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Predicting outcome of epilepsy after meningioma resection

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Background. Surgical excision is the standard treatment for intracranial meningiomas. Epilepsy is a major cause of morbidity in meningioma patients, but postoperative control of epilepsy is not achieved in a substantial fraction of patients. The purpose of this study was to define risk factors for postoperative epilepsy.

Methods. Patients treated for histologically confirmed intracranial meningioma at the University Hospital Zurich between 2000 and 2013 were retrospectively analyzed. Demographic, clinical, imaging, and electroencephalographic data were assessed. A binary regression model was applied to identify risk factors for postoperative epilepsy.

Results. Of the 779 patients analyzed, epileptic seizures occurred in 244 (31.3%) patients before surgery and in 204 (26.6%) patients after surgery. Of the 244 patients with preoperative epilepsy, 144 (59.0%) became seizure-free after surgery; of the 535 patients without preoperative seizures, 104 (19.4%) suffered from epilepsy after surgery. Risk factors for postoperative epilepsy were preoperative epilepsy (odds ratio [OR]: 3.46 [95% confidence interval {CI}: 2.32–5.16]), major surgical complications including CNS infections (OR: 5.89 [95% CI: 1.53–22.61]), hydrocephalus (OR: 3.27 [95% CI: 1.35–7.95]), recraniotomy (OR: 2.91 [95% CI: 1.25–6.78]), and symptomatic intracranial hemorrhage (OR: 2.60 [95% CI: 1.17–5.76]) as well as epileptiform EEG potentials (OR: 2.52 [95% CI: 1.36–4.67]), younger age (OR: 1.74 [(95% CI: 1.18–2.58]), and tumor progression (OR: 1.92 [95% CI: 1.16–3.18]). Postoperative improvement or recovery from preoperative neurologic deficits was associated with improved seizure control (OR: 0.46 [95% CI: 0.25–0.85], $P = .013$).

Conclusion. We suggest prospective validation of a score ("STAMPE2") based on clinical findings, EEG, and brain-imaging measures to estimate postoperative seizure risk and guide anticonvulsant treatment in meningioma patients.

Keywords: EEG, meningioma, postoperative epilepsy, STAMPE2.

Meningiomas are the most common intracranial tumors in adults, with an annual incidence per 100 000 of 10.26 and 4.55 for females and males, respectively,[1] and a prevalence of about 1.5% in autopsy and brain-imaging studies.[2–4] The vast majority of clinically silent incidental meningiomas are benign, both histologically and clinically,[5,6] but severe morbidity can accompany the disease course.[7] Surgery is required for histological diagnosis and therefore represents the standard first-line treatment for most patients with symptomatic meningiomas.[8] Complications and morbidity from meningioma surgery are, however, common.[9–11]

Epilepsy is a major cause of morbidity in meningioma patients, with onset before or after surgery.[12–14] Selection of patients who will require anticonvulsant treatment after meningioma resection is challenging because, despite advances in neurosurgery and radiation oncology during the past decades, factors predicting the outcome of epilepsy after meningioma resection are not well-defined in recent cohorts. Here we identify risk factors for postoperative epilepsy in a cohort of 779 consecutive patients who underwent surgery for meningioma between 2000 and 2013.

Patients and Methods

Subject Selection

This study was approved by the local ethics committee and was performed in accordance with the Declaration of Helsinki. Figure 1 (Consort chart) details the primary analysis population. A total of 897 patients were followed or treated for meningioma

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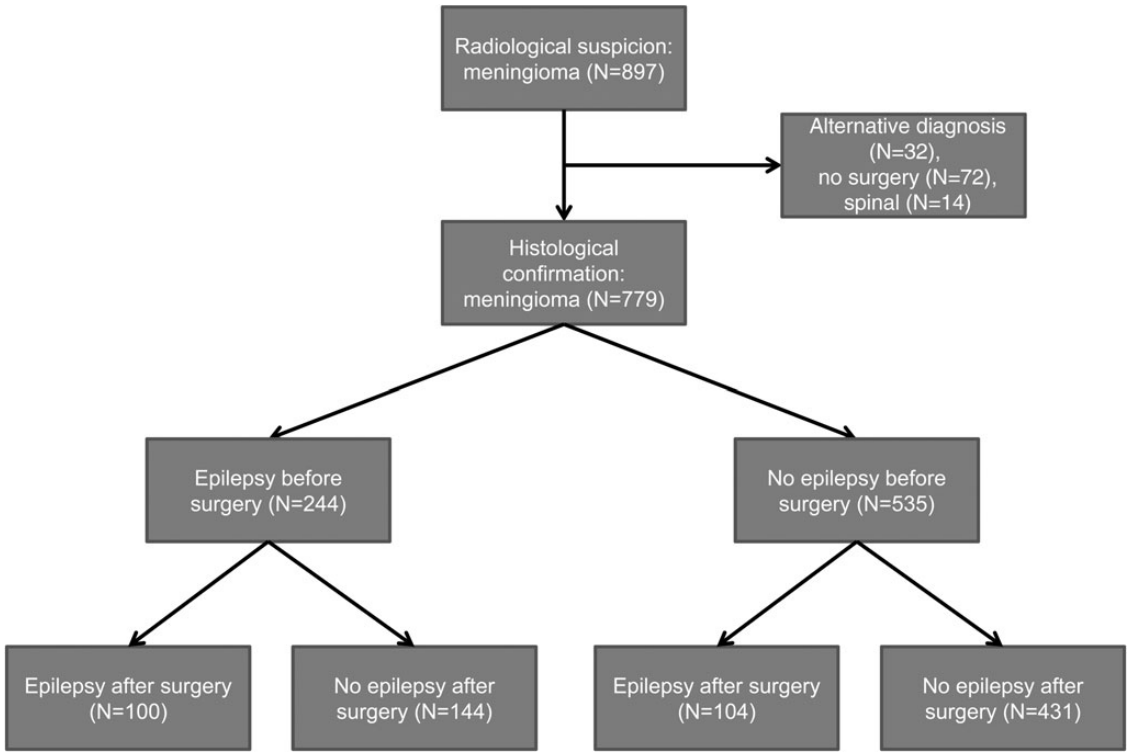

Fig. 1. Consort chart.

at the University Hospital Zurich between 2000 and 2013. Patients were identified by an automated search of the electronic chart system; 117 patients were excluded from further analysis because of spinal tumor location ($N = 13$) or lack of histological confirmation ($N = 104$). Subjects were further classified based on the occurrence of epileptic seizures before and after surgery.

Variables

Epilepsy was defined, according to criteria of the International League Against Epilepsy (ILAE), as a single seizure with a probability >60% for a second seizure within 10 years.[15] The term *postoperative epilepsy* was confined to patients with active postoperative epilepsy (ie, patients with documented postoperative epileptic seizures at any time during follow-up). The term *acute symptomatic postoperative seizures* was applied to seizures that occurred within 7 days of craniotomy according to the definition issued by the ILAE.[16]

Demographics, histopathological data, routine electroencephalography (EEG) parameters recorded over 20–30 minutes, and clinical course including neurological deficits, seizure history, surgical complications, and medication were obtained by reviewing the medical reports. The term *neurological deficit* refers to any deficits attributable to a focal cerebral lesion but not headache or seizures. An ordinal scale comprising the categories *better, worse*, and *unchanged* was applied. Imaging characteristics were complemented by review of cranial computer tomography (CT) and magnetic resonance imaging (MRI) scans. *Intracranial hemorrhage* was defined as the detection of hyperdensity on CT scans of at least 1 cm^3 diameter on 2 plains. Presence or absence of edema was defined as *hypodensity* on CT scans or as *T2 hyperintensity* on MRI scans. The term *ischemic stroke* was utilized according to the definition of the American Stroke Association for brain infarction attributable to ischemia and based on neuroimaging, and/or clinical evidence of permanent injury.[17] *Extent of resection* was defined by Simpson grade[18] and radiographically. *Radiographic gross total resection* (GTR) was defined as the absence of contrast enhancement on postoperative CT or MRI scans. *Tumor progression* was defined as an increase in diameter of contrast-enhancing lesions on CT or MRI scans at any time point after surgery. Interictal routine EEG measures during the entire follow-up period were analyzed. EEG recordings within 72 hours after documented seizures were considered postictal and were not included in analyses.

Statistical Methods

SPSS V22.0 was utilized for all statistical analyses. The chi-square test was performed for analysis of nominal variables, and the Mann-Whitney *U* test was performed for linearly scaled variables. Binary logistic regression was performed for multivariate testing of factors associated with postoperative epilepsy. Included in this model were age, World Health Organization (WHO) grade, tumor location, radiographic extent of resection, tumor progression at any time point, and the presence of preoperative seizures.

Results

Study Population

Patients undergoing surgical resection of intracranial meningioma ($N = 779$) were included in subsequent analyses (Figure 1).

Table 1. Demographic and clinical data

Age at diagnosis (y)	
Median	57
Range	18–90
Sex, *N* (%)	
Male	247 (31.8)
Female	532 (68.2)
WHO grade, *N* (%)	
I	638 (81.9)
II	119 (15.3)
III	22 (2.8)
Location[a], *N* (%)	
Convexity	167 (24.8)
Parasagittal	131 (20.2)
Skull base	260 (39.5)
Posterior fossa	81 (12.3)
Other	22 (3.3)
Maximal diameter[b], mm	
Median	40.0
Range	11–119
Simpson grade[c], *N* (%)	
1	143 (30.4)
2	221 (46.9)
3	41 (8.7)
4	55 (11.7)
5	11 (2.3)
Multiple meningiomas. *N* (%)	
Yes	118 (15.1)
No	661 (84.9)
Neurological deficit before surgery[d], *N* (%)	
Yes	379 (48.6)
No	389 (51.4)
Outcome of neurological deficits after surgery, *N* (%)	
Recovered	139 (36.7)
Residual deficit	124 (32.7)
Not improved	116 (30.6)
Epilepsy, *N* (%)	
Before surgery	244 (31.3)
After surgery	204 (26.2)
Epileptiform EEG potentials, *N* (%)	
Before surgery[e]	40 (15.8)
After surgery[f]	78 (22.9)
Tumor progression, *N* (%)	
Yes	203 (26.1)
No	576 (73.9)

[a]Not including patients with multiple meningiomas ($N = 661$).
[b]Documentation available for 694 patients (CT/MRI = 631/63).
[c]Documentation available for 468 patients.
[d]Not including headache and seizures.
[e]Documentation available for 253 patients.
[f]Documentation available for 340 patients.

Demographic and clinical data are summarized in Table 1. The median follow-up time after surgery was 67 (95% CI: 63–72) months, and 42 patients (5.4%) died. Simpson grade was documented in 468 patients, with Simpson grade 1/2 resection accomplished in 364 patients (77.3%). Imaging data were available for 694 patients, and among these radiographic GTR was achieved in 531 patients (76.5%). A subset of 129 patients (14.8%) underwent 2 or more meningioma resections. Co-treatments included preoperative intravascular embolization ($N = 392$, 47.8%), postoperative radiotherapy ($N = 118$, 15.1%), and systemic therapies ($N = 18$, 2.3%). Thirty-three patients (4.3%) were asymptomatic at diagnosis. Preoperative symptoms or signs in the other patients included headache ($N = 172$, 22.1%), epileptic seizures ($N = 244$, 31.2%), and neurological deficits ($N = 379$, 48.6%). In contrast, of the 72 patients with radiographic diagnosis of intracranial meningioma who did not undergo neurosurgery, 39 (54.1%) remained asymptomatic with respect to headache, epileptic seizures, and neurological deficits for a median follow-up of 71 months.

Clinical Correlates of Preoperative Epilepsy

The clinical characteristics of patients with preoperative epilepsy versus those without are summarized in Table 2. Localization at the cerebral convexity and epileptic discharges on EEG recordings were associated with epilepsy, whereas age, sex, WHO grade, tumor size, and the percentage of patients with multiple meningiomas were comparable in both groups. While localization at the skull base was not associated with preoperative epilepsy, further subclassification of this entity revealed an association of sphenoid wing meningiomas with epilepsy ($P = .032$). Preoperative epilepsy was less common among patients with petrous ridge ($P = .023$) or tuberculum sellae ($P = .018$) meningiomas, and no association with preoperative seizures was detected for cavernous sinus ($P = .584$), olfactory groove ($P = .215$), or suprasellar ($P = .079$) meningiomas. Among patients with preoperative epilepsy, tumors were less commonly associated with neurologic deficits, recovery from these deficits was more likely, and tumor recurrence or progression occurred less frequently. Only the secretory histological subtype was weakly associated with preoperative epilepsy ($P = .045$) (Supplementary material, Table S1). On brain imaging scans, edema was detected more frequently in patients with preoperative epilepsy, whereas hyperostosis was more frequent in patients without preoperative epilepsy, and no difference was apparent in the radiographic detection of tumor calcification as well as intraosseous, extracranial, or intra-axial growth (Supplementary material, Table S2). Recording of focal or background slowing on EEG was not associated with preoperative epilepsy (Supplementary material, Table S3) including frontal intermittent rhythmic delta activity (observed in 7 patients; data not shown).

Clinical Correlates of Postoperative Epilepsy

Of all patients undergoing meningioma resection ($N = 779$), 204 (26.3%) suffered from epilepsy after surgery (Figure 1). Acute symptomatic postoperative seizures, defined as seizures occurring within 7 days of craniotomy,[16] were associated with nonacute postoperative seizures in 29 (63%) of 46 cases, thus fulfilling the epilepsy-defining criteria of the ILAE.[15] Clinical characteristics of patients with postoperative epilepsy are summarized in Table 3. Younger age, higher WHO grade, tumor location at the cerebral convexity, multiple meningiomas, lack of postoperative improvement of preoperatively apparent

Table 2. Clinical characteristics of patients with versus without epilepsy before surgery

	Epilepsy before Surgery		*P*
	Yes *N* = 244 (31.3%)	No *N* = 535 (68.7%)	
Age at diagnosis, y			
Median	56	58	.265
Range	18–88	19–87	
Sex, *N* (%)			
Male	85 (34.8)	162 (30.3)	.214
Female	159 (65.2)	373 (69.7)	
WHO grade, *N* (%)			
I	200 (82.0)	438 (81.9)	.765
II	38 (15.6)	81 (15.1)	
III	6 (2.5)	16 (3)	
Location[a], *N* (%)			
Convexity	77 (35.9)	90 (19.1)	<.001
Parasagittal	39 (18.7)	92 (20.7)	.555
Skull base	81 (38.8)	179 (40.2)1	.733
Posterior fossa	9 (4.3)	72 (16.2)	<.001
Other	5 (1.9)	17 (3.8)	.347
Maximal diameter[b], mm			
Median	42	40	.088
Range	11–89	12–100	
Simpson grade[c], *N* (%)			
1	51 (35.9)	92 (28.2)	.295
2	57 (40.1)	162 (49.7)	
3	15 (10.6)	26 (8.0)	
4	15 (10.6)	39 (12.0)	
5	4 (2.8)	7 (2.1)	
Multiple meningiomas, *N* (%)			
Yes	35 (14.3)	90 (16.8)	.402
No	209 (85.7)	445 (83.2)	
Neurological deficit before surgery[d], *N* (%)			
Yes	104 (42.6)	275 (51.4)	.023
No	140 (57.4)	269 (48.6)	
Outcome of neurological deficits after surgery, *N* (%)			
Recovered	57 (54.8)	82 (29.8)	<.001
Residual deficit	19 (18.3)	105 (38.2)	
Not improved	28 (26.9)	88 (32.0)	
Epileptiform EEG potentials[f], *N* (%)			
Yes	25 (21.9)	15 (10.8)	.016
No	89 (78.1)	124 (89.2)	
Tumor progression, *N* (%)			
Yes	51 (20.9)	152 (28.4)	.027
No	193 (79.1)	383 (71.6)	

[a]*N* = 661, not including patients with multiple meningiomas.
[b]Documentation available for 694 patients (CT/MRI = 631/63).
[c]Documentation available for 468 patients.
[d]Not including headache and seizures.
[e]Patients with perioperative-onset neurologic deficits and a minimum follow-up of 1 year (*N* = 338).
[f]Documentation of preoperative EEG recordings available for 253 patients.

neurological deficits, epileptic discharges on EEG recordings, and tumor progression were associated with postoperative epilepsy. Further subclassification of skull base meningiomas into sphenoid wing, petrous ridge, tuberculum sellae, cavernous sinus, olfactory groove, and suprasellar meningiomas revealed no association between any of these tumor locations and postoperative epilepsy (data not shown).

Tumor diameter and Simpson grade did not differ in patients with or without postoperative epilepsy, although larger tumor diameter ($P = .057$) and higher Simpson grade ($P = .065$) favored postoperative epilepsy. The duration of surgery was not associated with postoperative epilepsy ($P = .111$) including acute symptomatic seizures ($P = .678$). We next evaluated surgical complications associated with postoperative epilepsy. Sensorimotor deficits with perioperative onset, CNS infections, clinically symptomatic intracranial hemorrhage, hydrocephalus, or recraniotomy for any reason were associated with postoperative epilepsy, whereas the frequencies of cranial nerve palsies, trigeminal neuralgias, and visual deficits were comparable in both groups (Table 4). Perioperative cardiovascular events including deep vein thrombosis, pulmonary embolism, myocardial infarction, and cardiac arrest were comparable between patients with and without postoperative epilepsy (data not shown).

We next assessed anticonvulsant drug therapies between patients with and without postoperative epilepsy (Supplementary material, Table S4). To allow for appropriate comparison of prescribed drugs, analysis was restricted to the first year of postoperative follow-up. The percentage of patients on anticonvulsants and the fraction with anticonvulsant polytherapy were larger among the cohort with postoperative epilepsy. Phenytoin was the most frequently prescribed anticonvulsant drug. More patients with postoperative epilepsy were on carbamazepine, but intake of all other evaluated drugs was balanced between the 2 groups.

Postoperative Control of Preoperative Onset Epilepsy

Among the 244 patients with preoperative epilepsy, 144 (59.1%) were seizure-free after surgery (Figure 1). Younger age, epileptic discharges on postoperative EEG recordings, and tumor progression were associated with persistent epilepsy after surgery, whereas there was no association with sex, WHO grade, tumor location (including further subclassification of skull base meningiomas; data not shown), tumor diameter, Simpson grade, multiple meningiomas, or preoperative neurologic deficits (Table 3). Postoperative complications associated with persistent epilepsy are summarized in Table 4. CNS infections and perioperative intracranial hemorrhages were associated with inferior postoperative control of preoperative-onset epilepsy. In addition, the association of hemorrhages with postoperative epilepsy was independent of neurologic symptoms arising from intracranial hemorrhage. Other postoperative complications including cranial nerve palsy, sensorimotor or visual deficits, ischemic stroke, hydrocephalus, and recraniotomy for any reason were comparable between patients with and without postoperative persistence of preoperative-onset epilepsy. Only fibrous meningioma was associated with postoperative control of preoperative epilepsy (Supplementary material, Table S1). Of note, radiographic GTR was achieved in 48 (90.6%) of 53 patients with fibrous meningioma as compared with 359 (74.5%) of 482 patients with other histological meningioma subtypes ($P = .009$), and fibrous meningiomas versus other subtypes were more frequently

Table 3. Clinical characteristics of patients with versus without epilepsy after surgery

				Epilepsy before Surgery					
				Yes $N = 244$ (31.3%)			No $N = 535$ (68.7%)		
	Epilepsy after Surgery			Epilepsy after Surgery					
	Yes $N = 204$ (26.2%)	No $N = 575$ (73.8%)	*P*	Yes $N = 100$ (41.0%)	No $N = 144$ (59.0%)	*P*	Yes $N = 104$ (19.4%)	No $N = 431$ (80.6%)	*P*
Age at diagnosis, y									
Median	54	58	<.001	53.5	58	.001	56.5	59	.025
Range	18-80	18-88		18–76	18–88		18–80	18–87	
Sex, *N* (%)									
Male	129 (36.8)	172 (29.9)	.071	35 (35.0)	50 (34.7)	.964	40 (38.5)	122 (28.3)	.043
Female	75 (63.2)	403 (70.1)		65 (65.0)	94 (75.3)		64 (61.5)	309 (71.7)	
WHO grade, *N* (%)									
I	158 (77.5)	480 (83.5)	<.001	82 (82.0)	118 (81.9)	.386	76 (73.1)	362 (84.0)	<.001
II	32 (15.7)	78 (15.1)		14 (14.0)	24 (16.7)		18 (17.3)	63 (14.6)	
III	14 (6.9)	8 (1.4)		4 (4.0)	2 (1.4)		10 (9.6)	6 (1.4)	
Location[a], *N* (%)									
Convexity	54 (31.6)	113 (22.2)	.007	28 (33.7)	49 (38.3)	.503	26 (32.9)	64 (17.3)	.013
Parasagittal	34 (21.5)	97 (19.6)	.667	17 (20.5)	22 (17.2)	.547	17 (21.5)	75 (20.2)	.798
Skull base	67 (42.4)	193 (38.9)	.544	34 (41.0)	47 (36.7)	.536	33 (41.8)	146 (39.4)	.677
Posterior fossa	6 (3.8)	75 (15.1)	<.001	3 (3.6)	6 (4.7)	.706	3 (3.8)	69 (18.6)	<.001
Other	1 (0.6)	21 (4.2)	.027	1 (1.2)	4 (3.1)	.65	0 (0.0)	17 (4.6)	.040
Maximal diameter, mm									
Median	41	40	.057	40	42	.427	40	41	.107
Range	10–96	11–100		15–90	10–90		10–96	10–100	
Simpson grade[b], *N* (%)									
1	30 (29.4)	113 (30.9)	.065	17 (30.4)	34 (39.5)	.456	13 (28.3)	79 (28.2)	.001
2	43 (42.2)	176 (48.1)		24 (42.9)	33 (38.4)		19 (41.3)	143 (51.1)	
3	8 (7.8)	33 (9.0)		5 (8.9)	10 (11.6)		3 (6.5)	23 (8.2)	
4	15 (14.7)	39 (10.7)		7 (12.5)	8 (9.3)		8 (17.4)	31 (11.1)	
5	6 (5.6)	5 (1.4)		3 (5.4)	1 (1.2)		3 (6.5)	4 (1.4)	
Multiple meningiomas, *N* (%)									
Yes	46 (22.5)	79 (13.7)	.003	17 (17.0)	18 (12.5)	.324	25 (24.0)	60 (13.9)	.011
No	158 (77.5)	496 (86.3)		83 (83.0)	126 (87.5)		79 (76.0)	371 (86.1)	
Neurological deficits before surgery[c], *N* (%)									
Yes	94 (46.1)	285 (49.6)	.392	44 (44.0)	60 (41.7)	.717	50 (48.1)	225 (52.2)	.450
No	110 (53.9)	290 (50.4)		56 (56.0)	84 (58.3)		42 (51.9)	206 (47.8)	
Postsurgical outcome of neurological deficits: *N* (%)									
Recovered	31 (32.9)	108 (37.9)	.011	19 (43.2)	38 (63.3)	.100	13 (26.0)	92 (40.9)	.010
Residual deficit	22 (23.4)	102 (35.8)		9 (20.5)	10 (16.7)		12 (24.0)	70 (31.1)	
Not improved	41 (43.7)	75 (26.3)		16 (36.3)	12 (20.0)		25 (50.0)	63 (28.0)	
Epileptiform EEG potentials[e], *N* (%)									
Yes	48 (29.6)	30 (16.9)	.005	25 (30.5)	13 (15.3)	.019	23 (27.8)	17 (18.3)	.096
No	114 (70.4)	148 (83.1)		57 (69.5)	72 (84.7)		57 (72.2)	76 (81.7)	
Tumor progression, *N* (%)									
Yes	74 (36.3)	129 (22.4)	<.001	29 (29.0)	22 (15.3)	.01	45 (43.3)	107 (24.8)	<.001
No	130 (63.7)	446 (77.6)		71 (71.0)	122 (84.7)		59 (56.7)	324 (75.2)	

[a]$N = 661$, not including patients with multiple meningiomas.
[b]Documentation available for 468 patients.
[c]Not including headache and seizures.
[d]Patients with perioperative-onset neurologic deficits and a minimum follow-up of 1 year ($N = 338$).
[e]Documentation of postoperative EEG recordings available for 340 patients.

Table 4. Association of epilepsy with neurologic complications from surgery

				Epilepsy before Surgery					
				Yes $N = 244$ (31.3%)			No $N = 535$ (68.7%)		
	Epilepsy after Surgery			Epilepsy after Surgery					
	Yes $N = 204$ (26.2%)	No $N = 575$ (83.8%)	*P*	Yes $N = 100$ (41.0%)	No $N = 144$ (59.0%)	*P*	Yes $N = 104$ (19.4%)	No $N = 431$ (80.6%)	*P*
Cranial nerve palsy, *N* (%)									
Yes	19 (9.3)	62 (10.8)	.555	10 (10.0)	9 (6.3)	.282	9 (8.7)	53 (12.3)	.393
No	185 (90.7)	513 (89.2)		90 (90.0)	135 (93.7)		95 (91.3)	378 (87.7)	
Trigeminal neuralgia, *N* (%)									
Yes	0 (0.0)	9 (1.6)	.122	0 (0.0)	1 (0.7)	N.A.	0 (0.0)	9 (2.1)	.217
No	204 (100.0)	566 (98.4)		100 (100.0)	143 (99.3)		104 (100.0)	422 (97.9)	
Sensorimotor deficit, *N* (%)									
Yes	40 (19.6)	66 (11.5)	.004	19 (19.0)	21 (14.6)	.359	21 (20.2)	45 (10.4)	.007
No	164 (80.4)	509 (88.5)		81 (81.0)	123 (85.4)		83 (79.8)	386 (89.6)	
Visual deficit, *N* (%)									
Yes	11 (5.4)	51 (8.9)	.115	7 (7.0)	7 (4.9)	.480	4 (3.8)	44 (10.2)	.054
No	193 (94.6)	524 (91.1)		93 (93.0)	137 (95.1)		100 (96.2)	387 (89.8)	
Stroke, *N* (%)									
Yes	13 (6.4)	23 (4.0)	.166	4 (4.0)	7 (4.9)	.750	9 (8.7)	16 (3.7)	.032
No	191 (93.6)	552 (96.0)		96 (96.0)	137 (95.1)		95 (91.3)	415 (96.3)	
CNS infection, *N* (%)									
Yes	10 (4.9)	6 (1.0)	.002	6 (6.0)	1 (0.7)	.015	4 (3.8)	5 (1.2)	.077
No	194 (95.1)	569 (99.0)		94 (94.0)	143 (99.3)		100 (96.2)	426 (98.8)	
Hemorrhage, *N* (%)									
Yes	63 (30.9)	153 (26.6)	.241	38 (38.0)	37 (25.7)	.040	25 (24.0)	116 (26.9)	.550
No	141 (69.1)	422 (73.4)		62 (62.0)	107 (74.3)		79 (76.0)	315 (73.1)	
Clinically symptomatic, *N* (%)									
Yes	40 (46.8)	74 (40.1)	.043	18 (47.4)	21 (56.8)	.416	22 (88.0)	53 (45.7)	<.001
No	23 (53.2)	79 (59.9)		20 (52.6)	16 (43.2)		3 (12.0)	63 (54.3)	
Hydrocephalus, *N* (%)									
Yes	13 (6.4)	14	.008	3 (3.0)	4 (2.8)	1.000	10 (9.6)	10 (2.3)	<.001
No	191 (93.6)	561		97 (97.0)	140 (97.2)		94 (90.4)	421 (97.7)	
Recraniotomy, *N* (%)									
Yes	16 (7.8)	21 (3.7)	.016	7 (7.0)	4 (2.8)	.130	9 (8.7)	17 (3.9)	.045
No	188 (92.2)	554 (96.3)		93 (93.0)	140 (97.2)		95 (91.3)	414 (96.1)	

located in the posterior fossa (30.2% vs 10.8%, $P < .001$) including the subgroup of patients with preoperative epilepsy (26.7% vs 2.4%, $P < .001$). Tumor characteristics on preoperative brain imaging scans were comparable between patients with and without postoperative persistence of epilepsy including radiographic extent of resection, presence of edema, calcification, and hyperostosis as well as intraosseous, extracranial or intraaxial growth (Supplementary material, Table S2). On postoperative EEG recordings, focal slowing, but not slowing of the background rhythm, was associated with persistence of preoperative epilepsy (Supplementary material, Table S3). Preoperative seizure semiology was not associated with postoperative epilepsy (Supplementary material, Table S5).

Postoperative New-onset Epilepsy

Of 535 patients without preoperative epilepsy, 104 patients (19.4%) suffered from epilepsy after meningioma resection (Figure 1). Younger age, male sex, higher WHO grade, tumor location at the cerebral convexity, higher Simpson grade, multiple meningiomas, and tumor progression were associated with new-onset epilepsy after meningioma surgery but not tumor diameter and recording of epileptic discharges on postoperative EEG (Table 3). Further subclassification of skull base meningiomas revealed a weak association of petrous ridge meningiomas with postoperative new-onset epilepsy ($P = .018$). Of note, petrous ridge meningiomas were associated with a lower rate of radiographic GTR ($P = .002$) and Simpson grade 1 or 2 resection

($P = .037$), whereas surgical complications and recurrence rates, age, sex, and WHO grade were not associated with petrous ridge meningiomas (data not shown). Surgical complications associated with postoperative-onset epilepsy included sensorimotor deficits, ischemic stroke, and symptomatic intracranial hemorrhage as well as hydrocephalus and recraniotomy but not cranial nerve palsies, trigeminal neuralgia, visual deficits, or CNS infections (Table 4). Anaplastic meningioma was the only histopathological subtype associated with new-onset epilepsy after surgery (Supplementary material, Table S1). On brain imaging scans, edema and intra-axial growth were more frequent, and hyperostosis was less frequent in patients with onset of epilepsy after surgery, but GTR, calcification, and intraosseous or extracranial growth were balanced between patients with and without onset of epilepsy after surgery (Supplementary material, Table S2). Focal or background slowing on EEG recordings occurred equally in patients with and without postoperative new-onset epilepsy (Supplementary material, Table S3).

Prophylactic Perioperative Anticonvulsant Therapy

Prophylactic perioperative anticonvulsant therapy was administered to 244 (45.6%) of 535 patients without preoperative epilepsy. The preferred drug utilized for prophylaxis was phenytoin ($N = 186$, 76.3%) followed by carbamazepine ($N = 15$, 6.2%), levetiracetam ($N = 14$, 5.7%), and valproate ($N = 11$, 4.5%). Prophylactic perioperative anticonvulsant intake was balanced between patients with versus without postoperative epilepsy ($P = .361$), but prophylactic anticonvulsant intake was associated with a higher rate of acute symptomatic postoperative seizures within 7 days after surgery ($P = .063$). Key clinical characteristics of patients receiving prophylactic anticonvulsants versus patients who did not receive seizure prophylaxis were not balanced. More patients receiving prophylactic anticonvulsant therapy suffered from WHO grade II or III meningiomas (23.8% vs 13.4%, $P = .002$), had documented epileptiform potentials on preoperative EEG (4.9% vs 1.0%, $P = .007$), or had a complicated postoperative course (30.3% vs 20.6%, $P = .010$) due to new-onset sensorimotor deficits, CNS infection, hydrocephalus, recraniotomy for any reason, or symptomatic intracranial hemorrhage. In contrast, among patients who did not receive prophylactic anticonvulsants, versus patients receiving prophylactic anticonvulsants more patients underwent Simpson grade 3–5 resection (26.9% vs 17.5%, $P = .046$), whereas the rate of patients with radiographic GTR ($P = .200$), edema on preoperative imaging scans ($P = .241$), younger versus older age ($P = .861$), multiple meningiomas ($P = .722$), and tumor location at the convexity ($P = .289$) were balanced between both groups.

Multivariate Modeling of Predictors of Postoperative Seizure Control

We applied a binary logistic regression model to identify predictors of postoperative seizure control. Univariate analyses of the association of variables included in this model with postoperative epilepsy are summarized in Supplementary material, Table S6. On multivariate analyses (Table 5), younger age, tumor progression, and preoperative epilepsy were predictive for postoperative epilepsy. Such an association was not identified for WHO grade, tumor location, or extent of resection. When tested as an additional single variable in this model, epileptic discharges on postoperative EEG recordings and edema on preoperative imaging scans were identified as a risk factor for postoperative epilepsy, and postoperative improvement or recovery from preoperative neurologic deficits was predictive for better seizure control. Surgical complications identified as risk factors for postoperative epilepsy, when tested as additional single variables, included sensorimotor deficits, CNS infections, hydrocephalus, and recraniotomy for any reason. Radiographic detection of intracranial hemorrhage was not predictive for poor postoperative seizure control, though favoring epilepsy. However, intracranial hemorrhage that was associated with neurological symptoms was a risk factor for epilepsy. No predictive role for postoperative seizure control was identified for preoperative neurologic deficits ($P = .736$), multiple meningiomas ($P = .151$), sex ($P = .741$), intra-axial growth ($P = .247$), or hyperostosis ($P = .438$) when tested as additional single variables in this model. Simpson grade was also not predictive ($P = .434$) when substituting for radiographic extent of resection.

We next applied this binary logistic regression model to detect independent risk factors for acute symptomatic perioperative seizures and included prophylactic anticonvulsant therapy and surgical complications (new-onset sensorimotor deficits, CNS infection, hydrocephalus, recraniotomy for any

Table 5. Multivariate analyses of predictors for postoperative seizure control[a]

	OR and 95% CI	*P*
Multivariate model		
Age: 18 y–54 y vs ≥55 y	1.74 (1.18–2.58)	.005
WHO grade: I vs II/III	1.01 (0.58–1.74)	.978
Tumor location convexity: yes vs no	1.40 (0.89–2.21)	.143
Radiographic extent of resection: gross total vs incomplete	0.89 (0.55–1.45)	.639
Tumor progression: yes vs no	1.92 (1.16–3.18)	.012
Preoperative epilepsy: yes vs no	3.46 (2.32–5.16)	<.001
Variables tested as additional single variables[b]		
Improvement of preoperative neurologic deficits: yes vs no	0.46 (0.25–0.85)	.013
Epileptic discharges[c]: yes vs no	2.52 (1.36–4.67)	.003
Edema before surgery[d]: yes vs no	1.63 (1.02–2.61)	.039
Surgical complications		
Sensorimotor deficits: yes vs no	1.80 (1.05–3.09)	.033
CNS infections: yes vs no	5.89 (1.53–22.61)	.010
Hydrocephalus: yes vs no	3.27 (1.35–7.95)	.009
Recraniotomy for any reason: yes vs no	2.91 (1.25–6.78)	.013
Radiographic intracranial hemorrhage: yes vs no	1.51 (0.97–2.31)	.058
Symptomatic intracranial hemorrhage: yes vs no	2.60 (1.17–5.76)	.018

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]$N = 623$ patients with complete datasets.
[b]Further variables are mentioned in the text.
[c]Postoperative EEG recordings ($N = 340$).
[d]Documentation available for 690 patients (CT/MRI = 629/61).

reason, or symptomatic intracranial hemorrhage) as additional covariates. Prophylactic anticonvulsant therapy in patients without preoperative epilepsy was not associated with perioperative seizure control in this model (odds ratio [OR]: 1.31 [95% confidence interval {CI}: 0.53–3.24]), $P = .560$]. Risk factors for acute symptomatic seizures were radiographic GTR (ie, more radical surgery [OR: 4.23{95% CI: 1.40–12.77}], $P = .011$) and surgical complications (OR: 3.18 [95% CI: 1.59–6.35], $P = .001$). Preoperative epilepsy was not predictive for perioperative seizure control, although it favored acute symptomatic seizures (OR: 2.32 [95% CI: 0.99–5.42], $P = .051$). Age ($P = .144$), WHO grade ($P = .408$), or tumor location at the convexity ($P = .273$) were not risk factors for acute symptomatic perioperative seizures. Edema was also not predictive for acute symptomatic seizures when included as an additional covariate in this model ($P = .084$).

Discussion

The efficacy of surgery on seizure control in meningioma patients is not well-defined. This retrospective analysis of the postoperative course of 779 consecutive meningioma patients indicates that predictors of poor postoperative seizure control include preoperative epilepsy, epileptiform potentials on postoperative EEG recordings, severe surgical complications including CNS infections, hydrocephalus, recraniotomy, and symptomatic intracranial hemorrhage as well as younger age and tumor progression at any time after initial surgery. In contrast, postoperative improvement of preoperative neurologic deficits predicted better seizure control.

Although the issue of poor postoperative seizure control in meningioma patients dates back to the onset of modern neurosurgery during the first half of the 20th century,[19] no prospective controlled trials have been conducted to evaluate the effects of surgery on seizure control. In retrospective series of meningioma patients dating from the introduction of microsurgical techniques, the reported frequencies of patients with postoperative epilepsy ranged from 20% to 26%.[12–14] These data compare well to our series (Table 1) and reflect both postoperative persistence and new onset of epilepsy. Of 244 patients with preoperative epilepsy, 100 (41.0%) suffered epilepsy after surgery, and 104 (19.4%) of 535 patients without preoperative epilepsy suffered new-onset postoperative epilepsy (Table 3).

EEG is a widely available technique and, epileptiform discharges on EEG recordings predict seizure recurrence upon withdrawal of antiepileptic drugs.[20] The utility of postoperative EEG recordings in meningioma patients has been questioned because a single retrospective study of 102 patients reported no association between EEG changes and epilepsy after meningioma resection.[21] However, postoperative epileptiform EEG potentials were recorded for only one patient in that series. In our series, postoperative epileptiform EEG potentials were recorded for 78 patients (Table 3) and were identified as an independent risk factor (OR: 2.52 [95% CI: 1.36–4.67], $P = .003$). We therefore suggest that EEG should be part of the routine clinical evaluation during the postoperative follow-up of meningioma patients, although an inherent limitation of our study was the lower frequency of patients receiving postoperative EEG ($N = 340$, Supplementary material, Table S2). Furthermore, only a small fraction of patients received both preoperative and postoperative EEG ($N = 116$), thus precluding comparisons of preoperative and postoperative EEG parameters.

Previous reports have emphasized a predictive role of tumor location for postoperative seizure control.[13,14] In support of these reports, we noted an association of convexity meningiomas with postoperative epilepsy (Table 3), but this was not an independent risk factor in the binary regression model (Table 5). Edema was reported to contribute to preoperative and postoperative epilepsy in 2 cohort studies of meningioma patients,[12,14] and our data support these reports (Supplementary material, Table S2). However, an inherent limitation of our study and of the above-mentioned reports is the assessment of edema mostly by CT. The lower resolution and sensitivity for detection of edema on CT scans compared with MRI precluded volumetric analyses and may have yielded an underestimation of the association of edema with epilepsy.

Measures to estimate postoperative seizure risk are required to guide anticonvulsant treatment and provide direct impact on the diagnosis of epilepsy according to the ILAE definition, which emphasizes the risk of seizure recurrence as an epilepsy-defining criterion.[15] Based on the analyses reported here, we suggest a simplified score to guide anticonvulsant treatment derived by arbitrarily assigning 1 point to predictors with an OR <2 and 2 points to an OR >2 and defining 2 points as an indication for postoperative anticonvulsant treatment (Table 6). The retrospective design of our study, however, precludes estimates regarding the efficacy of anticonvulsant treatments. In fact, postoperative epilepsy became apparent under more intense anticonvulsant treatment compared with patients without postoperative epilepsy (Supplementary material, Table S4). Therefore, prospective validation of the simplified score suggested in this document is required. Such prospective studies should include MRI-based preoperative and postoperative imaging for detailed analysis of tumor location, extent of resection, gliosis, peritumoral edema, and surgical complications.

Acute symptomatic perioperative seizures occur frequently after craniotomy, and therefore anticonvulsant drugs are commonly administered perioperatively as a means of prophylaxis, despite a lack of evidence supporting this practice.[22] In our series, a substantial fraction of 45.6% of the patients without preoperative epilepsy received perioperative anticonvulsant prophylaxis, but no association with the occurrence of acute

Table 6. STAMPE2: A clinical score to guide the indication for postoperative anticonvulsant therapy[a]

Sensorimotor Deficit	1 Point
Tumor progression	1 Point
Age <55 y	1 Point
Major surgical complication[b]	2 Point
Preoperative epilepsy	2 Point
Epileptiform potentials on postoperative EEG	2 Point
Edema	1 Point

[a]Anticonvulsant treatment should be implemented at a score of 2 points or higher.
[b]Hydrocephalus, recraniotomy for any reason and CNS infection.

symptomatic perioperative seizures was detected, thus further questioning the utility of anticonvulsant prophylaxis.

Considering that severe surgical complications occur in a substantial fraction of patients, even in the age of microsurgery (Table 4),[10,11,23] and that spontaneous growth arrest and stable clinical course are observed in some untreated meningiomas,[5,6] the question arises if prospective controlled trials should evaluate watchful waiting or radiotherapy as alternatives to surgery in selected subgroups of patients. Meningioma patients presenting with epilepsy as the only apparent symptom are good candidates for such a trial because modern anticonvulsant therapy is usually effective and well-tolerated. However, despite technical advances in brain imaging, concerns persist regarding the inclusion of patients in clinical trials without histological confirmation of the radiological diagnosis.

Supplementary Material

Supplementary material is available at *Neuro-Oncology Journal* online (http://neuro-oncology.oxfordjournals.org/).

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