CLINICAL ARTICLE

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The Natural History and Growth Rate of Meningiomas

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Objective : To evaluate the natural histories and growth rates of meningiomas, the authors perform this retrospective observational study and attempt to identify those factors predicting tumor growth.

Methods : Between 1993 and 2004, a total of 83 patients were diagnosed by computed tomography(CT) scans or magnetic resonance (MR) imaging as having an intracranial meningioma, and were treated by observation only using regular clinical and radiological examinations. Twenty-six of these 83 patients, with available data were included in this study. Follow up periods ranged from 9 to 137 months (mean, 55.6 mo.; median, 60 mo.). The tumor volumes, absolute growth rates, and tumor doubling times were calculated.

Results : Patient age and sex distributions were comparable to those of other studies, but exceptionally 16 meningiomas (62%) were located at the skull base in the present study. During follow-up monitoring, the majority of meningiomas grew, though 77% showed low absolute annual growth rates ($<1 cm^3/yr$). The tumor doubling times ranged from 2.87 to 201.72 years (mean, 42.91 yr). Based on imaging analysis, peritumoral edema and the absence of calcification were probable factors predicting tumor growth. Tumor-related symptoms seemed to be slightly related to tumor growth. Other factors, e.g., gender, age, tumor location, and T2-weighted signal intensities on MR imaging, were not significantly related to tumor growth.

Conclusion : This study shows that the majority of meningiomas are slow growing. However, variations in tumor growth are unexplained, thus individualized optimal treatment strategies should be provided in each meningioma.

KEY WORDS : Meningioma · Natural history · Growth rate.

Introduction

Meningiomas are common benign tumors and mainly developed during the sixth and seventh decades. The best way of dealing with them may be surgical resection, but their surgical resection is not always possible.

Many patients may show minimal neurological deficits or be asymptomatic due to the slow growth rates of most of these tumors. Thus, in terms of morbidity, surgery for meningiomas may place patients at risk despite advancements of microneurosurgical techniques. Moreover, because insufficient information is available on the natural history of these tumors, including symptomatic and asymptomatic meningiomas, optimal treatment options are often unclear. Several reports have analyzed the associations between tumor growth and clinical parameters, and there have been many debates concerning the factors that predict tumor growth. To provide a guide to treatment options in given patients, we retrospectively reviewed 26 meningioma patients, who were followed at our clinic, and measured the absolute growth rates and volume doubling times of these tumors and monitored clinical parameters.

Materials and Methods

Patient selection

A total of 83 patients were diagnosed by computed tomography or magnetic resonance(MR) image as having an intracranial meningioma and initially recommended to be treated conservatively between 1993 and 2003. Meningiomas were radiologically diagnosed by the presence of an extra-axial mass, with broad-based attachment along the dura or to the choroids plexus in the ventricles, which showed homogeneous and marked contrast enhancement. Serial follow-ups and clinical and imaging studies were conducted 3 months after the initial diagnosis, then at 6 months intervals during the first two years, and annually thereafter.

Of these 83 patients, three had associated multiple menin-

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Table 1. Overview of 26 cases

Patient no.	Sex/age (yr)	Symptom	Location	T2 signal	Calcification	Peritumoral brain edema	Follow-up time(mo)	Initial volume (cm^3)	Latest tumor volume(cm^3)
1	F/67	dizziness	Tentorial	high	No	No	60	1.32	1.63
2	F/54	dizziness	Parasellar	iso	No	No	24	1.31	2.13
3	M/61	dizziness	Parasellar	iso	Yes	No	19	19.04	22.48
4	F/72	dysarthria	FM	high	No	No	44	6.8	7.46
5	F/47	eyeball pain	Parasellar	high	No	No	90	4.55	4.68
6	F/73	facial nerve palsy	CPA	iso	No	No	9	4.7	5.25
7	M/62	headache	Falx	high	No	No	31	3.59	3.62
8	F/47	headache	CPA	iso	Yes	No	89	14.5	20.97
9	F/62	headache	convexity	high	Yes	No	87	3.77	4.29
10	F/44	headache	convexity	high	Yes	No	79	3.57	5.98
11	F/54	headache	Tentorial	low	No	No	30	2.12	2.41
12	F/57	headache	Trigonal	high	Yes	Yes	62	57.23	76.85
13	F/53	headache	Tentorial	low	No	No	36	38.73	39.21
14	F/64	headache	Parasellar	high	No	No	31	5.38	6.06
15	F/54	headache	Tentorial	iso	Yes	Yes	36	23.84	32.15
16	F/67	headache	Falx	high	Yes	No	29	11.39	18.81
17	M/55	hearing disturbance	Petroclival	high	No	Yes	60	23.45	31.04
18	M/57	hemiparesis	Parasagittal	high	Yes	Yes	137	102.51	108.27
19	M/67	hemiparesis	Frontobasal	iso	No	No	61	1.39	1.48
20	F/52	incidental	FM	iso	Yes	No	60	14.72	18.09
21	M/64	incidental	Sphenoid	high	Yes	Yes	60	22.99	25.78
22	F/60	incidental	Parasellar	high	No	No	37	11.79	12.98
23	F/43	syncope	Petroclival	high	Yes	Yes	70	26.26	55.06
24	F/66	trigeminal neuralgia	CPA	high	No	Yes	60	21.54	48.71
25	F/62	visual disturbance	Parasellar	low	No	No	49	3.19	3.78
26	F/37	visual disturbance	CPA	low	No	No	96	2.14	2.24

CPA, cerebellopontine angle; FM, foramen magnum; iso, isointense; low, hypointense; high, hyperintense; yes, present; no, absent

giomas, two had neurofibromatosis Type 2, and 18 patients underwent radiation therapy and five radiosurgery. Twenty-two patients elected to have surgical excision within 6 months of the initial neuroradiological diagnosis for various reasons in our or at another clinic, and 5 patients were lost to follow up after the initial diagnosis. Two patients could be followed by computed tomography(CT) scans only, and thus T2-signal intensities were unavailable in these cases. All of the above patients were excluded.

Thus, twenty-six patients with all data available composed the study population. Hospital charts, follow-up records, and imaging studies (CT and MR image) were analyzed retrospectively.

Data collection

Computed tomographic or MRI contrast enhanced scans were performed using 3- to 7-mm-thick slices and were used to determine tumor volumes, which were calculated using Osiris (Ver 4.18)[4,13]. To assess tumor growth, absolute growth rate and volume dou-bling times (tumor doubling times) were calculated, using the following :-

absolute growth rate (cm^3/yr) = $dV_{(latest-initial)}/t$

and

tumor doubling time (yr) = $(\log 2 \times t)/(\log V_{latest} - \log V_{initial})$

where V_{latest} is the tumor volume on last follow-up, $V_{initial}$ is the tumor volume at the initial radiological study, and t is the time interval between these two measures (expressed in years).

Statistical analysis

The Student's t-test was used to test for the significance of tumor growth differences between groups classified by the presence or absence of each clinical parameter.

Linear regression analysis was used to identify correlations between tumor growth and clinical parameters. During the statistical analysis, absolute growth rates and tumor doubling time were transformed to natural logarithms.

For all tests, a probability value of <0.05 was considered to indicate statistical significance.

Results

Demographic characteristics

The 26 study subjects comprised 20 (77%) women and 6 (23%)

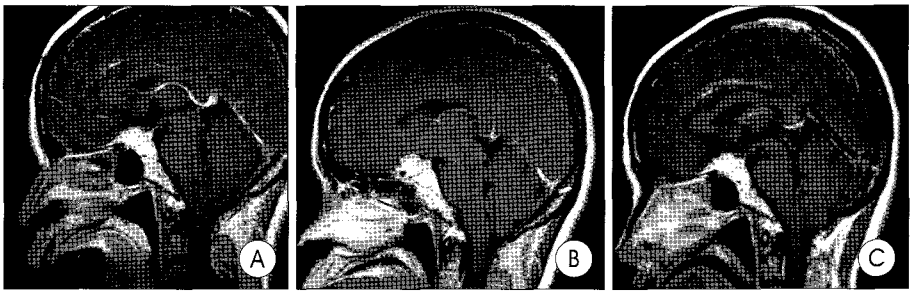

Fig. 1. Patient 5. Sagittal magnetic resonance image demonstraging a parasellar meningioma at the time of diagnosis (A), after 60 months (B), and after 90 months (C). There are no grossly significant changes in the size of the tumor.

Table 2. The results of Student's t-test with respect to the significance of differences in tumor growth in groups classified by the presence or absence of each clinical parameter. Only peritumoral edema and the absence of calcification are significantly related to the absolute volume growth. The scores in the mean were natural logarithms

Clinical parameters	Indices of tumor growth	Subgroups	Patients No.	Mean	SD	p
Peritumoral edema	Absolute volume growth	No edema	19	−1.7144	1.6265	.001
		edema	7	.6853	.9944	
	Tumor doubling time	No edema	19	3.0725	1.2862	.447
		edema	7	2.6391	1.2171	
Calcification	Absolute volume growth	calcification	15	−1.8799	.4556	.005
		No calcification	11	−3.832	.3822	
	Tumor doubling time	calcification	15	3.1969	.3536	.262
		No calcification	11	2.6270	.3207	
Age	Absolute volume growth	< 60 yr	14	−.8348	1.7380	.492
		> 60 yr	12	−1.3407	1.9561	
	Tumor doubling time	< 60 yr	14	3.0545	1.3432	.675
		> 60 yr	12	2.8407	1.2015	
Gender	Absolute volume growth	Male	6	−1.4146	2.2377	.606
		Female	20	−.9644	1.7326	
	Tumor doubling time	Male	6	3.6847	1.3468	.107
		Female	20	2.7372	1.1791	
Tumor-related symptom	Absolute volume growth	Sx(+)	9	−.1243	1.9268	.052
		Sx(−)	17	−1.5681	1.6016	
	Tumor doubling time	Sx(+)	9	2.8619	1.4433	.788
		Sx(−)	17	3.0056	1.1948	
T2-weighted signal intensities	Absolute volume growth	iso or low	11	−1.2579	1.7007	.659
		high	15	−.9293	1.9530	
	Tumor doubling time	iso or low	11	2.8046	1.2574	.610
		high	15	3.0667	1.2923	
Tumor location 1	Absolute volume growth	skull base	16	−.7158	1.8260	.219
		non skull base	10	−1.6324	1.7585	
	Tumor doubling time	skull base	16	2.9020	1.3958	.789
		non skull base	10	3.0419	1.0690	
Tumor location 2*	Absolute volume growth	Anterior/middle fossa	7	−1.1525	1.7098	.418
		Posterior fossa	9	−.3762	1.9397	
	Tumor doubling time	Anterior/middle fossa	7	3.3424	1.1309	.280
		Posterior fossa	9	2.5595	1.5466	

Sx (+), the presence of tumor-related symptoms; Sx (−), the absence of tumor-related symptoms; iso, isointense; low, hypointense; high, hyperintense; SD, standard deviation; p, probability. * tumor location 2 is the subdivision of the skull base group in tumor location 1

men. Subject ages at the time of diagnosis ranged from 37 to 73 years, with an overall mean age of 57.7 years. The mean follow-up period was 55.6 months (range, 9-137 mo). Most meningiomas were located cerebellopontine angle, tentorium, and parasellar area, followed by the convexity, foramen magnum, and petroclival regions. The most common presenting symptoms were headache (n=10, 38.5%), followed by dizziness (n=3, 11.5%), visual disturbance (n=2, 7.7%), hemiparesis (n=1, 3.8%), facial nerve palsy (n=1), and hearing disturbance (n=1) (Table 1).

In our study, 9 of the 26 patients had tumor-related symptoms, but were observed only. Retrospectively, it was difficult to evaluate the precise reasons for deciding on observation only. Three patients had already been diagnosed as having some other malignancy (advanced gastric cancer for one and thyroid cancers for the others). Two patients had a cardiac problem, and old age was a main factor in two cases. One patient with a large parasagittal meningioma refused surgery, and the reason was not evident in one patient.

Tumor growth rate

Average initial tumor volume was 16.6cm^3 (range, 1.31-102.51 cm^3/yr). Absolute growth rates ranged from 0.01 to 5.45cm^3/yr (mean, 1.13cm^3/yr), and the majority (77%) sh-owed a low absolute growth rate of <1cm^3/yr. Fig. 1 were the images of a case showing the minimal growth during the follow-up periods. Tumor doubling times ranged from 2.87 to 201.72 years (mean, 42.9 yr).

Statistical results

Principal Student's t-test results with respect to the significance of differences in tumor growth in groups classified by the presence or absence of

Table 3. The result of a linear regression analysis. The absolute growth rate is independently and significantly associated with peritumoral edema and the absence of calcification. The statistically removed clinical parameters are summarized below the table with their probabilities. This analysis using the absolute growth rate transformed to the natural logarithms. So, in the column of 'Mean', the negative value means that the mean value of the absolute growth rate of that group is smaller than the natural logarithmic constant 'e'. Negative calcification means the absence of calcification. R-squared was 0.5496

Variables	Coefficient	Standard Error	*t*	*p*	[95% confidence interval]	
Peritumoral edema	2.220	.641	3.46	0.002	.889	3.551
Negative Calcification	1.295	.554	2.34	0.029	.145	2.444
Gender	1.245	.633	1.97	0.062	−.067	2.559
Constant	−7.934	1.619	−4.90	0.000	−11.293	−4.575

p, probability, p = 0.635 >= 0.05 removing initial tumor volume, p = 0.835 >= 0.05 removing tumor-related symptoms, p = 0.470 >= 0.05 removing tumor location, p = 0.440 >= 0.05 removing T2-weighted signal intensities

each clinical parameter are summarized in the Table 2. The peritumoral edema and the absence of calcification were identified as being significantly related to tumor growth (p= 0.001 and p=0.005 respectively).

The tumor-related symptoms (e.g., visual disturbances, facial nerve palsy, hearing disturbance, and hemiparesis) appeared to be slightly related to tumor growth (p =0.052). Gender, age, tumor location, and T2- weighted signal intensities on MRI scans were not found to be related to tumor growth.

A linear regression analysis showed that the absolute growth rate was independently and significantly associated with peritumoral edema and the absence of calcification (p=0.002 and p=0.029, respectively) (Table 3). That is to say, the likelihood of tumor growth increased with an increase in peritumoral edema and a decrease in calcification.

Discussion

Although a considerable amount of literature is available on the growth of meningiomas, few reports have analyzed the associations between tumor growth and clinical parameters. And controversy still exists concerning factors predicting tumor growth. Moreover, methods of measuring tumors and of assessing tumor growth in the literature varies widely[14,16,17,21]. Olivero[17] and Niiro[16] analyzed tumor growth based on tumor diameter measurements. Jaaskelainen et al.[9] estimated the tumor growth rates of recurrent meningiomas by measuring volume doubling times; however, recent articles[10,14,20] have used volume doubling times together with volume growth and diameter growth rates.

To assess tumor growth in the present study, absolute growth rates and tumor doubling times were calculated, because the actual (absolute) growth is thought to be more important in terms of influencing patient symptomatics rather than relative growth. Moreover, tumor doubling times are believed to better reflect aggressive behavior[9].

Demographic characteristics

In this study, age and sex distributions were comparable to those of other studies[7,14,16,17,21]. However, in the present study, 16 meningiomas (62%) were located at the skull base, which is a slightly higher proportion than in other studies. This may be due to the fact patients and surgeons are more likely to avoid surgical intervention for these meningiomas, due to high morbidity and mortality, and probable difficulty of total surgical tumor resection[1,2,5,6,8,12].

Statistical analyses

The present study shows that the presence of peritumoral edema and the presence of calcification are positively and negatively related to tumor growth respectively.

In terms of the absolute annual growth rate, a significant difference was observed between patients with and without peritumoral edema. This finding correlated well with the general concept, that 'Generally, asymptomatic tumors are not associated with brain edema, but that growing tumors are'. However, in a previous article by Niiro et al.[16], in which the relation between peritumoral edema and meningioma growth rate was examined for the first time, no significant correlation was observed between peritumoral edema and tumor growth.

However, recent findings that peritumoral edema is associated with variable growth factors, e.g., vascular endothelial growth factor(VEGF), which is believed to induce tumor growth[4,19], indicate that peritumoral edema is a predictive factor of tumor growth.

Nakamura et al.[14] and Niiro et al.[16] concluded that the presence of calcification and iso or low signal intensities on T2-weighted MR images are associated with lower tumor growth. This suggestion corresponds to the finding that calcified tumors tend to have a reduced proliferating potential[15]. Moreover, hypointensity on T2-weighted images reflect harder, more fibrous tumor components[3,18], which is consistent with a low proliferative potential[15]. These findings indicate that calcifications and hypointensities are strong predictive factors of a lower tumor growth. However, in the present study, only the presence of calcification was found to be of significance.

Symptomatic meningiomas had slight higher absolute growth rates than asymptomatic meningiomas (p=0.052), as has been reported previously[9,11]. Although no significance was found between growth rate and tumor-related symptom in the present study, tumor-related symptoms are generally considered to be one predictive factors of tumor growth. Thus, we recommend that symptomatic patients who are only observed, should be followed carefully, clinically and radiologically.

The authors classified meningiomas according to locations into a skull-base group (n=16) and a non-skull-base group (n=10). The skull-base group was then subdivided to anterior/middle fossa (n=7) and posterior fossa (n=9). Meningiomas in the skull base group had a higher mean absolute growth rate (1.42cm^3/yr) than that those in the non-skull-base group (0.64cm^3/yr), but this was not statistically significant (P= 0.23). The tumor doubling time in the skull-base group was 63.16 years, compared with 59.22 years in the non-skull-base group (P=0.8). Meningiomas in the posterior fossa seemed to have a higher mean absolute growth rate (1.77cm^3/yr) than tumors in the anterior/middle fossa (0.98cm^3/yr) (p=0.39). Conversely, our results show meningiomas in the posterior fossa seemed to grow more rapidly than those in the anterior/middle fossa, but the size of the present study makes further studies mandatory.

Tumor doubling time is believed to be related to the aggressive behavior of the tumor, but in the present study, no clinical parameter was found to be significantly related to tumor doubling time. Concerning the view that tumor doubling times are significantly related to histologic grade[9], a study about histologic appearance of meningiomas, treated conservatively first and then surgically removed, seem to be mandatory.

The present study shows that most meningiomas show continuous growth, but that the majority tumors grow very slowly. Meningiomas with peritumoral edema or the absence of calcification are prone to grow more rapidly. Therefore, close observation, with clinical and radiological follow-ups at short intervals is mandatory for these tumors. Moreover, because tumor-related symptoms are believed to predict sluggish tumor growth, long term radiological follow-up monitoring should be considered for asymptomatic meningioma patients with calcification but without peritumoral edema.

Conclusion

This study shows that the majority of meningiomas are slow growing. However, observed variations in tumor growth rates are unexplained, as are study differences concerning the factors related to tumor growth. Further investigations of meningioma growth are mandatory, though the presence of peritumoral edema and the absence of calcification appear to be predictors of tumor growth.

Nevertheless, having considered all available data, it is apparent that individualized treatment strategies should be provided in each meningioma.

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Commentary

The authors have performed a retrospective study of twenty-six radiologically diagnosed intracranial meningiomas, studying their tumor volume, their absolute growth rates, and the tumor volume doubling times. It is noteworthy that in this study, peritumoral edema and the absence of calcification are probable factors predicting meningioma growth. However, the overall results are not very helpful. The results confirm that meningiomas grow slowly but with a very wide range of growth

rate and a wide range of tumor doubling time. This indicates, as everyone knows, that some meningiomas grow much faster than others. Personally I think that biological behavior of symptomatic menigiomas may different from that of incidental meningiomas, but authors evaluated all of the meningiomas, treated conservatively. It has something to be desired in this point. Anyway, this article emphasizes the biological behavior of meningiomas in general.

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