Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas

Clinical article

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Object. Seizures are a common presenting symptom and cause of morbidity for patients with malignant astrocytomas. The authors set out to determine preoperative seizure characteristics, effects of surgery on seizure control, and factors associated with prolonged seizure control in patients with malignant astrocytomas.

Methods. Cases involving adult patients who underwent primary resection of a hemispheric anaplastic astrocytoma (AA) or glioblastoma multiforme (GBM) at the Johns Hopkins Medical Institutions between 1996 and 2006 were retrospectively reviewed. Multivariate logistical regression analysis was used to identify associations with preoperative seizures, and multivariate proportional hazards regression analyses were used to identify associations with prolonged seizure control following resection.

Results. Of the 648 patients (505 with GBM, 143 with AA) in this series, 153 (24%) presented with seizures. The factors more commonly associated with preoperative seizures were AA pathology (p = 0.03), temporal lobe involvement (p = 0.04), and cortical location (p = 0.04), while the factors less commonly associated with preoperative seizures were greater age (p = 0.03) and larger tumor size (p = 0.001). Among those patients with a history of seizures, outcome 12 months after surgery was Engel Class I (seizure free) in 77%, Class II (rare seizures) in 12%, Class III (meaningful improvement) in 6%, and Class IV (no improvement) in 5%. Postoperative seizures were rare in patients without a history of preoperative seizures. The factor positively associated with prolonged seizure control was increased Karnofsky Performance Scale score (p = 0.002), while the factors negatively associated with seizure control were preoperative uncontrolled seizures (p = 0.03) and parietal lobe involvement (p = 0.005). Seizure recurrence in patients with postoperative seizure control was independently associated with tumor recurrence (p = 0.006).

Conclusions. The identification and consideration of factors associated with prolonged seizure control may help guide treatment strategies aimed at improving the quality of life for patients with malignant astrocytomas.

(DOI: 10.3171/2009.2.JNS081132)

Key Words • anaplastic astrocytoma • glioblastoma multiforme • glioma • seizure

MALIGNANT astrocytomas, which include AA (WHO Grade III) and GBM (WHO Grade IV), are the most common primary CNS tumor in adults. Despite advances in medical and surgical therapy, the median survival remains less than 2 years. This median survival has failed to significantly improve over the last decade. Nevertheless, most studies on malignant brain tumors are based on survival, and quality of life remains understudied. Because the length of survival is relatively dismal, it places an emphasis on whether surgery actually improves the quality of life for patients with malignant astrocytomas.

Seizures play an important role in patients’ quality of life. Seizures, which are commonly associated with low-grade gliomas, are also a well-known presenting sign in patients with malignant brain tumors. In fact, the incidence of seizures in patients with malignant astrocytomas ranges from 30 to 50%. Furthermore, many patients with brain tumors who develop seizures will continue to have seizures despite treatment with AEDs. Thus the presence of seizures dramatically affects the quality of life for patients with brain tumors. However, the factors that may contribute to seizure control, and thus improved quality of life, remain relatively understudied.

The aims of this study were therefore: 1) to identify the prevalence and characteristics of seizures in patients undergoing primary resection of malignant astrocytomas, 2) to understand the factors associated with preoperative seizures, 3) to evaluate the effects that resection has on seizure control, and 4) to discern the factors associated with prolonged seizure control.

Abbreviations used in this paper: AA = anaplastic astrocytoma; AED = antiepileptic drug; BCNU = carmustine; CCNU = lomustine; GBM = glioblastoma multiforme; IQR = interquartile range; KPS = Karnofsky Performance Scale; PCV = procarbazine, lomustine, vincristine.
Malignant astrocytoma seizure outcomes

Methods

Patient Selection

All cases involving adult patients undergoing primary resection of a supratentorial malignant astrocytoma at a single academic tertiary-care institution (Johns Hopkins Hospital) between 1996 and 2006 were retrospectively reviewed. Patients at least 18 years old with a tissue-proven diagnosis of a supratentorial WHO Grade III AA or Grade IV GBM17 were included in the study. Patients who underwent secondary resection or any revision resection, as well as those with infratentorial malignant astrocytomas and anaplastic oligodendrogliomas and those who underwent needle biopsy, were excluded from the analysis. These exclusion criteria were established to create a more uniform patient population with adequate follow-up in order to help understand the effects of resection on seizure control in patients presenting with primary malignant astrocytomas.

Recorded Variables

The clinical, operative, and hospital course records were reviewed. Information collected from neurosurgery and neurooncology clinical notes included patient demographic data, presenting symptoms, seizure characteristics, neuroimaging findings, and data on neurological function and adjuvant therapy. The pertinent seizure-related data included date of seizure onset, type of seizure (simple partial, complex partial, and/or generalized seizures), number of seizures, and the use of AEDs and steroid medication. Preoperative seizure control was defined as the complete absence of seizures in the month prior to surgery with the use of AEDs as previously published.5 Patients with uncontrolled seizures were those with more than 1 seizure in the month prior to surgery while being treated with a therapeutic level of AEDs.5 Preoperative KPS scores19 were assigned by the clinician at the time of evaluation and available in the chart for review in all cases. The MR imaging characteristics that were recorded included the lesion’s size (largest diameter based on FLAIR), specific lobe involvement, cortical or subcortical location, presence of a hemorrhagic component, and the degree of mass effect as assessed by an independent neuroradiologist. Extent of resection was retrospectively classified from dictated reports on MR images performed less than 48 hours after resection as either gross-total resection or subtotal resection by an independent neuroradiologist blinded to patient outcomes. Notably, extent of resection was not based on the surgeon’s intraoperative impressions, as this method would be more subjective and prone to bias. Operative data were reviewed for the use of motor stimulation mapping, language mapping, electrocorticography, and neuronavigation. Tumor recurrence was defined as significant progressive growth and/or recurrence on MR imaging.

The primary outcome variables were seizure status and seizure recurrence. Seizure status was evaluated at each postoperative visit using the Engel Classification of Seizures (Class I: seizure free; Class II: rare seizures; Class III: meaningful seizures; and Class IV: no seizure improvement or worsening).9 Seizure recurrence was defined as either a recurrence of seizures after at least 1 month without seizures or an increase in the frequency of seizures.

Surgical Procedure and Antiepileptic Treatment

In general, the aim of surgery was to achieve gross-total resection of the tumor when possible. Subtotal resection was performed mainly when the tumor involved eloquent brain as confirmed by intraoperative mapping and/or monitoring (awake/speech language mapping, direct cortical motor stimulation, and motor evoked or somatosensory evoked potentials). Extended resection beyond the tumor into normal brain parenchyma was not routinely performed. Motor and somatosensory evoked potentials were routinely used in the majority of cases, while surgical navigation (wand CT and/or MR imaging) was used in all cases after 2001. The use of motor mapping or electrocorticography largely depended upon the preference of the surgeon. Motor or speech mapping was primarily used when the tumor was near the speech or motor cortex, respectively. Electrocorticography was typically used when seizures were the patient’s primary problem.

There was no defined standard for the use of AEDs. In the preoperative period, AED treatment was typically only initiated in patients in whom seizures developed. Serum levels were checked and medication doses were adjusted to establish therapeutic, nontoxic levels. The choice of a specific AED was based on the clinician’s preference. Patients who experienced seizures despite a therapeutic level of a specific AED were prescribed additional AEDs. Patients without seizures were not routinely treated with AEDs. In the perioperative period, patients with preoperative seizures generally continued to be treated with their preoperative AED regimen. Patients without seizures were typically administered an AED for seizure prophylaxis immediately prior to surgery. Patients, regardless of preoperative seizures, who were continuing AED treatment at discharge, generally had their AED levels checked prior to discharge to establish therapeutic levels. Postoperatively, patients with preoperative seizures typically continued AED treatment for 3–6 months and were then weaned from the medication. If the patients had any evidence of seizures, AED treatment was continued indefinitely. Patients without preoperative seizures typically received AED treatment during the perioperative period and were weaned off of their AED 1–2 weeks after surgery. If seizures recurred, the patient's serum levels were checked, medication doses and regimens were adjusted accordingly, and MR imaging was performed to monitor for recurrence.

Statistical Analysis

All analyses were performed using JMP 7 (SAS Institute, Inc.) unless otherwise noted. Summary data were presented as means ± SDs for parametric data and as medians with IQRs for nonparametric data. Percentages were compared via the Fisher exact test. For intergroup comparison; the Student t-test was used for parametric...
data and the Mann-Whitney U-test for nonparametric data.

To understand the factors associated with preoperative seizures, we first performed univariate logistical regression analysis between preoperative patient characteristics and the presence of any seizures. All variables associated with seizures in univariate analysis \((p < 0.10)\) were then included into a stepwise multivariate logistical regression model. Probability values < 0.05 were considered significant. This same univariate and multivariate model was used to understand the factors associated with uncontrolled preoperative seizures.

Seizure control as a function of time was plotted using Kaplan–Meier plots and compared using log-rank analysis (Prism 5, GraphPad Software, Inc.). Loss of seizure control was defined as a decrease in seizure control such that the Engel classification was increased (for example, Engel Class I to II) following resection. Time was assessed from the date of resection.

To understand the factors associated with prolonged seizure control, univariate proportional hazards regression analysis (Cox model) was first performed to evaluate associations between radiographic, preoperative, operative, and pathological variables with postoperative seizure control at last follow-up. All variables associated with seizure control in univariate analysis \((p < 0.10)\) were then included in a stepwise multivariate proportional hazards regression model. Probability values < 0.05 were considered significant. For the purposes of this outcome analysis, Engel classification was dichotomized as Engel Class I (seizure free) versus Engel Class II–IV (seizures). This same multivariate proportional hazards regression model was also used to evaluate the association between seizure recurrence and tumor recurrence or progression.

**Results**

**Patient Population**

The patient information is summarized in Table 1. A total of 648 patients underwent primary resection of a malignant astrocytoma during the reviewed period. Of these patients, 143 (22%) had an AA and 505 (78%) had a GBM. The patients’ mean age was 55 ± 17 years at the time of surgery.

The median KPS score at presentation was 80 (IQR 80–90). One hundred fifty-three patients (24%) presented with seizures, 113 (17%) with signs of increased intracranial pressure (headache, nausea, vomiting), 150 (23%) with motor deficits, 101 (16%) with speech or language difficulty, 63 (10%) with visual deficits, and 46 (7%) with sensory deficits. The mean tumor size was 4.3 ± 1.6 cm; 279 (43%) of the tumors involved the frontal lobe; 121 (19%), the parietal lobe; 176 (27%), the temporal lobe; and 34 (5%), the occipital lobe. The tumor was located cortically in 243 (38%) and subcortically in 405 (63%) of the cases. Gross-total resection was achieved in 217 patients (33%). Surgical navigation was used in 363 patients (56%), evoked potentials in 544 (84%), motor mapping in 71 (11%), and electrocorticography in 52 (8%). There were no cases of perioperative mortality, but a new motor deficit developed in 27 patients (4%), a new visual deficit in 12 (2%), and a new language deficit in 24 (4%). At last follow-up, 371 patients (57%) had received postoperative radiation therapy; 151 (23%) Gliadel wafer implantation; and 173 (27%) temozolomide, 37 (6%) BCNU or CCNU, and 12 (2%) PCV chemotherapy.

**Patients With and Without Preoperative Seizures**

The results of the Fisher exact test comparing data obtained in patients with and without preoperative seizures are summarized in Table 1. Patients with any preoperative seizures were younger \((p = 0.001)\) and more commonly male \((p = 0.01)\) than patients without preoperative seizures. Patients with seizures also had fewer complaints of headache \((p = 0.01)\), as well as sensory \((p = 0.004)\), language \((p = 0.05)\), and visual deficits \((p = 0.03)\). Additionally, patients with seizures had tumors that were smaller \((p = 0.001)\), more commonly located along the cortical surface \((p < 0.001)\), and had an AA histological type \((p < 0.001)\). No other clinical, imaging, operative, or pathological variables were found to be significantly different between the two cohorts.

In comparison of patients with uncontrolled versus controlled seizures, patients with uncontrolled seizures presented with lower KPS scores \((p = 0.05)\) and more commonly with complex partial seizures \((p = 0.001)\). Interestingly, patients with uncontrolled seizures also had tumors that were significantly larger \((p = 0.005)\) and were more likely to have a hemorrhagic component \((p = 0.009)\). No other clinical, imaging, operative, or pathological variables were found to be significantly different between the 2 cohorts.

The majority of the 153 patients who presented with seizures were administered AEDs at the time of surgery (88%); 42 (27%) of 153 were treated with combination therapy, 102 (67%) received phenytoin, 13 (8%) leviteracetam, 12 (8%) divalproex sodium, 5 (3%) carbamazepine, 7 (5%) valproic acid, 4 (3%) lamotrigine, and 3 (2%) phenobarbital. Combination therapy was used in 10 (39%) of the 26 patients with uncontrolled seizures. There were no statistically significant differences in AED regimen between patients with preoperatively controlled and preoperatively uncontrolled seizures in this group of patients (Table 2). Of the 495 patients without preoperative seizures, AED treatment was initiated in 51 (10%) prior to surgery: phenytoin in 36 patients, levetiracetam in 6, divalproex sodium in 5, carbamazepine in 3, and valproic acid in 1.

**Factors Associated with Preoperative Seizures**

**Factors Associated with Any Preoperative Seizures.**

The factors that were associated with any preoperative seizures in univariate analysis were: age, male sex, KPS score, headache, motor deficit, sensory deficit, language deficit, visual deficit, AA histological type, temporal lobe location, increasing tumor size, and cortical tumor location. No other clinical, imaging, or pathological variables were found to be associated with preoperative seizures in this group of patients.

In multivariate analysis, the factors significantly as-
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## TABLE 1: Clinical and demographic characteristics of 648 patients (153 presenting with seizures and 495 without)*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean Age ± SD</th>
<th>Male Sex</th>
<th>Associated Sx</th>
<th>Seizure Duration</th>
<th>Imaging Findings</th>
<th>Tumor Pathology</th>
<th>Periop Outcomes</th>
<th>Adjuvant Tx</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (495 pts)</td>
<td>Any (153 pts)</td>
<td>Contr (127 pts)</td>
<td>Uncontr (26 pts)</td>
<td>Mean Age ± SD</td>
<td>Tumor Location</td>
<td>Extent of Resection</td>
<td>Radiation Tx</td>
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<tr>
<td></td>
<td></td>
<td>Any† (13 pts)</td>
<td>Uncontr‡ (10 pts)</td>
<td></td>
<td>Mean Age ± SD</td>
<td>Tumor Location</td>
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<td>Mean Age ± SD</td>
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<td>Uncontr‡ (10 pts)</td>
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<td>Mean Age ± SD</td>
<td>Tumor Location</td>
<td>Extent of Resection</td>
<td>Radiation Tx</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, values represent numbers of patients (%). Abbreviations: contr = controlled; IQR = interquartile range; NA = not applicable; pts = patients; uncontr = uncontrolled.
† Comparison between patients with and without preoperative seizures.
‡ Comparison between patients with uncontrolled seizures and no seizures preoperatively.
§ Statistically significant.
Factors Associated with Uncontrolled Preoperative Seizures.

Among patients with seizures, the factors that were associated with uncontrolled preoperative seizures in univariate analysis were: KPS score, duration of seizures, complex partial seizures, tumor size, and hemorrhagic component. No other clinical, imaging, or pathological variables were found to be associated with uncontrolled seizures in this data set.

In multivariate analysis, the factors significantly associated with uncontrolled preoperative seizures were complex partial seizures (OR 5.801, 95% CI 1.056–13.893, p = 0.03), tumor size (OR 1.558, 95% CI 1.041–2.332, p = 0.03), and hemorrhagic component (OR 12.857, 95% CI 1.867–18.537, p = 0.01; Table 3). The presence of complex partial seizures and a tumor with a hemorrhagic component made it, respectively, approximately 6 and 13 times more likely that a patient would develop uncontrolled seizures. Each centimeter increase in tumor size made it 1.5 times more likely that a patient would have uncontrolled seizures. Of note, tumor size > 3 cm (OR 2.750, 95% CI 1.011–7.9160, p = 0.01) had the strongest positive association with uncontrolled seizures.

Seizure Outcomes. Seizure control was recorded at each postoperative visit. For the purposes of this study, seizure control 6 and 12 months postoperatively was tabulated for patients for whom data were available (Table 4). Engel classification was determined for patients who presented with and without a history of seizures. Overall, the majority of patients remained seizure free (Class
Six months after surgery, 3% had rare seizures (Class II), 1% had meaningful seizures (Class III), and no patients had worsening seizures (Class IV). Twelve months after surgery, outcome in 5% was Class II, 2% Class III, and 1% Class IV. Among those patients who had no history of preoperative seizures, seizure occurrence was rare in the postoperative period, with 1% and 4% of these patients reporting seizures 6 and 12 months postoperatively, respectively. Only 2 (1%) of the patients in this group had meaningful seizures (Engel Class III and IV).

Among the patients with a history of seizures, Engel classification was determined to be Class I in 87%, Class II in 10%, Class III in 3%, and Class IV in 0% at 6 months after surgery. Twelve months postoperatively, outcome was Class I in 77%, Class II in 12%, Class III in 6%, and Class IV in 5%. Importantly, among the patients who presented with uncontrolled seizures, seizure occurrence was rare in the postoperative period, with and 4% of these patients reporting seizures 6 and 12 months postoperatively, respectively. Only 2 (1%) of the patients in this group had meaningful seizures (Engel Class III and IV).

The Kaplan-Meier method was used to plot seizure control in all cases. The median follow-up time for all patients was 13.7 months (IQR 8.9–20.3 months). The Kaplan-Meier plot of seizure control for patients who presented with seizures is depicted in Fig. 1. The 6-, 12-, and 18-month seizure-free survival rates were 85, 69, and 52%, respectively. For patients undergoing primary resection of a GBM (Fig. 2), the 6-, 12-, and 18-month seizure-free survival rates were 82, 73, and 50%. For patients undergoing primary resection of an AA, the 6-, 12-, and 18-month seizure-free survival rates were 91, 68, and 54%, respectively. There was no significant difference in seizure control between patients with GBM and AA (p = 0.47).

Factors Associated with Seizure Control. The factors associated with seizure control in univariate analysis were: KPS score, controlled seizures, motor deficit, language deficit, parietal lobe location, occipital lobe location, and tumor size. No other clinical, imaging, or pathological variables were found to be associated with seizure control in this data set. Of note, none of the AEDs was associated with postoperative seizure control in this data set.

In multivariate analysis, the factor significantly associated with seizure control was increased KPS score (RR 0.944, 95% CI 0.914–0.977, p = 0.002; Table 6). The factors more commonly associated with poor seizure control, on the other hand, were preoperative uncontrolled seizures (RR 2.748, 95% CI 1.131–6.368, p = 0.03) and parietal lobe involvement (RR 4.236, 95% CI 1.582–11.012,
p = 0.005). After we controlled for tumor histological type, these factors still remained independently associated with seizure control.

Each incremental increase in preoperative KPS score increased the chance of seizure control by 5%. Of note, KPS score ≥ 80 (RR 0.097, 95% CI 0.028–0.388) had the strongest association with seizure control, and increased seizure control more than 10 times. Patients with preoperative uncontrolled seizures and parietal lobe involvement, in contrast, had an almost 3- and 4-fold decreased chance of prolonged seizure control. Interestingly, patients who underwent gross-total resection of their malignant glioma had improved seizure control that trended toward but did not reach statistical significance (RR 0.581, 95% CI 0.270–1.085, p = 0.09). Also noteworthy is that complex partial seizures had no association with prolonged seizure control (p = 0.51).

Of note, the postoperative use of specific AEDs was not associated with postoperative seizure control in this data set (Table 5). In addition, the use of intraoperative electrocorticography was not associated with postoperative seizure control (RR 0.989, 95% CI 0.417–2.327, p = 0.31).

Seizure Recurrence and Tumor Recurrence. Seizures had worsened in 37 patients (24%) at last follow-up, and this worsening corresponded with tumor recurrence in 24 (65%). Patients who experienced a decrease in seizure control, as compared with those who maintained seizure control, were more likely to have tumor recurrence (p < 0.001). In fact, in multivariate proportional hazards regression analysis, loss of seizure control was independently associated with tumor progression (RR 2.662, 95% CI 1.300–6.063, p = 0.005). This was independent with uncontrolled seizures were presence of complex partial seizures, increasing tumor size, and hemorrhagic components in the tumor.

Overall, resection appears to control seizures in the majority of patients with malignant astrocytomas. The majority of patients remained seizure free (Class I outcome) 6 months (96%) and 12 months (92%) postoperatively. Of those with a history of seizures, 77% had Class I outcome, 12% Class II, 6% Class III, and 5% Class IV at 12 months after surgery. Of those with uncontrolled seizures, 56% had Class I outcome, 13% Class II, 19% Class III, and 13% Class IV at 12 months after surgery. Seizure occurrence was rare in the postoperative period for patients who did not have preoperative seizures. Importantly, the factor associated with prolonged seizure control was increased KPS score, while preoperative uncontrolled seizures and parietal lobe involvement were associated with poor seizure control. Patients who experienced a decrease in seizure control, as compared with those who maintained seizure control, were more likely to have tumor recurrence. In fact, loss of seizure control was independently associated with tumor recurrence.

Seizures in Patients With Malignant Astrocytomas

Duration of survival for patients with malignant astrocytomas remains dismal, with median survival times of less than 2 years.14,24 Prolonging survival remains a primary focus of many clinical studies, and little is known whether current treatments are effective, at improving quality of life for patients with these malignant tumors. Not surprisingly, seizures play an important role in patients’ quality of life.16 The incidence of seizures in patients with malignant astrocytomas varies between 30 and 50% in several series.14,24,27 The seizures manifest as simple or complex partial with or without secondary generalization, and their development adds substantial morbidity to patients with brain tumors.10,14,24,27 Moreover, medical management of seizures is rarely effective not only because patients with these tumors express multidrug-resistance proteins, but also because AEDs often interact with chemotherapeutic agents. Furthermore, the

### TABLE 5: Postoperative AED therapy in 153 patients who presented with seizures

<table>
<thead>
<tr>
<th>AED</th>
<th>No. of Pts</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenytoin</td>
<td>94 (61)</td>
<td>0.50</td>
</tr>
<tr>
<td>levetiracetam</td>
<td>23 (15)</td>
<td>0.43</td>
</tr>
<tr>
<td>divalproex sodium</td>
<td>4 (3)</td>
<td>0.28</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>8 (5)</td>
<td>0.41</td>
</tr>
<tr>
<td>valproic acid</td>
<td>3 (2)</td>
<td>0.46</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>10 (7)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

* Probability values are the result of univariate proportional hazards regression analysis.

### TABLE 6: Predictors of seizure control following resection in patients with malignant gliomas according to multivariate proportional hazards regression analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relative Risk (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>improved seizure control</td>
<td>0.944 (0.914–0.977)</td>
<td>0.002</td>
</tr>
<tr>
<td>greater KPS score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>decreased seizure control</td>
<td>2.748 (1.131–6.368)</td>
<td>0.03</td>
</tr>
<tr>
<td>uncontrolled preop seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>parietal lobe involvement</td>
<td>4.236 (1.582–11.012)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Discussion

In this study of patients undergoing primary resection of a malignant astrocytoma (AA or GBM), 24% of patients presented with seizures. Seizures were controlled with AED therapy in 83% of this patient group and uncontrolled in 17%. The factors significantly associated with preoperative seizures were AA histological type, temporal lobe involvement, and cortical location, while the factors less commonly present in patients with seizures were older age and larger tumor size. Among patients with seizures, the factors significantly associated with uncontrolled seizures were presence of complex partial seizures, increasing tumor size, and hemorrhagic components in the tumor.
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use of AEDs is associated with significant cognitive side-effects.31,33,36,38

The pathophysiology of tumor-related epileptogenesis remains poorly understood, but several mechanisms have been proposed. Malignant astrocytomas, as a result of their rapid progression, may cause acute tissue damage such as tissue necrosis or hemosiderin deposition.30 Tumors may also generate changes in peritumoral tissue by increasing the expression of gap junctions between neurons, eliciting aberrant neuronal migration, and increasing the concentration of epileptogenic glutamate neurotransmitters.1,32,42 Furthermore, tumors may alter the microenvironment by causing tissue hypoxia, decreasing pH, and increasing edema as result of their increased cellular metabolism.5,32 These potential effects, among others, may alter the balance between intracortical inhibitory and excitatory mechanisms, thus inducing epileptogenic activity.

Prior clinical studies on seizure control in patients with malignant astrocytomas are few and limited.15,24,40 Moots et al.24 studied 65 patients with malignant astrocytomas, and 29 of these patients presented with seizures. The authors found that patients with preoperative seizures were at risk for developing postoperative seizures. Wick and colleagues40 reviewed cases involving 73 of 107 patients with gliomas (including Grade II gliomas) who presented with seizures. They found that seizures recurred, regardless of AED therapy, with tumor progression or recurrence in the majority of cases. Hildebrand et al.15 studied 134 of 183 patients who presented with seizures. The majority of these patients had Grade II gliomas. The authors found that AEDs only deterred the development of secondary generalization. These studies and others did not have a uniform patient population in which the majority of patients had low-grade gliomas, which are associated with a higher incidence of seizures.5,15,22,28,39,40 In fact, the mechanism by which low- and high-grade gliomas elicit seizures may be distinctly different.30 Furthermore, many of these studies did not use multivariate analysis to evaluate factors independently associated with prolonged seizure control.15,22,28,39,40 Therefore, the factors associated with seizures and seizure control in patients with malignant astrocytomas remain poorly understood.

Factors Associated With Seizures

In this study, the factors positively associated with preoperative seizures were AA pathological type, temporal lobe involvement, and cortical location, whereas the factors negatively associated with seizures were older age, headache, and increasing tumor size. Among patients with seizures, patients who presented with complex partial seizures and larger tumors were more likely to have uncontrolled seizures.

Compared with patients with GBM, patients with AA had a 2-fold increased risk of preoperative seizures. Previous studies have found that slower growing tumors are associated with higher incidences of seizures, with 60–85% of patients with low-grade gliomas presenting with seizures as compared with 30–50% of patients with malignant astrocytomas.30 This higher incidence of seizures in association with slower growing tumors is thought to be due to the longer survival times of these patients, making the tumors more prone to cause epileptogenic activity. Others speculate that low-grade tumors, unlike their higher grade counterparts, can isolate nontumor brain regions through their slow growth, thus creating epileptogenic regions.32

In the present study, tumors, regardless of pathological type, that involved the cortical regions and/or the temporal lobe were more likely to be associated with preoperative seizures. This association between cortical regions and seizures supports the findings of previous studies of low-grade gliomas.5,15 The cortical region has a higher density of neurons, and consequently lesions in this area are more likely to cause epileptogenic activity than lesions in the white matter–dense subcortical regions.37 Likewise, the temporal lobe has also been found to be a region vulnerable to epileptogenesis. This is thought to be due to the unique network structures and neuronal plasticity that exist in the temporal lobe and, more specifically, the amygdala and hippocampal regions.3,22 Therefore, as with low-grade gliomas, malignant astrocytomas in this study that involved neuron-dense cortical and/or temporal lobe regions may have had an increased propensity to cause seizures.

Patients with brain tumors and seizures can have simple or complex partial seizures with or without generalization. Among patients with seizures, patients with complex partial seizures were more likely to have uncontrolled seizures in this study. In patients without brain tumors, uncontrolled seizures are more common in patients with complex partial seizures than simple partial seizures. Sporis et al.34 speculate that this is due to gene polymorphisms that render patients with complex partial seizures resistant to current AEDs. Likewise, this association between complex partial seizures and drug resistance has also been seen in patients with low-grade gliomas.5

The factors negatively associated with seizures in this study were older age and increasing tumor size. This study supports the finding that the incidence of epilepsy in patients without tumors decreases with increasing age.20 Younger patients with less developed brains may be more susceptible to epileptogenic activity.13,20,25 and this may explain why older patients with brain tumors have a decreased incidence of seizures. Furthermore, increasing tumor size was negatively associated with preoperative seizures. However, among patients with seizures, patients with uncontrolled seizures were likely to have larger tumors.

Seizure Control

Seizure control can be achieved in the majority of patients with malignant astrocytomas who present with seizures. At 12 months after surgery, outcome was Class I in 77% of the patients in our study, Class II in 12%, Class III in 6%, and Class IV in 5%. These results are similar to those of other studies on seizure control and low-grade gliomas.5,15,22,28,39,40 In fact, most of these studies report rates of complete seizure control ranging from 65 to 77%.5,15,22,28,39,40 Therefore, the majority of patients who present with seizures will be seizure free following resection.
Patients in this study with better preoperative functional status were more likely to have prolonged seizure control at last follow-up. In fact, patients with preoperative KPS scores ≥ 80 had a 10-fold increased chance of prolonged seizure control. Interestingly, previous studies of both low- and high-grade gliomas have found that patients with better preoperative functional status have prolonged survival. These factors may make these tumors less amenable to medical and surgical therapy. Besides uncontrolled seizures, parietal lobe involvement was also associated with decreased seizure control. These tumors may be in closer proximity to more eloquent areas, which may make them more difficult to resect and more likely to cause epileptogenic activity. Patients who underwent gross-total resection of malignant glioma in this study had prolonged seizure control that trended toward, but did not reach, statistical significance. Larger studies may be needed to elucidate the precise significance of this finding, but extensive resection may prolong seizure control by removing the epileptogenic focus. In fact, this association between extent of resection and seizure control has been demonstrated in patients with non–tumor-related temporal lobe epilepsies.

Tumor Recurrence and Seizure Control

In this study, seizure recurrence after initial postoperative seizure control was significantly associated with tumor progression. The exact mechanism underlying this finding is unknown, but intuitively it seems that lesions that cause seizures would continue to create these symptoms once the tumor recurs. Therefore, patients who redevelop seizures must be investigated for tumor recurrence.

Strengths and Limitations

Studies evaluating seizure characteristics and seizure control in patients undergoing resection of malignant astrocytomas are few and limited. The overwhelming majority of studies on resection of malignant astrocytomas have focused on factors associated with survival and recurrence, which have minimally changed despite advances in medical and surgical therapy. An understudied aspect is functional outcome and, more specifically, seizure control, which has been primarily limited to patients with low-grade gliomas. An understanding of these factors as they relate to malignant astrocytomas is important for several reasons. First, quality of life and the ability to resume activities of daily living are important for patients with malignant astrocytomas, and rival prolonged survival in many instances. Second, the effects of surgical therapy on seizure control for patients with malignant astrocytomas remain poorly understood. The ability to stratify risk in cases involving patients at risk for poor seizure control may help guide clinical decision making. Finally, developing strategies to prolong seizure control may provide a better approach to improving functional outcome for patients with malignant astrocytomas.

This study, however, has some limitations. Since all the patients in this study underwent resection of a malignant astrocytoma, it is difficult to discern whether surgery or AED treatment most contributed to seizure control. This study mainly shows that surgery in combination with AED therapy can provide adequate seizure control. Studies comparing surgery and AED therapy versus AED therapy alone are therefore needed. This study was also not designed to evaluate the effects of AEDs on seizure control for patients with malignant astrocytomas. This is because the complete preoperative AED administration history was not available in all cases, and the type of AEDs used varied drastically among patients, with choice of a particular AED often being the result of selection bias. Further studies on the control of seizures with specific AEDs are therefore necessary. This study was also not designed to evaluate the efficacy of electrocorticography because its use varied among physicians.

This study was not designed to evaluate the association between seizure control and the degree of resection, only whether gross-total resection was associated with seizure control. This was because the degree of resection was not routinely assessed in the radiology reports. Studies assessing the degree of resection and seizure outcomes may therefore provide useful insight. Additionally, it was hard to elucidate the effects that radiation and chemotherapy have on seizure control since many of these patients received these therapies. This study, however, showed no statistically significant associations between seizure control and patients’ having undergone any radiation or chemotherapy. This study is also inherently limited by its retrospective design, and therefore it is not appropriate to infer direct causal relationships from the results.

Despite these inherent limitations, we tried to create a uniform patient population by utilizing strict inclusion criteria. We included only patients who underwent primary resection of their tumor, and excluded patients (for example those with infratentorial tumors, those undergoing secondary resection, and those undergoing biopsies) in whom the effects of resection and seizure control might be masked. In addition, we used multivariate analyses to control for confounding variables in patients with malignant astrocytomas. Given these statistical controls and a relatively precise outcome measure, we believe our findings offer useful insights into the care of patients with seizures and malignant astrocytomas. Nevertheless, prospective studies are needed to provide better data to guide clinical decision making.
Malignant astrocytoma seizure outcomes

Treatment Recommendations

Seizures are not uncommon in patients with malignant astrocytomas. Seizures are more common in patients with AAs, temporal lobe tumors, and cortical tumor locations, whereas older patients and those with larger tumors are less likely to have seizures. Therefore, it may be plausible to initiate AED therapy in patients at risk for developing seizures (those with cortical tumor location, temporal lobe involvement, younger age). For patients who develop seizures, AED treatment should be started, but it should be realized that a significant percentage of patients will still have seizures despite therapeutic levels of AEDs. Patients with complex partial seizures, larger tumors, and hemorrhagic tumor components may be less responsive to AEDs. Despite this, AED therapy, in combination with surgery (where the aim is generally to achieve gross-total resection when it is safe to do so), appear to significantly reduce seizure frequency. Seizure control, however, is less likely to be achieved in patients with poor preoperative KPS, parietal lobe involvement, and uncontrolled preoperative seizures. Patients with these features should be counseled about their high risk of seizures despite surgery and AED therapy. Importantly, if seizures recur, there should be a high index of suspicion for tumor recurrence or progression.

Conclusions

Duration of survival for patients with malignant astrocytomas remains relatively dismal. This poor survival places an emphasis on understanding whether surgery actually improves the quality of life for patients with malignant astrocytomas. Seizures affect a patient's quality of life and are common in patients with brain tumors. An understanding of the seizure characteristics and the factors associated with prolonged seizure control may therefore provide insight into developing effective treatment strategies aimed at improving patients' quality of life.

Disclaimer

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

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Manuscript submitted September 7, 2008. Accepted February 26, 2009. Please include this information when citing this paper: published online April 3, 2009; DOI: 10.3171/2009.2.JNS081132. Address correspondence to: Alfredo Quiñones-Hinojosa, M.D., The Johns Hopkins Hospital, Department of Neurosurgery, Johns Hopkins University, CRB II, 1550 Orleans Street, Room 247, Baltimore, Maryland 21231. email: aquinon2@jhmi.edu.