의학석사 학위논문

Risk Factors of Preoperative Seizures and Predictors of Late Postoperative Seizures in Patients with Meningioma

수막종 환자에서 수술 전 경련의 위험인자 및 수술 후 지연성 경련의 예측인자

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이 논문을 의학석사 학위논문으로 제출함

2017년 4월

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황기환의 의학석사 학위논문을 인준함

2017년 6월

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Abstract

Objective: Seizures are common among patients with meningiomas and are considered to be a significant cause of morbidity and poor quality of life. We identified factors associated with the onset of preoperative seizures as well as predictors associated with late postoperative seizures.

Methods: Between July 2003 and December 2014, we retrospectively reviewed the medical records of 303 patients who underwent primary resection for supratentorial meningioma at Seoul National University Bundang Hospital. Univariate analysis and multivariate logistic regression analysis were performed to determine the association between seizure occurrence and prolonged seizure outcome after surgery.

Results: Forty-nine (16.2%), out of the 303 patients reviewed,

presented with preoperative seizures. The risk factors independently associated with preoperative seizures were absence of preoperative neurologic deficit (HR0.297, p=0.003), parasagittal or parafalcine location (HR2.197, p=0.023), and vasogenic edema (HR4.429, p=0.001). Among these patients, 33 (67.3%) were seizure free during the entire postoperative follow-up period (54.5 ±33.8 months). Of the 303 patients, we observed late postoperative seizures in 35 (11.6%) patients. The associated risk factors included history of preoperative seizure (HR3.956, p=0.002), bigger tumor size (HR1.041, p=0.002), and continuation of anti-epileptic drugs (HR4.741, p=0.001). We observed that meningiomas with a largest diameter of greater than 45.5mm were 4.2 times more likely to have late postoperative seizures than those with a diameter of less than 45.5mm. (HR4.191, 95% CI 1.9990 - 8.824, p<0.001). Ten patients (28.6%) experienced poor seizure control. The independently associated predictive factors were high grade meningiomas (WHO Grade II or III) (HR 10.663, p=0.035) and history of postoperative adjuvant therapy (HR12.581, p=0.042).

Conclusions: Identifying factors associated with preoperative or late postoperative seizures may help guide treatment strategies, ultimately improving the quality of life for patients with meningiomas.

Keywords: Meningioma; Microsurgery; Seizure; Risk factor; Outcome

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LIST OF ABBREVIATIONS

MNG, meningioma

AED, anti−epileptic drug

EOR, Extent of resection

GTR, gross total resection

MRI, magnetic resonance image

WHO, World Health Organization

ROC, receiver operating characteristic

C.I., confidential interval

HR, hazard ratio

Chapter 1. Introduction

Meningiomas are one of the most common intracranial tumors. It accounts for approximately 37.3% of all primary intracranial tumors in Korea, according to a nationwide epidemiologic study. [1] Seizures are one of the most commonly presenting symptoms, occurring in approximately 10 – 50% of patients with meningiomas. [2–6] The association between seizures and meningiomas has a long history. In 1935, Dr. Groff reported the incidence and character of epilepsy in a series of 291 meningiomas. [7] Since then, many articles have been published regarding this association; however, there are still many unanswered questions with respect to the risk factors of and ways to control seizures in patients with meningiomas.

Previous papers have suggested many possible factors that contribute to the development of seizures in patients with meningiomas. These include gender, tumor location, tumor size, peritumoral edema, histological type, Simpson's grade of resection, and so on. [4,5,8–10] However, to date, there has not been any studies sufficiently evaluating the factors that influence seizure development in these patients; the sample size in the majority of these studies was too small. Conversely, this study was able to include a large sample size. Herein, we suggest that peritumoral edema and tumor size play an important role in seizure occurrence.

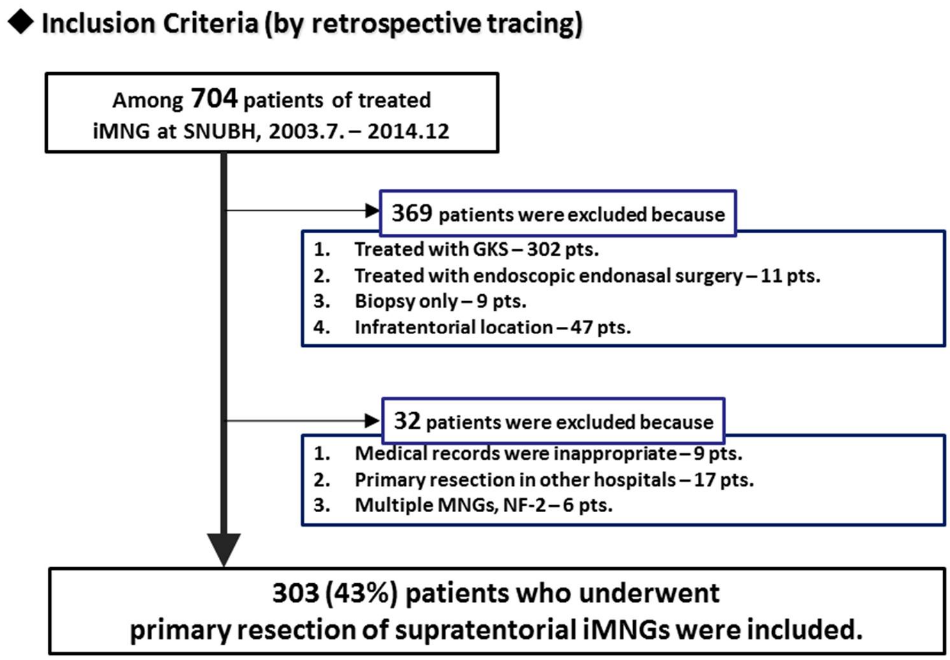
The purpose of this study was to (1) identify the incidence of seizures in patients undergoing primary resection of supratentorial meningiomas; (2) investigate the risk factors associated with preoperative seizures and predictors of late postoperative seizures; and (3) evaluate the predictive factors associated with the management of late postoperative seizures. Regardless of whether or not seizures can be managed with medical therapy, they are considered to be a significant cause of morbidity and poor quality of life. Therefore, proper understanding of these features is imperative to preventing seizure occurrence and guiding treatment strategies for patients with intracranial meningiomas. This is especially important considering the increase in meningioma detection due to the widespread availability of various neuroimaging modalities. [11,12]

Chapter 2. Materials and Methods

2.1. Patient population

This was a retrospective cohort study of patients with meningioma who underwent primary resection of supratentorial meningioma at Seoul National University Bundang Hospital (SNUBH) between July 2003 and December 2014. To determine the effect of non-benign pathology on seizure outcome, we included all patients with a tissue-proven diagnosis of meningioma, regardless of the World Health Organization (WHO) grade. Patients with infratentorial, recurrent, or multiple meningiomas were excluded from the analysis to create a more uniform patient population. A diagram of patient selection is shown in Figure 1.

Figure 1. Diagram of patient selection.



iMNG, intracranial meningioma; GKS, gamma knife surgery; pts, patients; NF−2, neurofibromatosis type 2

2.2. Data collection

The clinical, operative, and hospital course records were reviewed. Information collected from the medical records included the following: Patient demographics, presenting symptoms, seizure occurrences, neuroimaging, neurological function, histology, adjuvant therapy, and tumor recurrence.

The characteristics of magnetic resonance image (MRI) included the following: The size of lesions (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, cystic portion (any cystic meningiomas according to Nauta’s classification [13]), and calcification. The extent of resection (EOR) was confirmed using postoperative MRIs within the first 48 hours post-surgery as well as operative records: Simpson Grade I and II were defined as the gross total removal (GTR) of tumor and Simpson Grade III or above as non-GTR.

The primary endpoint variables were seizure status and control of seizure. The seizure status was assessed at each postoperative outpatient visit. Controlled seizure was defined as no recurrence of seizures for at least two years, whether on antiepileptic treatment or not. [14-16]

2.3. Anti-epileptic drugs (AEDs)

Preoperatively, patients were started on AEDs if they developed seizures. In the perioperative period, patients were generally continued on their same preoperative AEDs regimen. Postoperatively, patients with preoperative seizures were continued on AEDs for at least one or two months, and then weaned. AEDs were continued indefinitely if signs of seizures persisted.

To date, there have not been any established guidelines for using AEDs in patients undergoing surgery for meningioma without any history of preoperative seizures. In our institution, a standard seizure prophylaxis policy was constituted: Preoperative loading of AEDs and discontinuation at least one week postoperatively, if there is no evidence of clinical epilepsy. [10,17,18] The choice of specific AEDs was based on the preference of the clinician.

2.4. Postoperative seizures

For seizures appearing after surgery, a distinction is normally made between those occurring within one week after surgery (early seizures) and those occurring later (late seizures). [10,19] Likewise in this study, early postoperative seizure was defined as the onset of epilepsy within 1 week of surgery, and late postoperative seizure was defined as onset of epilepsy beyond the first week of surgery. Early seizures are considered to be an acute symptom and not associated with a similar risk of recurrence as late seizures. [10,20]

2.5. Statistical Analysis

All analyses were performed using SPSS 21 (IBM, Chicago, Illinois, USA). The categorical data were analyzed using Pearson chi-square test and Fisher's exact test. The continuous variables were presented as the mean ± standard deviation for parametric data. For an intergroup comparison, Student's t-test was used for parametric data and the Mann-Whitney U test for non-parametric data. The cut-off value was the point closest to the point of perfect classification (sensitivity and specificity), as determined by using a receiver operating characteristic (ROC) curve with a discrimination power of tumor diameter. Cox proportional hazards regression was used to determine the hazards ratio for the occurrence of late postoperative seizures.

All variables associated with seizures in univariate analysis ($p < 0.10$) were then included into a stepwise multivariate logistical regression model. P values of less than 0.05 were considered significant.

Chapter 3. Results

3.1. Patient population

The demographic information and clinical features of our study are presented in Table 1. A total of 303 patients underwent primary resection for supratentorial meningioma during the study period. The mean age was 54.1 ± 12.6 years at the time of surgery. A total of 215 (71.0%) patients were women. Forty-nine patients (16.2%) presented with seizures; while 70 (23.1%) patients presented with headaches, 49 (16.2%) with visual deficits, 40 (13.2%) with motor deficits, 16 (5.3%) with memory impairment, 15 (5.0%) with language difficulty and 27 (8.9%) with incidental findings. The average tumor size was 42.69 ± 16.35 mm. The tumor location was variable: 113 (37.3%) tumors in the cerebral convexity, 79 (26.1%) in the parasagittal/parafalcine area, 38 (12.5%) in the sphenoid wing, 32 (10.6%) in the tuberculum sella, 20 (6.6%) in the olfactory groove, 9 (3.0%) in the ventricle, 7 (2.3%) in the tentorial area, and 5 (1.7%) in the planum sphenoidale area. Gross total removal (GTR) was achieved in 215 (71.0%) patients. Postoperative, newly−developed neurologic deficit occurred in 34 (11.3%) patients.

Table 1. Demographic and clinical information of patients.

Characteristic		Characteristic	
Age (mean)	54.1 ±12.6	Perioperative Outcomes	
Female gender	215 (71.0%)	GTR	215 (71.0%)
First Presentation Symptom		Any Postoperative Complication	84 (27.7%)
Headache Seizure Visual deficit Motor deficit Incidentally Memory impairment Language deficit Dizziness Others	70 (23.1%) 49 (16.2%) 49 (16.2%) 40 (13.2%) 27 (8.9%) 16 (5.3%) 15 (5.0%) 11 (3.6%) 26 (8.6%)	Any Newly−developed Postoperative Neurologic deficit	34 (11.3%)
		WHO Grade	
		Grade I Grade II Grade III	251(82.8%) 44(14.5%) 8(2.6%)
		Postoperative Adjuvant Therapy	66 (21.8%)
Preoperative Neurologic deficit	114 (37.6%)	Of Grade I Of Grade II Of Grade III	36/251(14.3%) 22/44(50.0%) 8/8(100.0%)
Preoperative Embolization	174 (57.4%)		

Perioperative AEDs	
Valproate Levetiracetam Phenytoin Topiramate Oxcarbazepine No AEDs	237(78.2%) 49 (16.2%) 4 (1.3%) 3 (1.0%) 1 (0.3%) 9 (3.0%)
Radiographics	
Tumor size, mm (mean)	42.69±16.35
Tumor Location	
Convexity Parasagittal/Parafalcine Sphenoidal Tuberculum sella Planum sphenoidale Olfactory groove Tentorial Intraventricular	113 (37.3%) 79 (26.1%) 38 (12.5%) 32 (10.6%) 5 (1.7%) 20 (6.6%) 7 (2.3%) 9 (3.0%)
Cerebral edema	187 (61.7%)
High T2SI	86 (28.4%)
Cystic portion	20 (6.6%)
Calcification	167 (55.1%)

Tumor Recurrence	48 (15.8%)
Postoperative Seizures	35 (11.6%)
Follow up Duration, mo.	49.3 ± 31.6

Continuous variables are presented as mean ± standard deviation.
Categorical variables are presented as number (percentage).
GTR, gross total resection; AEDs, anti-epileptic drugs; SI, signal intensity

3.2. Factors associated with preoperative seizures

Patients with preoperative seizures were less frequently presented with preoperative neurologic deficit ($p=0.002$). They had tumors that caused vasogenic edema ($p<0.001$), which were presented with a cystic portion ($p=0.027$), commonly found in the parasagittal/parafalcine area ($p=0.003$), and less frequently in the tuberculum sella area ($p=0.009$). There was no gender difference ($p=0.195$).

The risk factors that were associated with preoperative seizures according to the multivariate analysis were absence of preoperative neurologic deficit (HR 0.297, 95% CI 0.133 – 0.661, $p=0.003$), parasagittal/parafalcine tumor location (HR 2.197, 95% CI 1.115 – 4.327, $p=0.023$), and presence of vasogenic edema (HR 4.429, 95% CI 1.780 – 11.021, $p=0.001$). No other clinical or imaging factors were found to be associated with preoperative seizures (Table 2).

Table 2. Risk factors of Preoperative seizures.

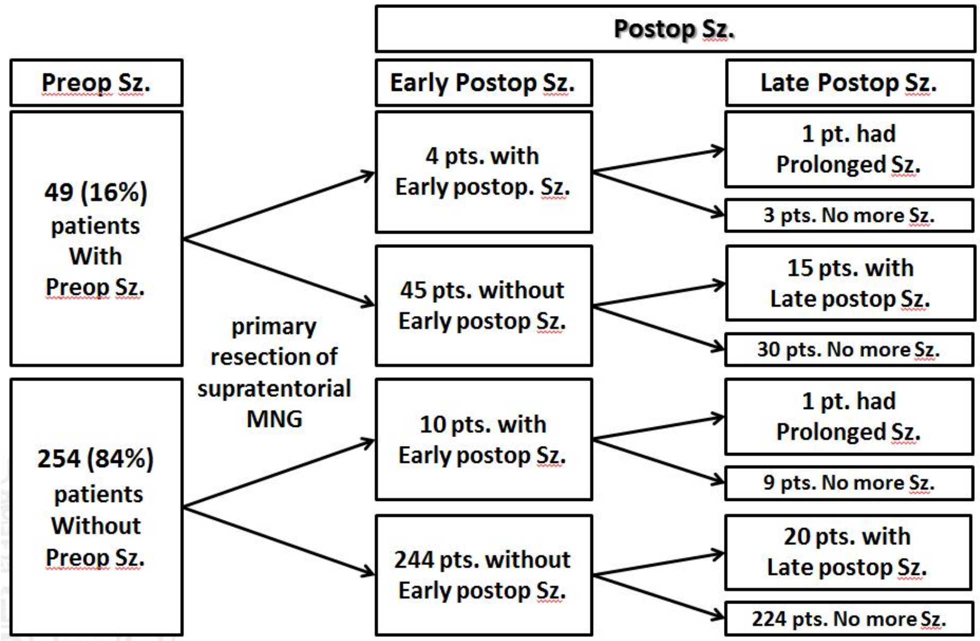
Variables	*HR (95% CI)*	*p value*
Preoperative Neurologic deficit	0.297 (0.133 – 0.661)	0.003
Parasagittal/Parafalcine Location	2.197 (1.115 – 4.327)	0.023
Vasogenic edema	4.429 (1.780 – 11.021)	0.001

Factors that are independently associated with any preoperative seizures in stepwise multivariate logistic regression analysis.
HR, Hazard ratio; CI, confidence interval

3.3. Seizure outcomes and early postoperative seizures

Seizure status and patient population are illustrated in Figure 2. In our study population, 49 (16.2%) out of the 303 patients experienced postoperative seizures. Among them, 19 (38.8%) patients had preoperative seizures, and 30 (11.8%) had no history of preoperative seizures. Early postoperative seizure within the 1st week after surgery occurred in 14 (4.6%) patients, and among them, 2 (14.3%) patients continued to have seizures during the long-term follow-up. Early postoperative seizures showed no association with history of preoperative seizures (p=0.254).

Figure 2. Seizure status and patient population.



Preop, preoperative; Sz, seizure; Postop, postoperative; Pt, patient

Of the 49 patients presented with seizures, the majority of them (33 patients, 67.3%) remained seizure free postoperatively (Engel Class I). Four (8.2%) patients had early postoperative seizures, and 1 (25.0%) of those patients experienced prolonged seizures beyond the first week after surgery throughout the long-term follow-up. The patient had convexity meningioma in the left precentral gyrus. With continued use of AEDs postoperatively, she had no seizures over the following 2 years.

Among the 254 patients without history of preoperative seizures, 10 (3.9%) patients had early postoperative seizures. Nine of them had no seizure recurrence after the 1^{st} week of surgery, and the remaining 1 (10%) patient continued to have seizures throughout the follow-up period. This patient had convexity meningioma near the sagittal sinus in the right postcentral gyrus; after subtotal removal of tumor, he had poorly controlled partial seizures. He was under AEDs adjustment via outpatient visits.

3.4. Late postoperative seizures and seizure control

Thirty-five (11.6%) patients of our study population had late postoperative seizures. Of the 49 patients presented with seizures, 15 (30.6%) patients had late postoperative seizures. Twenty (7.9%) of the 254 patients without history of preoperative seizures experienced late postoperative seizures (Figure 2). The mean interval between operation and late postoperative seizures was 17.6 ± 17.3 months. The first late postoperative seizure occurred during the first postoperative year in 17 (48.6%) patients and until the second postoperative year in 28 (80%) patients. Among the 35 patients, 14 (40.0%) patients were under prophylactic AEDs and 21 (60.0%) patients stopped AEDs on a specific time.

According to the univariate analysis, factors with $p < 0.10$ of late postoperative seizures were as follows (Table 3): Age (p=0.034), female gender (p=0.056), history of preoperative seizures (p<0.001), history of preoperative embolization (p=0.001), lager tumor size (p<0.001), tumor location other than tuberculum sella (p=0.035), history of postoperative adjuvant therapy (p=0.001), recurrence of tumor, and continuation of AEDs prophylaxis (p<0.001).

Table 3. Univariate analysis according to the occurrence of Late Postoperative seizures.

Variables	Late Postoperative Seizures, n (%)		
	No (n=268)	Yes (n=35)	p value
Age (mean)	54.69±12.59	49.89±12.02	0.034*
Female gender	195 (72.8%)	20 (57.1%)	0.056
Preoperative Neurologic deficit	102 (38.1%)	12 (34.3%)	0.665

Preoperative Seizures	34 (12.7%)	15 (42.9%)	0.000*
Preoperative Embolization	145 (54.1%)	29 (82.9%)	0.001*
Radiographics			
Tumor size (mm)	41.41±16.26	52.49±13.64	0.000*
Tumor Location			
Convexity	100 (37.3%)	13 (37.1%)	0.984
Parasagittal/Parafalcine	68 (25.4%)	11 (31.4%)	0.443
Sphenoidal	33 (12.3%)	5 (14.3%)	0.785
Tuberculum sella	32 (11.9%)	0 (0.0%)	0.035*
Planum sphenoidale	5 (1.9%)	0 (0.0%)	1.000
Olfactory groove	18 (6.7%)	2 (5.7%)	1.000
Tentorial	5 (1.9%)	2 (5.7%)	0.188
Intraventricular	7 (2.6%)	2 (5.7%)	0.279
Cerebral edema	161 (60.1%)	26 (74.3%)	0.104
T2SI High	72 (26.9%)	14 (40.0%)	0.105
Cystic portion	16 (6.0%)	4 (11.4%)	0.266
Calcification	147 (54.9%)	20 (57.1%)	0.798
Perioperative outcomes			
Non−GTR	76 (28.4%)	12 (34.3%)	0.468
High Grade (II/III)	43 (16.0%)	9 (25.7%)	0.154
Postop Complication	74 (27.6%)	10 (28.6%)	0.905
Postop new deficit	30 (11.2%)	4 (11.4%)	1.000
Postoperative Adjuvant Therapy	51 (19.0%)	15 (42.9%)	0.001*
Tumor Recurrence	39 (14.6%)	9 (25.7%)	0.089
AEDs Continuation	19 (7.1%)	14 (40.0%)	0.000*

Continuous variables are presented as mean ± standard deviation.
Categorical variables are presented as number (percentage).
*, statistical significance; GTR, gross total resection; AEDs, anti−epileptic drugs; SI, signal intensity

According to the binary logistic regression analysis, history of preoperative seizures (HR 3.956, 95% CI 1.637 – 9.558, p=0.002), larger tumor size (HR1.041, 95% CI 1.014 – 1.068, p=0.002), and continuation of AEDs (HR4.741, 95% CI 1.909 – 11.771, p=0.001) were significantly associated with late postoperative seizures (Table 4).

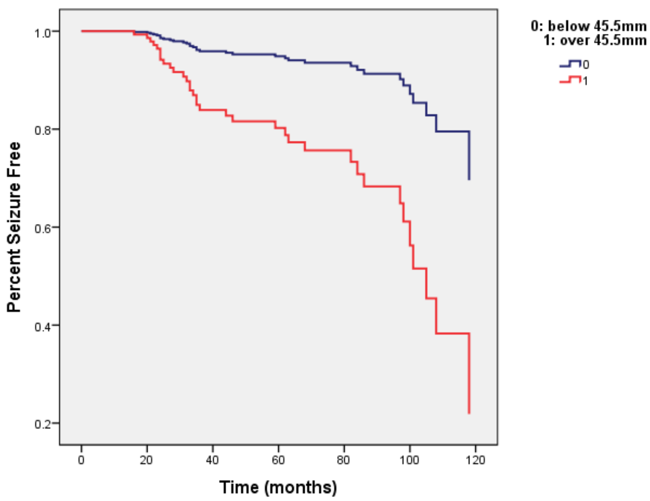
Table 4. Predictors of Late Postoperative Seizures.

Variable	Univariate (p−value)	Multivariate (p−value)	HR (95% CI)
Preoperative Seizures	0.000	0.002	3.956 (1.637–9.558)
Preoperative Embolization	0.001		
Tumor Size	0.000	0.002	1.041 (1.014–1.068)
Postoperative Adjuvant Therapy	0.001	0.065	2.187 (0.953–5.016)
AEDs Discontinuation	0.000	0.001	4.741 (1.909–11.771)
Tumor Recurrence	0.089		

All variables associated with late postoperative 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.
HR, hazard ratio; CI, confidence interval; AEDs, anti−epileptic drugs

We plotted the ROC curve and decided the most appropriate cut−off point for tumor diameter, which was 45.5mm. According to the Cox regression analysis, meningiomas with the largest diameter of greater than 45.5mm were shown to be a significant risk factor for late postoperative seizures (HR 4.191, 95% CI 1.990 – 8.824); meningiomas with the largest diameter of greater than 45.5mm were 4.2 times more likely to experience postoperative seizures than those with the largest diameter of less than 45.5mm (Figure 3).

Figure 3. Cox regression analysis evaluating the occurrence of late postoperative seizures according to tumor size.



Seizure management was assessed in according with the medical records. Controlled seizure was defined as no fits during a period of at least 2 years. Fifteen (42.9%) patients out of the 35 patients with late postoperative seizures had one episodic seizure attack and no recurrent seizures during the follow-up period. Among these 35 patients with late postoperative seizures, seizures were under control in 25 (71.4%) patients. The remaining 10 (28.6%) patients had poorly controlled seizures and with continued AED adjustments via outpatient visits. The factors associated with loss of seizure control according to the multivariate analysis were high grade meningioma, i.e. WHO Gr. II or Gr. III MNG (HR10.663, 95% CI 1.183 – 96.072, p=0.035), and history of postoperative adjuvant treatment (HR 12.581, 95% CI 1.099 – 144.068, p=0.042) (Table 5). The association between loss of seizure control and non-GTR of tumor (p=0.059), or tumor recurrence (p=0.081) trended toward but did not reach statistical significance.

Table 5. Predictors of Uncontrolled Late postoperative seizures.

Variable	Univariate (p value)	Multivariate (p value)	HR (95% CI)
High grade MNG (WHO Grade II or III)	0.001	0.035	10.663 (1.183 – 96.072)
Postoperative Adjuvant Therapy	0.001	0.042	12.581 (1.099 – 144.068)

Factors that are independently associated with any uncontrolled late postoperative seizures in stepwise multivariate logistic regression analysis. HR, Hazard ratio; CI, confidence interval; MNG, meningioma

Chapter 4. Discussion

4.1. Risk factors for Preoperative seizures

Here, we showed that peritumoral edema may be the factor most strongly related to preoperative seizures. Various studies in the past have reported a correlation between vasogenic edema and seizure occurrences. [2,3,5,10,21] It has been estimated that 30% − 60% of patients with meningiomas have signs of cerebral edema. [21−23] Although the pathogenesis of peritumoral edema of meningiomas still remains unknown, the breakdown of blood−brain barrier and pial invasion are believed to be associated. [22,24] It has also been 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. [22,24] Even so, the presence of edema usually suggests a more infiltrative type of meningioma, with a greater tendency to cause seizures. Moreover, peritumoral edema fluid contains a high concentration of glutamate, which may trigger hyperexcitability and epileptogenesis. [19]

Seizures occurred more often in patients with a tumor located in the parasagittal or parafalcine area, while showing less often in patients with a tumor located in the tuberculum sellae area. Many previously published studies described a high rate of preoperative seizures in the non-skull base lesions, such as parasagittal or convexity meningiomas. [2,4,5,10] Non-skull base meningiomas often grow for a long period of time, eventually reaching a considerable size before the occurrence of any neurological deficits; as such, they might contribute to the increasing amount of epileptogenic cortical gray matter. [4] In particular, the propensity for parasagittal/parafalcine meningiomas to cause seizures has been previously reported. [2,25] This area is adjacent to the sagittal sinus and meningiomas located in this area have a possibility to cause venous congestion and severe edema, which has been suggested to cause epileptogenesis.

Presence of preoperative neurologic deficits has been less frequently associated with preoperative seizures. This is an unexpected finding. However, considering the increase in meningioma detection and widespread availability of neuroimaging

[11,12], this may be explained by the diagnosis of the tumor prior to the occurrence of neurological deficits or just after a seizure attack. Otherwise, as mentioned above, meningiomas would reach a considerable size and involve epileptogenic cortical gray matter before the occurrence of any neurological deficits. Careful analysis and further investigation are needed.

4.2. Predictors of Late Postoperative seizures

In many previous studies, it has been suggested that there is no association between early and late postoperative seizures. [2,19,20] The occurrence of early postoperative seizures may be related to factors such as excessive intraoperative cortical stretching, as well as early-stage cerebral edema and postoperative electrolyte disorders. If these factors are avoided, early postoperative seizures may resolve without causing epileptogenic foci. [20] We focused on late postoperative seizures after the resection of meningioma and its outcome. According to the multivariate analysis, history of preoperative seizures, larger tumor size, and continuation of AEDs were significantly associated with the occurrence of late postoperative seizures.

Like our study, various reports have found a significant relationship between the history of preoperative seizures and the occurrence of postoperative seizures. [9,20,25-27]

A correlation between tumor size and seizure frequency of both preoperative seizures and postoperative seizures has been reported in many previous studies. [2,28] In our study, we found that tumors with a largest diameter of greater than 45.5mm have about 4.2 times the risk of developing postoperative seizures than those with less than 45.5mm diameter. Local pressure may increase with tumor size, leading to cortical compression, which is a suspected factor for epileptogenicity. [2,28] Tumor size has been associated with edema as a consequence of venous congestion or leptomeningeal tumor infiltration. [2]

History of preoperative embolization showed to be a possible risk factor for postoperative seizure, which was not significant in the multivariate analysis. To the best of our knowledge, there have only been a few studies that specifically addressed the association between seizure risk and embolization. Because various embolic materials were used in these studies, a direct comparison was inappropriate; however, a report of a new onset of seizures post-embolization was not uncommon. [29] Although the mechanism is not clear, the development of edema and inflammation surrounding the tumor may play a role. However, further studies are necessary.

Previous papers have suggested many other risk factors for postoperative seizures. The location of supratentorial meningioma may also influence the occurrence of postoperative seizures. [3,30] Moreover, incomplete resection of meningioma may continue to irritate the cortex and result in a higher incidences of postoperative seizures. [30] The association between tumor progression and postoperative seizures remains unclear; however, Chan et al. indicated that tumor progression involving the parasagittal area or convexity may be a significant risk factor for postoperative seizures. [31] There has also been a report that suggested permanent postoperative neurological deficits as a significant risk factor for late postoperative seizures. [19] However, we found no significant relationship between the abovementioned factors and postoperative seizures.

4.3. Effect of AEDs

To date, there have not been any defined guidelines or a clear consensus on the appropriate use of AEDs for postoperative seizures. Temkin had pointed out that traditional AEDs may reduce up to 40% to 50% of seizures in the first week after neurosurgery, as compared with a placebo or no treatment. [17] However, there has not been clear evidence showing that AEDs can effectively reduce the occurrence of late postoperative seizures. [10,15]

In our study, continuation of AEDs was independently associated with late postoperative seizures. Among the 35 patients who experienced late postoperative seizures, 14 (40.0%) patients continued receiving AEDs after the first postoperative week. Many possible factors were associated with the continuation of AEDs: Age, preoperative motor disturbance, Simpson grade, early postoperative seizures, new permanent postoperative neurologic deficits, postoperative radiotherapy, and tumor progression. [19] Therefore, a careful consideration regarding the use of AEDs is necessary. In particular, patients with a history of preoperative seizures or large tumor size may benefit from an extended use of AEDs of at least 18 months after surgery.

4.4. Limitations

There are several limitations to consider when interpreting our findings. First, there may be biases in patient selection, given the retrospective nature of this study. Second, this study was designed to neither evaluate patients who presented seizures nor the effects of surgery on prolonged seizure control. The duration and control of seizure before surgery and its own long-term follow-up may evaluate the seizure outcome for meningioma patients. Third, it is unclear to whether surgery or AEDs contributed to seizure management. Last, we did not evaluate the follow-up images after adjuvant radiotherapy, which may have changed from the immediate postoperative images.

Despite these limitations, our study represented large and homogeneous cohorts, who were treated surgically at a single institution. Moreover, we used a multivariate analysis to control for confounding variables. Even if our data are not completely new in the literature, we believe that our findings offer useful insights into the management of patients undergoing primary resection of meningioma. However, a well-designed prospective study is still needed to present better data to further assist clinical decision making.

Chapter 5. Conclusion

In this study, 49 (16%) out of 303 patients who underwent primary resection for supratentorial meningioma presented seizures. The factors significantly associated with preoperative seizures were absence of preoperative neurologic deficit, tumors of parasagittal/parafalcine location, and vasogenic edema on preoperative images. Among these 49 patients, the predictors significantly associated with late postoperative seizures were history of preoperative seizures, larger tumor size, and continuation of AEDs. It was suggested that meningiomas with the largest diameter of greater than 45.5mm were 4.2 times likely to experience late postoperative seizures than those with a diameter of less than 45.5mm. Of our patients with late postoperative seizures, 29% experienced uncontrolled seizures; high grade meningioma and history of postoperative adjuvant treatment were independent risk factors.

The identification of factors associated with preoperative and postoperative seizures may help guide treatment strategies, improving the quality of life for patients with meningiomas.

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국문초록

배경: 경련은 수막종 환자에서 흔한 증상이고, 질병 이환과 낮은 삶의 질의 중요한 원인 중 하나이다. 본 연구에서는 수술 전 경련의 위험 인자와 수술 후 지연성 경련의 예측 인자 및 그 결과를 고찰하였다.

방법: 2003년 7월부터 2014년 12월까지 분당서울대학교병원에서 천막상 수막종에 대한 일차치료로 미세수술을 받은 환자의 의무기록 및 영상학적 검사 소견을 후향적으로 정리하였다. 일변량 분석 및 다변량 로짓 회귀 분석을 통해 수술 후 경련 발생과 지연성 경련의 결과와 관련된 각종 요인들을 분석하였다.

결과: 총 303명의 환자를 분석하였다. 이 중 49 (16.2%)명의 환자가 진단 당시 경련을 주소로 내원하였다. 수술 전 경련과 관련된 독립적인 위험 인자는 수술 전 신경학적 장애의 부재 (HR0.297, p=0.003), 시상동인접부 또는 겸상수막 주변 위치 (HR2.197, p=0.023), 그리고 혈관성 뇌 부종 (HR4.429, p=0.001) 이었다. 수술 전 경련이 있었던 환자 중33 (67.3%) 명이 수술 후 추적관찰 기간 (54.5±33.8 개월) 중 경련이 없었다. 전체 303명 중 35 (11.6%)명이 수술 후 지연성 경련을 경

험하였고, 이와 관련된 예측 인자는 수술 전 경련의 과거력 (HR3.956, p=0.002), 큰 종양의 크기 (HR1.041, p=0.002), 그리고 항경련제의 지속 (HR4.741, p=0.001) 이었다. 최대 직경 45.5mm 이상의 수막종은 그 미만의 수막종보다 수술 후 지연성 경련의 위험이 약 4.2배 정도 증가하였다 (HR4.191, 95% CI 1.9990 - 8.824, p<0.001). 수술 후 지연성 경련을 경험한 35명 중 10 (28.6%)명의 경우 경련 조절이 잘 되지 않았었고, 이와 관련된 독립적인 예측 인자는 고등급 수막종 (WHO Grade II or III) (HR 10.663, p=0.035)와 수술 후 보조요법의 과거력 (HR12.581, p=0.042) 으로 확인되었다.

결론: 수술 전 또는 수술 후 지연성 경련 발생의 위험 인자를 고찰하고, 이를 대비하는 것은 수막종으로 수술 받는 환자의 삶의 질을 개선하는 치료 전략을 수립하는데 큰 도움이 될 것이다.

주요어: 수막종; 수술; 경련; 위험인자; 결과

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