Title
Perilesional Resection of Glioblastoma Is Independently Associated With Improved Outcomes

Journal
Neurosurgery, 86(1)

ISSN
0148-396X

Authors
Al-Holou, Wajd N
Hodges, Tiffany R
Everson, Richard G
et al.

Publication Date
2020

DOI
10.1093/neuros/nyz008

Peer reviewed

CNS Spotlight

Perilesional Resection of Glioblastoma Is Independently Associated With Improved Outcomes

Wajd N. Al-Holou, MD[*]
Tiffany R. Hodges, MD[†]
Richard G. Everson, MD[†]
Jacob Freeman, MD[†]
Shouhao Zhou, PhD[‡]
Dima Suki, PhD[†]
Ganesh Rao, MD[†]
Sherise D. Ferguson, MD[†]
Amy B. Heimberger, MD[†]
Ian E. McCutcheon, MD[†]
Sujit S. Prabhu, MD[†]
Frederick F. Lang, MD[†]
Jeffrey S. Weinberg, MD[†]
David M. Wildrick, PhD[†]
Raymond Sawaya, MD[†]

[*]Department of Neurosurgery, Wayne State University Medical School, Karmanos Cancer Institute, Detroit, Michigan; [†]Department of Neurosurgery, The University of Texas MD Anderson Cancer Center, Houston, Texas; [‡]Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas

Correspondence:
Raymond Sawaya, MD,
Department of Neurosurgery,
The University of Texas MD Anderson Cancer Center,
1515 Holcombe Blvd., Unit 442,
Houston, TX 77030-4009.
E-mail: rsawaya@mdanderson.org

Received, April 20, 2018.
Accepted, January 22, 2019.
Published Online, February 25, 2019.

BACKGROUND: Resection is a critical component in the initial treatment of glioblastoma (GBM). Often GBMs are resected using an intralesional method. Circumferential perilesional resection of GBMs has been described, but with limited data.

OBJECTIVE: To conduct an observational retrospective analysis to test whether perilesional resection produced a greater extent of resection.

METHODS: We identified all patients with newly diagnosed GBM who underwent resection at our institution from June 1, 1993 to December 31, 2015. Demographics, presenting symptoms, intraoperative data, method of resection (perilesional or intralesional), volumetric imaging data, and postoperative outcomes were obtained. Complete resection (CR) was defined as 100% resection of all contrast-enhancing disease. Univariate analyses employed analysis of variance (ANOVA) and Fisher's exact test. Multivariate analyses used propensity score-weighted multivariate logistic regression.

RESULTS: Newly diagnosed GBMs were resected in 1204 patients, 436 tumors (36%) perilesionally and 766 (64%) intralesionally. Radiographic CR was achieved in 69% of cases. Multivariate analysis demonstrated that perilesional tumor resection was associated with a significantly higher rate of CR than intralesional resection (81% vs 62%, multivariate odds ratio = 2.5, 95% confidence interval: 1.8-3.4, $P < .001$). Among tumors in eloquent cortex, multivariate analysis showed that patients who underwent perilesional resection had a higher rate of CR (79% vs 58%, respectively, $P < .001$) and a lower rate of neurological complications (11% vs 20%, respectively, $P = .018$) than those who underwent intralesional resection.

CONCLUSION: Circumferential perilesional resection of GBM is associated with significantly higher rates of CR and lower rates of neurological complications than intralesional resection, even for tumors arising in eloquent locations. Perilesional resection, when feasible, should be considered as a preferred option.

KEY WORDS: Circumferential dissection, Extent of resection, Glioblastoma, Intralesional resection, Neurological complications, Perilesional

Neurosurgery 86:112–121, 2020 DOI:10.1093/neuros/nyz008 www.neurosurgery-online.com

Currently, the standard-of-care treatment for glioblastoma (GBM) is maximal safe resection followed by temozolomide administration and radiation therapy.[1,2] Although GBM is an infiltrative disease and extends beyond the contrast-enhancing portion of the tumor, the goal of surgery is maximal resection of this enhancing component. The extent of resection correlates with survival, as initially described by Lacroix et al[4] and confirmed by several other studies.[3-6] Nonetheless, aggressive surgical resection must be balanced with the goal of minimizing neurological deficits.

A major tenet of oncological surgery outside the central nervous system is that resections should be conducted using an en bloc "no-touch" technique in which the mass is circumferentially removed without violation of its outer border and often with a margin of normal tissue.[7-13]

ABBREVIATIONS: CI, confidence interval; **CR,** complete resection; **GBM,** glioblastoma; **HR,** hazard ratio; **KPS,** Karnofsky Performance Scale; **OR,** odds ratio; **OS,** overall survival

This method is thought to prevent tumor spillage and to ensure complete removal of tumor cells. Historically, although en bloc resection with margins has not been a major tenet of neurosurgical oncology, recently, en bloc resection has been increasingly explored as a means of improving outcomes in certain pathologies. For example, en bloc resection of brain metastases is associated with decreased rates of recurrence and leptomengingeal disease compared with intralesional resection, wherein the pseudocapsule around the tumor is violated.[14-16] Furthermore, en bloc resection of pituitary adenomas is associated with improved outcomes and has been advocated by Oldfield et al.[17,18] Finally, recent work has also suggested that en bloc resection improves the outcome of patients with many other neurosurgical malignancies, including hemangioblastomas, and spinal tumors such as ependymomas, chordomas, and chondrosarcomas.[19-25]

For GBM, surgeons may remove the tumor in an intralesional fashion, often described as piecemeal, in which the contrast-enhancing portion of the tumor is entered, and the tumor is removed from the center toward the edges. This intralesional approach has been the mainstay of treatment because it is thought to be safer, as eloquent brain surrounding the tumor is approached only after the main mass is removed. In contrast, our group and others have previously described resecting GBMs using a perilesional circumferential dissection.[26,27] However, the safety and efficacy of this approach have not yet been reported. GBM is known to be infiltrative, and thus a true en bloc resection is not possible. However, we reasoned that following these same principles, using a perilesional resection technique to circumferentially dissect the brain–tumor interface would maximize extent of resection without increased neurological morbidity. We tested this hypothesis by analyzing the outcome of patients who underwent resection of treatment-naïve GBMs, comparing the perilesional and intralesional resection techniques.

METHODS

Patient Selection

We identified patients with newly diagnosed GBM who underwent initial resection at our institution from June 1, 1993, to December 31, 2015, from our prospectively collected departmental database. This observational study conforms to the strengthening the reporting of observational studies in epidemiology (STROBE) research reporting guidelines and was conducted under the auspices of an institutional review board-approved protocol. Waivers of informed consent and authorization were granted. Patients were only included if the tumor was newly diagnosed and previously untreated. To reduce bias in selection of a resection technique, we excluded 131 patients whose tumors were located primarily in deep locations or in locations that precluded perilesional resection, including tumors located mainly in the ventricle, thalamus/hypothalamus, insula, or deep within the posterior fossa. Overall, 1204 patients were included in the study.

Most demographic, preoperative, and perioperative clinical data were collected prospectively and entered into our Brain and Spine Center Database. These data included multiple intraoperative parameters, including whether the tumor was removed perilesionally or intralesionally. The remaining data were collected retrospectively. The following data were collected and reviewed: demographic data, preoperative data (including presenting symptoms), Karnofsky Performance Scale (KPS) score, and imaging data (including pre- and postoperative tumor volume using T1- and T2-weighted imaging [based on comparative computerized volumetric analyses of preoperative and postoperative magnetic resonance imaging scans]). For the purpose of analysis, tumor location defined as either within eloquent (located directly in cortex controlling motor, sensory, speech, or visual functions) or noneloquent brain (in noneloquent cortex or near eloquent cortex) was determined based on previous publications from our institution.[28] In addition, we recorded extent of tumor resection, extent of residual tumor, evidence of necrosis, hemorrhage, or cysts, and intraoperative data such as method of resection (perilesional or intralesional), blood loss, and type of anesthesia (either general or with patient awake). The choice of resection technique was determined by the surgeon, and it was classified and recorded in the charts/database prospectively by the surgeon at the end of the operation. We defined complete resection (CR) as 100% resection of all contrast-enhancing tumors. We also quantified postoperative data including neurological complications, seizures, and other complications such as infections and hemorrhages. Postoperative hemorrhages were recorded if they required surgical intervention. A neurological complication was counted if the patient developed new or worsening deficits postoperatively. Neurological complications that lasted beyond 30 d were considered long-term neurological complications. We defined perilesional resection as using a dissection technique in which the interface/pseudoplane between enhancing tumor and brain is identified initially, and then dissected circumferentially until the tumor specimen has been separated, which resulted in a single specimen.

Statistical Methods

The primary outcome studied was CR, and the secondary outcomes were neurological complications, intraoperative blood loss, non-neurological complications, and survival. Univariate analyses used ANOVA for continuous variables and the Fisher exact test for categorical variables. Multivariate analyses were performed using logistic regression. Odds ratios (ORs) with 95% confidence intervals (CIs) were reported. Any missing values were omitted from analysis.

Differences in patients' characteristics are noted in Table 1. We recognized that there is an inherent bias between the tumors that were resected perilesionally vs intralesionally, in that surgeons may have been more reluctant to use the perilesional method for tumors located in eloquent brain regions than for tumors in noneloquent areas. To adjust for this selection bias in choosing perilesional vs intralesional resection techniques, we applied a propensity score weighting method in our analysis.[29] This method aims to balance the baseline covariates to allow for homogenous distribution of the variables between the patient groups who underwent either perilesional or intralesional resection. The propensity scores were calculated on the basis of the projected probability of undergoing perilesional resection, given a patient's baseline characteristics. To estimate the propensity score for each patient, a multivariate logistic regression model was fitted with perilesional resection (yes $= 1$ vs no $= 0$) as the response and the baseline patient characteristics as the model covariates/predictors.

Overall survival time, defined as the time from date of diagnosis to the date of death, was estimated using the Kaplan–Meier method. The log-rank test was employed to determine the difference in survival times between groups. Variables tested in the survival analysis included

TABLE 1. Preoperative Presenting Characteristics of 1204 Patients, 1202 of Whom Underwent Either Perilesional Resection or Intralesional Resection of a Previously Untreated Glioblastoma

	Value			
Characteristic	All patients	Perilesional	Intralesional	*P* value
Total	1204 patients	436 (36%)	766 (64%)	
Median age	59.4 yr	60.5 yr	59.1 yr	NS
Sex				
Male	60%	59%	61%	NS
Female	40%	41%	39%	
Median tumor volume	28.9 cm^3	29.2 cm^3	28.9 cm^3	NS
Location				
Frontal	39%	41%	38%	NS
Temporal	37%	32%	39%	.02
Parietal	18%	18%	18%	NS
Functional location				
Eloquent	40%	34%	43%	.002
Noneloquent	60%	66%	57%	
Tumor characteristic				
Cystic	15%	15%	15%	NS
Necrotic	63%	59%	66%	.04
Hemorrhagic	11%	10%	12%	NS
Preoperative deficits				
All neurological deficits	72%	67%	74%	.01
Motor deficits	34%	30%	37%	.01
Speech deficits	33%	35%	32%	NS
Sensory deficits	16%	11%	19%	<.001
Visual deficits	22%	23%	21%	NS
Preoperative KPS score ≥ 70	92%	95%	91%	.02
Preoperative seizures	30%	27%	32%	NS

KPS, Karnofsky Performance Scale.
Data on resection technique were available in 1202 patients. Results of univariate analysis with *P* values are reported. $P < .05$ was considered significant, NS = not significant.

demographics such as age and sex, resection type, extent of resection, presence of neurological complications, KPS score, and location in eloquent brain. Cox proportional regression with propensity score weighting was applied to estimate hazard ratios (HRs) and their 95% CIs.

Data were analyzed using SPSS version 23.0 software (IBM Inc, Armonk, New York) and statistical software R version 3.3.2 with the packages Matching version 4.8-3.4 and survival version 2.38-1 (R Foundation for Statistical Computing, Vienna, Austria). *P* values of less than or equal to .05 were considered to be statistically significant.

Surgical Technique

Our standard technique involves using intraoperative ultrasound and stereotactic image guidance to identify the cortical margins of the tumor and its subcortical extension. Functional imaging and tractography as well as intraoperative mapping are vital to guiding our dissection and are used to identify surrounding functional tissue, including functional cortex and subcortical white matter. When performing an intralesional resection, the tumor is entered and resected until normal brain is identified visually or by tactile sensation or until functional tissue is identified by functional mapping. However, the brain–tumor interface can be difficult to identify as a result of progressive tissue swelling during the operation and an increase in bleeding surfaces. When performing a perilesional resection, we use the imaging and functional data obtained to perform volumetric and circumferential dissection of the tumor (Figures 1 and 2). The basis for this technique requires following a plane between the tumor and brain to maximize extent of resection and reduce transgression into subcortical white matter, which has been shown to be the most common source of postoperative deficits.[30] Tumors that extend to the cortical surface typically expand a gyrus. Using a transsulcal approach, the sulci that border this gyrus can then be used as the tumor margins for dissection. Otherwise, a transcortical approach can be used to define the tumor margin, especially for subcortical tumors. We use bipolar cautery and suction to dissect the tumor edge along a gliotic pseudoplane, which is often identifiable. Following this dissection pattern allows us to maximize tumor resection by minimizing transgression into the tumor, which also decreases bleeding. Along the edge of gyri, a subpial resection technique preserves the vascular integrity of the adjacent cortex and minimizes subcortical vascular injury. As we circumferentially surround the tumor with minimal brain retraction, we are able to coagulate feeding vessels and avoid vessels en passage. While approaching the deeper portions of the dissection, care is taken to stay on the tumor border. In addition, because the tumor is not "decompressed," computer-assisted surgical guidance is relatively well maintained, allowing for greater correlation at the depths of the dissection.

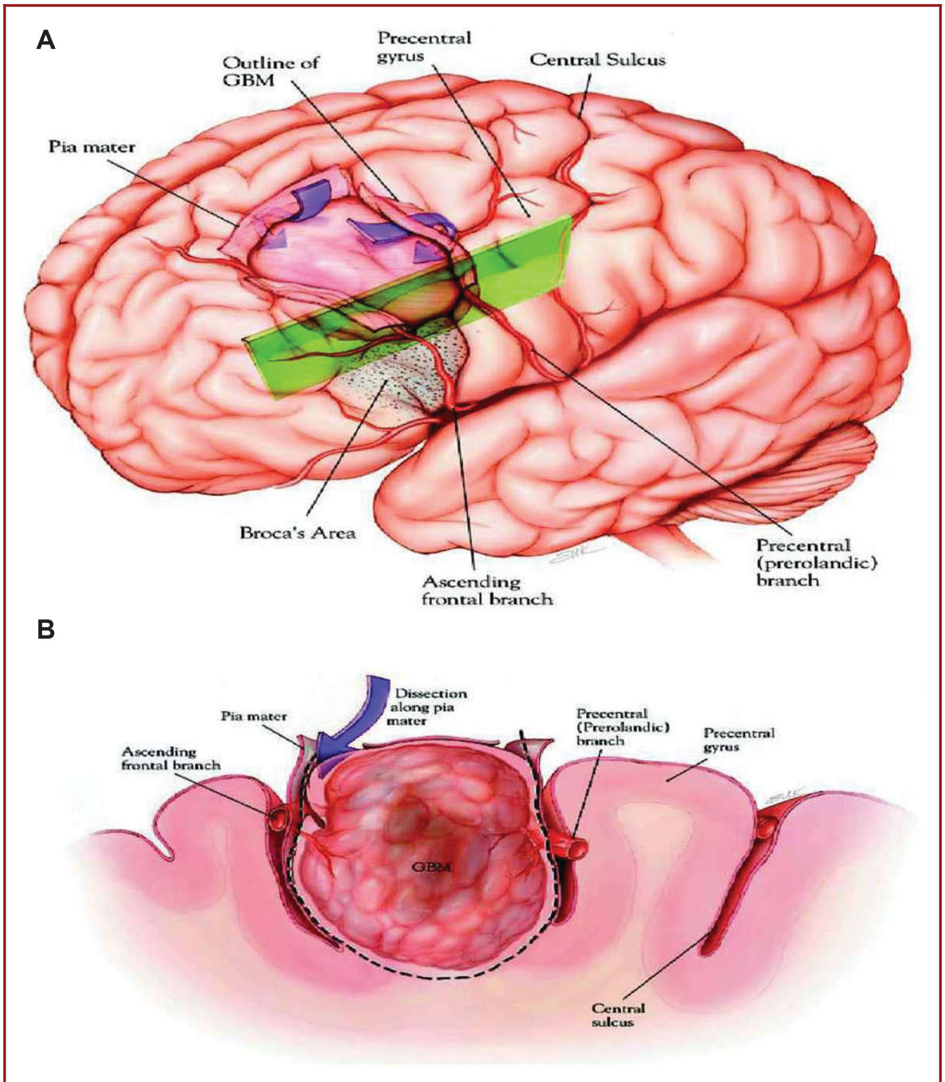

FIGURE 1. *Perilesional technique of GBM resection.* **A**, *A GBM in the left frontal lobe abutting Broca's area is shown. The expanded gyrus is identified, and its surrounding sulci are dissected. A perpendicular section at the level of the green plane in* **A** *is shown in* **B**: *the sulci are split to identify the large arteries, and the feeding vessels are coagulated and cut. After reaching the base of the sulcus, the inferior portion of the tumor is resected along the plane between the solid mass and the infiltrated brain. Reproduced with permission from Hentschel, S. J. and F. F. Lang, Current surgical management of glioblastoma. Cancer J, 2003.* ***9*** *(2): 113-125. (http://ovidsp.tx.ovid.com/sp-3.26.1a/ovidweb.cgi?&S = HKKPFPPKLKDDIGCKNCGKPBIBCBPPAA00&Link + Set = S.sh.22.23.26.29%7c7%7csl_10).*

RESULTS

We identified 1204 patients who met the inclusion criteria and underwent resection for newly diagnosed GBM (Table 1). Data on resection technique were available for 1202 patients. Perilesional resection was performed in 436 cases (36%), whereas 766 tumors (64%) were resected using an intralesional technique. There was no significant difference in median tumor volume between tumors resected perilesionally (29.2 cm^3) and those resected intralesionally (28.9 cm^3).

Degree of Resection

Of the tumors evaluated, 1095 had adequate preoperative and postoperative data recorded to assess degree of resection, and 754 (69%) had a CR with no residual contrast enhancement

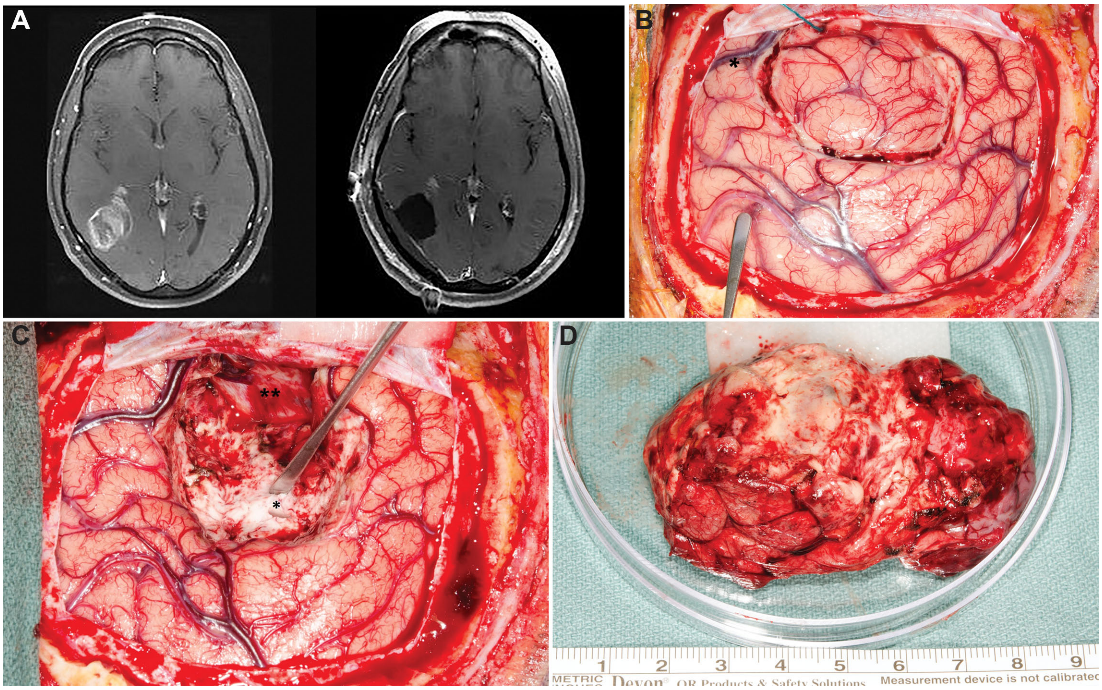

FIGURE 2. **A**, *Perilesional resection of a right temporo-occipital GBM. (Left) Preoperative axial T1-weighted postcontrast MR image. (Right) Postoperative axial T1-weighted postcontrast MR image.* **B**, *Intraoperative image of perilesional resection of the right temporo-occipital GBM shown in Figure 2, depicting craniotomy with inferiorly based dural flap exposing the temporo-occipital region overlying the tumor. The outline of the planned corticectomy can be seen. The Penfield #4 dissector is seen in the lower left (anterior superior) corner of the craniotomy. A large vein of Labbé is seen along the inferior edge of the planned resection (*).* **C**, *Depicts the resection cavity. The Penfield #4 dissector is within the cavity at the edge of a ventricular opening (*). The tentorium is seen in the depths of the cavity (**).* **D**, *Image of the GBM tumor specimen that was resected in a perilesional manner, as described above.*

noted on postoperative T1-weighted imaging (Figure 3). Of the perilesionally resected tumors, a CR was achieved in 81%, whereas only 62% of tumors that were resected in an intralesional fashion had a CR, which was statistically significant ($P < .001$; Table 2). This finding was confirmed with multivariate analysis with adjustment with propensity score weighting to balance for baseline covariates (OR = 2.5, 95% CI: 1.8-3.4, $P < .001$). The only other variable significantly associated with CR was smaller tumor volume (OR = 1.01, 95% CI: 1.01-1.02, $P < .001$).

Postoperative Neurological Complications

Of the 1204 patients included in the study, 155 (13%) patients developed a neurological complication after surgery. Univariate analysis revealed that patients who underwent perilesional resection had a significantly lower neurological complication rate than those who underwent intralesional tumor resection (9% and 15%, respectively, $P = .004$; Figure 4, Table 3). Multivariate analysis showed that perilesional resection continued to be significantly associated with a lower rate of neurological complications ($P = .03$), and eloquent location of the tumor was associated with a higher rate of neurological complications ($P = .02$; Table 4).

Long-Term Neurological Complications

Overall, 1157 patients had adequate clinical follow-up data to assess long-term neurological function. Eight percent of patients developed long-term neurological complications. Perilesional resection was associated with a lower rate of long-term neurological complications than intralesional resection (6% and 9%, respectively), but this was not significant. After multivariate analysis, only eloquent tumor location was significantly associated with long-term neurological complications ($P = .03$; Table 4).

Subgroup Analysis of Tumors in Eloquent Locations

Tumors in eloquent brain were less likely to undergo perilesional resection than tumors in noneloquent locations (31% and 40%, respectively, $P = .002$). Thus, we reasoned that a separate analysis of tumors in eloquent brain would best evaluate the impact of resection technique on outcomes. There was no significant difference in median tumor volume between tumors

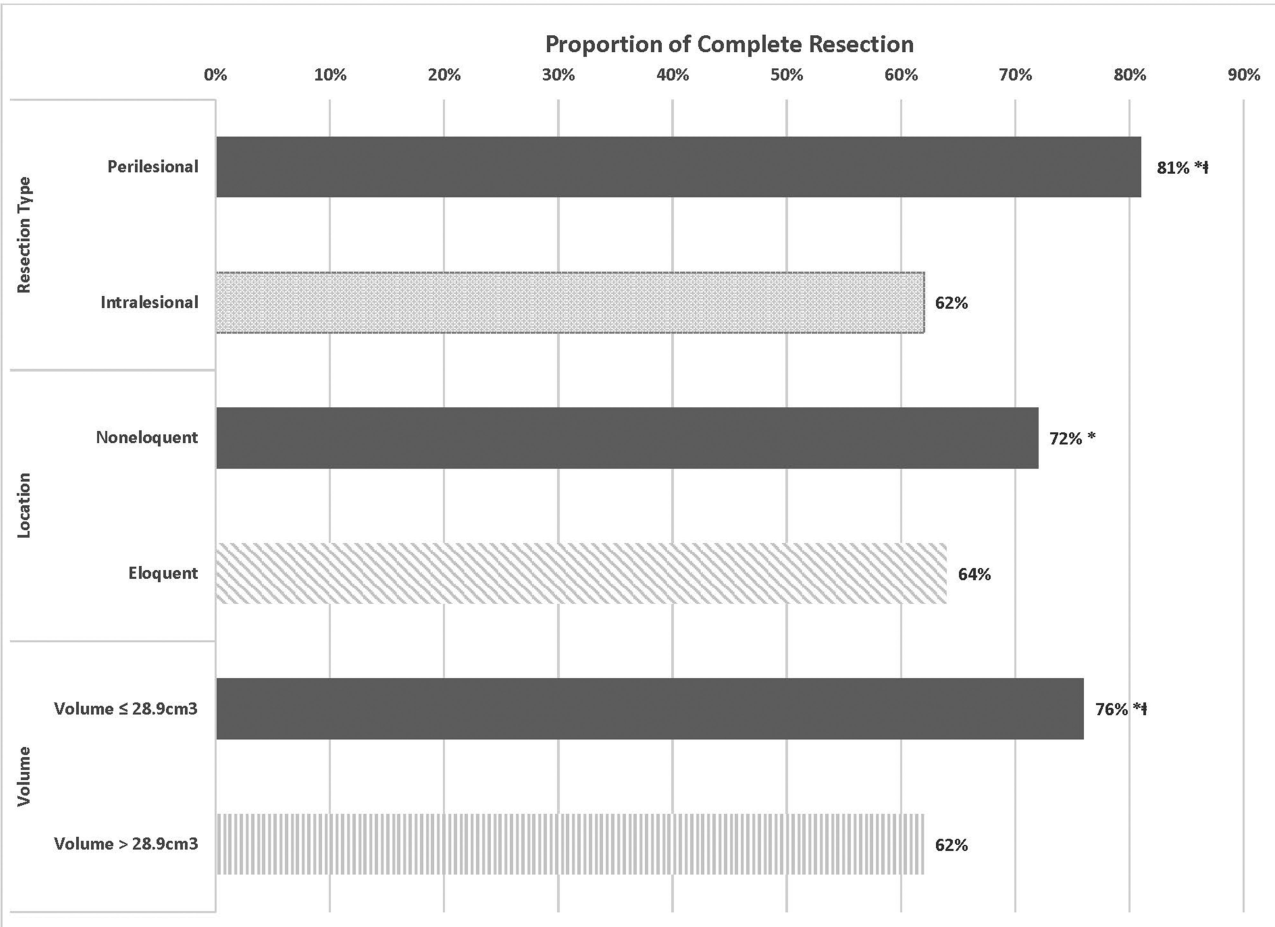

FIGURE 3. *Bar graph depicting the percentage of complete resection for each variable. Tumor volume is dichotomized for the purpose of visualization.* **Statistically significant based on univariate analysis.* *‡Statistically significant based on multivariate analysis.*

resected perilesionally (30.0 cm^3) and those resected intralesionally (31.0 cm^3).

Tumors in eloquent locations were evaluated in 479 patients. CR was attained in 64% of cases. The rate of CR was significantly greater in tumors resected perilesionally than in those resected intralesionally (79% and 58%, respectively; $P < .001$). This was confirmed with multivariate analysis (OR = 2.8, 95% CI: 1.7-4.6, $P < .001$). In this subgroup, 17% of patients had a postoperative neurological complication. Patients who underwent perilesional resection had a lower rate of neurological complications than those who underwent intralesional resection (11% and 20%, respectively), and this was the only significant variable identified based on both univariate and multivariate analyses (OR = 0.5, 95% CI: 0.2-0.9, $P = .02$).

Survival

The median overall survival (OS) time for this patient population was 13.8 mo (95% CI: 1.09-1.21). Patients who underwent perilesional resection had a longer median OS time (14.3 mo) than those who underwent intralesional resection (13.4 mo, HR = 0.89, 95% CI: 0.813-0.974, $P = .01$). Longer OS was also associated with CR (HR = 0.626, 95% CI: 0.565-0.683, $P < .001$), younger age (HR = 0.974, 95% CI: 0.968-0.976, $P < .001$), and a preoperative KPS score ≥ 70 (HR = 0.842, 95% CI 0.714-0.992, $P = .04$). The positive effect of perilesional resection was not significant ($P = .25$) when CR was included in the model, indicating that CR was more important to survival than resection technique. We also found similar results with comparable estimated HRs when subgroup analyses were performed for eloquent and noneloquent patients.

Other Surgical Outcomes

The mean intraoperative blood loss was 222 mL. After multivariate analysis, perilesional resection was the only factor associated with lower intraoperative blood loss (170 vs 251 mL for intralesional resection, $P < .001$). The overall postoperative

TABLE 2. Results of Univariate and Multivariate Analyses Evaluating Variables Associated With Complete Resection of a Previously Untreated Glioblastoma

	Univariate *P*-value	Multivariate *P*-value	Multivariate odds ratio (95% CI)
Age	.7		
Sex	.16	.1	0.8(0.6-1.1)
Perilesional resection	<.001	<.001	2.5(1.8-3.4)
Preoperative volume	<.001	<.001	1.01(1.01-1.02)
Eloquent location	.01	.24	0.8(0.6-1.1)
Preoperative neurological deficits	.11	.5	0.9(0.6-1.3)
Left-sided	.09	.06	0.7(0.5-1.01)
Preoperative KPS score ≥ 70	<.001	.1	1.7(0.9-3.3)
Location-frontal	.6		
Location-temporal	.3		

KPS, Karnofsky Performance Scale.
Odds ratios with 95% confidence intervals (CI) are reported. $P < .05$ was considered significant.

intracranial hemorrhage rate was 1.8%. The most common type of hemorrhage identified was intraparenchymal hemorrhage, which was identified in 0.9% of patients. CR was the only variable associated with a lower rate of intraparenchymal hemorrhage, after multivariate analysis ($P = .04$).

DISCUSSION

In the largest study to date evaluating circumferential perilesional resection for newly diagnosed GBM, we showed that perilesional resection is associated with a higher rate of CR of the contrast-enhancing disease along with decreased postoperative neurological morbidity. Furthermore, we showed that perilesional resection is safe and feasible in eloquent locations and is also associated with a lower rate of neurological complications. We believe this to be the largest study discussing the advantages of perilesional-style resection.

In many non-neurological systemic malignancies, en bloc resection using a "no-touch" technique is often standard and is associated with improved outcomes, and en bloc techniques are known to improve outcomes in many neurosurgical malignancies.[7-22,24,25,31,32] Many neurosurgeons resect GBMs from the center toward the edges in an intralesional/piecemeal fashion. Although GBM is an infiltrative tumor, thus making an authentic en bloc resection infeasible, we are proponents of performing a circumferential dissection in the gliotic plane surrounding the contrast-enhancing portion of GBMs, resulting in a circumferential perilesional resection. In addition, because the tumor is not "decompressed" during the dissection, computer-assisted image guidance is relatively well maintained throughout the procedure.[33] Although similar resection techniques have been described by many groups including our own,[26,27,33-35] data are sparse regarding patient outcomes. The only study describing patient outcomes with this technique evaluated a small patient population of 34 patients and found it to be associated with improved survival.[35]

Although GBM is an infiltrative disease and often contains contrast-enhancing and nonenhancing components,[36] the typical goal of surgery is maximal safe resection of the contrast-enhancing portion, and perilesional resection would facilitate these goals. In fact, our data show that perilesional resection was the only controllable variable significantly associated with a higher rate of CR.

We recognized that there may be a selection bias when choosing the perilesional technique. We were concerned that as a result of this bias, smaller tumors in noneloquent regions were more likely to be resected using perilesional resection. Yet we found that tumor size was similar in the 2 groups. We did find that a smaller percentage of tumors located in eloquent brain were resected using the perilesional technique. Thus, we performed an analysis evaluating only tumors in eloquent locations. Nevertheless, in this subgroup, perilesional technique was associated with a significantly higher rate of CR and a lower rate of neurological complications after multivariate analysis.

We found less difference in comparing resection techniques when evaluating long-term neurological complications. Perilesional resection was associated with lower rates of long-term neurological complications, but this was not significant. Thus, the difference between the resection techniques was most profound in short-term complications. This could be a result of a reduced frequency of complications for comparison. Regardless, these shorter-term neurological deficits can still result in major detriment to the quality of life and are associated with decreased survival time. Rahman et al[37] found that patients with new or worsened postoperative neurological deficits had significantly worse survival than those who lacked such deficits (9.2 and 14.7 mo, respectively), and importantly, this difference remained even in patients in whom the deficits improved at follow-up visits. McGirt et al[38] evaluated the presence of deficits at patient discharge, and found that the 2-yr survival rate for patients without surgically acquired deficits was 23% but was 0% and 8% for patients with speech or motor deficits, respectively.

Notably, we found that perilesional resection was significantly associated with a lower intraoperative blood loss. Anecdotally, in some cases when tumors are resected in an intralesional fashion, bleeding can be substantial and often does not abate until the tumor is completely resected. This issue is often avoided when a perilesional approach is employed. Furthermore, a CR was significantly associated with a lower rate of postoperative intraparenchymal hemorrhages. It is likely that residual tumor burden continues to be a source for potential hemorrhage.

Aggressive surgical resection must be balanced with the goal of minimizing neurological deficits. Any mechanism to decrease

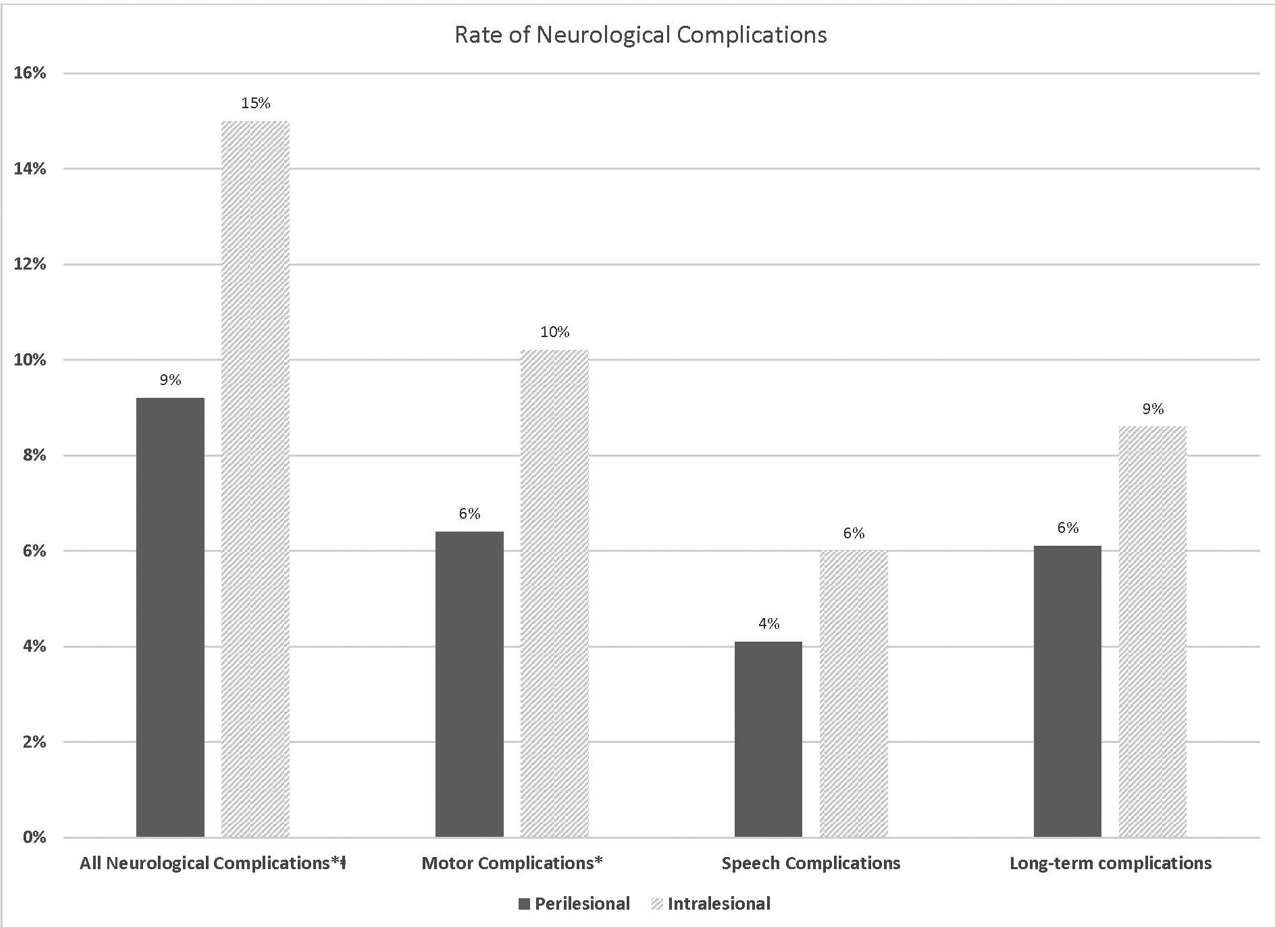

FIGURE 4. *The percentages of all neurological complications and specific subtypes are shown for the 2 resection techniques (perilesional and intralesional). * Statistically significant based on univariate analysis. ‡Statistically significant based on multivariate analysis. P < .05 was considered significant.*

deficits should be attempted.[39-43] We urge surgeons to contemplate the risks of neurological deficits before proceeding with aggressive resections, and to attempt any means to improve neurological outcomes. We routinely perform mapping when resecting tumors in or near eloquent regions.

Limitations

This study has several limitations. This is a retrospective review at a single institution, although most data were collected prospectively. There may be selection bias in the choice of using perilesional resection, as surgeons may limit its use in eloquent locations, but we tried to mitigate this bias by using a propensity score weighting method and by performing a subgroup analysis focusing on tumors in eloquent locations alone. Although a randomized trial might be the most definitive way to address this question, it is impractical, or unlikely to be successfully conducted.

CONCLUSION

Maximal safe resection has been shown to improve patient survival, but this must be balanced with minimizing neurological deficits. Surgeons should consider options that may improve the outcomes of our patients. Using the circumferential perilesional resection technique is significantly associated with higher rates of CR of GBM and a lower rate of neurological complications. Furthermore, in eloquent areas of the brain, the perilesional technique was safe and feasible and in fact, was also associated with a greater extent of resection and lower rates of neurological complications than intralesional resection. Perilesional resection

TABLE 3. The Proportions of All Postoperative Neurological Complications in Relation to Clinical Variables Potentially Affecting Morbidity in Patients Who Underwent Resection of a Previously Untreated Glioblastoma

Variable	Presence of postoperative neurological complications: Yes	No	Univariate analysis: *P* value
Overall	13%	87%	
Resection method			
Perilesional	9%	91%	.004
Intralesional	15%	85%	
Location			
Eloquent	17%	83%	<.001
Other	10%	90%	
Extent of resection			
Complete	12%	88%	.052
Incomplete	16%	84%	
Presence of preoperative deficits			
Preoperative deficit	14%	86%	.04
No deficit	10%	90%	
Tumor cyst presence			
Cyst	8%	92%	.02
No cyst	14%	86%	

Results of univariate analyses with *P* values are shown. $P < .05$ was considered significant, NS = not significant.

TABLE 4. Results of Multivariate Analysis Evaluating Postoperative Neurological Complications in Patients Who Underwent Resection of a Previously Untreated Glioblastoma

	Odds ratio (95% CI)	*P* value
All neurological complications		
Perilesional resection	0.6 (0.4-0.9)	.03
Eloquent location	1.7 (1.1-2.5)	.02
Long-term neurological complications		
Eloquent location	1.8 (1.04-3.2)	.03

Odds ratios with 95% confidence intervals (CI) are reported. $P < .05$ was considered significant.

of a GBM, when feasible, should be considered as a preferred option.

Disclosures

The database utilized for this study was supported, in part, by the Anne C. Brooks/Anthony Bullock III Distinguished Chair in Neurosurgery fund, awarded to Dr Raymond Sawaya. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol*. 2009;10(5):459-466.
2. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
3. Brown TJ, Brennan MC, Li M, et al. Association of the extent of resection with survival in glioblastoma. *JAMA Oncol*. 2016;2(11):1460-1469.
4. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95(2):190-198.
5. Li YM, Suki D, Hess K, Sawaya R. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? *J Neurosurg*. 2016;124(4):977-988.
6. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg*. 2011;115(1):3-8.
7. Altorki N, Skinner D. Should en bloc esophagectomy be the standard of care for esophageal carcinoma? *Ann Surg*. 2001;234(5):581-587.
8. Fengler SA, Pearl RK. Technical considerations in the surgical treatment of colon and rectal cancer. *Semin Surg Oncol*. 1994;10(3):200-207.
9. Nelson H, Petrelli N, Carlin A, et al. Guidelines 2000 for colon and rectal cancer surgery. *J Natl Cancer Inst*. 2001;93(8):583-596.
10. Neuhaus P, Thelen A, Jonas S, et al. Oncological superiority of hilar en bloc resection for the treatment of hilar cholangiocarcinoma. *Ann Surg Oncol*. 2012;19(5):1602-1608.
11. Nogueras JJ, Jagelman DG. Principles of surgical resection. Influence of surgical technique on treatment outcome. *Surg Clin North Am*. 1993;73(1):103-116.
12. Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic review of pelvic exenteration with en bloc sacrectomy for recurrent rectal adenocarcinoma: R0 resection predicts disease-free survival. *Dis Colon Rectum*. 2017;60(3):346-352.
13. Tamoto E, Hirano S, Tsuchikawa T, et al. Portal vein resection using the no-touch technique with a hepatectomy for hilar cholangiocarcinoma. *HPB (Oxford)*. 2014;16(1):56-61.
14. Patel AJ, Suki D, Hatiboglu MA, et al. Factors influencing the risk of local recurrence after resection of a single brain metastasis. *J Neurosurg*. 2010;113(2):181-189.
15. Patel AJ, Suki D, Hatiboglu MA, Rao VY, Fox BD, Sawaya R. Impact of surgical methodology on the complication rate and functional outcome of patients with a single brain metastasis. *J Neurosurg*. 2015;122(5):1132-1143.
16. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg*. 2008;108(2):248-257.
17. Jagannathan J, Smith R, DeVroom HL, et al. Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. *J Neurosurg*. 2009;111(3):531-539.
18. Oldfield EH, Vortmeyer AO. Development of a histological pseudocapsule and its use as a surgical capsule in the excision of pituitary tumors. *J Neurosurg*. 2006;104(1):7-19.
19. Abdulaziz M, Mallory GW, Bydon M, et al. Outcomes following myxopapillary ependymoma resection: the importance of capsule integrity. *Neurosurg Focus*. 2015;39(2):E8.
20. Hanbali F, Fourney DR, Marmor E, et al. Spinal cord ependymoma: radical surgical resection and outcome. *Neurosurgery*. 2002;51(5):1162-1174; discussion 1172-1174.
21. Hsieh PC, Xu R, Sciubba DM, et al. Long-term clinical outcomes following en bloc resections for sacral chordomas and chondrosarcomas: a series of twenty consecutive patients. *Spine (Phila Pa 1976)*. 2009;34(20):2233-2239.
22. Nakamura M, Ishii K, Watanabe K, et al. Long-term surgical outcomes for myxopapillary ependymomas of the cauda equina. *Spine (Phila Pa 1976)*. 2009;34(21):E756-E760.
23. Rachinger J, Buslei R, Prell J, Strauss C. Solid haemangioblastomas of the CNS: a review of 17 consecutive cases. *Neurosurg Rev*. 2009;32(1):37-48; discussion 47-48.
24. Varga PP, Szoverfi Z, Fisher CG, et al. Surgical treatment of sacral chordoma: prognostic variables for local recurrence and overall survival. *Eur Spine J*. 2015;24(5):1092-1101.

25. Zhou LF, Du G, Mao Y, Zhang R. Diagnosis and surgical treatment of brainstem hemangioblastomas. *Surg Neurol*. 2005;63(4):307-316; discussion 315-316.
26. Hentschel SJ, Lang FF. Current surgical management of glioblastoma. *Cancer J*. 2003;9(2):113-125.
27. Toms SA, Ferson DZ, Sawaya R. Basic surgical techniques in the resection of malignant gliomas. *J Neurooncol*. 1999;42(3):215-226.
28. Sawaya R, Hammoud M, Schoppa D, et al. Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. *Neurosurgery*. 1998;42(5):1044-1056; discussion 1055-1056.
29. Gelman A, Hill J. *Data Analysis Using Regression and Multilevel/Hierarchical Models*. Cambridge, NY: Cambridge University Press; 2007.
30. Trinh VT, Fahim DK, Shah K, et al. Subcortical injury is an independent predictor of worsening neurological deficits following awake craniotomy procedures. *Neurosurgery*. 2013;72(2):160-169.
31. Yoo H, Kim YZ, Nam BH, et al. Reduced local recurrence of a single brain metastasis through microscopic total resection. *J Neurosurg*. 2009;110(4):730-736.
32. Kim EH, Ku CR, Lee EJ, Kim SH. Extracapsular en bloc resection in pituitary adenoma surgery. *Pituitary*. 2015;18(3):397-404.
33. Germano IM. *Advanced Techniques in Image-Guided Brain and Spine Surgery*. New York: Thieme; 2002.
34. Hebb AO, Yang T, Silbergeld DL. The sub-pial resection technique for intrinsic tumor surgery. *Surg Neurol Int*. 2011;2(1):180.
35. Mangiola A, Maira G, De Bonis P, et al. Glioblastoma multiforme in the elderly: a therapeutic challenge. *J Neurooncol*. 2006;76(2):159-163.
36. Silbergeld DL, Chicoine MR. Isolation and characterization of human malignant glioma cells from histologically normal brain. *J Neurosurg*. 1997;86(3):525-531.
37. Rahman M, Abbatematteo J, De Leo EK, et al. The effects of new or worsened postoperative neurological deficits on survival of patients with glioblastoma. *J Neurosurg*. 2017;127(1):123-131.
38. McGirt MJ, Mukherjee D, Chaichana KL, Than KD, Weingart JD, Quinones-Hinojosa A. Association of surgically acquired motor and language deficits on overall survival after resection of glioblastoma multiforme. *Neurosurgery*. 2009;65(3):463-470; discussion 469-470.
39. Brown T, Shah AH, Bregy A, et al. A wake craniotomy for brain tumor resection: the rule rather than the exception? *J Neurosurg Anesthesiol*. 2013;25(3):240-247.
40. Sacko O, Lauwers-Cances V, Brauge D, Sesay M, Brenner A, Roux FE. Awake craniotomy vs surgery under general anesthesia for resection of supratentorial lesions. *Neurosurgery*. 2011;68(5):1192-1199; discussion 1198-1199.
41. De Benedictis A, Moritz-Gasser S, Duffau H. Awake mapping optimizes the extent of resection for low-grade gliomas in eloquent areas. *Neurosurgery*. 2010;66(6):1074-1084; discussion 1084.
42. Hervey-Jumper SL, Berger MS. Maximizing safe resection of low- and high-grade glioma. *J Neurooncol*. 2016;130(2):269-282.
43. Hervey-Jumper SL, Li J, Lau D, et al. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. *J Neurosurg*. 2015;123(2):325-339.

Video Abstract: Summary Video of Perilesional Resection of Glioblastoma Is Independently Associated With Improved Outcomes.

COMMENTS

The authors present a large series of patients with newly diagnosed GBM who were treated with intralesional or perilesional approaches. The hypothesis of this study was that although GBM is an infiltrative tumor, a pseudo "en bloc" approach can improve extent of resection and be safely performed. This approach has been previously reported by multiple groups but long-term follow-up data on a large cohort makes this study unique. The data suggests that this type of approach results in improved rate of complete removal, less blood loss, and no more morbidity than the usual school of intralesional debulking. This study is well-powered and the outcomes are not unexpected. Perilesional resection allows the surgeon to obtain a maximal or in some cases supramaximal resection which results in improved survival, albeit a marginal benefit in terms of total months. I think the authors have done a nice job of excluding deep lesions so that the groups are comparable. Despite this, there will be inherent biases in selection because not all tumors adjacent or within eloquent regions are equal, but I think given the large number of patients included in the study this limitation is acceptable. The authors themselves have certainly alluded to this in the limitation section. I personally subscribe to aggressive surgery for GBM but it is important to remember that this strategy has been tried and abandoned with other solid cancers exactly for the reason that cancer is not, at its most fundamental core, a purely surgical disease, but rather a systemic disease that requires systemic therapy for ultimate "cure". Certainly, the reported strategy by the authors results in a more complete gross resection but a word of caution to the overly zealous young or inexperienced surgeon is warranted in the discussion.

M. Yashar S. Kalani
Charlottesville, Virginia

The authors present a large cohort of glioblastoma patients to determine if extent of resection and other measures of patient outcome are improved using a perilesional resection versus an intralesional technique for resection of the tumor. The major limitation of this work is the obvious selection bias inherent in this retrospective study. Some tumors are more amenable to an en bloc resection while other lesions require an intralesional approach. This work adds to the growing body of literature supporting the importance of extent of resection in the outcomes of patients with gliomas. Nevertheless, it is important to remember that increasing resection volume at the expense of causing a new, permanent neurological deficit nullifies all of the survival benefits to the patient.

Randy L. Jensen
Salt Lake City, Utah