

Health related quality of life and cognitive status in patients with glioblastoma multiforme receiving escalating doses of conformal three dimensional radiation on RTOG 98-03

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Abstract The Radiation Therapy Oncology Group (RTOG) embarked on a phase I/II study of patients suffering from glioblastoma multiforme (protocol 98-03) to assess the impact of dose escalation with 3-D conformal techniques. The primary endpoints were feasibility and survival. This report describes the outcome of secondary endpoints (quality of life and neurocognitive function). Patients with supratentorial GBM were treated with a combination of carmustine (BCNU) and conformal irradiation (dose levels: 66, 72, 78, 84 Gy, respectively). Quality of Life was assessed with the Spitzer Quality of Life Index. Neurocognitive function was determined by the Mini Mental Status Examination. The latter tests were administered at the start of irradiation, at the end of irradiation

and then at 4 month intervals. Relatively high compliance was achieved with both of the tools (SQLI; MMSE). Overall rates of survival between baseline SQLI scores <7 and 7–10 were statistically significantly different [HR = 1.72, 95% CI (1.22, 2.4), $P = 0.0015$]. The significant impact of high SQLI score on survival was preserved in multivariate analysis. The component of this index which made the greatest contribution was the patient's independence. There was continual deterioration of neurocognitive function within the populations studied. No correlation was seen between dose escalation and the secondary endpoints studied. Radiation dose escalation and assessment of its impact on life quality and neurocognition can be carried out in a large international trial. Baseline

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SQLI is a statistically significant determinant of survival. Those who maintain independence have superior survival to those who are reliant on others.

Keywords Radiation dose · Neurocognition · QOL · GBM

Introduction

With approximately 12,000 cases diagnosed annually, glioblastoma multiforme (GBM) remains the most common primary brain tumor in adults in the United States [1]. Despite aggressive therapy, very few patients achieve long term survival. Fortunately, the number of long term survivors has increased with the advent of combined modality management including aggressive surgery, radiotherapy and temozolomide [2]. Prior to the reporting of phase III data from the European Organization for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCI-C) which led to the combination of radiotherapy and temozolomide as a standard of care, the Radiation Therapy Oncology Group (RTOG) embarked on a phase I–II dose escalation study using conformal irradiation (RTOG 98-03) for patients with newly diagnosed GBM. The rationale was based on the observation that most patients develop in-field recurrences and that safer techniques were being developed to facilitate the delivery of higher doses of radiotherapy in the target volume. Outcomes from this trial pertaining to feasibility, toxicity and survival are the subject of a separate manuscript [3]. The current report will describe the quality of life endpoints as well as results pertaining to neurocognitive impairment.

Materials and methods

Patient eligibility

Patients with supra-tentorial GBM were eligible to participate in RTOG 98-03 if they were at least 18 years of age, had Karnofsky Performance Status ≥ 60 and had a neurological functional score (NF) of 0-3 (Table 1). Patients underwent a range of surgical procedures. The extent of resection was categorized according to the surgeon’s

operative note and was not based on post-operative imaging studies. Adequate bone marrow reserve, acceptable hepatic and renal function, and a normal chest X-ray were also required. Therapy was to commence within 5 weeks of surgery.

Study design

All patients received carmustine (BCNU) 80 mg/m² on days 1, 2, 3 and 56, 57, 58. Subsequently, carmustine was administered every 8 weeks for a total of 6 cycles. The primary objective of the phase I component of the study was to establish the maximum tolerated dose (MTD) of radiotherapy (RT) as delivered in a dose-escalated fashion by three-dimensional (3-D) conformal techniques (Fig. 1). Accordingly, 46 Gy was given in 2 Gy fractions to the first Planning Target Volume (PTV₁) (defined as the gross tumor volume [GTV] + 1.8 cm margin) prior to a boost to the PTV₂ (defined as the GTV + 0.3 cm margin). The boost dose brought the total to 66, 72, 78 or 84 Gy (dose levels 1–4, respectively). Patients were stratified into 2 groups. For Group 1, the PTV₂ was <75 cc. For Group 2, the PTV₂ was ≥ 75 cc.

One dose level per group was open for accrual at a time, beginning with 66 Gy. Dose escalation then proceeded in a three step process. The first two criteria for dose escalation were only one or two irreversible CNS toxicities at the level of grade 3 or 4 and the absence of grade 5 toxicity in the first 14 evaluable patients. The third criterion for dose escalation required consideration of whether fewer than 9 of the first 14 patients who were progression free required steroids at the 3 month mark (relative to the initiation of

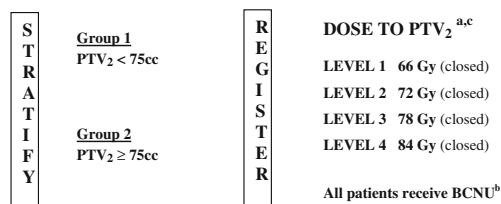


Fig. 1 Schema of RTOG 9803. *a* Radiation therapy to be administered in 2 Gy/day fractions. All patients will have a field reduction after 46 Gy. *b* BCNU (80 mg/m²) on days 1, 2, and 3 of the first week of radiotherapy repeated on days 56, 57 and 58. Then every 8 weeks for four cycles for a total of six cycles (maximum BCNU dose 1,440 mg/m²). *c* PTV₁ = CTV₁ + 3 mm (CTV₁ = gross tumor + 15 mm margin); PTV₂ = gross tumor + 3 mm margin

Table 1 RTOG neurological function status

0	No neurologic Sx; fully active at home/work without assistance
1	Minor neurologic Sx; fully active at home/work without assistance
2	Moderate neurologic Sx; fully active at home/work but requires assistance
3	Moderate neurologic Sx; less than fully active at home/work and requires assistance
4	Severe neurologic Sx; inactive and unable to work; requires complete assistance

therapy). Of note, in a re-analysis, a significant fraction of patients received steroids for what was later understood to be pseudo-progression. In such cases, this criterion was not used to define a dose limiting toxicity. Additionally, the dose level was to be de-escalated if more than 2 patients developed radiation necrosis within 1 year of follow-up.

Quality control assessment

The data collected from the 3-D treatment planning were submitted electronically to the Image Guided Therapy Center. This facilitated the evaluation of the quality assurance review for the planning target volumes, designated organs at risk and compliance with dosimetric guidelines.

Statistical analysis

The primary endpoint of this study was assessment of the rates of acute and late toxicity, steroid dependence and radio-necrosis. Toward this end, data pertaining to patient age, gender, KPS, Recursive Partitioning Analysis (RPA) class, extent of surgical resection, and mini-mental status were utilized. Secondary endpoints included survival (measured from the date of study entry until the date of death or last follow-up), and progression free survival (measured from the start of radiotherapy until the date of progression, death or last follow-up). The outcomes pertaining to those endpoints have been reported by Tsien and colleagues [3]. The secondary endpoints related to quality of life and neurocognitive function (NCF) are the subject of the present report. The former was assessed by the Spitzer Quality of Life Index (SQLI; a clinician rating scale with several domains) while the latter (i.e., NCF) was assessed with the Mini-Mental Status Examination (MMSE) [4, 5].

The SQLI is a general quality of life index that covers five domains of quality of life. It was designed by physicians to help them assess the relative benefits and risks of various treatments for serious illness and of supportive programs such as palliative interventions and hospice care. The SQLI was previously validated [6]. Specifically, SQLI was used in pretests and validation tests by more than 150 physicians to rate 879 patients. The median completion time was 1 min. The SQLI has convergent discriminant and content validity among cancer patients and patients with other chronic illnesses. The MMSE was validated for clinical practice and research in 1975 [7], albeit not specifically for patients with brain tumors undergoing radiotherapy. The SQLI and MMSE were scheduled prior to the start of irradiation (i.e., baseline), at the end of irradiation and then at 4 month intervals. Quality of life could only be determined among patients possessing sufficient neurocognitive function to be assessed. These tests were

administered by personnel trained with a computerized learning module. No formal attempt was made to *maintain* standards of quality assurance among data collectors after baseline competence was established.

Differences in SQLI and MMSE scores from baseline to follow-up time points were assessed using the Wilcoxon signed rank sum test, a non-parametric test. The difference between the baseline and follow-up assessments for SQLI and MMSE was evaluated by the reliable change (RC) index [8]. The Cox proportional hazards model was used to estimate the hazard ratio (HR) associated with overall survival. Failure for the endpoint “time to neurocognitive failure” was examined in two different ways. With one approach, the patient was considered to have failed upon the first report of an MMSE score below 23. With the second approach, the patient was considered to have failed when the MMSE score was lower than the age- and education—adjusted cutoff [9]. Since this endpoint is a cause-specific failure where death without neurocognitive failure is a competing risk, the cumulative incidence method [10] was used to estimate cumulative incidence of progression.

Results

Table 2 illustrates patient enrollment and eligibility for assessment. Of the six patients who were excluded from the study, five had progression of disease prior to initiation of therapy while one had misclassification of his disease volume (i.e., PTV₂ was actually <75 cc despite the fact that it was recorded as being ≥75 cc).

Pre-treatment characteristics of the patients are listed in Table 3. There were no significant differences between the respective cohorts in terms of age or prognostic factors. Most patients were in their sixth decade of life with a relatively high performance status (i.e., KPS ≥ 80). Most patients were deemed to be RPA Class IV. At the time of enrollment, most patients were judged to have normal mental status, and the majority had at least a partial resection. It is remarkable that a total resection was performed in 64% of the patients in Group 1 receiving 84 Gy though there is no clear reason that explains why more aggressive surgery was done on the patients in this group.

Table 4 shows compliance with the SQLI administration. Baseline data are available for 185 (91%) of the patients and unavailable for 18 (9%) patients (10—did not complete the questionnaire, 5—refused, and 3—due to institutional error). Data were collected at all five time points on seven patients, at four of five time points on 27 patients and at three time points on 47 patients. In 53 patients, the SQLI was assessed only once; usually at baseline ($n = 45$). Among the 185 patients with baseline assessments, 21 patients (11%) died before the 4 month

Table 2 Status of cases

	Group 1 (PTV ₂ < 75 cc)				Group 2 (PTV ₂ ≥ 75 cc)				Total
	66 Gy	72 Gy	78 Gy	84 Gy	66 Gy	72 Gy	78 Gy	84 Gy	
Total patients entered	22	23	27	23	35	24	35	20	209
Ineligible/no protocol rx	0	0	0	1	2	1	0	2	6
Eligible	22	23	27	22	33	23	35	18	203
With on-study information	22	23	27	22	33	23	35	18	203
With toxicity information	22	23	27	22	33	23	35	18	203
Date arm closed to accrual	5/31/2000	7/1/2001	4/5/2002	9/3/2003	12/13/2000	7/1/2001	12/20/2002	9/3/2003	

Table 3 Pretreatment characteristics

	Group 1 (PTV ₂ < 75 cc)				Group 2 (PTV ₂ ≥ 75 cc)			
	66 Gy (n = 22)	72 Gy (n = 23)	78 Gy (n = 27)	84 Gy (n = 22)	66 Gy (n = 33)	72 Gy (n = 23)	78 Gy (n = 35)	84 Gy (n = 18)
Age								
Median	56	56	59	53	54	56	54	50
Range	20–82	37–75	24–73	24–77	20–74	28–76	26–78	23–79
<50	8 (36%)	8 (35%)	8 (30%)	9 (41%)	12 (36%)	5 (22%)	12 (34%)	8 (44%)
≥50	14 (64%)	15 (65%)	19 (70%)	13 (59%)	21 (64%)	18 (78%)	23 (66%)	10 (56%)
KPS								
60–70	4 (18%)	3 (13%)	5 (19%)	2 (9%)	9 (27%)	2 (9%)	3 (9%)	5 (28%)
80–100	18 (82%)	20 (87%)	22 (81%)	20 (91%)	24 (73%)	21 (91%)	32 (91%)	13 (72%)
Gender								
Male	14 (64%)	12 (52%)	14 (52%)	16 (73%)	27 (82%)	18 (78%)	25 (71%)	13 (72%)
Female	8 (36%)	11 (48%)	13 (48%)	6 (27%)	6 (18%)	5 (22%)	10 (29%)	5 (28%)
Neurological function								
No symptoms	8 (36%)	7 (30%)	5 (19%)	4 (18%)	6 (18%)	3 (13%)	13 (37%)	2 (11%)
Minor symptoms	8 (36%)	12 (52%)	13 (48%)	11 (50%)	15 (45%)	11 (48%)	19 (54%)	9 (53%)
Moderate (fully active)	3 (14%)	3 (13%)	6 (22%)	5 (23%)	7 (21%)	7 (30%)	1 (3%)	3 (17%)
Moderate (not fully active)	3 (14%)	1 (4%)	3 (11%)	2 (9%)	5 (15%)	2 (9%)	2 (6%)	4 (22%)
Extent of surgery								
Biopsy	4 (18%)	1 (4%)	3 (11%)	4 (18%)	7 (21%)	4 (17%)	6 (17%)	4 (22%)
Partial resection	13 (59%)	13 (52%)	15 (56%)	4 (18%)	24 (73%)	13 (57%)	21 (60%)	5 (28%)
Total resection	4 (18%)	9 (39%)	7 (26%)	14 (64%)	2 (6%)	6 (26%)	8 (23%)	7 (39%)
Other	1 (5%)	0 (0%)	2 (7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Missing	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (11%)
Mental status								
Normal function	15 (68%)	18 (78%)	17 (63%)	17 (77%)	21 (64%)	16 (70%)	22 (63%)	10 (56%)
Minor confusion	7 (32%)	5 (22%)	10 (37%)	5 (23%)	10 (30%)	7 (30%)	13 (37%)	8 (44%)
Gross confusion, but awake	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (6%)	0 (0%)	0 (0%)	0 (0%)
RPA class								
III	8 (36%)	7 (30%)	2 (7%)	6 (27%)	6 (18%)	4 (17%)	10 (28%)	4 (22%)
IV	6 (27%)	11 (48%)	18 (67%)	12 (55%)	18 (55%)	10 (43%)	17 (48%)	9 (50%)
V	6 (27%)	5 (22%)	5 (18%)	3 (14%)	7 (21%)	9 (39%)	6 (17%)	4 (22%)
VI	2 (9%)	0 (0%)	1 (4%)	1 (5%)	2 (6%)	0 (0%)	1 (3%)	1 (6%)
Unknown	0 (0%)	0 (0%)	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)

assessment, 33 (18%) expired between the 4 and 8 month assessments, and 37 (20%) died between the 8 and 12 month assessments.

Table 5 documents the distribution of SQLI scores (possible range: 0–10) for patients who had data at baseline and at the end of irradiation. No significant differences were found when comparing these time points within either of the stratification groups ($PTV_2 < 75 \text{ cc}$ $> PTV_2 \geq 75 \text{ cc}$). No significant differences were found when comparisons were made between other intervals (e.g., 4 and 8 months) and baseline values (data not shown).

Figure 2 shows that baseline SQLI strongly predicted for survival. The rates of overall survival between baseline SQLI scores <7 and $7-10$ are statistically significantly different [HR = 1.72, 95% CI (1.22, 2.4), $P = 0.0015$]. Survival curves were also generated as a function of the components of the index (independence, overall outlook, activity, and wellness). Although, strictly speaking, “support” also constitutes one of the domains contributing to the SQLI it was not specifically examined because only 9 patients were classified as receiving support infrequently. Importantly, “Independence” (i.e., self-reliance versus

Table 4 Follow-up spitzer compliance

Baseline	End of RT	4 Mo. from RT start	8 Mo. from RT start	12 Mo. from RT start	Group 1 ($PTV_2 < 75 \text{ cc}$) ($n = 94$)	Group 2 ($PTV_2 \geq 75 \text{ cc}$) ($n = 109$)	Total
X	X	X	X	X	4	3	7
X	X	X	X		5	3	8
X	X	X		X	1	2	3
X	X	X			7	9	16
X	X		X	X	9	3	12
X	X		X		17	7	24
X	X			X	1	2	3
X	X				14	27	41
X		X	X	X	2	2	4
X		X	X		2	1	3
X		X			7	7	14
X			X	X	1	0	1
X			X		1	2	3
X				X	0	1	1
X					14	31	45
	X			X	0	1	1
	X				0	3	3
		X			1	2	3
			X		2	0	2
					6	3	9

Table 5 Distribution of spitzer scores for patients with both baseline and end of RT

Dose level	<i>n</i>	Group 1 ($PTV_2 < 75 \text{ cc}$)						<i>n</i>	Group 2 ($PTV_2 \geq 75 \text{ cc}$)					
		Baseline			End of RT				Baseline			End of RT		
		Mean	SD	Range	Mean	SD	Range		Mean	SD	Range	Mean	SD	Range
66 Gy	9	8.00	1.87	5–10	7.89	2.62	2–10	18	7.56	2.15	4–10	7.5	1.98	4–10
72 Gy	17	8.59	1.46	6–10	8.59	1.28	6–10	14	8.00	1.66	5–10	6.71	2.09	4–10
78 Gy	17	7.88	1.73	5–10	8.24	1.99	4–10	15	8.00	1.36	5–10	7.87	1.55	5–10
84 Gy	15	7.67	2.09	4–10	8.00	2.04	5–10	9	6.56	2.74	0–10	7.11	1.83	3–9
Total	58	8.05	1.77	4–10	8.22	1.90	2–10	56	7.63	1.98	0–10	7.34	1.88	3–10

Testing for difference of scores from baseline to end of RT

Group 1: $P = 0.37$ (Wilcoxon signed rank sum test)

Group 2: $P = 0.32$ (Wilcoxon signed rank sum test)

requiring assistance) was highly predictive of survival. The OS between self-reliant patients and those requiring assistance is statistically significantly different [HR = 1.88; 95% CI = (1.38, 2.55); $P < 0.0001$]. “Overall Outlook” (calm and positive versus confused or troubled) did

not reach statistical significance ($P = 0.06$; Fig. 2b and c). “Activity” (normal activity versus neither working nor studying) and “Wellness” (feeling well versus lacking energy or feeling ill) had no impact on overall survival within this data set.

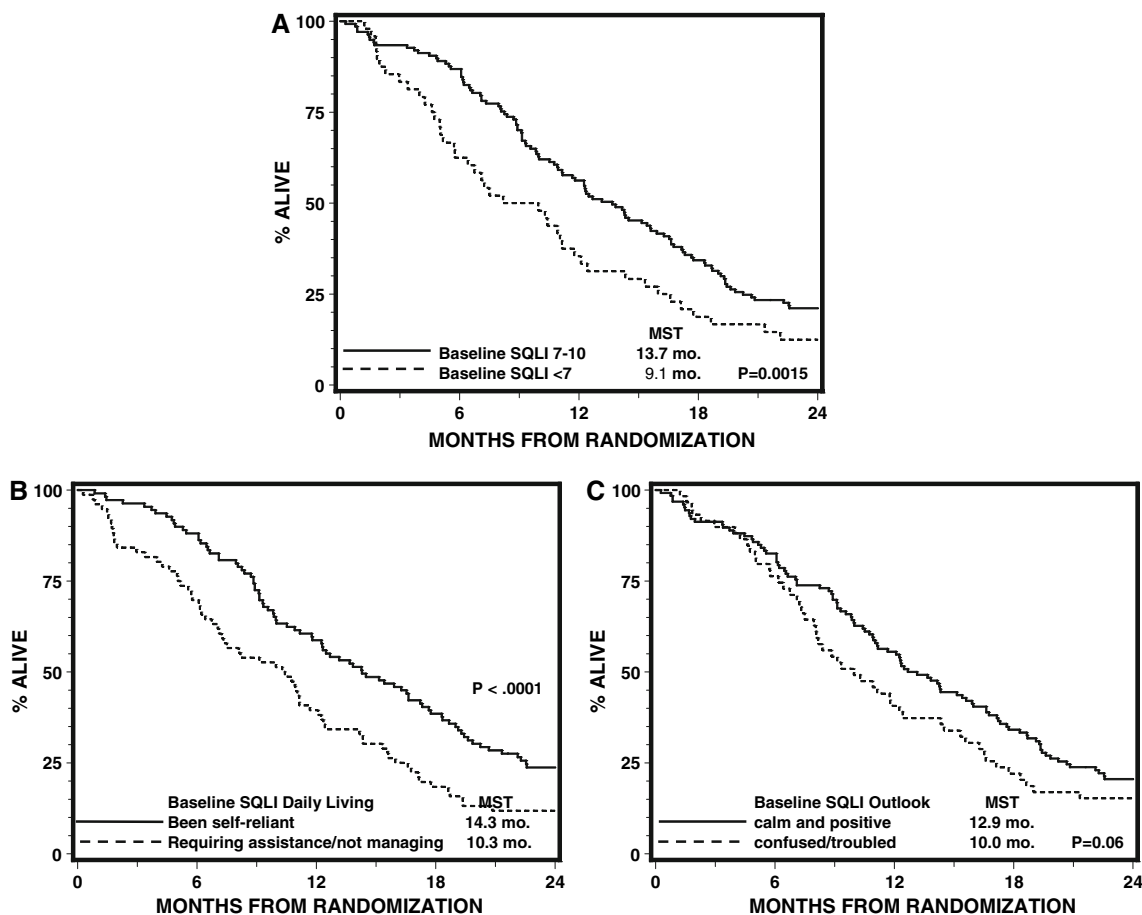


Fig. 2 Overall survival by SQLI scores (baseline and subdomains). **a** Overall survival by baseline SQLI score. **b** Overall survival by baseline SQLI daily living. **c** Overall survival by baseline SQLI outlook

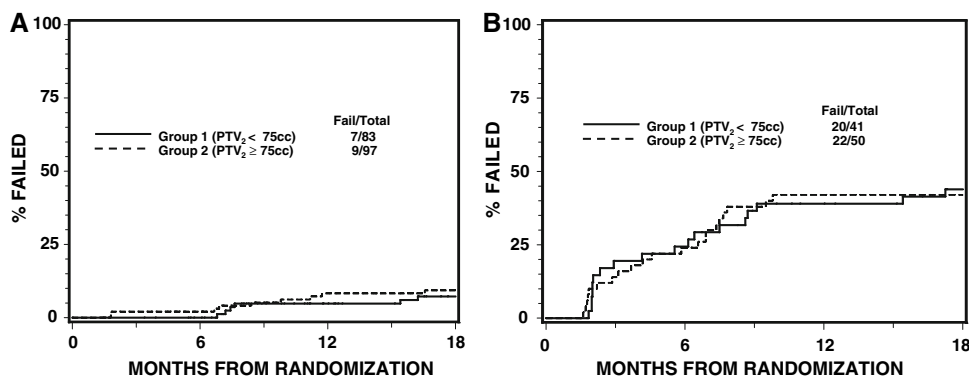


Fig. 3 Time to clinical neurocognitive failure with scoring according to absolute MMSE breakpoint or with adjustments for age and educational levels. **a** Time to clinical deterioration (MMSE < 23) by

group for baseline non-failures (MMSE ≥ 23 at baseline). **b** Time to clinical deterioration (MMSE < age/education cutoff) by group for baseline non-failures (MMSE ≥ age/education cutoff at baseline)

Table 6 Factors influencing overall survival: Cox proportional hazards multivariate analysis

Covariate	Comparison	HR (CI)	P-value
SQLI score	<7	–	–
	7–10	0.70 (0.49–0.99)	0.046
Gender	Male	–	
	Female	0.64 (0.46–0.91)	0.012
Age	<50	–	
	50+	2.26 (1.61–3.17)	<0.0001
Extent of surgery	Partial/total resection	–	
	Other (e.g., biopsy)	1.89 (1.27–2.82)	0.002

A Cox proportional hazard model was fitted to address the influence of SQLI baseline score, gender, age, and extent of surgery on survival (Table 6). After adjusting for gender, age, and extent of surgery, the overall survival between baseline SQLI scores <7 and scores between 7 and 10 were still statistically significantly different [HR (7–10 vs. < 7) = 0.70, 95% CI = (0.49, 0.99), P = 0.046]. Of note, Cox models with subscales were also performed. After adjusting for gender, age and extent of surgery, only the “independence” subscale was highly predictive of survival. “Outlook”, “activity” and “wellness” subscales did not have an impact on overall survival.

Table 7 shows patient compliance with administration of the MMSE. Only 5 patients did not have MMSE scores at baseline. (1—did not complete the questionnaire; 1—refusal; 1—institutional error; 2—unknown) Table 8 lists the pre-treatment characteristics by MMSE scores. Table 9

categorizes the same pre-treatment characteristics with attention to age and education levels of the patients studied in accordance with previous RTOG studies [11]. Figure 3 portrays the time to neurocognitive impairment according to either the absolute cut-point of 23 or age/education-adjusted scores, respectively. In either scenario, continual deterioration of neurocognitive function was evident though the level of neurocognitive impairment was more pronounced in the latter. Of note, there were only 7 and 11 patients with low MMSE scores at baseline in Group 1 and Group 2, respectively. Moreover, the median survival times of these patients with low MMSE scores were 6.4 and 3 months, respectively. Since small sample size may lead to unreliable conclusions, the estimates of clinical deterioration for patients with low MMSE scores at baseline were not detailed.

Discussion

Radiation therapy continues to play an important role in the treatment of glioblastoma. As more effective modalities for high-grade gliomas become available and long-term survival continues to improve [2], further attention has to be placed on identifying and quantifying the adverse effects of therapy on quality of life, cognition and neuropsychiatric functioning. Although the majority of GBM cases are associated with fatal consequences, an understanding of the morbidity of brain irradiation is critical in clinical decision-making.

Table 7 Follow-up MMSE compliance

Baseline	End of RT	4 Mo. from RT start	8 Mo. from RT start	12 Mo. from RT start	Group 1 (PTV ₂ < 75 cc) (n = 94)	Group 2 (PTV ₂ ≥ 75 cc) (n = 109)	Total
X	X	X	X	X	7	3	10
X	X	X	X		5	7	12
X	X	X		X	1	1	2
X	X	X			8	9	17
X	X		X	X	11	5	16
X	X		X		17	9	26
X	X				15	31	46
X		X	X	X	1	2	3
X		X	X		1	2	3
X		X		X	0	1	1
X		X			5	8	13
X			X		3	1	4
X				X	1	1	2
X					15	28	43
	X		X	X	0	1	1
		X			1	0	1
					3	0	3

Table 8 Pretreatment characteristics by MMSE score = 23 cutoff at baseline

	Group 1 (PTV ₂ < 75 cc)		Group 2 (PTV ₂ ≥ 75 cc)	
	MMSE ≥ 23 at baseline (baseline non-failures) (n = 83)	MMSE < 23 at baseline (baseline failures) (n = 7)	MMSE ≥ 23 at baseline (baseline non-failures) (n = 97)	MMSE < 23 at baseline (baseline failures) (n = 11)
Age				
Median	55	63	54	73
Range	20–82	55–77	20–74	37–79
		n (%)	n (%)	n (%)
Age				
<50		33 (40)	0 (0)	34 (35)
≥50		50 (60)	7 (100)	63 (65)
Gender				
Male		49 (59)	5 (71)	74 (76)
Female		34 (41)	2 (29)	23 (24)
KPS				
60–70		10 (12)	4 (57)	10 (10)
80–100		73 (88)	3 (43)	87 (90)
Neurological function				
No symptoms		22 (27)	0 (0)	23 (24)
Minor symptoms		43 (52)	0 (0)	53 (55)
Moderate (fully active)		13 (16)	4 (57)	15 (15)
Moderate (not fully active)		5 (6)	3 (43)	6 (6)
Mental status				
Normal function		65 (78)	0 (0)	67 (69)
Minor confusion		18 (22)	7 (100)	30 (31)
Gross confusion, but awake		0 (0)	0 (0)	0 (0)
RPA class				
III		23 (28)	0 (0)	23 (24)
IV		44 (53)	0 (0)	52 (54)
V		16 (19)	2 (29)	21 (22)
VI		0 (0)	4 (57)	0 (0)
Unknown		0 (0)	1 (14)	1 (1)

When the RTOG elected to launch protocol 98-03, the goal was to employ novel techniques of conformal irradiation to achieve safe dose-escalation. This analysis reports the results that pertain to the quality of life and neuro-cognitive function.

It is widely recognized that most studies on impairment of cognition and patient well-being following irradiation of gliomas are limited due to a variety of confounding factors including selection-bias, patient heterogeneity, small sample size and the use of outdated doses and volumes of irradiation [12, 13]. The current study used the best techniques that were available at the time for group-wide application, without resorting to detailed and prohibitively expensive formal neuropsychometric evaluation. Since that time, comprehensive neuropsychiatric batteries have emerged that are simultaneously affordable and easy to

administer [14]. Indeed these neuropsychiatric batteries have been incorporated into RTOG protocols. As noted by Meyers and Wefel [15], the MMSE is insufficient to assess the frontal-subcortical network dysfunction often associated with radiation therapy to the brain and thus studies relying on this kind of screening tool risk missing significant cognitive changes. While it is not possible to alter the methods of assessment utilized for this particular study it is fortunate that future research will include more sensitive neuropsychological measures.

Our data show that neither pre-treatment nor treatment-related factors (including the dose of radiation) had a meaningful effect upon life-quality or neurocognition. It must be acknowledged that the MMSE may not be sensitive enough to detect subtle differences between these groups. Putatively, dose-escalation is assumed to lead to

Table 9 Pretreatment characteristics by MMSE age/education cutoff at baseline

	Group 1 (PTV ₂ < 75 cc)		Group 2 (PTV ₂ ≥ 75 cc)	
	MMSE > age/education cutoff at baseline (baseline non-failures) (n = 41)	MMSE ≤ age/education cutoff at baseline (baseline failures) (n = 49)	MMSE > age/education cutoff at baseline (baseline non-failures) (n = 50)	MMSE ≤ age/education cutoff at baseline (baseline failures) (n = 58)
Age				
Median	55	56	55	53
Range	20–82	20–77	20–74	23–79
		<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
Age				
<50		18 (44)	15 (31)	13 (26)
≥50		23 (56)	34 (69)	37 (74)
Gender				
Male		27 (66)	27 (55)	39 (78)
Female		14 (34)	22 (45)	11 (22)
KPS				
60–70		5 (12)	9 (18)	5 (10)
80–100		36 (88)	40 (82)	45 (90)
Neurological function				
No symptoms		10 (24)	12 (24)	11 (22)
Minor symptoms		25 (61)	18 (37)	26 (52)
Moderate (fully active)		4 (10)	13 (27)	9 (18)
Moderate (not fully active)		2 (5)	6 (12)	4 (8)
Mental status				
Normal function		32 (78)	33 (67)	36 (72)
Minor confusion		9 (22)	16 (33)	14 (28)
Gross confusion, but awake		0 (0)	0 (0)	0 (0)
RPA class				
III		15 (37)	8 (16)	11 (22)
IV		21 (51)	23 (47)	23 (46)
V		5 (12)	13 (27)	15 (30)
VI		0 (0)	4 (8)	0 (0)
Unknown		0 (0)	1 (2)	1 (2)

increasing levels of cognitive impairment. For instance, Keibert et al. [16] reviewed the EORTC phase III study which compared the delivery of 59.4 vs. 45 Gy (conventional fractionation in both arms) among low grade glioma patients. Patients who received the higher total dose of irradiation tended to report lower levels of functioning and more symptom burden following the completion of irradiation compared to those who were treated with lower doses of radiotherapy. In the present study of GBM patients, a dose effect may have been obscured since all the doses employed may have been above the threshold needed to induce cognitive damage.

Neurocognitive abilities (as assessed via the MMSE) declined over time. Depending on the methodology used to determine neurocognitive function (e.g., absolute cut-off level on the test of 23, or, adjustments for age and

educational level), varying degrees of cognitive damage were manifest. As inferred from a similar study carried out by the RTOG in the context of brain metastases [11], it appears that that the preferable way to score neurocognitive outcome is by adjusting for age and education. Although it is difficult to isolate the contribution of irradiation alone to the neurocognitive impairment, it seems likely that the treatment is responsible for at least some component of the decline.

Several investigators have recently attempted to perform psychometric and/or quality of life assessments in high grade glioma patients. Bosma et al. [17] carried out evaluations of six neurocognitive domains at baseline (i.e., prior to radiotherapy) and at 8 and 16 months among patients suffering from high grade glioma. Fifteen of 32 patients suffered tumor recurrence before the 8 month follow-up

visit was reached. Patients manifesting recurrence had significantly more impairment (most notably executive functioning, information processing capacity and psychomotor speed) than those who were recurrence free; a finding that the authors associated with the use of anti-epileptic drugs in the former population. Recht and colleagues [18] used an independent living score (ILS) to retrospectively analyze a cohort of high grade glioma patients. They noted that individuals who were most intensively treated, including those whose tumors were totally resectable, had improved survival without compromising patient independence. Schmidinger et al. [19] restricted their analysis to 13 GBM patients surviving a minimum of 18 months. In this select group, eleven patients expressed high satisfaction with life in general despite various psychophysiological and cognitive impairments.

In the present study, baseline life quality was highly predictive of survival. Although it is unclear whether the SQLI can be segmented into domains [20], it appears that the driving force which explains the impact on survival in the current report is the patient's sense of independence. Recently, Tang and co-workers [21] used the Functional Independence Measure [22] (FIM) to assess patients with brain tumors at baseline and following a rehabilitation intervention. Those investigators demonstrated that patients with either primary or metastatic brain tumors could achieve functional gains following rehabilitation. What's more, high functional improvement was a significant predictor of longer survival among patients suffering from either brain metastases or glioblastoma multiforme.

Glioblastoma Multiforme is a notorious disease which, in and of itself, engenders a steady decline in patient function. Appropriate therapeutic goals are therefore not only restricted to the provision of extended survival but also attainment of an acceptable quality of life; ideally with preservation of useful levels of independence and neurocognition. In going forward, modern series will be most instructive if reporting is not restricted to survival outcome. Rather, insight into both QOL and neurocognitive function as well as interventions designed to optimize these factors will be welcomed by neuro-oncologists and the patients who benefit from their care.

References

1. Fisher JL, Schwartzbaum JA, Wrensch M, Wiemels JL (2007) Epidemiology of brain tumors. *Neurol Clin* 25:867–890. doi:10.1016/j.ncl.2007.07.002
2. Stupp R, Mason WP, van den Brent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 352:987–996. doi:10.1056/NEJMoa043330
3. Tsien C, Moughan J, Michalski JM et al (2009) A phase I/II conformal radiation dose escalation study in newly diagnosed patients with glioblastoma multiforme. RTOG trial 98-03. *Int J Radiat Oncol Biol Phys* 73:699–708. doi:10.1016/j.ijrobp.2008.05.034
4. Spitzer WO, Dobson AJ, Hall J et al (1981) Measuring the quality of life of cancer patients. A concise QL index for use by physicians. *J Chronic Dis* 34:585–597. doi:10.1016/0021-9681(81)90058-8
5. Tangalos EG, Smith GE, Ivnik RJ et al (1996) The mini mental status examination in general medical practice. Clinical utility and acceptance. *Mayo Clin Proc* 71:829–837. doi:10.4065/71.9.829
6. Addington-Hall JM, Macdonald LD, Anderson HD (1990) Can the spitzer quality of life index help to reduce prognostic uncertainty in terminal care? *BJC* 62:695–699
7. Folstein M, Folstein SE, Mchugh PR (1975) “Mini-mental state” a practical method of grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198. doi:10.1016/0022-3956(75)90026-6
8. Jacobson NS, Truax P (1991) Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. *J Consult Clin Psychol* 1991(59):12–19. doi:10.1037/0022-006X.59.1.12
9. Crum RM, Anthony JC, Bassett SS et al (1993) Population-based norms for the mini-mental state examination by age and educational level. *JAMA* 269:2386–2391. doi:10.1001/jama.269.18.2386
10. Kalbfleish JD, Prentice RL (1980) The statistical analysis of failure time data. John Wiley and Sons, New York, pp 167–169
11. Corn BW, Moughan J, Knisely JPS et al (2008) Prospective evaluation of quality of life and neurocognitive effects in patients with multiple brain metastases receiving whole brain radiotherapy with or without thalidomide on RTOG 01-18. *Int J Radiat Oncol Biol Phys* 71:71–78
12. Hochberg FH, Slotnick B (1980) Neuropsychologic impairment in astrocytoma survivors. *Neurology* 30:172–177
13. Archibald YM, Lunn D, Ruttan LA et al (1994) Cognitive functioning in long-term survivors of high grade glioma. *J Neurosurg* 80:247–253
14. Wefel JS, Witgert ME, Meyers CA (2008) Neuropsychological sequelae of non-central nervous system cancer and cancer therapy. *Neuropsychol Rev* 18:121–131. doi:10.1007/s11065-008-9058-x
15. Meyers CA, Wefel JS (2003) The use of mini-mental status examinations to assess cognitive functioning in cancer trials: no ifs, ands, buts, or sensitivity. *J Clin Oncol* 21:3557–3558. doi:10.1200/JCO.2003.07.080
16. Keibert GM, Curran D, Aaronson NK et al (1998) Quality of life after radiation therapy of cerebral low grade gliomas of the adult: results of a randomized phase III trial on dose response (EORTC Trial 22844). *Eur J Cancer* 34:1902–1909. doi:10.1016/S0959-8049(98)00268-8
17. Bosma I, Vos MJ, Heimans JJ et al (2007) The course of neurocognitive functioning in high grade glioma patients. *Neuro-oncology* 9:53–62. doi:10.1215/15228517-2006-012
18. Recht L, Glantz M, Chamberlain M, Hsieh CC (2003) Quantitative measurement of quality outcome in malignant glioma patients using an independent living score (ILS). Assessment of a retrospective cohort. *J Neurooncol* 61:127–136. doi:10.1023/A:1022187502917
19. Schmidinger M, Linzmayer L, Becherer A et al (2003) Psychometric and quality of life assessment in long-term glioblastoma survivors. *J Neurooncol* 63:55–61. doi:10.1023/A:1023740303162

20. Sloan JA, Loprinzi CL, Kross SA et al (1998) Randomized comparison of four tools measuring overall quality of life patients with advance cancer. *J Clin Oncol* 16:3662–3673
21. Tang V, Rathbone M, Dorsay JP, Jiang S, Harvey D (2008) Rehabilitation in primary and metastatic brain tumors. Impact of functional outcomes on survival. *J Neurol* 255:820–827. doi: [10.1007/s00415-008-0695-z](https://doi.org/10.1007/s00415-008-0695-z)
22. Keith RA, Granger CV, Hamilton BB, Sherwin FS (1987) The functional independence measure (FIM): a new tool for rehabilitation. *Adv Clin Rehabil* 1:6–18