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Factors Associated With Pre- and Postoperative Seizures in 1033 Patients Undergoing Supratentorial Meningioma Resection

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BACKGROUND: Risk factors for pre- and postoperative seizures in supratentorial meningiomas are understudied compared to other brain tumors.
OBJECTIVE: To report seizure frequency and identify factors associated with pre- and postoperative seizures in a large single-center population study of patients undergoing resection of supratentorial meningioma.
METHODS: Retrospective chart review of 1033 subjects undergoing resection of supratentorial meningioma at the author's institution (1991-2014). Multivariate regression was used to identify variables significantly associated with pre- and postoperative seizures.
RESULTS: Preoperative seizures occurred in 234 (22.7%) subjects. At 5 years postoperative, probability of seizure freedom was 89.9% among subjects without preoperative seizures and 62.2% with preoperative seizures. Multivariate analysis identified the following predictors of preoperative seizures: presence of $\geq$1 cm peritumoral edema (odds ratio [OR]: 4.45, 2.55-8.50), nonskull base tumor location (OR: 2.13, 1.26-3.67), greater age (OR per unit increase: 1.03, 1.01-1.05), while presenting symptom of headache (OR: 0.50, 0.29-0.84) or cranial nerve deficit (OR: 0.36, 0.17-0.71) decreased odds of preoperative seizures. Postoperative seizures after discharge were associated with preoperative seizures (OR: 5.70, 2.57-13.13), in-hospital seizure (OR: 4.31, 1.28-13.67), and among patients without preoperative seizure, occurrence of medical or surgical complications (OR 3.39, 1.09-9.48). Perioperative anti-epileptic drug use was not associated with decreased incidence of postoperative seizures.
CONCLUSIONS: Nonskull base supratentorial meningiomas with surrounding edema have the highest risk for preoperative seizure. Long-term follow-up showing persistent seizures in meningioma patients with preoperative seizures raises the possibility that these patients may benefit from electrocorticographic mapping of adjacent cortex and resection of noneloquent, epileptically active cortex.

KEY WORDS: Epilepsy, Meningioma, Predictor, Seizure, Surgery, Supratentorial, Complications

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Meningioma is the most common primary intracranial brain tumor, accounting for ~20% to 35% of all primary intracranial neoplasms.[1-3] The majority of meningiomas are benign, World Health Organization (WHO) grade I, and often amenable to surgical resection with excellent prognosis.[4-8] Seizures occur commonly among patients with supratentorial meningiomas, both pre- and postoperatively.[9] Recurrent seizures negatively impact patient quality of life,[10] affecting ability to drive,[11] employment, and independence, and can lead to significant comorbidities.[10,12-14] As such, seizure freedom represents an important outcome measure following meningioma resection, and one that has been relatively understudied.

Few studies exist investigating rates and predictors of pre- and postoperative seizure in meningioma.[15-18] A recent meta-analysis of seizures in supratentorial meningioma found

ABBREVIATIONS: AED, anti-epileptic drug; **CI,** confidence interval; **CN,** cranial nerve; **CVA,** cerebrovascular accident; **FLAIR,** Fluid-attenuated inversion recovery; **MRI,** magnetic resonance imaging; **OR,** odds ratio; **WHO,** World Health Organization

only 9 studies in the last 35 years, most relatively small in sample size, with detailed information regarding risk factors for seizure associated with meningiomas.[9] Pooling available data from 39 studies of seizure rates in meningioma, the authors reported a preoperative seizure rate of 29% of patients with supratentorial meningioma. For patients with preoperative seizures, seizure freedom was achieved in 69% of patients. For patients without preoperative seizures, new seizures occurred in 12% of patients postoperatively. Despite these prior studies, there is a need for additional studies examining both immediate and long-term seizure freedom following surgery, particularly studies with sufficient statistical power to identify robust predictors of pre- and postoperative seizures in meningioma resection.

Objectives

In this study, we examine patient clinical characteristics, tumor pathology, and neuroimaging variables to identify predictors of pre- and postoperative seizures in patients undergoing surgical resection of meningioma, and to characterize seizure incidence both in the immediate postoperative period and at long-term follow-up. To our knowledge, this is the largest single population study to date examining factors associated with seizure in supratentorial meningioma.

METHODS

Study Design, Setting, Size, and Participants

We performed a retrospective cohort chart review study of all adult patients undergoing surgical treatment for supratentorial meningioma at the author's institution from 1991 to 2014. Follow-up occurred through mid-2015. The study setting was a major academic medical center. The number of patients identified that met the inclusion criteria determined the study size. Patients were identified from an institutional database of all patients undergoing meningioma resection. Patient data was collected from the electronic medical record, pathology databases, and radiology archive systems. Criteria for inclusion in the study were adult patients who (1) had undergone surgical resection of a supratentorial meningioma in the study time period, (2) had adequate documentation in the medical record, including at least a tumor pathology report, an operative report, admission and discharge documentation, and (3) had not undergone treatment for meningioma outside of the author's institution. The author's institutional review board approved this study (IRB# 13–12587). The institutional review board deemed the research investigation to be low risk, and thus, did not require individual consent to be obtained from each patient.

Clinical and Tumor Variables

The outcomes measured were occurrence of seizure(s) preoperatively, during the immediate postoperative period prior to discharge, and postdischarge. The date of the first occurrence of seizure postoperatively was used for analysis of time to first seizure. Clinical variables analyzed included age at surgery, gender, anti-epileptic drug (AED) use, and presenting symptoms of headache, weakness, seizure, and cranial nerve (CN) deficit. Comorbid conditions analyzed included hypertension, diabetes mellitus type II, coronary artery disease, hyperlipidemia, prior myocardial infarction, prior cerebrovascular accident (CVA), chronic obstructive pulmonary disease, chronic kidney disease, prior radiation, and neurofibromatosis II. Tumor variables included tumor location and lateralization, tumor size, presence of peritumoral edema, tumor WHO grade, recurrence, and resection extent. Neurological complications included new postoperative weakness and new postoperative CN deficit. Medical/surgical complications included occurrence of deep venous thrombosis, pulmonary embolus, pneumonia, venous infarction, intracranial hemorrhage, CVA, cerebral edema/hydrocephalus, subdural hematoma, wound infection, and hyponatremia.

Data Sources and Measurements

All data were collected from the electronic or paper medical record. Follow-up data were collected from medical records of postdischarge follow-up clinic visits.

Tumor location was taken from the operative and radiology reports. Locations included were tuberculum/planum, convexity, falx/parasaggital, sphenoid wing, olfactory groove, tentorial (superior face), petroclival (if extended supratentorially), intraventricular, middle fossa, and multifocal. Multifocal meningiomas were included if 1 or more tumors were located supratentorially. The lateralization of unifocal tumors was recorded as left, right, or midline. Skull base location was defined as sphenoid wing, olfactory groove, tuberculum/planum, tentorial, petroclival, and middle fossa; convexity/parasagittal/falx included tumors with convexity and falx/parasagittal location. Tumor size on the preoperative magnetic resonance imaging (MRI) was routinely recorded in anterior–posterior, transverse, and craniocaudal coordinates. The maximum recorded tumor dimension was used as a proxy for tumor size. A binary tumor size cutoff of $\geq$3 cm or $<$3 cm was used based on the optimal threshold of a receiver operating characteristic curve of tumor size vs occurrence of pre- or postoperative seizure. Peritumoral edema was defined as hyperintensity on axial Fluid-attenuated inversion recovery (FLAIR) or T2-weighted MRI, and a binary cutoff derived from a prior study was applied based on the maximum perpendicular distance from the edge of the tumor to the edge of surrounding edema of $\geq$1 cm.[19] WHO grade of tumors was extracted from pathology reports and based on the grading system used at the time of treatment. The extent of resection was recorded as gross total or subtotal resection based on the postoperative radiology report. When recorded in the operative report, the Simpson grade of resection was used for determination of gross total (grade I-III) vs subtotal resection (grade IV). If Simpson grade was not recorded, then gross total vs subtotal resection was recorded based on the postoperative radiology report.

Bias

This retrospective study is limited by selection bias and observer bias. All patients treated at the author's institution who had information regarding the variables of interest in the chart were included. No patients were excluded who had information regarding the variables of interest in the chart, thus limiting selection bias. This study is also limited by observer bias in that only information that was recorded in the chart could be used. Any seizures or clinical variables that were not recorded, but did occur, could impact the results.

AED Practices

Patients at the author's institution are placed on an AED (levetiracetam or phenytoin) at the time of surgery if they have any of the

following criteria: frontal or temporal lobe location, size >2.5 cm, peritumoral edema, or if the pia is violated during the surgery. The AED, most commonly used, levetiracetam since 2001, phenytoin prior to 2001, is continued for 7 days postoperative and then discontinued if the patient does not have a seizure. This practice was developed based on the authors' experience and the duration of 7 days was based on data for patients with traumatic brain injury.[20]

Statistical Analysis

All statistical analyses were performed in JMP 12.0 (SAS, Cary, North Carolina). Univariate chi-squared analysis was performed on variables of interest in relation to outcome (presence of preoperative seizures, or occurrence of postoperative seizures). All univariate variables with P-value $\leq$ .20 were included in subsequent multivariate logistic regression. The Wald and effect likelihood ratio tests were used to determine statistically significant predictors with $P \leq .05$, and results reported as odds ratios (OR).

Kaplan–Meier survival analysis was used to study the time to first postoperative seizure. Subjects were censored based on their last follow-up clinical note date with clear documentation of seizure status; therefore, no minimum follow-up duration was used. A multivariate Cox proportional hazards regression of time to first postoperative seizure was performed on variables identified from univariate analysis of postoperative seizures to have a P-value $\leq$ .20. Patients who did not experience seizure were censored based on the date of last follow-up denoting seizure status.

TABLE 1. Patient Characteristics

Characteristics	n (%)
Gender	
Male	288 (28.0)
Female	742 (72.0)
Age	55.7 ± 13.9 (mean ± SD)
WHO class	
I	819 (81.1)
II	164 (16.3)
III	26 (2.6)
In-hospital AED use	
Yes	582 (74.6)
No	198 (25.4)
Preop seizure	
Yes	234 (22.7)
No	799 (77.3)
Postop seizure in hospital	
Yes	54 (5.9)
No	856 (94.1)
Postop seizure after discharge	
Yes	52 (13.8)
No	324 (86.2)
Median months follow-up	27.0 (48.8 ± 55.6, mean ± SD)

SD, standard deviation.

RESULTS

Participants

From a database of patients who underwent surgical treatment of meningioma at the author's institution during the study time period, a final sample of 1033 adult subjects were identified who fit all our inclusion criteria as described in the methods. Demographic and clinical characteristics of these subjects are presented in Table 1.

Preoperative Seizures

A total of 234 (22.7%) patients experienced preoperative seizures. Univariate analysis identified the following variables to be significantly associated with preoperative seizures (Table 2): male gender (P = .0015), lateral tumors (L/R vs midline, P = .0165), absence of headache as a presenting symptom (P < .0001), absence of a CN deficit as a presenting symptom (P < .0001), tumor location in the convexity/parasagittal/falx (P < .0001), tumor size ≥ 3 cm (P < .0001), and presence of ≥1 cm of peritumoral edema (P < .0001). Of these, multivariate logistic regression (Table 3) identified the following as significant predictors of preoperative seizures: the presence of ≥1 cm peritumoral edema (OR: 4.45, 95% confidence interval, CI: 2.55, 8.05, P < .0001), tumor location in the convexity/parasagittal/falx (OR: 2.13, 95% CI: 1.26, 3.67, P = .0046), older age (OR per year increase: 1.03, 95% CI: 1.01, 1.05, P = .0037), headache as a presenting symptom (OR: 0.50, 95% CI: 0.29, 0.84, P = .0085), CN deficit as a presenting symptom (OR: 0.36, 95% CI: 0.17, 0.71, P = .0027).

Patients presenting with headache were not more or less likely to have tumor size ≥ 3 cm (χ^2 = 0.084, P = .77), convexity/parasagittal location (χ^2 = 3.06, P = .08), peritumoral edema ≥ 1 cm (χ^2 = 2.38, P = .12), or WHO II/III pathology (χ^2 = 0.22, P = .64).

Preoperative seizure incidence was analyzed based on tumor localization. The highest seizure incidence was found for falx/parasagittal, convexity tumors (37.6%, 30.5%), followed by middle fossa, sphenoid wing, olfactory groove tumors, with intermediate incidence (28.9%, 15.9%, 15.0%), while tentorial (superior aspect), intraventricular, tuberculum, and supratentorially extending petroclival tumors had the lowest incidence (11.1%, 6.7%, 6.2%, 3.7%).

Postoperative Seizures

Postoperative seizures prior to discharge (in-hospital) and postdischarge were analyzed separately. Year of admission was not significantly associated with in-hospital or postdischarge seizures (χ^2 = 0.44, P > .5), suggesting that seizure rate did not change during the long study period. In the immediate postop period prior to discharge (median duration of postop stay: 4 days, 5.72 ± 6.63, mean ± standard deviation), 54 patients experienced seizures (5.9%). Univariate analysis identified variables significantly associated with immediate postop seizures (Table 4), including male gender (P = .0427), weakness as a presenting symptom (P < .0001), tumor location at

TABLE 2. Univariate Analysis of Preoperative Seizures

	Preop seizure, N (%)	*P*-value	
	No	Yes	
Gender			
Male	204 (25.6)	84 (36.2)	**.0015**
Female	594 (74.4)	148 (63.8)	
Comorbidities			
HTN	249 (33.2)	67 (30.5)	.4377
DM2	70 (9.3)	18 (8.2)	.5973
CAD	29 (3.9)	6 (2.7)	.4238
HLD	110 (14.7)	41 (18.6)	*.1555*
Prior MI	9 (1.2)	0 (0)	*.1024*
Prior CVA	8 (1.1)	3 (1.4)	.716
COPD	14 (1.9)	8 (3.6)	*.1218*
CKD	10 (1.3)	7 (3.2)	*.0666*
Prior radiation	36 (4.5)	10 (4.3)	.8797
NF2	5 (0.6)	2 (0.9)	.7074
Tumor side			
Left	298 (42.6)	114 (52.3)	**.0165**
Right	299 (42.7)	87 (39.9)	
Midline	103 (14.7)	17 (7.8)	
Presenting headache			
Yes	306 (38.3)	58 (24.8)	**<.0001**
No	493 (61.7)	176 (75.2)	
Presenting weakness			.3916
Yes	708 (88.6)	212 (90.6)	
No	91 (11.4)	22 (9.4)	
Presenting CN deficit			
Yes	271 (33.9)	27 (11.5)	**<.0001**
No	528 (66.1)	207 (88.5)	
WHO class			
I	641 (82.1)	178 (78.1)	*.1736*
II/III	140 (17.9)	50 (21.9)	
Tumor location			
Tuberculum/planum	183 (22.9)	12 (5.1)	**<.0001**
Convexity	173 (21.7)	76 (32.5)	
Falx/parasagittal	148 (18.5)	89 (38)	
Sphenoid wing	116 (14.5)	22 (9.4)	
Olfactory groove	34 (4.3)	6 (2.6)	
Tentorial	40 (5)	5 (2.1)	
Petroclival	26 (3.3)	1 (0.4)	
Intraventricular	14 (1.8)	1 (0.4)	
Middle fossa	32 (4)	13 (5.6)	
Multifocal	33 (4.1)	9 (3.8)	
Tumor location			
Convexity/falx	321 (41.9)	165 (73.3)	**<.0001**
Skull base	445 (58.1)	60 (26.7)	
Tumor size			
≥3 cm	334 (63.5)	128 (81.5)	**<.0001**
<3 cm	192 (36.5)	29 (18.5)	
Peritumoral edema			
≥1 cm	279 (43.5)	154 (76.2)	**<.0001**
<1 cm	362 (56.5)	48 (23.8)	

Abbreviations: HTN, hypertension; DM2, diabetes mellitus type 2; CAD, coronary artery disease; HLD, hyperlipidemia; MI, myocardial infarction; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NF2, neurofibromatosis type II; CN, cranial nerve; WHO, World Health Organization.
Significant *P*-values are shown in bold. *P*-values ≤ .20, to be included in multivariate analysis, are shown in italics.

TABLE 3. Multivariate Analysis of Preoperative Seizures

Variable	OR (95% CI)	*P*-value
Peritumoral edema ≥1 cm	4.45 (2.55, 8.05)	<.0001
Presenting CN deficit	0.36 (0.17, 0.71)	.0027
Age (per year increase)	1.03 (1.01, 1.05)	.0037
Convexity/parasagittal/falx	2.13 (1.26, 3.67)	.0046
Presenting headache	0.50 (0.29, 0.84)	.0085

Abbreviations: OR, odds ratio; CI, confidence interval; CN, cranial nerve; WHO, World Health Organization; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CKD, chronic kidney disease; HLD, hyperlipidemia.
Variables included in model: Peritumoral edema ≥1 cm, presenting CN deficit, age, convexity/parasagittal/falx, presenting headache, WHO II/III, COPD, prior MI, tumor size ≥3 cm, gender, CKD, HLD, tumor side. Whole model likelihood-ratio χ^2-test: $P < .0001$, area under the curve of the ROC curve: 0.78. Interactions tested included convexity/parasagittal/falx by tumor size ≥3 cm, convexity/parasagittal/falx by peritumoral edema ≥1 cm, and convexity/parasagittal/falx by presenting CN deficit, which were nonsignificant and did not alter the model; these interactions were excluded from the final model.

the convexity/parasagittal/falx ($P = .0013$), preoperative seizure ($P = .0091$). Postoperative complications were also significantly associated with immediate postop seizures, including new weakness ($P = .0004$), pneumonia ($P < .0001$), venous infarction ($P = .0005$), intracranial hemorrhage ($P = .0084$), CVA ($P = .0442$), and cerebral edema/hydrocephalus ($P = .0024$). For multivariate analysis, medical and surgical complications were combined into a single variable for occurrence of any medical/surgical complication. Male gender was associated with higher grade (WHO II/III) tumors in the whole sample (25.8% vs 16.2%, $\chi^2 = 12.01$, $P = .0005$).

After multivariate logistic regression (Table 5), weakness as a presenting symptom (OR 3.04, 95% CI: 1.31, 6.79, $P = .0135$), convexity/parasagittal/falx tumor location (OR 2.76, 95% CI: 1.24, 6.59, $P = .0091$), and any medical/surgical complication (OR 3.14, 95% CI: 1.29, 7.25, $P = .0122$) were significant independent predictors of in-hospital postoperative seizures. Weakness as a presenting symptom was significantly associated with in-hospital postoperative seizures, and not with preoperative seizures or seizures postdischarge. Patients presenting with weakness were more likely to have tumor size ≥3 cm (84.6% vs 65.5%, $\chi^2 = 11.59$, $P = .0007$), peritumoral edema ≥1 cm (67.0% vs 49.4%, $\chi^2 = 10.38$, $P = .0013$), tumor location in the convexity/parasagittal/falx (75.9% vs 45.6%, $\chi^2 = 11.36.43$, $P < .0001$), and WHO II/III pathology (32.7% vs 17.1%, $\chi^2 = 15.60$, $P < .0001$).

Subjects with at least 1 year of postoperative follow-up were included in univariate and multivariate analysis of seizures postdischarge (n = 373); of these, 51 patients experienced seizures postdischarge (13.7%), including 25 patients without preoperative seizures (8.6%, n = 291), and 26 patients with preoperative seizures (31.7%, n = 82). Univariate analysis identified the following variables to be significantly associated with postdischarge seizures: male gender ($P = .006$), tumor location

TABLE 4. Univariate Analysis of Postoperative Seizures

	In-hospital, n (%)		*P*-value	After discharge[a] n (%)		*P*-value
	No sz	Sz		No sz	Sz	
Gender						
Male	224 (26.3)	21 (38.9)	**.0427**	81 (25.3)	22 (44)	**.0061**
Female	629 (73.7)	33 (61.1)		239 (74.7)	28 (56)	
Comorbidities						
HTN	266 (32.7)	20 (37)	.5133	208 (36.6)	20 (29.4)	.2455
DM2	70 (8.6)	8 (14.8)	*.1228*	53 (9.3)	4 (5.9)	.3487
CAD	31 (3.8)	1 (1.9)	.4592	25 (4.4)	3 (4.4)	.9945
HLD	132 (16.2)	9 (16.7)	.9338	108 (19)	12 (17.6)	.7904
MI	9 (1.1)	0 (0)	.437	6 (1.1)	0 (0)	.3949
CVA	9 (1.1)	0 (0)	.437	8 (1.4)	0 (0)	.3251
COPD	18 (2.2)	0 (0)	.2692	12 (2.1)	3 (4.4)	.2366
CKD	14 (1.7)	2 (3.7)	.2947	12 (2.1)	1 (1.5)	.7249
Prior radiation	36 (4.2)	3 (5.6)	.6348	21 (3.6)	5 (7)	*.1669*
NF2	6 (0.7)	0 (0)	.5371	4 (0.7)	1 (1.4)	.5147
Tumor side						
Left	350 (46.2)	18 (37.5)	.6047	134 (48)	24 (50)	.3921
Right	308 (40.6)	23 (47.9)		107 (38.4)	21 (43.8)	
Midline	100 (13.2)	7 (14.6)		38 (13.6)	3 (6.3)	
Presenting headache						
Yes	320 (37.4)	18 (33.3)	.5503	118 (36.6)	18 (35.3)	.8522
No	536 (62.6)	36 (66.7)		204 (63.4)	33 (64.7)	
Presenting weakness						
Yes	85 (9.9)	16 (29.6)	**<.0001**	30 (9.3)	7 (13.7)	.3278
No	771 (90.1)	38 (70.4)		292 (90.7)	44 (86.3)	
Presenting CN deficit						
Yes	264 (30.8)	12 (22.2)	*.1814*	104 (32.3)	10 (19.6)	*.0676*
No	592 (69.2)	42 (77.8)		218 (67.7)	41 (80.4)	
WHO class						
I	680 (81)	44 (83)	.722	266 (84.2)	37 (74)	*.0765*
II/III	159 (19)	9 (17)		50 (15.8)	13 (26)	
Tumor localization						
Tuberculum/planum	170 (19.9)	3 (5.6)	**.0267**	74 (23)	2 (3.9)	**.0475**
Convexity	201 (23.5)	17 (31.5)		74 (23)	17 (33.3)	
Falx/parasagittal	193 (22.5)	21 (38.9)		71 (22)	15 (29.4)	
Sphenoid wing	116 (13.6)	6 (11.1)		39 (12.1)	6 (11.8)	
Olfactory groove	34 (4)	2 (3.7)		14 (4.3)	3 (5.9)	
Tentorial	37 (4.3)	2 (3.7)		11 (3.4)	3 (5.9)	
Petroclival	23 (2.7)	1 (1.9)		7 (2.2)	1 (2)	
Intraventricular	13 (1.5)	2 (3.7)		3 (0.9)	0 (0)	
Middle fossa	37 (4.3)	0 (0)		16 (5)	1 (2)	
Multifocal	32 (3.7)	0 (0)		13 (4)	3 (5.9)	
Tumor localization						
Convexity/falx	394 (47.8)	38 (70.4)	**.0013**	145 (46.9)	32 (66.7)	**.0109**
Skull base	430 (52.2)	16 (29.6)		164 (53.1)	16 (33.3)	
Tumor size						
≥3 cm	393 (67.4)	32 (80)	*.0981*	142 (63.1)	29 (80.6)	**.0409**
<3 cm	190 (32.6)	8 (20)		83 (36.9)	7 (19.4)	
Peritumoral edema						
≥1 cm	356 (48.8)	24 (54.5)	.4618	127 (44.4)	29 (65.9)	*.0078*
<1 cm	373 (51.2)	20 (45.5)		159 (55.6)	15 (34.1)	
In-hospital AED use						
Yes	510 (73.5)	42 (80.8)	.2482	196 (70.8)	43 (91.5)	**.0028**
No	184 (26.5)	10 (19.2)		81 (29.2)	4 (8.5)	
Preop seizure						
Yes	186 (21.7)	20 (37)	**.0091**	56 (17.4)	26 (51)	**<.0001**
No	670 (78.3)	34 (63)		266 (82.6)	25 (49)	

TABLE 4 – Continued.

	In-hospital, n (%)		*P*-value	After discharge[a] n (%)		*P*-value
	No sz	Sz		No sz	Sz	
In-hospital seizure						
Yes	n/a			23 (4.1)	13 (18.8)	**<.0001**
No	n/a			539 (95.9)	56 (81.2)	
Resection extent						
Gross total	613 (76.3)	35 (71.4)	.4343	232 (74.6)	32 (69.6)	.4679
Subtotal	190 (23.7)	14 (28.6)		79 (25.4)	14 (30.4)	
Recurrence						
Recurred	95 (11.6)	6 (11.3)	.9559	56 (17.9)	10 (22.2)	.49
Did not recur	726 (88.4)	47 (88.7)		256 (82.1)	35 (77.8)	
Neurological complications						
New weakness	36 (4.2)	8 (14.8)	**.0004**	24 (4.2)	6 (8.5)	*.1036*
New CN deficit	63 (7.4)	4 (7.4)	.9896	45 (7.8)	4 (5.6)	.5172
Medical/surgical complications						
DVT	8 (0.9)	1 (1.9)	.436	4 (0.7)	1 (1.4)	.5147
PE	2 (0.2)	0 (0)	.7221	1 (0.2)	0 (0)	.7258
Pneumonia	4 (0.5)	3 (5.6)	**<.0001**	2 (0.3)	0 (0)	.6196
Venous infarct	6 (0.7)	3 (5.6)	**.0005**	4 (0.7)	1 (1.4)	.5147
Intracranial hemorrhage	10 (1.2)	3 (5.6)	**.0084**	6 (1)	0 (0)	.3884
CVA	2 (0.2)	1 (1.9)	**.0442**	8 (1.4)	0 (0)	.3185
Cerebral edema/hydrocephalus	27 (3.2)	6 (11.1)	**.0024**	16 (2.8)	3 (4.2)	.4919
Hematoma	13 (1.5)	2 (3.7)	.2213	8 (1.4)	1 (1.4)	.9868
Wound infection	22 (2.6)	0 (0)	.233	15 (2.6)	4 (5.6)	*.1518*
Hyponatremia	9 (1.1)	1 (1.9)	.5842	2 (0.3)	0 (0)	.6196
Any med/surg complication	90 (10.5)	15 (27.8)	**.0001**	57 (9.9)	11 (15.5)	*.1437*

Abbreviations: HTN, hypertension; DM2, diabetes mellitus type 2; CAD, coronary artery disease; HLD, hyperlipidemia; MI, myocardial infarction; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; NF2, neurofibromatosis type II; CN, cranial nerve; WHO, World Health Organization; AED, anti-epileptic drug; DVT, deep vein thrombosis; PE, pulmonary embolism; CSF, cerebrospinal fluid.

[a]Only patients with at least 1 year of follow-up were included in univariate and multivariate analysis of seizures after discharge.

Significant *P*-values are shown in bold. *P*-values ≤ .20, to be included in multivariate analysis, are shown in italics.

at the convexity/parasagittal/falx ($P = .011$), tumor size ≥ 3 cm ($P = .041$), CN deficit ($P = .048$), presence of ≥1 cm peritumoral edema ($P = .008$), in-hospital AED use ($P = .003$), and presence of preoperative seizures ($P < .0001$). AED use was associated with increased occurrence of postdischarge seizures (18.0% vs 4.7%, $\chi^2 = 10.24$, $P = .0014$). In total, 37.1% received phenytoin alone, 50.8% received levetiracetam alone, and 12.1% some other type of AED or a combination. There was no significant difference between use of phenytoin alone vs levetiracetam alone in association with in-hospital or postdischarge seizure (in-hospital: $\chi^2 = 1.40$, $P = .24$; postdischarge: $\chi^2 = 0.75$, $P = .39$). In addition, stratification by gender, pathology, preoperative seizure, tumor size ≥3 cm, peritumoral edema ≥1 cm, resection extent, and tumor location failed to reveal an alternate association between AED use and seizure.

After multivariate logistic regression, preoperative seizures (OR 5.70, 95% CI: 2.57, 13.13, $P < .0001$) and postoperative in-hospital seizures (OR 4.31, 95% CI: 1.28, 13.67, $P = .0196$) were found to be significant independent predictors associated with postdischarge seizure. Neither extent of resection nor tumor recurrence was associated with greater postoperative seizure incidence.

Subgroup analysis of patients who did not have preoperative seizures identified the following significant univariate variables: any medical/surgical complication ($P = .0207$), WHO II/III ($P = .0119$), tumor location in the convexity/parasagittal/falx ($P = .0417$), and postop in-hospital seizure ($P = .0007$). Multivariate logistic regression revealed occurrence of postop in-hospital seizure (OR: 4.61, 95% CI: 1.23, 15.18, $P = .0248$) and any medical/surgical complication (OR: 3.39, 95% CI: 1.09, 9.48, $P = .0355$) to be significant independent predictors of postdischarge seizure among patients who did not have preoperative seizures.

Time to First Seizure and Seizure Freedom

In order to analyze the time course of when patients experience their first seizure after discharge, Kaplan–Meier survival analysis

TABLE 5. Multivariate Analysis of Postoperative Seizures

Variable	OR (95% CI)	*P*-value
In hospital, all patients[a]		
Convexity/parasagittal/falx	2.76 (1.24, 6.59)	.0091
Any medical/surgical complication	3.14 (1.29, 7.25)	.0122
Presenting weakness	3.04 (1.31, 6.79)	.0135
After discharge, all patients[b]		
Preop seizure	5.70 (2.57, 13.13)	<.0001
Postop in-hospital seizure	4.31 (1.28, 13.67)	.0196
After discharge, patients without preoperative seizure[c]		
Postop in-hospital seizure	4.61 (1.23, 15.18)	.0248
Any medical/surgical complication	3.39 (1.09, 9.48)	.0355

Abbreviations: OR, odds ratio; CI, confidence interval; DM2, diabetes mellitus type II; CN, cranial nerve; AED, anti-epileptic drug; WHO, World Health Organization, HTN, hypertension; COPD, chronic obstructive pulmonary disease.

[a]Variables included in model: convexity/parasagittal/falx, any medical/surgical complication, presenting weakness, DM2, age, preoperative seizure, tumor size ≥ 3 cm, new postoperative weakness, presenting CN deficit, gender. Whole model likelihood-ratio χ^2-test: $P = .0004$, area under the curve (AUC) of the ROC curve: 0.77. Interactions tested included convexity/parasagittal/falx by any medical/surgical complication, convexity/parasagittal/falx by presenting weakness, convexity/parasagittal/falx by preoperative seizure, which were found to be nonsignificant and were excluded from the final model.

[b]Variables included in model: preoperative seizure, postoperative in-hospital seizure, age, tumor size ≥ 3 cm, peritumoral edema ≥ 1 cm, AED use, gender, any medical/surgical complication, WHO II/III, prior radiation, convexity/parasagittal/falx, presenting CN deficit, new postoperative weakness. Whole model likelihood-ratio χ^2-test: $P = .0003$, AUC of the ROC curve: 0.77. Interactions tested included AED use by peritumoral edema ≥ 1 cm, AED use by tumor size ≥ 3 cm, AED use by WHO II/III, prior radiation by peritumoral edema ≥ 1 cm, which were found to be nonsignificant and were excluded from the final model.

[c]Variables included in model: age, HTN, COPD, presenting weakness, WHO II/III, convexity/parasagittal/falx, AED use, postoperative in-hospital seizure, any medical/surgical complication, new postoperative weakness. Whole model likelihood-ratio χ^2-test: $P = .021$, AUC of the ROC curve: 0.73. Interactions tested included AED use by WHO II/III, AED use by convexity/parasagittal/falx, postoperative in-hospital seizure by any medical/surgical complication, which were found to be nonsignificant and were excluded from the final model.

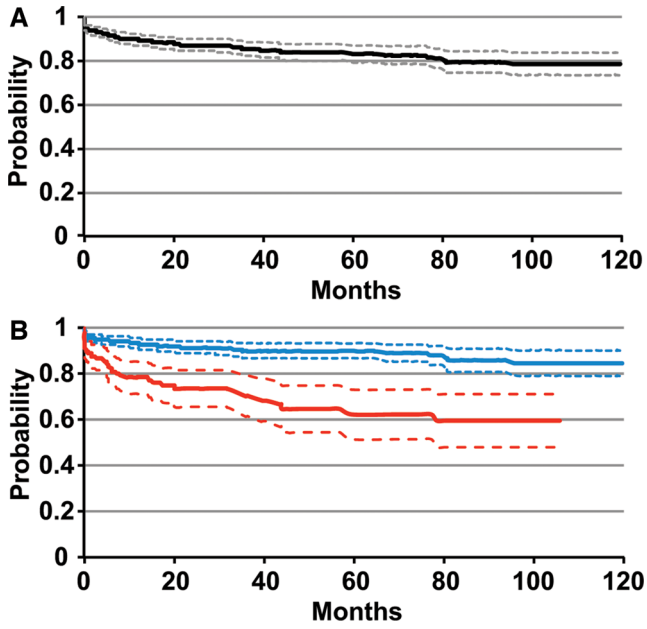

FIGURE. A, *Kaplan–Meier survival curve of seizure freedom for all patients. Time-to-event was defined as time to first postoperative seizure or censorship on the date of last follow-up. Patients who did not experience seizure were censored based on the date of last follow-up denoting seizure status.* **B**, *Kaplan–Meier survival curve of seizure freedom for patients, stratified by occurrence of preoperative seizures. The red curve represents patients who experienced preoperative seizures. The two curves are significantly different (Wilcoxon test: $\chi^2 = 26.7$, $P < .0001$).*

was performed on time-to-first-seizure (Figure A), combining both in-hospital and postdischarge seizures. Probabilities of not experiencing a postoperative seizure at 1, 12, 24, 36, 60, and 120 months were 94.3%, 89.6%, 87.1%, 85.2%, 83.3%, and 78.5%, respectively. Patients who did not experience seizure were censored based on the date of last follow-up denoting seizure status. There was a significant association between time-to-event and noncensorship (logistic fit, $\chi^2 = 4.32$, $P = .038$), indicating a slight bias toward longer follow-up for patients experiencing seizure, and possible overestimation of seizure occurrence in the long term.

Multivariate proportional hazards Cox regression on variables identified from univariate analysis of postoperative seizures (both pre- and postdischarge) to have $P < .20$ found the presence of preoperative seizures (relative risk: 2.58, 95% CI: 1.35, 5.01, $P = .0043$) and occurrence of any medical/surgical complication (relative risk: 2.65, 95% CI: 1.12, 5.82, $P = .0278$) to be significant independent predictors of experiencing a postoperative seizure. Variables included in this analysis were age, gender, report of weakness as a presenting symptom, report of a CN deficit as a presenting symptom, WHO grade II/III, tumor location in the convexity/parasagittal/falx, presence of ≥1 cm peritumoral edema, in-hospital AED use, tumor size ≥3 cm, new postoperative weakness, prior radiation, occurrence of any medical/surgical complication, and preoperative seizures. Cox regression repeated on the subgroup of patients who did not have preoperative seizures revealed the occurrence of any medical/surgical complication (relative risk: 4.22, 95% CI: 1.99, 8.46, $P = .0004$) to be the sole significant predictor of experiencing a postoperative seizure. The proportional hazards assumption for all significant covariates was met by determining the absence of crossing survival curves.

Stratifying patients based on absence vs presence of preoperative seizures revealed probabilities of not experiencing a postoperative seizure at 1, 12, 24, 36, and 60 months of 95.6% vs 89.1%, 93.2% vs 78.3%, 91.4% vs 73.5%, 89.9% vs 70.1%, and 89.9% vs 62.2%, respectively (Figure B).

DISCUSSION

Key Results

In this cohort of patients undergoing resection of supratentorial meningioma, the presence of >1 cm of peritumoral edema, nonskull base location, and greater age were identified as significant predictors of preoperative seizures, while presenting headache or CN deficit were associated with decreased odds. Weakness as a presenting symptom, nonskull base location, and occurrence of medical/surgical complications were found to be significantly associated with postoperative seizures prior to discharge. The presence of preoperative or postoperative in-hospital seizures was a significant predictor of postoperative seizures after discharge. Among patients without preoperative seizures, occurrence of postoperative in-hospital seizures and medical/surgical complications were significant predictors of postoperative seizures after discharge.

Interpretation by Topic Addressed

Factors Associated With Preoperative Seizure

Meningiomas that were larger than 3 cm in size, of higher grade, with convexity, falx or parasagittal location (nonskull base), and that had peritumoral edema ≥1 cm were more likely to be associated with preoperative seizure. These results suggest tumors exerting greater mass effect, and located close to the neocortex, to be more epileptogenic. Prior studies have shown similar results regarding tumor size, location, and peritumoral edema.[16,17,21,22]

In addition, we found that patients with presenting symptoms of headache or CN deficit had substantially reduced incidence of preoperative seizures. The latter is not surprising, as a finding of a CN deficit would indicate tumor location near the skull base and away from neocortex. On the other hand, the finding that headache, a symptom of mass effect, is inversely associated with preoperative seizures is surprising, but has been identified before in a smaller retrospective study.[17] This may be attributable to reporting bias of the more severe presenting symptom, ie, seizure, over headache. Alternatively, tumors detected on screening for headache may have been identified earlier, and may therefore have exerted less mass effect and been less epileptogenic. However, we found no association of headache with tumor size, edema, or tumor grade, although there was a trend toward skull base localization.

When we stratified preoperative seizure incidence based on tumor localization, we found that falx/parasagittal, convexity tumors had the highest incidence of seizures, followed by middle fossa, sphenoid wing, olfactory groove tumors with intermediate incidence, while tentorial (superior aspect), intraventricular, tuberculum, and superiorly extending petroclival tumors had the lowest incidence. This corresponds to proximity to neocortex, which is consistent with its known epileptogenicity. Interestingly, among skull base meningiomas, middle fossa tumors appeared to have a substantially higher rate of preoperative seizures, likely due to mass effect on the temporal lobe.[23]

Factors Associated With Postoperative Seizure

We studied factors associated with seizures in the immediate postoperative period while still admitted and after discharge with at least 1-year follow-up. Variables associated with in-hospital and postdischarge seizures differed: nonskull base location, presenting weakness, and occurrence of medical/surgical complications were associated with in-hospital seizures, while preop and in-hospital seizures were associated with seizures after discharge. The occurrence of any medical/surgical complication was independently associated with postdischarge seizure among patients who did not have preoperative seizure. On univariate analysis, the occurrence after surgery of new weakness, pneumonia, venous infarct, intracranial hemorrhage, CVA, and cerebral edema/hydrocephalus were significantly associated with in-hospital seizure but not postoperative seizure. Wound infection/recraniotomy and new weakness trended toward but did not reach significance in association with postdischarge seizure.

Male gender, nonskull base location, tumor size ≥3 cm, CN deficit, and peritumoral edema were also significantly associated with postdischarge seizures on univariate analysis. Subtotal resection was not associated with postoperative seizures, nor was tumor recurrence. Meningioma size as well as peritumoral edema have previously been associated with pre- and postoperative seizures.[17,21] The univariate association of increased postdischarge seizure occurrence in males may be due to gender differences in tumor characteristics. Male gender has been associated with more aggressive disease in anaplastic meningioma,[24] greater incidence of severe complication in intracranial meningioma surgery,[25] and in our study, higher grade tumors.

Stratification by tumor location largely mirrored that of preoperative seizures, with the exception of middle fossa tumors, which appeared to be associated with a substantially lower incidence of postoperative seizures both while in-hospital postresection and after discharge (0.0% and 5.9%); this is surprising, given the epileptogenic tendencies of the temporal lobe and the increased incidence of preoperative seizures with middle fossa tumors exerting mass effect on the temporal lobe (28.9%).

Interestingly, we found weakness as a presenting symptom to be significantly associated with in-hospital postoperative seizures on both univariate and multivariate analysis, but not with preoperative or postdischarge seizures. It is possible that the motor cortex is more sensitive and epileptogenic during the immediate perioperative setting, and that this subgroup of patients may benefit from AED prophylaxis in the perioperative period. Alternatively, this finding may reflect underrecognition of postoperative nonconvulsive seizures arising from nonmotor cortex, which may present subclinically. To our knowledge, this is the first report of such a finding in patients with meningioma.

Anti-Epileptic Prophylaxis

With regard to AED prophylaxis, we found an inverse relationship in univariate analysis between in-hospital AED use and postdischarge seizure freedom. This finding is likely

attributable to the fact that patients determined to be at risk for seizure were placed on AED prophylaxis while in the hospital. Subgroup analyses failed to identify an alternate relationship between AED use and postsurgical seizure, nor was there a significant difference between use of phenytoin alone and levetiracetam alone. The question of whether short-term AED prophylaxis in meningioma resection reduces the incidence of postoperative seizures is beyond the scope of this uncontrolled retrospective study, but warrants prospective, randomized controlled evaluation in the future. The authors are actively working to organize a multicentered randomized trial to test the efficacy of perioperative AED prophylaxis at this time.

Long-Term Seizure Freedom

As a measure of long-term seizure freedom, we studied the time to first seizure postoperatively. Overall, the probability of not experiencing a postoperative seizure through 5-year follow-up was roughly 90% in patients without a preoperative seizure, and 60% in patients with a preoperative seizure. These rates are similar to those previously reported.[16-18,26] Interestingly, the incidence of seizure did not plateau after surgery, but continued to slowly increase over time, even in patients who did not have a preoperative seizure. For those with preoperative seizures, this was even more pronounced, and is important information to relay when counseling patients and helping them establish expectations for their course.

The presence of preoperative seizures and medical/surgical complications were significant predictors of postoperative seizures in multivariate proportional hazards Cox regression of seizure freedom over time. The presence of preoperative seizures is inherently understandable as a predictive factor for postoperative seizure. Regarding medical/surgical complications, the sample sizes of each type of complication were too small to be included in multivariate modeling, but guidance can be drawn from the univariate analysis discussed above of the types of complications more likely to be associated with postop seizure.

Another interesting finding is the relatively poor long-term seizure freedom in patients with preoperative seizures. Only 62% of patients were seizure free at 5-year follow-up, suggesting room for improvement. These findings raise the possibility that patients with preoperative seizure may benefit from electrocorticographic mapping of adjacent cortex and resection of noneloquent, epileptically active cortex. At minimum, patients with persistent seizures may benefit from referral to an epilepsy center and evaluation for resection of adjacent epileptogenic cortex.

Strengths and Limitations

Our study represents a large single-institution sample of patients undergoing meningioma resection. Our large and relatively homogenous sample allowed us to utilize multivariate analyses to identify significant predictors of seizure and to characterize long-term seizure freedom following meningioma resection.

However, there are several limitations to this study. First, as a retrospective chart review study, we were limited by the availability of patient records and the quality of documentation, especially with long-term follow-up. Second, while we attempted to control for interactions among the variables studied by performing multivariate analysis, there may be unidentified confounders not accounted for in our analyses.

Comorbid conditions were based on admission notes that are limited by what was documented with regard to past medical history, leading to potential underreporting. Simpson grade of extent of resection was recorded in the operative note in 27% of cases, and our use of the postoperative MRI for determination of gross total resection is suboptimal; thus, our finding of a lack of association between resection extent and seizure occurrence should be interpreted with caution. Long-term follow-up data for postdischarge seizures was less reliable than data on preoperative and in-hospital seizures recorded in the admission and discharge notes, and may have resulted in underreporting of postdischarge seizures due to loss to follow-up. Conversely, our finding of an association between time-to-event and noncensorship in our Cox model may indicate a bias in our dataset in the long term toward overestimation of seizure occurrence. Given these caveats, our results regarding long-term seizure incidence should be interpreted with some caution.

Generalizability

The strengths of this study with regard to generalizability include the large size of the study and the consistency with prior studies on variables that were common between this study and prior studies reported in the literature including effect of tumor location, peritumoral edema, and tumor size (see above). However, the external validity of this study is limited by the fact that this was a single-institution analysis at a large tertiary academic neurosurgical center; the tumor characteristics, case complexity, and availability of imaging in our cohort may differ from the experience of other centers.

CONCLUSION

Seizures are a common occurrence both prior to and after meningioma resection, and can have a significant negative impact on patient quality of life. In this study, we found peritumoral edema, nonskull base location, and greater age to be associated with increased incidence of preoperative seizures. Weakness as a presenting symptom, nonskull base location, and medical/surgical complications were significant predictors of postoperative seizures while in house. Preoperative seizures and postoperative in-hospital seizures were significant predictors of postoperative seizures after discharge; among patients without preoperative seizures, in-hospital seizures and occurrence of medical/surgical complications were significant predictors of seizures after discharge. Complications associated with postsurgical seizures on univariate analysis included pneumonia, venous infarct, intracranial hemorrhage, CVA, and cerebral edema/hydrocephalus. Perioperative AED use was not meaningfully associated with seizure incidence, and prospective

randomized studies are needed to determine the efficacy of perioperative AED prophylaxis. Finally, long-term follow-up showing persistent seizures in meningioma patients with preoperative seizures raises the possibility that these patients may benefit from electrocorticographic mapping of adjacent cortex and resection of noneloquent, epileptically active cortex. These findings are useful for counseling patients on the short- and long-term incidence of seizures following meningioma resection, and in identifying patients who may be at higher risk for postoperative seizures.

Disclosure

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COMMENT

The authors have provided a detailed retrospective analysis of factors associated with seizure in 1033 patients who underwent surgery for meningioma. Overall, their methods were sound and their analysis was appropriate. Most of the findings were not surprising with the exception of the significant male preponderance in postoperative seizures. The strength of the paper is the very large number of cases in the series, the clear writing, and the thoughtful analysis. The acknowledged weaknesses are the retrospective analysis and the exclusive use of written records, without follow-up surveys or calls to confirm the long-term risk for postoperative seizures. This likely causes an under-reporting of seizures in the long-term follow-up group. Finally, the finding that preoperative weakness predicted seizures may reflect the epileptogenic nature of motor cortex, but may also reflect an under-reporting of non-motor seizures which are often more subtle in nature.

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