Intracranial mass lesions such as brain tumors have a well-established association with seizures. Lesion type and location are both relevant. Overall, 20%–40% of patients with brain tumors experience at least one seizure prior to diagnosis, and another 20%–45% will experience seizures at some point following diagnosis. Low-grade gliomas have been relatively more epileptogenic than malignant tumors. In patients harboring both brain tumors and refractory epilepsy, the challenge is to optimize therapy for both disease processes, which can evolve independently or in tandem.

Although GTR consistently appears to be a dominant factor for a good postoperative seizure outcome, some brain tumors may not be resectable, particularly in the case of large, infiltrative low-grade lesions. The role of chemotherapy and radiation for seizure control is not well defined in this context. Surgical strategies for optimizing epilepsy outcomes must be carefully considered in cases such as these.

Illustrative Case

History and Examination. A 4-year-old girl presented to our Comprehensive Epilepsy Center in Louisville having experienced about 3 months of generalized seizures, which were increasing in frequency. Neurological examination was nonfocal. Magnetic resonance imaging of the brain revealed an extensive diffuse nonenhancing area of abnormal signal involving the right frontal and temporal cortex and subcortical structures (Fig. 1). There was minimal mass effect and no restricted diffusion.

Operation. Eight months after the initial biopsy, the patient returned to surgery for an anterior temporal lob-
bectomy and amygdalohippocampectomy (Fig. 3). Intraoperative ECoG, used to localize areas of interictal spiking, guided further temporal and frontal cortical resection. Based on an additional tissue specimen from this procedure, the ultimate diagnosis of protoplasmic astrocytoma (WHO Grade II) was made.

Postoperative Course. The patient remained neurologically intact postoperatively. Seizure frequency decreased over the following 3 months with additional changes in medications and dosing. She has been seizure free on a regimen of clobazam, lacosamide, levetiracetam, and oxcarbazepine. No further adjuvant tumor therapy was initiated over this time.

Discussion

No study has demonstrated seizure outcomes similar or superior to those following subtotal tumor resection, when compared directly with GTR, except in 1 series of high-grade gliomas. This includes case series in which ECoG was used to localize interictal spikes intraoperatively and ictal onset extraoperatively. Although GTR is not always technically achievable, this limitation does not necessarily leave patients in these cases with ongoing uncontrolled epilepsy. However, the treatment factors that could predispose toward a good outcome in the context of STR have not been well established.

Authors of numerous retrospective case studies have reviewed seizure outcomes after brain tumor surgery from both pathological and anatomical perspectives. Representative results are summarized in Table 1. Many large studies of low-grade gliomas have been accumulated; only 1 has specifically focused on high-grade glioma. Glioneuronal tumors, specifically ganglioglioma and DNET, are often considered together because of their overlapping clinical and pathological characteristics, including epileptogenicity. Seizure outcomes have also been specifically examined for temporal lobe and insular cortex tumors are comparable to those achieved after surgery for nonneoplastic entities including vascular pathologies, such as cavernous malformation and arteriovenous malformation, and focal cortical dysplasia.

Oncological Perspective

Low-grade gliomas are the most common neoplastic pathology associated with pharmacoresistant epilepsy. A recent review of reports published between 1985 and 2010 revealed 773 patients with low-grade gliomas across 20 studies in which seizure outcomes after 6 months or more postoperatively were recorded. Gross-total resection was most predictive of complete seizure freedom, which was achieved in 357 (80%) of 448 patients who had undergone GTR. Only 100 (53%) of 187 patients who had undergone STR achieved an Engel Class I outcome.

<table>
<thead>
<tr>
<th>AUTHORS &amp; YEAR</th>
<th>PATHOLOGY</th>
<th>ENGEL CLASS I OUTCOMES (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Englert et al., 2012</td>
<td>low-grade glioma*</td>
<td>53</td>
</tr>
<tr>
<td>Englert et al., 2011</td>
<td>ganglioglioma/DNET*</td>
<td>55</td>
</tr>
<tr>
<td>Rowland et al., 2012</td>
<td>focal cortical dysplasia</td>
<td>55.8</td>
</tr>
<tr>
<td>Vale et al., 2012</td>
<td>mesial temporal sclerosis</td>
<td>78.9</td>
</tr>
</tbody>
</table>

* Treated with STR.
Other predictors of seizure freedom included good preoperative medical control of epilepsy, epilepsy duration < 1 year, and seizure semiology other than simple partial. There was no difference in seizure outcome between temporal lobe and extratemporal tumors. The use of intraoperative ECoG did not improve outcome, although its use was inconsistent within and across the various studies.

A subsequent large, single-institution retrospective analysis of 183 patients with low-grade gliomas showed consistent results, with 43 (78%) of 55 GTRs yielding an Engel Class I outcome, as compared with 52 (49%) of 105 STRs. Loss of heterozygosity on chromosome 19q and a lower Ki-67 index were pathological findings predicting better seizure outcomes in this study. The use of ECoG during surgery was based on surgeon preference. No additional treatment-related predictors of seizure freedom were identified.

Only 1 study27 has systematically examined seizure outcomes in patients with malignant glioma (WHO Grade III or IV), even though this lesion is the most common primary brain tumor in adults. Note, however, that only 153 (24%) of 648 patients initially presented with seizures, a much lower rate than has been observed in lower-grade pathologies. Seizures were more common in patients harboring anaplastic astrocytoma than glioblastoma multiforme. In this study, the extent of resection was not significantly associated with postoperative seizure freedom, although seizure recurrence after postoperative seizure freedom was strongly correlated with tumor recurrence. A higher Karnofsky Performance Scale score, a tumor location outside the parietal lobe, and the absence of preoperative uncontrolled seizures were factors that corresponded to a better postoperative seizure outcome in patients with preoperative seizures. Long-term outcome analyses in this population are limited by significantly worse overall survival compared with those for other pathologies.

A 2012 review of 39 studies on seizure outcome following resection of ganglioglioma or DNET14 documented an overall Engel Class I outcome post-GTR in 552 (87%) of 632 patients with 1 of these pathologies. The superiority of these results, as compared to an Engel Class I outcome post-STR in 88 (55%) of 160 patients, reached statistical significance. Other statistically significant factors included duration of epilepsy (< 1 year was associated with a better outcome) and seizure semiology. The preoperative presence of secondarily generalized seizures predicted a lower rate of seizure freedom than that in patients with partial seizures only. Outcomes were not significantly different when comparing a temporal versus an extratemporal tumor location. Neither did the use of intraoperative ECoG demonstrate a statistically significant effect in this analysis, although again its utilization was not standardized across the pooled studies.

A subsequent report30 describing 55 patients with epileptogenic ganglioglioma revealed 48 (87%) Engel Class I outcomes, consistent with prior studies, but did not show extent of resection to be a significant predictor of seizure outcome. Intraoperative ECoG, used in 42 patients, also did not affect outcome, and neither did a temporal versus an extratemporal tumor location. Another recent report, which was also limited to ganglioglioma pathology, demonstrated more seizures and more tumor progression with STR; ECoG was used in some patients according to individual surgeon preference. As in the low-grade glioma meta-analysis,32 duration of epilepsy < 1 year was associated with a better seizure outcome.

A more recent retrospective case study of pediatric patients with low-grade brain tumor diagnosis and associated seizures3 compared lesionectomy outcomes with the results of tailored resections, with a minimum follow-up of 1 year. Pathological diagnoses included mostly ganglioglioma and DNET, sometimes with associated focal cortical dysplasia identified. The tailored resection arm included only patients with temporal lobe tumors, in whom an extensive noninvasive preoperative epilepsy evaluation was performed. There were 5 right-sided and 6 left-sided tumors. A standard anterior temporal lobectomy with resection of mesial structures was performed and encompassed the tumor entirely. The use of ECoG was not mentioned. In the lesionectomy group, 17 of 20 patients underwent GTR; among these patients were 14 Engel Class I, 2 Engel Class II, and 1 Engel Class III outcomes. Two patients who underwent STR also achieved an Engel Class I outcome, and a third patient had an Engel Class II outcome. All 11 patients in the tailored resection group achieved Engel Class I outcomes.

Anatomical Perspective

Temporal lobe tumors have received specific attention, as mesial temporal structures are known to be associated with intractable epilepsy and are accessible within the surgical field. A recent systematic literature review of seizure outcomes following temporal lobe surgery for low-grade tumors34 demonstrated the best results when extended resection with corticectomy and hippocampectomy were performed. The study population all harbored WHO Grade I or II pathology, and patients were followed up for a minimum of 6 months postoperatively. Eighty-seven percent (294 of 338) of the patients had an Engel Class I outcome after surgery. This result was very similar to the 86.8% Engel Class I outcomes in patients who underwent GTR plus extended cortical resection and the 86% Engel Class I outcomes in patients who underwent GTR plus hippocampectomy. However, 78.6% (327 of 416) of the patients who underwent GTR alone also had Engel Class I outcomes. The difference with STR patients was highly significant; only 42.7% (70 of 164) of patients in this group had Engel Class I outcomes. The use of intraoperative and/or extraoperative ECoG or other adjuncts in the STR group was not standardized across the various studies pooled.

Two recent small case studies30,36 on insular tumors showed very good overall results for seizure control. One report on 11 patients,36 all with diagnosed low-grade glioma, demonstrated an Engel Class I outcome after a minimum of 3 total resections and 6 of 8 STRs. Another study36 of 24 patients included 13 WHO Grade I–III tumors and 11 nonneoplastic lesions. Seizure outcomes were reported according to the ILAE scale; 13 of 17 GTR cases had ILAE 1 or 2 outcomes, compared with 4 of 7 STR cases. Both studies suggested that good results are attainable with these technically very challenging lesions and that extent of resection also predicts a better outcome.
Nononcological Perspective

Comparison with other primary seizure disorders can help better contextualize tumor resection outcomes. Mesial temporal sclerosis is the most common preoperative diagnosis in adults undergoing epilepsy surgery, and its results stand as a de facto gold standard for assessing surgical seizure outcomes. A recent review of large modern studies revealed overall Engel Class I outcomes in 541 (78.9%) of 686 patients who had undergone surgery for this condition. Resection is, in general, somewhat more successful than other epilepsy operations, such as hemispherectomy for Rasmussen encephalitis (about 70% Engel Class I), Sturge-Weber syndrome (same), or hemimegalencephaly (approximately 50% Engel Class I). Palliative epilepsy interventions, such as vagus nerve stimulator placement or corpus callosotomy, are less likely to result in seizure freedom.

Seizure outcomes following subtotal tumor resection appear comparable to those after temporal lobe and extratemporal epilepsy operations in which the underlying etiology is focal cortical dysplasia. A recent meta-analysis encompassing 2014 patients with a pathological diagnosis of focal cortical dysplasia demonstrated an overall mean postoperative seizure freedom rate of 55.8 ± 16.2%. Similar to findings after tumor resections, the most important treatment-related factor in focal cortical dysplasia was complete resection of the anatomical or electrographic abnormality. This result was reflected both in the collective data and in 14 of 30 individually reviewed studies. Other favorable factors included partial seizures, temporal lobe location, abnormality on MRI, and more abnormal histology.

Frontal lobe epilepsy surgeries have been similarly reviewed. Among 1199 patients in 21 studies, overall Engel Class I outcomes over 48 months or longer were found in only 45.1%. The presence of an identifiable epileptogenic lesion preoperatively was a factor associated with a better postoperative seizure outcome. Among the 345 patients who had an identifiable epileptogenic lesion in the frontal lobe, GTR was strongly associated with a better outcome. One hundred thirty-eight (60.8%) of 227 GTR cases were classified as having Engel Class I outcomes over 48 months or longer. Findings were consistent with data in earlier, smaller studies but contrary to results in a similar study (226 patients) that showed no relationship between postoperative seizure control and choice of antiepileptic drug. Although no conclusions have been reached at this time, the use of specific agents such as levetiracetam may be a potential new, modifiable seizure outcome predictor after surgery.

Conclusions

Surgical control of epilepsy is an appropriate treatment goal in the setting of a nonresectable lesion together with medically intractable seizures. Regarding the case featured in this paper, we hypothesize that medications and surgery may have worked synergistically to ultimately achieve full seizure control, although we discovered little definitive data that would support this view. Unfortunately, prospective data are not available to guide treatment decisions. Tumor location in the temporal lobe appears to be associated with a more favorable outcome, although no conclusions can be drawn at this time regarding the utility of extended cortical and/or mesial temporal resection in unresectable lesions. Similarly, the role of ECoG remains undetermined because of its inconsistent utilization across case studies. Strategies to optimize outcome in the context of STR have not been fully developed. The prospective study of seizure control efficacy using adjuncts such as intraoperative and extraoperative ECoG may offer the best opportunity to optimize surgical outcomes.

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: Gump. Acquisition of data: Gump. Analysis and interpretation of data: Gump. Drafting the article: all authors. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Gump.

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Subtotal resection


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