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CLINICAL STUDY

Impact of removed tumor volume and location on patient outcome in glioblastoma

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Abstract Glioblastoma is an aggressive primary brain tumor with devastatingly poor prognosis. Multiple studies have shown the benefit of wider extent of resection (EOR) on patient overall survival (OS) and worsened survival with larger preoperative tumor volumes. However, the concomitant impact of postoperative tumor volume and eloquent location on OS has yet to be fully evaluated. We performed a retrospective chart review of adult patients treated for glioblastoma from January 2006 through December 2011. Adherence to standardized postoperative chemoradiation protocols was used as an inclusion criterion. Detailed volumetric and location analysis was performed on immediate preoperative and immediate postoperative magnetic resonance imaging. Cox proportional hazard modeling approach was employed to explore the modifying effects of EOR and eloquent location after adjusting for various confounders and associated characteristics, such as preoperative tumor volume and demographics. Of the 471 screened patients, 141 were excluded because they did not meet all inclusion criteria. The mean (±SD) age of the remaining 330 patients (60.6% male) was 58.9 ± 12.9 years; the mean preoperative and postoperative Karnofsky performance scores (KPSs) were 76.2 ± 10.3 and 80.0 ± 16.6, respectively. Preoperative tumor volume averaged 33.2 ± 29.0 ml, postoperative residual was 4.0 ± 8.1 ml, and average EOR was 88.6 ± 17.6%. The observed average follow-up was 17.6 ± 15.7 months, and mean OS was 16.7 ± 14.4 months. Survival analysis showed significantly shorter survival for patients with lesions in periventricular (16.8 ± 1.7 vs. 21.5 ± 1.4 mo, p = 0.03), deep nuclei/basal ganglia (11.6 ± 1.7 vs. 20.6 ± 1.2, p = 0.002), and multifocal (12.0 ± 1.4 vs. 21.3 ± 1.3 months, p = 0.0001) locations, but no significant influence on survival was seen for eloquent cortex sites (p = 0.14, range 0.07–0.9 for all individual locations). OS significantly improved with EOR in univariate analysis, averaging 22.3, 19.7, and 13.2 months for >90, 80–90, and 70–80% resection, respectively. Survival was 22.8, 19.0, and 12.7 months for 0, 0–5, and 5–10 ml postoperative residual, respectively. A hazard model showed that larger preoperative tumor volume [hazard ratio (HR) 1.05, 95% CI 1.02–1.07], greater age (HR 1.02, 95% CI 1.01–1.03), multifocality (HR 1.44, 95% CI 1.01–2.04), and deep nuclei/basal ganglia (HR 2.05, CI 1.27–3.3) were the most predictive of poor survival after adjusting for KPS and tumor location. There was a negligible but significant interaction between EOR and preoperative tumor volume (HR 0.9995, 95% CI 0.9993–0.9998), but EOR alone did not correlate with OS after adjusting for other factors. The interaction between EOR and preoperative tumor volume represented tumor volume removed during surgery. In conclusion, EOR alone was not an important predictor of outcome during GBM treatment once preoperative tumor volume, age, and deep nuclei/basal ganglia location were factored. Instead, the interaction between EOR and preoperative volume, representing reduced disease burden, was an important predictor of reducing OS. Removal of

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tumor from eloquent cortex did not impact postoperative KPS. These results suggest aggressive surgical treatment to reduce postoperative residual while maintaining postoperative KPS may aid patient survival outcomes for a given tumor size and location.

Keywords Glioblastoma · Extent of resection · Postoperative residual · EOR · Overall survival · Removed tumor volume

Introduction

Glioblastoma (GBM) is a World Health Organization grade IV astrocytic lesion, with median survival of approximately 1 year despite current surgical and adjuvant treatments [1, 2]. Maximizing extent of resection (EOR) has been shown in multiple studies to improve survival in patients with GBM and has been widely discussed as important in clinical intervention [3, 4]. Initial reports on EOR in GBM suggested that resection thresholds of ≥98% [5, 6], >95% [7], or >78% [8] conferred a significantly improved survival. Some studies have even endorsed >100% EOR [9, 10] or removing >50% of surrounding fluid-attenuated inversion recovery (FLAIR) abnormality to improve outcome [11]. Defining areas of active and residual tumor remains difficult with GBM, which is an infiltrative lesion with poor margins, and although greater EOR can improve survival, resection is limited by potential worsening of neurological deficit.

Preoperative tumor volume has been shown to affect outcome in a variety of neurological tumors including glioma [12] and meningioma [13]. Moreover, the volume of postoperative residual tumor has been shown to affect survival of patients with GBM [5, 14]. Postoperative residual volumes of <5 cm^3 have been reported to improve outcome [14]. Although the role of EOR in GBM patient survival has been the subject of considerable research, the impact of tumor location and clinical examination has been a limited area of focus. We hypothesized that tumor location, particularly an eloquent location, and postoperative volume also play important roles in patient outcomes after the treatment of GBM.

Methods

Patient population

After receiving approval from the Barrow Neurological Institute (BNI) Institutional Review Board (IRB), we undertook a retrospective chart review of patients with final diagnosis of GBM who presented from January 2006 through December 2011. Informed consent was waived by the IRB because of the retrospective nature of the study. Patients who underwent surgery followed by standard radiotherapy and chemotherapy were selected through a departmental database. Final pathology of confirmed GBM (ICD-9 code 191.9) was confirmed. Patients underwent primary resection by a variety of surgeons at the BNI. The use of intraoperative navigation, intraoperative MRI, cortical mapping, awake craniotomies, or other surgical adjuvants depended on surgeon preference. Evaluation of patient demographics, including age, sex, Karnofsky Performance Score (KPS), rate of postoperative chemotherapy or radiotherapy treatments (within 30 days of resection), length of follow-up, and death were evaluated. KPS was identified retrospectively via chart review by the primary author (WA). Change in KPS was defined as postoperative KPS–preoperative KPS.

Imaging variables

Preoperative and postoperative residual were assessed by calculation of user-generated regions of interest of contrast-enhancing areas of tumor seen on T1-weighted imaging using Osirix software (http://www.osirix-viewer.com/). Measurements of volume (cm^3) were made by a neurosurgeon (MAM). Areas that enhanced on postoperative T1 imaging that were not seen on postoperative non-contrasted T1 images were considered residual. EOR was calculated as: preoperative–postoperative volume divided by preoperative volume × 100. Tumor location was evaluated, including laterality (left, right, bilateral), location (frontal, temporal, parietal, occipital, periventricular, hippocampal, brainstem, deep nuclei/basal ganglia, cerebellar), and morphology (butterfly lesion, multifocal). Locations were not mutually exclusive, and each tumor could encompass multiple positions (e.g., frontotemporal lesions were coded as frontal and temporal). In addition, potential areas of eloquent cortex (motor, sensory, visual, speech areas) infiltrated by tumor or affected by surgical resection were assessed on anatomical imaging as previously used by one of the authors for the evaluation of arteriovenous malformations (RS). Eloquent areas included the sensorimotor strip, dominant hemisphere perisylvian language areas, basal ganglia/internal capsule, thalamus, calcarine visual cortex, and periventricular visual fibers.

Statistics

Descriptive statistics were used to measure means ± standard deviations for all variables, except where otherwise noted. Bivariate linear regression analysis with correlation using Spearman's ρ was performed during preliminary analysis to evaluate the effect of variables on overall

survival (OS). Then, variables with a 2-tailed $p < 0.15$ were entered into a multivariate, enter-method, linear regression. Kaplan–Meier survival analysis with Mantel–Cox log rank statistic was performed to evaluate the impact of various factors on survival distributions. To account for time-dependent effects expected in the treatment of patients with GBM and adjust for censored patients, a time-to-event Cox proportional hazards model with interaction terms was used to evaluate the effect of designated variables on OS. Preoperative volume and EOR were known to be important risk factors for modeling OS [5–8, 11, 14, 15], so the interaction between these primary variables was assessed in predicting OS. Importantly, the interaction between preoperative volume and EOR mathematically represented the impact of removed tumor burden in the statistical model as a continuous variable. We aimed to identify whether one risk factor had an effect as a modifier of another factor. The model was then developed by including various secondary confounders and associated predictors, such as tumor location and patient demographics. Preoperative tumor volume and EOR alone were sufficient and important compared with postoperative tumor volume. Postoperative volume or residual was not used because knowledge of the preoperative volume and EOR could predict residual. Statistical significance was defined as $p < 0.05$, and statistics were performed using SPSS (V20.0, Armonk, NY), and R (V3.3.2, http://www.r-project.org).

Results

Patient demographic and clinical characteristics

Initial screening identified 471 patients with GBM, but 141 were excluded because they did not meet the study criteria, including 5 pediatric patients (age < 18 years), 32 patients that only underwent biopsy, 3 patients that underwent chemotherapy before resection, 62 patients with incomplete preoperative or postoperative imaging, 3 patient with incomplete follow-up dates, and 36 who underwent previous resection. Baseline descriptive characteristics of the study group are presented in Table 1. A mean age of 58.9 ± 12.9 (median 59.2, range 19.7–84.9) was observed, and male patients accounted for 60.6% of cases. Mean preoperative KPS was 76.2 ± 10.3 and postoperative KPS was 80.0 ± 16.6, which was a significant increase postoperatively ($p = 0.0004$). Mean and median changes in KPS values (postoperative–preoperative) were 4.2 ± 17.8 and 10.0, respectively. KPS declined in 24.1% of patients, showed no change in 22.7%, and improved in 53.2% postoperatively. Patients uniformly received postoperative chemotherapy (89.4%) and/or radiotherapy (88.1%) within 1 month of follow-up, but the specific duration and types of therapies were not studied. The mean preoperative tumor volume was 33.2 ± 29.0 ml and the mean postoperative residual was 4.0 ± 8.1 ml (range 0.3–12.3 ml), a difference that was significant ($p = 0.0001$). The mean EOR was 88.6 ± 17.6% (median 96.0%, range 67.4–94.7%). Overall follow-up was 17.6 ± 15.7 months, overall death rate was 86.1%, and mean overall survival (OS) was 16.7 ± 14.3 months. 1-, 2- and 5-year OS rates were 59.3, 27.2, and 4.1%, respectively.

Table 1 Baseline characteristics of 330 patients with GBM

Variable	Frequency or value
Sex (male)	200 (60.6%)
Age (years)	58.9 ± 12.9
Karnofsky performance score (KPS)	
Preoperative KPS	76.2 ± 10.3
Postoperative KPS	80.0 ± 16.6
Immediate postoperative chemotherapy	295 (89.4%)
Immediate postoperative radiotherapy	294 (88.1%)
Preoperative tumor volume (ml)	33.2 ± 29.0
Postoperative residual (ml)	4.0 ± 8.1
Extent of resection (%)	88.6 ± 17.6
Follow-up (months)	17.6 ± 15.7
Overall death rate	284 (86.1%)
Overall survival (OS) (months)	16.7 ± 14.3

Tumor location characteristics

Approximately half of the tumors were right sided (50.9%), as compared with left sided (42.1%) or bilaterally located (7.0%) (Table 2; Fig. 1). Common locations included the frontal (40.0%), temporal (42.1%), parietal (30.0%), and periventricular (36.0%) areas. Lesions located in the occipital (15.2%), hippocampal (15.5%), and deep nuclei/basal ganglia (9.7%) regions were less common. Brainstem (1.2%) and cerebellar (0.9%) lesions were rare. Patients with butterfly lesions accounted for 6.7% of cases whereas those with multifocal lesions accounted for 17.3% of cases. Tumors with locations in eloquent (43.3%) cortex most often were in motor (18.8%), sensory (13.0%), or visual (26.4%) areas, whereas those in speech (7.6%) or memory (7.9%) cortex were more limited. Mean EOR and postoperative tumor volume varied greatly depending on tumor location (Table 3).

Predicting overall survival

Bivariate linear correlation and multivariate linear regression analysis were preliminarily used to study the impact of variables on OS (Table 4). Variables from the univariate analyses were entered into the multivariate model. Age ($\rho = -0.354$, $p = 0.0001$), postoperative KPS ($\rho = 0.258$,

Table 2 Tumor characteristics in 330 patients with GBM

Variable	Frequency
Side	
Left	139 (42.1%)
Right	168 (50.9%)
Bilateral	23 (7.0%)
Location	
Frontal	132 (40.0%)
Temporal	139 (42.1%)
Parietal	99 (30.0%)
Occipital	50 (15.2%)
Periventricular	117 (36.0%)
Hippocampal	51 (15.5%)
Brainstem	4 (1.2%)
Deep nuclei/basal ganglia	32 (9.7%)
Cerebellar	3 (0.9%)
Morphology	
Butterfly lesion	22 (6.7%)
Multifocal	57 (17.3%)
Functional impact	
Eloquent area	143 (43.3%)
Motor area	62 (18.8%)
Sensory area	43 (13.0%)
Visual area	87 (26.4%)
Speech area	25 (7.6%)
Memory area	26 (7.9%)

$p=0.0001$), postoperative residual ($\rho=-0.3$, $p=0.0001$), EOR ($\rho=0.318$, $p=0.0001$), periventricular ($\rho=-0.154$, $p=0.006$), deep nuclei/basal ganglia ($\rho=-0.168$, $p=0.002$), multifocal ($\rho=-0.191$, $p=0.001$), eloquent ($\rho=-0.144$, $p=0.01$), and motor ($\rho=-0.172$, $p=0.002$) locations were significantly associated with OS in a univariate analysis (Table 4). In a multivariate analysis, only age ($\beta=-0.225$, $p=0.001$), postoperative KPS ($\beta=0.187$, $p=0.001$), and a deep nuclei/basal ganglia location ($\beta=-0.133$, $p=0.045$) continued to show a significant effect on survival. Change in KPS (postoperative KPS–preoperative KPS) correlated with overall survival ($\rho=0.19$, $p=0.002$) on regression analysis (Fig. 2). The positive correlation indicates that improvement in KPS postoperatively predicted improved OS.

Change in KPS

Because the change in KPS influenced outcome, we analyzed the impact of factors influencing the change in KPS. Change in KPS correlated with location (parietal ($\rho=-0.153$, $p=0.009$), deep nuclei/basal ganglia ($\rho=-0.119$, $p=0.042$), eloquent area ($\rho=-0.208$, $p=0.0001$), motor area ($\rho=-0.194$, $p=0.001$), and sensory area ($\rho=-0.132$, $p=0.025$)), but not with surgical outcomes (EOR ($\rho=0.092$, $p=0.116$) or postoperative residual tumor volume ($\rho=-0.053$, $p=0.361$)) (Table S1). These specific locations (e.g., parietal, deep nuclei/basal ganglia, eloquent area, motor area, and sensory area) all correlated with worsened KPS after surgery on univariate regression analysis. No specific location correlated with improved KPS after surgery on univariate regression analysis, and no variable was predictive of change in KPS in a multivariate logistic regression—obviating any simple conclusion of the interaction between postoperative change in KPS and either patient or surgical factors.

Threshold for EOR

In light of previous studies evaluating thresholds for EOR, our preliminary analysis aimed to delineate a resection threshold similarly to prior studies [5–8, 10, 11, 14]. Patients with EOR > 90%, 80–90, 70–80, and <70% had mean survival of 22.3 ± 1.4, 19.7 ± 3.4, 13.3 ± 2.0, and 10.0 ± 2.1 months, respectively (log rank test, $p=0.0001$) (Fig. 3a). Similarly, residual postoperative volumes of 0, 0–5, 5–10, 10–20, and >20 ml were associated with mean survival of 22.8 ± 1.4, 19.0 ± 1.8, 12.7 ± 2.6, 17.9 ± 3.9, and 3.5 ± 0.9 months, respectively (log rank test, $p=0.0001$) (Fig. 3b). Regression analysis showed good correlation between EOR and postoperative residual ($R=0.702$, $p=0.001$). EOR of 78% correlated with postoperative residual of 7.4 ml (95% CI 1.4, 13.3), 95% EOR with 1.9-ml residual (95% CI −4.7, 8.5), and 98% EOR with 0.9-ml residual (95% CI −5.8, 7.6).

Statistical assessment to identify a threshold EOR or postoperative residual at which a significant difference in survival was observed did not define a single threshold, although this effect was seen in prior studies [6, 8]. All thresholds evaluated in our study demonstrated an incremental survival benefit, so that greater resection demonstrated statistically significantly improved survival benefit with no clear cutoff seen. In other words, no discrete threshold differentiated survival odds. Although no cutoff for EOR or postoperative residual could be identified, tumor location and preoperative volume were important factors affecting outcome, which likely explains why an EOR cutoff alone could not be clearly identified.

Survival analysis

Survival analysis for tumor characteristics was evaluated by log rank test (Fig. 3; Table 5). Lesions located in the periventricular (16.8 ± 1.7 vs. 21.5 ± 1.4 months, $p=0.03$), deep nuclei/basal ganglia (11.6 ± 1.7 vs. 20.6 ± 1.2 months, $p=0.002$), and multifocal (12.0 ± 1.4 vs. 21.3 ± 1.3, $p=0.0001$) locations were associated with significantly

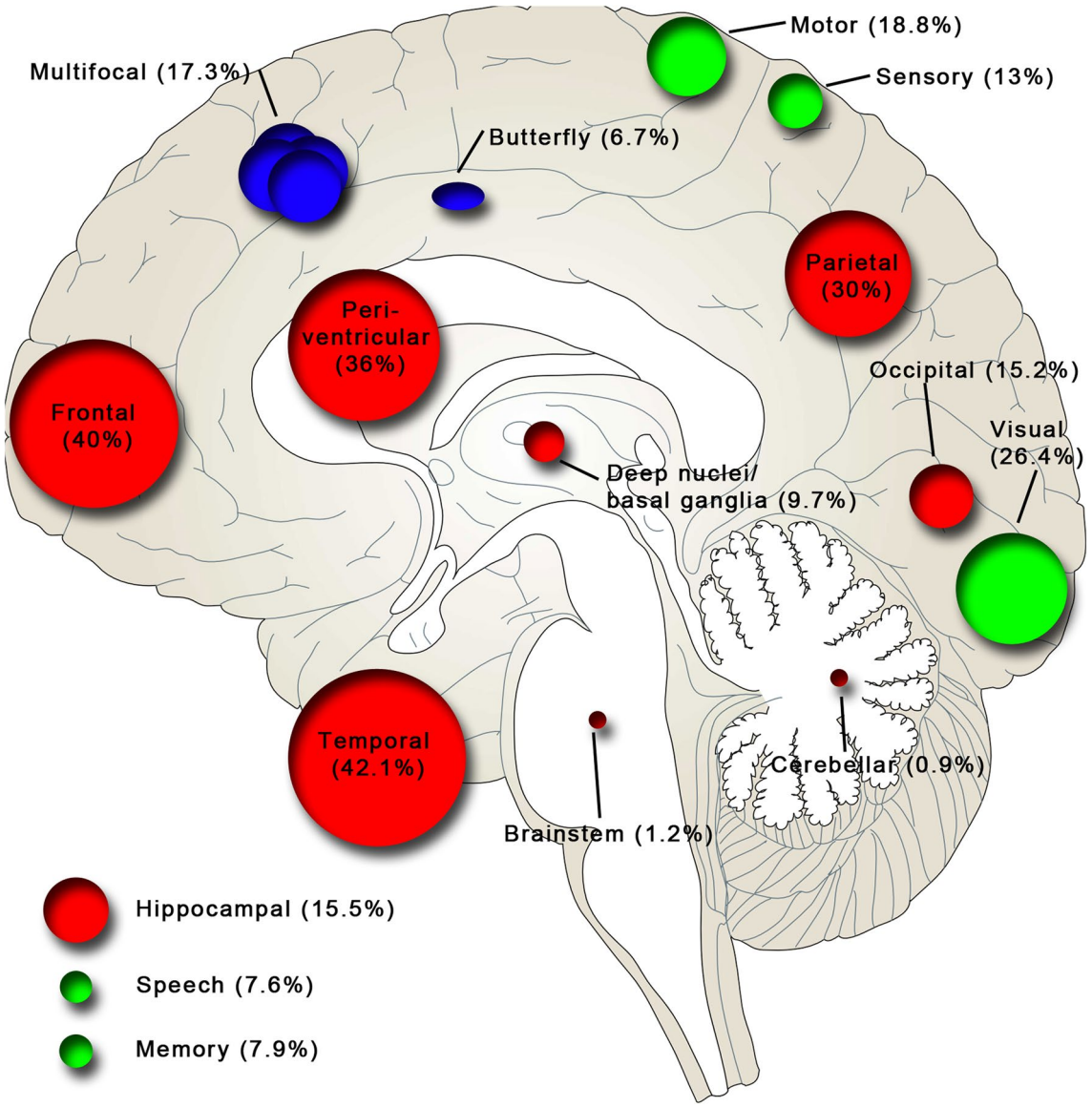

Fig. 1 Summary of survival and tumor locations. *Circle sizes* represent relative frequencies for tumor location (*red*), morphology (*blue*), and functional area (*green*)

worse OS. The results were not significant for bilateral (13.7 ± 4.1 vs. left: 20.5 ± 1.7 vs. right: 20.0 ± 1.5 months, p = 0.114), butterfly (14.2 ± 3.6 vs. 20.3 ± 1.1 months, p = 0.11), parietal lobe (23.2 ± 2.4 vs. 18.2 ± 1.1 months, p = 0.07), eloquent cortex (18.6 ± 1.9 vs. 20.6 ± 1.2 months, p = 0.14), or speech area (13.1 ± 2.8 vs. 20.3 ± 1.1 months, p = 0.07) tumors (i.e., survival of patients with lesions in these locations was not significantly longer or shorter). Many of these areas were non-mutually exclusive because of the invasiveness of tumors.

The information from all preliminary analyses helped in formulation of a planned statistical data model. A Cox proportional hazards model showed that preoperative tumor volume (HR 1.05, 95% CI 1.02–1.07), age (HR 1.02, 95% CI 1.01–1.03), multifocal lesions (HR 1.44, 95% CI 1.01–2.04), and deep nuclei/basal ganglia location (HR 2.06, 95% CI 1.27–3.33) were most predictive of survival (Table 6). Interestingly, a significant interaction between EOR and preoperative tumor volume, which logically represents removed tumor burden, was observed (HR 0.9995, 95% CI 0.9993–0.9998). Overall, the effect size of any variable was <5% except for deep nuclei/basal ganglia location, suggesting that deeper, unresectable tumors were distinct from tumors in eloquent cortex, which demonstrated substantially higher EOR (Table 3).

Table 3 Mean extent of resection and postoperative volume depending on tumor location

	EOR (%)	Postoperative residual (ml)
Side		
Left	89.7 ± 16.8	3.3 ± 7.3
Right	90.6 ± 14.1	3.4 ± 6.7
Both	67.4 ± 29.5	12.3 ± 15.1
Location		
Frontal	84.5 ± 21.5	6.4 ± 11.0
Temporal	87.6 ± 18.4	4.7 ± 8.4
Parietal	89.6 ± 13.0	3.3 ± 6.3
Occipital	92.7 ± 10.9	3.3 ± 6.7
Periventricular	84.8 ± 20.7	6.5 ± 11.3
Hippocampal	86.8 ± 21.1	6.2 ± 11.3
Brainstem	93.2 ± 8.6	0.5 ± 0.6
Deep nuclei/basal ganglia	79.9 ± 24.0	5.9 ± 7.9
Cerebellar	94.7 ± 9.1	0.3 ± 0.6
Butterfly	72.4 ± 26.0	10.4 ± 13.2
Multifocal	78.7 ± 24.1	7.1 ± 10.8
Functional impact		
Eloquence	85.8 ± 19.4	5.2 ± 9.2
Motor	81.9 ± 22.7	7.5 ± 12.4
Sensory	83.5 ± 21.9	5.4 ± 7.9
Visual	89.4 ± 13.3	4.6 ± 7.1
Speech	81.3 ± 18.7	10.5 ± 14.2
Memory	84.3 ± 19.2	5.0 ± 7.4

Evaluation of long-term survivors

For the 18 patients who lived longer than 48 months, a separate analysis was performed to identify predictive factors (Table S2). A significantly greater number of parietal lobe ($p = 0.02$) and lower number of multifocal ($p = 0.05$) lesions were found in long-term survivors. A greater number of cerebellar lesions ($p = 0.04$) were found in survivors, although the number of patients in either group with tumors in this location was quite small, making it difficult to draw a conclusion about the effect of cerebellar location. No other demographic, radiological, or functional variable was a significant predictor of long-term survival.

Discussion

The results of our study confirm other reported results regarding improved outcome in maximally resected tumors and provide new insight into the role of tumor location, morphology, and postoperative residual tumor, as well as changes in KPS. No specific threshold for EOR or postoperative residual was essential for improving OS, as the greater the EOR, the better the outcome statistically—indicating a graded, rather than step-like, influence of extent of surgical resection. A multivariate regression model was important in predicting survival for several previously supported variables. This model demonstrated that OS was best predicted by age, postoperative KPS, and deep nuclei/basal ganglia location. EOR alone did not significantly predict survival in our multivariate analysis, after accounting for other factors, supporting the observation that age, tumor location, and preoperative volume were influential. The final analysis using a hazard model showed that EOR had a strong interaction with preoperative tumor volume, demonstrating that the effect of decreased tumor burden is an important and previously undescribed factor in the meaningful treatment of GBM.

Two important multivariate analyses were used for understanding the interaction of survival predictors. A preliminary multivariate analysis demonstrated that age, postoperative KPS, and deep nuclei/basal ganglia location correlated with OS. We also noted that removal of tumor from eloquent cortex did not adversely impact KPS or OS. Older age [16], poorer postoperative KPS [17, 18], and deep nuclei/basal ganglia location compared with other areas [19–23] are well-known features of GBM. Interestingly, tumor eloquence, EOR, and tumor residual were not important factors as previously supported in the literature [5–8, 11, 14, 15]. This unexpected finding was further investigated with a final hazards model, allowing time-dependent analysis and adjustment for censored data, to further explore the relationship among tumor size, EOR, and survival. The hazards model allowed for a time-dependent analysis as well as generation of interaction variables. To that extent, OS was associated with preoperative volume, age, multifocal, deep nuclei/basal ganglia location, as well as notably a strong interaction between EOR and preoperative tumor volume, which represents removed tumor burden. EOR alone was not a significant predictor similarly to previous studies, and instead interaction with preoperative volume and adjustment for tumor location was important. Interestingly, the interaction between EOR and preoperative tumor volume reframes the important question in GBM resection, namely reduction of tumor burden, in affecting OS rather than any other clinical feature (e.g., age, volume, KPS, location) in isolation.

Preoperative tumor volume, tumor burden, age, and location were important predictive variables for OS. Although tumor burden importantly correlated with poor survival, the results identified that deep-seated or multifocal tumors are associated with poor survival—which can be explained by our model by the effects on KPS and larger postoperative volume or by effects not identified in our study, such as location-specific tumor biology. Operative resection in tumors in other eloquent locations commonly considered a poor prognostic factor, namely

Table 4 Factors predicting overall survival

	Univariate ρ	Univariate p value	Multivariate β[a]	Multivariate p value[a]
Sex (male)	−0.033	0.321		
Age	**−0.354**	**0.0001**	**−0.225**	**0.001**
Preoperative KPS	0.057	0.321		
Postoperative KPS	**0.258**	**0.0001**	**0.187**	**0.001**
Preoperative tumor volume	−0.091	0.102	0.116	0.113
Postoperative residual	**−0.3**	**0.0001**	−0.148	0.119
EOR	**0.318**	**0.0001**	−0.006	0.948
Side	−0.090	0.106	−0.085	0.182
Location				
Frontal	−0.056	0.32		
Temporal	−0.006	0.918		
Parietal	0.054	0.336		
Occipital	0.086	0.121	0.014	0.816
Periventricular	**−0.154**	**0.006**	−0.041	0.518
Hippocampal	−0.057	0.304		
Brainstem	−0.089	0.114	−0.065	0.28
Deep nuclei/basal ganglia	**−0.168**	**0.002**	**−0.133**	**0.045**
Cerebellar	0.010	0.852		
Butterfly lesion	−0.096	0.085	0.044	0.478
Multifocal	**−0.191**	**0.001**	−0.098	0.098
Functional impact				
Eloquent area	**−0.144**	**0.010**	−0.019	0.804
Motor area	**−0.172**	**0.002**	0.048	0.612
Sensory area	−0.081	0.147	−0.02	0.82
Visual area	−0.033	0.553		
Speech area	−0.095	0.088	−0.079	0.201
Memory area	−0.02	0.715		

Boldface variables are statistically significant

[a]Included univariate variables with $p < 0.15$, $R = 0.438$, $p = 0.0001$

hippocampal or eloquent cortex (i.e., motor, sensory, or speech), did not limit successful surgery, life expectancy, or postoperative KPS in our study. Importantly, the influence of eloquent cortex was minimal, both on OS and residual volumes. Thus, there is a dichotomous relationship for location in GBM—deeply seated and multifocal locations had strongly negative influence on survival, whereas eloquent cortex location, in our surgical series, did not. Improved KPS was also correlated with an improved OS, an effect that was seen regardless of tumor location. The results of this study confirm and support maximal reduction of tumor burden with careful regard to functionally eloquent cortex at least in regards to postoperative KPS.

Location, location, location

Specific tumor locations also played an important role in predicting OS, namely deep nuclei/basal ganglia, periventricular, and multifocality. Studies have shown better prognosis for GBM involving the frontal lobes [22, 23] and lateral ventricles [24] as well as poorer survival for cerebellar [19], disseminated [20], or butterfly [25] lesions. One study of 70 patients that measured T2 volume instead of enhancing T1 volume as a pattern of tumor cell invasiveness showed poorer survival with spread across the corpus callosum [21]. Tumor location in eloquent cortex was also an important factor in clinical decision making. In one study of 120 subjects in which 57.5% of patients had GBM in eloquent cortex [26], tumors in eloquent cortex were more predictive of higher postoperative residual volumes and lower EOR. However in our series, eloquent cortex did not influence OS, suggesting maximizing safe surgical resection could be achievable by a variety of providers. Nevertheless, eloquent cortex did not have as significant an impact on OS as tumor located in deep nuclei/basal ganglia. Functional reorganization of eloquent cortical functions may also

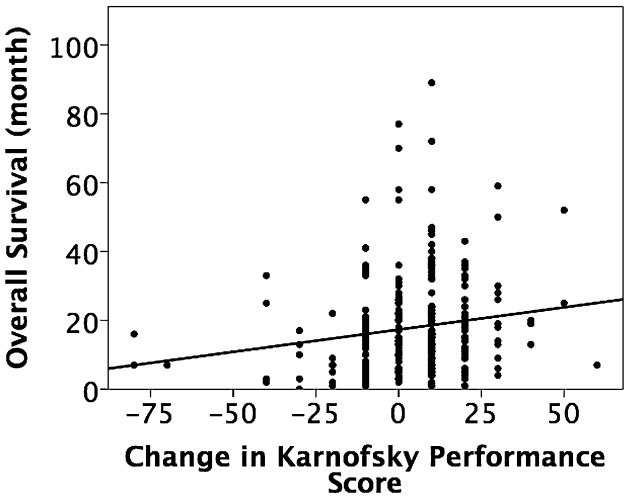

Fig. 2 Evaluation of Karnofsky performance score (KPS) in survival and residual tumor. A scatter plot is presented showing change in KPS, namely postoperative–preoperative score, correlated with overall survival (OS) ($\rho = 0.19$, $p = 0.002$). Improvement in KPS postoperatively was seen to predict improved overall survival. Among the sample, 24% of patients showed a decline in KPS, 47% were unchanged, and 29% improved

account for why lesions in such areas may not necessarily result in significant postoperative deficit [27].

The reasons for the anatomical localization of GBM remain unclear. Our results suggest that most tumors occur in a supratentorial region and that patients whose tumors required deeper surgical treatment fared worse. One study suggested that increased isocitrate dehydrogenase 1/2 (IDH1/2) mutation was associated with greater tumor resection and improved survival, because of its localization in the frontal lobes, younger patients, and with greater contrast-enhancing disease [22]. Other studies have supported the impact of genetic alterations on tumor location. Zhang et al. [28] supported increased p53 mutation in GBM tumors located in the frontal cortex as well as extending rostrally around the lateral ventricles while p53 wild-type tumors were more common in the temporal lobes. Similarly, Wang et al. [29] reported that low *O*-6-methylguanine-DNA methyltransferase (MGMT) upregulation was more common in the right temporoparietal lobe while high expression was mostly in the left frontal lobe. These results suggested that genetic and epigenetic changes, as well as GBM subtype, in the tumor could impact localization. With larger studies and registries, it may possible to better predict tumor mutational patterns based on tumor location and imaging characteristics. The use of MR spectroscopy to evaluate IDH1 mutation in gliomas is one example of this [30]. Further studies will be necessary to understand the genetic influence governing GBM formation.

Studies evaluating EOR

The results of our study confirm the importance of EOR, but also suggest that after taking tumor location and clinical exam into account, reduction of tumor burden was more predictive of OS. Increased EOR has been shown in multiple studies to predict improved patient outcome [5–8, 10, 11, 14]. In our results, EOR alone was unable to predict OS—presumably because of the larger influence of location and preoperative volume. The addition of preoperative tumor volume was an important consideration, which changed the key surgical variable to tumor burden. In addition to age, two of the four predictive variables

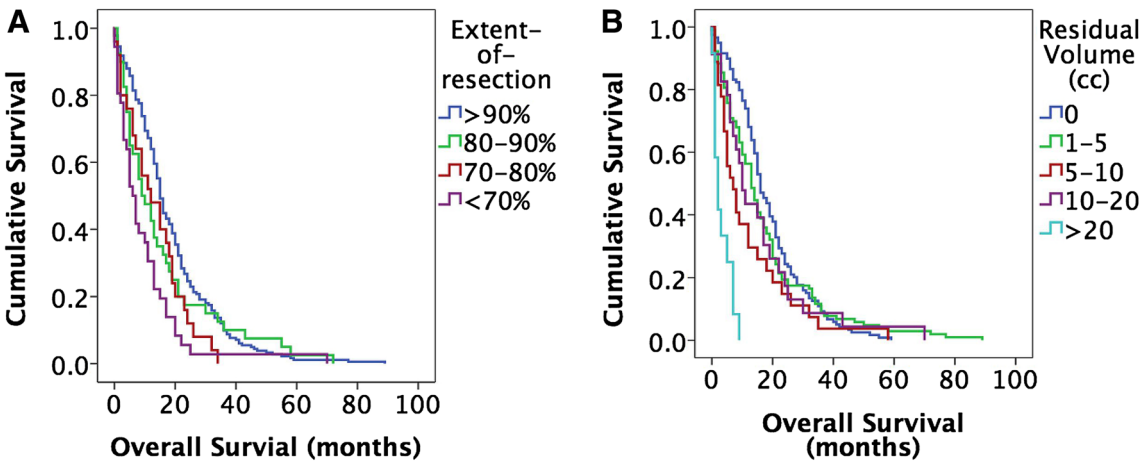

Fig. 3 Kaplan–Meier survival analysis. **a** Overall survival differed for patients with >90, 80–90, 70–80, and <70% EOR ($p = 0.0001$). Mean survival of 22.3 ± 1.4, 19.7 ± 3.4, 13.3 ± 2.0, and 10.0 ± 2.1 months, respectively, was observed. **b** Overall survival differed depending on postoperative residual tumor volumes ($p = 0.0001$). Mean survival of 22.8 ± 1.4, 19.0 ± 1.8, 12.7 ± 2.6, 17.9 ± 3.9, and 3.5 ± 0.9 months, respectively, was observed

Table 5 Kaplan–Meier survival analysis

Feature	Mean ± standard error survival (months)		Log rank (Mantel–Cox) test p value
	Absent feature	Present feature	
Location			
Side	Left : 20.5 ± 1.7; Right: 20.0 ± 1.5; Bilateral: 13.7 ± 4.1		0.114
Frontal	20.9 ± 1.5	18.8 ± 1.6	0.463
Temporal	19.5 ± 1.3	19.7 ± 1.7	0.902
Parietal	18.2 ± 1.1	23.2 ± 2.4	0.065
Occipital	19.9 ± 1.2	19.6 ± 2.3	0.980
Periventricular	**21.5 ± 1.4**	**16.8 ± 1.7**	**0.03**
Hippocampal	20.4 ± 1.3	16.7 ± 1.9	0.225
Brainstem	20.0 ± 1.1	8.7 ± 1.8	0.494
Deep nuclei/basal ganglia	**20.6 ± 1.2**	**11.6 ± 1.7**	**0.002**
Cerebellar	19.6 ± 1.1	45.0 ± 16.3	0.141
Butterfly	20.3 ± 1.1	14.2 ± 3.6	0.112
Multifocal	**21.3 ± 1.3**	**12.0 ± 1.4**	**0.0001**
Functional impact			
Eloquent	20.6 ± 1.2	18.6 ± 1.9	0.135
Motor deficit	20.4 ± 1.1	17.6 ± 3.2	0.168
Visual deficit	20.1 ± 1.3	18.9 ± 2.2	0.460
Speech deficit	20.3 ± 1.1	13.1 ± 2.8	0.069
Memory deficit	19.8 ± 1.1	19.1 ± 3.8	0.994
Sensory deficit	20.1 ± 1.2	17.5 ± 2.9	0.495

Boldface values are statistically significant

Table 6 Cox proportional hazards model of overall survival

Variable	Hazard ratio	95% CI lower	95% CI upper	p value
Preoperative tumor volume	**1.0473**	**1.0229**	**1.0724**	**<0.001**
EOR	0.9993	0.9886	1.0102	0.91
EOR × Preoperative tumor volume interaction	**0.9995**	**0.9993**	**0.9998**	**<0.001**
Age	**1.0188**	**1.0084**	**1.0293**	**<0.001**
Preoperative KPS	0.9960	0.9842	1.0079	0.51
Butterfly	0.9835	0.5831	1.6587	0.95
Multifocal	**1.4366**	**1.0110**	**2.0415**	**0.043**
Periventricular	1.1073	0.8321	1.4734	0.48
Hippocampal	0.9144	0.6314	1.3242	0.64
Brain stem	1.3150	0.3054	5.6622	0.71
Deep nuclei/basal ganglia	**2.0583**	**1.2712**	**3.3328**	**0.003**

Boldface values are statistically significant

for OS were tumor location variables. In understanding postoperative residual, preoperative volume was naturally an important factor. A single discrete threshold value for EOR has not been identified in previous studies of GBM. A limited number of these studies evaluated the effect of tumor location and clinical exam in predicting outcome, and no study concluded that location or KPS interacted with EOR or postoperative residual to alter outcome.

Limitations

One of the primary limitations of the study is the use of a population from a single institution; however, this included multiple attending surgeons and surgical techniques for resection in eloquent regions, including differential use of functional magnetic resonance imaging (fMRI) and intraoperative functional mapping for safe resection of eloquent region tumors. As such, multivariate analysis is the

determination of factors that influence outcome in this specific surgical population. Broad extrapolation of these results may not be warranted, especially with regard to preservation of KPS for tumors located in eloquent regions. In addition, although most patients underwent postoperative adjuvant chemotherapy and radiotherapy, the duration of therapy and use of secondary treatments during recurrence were not factored in this study. Likely these therapies play a key role in survival, and further studies using modern patients would be needed to validate our findings.

Some other limitations of this study include the retrospective nature of its data analysis as well as user-dependent, semi-quantitative evaluation of tumor volume. All volumetric calculations were reviewed by the senior author (MAM). All efforts were made to perform a comprehensive retrospective review and evaluate relevant variables, but the results of this study would need to be replicated for further validity. In addition, evaluation of preoperative and postoperative residuals measurements proved difficult to accomplish. Not all lesions showed adequate T1 enhancement so only the enhancing portion was considered as tumor. The nature of T2/FLAIR signal changes, reflective of tumor invasion and aggressiveness, were also not accounted in the radiographic evaluation of tumors. The evaluation of postoperative residual was based on user-derived regions of interest and could have been biased. In addition, localization of tumor in eloquent cortex depended on evaluation of lesions in specific locations with known critical structures (e.g., inferior frontal cortex for speech). However, postoperative evaluation of specific patient deficits was not performed, and only a global KPS score was available in the clinical record. Lastly, molecular markers of GBMs were unavailable at the time of this study.

Conclusion

The results of this study support the safe minimization of postoperative tumor volume as well as improvement of postoperative KPS depending on tumor location to lengthen OS. However, tumors with deep-seated, poorly accessible, or multifocal locations fared worse regardless of resection volume. No specific threshold of EOR or postoperative tumor residual was seen in improving OS, as preoperative volume demonstrated greater influence on OS. These results suggest that specific tumor locations may play an important role in further understanding the aggressive nature of GBM as well as affecting patient survival. This information from this study highlights that maximizing EOR and minimizing postoperative tumor residual are distinct surgical goals. Distinct genetic changes are likely to participate in tumor location and natural history. Further research is still needed in understanding the genetic and clinical heterogeneity of GBM to improve therapeutic approaches.

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Compliance with ethical standards

Conflict of interest Wala Al-Awad, MD, declares that he has no conflict of interest. Michael Karsy, MD, PhD, declares that he has no conflict of interest. Nader Sanai, MD, declares that he has no conflict of interest. Robert Spetzler, MD, declares that he has no conflict of interest. Yue Zhang, PhD, declares that he has no conflict of interest. Yizhe Xu, MS, declares that she has no conflict of interest. Mark A. Mahan, MD, declares that he has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was handled under an exemption.

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