mood State; PS, performance score; QOL, quality of life; SDS, Symptom Distress Scale.
[a]The sample sizes vary because of missing response variable and/or explanatory varibles.

Association of baseline patient characteristics and QOL measures with survival

The univariate association of survival with each baseline patient, disease, and QOL measure was determined. Among the patient characteristics, age, performance score, tumor location, and extent of resection were significantly associated with survival. Younger age ($P < 0.0001$), gross total resection ($P = 0.05$), anticonvulsant therapy ($P = 0.04$), higher MMSE score ($P = 0.01$), and tumor in the frontal lobe ($P = 0.03$) all tended to predict a better overall survival. In contrast, patients who required corticosteroid treatment ($P = 0.03$), had an ECOG performance score of 2 ($P = 0.0004$), or had a tumor in the occipital lobe ($P = 0.02$) tended to have worse survival.

There was no difference in survival between patients who completed at least one QOL assessment and those who did not complete any ($P = 0.60$). Two QOL measures had a statistically significant association with survival: SDS-fatigue ($P = 0.003$) and FACT-Br ($P = 0.01$). Patients who were less fatigued and those with higher overall QOL tended to survive longer.

Kaplan–Meier estimates for overall survival were compared between patients who had clinically impaired QOL (score ≤ 50) and those who did not (score > 50) for each of the five QOL measures. No significant difference in survival was found between the groups for the QOL measures of POMS-depression, ESS, LASA, and FACT-Br. Clinically impairing fatigue, as measured by SDS-fatigue, was associated with poorer survival although the difference between the two groups failed to achieve statistical significance ($P = 0.05$, Figure 1). The median survival of patients with an SDS-fatigue score of 50 or less was 8.4 months, as compared with 11.2 months for those with a score greater than 50.

CART analysis was used to identify potential interactions between patient, disease, and QOL measures and overall survival. SDS-fatigue ($P = 0.002$) was the QOL measure independently associated with overall survival (Table 4, variables of interest and variables found to be independently associated with overall survival listed): the less the patient was fatigued, the better survival

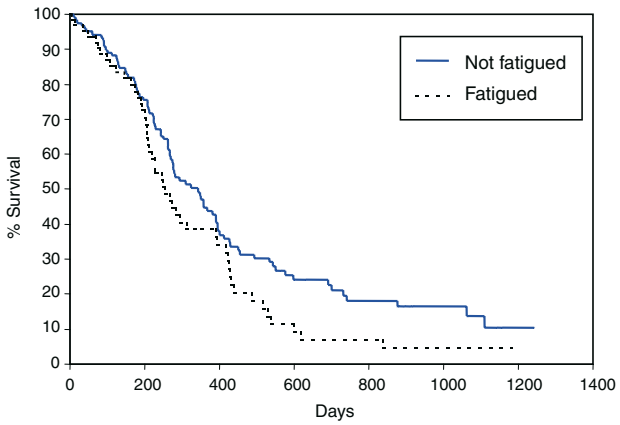


Figure 1. Comparison of survival between patients with Symptom Distress Scale-fatigue score ≤ 50 (fatigued) and those with a score > 50 (not fatigued) ($P = 0.05$).

Table 4. Final multivariate cox proportional hazards model for variables found to be independently associated with overall survival[a]

Variable	HR (95% CI)	*P*-value
Previous radiotherapy		
No	1.00	
Yes	1.18 (0.75–1.87)	0.47
Age	1.04 (1.02–1.06)	< 0.0001
Anticonvulsant therapy		
No	1.00	
Yes	0.53 (0.34–0.83)	0.005
Corticosteroid therapy		
No	1.00	
Yes	2.01 (1.31–3.08)	0.001
Extent of surgery		
Biopsy	1.00	
Subtotal resection	1.00 (0.59–1.69)	1.00
Gross total resection	0.64 (0.36–1.13)	0.13
MMSE	0.94 (0.89–0.98)	0.01
SDS-fatigue	0.99 (0.98–1.00)	0.002

CI, confidence interval; HR, hazard ratio; MMSE, Folstein Mini-Mental State Examination; SDS, Symptom Distress Scale.
[a]Population of 167 patients, 117 deaths. The sample size differs from 173 (number of patients with all five QOL measures) because six patients had missing values on one or more explanatory variables.

tended to be. Higher MMSE score, younger age, anticonvulsant therapy, and absence of corticosteroid therapy were all independent predictors of better overall survival.

Discussion

This NCCTG study prospectively evaluated the baseline QOL of adults with newly diagnosed high-grade gliomas. Whether the QOL of our patients was assessed at baseline could be questioned. The patients from N0074 had completed radiotherapy before proceeding to maintenance epidermal growth factor receptor inhibitor on study. The baseline QOL of these patients did not differ from that of the other patients except for a trend for increased levels of fatigue; therefore, these patients were included in the entire group for the 'baseline' analyses. Because surgical intervention (resection or biopsy) can have a positive [45] or negative [46] effect on QOL, assessing may not accurately reflect true 'baseline' QOL. However, the current NCCTG study is similar to the majority of studies that have tested QOL in patients with high-grade gliomas, with the baseline assessment being made post-operatively [8,47–52].

The results of our study indicate that performance status is closely related to QOL. This is consistent with the findings of Mackworth et al. [53] who used the Karnofsky performance scale (KPS) and a 20-min questionnaire covering 10 aspects of QOL to evaluate 200 patients with brain tumors. With more symptomatic patients (KPS, 50–80), KPS was sensitive to the QOL of patients. However, for relatively asymptomatic patients (KPS, 90–100), KPS was insensitive to QOL and the questionnaire provided a more definitive assessment of QOL. These results were confirmed during the development and validation of the FACT-Br, with KPS insensitive to QOL in patients with high KPS scores [9]. Klein et al. [51] studied post-surgically (before radiotherapy) 68 patients who had newly diagnosed gliomas and found a significant correlation between performance status and QOL. Osoba et al. [8,47] studied QOL in 105 patients with high-grade gliomas and noted significantly better QOL in patients with a KPS of 80 to 100 than in those with a KPS of 50 to 70. Although these disparate results may seem confusing, they could be explained by the lower performance status scores in the studies of Klein et al. (mean 76.7) and Osoba et al. (27% with a KPS of 50–70) and in our study (56% with an ECOG performance score of 1 or 2) than in the studies of Weitzner et al. [9] and Mackworth et al. [53]. Therefore, with these studies taken as a whole, performance scales do correlate with the QOL of a patient who has a brain tumor; however, performance scales do *not* provide a detailed assessment of the patient's QOL and are insensitive in high-performance patients.

Direct correlations between QOL and neurocognitive function have been found in long-term survivors of malignant brain tumors [8,47,54,55], in patients with newly diagnosed gliomas [51], and in patients with brain metastases [56]. In our study, increased fatigue, increased depression, and lower overall QOL scores correlated directly with lower MMSE scores. Others have reported similar findings, with deterioration in neurologic status associated with a decrease in QOL and an increase in fatigue [47]. This relation may be due to psychologic difficulties negatively influencing cognitive functioning [57], the negative effects of neurocognitive deficits on QOL [47], or both.

We found no differences in the baseline QOL of patients with anaplastic astrocytomas and those with glioblastomas (all $P > 0.10$). This is consistent with the findings of others who reported no significant differences in QOL between patients with grade 3 and those with grade 4 astrocytoma [48,52,55,58,59]. The lack of differences in QOL despite glioblastomas being more aggressive than anaplastic astrocytomas may be explained by the greater importance of neurocognitive function and disease status on QOL [47,55]. Although this would result in patients with anaplastic astrocytomas

and those with glioblastomas having similar levels of QOL initially and shortly after treatment, patients with glioblastomas would be expected to have a briefer period of stable QOL because of their shorter time to tumor progression and neurocognitive deterioration.

In the current study, tumors in the right hemisphere correlated with increased fatigue on univariate analyses. Various results have been reported, including left-sided tumors being associated with more depressive symptoms [52] and difficulties with communication [51], right-sided tumors having a negative effect on QOL in multiple dimensions [60] and patients suffering from more tension [61], and tumor laterality having no effect on QOL [62]. It may be that tumor laterality itself is not a sufficiently sensitive variable for analysis, and a larger number of patients may be needed to truly study the effect of laterality and specific tumor location [63] (e.g., superior frontal gyrus, frontotemporal region, or superior parietal lobe) on QOL.

One-third of our patients had an SDS fatigue score of 50 or less. Previous radiotherapy [64] in the cohort of patients treated on N0074 may have contributed to the fatigue but does not explain this finding completely. Osoba et al. [47] assessed the QOL of 41 patients with newly diagnosed high-grade gliomas and found that fatigue had the greatest symptom level of the nine symptom scales. A review of 488 patients with high-grade gliomas enrolled in three separate clinical trials found that fatigue was the most frequently reported symptom [59]. In addition, fatigue scored the highest (most difficulty with this symptom) of the tested symptom scales. The Nottingham health profile was used to measure QOL in 22 consecutive patients with high-grade gliomas who presented to Oulu Clinic [60]. Difficulties with 'energy' levels were much higher for patients with high-grade gliomas than for those with low-grade gliomas or benign brain tumors. In a cross-sectional questionnaire-based survey of 73 patients with primary brain tumors, 42% reported 'quite a bit low' or 'very low' energy levels on the FACT-Br [65]. Further analyses showed that increased levels of fatigue correlated strongly with decreased QOL. At the University of California, San Francisco, 60 adults with high-grade gliomas were evaluated at diagnosis and 2 weeks after radiotherapy [64]. POMS-SF was used to evaluate fatigue and the Multidimensional Quality of Life Scale-Cancer version 2 to evaluate overall QOL. Increased levels of fatigue were noted at diagnosis and a significant increase in the level of fatigue was seen after radiotherapy. There also was significant negative correlation between the fatigue scores and overall QOL and all but one of the QOL subscores.

Multivariate analyses found that the variables of age, baseline MMSE score, and corticosteroid and anticonvulsant therapy are predictors of overall survival [44,66,67]. Grade was not an independent prognostic variable, likely because of the small number and poorer-than-expected survival of patients with anaplastic astrocytoma [12.9 months, unpublished data). A novel finding is that increased fatigue, a QOL measure, is a significant negative prognostic factor. This may be explained by the close relation between fatigue and KPS in the patients in our study. Mackworth et al. [53] also found both QOL and KPS to be predictive of survival, although KPS was a much stronger predictor than QOL. Rogers et al. [62] used a self-administered 10-point Likert scale to assess the QOL of 430 patients with brain tumors and found that poorer scores on physical function, energy levels, and overall well-being were all predictive of worse survival. Another explantation is the close relation between fatigue and QOL [65], because many studies have reported a relation between QOL and disease status [8,47,55].

The increased levels of fatigue in many patients do provide an opportunity for intervention [68–70]. Therapies aimed at improving fatigue could improve QOL [64], suggesting that interventions for fatigue could improve survival [71]. This warrants further investigation and needs to be tested in well-designed prospective trials with a comprehensive QOL component.

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