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The natural history of intracranial meningiomas

Clinical article

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Object. Despite the increased detection of incidental or small meningiomas, the lesion's natural history is largely unknown.

Methods. One year or longer of follow-up was conducted in 244 patients with 273 meningiomas managed conservatively by a single surgeon between 2003 and 2008. Data were stratified according to age, sex, tumor location, symptoms, initial tumor diameter, calcification, MR imaging intensity, and edema. Linear tumor growth was defined as a 2-mm or larger increase in the maximum diameter in any direction of the tumor. Volumetric analysis (ImageJ version 1.43) was also conducted in 154 of 273 meningiomas for which complete radiological data were available in the form of DICOM files throughout the follow-up period. A volume increase greater than 8.2% was regarded as significant because the preliminary volumetry based on 20 randomly selected meningiomas showed that the average SD was 4.1%.

Results. Linear growth was observed in 120 tumors (44.0%) with a mean follow-up of 3.8 years. Factors related to tumor growth were age of 60 or younger ($p = 0.0004$), absence of calcification ($p = 0.027$), MR imaging T2 signal hyperintensity ($p = 0.021$), and edema ($p = 0.018$). Kaplan-Meier analysis and Cox proportional hazards regression analysis revealed that age 60 or younger (hazard ratio [HR] 1.54, 95% CI 1.05–2.30, $p = 0.026$), initial tumor diameter greater than 25 mm (HR 2.23, 95% CI 1.44–3.38, $p = 0.0004$), and the absence of calcification (HR 4.57, 95% CI 2.69–8.20, $p < 0.0001$) were factors associated with a short time to progression. Volumetric growth was seen in 74.0% of the cases. Factors associated with a higher annual growth rate were male sex ($p = 0.0002$), initial tumor diameter greater than 25 mm ($p < 0.0001$), MR imaging T2 signal hyperintensity ($p = 0.0001$), presence of symptoms ($p = 0.037$), and edema ($p < 0.0001$).

Conclusions. Although the authors could obtain variable results depending on the measurement method, the data demonstrate patients younger than 60 years of age and those with meningiomas characterized by hyperintensity on T2-weighted MR imaging, no calcification, diameter greater than 25 mm, and edema need to be observed more closely. Volumetry was more sensitive to detecting tumor growth than measuring the linear diameter.
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Key Words • **meningioma** • **growth rate** • **natural history** • **volumetry**

Meningiomas are the most common benign brain tumor.[5] The recent increase in access to CT and MR imaging to evaluate minor head injury, nonspecific neurological symptoms, or paranasal sinus symptoms has led to the increased detection of small or incidental meningiomas. With increased detection of these meningiomas, clinicians including neurosurgeons, neurologists, and primary care physicians today are commonly faced with the management dilemma as to when and what treatment should be given. To solve this dilemma, we need to know the natural history of meningiomas as well as risks and benefits of treatment. Among these factors, the natural history remains the single most important factor in the decision-making process.

Unfortunately, there is very little information regarding the natural history of intracranial meningiomas in the literature. Previous studies on the natural history are based on relatively small sample sizes, all studies limited to fewer than 70 samples, showing somewhat inconclusive results regarding the growth rate or prognostic factors for rapid growth.[2–4,6–11] The aim of the current study is to improve our understanding of meningioma's natural history to help clinicians provide a better therapeutic strategy for patients with meningiomas.

Methods

Patient Population

Between 2003 and 2009, 355 meningiomas in 316 patients were treated conservatively by the senior author (J.H.L.) at the Cleveland Clinic. We included in the study population patients with an established diagnosis of meningiomas made prior to 2003 who were conservatively managed if all radiographic (initial and subsequent) stud-

This article contains some figures that are displayed in color online but in black and white in the print edition.

Abbreviation used in this paper: HR = hazard ratio.

ies were available. The radiographic diagnosis of meningioma was made based on MR imaging evidence. Patients with neurofibromatosis were eliminated from this study. Follow-up was continued if conservative management was still chosen even when the tumor growth was observed. Overall, 1 year or longer of follow-up was accomplished in 77.2% of patients (244 of 316) and 0.5 year or longer follow-up was obtained in 93.3% of patients (295 of 316). The 244 patients harbored 273 tumors. We analyzed the data obtained in patients with 1 year or longer follow-up. All patient charts were retrospectively analyzed for data regarding age, sex, tumor location, symptoms, initial tumor diameter, calcification, MR imaging signal intensity, and peritumoral edema. Tumor locations were meticulously examined by MR imaging and classified into skull base or non–skull base, paramedian skull base or lateral skull base, or supra- or infratentorial (Table 1). Calcified tumors denote both partial and extensive intratumoral calcification.

Measurement of Tumor Growth

The maximum linear diameter of the tumor was measured for 273 meningiomas present in the 244 patients with at least 1 year of follow-up. Significant tumor growth was defined as a minimum increase of 2 mm in the maximum linear diameter in any direction. At least 2 views of axial, coronal, and sagittal planes were used to determine the maximum diameter.

Volumetric analysis size was also performed in 154 tumors for which complete radiological data were available in the form of DICOM files throughout the follow-up period. Using ImageJ Version 1.43 (http://rsbweb.nih.gov/ij/), the contour of the tumor in each slice image was traced using freehand tools and the actual area was measured. The tumor volume was calculated by multiplying each tumor area by the slice thickness of the image. Before starting the volumetry, 20 meningiomas were randomly chosen and their volumetric study was conducted 3 times with the software to calculate the means and SDs. Because the mean percentage of the SD to the mean was 4.1%, increases greater than 8.2% were defined as a significant volume growth. The annual growth rate (cm^3/year) was determined by actual volume growth divided by the period between the initial and the latest image.

Statistical Analysis

We performed Fisher exact tests for categorical variables and Wilcoxon tests for continuous variables. Kaplan-Meier analyses and log-rank tests for time-to-progression analysis were followed by multivariate Cox proportion hazard model to measure the independent association of variables with the time to progression. For time-to-progression analysis, the progression-free interval was defined as the time from the date on which the first image was taken to the date on which the follow-up image detects a significant volume growth for the first time. In cases without tumor growth, follow-up was censored at the date of the last radiological evaluation. All analyses

TABLE 1: Location of 273 conservatively treated meningiomas with 1 year or longer follow-up*

Location	No. of Lesions (%)	Skull Base or Non–Skull Base	Paramedian or Lat Skull Base	Supratentorial or Infratentorial
convexity	67 (24.5)	non–skull base	—	supratentorial
falx	30 (11.0)	non–skull base	—	supratentorial
parasagittal	29 (10.6)	non–skull base	—	supratentorial
petrosal	29 (10.6)			
superior	2 (0.7)	skull base	paramedian	infratentorial
ventral	12 (4.3)	skull base	paramedian	infratentorial
posterior	11 (4.0)	skull base	lateral	infratentorial
CPA	4 (1.5)	skull base	paramedian	infratentorial
anterior clinoid	20 (7.3)	skull base	paramedian	supratentorial
sphenoid wing	16 (5.9)	skull base	lateral	supratentorial
tentorial	13 (4.8)	skull base	paramedian	—
cavernous sinus	12 (4.4)	skull base	paramedian	supratentorial
tuberculum sellae	11 (4.0)	skull base	paramedian	supratentorial
petrotentorial, petroclival	9 (3.3)	skull base	paramedian	infratentorial
olfactory groove	7 (2.6)	skull base	paramedian	supratentorial
planum sphenoidale	7 (2.6)	skull base	paramedian	supratentorial
anterior cranial base	7 (2.6)	skull base	paramedian	supratentorial
foramen magnum	6 (2.2)	skull base	paramedian	infratentorial
clival	3 (1.1)	skull base	paramedian	infratentorial
posterior clinoid	2 (0.7)	skull base	paramedian	supratentorial
others†	5 (1.8)	—	—	—

* CPA = cerebellopontine angle; — = not applicable.

† These include torcular, transverse sinus, cerebellar convexity, ventricular, and pineal meningiomas (1 case each).

were performed with JMP Version 7.0.2 (SAS Institute). A p value < 0.05 was considered significant.

Results

Patient Characteristics

Of 273 tumors in 244 patients, linear growth was observed in 120 tumors (44.0%) with a mean follow-up duration of 3.8 years. Of these, 49 tumors (17.9%) were treated surgically and 23 tumors (8.4%) were treated with radiotherapy due to an increase in size or aggravating symptoms. In the rest of the cases we continued to observe the patients. The mean age of the 244 patients at the initial diagnosis was 60.5 (range 29–88) (Table 2). Tumor growth was observed more frequently in younger patients (median 56 vs 63 years of age, p = 0.0006). Although

TABLE 2: Characteristics of 273 conservatively treated meningiomas*

Characteristic	No. of Lesions			p Value
	All Tumors (%)	Linear Growth Present (%)	Linear Growth Absent (%)	
no. of lesions	273	120	153	
age (yrs)				0.0006
mean	60.5 ± 13.1	57.6 ± 14.0	62.8 ± 12.0	
median	60	56	63	
range	29–88	31–88	29–85	
no. of patients aged				
≤60 yrs	137 (50.2)	75 (54.7)	62 (45.3)	
>60 yrs	136 (49.8)	45 (33.0)	91 (77.0)	
sex				0.87
male	53 (19.4)	24 (45.2)	29 (54.8)	
female	220 (80.6)	96 (43.6)	124 (56.4)	
location				
skull base or not				0.62
skull base	129 (47.3)	59 (45.7)	70 (54.3)	
non–skull base	144 (52.7)	61 (42.3)	83 (57.5)	
paramedian or lat skull base				0.08
paramedian skull base	103 (79.8)	43 (41.7)	60 (58.3)	
lat skull base	26 (20.2)	16 (61.5)	10 (38.5)	
supra- or infratentorial*				0.08
supratentorial	208 (80.6)	100 (48.1)	108 (51.9)	
infratentorial	50 (19.4)	17 (34.0)	33 (66.0)	
initial tumor diameter (mm)				0.24
mean	19.8 ± 10.9	21.0 ± 12.5	18.7 ± 9.4	
median	18	19	18	
range	4–70	4–70	5–50	
≤25 mm	207 (75.8)	84 (40.6)	123 (50.4)	
>25 mm	66 (24.2)	36 (54.5)	30 (45.5)	
symptom				0.36
symptomatic	35 (12.8)	18 (51.4)	17 (48.6)	
incidental	238 (87.2)	102 (42.9)	136 (57.1)	
calcification				0.027
yes	61 (22.3)	19 (31.1)	42 (68.9)	
no	212 (77.7)	101 (47.6)	111 (52.4)	
MRI T2 signal intensity†				0.021
high	55 (20.4)	32 (58.2)	17 (48.6)	
iso/low	214 (79.6)	86 (40.2)	128 (59.8)	
peritumoral edema				0.018
yes	16 (5.9)	13 (81.3)	3 (18.7)	
no	257 (94.1)	107 (41.6)	150 (58.4)	

* Cases of tentorial, torcular, and transverse sinus meningioma were excluded. Mean values are presented ± SDs.
† Four patients with pacemakers were eliminated from the MR imaging analysis because their follow-up was performed with CT scanning.

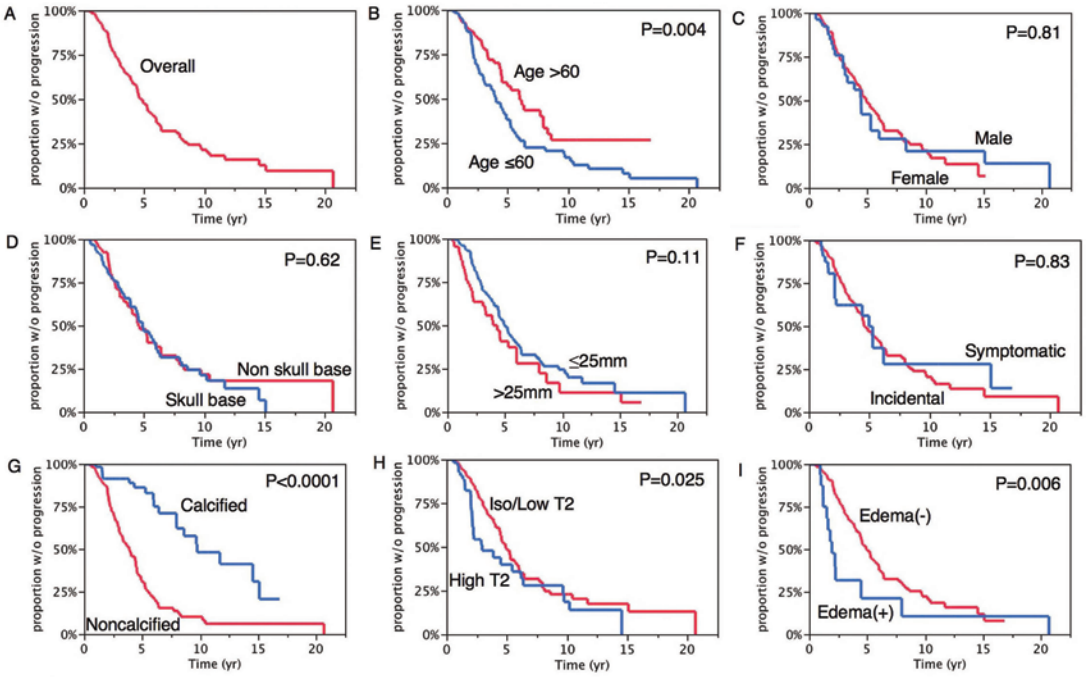

Fig. 1. Kaplan-Meier curves of time to progression in 273 conservatively managed meningiomas. Overall time to progression curve **(A)**. Time-to-progression curves stratified by age **(B)**, sex **(C)**, skull base location **(D)**, initial tumor size **(E)**, symptoms **(F)**, calcification **(G)**, T2 signal on MR imaging **(H)**, and edema **(I)**.

meningiomas are seen more frequently in women,[1] sex was not associated with the frequency of tumor growth in this follow-up period (p = 0.87).

Tumor Characteristics and Linear Meningioma Growth

As shown in Table 2, all common intracranial sites of origin are included in the study. In comparing tumor growth we did not find any significant differences between skull base and non–skull base, paramedian and lateral skull base, and supra- and infratentorial locations (p = 0.62, 0.08, and 0.08, respectively). The initial tumor diameter was not associated with tumor growth determined by a 2-mm or more increase in the linear diameter (median 19 vs 18 mm, p = 0.24). Two hundred thirty-eight tumors (87.2%) were asymptomatic. There was no significant difference in tumor growth frequency between symptomatic and incidental tumors (p = 0.36).

TABLE 3: Multivariate analysis of prognostic factors for time to progression in 273 meningiomas

Variable	HR (95% CI)	p Value
age ≤60 yrs	1.54 (1.05–2.30)	0.026
female sex	0.99 (0.60–1.70)	0.96
skull base location	0.90 (0.61–1.34)	0.62
initial tumor diameter >25 mm	2.23 (1.44–3.38)	0.0004
symptom	1.07 (0.60–1.82)	0.79
absence of calcification	4.57 (2.69–8.20)	<0.0001
MRI T2 hyperintensity	1.51 (0.95–2.34)	0.078
peritumoral edema	1.47 (0.72–2.74)	0.27

However, tumors without calcification were more prone to grow than tumors with calcification (p = 0.027). In addition, tumors with hyperintensity on T2-weighted MR imaging showed more frequent growth than tumors with iso- or hypointensity (p = 0.021). The presence of tumor-related edema was another significant risk factor for tumor growth (p = 0.018).

Time-to-Progression Analysis

Overall time-to-progression curve is shown in Fig. 1A. Approximately 40% of tumors exhibited significant growth in a 4-year follow-up duration. Kaplan-Meier analysis followed by log-rank test, stratified according to each characteristic, demonstrated that age 60 years or younger (p = 0.004), absence of calcification (p < 0.0001), hyperintensity on T2-weighted MR imaging (p = 0.025), and peritumoral edema (p = 0.006) were associated with significantly shorter time to progression. Whether the tumor was located in the paramedian or lateral skull base or whether the tumor was supra- or infratentorial was not associated with significant differences (p = 0.11 and 0.93, respectively; data not shown). Multivariate analysis using Cox proportional hazard model adjusting characteristics of patients and tumors showed that age 60 years or younger (HR 1.54, 95% CI 1.05–2.30, p = 0.026), initial tumor diameter greater than 25 mm (HR 2.23, 95% CI 1.44–3.38, p = 0.0004), and absence of calcification (HR 4.57, 95% CI 2.69–8.20, p < 0.0001) (Table 3) were significant prognostic factors for shorter time to progression.

Growth Rate by Volumetric Analysis

The results of volumetric analysis are shown in Table 4. The mean follow-up period in this subset was 3.6 years.

TABLE 4: Annual growth rate (cm³/year) of 154 meningiomas measured by volumetric anlaysis

Variables	No. of Lesions (%)	Annual Growth Rate (cm³/yr)*	p Value
age			0.80
≤60 yrs	81 (52.6)	0.10, 0.54 (0.21–0.86)	
>60 yrs	73 (47.4)	0.11, 0.83 (0.49–1.18)	
sex			0.0002
male	26 (16.9)	0.53, 1.34 (0.53–2.17)	
female	128 (83.1)	0.07, 0.53 (0.31–0.76)	
location			
skull base or not			0.29
skull base	74 (48.1)	0.15, 0.71 (0.37–1.06)	
non–skull base	80 (51.9)	0.09, 0.65 (0.32–0.98)	
paramedian or lateral skull base			0.74
paramedian skull base	59 (79.7)	0.19, 0.67 (0.35–0.98)	
lateral skull base	15 (20.3)	0.11, 0.91 (−0.40 to 2.23)	
supra- or infratentorial†			0.63
supratentorial	116 (78.9)	0.10, 0.73 (0.44–1.03)	
infratentorial	31 (21.1)	0.19, 0.61 (0.20–1.03)	
initial tumor diameter			<0.0001
≤25 mm	118 (76.6)	0.07, 0.33 (0.15–0.53)	
>25 mm	36 (23.4)	0.95, 1.80 (1.08–2.52)	
symptoms			0.037
symptomatic	21 (13.6)	0.33, 1.36 (0.25–2.47)	
incidental	133 (83.4)	0.09, 0.57 (0.35–0.79)	
calcification			0.074
yes	33 (21.4)	0.05, 0.51 (0.03–0.99)	
no	121 (78.6)	0.13, 0.72 (0.45–1.00)	
MRI T2 signal intensity			0.0001
high	40 (26.0)	0.35, 0.93 (0.39–1.47)	
iso/low	114 (74.0)	0.07, 0.59 (0.33–0.86)	
peritumoral edema			<0.0001
yes	11 (7.1)	1.38, 2.28 (0.47–4.09)	
no	143 (92.9)	0.08, 0.55 (0.34–0.77)	

* Data are presented in the following order: median, mean, and, parenthetically, 95% CI.
† Cases of tentorial, torcular, and transverse sinus meningioma were excluded.

Volumetric growth was observed in 74.0% (114 of 154) of tumors. Characteristics associated with a higher annual growth rate were male sex ($p = 0.0002$), initial diameter greater than 25 mm ($p < 0.0001$), presence of symptoms ($p = 0.037$), hyperintensity on T2-weighted MR imaging ($p = 0.0001$), and peritumoral edema ($p < 0.0001$).

Discussion

The authors of several studies have described the natural history of meningiomas, and they based their findings on samples ranging from 17 to 70 tumors.[2–4,6–11] Because of small sample sizes and the variety of the methods used to measure the tumor growth, information regarding the tumor growth rate and prognostic factors were inconclusive. Given that meningiomas are the most common benign brain tumors, the natural history information based on a large sample of lesions is of critical importance. Our study included 273 conservatively managed meningiomas in 244 patients. We studied the natural history of meningiomas using 3 methods: 1) linear diameter measurement, 2) time-to-progression analysis, and 3) volumetry. There are some potential selection biases in this retrospective study. First, there is a possibility that a very small number of patients who were lost to follow-up might have experienced tumor growth and undergone surgery at other hospitals. We usually schedule the first follow-up for 6 months after the date of the initial imaging study, and there were only 9 patients who did not show for their scheduled first follow-up visit for unknown reason. In addition, 22 of 72 lesions for which follow-up was shorter than 1 year were treated with surgery or radiotherapy due to an increase in the size of the tumor or worsening of symptoms, and therefore their follow-up

was stopped within 1 year. In our study, the follow-up rates were 77.2% for 1 year or longer and 93.3% for 6 months or longer, which we believe is sufficiently high for the purpose of depicting the natural course of meningiomas. Second, we cannot exclude the possibility that patients who had supposed tumor growth or neurological symptoms were more frequently referred to our institution by neurologists or primary care physicians whereas patients with stable meningiomas or no symptoms were observed locally without referral to our institution.

Various measurement methods such as maximum diameter analysis,[7–9] ellipsoidal approximation,[4] or volumetry[3,6] have been used in studies of meningioma natural history, resulting in inconsistency among studies in terms of probability and prognostic factors for tumor growth. Our data also demonstrated that we could get variable results depending on the method of study. However, young age, lack of calcification, initial diameter larger than 25 mm, hyperintensity on T2-weighted MR imaging, and the presence of edema were shown to be significant prognostic factors in at least 2 methods of study. Tumors with these characteristics may need to be observed more closely.

Additionally our analysis revealed that volumetry was more sensitive to detecting tumor growth. Similarly, the authors of previous studies have reported that volumetric growth was seen in 24.3%–90.3% of tumors[3,6,10] whereas linear diameter growth was observed in 22%–37.3% of tumors.[7–9] Volumetric analysis has increasingly been applied to the evaluation of the therapeutic effects of radiosurgery for intracranial benign tumors. Accurate volumetric quantification is important after radiosurgery because postirradiation tumor growth could indicate the high potential for the tumor cells to proliferate and the necessity of surgical intervention to prevent tumor progression. In the observation of incidental or small meningiomas, however, little is known regarding the clinical significance of volumetry. Also, although volumetry may more accurately describe the tumor growth kinetics in a research setting, there are some procedural problems from clinical standpoint. First, it takes longer to measure the volume than measure the diameter. In our experience, it takes 20–30 minutes to calculate the volume for each comparison, which may not be practical for daily use in an outpatient clinic setting. Second, some meningiomas have an unclear border with the brain parenchyma, the sagittal sinus, and the adjacent blood vessels (Fig. 2). These radiologically ambiguous findings can result in a large inter- and intraobserver bias.

Conclusions

The natural history study of meningiomas may provide different results depending on the method of study. Based on our data, however, intracranial meningioma growth was observed in 44.0% by the linear diameter measurement and in 74.0% by the volumetry within 4 years. The following factors were found to be significant based on at least 2 methods of study: young age (≤ 60 years), lack of calcification, hyperintensity on T2-weighted MR imaging, large size (> 25-mm diameter), and edema. Patients with these positive factors may need to be observed more closely. Although volumetry is more sensitive for detecting subtle growth, its everyday clinical application may be limited.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Lee, Oya, Sade. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting the article: all authors. Critically revising the article: Lee, Oya, Sade. Reviewed final version of the manuscript and approved it for submission: Lee.

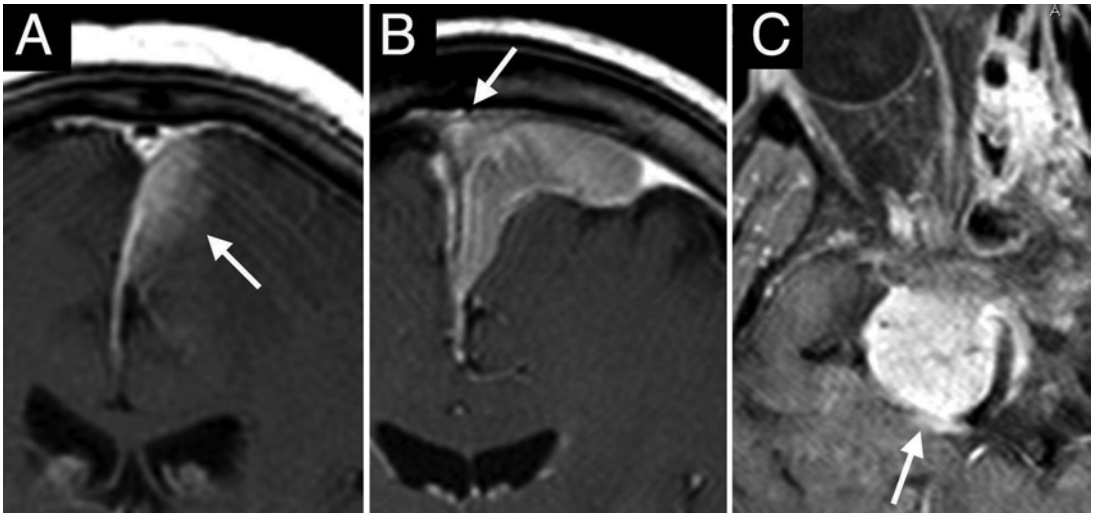

Fig. 2. Magnetic resonance images showing examples of unclear tumor borders. Unclear borders *(arrows)* between the tumor and the brain parenchyma **(A)**, the large venous sinus **(B)**, and the abutting blood vessel **(C)** may cause some technical problems in volumetry.

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