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Extent of Surgical Resection is Independently Associated with Survival in Patients with Hemispheric Infiltrating Low-grade Gliomas

OBJECTIVE: It remains unknown whether the extent of surgical resection affects survival or disease progression in patients with supratentorial low-grade gliomas.

METHODS: We conducted a retrospective cohort study (n = 170) between 1996 and 2007 at a single institution to determine whether increasing extent of surgical resection was associated with improved progression-free survival (PFS) and overall survival (OS). Surgical resection of gliomas defined as gross total resection (GTR) (complete resection of the preoperative fluid-attenuated inversion recovery signal abnormality), near total resection (NTR) (<3-mm thin residual fluid-attenuated inversion recovery signal abnormality around the rim of the resection cavity only), or subtotal resection (STR) (residual nodular fluid-attenuated inversion recovery signal abnormality) based on magnetic resonance imaging performed less than 48 hours after surgery. Our main outcome measures were OS, PFS, and malignant degeneration-free survival (conversion to high-grade glioma).

RESULTS: One hundred thirty-two primary and 38 revision resections were performed for low-grade astrocytomas (n = 93) or oligodendrogliomas (n = 77). GTR, NTR, and STR were achieved in 65 (38%), 39 (23%), and 66 (39%) cases, respectively. GTR versus STR was independently associated with increased OS (hazard ratio, 0.36; 95% confidence interval, 0.16–0.84; $P = 0.017$) and PFS (HR, 0.56; 95% confidence interval, 0.32–0.98; $P = 0.043$) and a trend of increased malignant degeneration-free survival (hazard ratio, 0.46; 95% confidence interval, 0.20–1.03; $P = 0.060$). NTR versus STR was not independently associated with improved OS, PFS, or malignant degeneration-free survival. Five-year OS after GTR, NTR, and STR was 95, 80, 70%, respectively, and 10-year OS was 76, 57, and 49%, respectively. After GTR, NTR, and STR, median time to tumor progression was 7.0, 4.0, and 3.5 years, respectively. Median time to malignant degeneration after GTR, NTR, and STR was 12.5, 5.8, and 7 years, respectively.

CONCLUSION: GTR was associated with a delay in tumor progression and malignant degeneration as well as improved OS independent of age, degree of disability, histological subtype, or revision versus primary resection. GTR should be safely attempted when not limited by eloquent cortex.

KEY WORDS: Astrocytoma, Extent of resection, Low-grade, Survival

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Intracranial hemispheric low-grade gliomas have a more favorable prognosis than their malignant counterparts. The median survival for patients with low-grade gliomas is between 5 and 10 years (9, 11, 16, 19, 22, 28), whereas the median survival for patients with glioblastomas is approximately 1 year (42). Despite long-term survival in many patients,

ABBREVIATIONS: CI, confidence interval; **FLAIR**, fluid-attenuated inversion recovery; **GTR**, gross total resection; **HR**, hazard ratio; **KPS**, Karnofsky Performance Scale; **LOH**, loss of heterozygosity; **MFS**, malignant degeneration-free survival; **MRI**, magnetic resonance imaging; **NTR**, near total resection; **OS**, overall survival; **PFS**, progression-free survival; **SD**, standard deviation; **STR**, subtotal resection; **WHO**, World Health Organization

50 to 75% of patients with low-grade gliomas eventually die as a result of either progression of low-grade tumor or degeneration to a malignant glioma (19). Unlike high-grade gliomas, little is known about the factors that may predict survival in patients with low-grade gliomas. An understanding of prognostic factors may help guide treatment paradigms and therapeutic strategies aimed at prolonging survival. Among several perioperative risk factors, only age and histology have generally been accepted as prognostic factors for patients with low-grade gliomas (6, 16, 17, 19).

For many solid organ tumors, gross total resection (GTR) with clear margins is associated with extended survival (14, 45). However, the effects of extensive resection on prolonging survival for patients with low-grade gliomas is less clear (26). In a recent literature review, Pouratian et al. (31) highlighted the inconsistent results of previous studies examining the effect of surgical resection of survival with low-grade gliomas. Evidence suggests that more aggressive resection is beneficial for pediatric patients; however, the benefit of extensive resection in adults is less clear (10, 30). Extensive resection of low-grade gliomas is made difficult because these tumors often involve eloquent areas (1), and margins between tumor and brain are often difficult to discern (24). Improvements in surgical adjuncts including intraoperative navigation (33), functional magnetic resonance imaging (MRI) (2, 29), cortical mapping (13, 35, 44), and intraoperative MRI (25) have been introduced at many centers to help achieve more extensive resection when possible. Nevertheless, it is not known whether extensive resection of low-grade gliomas affects survival or progression in adults. It remains difficult for the surgeon to weigh the increased risk of neurological deficit associated with more extensive surgical resection with an unknown survival advantage. We set out to determine whether the extent of surgical resection was associated with survival in our institutional experience with low-grade gliomas.

PATIENTS AND METHODS

Patient Selection

This retrospective cohort study was approved by the Johns Hopkins Institutional Review Board. We retrospectively identified all patients who underwent surgical resection for low-grade infiltrative astrocytomas or oligodendrogliomas at a single academic institution from 1996 to 2007. All cases were treated by 1 of 4 full-time faculty members. Presenting clinical, radiological, operative, and hospital course records were reviewed retrospectively. Outpatient clinic notes from both neurosurgical and neuro-oncology follow-up visits were reviewed and available for all patients. Tumor grade was histologically confirmed as World Health Organization (WHO) Grade II in all cases based on the WHO criteria (23). Low-grade oligodendrogliomas versus astrocytomas were identified by a single neuropathologist (PCB) for 150 (90%) cases reviewed in this study. The remaining cases (10%) were reviewed by 1 of 3 neuropathologists. Diagnosis of an oligodendroglioma was based on morphological characteristics; therefore, 1p19q status was assessed in the minority of specimens (3, 20). Only 3 cases diagnosed as oligodendrogliomas based on classic morphology failed to demonstrate 1p19q loss of heterozygosity (LOH).

Assessment, Treatment, and Outcome Measures

Intraoperative frameless neuronavigation was used in all cases after 2001. Awake mapping and intraoperative MRI were not used. The standard treatment paradigm for low-grade gliomas during the review period was to surgically excise and reserve external beam radiation therapy or chemotherapy for recurrence or high-grade transformation. During the reviewed time period, 18 patients deviated from our standard practice and received subtotal resection (STR) and adjuvant radiation therapy or chemotherapy immediately after surgery. These patients were not included in this analysis.

Tumor characteristics and extent of resection were assessed at the time of surgery by a neuroradiologist based on comparison of pre- and postoperative MRI scans obtained less than 48 hours after surgery. Preoperative fluid-attenuated inversion recovery (FLAIR) signal abnormality was used as a comparison to determine the extent of resection. Degree of resection was classified retrospectively from the neuroradiologist's report as: 1) GTR (complete resection of the preoperative FLAIR signal abnormality as seen from axial, coronal, or sagittal images); 2) near total resection (NTR) (thin residual FLAIR signal abnormality, 3 mm or less in thickness, around the rim of the resection cavity only as seen from axial, coronal, or sagittal images); or 3) STR (residual nodular FLAIR signal abnormality as seen from axial, coronal, or sagittal images) (Fig. 1). On postoperative MRI, increased signal observed within the cavity (postresection products) or within the brain extending into areas that were null of FLAIR signal on preoperative MRI studies (likely edema) was not considered indicative of residual tumor. The largest diameter measured from the preoperative FLAIR signal abnormality was used as a marker of tumor size.

Three outcome measures were assessed and defined as reported previously (38): overall survival (OS), progression-free survival (PFS), and malignant degeneration-free survival (MFS). OS was defined as the time from surgery to death. PFS was defined as the time from surgery to increase in tumor size on follow-up imaging or malignant degeneration. MFS was defined as the time from surgery to demonstration of gadolinium enhancement on follow-up imaging and/or WHO Grade III or IV tumor on subsequent biopsy. Patients with no known progression/malignant degeneration or death were censored as of their last clinical follow-up date.

Statistical Analysis

Parametric data were expressed as mean ± standard deviation and compared using the Student's *t* test. Nonparametric data were expressed as median and interquartile range and compared using the Mann-Whitney *U* test. The estimated Kaplan-Meier method was used to estimate OS, PFS, and MFS (15). Patients lost to follow-up were "censored" at the time of their last clinic visit. OS, PFS, and MFS were compared between GTR versus STR and NTR versus STR using multivariate proportional-hazards regression analysis (Cox model) (7) after adjusting for age, Karnofsky Performance Scale (KPS) status, tumor subtype (oligodendroglioma versus astrocytoma), mean tumor diameter, and primary versus revision resection.

RESULTS

Patient Population

Craniotomy was performed for hemispheric low-grade gliomas in 170 cases (132 primary resections and 38 revision resections). Patient characteristics are listed in Table 1. Median time from symptom onset to surgery was 0.26 years (range,

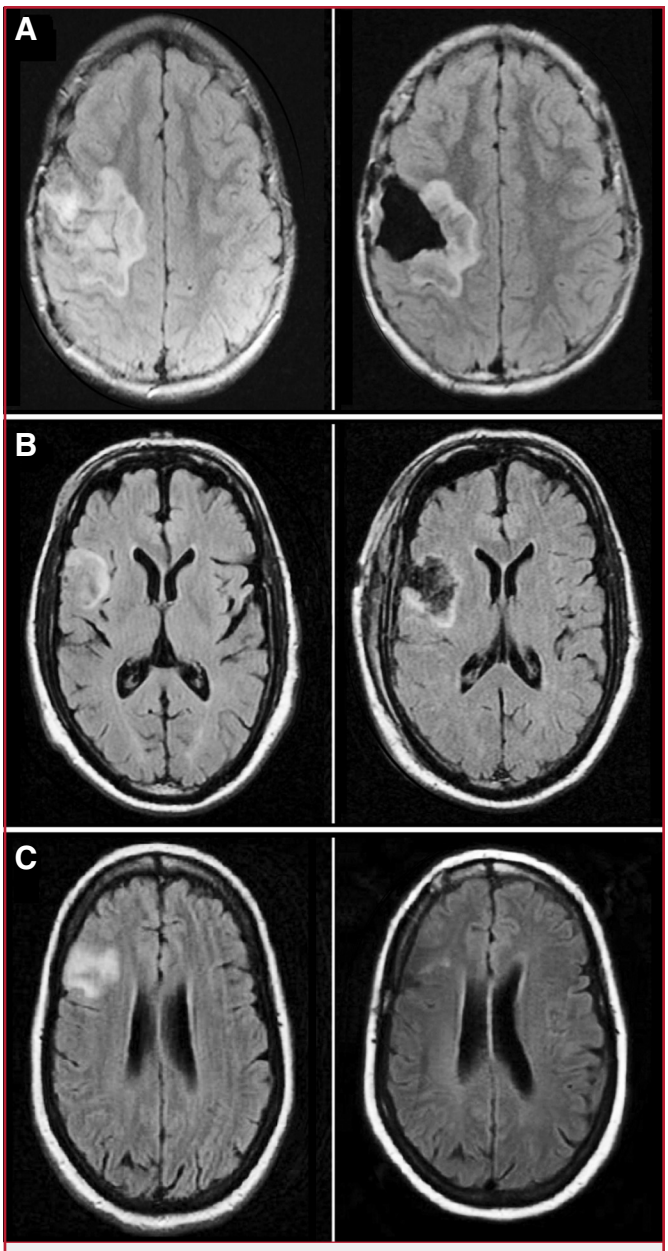


FIGURE 1. *Pre- and postoperative axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) scans in patients who underwent resection of Grade II fibrillary astrocytomas.* **A**, *depiction of subtotal resection (STR) with residual nodular FLAIR signal abnormality.* **B**, *near total resection (NTR) with a thin rim of residual FLAIR signal abnormality around the resection cavity only. A small amount of postsurgical contents can be seen within the posterior aspect of the resection cavity as a slightly elevated FLAIR signal, but it was not continuous with residual tumor FLAIR abnormality. Signal change resulting from retraction edema, postsurgical intracavitary contents, and residual tumor can be difficult to differentiate.* **C**, *gross total resection (GTR) with complete resection of the preoperative FLAIR signal abnormality. The very small degree of FLAIR signal on the postoperative MRI scan does not correspond to the preoperative tumor margin and was felt to represent retraction edema.*

0.1–8.3 years). Overall, GTR, NTR, and STR were achieved in 65 (38%), 39 (23%), and 66 (39%) cases, respectively. GTR was achieved in 53 (40%) primary resections and 12 (32%) revision resections. Revision resections were performed at a mean ± standard deviation of 48 ± 29 months after primary resection. A permanent surgically acquired neurological deficit occurred in 11 (6%) cases, and a transient deficit returning to baseline within 1 month postoperatively occurred in 8 (5%) cases. The incidence of a permanent surgically acquired deficit was similar for GTR (7.5%), NTR (5%), and STR (6%) (Table 1). Surgical-site infection occurred in 1 case (0.7%). There was no operative mortality. Thirty-four (20%) patients died during the follow-up period. The remaining patients were followed for a median of 4 years (interquartile range, 1.5–7.2 years; range, 1 month–12.5 years). Two- and 4-year follow-up was achieved in 73 and 50% of patients, respectively. Eight-year follow-up was achieved in 23% of patients.

Progression and malignant degeneration were identified in 70 (42%) and 40 (24%) cases, respectively. For all patients, median time to progression was 4.6 years and median time to malignant degeneration was 8.8 years. Median OS was 12 years.

Degree of Resection and Outcome

After adjusting for the effects of age, KPS status, histological subtype (astrocytoma versus oligodendroglioma), preoperative tumor diameter, and primary versus revision surgery, GTR versus STR was associated with improved OS (hazard ratio [HR], 0.36; 95% confidence interval [CI], 0.16–0.84; $P = 0.017$) (Fig. 2A; Table 2). An OS benefit was not observed with NTR versus STR ($P = 0.632$). Decreasing age, increasing KPS status, and oligodendroglioma versus astrocytoma were also independently associated with improved OS (Table 3). Five-year OS after GTR, NTR, and STR was 95, 80, and 70%, respectively; and 10-year OS was 76, 57, and 49%, respectively. Stratified by histological subtype, GTR versus STR was associated with improved OS for both astrocytomas (HR, 0.46; 95% CI, 0.17–0.99; $P = 0.049$) and oligodendrogliomas (HR, 0.42; 95% CI, 0.20–0.93; $P = 0.032$).

After adjusting for the effects of age, KPS status, histological subtype, tumor diameter, and primary versus revision surgery, GTR versus STR was independently associated with improved PFS (HR, 0.56; 95% CI, 0.32–0.98; $P = 0.043$) (Fig. 2B; Table 2). A PFS benefit was not observed with NTR versus STR ($P = 0.752$). Median time to tumor progression after GTR, NTR, and STR was 7, 4, and 3.5 years, respectively.

After adjusting for the effects of age, KPS status, histological subtype, tumor diameter, and primary versus revision surgery, GTR versus STR was associated with a trend of improved MFS (HR, 0.46; 95% CI, 0.20–1.03; $P = 0.060$) (Fig. 2C; Table 2). An MFS benefit was not observed with NTR versus STR ($P = 0.277$). Median time to malignant degeneration after GTR, NTR, and STR was 12.5, 5.8, and 7 years, respectively.

In a subset analysis, OS was compared between patients receiving GTR versus STR during the first 3 years of the study (1996–1999). GTR versus STR was also associated with improved OS in this early time period (HR, 0.31; 95% CI, 0.11–0.92; $P < 0.05$). Thus, the association of extent of resection

TABLE 1. Clinical and tumor characteristics of 170 low-grade glioma patients undergoing surgical resection[a,b]

Characteristic	STR (%) (n = 66)	NTR (%) (n = 39)	GTR (%) (n = 65)	*P* value[c]
Age (mean ± SD)	35 ± 14	36 ± 16	32 ± 15	0.296
Male	35 (53)	26 (66)	40 (62)	0.657
Preoperative KPS status				
Median	80	80	80	
Interquartile range	80–90	80–90	80–90	0.704
Presentation				
Seizure	41 (62)	27 (69)	47 (74)	0.307
Headache	19 (29)	8 (21)	13 (20)	0.393
Neurological deficit	6 (9)	4 (10)	5 (8)	0.682
Tumor location				
Frontal	34 (51)	27 (69)	41 (63)	0.227
Temporal	19 (28)	7 (18)	9 (14)	0.118
Parietal	10 (15)	3 (8)	12 (18)	0.373
Occipital	3 (5)	2 (5)	3 (5)	0.999
Preoperative tumor diameter (cm)	4.8 ± 1.8	4.6 ± 1.7	3.7 ± 1.8	0.010
Tumor subtype				
Astrocytoma	36 (55)	23 (58)	34 (52)	0.621
Oligodendroglioma	30 (45)	16 (42)	31 (48)	0.621
Surgery				
Primary resection	48 (73)	31 (80)	53 (82)	0.338
Revision resection	18 (17)	8 (20)	12 (18)	0.338
Intraoperative neurological navigation	43 (66)	19 (48)	39 (59)	0.902
Perioperative events				
Mortality	0 (0)	0 (0)	0 (0)	—
New permanent neurological deficit[d]	4 (6)	2 (5)	5 (7.5)	0.750
New transient neurological deficit[e]	3 (4)	2 (5)	3 (4)	0.999
Surgical site infection	0 (0)	0 (0)	1 (1.5)	0.382
Discharge to in-patient rehabilitation	5 (8)	2 (5)	8 (12)	0.267
Mean follow-up period (y)	3.9	3.7	4.5	0.140

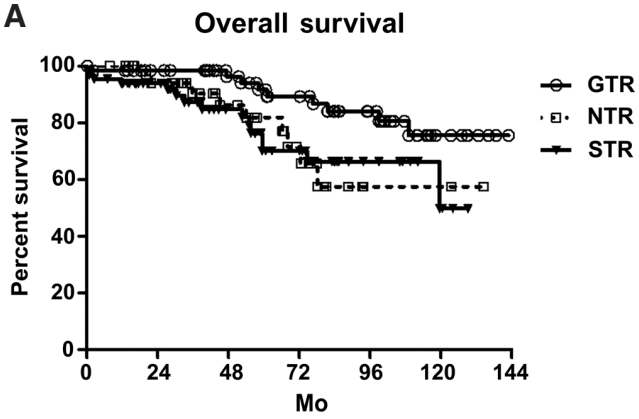
[a] STR, subtotal resection; NTR, near total resection; GTR, gross total resection; SD, standard deviation; KPS, Karnofsky Performance Scale.
[b] Patients receiving GTR had smaller tumor diameter versus NTR or STR.
[c] GTR versus STR or NTR.
[d] Permanent deficit (surgically acquired deficit still present at 3 mo).
[e] Transient deficit (surgically acquired deficit improved to baseline at 3 mo).

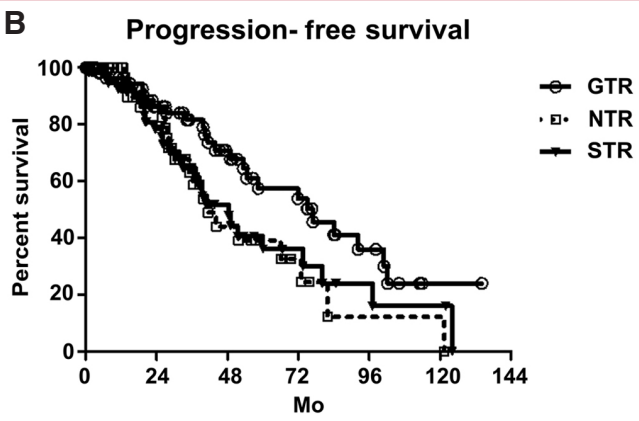
and OS does not simply reflect recent improvements in patient care during the later time period of the reviewed series.

DISCUSSION

In our experience of 170 cases of craniotomy for resection of hemispheric low-grade gliomas, we observed a survival benefit with GTR, independent of age, degree of disability, histological subtype (oligodendroglioma versus astrocytoma), tumor size (diameter), and primary versus revision surgery. GTR was also independently associated with improved PFS and a trend of improved MFS. These observations suggest that patients harboring tumors amenable to GTR may experience prolonged survival, delayed recurrence, and delay in malignant degeneration compared with patients in whom surgical goals, tumor characteristics, or tumor location prevented GTR. Our study, however, did not assess the effect of resection versus biopsy on survival. Although GTR versus STR was associated with prolonged survival, this observation cannot be applied to STR versus biopsy.

Currently, the role of surgery for hemispheric low-grade gliomas remains controversial. Many patients with these lesions are followed radiographically, and intervention occurs





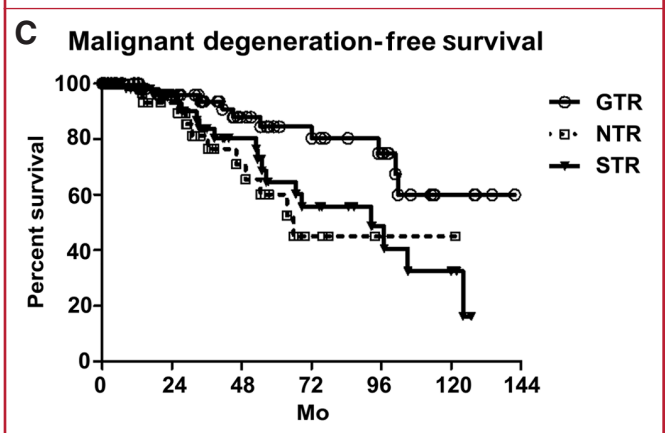


FIGURE 2. **A**, *overall survival (OS) after resection of low-grade infiltrating gliomas (World Health Organization [WHO] Grade II). Patients with GTR demonstrated improved overall survival compared with patients with STR ($P < 0.01$). NTR versus STR was not associated with improved OS.* **B**, *progression-free survival (PFS) after resection of low-grade infiltrating gliomas (WHO Grade II). Patients with GTR demonstrated improved PFS compared with patients with STR ($P < 0.05$). NTR versus STR was not associated with improved PFS.* **C**, *malignant degeneration-free survival (MFS) after resection of low-grade infiltrating gliomas (WHO Grade II). Patients with GTR demonstrated improved MFS compared with patients with STR ($P < 0.01$). NTR versus STR was not associated with MFS.*

only when clinical or radiographic progression becomes evident (24). The role that more aggressive resection has in prolonging survival for patients with low-grade gliomas remains unclear. This is because there is a lack of clear evidence supporting the benefits of GTR (19). In a review by Keles et al. (19), all but 5 studies were excluded from further review because of methodological limitations. These limitations included the inclusion of pilocytic astrocytomas, the surgeon's intraoperative determination of GTR, and small sample sizes, among others (19). The 5 higher quality studies that were further evaluated by Keles et al. (19) were also limited. Four of the 5 studies relied on intraoperative impression of extent of resection rather than neuroimaging (27, 32, 40, 43). The remaining study by Leighton et al. (22) was also limited because GTR and NTR were included in the same category. More recently, Pouratian et al. (31) reviewed the literature and summarized 11 studies that used multivariate analysis, included at least 100 patients, and assessed the effect of surgical resection of survival with low-grade gliomas. Within this review, there was no clear consensus on whether extensive resection affected survival or tumor progression. The impact that extensive resection and, more specifically, GTR have on survival for patients with low-grade gliomas remains poorly understood.

Several high-quality studies suggest that increasing extent of resection is associated with improved survival. Karim et al. (18) reported a prospective, randomized trial of high- versus low-dose radiation therapy in 343 patients and reported that extent of resection was the greatest prognosticator of overall survival. Sanford et al. (34) reported a prospective, nonrandomized, clinical trial of 516 patients correlating size of residual tumor with outcome. The 5-year OS rate was 99% with GTR, 95% with 1.5-cm^3 residual disease, 94% with 1.5- to 2.9-cm^3 residual disease, and 87% with 3-cm^3 residual disease. The 5-year PFS rate was 90% with GTR and 45 to 65% with any volume (1.5–3 cm^3) of residual disease (34). Most recently, Smith et al. (38) performed a retrospective volumetric analysis of extent of hemispheric low-grade glioma resection in 216 patients and found that patients with at least 90% resection had 5- and 8-year OS of 97 and 91%, respectively, whereas patients with less than 90% resection had 5- and 8-year OS rates of 76 and 60%, respectively.

The present study was designed with careful consideration of the limitations of many previous studies. Our study involved only adult patients (>18 years), and excluded cases of pilocytic astrocytomas (WHO Grade I), gemistocytic astrocytomas, and cases treated with up-front radiation or chemotherapy (n = 18) to create a more uniform study population. Pilocytic astrocytomas were excluded because these tumors are more benign, representing a separate histological entity, and would have led to longer survival times and better outcomes than WHO Grade II tumors (41). In addition, gemistocytic astrocytomas were excluded because they behave more aggressively than their WHO Grade II counterparts (12). Because oligodendrogliomas, particularly those with 1p19q LOH, have more benign courses, we separated these histological subtypes as a covariate in a multivariate analysis. Furthermore, for both

TABLE 2. Median survival and hazard ratios for gross total and near total versus subtotal resection[a,b]

	Progression-free survival			Malignant-free survival			Overall survival		
	Median time to progression (yr)	Hazard ratio (95% CI)	*P* value	Median time to malignant (y)	Hazard ratio (95% CI)	*P* value	Median time (y)	Hazard ratio (95% CI)	*P* value
GTR[c]	7.0	0.56 (0.32–0.98)	0.043	12.5	0.46 (0.20–1.03)	0.060	15	0.36 (0.16–0.84)	0.017
NTR[c]	4.0	1.01 (0.69–1.99)	0.752	5.8	1.57 (0.69–3.56)	0.277	11	0.87 (0.38–1.98)	0.632
STR	3.5			7.0			9.9		

[a] CI, confidence interval; GTR, gross total resection; NTR, near total resection; STR, subtotal resection.
[b] Adjusted for patient age, Karnofsky Performance Scale status, histological subtype (astrocytoma versus oligodendroglioma), preoperative tumor diameter, and primary versus revision resection.
[c] Survival compared with STR.

TABLE 3. Variables independently associated with overall survival after surgical resection of low-grade infiltrating gliomas (World Health Organization Grade II) in a multivariate proportional hazards analysis (Cox model)[a,b]

Variable	HR (95% CI)	*P* value
Age[c]	1.06 (1.03–1.09)	0.001
KPS status[c]	0.96 (0.92–0.99)	0.048
Oligodendroglioma	0.48 (0.20–0.86)	0.018
GTR[d]	0.36 (0.16–0.84)	0.017
NTR[d]	0.87 (0.38–1.98)	0.632

[a] HR, hazard ratio; CI, confidence interval; KPS, Karnofsky Performance Scale; GTR , gross total resection (complete resection of the preoperative fluid-attenuated inversion recovery [FLAIR] signal abnormality); NTR, near total resection (residual FLAIR signal abnormality around the rim of the resection cavity only); STR, subtotal resection (residual nodular FLAIR signal abnormality).
[b] Decreasing age, increasing KPS score, oligodendroglioma, and gross total resection were independently associated with improved overall survival.
[c] Increasing variable.
[d] Compared with STR.

oligodendrogliomas and astrocytomas, GTR versus STR was associated with an OS benefit. Because only 4 cases of oligodendrogliomas were proven not to have 1p19q LOH, a survival comparison between LOH-negative and LOH-positive was not possible. Nevertheless, OS and PFS were more favorable for the oligodendroglioma subtype. Furthermore, patients with extensive lesions crossing the midline, multifocal lesions, or lesions entirely invading eloquent cortex were selected for diagnostic biopsy and were not included in this study. Many of the STR patients in our series had solitary lesions invading the eloquent cortex, resulting in a planned STR. A smaller proportion received inadvertent STRs. However, these patients were not identifiable retrospectively. This difference in STR subgroups creates a potential bias that should be considered when interpreting these observations.

In addition to these exclusion criteria, we used a predetermined and strict definition of the extent of resection. GTR was defined as complete resection of all preoperative FLAIR signal abnormality. FLAIR signal abnormality was used because of its better delineation of residual pathological signal at the border of the resection cavity compared with conventional imaging techniques (8). We also adjusted for variables (age, KPS status, histology, tumor diameter, primary versus revision resection) (6, 16, 17, 19) that have been associated with outcome to evaluate the independent effect that GTR may have on survival and recurrence. It is important to highlight that our study does not provide volumetric analysis of postoperative tumor burden. Although our definition of GTR, NTR, and STR represent clinically relevant and easily applicable categories of resection, they do not allow for survival analysis for varying degrees of STR or NTR. In fact, although NTR versus STR was not associated with an OS, PFS, or MFS benefit based on an NTR definition of less than 3 mm of residual rim FLAIR signal, our study does not assess whether NTR defined as 4-, 2-, or less than 1-mm residual rim FLAIR signal would carry a different prognostic value. Recently, Smith et al. (38) demonstrated a survival benefit of NTR when using volumetric analysis. Nevertheless, given these controls and precise outcome measures, we feel that this study offers useful insight into the role that the extent of resection has on prolonging survival, delaying recurrence, and hindering malignant degeneration.

Although improved OS and PFS was observed with GTR versus STR, GTR was only associated with a trend ($P = 0.06$) of improved MFS when adjusting for potentially biasing factors. The practical utility of time to malignant degeneration is unclear for purposes of patient management, as progression of any type usually warrants action. However, the clinical relevance of time to malignant degeneration is of value because the majority of patients ultimately die as a result of transformed malignant lesions. It makes intuitive sense that GTR would prolong survival and recurrence as it has with other solid organ tumors (14, 45). Tumor recurrence commonly occurs close to the tumor margin, where there is increased tumor cell density at the periphery of the tumor, with a sharp falloff in cell numbers as the distance from the resection cavity increases (39).

Extensive resection decreases the number of remaining cells, theoretically decreasing the cumulative odds of malignant cellular degeneration and potentially prolonging survival (4, 5, 19). In a retrospective review of 461 cases of low-grade gliomas, Laws et al. (21) demonstrated a survival benefit with extensive resection but did not study progression. Shaw et al. (37) found no survival or progression benefit with extensive resection in a retrospective study of 126 patients with low-grade glioma. Shaw et al. (36) later performed a prospective observation study. Although this study demonstrated a benefit for survival and tumor progression on univariate analysis, an independent benefit was not apparent with extensive resection on multivariate analysis as observed in our series. In our institutional experience, we encountered minimal morbidity and mortality. Persistent postoperative neurological deficit occurred in only 11 (6%) cases and was similar between GTR and NTR or STR. This is likely because surgeons used intraoperative judgment when attempting more aggressive extent of resection. In cases in which tumor clearly invaded eloquent brain regions, less aggressive resection was attempted. In addition, there were no cases of perioperative mortality. As a result, extensive resection can be pursued safely when not limited by eloquent cortex.

Like the aforementioned retrospective studies, our study is inherently limited by its retrospective design and, as a result, no direct causal relationships can be inferred from these observations. Prospective studies examining extent of resection would ideally provide better data to guide clinical decision-making. We attempted to limit the bias associated with this approach by strictly defining the extent of resection into clinically relevant categories and controlling for each variable known to have an effect on survival. We understand that those patients in whom we obtained a more limited resection may reflect tumors that have already infiltrated beyond the point at which a safe resection could be carried out and, therefore, have a worse prognosis. Cases amenable to GTR may also represent a more favorable tumor biology, which may underlie both clearer tumor borders at resection and less aggressive progression. Furthermore, heterogeneity in tissue sampling or inconsistent enhancement among malignant degenerated lesions may have caused an artificially prolonged interval of MFS. It is important to note that the median follow-up period for this study was 4 years. Therefore, the accuracy of the estimated survival plot weakens beyond this time frame, requiring a greater intercohort difference to achieve significance. Given this large patient series, statistical control, and relatively precise outcome measure, we believe our findings offer useful insights into the interpretation of postoperative MRI scans and management of patients with low-grade gliomas. Our findings suggest that when low-grade gliomas are amenable to GTR, performing STR may result in decreased survival.

CONCLUSION

Previous studies evaluating the effects of extensive resection on survival for patients with low-grade gliomas are limited and inconclusive. In our experience, GTR of hemispheric low-grade gliomas was associated with improved survival independent of age, degree of disability, histological subtype, and subsequent resection. Our findings suggest that when low-grade gliomas are amenable to GTR, performing STR may result in decreased survival.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials or devices described in this article.

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COMMENTS

McGirt et al. reviewed in a retrospective fashion the extensive clinical experience of the Johns Hopkins' group in the surgical treatment of low-grade gliomas. The role of gross total resection for low-grade gliomas remains a controversial topic. For every article that seems to show a benefit, there are others that do not. However, as more outcome data accumulate, there seems to be a trend toward showing the benefit in terms of survival for total surgical resection. This study adds to the literature of relatively large numbers of patients who have undergone magnetic resonance imaging (MRI)-proven gross total resections and seem to do better than patients who have not.

McGirt et al. discuss a very interesting point. Perhaps the biology of the tumors amenable to gross total resections (i.e., contained) is different from that of tumors that are subtotally resected (i.e., diffuse). Interestingly, a recent microarray study (1) showed that a set of antimigratory genes are overexpressed in pilocytic astrocytomas (Grade I) versus diffuse astrocytomas (Grade II). It may be possible that a similar set of molecular signatures will identify the low-grade gliomas that are "contained" versus those that are more infiltrative. The implication of this differentiation would be that tumor biology (genes that regulate tumor invasion) provides a major determinant for neurosurgical skill in achieving gross total versus subtotal resections!

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Determining the impact of extent of resection (EOR) for low-grade gliomas on length of survival (LOS) has proven elusive. There are many significant variables that have equal or greater impact on LOS. Furthermore, survival curves for these patients are not "tight" bell-shaped curves, which are easily predictable. Rather, LOS is difficult to predict and long-term survivors are not uncommon. Even with malignant gliomas, which have a short LOS, well-defined prognostic factors, and rare long-term survivors, ferreting out the impact of surgery has not been easy.

There are unavoidable selection biases inherent in this study. As assessed preoperatively, gross total resection (GTR) was anticipated in all patients. Whether or not a tumor was "amenable to GTR" was a clinical judgment, made by the neurosurgeons preoperatively in this study. Therefore, patients who would have had a subtotal resection (STR) were excluded from this analysis. Furthermore, in the patients in whom a GTR was planned, but not accomplished, it is unclear why only STR was achieved. MRI assessment of the EOR in low-grade gliomas is problematic. For malignant gliomas, EOR is easier to assess, as it is based on postoperative contrast enhancement. With any glioma resection, there are fluid-attenuated inversion recovery (FLAIR) changes around the resection cavity. It is often difficult to determine whether these changes represent residual tumor or postsurgical edema. These MRI changes evolve over time and often increase after radiotherapy, sometimes making the determination of recurrent tumor versus treatment effect problematic.

The main conclusions of this study are that a more complete resection is better for LOS and results in delayed time to tumor progression or malignant degeneration. However, this study does not prove that STR is better than a biopsy or that a better STR is superior to a lesser STR. These are questions that will need to be addressed by future studies. It remains the onus of the individual neurosurgeon to decide what percentage of low-grade glioma resections warrant an open procedure over a biopsy, which means that an unclear benefit needs to be weighed against a known set of risks.

Daniel L. Silbergeld
Seattle, Washington

There have been a number of retrospective reports that examined the association between survival and EOR for low-grade gliomas. It is not surprising that McGirt et al. found that the absence of an abnormal FLAIR signal on the postoperative scan correlated with better prognosis. This advantage is lost with residual "nodular" tumor. Why the benefit of cytoreduction is so restricted to a radiographic GTR remains unknown, but similar findings have been reported previously.

Several questions remain when one is faced with these tumors. Does the importance of surgery change for tumors that do not have a 1p deletion or when the predominant histological subtype has an astrocytic phenotype? Because these lesions are anticipated to be more aggressive, should the absence of favorable biological markers influence the surgeon's strategy? What is the optimal adjuvant therapy, if any?

Postsurgical MRI scans for nonenhancing gliomas can be confusing. Some reports showed that residual FLAIR abnormalities did not change with chemotherapy although the clinical symptoms and positron emission tomography studies demonstrated improvement. It seems that FLAIR sequences are sensitive to increased extracellular water but are not specific for tumor. Since the European Organisation for Research and Treatment of Cancer trials showed that adjuvant radiotherapy can delay recurrence but not prolong survival, many oncologists are using chemotherapy for progressive disease. We still do not have a reliable noninvasive method of documenting a response to this treatment. Although I agree with the strategy of McGirt et al. for attempted GTR, this can only be accomplished for a minority of tumors. A significant majority of these patients will have residual tumor after surgery. This group needs our attention.

Joseph M. Piepmeier
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This article documents another, generally successful, attempt to use retrospective data to convince us of what we all suspect is true, namely, that EOR matters in glioma management. McGirt et al. admit to the shortcomings of the retrospective methodology necessarily used.

At one point, when the American College of Surgeons Oncology Group was contemplating an outcomes study of low-grade gliomas, the statisticians who were consulted declared that we would have to prospectively study more than 1000 patients for at least 10 years to reach Class I evidence status for the research. Retrospective studies such as this one add to the body of imperfect evidence that we all must use in our management recommendations.

Edward R. Laws, Jr.
Boston, Massachusetts

McGirt et al. reported their experience with low-grade gliomas in terms of how EOR affects survival. Although this has been a controversial issue in the past, there is mounting evidence, including the data from this study, that EOR has a significant impact on patient outcome. One of the added advantages, as seen in this retrospective analysis, is the impact that aggressive resection has on reducing the risk of malignant transformation. A recent study conducted by our group (1) demonstrated that after adjustment for the effects of age, Karnofsky Performance Scale, tumor location, and tumor subtype, EOR was a significant predictor of overall survival and showed a trend toward predicting progression-free survival. The volumetric EOR analysis revealed that patients with greater than 90% resection had an 8-year overall survival of 91% and a progression-free survival of 43%. This is in contradistinction to the patients with less than 90% resection, who had an 8-year overall survival of 60% and a progression-free survival of 21%. This study also demonstrated in a large series of patients that the EOR was directly related to a likelihood of malignant transformation. Thus, neurosurgeons can have a definite impact on the natural history of this disease by taking a more aggressive approach initially not only to affect time to tumor progression and overall survival but also to significantly decrease the risk of malignant transformation. Therefore, in their analysis, McGirt et al. have provided data to support the growing body of literature favoring an aggressive EOR in the treatment of low-grade gliomas and moving away from the more conservative approach of observation only after diagnosis.

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