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Original Article

Factors Associated with Recurrence of Intracranial Meningiomas After Surgical Resection: A Retrospective Single-Center Study☆

Chih-Chuan Yang [1], Cheng-Chia Tsai [1,2 *], Shiu-Jau Chen [1], Ming-Fu Chiang [1,2], Jui-Feng Lin [1], Chao-Kai Hu [1], Yun-kai Chan [1], Hsin-Yao Lin [1], Sheng-Yu Cheng [1]

[1] *Division of Neurosurgery, Department of Surgery, Mackay Memorial Hospital,* [2] *Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei, Taiwan*

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SUMMARY

Background: Meningioma is one of the most common primary brain neoplasms with poor outcomes. The present study was aimed to determine clinical and surgical characteristics of intracranial meningiomas associated with tumor recurrence and complications.

Methods: A total of 138 patients undergoing surgical resection of intracranial meningiomas between Jan 2003 and Dec 2014 were included and followed for the period of at least 12 months. The demographic and clinical characteristics possibly associated with tumor recurrence were assessed, including age, gender, clinical symptoms, pathology data, tumor parameters, preoperative and postoperative Karnofsky Performance Scale (KPS), complications and recurrence rate.

Results: One hundred and twenty one lesions were benign (classified as Grade I) and 17 were atypical/malignant (classified as Grade II/III). The patients were of a mean age of 60.5 years and a mean follow-up duration of 36.8 months (range, 16.3–62.9 months). The 1, 3, 5-year recurrence/tumor enlargement rates were 3.4%, 7.2%, and 15.7%, respectively. In multivariate analysis, symptoms of disturbance of consciousness and palpable cranial mass were associated with increased recurrence/tumor enlargement. In addition, patients with Simpson grade IV were more likely to have recurrence/tumor enlargement.

Conclusion: The pattern of intracranial meningioma in this series is typical to other studies. Presenting symptoms is suggested to be predictive of recurrence.

1. Introduction

Meningioma is one of the most common primary brain neoplasms, accounting for approximately 30% of tumors in central nerve system. It arises from the cells covering arachnoid layer of brain or spinal cord, characterized by a homogeneous enhancement of mass with a dural tail on magnetic resonance imaging. Based on World Health Organization (WHO) classification of tumor, meningiomas are graded into three categories on the basis of histological features[1]. Approximately 90% of meningiomas are benign (Grade I) and have slow growth, with incidence increasing with age[2]. However, some meningiomas are considered as atypical (Grade II) and malignant (Grade III), representing a major challenge to neurosurgeons.

Surgical resection is considered as an optimal therapeutic modality for symptomatic meningioma with the aim of complete removal of tumor. Although patients with benign meningiomas have high survival rates, patients with symptomatic meningiomas suffer from postoperative complications and long-term disability[2–4]. Recurrences after extent of surgical resection are reported more frequently in patients with higher-grade tumors[4]. In cases of recurrence or incompletely removed tumors, radiotherapy and radiosurgery are recommended. Nevertheless, the factors associated with recurrent meningiomas remain sketchy.

In the present study, we determined the recurrence rate and predictive factors for recurrence of meningiomas. We reviewed and presented the results of the clinical outcomes of the patients treated conservatively in our department over a period of 12-year. We compared the characteristics of intracranial meningiomas in our series with the pattern reported in the literatures.

☆ Conflicts of interest: All contributing authors declare that they have no conflicts of interest.

* Correspondence to: Cheng-Chia Tsai, Division of Neurosurgery, Department of Surgery, Mackay Memorial Hospital, Taipei, Taiwan.
E-mail address: ycc.mmh@gmail.com (C.-C. Tsai).

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2. Materials and methods

2.1. Patients

Patients undergoing surgery for meningioma at Mackey memorial hospital between Jan 2003 and Dec 2014 were included. The study protocol was reviewed and approved by institutional review board (IRB approval number: 15MMHIS077). All patients were diagnosed with meningioma using magnetic resonance imaging (MRI), radiological modalities and computed tomographic (CT) scanning incorporating with the results of histopathological examination. Exclusion criteria were previous radiation therapy, recurrence of meningioma and presence of other malignancy.

2.2. Clinical parameters and outcome assessment

The demographic and clinical characteristics possibly associated with tumor recurrence were assessed, including age, gender, clinical symptoms, pathology data, tumor parameters, preoperative and postoperative Karnofsky Performance Scale (KPS), post-surgery complications and recurrence rate[5]. Focal neurologica deficit were defined as impaired function of cranial nerve, including facial palsy, hemifacial spasm, anosmia, hearing loss and ptosis.

Tumor locations were classified into following sublocations based on radiologic studies using CT or MRI, which included parasagittal, convexity, sphenoid ridge, olfactory groove, parafalcine, posterior fossa, middle fossa, cerebellopontine angle, tuberculum sella, planum sphenoidale, tentorial and intraventricular. T1-weighted MRI and CT scanning were employed to determine the maximal size of the tumor. The extent of surgical removal of tumor was classified using Simpson's scale into 5 grades[6]. All meningiomas were graded according to the WHO classification system. KPS was utilized to evaluate the pre- and post-operative clinical status. Patients with KPS above 70 were considered as in good performance status.

2.3. Statistical analysis

The cumulative recurrence and tumor enlargement rate were performed using the Kaplan–Meier estimates. The factors associated with recurrence/tumor enlargement were examined using the Cox proportional hazard model. When there were two or more factors with p-value less than 0.2 in the univariable Cox proportional hazard models, the factors would be included into the multivariable model by using backward conditional method. The continuous data between two age groups were tested with the independent two samples *t*-test and the Mann–Whiney *U* test, respectively for normal-distributed and non-normal distributed continuous data. The Fisher's exact test was employed to test with the associations of age group versus categorical data. A p-value less than 0.05 was considered as statistical significance. Statistical analyses were performed using the software IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, New York).

3. Results

A total of 138 patients with intracranial meningioma were enrolled in the study, including 95 females (68.8%) and 43 males (31.2%), with a mean age of 60.5 years (SD = 12.2 years). 36 (26.1%) patients had a preoperative embolization before operation. The most frequent presenting symptom of these patients was motor deficit (n = 45, 32.6%), followed by headache (n = 38, 27.5%) and dizziness (n = 30, 21.7%) (Table 1). Of 138 patients, 60 had tumors located in convexity (43.5%), 19 patients had parasagittal meningioma (13.8%), and 13 patients were with the tumors located in sphenoid ridge (9.4%). The pathology results showed that 87.7% (n = 121) of meningiomas were benign (Grade I). 8 patients who had focal neurologica deficit were defined as impaired function of cranial nerve, including 2 facial palsy, 1 hemifacial spasm, 2 anosmia, 2 hearing loss and 1 ptosis. Detailed clinical demographics and characteristics of the patients were summarized and presented in Table 1.

Table 1
Demographic and clinical data for the 138 patients with intracranial meningiomas.

	N = 138
Age† (year)	60.5 (12.2)
Gender	
Female	95 (68.8%)
Male	43 (31.2%)
Tumor volume‡ (mm^3)	32.0 (13.5, 62.5)
TAE before operation	36 (26.1%)
KPS before operation	
≤70 (dependent)	59 (42.8%)
>70 (undependent)	79 (57.2%)
Follow-up duration after operation‡ (month)	36.8 (16.3, 62.9)
Presenting symptoms	
Motor deficit	45 (32.6%)
Headache	38 (27.5%)
Dizziness	30 (21.7%)
Change in behavior/memory	19 (13.8%)
Seizure	19 (13.8%)
Visual disturbance	16 (11.6%)
Disturbance of consciousness	15 (10.9%)
Nausea/vomiting	13 (9.4%)
Incidental	12 (8.7%)
Language dysfunction	9 (6.5%)
Focal neurologic deficit	8 (5.8%)
Palpable cranial mass	4 (2.9%)
Sensory alteration	4 (2.9%)
Syncope	2 (1.4%)
Tumor location	
Convexity	60 (43.5%)
Parasagittal	19 (13.8%)
Sphenoid ridge	13 (9.4%)
Parafalcine	10 (7.2%)
Olfactory groove	8 (5.8%)
Posterior fossa	8 (5.8%)
Middle fossa	6 (4.3%)
Cerebellopontine angle	5 (3.6%)
Tuberculum sella	4 (2.9%)
Planum sphenoidale	3 (2.2%)
Tentorial	1 (0.7%)
Intraventricular	1 (0.7%)
Pathology	
Grade I: benign	121 (87.7%)
Grade II: atypical	9 (6.5%)
Grade III: malignant	8 (5.8%)
Simpson grade	
I	52 (37.7%)
II	61 (44.2%)
III	8 (5.8%)
IV	17 (12.3%)

Data are presented by number with percentage except for †age is presented by mean with standard deviation and ‡ non-normal distributed continuous data (tumor volume and follow-up duration after operation) are presented by median with inter-quartile range.

The median hospitalized duration after operation was 12 days (IQR in 10–18 days), and 16 patients treated with radiotherapy after operation (11.6%). The majority of post-operative complications included 16 intracerebral hematoma (11.6%) and 10 pneumonia (7.2%). At the time of discharge, 88 (63.8%) of the patients had Karnofsky scores over 70 (undependent). In addition, ninety-nine patients (71.7%) had improved outcome but 17 (12.3%) had deteriorated outcome (Table 2).

We examined the recurrence/tumor enlargement rate of each time point. As shown Fig. 1, the 1, 3, 5-year recurrence/tumor enlargement rates were 3.4%, 7.2%, and 15.7%, respectively.

Table 2
Clinical outcomes.

	N = 138
Duration of hospitalization after operation (day)	12 (10, 18)
Radiotherapy after operation	16 (11.6%)
Postoperative complications	
Intracerebral hematoma	16 (11.6%)
Pneumonia	10 (7.2%)
Urinary tract infection	5 (3.6%)
Cranial nerve injury	5 (3.6%)
Seizure	3 (2.2%)
Hydrocephalus	2 (1.4%)
Wound infection	2 (1.4%)
CNS infection	2 (1.4%)
Others	15 (10.9%)
KPS on discharge	
≤70 (dependent)	50 (36.2%)
>70 (undependent)	88 (63.8%)
Outcome at discharge	
Improved	99 (71.7%)
Same	22 (15.9%)
Deteriorated	17 (12.3%)

Data are presented by number with percentage except for ‡ the duration of hospitalization after operation is presented by median with inter-quartile range.

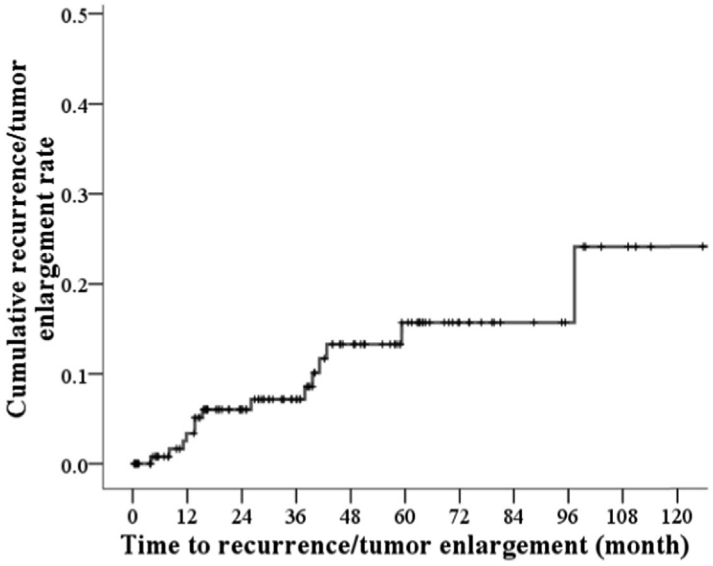
Univariable analyses revealed significant associations for recurrence/tumor enlargement versus two presenting symptoms of disturbance of consciousness and palpable cranial mass. Patients with Simpson grade IV were more likely to have recurrence/tumor enlargement compare to those with the other grades. The significance was observed in the multivariable analysis (Table 3).

We next stratified the population by age over 65 years, resulting in 85 (61.6%) aged < 65 years and 53 (38.4%) aged ≥ 65 years. The results showed a significantly high incidence of headache in the patients aged <65 years compared with that of the patients aged ≥65 years (36.5% vs. 13.2%, p = 0.003). Meningioma patients aged ≥65 years were more likely to have disturbance of consciousness (20.8% vs. 4.7%, p = 0.005). Our data showed that preoperative embolization before operation was more frequently indicated to younger patients with meningiomas (32.9% vs. 15.1%, p = 0.028). In-hospital length of stay was significantly longer in patients aged ≥65 years than the younger ones (medians of 14 vs. 11 days, p < 0.001) (Table 4). With fixing the conditions of preoperative embolization and Karnofsky scoring before operation, the association between age and Karnofsky scoring on discharge remained statistically significant (p = 0.013), and each 10 years increasing of age would resulted in 3.74 decreasing of Karnofsky scoring on discharge.

4. Discussion

Meningioma is a common brain tumor type occurring at all ages with a peak incidence in sixth and seven decade of life. Our study showed a mean age of 60.5 years at diagnosis for the meningioma patients, which is in agreement with other Asian studies[7–10]. Mean age at diagnosis of meningiomas has been suggested to be less in African-origin population ranging from 39.9 to 45.7 than Caucasian ranging from 57 to 59.1[11–15]. In addition to age distribution, increasing evidence has highlighted a sex disparity in meningiomas with a ratio of males to females ranging from 1:1.1 to 1:3.8. It has been reported that the female preponderance in the African-origin population is less than that in other ethnic groups[16]. Our results showing a male-to-female ratio of 1:2.2 were in agreement with previous studies in Caucasian populations[17,18]. Interestingly, a recent population-based study has reported an absence of female predominance among patients with intracranial meningiomas undergoing surgery[18]. The differences are possibly explained by different genetic, environmental or other factors. We noted a similar sex difference stratified by age <65 and age ≥65, whereas there was a higher male-to-female ration in patients age <65 (1:2.0).

Location of the meningioma is suggested to be a determining factor in surgical resectability and prognosis. Meningiomas are frequently found in the convexity, parasagittal, and falx regions[17,19]. Less common locations for meningiomas include olfactory groove,



	Time (month)								
	12	24	36	48	60	72	84	96	108
Recurrence/tumor enlargement rat	0.034	0.061	0.072	0.133	0.157	0.157	0.157	0.157	0.241
Number of cumulative events	4	7	8	12	13	13	13	13	14
Number of remaining cases	111	88	68	49	34	19	13	10	6

Fig. 1. The cumulative recurrence/tumor enlargement rate by the Kaplan–Meier estimates.

Table 3
The risk factor of recurrence/tumor enlargement.

	Risk of recurrence/tumor enlargement			
	Crude HR (95% CI)	p-value	Adjusted HR (95% CI)	p-value
Age (≥65 years vs. <65 years)	1.49 (0.51, 4.31)	0.464		
Gender (male to female)	1.05 (0.33, 3.37)	0.937		
Presenting symptoms				
Disturbance of consciousness	7.31 (2.44, 21.94)	<0.001*	5.36 (1.40, 20.59)	0.014*
Palpable cranial mass	18.83 (3.59, 98.61)	0.001*	19.43 (3.06, 123.21)	0.002*
Tumor volume (mm^3)	1.01 (1.00, 1.02)	0.091		
Pathology grade				
I: benign	Reference			
II: atypical	2.88 (0.62, 13.35)	0.178		
III: malignant	3.66 (0.79, 16.97)	0.098		
Simpson grade				
I	Reference		Reference	
II	0.85 (0.17, 4.23)	0.845	1.25 (0.24, 6.60)	0.793
III	4.62 (0.77, 27.88)	0.095	2.76 (0.38, 19.94)	0.314
IV	8.06 (1.96, 33.07)	0.004*	5.06 (1.20, 21.34)	0.027*
TAE before operation	1.05 (0.33, 3.37)	0.933		
Karnofsky scoring before operation	1.49 (0.49, 4.50)	0.483		

* p-value <0.05.

sphenoid wing and posterior fossa[17,20]. A recent study conducted in Nigeria reported a different anatomical distribution of meningiomas[16]. The common locations of intracranial meningiomas have been suggested to vary among reports[21,22]. In our study, the common anatomical location of meningioma was cerebral convexity followed by parasagittal region. This finding is in agreement with previous studies that meningiomas in adults are found commonly located in cerebral convexity. We also found tumors located within tentorium (0.7%) and ventricle (0.7%), which are considered to be more common in children[23,24].

Most of intracranial meningiomas are histologically graded as benign, whereas 5–10% of meningiomas exhibit aggressive behavior as high-grade (WHO grade II/III)[2,25]. In our series, the distribution of tumor types was similar to other studies, showing a predominance of benign meningiomas (87.7%). Despite of being a slow-growing histologically benign tumor, recurrence rates of meningiomas after surgery with unfavorable clinical course remain high. Atypical and malignant meningiomas has been reported to exhibit higher recurrence rate compared with that of benign tumors (WHO grade I)[26,27]. However, a significant number of meningioma relapses occur among benign meningiomas[28]. In addition to WHO grading, Simpson grading system describing the completeness of resection is suggested as a predictor of meningioma progression and recurrence. In our series, the overall recurrence rate was 24.1%. Univariable analysis revealed that Simpson grade IV was significantly associated with recurrence risk compared with the other grades. The finding is similar to previous studies focusing on the relationship of Simpson grade and meningioma control[29–31]. Several factors have been associated with high risk for meningioma recurrence, including peritumoral brain edema, cellular pleomorphism, neovascularization, presence of macronuclei and brain invasion[32–35]. In the present study, we found that meningioma patients with presenting symptoms, namely disturbance of consciousness and palpable cranial mass had an increased tendency to recur after surgery. It is suggested

Table 4
The associations of patient characteristics and clinical outcomes with age.

	Age		p-value
	<65 years	≥65 years	
Gender			
Female	57 (67.1%)	38 (71.7%)	0.706
Male	28 (32.9%)	15 (28.3%)	
Presenting symptoms			
Motor deficit	24 (28.2%)	21 (39.6%)	0.193
Sensory alteration	2 (2.4%)	2 (3.8%)	0.638
Headache	31 (36.5%)	7 (13.2%)	0.003*
Dizziness	16 (18.8%)	14 (26.4%)	0.298
Nausea/vomiting	10 (11.8%)	3 (5.7%)	0.370
Syncope	1 (1.2%)	1 (1.9%)	1.000
Seizure	13 (15.3%)	6 (11.3%)	0.616
Disturbance of consciousness	4 (4.7%)	11 (20.8%)	0.005*
Language dysfunction	6 (7.1%)	3 (5.7%)	1.000
Visual disturbance	12 (14.1%)	4 (7.5%)	0.286
Focal neurologic deficit	5 (5.9%)	3 (5.7%)	1.000
Change in behavior/ Memory	9 (10.6%)	10 (18.9%)	0.207
Palpable cranial mass	1 (1.2%)	3 (5.7%)	0.158
Incidental	8 (9.4%)	4 (7.5%)	0.767
Simpson grade			
I	29 (34.1%)	23 (43.4%)	0.559
II	40 (47.1%)	21 (39.6%)	
III	4 (4.7%)	4 (7.5%)	
IV	12 (14.1%)	5 (9.4%)	
Tumor location			
Parasagittal	12 (14.1%)	7 (13.2%)	0.307
Parafalcine	8 (9.4%)	2 (3.8%)	
Convexity	31 (36.5%)	29 (54.7%)	
Olfactory groove	6 (7.1%)	2 (3.8%)	
Sphenoid ridge	11 (12.9%)	2 (3.8%)	
Tuberculum sella	3 (3.5%)	1 (1.9%)	
Planum sphenoidale	2 (2.4%)	1 (1.9%)	
Cerebellopontine angle	3 (3.5%)	2 (3.8%)	
Tentorial	0 (0.0%)	1 (1.9%)	
Middle fossa	2 (2.4%)	4 (7.5%)	
Posterior fossa	6 (7.1%)	2 (3.8%)	
Intraventricular	1 (1.2%)	0 (0.0%)	
Pathology			
Grade I: benign	77 (90.6%)	44 (83.0%)	0.405
Grade II: atypical	4 (4.7%)	5 (9.4%)	
Grade III: malignant	4 (4.7%)	4 (7.5%)	
Tumor volume (mm^3)‡	33.3 (13.5, 63.6)	32.0 (13.5, 60.0)	0.439
TAE before operation	28 (32.9%)	8 (15.1%)	0.028*
Karnofsky scoring before operation			
≤70 (dependent)	26 (30.6%)	33 (62.3%)	<0.001*
>70 (undependent)	59 (69.4%)	20 (37.7%)	
Karnofsky scoring on discharge			
≤70 (dependent)	21 (24.7%)	29 (54.7%)	0.001*
>70 (undependent)	64 (75.3%)	24 (45.3%)	
Radiotherapy after operation	10 (11.8%)	6 (11.3%)	1.000
Postoperative complications			
Intracerebral hematoma	9 (10.6%)	7 (13.2%)	0.785
Wound infection	2 (2.4%)	0 (0.0%)	0.523
CNS infection	1 (1.2%)	1 (1.9%)	1.000
Pneumonia	5 (5.9%)	5 (9.4%)	0.507
Urinary tract infection	2 (2.4%)	3 (5.7%)	0.372
Seizure	1 (1.2%)	2 (3.8%)	0.558
Hydrocephalus	2 (2.4%)	0 (0.0%)	0.523
Cranial nerve injury	4 (4.7%)	1 (1.9%)	0.649
Others	7 (8.2%)	8 (15.1%)	0.263
Outcome at discharge			
Improved	67 (78.8%)	32 (60.4%)	0.069
Same	10 (11.8%)	12 (22.6%)	
Deteriorated	8 (9.4%)	9 (17.0%)	
Duration of hospitalization after operation (day)‡	11 (10, 18)	14 (10, 22)	<0.001*

* p-value <0.05.
Data are presented by number with percentage except for ‡ non-normal distributed continuous data (tumor volume, duration of hospitalization after operation) are presented by median with inter-quartile range.

that presenting symptoms upon diagnosis may stand as predictor for recurrence after surgery incorporating with other tools. However, further study in large population is required to confirm this finding. In this series, tumor size and location were found to have no influence on meningioma relapse. Moreover, association of patient gender and age with recurrence was insignificant.

The incidence rate of meningiomas increases significantly in people over 65[36]. An age of >60 years at diagnosis has been reported to be a predictor of worse outcomes among advanced meningioma patients. In our series, there were postoperative complications in 60 of 138 patients (43.3%) with a majority of complications related to surgery, including hematoma, infections, seizure and cranial nerve injury. This finding is agreed with a previous series showing a morbidity rate of 37%[37]. However, the morbidity rates were comparable between two groups, aged <65 years and aged ≥65 years. A significant difference was observed in the duration of hospitalization between two age groups. It is indicated that age over 65 serves as a predictor for poor outcome.

This study had several limitations. Firstly, the nature of retrospective study design is likely to be bias. Second of all, a mean follow-up duration of 36.8 months may lead to underestimating late recurrences that may occur in 4 years after surgery. A final limitation is that of the small number of trials as well as heterogeneity of treatments. In this series, the tumor location, histological characteristic and grades as well as age and sex distribution were similar and comparable to other studies. The results suggest that presenting symptom may represent a predictive factor for recurrence. A multicenter study is required to elucidate the postoperative morbidity of intracranial meningiomas.

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