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Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma

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Introduction. Surgery is first-line therapy for glioblastoma, and there is evidence that gross total resection is associated with improved survival. Gross total resection, however, is not always possible, and relationships among extent (percent) of resection (EOR), residual volume (RV), and survival are unknown. The goals were to evaluate whether there is an association between EOR and RV with survival and recurrence and to establish minimum EOR and maximum RV thresholds.

Methods. Adult patients who underwent primary glioblastoma surgery from 2007 to 2011 were retrospectively reviewed. Three-dimensional volumetric tumor measurements were made. Multivariate proportional hazards regression analysis was used to evaluate the relationship between EOR and RV with survival and recurrence.

Results. Of 259 patients, 203 (78%) died and 156 (60%) had tumor recurrence. The median survival and progression-free survival were 13.4 and 8.9 months, respectively. The median (interquartile range) pre- and postoperative tumor volumes were 32.2 (14.0–56.3) and 2.1 (0.0–7.9) cm^3, respectively. EOR was independently associated with survival (hazard ratio [HR], 0.995; 95% confidence interval [CI]: 0.990–0.998; $P = .008$) and recurrence (HR [95% CI], 0.992 [0.983–0.998], $P = .005$). The minimum EOR threshold for survival ($P = .0006$) and recurrence ($P = .005$) was 70%. RV was also associated with survival (HR [95% CI], 1.019 [1.006–1.030], $P = .004$) and recurrence (HR [95% CI], 1.024 [1.001–1.044], $P = .03$). The maximum RV threshold for survival ($P = .01$) and recurrence ($P = .01$) was 5 cm^3.

Conclusion. This study shows for the first time that both EOR and RV are significantly associated with survival and recurrence, where the thresholds are 70% and 5 cm^3, respectively. These findings may help guide surgical and adjuvant therapies aimed at optimizing outcomes for glioblastoma patients.

Keywords: extent of resection, GBM, glioblastoma, residual, surgery, survival, volumetric.

Patients with glioblastoma (GB) have disparate survival times, where some patients survive for only a few months, while other patients survive for several years.[1–6] This disparity in survival among individual patients with GB has been attributed to a combination of different clinical risk factors, including age, neurological function, extent of resection (EOR), and use of adjuvant therapies.[1–7] Among these factors, the only potentially modifiable risk factor for patients with GB is EOR.[8–12] While several studies have shown that gross total resection (GTR) is associated with prolonged survival, GTR is not always possible and may lead to surgically acquired motor and language deficits and a decrease in overall survival.[13] It remains unclear whether increasing percent EOR and decreasing residual volume (RV) are associated with prolonged survival and delayed recurrence.

This association between increasing EOR and RV is unclear because previous studies have not used volumetric analyses, which makes it impossible to accurately measure percent resection.[3,9–11,14–19] As a result, these previous studies

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have categorized patients into GTR and subtotal resection (STR).[3,9–11,14–19] The GTR group in these studies consists of heterogeneous patients with percent resections that range from 90% to 100%, while that of the STR group ranges from 0% to 99%.[3,9–11,14–19] In addition, several of these studies included patients prior to the adoption of temozolomide as a standard of care, and their results might be altered in a more modern patient cohort.[3,9–11,14–19] Importantly, a threshold for the minimum EOR and maximum postoperative RV have also yet to be established in a modern patient cohort. This study seeks to address these limitations in a modern, large, and more homogeneous surgical series at a tertiary care center.

An understanding of the thresholds for minimum EOR and maximum RV may help guide surgical strategies aimed at optimizing outcomes for patients with GB. EOR and RV thresholds are not necessarily congruent where EOR is dependent on preoperative tumor volume and RV may be more affected by tumor location. These distinct thresholds could serve as useful surgical goals, and for surgeries where these goals are not possible, more aggressive adjuvant therapies could be implemented. The goals of this study were therefore to (i) evaluate whether EOR and postoperative RV were each independently associated with survival and recurrence and (ii) identify the minimum EOR and maximum postoperative RV thresholds that are associated with prolonged survival and delayed recurrence for patients undergoing surgery of an intracranial GB (Fig. 1).

Materials and Methods

Institutional review board approval was obtained prior to the start of this study (#36875).

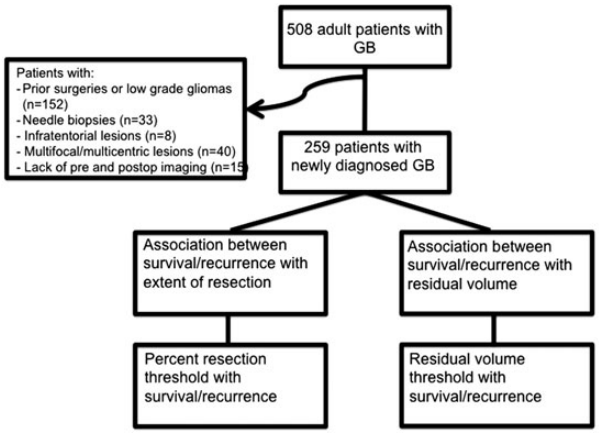

Fig. 1. Schematic diagram of the patients included and the methodology used in the study. There were a total of 508 patients who underwent intracranial GB surgery at a single tertiary care institution from 2007 to 2011. Of these 508 patients, 259 who underwent nonbiopsy surgical resection of a primary or newly diagnosed GB were included in the study. The goals of the study were to identify whether there was an association between increasing percent resection and decreased residual volume with survival and recurrence and to establish a minimum percent resection and maximum residual volume threshold.

Patient Selection

From 2007 to 2011, there were a total of 508 adult patients (age >18 y) who underwent surgery for an intracranial GB at a single academic tertiary care institution. The diagnosis of a GB was based on the World Health Organization (WHO) classification system and determined by a neuropathologist in all cases.[20,21] Patients ($n = 152$) with prior resections and/or previous lower-grade gliomas were excluded, as well as those with needle biopsies ($n = 33$). Among those remaining, patients with multifocal or multicentric lesions ($n = 40$) as well as infratentorial lesions ($n = 8$) were excluded. Furthermore, patients without pre- and postoperative MRI were also excluded ($n = 15$). In total, 259 patients met the inclusion criteria (Fig. 1).

Recorded Variables

The clinical records of the included patients were retrospectively reviewed. The information collected from clinical notes included demographics, comorbidities, presenting symptoms, hospital course, postoperative neurological function, and adjuvant therapy. An eloquent location was defined as a tumor involving motor, language, and/or somatosensory regions. This corresponds to grade 3 by Sawaya et al.[22] Deep-seated tumors were tumors located in the basal ganglia and/or thalamus. The pre- and postoperative MRIs were obtained and reviewed for each patient. The preoperative volume was measured using T1-weighted gadolinium-enhanced MRI (1.5–3 mm axial cuts) obtained on the day of or prior to surgery. Using OsiriX software, the area of contrast enhancement was calculated for each axial section, and the tumor volume was quantified based on the sum of axial areas in a semiautomated manner (Fig. 2, Supplementary material, Video 1). The RV was calculated in the same manner by evaluating MRI obtained within 48 h of surgery. The exception was that the volume of blood products rather than residual tumor was confirmed by comparing T1-weighted gadolinium-enhanced and non-enhanced MRI. Tumor identification on MRI was made by a clinician blinded to patient outcomes, and the area and volumes were computed by OsiriX software. The EOR was calculated using the following formula: (preoperative – postoperative tumor volume)/preoperative tumor volume. Since these measurements were dependent on contrast enhancement, patients with preoperative non-contrast-enhancing GB were excluded.

The date of death was obtained using the Social Security Death Index database.[23] Time to death was calculated from time from surgery to death. Patients whose deaths were unconfirmed at last follow-up were censored at the time of their last clinic visit. Tumor recurrence was defined as any definitive evidence of tumor recurrence or progressive growth on MRI (T1 with gadolinium) by a neuroradiologist blinded to outcomes. Tumor recurrence, as opposed to pseudoprogression, was based radiographically on repeated MRIs where tumor recurrence was characterized by an increase in tumor size and/or contrast on serial imaging, as previously described.[24] Patients who had surgery where no active tumor was found were not classified as having recurred. Patients with tumors not confirmed as having recurred were classified as lost to follow-up at the time of their last MRI.

General Treatment Strategy

The general treatment goal was to achieve maximal resection without causing an iatrogenic deficit. A resection was typically stopped when the tumor involved functional areas as confirmed by intraoperative mapping, monitoring (awake/speech language mapping, direct cortical/subcortical stimulation, motor evoked or somatosensory evoked potentials), and/or surgical navigation. Motor and somatosensory evoked potentials and surgical navigation were typically used for tumors near motor and/or somatosensory cortex. The use of other surgical adjuncts, including cortical and subcortical mapping, ultrasound, and functional imaging, largely depended upon the preference of the surgeon. Patients typically underwent gadolinium-enhanced MRI at 1- to 3-month intervals and/or if new or

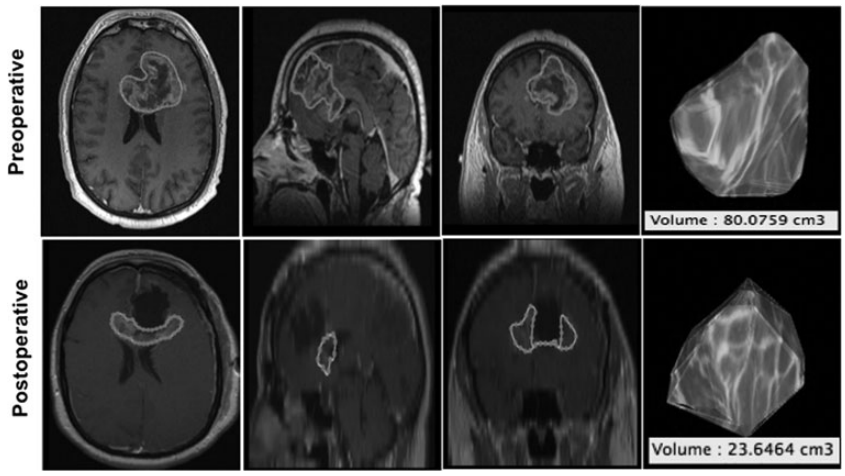

Fig. 2. Volumetric measurements. The pre- and postoperative MRIs were obtained and reviewed for each patient. All patients underwent axial MRI with gadolinium at 1.5- to 3-mm intervals on the day prior to or on the day of surgery and within 48 h of surgery. Using OsiriX software, the area of contrast enhancement was measured for each axial section, and tumor volume was quantified based on the sum of axial areas in a semiautomated manner.

progressive neurological symptoms occurred. The use of adjuvant radiation and/or chemotherapy was determined by a multidisciplinary team, which included the surgeon, radiation oncologist, medical oncologist, and the patients themselves.

Statistical Analysis

Summary data were presented as mean ± standard deviation for parametric data and as median (interquartile range [IQR]) for nonparametric data. Pearson's correlation coefficient was used to assess whether there was a correlation between EOR and RV. The Bland–Altman plot was used to assess interobserver reliability for measuring RV and EOR.[25] In this analysis, 2 clinicians blinded to each other's results measured the RV and EOR of 15 randomly chosen patients in this database, and the bias was assessed using the Bland–Altman technique. Multivariate proportional hazards regression analysis was used to identify whether an association between EOR and RV with survival existed. This was done after controlling for pre- (age, KPS)[2,4,6,9] and postoperative factors (carmustine wafer implantation,[26–29] temozolomide chemotherapy,[7] radiation therapy[30]) known to be associated with survival. In order to identify the thresholds for EOR and RV, EOR and RV were dichotomized in increments of 5% resection and 1 cm^3 RV, respectively. Values with $P < .05$ in these analyses were considered statistically significant, with the exception of EOR and RV thresholds. In order to establish a more significant association with EOR and RV threshold, a $P < .01$ was used as previously described.[11] These same analyses were used to evaluate whether an association between EOR, RV, and tumor recurrence existed. Overall survival and progression-free survival (PFS) were plotted using the Kaplan–Meier method, and log-rank analysis was used to compare Kaplan–Meier plots (GraphPad Prism 5). JMP9 (SAS) was used unless otherwise specified.

Results

Pre-, Peri-, and Postoperative Patient Characteristics

The pre-, peri-, and postoperative characteristics of the 259 patients in this study are summarized in Table 1. The average age of the patients was 59.6 ± 13.7 years at the time of surgery, and 159 patients (61%) were male. The median (IQR) KPS prior to surgery was 80 (70–90); 95 patients (37%) presented with headaches, 84 (32%) with seizures, 89 (34%) with language deficits, 78 (30%) with motor deficits, and 75 (29%) with confusion/memory loss. The median (IQR) preoperative contrast-enhancing tumor volume was 32.2 (14.0–56.3) cm^3. One hundred eighteen (46%) tumors involved eloquent cortex, 135 (52%) involved the left hemisphere, and 28 (11%) were deep seated.

Perioperatively, 64 patients (22%) had carmustine wafers placed at the time of surgery. The median (IQR) postoperative RV was 2.1 (0–7.9) cm^3 (range, 0–58 cm^3) (Supplementary material, Fig. S2). The mean ± standard error of the mean (SEM) EOR was 81.0 ± 1.6% (range, 5%–100%) (Supplementary material, Fig. S1). Among the patients who had carmustine wafers placed at the time of surgery, 40 (63%) had >90% resection, 13 (20%) had 80%–89% resection, 4 (9%) had 70%–79% resection, 3 (5%) had 60%–69% resection, and 4 (6%) had <60% resection. Following surgery, 15 (6%), 8 (3%), and 11 (4%) incurred a new motor, language, and vision deficit, respectively. Vascular injury was attributed to the new motor, language, and vision deficit in 4 (27%), 4 (50%), and 4 (36%), respectively. The remainder was most likely due to parenchymal injury from extending the resection into eloquent cortex/tracts in order to maximize resection. At last follow-up, the motor, language, and vision deficits persisted in 8 (3%), 5 (2%), and 6 (2%) at a median (IQR) follow-up time of 6.7 (4.5–8.1) months. The median (IQR) hospital length of stay was 4 (3–8) days.

At last follow-up, 169 patients (65%) underwent temozolomide chemotherapy and 185 (71%) underwent radiation therapy. Of the patients who did not undergo temozolomide chemotherapy, 40 (15%) underwent other types of chemotherapy, 23 (9%) were determined to not be candidates for chemotherapy (thrombocytopenia, poor functional status, etc), and 27 (10%) were lost to follow-up and may have had their adjuvant therapy at another hospital and their records were not available for review. One hundred sixty-two patients (63%) underwent temozolomide/radiation therapy according to the Stupp protocol.[7] Two hundred three patients (78%) died at last follow-up, where the median survival was 13.4 months. The 6-, 12-, 18-, and 24-month survival rates were 79.0%, 58.9%, 32.9%, and 19.3%, respectively (Fig. 3A).

Table 1. Pre-, peri-, and postoperative characteristics of patients undergoing surgery of a newly diagnosed intracranial glioblastoma from 1997 to 2011

Study Population ($N = 259$)	
Characteristics	
Age, y[a]	59.6 ± 13.7
Male, *n*	159 (61%)
Karnofsky Performance Score[b]	80 (70–90)
Preoperative symptoms, *n*	
Seizures	84 (32%)
Headaches	95 (37%)
Nausea/vomiting	28 (11%)
Motor deficit	78 (30%)
Sensory deficit	12 (5%)
Language deficit	89 (34%)
Visual deficit	40 (15%)
Gait deficit	32 (12%)
Confusion/memory loss	75 (29%)
Radiographic characteristics	
Tumor volume, cm^3[b]	32.2 (14.0.–56.3)
Left hemisphere, *n*	135 (52%)
Eloquent cortex	118 (46%)
Deep-seated	28 (11%)
Surgical variables	
Needle biopsy, *n*	0 (0%)
Postoperative tumor volume, cm^3[b]	2.1 (0–7.9)
Percent resection[c]	81.0 ± 1.6
Perioperative variables, *n*	
Motor deficit	15 (6%)
Language deficit	8 (3%)
Vision deficit	11 (4%)
Length of hospital stay, days[b]	4 (3–8)
Adjuvant therapy, *n*	
Carmustine wafers	64 (25%)
Temozolomide	169 (65%)
Radiation therapy	185 (71%)
Survival	
Died at last follow-up, *n*	203 (78%)
Follow-up, mo[b]	12 (2–19)
Median survival, mo	13.4
6-mo survival rate	79.0
12-mo survival rate	58.9
18-mo survival rate	32.9
24-mo survival rate	19.3
Recurrence	
Tumor recurrence, *n*	156 (60%)
Median progression free survival, mo	8.9
6-mo survival rate	73.3
12-mo survival rate	29.7
18-mo survival rate	14.3
24-mo survival rate	6.6

[a]Mean ± SD.
[b]Median (IQR).
[c]Mean ± SEM.

One hundred fifty-six patients (60%) had tumor recurrence, where the median PFS was 8.9 months. The 6-, 12-, 18-, and 24-month PFS rates were 73.3%, 29.7%, 14.3%, and 6.6%, respectively (Fig. 3B). The median (IQR) follow-up time for surviving patients was 12 (2–19) months.

Interobserver Reliability

The Bland–Altman plot[25] was to assess interobserver reliability for measuring EOR and RV in a sample dataset of 15 patients with GB. The bias ± SD EOR and RV were −0.5 ± 1.6% and 0.09 ± 0.25 cm^3, respectively.

Association Between Percent of Resection and Survival

In univariate analysis, EOR was associated with survival (hazard ratio [HR], 0.992; 95% confidence interval [CI], 0.988–0.998; $P = .0007$). In multivariate analysis, after controlling for factors previously known to be associated with survival (age, KPS, carmustine wafer implantation, temozolomide, and radiation therapy), EOR remained significantly associated with survival (HR [95% CI], 0.995 [0.990–0.998], $P = .008$; Table 2). In order to make the HR more clinically interpretable, the EOR was rescaled so that the HR represented the effect of a 5% increment in EOR. For each 5% EOR increment, the HR or risk of death decreased by ~5.2% (HR [95% CI], 0.948 [0.918–0.978], $P = .0005$). In further multivariate models, EOR remained significantly associated with survival even after controlling for deep-seated tumors (HR [95% CI], 0.993 [0.988–0.998], $P = .008$) and eloquent location (HR [95% CI], 0.991 [0.986–0.996], $P = .003$). Of note, preoperative volume itself was not significantly associated with survival (HR [95% CI], 1.003 [0.999–1.006], $P = .20$). Even after controlling for preoperative tumor volume, EOR remained significantly associated with survival (HR [95% CI], 0.992 [0.987–0.997], $P = .003$).

In order to determine the minimum EOR associated with prolonged survival, EOR was dichotomized in increments of 5% resection. The minimum EOR that was significantly associated with prolonged survival in multivariate analysis was >70% resection (HR [95% CI], 0.631 [0.462–0.875], $P = .0006$; Table 2). The median survival for patients with >70% tumor resection was 14.4 months compared with 10.5 months for patients with ≤70% resection ($P = .0003$; Fig. 4A). The 6-, 12-, and 24-month overall survival rates for patients with >70% tumor resection were 83.3.3%, 64.7%, and 20.3.5%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≤70% tumor resection were 65.5%, 38.7%, and 15.5%, respectively.

Association Between Percent of Resection and Recurrence

In univariate analysis, EOR was associated with tumor recurrence (HR [95% CI], 0.994 [0.991–0.998], $P = .01$). In multivariate analysis, after controlling for factors previously known to be associated with survival, EOR remained significantly associated with recurrence (HR [95% CI], 0.992 [0.983–0.998], $P = .005$; Table 2). In order to make the HR more clinically interpretable, the EOR was rescaled so that the HR represented the effect of a 5% increment in EOR. For each 5% EOR increment, the HR or risk of recurrence decreased by 3.2% (HR [95% CI], 0.968 [0.937–0.988], $P = .004$). The minimum EOR that was significantly associated with

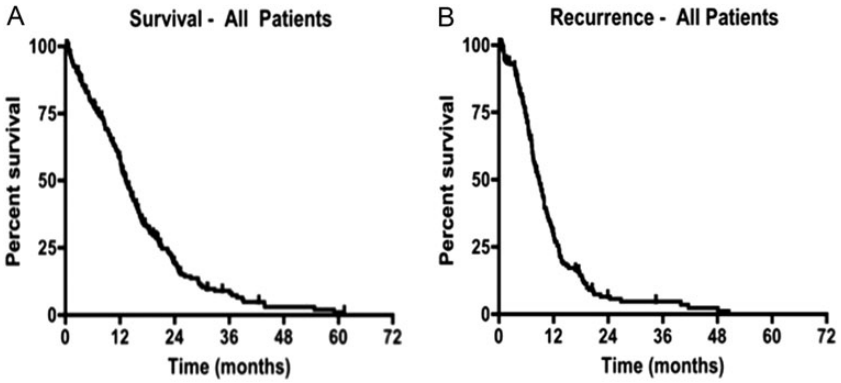

Fig. 3. Survival and recurrence for all included patients who underwent nonbiopsy surgery of a newly diagnosed intracranial GB from 2007 to 2011 at a single tertiary care institution. (A) Survival of all patients. The median survival for all included patients was 13.4 months. The 6-, 12-, 18-, and 24-month overall survival rates were 79.0%, 58.9%, 32.9%, and 19.3%, respectively. (B) Recurrence of all patients. The median PFS of all included patients was 8.9 months. The 6-, 12-, 18-, and 24-month PFS rates were 73.3%, 29.7%, 14.3%, and 6.6%, respectively.

Table 2. Multivariate associations of percent tumor resection with survival and recurrence for adult patients with newly diagnosed intracranial GB

Percent Resection and Survival		
Variables	Hazard Ratio (95% CI)	*P*
Univariate analysis with survival		
Increasing percent EOR	0.992 (0.988–0.998)	.0007
Multivariate analysis with survival		
Increasing percent EOR	0.995 (0.990–0.998)	.008
Increase in resection by 5% increments[a]	0.948 (0.918–0.978)	.0005
>70% resection[b]	0.631 (0.462–0.875)	.0006
Factors controlled for in multivariate analysis		
Increasing age	1.025 (1.014–1.037)	<.0001
Increasing KPS	0.982 (0.971–0.993)	.001
Carmustine wafer	1.045 (0.767–1.542)	.61
Radiation therapy	0.878 (0.526–1.511)	.63
Temozolomide chemotherapy	0.385 (0.237–0.653)	.006
Percent Resection and Recurrence		
Univariate analysis with recurrence		
Increasing percent EOR	0.994 (0.991–0.998)	.01
Multivariate analysis with recurrence		
Increasing percent EOR	0.992 (0.983–0.998)	.005
Increase in resection by 5% increments[a]	0.968 (0.937–0.988)	.004
>70% resection[b]	0.631 (0.462–0.875)	.007
Factors controlled for in multivariate analysis		
Increasing age	1.000 (0.987–1.013)	.98
Increasing KPS	0.991 (0.978–1.005)	.21
Carmustine wafer	0.891 (0.599–1.298)	.55
Radiation therapy	0.939 (0.423–2.045)	.08
Temozolomide chemotherapy	0.730 (0.372–1.655)	.04

These factors were independent of perioperative variables previously shown to be associated with survival (age, KPS, temozolomide chemotherapy, and radiation therapy).

[a]In a separate multivariate model, percent of resection was categorized into increments of 5% resection to evaluate the hazard ratio for every 5% resection.

[b]In a separate multivariate model, percent resection was dichotomized and included in the multivariate analysis to find the minimum percent resection significantly associated with survival ($P < .01$).

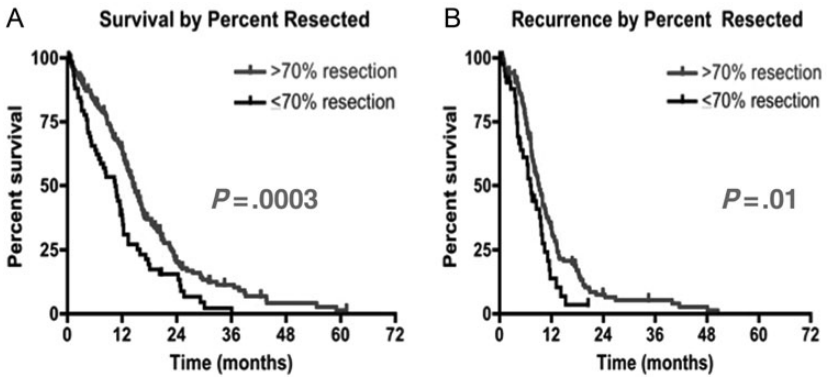

Fig. 4. Survival and recurrence by percent tumor resection. (A) Survival by percent resection. The median survival for patients with >70% tumor resection was 14.4 months compared with 10.5 months for patients with ≤70% resection ($P = .0003$). The 6-, 12-, and 24-month overall survival rates for patients with >70% tumor resection were 83.3.3%, 64.7%, and 20.3.5%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≤70% tumor resection were 65.5%, 38.7%, and 15.5%, respectively. (B) PFS by percent resection. The median PFS for patients with >70% tumor resection was 9.0 months compared with 7.1 months for patients with ≤70% resection ($P = .01$). The 6-, 12-, and 24-month PFS rates for patients with >70% tumor resection were 76.5%, 33.6%, and 7.6%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≤70% tumor resection were 61.0%, 13.8%, and 3.4%, respectively.

prolonged PFS in multivariate analysis was >70% resection (HR [95% CI], 0.631 [0.462–0.875], $P = .007$; Table 2). The median PFS for patients with >70% tumor resection was 9.0 months compared with 7.1 months for patients with ≤70% resection ($P < .0001$; Fig. 4B). The 6-, 12-, and 24-month PFS rates for patients with >70% tumor resection were 76.5%, 33.6%, and 7.6%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≤70% tumor resection were 61.0%, 13.8%, and 3.4%, respectively.

Association Between Residual Volume and Survival

In univariate analysis, RV was associated with survival (HR [95% CI], 1.026 [1.015–1.035], $P < .0001$). In multivariate analysis, after controlling for factors previously known to be associated with survival, RV remained significantly associated with survival (HR [95% CI], 1.019 [1.006–1.030], $P = .004$; Table 3). In order to make the HR more clinically interpretable, the RV was rescaled so that the HR represented the effect of a 5 cm^3 increment in RV. For each 5 cm^3 increment, the HR or risk of death increased by ∼15% (HR [95% CI], 1.147 [1.053–1.261], $P = .001$). In further multivariate models, RV remained significantly associated with survival even after controlling for deep-seated tumors (HR [95% CI], 1.023 [1.012–1.033], $P = .0001$) and eloquent location (HR [95% CI], 1.026 [1.015–1.036], $P = .0001$). Moreover, even after controlling for preoperative tumor volume, RV remained significantly associated with survival (HR [95% CI], 1.028 [1.015–1.040], $P = .001$).

In order to determine the maximum RV associated with prolonged survival, RV was dichotomized in increments of 1 cm^3. The maximum RV significantly associated with prolonged survival in multivariate analysis was 5 cm^3 (HR [95% CI], 0.725 [0.534–0.991], $P = .01$; Table 3). The median survival for patients with <5 cm^3 of residual tumor volume was 14.4 months compared with 10.5 months for patients with ≥5 cm^3 RV ($P = .0003$; Fig. 5A). The 6-, 12-, and 24-month overall survival rates for patients with >70% tumor resection were 83.3.3%, 64.7%, and 20.3.5%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≤70% tumor resection were 65.5%, 38.7%, and 15.5%, respectively.

Association Between Residual Volume and Recurrence

In univariate analysis, RV was associated with recurrence (HR [95% CI], 1.028 [1.007–1.047], $P = .009$). In multivariate analysis, after controlling for factors previously known to be associated with survival, RV remained significantly associated with recurrence (HR [95% CI], 1.024 [1.001–1.044], $P = .03$; Table 3). In order to make the HR more clinically interpretable, the RV was rescaled so that the HR represented the effect of a 5 cm^3 increment in RV. For each 5 cm^3 increment, the HR or risk of recurrence increased by ∼13% (HR [95% CI], 1.127 [1.025–1.255], $P = .01$). The maximum RV that was significantly associated with prolonged PFS in multivariate analysis was <5 cm^3 (HR [95% CI], 0.783 [0.546–0.984], $P = .01$; Table 3). The median PFS for patients with <5 cm^3 RV was 9.2 months compared with 7.5 months for patients with ≥5 cm^3 RV ($P = .005$; Fig. 5B). The 6-, 12-, and 24-month PFS rates for patients with <5 cm^3 RV were 75.7%, 31.8%, and 6.6%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≥5 cm^3 RV were 67.2%, 14.3%, and 0.0%, respectively.

Correlation Between Percent of Resection and Residual Volume

The correlation between EOR and RV was −0.607 (95% CI: −0.679 to −0.524, $P < .0001$) for all patients with GB. The coefficient of determination (r^2) was 0.369.

In multivariate proportional hazards regression analysis including both EOR and RV in the same model, both EOR (HR [95% CI], 0.993 [0.989–0.998], $P = .03$) and RV (HR [95% CI], 1.017 [1.002–1.030], $P = .02$) remained significantly associated with survival. Moreover, when using the EOR and RV categorized in 5% and 5 cm^3 increments, respectively, EOR (HR [95% CI], 0.956 [0.914–0.995], $P = .02$) and RV (HR [95% CI], 1.027 [1.015–1.173], $P = .01$) remained significantly associated with survival.

Table 3. Multivariate associations of residual tumor volume with survival and recurrence for adult patients with newly diagnosed intracranial GB

Variables	Hazard Ratio (95% CI)	*P*
RV and Survival		
Univariate analysis with survival		
Increasing RV	1.026 (1.015–1.035)	<.0001
Multivariate analysis with survival		
Increasing RV	1.019 (1.006–1.030)	.004
Increase in RV by 5 cm^3 increments[a]	1.147 (1.053–1.261)	.001
RV <5 cm^3[b]	0.725 (0.534–0.991)	.01
Factors controlled for in multivariate analysis		
Increasing age	1.027 (1.016–1.039)	<.0001
Increasing KPS	0.984 (0.973–0.995)	.006
Carmustine wafer	1.141 (0.798–1.610)	.46
Radiation therapy	1.151 (0.670–1.921)	.60
Temozolomide chemotherapy	0.405 (0.250–0.687)	.006
RV and Recurrence		
Univariate analysis with recurrence		
Increasing RV	1.028 (1.007–1.047)	.009
Multivariate analysis with recurrence		
Increasing RV	1.024 (1.001–1.044)	.03
Increase in RV by 5 cm^3 increments[a]	1.127 (1.025–1.255)	.01
RV <5 cm^3[b]	0.783 (0.546–0.984)	.01
Factors controlled for in multivariate analysis		
Increasing age	1.002 (0.989–1.016)	.77
Increasing KPS	0.995 (0.981–1.010)	.51
Carmustine wafer	0.946 (0.636–1.380)	.78
Radiation therapy	0.923 (0.417–2.001)	.84
Temozolomide chemotherapy	0.526 (0.296–1.028)	.05

These factors were independent of perioperative variables previously shown to be associated with survival (age, KPS, temozolomide chemotherapy, and radiation therapy).
[a]In a separate multivariate model, RV was categorized into increments of 5 cm^3 to evaluate the hazard ratio for every 5 cm^3 increase in residual tumor.
[b]In a separate multivariate model, residual tumor volume was dichotomized and included in the multivariate analysis to find the minimum RV significantly associated with survival ($P < .01$).

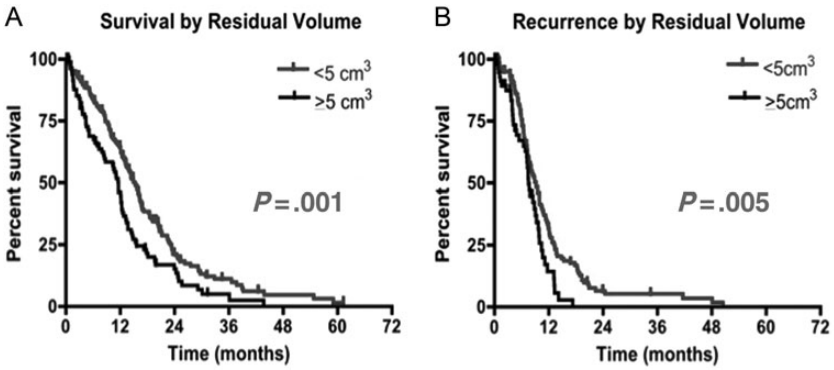

Fig. 5. Survival and recurrence by residual tumor volume. (A) Survival by residual tumor volume. The median survival for patients with <5 cm^3 of residual tumor volume was 15.3 months compared with 11.6 months for patients with ≥5 cm^3 of residual volume ($P = .001$). The 6-, 12-, and 24-month overall survival rates for patients with <5 cm^3 of residual tumor volume were 84.1%, 64.5%, and 21.2%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≥5 cm^3 of residual tumor volume were 68.8%, 46.2%, and 15.2%, respectively. (B) Recurrence by residual volume. The median PFS for patients with <5 cm^3 RV was 9.2 months compared with 7.5 months for patients with ≥5 cm^3 RV ($P = .005$). The 6-, 12-, and 24-month PFS rates for patients with <5 cm^3 RV were 75.7%, 31.8%, and 6.6%, respectively. In comparison, the 6-, 12-, and 24-month overall survival rates for patients with ≥5 cm^3 RV were 67.2%, 14.3%, and 0.0%, respectively.

Discussion

Of the 259 patients in this study who underwent nonbiopsy surgery from 2007 to 2011 for a newly diagnosed intracranial GB, 203 (78%) died and 156 (60%) died and had tumor recurrence at last follow-up. The median survival and PFS were 13.4 and 8.9 months, respectively. The average pre- and postoperative tumor volumes were 32.2 and 2.1 cm^3, respectively. This correlated with an average percent resection of 81.0%. The correlation between EOR and RV was −0.607, and the coefficient of determination was 0.369. In multivariate analyses, EOR and RV were each independently associated with survival and recurrence. The minimum EOR and the maximum RV thresholds that were significantly associated with survival were 70% resection and 5 cm^3, respectively.

GBs are characterized by their ability to invade and infiltrate surrounding parenchyma, making curative resection difficult. There have been an increasing number of studies in recent years demonstrating an association between EOR and survival.[3,9–11,14–19] Laws[17] and Buckner[15] each independently showed that surgical resection rather than biopsy was associated with prolonged survival for patients with high-grade gliomas.[17] Other studies have found that GTR was associated with longer survival in patients compared with those patients who underwent non-GTR.[10–12,18,31,32] Brown et al[14] studied 124 patients with GB in 2006 and found that GTR was associated with significantly longer survival times and improved quality of life compared with less resection. Likewise, Schneider et al[18] evaluated 31 patients with GB who underwent intraoperative MRI in 2005 and found that patients who underwent GTR had better survival times than patients who underwent non-GTR. This non-GTR cohort in these studies, however, included patients with heterogeneous amounts of resection that ranged from 0% to 99%.[18,31,32] More recently, we studied 700 patients with GB operated on between 1996 and 2006.[10] We showed that survival was different among patients who underwent GTR, near total resection (NTR), and STR.[10] Patients who underwent GTR had improved survival compared with patients who underwent NTR, and patients who underwent NTR had improved survival compared with patients who underwent STR.[10] Nevertheless, since the majority of these studies divided patients into either GTR or non-GTR cohorts, it is difficult to assess the effects that increasing volumetric resection had on survival. The ability to truly assess EOR therefore requires 3-dimensional volumetric measurements and analyses.

Large-scale volumetric studies on patients with GB are few and limited.[9,11,12] Lacroix et al[9] in 2001 examined 416 patients with primary and recurrent GB who were operated on between 1993 and 1999. The median pre- and postoperative tumor volumes in this study were 34 and 0.68 cm^3, respectively.[9] The mean EOR was 89%.[9] They found that increased EOR was independently associated with prolonged survival, where a threshold of 98% was needed to confer a significant survival advantage.[9] More recently, Sanai et al[11] in 2011 evaluated 500 patients with newly diagnosed GB between 1997 and 2009. The pre- and postoperative tumor volumes of the patients in this study were 65.8 and 2.3 cm^3, respectively.[11] The mean EOR was 96%.[11] Similar to the previous study, Sanai and colleagues found that increased EOR was independently associated with prolonged survival, but a threshold of only 78% was needed to confer a significant survival advantage.[11] Orringer et al[12] evaluated 46 patients with GB from 2006 to 2009 and found that >90% resection was associated with improved survival at 1 year. These studies, however, are limited because they were underpowered,[12] used nonautomated techniques,[11] included patients prior to the adoption of temozolomide as standard of care,[9,11] had patients over a long time frame,[11] and did not evaluate tumor recurrence.[9,11,12] The questions therefore remain whether volumetric EOR and RV are each independently associated with prolonged survival in a more modern cohort of patients, which takes into account new adjuvant therapy regimens.

This study established a threshold of 70% resection to have a significant impact on survival and recurrence. This is lower than the 98% and 78% thresholds established by Lacroix et al[9] and Sanai et al,[11] respectively. The reason for the lower threshold in this study could be because the patients in this study were operated on during a more recent time period. Temozolomide became the standard of care after 2005.[7] All of the patients in Lacroix's study and a significant number of the patients in Sanai's study predated the adoption of temozolomide as standard of care.[9,11] Temozolomide and other more modern adjuvant therapies may therefore be more effective at treating larger RV, and therefore less extensive resection is required. Additionally, the range of percent resection in this study was larger than in previous studies.[9,11] The ranges of EOR in Lacroix's and Sanai's studies were 71%–100% and 10%–100%, respectively.[9,11] The range in our study was 5%–100%, which may be able to better detect differences in outcomes for patients with less percent resection.

More important than EOR is the postoperative RV. This is because it makes intuitive sense that patients with the same EOR may have disparate RVs, since EOR is dependent on the preoperative tumor volume. This study showed that while EOR and RV are highly inversely correlated where increased EOR is associated with decreased RV, the inverse relationship was present only 37% of the time. EOR and RV are therefore not correlated in the majority of patients, which places an emphasis on understanding EOR and RV separately. Prior studies have yet to evaluate RV and establish an RV threshold. This study showed that postoperative RV, unlike preoperative tumor volume, was significantly associated with survival. Patient survival was impacted by how much postoperative residual tumor remained rather than how much preoperative tumor was present. This shows that surgery itself can have an impact on survival, regardless of the preoperative tumor burden. After surgery, an RV is established and represents the patient's tumor burden. It seems intuitive that the higher the tumor burden, the worse the outcome. A larger RV may have not only a larger number of tumor cells, but a greater number of tumor stem cells, which may make larger RV more resistant to adjuvant therapies, including radiation and chemotherapy.[33]

This study is important because it shows that GTR does not have to be achieved at the risk of causing an irreversible deficit. The development of iatrogenic deficits in itself is associated with worse outcomes.[13] In fact, 8 (3%) and 5 (2%) patients developed a new motor and/or language deficit, respectively, that was believed to be due to permanent injury to the cortex/cortical tracts in order to maximize resection in this study. Despite the use of mapping and other modalities, these deficits can still occur.[34] Therefore, a balance must be achieved between extensive resection and decreased RV with avoidance of iatrogenic deficits.

Strength and Limitations

We believe that this study provides several useful insights. First, the potential benefits of increased EOR and decreased RV for patients with GB are poorly understood. This study shows that patients with GB who underwent increased EOR and/or had decreased RV had improved survival and delayed recurrence independent of age, KPS, and adjuvant therapies. Second, this study established a 70% resection threshold, which is the minimum EOR associated with survival. This is lower than previous studies and shows that surgical resection is still important even when GTR cannot be achieved. This lower threshold may reflect advancements in adjuvant therapies. Third, this study has also established a 5 cm^3 threshold for postoperative RV. Prior studies have yet to report an RV threshold, which may be more important than EOR. Lastly, this study may provide useful information to help guide treatment strategies aimed at prolonging survival and delaying recurrence for patients with GB. This may help guide surgical and adjuvant therapies based on these established benchmarks of resection and RV.

This study, however, has some limitations. One important limitation of this study, as well as of previous volumetric studies,[9,11,12] is the uncertainty that exists with the tumor volume measurements. These 3-dimensional volumetric measurements were based on 2-dimensional imaging and were further limited by slice thickness and imaging resolution to the voxel level. These measurements may have over- or underestimated EOR and/or RV. While these measurements were consistent between evaluators, it remains unclear how precise or accurate these measurements are, which can limit the findings of this study. This includes accurately measuring a 5% differential in EOR and 1 cm^3 RV. In order to minimize these potential errors, tumor measurements were done in a semiautomated fashion to the best of our abilities and with the current imaging protocols and available software at our institution. Another limitation is that these findings apply only to patients undergoing nonbiopsy surgery of primary GB. These findings may not be applicable to patients with recurrent tumors, prior low-grade gliomas, infratentorial lesions, and surgeries where no active tumor is found. Also, it may not apply to patients with non-contrast-enhancing GB, since these tumors were excluded. Moreover, in order to establish the resection threshold associated with survival, repeated testing was done in multivariate analyses. The limitation with this statistical technique is that type I error increases with repeated testing. We attempted to minimize this by basing our threshold around the threshold established by Sanai et al.[11] This limitation makes it necessary for future prospective studies to help confirm this threshold. This process is currently ongoing at our institution. Furthermore, a significant number of patients in this study did not receive triple combinatorial adjuvant therapy (carmustine wafer, temozolomide, radiation). Some of these patients received non-temozolomide adjuvant therapy or were poor candidates for adjuvant therapy; others were lost to follow-up and had their adjuvant care at another hospital, and it was therefore difficult to determine whether they received adjuvant therapy, since their records were not available to review. The relevance of this study's findings may be altered if all patients received the most aggressive treatment regimens. Finally, this study is inherently limited because of its retrospective design. It is therefore not appropriate to infer direct causal relationships. There may be an inherent bias associated with patient selection, where patients who were offered more aggressive surgeries may have a propensity for better outcomes. However, we tried to create a uniform patient population by utilizing strict inclusion criteria and controlling for potential confounding variables. Given these statistical controls, multivariate analyses, and relatively precise outcome measures, we believe our findings offer useful insights for patients undergoing intracranial GB surgery. Nonetheless, prospective studies are needed to provide better data to guide clinical decision making.

Conclusion

Patients with GB have a dismal prognosis. The only potentially modifiable risk factor associated with survival is extent of tumor resection. While there are several studies demonstrating an association between GTR and prolonged survival for patients with GB, GTR is not always possible. This study showed that increased EOR and decreased RV are each independently associated with prolonged survival and delayed recurrence. Moreover, this study shows that the minimum EOR and maximum RV associated with survival and recurrence is 70% and 5 cm^3, respectively. These thresholds may serve as minimum surgical goals when safe to do so and/or may guide adjuvant therapies. However, it should be noted that there is inherent uncertainty in the tumor volume measurements in this study because calculations are based on 2-dimensional imaging and were further limited by slice thickness.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

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