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The meningioma surface factor: a novel approach to quantify shape irregularity on preoperative imaging and its correlation with WHO grade

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OBJECTIVE Atypical and anaplastic meningiomas account for 20% of all meningiomas. An irregular tumor shape on preoperative MRI has been associated with WHO grade II–III histology. However, this subjective allocation does not allow quantification or comparison. An objective parameter of irregularity could substantially influence resection strategy toward a more aggressive approach. Therefore, the aim of this study was to objectively quantify the level of irregularity on preoperative MRI and predict histology based on WHO grade using this novel approach.

METHODS A retrospective study on meningiomas resected between January 2010 and December 2018 was conducted at two neurosurgical centers. This novel approach relies on the theory that a regularly shaped tumor has a smaller surface area than an irregularly shaped tumor with the same volume. A factor was generated using the surface area of a corresponding sphere as a reference, because for a given volume a sphere represents the shape with the smallest surface area possible. Consequently, the surface factor (SF) was calculated by dividing the surface area of a sphere with the same volume as the tumor with the surface area of the tumor. The resulting value of the SF ranges from > 0 to 1. Finally, the SF of each meningioma was then correlated with the corresponding histopathological grading.

RESULTS A total of 126 patients were included in this study; 60.3% had a WHO grade I, 34.9% a WHO grade II, and 4.8% a WHO grade III meningioma. Calculation of the SF demonstrated a significant difference in SFs between WHO grade I (SF 0.851) and WHO grade II–III meningiomas (SF 0.788) ($p < 0.001$). Multivariate analysis identified SF as an independent prognostic factor for WHO grade (OR 0.000009, 95% CI 0.000–0.159; $p = 0.020$).

CONCLUSIONS The SF is a proposed mathematical model for a quantitative and objective measurement of meningioma shape, instead of the present subjective assessment. This study revealed significant differences between the SFs of WHO grade I and WHO grade II–III meningiomas and demonstrated that SF is an independent prognostic factor for WHO grade.

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KEYWORDS meningioma; MRI; shape; irregularity; WHO grade; surface factor; oncology

MENINGIOMAS are among the most common intracranial tumors. After resection, meningiomas are graded histopathologically according to the WHO classification, with 80.6% reported as WHO grade I, 17.6% as WHO grade II, and 1.7% as WHO grade III.[1] The local control rate and outcome is generally favorable in patients with benign meningiomas (WHO grade I), whereas prior studies show a reduced local control rate in atypical meningiomas (WHO grade II) and malignant behavior with the need for adjuvant treatment in anaplastic meningiomas (WHO grade III).[2] Reports on recurrence rates vary in the literature but are as high as 29%–52% for WHO grade II and 50%–94% for WHO grade III meningiomas.[3] Furthermore, a 5-year survival rate of 78% has been shown for WHO grade II meningiomas and a 10-year survival rate of 54% for WHO grade III meningiomas.[1,4] The extent of

ABBREVIATIONS ROC = receiver operating characteristic; SF = surface factor.
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resection represents the most relevant predictor for recurrence in meningiomas.[2,5–7] At the same time, recurrence seems to have a significantly worse effect on survival for WHO grade II–III meningiomas than for WHO grade I meningiomas.[2,8–10] Therefore, a method for reliable preoperative identification of potential atypical or anaplastic meningiomas could help to improve outcomes by enhancing surgical radicality toward a complete resection, including adjacent dura, venous sinus, and bony structures.

Preoperative MRI features like tumor volume, perilesional edema, and others have been previously correlated with WHO grading. Among other meningioma characteristics, an irregular tumor shape has consistently been associated with WHO grade II–III histology.[11–17] As reported in these publications, the tumor shape was divided into arbitrary chosen categories, e.g., round, irregular, or mushroom shaped. However, these classifications are subjective and do not allow generalization of the results or to quantification and comparison of the irregularity. Also, it is important to note that atypical or anaplastic meningiomas are rare diseases for many institutions.[2] Consequently, the experience of clinicians, including radiologists, in subjective interpretation of preoperative MRI images of suspected WHO grade II or III meningiomas can be limited. Therefore, a reliable objective parameter characterizing this histology could be beneficial.

Thus, the aim of this study was to quantify meningioma shape irregularities on preoperative MRI and to create a reproducible and objective parameter that may offer a novel approach for predicting the WHO grade of a meningioma.

Methods

We conducted a retrospective analysis of patients with meningiomas by using data drawn from institutional tumor databases from two neurosurgical centers. Patients who underwent surgical resection for meningioma between January 1, 2010, and December 31, 2018, were included. The study was approved by the ethics committee of the Karl Landsteiner University of Health Sciences, Krems, Austria, and acknowledged by the Medical University of Innsbruck, Innsbruck, Austria.

Patient Selection

During the study period, patients with convexity, parasagittal, falcine and tentorial meningiomas without skull base contact were included. Eligible patients were ≥ 18 years old, with a histologically verified meningioma and available preoperative imaging (contrast-enhanced T1-weighted MRI, slice thickness ≤ 2 mm, maximum 7 days before surgery). Exclusion criteria were prior meningioma treatment (e.g., radiation, embolization), previous neurosurgical procedures in proximity to the meningioma, large superficial cysts, and meningioma en plaque.

Neurosurgical center one included patients with meningiomas of all WHO grades in a consecutive order. During the study period 129 patients met the inclusion criteria, and 24 patients were excluded due to pretreatment, large superficial cysts, or en plaque meningioma. Therefore, 105 patients from center one were included in this study.

Neurosurgical center two included patients with meningiomas of WHO grade II and III in a consecutive order. During the study period 41 patients met the inclusion criteria, and 20 patients were excluded due to pretreatment, large superficial cysts, or en plaque meningioma. Therefore, 21 patients from center two were included in this study.

In total, 126 patients were included by the participating centers. As reported in previous studies, WHO grade II and III meningiomas were grouped together for analysis.[11,13]

WHO Grade

Depending on the date of surgery, initial histopathological workup was performed using the WHO 2007 or the WHO 2016 criteria for classification of CNS tumors.[3,18] To ensure a uniform classification, all histopathological results using the WHO 2007 classification were checked for brain invasion. In cases of documented brain invasion, tissue samples were analyzed by a neuropathological reference institute and regraded with the WHO 2016 classification.

Surface Factor

An irregular meningioma shape has been shown in various studies to correlate with WHO grade II–III histology.[11–17] In general, describable parameters for a 3D shape are volume and surface area. The idea behind our approach relies on the conclusion that a regularly shaped tumor has a smaller surface area than an irregularly shaped tumor with the same volume. To be able to create a usable factor, it was necessary to compare the surface area of the tumors not with each other, but with a reference shape. Because for a given volume a sphere represents the shape with the smallest surface area possible, a sphere was used as a reference shape in our approach to describe shape irregularity of meningiomas.

First, a volumetric analysis was performed by a blinded investigator to determine the volume (semiautomated segmentation) and the surface area of the tumor by using 3D Slicer (version 4.10.2; https://www.slicer.org) with anonymized datasets.[19] Second, the individual tumor volume was used to calculate the surface area of a sphere with a volume identical to that of the tumor. The relevant information at this point consisted of the difference in the surface area of the tumor and the sphere, as any irregularity or shape deviation of the tumor leads to an increase in surface area. The higher the degree of tumor shape irregularity or deviation from a regularly formed shape like a sphere, the higher was the resulting difference. Third, to be able to express and quantify the degree of measured irregularity, it was necessary to create a factor displaying a defined value, which we termed the "surface factor" (SF). This was achieved by using the following formula:

$$SF = SA_{sphere}/SA_{tumor},$$

where SA_{sphere} is the surface area of a sphere with the same volume as the tumor and SA_{tumor} is the surface area of the tumor.

The resulting value of the SF ranges from > 0 to 1, with the value 1 showing a hypothetical tumor with a spherical

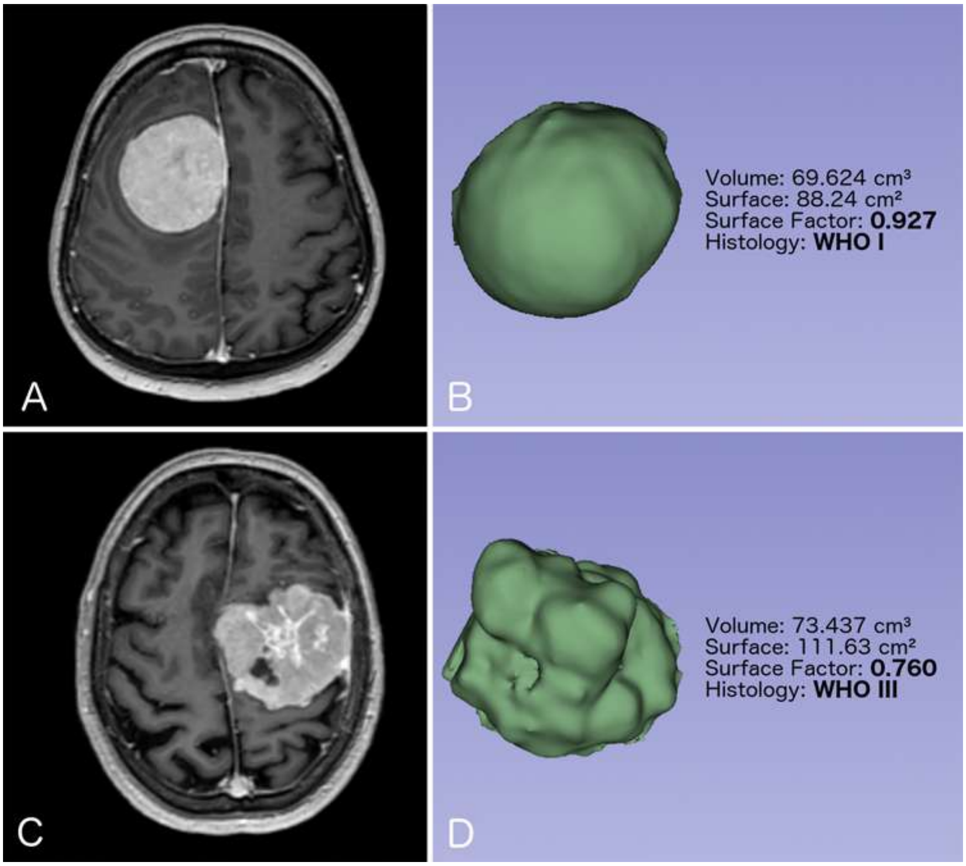

FIG. 1. The SF demonstrated in two representative cases. **A:** Contrast-enhancing T1-weighted MR image of a 54-year-old female patient showing a parasagittal meningioma displaying a regular shape. **B:** 3D model created with 3D Slicer (version 4.10.2; https://www.slicer.org). The SF shows a value of 0.927. Postoperatively a WHO grade I meningioma was diagnosed. **C:** Contrast-enhancing T1-weighted MR image of a 52-year-old female patient showing a convexity meningioma displaying an irregular shape. **D:** 3D model created with 3D Slicer (version 4.10.2; https://www.slicer.org). The SF shows a value of 0.760. Postoperatively a WHO grade III meningioma was diagnosed.

shape. The higher the degree of irregularity, the lower is the calculated SF.

Finally, the SF of each meningioma was then correlated with the corresponding histopathological grading. Two representative cases are displayed in Fig. 1 to demonstrate this process.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics (IBM SPSS Statistics for Windows, version 25.0, IBM Corp.). Normal distribution was tested with the Kolmogorov-Smirnov test, and metric data were described using mean ± standard deviation if normally distributed. Skewed metric data were summarized using median and range. Categorical data are presented as absolute frequencies and percentages. To test for differences between two groups for metric and normally distributed data, Student t-tests were used. For metric but skewed distribution, Mann-Whitney U-tests were used. Cutoff values were assessed using receiver operating characteristic (ROC) curve analysis and calculation of the Youden index. Univariate and multivariate logistic regression were performed to test for possible predictors of WHO grade. All univariable-tested variables were included in the multivariate regression model. Furthermore, to rule out multicollinearity between metrical variables (SF, volume, and surface), a stepwise forward and backward regression was performed. A p value < 0.05 was considered to indicate statistical significance.

Results

Patient Characteristics

This study cohort consisted of 81 female (64.3%) and 45 male patients (35.7%). Median age was 63 years (range 25–84 years). The majority of the tumors were located at the convexity (n = 68, 54%), followed by parasagittal (n = 45, 35.7%), falcine (n = 10, 7.9%), and tentorial meningiomas (n = 3, 2.4%). Altogether, 76 tumors (60.3%) were diagnosed as WHO grade I, 44 as WHO grade II (34.9%), and 6 as WHO grade III (4.8%) meningiomas. Demographic, radiological, and histological data are shown in Table 1.

Differences Between WHO Grade I and WHO Grade II–III Meningiomas

The sex distribution showed a predominance of female

TABLE 1. Patient characteristics

Parameter	Values
Total no. of pts	126 (100)
Sex	
Female	81 (64.3)
Male	45 (35.7)
Age, yrs	63.1 (25.4–84.3)
Meningioma	
Location	
Convexity	68 (54)
Parasagittal	45 (35.7)
Falcine	10 (7.9)
Tentorial	3 (2.4)
Histology: WHO grade	
I	76 (60.3)
II	44 (34.9)
III	6 (4.8)

Pt = patient.
Values are presented as number of patients (%) or median (range).

TABLE 2. Difference between WHO I and WHO II–III meningiomas

Parameter	WHO I	WHO II–III	p Value
Pts	76 (60.3%)	50 (39.7%)	
Sex			
Female	54 (71.1%)	27 (54.0%)	**0.051**
Male	22 (28.9%)	23 (46.0%)	
Age, yrs	60.8 (26.7–83.7)	64.7 (25.4–84.3)	0.354
Meningioma			
Location			0.879
Convexity	43 (56.6%)	25 (50%)	
Parasagittal	25 (32.9%)	20 (40%)	
Falcine	6 (7.9%)	4 (8%)	
Tentorial	2 (2.6%)	1 (2%)	
Vol, cm^3	30.6 (0.6–157)	43.2 (1.5–173)	**0.029**
Surface area, cm^2	60.7 ± 40.0	83.3 ± 47.3	**0.005**

Values are presented as number of patients (%), median (range), or mean ± SD. Boldface type indicates statistical significance.

patients with WHO grade I meningiomas (n = 54; 71.1%) in comparison to those with WHO grade II–III meningiomas (n = 27; 54%), but this finding did not reach statistical significance (p = 0.052). No differences in tumor grade distribution were associated with age or tumor location. WHO grade I meningiomas were significantly smaller than WHO grade II–III meningiomas, with a median volume of 30.6 cm^3 (range 0.6–157.0 cm^3) and 43.2 cm^3 (range 1.5–173.0 cm^3; p = 0.029), respectively. Tumor surface also differed significantly between WHO grade I and WHO grade II–III meningiomas with 60.7 ± 40.0 cm^2 and 83.3 ± 47.3 cm^2 (p = 0.005). Characteristics of WHO grade I and WHO grade II–III meningiomas are shown in Table 2.

Surface Factor

There was a significant difference between the SFs of WHO grade I and WHO grade II–III meningiomas, which were 0.851 ± 0.066 and 0.788 ± 0.089, respectively ($p < 0.001$). When the analysis was stratified by location, the SF showed significant differences for convexity and parasagittal meningiomas. In convexity meningiomas, the SF was 0.850 ± 0.058 for WHO grade I and 0.788 ± 0.92 for WHO grade II–III meningiomas (p = 0.005). For parasagittal meningiomas, the SF was 0.841 ± 0.078 for WHO grade I and 0.780 ± 0.093 for WHO grade II–III histology (p = 0.022). Falcine meningiomas accounted for 10 cases, and the SF did not reach statistical significance (WHO grade I 0.886 ± 0.065, WHO grade II–III 0.836 ± 0.038; p = 0.204). Only 2 cases were tentorial meningiomas and a further analysis of these was therefore not reasonable. Results after calculation of the SF are summarized in Table 3. The ability of the SF to discriminate preoperatively between WHO grade I and WHO grade II–III meningiomas was tested with an ROC analysis, which resulted in an area under the ROC curve of 0.713 (95% CI 0.62–0.81; $p < 0.001$). The highest Youden index was found at a cutoff value of 0.800, with a sensitivity of 52.0% for WHO grade II–III meningioma with a positive predictive value of 70.3%, and achieved a specificity of 85.5% for WHO grade I meningiomas and a negative predictive value of 73.3%.

Brain Invasion

Histological evidence of brain invasion was found in 8 meningiomas (WHO grade II, n = 7; WHO grade III, n = 1). Additionally, SF differed significantly between patients with and without histological evidence of brain invasion (p = 0.049). In meningiomas with brain invasion, the median SF was significantly lower: 0.759 (0.601–0.906) in comparison to 0.845 (0.555–0.973) without brain invasion.

Univariate regression showed a significant relation between SF and brain invasion (OR 0.00127, CI 0.000–0.288; p = 0.023).

Univariate and Multivariate Analysis

In univariate analysis, SF (OR 0.000021, CI 0.000–0.005; p = 0.001), volume (OR 1.0, CI 1.0–1.02; p = 0.042), and surface area (OR 1.012, CI 1.003–1.021; p = 0.006) showed statistical significance for prediction of WHO grade. Age, sex, and location did not reach statistical significance. A multivariate model analysis was performed, including all univariate tested variables. With this approach, only SF remained a significant predictor for WHO grade (OR 0.000009, CI 0.000–0.159; p = 0.020). To rule out possible multicollinearity affecting obtained results, especially between SF, volume, and surface area, we also performed a stepwise forward and backward regression, which consistently showed only SF as a prognostic factor. Detailed results of univariate and multivariate analysis are depicted in Table 4.

Discussion

Our study proposes a mathematical model for a quan-

TABLE 3. Comparison of SF for WHO grade I and WHO grade II–III meningiomas

Parameter	WHO Grade		p Value
	I	II–III	
SF			
All locations	0.851 ± 0.066	0.788 ± 0.089	**<0.001**
Meningioma location			
Convexity	0.850 ± 0.058 (n = 43)	0.788 ± 0.092 (n = 25)	**0.005**
Parasagittal	0.841 ± 0.078 (n = 24)	0.780 ± 0.093 (n = 21)	**0.022**
Falcine	0.886 ± 0.065 (n = 6)	0.836 ± 0.038 (n = 4)	0.204

SF values are presented as mean ± SD. Boldface type indicates statistical significance.

titative and objective measurement of meningioma shape, which correlates with the WHO grade of meningiomas, instead of the subjective assessment used currently. The preoperative identification of potential atypical or anaplastic meningiomas could help to improve outcome by enhancing surgical radicality.

Irregular meningioma shapes have been shown to correlate with WHO grade II–III histology in various studies.[11–17] The tumor shape has been assessed subjectively and classifications were created on arbitrary strata. To our knowledge there has never been a description about a way to express or compare the degree of irregularity. Therefore, our intention was to address objective data on shape irregularity of meningiomas on preoperative MRI with a focus on the clinical wish to predict the WHO grade.

The idea behind our approach relies on the conclusion that a regularly shaped tumor has a smaller surface area than an irregularly shaped tumor with the same volume. Because a sphere represents the shape with the smallest surface area possible for a given volume, we used the surface area of the sphere as a reference to create the SF. This step was necessary to create a defined value that is comparable between different cases and does not mean that a meningioma needs to resemble a sphere. Instead, our results demonstrate that the deviation of the lowest surface area possible is higher in WHO grade II–III meningiomas than in WHO grade I meningiomas.

WHO grade I meningiomas have been found to be relatively common, but WHO grade II and III meningiomas accounted for only 19.4% of all meningiomas in epidemiological studies.[1] As we therefore expected limited patient numbers for the group of patients with WHO grade II or III meningiomas, consecutive patients with WHO grade II and III meningiomas of a second center were included in this study in order to increase the value of our statistical analysis. Furthermore, WHO grades II and III were grouped together as WHO grade II–III meningiomas for analysis, which has also been done in previous studies because anaplastic meningioma is a rare disease.[2,11,13]

Calculation of the SF showed a significant difference between WHO grade I and WHO grade II–III meningiomas with (SF 0.851 and 0.788, respectively, $p < 0.001$). Subanalysis by location showed significant differences for convexity and parasagittal meningiomas but not for falcine meningiomas. However, the number of patients in the present study with falcine and tentorial meningiomas was low, and therefore the value of the subanalysis for these meningiomas was limited. The effects of different meningioma location on the SF therefore provides an interesting topic for future research.

Additionally, an analysis of SF and histological evidence of brain invasion showed a significant difference between meningiomas with and without brain invasion ($p = 0.049$). This correlation was partly expected as brain

TABLE 4. Univariate and multivariate analysis

Parameter	Univariate		Multivariate	
	OR (95% CI)	p Value	OR (95% CI)	p Value
SF	0.000* (0.000–0.005)	**0.001**	0.000† (0.000–0.159)	**0.020**
Pts				
Age, yrs	1.014 (0.99–1.04)	0.287	1.006 (0.98–1.04)	0.674
Sex	2.09 (0.9–4.40)	0.052	1.3 (0.56–3.03)	0.537
Meningioma				
Volume, cm^3	1.0 (1.0–1.02)	**0.042**	1.02 (0.95–1.09)	0.569
Surface area, cm^2	1.012 (1.003–1.021)	**0.006**	0.99 (0.93–1.05)	0.657
Localization‡			—	0.944

Boldface type indicates statistical significance.

* Exact value is 0.000021.

† Exact value is 0.000009.

‡ Global category, each subcategory did not reach significance.

invasion represents a criterion for WHO grade II meningiomas. Furthermore, a smaller SF indicates a larger meningioma surface area, resulting in increased contact with the brain surface. These findings offer a possible explanation for a higher probability of brain invasion. After ROC analysis, the highest Youden index was found at a cutoff value of 0.800. The resulting sensitivity of 52% for WHO grade II–III meningiomas, with a positive predictive value of 70.3% and specificity of 85.5% for WHO grade I meningiomas with a negative predictive value of 73.3%, clarifies the need for additional data. Also, the role of this cutoff value remains unclear. One possibility would be the establishment of a new cutoff value with higher sensitivity for WHO grade II–III meningiomas to serve as a screening parameter on preoperative MRI. Another approach would be the definition of risk ranges for SF values of meningiomas to divide patients into groups according to their risk of WHO grade II–III pathology. However, higher patient numbers as well as detailed analyses of subgroups are necessary for further sufficient evaluation of cutoff values.

Moreover, a multivariate regression analysis was performed to identify possible predictors of WHO grade. Histological evidence of brain invasion was excluded from this model as it is not available preoperatively and represents a criterion for WHO grade. SF, surface area, and volume of the meningioma were significantly related to WHO grade in univariate analysis. However, only SF was identified as an independent predictor of WHO grade in our multivariate regression model (OR 0.000009, CI 0.000–0.159; p = 0.020; Table 4).

Concerning the predictive value of the SF, it is also important to keep in mind that other predictors exist on preoperative MR images.[11] Furthermore, differentiation of WHO grades has been successfully performed with histogram analysis of T1-weighted sequences or diffusion tensor imaging.[20] Combining these features in a model could increase the accuracy of preoperative determination of the WHO grade of meningiomas by using MRI.

Regarding the practicability of the SF for everyday use, major facilitation can be expected with the increasing use of artificial intelligence (AI) in diagnostics. As automated volumetric analysis of brain tumors moves from the experimental to the implementation phase, an automated calculation of the SF seems feasible and would offer exciting possibilities for further AI-based validation and research.

Study Limitations

This study has some limitations. First, the retrospective study design must be considered a limitation. Second, the low patient numbers, especially for patients with WHO grade III meningioma, force individual research groups and small collaborative networks to take measures to increase their statistical value. Therefore, WHO grade II and III meningiomas of a second center were included in this study, which results in a potential selection bias. Also, WHO grade II and III tumors were grouped, which does not allow differentiation between them. However, one must keep in mind that the aim of this study was to test a novel approach. Future research needs to be done with higher patient numbers to validate this method and to analyze potential differences in the SFs of different meningioma types.

Conclusions

With the SF, we propose a mathematical model for a quantitative and objective measurement of meningioma shape, instead of the present method of subjective assessment. Furthermore, we demonstrated significant differences between the SF of WHO grade I and WHO grade II–III meningiomas and proved SF as an independent prognostic factor for WHO grade. These findings represent a step toward reliable radiological prediction of the WHO grade of meningiomas. This predictive tool may substantially influence future treatment strategies by enhancing surgical radicality in patients with suspected WHO grade II–III meningiomas and translate into better neurooncological outcome.

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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: Popadic, Scheichel. Acquisition of data: Popadic, Pinggera, Kitzwoegerer, Roetzer. Analysis and interpretation of data: Popadic, Scheichel, Kitzwoegerer, Roetzer, Oberndorfer, Freyschlag. Drafting the article: Marhold, Popadic, Scheichel. Critically revising the article: Marhold, Popadic, Scheichel, Pinggera, Ungersboeck, Oberndorfer, Sherif, Freyschlag. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Marhold. Statistical analysis: Popadic, Scheichel, Weber. Administrative/technical/material support: Popadic. Study supervision: Marhold, Popadic.

Supplemental Information

Previous Presentations

The first results of a single-center experience with the surface factor have been presented at the Annual Scientific Meeting of the OEGNC (Austrian Society of Neurosurgeons), Vienna, Austria, 2019. Parts of this study have been presented as an E-poster (no. 2739) at the Annual Scientific Meeting of the AANS, Boston, MA, 2020.

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