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ORIGINAL ARTICLE - BRAIN TUMORS

Growth prediction in asymptomatic meningiomas: the utility of the AIMSS score

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Abstract

Background Management of asymptomatic meningiomas represents a challenge due to the absence of a solid consensus on which is the best management strategy. There are various known factors predicting meningiomas growth risk. However, the Asian Intracranial Meningioma Scoring System (AIMSS) is the only described score to quantify such risk thus emerging as a potential tool for management decisions. This study aims to validate this score on our series of asymptomatic meningiomas.

Method We performed a retrospective review of asymptomatic meningiomas diagnosed at our institution between January 2008 and October 2016 and followed by an annual cerebral Magnetic Resonance Imaging (MRI). For each lesion, the AIMSS score was calculated thus classifying them in low (0–2), intermediate (3–6) or high risk (7–11) of rapid growth (>2cm^3/year). We investigated the correlation between the expected Average Growth Rate (AGR) according to the score and the one obtained in our study. The mean growth velocity over the different risk groups was also compared.

Results Overall, 69 asymptomatic meningiomas found incidentally in 46 patients were included in the study; 31 were assigned to the low-risk group, 34 to the intermediate-risk group and 4 to the high-risk group. Attending to the AGR, 0% showed rapid growth in the low-risk group, 12% in the intermediate-risk group, and 25% in the high-risk group. The mean growth velocity showed a significant difference over the different risk groups ($p < 0{,}001$).

Conclusions According to our finding, the AIMSS score is a valid tool to estimate the risk of rapid growth of asymptomatic meningiomas. It is especially useful distinguishing between low- and intermediate-risk meningiomas. This feature would allow physicians to adjust the periodicity of radiological and clinical controls. Adding more known risk factors of rapid growth to the score might improve its predictive capabilities with the high-risk group.

Keywords Growth risk · Asymptomatic meningioma · AIMSS score · Risk of rapid growth · Average growth rate

Background

Meningiomas are the most common central nervous system tumors in adults, accounting for 35% of the total primary brain tumors [3, 6, 11, 18]. It is recommended to treat them when they produce symptoms clearly attributed to their location. Surgical removal is the main treatment option, with radiotherapy or radiosurgery usually being reserved for lesions difficult to access, patients medically not fit for surgical resection, or lesions not completely removed with surgery [1, 5].

However, the management strategy for these tumors becomes less clear when they do not produce symptoms and have been diagnosed by chance. According to autopsy studies, around 2–3% of the population may harbor one of these so-called incidental meningiomas [11]. Over the past decades, the increasing widely available access to image diagnostic studies and the raising age of the population have translated into a growing number of asymptomatic meningiomas being diagnosed incidentally [1, 13, 24]. As stated by Islim et al., incidental discovery accounts for 30% of newly diagnosed intracranial meningiomas [8].

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Most of these incidental meningiomas, especially those smaller than 25 mm in diameter, are thought to grow quite slowly or show no growth over the 5-year period following their discovery and only a small proportion of them (around 3–6%) later become symptomatic over the follow-up period [5, 14, 23]. However, some clinical series show a greater proportion of meningiomas presenting growth or developing relevant symptoms. A meta-analysis by Islim et al. reported growth in around 25% of incidental meningiomas [8]. Jadid et al., on the other hand, extrapolated data from Kaplan-Meyer analyses of their series and assuming a uniform progression rate maintained that the proportion of meningiomas presenting growth after 15 years of follow-up can reach up to 75% [9]. However, Nakasu et al. stated that the growing pattern of meningiomas fits an S-shaped curve rather than a linear model, which contradicts the assumption that the progression rate is uniform and does not decrease [12]. Accordingly, most symptomatic meningiomas would be diagnosed on the rise phase of the curve. In this stage, the decompensation of the intracranial pressure and the acute compression of the surrounding brain caused by the rapid growth could be the cause of symptoms appearance. Therefore, when diagnosing an asymptomatic meningioma, it would be key to establish in which supposed phase of the growing sigmoid curve is located. A small-size asymptomatic meningioma is likely could either be in the static initial phase or in the static later phase. Both would imply a short-term low risk of rapid growth but the follow-up strategy should differ from one another since, in a midterm future, the first one can easily enter into the rise phase and present a rapid growth.

The aforementioned variability among different studies could also be partially explained by a lack of standardized definition of significant growth. Furthermore, the best size parameter for the follow-up of these lesions is still a matter of debate. There is a general acceptance about volume being a more precise marker than the largest diameter. It is also widely believed that the follow-up time must be taken into account to increase precision. Moreover, relative growth might be more appropriate than absolute growth based on the oncological concept of "doubling time," but many of the available literature focuses on absolute growth (AGR) considering it a more clinically relevant measure of incidental meningioma growth. The fact that the likeliness of a lesion to become symptomatic and end up requiring treatment is more related with absolute growth than with relative growth might explain this preference [8].

Considering all the above controversy, the decision-making about the best management strategy might result more challenging in asymptomatic meningiomas than with their symptomatic counterparts. Some authors support a conservative management option where treatment is offered whenever there is a significant growth on serial imaging studies or new neurological symptoms are noticed on clinical follow-up [12]. Other authors, on the other hand, favor active treatment based on the estimated probability of the tumor presenting significant growth in the future and/or its likely ease to produce symptoms or complications in case that growth would take place [22]. Several predictive factors such as age (< 60 years old), gender (male), large tumor size, absence of calcifications, peritumoral edema, hyperintensity on T2 MRI, non-skull base location, and irregular tumor morphology have been related to size progression of asymptomatic meningiomas [1, 5, 8, 10, 12, 15, 19, 24]. However, neither the conservative management option nor the active treatment one based on predictive factors of growth and/or symptom development is yet clearly standardized among treating physicians [8]. This situation may lead to some controversies in daily clinical practice. For example, the optimal time interval between radiological controls when a conservative strategy is chosen is not well established [10]. Moreover, most authors agree that large size and important growth are indications for treatment but, as aforementioned, neither of these conditions is uniformly defined, with various criteria among different studies [7, 17, 19, 20, 22]. Furthermore, not all the lesions that show growth necessarily end up producing relevant symptoms, which is nowadays the only firm indication to treat such lesions [8].

Recently, in an attempt to unify all these criteria, Lee et al. published the Asian Intracranial Meningioma Scoring System (AIMSS) with the aim to estimate the risk of rapid growth of a given intracranial asymptomatic meningioma. This score evaluates volume, calcifications, peritumoral edema, and intensity on T2-MRI and classifies meningiomas as low, intermediate, or high risk of rapid growth. However, the authors already pointed out the possible lack of external validity due to a great number of enrolled patients with large lesions who required a follow-up strategy due to their suboptimal medical condition for surgical removal [11]. Furthermore, apart from the original series, few authors have tried to validate the findings and accuracy of the score [12, 16]. Our study aims to provide such external validation and evaluate the potential usefulness of the AIMSS score in the daily practice with asymptomatic meningiomas in a standard neurosurgical unit without the limitations of the more specific population described by Lee et al. We also seek to investigate the correlation between the AIMSS score, its defined groups, and the risk of rapid tumor progression in terms of absolute growth rate (AGR) with the aim to identify the subgroup of lesions that might benefit the most from the application of this scale The risk factors of rapid tumor growth included in the AIMSS score are also thoroughly reviewed in order to identify the most useful ones.

Methods

A retrospective analysis of all patients diagnosed at our institution of asymptomatic meningioma from January 2008 to

October 2016 was performed. Clinical and radiological follow-up was conducted since diagnosis until active treatment or until October 2018 if no treatment was required before. Active treatment was offered whenever new symptoms clearly attributable to the meningioma appeared or whenever a significant growth was detected on imaging studies at any time during the follow-up period. A significant growth was defined by an increase in the diameter of at least 5 mm between radiological controls.

Radiological follow-up was performed with an initial brain magnetic resonance imaging (MRI), followed by MRI at 6 months and then a new MRI every year. Standard MRI for our series included sequences weighted on T1, T1 after gadolinium administration, T2, and T2 FLAIR. A non-contrast head CT scan was also performed within the first year after diagnosis in those cases where the CT scan was not the initial diagnostic imaging study.

Patients followed less than 2 years without significant growth, those in which MRI and/or CT scan could not be performed, those who had previously received radiotherapy, and those harboring a NF-2 mutation were excluded from the analysis.

For every meningioma, the AIMSS score was calculated considering the four radiological parameters originally described by the authors [9]: tumor diameter, presence or absence of calcifications, presence or absence of peritumoral edema, and lesion's signal on T2W-MRI compared with normal brain, defined as iso/hyperintense or hypointense. The diameter was calculated in centimeters based on the volume's measurement assuming that meningiomas are perfect spheres. The volume was measured by manual segmentation on T1W-MRI post-Gadolinium sequence using Iplannet (Iplan 3.0 cranial planning software, Brainlab AG, Munich, Germany). The presence of calcifications was determined on the CT scan and classified dichotomically as present or absent. The presence of peritumoral edema (present/absent) was evaluated on T2W FLAIR MRI and the intensity signal on T2 (hypo/iso-hyperintense) was determined on plain T2W-MRI. Considering the resulting overall AIMSS score, each meningioma was classified as either low risk (scores 0–2; < 0% estimated risk of rapid growth), intermediate risk (scores 3–6; 10–50% estimated risk of rapid growth), or high risk (scores 7–11; > 50% estimated risk of rapid growth). Next, considering the volume measured on the first and last available MRI, the total growth in cm^3 of every lesion and the absolute growth rate (AGR) in cm^3/year during its follow-up period were calculated. All these measurements were made by a single author (FBB).

Then, for each previously defined risk group, the percentage of meningiomas with rapid growth (defined as > 2 cm^3/year) and the mean AGR was calculated. Due to the non-normal distribution of the variables (determined by the Kolmogorov-Smirnoff), the non-parametric statistic Kruskal-Wallis test was used for comparisons. Statistical significant difference was defined as $p < 0.05$.

Results

Overall, sixty-nine asymptomatic meningiomas found incidentally in forty-six patients (36 women, 10 men) were included in the study. Mean age at diagnosis was 59, ranging from 38 to 81 years old. Thirty-three of these meningiomas (48%) were found in patients with multiple lesions. The follow-up time period ranged from 2 to 10 years. The volume of the lesions at the beginning of the follow-up comprised between 0.1 cm^3 and 15.4 cm^3 (Fig. 1). From the sixty-nine meningiomas included, twenty-five (36%) presented calcifications, six (9%) presented peritumoral edema, and forty-one (60%) presented iso- or hyperintensity on T2-MR compared with normal surrounding brain at the time of diagnosis (Fig. 2; Table 1). Attending to their location, twenty-four of these meningiomas (35%) were found in the skull base, while the rest of them were found in other non–skull base locations, such as convexity, falx cerebri, sagittal sinus, or ventricles.

According to their AIMSS score, thirty-one meningiomas (45%) were classified as low risk, thirty-four (49%) were assigned to the intermediate-risk group, and only four lesions (6%) were considered as high risk. The mean age at diagnosis was 58 years at the low-risk group, 60 years at the intermediate-risk group, and 64 years at the high-risk group, with no statistical differences between them ($p = 0.3818$).

Regarding the AGR, none of the thirty-one meningiomas in the low-risk group showed a rapid growth; four out of the thirty-four meningiomas in the intermediate-risk group (12%) showed a rapid growth and one of the four lesions in the high-risk group did so (25%). The mean AGR was 0.1 cm^3/year in the low-risk group, 0.74 cm^3/year in the intermediate-risk group, and 0.78cm^3/year in the high-risk group. In the subgroup analyses, we noticed that the difference was established between the low-risk group and intermediate-risk group ($p < 0.001$), while no significant difference could be established between the low-risk group and high-risk group ($p = 0.117$) or intermediate-risk group and high-risk group ($p = 1$) (Table 2).

Overall, out of the entire series, five meningiomas out of sixty-nine (7%) showed rapid growth (Table 3). Only two meningiomas (3%) presented new clinical symptoms during the study follow-up. One of them, which showed a 2-cm^3 growth in 6 months (main growth velocity of 4 cm^3/year), scored 4 points on the initial AIMSS and was therefore classified in the intermediate-risk group. The other case with clinical worsening also obtained an initial AIMSS score of 4 points being classified in the intermediate-risk group as well. However, contrary to its previous counterpart, this lesion did

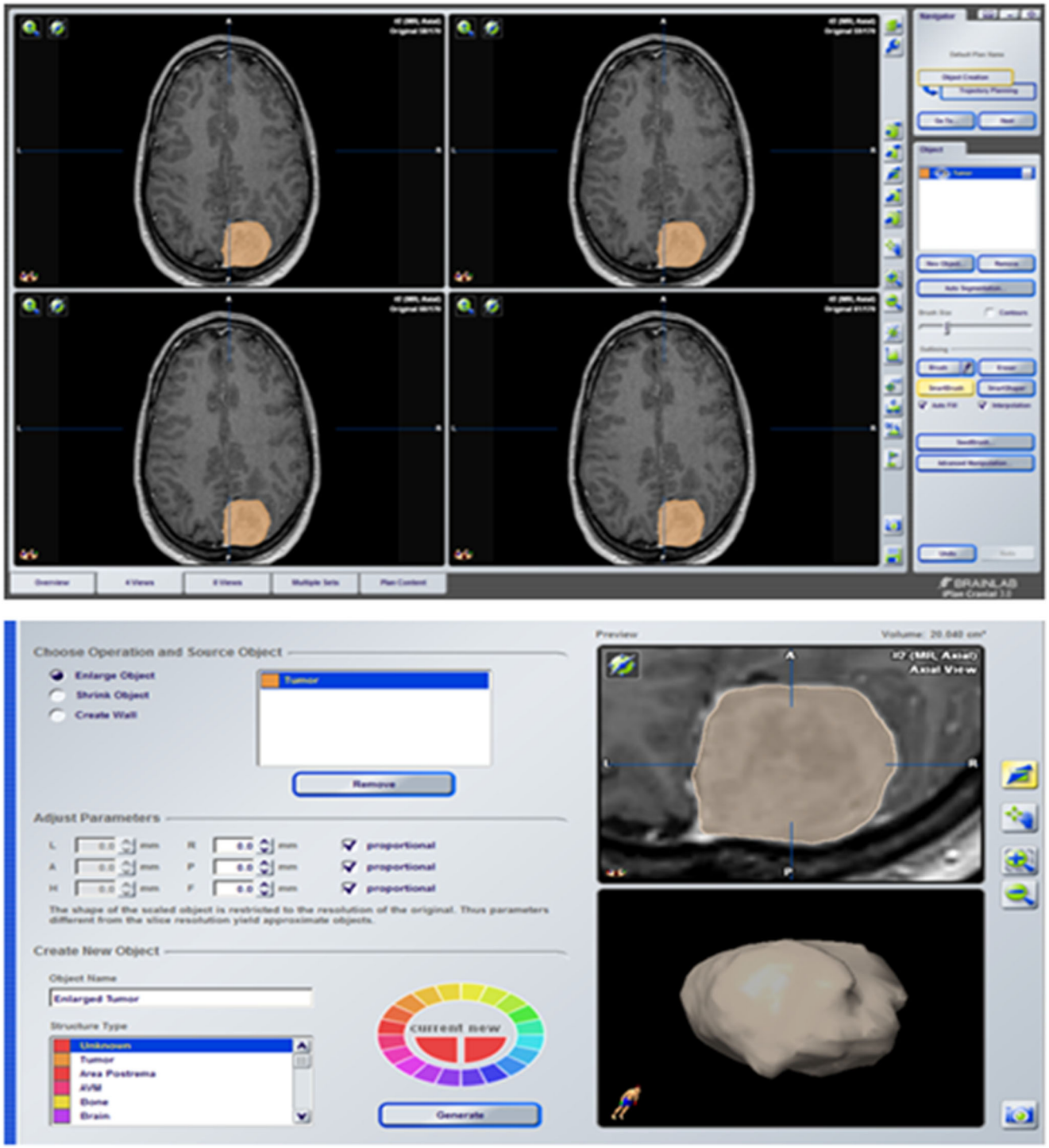

Fig. 1 Calculating a lesion's volume by using manual segmentation with Iplannet (Iplan 3.0 cranial planning software, Brainlab AG, Munich, Germany), which allows to highlight the uptaking component of the lesions in the T1W-MR post-Gadolinium sequence. A 3D reconstruction of every lesion is performed to calculate its volume

not present a rapid growth (total growth of 3.2 cm^3 in 4 years, main growth velocity of 0.8 cm^3/year). Nevertheless, it was surgically resected due to the symptom appearance, obtaining a WHO grade I.

Summarizing, six meningiomas from our series ended up requiring surgery: the aforementioned five cases that shown rapid growth listed in Table 3 and the one that became symptomatic despite not showing rapid growth.

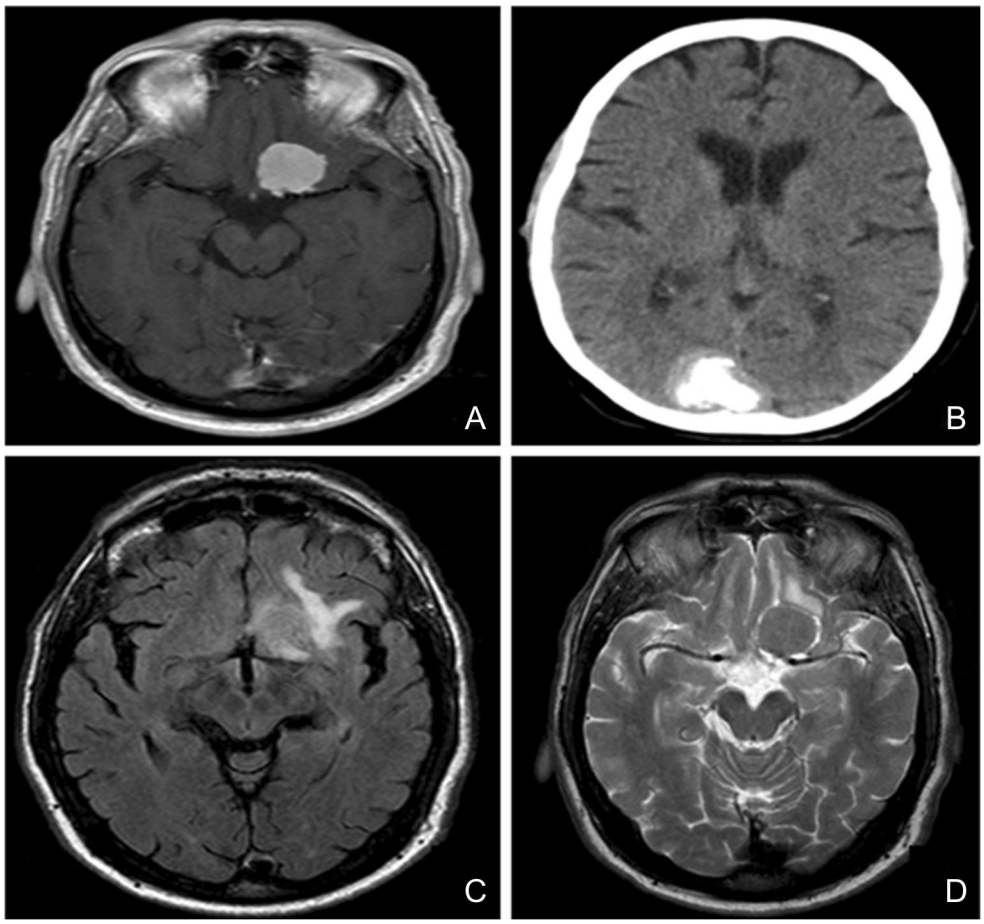

Fig. 2 Obtaining the different parameters to calculate the AIMSS. **a** T1W-MR post-Gadolinium sequence, used to calculate the volume and diameter of the lesions. **b** CT scan, used to establish the presence of calcifications (as seen on this example). **c** T2W-MRI FLAIR sequence, used to establish the presence of peritumoral edema (as seen on this image). T2W-MRI can also be used for that purpose. **d** T2W-MRI sequence, used to determine the intensity of the meningioma in comparison with the surrounding normal brain (isointense in this particular case)

Table 1 AIMSS calculation according to its four parameters and results obtained in our sample

Parameter	AIMSS score	Total number	Percentage
Diameter (approximate volume)			
≤2.5 cm (8.18 cm^3)	0	62	90
2.5–4 cm	3	7	10
>4 cm (33.49 cm^3)	6	0	0
Calcifications			
Yes	0	25	36
No	2	44	64
Peritumoral edema			
Yes	1	6	9
No	0	63	91
Intensity on T2			
Iso- or hyperintense	2	41	60
Hypointense	0	28	40

The score ranges from 0 to 11, with a higher score indicating a higher risk of growth

Discussion

Diagnosis of asymptomatic meningiomas has been on the rise over the last decades and their management is not fully standardized among professionals. Most physicians agree on the need to follow these lesions periodically with radiological imaging studies in an outpatient setting. However, the periodicity of those controls and the treatment algorithm may vary widely among different medical centers. Before the AIMSS was published, many studies described different risk factors that showed a correlation with an increased risk of tumor growth, but there was no score or classification to calculate such risk for decision-making.

The AIMSS classification gives each meningioma a score from 0 to 11 taking into account 4 different radiological characteristics (size, calcifications, edema, and intensity on T2-MRI) and allocates them into 3 different groups according to their risk of rapid growth: low (scores 0–2), intermediate (3–6), and high (7–11). Previously, to the AIMSS publication, the AGR had shown to be the most reliable marker to establish the risk of future growth, because lesions that have already grown fast are supposed to be in the rising phase of the sigmoid curve and, therefore, they are presumed to continue growing in the short-term future. The cut-off value of AGR established at

Table 2 Summary of AIMSS risk groups and their associated risk of rapid growth

Risk group	AIMSS score	Estimated risk of rapid growth (%)	Number of lesions	Lesions presenting rapid growth	Mean growth velocity (cm^3/year)	*p*
Low	0–2	< 10	31 (45%)	0 (0%)	0.1	$p < 0.001$
Intermediate	3–6	10–50	34 (49%)	4 (12%)	0.74	$p < 0.001$
High	7–11	> 50	4 (6%)	1 (25%)	0.78	$p = 0.117$

Overall number of meningiomas, lesions presenting rapid growth, and mean growth velocity in each group. Notice the statistically significant difference in the mean growth velocity between low- and intermediate-risk groups, while no difference could be established between low- or intermediate-risk groups and high-risk group

2 cm^3/year permitted to differentiate the lesions with a proclivity towards a linear growth (AGR < 2 cm^3/year) from the ones with a tendency to exponential growth (AGR > 2 cm^3/year) [11, 12].

Our study has evaluated the validity of the AIMSS score in a sample of asymptomatic meningiomas yielding interesting results. According to our data, the AIMSS score shows good capability differentiating between low- and intermediate-risk lesions. Therefore, it can be a good tool to establish the periodicity in which the radiological controls should be performed when a follow-up strategy is chosen. Whenever a lesion falls into the low-risk group, its radiological controls could be further spaced in time thus leading to savings on imaging studies and most likely diminishing the patient's perception of chronic illness and medical dependence. In all, it would most likely diminish the anxiety felt by low-risk patients that would otherwise be clinically and radiologically controlled unnecessarily more often. Nevertheless, it should be noted that the score suggests the likely growth velocity of a given lesion, but it does not reveal if a lesion will grow at all or not.

On the other hand, our investigation failed to demonstrate a significant difference in the risk of rapid growth between the high-risk group and the other two groups of risk. This is most likely explained by the fact that there were only 4 meningiomas initially classified in the high-risk group, which might have prevented us from observing statistically significant differences. This limited number of high-risk lesions might obey to the nature of the score itself and the quite significant importance it grants to tumor size. Even if a lesion meets all the requirements (calcifications, peritumoral edema, and signal on T2), to be classified as high risk, its size should also score at least 3 points (> 25 mm) to be finally allocated in the high-risk group. With such size plus peritumoral edema, many meningiomas may have already been symptomatic and thus excluded from our study. Furthermore, as mentioned before, a large size is one of the most predictive factors of a meningioma future rapid growth and thus its likelihood of becoming symptomatic. Therefore, the temporal window in which they have a size large enough to be in the high-risk group but without producing symptoms could be quite limited and thus their incidental diagnosis during that limited time unlikely. As mentioned by Lee EJ et al. in their study, the inclusion of a large number of patients in the creation of the AIMSS with big non-operated meningiomas because of bad medical condition could explain why they got enough high-risk group meningiomas to demonstrate statistical differences with the other risk groups [11]. We have not been able to obtain these results because we stop following such inoperable patients in which a neurosurgical therapy cannot be applied. In sum, considering all the above and our own results, it seems like the size is the least useful parameter of the AIMSS score [1, 5, 12, 15, 16, 19, 24].

The findings of our study match with the results published by Nakasu et al., who report that the growth of meningiomas fit an S-shaped curve rather than a linear growth model [12]. Accordingly, most symptomatic meningiomas would be diagnosed in the rise phase of the curve. In this stage, the decompensation of the intracranial pressure and the acute compression of the surrounding brain caused by the rapid growth could be the cause of symptom appearance. Therefore, when diagnosing an asymptomatic meningioma, it would be important to establish in which supposed phase of the growing sigmoid curve is located. Radiological signs cited above can help

Table 3 Characteristics of the meningiomas that showed rapid growth

Gender	Age	Location	Multiple	AIMSS	Follow-up (months)	Total growth (cm^3)	AGR (cm^3/year)	Symptoms appearance	WHO grade
Male	70	Skull base	No	4	6	2	4	Yes	I
Male	38	Convexity	Yes	8	30	5,8	2,3	No	II
Female	57	Convexity	Yes	4	42	12,3	3,5	No	I
Female	63	Convexity	No	4	72	13,8	2,3	No	II
Male	65	Convexity	Yes	3	108	18,6	2,1	No	I

All of them were surgically removed

with this purpose. A small-size meningioma is likely to be in the static initial phase, while the presence of calcifications could indicate it being in the static later phase. Both characteristics show a low risk of rapid growth. On the contrary, the presence of surrounding edema and the hyperintensity in T2 could be factors indicating a meningioma on the rise phase of the growing curve and thus presenting exponential growth. Lesions encountered in that phase that have presented rapid growth are presumed to continue growing in the near future and end up producing symptoms in case they have not done it yet. Attending to that theory, the role of the physician would be to follow up strictly the asymptomatic lesions located in the presumed rise phase, as well as treating the symptomatic ones, which are presumed to be in the rise phase. A laxer follow-up strategy could be adopted with lesions presumed to be in the static phase. Nonetheless, it should be considered that in a midterm future, they can turn into the rise phase and develop a rapid growth or keep growing slowly even being in the static phase till being clinically significant. For that reason, and despite the statement by Islim et al. regarding meningioma progression and subsequent treatment intervention in the vast majority of cases within 5 years of diagnosis [8], patients should always be followed even if they are at the low-risk group.

The study's failure to demonstrate the high risk of rapid growth in the high-risk group of lesions prevents us from establishing surgical indication in patients that are still asymptomatic but have predictive factors suggesting a likely future growth of their lesion. Considering the prognostic factors of meningioma surgery (younger age, smaller tumor size, and better preoperative performance status), it would be preferable to operate patients in better clinical condition in order to achieve better results in terms of morbidity and mortality. Moreover, a better outcome is directly related to a major percent of lesion removal, which is also linked to the tumor size and invasion of surrounding structures [1, 2, 4, 21]. Hence, once we suspect that an asymptomatic meningioma may end up needing surgery at some point, it would be better to operate on it as soon as possible. Unfortunately, our investigation found that the AIMSS score would not provide much evidence for such suspicion. Future research regarding the management of asymptomatic meningiomas should consider broadening the AIMSS score. Adding other prognostic factors previously related to rapid meningioma growth but not investigated by Lee et al. in their study might improve the AIMSS ability of telling apart low-, intermediate-, and high-risk lesions.

The present work shows the usefulness and applicability of the AIMSS score to establish the follow-up strategy of asymptomatic meningiomas in the current clinical practice in a standard neurosurgical unit and aims to compensate the possible lack of external validity that Lee et al. mention in the original work, performed in a more specific population [11]. It also specifies the subgroup of lesions in which it is more useful. Attending to our findings, the score can be used to distinguish between low-risk and intermediate-risk lesions, but its usefulness to detect high-risk lesions has not been proved. We also found that the size is a good predicting factor but its usefulness in the current clinical application of the score is questionable since few large meningiomas are asymptomatic. Our results suggest that the most useful factors to be used in the daily clinical practice are the presence of calcifications, edema, and intensity on T2.

Nevertheless, our study has some limitations worth mentioning. Patient data were collected retrospectively and some surgical indications, despite relying on international and national guidelines, may have not been fully standardized. Another issue is the sample size and the limited number of meningiomas classified as high risk according to the AIMSS score. However, this small number of high-risk meningiomas may obey to weaknesses of the AIMSS score itself. Furthermore, despite the overall number of cases being limited, the results reached statistical significance for low- and intermediate-grade meningiomas. Finally, both the AIMSS score and the AGR were reviewed by a single author (FBB). Nevertheless, FBB implemented the AIMSS score and the AGR while being blinded to clinical management and outcome. In any case, the results here proposed should be validated with a prospective cohort of patients; thus, further studies are still needed.

Conclusions

Anticipating asymptomatic meningioma's risk of rapid growth is a crucial factor to offer each patient the best management option right at the initial diagnosis. The AIMSS score has been recently proposed as a good tool for that purpose. However, our results suggest that its bigger strength relies on distinguishing between low- and intermediate-risk lesions. This feature would allow the physician to adjust the periodicity of the radiological and clinical controls, but the score would fall short in pointing out those meningiomas at a high risk for rapid growth. Further studies amplifying the number of prognostic factors included in the score could overcome this drawback and increase the score's capacity of distinction between high-risk lesions and the other two risk groups.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name of institute/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

For this type of study, formal consent is not required.

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