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Impact of extent of resection for recurrent glioblastoma on overall survival

Clinical article

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Object. Extent of resection (EOR) has been shown to be an important prognostic factor for survival in patients undergoing initial resection of glioblastoma (GBM), but the significance of EOR at repeat craniotomy for recurrence remains unclear. In this study the authors investigate the impact of EOR at initial and repeat resection of GBM on overall survival.

Methods. Medical records were reviewed for all patients undergoing craniotomy for GBM at the University of California San Francisco Medical Center from January 1, 2005, through August 15, 2009. Patients who had a second craniotomy for pathologically confirmed recurrence following radiation and chemotherapy were evaluated. Volumetric EOR was measured and classified as gross-total resection (GTR, > 95% by volume) or subtotal resection (STR, ≤ 95% by volume) after independent radiological review. Overall survival was compared between groups using univariate and multivariate analysis accounting for known prognostic factors, including age, eloquent location, Karnofsky Performance Status (KPS), and adjuvant therapies.

Results. Multiple resections were performed in 107 patients. Fifty-two patients had initial GTR, of whom 31 (60%) had GTR at recurrence, with a median survival of 20.4 months (standard error [SE] 1.0 months), and 21 (40%) had STR at recurrence, with a median survival of 18.4 months (SE 0.5 months) (difference not statistically significant). Initial STR was performed in 55 patients, of whom 26 (47%) had GTR at recurrence, with a median survival of 19.0 months (SE 1.2 months), and 29 (53%) had STR, with a median survival of 15.9 months (SE 1.2 months) ($p = 0.004$). A Cox proportional hazards model was constructed demonstrating that age (HR 1.03, $p = 0.004$), KPS score at recurrence (HR 2.4, $p = 0.02$), and EOR at repeat resection (HR 0.62, $p = 0.02$) were independent predictors of survival. Extent of initial resection was not a statistically significant factor ($p = 0.13$) when repeat EOR was included in the model, suggesting that GTR at second craniotomy could overcome the effect of an initial STR.

Conclusions. Extent of resection at recurrence is an important predictor of overall survival. If GTR is achieved at recurrence, overall survival is maximized regardless of initial EOR, suggesting that patients with initial STR may benefit from surgery with a GTR at recurrence.

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Key Words • **glioblastoma** • **survival** • **craniotomy** • **extent of resection** • **oncology**

Glioblastoma, the most common primary malignant brain tumor in adults, is associated with a uniformly poor prognosis.[3,19] Despite advances in adjuvant therapy over the past 2 decades there has been little improvement in outcomes, with the median duration of survival remaining at 12–15 months.[7,18] Standard therapy for newly diagnosed GBM involves resection when possible, and multiple studies over the past decade have shown that EOR is an important prognostic factor for overall survival.[6,8,12] Recently, an EOR threshold for the primary treatment of GBM has been reported in the literature, demonstrating significant improvement in survival with greater than 78% resection and incremental improvements with increasing EOR, based on volumetric assessment of enhancing tumor.[12] The appreciation for the importance of achieving a maximal resection has led

Abbreviations used in this paper: EOR = extent of resection; GBM = glioblastoma; GTR = gross-total resection; KPS = Karnofsky Performance Status; RTOG = Radiation Therapy Oncology Group; SE = standard error; STR = subtotal resection; TMZ = temozolomide.

This article contains some figures that are displayed in color online but in black-and-white in the print edition.

to the development of new technologies aimed at improving the safety and completeness of resections, including neuronavigation, functional mapping, intraoperative vital dyes, and intraoperative MRI.[5,11,14,16]

With improvements in surgical techniques, many patients are now surviving to recurrence with good functional status. Upon recurrence there are limited effective options for treatment, but anecdotal experience suggests that in highly functional patients minimizing tumor burden may facilitate the efficacy of subsequent therapy. To date, the impact of EOR at repeat craniotomy for recurrence has not been fully investigated. Although a small number of studies have examined the effect of repeat resection on survival, none of them have addressed the effect of EOR accounting for both the initial and repeat resection.[6,8] In this study we report outcomes for our series of 107 consecutively treated GBM patients who have undergone 2 or more craniotomies for tumor resection. The primary focus of this study is the prognostic importance of EOR at repeat surgery for recurrence and the relative impact of EOR at each resection.

Methods

Patient Data Acquisition

We performed a retrospective review of all cases in which patients underwent a craniotomy for resection of a GBM at the University of California San Francisco Medical Center from January 1, 2005 to August 15, 2009. A database of patients undergoing craniotomy for a brain tumor was generated from the operating room log and cross-referenced with a pathology database containing identifiers for all patients with a histopathologically confirmed diagnosis of GBM according to the World Health Organization classification system. Medical records were reviewed to identify patients with a primary GBM who underwent resection and for whom complete medical records were available. Patients with known secondary GBM, incomplete medical records, or who underwent biopsy only were excluded from this study.

During the study period 354 adult patients with a new diagnosis of primary GBM underwent resective surgery. Of these, 107 patients underwent one or more additional craniotomies for treatment of recurrent disease, with histopathologically confirmed recurrent tumor at the time of repeat resection, and these 107 patients were included in this study. A review of patient charts was conducted to obtain demographic information, including age, sex, presenting symptoms, and pre- and postoperative KPS scores. Additionally, preoperative imaging was reviewed to determine tumor location and size. All tumors were classified as located in eloquent or noneloquent cortex. Eloquence was defined by radiological tumor location and confirmed by the presence of a positive intraoperative map in patients undergoing motor and/or speech mapping during resection. For patients who were not candidates for intraoperative mapping, eloquence was defined by the location of the tumor and an associated preoperative deficit corresponding to the tumor location. All patients underwent postoperative MRI within 48 hours of each surgery and clinical follow-up with assessment of functional status at 6 weeks postoperatively. After resection, patients received radiotherapy and adjuvant chemotherapy. For most patients, primary therapy following initial resection consisted of fractionated 3D-conformal radiotherapy and TMZ in accordance with the Stupp protocol.[18] A minority of patients received a second chemotherapeutic agent in addition to TMZ as part of a clinical study, as indicated in *Results* (see Table 1). Following recurrence, some patients received further adjuvant chemotherapy as indicated.

The extent of resection for each procedure was retrospectively reviewed by a single, experienced neuroradiologist blinded to clinical information. Volumetric analysis of the contrast-enhancing tumor calculated by the reviewing neuroradiologist was used to assess the EOR. T1-weighted pre- and postcontrast images from the preoperative and postoperative scans were used to identify the contrast-enhancing tumor while accounting for intrinsically T1 hyperintense blood products postresection. The pre- and postcontrast T1-weighted images from before and immediately after the resection were transferred to an imaging workstation offline (AW Workstation, GE Healthcare) and regions of interest were manually drawn on each postcontrast T1-weighted image by the reviewing neuroradiologist. Volumetric EOR was calculated based on the difference in preoperative and postoperative contrast-enhancing tumor volumes (expressed as a percentage) and the EOR for each patient was classified as GTR (> 95% resection by volume) or STR (≤ 95% resection by volume).

The primary end point used for this study was overall survival, calculated as the time from diagnosis to death. Additionally, the time to reoperation, calculated as the time between the first and second resection, and the survival from reoperation, calculated as the time from the second resection until death, were evaluated as secondary measures. Official death records were obtained from the Social Security Death Index. At the time of the data analysis, 5 patients (5%) were known by recent clinical follow-up to be alive and were appropriately censored in the survival analysis. Another 2 patients (2%) were lost to follow-up without available records of death. All medical record and imaging reviews were conducted with approval from the University of California, San Francisco, Committee on Human Research.

Data Analysis and Statistical Methods

Patients were divided into 4 groups based on EOR at initial surgery (GTR vs STR) and subsequently at second surgery within each initial group (see Fig. 1). Differences in demographic variables between groups were compared using an independent-groups ANOVA for continuous variables, the Kruskal-Wallis test for ordinal variables, and the Pearson chi-square test for dichotomous variables. The Kaplan-Meier method was used to estimate overall survival for each group, and a log-rank test was performed to determine statistically significant differences between groups. Mean time to reoperation and mean duration of survival from reoperation were compared between groups using an independent-groups ANOVA with a posthoc Bonferroni correction. For these statistical tests, significance was accepted at $p = 0.05$.

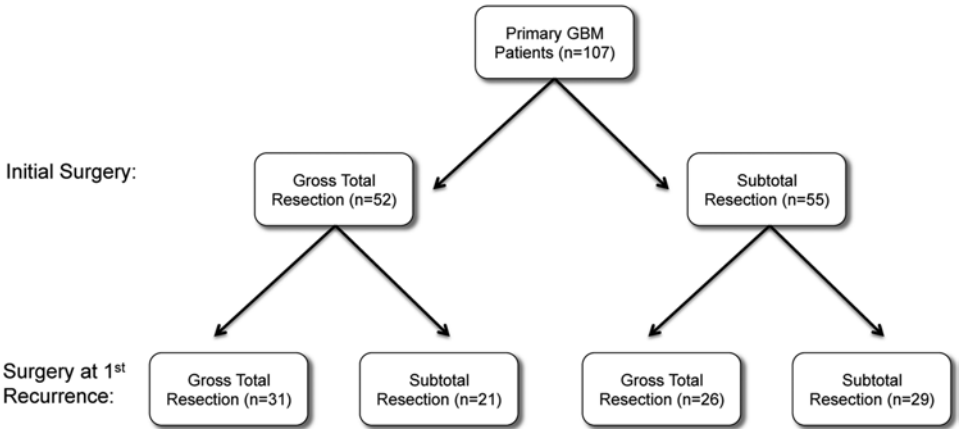

Fig. 1. Graphical depiction of patient stratification into 4 groups based on EOR at initial operation and recurrence.

To assess the relative impact of multiple variables on overall survival, a Cox proportional hazards model was constructed. Each variable was first tested independently in univariate analysis using the Kaplan-Meier method log-rank test for dichotomous variables and a univariate Cox regression for continuous variables. Variables with significance at the $p = 0.20$ level were selected for inclusion in the multivariate model and were entered in a forward stepwise fashion. Only variables with significance at the $p = 0.02$ level were accepted in the final model. All statistical tests were performed using SPSS version 19 (IBM).

Results

Clinical Characteristics

The clinical characteristics at presentation are summarized for each EOR group in Table 1. There were 31 patients who had GTR at the first and second resection, 21 patients who had GTR followed by STR at recurrence, 26 patients who had STR followed by GTR at recurrence, and 29 patients who had STR at the first and second resection, as shown in Fig. 1. There were no significant differences in age, sex, tumor location, or eloquence of tumor location between groups. The initial median KPS score was 90 for all groups. The median KPS score at recurrence was 90 for all groups except the STR/STR group, in which the median KPS score was 80. All patients received standard conformal radiotherapy and TMZ following initial resection. An equivalently small fraction of patients in each group received an additional experimental agent following initial resection. A number of adjuvant chemotherapy regimens were given for recurrence in addition to repeat resection. As seen in Table 1, there were no significant differences in the number of patients in each group receiving secondary chemotherapeutic agents.

Survival Outcomes

The overall survival for patients in each EOR group is summarized in Table 2. The median actuarial survival for patients with GTR followed by GTR was 20.4 months (SE 1.0 months) with 1- and 2-year survival rates of 87% and 32%, respectively. In patients with GTR followed by STR, the median actuarial survival was 18.4 months (SE 0.5 months) with 1- and 2-year survival rates of 81% and 33%, respectively. The median actuarial survival for patients with STR followed by GTR was 19.0 months (SE 1.2 months) with 1- and 2-year survival rates of 88% and 36%, respectively. In patients with STR followed by STR, the median actuarial survival was 15.9 months (SE 1.2 months) with 1- and 2-year survival rates of 61% and 4%, respectively. Kaplan-Meier survival curves for each group are shown in Figs. 2 and 3. There was no statistically significant difference in survival between the 2 groups with an initial GTR; however, for patients with an initial STR, the group with STR at recurrence demonstrated significantly decreased survival compared with GTR at recurrence (median survival 15.9 vs 19.0 months, $p = 0.004$). For patients with an initial STR followed by GTR at recurrence, overall survival was not significantly different from patients with an initial GTR.

The duration of progression-free survival, as measured by time from initial to repeat resection, was significantly increased for initial GTR compared with STR (mean 11.3 vs 6.7 months, $p = 0.009$). For patients with initial GTR, there was no statistically significant difference in survival following repeat resection based on the EOR in the surgery for recurrence (mean survival from reoperation 11.5 vs 8.5 months, $p = 0.2$). In contrast, for patients with initial STR, survival following repeat resection was significantly increased for GTR compared with STR at reoperation (mean 16.7 vs 7.4 months, $p = 0.001$). As shown in Fig. 4, the extended survival following GTR at recurrence for patients with initial STR results in a total survival similar to that of patients with initial GTR, and significantly increased survival compared with patients with STR followed by STR.

Prognostic Factors

To determine the independent impact of EOR on overall survival, a multivariate Cox regression model was constructed utilizing previously characterized prognostic factors. Patient age, sex, KPS score, eloquent tumor location, primary and secondary chemotherapy, and both initial and repeat EOR were examined as prognostic factors for survival using univariate analysis, as shown in Table 3. Only age, KPS, and EOR were significant at the p =

TABLE 1: Patient demographics of EOR groups*

Characteristic	Initial GTR		Initial STR		p Value
	GTR at Recur	STR at Recur	GTR at Recur	STR at Recur	
no. of patients	31	21	26	29	
age, mean (yrs)	54.4	53.2	54.4	52.7	0.91
sex					
male	20 (64.5)	10 (48)	10 (38.5)	11 (38)	0.65
female	11 (35.5)	11 (52)	16 (61.5)	18 (62)	
tumor location					
frontal	13 (42)	12 (57)	11 (42)	12 (41)	0.90
temporal	3 (10)	3 (14)	4 (15)	6 (21)	
parietal	13 (42)	6 (29)	10 (39)	10 (35)	
occipital	2 (6)	0 (0)	1 (4)	1 (3)	
eloquent location	13 (42)	10 (48)	10 (39)	10 (35)	0.82
median KPS					
initial	90	90	90	90	0.52
recurrence	90	90	90	80	0.001
primary chemotherapy					
TMZ	27 (87)	20 (95)	23 (88.5)	29 (97)	0.49
TMZ + erlotinib	4 (13)	1 (5)	3 (11.5)	1 (3)	
secondary chemotherapy					
none	9 (29)	5 (24)	8 (31)	7 (24)	0.35
bevacizumab	6 (20)	8 (38)	5 (19)	8 (28)	
bevacizumab + irinotecan	3 (9)	4 (19)	7 (27)	3 (10)	
lomustine	0 (0)	0 (0)	0 (0)	2 (7)	
other	10 (32)	2 (10)	3 (11)	5 (17)	

* Values represent numbers of patients (%) unless otherwise indicated. Abbreviation: Recur = Recurrence.

0.20 level and were included in the multivariate model. Hazard ratios from the multivariate results for each factor are shown in Table 4. When adjusting for all factors, only age, KPS score at recurrence, and EOR at repeat resection were statistically significant predictors of overall survival. There was a trend toward significance for the KPS score at presentation. Initial EOR was not significant when EOR at recurrence was included in the model.

Discussion

The importance of EOR as a prognostic factor for gliomas remains a topic of debate in neurooncology. Although Class I data are limited, numerous retrospective studies suggest that more complete resection is a predictor of increased survival for patients with high-grade and low-grade gliomas.[6,8,10,12,15,17] Evidence of the importance of resection compared with biopsy dates back to early studies by the RTOG. The original RTOG recursive partitioning analysis identified 6 survival groups for high-grade gliomas, with resection versus biopsy stratifying patients into median survival groups of 17.7 and 10.8 months, respectively.[2,13] The Glioma Outcomes Project[7] reported similar results for resection versus biopsy of anaplastic astrocytoma and

TABLE 2: Patient outcomes of EOR groups*

Outcome	Initial GTR		Initial STR		p Value
	GTR at Recur	STR at Recur	GTR at Recur	STR at Recur	
overall survival					
median, mos	20.4	18.4	19.0	15.9	0.004†
1-yr survival (%)	87	81	88	61	
2-yr survival (%)	32	33	36	4	
mean time to reoperation (mos)	11.1 ± 1.6	11.8 ± 2.0	6.1 ± 0.5	7.3 ± 1.0	0.009
mean survival from reoperation (mos)	11.5 ± 1.3	8.5 ± 1.1	16.7 ± 2.9	7.4 ± 0.8	0.001†

* Mean values are presented ± SE.
† For STR vs GTR at recurrence after initial STR.

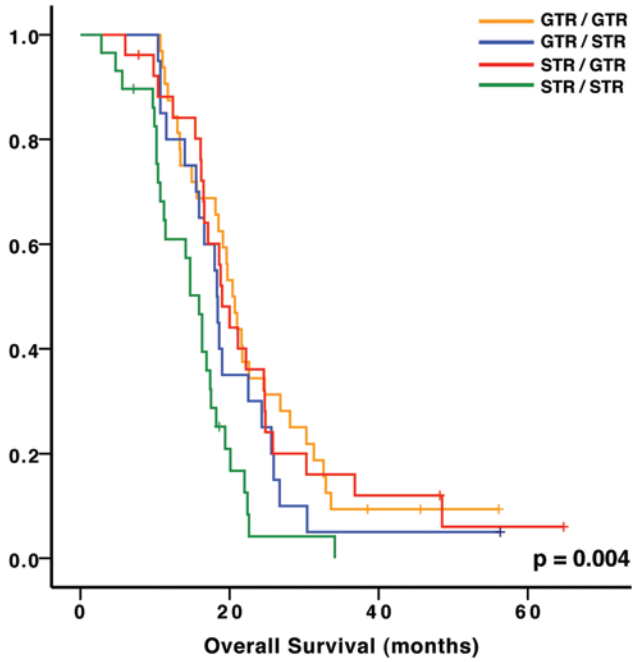

Fig. 2. Overall survival stratified by EOR. Kaplan-Meier curves are shown for overall survival from diagnosis stratified by EOR group. Differences between groups were compared using the log-rank test with significantly decreased survival in the STR/STR group as indicated. (p = 0.004 for comparison with STR/GTR group)

GBM. Lacroix[6] and colleagues first demonstrated evidence that not only resection but extent of the resection predicted survival in their prospectively collected series of 416 GBM patients, including 233 previously untreated patients analyzed independently. They showed a hazard ratio of 1.4 for patients who underwent STR compared with GTR at first intervention, which proved to be an independent predictor of survival in univariate and multivariate analysis. Subsequently, multiple other groups have demonstrated increased overall survival associated with greater EOR for GBM in all patients[8–10,17] and specifically in the elderly,[4] who are often thought to have poor outcome regardless of intervention. In addition, evidence from low-grade gliomas suggests that greater EOR results in improved overall survival, progression-free survival, and malignant progression–free survival.[1,10,15] Recently, Sanai et al.[12] reported on EOR thresholds for GBM, demonstrating improved overall survival associated with greater than 78% resection and incremental increases with more extensive resection.

To date, published studies of the impact of EOR on survival have primarily focused on the initial resection. However, in the modern era of aggressive interventions and clinical trials, many patients with good functional status will undergo a second resection at tumor recurrence. In one study of the impact of EOR, McGirt and colleagues[8] reported on a subset of patients undergoing repeat craniotomy for recurrence, with improved survival associated with increased EOR; however, they did not account for the initial EOR independently in their analysis of overall survival from the time of diagnosis. In this study we have, for the first time, evaluated the impact of EOR independently at initial and repeat craniotomy with an analysis of the cumulative effect on overall survival. Our findings demonstrate that if GTR is achieved at initial resection, the EOR at repeat craniotomy does not affect overall survival. If, however, the initial resection is subtotal, the EOR at repeat craniotomy does significantly impact overall survival. Importantly, if GTR is achieved at repeat resection, the overall survival is statistically no different regardless of initial EOR. This conclusion is further supported by the multivariate regression, which identifies only extent of repeat resection, not the initial EOR, as an independent predictor of survival. Based on these results, patients with good functional status who have undergone previous STR would likely benefit from repeat resection with the goal of GTR at progression. Surgical adjuncts such as intraoperative navigation, functional mapping, and intraoperative MRI may be of use to maximize the repeat resection.[5,11,14,16]

The results of this study do not challenge, but rather support, the previously published data on initial EOR. In

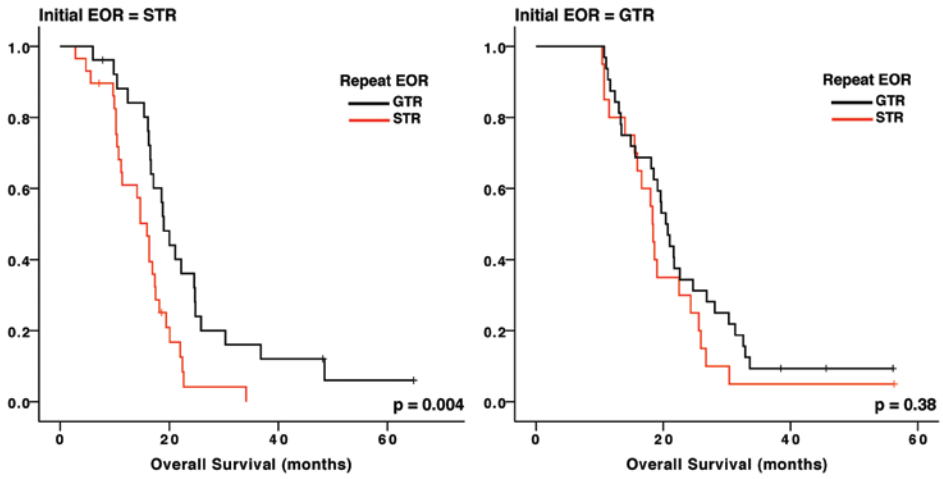

Fig. 3. Overall survival separated by initial EOR. Kaplan-Meier curves are shown for overall survival separated by initial EOR. Differences between groups were compared using the log-rank test. Significantly decreased survival in the STR group after recurrence was seen among patients with an initial STR (**left**, p = 0.004). No differences in survival were seen for STR versus GTR for patients with an initial GTR (**right**, p = 0.38).

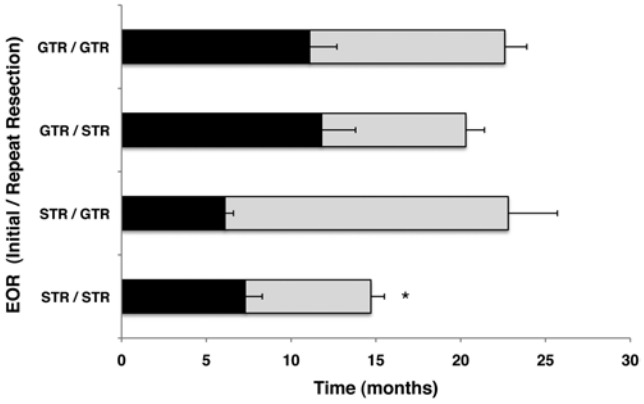

Fig. 4. Time to reoperation and time from reoperation. Graphical depiction of the overall survival for each EOR group divided into survival from initial operation to reoperation *(black bar)* and time from reoperation to death *(gray bar)*. Results are depicted as mean plus standard error. * Significantly decreased survival ($p < 0.01$).

TABLE 3: Univariate analysis of overall survival*

Variable	Median Survival (mos)	95% CI	p Value
sex			0.52
male	18.2	16.9–19.5	
female	19.0	15.0–23.0	
eloquent location			0.48
noneloquent	18.2	16.7–19.7	
eloquent	21.1	15.7–26.5	
initial KPS			0.13
>70	18.1	16.3–19.9	
≤70	25.6	18.7–32.4	
KPS at recurrence			0.004
>70	18.6	17.2–20.0	
≤70	16.1	7.0–25.2	
initial EOR			0.12
subtotal resection	16.9	15.7–18.1	
total resection	19.1	16.8–21.3	
repeat EOR			0.01
subtotal resection	16.6	14.5–18.6	
total resection	20.0	17.9–22.1	
primary treatment			0.85
TMZ	18.5	17.2–19.8	
TMZ + erlotinib	16.3	1.7–30.9	
secondary treatment			0.40
none	16.6	12.2–21.0	
bevacizumab	21.0	18.4–23.6	
bevacizumab + irinotecan	18.8	13.9–23.7	
lomustine	18.2	—	
other	18.3	13.3–23.3	
age (HR)†	1.03	1.01–1.05	0.01

* — = Insufficient data points to calculate confidence interval.
† Hazard ratio per 1-yr increment calculated by univariate Cox regression.

TABLE 4: Multivariate analysis of overall survival

Variable	HR	95% CI	p Value
age (per 1-yr increment)	1.03	1.01–1.05	0.004
initial KPS			
KPS >70	1.00		
KPS ≤70	0.39	0.16–0.91	0.03
KPS at recurrence			
KPS >70	1.00		
KPS ≤70	2.40	1.18–4.99	0.02
initial EOR			
STR	1.00		
total resection	0.72	0.47–1.10	0.13
repeat EOR			
STR	1.00		
total resection	0.62	0.41–0.93	0.02

our multivariate analysis, initial EOR was not an independent predictor of survival because patients with an initial STR could still achieve the same prolonged survival as patients with an initial GTR based primarily on the EOR at repeat resection. However, it is important to note that patients with an initial GTR had a maximized overall survival regardless of EOR at recurrence. This means that the best survival outcome is associated with an initial GTR or a GTR at recurrence for patients with an initial STR. Since it is often easiest to achieve a safe, maximal resection in previously undisturbed tissue, the goal of initial resection remains a GTR. For many patients who will undergo only a single surgery and have a more rapid functional decline, greater EOR at initial intervention is even more important for its impact on overall survival. The novel finding in this study is that, in the subset of patients who maintain good functional status at recurrence, a second operation with a GTR can maximize survival despite an incomplete initial resection.

Of note, our conclusions are subject to the limitations of a retrospective study. In particular, there may be a selection bias for patients included in this study and their distribution in the EOR groups. By the nature of the design, this study is limited to patients with sufficient functional status to safely undergo 2 or more surgeries and adjuvant chemotherapy. This group is younger, with a better initial KPS score and longer median survival, than patients in previous studies of EOR, which included all patients undergoing a craniotomy at initial diagnosis.[6,12] These factors must be considered when applying the results of this study to risk-stratification to based on EOR.

In this study EOR was graded as GTR or STR based on a volumetric cutoff determined by the independent blinded review of a single neuroradiologist. Previous studies on the impact of EOR at initial diagnosis have used a continuous measure to demonstrate a minimum threshold for improvement in survival with an increasing benefit of greater resection above the threshold.[6,12,15,17] We elected to evaluate EOR as a dichotomous effect of GTR, defined as volumetric resection greater than 95% of the contrast enhancement, compared with any lesser resection. Although

an exact EOR was calculated for all patients, analyzing EOR from the first and second surgeries as continuous variables would require a significantly larger data set to resolve differences between a large number of possible combinations of initial and repeat EOR. Given the size of our patient groups, it was necessary to simplify the analysis to evaluate the relative impact of each resection on overall survival. We do not intend to imply that only GTR improves survival and we acknowledge that, as has been shown for initial resection, there may be a threshold effect to varying extents of repeat resection. However, the data do clearly demonstrate that if GTR is achieved at the second resection, the overall survival is maximized.

Conclusions

The results of this study confirm previous reports of a survival advantage for GBM patients with a more complete resection and now extend the indications for aggressive resection to surgery for recurrence. Furthermore, the data suggest that GTR at recurrence may be able to overcome the negative effect on survival of an incomplete initial resection. Recent advancements in surgical technologies, including functional mapping, intraoperative imaging, and vital dyes, have made the ability to achieve a GTR safer and more reliable. With a new emphasis on the importance of achieving a GTR at repeat resection, our study suggests that functional patients with recurrent disease should undergo reoperation with access to the most advanced technologies to maximize extent of resection and prolong survival.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Parsa, Bloch. Acquisition of data: Bloch, Han, Sun, Aghi, McDermott, Berger. Analysis and interpretation of data: Parsa, Bloch, Cha, Sun. Drafting the article: Parsa, Bloch, Han. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Parsa. Statistical analysis: Bloch.

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