A Prospective Study of Quality of Life in Adults with Newly Diagnosed High-grade Gliomas: The Impact of the Extent of Resection on Quality of Life and Survival

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OBJECTIVE: To describe the quality of life (QOL) over time for adults with newly diagnosed high-grade gliomas and to examine the relationship between QOL and outcome data collected in three prospective cooperative group clinical trials.

METHODS: The QOL study was a companion protocol for three Phase II high-grade glioma protocols. Five self-administered forms were completed by patients to assess QOL at study entry, 2 months, and 4 months after enrollment.

RESULTS: QOL data were available for baseline, first, and second subsequent follow-up evaluations for 89%, 71%, and 69% of patients, respectively. A significant proportion of patients (47.1%) experienced impaired QOL (QOL $\leq$ 50) in at least one measure at subsequent evaluations, whereas most patients (88%) with impaired QOL at baseline continued to have impaired QOL at subsequent evaluations. On multivariable analyses, baseline QOL measures were predictive of QOL at the time of follow-up. In addition, patients who underwent a gross total resection were much less likely to have impaired QOL ($P = 0.006$), were less likely to experience worsening depression ($P = 0.0008$), and were more likely to have improved QOL ($P = 0.003$) at their first follow-up evaluation. Changes in QOL measures over time were not found to be associated with survival in multivariable analyses that adjusted for known prognostic variables; variables that were independently associated with improved survival were better performance status ($P < 0.001$), younger age ($P < 0.001$), and greater extent of resection ($P < 0.001$).

CONCLUSION: Baseline QOL was predictive of QOL over time. Gross total resection was associated with longer survival and improved QOL over time for patients with high-grade gliomas.

KEY WORDS: Glioblastoma, High-grade glioma, Prospective studies, Quality of life, Radiotherapy resection

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High-grade gliomas are extremely aggressive tumors, and despite intensive treatment with surgery, radiotherapy, and chemotherapy, the vast majority of patients invariably have tumor recurrence, with the median survival time ranging from 1 to 3 years after initial diagnosis (18). 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 (22, 43). Fatigue, depression, cognitive impairment, and excessive daytime somnolence can seriously impair the QOL of patients with high-grade brain tumors (31). However, because all these psychosocial difficulties are potentially amenable to treatment, it is important to establish QOL in this patient population for comparison when designing future therapeutic trials. A few reports have begun to describe the QOL of high-grade glioma patients, but much work is left to be done, in part because of the unique challenges presented by high-grade gliomas in assessing patient QOL (21, 64). The primary objective of our study was to prospectively assess the QOL of patients with newly diagnosed high-grade gliomas and to examine the relationship between QOL and outcome.

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PATIENTS AND METHODS

Patients

This project, the Glioma QOL study, was a companion protocol for three institutional review board-approved high-grade glioma treatment protocols (98-72-51, 98-72-52, N0074). The 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 preirradiation chemotherapy (carmustine, cisplatin, and etoposide) followed by the same chemotherapy delivered concurrently with radiation therapy (48). Twenty-nine patients were enrolled between February 1999 and April 2001.

In NCCTG 98-72-52, patients with glioblastomas received one cycle of preirradiation chemotherapy (carmustine, cisplatin, and etoposide) followed by the same chemotherapy delivered concurrently with radiation therapy (40). Radiotherapy was followed by four cycles of carmustine. 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 starting 2 to 5 weeks after radiotherapy was completed for patients with glioblastomas (62). ZD1839 was continued for up to 2 years, or until tumor progression. Ninety-eight patients were enrolled between May 2001 and August 2002.

Assessment

QOL is a multidimensional construct that is best measured with several different instruments (22, 43). The Glioma QOL study used five self-administered forms. These instruments were completed by the patient (after receiving instructions on how to complete the forms) within 72 hours after study entry. Patients also underwent testing with the Folstein Mini-Mental State Examination (19). The Eastern Cooperative Oncology Group performance score, 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, and depression.

The study forms were also completed before each 8-week cycle while receiving treatment in conjunction with a physical examination that included a neurological examination and computed tomography or magnetic resonance imaging. The median follow-up for the 24 patients still alive is 31.2 months. Collectively, patients completed the QOL tools and the Mini-Mental State Examination in approximately 30 minutes.

The QOL tools and the aspect of QOL they measure (listed below) were predefined in the protocol and are reported only as such in this manuscript. Exploratory QOL analyses not predefined in the protocol (i.e., subscales of the Profiles of Mood States short form [POMS-SF]) will be deferred for future reports.

Overall QOL

A simple five-item linear analog scale assessment (LASA) and the Functional Assessment of Cancer Therapy-Brain (FACT-Br, version 4) were used. LASA-type measures have been shown to be effective for obtaining valid and reliable measures of QOL domains in numerous studies and oncology clinical applications (11, 38, 44, 66). The LASA measures assessed the five domains of overall QOL, physical, emotional, spiritual, and intellectual well-being (54). The FACT-Br (65) 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 (11). 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. It has been used successfully in clinical trials dealing with brain tumors (i.e., meningiomas) (29), although completion rates have been indicated as a particular challenge in high-grade glioma patients (51).

Fatigue

The POMS-SF and the Symptom Distress Scale (SDS) were used to measure fatigue. The POMS-SF is a shortened version of the POMS, a questionnaire that has been well validated in cancer populations (5, 10, 60). The POMS-SF is a 30-item (6 subscales) self-administered questionnaire that has been used in many patient populations, (3, 17) including those with cancer (50, 63). The six subscales include tension, depression, anger, vigor, fatigue, and confusion. The fatigue subscale has been found to be a sensitive measure of fatigue in cancer patients (34, 41). The SDS is a 13-item self-administered questionnaire developed to measure common physical concerns of cancer patients (37) and has extensive application in oncology studies (4, 20). The SDS fatigue question was used to assess fatigue.

Excessive Daytime Somnolence

The Epworth Sleepiness Scale is a simple eight-item self-administered questionnaire that provides sleep propensity results comparable with the multiple sleep latency test (9, 28). This scale has proven reliability (26, 27) and clinical usefulness (24) in assessing excessive daytime somnolence and its response to therapy.

Depression

The depression scale of the POMS-SF was used to assess self-reported items related to depression.

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 (45, 55, 56). In all cases, 0 reflected the worst QOL and 100 reflected the best. By using the transformed scores, we were able to compare scores designed to evaluate the same construct and to 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

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summarized as the means ± 1 standard deviation, the median (min, max), or both. Categorical baseline and disease variables were summarized as frequency (percentage). Because some of the variables had skewed distributions, comparisons of continuous variables among the three protocol 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 Fisher's exact test. Univariate associations between the QOL measures and continuous baseline patient and disease variables were measured with the Spearman rank correlation coefficient. 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. Clinically impaired QOL was defined as a score of 50 or less for each QOL measure (6, 23, 55). Backward stepwise logistic regression was used to ascertain baseline patient, disease, and treatment characteristics that were associated with impaired QOL for each of the six QOL measures.

Time-to-event distributions (e.g., survival, time to progression) were estimated with Kaplan-Meier curves (30) and were compared with log-rank tests (36). The extent of surgery (i.e., gross total resection [GTR], subtotal resection, biopsy) was defined by the radiologist and treating oncologist using postoperative imaging (i.e., magnetic resonance imaging) (1). Time was measured from the date of the surgical procedure or biopsy to the date of the event or the date of the last follow-up examination. Progression was declared if the neurological 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 the baseline. If a patient died without documentation of being progression free, the patient was assumed to have progressed on the date of death. Cox proportional hazards models (13) 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 (16) and Cox model backward-selection procedures (52) 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 were considered to be valid prognostic indicators in the multivariable analyses. All statistical tests were two sided. To protect against spurious findings resulting from multiple analyses, a P value ≤ 0.01 was considered statistically significant for nonbootstrapped analyses.

RESULTS

QOL Responses

There were 220 patients accrued to the three trials. QOL data were available for baseline, first, and second subsequent follow-up evaluations for 89% (196 of 220), 71% (127 of 179), and 69% (85 of 124) of evaluable patients, respectively. Per the dictates of the protocol, the first and second follow-up evaluations occurred at 2 and 4 months after enrollment. There were no significant differences in the completion rates of the QOL forms among the three studies (all studies, $P \geq 0.10$). QOL data collected at the third follow-up evaluation or later were not ana-

TABLE 1. Summary of baseline characteristics for patients with at least one follow-up examination with quality of life data[a]

Variable	All patients (n = 124)
Age (yr)	
Median (min, max)	55 (19, 79)
Mean ± SD	54 ± 12
MMSE	
Median (min, max)	29 (11, 30)
Mean ± SD	28 ± 3
Sex, no. of patients (%)	
Female	42 (34)
Male	82 (66)
Performance score, no. of patients (%)	
0	59 (48)
1	56 (45)
2	9 (7)
Extent of resection, no. of patients (%)	
Biopsy	22 (18)
Subtotal resection	53 (43)
Gross total resection	49 (40)
Tumor grade, no. of patients (%)	
3	21 (17)
4	103 (83)
Tumor location, no. of patients (%)	
Temporal	29 (23)
Frontal	36 (29)
Parietal	15 (12)
Occipital	2 (2)
Other/mixed	42 (34)
Side, no. of patients (%)	
Right	74 (60)
Left	50 (40)
Anticonvulsant therapy, no. of patients (%)	
Yes	95 (77)
No	29 (23)
Corticosteroid therapy, no. of patients (%)	
Yes	73 (59)
No	51 (41)

[a] SD, standard deviation; MMSE, Folstein Mini-Mental State Examination.

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lyzed because of the low completion rate of the QOL measures (45–49% at the third evaluation).

There were no statistically significant differences in any of the measured baseline variables between patients who had follow-up QOL data and those who did not, except for the Mini-Mental State Examination. There was a statistically significant difference ($P = 0.005$) but not a clinically significant difference with a median Mini-Mental State Examination of 29 and 28 for those with and without QOL data over time, respectively (7, 61).

TABLE 2. Summary of quality of life data over time[a]

QOL measure	Distressed (%)	Mean	Median (min, max)
SDS—fatigue			
Baseline	14	73	80 (20, 100)
Evaluation 1	13	69	80 (20, 100)
Evaluation 2	16	68	80 (20, 100)
POMS—fatigue			
Baseline	21	70	75 (5, 100)
Evaluation 1	27	62	70 (0, 100)
Evaluation 2	25	62	65 (0, 100)
LASA—QOL			
Baseline	28	71	75 (25, 100)
Evaluation 1	30	69	75 (0, 100)
Evaluation 2	32	70	75 (25, 100)
FACT—Br			
Baseline	3	75	76 (36, 98)
Evaluation 1	7	72	73 (33, 100)
Evaluation 2	9	72	73 (34, 96)
POMS—depression			
Baseline	8	82	90 (20, 100)
Evaluation 1	5	82	85 (20, 100)
Evaluation 2	4	84	90 (5, 100)
ESS			
Baseline	17	67	67 (17, 96)
Evaluation 1	24	64	67 (4, 96)
Evaluation 2	33	63	67 (0, 96)

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

Comparison of Baseline Characteristics and QOL Scores Across Studies

The baseline characteristics of patients (*Table 1*) who completed a baseline and at least one follow-up QOL assessment were compared across the three studies and were compiled. There was a trend for patients in 98-72-51 (Grade 3 astrocytomas) to be younger ($P = 0.02$) and to have GTR of the tumor less often ($P = 0.05$) than patients in 98-72-52 and N0074 (glioblastomas in both studies), but for all other baseline variables, there were no significant differences between the studies. Baseline QOL scores and changes in QOL scores also were compared across studies, and no significant differences were found; therefore, patients from all three studies were pooled for the remaining analyses of QOL. However, previous radiation (yes versus no) was included as a covariate in the multivariable models as an adjusting variable.

Changes of QOL Over Time and Association with Baseline Characteristics

The average score for a healthy population of persons is 70 to 80 for each of the QOL measures (6, 23, 54). Furthermore, a 10-point difference in a given QOL score is considered clinically significant (42, 45, 55). Although the QOL scores of these patients with high-grade gliomas did not on average seem to differ considerably from those of a healthy population, a significant proportion had impaired (i.e., distressed) QOL (QOL ≤ 50) at baseline and further evaluations (*Table 2*) (6, 23).

Analyzing all patients combined (impaired and nonimpaired QOL at baseline) found only POMS-fatigue had a clinically and statistically significant ($P = 0.002$) change with time, with a mean improvement in score of 10.3 points (± 27.0; range improvement of 90 points to a loss of 45 points) at the second evaluation. There was a statistically significant ($P = 0.002$) and nearly clinically significant change in POMS-fatigue at the first evaluation, with a mean improvement in score of 7.6 points (± 23.8; range improvement of 65 points to a loss of 50 points).

Stratifying patients by QOL status at baseline (i.e., impaired versus nonimpaired) found that nearly half (47.1%) of nonimpaired patients experienced impaired QOL at subsequent evaluations in at least one measure, whereas most patients (88%) with impaired QOL at baseline continued to have impaired QOL at subsequent evaluations (*Table 3*). Analysis of the individual measures (e.g., SDS, the Epworth Sleepiness Scale, etc.) revealed that patients with impaired QOL at baseline experienced a further worsening of QOL with time, whereas patients who were not distressed at baseline generally experienced an improvement in their scores (*Table 3*) over time. There were statistically significant differences in the changes in QOL over time between the patients

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TABLE 3. Changes in quality of life data over time by baseline status[a]

Measured difference (follow-up score minus baseline score)	First evaluation			Second evaluation		
	Baseline distress	No baseline distress	*P* value	Baseline distress	No baseline distress	*P* value
SDS—fatigue			0.0001			0.0002
No.	16	96		9	65	
Mean ± SD	−17.5 ± 22.9	7.7 ± 16.8		−20.0 ± 20.0	10.5 ± 17.7	
Median (min, max)	−20 (−60, 20)	0 (−20, 60)		−20 (−40, 20)	0 (−20, 60)	
LASA			<0.0001			0.0002
No.	33	83		19	55	
Mean ± SD	−12.7 ± 20.4	7.2 ± 18.3		−12.8 ± 16.9	8.6 ± 22.0	
Median (min, max)	−12.5 (−50, 25)	0 (−25, 62.5)		−18.8 (−31.3, 25)	0 (−37.5, 62.5)	
ESS			0.06			0.02
No.	19	85		12	60	
Mean ± SD	−4.5 ± 18.6	5.8 ± 13.8		−9.5 ± 20.6	8.1 ± 19.4	
Median (min, max)	0 (−41.7, 25)	4.2 (−25, 41.7)		−5.7 (−48.8, 20)	4.2 (−29.1, 62.5)	
FACT—Br			0.008			0.22
No.	4	103		2	71	
Mean ± SD	−11.2 ± 5.8	2.6 ± 10.1		−6.0 ± 8.5	3.4 ± 12.4	
Median (min, max)	−11.9 (−17.4, −3.4)	1.6 (−20.8, 34.8)		−6 (−12, 0)	2.7 (−26.1, 29.8)	
POMS—depression			<0.0001			0.03
No.	9	97		6	66	
Mean ± SD	−28.3 ± 15.2	2.2 ± 14.3		−19.2 ± 34.3	−0.9 ± 15.5	
Median (min, max)	−30 (−45, −5)	0 (−40, 45)		−20 (−55, 40)	0 (−35, 55)	
POMS—fatigue			0.0004			0.002
No.	23	85		12	63	
Mean ± SD	−9.3 ± 26.6	12.2 ± 20.9		−13.3 ± 23.3	14.8 ± 25.5	
Median (min, max)	−15 (−50, 45)	10 (−30, 65)		−22.5 (−45, 25)	15 (−40, 90)	

[a] SD, standard deviation; SDS, Symptom Distress Scale; LASA, linear analog scale assessment; ESS, Epworth Sleepiness Scale; FACT—Br, Functional Assessment of Cancer Therapy—Brain; POMS, Profiles of Mood State. A negative value represents a worsening in score and a positive value indicates an improvement in score. *P* value is the Wilcoxon rank-sum test.

with impaired versus nonimpaired QOL at baseline for many measurements, including SDS-fatigue (first and second evaluation), LASA overall QOL (first and second evaluation), FACT-Br overall QOL (first evaluation), POMS-depression (first evaluation with a trend at the second evaluation), and POMS-fatigue (first and second evaluation). Those patients not distressed at baseline had significant improvements in SDS-fatigue (second evaluation) and POMS-fatigue (first and second evaluation), with the mean scores for all other measures either stable or trending toward improvement with time. Those patients with impaired QOL at baseline had significant worsening of SDS-fatigue (first and second evaluation), LASA overall QOL (first and second evaluation), FACT-Br overall QOL (first evaluation), POMS-depression (first and second evaluation), and POMS-fatigue (second evaluation), with the mean scores for all other measures either stable or worsening with time. Although the sample size was small, the worsening of scores in SDS-fatigue and POMS-depression for those patients with impaired QOL at baseline were striking, with mean losses of 17.5 to 28.3.

Association Between QOL Measures at Follow-up and Baseline Characteristics

The data were analyzed to determine whether there was an association between impaired QOL at the first follow-up evaluation and the baseline patient characteristics variables listed in *Table 1*. The results of the multivariable analyses are listed in *Table 4*. Baseline QOL scores were predictive of impaired QOL at follow-up (e.g., worse QOL at baseline was predictive of impaired QOL at follow-up), and all measures achieved statistical significance at the 0.01 level except POMS-depression ($P = 0.02$). In addition, patients who underwent a GTR were much less likely to have impaired QOL at the first follow-up evaluation ($P = 0.006$).

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The data were also analyzed to determine whether there was an association between baseline patient characteristics and improvement or worsening of QOL at the first follow-up evaluation. The results of the multivariable analyses are listed in *Table 5* and again reveal a strong correlation between baseline QOL scores and QOL at first follow-up evaluation (e.g., patients with worse QOL at baseline were more likely to have worsening of QOL at follow-up). Extent of surgical resection again was predictive with biopsy-only patients more likely to have worse depression ($P = 0.0008$) and less likely to have improved QOL ($P = 0.003$) at the first follow-up evaluation.

Association of Baseline Patient Characteristics and QOL Measures with Progression-free Survival

The univariate association of progression-free survival with each patient (age, sex, performance status), disease (tumor location, tumor laterality, tumor grade), treatment (extent of resection, corticosteroid use, anticonvulsant use, radiotherapy timing), and QOL (QOL scores, QOL changes over time, and clinically impaired patients with QOL scores of ≤ 50) variable was determined. Consistent with other NCCTG studies, older age ($P = 0.0007$; hazard ratio [HR], 1.03; 95% confidence interval [CI], 1.01–1.04) predicted a worse progression-free survival (8). In addition, a clinically significant decline in POMS depression score (i.e., worsening) between baseline and the first evaluation ($P = 0.008$; HR, 1.85; 95% CI, 1.17–2.9) and between the first and the second follow-up evaluation ($P = 0.011$; HR, 2.13; 95% CI, 1.19–3.83) correlated with a worse progression-free survival. However, only age was found to be independently associated with progression-free survival ($P = 0.002$; HR, 1.03; 95% CI, 1.01–1.05) in the multivariable analysis; specifically, POMS-depression was not found to be independently associated with progression-free survival after adjusting for the other variables.

Association of Baseline Patient Characteristics and QOL Measures with Survival

The univariate associations of survival with each baseline patient (age, sex, performance status), disease (tumor location, tumor laterality, tumor grade), treatment (extent of resection, corticosteroid use, anticonvulsant use, radiotherapy timing), and QOL (QOL scores, QOL changes over time, and clinically impaired patients with QOL scores of ≤ 50) variable was determined. Of the QOL measures, a clinically significant decline in POMS depression score between baseline and the first follow-up evaluation was predictive of a worse survival ($P = 0.002$; HR, 2.12; 95% CI, 1.33–3.36). The POMS depression score also predicted a worse survival for patients clinically distressed at the first ($P = 0.002$; HR, 3.89; 95% CI, 1.66–9.13) and second ($P = 0.002$; HR, 7.26; 95% CI, 2.09–25.24) follow-up evaluations. Among the patient characteristics, older age ($P < 0.0001$; HR, 1.04; 95% CI, 1.02–1.06) predicted a worse overall survival. There was a trend for patients with a GTR ($P = 0.054$; HR, 0.68; 95% CI, 0.46–1.01) to have a better survival and for those with an Eastern Cooperative Oncology Group performance score of 2 ($P = 0.052$; HR, 2.06; 95% CI, 0.99–4.27) to have worse survival. However, on multivariable analyses, the only variables independently associated with overall survival were age ($P < 0.001$; HR, 1.05; 95% CI, 1.03–1.07), GTR ($P < 0.001$; HR, 0.30; 95% CI, 0.16–0.59), Eastern Cooperative Oncology Group performance score of 2 ($P < 0.001$; HR, 7.4; 95% CI, 2.87–19.11), with a trend for those patients with a decline in POMS depression score between baseline and the first follow-up ($P = 0.03$; HR, 1.77; 95% CI, 1.05–2.99).

TABLE 4. Final logistic regression models for determining variables independently associated with impaired quality of life (score ≤50) at first follow-up evaluation[a]

QOL measure	Variable	OR (95% CI)	*P* value
SDS—fatigue	Baseline fatigue	0.96 (0.93–0.98)	0.0004
POMS—depression	Baseline depression	0.95 (0.92–0.99)	0.02
ESS	Baseline ESS	0.91 (0.87–0.95)	<0.0001
	PS		
	0	1.00	
	1	3.40 (0.93–12.47)	0.06
	2	14.89 (1.90–116.88)	0.01
LASA overall	Baseline LASA	0.95 (0.92–0.97)	0.0001
	Corticosteroid use		
	No	1.00	
	Yes	3.49 (1.29–9.46)	0.01
	Extent of resection		
	Biopsy	1.00	
	Gross total resection	0.14 (0.04–0.57)	0.006
	Subtotal resection	0.56 (0.17–1.91)	0.35
FACT—Br	Baseline FACT	0.93 (0.87–0.98)	0.01
POMS—fatigue	Baseline fatigue	0.96 (0.94–0.98)	0.0004

[a] QOL, quality of life; OR, odds ratio; CI, confidence interval; SDS, Symptom Distress Scale; POMS, Profiles of Mood State; ESS, Epworth Sleepiness Scale; PS, performance score; LASA, linear analog scale assessment; FACT—Br, Functional Assessment of Cancer Therapy—Brain.

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TABLE 5. Final logistic regression models for determining variables independently associated with significant (change of 10 points or more) improvement or worsening of quality of life at first follow-up evaluation[a]

QOL measure	Variable	OR (95% CI)	*P* value
SDS—fatigue			
Fatigue improved	Baseline fatigue	0.92 (0.89–0.95)	<0.0001
	Tumor location		
	Frontal	10.90 (1.75–67.96)	0.01
	Temporal	4.63 (0.66–32.78)	0.12
	Parietal	1.57 (0.13–18.46)	0.72
Fatigue worsened	Baseline fatigue	1.05 (1.02–1.08)	0.0006
POMS—depression			
Depression improved	Baseline depression	0.91 (0.88–0.95)	<0.0001
Depression worsened	Extent of resection		
	Biopsy	1.00	
	Gross total resection	0.10 (0.03–0.38)	0.0008
	Subtotal resection	0.11 (0.03–0.39)	0.0008
ESS			
ESS improved	Baseline ESS	0.94 (0.91–0.97)	0.0002
ESS worsened	Baseline ESS	1.03 (1.00–1.05)	0.04
LASA overall			
LASA improved	Baseline LASA	0.89 (0.85–0.94)	<0.0001
	PS		
	0	1.00	
	1	0.15 (0.03,–0.70)	0.02
	2	0.57 (0.06,–5.30)	0.62
	GBM		
	No	1.00	
	Yes	0.11 (0.02–0.71)	0.02
	Tumor location		
	Frontal	0.22 (0.04–1.16)	0.07
	Temporal	0.28 (0.05–1.66)	0.16
	Parietal	7.04 (1.06–46.85)	0.04
	Extent of resection		
	Biopsy	1.00	
	Gross total resection	21.88 (2.78–172.45)	0.0003
	Subtotal resection	11.28 (1.43–88.90)	0.02
	Corticosteroid use		
	No	1.00	
	Yes	0.03 (0.01–0.16)	<0.0001
LASA worsened	Baseline LASA	1.03 (1.00–1.05)	0.02
FACT—Br			
FACT improved	Baseline FACT	0.93 (0.89–0.97)	0.001
FACT worsened	Anticonvulsant use		
	No	1.00	
	Yes	5.83 (1.28–26.61)	0.02
POMS—fatigue			
Fatigue improved	Baseline fatigue	0.95 (0.93–0.97)	<0.0001
Fatigue worsened	Baseline fatigue	1.05 (1.03–1.08)	<0.0001
	PS		
	0	1.00	
	1	3.57 (1.37–9.31)	0.009
	2	1.37 (0.17–11.07)	0.77

[a] QOL, quality of life; OR, odds ratio; CI, confidence interval; SDS, Symptom Distress Scale; POMS, Profiles of Mood State; ESS, Epworth Sleepiness Scale; LASA, linear analog scale assessment; PS, performance score; GBM, glioblastoma multiforme; FACT—Br, Functional Assessment of Cancer Therapy—Brain.

DISCUSSION

Because the expected lifespan of a high-grade glioma patient is quite short, one would expect issues related to QOL to be even more significant. Unfortunately, the literature regarding QOL in high-grade gliomas is not extensive, and is even more limited if one restricts a review to studies prospectively evaluating multiple aspects of QOL (31, 64), possibly because of the inherent difficulties of studying QOL in high-grade glioma patients (51). Therefore, the goal of this study was to establish QOL quantitatively and qualitatively in this patient population. Patients prospectively underwent evaluation of multiple aspects of QOL using five different measures. Significant levels of impaired QOL at baseline and follow-up evaluations were found. The results also indicate that over time, patients with impaired QOL at baseline had further worsening of their QOL, whereas patients not distressed at baseline had significant improvement in their QOL scores. Thus, baseline QOL consistently was a predictor of QOL over time for each of the measures.

Multivariable analyses found that age, performance status, and extent of resection independently associated with overall survival, whereas none of the QOL measures were associated independently with survival. These findings are consistent with previous research, because age and performance status are well established prognostic factors for high-grade gliomas (8, 14), but the independent impact of surgical resection on survival is somewhat more controversial (25). A review of three consecutive prospective Radiation Therapy Oncology Group trials did find a significant association be-

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tween GTR and survival that remained independently significant in multivariable analyses (53). One of the best conducted analyses of the impact of the extent of resection was performed by the M. D. Anderson Cancer Center (32). Analyzing prospectively collected imaging, volumetric, and other tumor characteristic data, the authors found GTR to be independently associated with survival and to be especially significant for patients with otherwise favorable characteristics (e.g., younger, better performance status).

A more novel finding is the significant association between extent of resection and QOL of high-grade glioma patients. A few studies have reported improved QOL after tumor resection, but with significant limitations, such as using a measure that evaluates only one aspect of QOL (46) (e.g., Hospital Anxiety and Depression Scale). Other studies have used an extremely insensitive measure (35, 65), such as the Karnofsky performance score, to define QOL (2). In contrast, our report found improved QOL for high-grade glioma patients who underwent GTR on follow-up after extensive testing of QOL using five different measures to evaluate several different aspects of QOL. Although this is an important finding, it is uncertain why patients would have better QOL after greater tumor resection. In our multivariable analyses, we accounted for many variables, including tumor grade, tumor laterality, and tumor location (e.g., frontal lobe, parietal lobe, etc.). However, it may be that tumor location (as we defined it) is not a sufficiently sensitive variable for analyses, and a more specific definition of tumor location (33) (e.g., superior frontal gyrus, frontotemporal region, superior parietal lobe, etc.) may have revealed a more significant correlation between QOL and tumor location. Another possible explanation is that patients perceived a better outcome after a GTR (compared with other high-grade glioma patients) and therefore had a superior QOL (12, 15). It is also possible the GTR patients had better independence and less disability at least on early follow-up and therefore had better QOL (49). In addition, GTR patients inherently have much less peritumoral edema and its associated difficulties (58, 59) during and shortly after radiotherapy than biopsy only patients.

In conclusion, high-grade glioma patients with impaired QOL at diagnosis tend to continue to have impaired QOL over time, and interventions to improve QOL (39, 47, 57) are needed for these distressed patients. These interventions should be tested in well-designed prospective trials with comprehensive QOL measures. In addition, greater tumor resection is associated not only with improved survival, but also with improved QOL. Therefore, when counseling high-grade glioma patients about surgical options, one should take into account the impact of GTR on QOL.

REFERENCES

1. Albert FK, Forsting M, Sartor K, Adams HP, Kunze S: Early postoperative magnetic resonance imaging after resection of malignant glioma: objective evaluation of residual tumor and its influence on regrowth and prognosis. **Neurosurgery** 34:45–61, 1994.
2. Ammirati M, Vick N, Liao YL, Ciric I, Mikhael M: Effect of the extent of surgical resection on survival and quality of life in patients with supratentorial glioblastomas and anaplastic astrocytomas. **Neurosurgery** 21:201–206, 1987.
3. Baradell JG: Clinical outcomes and satisfaction of patients of clinical nurse specialists in psychiatric-mental health nursing. **Arch Psych Nurs** 9:240–250, 1995.
4. Boehmke MM: Measurement of symptom distress in women with early-stage breast cancer. **Cancer Nurs** 27:144–152, 2004.
5. Braslis KG, Santa-Cruz C, Brickman AL, Soloway MS: Quality of life 12 months after radical prostatectomy. **Br J Urol** 75:48–53, 1995.
6. Bretscher M, Rummans T, Sloan J, Kaur J, Bartlett A, Borkenhagen L, Loprinzi CL: Quality of life in hospice patients: A pilot study. **Psychosomatics** 40:309–313, 1999.
7. Brown PD, Buckner JC, O'Fallon JR, Iturria NL, Brown CA, O'Neill BP, Scheithauer BW, Dinapoli RP, Arusell RM, Curran WJ, Abrams R, Shaw EG: Effects of radiotherapy on cognitive function in patients with low-grade glioma measured by the Folstein mini-mental state examination **J Clin Oncol** 21:2519–2524, 2003.
8. Buckner JC, Schomberg PJ, McGinnis WL, Cascino TL, Scheithauer BW, O'Fallon JR, Morton RF, Kuross SA, Mailliard JA, Hatfield AK, Cole JT, Steen PD, Bernath AM: A phase III study of radiation therapy plus carmustine with or without recombinant interferon-α in the treatment of patients with newly diagnosed high-grade glioma. **Cancer** 92:420–433, 2001.
9. Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S: Guidelines for the multiple sleep latency test (MSLT): A standard measure of sleepiness. **Sleep** 9:519–524, 1986.
10. Cassileth BR, Soloway MS, Vogelzang NJ, Chou JM, Schellhammer PD, Seidmon EJ, Kennealey GT: Quality of life and psychosocial status in stage D prostate cancer: Zoladex Prostate Cancer Study Group. **Qual Life Res** 1:323–329, 1992.
11. Cella DF: Quality of life outcomes: Measurement and validation. **Oncology (Huntington)** 10[11 Suppl]:233–246, 1996.
12. Chen ML: Pain and hope in patients with cancer: A role for cognition. **Cancer Nurs** 26:61–67, 2003.
13. Cox DR: Regression models and life tables. **J Royal Stat Soc B** 34:187–220, 1972.
14. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, Chang CH, Rotman M, Asbell SO, Krisch RE: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. **J Natl Cancer Inst** 85:704–710, 1993.
15. Dias L, Chabner BA, Lynch TJ Jr, Penson RT: Breaking bad news: A patient's perspective. **Oncologist** 8:587–596, 2003.
16. Efron B: Bootstrap methods: Another look at the jacknife. **Ann Stat** 7:1–26, 1979.
17. Faulx AL, Catanzaro A, Zyzanski S, Cooper GS, Pfau PR, Isenberg G, Wong RC, Sivak MV Jr, Chak A: Patient tolerance and acceptance of unsedated ultrathin esophagoscopy. **Gastrointest Endosc** 55:620–623, 2002.
18. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. **Cancer** 71:2585–2597, 1993.
19. Folstein MF, Folstein SE, McHugh PR: "Mini-mental state": A practical method for grading the cognitive state of patients for the clinician. **J Psychiatr Res** 12:189–198, 1975.
20. Ganz PA, Moinpour CM, Pauler DK, Kornblith AB, Gaynor ER, Balcerzak SP, Gatti GS, Erba HP, McCoy S, Press OW, Fisher RI: Health status and quality of life in patients with early-stage Hodgkin's disease treated on Southwest Oncology Group Study 9133. **J Clin Oncol** 21:3512–3519, 2003.
21. Gilbert M, Armstrong T, Meyers C, Issues in assessing and interpreting quality of life in patients with malignant glioma. **Semin Oncol** 27[3 Suppl 6]:20–26, 2000.
22. Gotay CC, Korn EL, McCabe MS, Moore TD, Cheson BD: Quality-of-life assessment in cancer treatment protocols: Research issues in protocol development. **J Natl Cancer Inst** 84:575–579, 1992.
23. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting: Methods to explain the clinical significance of health status measures. **Mayo Clin Proc** 77:371–383, 2002.
24. Hardinge FM, Pitson DJ, Stradling JR: Use of the Epworth Sleepiness Scale to demonstrate response to treatment with nasal continuous positive airways pressure in patients with obstructive sleep apnoea. **Respir Med** 89:617–620, 1995.
25. Jeremic B, Milicic B, Grujicic D, Dagovic A, Aleksandrovic J, Nikolic N: Clinical prognostic factors in patients with malignant glioma treated with combined modality approach. **Am J Clin Oncol** 27:195–204, 2004.
26. Johns MW: A new method for measuring daytime sleepiness: The Epworth sleepiness scale. **Sleep** 14: 540–545, 1991.
27. Johns MW: Reliability and factor analysis of the Epworth Sleepiness Scale. **Sleep** 15:376–381, 1992.

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28. Johns MW: Daytime sleepiness, snoring, and obstructive sleep apnea. The Epworth Sleepiness Scale. **Chest** 103:30–36, 1993.
29. Kalkanis SN, Quiñones-Hinojosa A, Buzney E, Ribaudo HJ, Black PMcL: Quality of life following surgery for intracranial meningiomas at Brigham and Women's Hospital: A study of 164 patients using a modification of the functional assessment of cancer therapy-brain questionnaire. **J Neuro-Oncol** 48:233–241, 2000.
30. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. **J Am Stat Assoc** 53:457–481, 1958.
31. Klein M, Taphoorn MJ, Heimans JJ, van der Ploeg HM, Vandertop WP, Smit EF, Leenstra S, Tulleken CA, Boogerd W, Belderbos JS, Cleijne W, Aaronson NK: Neurobehavioral status and health-related quality of life in newly diagnosed high-grade glioma patients. **J Clin Oncol** 19:4037–4047, 2001.
32. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, Lang FF, McCutcheon IE, Hassenbusch SJ, Holland E, Hess K, Michael C, Miller D, Sawaya R: A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. **J Neurosurg** 95:190–198, 2001.
33. Levine DN, Grek A: The anatomic basis of delusions after right cerebral infarction. **Neurology** 34:577–582, 1984.
34. Lovely MP, Miaskowski C, Dodd M: Relationship between fatigue and quality of life in patients with glioblastoma multiforme. **Oncol Nurs Forum** 26:921–925, 1999.
35. Mackworth N, Fobair P, Prados MD: Quality of life self-reports from 200 brain tumor patients: Comparisons with Karnofsky performance scores **J Neuro-Oncol** 14:243–253, 1992.
36. Mantel N: Evaluation of survival data and two new rank order statistics arising in its consideration. **Cancer Chemother Rep Part 1** 50:163–170, 1966.
37. McCorkle R, Quint-Benoliel J: Symptom distress, current concerns and mood disturbance after diagnosis of life-threatening disease. **Soc Sci Med** 17:431–438, 1983.
38. McCormack HM, Horne DJ, Sheather S: Clinical applications of visual analogue scales: A critical review. **Psychol Med** 18:1007–1019, 1988.
39. Meyers CA, Weitzner MA, Valentine AD, Levin VA: Methylphenidate therapy improves cognition, mood, and function of brain tumor patients. **J Clin Oncol** 16:2522–2527, 1998.
40. Moynihan TJ, O'Fallon JR, Krook JE, Schomberg P, Dinapoli R, Kazem I, Scheithauer B, Buckner JC: A phase II trial of pre-irradiation chemotherapy with BCNU, cisplatin and oral etoposide combined with radiation therapy in the treatment of glioblastoma (GBM). **Proc Am Soc Clin Oncol** 21:77, 2002 (abstr).
41. Nail LM, King KB: Symptom distress fatigue. **Semin Oncol Nurs** 3:257–262, 1987.
42. Norman GR, Sloan JA, Wyrwich KW: Interpretation of changes in health-related quality of life: The remarkable universality of half a standard deviation. **Medical Care** 41:582–592, 2003.
43. Osoba D: Lessons learned from measuring health-related quality of life in oncology. **J Clin Oncol** 12:608–616, 1994.
44. Osoba D, Aaronson NK, Muller M, Sneeuw K, Hsu MA, Yung WK, Brada M, Newlands E: The development and psychometric validation of a brain cancer quality-of-life questionnaire for use in combination with general cancer-specific questionnaires. **Qual Life Res** 5:139–150, 1996.
45. Osoba D, Rodrigues G, Myles J, Zee B, Pater J: Interpreting the significance of changes in health-related quality-of-life scores. **J Clin Oncol** 16:139–144, 1998.
46. Pringle AM, Taylor R, Whittle IR: Anxiety and depression in patients with an intracranial neoplasm before and after tumour surgery. **Br J Neurosurg** 13:46–51, 1999.
47. Raison CL, Miller AH: Depression in cancer: New developments regarding diagnosis and treatment **Biologic Psychiatr** 54:283–294, 2003.
48. Rao R, Fitch TR, Schomberg P, Dinapoli R, Nordstrom K, Boeve BF, Rummans TA, Tang-Wai DF, Scheithauer B, O'Fallon J, Maurer MJ, Buckner JC: A phase II trial of pre-irradiation chemotherapy with BCNU, cisplatin and oral etoposide combined with radiation therapy in the treatment of grade 3 astrocytoma (anaplastic astrocytoma). **Neuro-Oncol** 4:374, 2002.
49. Recht L, Glantz M, Chamberlain M, Hsieh CC: Quantitative measurement of quality outcome in malignant glioma patients using an independent living score (ILS) assessment of a retrospective cohort. **J Neuro-Oncol** 61:127–136, 2003.
50. Regine WF, Schmitt FA, Scott C, Dearth CS, Patchell R, Nichols RC Jr, Gore E, Franklin RL III, Suh JH, Mehta MP: Feasibility of neurocognitive outcome evaluations in patients with brain metastases in a multi-institutional cooperative group setting: Results of radiation therapy oncology group (RTOG) trial BR-0018. **Int J Radiat Oncol Biol Phys** 54[2 Suppl]:49, 2002 (abstr).
51. Roa W, Brasher PM, Bauman G, Anthes M, Bruera E, Chan A, Fisher B, Fulton D, Gulavita S, Hao C, Husain S, Murtha A, Petruk K, Stewart D, Tai P, Urtasun R, Cairncross JG, Forsyth P: Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. **J Clin Oncol** 22:1583–1588, 2004.
52. Sauerbrei W, Schumacher M: A bootstrap resampling procedure for model building: Application to the Cox regression model. **Stat Med** 11:2093–2109, 1992.
53. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, Isaacson S, Rotman M, Asbell SO, Nelson JS: Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: Results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. **Int J Radiat Oncol Biol Phys** 26:239–244, 1993.
54. Sloan JA, Cella D, Frost M, Guyatt GH, Sprangers M, Symonds T: Clinical Significance Consensus Meeting: Assessing clinical significance in measuring oncology patient quality of life—Introduction to the symposium, content overview, and definition of terms. **Mayo Clin Proc** 77:367–370, 2002.
55. Sloan JA, Dueck A: Issues for statisticians in conducting analyses and translating results for quality of life end points in clinical trials. **J Biopharmaceut Stat** 14:73–96, 2004.
56. Sloan JA, Loprinzi CL, Kuross SA, Miser AW, O'Fallon JR, Mahoney MR, Heid IM, Bretscher ME, Vaught NL: Randomized comparison of four tools measuring overall quality of life in patients with advanced cancer. **J Clin Oncol** 16:3662–3673, 1998.
57. Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S: Cancer-related fatigue: evolving concepts in evaluation and treatment. **Cancer** 98:1786–1801, 2003.
58. Streffer JR, Bitzer M, Schabet M, Dichgans J, Weller M: Response of radiochemotherapy-associated cerebral edema to a phytotherapeutic agent, H15. **Neurology** 56:1219–1221, 2001.
59. Sultanem K, Patrocinio H, Lambert C, Corns R, Leblanc R, Parker W, Shenouda G, Souhami L: The use of hypofractionated intensity-modulated irradiation in the treatment of glioblastoma multiforme: Preliminary results of a prospective trial. **Int J Radiat Oncol Biol Phys** 58:247–252, 2004.
60. Swain SM, Rowland J, Weinfurt K, Berg C, Lippman ME, Walton L, Egan E, King D, Spertus I, Honig SF: Intensive outpatient adjuvant therapy for breast cancer: Results of dose escalation and quality of life. **J Clin Oncol** 14:1565–1572, 1996.
61. Tangalos EG, Smith GE, Ivnik RJ, Petersen RC, Kokmen E, Kurland LT, Offord KP, Parisi JE: The Mini-Mental State Examination in general medical practice: Clinical utility and acceptance. **Mayo Clin Proc** 71:829–837, 1996.
62. Uhm JH, Ballman KV, Krause JC, Buckner JC, James D, Scheithauer BW, O'Fallon JR, Jaeckle KA: Phase II study of ZD1839 in patients with newly diagnosed grade 4 astrocytoma. **Proc Am Soc Clin Oncol** 22[14 Suppl]:108s, 2004 (abstr).
63. Waldon EG: The effects of group music therapy on mood states and cohesiveness in adult oncology patients. **J Music Ther** 38:212–238, 2001.
64. Walker M, Brown J, Brown K, Gregor A, Whittle IR, Grant R: Practical problems with the collection and interpretation of serial quality of life assessments in patients with malignant glioma. **J Neuro-Oncol** 63:179–186, 2003.
65. Weitzner MA, Meyers CA, Gelke CK, Byrne KS, Cella DF, Levin VA: The Functional Assessment of Cancer Therapy (FACT) scale: Development of a brain subscale and revalidation of the general version (FACT-G) in patients with primary brain tumors. **Cancer** 75:1151–1161, 1995.
66. Wewers ME, Lowe NK: A critical review of visual analogue scales in the measurement of clinical phenomena. **Res Nurs Health** 13:227–236, 1990.

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COMMENTS

The authors report their simultaneous assessment of quality of life (QOL) issues in a variety of patients undergoing multimodality management for high-grade malignant gliomas. What have we learned? Patients with brain cancer are likely to have deterioration in their QOL

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and/or depression during the course of their illness, a feature with which most of us who care for such patients are quite familiar. The paper provides more objective measurements of this, and may thereby set a standard for subsequent reporting of such issues in other clinical trials. As in most such reports, the authors tend to get sucked into the discussion of big resections versus small resections and biopsy. Gross total resections of malignant gliomas are, in my experience, quite a remarkable event, and require definition as to whether they are talking about the contrast-enhancing component of the tumor, the T2 signal abnormality (the area of brain infiltrated with tumor), or exactly what gross total or subtotal resection means and how to define it by postoperative magnetic resonance imaging scan. Because the average glioma might have 108 cells in it, and a 99% reduction still leaves you with 106, I still do not believe that there is substantive data which defines the value of the surgical resection volume when the location, the tumor growth pattern, the histology, and the preoperative neurological symptoms are controlled. Certainly, we do what we can, and for patients with lobar tumors without deep invasion, with tight contrast enhancing and T2 borders which correspond to each other, we should aim for maximal resection and try to improve our patient's QOL, at least for a period of time. After that, we need radical new thinking. Comprehensive meta-analyses of the value of contemporary chemotherapeutic protocols provide little comforting evidence that we are providing a major benefit. Targeted therapies based on molecular knowledge may provide a better strategy.

L. Dade Lunsford
Pittsburgh, Pennsylvania

There is an increase in Class 2 evidence that major resection improves survival in patients with malignant gliomas. Neurosurgeons and radiation oncologists have also suspected that major resection and aggressive radiation improve the QOL in patients with these devastating disorders: there is less edema, less mass effect, and greater opportunity to use new therapeutic agents if the enhancing mass is removed. There are a number of adjuncts to help this removal—image-guided surgery, brain mapping, and intraoperative imaging—but the major point is that they make a difference for patients. Critics, of course, say that these techniques are not a "home run," that they do not cure a glioblastoma or malignant glioma. However, they miss the fact that nothing else does either, and that, at the moment, the only treatments we can offer that make a difference are aggressive surgery and aggressive radiation. If we want to help the actual patient in front of us, these are the methods we should use. Chemotherapy, unfortunately, is not presently in the mixture of proven advantage, although most of the critics of surgery and radiation believe that this will someday make a major difference. Most neurosurgeons who advocate major resection do not believe that they are curing malignant gliomas; however, they are giving the best treatment possible today. Hopefully the development of new biological agents will be the "home run" we all want, but, in the meantime, surgery and radiation are the best we can offer.

Peter McL. Black
Boston, Massachusetts

This is a very timely article from a group of investigators who have a great deal of experience managing patients with gliomas. In particular, we, as neurosurgeons, fail to appreciate the impact that this disease has on the QOL, especially in the newly diagnosed situation. Not only are physical limitations placed on the patient from the lesion, but newly diagnosed gliomas are also likely to be associated with significant degrees of depression, often requiring medication. This article is critical, because QOL was assessed with a number of different measures into three high-grade glioma treatment protocols involving more than 200 patients. One of the most important messages in this study is that patients who have a gross total resection, based on postoperative imaging, were indeed less likely to have impairment of their QOL at the initial follow-up examination compared with their baseline. These patients were also less likely to be depressed. When both factors are considered, especially in the high-grade glioma population, in which life can be very short, it is indeed an important observation. Thus, we as surgeons must strive to achieve an aggressive surgical resection, not only to improve time to tumor progression and survival, but also to positively impact on the QOL. The authors have made an excellent contribution to the literature.

Mitchel S. Berger
San Francisco, California

The authors have assessed QOL for adults with newly diagnosed high-grade gliomas, and have examined the relationship between the QOL and the number of standard variables in three prospective cooperative Phase II clinical trials. This type of QOL information is particularly important as authoritative data is lacking and too often clinical trials concentrate on purely the length of survival and neglect the importance of the quality of the survival time for the patient.

The authors have reported that the variables independently associated with the improved survival include better performance status at the time of diagnosis, younger age, and greater extent of resection. Not unexpectedly, the studies show that the baseline of the QOL was predictive of the QOL over time and the gross total resection was associated with not only longer survival, but also improved QOL over time for patients with high-grade gliomas.

This type of Phase II data does not provide conclusive evidence regarding the value of tumor resection in terms of survival, as the ability to obtain a gross total resection of the tumor may just be a surrogate measure for the biological behavior of those tumors able to be resected that result in improved survival and QOL. Although I personally am convinced that the extent of tumor resection is of oncological value in itself by reducing tumour burden, and consequently increasing the chance of efficacy of adjuvant therapies, Phase II data alone is not absolute proof of the association. Nevertheless, it is improbable that a prospective randomized control trial of the value of resection in high-grade glioma is feasible and prospective Phase II trials and retrospective studies for both high- and low-grade tumors will probably have to suffice (1).

A further limitation in the study, noted by the authors themselves, relates to the association between tumor position and QOL. As the authors describe, it is likely that the tumor location as defined in this study was not a sufficiently sensitive variable for analysis. It is evident in neurosurgical practice that patients with tumors involving eloquent regions have a much impaired QOL compared with patients who have tumors located in easily resectable locations.

Although the authors are "uncertain" why patients would have a better QOL after greater tumor resection, neurosurgical experience certainly supports this finding as those patients with a gross microscopic resection tolerate adjuvant therapies much better and have less problems with postoperative edema.

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