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Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival

Clinical article

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Object. The extent of resection (EOR) is a known prognostic factor in patients with glioblastoma. However, gross-total resection (GTR) is not always achieved. Understanding the factors that prevent GTR is helpful in surgical planning and when counseling patients. The goal of this study was to identify demographic, tumor-related, and technical factors that influence EOR and to define the relationship between the surgeon's impression of EOR and radiographically determined EOR.

Methods. The authors performed a retrospective review of the electronic medical records to identify all patients who underwent craniotomy for glioblastoma resection between 2006 and 2009 and who had both preoperative and postoperative MRI studies. Forty-six patients were identified and were included in the study. Image analysis software (FIJI) was used to perform volumetric analysis of tumor size and EOR based on preoperative and postoperative MRI. Using multivariate analysis, the authors assessed factors associated with EOR and residual tumor volume. Perception of resectability was described using bivariate statistics, and survival was described using the log-rank test and Kaplan-Meier curves.

Results. The EOR was less for tumors in eloquent areas ($p = 0.014$) and those touching ventricles ($p = 0.031$). Left parietal tumors had significantly greater residual volume ($p = 0.042$). The average EOR was 91.0% in this series. There was MRI-demonstrable residual tumor in 69.6% of cases (16 of 23) in which GTR was perceived by the surgeon. Expert reviewers agreed that GTR could be safely achieved in 37.0% of patients (17 of 46) in this series. Among patients with safely resectable tumors, radiographically complete resection was achieved in 23.5% of patients (4 of 17). An EOR greater than 90% was associated with a significantly greater 1-year survival (76.5%) than an EOR less than 90% ($p = 0.005$).

Conclusions. The authors' findings confirm that tumor location affects EOR and suggest that EOR may also be influenced by the surgeon's ability to judge the presence of residual tumor during surgery. The surgeon's ability to judge completeness of resection during surgery is commonly inaccurate. The authors' study confirms the impact of EOR on 1-year survival.

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Key Words • glioblastoma multiforme • resection • astrocytoma • neoplasm

While controversy has surrounded glioblastoma surgery since the early days of modern neurosurgery, a growing body of evidence suggests that EOR is a key prognostic factor.[11,18] Neurosurgeons, therefore, often play a central role in determining patient outcome by maximizing resection. Radiographically complete resection, defined as the absence of tumor on MRI, is the ideal surgical result because it is associated with the best possible outcome and prognosis. However, in cases in which radiographically complete resection carries a high risk of neurological deficit, a subtotal resection may be desired.[27] Even in cases in which subtotal resection is determined to offer the best possible outcome, substantial evidence suggests that cytoreductive surgery is beneficial when at least 78% of the tumor can be removed.[18] Distinguishing the factors that determine the resectability of a given glioblastoma is important in defining a surgical plan and in formulating patient expectations. Currently, there is a paucity of studies that critically examine the factors associated with the likelihood of maximum resection.[22]

Execution of surgical plans requires accurate intraoperative judgment of the EOR. Given the infiltrative nature of gliomas and the visual and textural similarity between tumor and normal brain, judging EOR poses a substantial challenge to the surgeon. Early studies using postoperative MRI highlighted the disparity between the surgeon's

Abbreviations used in this paper: ACE-27 = Adult Comorbidity Evaluation-27; EOR = extent of resection; GTR = gross-total resection.

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estimate of EOR and radiographically determined EOR.[1] Since estimation of EOR was last reported in the literature, substantial advances in MRI, improvement in the quality of frameless stereotactic navigation systems, and an increasing body of knowledge demonstrating the clear benefits of maximum resection have emerged.[11,18]

Therefore, we sought to identify factors affecting EOR and assess the ability of neurosurgeons to estimate EOR in the modern neurosurgical environment through multivariate statistics. Specifically, we examine the relevance of patient and tumor characteristics that neurosurgeons consider when determining the goals of cytoreductive surgery. In addition, the relationship between the surgeon's impression of EOR and radiographically determined EOR is defined.

Methods

This study was reviewed and approved by the Medical Sciences Institutional Review Board of the University of Michigan.

Patient Population

Electronic medical records were queried retrospectively to identify all consecutive patients who underwent craniotomy for tumor resection of a glioblastoma (WHO Grade IV astrocytoma) diagnosed by pathological examination during the period January 2006 to December 2009. Inclusion criteria set a priori consisted of patients of any age or sex undergoing craniotomy for resection. Patients who had any additional brain pathology that required additional surgical and/or medical treatment or terminal disease that may have affected survival were excluded from analysis to avoid potential confounding factors. In addition, patients without sufficient preoperative and/or postoperative MRI studies were excluded, as these images were critical for objective measurement of tumor volume.

Tumor Measurements

Semiautomated segmentation tools and volumetric analysis were used throughout this study to minimize the subjective component of estimating EOR. Each volume measurement in this study represents an average of measured volumes from 3 individual investigators blinded to all aspects of the cases analyzed. Tumor volumes were measured in detail using FIJI (Fiji Is Just ImageJ; http://fiji.sc/wiki/index.php/Fiji), which is an open source image-processing package based on ImageJ software (National Institutes of Health). Tumor measurements were assessed using the following 3 MRI sequences: preoperative T1-weighted imaging with contrast, postoperative T1-weighted imaging without contrast, and postoperative T1-weighted imaging with contrast. All postoperative MRI studies were obtained within 48 hours of surgery. Within the FIJI software, the "Segmentation Editor" function was used to meticulously outline the area of tumor in each slice of the MRI sequence. Next, the outlined tumor slices from the MRI sequence were transitioned onto another image file to obtain a new sequence that only contained the selected tumor areas from each slice. The "3D Objects Counter" function was then used to generate a 3D image of the tumor (through the combination of outlined tumor slices) and to determine the total number of voxels in each selection (volume of tumor in each slice). Using the original MRI sequence profile, the total number of voxels in our tumor selections was converted to a volumetric measurement of cubic millimeters.

Slice thickness of the MRI sequence and pixel spacing were accounted for in our measurements and calculation of tumor volumes. For the 3D sequences, we simply multiplied the number of voxels by the voxel dimensions as follows: number of voxels × pixel spacing × slice thickness = total tumor volume. Voxel dimensions were obtained as follows in the sequence information stored in the MRI: "pixel spacing" was used as the x and y dimensions, and "slice thickness" was used as the z dimension. These values were calculated in millimeters. For the 2D sequences, we had to account for gaps in the slices in addition to what we had done for the 3D sequences. Voxel dimensions for the tumor selections were the same as those obtained in the 3D sequences. However, for these sequences, we counted the number of slices within a tumor volume to eventually calculate the amount unseen due to gaps. For example, if a 20-slice sequence had tumor present on 7 slices, tumor would be missing in 7 – 1, or 6 gaps. We divided the number of voxels in our tumor selections by the number of slices with tumor and multiplied that by the number of gaps (calculated as explained above). This offered an approximation of the number of tumor voxels that were not seen due to gaps between slices. These voxels had a different thickness (z dimension) because the gaps were a different size from the slice, and this thickness was accounted for using the "spacing between slices" entry in the MRI sequence information. This value was used as the thickness of the gaps (z dimension), or the unseen tumor between the slices. Hence, the equation used to calculate total tumor volume in 3D sequences is as follows: tumor volume in selections + tumor volume in gaps = total tumor volume. Tumor volume in selections = number of voxels × pixel spacing × slice thickness + tumor volume gaps = number of voxels/number of slices within tumor × number of gaps × pixel spacing × spacing between slices. This method was verified by a neuroradiologist blinded to the goals of the study.

Patient Data

To identify potential factors associated with EOR, patient demographics, baseline clinical variables, and tumor characteristics were recorded. Patient demographics and baseline clinical variables of interest included age at time of surgery, sex, and ACE-27 score.[5] Based on preoperative MRI findings, tumor location was assessed and categorized as left versus right side of brain, specific lobe of brain (categorized as left frontal, right frontal, left parietal, right parietal, left temporal, right temporal, left occipital, or right occipital lobe), eloquent versus noneloquent brain (defined by the Spetzler-Martin grading scale),[20] and proximity to ventricles (touching ventricles vs not touching ventricles). If the tumor involved more

than one lobe of the brain, it was categorized by the lobe in which the majority of the tumor was located. Initial tumor size and residual tumor volume were measured using FIJI and were recorded in cubic millimeters. Handedness and whether tumor resection was performed awake were also recorded.

In this study, our main concerns were postoperative outcomes for EOR and volume of residual tumor (in mm^3). The EOR was reported as the percentage resected and was determined using the following equation: (initial tumor size – residual tumor size)/initial tumor size. Another outcome of interest was 1-year survival to evaluate the prognostic relationship of EOR. One-year and 2-year survival were determined via review of medical records. In patients in whom there was no date of death available but the patient had a progress note dated at least 1 year after the date of surgery, the patient was determined to have 1-year survival. If the patient did not have a recorded date of death or a postoperative note of any sort in the medical record, the patient was determined to be lost to follow-up.

Preoperative Judgment and Intraoperative Perception of Total Resection

Preoperative judgment of whether total resection was possible without causing neurological deficit was obtained via post hoc examination of preoperative MRIs by senior neurosurgeons who were blinded to any knowledge of patient history, patient identity, and goals of the study. The surgeons were asked, "Is it reasonable to expect that this lesion could be completely removed without causing permanent neurologic deficit?" A binomial answer of yes or no was recorded. Intraoperative perception of total resection (gross total vs subtotal) by the attending neurosurgeon was determined via retrospective evaluation of operative notes.

Statistical Analysis

Identifying Factors Associated With EOR. To identify factors associated with EOR and residual tumor volume, we first used univariate statistics to describe our data. Second, we used ANOVA to assess for significant associations between explanatory covariates of interest and continuous outcomes (EOR and residual volume). Third, multivariate ANCOVA models of EOR and residual volume by various covariates were fit and were adjusted for the covariates found to be significantly associated with the outcome of interest in ANOVA models. A p value threshold of 0.200 was used as an identifier for potential confounders in ANOVA models, and confounders were adjusted for as mentioned.

Preoperative Judgment for Total Resection. Basic descriptive statistics were used to compare the level of agreement between the 2 data sets from each neurosurgeon. In addition, data from the 2 senior neurosurgeons were combined to stratify patients into one of 3 groups to allow further statistical analysis: a group in which both neurosurgeons answered no, a group in which one answered no and the other answered yes, and a group in which both answered yes. We then used a log-rank test and created a Kaplan-Meier curve to evaluate whether there is prognostic significance in preoperative judgment of resectability for 1- and 2-year survival (stratified by the 3 groups mentioned). The Cox proportional hazards model was then used to analyze for the hazard ratio of preoperative judgment of resectability. Sensitivity, specificity, positive predictive value, and negative predictive value of preoperative judgment of resectability were then calculated and are reported as percentages.

Intraoperative Perception for Total Resection. Bivariate chi-square tests were used to describe the frequency with which neurosurgeons perceived total resection stratified by measured EOR. In addition, ANOVA was used as a supplemental analysis to describe this same phenomenon and provide values for EOR and residual tumor when total resection was perceived.

One- and 2-Year Survival Analysis by EOR. We calculated univariate statistics using the log-rank test to identify significant associations between EOR and 1- and 2-year survival. A Kaplan-Meier survival curve was constructed using the log-rank test stratified by EOR.

For all statistics, results with $p < 0.050$ were considered significant. All statistical analyses were run using SAS version 9.2 software (SAS Institute). Kaplan-Meier survival curves were constructed with the use of GraphPad Prism 5 software (GraphPad Software, Inc.).

Results

A total of 100 consecutive patients with glioblastoma were identified. Forty-six patients met the set criteria and had sufficient preoperative and postoperative MRI studies for objective measurements of tumor volume. Of the 46 patients, 44 patients (95.7%) were right-handed. Three (6.5%) of the surgeries were performed when the patient was awake.

Demographic and Tumor-Related Factors Associated With EOR

Factors influencing EOR and residual tumor volume were identified by ANOVA (Table 1). The mean EOR was 91.0% among all 46 patients. Tumors arising in an eloquent location were significantly associated with EOR ($p = 0.008$). Patients with tumors located in eloquent areas of the brain had a mean EOR of 84.2% compared with 95.3% for tumors located in noneloquent areas. Proximity to the ventricles was also significantly associated with EOR ($p = 0.041$). The mean EOR for tumors touching the ventricles was significantly less than that for tumors not touching ventricles (85.9% vs 94.5%). Age, sex, side of the tumor, and lobe were not significantly associated with EOR. There seemed to be a trend toward lower EOR values with increasing ACE-27 scores, but this was not statistically significant.

As seen in Table 1, the mean volume of residual tumor among all patients was 3294.9 mm^3. Similar to EOR, eloquent location ($p = 0.012$) and proximity to ventricles ($p = 0.004$) were significantly associated with residual tumor volume. Patients with tumors located in eloquent areas had a mean residual tumor volume of 5960.8 mm^3

TABLE 1: Analysis of variance between demographic and medical covariates and tumor EOR in patients with glioblastoma who underwent craniotomy for tumor resection

Parameter	No. of Patients (%)	% EOR		Residual Tumor Vol (mm^3)	
		Mean ± SD	p Value	Mean ± SD	p Value
total	46	91.0 ± 14.2		3,294.9 ± 5,873.5	
age (yrs)			0.515		0.622
<35	9 (19.6)	94.7 ± 12.3		2,313.0 ± 4,858.4	
35–55	19 (41.3)	88.3 ± 17.7		4,303.9 ± 7,751.3	
>55	18 (39.1)	91.9 ± 10.5		2,720.7 ± 3,820.4	
sex			0.632		0.724
male	23 (50.0)	89.9 ± 11.9		2,984.6 ± 5,896.2	
female	23 (50.0)	92.0 ± 16.3		3,605.2 ± 5,966.3	
ACE-27 score			0.316		0.662
0	23 (50.0)	93.8 ± 12.0		2,511.9 ± 5,988.7	
1	21 (45.7)	88.7 ± 16.0		4,151.5 ± 6,023.0	
2	2 (4.3)	81.8 ± 16.4		3,304.6 ± 2,888.3	
tumor side			0.413		0.228
rt	19 (41.3)	92.4 ± 11.4		2,411.3 ± 4,416.2	
lt	27 (58.7)	88.9 ± 17.5		4,550.5 ± 7,432.3	
lobe			0.612		0.121
lt frontal	6 (13.0)	97.9 ± 4.5		1,836.5 ± 3,486.3	
rt frontal	9 (19.6)	92.3 ± 14.1		1,972.1 ± 4,937.0	
lt parietal	4 (8.7)	87.9 ± 16.3		11,536.8 ± 12,375.1	
rt parietal	3 (6.5)	97.7 ± 9.4		3,826.3 ± 8,012.9	
lt temporal	6 (13.0)	85.6 ± 25.2		1,299.3 ± 2,068.7	
rt temporal	13 (28.3)	91.0 ± 11.0		2,474.9 ± 3,808.1	
lt occipital	3 (6.5)	78.7 ± 17.1		7,166.2 ± 8,041.4	
rt occipital	2 (4.3)	94.4 ± 3.9		1,851.4 ± 1,108.2	
eloquent location			0.008		0.012
yes	18 (39.1)	84.2 ± 18.1		5,960.8 ± 7,274.4	
no	28 (60.9)	95.3 ± 8.8		1,581.1 ± 4,049.1	
touching ventricle			0.041		0.004
yes	18 (39.1)	85.9 ± 17.2		6,169.8 ± 7,623.6	
no	28 (60.9)	94.5 ± 10.5		1,271.8 ± 3,030.1	
initial tumor size (mm^3)			0.664		0.048
<10,000	9 (19.6)	87.3 ± 21.7		632.0 ± 1,555.7	
10,000–25,000	13 (28.3)	94.9 ± 9.9		890.6 ± 1,672.0	
25,000–40,000	8 (17.4)	86.8 ± 16.3		4,786.8 ± 6,090.5	
40,000–55,000	5 (10.9)	90.4 ± 13.1		4,771.3 ± 6,397.6	
>55,000	11 (23.9)	92.6 ± 10.3		6,559.0 ± 8,895.3	

compared with 1581.1 mm^3 for tumors located in noneloquent areas. Patients with tumors involving or touching the ventricles had a much larger mean residual tumor volume compared with tumors not in proximity to the ventricles (6169.8 mm^3 vs 1271.8 mm^3). In addition, the initial size of the tumor was associated with a mean residual tumor volume ($p = 0.048$). There was a noticeable trend in that larger tumors resulted in a greater residual tumor volume. Patients with tumors greater than 55,000 mm^3 had a mean residual tumor volume of 6559.0 mm^3. Tumors with an initial size of less than 10,000 mm^3, 10,000–25,000 mm^3, 25,000–40,000 mm^3, and 40,000–50,000 mm^3 had residual tumor volumes of 632.0 mm^3, 890.6 mm^3, 4786.8 mm^3, and 4771.3 mm^3, respectively.

To correct for potential confounders in ANOVA, a multivariate ANCOVA was performed. As seen in Table 2, both eloquent location ($p = 0.014$) and proximity to the ventricles ($p = 0.031$) remained significant factors in determining EOR. However, eloquent location, proximity to ventricles, and initial tumor size were no longer significantly associated with residual tumor volume after adjusting for specific tumor location. Rather, tumors located in the left parietal lobe were significantly associated with higher residual tumor volume ($p = 0.042$) and had the

TABLE 2: Multivariate ANCOVA models for EOR resection by covariate factors adjusted for potential confounders in patients with glioblastoma who underwent craniotomy for tumor resection*

	% EOR		Residual Tumor Vol (mm^3)	
Descriptive	Mean ± SD	p Value	Mean ± SD	p Value
lobe				
lt frontal			1,836.5 ± 3,486.3	0.883
rt frontal			1,972.1 ± 4,937.0	ref
lt parietal			11,536.8 ± 12,375.1	0.042
rt parietal			3,826.3 ± 8,012.9	0.898
lt temporal			1,299.3 ± 2,068.7	0.783
rt temporal			2,474.9 ± 3,808.1	0.867
lt occipital			7,166.2 ± 8,041.4	0.260
rt occipital			1,851.4 ± 1,108.2	0.628
eloquent location				
yes	84.2 ± 18.1	0.014	5,960.8 ± 7,274.4	0.154
no	95.3 ± 8.8	ref	1581.1 ± 4049.1	ref
touching ventricle				
yes	85.9 ± 17.2	0.031	6,169.8 ± 7,623.6	0.105
no	94.5 ± 10.5	ref	1,271.8 ± 3,030.1	ref
initial tumor size (mm^3)				
<10,000			632.0 ± 1,555.7	ref
10,000–25,000			890.6 ± 1,672.0	0.746
25,000–40,000			4,786.8 ± 6,090.5	0.282
40,000–55,000			4,771.3 ± 6,397.6	0.608
>55,000			6,559.0 ± 8,895.3	0.684

* ref = reference.

TABLE 3: Comparison between radiographically determined EOR and surgeon's intraoperative judgment of resection in patients with glioblastoma who underwent craniotomy for tumor resection*

	No. of Patients (%)	
% EOR on MRI†	MRI-Determined EOR	Surgeon-Perceived GTR‡
100	8 (17.4)	7 (87.5)
99–90	22 (47.8)	13 (59.1)
89–80	8 (17.4)	2 (25.0)
79–70	4 (8.7)	0 (0.0)
69–60	3 (6.5)	1 (33.3)
59–50	0 (0.0)	0 (NA)
49–40	0 (0.0)	0 (NA)
39–30	1 (2.2)	0 (0.0)
total	46 (100)	23 (50.0)

* NA = not applicable.

† p = 0.021 for the group of patients in whom surgeons perceived GTR had been achieved versus the group of patients in whom surgeons predicted a subtotal resection.

‡ Percentages in this column are based on the number of patients per category of MRI-determined EOR.

highest mean residual tumor volume (11,536.8 mm^3) of any other group of tumors separated by location in our series (Table 2).

Preoperative and Intraoperative Perception of Resectability

The surgeon's perception of EOR was compared with the MRI-defined EOR. In 50% of cases in our series (23 of 46), the surgeon reported that complete tumor resection was achieved (Table 3). Radiographically complete resection was achieved in 17.4% of patients (8 of 46) in this series, and in 30.4% of patients (7 of 23) in whom surgeons believed a GTR had been accomplished. There was a significant difference in EOR between the group of patients in whom surgeons perceived GTR had been achieved and the group of patients in whom surgeons predicted a subtotal resection ($p = 0.021$). When resection was less than 90%, surgeons were less likely to report total resection (Table 3). As seen in Table 4, in cases in which the neurosurgeon believed that a total resection was achieved, the mean EOR was 97.4%. When the resection was believed to be incomplete, the mean EOR was 84.5%. This difference was statistically significant ($p = 0.001$). In addition, when GTR was perceived, significantly less residual tumor volume remained than in those cases in which subtotal resection was perceived (806.4 mm^3 vs 5783.4 mm^3) ($p = 0.003$).

Accuracy of the surgeon's intraoperative ability to assess EOR was quantified. The sensitivity, or the proportion of patients with MRI-confirmed subtotal resection in whom surgeons believed there was a subtotal resection, was 57.9%. The specificity, or the proportion of patients with radiographically complete resection in whom surgeons believed that there was a complete resection, was 87.5%. The positive predictive value, or the proportion of patients in whom surgeons perceived a subtotal resection and who had MRI-confirmed subtotal resection, was 95.7%. The negative predictive value, or the proportion of patients in whom surgeons believed the resection was complete and who had radiographically complete resections, was 30.4%.

Surgical Outcome and the Safety of GTR

The patients in this series were nearly evenly distributed among the 3 groups, based on the predicted safety of GTR (Table 5). Expert reviewers agreed that GTR could be safely achieved in 37.0% of patients (17 of 46) and that GTR was unsafe in 34.8% of patients (16 of 46). The reviewers disagreed about the safety of GTR in 28.3% of patients (13 of 46). There was no significant difference in EOR between the groups, although there was a trend toward greater EOR in patients in whom reviewers agreed or one surgeon judged that GTR could be safely achieved ($p = 0.116$). Survival was significantly greater in patients with unanimously resectable tumors at 2 years ($p = 0.039$), but there was no significant difference in survival between the groups at 1 year ($p = 0.252$) (Table 5). Of the patients with unanimously judged totally resectable tumors, 53.3% of the patients were alive at 2-year

TABLE 4: Comparison between EOR and surgeon perception of obtaining a GTR among patients with glioblastoma who underwent craniotomy for tumor resection

Parameter	No. of Patients	% EOR		Residual Tumor Vol (mm^3)	
		Mean ± SD	p Value	Mean ± SD	p Value
overall	46	91.0 ± 14.2		3,294.9 ± 5,873.5	
perception of total resection			0.001		0.003
yes	23	97.4 ± 8.4		806.4 ± 2,664.4	
no	23	84.5 ± 15.9		5,783.4 ± 7,107.5	

follow-up, compared with 30.8% in the equivocal group and 26.7% in the unanimously unsafe group.

Subtotal Resection in Patients With Resectable Tumors

Among the 37.0% of patients with tumors in whom reviewers agreed that GTR was safe, radiographically complete resection was achieved in 23.5% of patients (4 of 17). Surgeons achieved an EOR of less than 90% in 5 patients in whom GTR was deemed to be safe (Table 6). Among these patients, none of the tumors were in eloquent locations and only 1 tumor was touching the ventricle.

One- and 2-Year Survival by EOR

Survival analysis was performed for 43 of the 46 patients in this study (3 patients were lost to follow-up). There was a significant difference in survival at 1 year among the 4 subgroups (p = 0.043) (Table 7 and Fig. 1). An EOR of 100%–90% was associated with 81.5% 1-year survival compared with 37.5% in the 89%–80% range, 25.0% in the 79%–70% range, and 25.0% in the less than 70% subgroup. At 2 years, there was no longer a significant difference in survival among the subgroups (p = 0.350), but the trend toward better survival rates with greater EOR is still seen. The survival rate at 2 years was 40.7% for patients with greater than 90% EOR compared with 37.5%, 25.0%, and 25.0% in the groups with EORs of 89%–80%, 79%–70%, and less than 70%, respectively.

TABLE 6: Patients in whom safe GTR was deemed possible with an actual EOR less than 90%

Case No.	Tumor Location	Age (yrs), Sex	Initial Tumor Size (mm^3)	Residual Tumor Size (mm^3)	Extent of Resection (%)
1	lt occipital	56, M	17,945	5,347	70.2
2	rt temporal	48, M	33,288	8,429	75.3
3	rt frontotemporal	60, M	14,627	2,333	84.1
4	rt temporal	50, M	774	335	84.2
5	rt frontal	54, F	3,513	513	87.2

Discussion

An expanding body of evidence suggests that EOR influences survival in patients with glioblastoma.[11,17,18] Consequently, the guiding principle in modern glioblastoma surgery is to achieve maximal safe resection.[16,26] Given the nuances involved in defining maximal safe resection, a variety of factors are considered both before and during an operation. In this study, we used volumetric analysis and statistical methods to quantitatively examine the factors that influence EOR. Three general categories of factors were examined: patient related, tumor related, and technical.

Patient-related factors, such as age, sex, and comorbidity status (ACE-27 score) did not have a significant effect on EOR. Given the lack of an effect of age on EOR, it is likely that the well-documented prognostic effects of age on survival of patients with glioblastomas[23] is not related to the surgical results that can be achieved. In addition, the observation that comorbidity status was not associated with EOR suggests that with modern surgical practice and improved postoperative management, good surgical outcomes can be expected, even for patients with substantial comorbidities. However, our ability to assess the full effects of comorbidity status on surgical outcome may have been compromised by our relatively small group of patients with extensive comorbidities. It is also possible that patients with an unfavorable medical risk profile were not offered surgery, raising the possibility for selection bias in our sample.

TABLE 5: Expert perception of tumor resectability in patients with glioblastoma who underwent craniotomy for tumor resection

Parameter	Total No. of Patients (%)	% EOR		No. of Patients Included in Survival Analysis (%)*	1-Yr Survival		2-Yr Survival	
		Mean ± SD	p Value		No. of Patients (%)	p Value	No. of Patients (%)	p Value
resectability			0.116			0.252		0.039
unsafe GTR	16 (34.8)	85.2 ± 18.7		15 (34.9)	8 (53.3)		4 (26.7)	
equivocal	13 (28.3)	95.5 ± 9.7		13 (30.2)	7 (53.8)		4 (30.8)†	
safe GTR	17 (37.0)	92.9 ± 10.6		15 (34.9)	12 (80.0)		8 (53.3)‡	
total	46			43	27 (62.8)		16 (37.2)	

* Three patients were lost to follow-up.
† Hazard ratio 0.691 (p = 0.517) compared with the unsafe GTR group.
‡ Hazard ratio 0.311 (p = 0.085) compared with the unsafe GTR group.

TABLE 7: Univariate log-rank test for 1- and 2-year survival stratified by EOR*

% EOR*	No. of Patients (%)	No. of Patients (%)	
		1-Yr Survival	2-Yr Survival
100–90	27 (62.8)	22 (81.5)	11 (40.7)
89–80	8 (18.6)	3 (37.5)	3 (37.5)
79–70	4 (9.3)	1 (25.0)	1 (25.0)
<70	4 (9.3)	1 (25.0)	1 (25.0)
total	43	27 (62.8)	16 (37.2)

* p = 0.043 and p = 0.350 for differences in survival at 1 and 2 years, respectively.

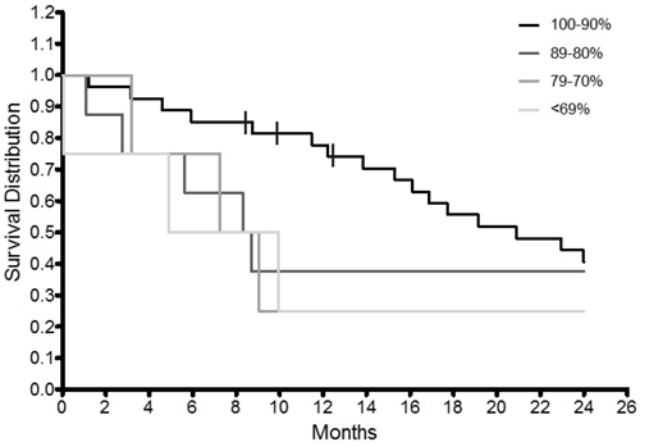

Fig. 1. Kaplan-Meier survival curve representing patients who underwent craniotomy for glioblastoma stratified by EOR. The EOR was associated with a significant difference in mortality at 1 year (p = 0.043), but not at 2 years (p = 0.350), among the 4 groups.

In contrast, tumor-related factors (eloquent location, superficial vs deep location, and size) were found to have a statistically significant effect on EOR. The covariates associated with a lesser EOR in this study confirm previously published results.[9,12,24] Given the poor median survival for patients with glioblastoma,[18] preserving the best possible quality of life after diagnosis is of paramount importance. Consequently, the risk of aggressive tumor resection within eloquent areas is rarely justified by the oncological benefits of cytoreduction. This principle likely explains the finding that EOR was lesser among tumors involving eloquent regions in this series. In addition, tumors centered within the left parietal lobe had a lesser EOR, resulting in a significantly larger residual volume, most likely because of their proximity to eloquent motor and language cortical regions. The finding that EOR was least among tumors that were adjacent to ventricles likely reflects the relative technical complexity and greater surgical risk of approaching deep, rather than superficial, lesions. It may also reflect the difficulty of operating on tumors involving white matter tracts, as suggested in a study evaluating the resectability of low-grade gliomas.[24] A lesser EOR among periventricular tumors may be a factor contributing to the observation that survival is poorer in patients with periventricular glioblastomas than in those with superficial lesions.[3]

Technical factors that complicate glioblastoma surgery have been recognized since the earliest days of modern neurosurgery.[4] Among the greatest challenges of glioblastoma resection is differentiating tumor tissue from normal brain, especially at tumor margins.[21] Cues such as tissue texture and discoloration, bleeding and vascularity of resection planes, and proximity to anatomical landmarks are used to judge completeness of resection.[2,15] Based on previous nonvolumetric analyses[1] and our experience, we hypothesized that the use of visual and textural clues would lead to highly variable surgical outcomes. The average EOR in the cohort examined here (91.0%) suggests that visual and textural clues can and are generally effective in tumor debulking. However, the wide variability of observed EOR in our series, the proportion of patients undergoing EOR less than 90% (34.8%), and the rarity of radiographically complete resection (8 [17.4%] of 46 patients) raises the possibility that maximum resection was not always achieved in our study.

When associated with a high risk of disabling neurological deficits, radiographically complete resection is not the objective of glioblastoma resection.[7] To separate the cases in which GTR was considered the optimal outcome from those in which the EOR might have been intentionally limited to reduce the risk of postsurgical morbidity, the resectability of each tumor was judged by 2 experienced neurosurgeons blinded to the objectives of the study. Interestingly, the reviewers agreed about the safety of GTR only 71.7% of the time, suggesting a strong subjective component in the determination of surgical goals. Given the frequency of disagreement between the reviewers, our designation of resectability might have been strengthened by including the opinions of a large number of experts. Nonetheless, the opinions of 2 experts who categorized cases based on resectability enabled us to critically compare the resectability of a tumor with EOR, a quantitative measure of surgical outcome. Furthermore, this analysis enabled a focused examination of the EOR in cases in which GTR was considered safe and feasible.

Among the cases in which the reviewers agreed that GTR could be safely achieved, it was achieved in only 4 of 17 patients. The 5 patients with resectable tumors in whom EOR was less than 90% represent the clearest examples of suboptimal surgical outcomes. In 2 patients with resectable tumors, EOR was below the 78% threshold suggested as the minimal surgical intervention necessary to confer a survival benefit.[18] To our knowledge, our analysis is the first to quantify the relative rarity of optimal surgical outcome in a series of patients with glioblastomas in whom GTR was considered feasible and safe.

Assuming the surgeons caring for the patients with safely resectable tumors were guided by the idea that maximal, safe resection should be performed in patients with glioblastomas, it is surprising that optimal surgical results were not achieved in more patients. Given the technical challenge of judging EOR intraoperatively, we hypothesized that surgeons were limited by their ability to determine when radiographically complete resection had been accomplished. To test this hypothesis, we calcu-

lated the negative predictive value of the surgeon's judgment of completeness of resection. As expected, we observed a negative predictive value of just 30.4%. In other words, the surgeons incorrectly suggested that GTR had been achieved at the time of surgery in 69.6% of cases. Interestingly, a recent volumetric analysis of EOR in a large series of patients with gliomas confirms our observation that GTR is achieved in approximately one-third of cases.[10] Our observation that the surgeon's perception of EOR often differs from the radiographically determined EOR is consistent with several nonvolumetric analyses as well.[1,14]

In our study, we categorized the surgeon's subjective perception of EOR into 2 exclusive classes: GTR and subtotal resection. We acknowledge, however, that the surgeon's perception of EOR is often nuanced. The binary categorization of cases into GTR and subtotal resection may not truly reflect the spirit of the surgeon's intraoperative judgment of the EOR. On the basis of operative notes alone it is not possible to determine the certainty with which a surgeon could categorize a resection as gross total versus subtotal. To gauge the surgeon's ability to judge EOR more finely, it would have been optimal to ask surgeons at the end of each case what percentage of tumor they deemed had been removed and how certain they were about that judgment.

We also acknowledge that determining the EOR from volumetric methods, including the one used in this study, may over- or underestimate the true volume of residual tumor. Due to their infiltrative nature, delineating the boundaries of glioblastomas and calculating their volumes on MRI is notoriously difficult.[6] To limit the subjectivity introduced when segmenting a poorly defined lesion, we used a semiautomated segmentation method similar to ones that have been described in the literature.[8,13,21] However, semiautomated methods of differentiating tumor from normal brain are more effective for well-delineated lesions. Given the variability in the invasiveness of glioblastomas from patient to patient, it is possible that the accuracy of the volumetric method was similarly variable among the cases studied.

Moreover, the use of pre- and postoperative T1-weighted images introduces the possibility of underestimating tumor volume by excluding nonenhancing infiltrative portions of the tumor that are better demonstrated on FLAIR sequences. On the other hand, including regions of largely noninfiltrated normal brain that enhance on postoperative MRI studies due to surgical manipulation may overestimate residual tumor volume. We elected to use contrast-enhanced T1-weighted imaging for our volumetric analysis, primarily to facilitate comparison of our study with other published volumetric analyses of glioblastoma surgery.[18,21]

Kaplan-Meier analysis of our cohort is consistent with the existing evidence linking EOR to survival. As Sanai et al.[18] reported, we observed a stepwise improvement in survival with greater EOR. The survival data reported here, in conjunction with the existing evidence supporting the importance of maximizing EOR to prolong glioblastoma patient survival, support the practice of achieving maximum resection whenever possible.

Given the impact of EOR on survival and the formidable challenge of determining completeness of resection during surgery, our data provide justification for the use of existing technology available for maximizing EOR. Class I evidence supporting the use of iMRI has recently emerged from a randomized controlled trial. Senft et al.[19] achieved GTR in 96% of patients when iMRI was used and in 68% of patients when iMRI was not used. While frameless stereotactic navigation has not been shown to improve EOR,[25] neuronavigation incorporating diffusion-tensor imaging has been shown to more than double the chances of achieving GTR.[27] Magnetic resonance imaging–independent methods for improving EOR have shown success in clinical trials as well. In a landmark Phase III clinical trial, 5-aminolevulinic acid–guided resection was shown to improve EOR and 6-month progression-free survival in patients with malignant gliomas.[21] Improvements in existing technologies for maximizing resection and the emergence of alternative technologies designed to maximize EOR will pave the road toward ensuring more uniform and complete resection for all patients with glioblastomas in the future.

Our ability to generalize the findings of this case series to clinical practice may be limited by the relatively small sample size and selection bias within our cohort. The sample size was compromised by the fact that many patients who underwent surgery for glioblastoma at our institution did not have adequate preoperative and postoperative studies required for volumetric analysis. Postoperative imaging may be performed to evaluate for the presence of resectable residual tumor or to explain the appearance of postoperative neurological deficits. Therefore, neurologically intact patients who are unlikely candidates for reoperation may have been underrepresented in our cohort, representing a possible selection bias. Until recently, it has not been considered standard practice at our institution to obtain routine postoperative MRI studies to evaluate EOR. As comparative imaging becomes more common, it may become feasible to validate our findings with a larger, more representative cohort of patients with glioblastoma.

Conclusions

As EOR has emerged as a predictor of survival in patients with glioblastomas, it becomes necessary to understand the factors that predict surgical outcome. Our data suggest that the ability to achieve maximum EOR may be compromised by tumor-related and technical factors. Given the formidable challenge of clinically evaluating the presence of residual tumor during surgery, the use of technologies designed to improve the chance of achieving maximal safe resection of glioblastomas may be justified.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Sagher, Orringer, Lau. Acquisition of data: Lau, Khatri, Zamora-Berridi, Zhang, Wu.

Analysis and interpretation of data: Sagher, Orringer, Lau, Khatri, Chaudhary. Drafting the article: Orringer, Lau, Khatri. 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: Sagher. Study supervision: Sagher.

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