JNS

CLINICAL ARTICLE

J Neurosurg 127:971–980, 2017

A novel weighted scoring system for estimating the risk of rapid growth in untreated intracranial meningiomas

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OBJECTIVE Advances in neuroimaging techniques have led to the increased detection of asymptomatic intracranial meningiomas (IMs). Despite several studies on the natural history of IMs, a comprehensive evaluation method for estimating the growth potential of these tumors, based on the relative weight of each risk factor, has not been developed. The aim of this study was to develop a weighted scoring system that estimates the risk of rapid tumor growth to aid treatment decision making.

METHODS The authors performed a retrospective analysis of 232 patients with presumed IM who had been prospectively followed up in the absence of treatment from 1997 to 2013. Tumor volume was measured by imaging at each follow-up visit, and the growth rate was determined by regression analysis. Predictors of rapid tumor growth (defined as ≥ 2 cm^3/year) were identified using a logistic regression model; each factor was awarded a score based on its own coefficient value. The probability (P) of rapid tumor growth was estimated using the following formula:

$$\mathrm{P}\,(\%) = \left[\frac{1}{1+e^{-(\mathrm{intercept} + \mathrm{b1} \times \mathrm{total\ score})}}\right] \times 100\,(\%). \quad \text{[Eq. 1]}$$

RESULTS Fifty-nine tumors (25.4%) showed rapid growth. Tumor size (OR per cm^3 1.07, p = 0.000), absence of calcification (OR 3.87, p = 0.004), peritumoral edema (OR 2.74, p = 0.025), and hyperintense or isointense signal on T2-weighted MRI (OR 3.76, p = 0.049) were predictors of tumor growth rate. In the Asan Intracranial Meningioma Scoring System (AIMSS), tumor size was categorized into 3 groups of < 2.5 cm, ≥ 2.5 to < 4.0 cm, and ≥ 4.0 cm in diameter and awarded a score of 0, 3, and 6, respectively; the parameters of calcification and peritumoral edema were categorized into 2 groups based on their presence or absence and given a score of 0 or 2 and 1 or 0, respectively; and the signal on T2-weighted MRI was categorized into 2 groups of hypointense and hyperintense/isointense and given a score of 0 or 2, respectively. The risk of rapid tumor growth was estimated to be < 10% when the total score was 0–2, 10%–50% when the total score was 3–6, and ≥ 50% when the total score was 7–11 (Hosmer-Lemeshow goodness-of-fit test, p = 0.9958). The area under the receiver operating characteristic curve was 0.86.

CONCLUSIONS The authors suggest a weighted scoring system (AIMSS) that predicts the specific probability of rapid tumor growth for patients with untreated IM. This scoring system will aid treatment decision making in clinical settings by screening out patients at high risk for rapid tumor growth.

https://thejns.org/doi/abs/10.3171/2016.9.JNS161669

KEY WORDS meningioma; natural history; incidental finding; factor analysis; risk assessment; oncology

Intracranial meningiomas (IMs) are the most common central nervous system tumors in adults and account for up to 35% of all primary brain tumors.[2,3,15] There is a linear increase in the incidence of these tumors with age.[15] The recent rapid shift toward an aging society, along with advances in neuroimaging techniques, has contributed to the increased frequency of detection for asymptomatic IMs.[11] Although most IMs grow slowly, some grow exponentially over a short time. Not only can the opportunity for radiosurgery be missed in patients with rapidly growing IMs, but neurological symptoms can also quickly develop in these patients. Therefore, correctly assessing a

ABBREVIATIONS AGR = absolute growth rate; AIMSS = Asan Intracranial Meningioma Scoring System; AUC = area under the receiver operating characteristic curve; CT = computed tomography; IM = intracranial meningioma; RGR = relative growth rate; SI = signal intensity; T2W-MRI = T2-weighted MRI.

SUBMITTED June 26, 2016. **ACCEPTED** September 19, 2016.

INCLUDE WHEN CITING Published online January 13, 2017; DOI: 10.3171/2016.9.JNS161669.

tumor's growth potential is paramount for the appropriate and timely management of asymptomatic IMs. Several authors have studied the natural history of IMs[4,5,8,11,13,14,16–19] and have suggested similar clinicoradiological parameters as risk factors for tumor growth. These include young age at diagnosis,[11,16] peritumoral edema,[5,16] absence of calcification,[5,8,11,13,16] and hyperintense signal on T2-weighted MRI (T2W-MRI).[13,16–18] However, the relative influence of each parameter on tumor growth and the use of corresponding weights for predicting overall risk have not been reported. The aims of this study were as follows: 1) to investigate the natural history of IMs using volumetric assessment and statistical techniques, 2) to determine the risk factors for rapid tumor growth and their respective influential weights, and 3) to design a novel scoring system for estimating overall risk of rapid tumor growth to help clinicians better develop a therapeutic strategy.

Methods

Patient Population

Between 1997 and 2013, a total of 1380 adult patients (age > 20 years) with a presumed diagnosis of IM (based on neuroimaging analysis) were treated by the senior author (J.H.K.) at Asan Medical Center. Among these, 918 patients (66.5%) underwent resection and 135 patients (9.8%) underwent stereotactic radiosurgery soon afterward. A total of 327 patients (23.7%) underwent prospective follow-up with the senior author but did not undergo active treatment. Our institutional review board granted a waiver for informed consent and approved the study protocol and chart review. Seven patients for whom gadolinium-enhanced imaging was not performed, 9 patients with multiple IMs, and 4 patients who were eventually diagnosed with another disease upon pathological examination were excluded from the study. Patients were followed up with serial neuroimaging studies, initially at 6 months or 1 year after diagnosis and then 1 year or every other year until significant tumor growth that merited therapeutic intervention was observed or until aggravation of clinical symptoms or the development of new symptoms. Among the patients who did not reach an end point, those with a follow-up duration ≤ 2 years (n = 75) were excluded. Thus, the final number of patients included in the study was 232.

Thirty-two patients (13.8%) presented with neurological symptoms such as hemiparesis (n = 12), visual disturbance (n = 10), cognitive dysfunction (n = 5), hemihypesthesia (n = 3), facial hypesthesia (n = 1), and dysarthria (n = 1). Although these symptoms were attributed to the tumors, most were mild, and the patients refused to undergo treatment out of fear of posttreatment symptom deterioration or because of comorbidity and poor performance status. Over a mean follow-up period of 47 months, the development of new neurological symptoms or the aggravation of existing symptoms was observed in 40 patients (17.2%). Forty-five patients eventually dropped out of the imaging surveillance. Resection was performed in 27 patients, stereotactic radiosurgery in 14 patients, and external beam fractionated radiotherapy in 4 patients over a mean duration of 36 ± 26 months (range 7–128 months) after the diagnosis of IM. Three patients who had cerebrospinal fluid diversion because of obstructive hydrocephalus continued with follow-up examinations of the tumors. The demographic features of the patients and the tumor characteristics are summarized in Table 1. Complete clinicoradiological data were available for 221 patients, except for computed tomography (CT) and T2W-MRI data for 5 and 6 patients, respectively. Data pertaining to these 221 patients were used to develop the scoring system for estimating the risk of rapid tumor growth.

Determination of the Tumor Growth Rate

Approximately half of all patients (n = 116) were followed up alternately with CT and MRI studies, and the other half underwent surveillance with the same imaging modality. A total of 109 (47%) patients were consistently followed up with MRI and 3% of patients (n = 7) with CT. At each follow-up examination, all tumors were volumetrically measured during enhanced imaging using 1.5- to 5-mm-thick slices; the slices were then analyzed using ImageJ software, an image-processing program developed at the National Institutes of Health. The tumors were roughly contoured in manual mode for each slice, and the actual areas were automatically selected based on the contrast of the image. Tumor volume was calculated by multiplying each tumor area by the slice thickness. To minimize measurement error, the volume was measured 3 times at each follow-up visit and the mean values were recorded.

The absolute growth rate (AGR) was defined as the increase in tumor volume (cm^3) per year, whereas the relative growth rate (RGR) was defined as the percent increase in volume per year. Tumor volumes measured at each follow-up imaging exam were used to track tumor growth, regardless of the imaging modality used. Tumor volume determined from CT data tended to be slightly underestimated when compared with that from MRI data. We overcame the discrepancy between CT and MRI measurements by using the following methods. The growth rates for each tumor were statistically determined by regression analysis using a linear mixed-effects model with random intercepts and slopes. A random coefficient model assumes that each individual has a different intercept and slope. The sum of the regression coefficients of fixed and random effects for the slope estimated from the mixed model represented the average growth rate of each tumor. Tumor doubling time was also calculated using each regression equation. Spaghetti plots of tumor volume (cm^3) over time were generated using observed data (Fig. 1). The growth patterns of each tumor were statistically fitted to linear and exponential curves or unclassified and chosen based on the Akaike information criterion.

Identification of Factors Associated With Rapid Tumor Growth

The definition of significant tumor growth used in previous studies has shown wide variability. Most definitions were based on a certain extent of growth, such as an increase in the maximal diameter > 2 mm or an increase in volume > 15% from the previous value. The time taken for growth to occur was not considered. However, we believe that the rate of tumor growth is of greater clinical significance than the extent of growth. The entire cohort

TABLE 1. Demographic characteristics of patients with IM in the slow-growth and rapid-growth groups

Characteristic	All		Slow-Growth Group (<2 cm³/yr)		Rapid-Growth Group (≥2 cm³/yr)		p Value
	No.	%	No.	%	No.	%	
Total	232		173	74.6	59	25.4	
Mean age in yrs (± SD)	60 ± 10		59 ± 10		63 ± 11		0.010
Male sex	40	17.2	23	13.3	17	28.8	0.006
Neurological deficit on presentation	32	13.8	13	7.5	19	32.2	0.000
Initial tumor size in cm³ (± SD)	11.5 ± 19.3		6.6 ± 13.0		26.5 ± 27.5		0.000
>8.18 (approximately a 2.5-cm-diameter sphere)	73	31.5	31	17.9	42	71.2	0.000
Tumor location							
Eloquent	133	57.3	92	52.6	42	71.2	0.013
Infratentorial	35	15.1	27	15.6	8	13.6	0.704
Skull base	54	23.3	39	22.5	15	25.4	0.651
Calcification	91 (5*)	40.1	78 (5*)	46.4	13	22.0	0.001
Edema	46	19.8	21	12.1	25	42.4	0.000
Arachnoid plane	96	41.4	80	46.2	16	27.1	0.010
T2W-MRI	(6*)		(5*)		(1*)		
Hyperintense	30	13.3	20	11.9	10	17.2	0.302
Isointense	150	66.4	108	63.1	44	75.9	0.076
Hypointense	46	20.4	42	25.0	4	6.9	0.003
Mean AGR in cm³/yr (± SD)	2.2 ± 4.6		0.4 ± 0.5		7.3 ± 6.0		0.000
Mean RGR in %/yr (± SD)	20.4 ± 38.7		9.7 ± 18.5		50.8 ± 60.3		0.000
Mean tumor doubling time in yrs (± SD)	18.0 ± 35.3		22.8 ± 39.7		3.7 ± 3.4		0.000
Symptom aggravation	40	17.2	11	6.4	29	49.2	
Mean time to start of symptoms in mos (range)	27 (6–86)		34 (6–86)		25 (7–81)		0.000
Therapeutic intervention	48	20.7	20	11.6	28	47.5	0.000
Mean follow-up duration in mos (range)	47 (6–151)		48 (18–151)		35 (7–84)		0.000

* Number of patients with missing data for each variable.

was categorized into either the slow-growth or the rapid-growth group using various standards for the rate of volume increase; rate of volume increase refers to the growth criteria used in previous studies,[6,11,17] such as 1 cm³ per year, 2 cm³ per year, 15% per year, or 33% per year (which approximately corresponds to a 10% increase in length per year). The standard that best showed a sharp contrast between the 2 groups in terms of tumor characteristics and growth patterns was 2 cm³ per year. Only tumors with a growth rate > 2 cm³ per year showed explosive growth in a short time. Since we hoped to design a specific screening tool for tumors requiring early therapeutic intervention, we considered an AGR of ≥ 2 cm³ per year as the criterion defining rapid growth.

Taking the results of previous studies into consideration, we evaluated growth rate with respect to the following clinicoradiological parameters: age, sex, initial tumor size, tumor location, presence of neurological symptoms, calcification, peritumoral edema, arachnoid plane between brain and tumor, and signal intensity (SI) on T2W-MRI. Tumor location was examined with regard to 3 aspects: eloquent versus noneloquent, superficial versus skull base, and supratentorial versus infratentorial. The presence of calcification was evaluated on standard CT. Tumor T2W-MR images were graded as having a hyperintense, isointense, or hypointense signal as compared with gray matter, and the significance of each SI on the growth rate was separately assessed.

Statistical Methods

All analyses were performed with R-3.0.2 statistical software (http://www.r-project.org), with a p value < 0.05 considered to be significant. We used the Pearson chi-square test for categorical variables and the Mann-Whitney U-test (2-tailed) for continuous variables. The growth rate was determined by the linear mixed-effects model as described earlier. All candidate predictors that correlated with rapid tumor growth on univariable logistic regression analysis were factored in the multivariable logistic regression analysis. Predictors of rapid growth rate within the resampled data (number of repetitions = 200), identified on multivariable analysis using a backward step-down variable selection strategy, were included in the logistic regression model with the following equation:

$$\text{Probability (Y)} = \frac{1}{1 + e^{-(b_0 + b_1 \times X_{1i} + b_2 \times X_{2i} + \ldots + bp \times Xpi)}}, \quad \text{[Eq. 2]}$$

where i = 1, . . . n and p = number of covariates. The coefficient of each parameter was determined by fitting the logistic regression model to the observed data. To develop

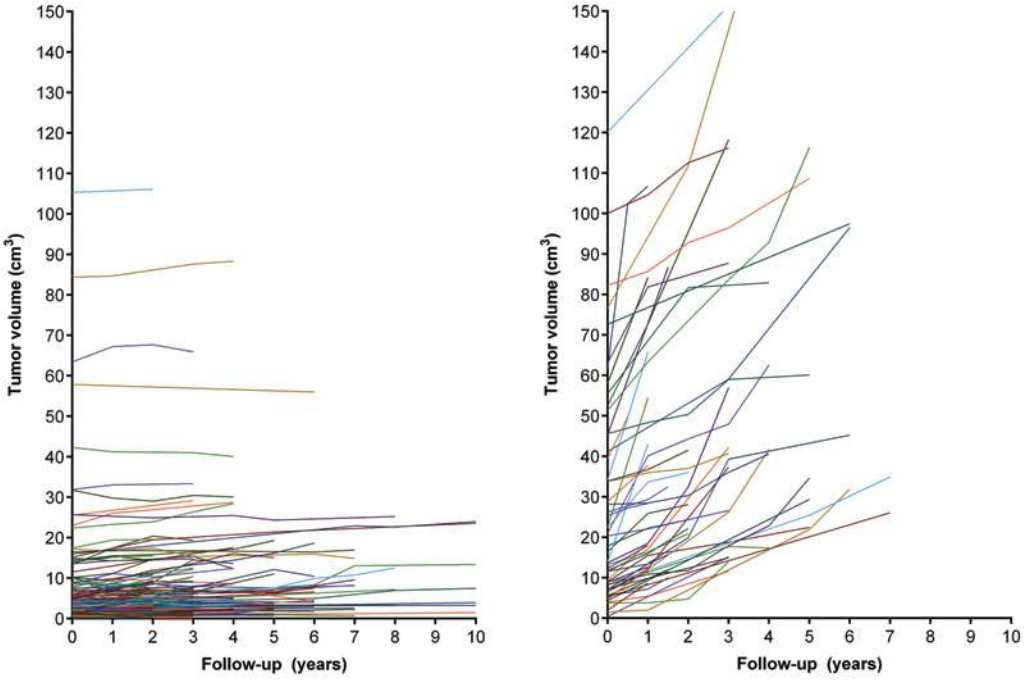

FIG. 1. Spaghetti plots of tumor volume versus time in the slow-growth (**left**) and rapid-growth (**right**) groups. The growth features of the rapid-growth group are in sharp contrast to those of the slow-growth group. Tumors in the rapid-growth group show explosive growth with a mean AGR of 7.3 cm^3 per year, whereas most tumors in the slow-growth group are stationary with a mean AGR of 0.4 cm^3 per year. Figure is available in color online only.

a scoring system, which was named the Asan Intracranial Meningioma Scoring System (AIMSS), with selected variables, the smallest coefficient value (b1) in the logistic regression model was modified to 1 in the scoring system, and then coefficient values for the other variables were proportionally converted to the nearest integer. The probability (P) of rapid tumor growth at each score was estimated with the following formula:[14]

$$P_{\text{rapid tumor growth}}(\%) = \left[\frac{1}{1+e^{-(\text{intercept}+b1\times\text{total score})}}\right]\times 100(\%). \quad \text{[Eq. 3]}$$

The calibration ability of our scoring system was analyzed using the Hosmer-Lemeshow goodness-of-fit test. Intraclass correlation was estimated between the logistic regression model and the scoring system. The area under the receiver operating characteristic curve (AUC) was estimated for both the logistic regression model and the scoring system. All internal validations were performed using 1000 bootstrap samples to estimate the bias-corrected concordance index for describing the predictive accuracy of the model.

External Validation

To validate the generalizability of our scoring system, an additional 50 patients with IMs who qualified for the study under our inclusion and exclusion criteria were analyzed using the AIMSS. The patients were randomly selected from among those who underwent conservative management for IMs by another author (S.H.H.).

Results

Growth Rates and Patterns of IMs

For the entire study cohort of 232 patients, growth patterns were statistically fitted to a straight line with a mean slope of 2.2 cm^3 per year. According to the definition, 25.4% of tumors (n = 59) belonged to the rapid-growth group (≥ 2 cm^3/year) and the remainder belonged to the slow-growth group. The demographic characteristics for the entire cohort disaggregated by study group are summarized in Table 1. The growth characteristics for IMs in the 2 groups were distinctly different from each other. The AGRs of the slow-growth and rapid-growth groups were 0.4 ± 0.5 and 7.3 ± 6.0 cm^3 per year, respectively. Most tumors (67.1%, n = 116) in the slow-growth group showed linear growth, although the remainder were static with an AGR of < 0.1 cm^3 per year. Most tumors (67.8%, n = 40) in the rapid-growth group also showed linear growth. However, 22.0% (n = 13) of the tumors showed exponential growth, whereas 6 tumors initially showed linear or exponential growth and eventually reached a plateau during the follow-up period (Fig. 1). To determine the relationship between tumor size and growth rate, the diameter of each tumor was inversely calculated from the tumor volume based on the assumption that the tumors were perfect spheres. The imaginary diameter ranged from 0.7 to 6.1 cm (mean 2.3 cm, median 3.5 cm); the relationship between tumor diameter and growth rate is presented in Fig. 2. In the rapid-growth group, the AGRs increased in proportion to the diameter with a mean slope of 2.8 cm^3 per year per diameter (cm), whereas those in the slow-growth group were almost stationary, regardless of the diameter

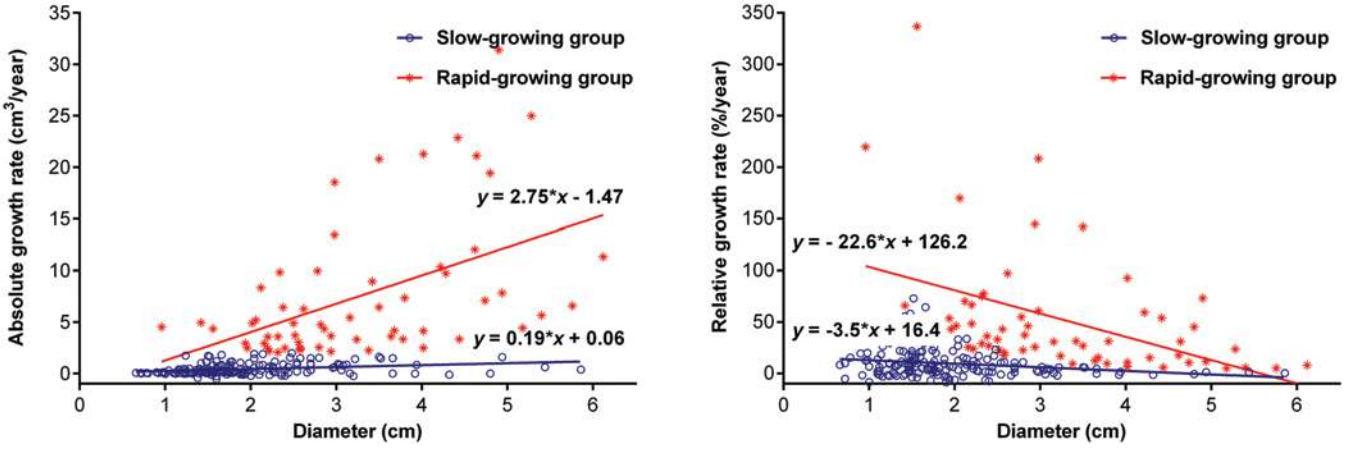

FIG. 2. Tumor growth rates disaggregated by tumor diameter in the slow-growth and rapid-growth groups. In the rapid-growth group, AGR shows a linear increase, and RGR decreases with respect to increasing tumor diameter. However, the AGR and RGR for the slow-growth group are almost static, regardless of any diameter change. This implies that the growth potentials of the 2 groups are quite different. Figure is available in color online only.

increase. A negative correlation between the RGR and diameter was observed in both the groups.

Clinicoradiological Correlates of Rapid Tumor Growth

On univariable analysis using a logistic regression model, old age ($p = 0.002$), male sex ($p = 0.002$), neurological deficit at presentation ($p < 0.001$), larger tumor ($p < 0.001$), tumor location in eloquent region ($p = 0.008$), absence of calcification ($p = 0.011$), peritumoral edema ($p < 0.001$), and hyperintense or isointense signal on T2W-MRI ($p = 0.005$) were associated with rapid tumor growth. However, on multivariable analysis, larger tumor (OR per cm^3 1.07, 95% CI 1.04–1.10, $p = 0.000$), absence of calcification (OR 3.87, 95% CI 1.54–9.74, $p = 0.004$), peritumoral edema (OR 2.74, 95% CI 1.14–6.59, $p = 0.025$), and hyperintense or isointense signal on T2W-MRI (OR 3.76, 95% CI 1.01–14.07, $p = 0.049$) were the only independent predictors of rapid tumor growth. An increase in tumor volume by 10 cm^3 was associated with an approximately 2-fold increase in the risk for rapid tumor growth (approximately 1.07[10]).

AIMSS Estimation of Risk of Rapid Tumor Growth

Tumor size, calcification, peritumoral edema, and SI on T2W-MRI were included as parameters in AIMSS. Data pertaining to 221 patients were used for developing the scoring system. Tumor size was presented as a diameter that was calculated from the respective volumes and then initially categorized into 6 groups at intervals of 0.5–1 cm from 2.5 cm; calcification and peritumoral edema were categorized into 2 groups according to whether the parameter was present or absent; and SI on T2W-MRI was categorized into 2 groups of hypointense and hyper-/isointense signals. However, when the data were fitted to the logistic regression model using the above categories, the coefficient values (or influential weight) of some neighboring categories for tumor size were found to be similar. Thus, the tumor size was recategorized into 3 groups that exhibited distinctly different coefficient values (≤ 2.5 cm, > 2.5 cm to ≤ 4 cm, and > 4 cm). Then, the fitting process was repeated and the final model presented (Table 2). The coefficient value of peritumoral edema (0.67) was modified to 1 in the scoring system, and the values of the other parameters were proportionally converted to the nearest integer. The total score ranged from 1 to 11, and the probability (P) of rapid tumor growth at each score was estimated using the following formula (Table 3):

$$P_{\text{rapid tumor growth}}(\%) = \left[\frac{1}{1+e^{-(\text{intercept}+0.67\times\text{total score})}}\right]\times 100(\%). \quad \text{[Eq. 4]}$$

According to the scoring system, the risk of rapid tumor growth (≥ 2 cm^3/year) was < 10% with a score of 0–2, 10%–50% with a score of 3–6, and > 50% or more with a score of 7–11. The estimated risk and the observed values for each score were almost analogous ($R^2 = 0.463$, Hosmer-Lemeshow goodness-of-fit, $p = 0.9958$). The scoring system reflected well the logistic regression model (95% CI for the intraclass correlation 0.998–0.999), and both had good predictive power. The AUCs of the logistic regression model and scoring system were 0.86 (95% CI 0.81–0.92) and 0.86 (95% CI 0.80–0.91), respectively.

Generalizability of the Scoring System

To assess the generalizability of our scoring system, external validation was performed using an additional data set of 50 patients (Supplementary Table 1). The observed values of rapid tumor growth at each score were comparable to the values estimated by the scoring system (Table 4). The AUC of the scoring system was 0.87 (95% CI 0.76–0.99).

Discussion

Natural History of IMs

Several authors have studied the natural history of IMs; the reported annual tumor growth rates have ranged from 0.01 to 1.15 cm in length[14,18] and from 0.01 to 10.3 cm^3 in volume (Table 5).[4,5,11,16] However, most of these were

TABLE 2. Coefficient (b) of each parameter as estimated using multinominal logistic regression and its conversion to a score in the AIMSS

Parameter	b (SE)*	p Value	OR	95% CI	Score
Intercept	−4.14 (0.69)	<0.0001			
Tumor diameter (cm)†					
≤2.5 (approximately 8.18 cm^3)	0				0
>2.5 to ≤4.0	2.10 (0.46)	<0.0001	8.18	3.32–20.19	3
>4.0 (approximately 33.49 cm^3)	3.91 (0.73)	<0.0001	50.31	11.96–211.66	6
Calcification					
Present	0				0
Absent	1.45 (0.50)	0.004	4.27	1.61–11.35	2
Peritumoral edema					
Present	0.67 (0.47)	0.155	1.96	0.78–4.93	1
Absent	0				0
SI on T2W-MRI					
Hypointense	0				0
Hyper- or isointense	1.07 (0.64)	0.095	2.90	0.83–10.15	2

SE = standard error.
* Coefficient (b) is equal to each parameter's influential weight.
† Tumor diameter is inversely calculated from the volume based on the assumption that the tumors are perfect spheres.

small-scale studies with < 70 patients,[4,5,8,11,13,14,19] and some included only small- to medium-sized tumors.[4,11] Several studies defined significant tumor growth based on a change in tumor diameter, even though this method is less sensitive than evaluating a change in volume and is inappropriate for irregularly shaped tumors.[8,13,14,18] Moreover, most studies did not take into account the time frame of tumor growth. For instance, an increase of 2 mm in length over 10 years was treated the same as a 2-mm increase over 1 year.[5,8,13,14,16,18] Although some studies have analyzed tumor growth rate, it was calculated using only the initial and last values, which assumes linear tumor growth.[4,11,16,19] However, such an approach may not represent the growth potential of tumors and may have misled the analysis of risk factors associated with tumor growth.

To overcome the shortcomings of these previous studies, we studied the natural history of IMs in a large cohort encompassing various-sized tumors (0.2–120.1 cm^3) by using volumetric assessment. Tumor volume was determined during every imaging examination, and the tumor growth rate was estimated using regression analysis so that all observed values were reflected in the outcome. Although the mean AGR (2.2 cm^3/year) in the current study was considerably higher than that reported in previous studies, the difference is likely attributable to the presence of several patients (10.8%) with large-sized tumors (≥ 30 cm^3) and of some (5.2%) extremely rapidly grow-

TABLE 3. Probability of rapid tumor growth, as estimated by the AIMSS and compared with the observed value

Score	Estimated Risk (%)	Observed Risk (%)* n = 221	Risk Group
0	2	0 (0/17)	Low (<10%)
1	3	0 (0/3)	
2	6	6 (3/53)	
3	11	0 (0/4)	Intermediate (10%–50%)
4	19	15 (11/72)	
5	31	31 (3/16)	
6	47	50 (3/6)	
7	64	60 (12/20)	High (>50%)
8	77	69 (9/13)	
9	87	86 (6/7)	
10	93	80 (4/5)	
11	96	100 (5/5)	

Hosmer-Lemeshow goodness-of-fit, p = 0.9958.
* Value represented as % observed risk (no. of patients with rapid growth tumors/no. of patients at each score).

TABLE 4. External validation of scoring system using data from 50 additional patients

Score	Estimated Risk (%)	Observed Value (%)*	Risk Group
0	2	0 (0/4)	Low (<10%)
1	3	0 (0/0)	
2	6	0 (0/12)	
3	11	100 (1/1)	Intermediate (10%–50%)
4	19	19 (4/21)	
5	31	33 (1/3)	
6	47	50 (1/2)	
7	64	100 (2/2)	High (>50%)
8	77	100 (3/3)	
9	87	0 (0/0)	
10	93	100 (1/1)	
11	96	100 (1/1)	

* Value represented as % observed risk (no. of patients with rapid growth tumors/no. of patients at each score).

TABLE 5. Natural history of IMs in the literature

Authors & Year	No. of Patients	Mean FU in Mos (range)	Mean Tumor Size (range)	Method of Tumor Size Measurement	Mean GR (range)		Definition of Significant Growth (% tumors)	Factors Associated w/ Rapid Growth	Factors Associated w/ Slow Growth	Failure Rate
					Absolute	Relative				
Firsching et al., 1990	17	25 (2–89)	4.8 cm^3 (0.1–35.5)	Vol	0.12 cm^3/yr (0.01–0.65)	3.6%/yr (0.5–21)		None	None	0
Olivero et al., 1995	45	32 (3–180)	2.2 cm (0.5–5.0)	Lng	0.24 cm/yr (0.01–1.0)	NA	Any Lng Δ (22%)	NA	NA	0
Niiro et al., 2000	40	38 (6–97)	2.6 cm (1.0–6.0)	Lng	NA	NA	Any Lng Δ (35%)	Size >3 cm, hyperintensity on T2W-MRI, male sex	Calcification	12.5%
Nakamura et al., 2003	41	43 (6–105)	9 cm^3 (0.1–29.3)	Vol	0.80 cm^3/yr (0.03–2.62)	15%/yr (0.5–73)	Vol Δ >1 cm^3/yr (34%)	Young age	Calcification, hypointensity or isointensity on T2W-MRI	12.8%
Yano & Kuratsu, 2006	67	(60–163)	2.3 cm (0.5–6.0)	Lng	0.19 cm/yr (0.04–1.15)	NA	Any Lng Δ (37%)	Hyperintensity on T2W-MRI	Calcification	NA
Hashiba et al., 2009	70	39 (12–123)	10 cm^3 (0.6–6.9)	Vol	(0.0–10.3) cm^3/yr	0%–93%/yr	Vol Δ >15% (63%)	PTE ∝ exp growth	Calcification	4.2%
Sughrue et al., 2010	357	55	≤2.5 cm in 58% of patients	Lng	NA	NA	Lng Δ >10%/yr (24%)	Hyperintensity on T2W-MRI	NA	NA
Oya et al., 2011	273	46 (Lng), 43 (vol)	2.0 cm (0.4–7.0)	Lng in 44%, vol in 56%	0.68 cm^3/yr, (0.03–4.09)	NA	Lng Δ ≥2 mm (44%), vol Δ >8.2% (74%)	Young age ≤60 yrs, hyperintensity on T2W-MRI, PTE, size >2.5 cm	Calcification	26.4%
Jadid et al., 2015	65	74 (6–240)	2.4 cm (0.6–7.0)	Lng	NA	NA	Lng Δ >2 mm (35%)	None	Calcification	27.7%

Exp = exponential; FU = follow-up; GR = growth rate; Lng = length; NA = non-applicable; PTE = peritumoral edema; vol = volume; Δ = increment; ∝ = correlation.

ing tumors (≥ 10 cm^3/year). When separate analyses were performed for the slow-growth and rapid-growth groups based on the 2-cm^3/year cutoff, the growth feature of tumors in the slow-growth group was similar to that reported in the literature. Tumors in the slow-growth group were either static or grew in a linear pattern with a mean AGR of 0.4 cm^3 per year. On the other hand, the mean AGR of tumors in the rapid-growth group was 7.3 cm^3 per year. Despite such explosive growth, most tumors in the rapid-growth group exhibited a linear growth pattern, and only some tumors showed exponential growth. It is conceivable that some tumors with a linear growth pattern actually had an exponential growth rate. This assumption is likely to be true for tumors that were treated immediately after the first follow-up examination, owing to the evidence of explosive growth. Shorter intervals between follow-up imaging studies may have identified an exponential growth rate more often.

Clinicoradiological Factors Associated With the Growth Potential of Meningiomas

Various clinicoradiological factors have been reported to be associated with tumor growth. Although age was not a significant factor in our study, a younger age has been shown to be associated with higher growth potential.[11,16,19] However, in a study of elderly patients (age > 70 years), as many as 35% of patients experienced significant tumor growth and 12.5% of patients became symptomatic.[13] Therefore, a definitive association between age and tumor growth is yet to be determined. Several authors reported that larger tumors have a higher risk of growth than small tumors,[13,16,19] which is consistent with our findings. Tumors located distally to the skull base tend to have a much higher growth potential than those within the skull base.[7,9,10] However, some authors have reported the opposite.[1] We did not observe a correlation between tumor location and growth potential. A number of radiological features have been consistently linked to growth potential: peritumoral edema[5,16] and hyperintense signal on T2W-MRI[13,16–18] have been associated with rapid tumor growth, whereas the presence of calcification[5,8,11,13,16,18] and hypointense signal on T2W-MRI[11] tend to be associated with low growth potential. These results are supported by pathological examination, which showed a direct correlation between the radiological features and the MIB-1 labeling index (cell proliferation marker).[12] Peritumoral edema was strongly related to a higher MIB-1 labeling index, whereas hypointense signal and calcification were significantly associated with a lower MIB-1 labeling index. In the current study, peritumoral edema was a risk factor for significant tumor growth, whereas calcification was associated with a low risk of tumor growth, which is consistent with earlier reports. Hypointensity of the tumor suggested little potential for growth as a distinct predictor from the presence of calcification, whereas hyperintensity and isointensity indicated considerable potential for growth over the next few years.

A Cutoff Point of 2 cm^3 per Year as a Standard for Rapid Growth

The cutoff growth rate of 2 cm^3 per year used for risk factor analysis and subsequent development of the scoring system is a relatively high standard for significant tumor growth compared with those used in previous studies, i.e., 1 cm^3 per year, 15% per year, and 33% per year increase in volume (which is equivalent to a 10% per year increase in length).[6,11,17] Establishing a standard for rapid growth may be a little subjective; however, we defined a volume increase ≥ 2 cm^3 per year as the standard for rapid tumor growth for the following reasons. First, we perceived that all IMs could be divided into 2 groups with distinctly different growth potential (Fig. 1), namely a slow- and linear-growth group and a rapid- and exponential-growth group. Our aim was to develop a screening tool to identify tumors at high risk for explosive growth; therefore, we established a rather high cutoff for rapid growth. Second, 2 cm^3 per year was initially considered a candidate for the cutoff point because it was close to the mean growth rate in our cohort, which included patients with a wide range of tumors. Later, our statistical analysis using various cutoff points (1 cm^3/year, 2 cm^3/year, 15%/year, and 33%/year) demonstrated that 2 cm^3 per year was the standard that best showed a sharp contrast between slow-growth and rapid-growth groups in terms of tumor characteristics and growth patterns. Lastly, all tumors with a growth rate < 2 cm^3 per year showed nonthreatening linear growth in our series. Thus, these tumors certainly do not require early therapeutic intervention. For these reasons, we determined 2 cm^3 per year to be the standard cutoff point when screening tumors at risk for significant growth. Nevertheless, if the goal is to select tumors with growth potential, future studies may choose to estimate risk based on a lower cutoff to yield higher sensitivity.

Clinical Significance and Application of the AIMSS

Previous studies on the natural history of IMs sought to identify factors associated with tumor growth; however, none of them addressed the issue of relative weights for various risk factors on tumor growth. With this issue in mind, we designed a novel scoring system that estimates the overall risk for rapid IM growth based on the patient's clinicoradiological characteristics. Hashiba et al.[6] developed a scoring system based on 3 parameters: peritumoral edema, loss of arachnoid plane, and irregular tumor shape. The total score ranged from 0 to 3. However, all parameters were allotted the same weight (score of 1). Moreover, the risk of tumor growth at each score was presented as the value of the MIB-1 labeling index, which is not an intuitive way to explain the risk for both primary care clinicians and patients. Therefore, our scoring system awards a weight to each parameter and estimates the specific probability of a tumor growth rate ≥ 2 cm^3 per year using a statistical model. The good predictive power of the AIMSS was verified by internal and external validation; thus, it may be a useful tool to assess the need for early treatment based on the risk to the patient.

Nonetheless, because the weight of a larger tumor was exceptionally high in the AIMSS and the obtainable score ranges differed according to the tumor size group, the risk for small-sized to medium-sized tumors can be underestimated when the cutoff value for early treatment is fixed to only 1 score. To avoid this, we separately assessed the

sensitivity and specificity of the score for each tumor size group (Supplementary Table 2). Based on our analysis, we suggest that the following scores indicate the need for early treatment: score ≥ 4 for tumors ≤ 2.5 cm (approximate volume of 8.18 cm^3), score ≥ 6 for tumors between > 2.5 cm and ≤ 4.0 cm, and a score ≥ 8 for tumors > 4.0 cm in diameter (approximate volume of 33.49 cm^3; Fig. 3). If patients who are deemed to require early treatment are reluctant to undergo treatment, we recommend close follow-up.

Study Limitations

The current study is a retrospective analysis of patients with untreated IMs from a single institute—a major medical center in Korea where the patients at high risk tend to be concentrated. This study enrolled many patients with large-sized IMs who were obliged to undergo follow-up because of comorbidity and poor performance status; thus, they may not be representative of the population at large. A prospective large-scale study needs to be performed with long-term follow-up for improved understanding of the natural history of IMs. Moreover, a risk estimation based on quantitative analysis of radiological parameters would enable much better prediction. Lastly, incorporating tumor shape, which has been identified as another risk factor in the literature, as a parameter in the scoring system would permit more exact estimation.

Conclusions

The risk factors for rapid growth of IMs are a larger tumor size, peritumoral edema, absence of calcification, and hyperintense or isointense signal on T2W-MRI. A scoring system that integrates the relative weights of these risk factors provides a better estimate of the overall risk of rapid tumor growth with good predictive power. Our scoring system will help clinicians to screen patients with IMs who may require early treatment and thus facilitate optimal and timely treatment in these patients.

Acknowledgments

We gratefully acknowledge technical support from the Biomedical Imaging Infrastructure, Department of Radiology, and statistical support from the Department of Clinical Epidemiology and Biostatics (Seunghee Baek, PhD), Asan Medical Center, Seoul, Korea.

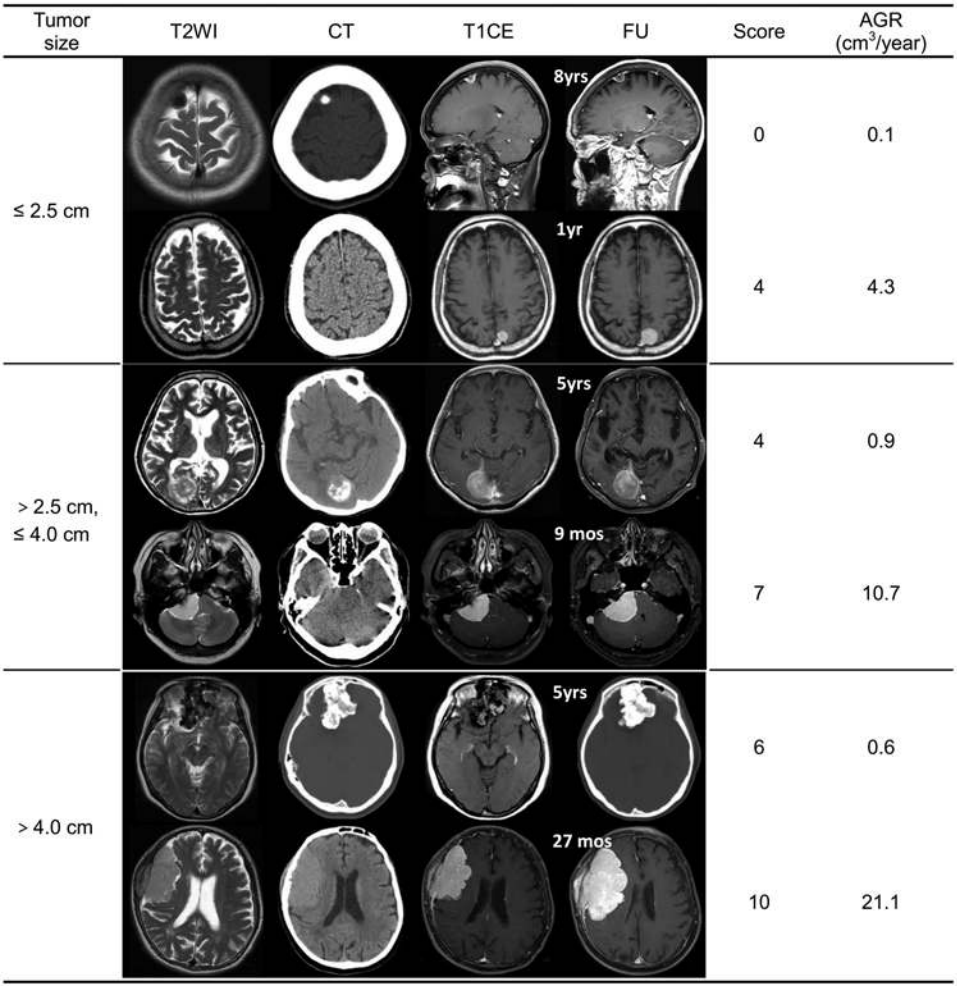

FIG. 3. Clinical application of the scoring system is presented according to tumor size. The *upper row* of images in each group shows a patient at low risk for rapid tumor growth, and the lower row of images shows a patient at high risk. FU = follow-up duration; T1CE = T1-weighted contrast-enhanced image.

References

1. Aguiar PH, Tsanaclis AM, Tella OI Jr, Plese JP: Proliferation rate of intracranial meningiomas as defined by the monoclonal antibody MIB-1: correlation with peritumoural oedema and other clinicoradiological and histological characteristics. **Neurosurg Rev 26:**221–228, 2003
2. Claus EB, Bondy ML, Schildkraut JM, Wiemels JL, Wrensch M, Black PM: Epidemiology of intracranial meningioma. **Neurosurgery 57:**1088–1095, 2005
3. Fathi AR, Roelcke U: Meningioma. **Curr Neurol Neurosci Rep 13:**337, 2013
4. Firsching RP, Fischer A, Peters R, Thun F, Klug N: Growth rate of incidental meningiomas. **J Neurosurg 73:**545–547, 1990
5. Hashiba T, Hashimoto N, Izumoto S, Suzuki T, Kagawa N, Maruno M, et al: Serial volumetric assessment of the natural history and growth pattern of incidentally discovered meningiomas. **J Neurosurg 110:**675–684, 2009
6. Hashiba T, Hashimoto N, Maruno M, Izumoto S, Suzuki T, Kagawa N, et al: Scoring radiologic characteristics to predict proliferative potential in meningiomas. **Brain Tumor Pathol 23:**49–54, 2006
7. Hashimoto N, Rabo CS, Okita Y, Kinoshita M, Kagawa N, Fujimoto Y, et al: Slower growth of skull base meningiomas compared with non-skull base meningiomas based on volumetric and biological studies. **J Neurosurg 116:**574–580, 2012
8. Jadid KD, Feychting M, Höijer J, Hylin S, Kihlström L, Mathiesen T: Long-term follow-up of incidentally discovered meningiomas. **Acta Neurochir (Wien) 157:**225–230, 2015
9. Kasuya H, Kubo O, Tanaka M, Amano K, Kato K, Hori T: Clinical and radiological features related to the growth potential of meningioma. **Neurosurg Rev 29:**293–297, 2006
10. McGovern SL, Aldape KD, Munsell MF, Mahajan A, DeMonte F, Woo SY: A comparison of World Health Organization tumor grades at recurrence in patients with non-skull base and skull base meningiomas. **J Neurosurg 112:**925–933, 2010
11. Nakamura M, Roser F, Michel J, Jacobs C, Samii M: The natural history of incidental meningiomas. **Neurosurgery 53:**62–71, 2003
12. Nakasu S, Nakajima M, Matsumura K, Nakasu Y, Handa J: Meningioma: proliferating potential and clinicoradiological features. **Neurosurgery 37:**1049–1055, 1999
13. Niiro M, Yatsushiro K, Nakamura K, Kawahara Y, Kuratsu J: Natural history of elderly patients with asymptomatic meningiomas. **J Neurol Neurosurg Psychiatry 68:**25–28, 2000
14. Olivero WC, Lister JR, Elwood PW: The natural history and growth rate of asymptomatic meningiomas: a review of 60 patients. **J Neurosurg 83:**222–224, 1995
15. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al: CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008–2012. **Neuro Oncol 17 (Suppl 4):**iv1–iv62, 2015
16. Oya S, Kim SH, Sade B, Lee JH: The natural history of intracranial meningiomas. **J Neurosurg 114:**1250–1256, 2011
17. Sughrue ME, Rutkowski MJ, Aranda D, Barani IJ, McDermott MW, Parsa AT: Treatment decision making based on the published natural history and growth rate of small meningiomas. **J Neurosurg 113:**1036–1042, 2010
18. Yano S, Kuratsu J: Indications for surgery in patients with asymptomatic meningiomas based on an extensive experience. **J Neurosurg 105:**538–543, 2006
19. Yoneoka Y, Fujii Y, Tanaka R: Growth of incidental meningiomas. **Acta Neurochir (Wien) 142:**507–511, 2000

Disclosures

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

Conception and design: EJ Lee, Park. Acquisition of data: JK Lee. Analysis and interpretation of data: EJ Lee, YH Kim, Cho. Drafting the article: EJ Lee. Critically revising the article: JH Kim, EJ Lee, Park, YH Kim. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: JH Kim. Statistical analysis: EJ Lee. Administrative/technical/material support: JH Kim, Hong. Study supervision: JH Kim, CJ Kim.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables 1 and 2. https://thejns.org/doi/suppl/10.3171/2016.9.JNS161669.

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