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# Seizures in surgically resected atypical and malignant meningiomas: Long-term outcome analysis

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ABSTRACT

*Purpose:* Seizures in rare atypical and malignant meningiomas were significantly under-studied. Our aim was to examine the rates, predictors, and seizure control in these meningiomas, and to analyze associations between clinical characteristics and seizure free survival (SFS) following surgical resection in an Asian population.
*Methods:* We retrospectively analyzed 102 patients with atypical or malignant meningiomas. Seizures occurring before and after the operation were reviewed. We compared demographic data and clinical characteristics including anti-epileptic drug (AED) treatment to extract potential risk factors for seizures.
*Results:* Preoperative and postoperative early seizures occurred in 15 (14.7%) and 13 (12.7%) patients, respectively. All preoperative seizures occurred with tumors located at the convexity or parasagittal area ($P = .001$) and were influenced by peritumor edema ($P = .027$). Preoperative seizures were predictive of early seizures occurrence postoperatively ($P = .016$). Twenty-one patients (20.6%) had late seizures postoperatively. SFS was influenced by preoperative seizures, tumor location, AED use, and tumor relapse ($P = .003$, .001, .013, and .046, respectively). Among 15 patients with preoperative seizures, malignant meningiomas were associated with shorter SFS than atypical meningiomas ($P = .001$). Fifty one of 87 patients without preoperative seizures had prophylactic AEDs, and none had early seizures ($P = .001$). Gross total resection (GTR) of tumors induced more new-onset seizure than subtotal resection ($P = .045$).
*Conclusion:* Convexity and parasagittal area tumors as well as peritumor edema induce seizures. Preoperative seizures and tumor relapse predict seizures postoperatively. AEDs treatment improves SFS, and prophylactic AEDs eliminate early seizures after surgery. GTR has negative impact to seizure control.

## 1. Introduction

Meningiomas, one of the most common intracranial tumors, have an annual incidence of 6 per 100,000 people (Modha and Gutin, 2005). The World Health Organization (WHO) graded meningiomas based on histological standards: around 90% are benign (WHO grade I), 5–7% are atypical (WHO grade II), and only 1–3% are considered anaplastic or malignant (WHO grade III) (Louis et al., 2007). The rarity of the atypical and malignant subtypes has limited the amount of available data on the clinical behavior, outcomes, and optimal treatment of these tumors (Kaur et al., 2014).

Brain tumor-related seizures are usually refractory to pharmacological treatment alone, and surgical or radiological treatment of the underlying tumor is the mainstay of the treatment for the seizures (Michelucci et al., 2013). Among patients with meningiomas that undergo surgery, 10–50% have seizures as the first neurologic symptom (Lieu and Howng, 2000). Seizures also occur peri-and post-operatively, despite antiepileptic drugs (AEDs) therapy, and cause morbidity in meningioma patients (Chozick et al., 1996). Previous studies indicated that seizures diminishes quality of life in patients with benign meningiomas (Tanti et al., 2017). However, details regarding the incidence, prognostic factors, and treatment of seizures in meningiomas, especially in atypical and malignant subtypes, have remained understudied, despite of advances in neurology, neurosurgery, and radiation oncology during the past decades.

Traditionally, AEDs have been used for seizure prophylaxis in patients undergoing craniotomy for resection of meningiomas (Chozick et al., 1996; Tsuji et al., 1993). However, the efficacy of prophylactic AEDs in reducing the frequency of new-onset seizures in patients undergoing brain tumor surgery remains controversial (Glantz et al.,

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2000; Sayegh et al., 2014). It is challenging to select patients who need anticonvulsant treatment after meningioma resection because factors predicting the outcome of seizures after meningioma resection are not well-defined.

Awareness and understanding of the complex factors and their importance in seizure-related WHO grade II/III meningiomas can aid clinical decisions and improve quality of life for these patients. This study aimed to clarify the clinicopathological factors associated with seizures and their importance in patients with atypical and malignant meningiomas to establish optimal treatment strategies.

## 2. Materials and methods

### 2.1. Patients

The records for all patients who were treated for atypical and malignant meningiomas between June 2001 and November 2009 at Chung Gang Memorial Hospital were retrospectively reviewed. This study was approved by Chang Gung Medical Foundation Institutional Review Board, and because of the retrospective nature the requirement of informed patient consent was waived.

Clinical information was retrospectively obtained from patient medical records, radiologic data including computer tomography (CT) and magnetic resonance imaging (MRI) scans, and pathologic specimens. All specimens were classified using the latest 2007 WHO criteria retrospectively. Presence or absence of peritumoral edema was defined as hypodensity on CT scans or as T2 hyperintensity on MRI scans.

The term “preoperative seizure” was confined to an initial symptom that led to the diagnosis of the tumor. The term “post-operative early seizure” (early seizure) was applied to early-onset seizure(s) that occurred within 7 days of craniotomy. “Post-operative late seizure” (late seizure) was defined to patients with documented seizure(s) from the 8th day after the surgery to any time later during follow-up.

Because the goal of this study was to analyze de novo seizures among atypical and malignant meningiomas, we excluded patients with confounding neurosurgical histories and patients with tumor recurrence after being treated previously for meningiomas.

### 2.2. Surgery and adjuvant radiotherapy

All patients underwent surgical resection to brain tumors after image diagnosis. The degree of resection which was divided to gross total resection (GTR) and subtotal resection(STR) was determined based on the intra-operative impression of the surgeon and the radiographic evidence obtained post-operatively. Radiotherapy (54–60 Gy, delivered in 27–30 fractions) was within 6 months after surgery (before any signs of tumor relapse).

### 2.3. Follow-up evaluation

The mean follow-up time was 77.7 months (range, 5–192 months). We defined disease relapse as recurrence of tumors after GTR or enlarged residual tumor after STR. Gadolinium-enhanced MRI was used as radiological evidence in all case assessments. Seizure-free survival (SFS) was calculated from the 8th day after surgery to the time of seizure occurrence.

### 2.4. Statistical analysis

Univariate analysis of different variables was used to obtain an overview of the distribution of the data. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for all variables to assess impacts on seizures occurrence. Statistical significance was determined by the 2-tailed $\chi^2$ test. Only significant variables in univariate analysis ($P < .05$) were included in multivariate regression analysis. SFS analysis was performed with Kaplan-Meier method, and comparisons between groups were performed using log-rank tests. Values of $P < .05$ were considered statistically significant. Statistical analysis was performed using the SPSS software package (version 19; SPSS Inc. IBM Corporation).

**Table 1**
Patient Demographics and Tumor Characteristics.

| All patients | Total Number (%) 102 | WHO Grade II 86 | WHO Grade III 16 |
|---|---|---|---|
| Gender | | | |
| Male | 45(44.1) | 39 | 6 |
| Female | 57(55.9) | 47 | 10 |
| Age | | | |
| Mean ± SD | 57 ± 17 | 56 ± 17 | 66 ± 13 |
| Tumor Diameter (cm) | | | |
| Mean ± SD | 5.2 ± 2.0 | 5.1 ± 2.1 | 5.5 ± 1.5 |
| Location | | | |
| Covexity | 33(32.4) | 31 | 2 |
| Parasagittal | 32(31.4) | 24 | 8 |
| Skull base | 29(28.4) | 26 | 3 |
| Posterior fossa | 8(7.8) | 5 | 3 |
| Peritumor Edema | | | |
| Yes | 47(46.1) | 37 | 10 |
| No | 55(53.9) | 49 | 6 |
| MIB-1 index | | | |
| Mean ± SD | 8.6 ± 6.1 | 7.2 ± 3.9 | 16.1 ± 9.5 |
| Surgical Resection | | | |
| GTR | 69(67.7) | 57 | 12 |
| STR | 33(32.3) | 29 | 4 |
| Preoperative Seizure | | | |
| Yes | 15(38.1) | 12 | 3 |
| No | 87(61.9) | 74 | 13 |
| Early Seizure | | | |
| Yes | 13(23.8) | 10 | 3 |
| No | 89(76.2) | 76 | 13 |
| Late Seizure | | | |
| Yes | 21(23.8) | 19 | 2 |
| No | 81(76.2) | 67 | 14 |

Abbreviations;: SD, Standard Deviation; WHO, World Health Organization; GTR, Gross Total Resection; STR, Subtotal Removal; RT, Radiotherapy.

## 3. Results

### 3.1. Patient demographics and tumor characteristics

A total of 102 (45 males and 57 females) with a mean age of 57 ± 1.6 years at the time of surgery were included in the analysis. Tumors were stratified into atypical and malignant subgroups and were also divided into four categories based on anatomic location: convexity, parasagittal, skull base, and posterior fossa. The mean diameter of the tumors was 5.2 cm, and imaging-verified peritumor edema was present in 47 patients. Demographic and clinical data are presented in Table 1.

### 3.2. Clinical parameters correlate with preoperative and early seizures

Preoperative seizures occurred in 15 patients (14.7%). All the patients had first-line AED monotherapy initially, including Valproic acid, Levetiracetam or Phenytoin. Eight patients were responsive to one AED, while other 7 patients were refractory to single anticonvulsant and needed two or more AEDs. The operations to the tumors were all undergone within 5 days after initial seizure onset. Univariate analysis showed that pre-operative seizures was significantly correlated with peritumor edema (OR, 3.90; 95% CI, 1.15–13.21; $P = .027$). All patients with preoperative seizures had tumors in convexity or parasagittal areas ($P = .001$). Patient’s age, sex, tumor size, or histopathology grade were not risk factors (Table 2).

Sixty-three of 102 patients had regular first-line AED monotherapy within 7 days after tumor resection (perioperative period). The AED treatment of the 15 patients with preoperative seizures was also