Low-grade gliomas account for approximately 15% of all primary brain and CNS tumors in adults. These gliomas are classified based on histology and include WHO Grade I and II gliomas. Grade II gliomas present their own set of therapeutic challenges and will be discussed further. The most common subtypes of Grade II gliomas are astrocytoma, oligodendroglioma, and oligoastrocytoma. The majority of adults with these tumors are diagnosed between the ages of 20 and 64 years, with a median age of 39 years, and the diagnosis is frequently made among otherwise healthy and productive people. Although LGGs are more histologically and radiographically benign than their high-grade counterparts, many patients eventually die of their disease due to tumor progression and/or malignant transformation. The average overall survival for patients with LGGs is...
approximately 6 years, but up to one-fourth of patients live 20 years after diagnosis, which emphasizes the importance of maintaining patient quality of life when intervening.

Favorable prognostic factors in a 2006 analysis of patients with LGGs included female sex, younger age, Caucasian race, histology, and surgery as the initial treatment. Extent of resection is now a widely accepted factor that influences overall survival, progression-free survival, and malignant transformation in these gliomas. Gross-total resection of LGGs may lower the rate of histological progression nearly 2-fold and alter the natural history of the disease by decreasing tumor burden and therefore its oncological potential. Even if GTR is not achieved, maximal tumor resection has proven more effective than minimal resection at extending overall and progression-free survival. Postoperative neurological deficits have become increasingly uncommon with the use of specialized preoperative and intraoperative neuroimaging. As well as intraoperative motor and speech mapping. When deficits do occur, they are usually temporary, and patients tend to recover fully without adverse affects on their long-term quality of life.

Persistent seizures can also adversely affect quality of life in this patient population. Although LGGs can cause headaches or progressive neurological decline such as weakness, sensory loss, apraxia, or aphasia, 60%–80% of patients harboring LGGs initially experience a seizure; thus, seizures are the most common presenting symptom. Generalized seizures are the most common type and are often medically refractory. Some authors advocate for the use of intraoperative electrocorticography to assist in the resection of epileptogenic foci beyond the actual tumor boundaries and maximize long-term seizure control. Given all the available data, traditional treatment options including observation with serial neuroimaging or diagnostic biopsy followed by observation, radiation, and/or chemotherapy alone, are now frequently reserved for patients with medical comorbidities who are unable to tolerate aggressive surgery.

Maintaining a satisfactory quality of life for patients with LGGs is paramount. Whenever feasible, early and maximal resection should be considered. The purpose of this case series is to describe the modalities used at our institution to achieve reasonable clinical and surgical outcomes in patients whose epileptogenic tumors were considered high surgical risk by referring providers, due to the presumed infiltration of eloquent cortex and their relative diffuse character on imaging.

Methods

Study Cohort

From 2008 to 2011, a total of 52 patients underwent awake cortical mapping for maximal tumor resection given the proximity of their lesions to functional cortex. Seven patients with nonenhancing or minimally enhancing mass lesions on MRI were referred for biopsy only by referring neurosurgeons due to obvious tumor invasion into the presumed functional cortex and their relative diffuse nature on imaging. These patients underwent fMRI, DTI, and MR perfusion, followed by awake craniotomy with intraoperative neurophysiological testing by the senior author (A.A.C.G.). For 6 patients this represented an initial diagnosis, and in 1 patient this was a recurrence of a previously resected LGG. All patients were primarily English speaking and did not have any significant neurological deficits, including motor, sensory, or language dysfunctions, making them eligible for demanding intraoperative evaluations. One patient suffered from mild bradykinetic hand movements as well as intermittent visual hallucinations (Case 6), and 1 demonstrated a slight expressive aphasia (Case 3).

Preoperative Neuroimaging

Patients underwent preoperative fMRI evaluation using a 3-T system (Siemens Trio Tim, Siemens Medical) with either an 8- or 12-channel array radiofrequency coil because 3-T fMRI maps more accurately correlate with intraoperative cortical stimulation than 1.5-T maps, due to increased spatial resolution. Each patient was initially neurologically assessed by the radiologist, and hand dominance was determined using the Edinburgh Handedness Survey. A preprocedure practice session for each task was performed to assess patient cooperation and understanding. Field mapping was performed using axial 3.5-mm gradient echo field maps. The blood oxygen-level dependent signal, which indirectly measures neural activity via local tissue hemodynamic responses, was acquired with axial 3.5-mm single-shot gradient recalled echo–echo planar imaging during standardized task paradigms. Specifically, patients performed bilateral self-paced finger-tapping (gross motor test), unilateral hand/ball manipulation (fine motor test), tongue tapping, and language tasks consisting of word generation, covert naming, rhyming, and reading. Real-time prospective motion correction was performed by application of the Prospective Acquisition CorrEction (PACE) algorithm (Siemens). Moreover, during acquisition of fMRI images, continuous visual and auditory monitoring was performed as well as real-time supervision of task performance and head motion by a radiologist. The echo planar imaging fMRI raw data were processed offline using AFNI (http://afni.nimh.nih.gov/afni).

The first 8 volumes were discarded to allow system equilibration, and the time series data were slice, timing, and motion corrected using standard 3D volumetric least-squares affine techniques. Time series data from the functional runs were spatially smoothed with a low-pass filter kernel of 5 mm full width at half maximum. Hemodynamic response functions for each voxel were estimated through general linear modeling; computations were performed with the use of the AFNI function 3dDeconvolve incorporating baseline correction, retrospective head motion correction using the 3D motion parameters detected in the Prospective Acquisition CorrEction algorithm, outlier correction, and detrending. The impulse response functions were computed from the deconvolution and the area under the impulse response functions converted to baseline signal change for each stimulus event. The AFNI program AlphaSim was used to compute the
corrected Type I error. The criteria input to AlphaSim included voxel size (3.5 × 3.5 × 3.5 mm) and desired probability threshold (p = 0.05), and a minimum cluster size threshold of 25 voxels provided a corrected overall α of p < 0.05. A Monte Carlo simulation (1000 trials) was run in AlphaSim, which outputs the corrected Type I error (α). Display thresholds for interpretation of fMRI maps were set to p < 0.001.

Each preoperative neuroimaging session also included DTI to delineate the course of critical white matter tracts and DSC–MR perfusion imaging to identify tumor foci with relatively increased regional blood volume indicative of greater malignant potential. Diffusion tensor imaging was performed using axial 3.5-mm spin echo–echo planar imaging acquisitions with 48 or 64 directions. Perfusion imaging was performed using a DSC technique, with online as well as calculated maps. An intravenous injection of approximately 20 ml of gadobenate dimeglumine (MultiHance, Bracco Diagnostics, Inc.) was administered for each MRI study, delivered at a rate of 4 ml/sec for perfusion purposes. Standard acquired anatomical brain MRI sequences included: precontrast sagittally acquired 1-mm 3D sampling perfection with application-optimized contrasts using different flip angle evolutions (SPACE) T2 turbo spin echo whole brain with 1-mm axial and coronal reformats; sagittally acquired 1-mm 3D T1 magnetization-prepared rapid acquisition with gradient echo (MPRAGE) with 1-mm axial and coronal reformats; axial fast low-angled shot (FLASH); sagittally acquired 1-mm 3D FLAIR whole brain with 1-mm axial reformats; sagittally acquired 1-mm 3D T1 magnetization-prepared rapid acquisition with gradient echo, with 1-mm axial and coronal reformats; and postcontrast sagittally acquired 1-mm 3D T1 magnetization-prepared rapid acquisition with gradient echo, with 1-mm axial and coronal reformats; and postcontrast axial FLASH. Susceptibility-weighted MR images, when available, were used to retrospectively guide correction of large, spurious hemodynamic response functions due to larger draining veins. Color-coded fMRI activation maps were acquired and overlaid onto standard 3D anatomical brain MRI sequences. All relevant anatomical MRI sequences were uploaded into our neuronavigation system and functional sequences were displayed on our large-scale operating room view screens.

Awake Craniotomy and Neurophysiological Evaluation

All operations were performed in collaboration with an experienced neuroanesthesiologist and an operating team that was familiar with the workflow and goals of awake craniotomy. The patient was moved onto the operating room bed in the supine position, and intravenous access, an arterial line, and a Foley catheter (using lidocaine jelly for anesthesia) were placed while we carefully explained each step to the patient. Additionally, pneumatic compression devices were placed on the lower extremities to prevent deep venous thrombosis, and an air warmer blanket (Bair-Hugger, Augustine Medical) was placed over the patient to strictly control the temperature to 36°C. Our neuroanesthesiologist administered intravenous sedation, primarily remifentanil (0.05–0.1 μg/kg/min) and dexmedetomidine (0.7–2.0 μg/kg/hour). We infiltrated the scalp with 0.5% lidocaine with epinephrine in a 1:200,000 ratio along the trajectory of supraorbital and occipital nerves (regional scalp anesthesia) as well as at the skull clamp pin sites. The patient was then placed in a skull clamp (Mayfield, Integra LifeSciences) with 1 pin behind the ear on the side of interest and 2 pins along the contralateral superior temporal line. This method of skull clamp placement provided an ample amount of space for an ipsilateral craniotomy without any interference from the pins.

The headholder was then secured, with the head turned approximately 45° to the side opposite the surgery and the neck in a neutral position. A large exposure that includes both the lesion and the surrounding cortex is necessary for intraoperative monitoring and should be a key factor in planning the incision. A generous pterional/trauma flap incision was typically marked extending from the root of the zygoma, approximately 1 cm in front of the tragus to just beyond the midline of the forehead and behind the hairline. Neuronavigation was registered using a StealthStation TREON (Medtronic Navigation) with the surface-matching Tracer method previously described. When draping, the sheets were adjusted so that the patient’s face was unobstructed and he or she had a clear view of the anesthesiologist and/or the examiner. We performed the awake craniotomy procedure as previously described by Berger and colleagues.

Upon opening of the dura, the patient’s sedation was decreased, and the patient was allowed to wake up until he or she was fully conscious and cooperative. A subdural strip electrode was placed on the cortex in close proximity to the area of examination to monitor for afterdischarges. Exposed cortex underwent direct electrical stimulation with a Ojemann cortical stimulator approximately every 1 cm for approximately 2 seconds in the region of the tumor and in the immediate surrounding cortex. Stimulation intensity at each site was initiated at 2 mA and was gradually increased in 1-mA increments until a clinical response was observed, afterdischarges occurred, or a maximum of approximately 10 mA was reached.

Functional tissue was marked with plastic tags customized to that function (such as “Ha” for hand, “Le” for leg) as previously described. If a seizure occurred during stimulation, cold saline was gently irrigated over the discharging cortex until the event ceased. It is important not to wash away the plastic tags that have already been placed on the identified functional areas. Stimulation was then resumed at a lower threshold than that which had caused the seizure. A total of 3 noncontiguous trials were performed in each presumed eloquent area to increase the statistical probability that the stimulation finding represented real functional anatomy. For motor mapping, the examiner gauged the patient’s responses by direct visualization as well as by self-reported movement by the patient upon questioning. We recommend the use of both assessments because subtle patient movement can be visually obscured by drapes and other equipment (such as intravenous lines and Bair Hugger therapy), but reported accurately by the patient. If a discrepancy occurs, fully uncovering the body part of interest and repeating stimu-
lation can usually confirm the self-reported movement. Although no neurolinguistic standard currently exists for intraoperative testing, we assessed language using a routine battery of tests for reading, naming, comprehension, and motor speech that match the fMRI paradigms and have been previously described. Areas related to speech and language were highly variable between patients as previously noted.

The operating microscope was then used to complete tumor removal based on entry corticotomies that had the least perceived morbidity on the basis of the mapping information. During the duration of tumor resection, an examiner performed brief serial neurological examinations approximately every 10 minutes on the patient. Periodically we would use direct electrical stimulation to the areas immediately adjacent to our working space to ensure that we could continue safely. Areas of language function were generously respected by leaving a 7- to 10-mm rim of cortex around the central site of importance, which has been previously recommended. Subcortical mapping followed a similar procedure as cortical mapping and was used to help delineate the exact location of the corticospinal tract. We continued tumor resection until normal brain was encountered as defined by neuronavigation, direct electrical stimulation revealed functional cortex, or the patient began to experience a minor deficit. We were able to resect tumor in classical areas of eloquence because these areas did not show functional activity with direct electrical stimulation, due to the probable cortical reorganization of function in response to a slowly progressive pathological process.

For tumors with an insular extension, we completed a wide sylvian fissure dissection and removed tumor along the lateral aspect of the insula before sedation was decreased. This initial resection then determined the need for mapping of function along the inferior frontal and superior temporal gyri to find safe corridors in these regions to perform corticotomies. These corticotomies increased the working zone and improved the angles so we were able to remove tumor not accessible through the transylvanian approach.

**Results**

Table 1 shows the basic demographics of our patients as well as the initial clinical presentation and baseline neurological examination results in the 7 patients who underwent our protocol. All patients had initially presented with seizures, and 3 patients had been diagnosed with medically refractory epilepsy. The most common tumor location was the frontoparietal region. Follow-up ranged from 13 to 57 months (mean 31 months).

Table 2 shows the results of preoperative neuroimaging and intraoperative neurophysiology, as well as the clinical outcomes and extent of resection. Extent of resection was assessed by evaluation of residual signal abnormalities on T2-weighted sequences from postoperative 3-T MR images. Functional MRI demonstrated either motor activation and/or speech/language activation in all 7 patients, with overall qualitatively good agreement (approximately 86%) between fMRI and subsequent intraoperative neurophysiology (6 of 7 patients). One patient (Case 2) showed robust activation in all motor and language tasks, but demonstrated no significant activation in or near the tumor margins. However, during intraoperative direct electrical stimulation, functional tissue was identified in the posterior inferior frontal gyrus within the borders of the neuroimaging-defined tumor. Specifically, anomia was elicited during object naming tasks (Table 2). The disparity between fMRI and direct electrical stimulation findings likely reflects an altered hemodynamic response function in abnormal cortex, which is obscured due to the signal averaging approaches used to generate the fMRI maps. Subtle differences in hemodynamic response functions can be detected with fMRI techniques, but these may be impractical for routine preoperative mapping. Diffusion tensor imaging demonstrated subcortical white matter tract displacement due to vasogenic edema in 4 patients, and fiber tract disruption suggestive of tumor infiltration in 3 patients. Among the patients who underwent MR perfusion imaging, only 1 (Case 3)—who had been diagnosed with a recurrent Grade II oligodendroglioma in 2011 after initial resection in 2002—demonstrated increased perfusion within the tumor boundaries. Her final pathological analysis correlated with this finding by demonstrating focal areas of nuclear pleomorphism and numerous mini-gemistocytes, suggesting early anaplasia.

Only 1 patient developed a mild permanent expressive aphasia (that is, still present at last available follow-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Presentation*</th>
<th>Location</th>
<th>Final Pathology†</th>
<th>Adjuvant Therapy</th>
<th>Follow-Up (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29, M</td>
<td>generalized seizure</td>
<td>rt frontoparietal lobe</td>
<td>oligodendroglioma</td>
<td>radiation</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>20, F</td>
<td>intractable epilepsy</td>
<td>lt insula</td>
<td>astrocytoma</td>
<td>radiation/temozolomide</td>
<td>37</td>
</tr>
<tr>
<td>3</td>
<td>41, F</td>
<td>intractable epilepsy</td>
<td>lt frontoparietal lobe</td>
<td>oligodendroglioma</td>
<td>radiation/temozolomide</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>53, M</td>
<td>focal seizure</td>
<td>rt frontoparietal lobe</td>
<td>oligoastrocytoma</td>
<td>radiation</td>
<td>57</td>
</tr>
<tr>
<td>5</td>
<td>27, M</td>
<td>intractable epilepsy</td>
<td>rt frontoparietal lobe</td>
<td>oligodendroglioma</td>
<td>radiation</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>36, F</td>
<td>focal seizures</td>
<td>rt insula</td>
<td>oligodendroglioma</td>
<td>radiation</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>40, M</td>
<td>generalized seizure</td>
<td>lt insula</td>
<td>oligodendroglioma</td>
<td>none</td>
<td>25</td>
</tr>
</tbody>
</table>

* The baseline examination results in all patients were normal.
† Pathology was WHO Grade II in all cases.
### TABLE 2: Preoperative imaging, intraoperative mapping, and subsequent outcomes*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>fMRI</th>
<th>DTI</th>
<th>Perfusion MRI</th>
<th>Intraoperative Mapping</th>
<th>Extent of Resection†</th>
<th>Neurological Outcome</th>
<th>Seizure Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>motor activation at superomedial tumor margin (hand movement) &amp; at anteroinferior tumor margin (tongue movement)</td>
<td>no WMT infiltration</td>
<td>no increased perfusion</td>
<td>stimulation of superoposterior tumor, Lt hand tingling/movement</td>
<td>STR</td>
<td>temporary lt face/arm weakness; temporary lt tongue/face/arm sensory deficits</td>
<td>seizure free on 1 agent</td>
</tr>
<tr>
<td>2</td>
<td>no significant peritumoral activation</td>
<td>no WMT infiltration</td>
<td>no increased perfusion</td>
<td>stimulation of posterior margin of tumor, naming</td>
<td>STR</td>
<td>temporary speech deficits</td>
<td>seizure free on 2 agents</td>
</tr>
<tr>
<td>3</td>
<td>motor activation at posterior tumor margin, S/L activation at anteromedial tumor margin</td>
<td>WMT infiltration</td>
<td>increased perfusion at enhancing &amp; deep white matter margins</td>
<td>stimulation of posterior tumor margin, rt face/tongue movement</td>
<td>GTR</td>
<td>permanent mild expressive aphasia</td>
<td>seizure free on 2 agents</td>
</tr>
<tr>
<td>4</td>
<td>S/L activation at inferolateral tumor margin</td>
<td>inferior WMT infiltration</td>
<td>no increased perfusion</td>
<td>stimulation of posterior tumor margin, Lt hand/arm movement</td>
<td>STR</td>
<td>temporary lt face/arm/leg weakness</td>
<td>seizure free on 1 agent</td>
</tr>
<tr>
<td>5</td>
<td>motor activation at superior lateral tumor margin, activation displaced laterally by tumor; S/L activation at anterior tumor margin</td>
<td>no WMT infiltration</td>
<td>not available</td>
<td>stimulation of superomedial tumor, leg/thigh movement</td>
<td>STR</td>
<td>no temporary or permanent deficits</td>
<td>seizure free on no meds</td>
</tr>
<tr>
<td>6</td>
<td>motor activation at posteroinferior tumor margin</td>
<td>WMT infiltration</td>
<td>no increased perfusion</td>
<td>stimulation of posterior tumor margin, Lt hand movement</td>
<td>STR</td>
<td>temporary mild lt face/hand weakness</td>
<td>1–2 seizures/wk on 1 agent</td>
</tr>
<tr>
<td>7</td>
<td>S/L activation at anterosuperior tumor margin</td>
<td>no WMT infiltration</td>
<td>no increased perfusion</td>
<td>stimulation of anterosuperior tumor, expressive speech</td>
<td>STR</td>
<td>temporary expressive aphasia</td>
<td>seizure free on 1 agent</td>
</tr>
</tbody>
</table>

* S/L = speech/language; WMT = white matter tract.
† Subtotal resection defined as removal of more than 80% of the tumor on imaging.
However, temporary neurological deficits were common, developing immediately postoperatively or within 2 days of the operation. Four of the 7 patients experienced mild to moderate postoperative deficits in motor and sensory function and sensation, and 2 patients developed temporary expressive aphasia, one leading to permanent expressive aphasia. Four of these patients subsequently improved to baseline levels by the last follow-up evaluation. Immediate postoperative seizures occurred in 3 patients, including 2 who experienced intraoperative seizures with stimulation. Of these 3 patients, 1 required a dose increase of a single antiepileptic drug, 1 required a second agent, and 1 required 2 additional agents before postoperative seizures were controlled. Long-term seizure control was excellent in 1 patient with prior intractable epilepsy who was seizure free on no medication, very good in 3 patients who were seizure free on a single drug, satisfactory in 2 patients with prior intractable epilepsy who were seizure free on 2 drugs, and poor in 1 patient who continued to have 1 to 2 seizures a week. She made the choice to continue on a low dose of a single drug and did not wish to try other medications or a higher dose of her current medication due to fear of side effects.

The most common final pathology was Grade II oligodendroglioma. One patient underwent GTR and 6 patients underwent STR (> 80%) of their tumors. Four patients subsequently received postoperative radiation, 2 patients received postoperative radiation and chemotherapy in the form of temozolomide, and 1 patient did not receive any adjuvant treatment. No patient’s tumor had progressed or recurred at the last follow-up evaluation.

Illustrative Cases

Case 2

This 20-year-old woman presented with medically refractory complex focal seizures for several months, characterized by speech arrest and subsequent impaired consciousness. Initial brain MRI revealed a diffuse lesion in the left insular region suspected to be a low- or intermediate-grade glioma (Fig. 1). The patient underwent stereotactic biopsy of the slightly enhancing edge of the tumor at an outside institution and was given a diagnosis of Grade II astrocytoma. Her local providers advised that resection was too risky given the location and “infiltrating” nature of the tumor.

The patient was referred to Indianapolis Methodist Hospital for a second opinion regarding further therapy. Given her age and the debilitating nature of her epilepsy, the patient sought an aggressive resection. Preoperative fMRI demonstrated robust activation areas for both motor and language tasks that did not significantly overlap with the tumor mass. Additionally, DTI did not suggest tumor infiltration of the surrounding white matter tracts (Fig. 2), and MR perfusion did not identify any significant tumor foci harboring relatively increased blood volume, even in the region of slight contrast enhancement.

The patient underwent awake craniotomy following the protocol described above. We first removed the tumor through the transtemporal route and then mapped the inferior frontal cortex to avoid the Broca area and complete a corticotomy in the region to remove the extension of the tumor in the frontal lobe (Fig. 2D). Subcortical mapping assisted with additional tumor resection along the posterior superior aspect of the tumor. Resection was stopped when motor pathways were encountered. More than 90% of the tumor was removed (Fig. 3). This patient tolerated the procedure well, but suffered from temporary expressive speech difficulty, mainly with verbal fluency and object naming, which manifested fully by the second postoperative day and lasted for a few weeks. She was markedly improved at her 1-month follow-up and ultimately recovered to her baseline level. Final histopathological evaluation of the tumor was consistent with Grade II astrocytoma with small areas of increased mitosis. She subsequently underwent adjuvant radiation and chemotherapy (temozolomide). She has remained seizure free (Engel Class I outcome) on 2 agents, and no further tumor progression has been noted at serial follow-up appointments up to 37 months. In this case, aggressive resection allowed for optimal control of her seizures and a more accurate assessment of tumor behavior, which allowed us to tailor her adjuvant therapy.

Case 4

This 53-year-old man presented with focal motor seizures and was found to have a right frontal lesion suspected to be an LGG infiltrating the motor cortex (Fig. 4). He underwent the above preoperative protocol and DTI,
which revealed preservation of corticospinal tracts. Fractional anisotropy maps showed focal infiltration of the U-fibers at the inferior margin (Fig. 5). He therefore underwent an awake craniotomy. Stimulation of the cortex just posterior to the tumor led to left hand and arm movement. We microsurgically removed the tumor (oligoastrocytoma Grade II) as subcortical stimulation and frequent intraoperative examinations were performed. The majority of the tumor was removed as evident on postoperative MRI (Fig. 6). The patient did not suffer from any deficit intraoperatively, but demonstrated delayed (postoperative Day 1) left-sided weakness that resolved within 2 weeks after surgery. He remains seizure free on 1 medication and subsequently underwent radiation treatment. He demonstrated no tumor recurrence at last follow-up (57 months).

**Discussion**

Low-grade intrinsic brain tumors represent a thera-
neurooncologists. The risk of resection can be substantial due to the vicinity of the tumor relative to the surrounding functional cortex and vascular structures. The major goals of surgery are to avoid neurological morbidity, relieve any mass effect (which is rare), provide a diagnosis (and avoid sampling error), control seizures, and decrease the likelihood of recurrence and malignant transformation by cytoreduction. An accurate diagnosis and chromosomal analysis, specifically for loss of heterozygosity 1p and 19q and for methylation of the MGMT promoter, assists in decisions regarding additional therapy.

Although some general guidelines for adjuvant therapy exist, there are no universally agreed-upon guidelines for radiotherapy, chemotherapy, and particularly surgery for LGGs. Emerging literature strongly suggests that a greater extent of resection portends better oncological outcomes, specifically longer overall patient survival, longer progression-free survival, and decreased malignant transformation. Given this defendable trend, we have described our protocol for attempting to maximize the extent of resection without undue morbidity using specialized neuroimaging protocols and intraoperative neurophysiological monitoring in cases otherwise considered “high surgical risk” by referring neurosurgeons.

The definition of high risk is subjective and controversial and is affected by the surgeon’s experience and the availability of appropriate technology. We maximized our chances of identifying the functional cortex by first creating a roadmap with fMRI and DTI. In our series, fMRI subjectively corresponded to 100% of the intraoperative motor mapping and 86% of the intraoperative speech and language mapping performed in our patients, consistent with prior studies in demonstrating a slightly reduced accuracy of fMRI for predicting critical language cortex. Functional MRI mapping can sometimes be significantly compromised, both at the tumor margins and in normal vascular territories somewhat removed from the tumor; loss of regional cerebral vasoactivity near these tumors is believed to be a major contributing factor. Moreover, alterations in the hemodynamic response functions of abnormal cortex may be averaged out using conventional fMRI techniques, but can be elucidated with additional fMRI approaches. Such effects can result in the underestimation of genuine neuronal function surrounding tumor margins and reduce the

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**Fig. 4.** Case 4. Preoperative axial T2-weighted MR images in a 53-year-old man who presented with focal motor seizures and was found to have a right frontal lesion suspected to be an LGG infiltrating the motor cortex.

**Fig. 5.** Case 4. Three-dimensional reconstruction of DTI reveals preservation of corticospinal tracts. Descending fibers are shown in blue.

**Fig. 6.** Case 4. Postoperative axial T2-weighted MRI sequences demonstrate reasonable resection of the mass without any complications.
diagnostic accuracy of fMRI mapping, again illustrating the complementary nature of fMRI and intraoperative mapping in these challenging cases.

Diffusion tensor imaging and DSC–MR perfusion imaging also assist in characterizing more or less aggressive tumor imaging features. Diffusion tensor imaging evaluation allowed for a more thorough tumor resection in those cases that illustrated white matter tract displacement, as opposed to tract infiltration and disruption, helping direct our subcortical stimulation intraoperatively. Dynamic susceptibility contrast–MR perfusion imaging accurately predicted which tumor had greater malignant potential (focal areas of anaplasia), prompting a slightly more aggressive approach during the corresponding resection. We were able to achieve GTR in this particular patient (Case 3), but at the cost of a mild permanent speech deficit.

Awake mapping techniques such as ours can increase the extent of resection compared with traditional craniotomy techniques under general anesthesia, with 1 study showing a decrease in residual tumor volume from an average of 29 to 1.6 cm³ after adopting intraoperative neurophysiological monitoring. In our study, GTR or STR (defined as more than 80% but less than 100% on neuroimaging) was achieved in all patients. Given the typical young and productive patient with LGG, neurological outcomes are as important as oncological outcomes. Awake mapping techniques may decrease the risk of permanent postoperative neurological deficits, particularly with regard to language. Concordantly, only 1 of our patients developed a long-term deficit, in the form of a mild expressive aphasia. In particular, this single patient had a recurrent glioma requiring a second craniotomy in the setting of superficial and deep scarring, with preoperative DSC–MR perfusion images identifying tumor foci harboring relatively increased blood volume, features suggestive of more aggressive biological behavior. This approximately 12% rate of permanent injury is somewhat higher than the 3%–6% rate commonly reported in the literature and may be due to our small sample size.

Seizure outcomes in our series were excellent, with all but 1 patient becoming seizure-free. All 3 patients with preoperative intractable epilepsy became seizure-free postoperatively, although 2 of the 3 patients did require long-term anticonvulsant medications. This may be a reflection of the amount of tumor resected because seizure control appears to improve with larger extent of tumor resection. However, this result may also reflect postoperative treatment with radiation and chemotherapy, which have also—independent of each other—shown an impact on postoperative seizure occurrence. Six of 7 patients decided on postoperative adjuvant therapy based on a detailed discussion with our neurooncologist, with 4 receiving radiation therapy and 2 receiving both radiotherapy and temozolomide. Early postoperative radiation therapy has shown a progression-free survival advantage of approximately 2 years without showing an overall survival advantage in patients with LGGs. The addition of chemotherapy to radiotherapy has demonstrated an overall and progression-free survival advantage after the first 2 years of therapy. A Phase II trial examining the specific chemotherapeutic agent temozolomide demonstrated a 61% response rate of LGGs to therapy as well as a reasonable tolerability among patients. Low-grade gliomas with particular markers, including 1p19q codeletion and MGMT promoter methylation, may predict a favorable response to the drug. Taking into account such data, we believe that the high rate (86%) of patients who received adjuvant therapy in this series is based on a solid and somewhat controversial foundation.

Our treatment paradigm is similar to that used by other institutions and remains a powerful tool to maximize tumor resection among patients harboring LGGs that are considered difficult to remove due to the tumor’s location and diffuse character. Our strategies include: 1) use of preoperative DTI and functional imaging to assess for degree of functional cortex and white matter tract infiltration; 2) employing awake craniotomy with intraoperative cortical and subcortical mapping to maximize tumor resection while minimizing morbidity, if the majority of the mentioned functional areas are not affected; and 3) using transsulcal or transsylvian routes as well as transcortical routes in stimulation-confirmed noneloquent areas to minimize violation of normal cortex. We plan to include the expanded use of electrocorticography to resect epileptogenic zones adjacent to the tumor and the use of intraoperative MRI, which could provide immediate feedback regarding the extent of resection, potentially increasing our rate of GTR.

Conclusions

Individualized preoperative neuroimaging, including anatomical MRI, fMRI, DTI, and MR perfusion, followed by an awake craniotomy with intraoperative direct cortical stimulation and functional mapping, may be able to maximize the extent of resection and preserve long-term neurological function. This approach may also prevent progression and/or malignant transformation and optimize seizure control in diffuse LGGs infiltrating the functional cortex that have been traditionally believed to be too risky to remove.

Disclosure

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Cohen-Gadol, Wilden, Mosier. Acquisition of data: Cohen-Gadol, Wilden, Mosier, O’Neill. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Study supervision: Cohen-Gadol.

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