Surgical treatment of drug-resistant epilepsy caused by gliomas in eloquent areas: experience report

Tratamento cirúrgico de epilepsias refratárias causadas por gliomas localizados em áreas eloquentes: uma série de casos brasileiros

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ABSTRACT

Drug-resistant epilepsy associated with central nervous system tumors is generally caused by low grade gliomas. This group of tumors is usually found in brain eloquent areas, such as the insular lobe, rolandic cortex and supplementary motor area and, historically, possess a greater risk of postoperative deficits. **Objective:** The aim of this investigation was to present our surgical experience on patients with drug-resistant epilepsy caused by gliomas in eloquent areas. We retrospectively investigated variables that impact seizure control, such as tumor location, extent of resection, invasion into the lenticulostriate arteries in the patient, especially those with insular gliomas. **Methods:** Out of 67 patients with eloquent area brain tumors operated on in our service between 2007 and 2016, 14 patients had symptoms of drug-resistant epilepsy. Volumetric analysis, extent of resection (EOR), type of approach and mapping, among other factors were correlated with the 12-month postoperative seizure outcome. **Results:** Univariate analysis showed that the factors showing statistical relevance with seizure control were preoperative volume (p = 0.005), EOR (p = 0.028) and postoperative volume (p = 0.030). **Conclusion:** There was a statistically significant association between the EOR and the Engel score for epilepsy control: an EOR < 70 was associated with Engel II, III, IV and an EOR > 90 was associated with Engel I. Eloquent area gliomas can safely be resected when surgeons use not only microsurgical anatomy concepts but also brain mapping. **Keywords:** Drug resistant epilepsy; brain neoplasms; brain mapping; glioma.

RESUMO

Epilepsia refratária secundária a tumores cerebrais são geralmente causadas por gliomas de baixo grau. Esse grupo de tumor é frequentemente localizado em áreas eloquentes do cérebro como na insula, córtex rolândico e área motora suplementar; e sua ressecção apresenta alto risco de déficits neurológicos no pós operatório. **Objetivo:** O objetivo do estudo consiste em apresentar nossa experiência no tratamento cirúrgico de pacientes com epilepsia refratária secundária a gliomas em áreas eloquentes. **Métodos:** O estudo consiste em investigação retrospectiva de variáveis que interferem no controle de crises, tais como localização do tumor, grau de ressecção, invasão tumoral de artérias lenticulo estriadas, principalmente em gliomas insulares. Dentre 67 pacientes portadores de gliomas em área eloquente operados no período de 2007 a 2016, 14 doentes apresentavam epilepsia refratária associada. Análise volumétrica do tumor, grau de ressecção, acesso cirúrgico, bem como o uso de mapeamento cortical intraoperatorário foram correlacionados com desfecho de controle de crises epilépticas em 12 meses. **Resultados:** Em análise univariada os fatores relacionados com controle de crises em 12 meses foram volume tumoral pré operatório (p = 0.005), grau de ressecção (p = 0.028) e volume tumoral pós operatório. **Conclusão:** O grau de ressecção apresentou significância estatística em relação ao controle de crises conforme escala de Engel. Ressecções menores que 70% apresentaram correlação com Engel II, III e IV; enquanto ressecções maiores que 90% apresentaram correção positiva com Engel I. Gliomas em áreas eloquentes podem ser ressecados de forma segura desde que seja realizada por equipe experiente com conhecimento acurado da anatomia microcirúrgica e emprego de mapeamento cortical intraoperatorário. **Palavras-chave:** Epilepsia refratária; neoplasias encefálicas; mapeamento encefálico; glioma.

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The International League Against Epilepsy (ILAE) defines drug-resistant epilepsy as "failure of adequate trials of two tolerated and appropriately chosen anti-epileptic drug schedules (whether as monotherapy or in combination) to achieve seizure freedom". Drug-resistant epilepsy may result in cognitive impairment, diminished quality of life, and even neuropsychological damage or death.2,3

Drug-resistant epilepsy secondary to central nervous system tumors is generally caused by low grade gliomas.4,5,6,7,8,9 This group of tumors is usually found in brain eloquent areas, such as the insular lobe, rolandic cortex and supplementary motor area.6 Performing surgery on patients with this condition has potential not only to treat drug-resistant epilepsy4,5,6,7,8 but also to improve overall survival1,2,11,12,13,14. However, operating on tumors in the so-called eloquent areas carries a significant risk of postoperative deficits. Refined surgical techniques, based on microneuro-surgical anatomy4,5,15,16,17 and brain mapping, have permitted safe resection with minimal risk18,19,20,21,22,23.

In the present study, we reviewed our surgical experience in resection of low-grade gliomas in eloquent areas causing drug-resistant epilepsy, and determined the most relevant variables related to seizure control.

METHODS

Patient population

The study was approved by the Institutional Review Board of the Federal University of Rio Grande do Sul. All patients provided written informed consent.

From 67 eloquent area brain tumors operated on between 2007 and 2016, 14 patients had symptoms of drug-resistant epilepsy. The cases were individually analyzed according to the tumor’s location; while insular gliomas were classified based on the Yaşargil24 and Berger-Sanai25 criteria. The histological tumor type was defined according to the 2016 World Health Organization classification.26 Handedness and language dominance were determined using the Portuguese Edinburgh Handedness Inventory.27

Several eloquent cortical and subcortical regions have been identified in brain mapping studies. We focused on tumors within or adjacent to those eloquent areas, such as the rolandic cortex, supplementary motor area, corona radiata, internal capsule, uncinate fasciculus, dominant temporal, dominant mid-to-posterior frontal, and dominant mid-to-anterior parietal lobes.28

For functional outcomes assessment, we applied the following preoperative tests: the Picture Naming Test and the Boston Diagnostic Aphasia Examination29, as well as the Karnofsky Performance Status scale.30 The clinical outcome in the immediate and six-month postoperative period was categorized as “normal”, “motor deficit” or “speech disorder”.

To evaluate seizure control in the follow-up, we used the Engel outcome scale, which was dichotomized as class I versus class II-IV, 12 months after surgery. As well, we categorized seizures using the following parameters: type of crisis according to the 2017 ILAE classification, seizure frequency (daily, weekly or monthly) and duration (more or less than one year before surgery).31

Surgical technique

Over the years, we have experienced significant technological advancement in resecting tumors in eloquent brain areas. In the first patient from our series, operated on in 2007, the patient presented with a left insular low grade glioma. The tumor was resected through a transsylvian approach based only on microsurgical anatomic landmarks for insular tumors.

From 2008, we had somatosensory and motor evoked potentials with subcortical electric stimulation become available using the Nicolet Endeavor system (Cardinal Healthcare) to define the medial limits of the resection. We assumed that an electromyographic response in the contralateral body with 7 mA of subcortical stimulation was the medial limit for safe resection as it is close to the motor tract. For tumors located on or near the rolandic cortex or supplementary motor area we used mapping of the motor cortex with an anesthetized patient.

In 2010, for insular tumors in the dominant hemisphere, we used awake surgery with a transsylvian approach. For insular tumors extending beyond the insula into the frontal and temporal lobes, we used a transcortical approach where silent mapping permitted. From 2010 to 2014, for purely insular tumors located in the dominant hemisphere, we used awake surgery with a transsylvian approach. For insular tumors extending beyond the insula into the frontal and temporal lobes, we used a transcortical approach where silent mapping permitted.

Our parameters of intraoperative cortical and subcortical electrical stimulation were used according to the methodology described by Duffau23,31. In patients with insular gliomas undergoing awake surgery, our medial limit for resection was identified primarily through altered speech patterns, such as paraphasia due to electric subcortical stimulation of the inferior fronto-occipital fasciculus. To evaluate the potential involvement of lenticulostriate arteries with the medial aspect of the tumor, we carried out an accurate analysis of the coronal and axial T2- and T1-weighted magnetic resonance (MR) images and considered that tumors that entangled these vessels could not be entirely resected. All patients undergoing awake surgery were submitted to a prior simulation of the surgical procedure.

Volumetric analysis

Until 2013, we estimated the tumor’s volume using the three largest diameters (D1, D2 and D3) of the tumor on T2-weighted MR images. Then, we applied the formula D1 x D2 x D3 / 2.
Since 2014, we have used the OsiriX (Pixmeo SARL, Geneva, Switzerland) via stored files of MR images in DICOM format (digital imaging and communications in medicine).

The EOR was classified as < 70%, 70-90%, > 90% or gross total resection. The residual tumor volume was subdivided into four categories: < 10 cm³, 10-19 cm³, 20-29 cm³ and > 30 cm³. Eight repeated surgical procedures were required due to tumor recurrence. We have not included data from these new surgeries in our statistical analysis.

**Statistical analysis**
A descriptive analysis of the data was performed. Categorical variables are shown as absolute (n) and relative (%) frequencies. Association chi-squared tests and Fisher’s exact test were applied to compare all categorical variables. Mann-Whitney tests were applied to compare the distributions in quantitative variables related to the Engel variable.

Survival analysis discriminating the Engel and EOR variables were applied to show the mean, median and the 95% confidence intervals. Mean time until death was assessed by the log-rank test in each survival analysis. Statistical analysis was performed using SPSS for Windows 18.0 (SPSS Inc., Chicago, IL, USA). A two-tailed p-value < 0.05 was considered significant.

**RESULTS**

**Patient population**
The patients’ demographic background, preoperative clinical condition, brain mapping type, surgical approach, volumetric analysis of T2-weighted MR images, histological findings, EOR and postoperative status are presented in Table 1.

| Characteristics                          | Engel | p-value* |
|------------------------------------------|-------|----------|
|                                          | I     | II, III or IV |
|                                          | n = 11 (78.6) | n = 3 (21.4) |
| Sex                                      |       |          |
| Female                                   | 3 (60) | 2 (40) | 0.505 |
| Male                                     | 8 (88.9) | 1 (11.1) | |
| Diagnostic (months)                      | 20.0 (40.4) | 8.0 [1.0; 140.0] | 15.0 (10.8) | 18.0 [3.0; 24.0] | 0.456 |
| Age                                      | 35.3 (12.4) | 35.0 [13.0; 53.0] | 32.7 (15.5) | 28.0 [20.0; 50.0] | 0.769 |
| Preoperative volume (cm³)                | 46.1 (19.8) | 39.0 [26.0; 98.0] | 17.3 (7.0) | 18.0 [10.0; 24.0] | 0.005 |
| Seizure classification                   |       |          |
| Focal aware                              | 3 (100) | 0 (0) | 0.140 |
| Focal clonic seizures                    | 0 (0) | 1 (100) | |
| Focal impaired awareness                 | 0 (0) | 1 (100) | |
| Focal sensory (olfactory)                | 2 (100) | 0 (0) | |
| Focal to bilateral tonic-clonic          | 6 (85.7) | 1 (14.3) | |
| Seizure frequency                        |       |          |
| Daily                                    | 3 (75) | 1 (25) | > 0.999 |
| Monthly                                  | 2 (66.7) | 1 (33.3) | |
| Weekly                                   | 6 (85.7) | 1 (14.3) | |
| Duration                                 |       |          |
| < 1 year                                 | 8 (88.9) | 1 (11.1) | 0.505 |
| > 1 year                                 | 3 (60) | 2 (40) | |
| Preoperative EEG pattern                 |       |          |
| Epileptic                                | 6 (66.7) | 3 (33.3) | 0.607 |
| Normal                                   | 4 (100) | 0 (0) | |
| Slow                                     | 1 (100) | 0 (0) | |
| Location                                 |       |          |
| Insula                                   | 8 (100) | 0 (0) | 0.053 |
| Motor and/or premotor                    | 3 (60.0) | 2 (40.0) | |
| Frontal gyrus                            | 0 (0) | 1 (100) | |
| Tumor enhancement                        |       |          |
| No                                       | 9 (81.8) | 2 (18.2) | >0.999 |
| Yes                                      | 2 (66.7) | 1 (33.3) | |

Continue
| Characteristics | Engel          | p-value* |
|-----------------|---------------|----------|
|                 | I             | II, III or IV |       |
|                 | n = 11 (78.6) | n = 3 (21.4) |       |
| **Histological grade** |               |           |       |
| 2 - Diffuse astrocytoma NOS | 8 (80) | 2 (20) | 0.665 |
| 3 - Anaplastic astrocytoma NOS | 1 (50) | 1 (50) |       |
| 4 - Glioblastoma with primitive neuroectodermal tumor-like components | 1 (100) | 0 (0) |       |
| Ganglioglioma | 1 (100) | 0 (0) |       |
| **Surgical approach** |               |           |       |
| Transcortical | 2 (66.7) | 1 (33.3) | 0.449 |
| Transsylvian | 5 (100) | 0 (0) |       |
| Transsylvian/transcortical | 1 (100) | 0 (0) |       |
| **Mapping** |               |           |       |
| Motor | 3 (75) | 1 (25) | >0.999 |
| Motor awake | 3 (100) | 0 (0) |       |
| Motor/language (awake) | 2 (66.7) | 1 (33.3) |       |
| No | 3 (100) | 0 (0) |       |
| **EOR** |               |           |       |
| < 70% | 1 (33.3) | 2 (66.7) | 0.028 |
| 70 - 89 | 0 (0) | 0 (0) |       |
| ≥ 90% | 9 (100) | 0 (0) |       |
| Supratotal | 1 (50) | 1 (50) |       |
| **Immediate postoperative** |               |           |       |
| Aphasic and hemiplegic | 1 (100) | 0 (0) | 0.275 |
| Hemiparesis | 2 (66.7) | 1 (33.3) |       |
| No | 8 (88.9) | 1 (11.1) |       |
| Worse aphasia | 0 (0) | 1 (100) |       |
| **Follow-up (6 months)** |               |           |       |
| Motor aphasia and hemiparetic / Karnofsky Performance Status 60 | 1 (100) | 0 (0) | 0.392 |
| No / Karnofsky Performance Status 100 | 10 (83.3) | 2 (16.7) |       |
| No Karnofsky Performance Status 70 | 0 (0) | 1 (100) |       |
| **Postoperative volume** |               |           |       |
| Partial resection | 1 (33.3) | 2 (66.7) | 0.030 |
| Supratotal resection | 1 (50) | 1 (50) |       |
| Total resection | 9 (100) | 0 (0) |       |
| **Sanai** |               |           |       |
| “Giant” | 2 (100) | 0 (0) |       |
| Zone 1 | 4 (100) | 0 (0) |       |
| Zone 1+4 | 1 (100) | 0 (0) |       |
| Zone 3+4 | 1 (100) | 0 (0) |       |
| **Yasargil** |               |           |       |
| 3A | 1 (100) | 0 (0) |       |
| 3B | 3 (100) | 0 (0) |       |
| 5A | 3 (100) | 0 (0) |       |
| 5B | 1 (100) | 0 (0) |       |
| **Lenticulostriate arteries involvement** |               |           |       |
| No | 7 (100) | 0 (0) |       |
| Yes | 1 (100) | 0 (0) |       |
| **Additional treatment** |               |           |       |
| Chemotherapy | 0 (0) | 1 (100) | 0.392 |
| Chemotherapy plus radiotherapy | 2 (66.7) | 1 (33.3) |       |
| No | 4 (80) | 1 (20) |       |
| Second and third surgery procedure / chemotherapy plus radiotherapy | 4 (100) | 0 (0) |       |
| Second surgery procedure – radiotherapy | 1 (100) | 0 (0) |       |
| **Status** |               |           |       |
| Alive | 6 (75) | 2 (25) | >0.999 |
| Deaths | 5 (83.3) | 1 (16.7) |       |
This study included nine male and five female patients, and seizure was the primary symptom among them. Their period of refractory epilepsy ranged from 2–15 months. For statistical analysis, we categorized the refractory period into less than, and more than, one year. Five (35.7%) patients had refractory seizures for more than one year. Of these, four were referred after brain biopsy for oncological treatment.

Seven (50%) patients had insular gliomas, one of whom had a histological diagnosis of glioblastoma with primitive neuroectodermal tumor-like components. One (7.1%) patient had an insular ganglioglioma. The 6 (35.7%) remaining patients had low grade gliomas located in the supplementary motor area (n = 5; 28–35.7%) and Broca’s area (n = 1; 7.1%). Tumor volume ranged from 13 cm³ to 53 cm³.

**Surgical technique and postoperative course**

Motor mapping was used in all patients with tumors located in the rolandic cortex or supplementary motor area. In three of these, the patients were submitted to awake craniotomies, and the other two were anesthetized. For the anesthetized patients, the tumors were completely resected, and patients did not show any motor or speech dysfunction at the six-month follow-up. For the three patients who underwent awake surgery, gross total resection was achieved in two of them and partial resection in the last one. At six months, there was no neurological dysfunction in any of these patients.

Regarding surgery on insular gliomas presenting with drug-resistant epilepsy, only our first patient developed permanent mild aphasia and hemiparesis, probably related to the disruption of the inferior fronto-occipital fasciculus and arcuate fasciculus. There was no neurophysiologic intraoperative monitoring available at that time; however, the high frequency of seizures justified the procedure. All other patients with insular gliomas had no permanent deficit. Apart from one patient (Figure 1), whose tumor harbored lenticulostriate arteries in the medial portion, the EOR was > 90% in all patients (Figure 2).

The surgical approach to insular gliomas did not influence the final result regarding the EOR and neurological preservation. However, the transsylvian corridor approach to middle cerebral artery manipulation caused intense headache, discomfort and prolonged brain mapping. Therefore, we preferred a transcortical approach with subpial resection.

The patient with a tumor in Broca’s area was a native Portuguese speaker, but also fluent in English and Spanish. During intraoperative subcortical stimulation of the inferior frontal gyrus he presented with the language switching phenomenon and started answering questions in English. Thus, we performed only partial resection of the lesion.

For the insular gliomas, we used the Yaşargil and Berger-Sanai classifications. However, there was no statistical correlation between these classification systems and the EOR (Table 2). The glioma of the insula on which partial resection was performed due to the involvement of lenticulostriate arteries was classified as Yaşargil 5B, or giant tumor in the Berger-Sanai classifications. Neither of these classification systems consider the involvement of these arteries, an important aspect to be considered for the degree of resection in insular gliomas. When we compared these two classification systems, we noted that all giant tumors were classified as 5A in the Berger-Sanai Classification or 5B tumors in the Yaşargil Classification.

Cortical and subcortical mapping was performed in 13 patients. The first patient of the series was operated on without stimulation, as this was not available. For the other two patients (a right insular low grade glioma and a left insular ganglioglioma), neurophysiological monitoring was not considered necessary due to the relatively low risk for development of permanent postoperative neurological deficits.

Gross total resection (EOR > 90%) was achieved in 11 (78.5%) patients.

**Predictive factors of postoperative seizure**

When analyzing the effect of surgery on seizure control in our drug-resistant epilepsy patients, we achieved good outcomes in seizure control. For comparison analysis, we divided postoperative seizures into two groups, either Engel I or Engel II, III and IV (Table 1). In the one-year follow up, 78.6% of patients presented with good seizure control and, of the remaining 21.4%, one was classified as Engel II and two as Engel III. The patients classified as Engel I and II maintained the same anti-epileptic drug doses after surgery. The patient who still had drug-resistant epilepsy even after surgery did not reduce their frequency of seizures after new anti-epileptic drug regimens.

In patients who had tumor recurrence, all occurred at least one year after surgery and the predominant symptom was an increase in seizure frequency. Even with no statistical relevance, the survival rate was higher in the Engel II, III and IV group. The survival analysis showed a mean of 103 months in the Engel I group and 140.4 months in the Engel II, III and IV group (p = 0.295) (Table 3).
Regarding insular gliomas, there was no correlation between the type of classification and the EOR. However, the involvement of lenticulostriate arteries by the tumor is an important limiting factor to achieving gross total resection.

**DISCUSSION**

Drug-resistant epilepsy prevalence varies between 15.6% and 37% among people with epilepsy. Those patients may have structural abnormalities that explain the frequency of this crisis without complete response to the pharmacological treatment.

**Eloquent areas and intraoperative brain mapping**

Low grade gliomas are commonly located in eloquent areas of the brain and it has already been demonstrated that intraoperative functional mapping may improve long-term survival in those with low grade gliomas located in eloquent brain regions. Chang et al. conducted a retrospective study with a long-term follow-up of 281 adult patients with hemispheric infiltrative low grade gliomas who underwent surgical treatment. More than half of the patients harbored tumors that directly involved the presumed eloquent areas. However, they also defined "false eloquent areas" adjacent to eloquent brain, based on the intraoperative monitoring. Therefore, those standard eloquent areas postulated in the basic anatomy may not represent a functionally relevant region, suggesting that mapping can drastically change the long-term prognosis for these patients.
In our series, three patients had partial resection surgery for tumors located in Broca’s area, in the left insular glioma with lenticulostriate arteries involvement and in the primary motor cortex. The patients were discharged without new neurological deficits; however, the oncological gross total resection could not always be achieved. Expertise in microsurgical anatomy, in addition to the brain mapping technique, is the gold standard treatment for eloquent area gliomas. It provides neurological preservation with maximal surgical resection, as subtotal resection is associated with the recurrence of gliomas of a higher grade.

One interesting finding involved a patient with a tumor in the inferior frontal gyrus. Cortical and subcortical language organization in bilingual patients with epilepsy, or those who developed language switching brain tumors, has been studied previously. All the authors identified language-common areas and language-specific areas by stimulating cortical structures, while Bello et al. also identified language-specific white matter fiber tracts by stimulating subcortical structures. In our case, the patient switched language from their native Portuguese to English during stimulation of the left inferior frontal gyrus.

The activation of different languages is usually found to occur within the same region, or dependent on the intensity of cortical stimulation. It has been observed that lexical processing is related to declarative memory and is similar for both native and second languages, while sentence processing depends on procedural memory, which can differ between native and second languages.

**Predictive factors of seizure control**

This study selected patients with tumors in eloquent areas who also had refractory epilepsy, and studied the surgical impact on the Engel Class. Although the correlation of epilepsy with glioma surgery has been studied before, only one previous study correlated refractory epilepsy with gliomas in eloquent areas. Studying this subgroup of patients is important because tumor resection is avoided in eloquent areas considering the high risk of sequelae and their negative impact on quality of life. However, this consideration must be balanced against the lowered quality of life of this population due to refractory epilepsy. In these patients, the need for surgery, regardless of the neuro-oncological premise, is mandatory. We have shown in our patients that the preoperative tumor volume and degree of resection were determinants for seizure control. In accordance with our findings, Ius et al. and Chang et al. demonstrated a statistically significant correlation between the EOR and seizure control.

Although we did not find a statistically significant correlation between early surgery and seizure control, we believe this was due to the small number of patients in our series. Ius et al. correlated monthly seizures and preoperative normal EEGs with better postoperative seizure control. They also measured the preoperative volumetric difference on T2- and T1-weighted MR images and their volumetric of the EOR and this T2- and T1-weighted difference. They found a higher correlation using this method than using volumetric analysis on T2- or T1-weighted images. They concluded that a less invasive tumor offered a better chance of greater EOR and, by extension, a better chance for postoperative seizure control. In this sense, the invasive tumor determined in T2-weighted images was considered by these authors as a new predictive index. This understanding favors resection based on preoperative T2-weighted images. This is the conceptual basis we have used in recent years regarding patients undergoing awake surgery in which the border of tumor resection is determined by function instead of anatomy.

We did not use intraoperative electrocorticography in our patients but performed tumor resection based on anatomy brain mapping. The electrocorticography would not have altered the degree of resection because a functional area would not have been resected anyway. In addition, we wanted to avoid intraoperative seizures after stimulation. In our hospital, we reserved electrocorticography for extra-temporal refractory epilepsy due to cortical dysplasia.

**Study limitations**

The limited sample size prevented COX regression analysis in evaluating the predictors of the Engel outcome in our series. We also did not use molecular biology analysis to
identify gliomas or correlate any specific marker that may have predicted the prognosis of epileptic seizures. Performing a randomized prospective study on this group of patients with the objective of searching for credible evidence would not be modified to create a unique study group. On the other hand, if we compare the first few in a series of patients operated on without brain mapping by one neurosurgeon with the more recent patients in the series operated on, and brain mapped, by the same surgeon, we would be failing to account for any learning curve variables that would be expected to impact the more recent patients in a positive way.

In conclusion, there is a relevant correlation between EOR and the Engel scale. An EOR < 70 is associated with Engel II, III, IV and an EOR > 90 is associated with better seizure control (Engel I). Due to oncological factors, patients with refractory epilepsy should be operated on earlier than patients without structural lesions.

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