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Risk factors associated with higher WHO grade in meningiomas: a multicentric study of 552 skull base meningiomas

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The histological grade is crucial for therapeutic management, and its reliable preoperative detection can significantly influence treatment approach. Lacking established risk factors, this study identifies preoperative predictors of high-grade skull base meningiomas and discusses the implications of non-invasive detection. A multicentric study was conducted on 552 patients with skull base meningiomas who underwent primary surgical resection between 2014 and 2019. Data were gathered from clinical, surgical and pathology records and radiological diagnostics. The predictive factors of higher WHO grade were analysed in univariate analysis and multivariate stepwise selection logistic regression analysis. Histological analysis revealed 511 grade 1 (92.6%) and 41 grade 2 (7.4%) meningiomas. A prognostic model predicting the probability of WHO grade 2 skull base meningioma (AUC 0.79; SE 0.04; 95% Wald Confidence Limits (0.71; 0.86)) based on meningioma diameter, presence of an arachnoid plane and cranial nerve palsy was built. Accurate preoperative detection of WHO grade in skull base meningiomas is essential for effective treatment planning. Our logistic regression model, based on diameter, cranial nerve palsy, and arachnoid plane, is tailored for detecting WHO grade 2 skull base meningiomas, even in outpatient settings.

Keywords Meningioma, Skull base, Surgery, Tumor grading, Risk factors, Case series

Meningiomas are the most common primary intracranial tumours, accounting for 36.1% of all central nervous system tumours[1]. They are classified into three histopathological grades by the World Health Organization (WHO), with 88–94% classified as grade 1 (benign), 5–7% as grade 2 (atypical), and 1–2% as grade 3 (anaplastic)[2,3]. High-grade meningiomas (grade 2 and 3; HGM) exhibit aggressive clinical behaviour, with rapid progression, high recurrence rates (RR), and the potential to metastasize[4]. The documented RR at 5 years after radical resection were 3% for grade 1, 38% for grade 2, and 78% for grade 3 meningiomas, with corresponding median times to recurrence of 7.5, 2.4, and 3.5 years[5]. Moreover, documented actuarial 5- and 10-year survival rates are 95% and 79% for atypical meningiomas, and 64.3% and 34.5% for anaplastic meningiomas[6].

The occurrence of HGM is significantly less frequent at the skull base compared to non-skull base locations[7–12]. Although predictive factors for higher WHO grade in meningiomas have been thoroughly studied, risk factors (RF) associated with a higher WHO grade in skull base meningiomas (SBMs) are not well established[7–9,13,14].

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This study aims to identify specific preoperative RF predictive of high-grade SBMs and to discuss the therapeutic consequences of preoperative non-invasive detection of HGM within this surgically challenging subgroup.

Materials and methods

A multicentric study was conducted on 552 consecutive patients who underwent primary SBM resection between 2014 and 2019, with data collected retrospectively from January 1, 2014, to June 30, 2018, and prospectively from July 1, 2018, to December 31, 2019. Patients with a history of previous cranial irradiation, meningiomatosis, multiple meningiomas, neurofibromatosis type II, or similar conditions predisposing to meningiomas were excluded. The study included data from six neurosurgical centres in the Czech Republic, namely Military University Hospital Prague (260 patients), Pilsen University Hospital (76 patients), Liberec Hospital (69 patients), Ceske Budejovice Hospital (63 patients), University Hospital Olomouc (44 patients), and University Hospital Ostrava (40 patients). Clinical, surgical, pathology records and radiological diagnostics were used to collect the data, which were subsequently anonymised. The radiological evaluation was conducted by two independent senior radiologists (VS, JM). They assessed various radiologic factors, including the diameter, volume, and location of the tumour, as well as characteristics such as oedema, shape, presence of an arachnoid plane, invasive tumour-brain interface, margins, vessel encasement, vessel narrowing, cavernous sinus invasion, enhancement, capsular enhancement, presence of a dural tail, cysts, sunburst sign, bone invasion, and hyperostosis. The extent of resection (EOR) was estimated using the Simpson grading system in the surgical records, and subsequently verified on early baseline postoperative magnetic resonance imaging (MRI)[15]. Histopathological analysis was performed using the 2007 and 2016 WHO classifications[16,17]. Surgical morbidity, mortality, and the evolution of preoperative neurological deficits were recorded, while specific details regarding clinical outcomes and associated RF have been subject to a previous study[18]. Clinical and radiological follow-up were conducted according to individual department protocols, but at least once a year. Tumour progression or recurrence, along with subsequent therapeutic interventions, were systematically documented. Preoperative RF of higher WHO grade were analysed.

Ethics approval and consent to participate

This study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The experimental protocol was approved by the Ethical Committee of the University Hospital in Ostrava, Czech Republic (reference number 530/2018). Due to the nature of the study, only general informed consent for the use of anonymised data for research purposes was obtained from all individual participants, as approved by the Ethical Committee of University Hospital in Ostrava, Czech Republic (reference number 530/2018).

Statistical analysis

Results are presented descriptively as mean ± standard deviation, median and interquartile range, respectively for numerical variables and absolute and relative frequencies for qualitative variables. Inferential statistical analysis was performed using logistic regression (univariate and multivariate stepwise selection). Group comparisons were conducted using Wilcoxon Rank Sum tests and the Kruskal–Wallis test for more than two groups. Correlation analysis was performed using the Spearman rank correlation coefficient because not all correlations were linear and the chi-square test was used to determine the strength of the relationship between the two qualitative variables. All main results were presented with 95% confidence intervals. The statistical software used for all analyses was SAS version 9.4. A p-value of < 0.05 was considered statistically significant and all tests were performed as two-sided. No adjustments for multiple comparisons were made as there was no single primary hypothesis.

Potential preoperative predictors included in our analysis: 1. age, 2. gender, 3. GCS, 4. KPS, 5. subjective symptoms, 6. objective deficit, 7. cognitive deficit, 8. higher cortical function deficit (excluding speech), 9. speech disorder, 10. cerebellar deficit, 11. motor deficit, 12. somatosensory deficit, 13. epileptic seizure, 14. other deficits, 15. cranial nerve (CN) deficit, 16. CN1 deficit, 17. CN2 deficit, 18. CN3 deficit, 19. CN4 deficit, 20. CN5 deficit, 21. CN6 deficit, 22. CN7 deficit, 23. CN8 deficit, 24. CN9 deficit, 25. CN10 deficit, 26. CN11 deficit, 27. CN12 deficit, 28. location dichotomised (supratentorial vs. infratentorial), 29. exact location, 30. diameter, 31. volume, 32. arachnoid cistern of meningioma origin, 33. irregular shape, 34. invasive tumour-brain interface, 35. irregular margins, 36. arachnoid plane, 37. peritumoral oedema, 38. contrast enhancement, 39. capsular enhancement, 40. dural tail, 41. contact with CN, 42. major vessel encasement, 43. major vessel narrowing, 44. cavernous sinus invasion, 45. sunburst sign, 46. intra- or peritumoral cysts, 47. bone invasion, 48. hyperostosis.

In total, 48 potential predictors were considered in the model. To ensure the most robust and statistically sound model, we used the stepwise selection method in SAS PROC LOGISTIC. This method incorporates elements of both forward selection and backward elimination, starting with the best single predictor and iteratively adding or removing predictors based on their contribution to the model's statistical significance (using a p-value threshold of < 0.05).

A plot of the ROC curve for the fitted model was produced by ROC option in the PROC LOGISTIC statement using the default methodology. ROC curve was calculated in all point/results of obtained multivariate predictor for included 552 subjects (therefore 552 cut-offs were used in ROC curve – for these 552 points sensitivity a false positivity were calculated and plotted in ROC curve).

Results

Between 2014 and 2019, a total of 552 consecutive patients underwent surgical resection for SBMs. Of these, 423 (76.6%) were women and 129 (23.4%) were men. The mean age of patients at surgery was 56.8 years (range

Preoperative neurological status	No	%	CN deficits (partial or complete)	No	%
Mean GCS	14.9	-	CN1 (Olfactory)	63	11.4
Mean KPS	90	-	CN2 (Optic)	135	24.5
Objective deficit	355	64.3	CN3 (Oculomotor)	19	3.4
Cognitive deficit	62	11.2	CN4 (Trochlear)	6	1.1
Higher cortical function deficit (except for speech)	25	4.5	CN5 (Trigeminal)	6	1.1
Speech disorder	22	4.0	CN6 (Abducens)	11	2.0
Cerebellar deficit	21	3.8	CN7 (Facial)	21	3.8
Motor deficit	45	8.2	CN8 (Vestibulocochlear)	21	3.8
Somatosensory deficit	7	1.3	CN9 (Glossopharyngeal)	7	1.3
Epileptic seizure	60	10.9	CN10 (Vagus)	6	1.1
Other	4	0.7	CN11 (Accessory)	1	0.2
Cranial nerve (CN) deficit	219	39.7	CN12 (Hypoglossal)	4	0.7

Table 1. Preoperative clinical characteristics.

Location	No	%	Characteristic	No	%
Olfactory groove	63	11.4	Irregular shape	98	17.8
Planum sphenoidale	58	10.5	Invasive tumor-brain interface	79	14.3
Tuberculum sellae	55	10.0	Irregular margins	131	23.7
Sella turcica	3	0.5	Arachnoid plane	213	38.6
Sphenoorbital	39	7.1	Peritumoral edema	236	42.8
Sphenoid wing, medial variant	84	15.2	Contrast enhancement – homogeneous	443	80.3
Sphenoid wing, middle variant	39	7.1	Contrast enhancement – heterogeneous	109	19.8
Sphenoid wing, lateral variant	43	7.8	Capsular enhancement	85	15.4
Frontobasal	15	2.7	Dural tail	323	58.5
Cavernous sinus	9	1.6	CN - contact	98	17.8
Middle cranial fossa	28	5.1	Major vessel – contact	234	42.4
Posterior clinoid process	8	1.4	Major vessel – 360° encasement	87	15.8
Petrous	30	5.4	Major vessel – narrowing	9	1.6
Petroclival	14	2.5	Cavernous sinus invasion	36	6.5
Clival	5	0.9	Sunburst sign	179	32.4
Cerebellopontine angle	43	7.8	Intra- or peritumoral cysts	54	9.8
Jugular foramen	3	0.5	Bone invasion	129	23.4
Foramen magnum	13	2.4	Hyperostosis	102	18.5

Table 2. Radiologic characteristics[18]. Creative Commons Attribution 4.0 International License.

20–85, median: 58). Preoperative clinical characteristics of the cohort are summarized in Table 1. Objective preoperative neurological deficits were observed in 355 patients (64.3%). In terms of location, 452 meningiomas (81.9%) were supratentorial and 100 (18.1%) were infratentorial. The average diameter and volume were 3.1 cm and 22.7 cm^3, respectively. Further details on radiological characteristics are provided in Table 2. Simpson grade (S) was I in 87 (16.9%), SII in 321 (58.2%), SIII in 34 (6.2%), SIV in 109 (19.7%), and SV in 1 (0.2%) patient. Histological analysis revealed grade 1 meningiomas in 511 (92.6%) and grade 2 in 41 (7.4%) cases. Surgery-related mortality occured in seven cases (1.3%) and permanent neurological deficits were observed in 73 (13.2%) patients. Overall survival (OS) rate at 2 years was 98.1% with an average follow-up of 27.7 months.

Among 41 patients with atypical meningiomas, 31 (75.6%) underwent GTR, and 10 (24.4%) underwent STR. In the GTR group, 5 patients (16.1%) experienced recurrence; 3 of these (9.7%) underwent reresection, 1 (3.2%) received SRS, and 1 patient (3.2%) required RT following reresection. The mean follow-up for the GTR group was 76.2 months. Among the STR group, 1 patient (10%) underwent a reresection followed by recurrence, 4 patients (40%) received SRS, and 2 patients (20%) were treated with RT. At the last follow-up (mean follow-up: 35 months), 3 patients (30%) experienced disease progression, while seven (70%) remained stable.

Risk factors associated with a higher probability of WHO grade 2 SBM

The RF associated with a higher probability of WHO grade 2 SBM in univariate analysis and multivariate stepwise selection analysis are listed in Tables 3 and 4, respectively. According to the multivariate analysis, the presence of CN palsy ($p < 0.0001$), larger diameter ($p < 0.0001$), and absence of the arachnoid plane ($p = 0.0127$) were found to be significantly associated with a higher probability of WHO grade 2 SBM. The parameter Glasgow Coma Scale was excluded from the analysis due to non-significance (according to the Wald criterion). Based on these

Risk factors for WHO grade 2 SBM	*p*	
Diameter	W	< 0.0001
Volume	W	< 0.0001
Contact with cranial nerve	Chi	< 0.0001
Irregular shape	Chi	0.0002
Dural tail	Chi	0.0002
Invasive tumour-brain interface	Chi	0.0016
Length of symptoms/signs	W	0.0085
Gender	Chi	0.0138
Higher cortical function deficit (w/o speech)	Chi	0.0141
Nodularity	Chi	0.0166
Arachnoid plane	Chi	0.0229
Hyperostosis	Chi	0.0233
Cognitive deficit	Chi	0.0239
Oedema	Chi	0.0374
Cranial nerve palsy	Chi	0.0376
Sunburst sign	Chi	0.0479
Arachnoid cistern of meningioma origin	Chi	0.0490

Table 3. Univariate analysis: risk factors associated with higher probability of WHO grade 2 SBM (chi – chi-square test, W – Wilcoxon test).

Summary of stepwise selection process						
	Effect			Score	Wald	
Step	Entered	Removed	Number In	Chi-Square	Chi-Square	P-value
Risk factors for WHO grade 2 SBM						
1	Cranial nerve palsy		1	29.1994		< 0.0001
2	Diameter		2	16.2665		< 0.0001
3	Arachnoid plane		3	6.2116		0.0127
4	GCS		4	23.8328		0.0002
5		GCS	3		0.5010	0.9921

Table 4. Multivariate stepwise selection analysis: risk factors associated with higher probability of WHO grade 2 SBM.

results, a predictive logistic regression model was created with an area under the curve (AUC) of 0.79 (SE 0.04; 95% Wald Confidence Limits (0.71; 0.86); Fig. 1):

$$\text{Risk score (below f(X))} = -4.6995 + 1.3430 \times \text{CN palsy (0/1)} - 1.0041 \times \text{arachnoid plane (0/1)} + 0.0587 \times \text{diameter (mm)}$$

The probability of WHO grade 2 SBM is then calculated as $y = \frac{1}{1+e^{-f(X)}}$

Sub-analysis of predictive factors in the 2007 and 2016 WHO classifications

To address the issue of using two different WHO classifications and the challenges of retrospectively assessing the invasion parameter, we conducted a sub-analysis by dividing the cohort into two groups based on the time of surgery. The first group consisted of 222 patients treated between January 2014 and August 2016, classified under the 2007 WHO criteria, while the second group included 330 patients treated between September 2016 and December 2019, classified under the 2016 WHO criteria. Using a multivariate logistic regression model with three key predictors (CN palsy, arachnoid plane, and tumour diameter), we found that the coefficients for these predictors in both subgroups were very similar to those derived from the entire cohort of 552 patients (Supplement 1: Sub-analysis of predictive factors in the 2007 and 2016 WHO classifications). The 95% confidence intervals showed substantial overlap across the groups, indicating consistent results. In the older cohort (2007 WHO classification), CN palsy (OR: 3.12, $p = 0.0279$), an intact arachnoid plane (OR: 0.34, $p = 0.0484$), and tumour diameter (OR: 1.07, $p = 0.0018$) remained significant predictors. The OR and confidence intervals were slightly different from the full cohort, but the significance and direction of effects were consistent. In the more recent cohort (2016 WHO classification), CN palsy (OR: 4.14, $p = 0.0035$) and tumour diameter (OR: 1.05, $p = 0.0071$) continued to be significant. Although the arachnoid plane predictor trended toward significance, it did not reach statistical significance (OR: 0.37, $p = 0.0944$).

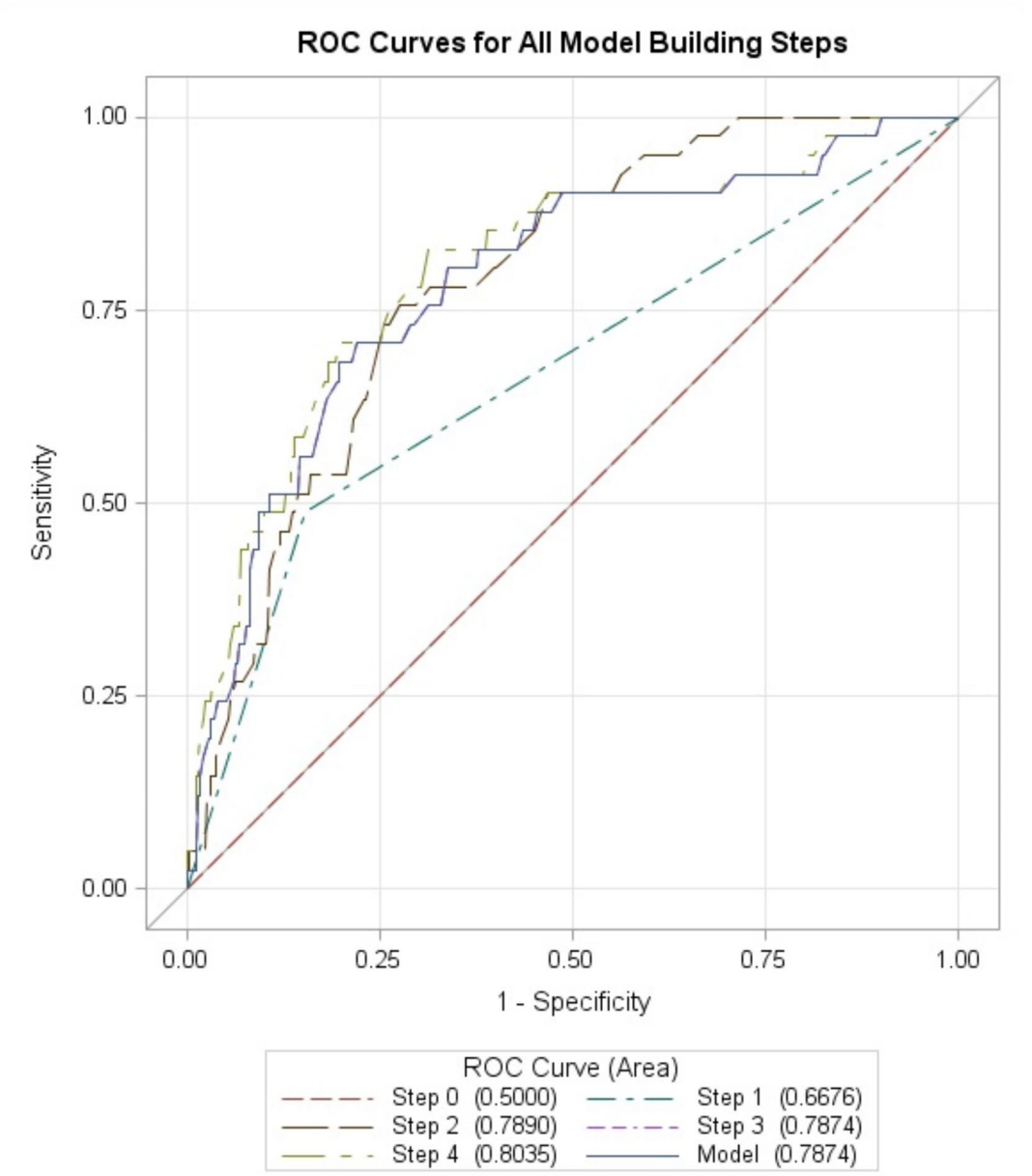


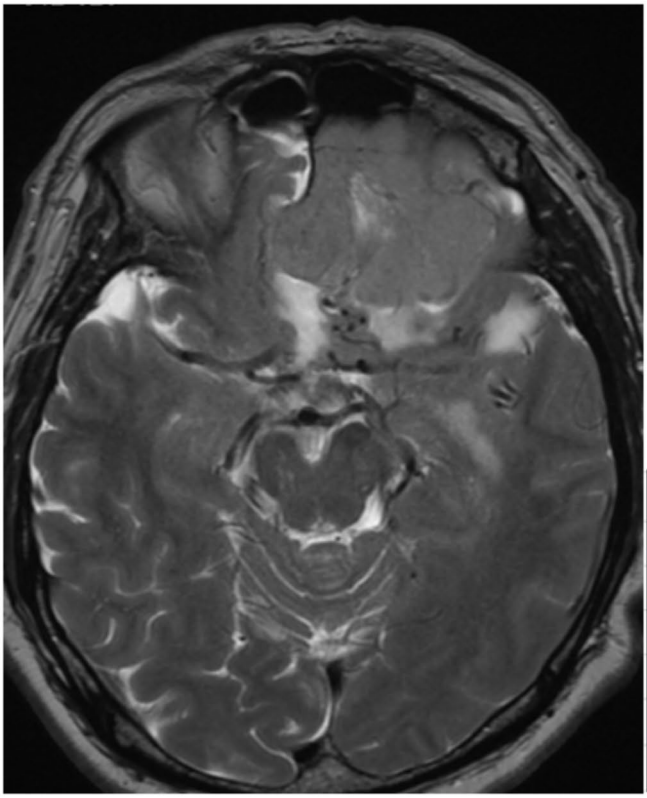
Fig. 1. Receiver operating characteristic (ROC) model predicting probability of WHO grade 2 SBM (AUC 0.79; 95%Wald Confidence Limits (0.71; 0.86)).

Discussion

Histological grading stands as a cornerstone in the prognostication and therapeutic decision-making for meningiomas. For WHO grade 2 meningiomas, studies report 5-year OS rates ranging from 78.4 to 95.0%, with 10-year OS rates ranging from 53.3 to 89.6%[6,19–21]. However, the reported PFS rates at 5 and 10 years are 48.4% and 22.6%, respectively, indicating a considerable risk of recurrence[19]. WHO grade 3 meningiomas exhibit even poorer survival outcomes, with 5-year OS rates ranging from 35.0 to 64.5% and 10-year OS rates from 14.2 to 34.5%[6,19,21,22]. The PFS for these patients is particularly low, with 5- and 10-year PFS rates of 8.4% and 0%, respectively[19]. RR are high, with only 29% of patients remaining recurrence-free at 5 years[21].

Preoperative risk factors associated with higher WHO grade

The preoperative detection of higher histological grades in meningiomas plays a pivotal role in guiding treatment strategies and improving patient outcomes. Various RF for HGM were investigated, encompassing epidemiological and clinical factors, conventional and advanced MRI features, SPECT, PET, and blood biomarkers[7,8,23–26]. Herein, we analysed epidemiological, clinical and radiological RF associated with higher probability of WHO grade 2 SBM in a cohort of 552 patients who underwent primary surgical resection of SBM. According to multivariate analysis larger meningioma diameter, absence of the arachnoid plane, and preoperative



70-year-old patient dignosed with grade 2 SBM

Neurologic Examination Findings:

- mental alterations
- speech disorder
- **hyposmia**

MRI Findings:

- SBM **without an arachnoid plane**
- measuring **60 mm** in diameter

Risk of a Higher WHO Grade: 54.13%

Calculator	
CN palsy (0/1)	1
Arachnoid plane (0/1)	0
Diameter (mm)	60
Risk score	0,17
y	0,54
Risk of higher WHO grade (%)	54,13

Fig. 2. Case example.

CN palsy were associated with a higher probability of WHO grade 2 SBM. Higher meningioma diameter, volume and volumetric growth were previously well documented as predictors of higher WHO grade[10,27,28]. Similarly, although inconsistently defined characteristics of the meningioma-brain interface e.g. incomplete CSF cleft[29], indistinct tumour-brain interface[30], lower grade of rim-pattern on FLAIR[31], pial invasion[29], and parenchymal invasion[29] were associated with higher WHO grade. Finally, the higher frequency of preoperative CN palsy in HGM could be explained by rapid and aggressive SBM growth. Likewise, Varlotto et al. documented an association of preoperative paresis with HGM histology[14]. We developed the logistic regression multivariate model estimating probability of WHO grade 2 SBM and transformed it into a surgeon-friendly Excel function. Its major advantage is quick applicability based on easily accessible preoperative RF. Furthermore, considering meningioma diameter as a continuous variable avoids categorization and enhances result accuracy. An example case is provided in Fig. 2 to illustrate its application.

Additionally, numerous other RF associated with higher histologic grade have been delineated in the literature. These patient- and tumour- related factors can be categorized into those readily accessible during routine examination and those requiring additional time and expertise for their extraction through advanced techniques and specialized procedures. Epidemiological biomarkers, most commonly older age[7,24,27,30] and male sex, are identified as RF for HGMs[8–10,32]. Moreover, specific tumour locations, particularly non-skull base meningiomas[7,9], and the presence of peritumoral oedema are commonly associated with a higher probability of HGMs[13,32]. RF not easily accessible during routine examination encompass the following. Lin et al. compared the effectiveness of diffusion kurtosis imaging (DKI), diffusion tensor imaging, and diffusion-weighted imaging metrics in grading meningiomas. The results revealed that DKI metrics were significantly higher in HGM, while mean diffusivity and apparent diffusion coefficient (ADC) were lower in HGM. Mean kurtosis emerged as the most effective parameter in differentiating HGM from low-grade meningiomas (LGM)[33]. Perfusion MRI is commonly used in neuro-oncology due to the strong association between tumour neo-angiogenesis and grading. Zikou et al. analysed dynamic susceptibility contrast metrics and reported the lesion/normal and peritumoral/normal relative cerebral blood volume ratios were significantly lower in LGM. Additionally, the fractional anisotropy ratios were significantly higher in LGM[34]. Dynamic contrast-enhanced MRI parameters were studied by Utomo et al. Time to maximum was lower and time-intensity curve, maximum slope of increase, maximum contrast enhancement ratio, slope were higher in HGM[35]. MR spectroscopy was examined by Lin et al., who observed a significantly higher choline/ N-acetylaspartate ratio in HGM[36]. Recently, there has been a noticeable increase in the number of studies applying radiomics and machine learning techniques for non-invasive grade detection. For instance, Hu et al. reported that the best performing multiparametric radiomic models were based on conventional MRI, ADC map, and SWI, achieving AUC values of 0.84 and 0.81[37]. Similarly, Zhang et al. trained the pyramid scene parsing network to identify meningiomas, while using the deep residual network

model for grading. For grade classification, the accuracy rates for the training and test datasets were 99.93% and 81.52%, respectively[38].

Optimizing treatment strategies with preoperative WHO grade detection

Reliable preoperative detection of HGM would necessitate substantial adjustments in treatment strategies to enhance therapeutic efficacy.

Observation

Given the poor prognosis and rapid progression of HGM, observation is of limited value in therapeutic strategies. Jääskeläinen et al. reported mean doubling times of 415 days for grade1, 178 days for grade 2, and 205 days for grade 3 meningiomas[39]. Furthermore, Soon et al. identified a significantly higher volumetric growth rate in grade 2 meningiomas compared to grade 1, with a threshold of 3 cm^3/year suggesting a HGM[28]. High suspicion of HGM on initial imaging would warrant immediate surgical resection without prior follow-up MRI. In cases of uncertainty, follow-up imaging at short intervals (e.g., 2–3 months) would be recommended.

Surgical resection

The recommended first-line treatment for HGM is prompt maximal safe surgical resection even in high-risk areas or incidental findings. Multiple studies emphasize the importance of EOR in improving survival outcomes for both grade 2 and grade 3 meningiomas. GTR has been consistently linked to better outcomes, including a higher 5-year OS rate (91.3% with GTR vs. 78.2% with STR in grade 2; 95% with GTR vs. 86% with STR vs. 67% with PR for HGM)[22,40], a higher 10-year OS rate (87% with GTR vs. 75% with STR in grade 2)[20] and significantly prolonged PFS[41,42]. SI resection has been shown to significantly improve both 5- and 10-year OS rates[6,19]. In atypical meningiomas, GTR provided a markedly higher 10-year local control rate compared to STR or an unknown resection extent (87% vs. 17%; $p = 0.02$)[20]. Additionally, a higher EOR was associated with longer OS ($p = 0.057$) and significantly reduced recurrence-free survival (OR 2.406; 95% CI 1.092 to 5.457; $p = 0.012$)[21]. Interestingly, Sughrue et al. reported a median survival of 107 months for near-total resection (NTR) compared to 50 months for GTR. However, the functional benefit of a smaller EOR should be interpreted cautiously, as all STR removed over 90% of the tumour, leaving only inoperable portions in high-risk areas (e.g., motor strip, cavernous sinus, internal carotid artery). These findings suggest that aggressive efforts to remove the final 1–5% of the tumour likely do not significantly improve survival[43]. Moreover, aggressive resection of malignant meningiomas appears to carry a higher risk of neurological morbidity compared to lower-grade meningiomas, regardless of the EOR[43,44]. Aizer et al. highlighted that GTR was associated with a 61% and 65% reduction in all-cause mortality for atypical and malignant meningiomas, respectively[22]. While aggressive resection may increase morbidity, the significant survival benefit suggests that GTR[22] or at least NTR[43] should be pursued when feasible. To facilitate maximal resection techniques such as wider craniotomy, extensive dural resection, and removal of infiltrated bone, dural venous sinus or invaded brain parenchyma in non-eloquent areas should be considered. The use of intraoperative MRI has been demonstrated to improve the EOR, particularly advantageous for cavernous sinus lesions and meningiomas extending into extracranial compartments. This facilitates additional safe resection and enhances the suitability for radiotherapy[45]. Furthermore, 5-ALA-induced fluorescence has been proposed to differentiate recurrent tumour from scar tissue and confirm complete removal in invasive meningiomas near critical neurovascular structures[46]. In addition to the well-established role of electrophysiological monitoring, the utilization of novel intraoperative technologies, such as augmented reality, shows promise in aiding complication avoidance, particularly in lesions adjacent to intricate anatomical structures[47].

Radiotherapy

The 2021 European Association of Neuro-Oncology guidelines recommend adjuvant radiotherapy for all grade 3 meningiomas and partially resected grade 2 meningiomas. Radiotherapy should also be considered for grade 2 meningiomas even after radical resection[48]. While malignant meningiomas are usually treated with maximal resection followed by RT[48,49], the optimal treatment for atypical meningiomas remains unclear[48,50]. The NRG Oncology/RTOG 0539 trial for high-risk meningiomas (new or recurrent grade 3, recurrent grade 2, and new grade 2 after STR) treated with intensity-modulated RT (60 Gy high dose and 54 Gy low dose in 30 fractions) reported a 3-year PFS of 59.2%, 3-year local control of 68.9%, and OS of 78.6%. Most adverse events were grades 1 to 3, with one grade 5 necrosis-related event, supporting the use of postoperative intensity-modulated RT[51]. For intermediate-risk meningiomas (recurrent WHO grade 1 and newly diagnosed WHO grade 2 after GTR), the same trial showed a 3-year PFS of 93.8%, a 3-year OS of 96%, and a local failure rate of 4.1%, demonstrating the effectiveness of fractionated RT (54 Gy in 30 fractions) with minimal adverse events[52]. Rydzewski et al. found 5-year OS rates of 85.5% for grade 1, 75.9% for grade 2, and 55.4% for grade 3 meningiomas. GTR and adjuvant RT significantly improved survival in atypical meningiomas, especially when combined (GTR plus RT: hazard ratio, 0.47; $P = 0.002$)[50]. A phase II study (EORTC 22042–26042) on grade 2 meningiomas treated with high-dose RT (60 Gy in 2 Gy fractions) after GTR reported a 3-year PFS of 88.7%, with 14.3% treatment failures and a 3-year OS of 98.2%. Late grade 3 or higher adverse events were observed in 14.3% of patients[53]. The results of the ROAM/EORTC-1308 trial to assess whether early adjuvant radiotherapy (60 Gy in 30 fractions) reduces tumour recurrence after complete resection of atypical meningioma are still pending[54]. Similarly, the ongoing NRG-BN003 trial in the US, a phase III randomized study, is assessing whether intensity-modulated RT (59.4 Gy in 33 daily 1.8 Gy fractions) after GTR of WHO grade 2 meningiomas improves PFS compared to observation. US and European trials indicate that adjuvant fractionated RT may benefit patients with intermediate and high-risk meningiomas, with acceptable toxicity[48]. Since adjuvant RT is recommended for any EOR in HGM, reliable preoperative grade detection is crucial. It enables early collaboration between the

surgeon and radiation oncologist, allowing them to assess and minimize surgical risks and potential radiation side effects. This approach facilitates timely initiation of radiation, reduces irradiated volumes, and improves the preservation of organs at risk.

Stereotactic radiosurgery

The role of SRS in the treatment of HGM is still to be determined. Gagliardi et al. conducted a systematic review and meta-analysis encompassing 42 studies (27 RT, 15 SRS; 2,853 patients; 3,077 HGM). Adjuvant RT compared to SRS, resulted in a higher overall RR (RT vs. SRS: 38% vs. 25% $p = 0.01$) but better 5-year local control (55% vs. 26%, $p = 0.01$) and 5-year-PFS (62% vs. 40%, $p = 0.008$), suggesting a potentially longer time to recurrence. However, it's important to consider that the SRS group had a shorter follow-up period, a higher proportion of grade 3 lesions, and a smaller EOR. No significant differences were observed in salvage regimens (RT vs. SRS: RR 46% vs. 24%, $p = 0.39$; mortality 34% vs. 12%, $p = 0.54$; 5-year OS 49% vs. 83%, $p = 0.90$; 5-year PFS 39% vs. 50%, $p = 0.66$)[41]. According to Kim et al., 35 patients with 49 HGM were treated with SRS at an average marginal dose of 16 Gy. Local tumour control rates for atypical meningiomas were 78% at 1 year, 53% at 2 years, and 36% at 3 years, while for anaplastic 35% at 1 year and 10% at 2 years. SRS may be a viable option for atypical meningiomas, but more aggressive treatment is required for anaplastic meningiomas[55]. Shepard et al. conducted a retrospective multicentre study of 271 patients treated with SRS for atypical (85.9%) or malignant (14.0%) meningiomas. Most received single-fraction SRS (97.4%) with a mean dose of 14.8 Gy. SRS was used as adjuvant treatment in 31.4%, salvage therapy in 67.2%, and primary therapy in 1.5% of cases. The 5-year PFS and OS rates were 33.6% and 77.0%, respectively. No significant difference in PFS/OS was found between adjuvant and salvage SRS, but a shorter interval between surgery and SRS improved PFS for atypical meningiomas (HR = 0.99, $P = 0.02$)[56]. The same advantages of preoperative grade detection for RT also apply to SRS, with even greater importance given the high radiation doses delivered in just 1–5 fractions.

Strenghts and limitations

The study's main strengths include its multicentric design and relatively large patient cohort, with all surgically treated meningiomas included to avoid selection bias. Surgeries were performed in six neurosurgical departments within a geographically well-defined area, ensuring equal patient access to healthcare. Limitations include the partly retrospective nature of the study and relatively short postoperative follow-up. Additionally, changes to WHO grading systems in 2000, 2007, 2016, and 2021 need to be taken into account, as some meningiomas in this study were graded according to the 2007 while others were graded using the 2016 classification. To address this, we conducted a sub-analysis of predictive factors for grade 2 meningiomas in the 2007 and 2016 WHO classification cohorts.

Conclusion

Various RF have been associated with an increased probability of a higher WHO grade, including epidemiological, clinical, and both conventional and advanced radiological parameters. Herein, we have developed a logistic regression model to estimate the probability of a WHO grade 2 SBM based on meningioma size, the presence of CN palsy, and the presence of the arachnoid plane (AUC 0.79). The primary advantage of this model lies in its focus on surgically challenging SBM and its ease of application, utilizing readily accessible parameters even in outpatient settings. Reliable preoperative detection of higher WHO grade in meningiomas would result in significant adjustments to treatment strategies, thereby enhancing therapeutic efficacy. With minimal reliance on observation, the preferred approach involves prompt maximal safe surgical resection, even in high-risk areas or incidental findings, followed by timely adjuvant radiotherapy in most cases. Adjuvant radiotherapy would be considered already in surgical planning, leading to reduced irradiated volumes and better preservation of organs at risk.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

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Author contributions

MM: Substantial contributions to the conception or design of the study, data acquisition and drafting of the manuscript. Final approval of the version to be published. VS, JM: Substantial contributions to the conception or design of the study and radiologic evaluation of the imaging studies. Final approval of the version to be published.LP: Statistical analysis and interpretation of the results. Final approval of the version to be published. VP, PB, JF, MV, RL, SR: Substantial contributions to the conception or design of the study and the data acquisition. Final approval of the version to be published.MC: Substantial contributions to the manuscript, analysis, and interpretation of the data. Final approval of the version to be published.DN: Substantial contributions to the study design, revising the manuscript critically for important intellectual content and final approval of the version to be published.VB: Substantial contributions to the study design, revising the manuscript critically for important intellectual content and final approval of the version to be published.

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Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

All procedures performed in studies involving human participants were in accordancewith the ethical standards of the Ethical Committee of the University Hospital in Ostrava(reference number 530/2018) and with the 1964 Helsinki Declaration and its lateramendments or comparable ethical standards

Consent to participate

General informed consent to the use of the anonymised data for research purposes wasobtained from all individual participants included in the study

Consent for publication

The authors affirm that human research participant provided informed consent for publication of the image in Fig. 2.

Additional information

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