Morphological Characteristics of Brain Tumors Causing Seizures

Jong Woo Lee, MD, PhD; Patrick Y. Wen, MD; Shelley Hurwitz, PhD; Peter Black, MD, PhD; Santosh Kesari, MD, PhD; Jan Drappatz, MD, PhD; Alexandra J. Golby, MD, PhD; William M. Wells III, PhD; Simon K. Warfield, PhD; Ron Kikinis, PhD; Edward B. Bromfield, MD†

Objective: To quantify size and localization differences between tumors presenting with seizures vs non-seizure neurological symptoms.

Design: Retrospective imaging survey. We performed magnetic resonance imaging–based morphometric analysis and nonparametric mapping in patients with brain tumors.

Setting: University-affiliated teaching hospital.

Patients or Other Participants: One hundred twenty-four patients with newly diagnosed supratentorial glial tumors.

Main Outcome Measures: Volumetric and mapping methods were used to evaluate differences in size and location of the tumors in patients who presented with seizures as compared with patients who presented with other symptoms.

Results: In high-grade gliomas, tumors presenting with seizures were smaller than tumors presenting with other neurological symptoms, whereas in low-grade gliomas, tumors presenting with seizures were larger. Tumor location maps revealed that in high-grade gliomas, deep-seated tumors in the pericallosal regions were more likely to present with nonseizure neurological symptoms. In low-grade gliomas, tumors of the temporal lobe as well as the insular region were more likely to present with seizures.

Conclusions: The influence of size and location of the tumors on their propensity to cause seizures varies with the grade of the tumor. In high-grade gliomas, rapidly growing tumors, particularly those situated in deeper structures, present with non–seizure-related symptoms. In low-grade gliomas, lesions in the temporal lobe or the insula grow large without other symptoms and eventually cause seizures. Quantitative image analysis allows for the mapping of regions in each group that are more or less susceptible to seizures.

Arch Neurol. 2010;67(3):336-342

Seizures are encountered in a majority of patients with primary brain tumors and are a major cause of morbidity in these patients.1,2 Thirty percent to 50% of patients experience a seizure by the time their tumors are diagnosed, and an additional 6% to 45% of patients who do not initially present with seizures eventually develop them.3-5 Characteristics of brain tumors and their mechanism in causing seizures in patients are incompletely understood.6-8 Low-grade, well-differentiated gliomas,1,6-9 cortically located tumors,3,10,14 and location in the temporal/frontal/motor/sensory cortices8,15,17 are more frequently associated with seizures.

Although there is a high incidence of seizures in these patients, treatment strategies remain poorly defined. Prophylactic anticonvulsant therapy, shown to be ineffective in preventing seizures in patients with brain tumors in multiple large-scale studies,12,18-20 is not recommended by the American Academy of Neurology.5 Nonetheless, prophylaxis remains a widespread practice21 because of difficulty in determining which patients are at greatest risk for seizures. Determination of morphometric factors influencing seizures would help in identifying patients at greatest risk for early, targeted treatment and prevent potentially toxic, unnecessary treatment in patients at minimal risk.

Although studies examining brain tumors in relationship to epilepsy have localized tumors to a particular lobe,10 few studies have performed quantitative volumetric or spatial mapping analysis of tumors in relation to their epileptogenic potential. Regions within a particular lobe are likely to exhibit different epileptogenic potential to tumor invasion and tumors frequently affect multiple contiguous lobes.6
Modern imaging techniques allow for analysis of lesions over a large group of subjects through registration and mapping techniques. In this study, we used these techniques to examine the size and location of primary supratentorial glial brain tumors and characterized their propensity to cause seizures at presentation.

This retrospective study examined patients who underwent surgical evaluation of a brain tumor at the Brigham and Women’s Hospital between January 2005 and September 2007. Inclusion criteria were age 18 years or older, new diagnosis of brain tumor, supratentorial location, pathologically proven glial tumor, and preoperative acquisition of high-quality volumetric magnetic resonance imaging (MRI) scan. Tumors were designated “low grade” (World Health Organization grade I or II) or “high grade” (World Health Organization grade III or IV).

A total of 81 patients presented with low-grade gliomas during the study period. Of these, 24 patients were excluded from the analysis because of lack of access to preoperative volumetric MRI scans (13 patients), unclear clinical history (2 patients), clinical or radiological suspicion of higher-grade lesion than suggested from pathological examination (3 patients), poorly defined lesion (1 patient), suspicion of neuroglial component (1 patient), and inconclusive pathological examination (6 patients).

All 57 patients with low-grade glioma who met the criteria were analyzed. Because of their vastly larger numbers, 67 consecutive patients with high-grade gliomas who obtained identical MRI sequences between the dates March 24, 2005, and May 20, 2006, from 317 eligible patients during the study period, were selected. Patient records were reviewed to determine the presenting symptom. Approval for this study was obtained from the local human research institutional review board.

**IMAGE ACQUISITION**

Patients with low-grade tumors underwent preoperative imaging with 1 of several MRI scanners from which T2 and volumetric T1 images were obtained: 0.5-T MRI (Signa SP; GE Medical Systems, Milwaukee, Wisconsin); 1.5-T General Electric Signa Excite scanner; and 3-T General Electric Signa scanner. Patients with high-grade tumors underwent imaging with a 1.5-T General Electric Signa scanner.

**IMAGE PROCESSING**

Tumors were manually segmented from the MRI by a blinded rater using standard image processing software to create a lesion mask (3D Slicer; www.slicer.org and MNI Display; www.bic.mni.mcgill.ca). For low-grade tumors, T2-weighted images were resampled and registered into T1-weighted space; the tumor margin was determined by the extent of T2 signal abnormality. For high-grade gliomas, tumor margin was delineated by the area of contrast enhancement on the volumetric T1-weighted image.

Magnetic resonance images were transformed into a standardized coordinate space based on the Talairach atlas to account for differences in brain orientation and differences in intracranial volume. Automatic registration using linear affine transformation was performed from the T1-weighted images. Because distortions of the anatomy caused the registration procedure to fail at times, registration validity was checked by selecting 6 points on both the template and the target brains (maximal anterior and posterior cortical extent along the anterior-posterior commissure line, upper and lower extent along the perpendicular line through the anterior commissure, left and right extent along the third axis formed by the 2 previous lines); if the root mean square was greater than 5 mm, registration was reperformed using the manually selected coordinates (MNI Register; www.bic.mni.mcgill.ca). Tumor volumes were calculated after registration (MATLAB; MathWorks, Natick, Massachusetts).

**STATISTICAL ANALYSES**

Logistic regression was used to estimate odds ratios and 95% confidence intervals for patient characteristics. SAS version 9.1 was used (SAS Institute, Cary, North Carolina). To assess the localization value of the tumors causing seizures, a χ² statistic map was calculated. At each voxel, the group of patients presenting with a tumor at that voxel was determined. From this group, the number of patients who presented with seizures, as compared with the expected number (the product of the number of patients with a tumor at that voxel and the ratio of the patients presenting with seizures in the study population), was used to calculate the χ² statistic. In voxels where the number of patients with seizures exceeded the number of patients without seizures, a higher value of χ² is indicative of a stronger likeliness that patients with a tumor at that location would present with seizures than at other locations. A complementary χ² map was calculated to determine “protective” locations, eg, where presentation with seizures is less likely.

To assess the significance of the χ² statistic, a nonparametric mapping method based on permutation testing was used, which requires making minimal assumptions regarding our data. The χ² was used as an omnibus statistic. The χ² map was masked to include only voxels that exceeded the threshold level of 2. These were grouped into discrete clusters using a 6-connectivity model, and a cluster mass was calculated. Thereafter, the labeling of each patient as “seizure” vs “no seizure” was randomly reassigned. Analysis was performed using MATLAB version 7.6 (R2008a).

**RESULTS**

One hundred twenty-four patients were included in this study. Their main clinical and pathological characteristics are listed in Table 1. Odds ratios regarding these characteristics are listed in Table 2. Patients with presumed low-grade gliomas not included in the study were compared with patients who were included. Of the 24 patients, 15 were male, 14 had left-sided tumors, 7 had temporal tumors, and 15 had seizures; their average age was 46.3 years (range, 18-83 years). The age of the excluded patients was higher than the included group, but the other characteristics did not differ significantly.

Patients with low-grade tumors were more likely to present with seizures than patients with high-grade tumors. Age was significantly protective overall (P = .02) with a reduction in likelihood of 23% per decade. However,
subgroup analysis revealed that patients with high-grade tumors were significantly older than those with low-grade tumors.

LOBE INVOLVEMENT

Patients with tumors involving the temporal lobe were more than twice as likely to present with seizures. This tendency was significant in low-grade tumors and there was a similar but slightly weaker tendency in patients with high-grade tumors. Low-grade tumors in the temporal lobe were more likely to present with seizures (16 of 20 patients). High-grade tumors in the temporal lobe were neither more nor less likely to present with seizures (14 of 29 patients).

VOLUME AND SEIZURES

There was significant qualitative interaction between tumor volume and grade (P = .004). Tumor volume was predictive of presenting with seizures in patients with low-grade tumors (P = .01), with a 3% increase in likelihood per cubic centimeter (Figure 1). In high-grade tumors, there was a slight tendency for tumor volume to be protective in relation to seizure presentation (P = .13).

LOCATION MODELING

The aggregate of all the tumors generated from the sum of the binary tumor masks is shown for high-grade (Figure 2A) and low-grade (Figure 2B) gliomas. The χ² maps of high-grade tumors were created indicating where seizures were more likely to occur and where other neurological symptoms were more likely to occur. Cluster analysis revealed 1 cluster that reached statistical significance (P < .05) to indicate regions where patients were more likely to present with nonseizure neurological symptoms (Figure 3). The cluster was located in the frontal pericallosal region and was 70.4 cm³ in volume. No clusters of significant size were found indicating where seizures were more likely to occur, including the temporal region.

The χ² maps of low-grade tumors indicating where seizures were more likely to occur and where other neurological symptoms were more likely to occur were created. Significant clusters where patients were more likely to present with seizures were found in the right hemisphere (size 56.5 cm³) and in the left hemisphere (size 70.4 cm³) (Figure 4A). Clusters in both hemispheres involved the temporal lobe, while the right hemisphere cluster included the insular region. There were no statistically significant clusters to denote regions where patients were more likely to present with nonseizure neurological symptoms.

Because of concern of uneven spatial distribution of the low-grade tumors between the 2 hemispheres, cluster analysis was repeated after inverting all right hemispheric tumors across the midline to simulate 58 left hemispheric tumors. This revealed a single significant cluster of 115.6 cm² that included the insular as well as most of the temporal lobe (Figure 4B).

SEIZURE SEMIOLOGY

Of the 26 patients with high-grade tumors with seizures, 11 patients had generalized convulsions; 7 had simple partial seizures; and 7 had complex partial seizures. There was insufficient information to determine accurate seizure semiology in 1 patient. Of the 35 patients with low-grade tumors and seizure presentations, 21 had generalized convulsions; 10 had simple partial seizures; and 4 had complex partial seizures. No significant differences were seen between the 2 groups (P = .24).

COMMENT

We examined the effects of glioma size and location on propensity to generate seizures as an early symptom using quantitative image analysis techniques.

SEIZURES AND SIZE OF TUMOR

In this study, 34% of patients with high-grade tumors and 62% of those with low-grade tumors presented with seizures, consistent with the previously reported values.1-3,38,50-38 High- and low-grade tumors differ in terms of their relationship between seizure size/location and the propensity to present with seizures. High-grade tumors
presenting with seizures are likely to be smaller than those presenting with other symptoms. We postulate that rapidly growing tumors cause symptoms related to mass effect, such as headache, cognitive deficits, or focal weakness, rather than seizures. The reverse was found with low-grade tumors, where large tumors were more likely to present with seizures than small tumors. We postulate that large tumor size is indicative of the long duration of silent growth, allowing more time for seizures to develop.

Table 2. Odds Ratios and 95% Confidence Intervals for Patient and Tumor Characteristics to Predict Presentation With Seizures

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22 (35)</td>
<td>35 (57)</td>
<td>2.51 (1.22-5.19)</td>
</tr>
<tr>
<td>High</td>
<td>41 (65)</td>
<td>26 (43)</td>
<td>0.40 (0.19-0.82)</td>
</tr>
<tr>
<td>Age per decade, y, median (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>50 (18-88)</td>
<td>42 (18-88)</td>
<td>0.77 (0.61-0.96)</td>
</tr>
<tr>
<td>Low grade</td>
<td>38 (18-64)</td>
<td>38 (18-56)</td>
<td>1.00 (0.80-1.66)</td>
</tr>
<tr>
<td>High grade</td>
<td>57 (21-88)</td>
<td>55 (26-88)</td>
<td>0.80 (0.59-1.10)</td>
</tr>
<tr>
<td>Tumor volume, median (range), per 10 cm³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>41 (1.0-166)</td>
<td>35 (0.3-205)</td>
<td>1.05 (0.96-1.15)</td>
</tr>
<tr>
<td>Low grade</td>
<td>14 (1.0-87)</td>
<td>38 (0.3-305)</td>
<td>1.31 (1.06-1.60)</td>
</tr>
<tr>
<td>High grade</td>
<td>47 (2.6-167)</td>
<td>30 (2.9-145)</td>
<td>0.89 (0.74-1.04)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>28 (44)</td>
<td>33 (54)</td>
<td>1.47 (0.73-2.99)</td>
</tr>
<tr>
<td>Low grade</td>
<td>5 (23)</td>
<td>17 (49)</td>
<td>3.21 (0.97-10.63)</td>
</tr>
<tr>
<td>High grade</td>
<td>23 (56)</td>
<td>16 (62)</td>
<td>1.25 (0.46-3.41)</td>
</tr>
<tr>
<td>Temporal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>18 (29)</td>
<td>31 (51)</td>
<td>2.58 (1.23-5.43)</td>
</tr>
<tr>
<td>Low grade</td>
<td>4 (18)</td>
<td>16 (46)</td>
<td>3.79 (1.06-13.51)</td>
</tr>
<tr>
<td>High grade</td>
<td>14 (34)</td>
<td>15 (58)</td>
<td>2.63 (0.96-7.23)</td>
</tr>
<tr>
<td>Hippocampal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>4 (6.4)</td>
<td>8 (13.1)</td>
<td>2.23 (0.63-7.82)</td>
</tr>
<tr>
<td>Low grade</td>
<td>2 (9.1)</td>
<td>5 (14.3)</td>
<td>1.67 (0.29-9.44)</td>
</tr>
<tr>
<td>High grade</td>
<td>2 (4.9)</td>
<td>3 (11.5)</td>
<td>2.54 (0.40-16.37)</td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>40 (63)</td>
<td>51 (84)</td>
<td>2.93 (1.25-6.86)</td>
</tr>
<tr>
<td>Low grade</td>
<td>19 (86)</td>
<td>29 (83)</td>
<td>0.78 (0.17-3.43)</td>
</tr>
<tr>
<td>High grade</td>
<td>21 (51)</td>
<td>22 (85)</td>
<td>5.24 (1.53-17.91)</td>
</tr>
<tr>
<td>Left hemisphere</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>37 (59)</td>
<td>32 (52)</td>
<td>0.78 (0.38-1.58)</td>
</tr>
<tr>
<td>Low grade</td>
<td>12 (55)</td>
<td>17 (49)</td>
<td>0.79 (0.27-2.29)</td>
</tr>
<tr>
<td>High grade</td>
<td>25 (61)</td>
<td>15 (58)</td>
<td>0.87 (0.32-2.37)</td>
</tr>
</tbody>
</table>

a Interaction with grade, P=.004.
b Interaction with grade, P=.05.

Figure 1. Tumor volume and grade.

Figure 2. Summed statistic image. At each voxel, the number of patients presenting with tumors is calculated. A, High-grade tumors. B, Low-grade tumors.
Small low-grade tumors are sometimes found on imaging studies acquired to evaluate nonspecific symptoms that may be unrelated, as was the case in 7 patients. Whether tumors were completely incidental or whether they contributed to the presenting symptom is difficult to determine.

**LOCATION OF THE TUMOR**

Patients with high-grade tumors in the pericallosal region, likely representing so-called butterfly gliomas, were significantly less likely to present with seizures. Such deeply seated, rapidly growing tumors are more likely to cause symptoms due to mass effect rather than seizures.

Patients who presented with high-grade tumors in the temporal lobes were not more likely to present with seizures than other neurological symptoms. However, in comparison with the relatively low rates of seizures in deeply seated pericallosal tumors, this result indicates a relative increase in the epileptogenicity in this region. In contrast, patients with low-grade tumors were more likely to present with seizures if their tumors were located in the temporal lobe.

Patients with tumors in the insular cortex were also more likely to present with seizures. The insular cortex is often a region of seizure spread in temporal lobe epilepsy. Clinically, seizures originating from the insular region are difficult to distinguish from those arising from elsewhere in the temporal lobe and 10% of patients initially thought to have temporal lobe epilepsy may in fact have seizures originating in the insular cortex, though detailed investigation revealed distinct clinical differences. In a recent large retrospective review of 51 insular grade II gliomas, 50 patients presented with seizures and 45 patients had normal neurological examination results. High frequency of preoperative seizures has been reported in other smaller series describing low-grade insular tumors. These results suggest that tumors located in the insular cortex are likely to be clinically silent until the patient experiences a seizure.

**ASYMMETRY OF LOW-GRADE TUMORS**

Although the number of patients with low-grade tumors in the left hemisphere was equal to the number of right hemisphere tumors, and the volumes of the tumors in both hemispheres were comparable, the aggregate tumor image (Figure 2B) revealed that the distribu-
tion of the tumors was not identical; a large number of tumors were located in the right insular region, many of which presented with seizures. We are unaware of any studies in the literature that have systematically examined this asymmetry, though similar asymmetries have been found in some studies.41,43

Although volumes of regions of significance were similar over both hemispheres, regions of highest correlation with seizure presentation were located over the right hemisphere. It is possible that left hemisphere tumors are less likely to present with seizures, perhaps because of increased presentation with other neurological findings as a result of greater eloquence of the dominant hemisphere.

LIMITATIONS

Because of the retrospective nature of this study, we were unable to control for a number of factors. Magnetic resonance imaging scanning parameters were not homogeneous over the duration of this study. This is a historical artifact representing the development of imaging technology at our institution. We minimized the influence of this variability by selecting only patients who had received volumetric T1-weighted scans to obtain the highest-resolution images available at the time.

No regions of significantly increased risk for seizures were found for low-grade tumors in other areas where small tumors are believed to typically cause seizures (motor/sensory cortices, hippocampus). We also did not find that occipital tumors are unlikely to present with seizures. These negative findings may be due to a low number of tumors at those locations in our study.

It is likely that the tumor extends beyond the edge of the enhancing lesion in high-grade gliomas and that T2 signal changes in low-grade gliomas in some areas may represent an edematous process rather than tumor. However, these methods result in boundaries that are easily identified and provide reasonable delineation of tumors.

The registration procedure in patients with large lesions is challenging,40 causing automated registration to fail when tumors substantially distort cortical structure. We chose to correct the registration errors manually, which decreases interrater reproducibility as compared with automated techniques; such automated registration procedures are not yet well established.

We used a clustering algorithm rather than a voxel-based statistic. The cluster mass test is known to have increased sensitivity and specificity compared with tests based on voxel intensity when the signal is spatially extended.47-49 and as a result, these tests are more powerful than single-threshold approaches but result in reduced localizing power. We chose a low primary threshold level ($\chi^2 = 2$), resulting in large clusters emphasizing the high spatial correlation between adjacent voxels in our population; in doing so, we were unable to detect intense focal signals. The optimal selection of primary thresholds with permutation labeling remains to be resolved.27

Despite these limitations, volumetric imaging analysis is useful to localize regions that are particularly susceptible to seizures, as well as define regions that are relatively protective against seizures. Future studies using similar techniques may be used to identify patients who are at greater and lower risk for seizures prospectively and postoperatively, allowing for early selection of patients for targeted antiepileptic drug therapy.

Accepted for Publication: October 23, 2009.
Correspondence: Jong Woo Lee, MD, PhD, Department of Neurology, Brigham and Women’s Hospital, Boston, MA 02115 (jlee36@partners.org).


Financial Disclosure: None reported.

Funding/Support: This study was supported by funding from the National Epifellows Foundation (Dr Lee), grant U41 RR019703 from the National Center for Image-Guided Therapy, and grants P50CA67165-11 and P41RR13218 from the National Institutes of Health.

REFERENCES


