Seizure Control for Patients Undergoing Meningioma Surgery

Kaisorn L. Chaichana[1], Courtney Pendleton[1], Hasan Zaidi[2], Alessandro Olivi[1], Jon D. Weingart[1], Gary L. Gallia[1], Michael Lim[1], Henry Brem[1], Alfredo Quiñones-Hinojosa[1]

Key words
- Brain tumor
- Engel
- Function
- Meningioma
- Resection
- Seizures
- Surgery

Abbreviations and Acronyms
AED: Antiepileptic drug
CI: Confidence interval
IQR: Interquartile range
KPS: Karnofsky performance scores
MRI: Magnetic resonance imaging
OR: Odds ratio
RR: Relative risk

From the [1]Department of Neurosurgery, Neuro-Oncology Outcomes Laboratory, Johns Hopkins University, Baltimore, Maryland; and [2]Department of Neurosurgery Barrow Neurological Institute, Phoenix, Arizona, USA

To whom correspondence should be addressed: Kaisorn L. Chaichana, M.D. [E-mail: kaisorn@jhmi.edu]

*Citation: World Neurosurg. (2013) 79, 3/4:515-524.
http://dx.doi.org/10.1016/j.wneu.2012.02.051*

*Journal homepage: **www.WORLDNEUROSURGERY.org***

*Available online: **www.sciencedirect.com***

■ OBJECTIVE: **Seizures are common among patients with meningiomas and are a significant cause of morbidity and poor quality of life. The factors associated with the onset of seizures as well as factors associated with seizure control remains poorly understood.**

■ METHODS: **Adult patients who underwent primary resection of a supratentorial World Health Organization grade I meningioma at a single institution between 1996 and 2006 were retrospectively reviewed. Multivariate logistical regression analyses were used to identify associations with preoperative seizures, and multivariate proportional hazards regression analyses were used to identify associations with prolonged seizure control after surgical resection.**

■ RESULTS: **Of the 626 patients in this series, 84 (13%) presented with seizures. The factors independently associated with preoperative seizures were Karnofsky performance score ≤80 ($P < 0.0001$), absence of headaches ($P = 0.0006$), and vasogenic edema ($P = 0.007$). At 48 months postoperatively, 90% were Engel class I, 3% were class II, 0 were class III, and 7% were class IV. The factors independently associated with decreased seizure control after surgical resection were uncontrolled preoperative seizures ($P = 0.04$), parasagittal tumors ($P = 0.03$), and tumors along the sphenoid wing ($P = 0.05$). The association between seizure recurrence and tumor recurrence trended toward but did not achieve statistical significance ($P = 0.11$).**

■ CONCLUSIONS: **With the widespread availability of various neuroimaging modalities, there will be increased detection of intracranial meningiomas. The identification and consideration of factors associated with seizure onset and prolonged seizure control may help guide treatment strategies aimed at improving the quality of life for patients with meningiomas.**

INTRODUCTION

Intracranial meningiomas account for 20% of all brain tumors, with an incidence of 6 cases per 100,000 persons per year (18, 26). With the widespread availability of neuroimaging, more meningiomas are being detected (18, 26). One of the most common presenting symptoms is epilepsy, where 10%–50% of patients present with seizures as their first symptom (5, 7, 14, 19). Although the majority of these seizures can be controlled with antiepileptic drug (AED) therapy, some seizures persist despite various AED regimens (5, 7, 14, 19). The presence of seizures, regardless whether or not they are controlled with medical therapy, has a tremendous impact on a patient's quality of life (2, 4). Unanswered questions still remain regarding the ability for surgical resection to control seizures in patients with meningiomas.

Therefore, the aims of this study were to (1) identify the prevalence and characteristics of seizures in patients undergoing primary resection of supratentorial meningiomas, (2) understand the factors associated with preoperative seizures, (3) evaluate the effects that surgical resection has on seizure control, and (4) discern the factors associated with prolonged seizure control. An understanding of these features may help guide treatment strategies aimed at improving seizure control for patients with intracranial meningiomas. This is especially relevant given the increase in meningioma detection as a result of the widespread availability of various neuroimaging modalities (18, 26).

MATERIALS AND METHODS

Patient Selection

All adult patients (aged >18 years) undergoing primary resection of a supratentorial meningioma at a single academic tertiary care institution between 1996 and 2006 were retrospectively reviewed. Patients with a tissue-proven diagnosis of a supratentorial World Health Organization grade I meningioma (12) were included in the study. Patients with higher grade (grade II or III), recurrent, and/or infratentorial meningiomas were excluded from the analysis. This was done to create a more uniform patient population with adequate follow-up to help understand the effects of surgical resection on seizure control in patients presenting with meningiomas.

Recorded Variables

The clinical, operative, and hospital course records were reviewed. Information collected from clinical notes included patient demographics, presenting symptoms, seizure characteristics, neuroimaging, 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 1 month before surgery with the use of AEDs, as previously published (4, 6). Patients with uncontrolled seizures were those with more than one seizure in the month before surgery while being treated with a therapeutic level of AEDs (4, 6). Preoperative Karnofsky performance scores (KPS) (13) were assigned by the clinician at the clinic visit before surgery. The magnetic resonance imaging (MRI) characteristics that were recorded included the lesion's size (largest diameter based on gadolinium enhancement, excluding the dural tail if present), location of tumor (convexity, parasagittal/parafalcine, sphenoid wing, planum sphenoidale, olfactory groove, intraventricular), presence of vasogenic edema, venous sinus involvement, and the degree of mass effect by an independent neuroradiologist. Extent of resection was retrospectively classified based on the Simpson criteria from postoperative MRIs within 48 hours of surgery and operative report (24).

The primary outcome variables were seizure status and duration of seizure control. The 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 a 1-month period without seizures or an increase in the frequency of seizures.

Surgical Procedure and Antiepileptic Treatment

In general, the aim of surgery was to achieve a Simpson grade I resection when possible. Subtotal resection was performed mainly when the tumor involved nerves and/or vessels. Motor and somatosensory-evoked potentials were routinely used in most patients and surgical navigation (computed tomography and/or MRI wand) was used in all patients after 2001.

There was no defined standard for the use of AEDs. In the preoperative period, patients were typically only started on AEDs if they developed seizures. Patients on AEDs had serum levels checked, and medication doses were then adjusted to establish therapeutic, nontoxic levels. The choice of a specific AED was based on the preference of the clinician. In cases where a patient continued having seizures despite a therapeutic level of a specific AED, additional AEDs were started. Patients without seizures were not routinely given AEDs. In the perioperative period, patients with preoperative seizures were generally continued on their same preoperative AED regimen. Patients without seizures were typically given AED for seizure prophylaxis immediately before surgery. Patients, regardless of preoperative seizures, generally had their AED levels checked before discharge to establish therapeutic levels. Postoperatively, patients with preoperative seizures were continued on their AED typically for 1–2 months and then weaned. If the patients had any evidence of seizures, their AEDs were continued indefinitely. Patients without preoperative seizures were typically weaned off of their AED 1–2 weeks after surgery. If seizures recurred, the serum levels were checked, medication doses and regimens were adjusted accordingly, and patients received MRI neuroimaging to monitor for recurrence.

Statistical Analysis

All analyses were performed using JMP 9 (SAS Institute, Carey, North Carolina, USA) unless otherwise noted. Summary data were presented as mean ± standard deviation for parametric data and as median (interquartile range [IQR]) for nonparametric data. Percentages were compared by Fisher exact test. For intergroup comparison, the Student's *t*-test was used for parametric data and the Mann-Whitney U test for nonparametric data.

To understand the factors associated with preoperative seizures, univariate logistical regression analysis was first performed 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. Values with $P < 0.05$ 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 (GraphPad Prism 5; GraphPad Software, La Jolla, California, USA). Loss of seizure control was defined as a decrease in seizure control, whereby the patient increased in Engel classification (i.e., Engel class I–II) after surgical resection. Time was assessed from the date of surgical 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 pathologic 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. Values with $P < 0.05$ 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).

RESULTS

Patient Population

The patient information is summarized in **Table 1**. A total of 626 patients underwent primary resection of a supratentorial grade I meningioma during the reviewed period. Average age was 53.9 ± 14.2 years at the time of surgery. A total of 456 patients (73%) were women.

For all patients, median KPS at presentation was 90 (range, 80–90). Eighty-four patients (13%) presented with seizures, 258 (41%) with headaches, 45 (7%) with motor deficits, 19 (3%) with speech

TUMOR

Table 1. Patient Characteristics in 84 and 542 Patients presenting with and without Seizures

Characteristics	No Seizures, *n* (%)	Preoperative Seizures: Any, *n* (%)	Controlled, *n* (%)	Uncontrolled, *n* (%)	*P* Value: Associated with any Seizure*	Associated with Uncontrolled Seizures†
Age	54 ± 14	52 ± 14	52 ± 13	51 ± 16	0.11	0.25
Female	405 (75)	53 (63)	31 (60)	22 (69)	0.03	0.53
Associated symptoms						
KPS	90 (80–90)	80 (80–90)	80 (80–90)	80 (80–90)	0.0001	0.0001
Headache	234 (43)	24 (29)	13 (25)	11 (34)	0.01	0.36
Motor deficit	37 (7)	8 (10)	4 (8)	4 (13)	0.37	0.27
Language deficit	16 (3)	3 (4)	3 (6)	0 (0)	0.73	0.99
Visual deficit	107 (20)	12 (14)	5(12)	6 (19)	0.30	0.99
Seizure type						
Simple partial	N/A	55 (65)	31 (60)	24 (75)	N/A	0.17
Complex partial	N/A	7 (8)	3 (6)	4 (13)	N/A	0.42
Secondary generalized	N/A	22 (35)	18 (35)	4 (13)	N/A	0.04
Seizure duration						
1 seizure ever	N/A	52 (62)	52 (100)	0 (0)	N/A	0.0001
≥1/week	N/A	20 (24)	0 (0)	20 (63)	N/A	0.0001
≥1/month	N/A	12 (14)	0 (0)	12 (38)	N/A	0.001
Radiographics						
Tumor size	3.4 ± 1.6	3.9 ± 1.6	4.0 ± 1.2	3.7 ± 2.0	0.04	0.58
Tumor location						
Convexity	155 (29)	30 (36)	19 (37)	11 (34)	0.20	0.55
Parasagittal/parafalcine	133 (25)	27 (32)	14 (27)	13 (41)	0.14	0.06
Sphenoid wing	111 (20)	15 (18)	9 (17)	6 (19)	0.66	0.99
Olfactory groove	29 (5)	2 (2)	2 (4)	0 (0)	0.41	0.40
Planum sphenoidale	22 (4)	3 (4)	3 (6)	0 (0)	0.99	0.63
Tuberculum sella	51 (9)	1 (1)	1 (2)	0 (0)	0.009	0.10
Tentorial	31 (6)	3 (4)	2 (4)	1 (3)	0.24	0.99
Intraventricular	10 (2)	2 (2)	2 (4)	0 (0)	0.67	0.99
Cerebral edema	147 (27)	39 (46)	24 (46)	15 (47)	0.0003	0.99
Cystic	31 (6)	6 (7)	4 (8)	2 (6)	0.62	0.71
Sinus invasion	73 (13)	15 (18)	9 (17)	6 (19)	0.31	0.29
Perioperative outcomes						
Extent of resection						
Simpson I	162 (30)	28 (33)	18 (33)	10 (31)	0.53	0.69
Simpson II	209 (39)	25 (30)	17 (31)	8 (25)	0.15	0.14
Simpson III	80 (15)	15 (18)	8 (15)	7 (22)	0.51	0.31
Simpson IV	89 (16)	16 (19)	9 (17)	7 (22)	0.53	0.46
Simpson V	2 (4)	0 (0)	0 (0)	0 (0)	0.99	0.99

Continues

TUMOR

Table 1. Continued

Characteristics	No Seizures, *n* (%)	Preoperative Seizures: Any, *n* (%)	Preoperative Seizures: Controlled, *n* (%)	Preoperative Seizures: Uncontrolled, *n* (%)	*P* Value: Associated with any Seizure*	*P* Value: Associated with Uncontrolled Seizures†
New deficit						
Motor deficit	27 (5)	6 (7)	2 (4)	4 (13)	0.43	0.09
Visual deficit	27 (5)	2 (2)	1 (2)	1 (3)	0.41	0.99
Language deficit	13 (2)	2 (2)	1 (2)	1 (3)	0.99	0.56
Adjuvant therapies						
Preoperative embolization	7 (1)	1 (1)	1 (2)	0 (0)	0.99	0.99

Of these 84 patients with seizures, 52 and 32 patients had seizures that were controlled and noncontrolled before surgery.
KPS, Karnofsky performance score; N/A, not applicable.
*P value between patients with and without preoperative seizures.
†P value between patients with uncontrolled seizures and no seizures preoperatively.

or language difficulty, and 119 patients (19%) with visual deficits. The average size of the tumor was 3.5 ± 1.6 cm, and 185 tumors (30%) involved the cerebral convexity, 160 (26%) the parasagittal/parafalcine region, 126 (20%) the sphenoid wing, 31 (5%) the olfactory groove, 25 (4%) the planum sphenoidale, 52 (8%) the tuberculum sella, 34 (5%) the tentorial region, and 12 tumors (2%) were intraventricular. Simpson grade I resection was achieved in 190 patients (30%), grade II in 234 (37%), grade III in 95 (15%), grade IV in 105 (2%), and grade V in 2 patients (0.3%). A new motor deficit occurred in 33 patients (5%), visual deficit in 29 (5%), and language deficit in 15 patients (2%).

Patients with and without Preoperative Seizures

The results of the Fisher exact test between patients with and without preoperative seizures are summarized in **Table 1**. Patients with preoperative seizures were less commonly women ($P = 0.03$), presented with lower KPS ($P = 0.0001$), but less frequently presented with headaches ($P = 0.01$). Patients with seizures also had larger tumors ($P = 0.04$), tumors that caused vasogenic edema ($P = 0.0003$), but less frequently involved the tuberculum sella ($P = 0.009$). No other clinical, imaging, operative, or pathologic variables were found to be significantly different between the two cohorts.

When comparing patients with uncontrolled versus controlled seizures, patients with uncontrolled seizures presented with lower KPS ($P = 0.0001$) and seizures that were less frequently generalized ($P = 0.03$). No other clinical, imaging, operative, or pathologic variables were found to be significantly different between the two cohorts.

All patients who presented with seizures were administered AEDs at the time of surgery (100%); 44 (52%) received phenytoin, 22 (26%) levetiracetam, 9 (11%) divalproex sodium, 9 (11%) carbamazepine, 2 (2%) lamotrigine, and 2 (2%) phenobarbital. Combinatorial therapy was used in 13 patients (39%). The only significant difference in AED therapy between patients with controlled and uncontrolled seizures was that patients with uncontrolled seizures more commonly received combinatorial therapy ($P = 0.0003$) (**Tables 2** and **3**).

Table 2. The Use of Preoperative Antiepileptic Drugs in Patients Who Presented with Seizures

Preoperative Antiepileptic Drug	Controlled Seizures ($n = 52$)	Uncontrolled Seizures ($n = 32$)	*P* Value
Phenytoin	28 (54%)	16 (50%)	0.82
Levetiracetam	12 (23%)	10 (31%)	0.45
Divalproex sodium	4 (8%)	5 (16%)	0.29
Carbamazepine	4 (8%)	5 (16%)	0.29
Lamotrigine	1 (2%)	1 (3%)	0.99
Phenobarbital	1 (2%)	1 (3%)	0.99
Combinatorial therapy	2 (4%)	11 (34%)	0.0003

P values are the Fisher exact test between patients with and without preoperative controlled seizures.

Factors Associated with Preoperative Seizures

Factors Associated with Preoperative Seizures. In univariate analysis, the factors that were associated with any preoperative seizures were younger age, male gender, decreasing KPS, absence of headaches, decreasing tumor size, presence of cerebral edema, and increasing midline shift. The factors that were associated with any preoperative seizures in multivariate analyses (**Table 4**) were KPS ≤80 (odds ratio [OR] 2.917, 95% confidence interval [CI] 1.245–3.663, $P < 0.0001$), absence of headaches (OR 2.054,

Table 3. The Use of Postoperative Antiepileptic Drugs in Patients Presenting With Seizures

Postoperative Antiepileptic Drug	Seizures	*P* Value
Phenytoin	44 (52%)	0.66
Levetiracetam	11 (13%)	0.37
Divalproex sodium	10 (12%)	0.15
Carbamazepine	14 (17%)	0.16
Lamotrigine	5 (6%)	0.52
Combinatorial therapy	8 (10%)	0.46

P values are the result of univariate proportional hazards regression analysis.

95% CI 1.248–4.381, $P = 0.0006$), and presence of vasogenic edema (OR 2.681, 95% CI 1.600–10.309, $P = 0.007$). No other clinical, imaging, or pathologic variables were found to be associated with preoperative seizures in this group of patients.

Factors Associated with Uncontrolled Preoperative Seizures. In univariate analysis, among patients with seizures, the factors associated with uncontrolled preoperative seizures were decreasing KPS, parafalcine/ parasagittal tumor location, and cerebral edema. The factors that were associated with uncontrolled preoperative seizures in multivariate analyses (**Table 4**) were KPS ≤80 (OR 3.254, 95% CI 1.008–5.035, $P = 0.003$) and the presence of vasogenic edema (OR 1.845, 95% CI 1.043–2.428, $P = 0.04$). No other clinical, imaging, or pathologic variables were found to be associated with uncontrolled preoperative seizures in this group of patients. In subgroup analysis, the effect of KPS on preoperative seizures was evaluated after controlling for vasogenic edema and preoperative motor and language deficits. This was to evaluate whether the KPS was truly associated with seizures and not a bystander of tumor-related variables. In this analysis, preoperative KPS remained significantly associated with preoperative seizures ($P = 0.002$).

Seizure Outcomes

Seizure control was recorded at each postoperative visit. For the purposes of this study, seizure control for patients with seizures was tabulated using Engel classification at 6, 12, 24, and 48 months after surgery for those patients for whom data were available (**Table 5**). Overall, for all patients who presented with seizures, the majority of patients remained seizure-free (class I) at 6 (90%), 12 (92%), 24 (87%), and 48 months (90%) postoperatively. At 6 months postoperatively, 2% of patients had rare seizures (class II), 6% had meaningful seizures (class III), and 2% had worsening seizures (class IV). At 48 months postoperatively, 3% of patients had rare seizures (class II), 0 had meaningful seizures (class III), and 7% had worsening seizures (class IV).

Among patients with controlled preoperative seizures, their occurrence was rare in the postoperative period, where only 6% of patients reported seizures at 6 and 48 months postoperatively. The majority of patients remained seizure-free (class I) at 6 (95%), 12 (89%), 24 (84%), and 48 months (94%) postoperatively. At 6 months postoperatively, 3% had rare seizures (class II), 3% had meaningful seizures (class III), and no patients had worsening seizures (class IV). At 48 months postoperatively, no patients had rare seizures (class II), no patients had meaningful seizures (class III), but 6% had worsening seizures (class IV).

For patients with uncontrolled preoperative seizures, the majority of patients also remained seizure-free after surgery. At 6, 12, 24, and 48 months postoperatively, 83%, 70%, 93%, and 83% reported being seizure-free, respectively. Seventeen percent and 16% of patients reported seizures at 6 and 48 months postoperatively. At 6 months postoperatively, 0 had rare seizures (class II), 13% had meaningful seizures (class III), and 4% of patients had worsening seizures (class IV). At 48 months postoperatively, 8% of patients had rare seizures (class II), no patients had meaningful seizures (class III), and 8% had worsening seizures (class IV).

The Kaplan-Meier method was used to plot seizure control for all patients. The median (IQR) follow-up time for all patients was 29 months (range, 5–72 months). The Kaplan-Meier plot of seizure control for patients who presented with seizures is depicted in **Figure 1**. The seizure-free survival rates for 6, 12, 24, and 48 months were 91%, 84%, 77%, and 74%, respectively. For patients with controlled preoperative seizures (**Figure 2**), the seizure-free rates for 6, 12, 24, and 48 months were 95%, 90%, 83%, and 83%. For patients with uncontrolled preoperative seizures (**Figure 2**), the seizure-free rates for 6, 12, 24, and 48 months were 84%, 73%, 67%, and 59%. In log-rank analysis, these seizure-free survival rates were statistically different between patients with and without preoperative controlled seizures ($P = 0.05$) (**Figure 2**).

Factors Associated with Seizure Control

The factors that were associated with loss of seizure control in multivariate analyses were tumors located in the parasagittal/ parafalcine location (relative risk [RR] 5.634, 95% CI 1.164–8.977, $P = 0.03$), sphenoid wing tumors (RR 3.307, 95% CI 1.004–6.576, $P = 0.05$), and uncontrolled

Table 4. Predictors of Preoperative Seizures in Patients with Supratentorial Meningiomas

Multivariate Association Variables	Odds Ratio (95% CI)	*P* Value
Associated with any seizures		
KPS ≤80	2.917 (1.245–3.663)	<0.0001
Absence of headaches	2.054 (1.248–4.381)	0.0006
Vasogenic edema	2.681 (1.600–10.309)	0.007
Associated with uncontrolled seizures		
KPS ≤80	3.254 (1.008–5.035)	0.003
Vasogenic edema	1.845 (1.043–2.428)	0.04

Factors that are independently associated with any preoperative seizures and uncontrolled preoperative seizures in stepwise multivariate logistical regression analyses.
CI, confidence interval.

TUMOR

Table 5. Seizure Status, Stratified by Preoperative Seizure Status, at 6, 12, 24, and 48 Months After Surgery

	Any Seizures (month)				Controlled Seizures (month)				Uncontrolled Seizures (month)			
	6	12	24	48	6	12	24	48	6	12	24	48
Number of patients	62	55	45	29	39	35	31	17	23	20	14	12
Engel class												
I	56 (90%)	45 (82%)	39 (87%)	26 (90%)	37 (95%)	31 (89%)	26 (84%)	16 (94%)	19 (83%)	14 (70%)	13 (93%)	10 (83%)
II	1 (2%)	3 (5%)	3 (7%)	1 (3%)	1 (3%)	2 (6%)	2 (6%)	0 (0)	0 (0)	1 (5%)	1 (7%)	1 (8%)
III	3 (6%)	4 (7%)	1 (2%)	0 (0)	1 (3%)	2 (6%)	1 (3%)	0 (0)	3 (13%)	2 (10%)	0 (0)	0 (0)
IV	1 (2%)	3 (5%)	2 (4%)	2 (7%)	0 (0)	0 (0)	2 (6%)	1 (6%)	1 (4%)	3 (15%)	0 (0)	1 (8%)

preoperative seizures (RR 2.170, 95% CI 1.045–6.356, $P = 0.04$) (**Table 6**). No other clinical, imaging, or pathologic variables were found to be associated with preoperative seizures in this group of patients. Important, decreasing Simpson grade ($P = 0.86$), increasing tumor size ($P = 0.44$), or improved resection ($P = 0.53$) was not associated with prolonged seizure control ($P = 0.86$).

Postoperatively, among patients with preoperative seizures, 44 (52%) received phenytoin, 11 (13%) levetiracetam, 10 (12%) divalproex sodium, 14 (17%) carbamazepine, 5 (6%) lamotrigine, and 8 (10%) received combinatorial AED therapy. None of these AEDs was associated with postoperative seizure control (**Table 3**). At a median (IQR) follow-up time of 27 months (range, 5.3–54.5 months), 28 (33%) were weaned off of their AED. In subgroup analysis, comparing patients who were and were not able to wean off their AED, there were no differences between the type of AED and whether they were weaned off the AED ($P > 0.05$). However, 21 patients (40%) with controlled preoperative seizures were weaned off of their AEDs, whereas 7 patients (22%) with uncontrolled preoperative seizures were weaned off of their AEDs ($P = 0.006$).

Seizure Recurrence and Tumor Recurrence

Seizures worsened in 14 patients (17%) at last follow-up, and it corresponded with tumor recurrence in 4 patients (33%). An association between worsened seizure control and tumor recurrence trended toward but did not reach statistical significance ($P = 0.07$). Furthermore, in proportional hazards regression analysis, the association between loss of seizure control and tumor recurrence trended toward but did not achieve statistical significance (RR 1.976, 95% CI 0.882–6.186, $P = 0.11$).

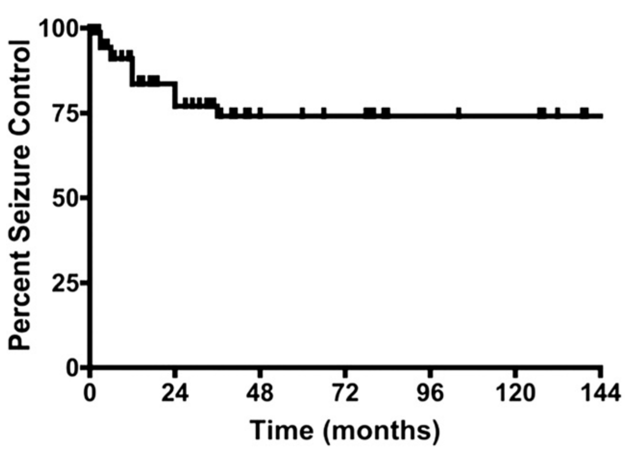

Figure 1. Seizure control for all patients. Kaplan-Meier plot of seizure control for patients who presented with seizures and underwent resection of a supratentorial meningioma. The seizure-free survival rates for 6, 12, 24, and 48 months were 91%, 84%, 77%, and 74%, respectively.

DISCUSSION

In this study of 626 patients undergoing primary resection of a supratentorial meningioma, 84 (13%) presented with seizures. Of the patients presenting with seizures, 62% were controlled on AEDs, whereas 38% were uncontrolled. The factors significantly associated with preoperative seizures were preoperative KPS ≤80, absence of headaches, and vasogenic edema on preoperative neuroimaging. Among patients with seizures, the factors significantly associated with uncontrolled seizures were preoperative KPS ≤80 and vasogenic edema. Surgical resection appeared to control seizures in the majority of patients with supratentorial meningiomas. Among patients who presented with seizures, the majority remained seizure-free (class I) at 12 (92%), 24 (87%), and 48 months (90%) postoperatively. Among those with a history of uncontrolled seizures, the majority also remained seizure-free (class I) at 12 (70%), 24 (93%), and 48 months (83%) postoperatively. The factors associated with poor seizure control included uncontrolled preoperative seizures, parasagittal/parafalcine tumors, and sphenoid wing tumors. Tumor recurrence appeared to be associated with loss of seizure control, but did not reach statistical significance.

Seizure in Patients with Meningiomas

Intracranial meningiomas are common intracranial tumors. Patients with these tu-

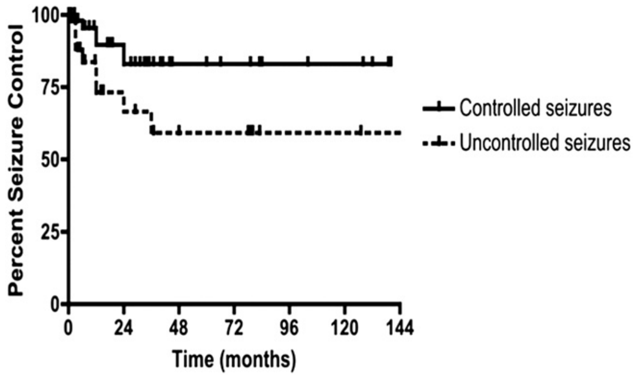

Figure 2. Seizure control for patients who presented with drug-controlled versus uncontrolled seizures. Patients with controlled preoperative seizures had seizure-free rates for 6, 12, 24, and 48 months of 95%, 90%, 83%, and 83%, respectively. Patients with uncontrolled preoperative seizures had seizure-free rates for 6, 12, 24, and 48 months of 84%, 73%, 67%, and 59%. In log-rank analysis, these seizure-free survival rates were statistically different between patients with and without preoperative controlled seizures (P = 0.05).

mors often present with seizures, with reported incidence rates ranging from 10%–50% in several series (5, 7, 14, 19). The pathophysiology of these seizures is assumed to be due a combination of tumor-caused mass effect on epileptogenic cortex, acid/base derangements from cerebral edema, and/or disturbances of neurotransmitter pathways (3, 22). These seizures often manifest as simple or complex partial seizures with or without secondary generalization (10). Their development adds substantial morbidity to one's quality of life and activities of daily living (10). In addition, the use of AED may itself also cause significant morbidity with significant consequences (21, 25, 27, 28). With an increase in meningioma detection with widespread availability of various radiographic modalities, predicting seizure onset and factors associated with seizure control are increasingly important.

Prior clinical studies on seizure characteristics and control for patients with intracranial meningiomas are few and limited. Lieu and Howng (14) studied 59 patients with meningiomas and found that surgical resection stopped seizures in 62.7% of these patients at follow-up times ranging from 12 months to 12 years. They found that supratentorial location, convexity location, and evidence of peritumor edema were associated with preoperative seizures, whereas the presence of edema was associated with postoperative seizures. Kawaguchi et al. (11) studied 27 patients with parasagittal meningiomas and seizures. They found that the presence of edema was associated with seizures, independent of tumor location or histology. Ramamurthi et al. (19) evaluated 37 patients with seizures and found that seizures recurred in half of the patients. These studies often lacked a uniform patient population in which patients with infratentorial tumors, pediatric patients, and different pathologic grades were all included into the same study (11, 14, 19). Furthermore, these studies did not use multivariate analyses to evaluate factors independently associated with prolonged seizure control (11, 14, 19). Therefore, the factors associated with seizures and seizure control for patients with meningiomas remain poorly understood.

Table 6. Predictors of Poorer Seizure Control After Surgical Resection in Patients with Meningiomas After Stepwise Multivariate Proportional Hazards Regression Analyses

Multivariate Association with Loss of Seizure Control		
Variable	Relative Risk (95% CI)	P Value
Parasagittal tumor location	5.634 (1.164–8.977)	0.03
Sphenoid wing tumor location	3.307 (1.004–6.576)	0.05
Uncontrolled preoperative seizures	2.170 (1.045–6.356)	0.04

CI, confidence interval.

Factors Associated with Seizures and Seizure Control

In the present study, the factors positively associated with preoperative seizures were KPS ≤80, absence of headaches, and cerebral edema. Among patients with seizures, patients with KPS ≤80 and cerebral edema were associated with uncontrolled preoperative seizures. At last follow-up, patients were less likely to have prolonged seizure control if their tumor involved parasagittal/parafalcine location, sphenoid wing location, and presence of cerebral edema.

Patients with a KPS ≤80 had an almost threefold higher risk of having preoperative seizures than patients who presented with higher KPS. Among patients with seizures, patients with a KPS ≤80 were also more than three times likely to have uncontrolled seizures. Not surprisingly, this emphasizes the impact of seizures on a patient's quality of life (10). A patient's quality of life is significantly worsened by the presence of seizures (10). This association between lowered KPS and seizures may also be multifactorial. Patients with tumors with more pial invasion, vasogenic edema, and mass effect on eloquent areas (i.e., motor cortex) may theoretically have tumors, which cause both seizures and lowered KPS. However, this was not seen in our multivariate analyses, and the lower KPS was still seen despite controlling for vasogenic edema and preoperative deficits. Besides decreased KPS, the absence of headaches was also associated with having preoperative seizures but not uncontrolled seizures (17). Patients without headaches were twofold more likely to have seizures than patients with headaches. Patients with meningiomas typically either present with signs of mass effect including headaches or other

TUMOR

symptoms such as seizures (17). In our patient population, patients with seizures were less likely to have headaches.

The presence of cerebral edema was significantly associated with seizures, as has been seen in other studies (11, 15, 23). Patients with cerebral edema on preoperative imaging were almost three and two times more like to have preoperative seizures and preoperative uncontrolled seizures compared with patients without edema, respectively. It has been estimated that 30%–60% of patients with meningiomas have signs of cerebral edema (11, 15, 23). This is primarily believed to be due to breakdown of the blood-brain barrier as well as pial invasion (11, 15, 23). Other investigators have postulated that edema formation is due to mechanical factors from tumor compression on brain parenchyma or draining veins, excretion of vasogenic factors such as vascular endothelial growth factor, or hypoplasia of draining vessels (11, 15, 23). Nevertheless, the presence of edema usually signifies a more infiltrative type of meningioma, with a greater propensity to cause seizures.

Seizure Control

Surgical resection controlled seizures in most patients who presented with seizures. Ninety percent of patients who presented with seizures had no seizures and 3% had rare seizures at 48-month follow-up. As with this study, prior studies have found that with surgical resection of meningiomas, patients have seizure cessation rates that vary between 60% and 90% (7, 8, 14). The exact duration and extent of seizure control for these patients, however, remains unstudied. Nevertheless, the majority of patients with meningiomas who present with seizures will be seizure-free after surgical resection.

The factors associated with poor seizure control in this study were uncontrolled preoperative seizures, parasagittal tumor location, and sphenoid wing tumors. Patients with poorly controlled preoperative seizures were more than two times likely to have seizure recurrence after surgery. This has been seen in other studies as well (8, 19). This propensity for seizure recurrence, regardless of extent of resection, may be due to the lowered seizure threshold for these patients. This lowered threshold may make it easier for precipitating factors to elicit seizures (7, 8, 19). This may also emphasize the need for early surgical resect of tumors at risk of causing seizures. If seizures were to become uncontrolled, there is a decreased likelihood of establishing control after surgical resection. Besides uncontrolled preoperative seizures, patients with tumors located in the parasagittal/parafalcine or sphenoid wing location had a six- and threefold decreased likelihood of having prolonged seizure control, respectively. These areas represent supratentorial locations where it is difficult to achieve radical resection with minimal brain manipulation (1, 20). Resection of these tumors may have a lower rate of Simpson grade I resection and/or higher rates of pial violation, which may lower a patient's seizure threshold. This may make patients more prone to developing late onset seizures.

Tumor Recurrence and Seizure Control

In the present study, the association between seizure recurrence after initial postoperative seizure control and tumor recurrence trended toward but did not reach statistical significance. Some studies have found an association between tumor recurrence and seizure recurrence (7), whereas others have not (8, 19). The exact mechanism of this finding is unknown, but it seems intuitive that lesions that cause seizures will continue to create these symptoms once the tumor recurs. Therefore, patients who redevelop seizures should be investigated for tumor recurrence. Interestingly, 10 patients had worsened seizures and no evidence of tumor recurrence. The source of this recurrence had been attributed to their prior predisposition to developing seizures (16). An alternate explanation, which was not explored in these patients, is that they may have an alternate seizure focus (i.e., mesial temporal sclerosis) that can be causing the seizures.

Clinical Implications

The findings in the present study may have important clinical implications, although the factors may not be identifiable. Patients with meningiomas, especially those discovered incidentally, also with poor performance status, absence of headaches, and/or vasogenic edema on MRI, are at risk of developing seizures if they have not yet had seizures. These patients may benefit from earlier surgical intervention before seizures occur rather than prolonged surveillance as the development of uncontrolled seizures may impede prolonged seizure control. In addition, the majority patients who have seizures and undergo surgical resection will have prolonged seizure-free control. The patients at greatest risk of seizure recurrence are those with tumors in the parasagittal or sphenoid wing tumor location or those with preoperative uncontrolled seizures. These patients may benefit from more aggressive surgery aimed at complete resection or adjuvant therapy including radiotherapy. They may also benefit from a more prolonged antiepileptic course. Patients will also be treated with preoperative and postoperative AEDs if they present with seizures. The present study shows that most patients can be weaned off AEDs.

Strengths and Limitations

Studies evaluating seizure characteristics and seizure control for patients with meningiomas are few and limited. The majority of studies on meningiomas have focused on factors associated with extent of resection and recurrence, whereas an understudied aspect is functional outcome and, more specifically, seizure control. An understanding of these factors is important for several reasons. First, there has been an increase in meningioma detection in recent years due to widespread availability of MRI (18, 26). Many of these patients may develop seizures. The ability to predict which patients are at highest risk of seizures is important as the development of seizures can have a significant impact on an individual's quality of life and the ability to resume activities of daily living. Second, the effects of surgical therapy on seizure control for patients with meningiomas remain poorly understood. Little is known about long-term seizure control for patients undergoing meningioma surgery. Finally, the ability to risk stratify patients with meningiomas and poor seizure control may help guide clinical decision making to improve functional outcome for patients harboring these tumors.

This study, however, has some additional limitations. One limitation is that the present study is based on a retrospective design, which is susceptible to inherent biases. This emphasizes the need for a prospectively followed cohort. In addition, because all the patients in this study underwent surgical resection of a meningioma, it is difficult to discern whether surgery or AED treatment most contributed to seizure control. This study mainly shows that surgery in combination with AEDs can provide adequate seizure control. Important, a significant percentage of patients can be completely weaned from their AEDs. Last, this study was not designed to evaluate the efficacy of perioperative AEDs for patients who did not present with seizures or the incidence of immediate postoperative seizures. This study was mainly designed to study those patients who presented with seizures and the effects of surgery on prolonged seizure control.

Despite these inherent limitations, we tried to create a uniform patient population by using strict inclusion criteria, and therefore it may not apply to all patients with meningiomas. We included only patients who underwent primary surgical resection of their tumor, and excluded variants that may mask the effects of surgical resection and seizure control including infratentorial tumors, secondary resection, patients undergoing biopsies, and patients with atypical or malignant meningiomas. In addition, we used multivariate analyses to control for confounding variables. Given these statistical controls and a relatively precise outcome measure, we believe that our findings offer useful insights into the management of patients with seizures and meningiomas. However, prospective studies are needed to provide better data to guide clinical decision making.

Treatment Recommendations

Seizures are not uncommon among patients with meningiomas. Seizures are more common in patients with poor preoperative functional status, absence of signs of increased intracranial pressure, and cerebral edema. Therefore, it may be plausible to start AEDs or even offer early surgery for these patients at risk of developing seizures rather than prolonged surveillance. For patients who develop seizures, AEDs should be started, but it should be realized that a significant percentage of patients will still have seizures despite therapeutic levels of AEDs. The patients most at risk of still having seizures despite appropriate AEDs are those with poor preoperative functional status and cerebral edema on preoperative neuroimaging. These patients may benefit from earlier surgical intervention. Despite this, AEDs, in combination with surgery (where the aim is to generally achieve gross total resection when it is safe to do so), appear to significantly reduce seizure frequencies. In fact, 90% of patients with preoperative seizures will have prolonged seizure control. Seizure control, however, is less likely to be achieved in patients with previously uncontrolled seizures, and for tumors located in the parasagittal or sphenoid wing. Patients with these features should be counseled about their high risk of seizures despite surgery and AED therapy. These patients may benefit from more aggressive surgery or adjuvant therapy. Patients without these factors (uncontrolled preoperative seizures, parasagittal tumors, sphenoid wing tumors) may be better candidates to wean off AED therapy. The electroencephalogram may be useful to help in weaning patients with controlled or uncontrolled preoperative seizures from AEDs. It is also important that if seizures recur, there should be a high index of suspicion for tumor recurrence or progression. These findings, presented in this study, are novel and have yet to be elucidated in previous studies using multivariate analyses.

CONCLUSIONS

Seizures contribute to a patient's quality of life, and are not uncommon among patients with meningiomas. An understanding of factors associated with seizures and prolonged seizure control may therefore provide insight into developing effective treatment strategies aimed at improving patients' quality of life. In addition, with an increase in incidentally discovered meningiomas with the wide use of neuroimaging, the importance of predicting seizures and seizure control is more apparent.

REFERENCES

1. Alvernia JE, Dang ND, Sindou MP: Convexity meningiomas: study of recurrence factors with special emphasis on the cleavage plane in a series of 100 consecutive patients. J Neurosurg 115:491-498, 2011.

2. Aydemir N, Ozkara C, Unsal P, Canbeyli R: A comparative study of health related quality of life, psychological well-being, impact of illness and stigma in epilepsy and migraine. Seizure 20:679-685, 2011.

3. Beaumont A, Whittle IR: The pathogenesis of tumour associated epilepsy. Acta Neurochir (Wien) 142:1-15, 2000.

4. Chaichana KL, Parker SL, Olivi A, Quinones-Hinojosa A: Long-term seizure outcomes in adult patients undergoing primary resection of malignant brain astrocytomas. Clinical article. J Neurosurg 111:282-292, 2009.

5. Chan RC, Thompson GB: Morbidity, mortality, and quality of life following surgery for intracranial meningiomas. A retrospective study in 257 cases. J Neurosurg 60:52-60, 1984.

6. Chang EF, Potts MB, Keles GE, Lamborn KR, Chang SM, Barbaro NM, Berger MS: Seizure characteristics and control following resection in 332 patients with low-grade gliomas. J Neurosurg 108:227-235, 2008.

7. Chow SY, Hsi MS, Tang LM, Fong VH: Epilepsy and intracranial meningiomas. Zhonghua Yi Xue Za Zhi (Taipei) 55:151-155, 1995.

8. Chozick BS, Reinert SE, Greenblatt SH: Incidence of seizures after surgery for supratentorial meningiomas: a modern analysis. J Neurosurg 84:382-386, 1996.

9. Engel J Jr: A proposed diagnostic scheme for people with epileptic seizures and with epilepsy: report of the ILAE Task Force on Classification and Terminology. Epilepsia 42:796-803, 2001.

10. Jacoby A, Wang W, Vu TD, Wu J, Snape D, Aydemir N, Parr J, Reis R, Begley C, de Boer H, Prilipko L, Baker G: Meanings of epilepsy in its sociocultural context and implications for stigma: findings from ethnographic studies in local communities in China and Vietnam. Epilepsy Behav 12:286-297, 2008.

11. Kawaguchi T, Kameyama S, Tanaka R: Peritumoral edema and seizure in patients with cerebral convexity and parasagittal meningiomas. Neurol Med Chir (Tokyo) 36:568-573 [discussion 573-574], 1996.

12. Kleihues P, Louis DN, Scheithauer BW, Rorke LB, Reifenberger G, Burger PC, Cavenee WK: The WHO classification of tumors of the nervous system. J Neuropathol Exp Neurol 61:215-225 [discussion 226-229], 2002.

13. Lamborn KR, Chang SM, Prados MD: Prognostic factors for survival of patients with glioblastoma: recursive partitioning analysis. Neuro Oncol 6:227-235, 2004.

14. Lieu AS, Howng SL: Intracranial meningiomas and epilepsy: incidence, prognosis and influencing factors. Epilepsy Res 38:45-52, 2000.

15. Lobato RD, Alday R, Gomez PA, Rivas JJ, Dominguez J, Cabrera A, Madero S, Ayerbe J: Brain oedema in patients with intracranial meningioma. Correlation between clinical, radiological, and histological factors and the presence and intensity of oedema. Acta Neurochir (Wien) 138:485-493 [discussion 493-494], 1996.

16. Lwu S, Hamilton MG, Forsyth PA, Cairncross JG, Parney IF: Use of peri-operative anti-epileptic drugs

in patients with newly diagnosed high grade malignant glioma: a single center experience. J Neurooncol 96:403-408, 2010.

17. Lynam LM, Lyons MK, Drazkowski JF, Sirven JI, Noe KH, Zimmerman RS, Wilkens JA: Frequency of seizures in patients with newly diagnosed brain tumors: a retrospective review. Clin Neurol Neurosurg 109:634-638, 2007.

18. Porter KR, McCarthy BJ, Freels S, Kim Y, Davis FG: Prevalence estimates for primary brain tumors in the United States by age, gender, behavior, and histology. Neuro Oncol 12:520-527, 2010.

19. Ramamurthi B, Ravi B, Ramachandran V: Convulsions with meningiomas: incidence and significance. Surg Neurol 14:415-416, 1980.

20. Raza SM, Gallia GL, Brem H, Weingart JD, Long DM, Olivi A: Perioperative and long-term outcomes from the management of parasagittal meningiomas invading the superior sagittal sinus. Neurosurgery 67:885-893 [discussion 893], 2010.

21. Salmaggi A, Boiardi A, Gelati M, Russo A, Calatozzolo C, Ciusani E, Sciacca FL, Ottolina A, Parati EA, La Porta C, Alessandri G, Marras C, Croci D, De Rossi M: Glioblastoma-derived tumorospheres identify a population of tumor stem-like cells with angiogenic potential and enhanced multidrug resistance phenotype. Glia 54:850-860, 2006.

22. Shamji MF, Fric-Shamji EC, Benoit BG: Brain tumors and epilepsy: pathophysiology of peritumoral changes. Neurosurg Rev 32:275-284 [discussion 284-286], 2009.

23. Simis A, Pires de Aguiar PH, Leite CC, Santana PA Jr, Rosemberg S, Teixeira MJ: Peritumoral brain edema in benign meningiomas: correlation with clinical, radiologic, and surgical factors and possible role on recurrence. Surg Neurol 70:471-477 [discussion 477], 2008.

24. Simpson D: The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 20:22-39, 1957.

25. Sisodiya SM, Lin WR, Harding BN, Squier MV, Thom M: Drug resistance in epilepsy: expression of drug resistance proteins in common causes of refractory epilepsy. Brain 125(Pt 1):22-31, 2002.

26. Surawicz TS, McCarthy BJ, Kupelian V, Jukich PJ, Bruner JM, Davis FG: Descriptive epidemiology of primary brain and CNS tumors: results from the Central Brain Tumor Registry of the United States, 1990–1994. Neuro Oncol 1:14-25, 1999.

27. Taphoorn MJ: Neurocognitive sequelae in the treatment of low-grade gliomas. Semin Oncol 30(Suppl 19):45-48, 2003.

28. Vecht CJ, Wagner GL, Wilms EB: Interactions between antiepileptic and chemotherapeutic drugs. Lancet Neurol 2:404-409, 2003.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received 30 October 2011; accepted 03 February 2012

Citation: World Neurosurg. (2013) 79, 3/4:515-524.
http://dx.doi.org/10.1016/j.wneu.2012.02.051

Journal homepage: ***www.WORLDNEUROSURGERY.org***

Available online: ***www.sciencedirect.com***

1878-8750/$ - see front matter