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CLINICAL PRESENTATION AND RADIOLOGIC PATTERNS OF WHO GRADE I VS GRADE II MENINGIOMAS

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Abstract: Meningiomas are the most common benign tumor of the central nervous system, accounting for 53.3% and 37.6% of all central nervous system tumors (1). The World Health Organization (WHO) Grade I meningiomas account for 80.5% of all meningiomas and are considered benign meningiomas; the WHO Grade II meningiomas account for 17.7 % of all meningiomas and exhibit more aggressive behavior.

Methods: In the period 2015-2022, a retrospective single-center study at the clinic of neurosurgery at the Clinical Center University of Sarajevo was conducted, which included patients with a pathohistological finding of WHO Grade I or II meningioma. Depending on the pathohistological grade of the tumor, patients were divided into two groups: Grade I and Grade II patients. Patients were examined clinically and radiologically. Clinical data collected included in the study: Gender, age, number of symptoms before surgery, whether patients were symptomatic or asymptomatic, pre-operative Eastern Cooperative Oncology Group,and Karnopsky performance scale. Pre-operative contrast magnetic resonance imaging of the head measured tumor volume, temporal muscle thickness (TMT), sagittal midline shift, and surrounding cerebral edema.

Results: A total of 80 patients were enrolled in the study, 68 with WHO Grade I and 12 with WHO Grade II meningiomas. We found that patients with Grade I meningioma were younger and that the mean thickness of the temporal muscle was statistically thicker than in patients with Grade II. Increasing TMT was significantly and positively associated with Grade I tumors and negatively associated with Grade II tumors (p = 0.032).

Conclusion: This study demonstrates that TMT can serve as a radiologic pre-operative indicator of meningioma grade and provide valuable guidance to neurosurgeons in surgical planning. Further studies are needed to validate these results.

Keywords: Meningioma; World Health Organization; pre-operative indicator; grade

INTRODUCTION

Meningiomas are the most common benign tumor of the central nervous system, accounting for 53.3% and about 37.6% of all central nervous system tumors (1). The World Health Organization (WHO) Grade I meningioma's account for 80.5% of all meningiomas and are considered benign meningiomas; WHO Grade II meningioma's account for 17.7% of all meningiomas and have a more aggressive behavior. Of all WHO Grade II meningiomas, most are located on the convex side of the brain, and they are rare at the base of the skull, where Grade I meningiomas predominate (1, 2). Complete resection of the tumor and dural attachment remains the primary goal of treatment. However, this goal cannot

always be achieved because meningiomas can involve eloquent brain regions or structures where resection of the tumor can result in damage to the affected structures, such as at the base of the skull. In the surgical treatment of WHO Grade II meningiomas, the 5-year disease-free progression rate is between 50% and 90% if total resection is achieved; if subtotal resection is performed, the rate is 30-70% (3). The classification used to describe the extent of resection of tumors is known as the Simpson classification. It includes gross total resection as Simpson Grades I to III and subtotal resection as Simpson Grades IV and V (4). Simpson's Grades I to III include gross total resection, but the impact on clinical outcomes varies widely between rates: 5 years after surgery, rates range from 74% to 85% for Simpson's I and 34-89% for Simpson's II and are much lower for Simpson's Grade III (5, 6). When resecting meningiomas, the neurosurgeon must decide on the extent of Simpson's resection and possible neurological deterioration; there must be an onco-functional balance that includes all factors that can affect the patient's quality of life. The decision must take into account the possibility of meningioma recurrence and the possibility of reoperation. The aim of this paper is to evaluate the clinical and radiologic features of WHO Grade I and II meningiomas to perform aggressive resection in preoperatively suspected WHO grade meningiomas to achieve a better progression-free time.

METHODS

A retrospective single-center study was conducted at the clinic of neurosurgery at the Clinical Center University of Sarajevo in the period 2015–2022. Inclusion criteria were patients older than 18 years; surgically treated and pathophysiologically proven to be a Grade I or II meningioma according to the WHO classification of tumors, intracranial tumor localization, pre-operative magnetic resonance imaging (MRI) of the head with contrast. Exclusion criteria were patients who underwent surgery with computed tomography of the brain only, spinal localization of the tumor, recurrent meningiomas, meningiomas with multiloculated localization, pathohistological findings without a definitive diagnosis of Grade I or Grade II meningioma. Due to the retrospective design of the study, informed consent of the patients was not required. The study is approved by the Ethical Committee of Clinical Center of Sarajevo University. Patients were divided into two groups according to the pathohistological grade of the tumor: Grade I and Grade II patients. Patients were examined clinically and radiologically. Clinical data collected included in the study: Gender, age, number of symptoms before surgery, whether patients were symptomatic or asymptomatic, and pre-operative Eastern Cooperative Oncology Group (ECOG) and Karnopsky performance scale. Tumor volume, temporal muscle thickness (TMT), sagittal midline shift, and surrounding brain edema were measured on pre-operative contrast MRI of the head. Meningioma volume was calculated using the 1/2ABC formula, where "A" was defined as the greatest longitudinal length and "B" as the maximum width, and it was measured from the internal table of the skull to the cortex perpendicular to A on the same slide. "C" was the height of the meningioma. TMT was measured bilaterally perpendicular to the long axis of the temporal muscle at the slice on the T1w gadolinium contrast-enhanced MRI scan above the orbital roof and calculated using the average values for the left and right sides. Sagittal midline shift was measured as the perpendicular of the falx cerebri (midline) to the septum pellucidum. Cerebral edema is analyzed in the T2w MRI sequence, and hypersignal is assumed to be cerebral edema (Figure 1). All measurements were performed by two

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researchers. The statistical analysis was performed in R 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria). Descriptive summaries are given as mean (± SD), median interquartile range (IQR), and range (min-max) for numeric

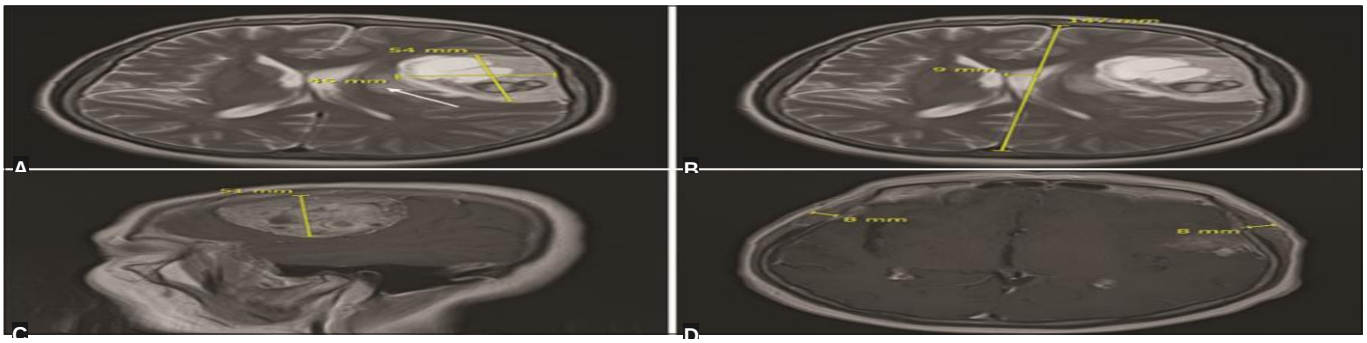

FIG URE 1 . Radiological measurements. (A) On the axial T2w sequence

TABLE 1. Patient characteristics TABLE 3. Tumor characteristics

Tumor grade

Variable	Grade I (n=68)	Grade II (n=12)	p-value
Tumor volume (cm3)			0.0593
Mean (±SD)	41 (±36)	60 (±34)	
Median (IQR)	35 (16-49)	66 (29-76)	
Range	1-170	6-113	
Cerebral edema, n (%)	50 (74)	10 (83)	0.72
Midline shift, n (%)	43 (63)	6 (50)	0.52
Temporal muscle thickne ss (mm)			<0.0013
Mean (±SD)	7.36 (±1.66)	5.22 (±1.34)	
Median (IQR)	7.35 (6.10-8.43)	5.00 (4.43-5.65)	
Range	3.90-10.90	3.50-8.30	

1Eastern cooperative oncology group score
2Fisher's exact test
3Wilcoxon rank-sum test
SD: Standard deviation, IQR: Interquartile range

With the white arrow is brain edema shown, and the measurement of the tumor volume with longitudinal length and width of it. (B) On the axial T2w sequence, the measurement of the midline sagittal structure shift is shown. (C) On the sagittal T1w CE, the measurement of the head-feet diameter of the tumor is shown. (D) On the axial T1w CE sequence, the measurement of temporal muscle thickness is shown. Variables. Ordinal and categorical variables are reported in absolute and relative numbers within each stratum, and ordinal variables are summarized as median (IQR). The significance threshold was set at $\alpha = 0.05$, with lower p-values at this level being considered statistically significant. Univariate logistic regression was performed to determine the association with the outcome (tumor grade) for each variable, and variables with a $p < 0.2$ were included in the multivariate model. Variables with high collinearity and perfect categorical discriminators were excluded before model fitting as the

number of observations in the Grade 2 stratum was low. The multivariate logistic regression model was fitted to the data, and a stepwise backward selection was performed using the Akaike information criterion, excluding variables with low predictive value. The odds ratios and 95% confidence intervals are given as the results of the multivariate model.

RESULTS

In this retrospective observational study of patients with meningiomas, we analyzed the association between tumor grade and various demographic, clinical, and radiological characteristics in 80 patients, 68 of whom had Grade I and 12 Grade II tumors (Tables 1-3). The distribution of gender showed no significant difference between the two groups (p = 0.3), with 17% of Grade I and 42% of Grade II patients being male. Age showed a statistically significant difference (p = 0.003), with Grade I patients having a mean age of 57 years (± 12), while the mean age of Grade II patients was 69 years (± 8). Clinical symptoms were present in 88% of Grade I patients and 92% of Grade II patients, with no significant difference (p > 0.9). There was a non-significant trend in the number of symptoms (p = 0.093), with Grade I patients tending to Have a higher number of symptoms. Tumor location did not differ significantly between the two groups (p = 0.72), and the most common locations were frontal (25% in both strata) and parietal (16% of Grade I patients and 25% of Grade II patients). Pre-operative performance status, as Assessed by the ECOG scale, showed no significant differences between Grade I and Grade II patients (p = 0.4 each). Pre-operative functional assessment results using the Karnofsky scale showed a lower median score of 70 (IQR 58-75) in Grade II patients compared to Grade I patients with a median score of 80 (IQR 70-90), with no statistically significant difference (p = 0.081). Tumor volume approached significance (p = 0.059), with Grade II tumors having a larger median volume of 66 cm^3 (IQR 29-76) than Grade I tumors with a median volume of 35 cm^3 (IQR 16-49). Cerebral edema and midline shift showed no significant differences (p = 0.7 and p = 0.5, respectively). In particular, TMT showed a highly significant difference (p < 0.001), with Grade I patients having a median thickness of 7.35 mm (IQR 6.10-8.43) and Grade II patients having a median thickness of 5.00 mm (IQR 4.43-5.65). The exponentiated coefficients (interpreted as odds ratios in the logistic regression model) together with the 95% confidence intervals are shown in Table 2. Gender, age, number of symptoms, pre-operative ECOG and Karnofsky scale scores, and TMT were included in the final model. There is a positive correlation between male gender and higher tumor grade, although we report a very wide confidence interval of 0.75-200, with a p = 0.11. Similarly, there is a positive correlation between increasing age and higher tumor grade, although also not statistically significant (p = 0.14). The increasing number of symptoms present is more strongly associated with Grade I tumors and was found to be statistically significant (p = 0.008). There was also a non-significant association between a higher ECOG score and Grade I tumors (p = 0.12), while an increasing Karnofsky score was significantly associated with Grade I tumors (p = 0.046). Finally, increasing TMT was significantly and positively associated with Grade I tumors and negatively associated with Grade II tumors (p = 0.032) (Table 4.).

DISCUSSION

In this study, we have shown that the clinical and radiologic features of Grade I or II meningiomas are almost identical.

TABLE 4. Multivariable logistic regression model

Variable	OR[1]	95% CI[1]	p-value
Sex (male)	8.63	0.75-200	0.11
Age	1.09	0.98-1.24	0.14
Number of symptoms	0.11	0.01-0.46	0.008
Pre-operative ECOG	0.04	0.00-1.20	0.12
Pre-operative Karnofsky scale	0.79	0.58-0.95	0.046
Temporal muscle thickness (mm)	0.37	0.12-0.79	0.032

[1]OR=Odds Ratio,CI=Confidence Interval, ECOG: Eastern cooperative oncology group We found that patients with a Grade I meningioma were younger and that the mean thickness of the temporal muscle was statistically thicker than in patients with a Grade II meningioma. In our study, we showed that patients who underwent surgery for WHO Grade I meningioma were younger than patients in the WHO Grade II group, $p < 0.05$. The Previous published studies have reported that in the series, the age of patients with WHO Grade II and III meningioma was significantly younger than that of patients with WHO Grade I meningioma. However, Magill et al. found that patient age was not a predictor of WHO Grade II meningiomas (7, 8). In another study published in Norway in 2019 with a study population of 1355 patients diagnosed with WHO Grade I meningioma, the mean age was 58 ± 13.2 years, similar to our results. This study also found that patient age was identified as an independent prognostic factor for overall survival (OS) (9). However, in our multivariable logistic regression model, increasing age and higher tumor grade are indicated, although also not statistically significant. TMT has been proposed as a new surrogate marker for skeletal muscle mass in malignant head and neck tumors. In a study analyzing TMT in 261 newly diagnosed gliomas from 2016 to 2022, TMT was found to be a positive biomarker for clinical prognosis in gliomas, with patients with thicker TMT having longer OS (10). In a meta-analysis that included 19 studies involving 4570 patients with brain tumors, it was found that sarcopenia or thinner TMT is an independent prognostic factor for OS in primary and secondary brain tumors, and that TMT should be included as a general tool in the pre-operative assessment of patients (11). In our study, there was a highly significant difference in TMT ($p < 0.001$), with WHO Grade I patients having a median thickness of 7.35 mm (IQR 6.10-8.43) and Grade II patients having a median thickness of 5.00 mm (IQR 4.43-5.65). However, this finding should be taken with caution as it is known that as patients age their TMT becomes thinner, our WHO Grade II meningioma group was significantly older at 57 versus 68 years (12). As for pre-operative meningioma volume, patients in the WHO Grade II group had larger meningioma volume, but there was no statistical difference between the groups. Conventionally, the larger size of the meningioma preoperatively was an indicator of larger meningioma (13). In some studies, such as Magill et al., they found a cut-off associated with the risk of WHO Grade II meningioma of 3.2 cm (8). In contrast, a systematic review published by Fountain et al. (14) as part of a literature search included four studies that provided limited evidence for the correlation of volumetric growth rates with histologic diagnosis. Perifocal brain edema is a clinical feature of most brain tumors, whether primary or secondary. Perifocal cerebral edema also occurs in meningiomas.

Previously, WHO Grade II and III meningiomas have been reported to have larger perifocal edema (15). In our study, the presence of perifocal cerebral edema was not a statistical difference between WHO Grade I and II. Meningiomas are thought to have a specific pathophysiologic mechanism that leads to perifocal edema; one of these theories is glymphatic system dysfunction (16). The glymphatic system has recently been recognized as a pathway for the removal of waste products and maintenance of fluid balance in the parenchymal interstitium of the brain (17, 18). The subtypes of WHO Grade I meningiomas: Angiomatous and microcystic meningiomas, which, due to their peculiar characteristics, produce giant perifocal brain edema that can mimic the edema of a highgrade meningioma (19). In our study, the location of the tumor did not show a specific localization of WHO Grade I or II meningiomas. Most of the WHO Grade II meningiomas were located in the frontoparietal area. As previously mentioned, most skull base meningiomas are WHO Grade Me meningiomas, whereas non-skull base meningioma and male sex are considered risk factors for Grade II meningiomas (20). We found no difference between the sexes of patients in these two groups. In a population-based study using data from a US national database of more than 450,000 patients diagnosed with meningiomas, the female sex was shown to be associated with a higher risk of meningiomas at all tumor grades, especially for WHO Grade I meningiomas (21). This study had limitations regarding the retrospective study design and the change in the WHO criteria for the diagnosis of meningiomas between 2016 and 2021 of the WHO classification of central nervous system tumors. The sample of patients with WHO Grade II was also small.

CONCLUSION

This study shows that the thickness of the temporal muscle can serve as a radiologic pre-operative indicator of the degree of meningioma, providing neurosurgeons with valuable information for surgical planning. Further studies are needed to validate these results.

Tumor grade

Variable	Grade I (n=68) (%)	Grade II (n=12) (%)	p-value
Sex, n (%)			0.32
Female	51 (75)	7 (58)	
Male	17 (25)	5 (42)	
Age			0.0033
Mean (±SD)	57 (±12)	69 (±8)	
Median (IQR)	59 (48-65)	65 (62-76)	
Range	29-83	57-81	
Clinical symptoms, n (%)	60 (88)	11 (92)	>0.92
Number of symptoms, n (%)			0.0932
0	8 (12)	1 (8.3)	
1	19 (28)	8 (67)	
2	15 (22)	1 (8.3)	
3	26 (38)	2 (17)	
Pre-operative ECOG, n (%)	1		0.42

0 15 (22) 3 (25)
1 28 (41) 5 (42)
2 14 (21)2 (17)
3 11 (16)1 (8.3)
4 0 (0) 1 (8.3)
Pre-operative Karnofsky scale 0.0813
Median (IQR) 80 (70-90)
1Eastern cooperative oncology group score
2Fisher's exact test
3Wilcoxon rank-sum test 70 (58-75)
SD: Standard deviation, IQR: Interquartile cooperative oncology group
TABLE 2. Tumor location range, ECOG: Eastern
Tumor grade
Variable Grade I (n=68) (%) Grade II (n=12) (%) p-value
Tumor location, n (%) 0.7 2
Clinoidal 1 (1.5) 0 (0)
Falcotentorial 1 (1.5) 0 (0)
Frontal 17 (25) 3 (25)
Frontobasal 3 (4.4)0 (0)
Frontoparietal 6 (8.8) 3 (25)
Frontotemporal 4 (5.9)0 (0)
Frontotemporoparietal 3 (4.4)2 (17)
Occipital 3 (4.4)0 (0)
Olfactorius 3 (4.4)0 (0)
Parietal 11 (16)3 (25)
Parietooccipital 3 (4.4)0 (0)
Petroclival 1 (1.5) 0 (0)
Pontocerebellar 1 (1.5) 1 (8.3)
Skull base 4 (5.9)0 (0)
Temporal 6 (8.8) 0 (0)
Ventricular 1 (1.5)
1Eastern cooperative oncology group score
2Fisher's exact test
3Wilcoxon rank-sum test 0 (0)

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