William A. Hall, MD*
 Stephanie L. Pugh, PhD[‡]
 Jeffrey S. Wefel, PhD[§]
 Terri S. Armstrong, PhD[¶]
 Mark R. Gilbert, MD^{||}
 David G. Brachman, MD[#]
 Maria Werner-Wasik, MD**
 Merideth M. Wendland, MD**
 Paul D. Brown, MD^{§§}
 Samuel T. Chao, MD^{¶¶}
 Kevin S. Roof, MD^{|||}
 H. Ian Robins, MD^{##}
 Minesh P. Mehta, MD***
 Walter J. Curran, Jr, MD⁺⁺⁺
 Benjamin Movsas, MD^{§§§}

*Department of Radiation Oncology, Medical College of Wisconsin, Milwaukee, Wisconsin and Clement J. Zablocki, VA, Medical Center, Milwaukee, Wisconsin; [‡]NRG Oncology Statistics and Data Management Center, Philadelphia, Pennsylvania; [§]Department of Neuro-Oncology, University of Texas MD Anderson Cancer Center, Houston, Texas; [¶]Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; ^{||}Center for Cancer Research, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; [#]Department of Radiation Oncology, University of Arizona, St. Joseph's Hospital Medical Center and Barrow Neurological Institute, Phoenix, Arizona; ^{**}Department of Radiation Oncology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania; ^{††}Department of Radiation Oncology, Willamette Valley Cancer Institute, Eugene, Oregon; ^{§§}Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota; ^{¶¶}Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, Ohio; ^{|||}Department of Radiation Oncology, Southeast Cancer Control Consortium, Inc, CCOP, Winston Salem, NC, North Carolina; ^{##}Departments of Medicine, Human Oncology, and Neurology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; ^{***}Miami Cancer Institute, Baptist Health, Kendall, Florida; ⁺⁺⁺Winship Cancer Institute, Emory University, Atlanta, Georgia; ^{§§§}Department of Radiation Oncology, Henry Ford Hospital, Detroit, Michigan

This study has been presented as an oral presentation at the 2014 Society of Neuro-oncology meeting in Miami, Florida, November 13 to 16, 2014, and the 2015 American Society of Radiation Oncology (ASTRO) meeting in San Antonio, Texas, October 18 to 21, 2015, both as oral presentations.

Correspondence:

William A. Hall, MD,
 Department of Radiation Oncology,
 Medical College of Wisconsin,
 8701 W Watertown Plank Rd,
 Milwaukee, WI 53226.
 E-mail: whall@mcw.edu

Received, June 23, 2017.

Accepted, February 15, 2018.

Published Online, March 30, 2018.

Copyright © 2018 by the
 Congress of Neurological Surgeons

Influence of Residual Disease Following Surgical Resection in Newly Diagnosed Glioblastoma on Clinical, Neurocognitive, and Patient Reported Outcomes

BACKGROUND: The influence of subtotal resection (STR) on neurocognitive function (NCF), quality of life, and symptom burden in glioblastoma is unknown. If bevacizumab preferentially benefits patients with STR is unknown.

OBJECTIVE: To examine these uncertainties.

METHODS: NCF and patient reported outcomes (PRO) were prospectively collected in NRG Oncology RTOG 0525 and 0825. Changes in NCF and PRO measures from baseline to prespecified times were examined by Wilcoxon test, and mixed effects longitudinal modeling, to assess differences between patients who received STR vs gross-total resection. Changes were also compared among STR patients on 0825 receiving placebo vs bevacizumab to assess for a preferential therapeutic effect. Overall survival between STR and gross-total resection patients was compared using the Kaplan–Meier method.

RESULTS: A total of 427 patients were eligible with STR present in 37%. At baseline, patients with STR had worse NCF, worse MD Anderson Symptom Inventory Brain Tumor Neurological Factor ratings ($P = .004$), and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire ($P = .002$). Longitudinal multivariate analysis associated STR with worse NCF (Hopkins Verbal Learning Test–Revised Delayed Recognition [$P = .048$], Trail Making Test Part A [$P = .035$], and Controlled Oral Word Association [$P = .049$]). One hundred eighty-three STR patients from 0825 were analyzed (89 bevacizumab, 94 placebo); bevacizumab failed to demonstrate improvement in select NCF or PRO measures.

CONCLUSION: STR patients had worse NCF and PROs before therapy. During adjuvant therapy, STR patients had worse objective NCF, despite accounting for tumor location. STR did not result in a detriment to OS. The addition of bevacizumab did not preferentially improve PRO or NCF outcomes in STR patients.

KEY WORDS: Resection status and quality of life, Resection extent and neurocognitive function, Glioblastoma resection, Glioblastoma and extent of resection, Extent of resection in GBM, Quality of life GBM, patient reported outcomes GBM, Bevacizumab and GBM, Glioblastoma and radiation therapy, Glioblastoma and surgical resection

Neurosurgery 84:66–76, 2019

DOI:10.1093/neuros/nyy003

www.neurosurgery-online.com

Glioblastoma (GBM) is a highly infiltrative and aggressive malignancy with overall survival (OS) rates that remain dismal.^{1,2} Attempts to improve OS in newly diagnosed GBM using dose dense schedules of chemotherapy or novel

ABBREVIATIONS: COWA, Controlled Oral Word Association; EORTC-QLQ, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; GBM, glioblastoma; GTR, gross-total resection; HVL-T-R, Hopkins Verbal Learning Test–Revised; KPS, Karnofsky Performance Status; MDASI-BT, MD Anderson Symptom Inventory Brain Tumor; MRI, magnetic resonance imaging; NCF, neurocognitive function; NIH, National Institutes of Health; OS, overall survival; PFS, progression-free survival; PROs, patient reported outcomes; QOL, quality of life; STR, subtotal resection; TMT, Trail Making Test

Supplemental digital content is available for this article at www.neurosurgery-online.com.

targeted agents including bevacizumab have largely failed.^{3,4} Exciting advances in surgical techniques including 5-ALA guided surgery and intraoperative magnetic resonance imaging (MRI)-assisted surgery have recently emerged; however, quantifying the precise benefits of these technologies is challenging.⁵ Several publications have described an extent of resection “threshold” that distinguishes patients with higher median OS.⁶⁻⁸ Yet others have used accelerated failure time modeling and have recommended a maximum safe resection approach.⁹ Notable is that more extensive resections may carry a higher risk of morbidity and neurological impairment. Additionally, in these patients with relatively short anticipated survival, an understanding of the influence of interventions on neurocognitive function (NCF) and patient reported outcomes (PROs), and quality of life (QOL) seems highly prudent. Nevertheless, only a limited number of small series have examined the relationship between resection status and such endpoints in patients with GBM.¹⁰⁻¹² Changes in the normal brain function, specifically in NCF, are important in assessing the consequence of aggressive resection; further, NCF has an important role in GBM prognosis.¹³ However, there is a paucity of data examining the impact of subtotal resection (STR), relative to gross-total resection (GTR) on NCF in large cohorts of prospectively collected data. There are no published manuscripts, to the best of our knowledge, which have collectively examined NCF and PROs as influenced by the extent of resection.

NRG Oncology 0525 was a phase III randomized clinical trial comparing conventional adjuvant temozolomide chemotherapy with dose intensive temozolomide.⁴ NRG Oncology RTOG 0825 was phase III randomized clinical trial evaluating the use of bevacizumab in patients with newly diagnosed GBM.³ These clinical trials were 2 of the largest clinical trials in GBM ever conducted, and both were the first to collect detailed data examining NCF and PROs.^{14,15} These data provided the first opportunity to examine the relationship between the extent of resection and the NCF and PRO metrics over time.

Bevacizumab is a humanized monoclonal antibody against Vascular Endothelial Growth Factor A (VEGF-A) and preclinical data suggest that its therapeutic benefit is likely secondary to normalization of tumor vasculature.^{16,17} The clinical trial NRG Oncology RTOG 0825 demonstrated that the addition of bevacizumab to the upfront treatment of newly diagnosed GBM did not improve OS or NCF or PRO metrics.^{3,15} However, the possibility that STR patients may have intact tumor vasculature lead to the hypothesis that bevacizumab may preferentially improve clinical metrics in these patients.¹⁷ This analysis sought to simultaneously examine the influence of bevacizumab in only those patients with a STR.

METHODS

Sample

This was a posthoc exploratory analysis conducted using the merged dataset from the companion studies of NRG Oncology RTOG 0525 and NRG Oncology RTOG 0825 in which NCF and PRO data were

prospectively collected. The merger of the 0525 and 0825 datasets was felt to be appropriate to add statistical power given extremely similar inclusion criteria of the 2 parent studies. The primary analysis for each subcomponent of the publication has been previously presented.^{14,15} Patients were included from only the control arm of 0825 to avoid the known influence and potential confounding factor of bevacizumab on NCF and PRO metrics.¹⁵ All patients who participated in these subcomponents could speak English and had histopathologically confirmed GBM (World Health Organization grade IV). All patients provided written informed consent for participation in each of the clinical trials. Eligible patients with unknown resection status or biopsies only were removed from the analysis. Patients with biopsies only were removed secondary to their ineligibility for study participation. The distinction of GTR and STR was made by the accruing site and was based on postoperative computed tomography or MRI reports from the accruing site. The reason for STR was based on the discretion of the surgeon at the accruing center, and was likely secondary to tumor in more eloquent locations. Radiation therapy treatment specifications were the same in both clinical trials RTOG 0525 and RTOG 0825.

Study Design

The objective of this study was to compare changes in QOL, symptom burden, and NCF between 2 cohorts of patients, STR and GTR, in NRG Oncology RTOG 0525 and NRG Oncology RTOG 0825. Patients were only eligible for this portion of the clinical trial if they had not demonstrated radiographic progression during therapy. In addition, another objective of this study was to examine if the addition of bevacizumab preferentially improved QOL, symptom burden, and NCF metrics in patients with a STR. There were a total of 4 follow-up time points of interest for data collection: prior to cycles 1, 4, and 10, corresponding to 6, 21, and 42 wk from the start of treatment in NRG Oncology RTOG 0525 and at 6, 22, and 46 wk from the start of treatment in NRG Oncology RTOG 0825. Because of the 4 wk discrepancy in the last follow-up time point, these data were only incorporated into certain analyses in which an adjustment for the study variable (0525 vs 0825) could be included. Each patient's change from baseline to these follow-up time points (prior to cycles 1, 4 in NRG Oncology RTOG 0525, and 6 and 22 wk in NRG Oncology RTOG 0825) was calculated. Patients who had undergone STR were then selected from NRG Oncology RTOG 0825 to compare the placebo vs the bevacizumab arms.

Outcome Measures

The results of these companion clinical trials of NRG Oncology RTOG 0525 and RTOG 0825 have been previously reported.^{14,15} Health-related QOL was evaluated using the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30/BN20 (EORTC-QLQ-C30/BN20) developed and validated for use in a cancer patient population.^{18,19} For this analysis, prespecified domains were global QOL and cognitive function from the EORTC-QLQ-C30 and communication deficit and motor dysfunction from the BN20. Symptom burden and interference were assessed using the MD Anderson Symptom Inventory Brain Tumor (MDASI-BT), which was developed and validated for use in this patient population.^{14,20} Symptom severity, cognitive factor, neurological factor, and interference were prespecified for this analysis.

NCF was assessed using the Hopkins Verbal Learning Test–Revised (HVLT-R; Total Recall, Delayed Recall, and Delayed Recognition),²¹ the Trail Making Test (TMT; Part A and Part B)²² and the Controlled Oral

Word Association (COWA) test.²³ The NCF tests were administered by a health care professional (eg, nurse, psychologist) who was trained and certified by the study neuropsychologist (J.S.W.). The Clinical Trial Battery Composite score, calculated using the standardized HVLT-R, TMT Parts A and B, and COWA scores, was also assessed.

Statistical Methods

After conducting a normality test, either the *t*-test or Wilcoxon test was used to assess resection status differences at these time points. Mixed effects models with random intercepts and slopes were used to assess changes across time. Adjustment was made for resection status (STR vs GTR), study (0525 vs 0825), and any baseline characteristics that were significantly different (at the $\alpha = 0.05$ level) between type of resection status. Other covariates that were considered for inclusion were age (<60 vs ≥ 60 yr old), RPA (recursive partitioning analysis) class (III vs IV vs V), MGMT (O⁶-methylguanine-DNA-methyltransferase) status (methylated vs unmethylated), neurological function (no symptoms vs at least some symptoms), gender (male vs female), Karnofsky Performance Status scale (KPS; 60-80 vs 90-100), tumor laterality (right vs left), tumor location, temozolomide dosing (days 1-5 vs days 1-21), baseline anticonvulsant use (yes vs no), and baseline steroid use (yes vs no). Models were built as follows: covariates significant in a univariable model at the 0.10 level were considered for inclusion in the multivariable model. Covariates were removed one at a time, beginning with the covariate with the highest corresponding *P*-value, until all covariates remaining were significant at the 0.05 level. Higher alpha levels were used in the model building process due to its exploratory nature.

The effect of time from surgery to start of treatment, tumor laterality, and tumor location on baseline NCF and PRO metrics was examined using a linear regression model. The change from baseline to 2 of the follow-up time points (prior to cycles 1 and 4 in 0825) was calculated as follow-up—baseline. After conducting a normality test, either the *t*-test or Wilcoxon test were used to assess resection status differences at these time points. To adjust for the multiple domains being analyzed, while accounting for the correlated nature of these domains, a significance level of 0.01 was used.

OS and progression-free survival (PFS) for the cohort as a whole were estimated using the Kaplan–Meier method. Differences between the STR and GTR patients were assessed using the log rank test. A Cox proportional hazards model was used to calculate hazard ratios.

RESULTS

Patient Cohort

A total of 427 eligible patients who participated in the NCF and PRO components of NRG Oncology RTOG 0525 and the control arm of NRG Oncology RTOG 0825 with either an STR or GTR were included in the initial portion of the analysis (Figure 1A). Patients with unknown resection status or biopsies only were removed. A second cohort of patients were analyzed, those with STR on NRG Oncology RTOG 0825, this consisted of a total of 183 patients (94 patients in the control arm and 89 patients in the treatment arm; Figure 1B). Complete patient characteristics, with statistical comparisons between the different arms of the studies, are in Tables 1 and 2. There were more patients who underwent a GTR ($n = 268$) compared to STR

($n = 159$). Both groups were similar with respect to all patient and clinical characteristics except KPS. A total of 60.4% of patients with a STR had a KPS of 90 to 100 compared to 70.5% of patients with a GTR (Table 1; $P = .032$). The characteristics of the patients with a STR that were analyzed from NRG Oncology RTOG 0825 can be seen in Table 2. There were no statistically significant differences seen amongst the patient cohorts in this subgroup.

NCF and PRO Comparison

Comparing the baselines scores from the various metrics measured for patients with STR in comparison to those with GTR, STR patients were found to have worse NCF (HVLT-R Total Recall [median score -1.5 for STR vs -1.0 for GTR, $P = .004$], COWA [-1.1 vs -0.8 for STR and GTR, respectively, $P = .007$]; worse MDASI-BT Cognitive Factor ratings (1.0 vs 0.5 for STR and GTR, respectively, $P = .006$); and worse EORTC-QLQ Cognitive Function scale ratings (66.7 vs 83.3 for STR and GTR, respectively, $P = .002$) at baseline. Those baseline comparisons reaching statistical significance are summarized in Table 3. Of note there were multiple baseline comparisons for each domain that did not reach statistical significance that are listed in the footer of Table 3.

When the discrete time point analysis was performed examining patient changes from baseline to the 6-, and the 22-wk time points, there were no statistically significant differences between the patients achieving a GTR as compared to STR (Tables, Supplemental Digital Content 1-6). On longitudinal multivariate analysis, several factors emerged as significantly associated with STR. The presence of STR was associated with worse NCF (HVLT-R Delayed Recognition [estimate = -0.018 , $P = .048$], TMT Part A [-0.046 , $P = .035$], and COWA [-0.0086 , $P = .049$]) in patients without progressive disease. These differences can be seen in Table 4 along with graphical representation showing longitudinal trends in Figure 2. These differences were independent of tumor location and laterality, as both variables were accounted for in the statistical models. Resection status was not significantly associated with QOL or symptom burden over time.

Bevacizumab Subgroup Analysis

Patients with a STR only in NRG Oncology RTOG 0825 ($n = 183$) were examined from both the control and bevacizumab arms ($n = 94, 89$, respectively). The median change score was analyzed from baseline to 22 wk, comparing the control arm to those patients in the treatment arm (bevacizumab). The objective of this analysis was to examine if the addition of bevacizumab had a preferential benefit for patients with STR. There were no differences in any of the selected metrics of NCF, EORTC QLQ, or MDASI-BT for those patients with STR who received bevacizumab as compared to placebo (Tables, Supplemental Digital Content 7-9).

TABLE 1. Baseline Patient Characteristics

	Partial resection (n = 159)	Total Resection (n = 268)	P-value ^a
Age (yr)			
Mean	57.3	56.2	.37 ^b
Std. dev.	12.1	12.4	
Median	59	57	
Min - max	19 - 82	20 - 84	
Q1 - Q3	50 - 66	50 - 64	
Gender			
Male	98 (61.6%)	150 (56.0%)	.25
Female	61 (38.4%)	118 (44.0%)	
KPS			
60-80	63 (39.6%)	79 (29.5%)	.032
90-100	96 (60.4%)	189 (70.5%)	
Neurological function			
No symptoms vs at least some			.053
No symptoms	47 (29.6%)	104 (38.8%)	
Minor symptoms	72 (45.3%)	118 (44.0%)	
Moderate symptoms	40 (25.2%)	45 (16.8%)	
Severe symptoms	0 (0.0%)	1 (0.4%)	
MGMT			
Methylated vs unmethylated			.52
Methylated	44 (27.7%)	78 (29.1%)	
Unmethylated	109 (68.6%)	167 (62.3%)	
Unknown	6 (3.8%)	23 (8.6%)	
RPA class			
III	30 (18.9%)	51 (19.0%)	.31
IV	97 (61.0%)	178 (66.4%)	
V	32 (20.1%)	39 (14.6%)	
Lateralization of tumor			
Right vs left			.22
Right side only	80 (50.3%)	155 (57.8%)	
Left side only	74 (46.5%)	112 (41.8%)	
Bilateral	4 (2.5%)	1 (0.4%)	
Unknown	1 (0.6%)	0 (0.0%)	
Tumor location			
Single vs multiple			.18
Frontal	43 (27.0%)	78 (29.1%)	
Temporal	44 (27.7%)	75 (28.0%)	
Parietal	24 (15.1%)	44 (16.4%)	
Occipital	0 (0.0%)	5 (1.9%)	
Other	0 (0.0%)	1 (0.4%)	
Multiple	48 (30.2%)	65 (24.3%)	
Days from surgery to start of treatment			
Mean	28.6	28.6	.91 ^b
Std. dev.	5.0	5.5	
Median	29	28	
Min - max	3 - 36	10 - 64	
Q1 - Q3	25 - 33	25 - 33	
Steroid use			
No	33 (20.8%)	62 (23.1%)	.57
Yes	126 (79.2%)	206 (76.9%)	
Anticonvulsant use			
No	46 (28.9%)	64 (23.9%)	.25
Yes	113 (71.1%)	204 (76.1%)	
TMZ dose			
TMZ d 1-5	127 (79.9%)	209 (78.0%)	.64
TMZ d 1-21	32 (20.1%)	59 (22.0%)	
Treatment arm			
0525 arm 1	33 (20.8%)	63 (23.5%)	.64
0525 arm 2	32 (20.1%)	59 (22.0%)	
0825 arm 1	94 (59.1%)	146 (54.5%)	

TABLE 1. *continued*

	Partial resection (n = 159)	Total Resection (n = 268)	P-value ^a
Study			
0525	65 (40.9%)	122 (45.5%)	.35
0825	94 (59.1%)	146 (54.5%)	

TMZ, temozolomide; Std. dev., standard deviation; KPS, Karnofsky performance score; MGMT, O⁶-methylguanine-DNA-methyltransferase; Q1, first quartile; Q3, third quartile; RPA, recursive partitioning analysis

^aP-value from Chi-Square test

^bP-value from t-test assuming equal variances

OS and PFS Comparison

Finally, OS and PFS were examined for all patients, comparing STR to GTR. No statistically significant difference in OS was seen. A significant improvement in PFS was observed in the GTR cohort (Figure 3; hazard ratio of 0.76 [95% confidence interval: 0.61, 0.94], $P = .010$).

DISCUSSION

Our understanding of the influence of therapeutic interventions in GBM is in need of considerable expansion. OS and PFS are critical endpoints; however, short of the recently published EF-14 trial, major clinical breakthroughs in GBM have been limited.²⁴ Considering the dismal outcomes in GBM, there is a need for improved understanding of current interventional strategies on NCF and PROs. This enables evaluation of interventions beyond just their influence on OS and PFS. Such an understanding might enable a more refined evaluation of both existing, and innovative therapeutic interventions. The precise influence of surgical resection in GBM is moderately controversial; however, most evidence supports a maximum safe resection.^{5-7,9} Yet the relationship between the presence of residual disease following surgical resection on patient outcomes such as QOL, symptom burden, and NCF remains largely unknown in GBM. Moreover, the ability of bevacizumab to preferentially improve NCF and PROs in those patients with an STR is also unknown. In the current report, a combined, posthoc, exploratory analysis of NRG Oncology RTOG 0525 and NRG Oncology RTOG 0825 is presented with the objective of addressing these questions.

These findings demonstrate that residual disease following STR has important implications in GBM. At baseline, patients with STR had worse NCF, MDASI-BT and worse EORTC-QLQ scale ratings, compared to GTR. This is likely secondary to tumor in more eloquent locations. Such differences in baseline scores may have important consequences for interpretation of future studies examining these endpoints. Possibly more interesting are the results of the longitudinal multivariate analysis in which patients with STR demonstrated worse NCF. This finding supports the widely held dictum in neuro-oncology that “tumor in the brain is

bad for cognition.” Critical to this result is that collection of these NCF and PRO metrics was suspended if radiographic progression was demonstrated. This means that such declines were measured, for this analysis, in patients without clinical or radiographic evidence of progression. This removes tumor progression as a variable that could have accounted for NCF decline. This finding expands on and agrees with previously published data suggesting that NCF worsening precedes radiographic progression.²⁵ The inclusion of NCF tests may allow identification of patients at risk for tumor progression before MRI evidence of tumor progression develops or differential impact on cognition from subsequent therapy. Moreover, the ability to measure these declines provides compelling data for a potentially novel endpoint for clinical trials, especially as OS did not vary between the GTR and STR patients.

Several nonstatistically significant findings of the study are worthy of mention. No significant influence of the time from surgery to the start of chemo-radiation therapy and baseline NCF, PRO, or QOL metrics or longitudinal metrics was observed. This is despite the potential for rapid tumor growth as illustrated in previously published series.²⁶ Upon the revelation that patients with STR appeared to have worse select NCF and PRO metrics longitudinally, the influence of bevacizumab on these metrics was examined only in those patients with STR. The hypothesis was that the addition of bevacizumab in patients with STR may result in preferential improvement in these metrics. This was suspected secondary to the mechanism of action of bevacizumab, which centers on normalization of tumor vasculature. To this end a small, hypothesis generating, exploratory analysis of only those patients with STR was conducted. In this cohort, the change from baseline to 22 wk between patients receiving bevacizumab as compared to those patients receiving placebo was examined. Unfortunately, no preferential benefit was seen in those patients receiving bevacizumab with STR without demonstration of radiographic progression. This was consistent with the findings of the cohort as a whole.¹⁵ Given the absence of any benefit to bevacizumab in this smaller sub-group, we elected not to continue conducting exploratory analyses with bevacizumab as additional hypothesis driven subgroup analyses could not be formulated.

The influence of STR on OS and PFS was also examined; however, this was not the primary objective of this study and

TABLE 2. Baseline Characteristics by Treatment Arm for 0825 STR Patients

	Control (n = 94)	Bev (n = 89)	P-value ^a
Age (yr)			
Mean	57.6	59.3	.29 ^b
Std. dev.	11.7	10.4	
Median	58.5	60	
Min - max	19 - 82	29 - 82	
Q1 - Q3	51 - 66	54 - 66	
Gender			
Male	63 (67.0%)	53 (59.6%)	.29
Female	31 (33.0%)	36 (40.4%)	
KPS			
60-80	40 (42.6%)	32 (36.0%)	.36
90-100	54 (57.4%)	57 (64.0%)	
Neurological function			
No symptoms	26 (27.7%)	21 (23.6%)	.53
Minor symptoms	41 (43.6%)	48 (53.9%)	
Moderate symptoms	27 (28.7%)	20 (22.5%)	
MGMT			
Methylated	24 (25.5%)	22 (24.7%)	.99
Unmethylated	70 (74.5%)	64 (71.9%)	
Unknown (indeterminate, invalid)	0 (0.0%)	3 (3.4%)	
RPA class			
III	14 (14.9%)	9 (10.1%)	.41
IV	58 (61.7%)	63 (70.8%)	
V	22 (23.4%)	17 (19.1%)	
Lateralization of tumor			
Right side only	44 (46.8%)	48 (53.9%)	.28
Left side only	46 (48.9%)	36 (40.4%)	
Bilateral	3 (3.2%)	4 (4.5%)	
Unknown	1 (1.1%)	1 (1.1%)	
Tumor location^c			
Frontal	21 (22.3%)	18 (20.5%)	.20
Temporal	23 (24.5%)	15 (17.0%)	
Parietal	16 (17.0%)	11 (12.5%)	
Occipital	0 (0.0%)	2 (2.3%)	
Other	0 (0.0%)	2 (2.3%)	
Multiple	34 (36.2%)	40 (45.5%)	
Days from surgery to start of treatment^c			
Mean	29.1	29.2	.92 ^b
Std. dev.	5.0	5.7	
Median	30	30	
Min - max	3 - 36	7 - 39	
Q1 - Q3	26 - 33	26 - 34	
Steroid use			
No	21 (22.3%)	20 (22.5%)	.98
Yes	73 (77.7%)	69 (77.5%)	
Anticonvulsant use			
No	25 (26.6%)	21 (23.6%)	.64
Yes	69 (73.4%)	68 (76.4%)	

TMZ, temozolomide; Std. dev., standard deviation; KPS, Karnofsky performance score; MGMT, O⁶-methylguanin-DNA-methyltransferase; Q1, first quartile; Q3, third quartile; RPA, recursive partitioning analysis

^aP-value from Chi-Square test

^bP-value from t-test assuming equal variances

^cOne patient on the Bev arm is missing and not included in the test between arms

TABLE 3. Significant Baseline Distribution Differences for Net Clinical Benefit Metrics

	Partial resection (n = 159)	Total resection (n = 268)	P-value ^a
NCF			
HVLT-R Total Recall (n = 148)		(n = 242)	
Mean	-1.7	-1.2	
Std. dev.	1.7	1.5	
Median	-1.5	-1.0	.0031
Min - max	-6.4 - 1.6	-6.2 - 2.0	
Q1 - Q3	-2.9 - -0.3	-2.1 - 0.1	
COWA (n = 149)		(n = 245)	
Mean	-1.1	-0.7	
Std. dev.	1.3	1.3	
Median	-1.1	-0.8	.0055
Min - max	-4.1 - 2.1	-3.7 - 5.0	
Q1 - Q3	-1.9 - -0.4	-1.5 - 0.1	
MDASI-BT			
Neurological factor (n = 149)		(n = 250)	
Mean	1.3	1.0	
Std. dev.	1.6	1.5	
Median	0.7	0.3	.0039
Min - max	0.0 - 8.0	0.0 - 9.3	
Q1 - Q3	0.0 - 1.7	0.0 - 1.3	
EORTC QLQ C30/BN20			
Cognitive function (n = 149)		(n = 249)	
Mean	70.1	77.4	
Std. dev.	24.5	23.1	
Median	66.7	83.3	.0015
Min - max	0.0 - 100.0	0.0 - 100.0	
Q1 - Q3	66.7 - 83.3	66.7 - 100.0	

HVLT-R, Hopkins Verbal Learning Test-Revised; COWA, Controlled Oral Word Association; Q1, first quartile; Q3, third quartile; Std. dev., standard deviation

^aP-value from 2-sided Wilcoxon test using the normal approximation

Nonstatistically significant NCF baseline differences examined included: HVLT-R Delayed Recall, HVLT-R Delayed Recognition, TMT Part A, TMT Part B.

Nonstatistically significant MDASI-BT baseline differences examined included: Symptoms Severity, Neurological Factor, and Interference scores.

Nonstatistically significant baseline differences in the EORTC QLQ C30/BN20 include: Global QOL, Communication Deficit, Motor Dysfunction

should be interpreted with caution. This analysis showed no difference with regard to OS for those patients with STR vs GTR. Patients with STR did have inferior PFS. Given there was no volumetric analysis performed to examine for a “threshold effect” of the extent of surgical resection these OS data are difficult to interpret. These OS comparisons should be interpreted with caution as this was not the primary focus of the analysis and the lack of volumetric analysis makes any firm conclusions from these data limited. These data support a maximum safe resection approach in terms of superior PFS^{5,7,9}.

Limitations

There are limitations of this analysis that merit discussion. This analysis included only those patients with a high enough

TABLE 4. Multivariable Longitudinal Analysis

Effect	Estimate (std dev)	P-value
HVLT-R Delayed Recognition Multivariable Model		
Intercept	-0.22 (0.73)	.76
Time	-0.066 (0.033)	.046
Surgery (total resection)	-0.095 (0.20)	.63
Time*surgery (total resection)	0.018 (0.0089)	.048
Gender (male)	0.48 (0.14)	.0004
KPS (90-100)	-0.61 (0.19)	.0014
Tumor laterality (right side)	-0.94 (0.18)	<.0001
Study (0825)	0.30 (0.18)	.092
TMT Part A Multivariable Model		
Intercept	-4.82 (1.16)	<.0001
Time	0.052 (0.013)	<.0001
Surgery (total resection)	0.073 (1.03)	.94
Time*surgery (total resection)	-0.046 (0.022)	.035
KPS (90-100)	-0.63 (0.17)	.0002
RPA III (V)	2.91 (1.10)	.58
RPA IV (V)	1.75 (0.92)	.0086
Study (0825)	0.37 (0.53)	.47
COWA Multivariable Model		
Intercept	-0.91 (0.21)	<.0001
Time	0.0090 (0.0025)	.0003
Surgery (total resection)	-0.36 (0.12)	.0034
Time*surgery (total resection)	-0.0086 (0.0043)	.049
Gender (male)	0.28 (0.12)	.18
KPS (90-100)	-0.40 (0.15)	.0062
Tumor laterality (right side)	-0.63 (0.11)	<.0001
RPA III (V)	0.73 (0.23)	.0016
RPA IV (V)	0.45 (0.18)	.012
Study (0825)	-0.031 (0.12)	.79

Study, surgery, interaction, and KPS were forced into the model.

Reference levels are in parentheses.

performance status to enroll in the clinical trials NRG Oncology RTOG 0525 and 0825. This may not be an accurate reflection of a typical GBM population. The studies did not perform central imaging analysis and as mentioned previously volumetric analysis of residual tumor was unknown. The absence of central imaging analysis prevented any ability to analyze the influence of residual tumor volume on OS or examine radiation dose distribution and its relation to the included metrics. Finally this is a posthoc exploratory analysis, which has inherent limitations. While we attempted to statistically control for nearly all potential confounders, data on some clinical metrics, such as steroid dosing was limited and was not able to be retrospectively ascertained with accuracy.

Limitations to this data notwithstanding there are some potentially novel and intriguing aspects to this analysis that may carry clinical implications. For the first time we have shown that NCF and PRO metrics change on longitudinal multivariate analysis amongst patients with STR compared to GTR. Given these results, patients with STR may need to be more closely monitored for cognitive decline. In addition, the presence of STR should be

accounted for in future studies examining NCF and PRO metrics. Furthermore, given that NCF tests were more sensitive to the detection of this decline, when compared with PROs, inclusion of neuropsychologists in the care of these patients may be of clinical benefit. Despite hypothetical benefits, we are seeing no signal for a preferential benefit to bevacizumab use in STR patients.^{3,15} Finally our data demonstrate a PFS benefit associated with GTR supporting a maximum safe resection approach.

CONCLUSION

These analyses demonstrate that NCF and PRO metrics differ in those patients achieving a STR as compared with a GTR. This is despite the absence of radiographic progression or difference in OS. These findings warrant additional investigation and validation in independent cohorts. These data provide important information about the impact of STR on NCF and PRO metrics. Moreover, they provide compelling data for a potentially novel endpoint for GBM clinical trials.

Disclosures

This project was supported by grants U10CA21661, U10CA180868, U10CA180822, U10 CA37422, and UG1CA189867 from the National Cancer Institute, Merck & Co, and Genentech. This publication was supported by the National Center for Research Resources and the National Center for Advancing Translational Sciences, National Institutes of Health (NIH), through Grant Number UL1TR001436. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Dr Wefel reports consulting roles with Genentech, Roche, Bayer, VFW, Angiochem, Juno, Novocure, Cogstate, and Vanquish Oncology. Dr Wendland reports employment at US Oncology. Dr Chao reports honoraria from Zeiss and Abbvie, and travel expenses and speaking fees from Varian. Dr Roof reports Amgen, Merck, and Halyard Health Inc stock. Dr Mehta reports a leadership role and stock/ownership interest with Pharmacyclics, consulting roles with Varian medical Systems, Agenus, Insys Therapeutics, Remedy Pharmaceuticals, IBA, AstraZeneca, and Oncocutics, research funding to his institution from Novocure and Novelos, a patent, and is a member of a data safety monitoring board for Monteris Medical. Dr Movsas reports research funding to institution from Varian Inc and Philips Inc, patents, and travel expenses from Varian Inc. Dr Brachman reports a patent or intellectual property interest in GammaTile. Dr Hall reports institutional research support from Elekta and grant funding from the American Cancer Society.

REFERENCES

1. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. *Neuro Oncol.* 2012;14(suppl 5):v1-v49.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med.* 2005; 352(10):987-996.
3. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med.* 2014; 370(8):699-708.
4. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol.* 2013;31(32):4085-4091.
5. Barone DG, Lawrie TA, Hart MG. Image guided surgery for the resection of brain tumours. *Cochrane Database Syst Rev.* 2014;1: Jan 28;(1):CD009685.

6. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg.* 2011;115(1):3-8.
7. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg.* 2001;95(2):190-198.
8. Pope WB, Sayre J, Perlina A, Villablanca JP, Mischel PS, Cloughesy TF. MR imaging correlates of survival in patients with high-grade gliomas. *AJNR Am J Neuroradiol.* 2005;26(10):2466-2474.
9. Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. *J Clin Oncol.* 2014;32(8):774-782.
10. Jakola AS, Unsgard G, Solheim O. Quality of life in patients with intracranial gliomas: the impact of modern image-guided surgery. *J Neurosurg.* 2011;114(6):1622-1630.
11. Sagberg LM, Solheim O, Jakola AS. Quality of survival the 1st year with glioblastoma: a longitudinal study of patient-reported quality of life. *J Neurosurg.* 2016;124(4):989-997.
12. Budrukkar A, Jalali R, Dutta D, et al. Prospective assessment of quality of life in adult patients with primary brain tumors in routine neurooncology practice. *J Neurooncol.* 2009;95(3):413-419.
13. Johnson DR, Sawyer AM, Meyers CA, O'Neill BP, Wefel JS. Early measures of cognitive function predict survival in patients with newly diagnosed glioblastoma. *Neuro Oncol.* 2012;14(6):808-816.
14. Armstrong TS, Wefel JS, Wang M, et al. Net clinical benefit analysis of radiation therapy oncology group 0525: a phase III trial comparing conventional adjuvant temozolomide with dose-intensive temozolomide in patients with newly diagnosed glioblastoma. *J Clin Oncol.* 2013;31(32):4076-4084.
15. Wefel JS, Armstrong TS, Won MM. Neurocognitive function (NCF) outcomes in patients with glioblastoma (GBM) enrolled in RTOG 0825. *J Clin Oncol.* 2013;31(15):2004-2004.
16. Ferrara N, Hillan KJ, Novotny W. Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *Biochem Biophys Res Commun.* 2005;333(2):328-335.
17. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science.* 2005;307(5706):58-62.
18. Efficace F, Bottomley A. Health related quality of life assessment methodology and reported outcomes in randomised controlled trials of primary brain cancer patients. *Eur J Cancer.* 2002;38(14):1824-1831.
19. Taphoorn MJ, Claassens L, Aaronson NK, et al. An international validation study of the EORTC brain cancer module (EORTC QLQ-BN20) for assessing health-related quality of life and symptoms in brain cancer patients. *Eur J Cancer.* 2010;46(6):1033-1040.
20. Armstrong TS, Mendoza T, Gning I, et al. Validation of the M.D. Anderson Symptom Inventory Brain Tumor Module (MDASI-BT). *J Neurooncol.* 2006;80(1):27-35.
21. Shapiro AM, Benedict RH, Schretlen D, Brandt J. Construct and concurrent validity of the Hopkins Verbal Learning Test – Revised. *Clin Neuropsychol.* 1999;13(3):348-358.
22. Tombaugh TN. Trail Making Test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol.* 2004;19(2):203-214.
23. Ruff RM, Light RH, Parker SB, Levin HS. Benton controlled Oral Word Association Test: reliability and updated norms. *Arch Clin Neuropsychol.* 1996;11(4):329-338.
24. Stupp R, Taillibert S, Kanner AA, et al. Maintenance therapy with tumor-treating fields plus temozolomide vs temozolomide alone for glioblastoma. *JAMA.* 2015;314(23):2535-2543.
25. Meyers CA, Hess KR. Multifaceted end points in brain tumor clinical trials: cognitive deterioration precedes MRI progression. *Neuro Oncol.* 2003;5(2):89-95.
26. Pirzkall A, McGue C, Saraswathy S, et al. Tumor regrowth between surgery and initiation of adjuvant therapy in patients with newly diagnosed glioblastoma. *Neuro Oncol.* 2009;11(6):842-852.

Supplemental digital content is available for this article at www.neurosurgery-online.com.

Supplemental Digital Content 1. Table. Change from Baseline to 6 wk for NCF for RTOG 0525 and RTOG 0825.

Supplemental Digital Content 2. Table. Change from Baseline to 6 wk for MDASI-BT for RTOG 0525 and RTOG 0825 Arm 1.

Supplemental Digital Content 3. Table. Change from Baseline to 6 wk for EORTC QLQ C30/BN20 for RTOG 0525 and RTOG 0825 Arm 1

Supplemental Digital Content 4. Table. Change from Baseline to 22 wk for NCF for RTOG 0525 and RTOG 0825 Arm 1.

Supplemental Digital Content 5. Table. Change from Baseline to 22 wk for MDASI-BT for RTOG 0525 and RTOG 0825 Arm 1.

Supplemental Digital Content 6. Table. Change from Baseline to 22 wk for EORTC QLQ C30/BN20 for RTOG 0525 and RTOG 0825 Arm 1.

Supplemental Digital Content 7. Table. Change from Baseline to 22 wk for NCF for RTOG 0825 Control vs Treatment.

Supplemental Digital Content 8. Table. Change from Baseline to 22 wk for MDASI-BT for RTOG 0825 Control vs Treatment.

Supplemental Digital Content 9. Table. Change from Baseline to 22 wk for EORTC QLQ C30/BN20 for RTOG 0825 Control vs Treatment.