ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Advances in the Surgical Management of Low-Grade Glioma

Todd Hollon, MD, Shawn L. Hervey-Jumper, MD, Oren Sagher, MD, and Daniel A. Orringer, MD

Over the past 2 decades, extent of resection has emerged as a significant prognostic factor in patients with low-grade gliomas (LGGs). Greater extent of resection has been shown to improve overall survival, progression-free survival, and time to malignant transformation. The operative goal in most LGG cases is to maximize extent of resection, while avoiding postoperative neurologic deficits. Several advanced surgical techniques have been developed in an attempt to better achieve maximal safe resection. Intraoperative magnetic resonance imaging, fluorescence-guided surgery, intraoperative functional pathway mapping, and neuronavigation are some of the most commonly used techniques with multiple studies to support their efficacy in glioma surgery. By using these techniques either alone or in combination, patients harboring LGGs have a better prognosis with less surgical morbidity following tumor resection.

Semin Radiat Oncol 25:181-188

Introduction

Low-grade gliomas (LGGs) constitute approximately 15% of the nearly 19,000 primary brain tumors diagnosed in adults each year.[1,2] Most LGGs are detected in healthy patients with good neurologic status following a seizure. LGGs tend to occur in locations adjacent to eloquent areas of the cortex.[3] A common location for these tumors in adults is in the supratentorial region, frequently involving the supplementary motor cortex and insula. This presents a formidable operative challenge for neurosurgeons, as the location of tumors near eloquent cortex limits extent of resection and increases the likelihood of postoperative neurologic deficits.[4-7]

Although recent advances have been made in chemotherapy and radiation therapy for LGG, surgical resection remains essential to its management. A growing body of literature supports the claim that a greater extent of resection leads to a significant survival benefit.[8-19] Extent of tumor resection has become a strong predictor of patient outcomes, alongside patient age, performance status, tumor histology, and molecular genetics (isocitrate dehydrogenase-1 and 1p/19q codeletion status).[4,6,20] Over the past 2 decades, surgeons have emphasized the importance of maximizing extent of resection and its effect on overall survival, progression-free survival, and time to malignant transformation.

Maximizing the extent of resection while preserving neurologic function is the central tenet of LGG surgery. In light of the fact that LGGs occur in younger patients with good neurologic function near eloquent areas of the brain, advanced surgical techniques have been developed to aid in improving the extent of resection of LGG because of the difficulties in distinguishing tumor tissue from normal brain intraoperatively. In the following review, we examine the current literature describing the role of extent of resection in the management of LGG, highlighting the most significant studies that demonstrate its importance for overall prognosis. In addition, we provide an overview as well as supporting evidence for the use of advanced surgical techniques in the operative treatment of LGG.

Evidence for Extent of Resection

A review of the neurosurgical literature since 1990 produced 17 studies analyzing the efficacy of extent of resection on progression-free and overall survival in LGG (Table 1).[9-19,21-26] The evidence before 1990 is ambivalent; although many studies demonstrated a trend toward greater overall survival

Department of Neurosurgery, University of Michigan, Ann Arbor, MI.
The authors declare no conflicts of interest.
Address reprint requests to Daniel A. Orringer, MD, Department of Neurosurgery, University of Michigan, 1500 East Medical Center Dr, Room 3552 TC, Ann Arbor, MI 48109-5338. E-mail: dorringe@med.umich.edu

http://dx.doi.org/10.1016/j.semradonc.2015.02.007
1053-4296/

Table 1 Overview of Literature on Extent of Resection in Low-Grade Glioma

Overall Survival	Nonvolumetric Studies	No. of Patients	Volumetric Studies	No. of Patients
Benefit	North et al[70]	77	van Veelen et al[18]	75
	Philippon et al[13]	179	Claus et al[8]	156
	Rajan et al[14]	82	Smith et al[17]	216
	Leighton et al[11]	167	Sanai et al[15]	104
	Nakamura et al[12]	88		
	Yeh et al[19]	93		
	McGirt et al[25]	170		
	Ahmadi et al[71]	130		
	Chaichana et al[22]	191		
	Jakola et al[10]	153		
No benefit	Whitton and Bloom[26]	88	None to date	
	Bauman et al[21]	401		
	Johannesen et al[24]	993		

in patients who received gross total resection, these trends did not reach statistical significance.[27,28] It should be noted that most of the pre-1990 studies relied on the neurosurgeon's intraoperative judgment to gauge extent of resection. Several studies have since suggested that a surgeon's intraoperative assessment of tumor removal is unreliable when compared with residual tumor identified on postoperative imaging.[29,30] With the advent of magnetic resonance imaging (MRI) and the routine practice of obtaining postoperative imaging, it is now feasible to obtain a more reliable assessment of postoperative residual tumor volume and extent of resection.

Studies evaluating extent of resection can be divided into volumetric (ie, quantitative volumetric analysis used to determine percentage of extent of resection) and nonvolumetric (qualitative assessment of residual tumor, commonly divided into gross total, subtotal, and biopsy) categories. Of the 13 nonvolumetric studies, 10 demonstrated that extent of resection is associated with improved 5- and 10-year rates of overall survival in a statistically significant fashion.[8-19,22,25] Statistical significance was reached on both univariate and multivariate analyses for all studies showing a positive benefit for extent of resection. The 3 studies that were not statistically significant did reveal a consistent trend toward improved overall survival with greater extent of resection.[21,24,26]

A recent study by Jakola et al[10] examined different LGG treatment approaches by comparing 2 population-based parallel cohorts treated at either hospital A (favoring biopsy and observation) or hospital B (favoring early resection following diagnosis). A total of 153 patients were included in the study (66 from hospital A and 87 from hospital B). Median follow-up was approximately 7 years in both the groups. The overall survival was significantly better in patients receiving early resection (5.9-year median survival in the cohort favoring biopsy vs no median survival reached in the cohort favoring early resection, as more than 50% of patients were still alive). The estimated 5-year survival was 60% and 74%, correspondingly. The survival benefit remained after multivariate analysis using known prognostic factors, including age more than 40 years, maximum tumor diameter of 6 cm or more, tumor crossing midline, neurologic deficit, and astrocytoma histology.[6] Moreover, malignant transformation was significantly decreased in the group favoring early resection, indicating that early surgical intervention may improve overall survival by altering the natural history of LGGs.

The 4 volumetric-based studies reviewed determined that extent of resection is a prognostic factor for overall survival.[8,15,17,18] The largest study examined 216 patients with hemispheric LGGs.[17] Patients with $\geq$90% tumor resection had a 5- and 8-year overall survival rate of 97% and 91%, respectively; patients with less complete resection had a survival rate of 76% and 60%, respectively. After correcting for multiple confounding variables (patient age, Karnofsky performance status, tumor location, and histologic subtype), the extent of resection was significantly correlated with overall survival, along with preoperative and postoperative tumor volume. This was the first study to demonstrate an improved outcome in patients with LGGs, as predicted by greater extent of resection. Collectively, the body of literature examining extent of resection supports operative intervention as a mainstay treatment for LGGs. Maximizing extent of resection while preserving functional brain regions should be the operative goal in most patients with LGGs.

Advanced Surgical Techniques

Understanding the Role of Advanced Surgical Techniques

The objective of LGG surgery is twofold: (1) maximize tumor removal and (2) minimize surgical morbidity and postoperative neurologic deficits. Modern surgical techniques have emerged in an attempt to better navigate these 2 operative obstacles. Several randomized controlled trials have now been reported, supporting their efficacy.[31-34] The major techniques are summarized in Table 2. Most techniques have been developed to preferentially serve one objective over the other. For example, intraoperative MRI (iMRI) is a technique that was developed in the 1990s to identify residual tumor radiographically during tumor resection. This technique serves the purpose of maximizing tumor removal by providing updated

Table 2 Advanced Surgical Techniques in Glioma Surgery

Identification of tumor
Fluorescence-guided surgery
Intraoperative MRI
Intraoperative ultrasound
Intraoperative microscopy
Mapping functional pathways
Direct stimulation
Cortical stimulation
Subcortical stimulation
Awake craniotomy with stimulation
Functional imaging
Functional MRI
Magnetoencephalography
Positron emission tomography
Neuronavigation with functional imaging

data on extent of resection. However, currently available iMRI does not provide real-time information on functional pathways.[32] When tumors occur near eloquent areas, functional mapping serves to delineate a safe operative margin, and consequently, it largely determines and improves extent of resection.[5]

A review of the most promising surgical techniques and technologies that aid in the identification of tumor tissue is described. In addition, several techniques dedicated to identifying functional pathways and eloquent areas are reviewed. In conclusion, the utility of a multimodal approach combining several of these techniques is discussed.

Intraoperative MRI

For more than 2 decades, iMRI has been used to detect tumors intraoperatively.[35,36] The advantage of iMRI over traditional neuronavigation (which uses preoperative imaging) is its ability to provide real-time accuracy, addressing brain shifts during surgery secondary to cerebrospinal fluid loss, tumor removal, and brain edema. Multiple studies have shown increased extent of resection in LGG surgery using iMRI.[8,32,37-40] Claus et al[8,23] performed a retrospective study evaluating progression-free and overall survival rates for 156 patients who underwent resection of LGGs using iMRI compared with age- and histology-adjusted controls obtained from the Surveillance, Epidemiology, and End Results (SEER) registry. The 1-, 2-, and 5-year death rates were 1.9%, 3.6%, and 17.6%, respectively. These results show a significant decrease in death rates when compared with SEER-matched controls (10%, 16%, and 29%, correspondingly).

Senft et al performed a randomized, controlled trial evaluating the effect of iMRI in glioma surgery. Patients were randomized to either iMRI-guided surgery (study group) or conventional microsurgery with neuronavigation (control group).[32] The primary end point was extent of resection, with secondary end points of postoperative tumor volume and progression-free survival at 60 months. A total of 49 patients were included in the data analysis, with 24 patients in the iMRI group and 25 patients in the control group. Significantly more patients who underwent iMRI-guided surgery had complete tumor resection (96%) when compared with the control group (68%). Although there was no statistically significant difference in progression-free survival between the 2 groups, the data did show that complete resection was a strong predictor of 6-month progression-free survival. There was no difference in postoperative neurologic deficits between both the groups. Importantly, no patient in whom residual tumor was identified intraoperatively and subsequently underwent further resection after scanning developed postoperative neurologic deficits. An early concern that iMRI may lead to a greater risk of postoperative neurologic deficits due to more aggressive resections has not been realized. A review of surgical results did not show iMRI-guided surgery to result in additional neurologic deficits, including cases where intraoperative imaging resulted in further, more aggressive resection.[37] Results to date support the use of iMRI as an important tool for maximizing extent of resection without producing additional surgical morbidity.

Fluorescence-Guided Glioma Surgery

Low-grade primary brain neoplasms frequently resemble surrounding tissue, making it difficult to delineate normal tissue from abnormal tissue. Fluorescence-guided surgery was developed in an attempt to label tumor tissue with a fluorescent biomarker to aid in the intraoperative identification of tumor tissue. There are 2 agents that have received the greatest amount of attention: fluorescein sodium and 5-aminolevulinic acid (5-ALA). Although fluorescein sodium has been studied in glioma surgery,[41] it suffers from significant nonspecific staining. Presently, it has minimal value in LGG surgery and is not discussed in detail here.

The agent 5-ALA is a naturally occurring amino acid precursor in the heme biosynthesis pathway. Exogenous administration of 5-ALA acts as a prodrug to the production of fluorescent porphyrins (especially protoporphyrin IX) within glioma cells as well as other malignant tumors. 5-ALA fluorescence is particularly high in malignant glioma for 2 major reasons. As a water-soluble amino acid, 5-ALA does not readily pass the blood-brain barrier, thereby preventing accumulation in healthy brain. The breakdown of the blood-brain barrier that occurs in glioma results in intracellular accumulation of 5-ALA in glioma tissue. Additionally, the heme biosynthesis pathway is upregulated in malignant glioma, producing a favorable kinetic environment for the production of fluorescent porphyrins from exogenous 5-ALA.

The amino acid 5-ALA is given either intravenously or orally 3 hours before the induction of general anesthesia. This allows for tumor resection to occur at the peak fluorescent time of 6 hours following administration. Protoporphyrin IX emits a red-violet light (wavelength: 635-704 nm) when excited by blue light (wavelength: 400-410 nm).[42-44] The operative microscope can be equipped with white light for standard microsurgery as well as a blue light both for fluorescent excitation and optimal visualization of red-violet light emitted from tumor tissue (Fig. 1).

In 2006, Stummer et al[33] completed a randomized, controlled trial comparing resection of malignant glioma using 5-ALA vs resection under standard white light. Primary end

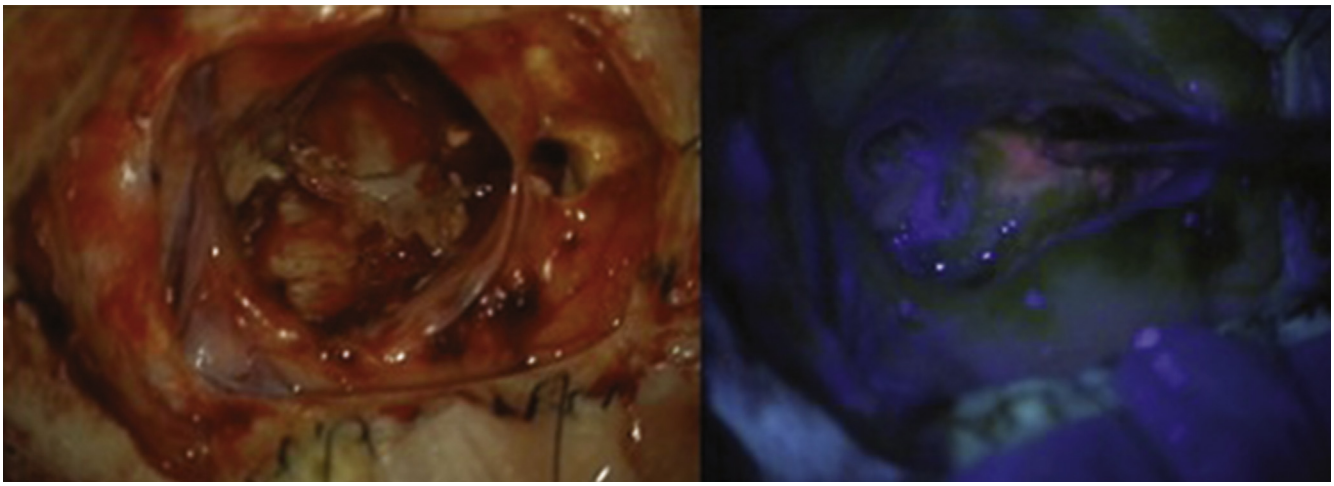

Figure 1 Fluorescence-guided surgery using 5-ALA. Left: Standard white light intraoperative photograph using the operative microscope. Corticectomy has been performed, and the tumor is internally debulked. Resection cavity is visualized without clear tumor-brain interface. Right: Red-violet 5-ALA fluorescence is clearly visualized under blue filter within residual tumor. Note this photograph was taken of a malignant glioma. The 5-ALA fluorescence in LGG requires confocal microscopy.

points were number of patients without a contrast-enhancing tumor on early postoperative MRI and 6-month progression-free survival. A total of 270 patients were included in the final analysis: 139 in the 5-ALA group and 131 in the white light group. The trial was terminated at interim analysis as defined by the study. Complete resection of a contrast-enhancing tumor was achieved in 90% of patients receiving 5-ALA when compared with 36% of patients in the white light group. The 5-ALA group had a statistically significant greater 6-month progression-free survival (41%) when compared with the white light group (21%). No difference was noted in post-operative neurologic deficits or adverse events between both the groups. The study was not powered to assess overall survival.

The literature on 5-ALA and fluorescence-guided glioma surgery has been largely limited to high-grade glioma. In most LGGs, no visible fluorescence can be detected under standard microsurgical conditions. Intraoperative confocal microscopy has been used in an attempt to visualize 5-ALA tumor fluorescence in LGGs during microsurgical resection.[45] An initial study involving 10 patients confirmed that no macroscopic fluorescence was detected at any point during the procedure. All patients in this study had intraoperative fluorescence detected using the confocal microscope, and greater than 90% extent of resection was achieved in 9 of 10 patients. Although these results are promising, a limitation of this technique is that in 4 patients, no fluorescence was detected at the tumor-cavity margin. A possible explanation for this limitation lies in the inherent problem with any technique that relies on dye delivery. In addition to heterogeneous delivery and nonspecific staining, labeling specificity for tumor tissue progressively diminishes as resection proceeds toward the tumor-normal brain margin in infiltrative tumors such as glioma. For this reason, various approaches to label-free techniques for tumor detection are under development.[46] Despite these limitations, fluorescence-guided surgery has emerged as an important component in the brain tumor surgeon's armamentarium for the treatment of glioma.

Intraoperative Functional Mapping

The variability of functional pathways in the human brain has been well described.[47-53] Reliance on anatomical landmarks for localization of eloquent cortex, such as the primary motor cortex, has proven to be inadequate in clinical practice and lacks the precision necessary to minimize postoperative deficits.[54,55] Mass effect from adjacent tumor can distort tissues, and the plasticity of functional pathways allows for significant reorganization. Moreover, functional motor fibers have been found to travel directly through tumor tissue in LGGs, making intratumoral resection vulnerable to postoperative deficits.[56,57] This variability has necessitated the use of techniques that can reliably localize functional pathways when tumor tissue is located near eloquent areas.

The oldest and best-described technique for identifying functional pathways is by direct cortical stimulation. The technique was developed in the 1930s by Penfield and Boldrey,[58] and it was largely used in epilepsy surgery. This technique involves the application of a depolarization current using a bipolar stimulation device. Direct stimulation depolarizes a focal area of cortex, exciting local neurons and inducing either focal excitation or inhibition of function. Numerically marked stimulation sites separated by 1 cm are placed on the surgical field (Fig. 2). To improve accuracy and limit subclinical seizure activity, continuous electrocorticography is used to determine the threshold intensity at which potential epileptiform activity occurs. All language testing is repeated at least 2 times, and a positive site is defined as the inability to reliably count, name objects, or read words during stimulation.[51] Language testing identifies sites responsible for speech arrest, anomia, and alexia with stimulation testing. Speech arrest is defined as discontinuation in number counting

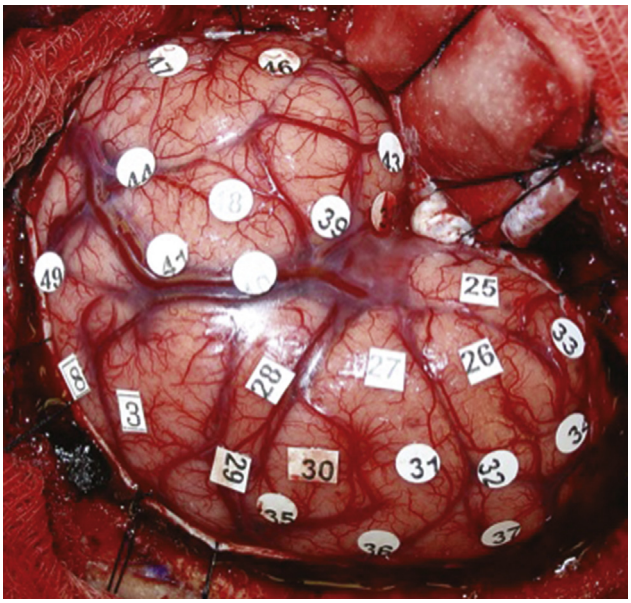

Figure 2 Intraoperative mapping of functional pathways by direct cortical stimulation. A left pterional craniotomy was performed to expose inferior frontal and posterior temporal regions for language mapping. Stimulation sites are numerically marked and recorded as either positive or negative mapping sites. Resection proceeds after a safe location for the corticectomy has been identified. (Color version of figure is available online.)

without simultaneous motor response. Dysarthria can be distinguished from speech arrest by an absence of involuntary muscle contractions affecting speech. To identify reading sites, the same stimulation is applied during a slide presentation of words.

Awake craniotomy for functional pathway mapping requires an experienced neuroanesthesiologist to administer the anesthesia. Patients are typically premedicated with midazolam and fentanyl before positioning for patient comfort and anxiolysis. Sedation is achieved with propofol and remifentanil. A scalp block using lidocaine and bupivacaine with sodium bicarbonate and epinephrine is applied by the neurosurgeon, to reduce discomfort. When positioning, preparing, and draping the patient, it is important to allow the patient direct visual access to the anesthesiologist and intraoperative tester. After skin incision and removal of the bone flap, all sedatives are discontinued. Topical ice-cold Ringers lactate solution is made available on the surgical field, as it has been shown to prevent or stop stimulation-induced seizure activity.[59]

The use of awake craniotomies in brain tumor surgery has been shown to decrease postoperative neurologic deficits and surgical morbidity, while safely delineating an operative margin for resection.[5] Early mapping techniques used in epilepsy surgery involved large craniotomies to widely expose the cortex in order to identify positive controls that generated speech arrest, motor stimulation, or inhibition. This technique has been largely abandoned in brain tumor surgery in favor of "negative" mapping, in which cortical stimulation proceeds by identifying areas that fail to produce neurologic symptoms.[51] Intraoperative stimulation and identification of eloquent cortex increases the risk of postoperative neurologic deficits, likely because of tumor proximity to these areas. Negative mapping is a safe alternative, allowing for tailored craniotomies, shorter operative times, and fewer postoperative deficits.[5,51] Using this technique, long-term language function after intraoperative stimulation was evaluated in a series of 250 consecutive patients with glioma with World Health Organization grade II-IV–dominant hemisphere gliomas.[51] Of the patients, 58% had at least 1 functional language site identified, and long-term language disability was 1.6%.

A recent meta-analysis of 90 studies and 8091 patients was completed to determine the effect of intraoperative stimulation (cortical and subcortical) brain mapping on patient outcomes after glioma surgery.[60] Severe neurologic deficits were observed in 3.4% of patients after resections with intraoperative stimulation mapping and in 8.2% of patients after resections without mapping. In addition to this significant decrease in surgical morbidity, gross total resection was achieved in operations with intraoperative stimulation in 75% of cases, whereas only 58% of operations performed without intraoperative mapping resulted in gross total resection. This finding provides evidence that mapping functional pathways in tumors adjacent to eloquent cortex serves not only to achieve its primary objective of reducing postoperative neurologic deficits but also to increase extent of resection and reduce postoperative residual tumor.

Frameless Stereotactic Neuronavigation

Neuronavigation has become a ubiquitous tool in brain tumor surgery.[61] Improvements in cross-sectional imaging modalities such as computed tomography and MRI have made possible 3-dimensional reconstructions of anatomical structures. Neuronavigation is the process by which anatomical landmarks in and around the operative field are spatially registered to a corresponding reconstructed 3-dimensional model generated from preoperative or intraoperative cross-sectional imaging. Using a handheld optical or electromagnetic detector probe, anatomical landmarks are localized using a tracking system. The most common tracking system uses dual infrared cameras to track the position of the handheld surgical probe relative to a reference frame fixed to either the patient or a rigid head holder.

Standard neuronavigation in brain tumor surgery is used mainly for optimizing the surgical approach to the tumor before opening the dura. Scalp incision and craniotomies can be accurately tailored to allow for minimal tissue injury and bony removal. A randomized, controlled trial was completed to evaluate the importance of neuronavigation for cytoreduction of solitary intracerebral contrast-enhancing tumors.[62] A total of 45 patients were enrolled in the study. There was no statistically significant difference in extent of resection between patients who underwent surgery with or without standard neuronavigation. The results of this study highlight some of the limitations of neuronavigation in brain tumor surgery. With opening of the dura, cerebrospinal fluid egress allows for significant shifts in intracranial contents. Additionally, as tumor resection proceeds, a tumor cavity develops, leading to distortion of surrounding structures, including eloquent

cortex and functional pathways. In the absence of an updated navigational data set, traditional rigid registration methods do not account for these intraoperative anatomical changes.

Because of these inherent limitations, neuronavigation is best used as an adjunct to other surgical or imaging techniques. A particular strategy involves the integration of standard neuronavigation with functional noninvasive neuroimaging such as functional MRI, diffusion tensor imaging (DTI), or magnetoencephalography (MEG). Wu et al[34] performed a randomized, controlled trial evaluating the use of DTI-based functional neuronavigation in patients with gliomas involving the pyramidal tracts. The study demonstrated a significant decrease in postoperative motor deterioration in patients using DTI-based functional neuronavigation (9.8%) compared with standard neuronavigation (18.6%) in patients with LGG. The study group also had 13% of patients show improvement in their postoperative motor function compared with only 1% in the control group. There was no difference in extent of resection in patients with LGG.

Resting-state coherence measured with MEG is capable of mapping functional connectivity of the brain. Tarapore et al[63] measured resting whole-brain MEG recordings from 79 patients with unilateral gliomas near or within sensory, motor, or language areas during the preoperative and postoperative periods. Patients with baseline decreased functional connectivity had a 29% rate of new neurologic deficits 1 week after surgery, and 0% at 6-month follow-up. However, patients with increased functional connectivity had a 60% rate of new deficits at 1 week and 25% at 6 months. Tumors with decreased resting-state connectivity have a relatively low risk of postoperative neurologic deficits, whereas those with increased resting-state connectivity are associated with higher risk of postoperative neurologic deficits.

Neuronavigation is an essential component of brain tumor surgery. The technique will continue to improve, as methods are developed to integrate functional imaging into navigational data sets that are able to account for intraoperative brain shift and anatomical changes during tumor resection.

Conclusion

Each of the aforementioned advanced techniques has a role in safely maximizing extent of resection in LGG surgery. Deciding which technique is optimal for a given surgery remains nuanced and complex. Lesions located near eloquent areas should prompt neurosurgeons to pursue noninvasive functional imaging or intraoperative mapping or both. Candidacy for awake craniotomy depends on tumor location and the patient's ability to cooperate during surgery. Awake mapping should be strongly considered in dominant hemisphere LGG with involvement of language pathways. iMRI and fluorescence-guided surgery are ideal for large LGGs occurring in noneloquent areas. This strategy facilitates maximal resection in patients at lower risk for postoperative neurologic deficits. Several studies have examined the use of a multimodal approach in glioma surgery.[64-69] Good operative results have been reported with iMRI or 5-ALA-guided surgery integrated with functional mapping techniques. This allows both for delineation of tumor tissue and identification of functional pathways in a single operation. The decision to use advanced surgical techniques for any given patient harboring a LGG can only be made by an experienced neurosurgeon following an extensive preoperative evaluation to provide optimal surgical care.[2]

References

1. Barnholtz-Sloan JS, Sloan AE, Schwartz AG: Chapter 25: Cancer of the brain and other central nervous system. In: Gloeckler-Ries LA, Young JL, Eisner MP, et al.(eds): SEER Survival Monograph: Cancer Survival Among Adults: U.S. SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD, National Cancer Institute, 204-215, 2007⟨http://seer.cancer.gov/archive/publications/survival/⟩. [SEER Program, NIH Pub. No. 07-6215]
2. Bondy ML, Scheurer ME, Malmer B, et al: Brain tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium. Cancer 113:1953-1968, 2008
3. Duffau H, Capelle L: Preferential brain locations of low-grade gliomas. Cancer 100:2622-2626, 2004
4. Chang EF, Clark A, Jensen RL, et al: Multiinstitutional validation of the University of California at San Francisco Low-Grade Glioma Prognostic Scoring System. Clinical article. J Neurosurg 111:203-210, 2009
5. Kim SS, McCutcheon IE, Suki D, et al: Awake craniotomy for brain tumors near eloquent cortex: Correlation of intraoperative cortical mapping with neurological outcomes in 309 consecutive patients. Neurosurgery 64:836-846, 2009
6. Pignatti F, van den Bent M, Curran D, et al: Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol 20:2076-2084, 2002
7. Sawaya R, Hammoud M, Schoppa D, et al: Neurosurgical outcomes in a modern series of 400 craniotomies for treatment of parenchymal tumors. Neurosurgery 42:1044-1056, 1998
8. Claus EB, Horlacher A, Hsu L, et al: Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer 103:1227-1233, 2005
9. Ius T, Isola M, Budai R, et al: Low-grade glioma surgery in eloquent areas: Volumetric analysis of extent of resection and its impact on overall survival. A single-institution experience in 190 patients: Clinical article. J Neurosurg 117:1039-1052, 2012
10. Jakola AS, Myrmel KS, Kloster R, et al: Comparison of a strategy favoring early surgical resection vs a strategy favoring watchful waiting in low-grade gliomas. J Am Med Assoc 308:1881-1888, 2012
11. Leighton C, Fisher B, Bauman G, et al: Supratentorial low-grade glioma in adults: An analysis of prognostic factors and timing of radiation. J Clin Oncol 15:1294-1301, 1997
12. Nakamura M, Konishi N, Tsunoda S, et al: Analysis of prognostic and survival factors related to treatment of low-grade astrocytomas in adults. Oncology 58:108-116, 2000
13. Philippon JH, Clemenceau SH, Fauchon FH, et al: Supratentorial low-grade astrocytomas in adults. Neurosurgery 32:554-559, 1993
14. Rajan B, Pickuth D, Ashley S, et al: The management of histologically unverified presumed cerebral gliomas with radiotherapy. Int J Radiat Oncol Biol Phys 28:405-413, 1994
15. Sanai N, Polley MY, Berger MS: Insular glioma resection: Assessment of patient morbidity, survival, and tumor progression. J Neurosurg 112:1-9, 2010
16. Shaw E, Arusell R, Scheithauer B, et al: Prospective randomized trial of low- versus high-dose radiation therapy in adults with supratentorial low-grade glioma: Initial report of a North Central Cancer Treatment Group/Radiation Therapy Oncology Group/Eastern Cooperative Oncology Group study. J Clin Oncol 20:2267-2276, 2002
17. Smith JS, Chang EF, Lamborn KR, et al: Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. J Clin Oncol 26:1338-1345, 2008

18. van Veelen ML, Avezaat CJ, Kros JM, et al: Supratentorial low grade astrocytoma: Prognostic factors, dedifferentiation, and the issue of early versus late surgery. J Neurol Neurosurg Psychiatry 64:581-587, 1998
19. Yeh SA, Ho JT, Lui CC, et al: Treatment outcomes and prognostic factors in patients with supratentorial low-grade gliomas. Br J Radiol 78:230-235, 2005
20. Weiler M, Wick W: Molecular predictors of outcome in low-grade glioma. Curr Opin Neurol 25:767-773, 2012
21. Bauman G, Lote K, Larson D, et al: Pretreatment factors predict overall survival for patients with low-grade glioma: A recursive partitioning analysis. Int J Radiat Oncol Biol Phys 45:923-929, 1999
22. Chaichana KL, McGirt MJ, Laterra J, et al: Recurrence and malignant degeneration after resection of adult hemispheric low-grade gliomas. J Neurosurg 112:10-17, 2010
23. Claus EB, Black PM: Survival rates and patterns of care for patients diagnosed with supratentorial low-grade gliomas: Data from the SEER program, 1973-2001. Cancer 106:1358-1363, 2006
24. Johannesen TB, Langmark F, Lote K: Progress in long-term survival in adult patients with supratentorial low-grade gliomas: A population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. J Neurosurg 99:854-862, 2003
25. McGirt MJ, Chaichana KL, Attenello FJ, et al: Extent of surgical resection is independently associated with survival in patients with hemispheric infiltrating low-grade gliomas. Neurosurgery 63:700-708, 2008
26. Whitton AC, Bloom HJ: Low grade glioma of the cerebral hemispheres in adults: A retrospective analysis of 88 cases. Int J Radiat Oncol Biol Phys 18:783-786, 1990
27. Laws ER, Taylor WF, Clifton MB, et al: Neurosurgical management of low-grade astrocytoma of the cerebral hemispheres. J Neurosurg 61:665-673, 1984
28. Piepmeier JM: Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. J Neurosurg 67:177-181, 1987
29. Albert FK, Forsting M, Sartor K, et al: Early postoperative magnetic resonance imaging after resection of malignant glioma: Objective evaluation of residual tumor and its influence on regrowth and prognosis. Neurosurgery 34:45-61, 1994
30. Orringer D, Lau D, Khatri S, et al: Extent of resection in patients with glioblastoma: Limiting factors, perception of resectability, and effect on survival. J Neurosurg 117:851-859, 2012
31. Barone DG, Lawrie TA, Hart MG: Image guided surgery for the resection of brain tumours. Cochrane Database Syst Rev 1:CD009685, 2014
32. Senft C, Bink A, Franz K, et al: Intraoperative MRI guidance and extent of resection in glioma surgery: A randomised, controlled trial. Lancet Oncol 12:997-1003, 2011
33. Stummer W, Pichlmeier U, Meinel T, et al: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. Lancet Oncol 7:392-401, 2006
34. Wu JS, Zhou LF, Tang WJ, et al: Clinical evaluation and follow-up outcome of diffusion tensor imaging-based functional neuronavigation: A prospective, controlled study in patients with gliomas involving pyramidal tracts. Neurosurgery 61:935-949, 2007
35. Black PM, Alexander E, Martin C, et al: Craniotomy for tumor treatment in an intraoperative magnetic resonance imaging unit. Neurosurgery 45:423-433, 1999
36. Knauth M, Wirtz CR, Tronnier VM, et al: Intraoperative MR imaging increases the extent of tumor resection in patients with high-grade gliomas. Am J Neuroradiol 20:1642-1646, 1999
37. Nimsky C, Fujita A, Ganslandt O, et al: Volumetric assessment of glioma removal by intraoperative high-field magnetic resonance imaging. Neurosurgery 55:358-371, 2004
38. Nimsky C, Ganslandt O, Tomandl B, et al: Low-field magnetic resonance imaging for intraoperative use in neurosurgery: A 5-year experience. Eur Radiol 12:2690-2703, 2002
39. Schneider JP, Schulz T, Schmidt F, et al: Gross-total surgery of supratentorial low-grade gliomas under intraoperative MR guidance. Am J Neuroradiol 22:89-98, 2001
40. Schneider JP, Trantakis C, Rubach M, et al: Intraoperative MRI to guide the resection of primary supratentorial glioblastoma multiforme—a quantitative radiological analysis. Neuroradiology 47:489-500, 2005
41. Li Y, Rey-Dios R, Roberts DW, et al: Intraoperative fluorescence-guided resection of high-grade gliomas: A comparison of the present techniques and evolution of future strategies. World Neurosurg 82:175-185, 2014
42. Ishihara R, Katayama Y, Watanabe T, et al: Quantitative spectroscopic analysis of 5-aminolevulinic acid-induced protoporphyrin IX fluorescence intensity in diffusely infiltrating astrocytomas. Neurol Med Chir (Tokyo) 47:53-57, 2007
43. Stummer W, Reulen HJ, Novotny A, et al: Fluorescence-guided resections of malignant gliomas—an overview. Acta Neurochir Suppl 88:9-12, 2003
44. Stummer W, Stocker S, Wagner S, et al: Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 42:518-526, 1998
45. Sanai N, Snyder LA, Honea NJ, et al: Intraoperative confocal microscopy in the visualization of 5-aminolevulinic acid fluorescence in low-grade gliomas. J Neurosurg 115:740-748, 2011
46. Ji M, Orringer DA, Freudiger CW, et al: Rapid, label-free detection of brain tumors with stimulated Raman scattering microscopy. Sci Transl Med 5:3005954, 2013
47. Herholz K, Thiel A, Wienhard K, et al: Individual functional anatomy of verb generation. Neuroimage 3:185-194, 1996
48. Ojemann G, Ojemann J, Lettich E, et al: Cortical language localization in left, dominant hemisphere. An electrical stimulation mapping investigation in 117 patients. J Neurosurg 71:316-326, 1989
49. Ojemann GA: Individual variability in cortical localization of language. J Neurosurg 50:164-169, 1979
50. Ojemann GA, Whitaker HA: Language localization and variability. Brain Lang 6:239-260, 1978
51. Sanai N, Mirzadeh Z, Berger MS: Functional outcome after language mapping for glioma resection. N Engl J Med 358:18-27, 2008
52. Seitz RJ, Huang Y, Knorr U, et al: Large-scale plasticity of the human motor cortex. Neuroreport 6:742-744, 1995
53. Wunderlich G, Knorr U, Herzog H, et al: Precentral glioma location determines the displacement of cortical hand representation. Neurosurgery 42:18-27, 1998
54. FitzGerald DB, Cosgrove GR, Ronner S, et al: Location of language in the cortex: A comparison between functional MR imaging and electrocortical stimulation. Am J Neuroradiol 18:1529-1539, 1997
55. Quiñones-Hinojosa A, Ojemann SG, Sanai N, et al: Preoperative correlation of intraoperative cortical mapping with magnetic resonance imaging landmarks to predict localization of the Broca area. J Neurosurg 99:311-318, 2003
56. Ojemann JG, Miller JW, Silbergeld DL: Preserved function in brain invaded by tumor. Neurosurgery 39:253-259, 1996
57. Skirboll SS, Ojemann GA, Berger MS, et al: Functional cortex and subcortical white matter located within gliomas. Neurosurgery 38:678-685, 1996
58. Penfield W, Boldrey E: Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain 60:389-443, 1937
59. Sartorius CJ, Berger MS: Rapid termination of intraoperative stimulation-evoked seizures with application of cold Ringer's lactate to the cortex. Technical note. J Neurosurg 88:349-351, 1998
60. De Witt Hamer PC, Robles SG, Zwinderman AH, et al: Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. J Clin Oncol 30:2559-2565, 2012
61. Orringer DA, Golby A, Jolesz F: Neuronavigation in the surgical management of brain tumors: Current and future trends. Expert Rev Med Devices 9:491-500, 2012
62. Willems PW, Taphoorn MJ, Burger H, et al: Effectiveness of neuronavigation in resecting solitary intracerebral contrast-enhancing tumors: A randomized controlled trial. J Neurosurg 104:360-368, 2006
63. Tarapore PE, Tate MC, Findlay AM, et al: Preoperative multimodal motor mapping: A comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. J Neurosurg 117:354-362, 2012

64. Della Puppa A, De Pellegrin S, d'Avella E, et al: 5-aminolevulinic acid (5-ALA) fluorescence guided surgery of high-grade gliomas in eloquent areas assisted by functional mapping. Our experience and review of the literature. Acta Neurochir (Wien) 155:965-972, 2013
65. Feigl GC, Ritz R, Moraes M, et al: Resection of malignant brain tumors in eloquent cortical areas: A new multimodal approach combining 5-aminolevulinic acid and intraoperative monitoring. J Neurosurg 113:352-357, 2010
66. González-Darder JM, González-López P, Talamantes F, et al: Multimodal navigation in the functional microsurgical resection of intrinsic brain tumors located in eloquent motor areas: Role of tractography. Neurosurg Focus 28:E5, 2010
67. Nossek E, Korn A, Shahar T, et al: Intraoperative mapping and monitoring of the corticospinal tracts with neurophysiological assessment and 3-dimensional ultrasonography-based navigation. Clinical article. J Neurosurg 114:738-746, 2011
68. Prabhu SS, Gasco J, Tummala S, et al: Intraoperative magnetic resonance imaging-guided tractography with integrated monopolar subcortical functional mapping for resection of brain tumors. Clinical article. J Neurosurg 114:719-726, 2011
69. Schucht P, Beck J, Abu-Isa J, et al: Gross total resection rates in contemporary glioblastoma surgery: Results of an institutional protocol combining 5-aminolevulinic acid intraoperative fluorescence imaging and brain mapping. Neurosurgery 71:927-936, 2012
70. North CA, North RB, Epstein JA, et al: Low-grade cerebral astrocytomas. Survival and quality of life after radiation therapy. Cancer 66:6-14, 1990
71. Ahmadi R, Dictus C, Hartmann C, et al: Long-term outcome and survival of surgically treated supratentorial low-grade glioma in adult patients. Acta Neurochir 151:1359-1365, 2009