The relationship between molecular subtypes and MR perfusion in patients with brain meningioma

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Abstract:

Background and Objective: Meningiomas are the most common primary brain tumors, accounting for 15 to 20% of all primary brain tumors. Differentiating between malignant and benign meningiomas before surgery is essential for treatment planning and prognostic assessment. One proposed method for differentiating malignant from benign meningiomasis magnetic resonance perfusion (MR perfusion), but limited studies have been conducted in this respect. Therefore, this study aimed to determine the relationship between molecular subtypes and MR perfusion in patients with meningiomas.

Materials & Methods: In this cross-sectional study, all patients with brainmeningiomas referred to Sina Hospital in Tehran between 2021 and 2024 were evaluated prospectively. MR perfusion was done for patients. After brain surgery, pathological samples were obtained from the patients, and in addition to determining the conventional tumor grade, molecular studies including Ki-67, EGFR amplification, and S100 were performed by the pathologist, and the results were recorded. The relationship between MR perfusion parameters (relative cerebral blood volume (rCBV), relative cerebral blood flow (rCBF), and mean transit time) with tumor-related data was assessed. The significance level was considered less than 0.05.

Results: Twenty-five patients were studied. The mean age was 55.08±12.07 years, and 17 patients (68%) were female. The most common presentation (76%) was headache. The findings showed that rCBV and rCBF were statistically significantly different between low-grade and high-grade tumors (P-values < 0.05). Although the calculated cut-offs for rCBV and rCBF (7.55 and 6.94, respectively) were useful for differentiating the different grades of disease, neither was statistically significant (P-value: 0.05 and P-value: 0.1, respectively). Also, patients with higher Ki67 levels had higher rCBV and rCBF (P-value < 0.05 for both).

Conclusion: MR perfusion values (rCBV and rCBF) have statistically significant differences between different grades of meningioma.

***Keywords:** Benign Meningiomas, Magnetic resonance imaging, Meningioma, Malignant Meningiomas*

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Background and Objective

Meningiomas represent the most prevalent type of intracranial tumors, accounting for 30% of all primary brain neoplasms. These tumors predominantly affect middle-aged individuals and are believed to arise from arachnoid cap cells.[1,2]

While the majority of meningiomas are classified as benign, it is important to note that up to 20% of these tumors are atypical or malignant. In such instances, these variants exhibit a more aggressive nature accompanied by a higher likelihood of recurrence. The degree of initial tumor resection, in conjunction with the histological grade, serves as significant predictors of tumor recurrence. Consequently, an understanding of the histological grade before the surgery is essential for effectively planning surgical interventions and radiotherapy.[3,4]

Meningioma recurrence risk has primarily been associated with the World Health Organization histopathological grade and the extent of surgical resection. However, the importance of molecular characteristics in evaluating meningioma aggressiveness and recurrence risk were described recently. Investigation of the relationship between these subtypes and imaging findings before the surgical resection can be utilize for beter management of patients. The routine diagnostic approach for meningioma involves conducting a brain magnetic resonance imaging (MRI), with or without the use of intravenous contrast. This method is typically effective in detecting meningiomas; however, it may not facilitate the differentiation between various subtypes of typical meningiomas, nor between typical and atypical or malignant meningiomas, utilizing conventional MRI sequences.[5-7] Magnetic resonance perfusion (MR perfusion) has the potential to aid in distinguishing a primary neoplastic process from a mass. Nevertheless, there is a paucity of research examining the correlation between the molecular subtypes of brainmeningiomas and MR perfusion findings. Consequently, this study's objective was to explore the relationship between molecular subtypes of meningioma and MR perfusion parameters.[5,8-10]

Materials and Methods

It was a cross-sectional prospective study that was conducted on all patients with brainmeningiomas referred to Sina Hospital in Tehran between 2021 and 2024. All patients presenting with newly diagnosed brain meningioma who were referred to the Sina Hospital and were candidate for surgical intervention were included in this study. The exclusion criteria were age less than 18 years or more than 75 years; not previously received care at this center, incomplete medical information; not having consent to participate in the study; psychological disorders; concurrent malignant diseases; pregnancy; concurrent brain lesions other than meningioma; history of stroke; previously history of brain surgery; recurrent meningioma; multiple meningiomas; history of neurofibromatosis; meningiomas secondary to radiotherapy; prior adjuvant therapy for meningioma before surgical intervention; requiring emergency surgery for meningioma; Karnofsky Performance Status (KPS) less than 70; and modified Rankin Scale (mRS) greater than 2.

Following evaluation against the predefined criteria, eligible patients who met the inclusion criteria underwent brain MR perfusion imaging after hospitalization. The imaging data were processed and analyzed at the Imaging Center of Imam Khomeini Hospital, Tehran University of Medical Sciences.

Brain MR perfusion was conducted at the hospital utilizing a General Electric Discovery 750 GEM 3-Tesla device. To enhance coordination and analysis, a member of the Radiology Department served as a collaborative partner on the project.

The patients underwent examination by a neurosurgeon, during which demographic information was systematically recorded using a checklist. Subsequently, surgical procedures were conducted on the patients. Following the surgical intervention, conventional tumor grading was performed,

alongside molecular assessments, including ki67, epidermal growth factor receptor (EGFR) amplification, and S100. These analyses were conducted by a pathologist at the hospital, and the findings were duly documented.

All tumor-related pathological data were independently reviewed and recorded by two pathologists. All MR perfusion (MRP) procedures were performed in collaboration with the Imaging Department of Imam Khomeini Hospital. The imaging findings for each patient were subsequently received, analyzed, and archived. Upon completion of the study, all patient data were comprehensively reviewed, and the final analysis was conducted.

Using the repeated-measures formula and related statistical calculations, with a Type I error rate of 5% and a study power of 80%, and based on findings from previous studies, the minimum required sample size for this study was initially estimated at 45 participants. After accounting for an anticipated dropout rate of at least 10%, the adjusted required sample size was approximately 50 participants. However, due to the limited number of referrals to Sina Hospital, the small number of eligible patients, the high cost of laboratory tests, and financial constraints, the final sample size was set at 25 patients, with the approval of the department's Vice Chancellor for Research.

Statistical Methods

The collected data were analyzed using SPSS version 26 software. The statistical indicators of mean and standard deviation for continuous variables and frequency (number and percentage) for categorical variables were used to describe the data. The ANOVA (pairwise Bonferroni) test was used to examine the differences between groups in continuous variables. The statistical significance level in this study was considered less than 0.05.

Ethical consideration

This study was approved by the ethical committee of Tehran University of Medical Science (IR.TUMS.SINAHOSPITAL.REC.1401.054).

Findings

Twenty-five patients were evaluated. The mean age of the participants was 55.08 ± 12.07 years, and 32% were male (n = 8) and 68% were female (n = 17). The data on presentation, location, and type of tumor are presented in Table 1.

Clinically, headache emerged as the most prevalent symptom, observed in 19 patients (76%). Additional reported symptoms included visual loss in 4 patients (16%), seizures in 1 patient (4%), and limb weakness in 1 patient (4%). In terms of tumor type, meningothelioma and atypical meningioma were identified as the most common, each accounting for 8 cases (32%). Transitional meningioma was observed in 6 cases (24%), and anaplastic meningioma in 3 cases (12%). Based on the Traditional Grading System, 12 patients (48%) were classified as grade 1, 10 patients (40%) as grade 2, and 3 patients (12%) as grade 3. Tumor location data are presented in Figure 2.

Ki67 was greater than 10% in 4 patients (16%), 5-10% in 1 patient (4%), and less than 5% in 20 patients (80%). In patients with Grade 1, 2, and 3, 9 patients (75%) had Ki67 less than 5%, three patients had Ki67 greater than 10%, and Ki67 was greater than 10% in one case, respectively. EGFR was negative in all patients, and S100 was strongly positive in only one with Grade 2 (4%).

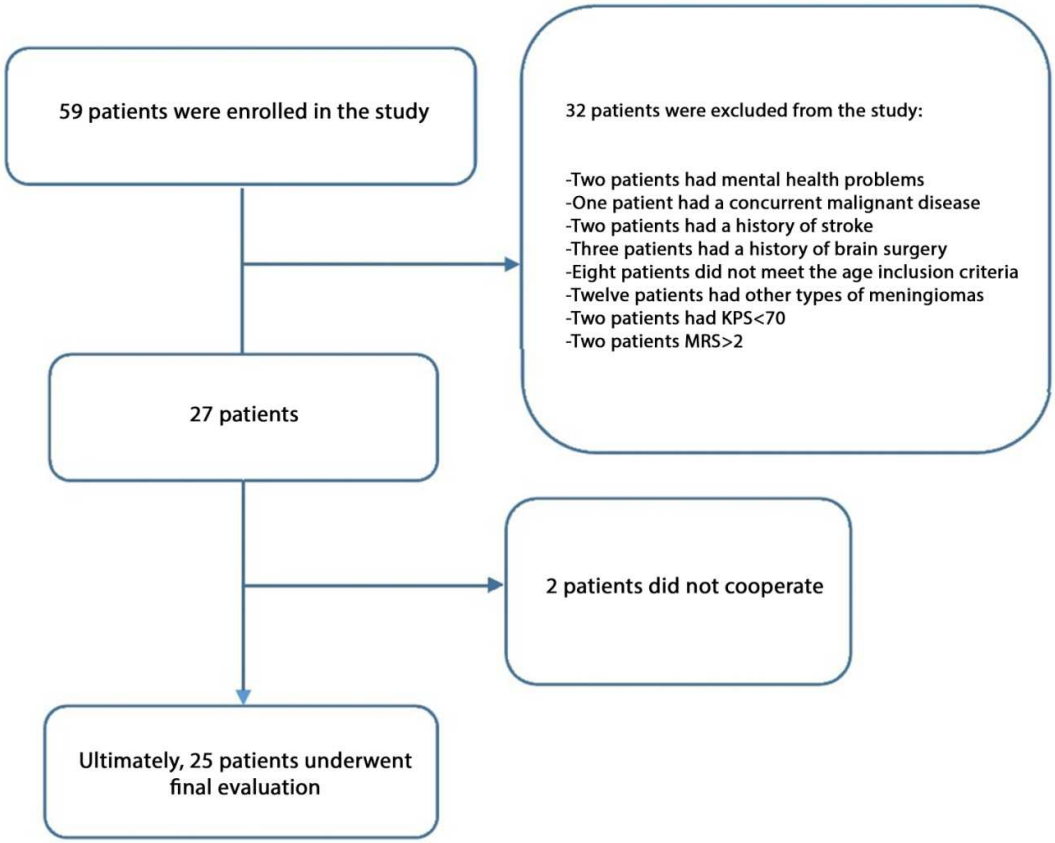

Diagram 1 - CONSORT chart

Table 1- Comparison of MRI perfusion parameters between different tumor grades

	Grade						
	1		***2***		***3***		
Variable	***Mean***	***Standard Deviation***	***Mean***	***Standard Deviation***	***Mean***	***Standard Deviation***	***Probability Value***
rCBV	*6.96*	*2.36*	*7.33*	*2.72*	*29.00*	*2.00*	*<0.001*
rCBF	*4.52*	*1.73*	*16.39*	*23.95*	*44.67*	*6.03*	*0.001*
MTT (Sec)	*17.63*	*9.26*	*17.06*	*11.01*	*23.67*	*4.04*	*0.573*

P-value based on ANOVA (Pairwise comparison by Bonferroni Test)

The mean value of MR perfusion parameters, including rCBV, rCBF, and MTT of all patients, were 9.74±7.64, 19.08±13.61, and 18.15±9.44, respectively.

Table 1 presents the association between Magnetic Resonance (MR) perfusion parameters and meningioma tumor grade. Both relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) demonstrated statistically significant correlations with tumor grade. In contrast, mean transit time (MTT) did not show a significant association with tumor grade.

The relationship between meningioma histological subtypes and MR perfusion parameters is summarized in Table 2. A statistically significant difference in rCBV was observed across the histological groups. Post hoc pairwise comparisons indicated that rCBV values were significantly higher in anaplastic tumors compared to all other subtypes ($P < 0.001$). Similarly, rCBF also differed significantly among the histological groups ($P = 0.005$). However, no statistically significant differences in MTT were detected among the histological subtypes (all $P > 0.05$).

To establish diagnostic cut-off values for meningioma grading, Receiver Operating Characteristic (ROC) analysis was performed. Based on the parameters that exhibited significant differences between tumor grades (as detailed in Table 3), ROC curves were generated. Given the limited sample size of Grade 3 meningiomas (n=3), patients with Grade 2 and Grade 3 tumors were grouped together as "Grade 2/3" for statistical analysis. Subsequent interpretation is based on the results derived from this combined cohort.

Interpretation of Relative Cerebral Blood Volume (rCBV) Cut-off Analysis Results

The area under the curve (AUC) for rCBV was 0.731, suggesting a moderate to good level of diagnostic accuracy for grading differentiation based on rCBV measurements. The standard error associated with this AUC value was 0.106. The p-value was at 0.050, on the statistical significance threshold ($p \leq 0.05$). This may be attributed to the limited sample size used in the analysis.

The optimal cut-off for detecting various grades of meningioma for rCBV was 7.55.

In this Cut off:

Sensitivity: 83.3% (indicating that 83.3% of Grade 2/3 tumors were correctly identified).

Specificity: 30.8% (indicating that 30.8% of Grade 1 tumors were correctly identified).

A cut-off value of 7.55 for relative cerebral blood volume (rCBV) was evaluated for its diagnostic performance in differentiating Grade 1 from Grade 2/3 meningiomas. This proposed cut-off of 7.55 for rCBV offers a high sensitivity (83.3%), suggesting a robust ability to detect high-grade (Grade 2/3) meningiomas. However, its comparatively low specificity (30.8%) implies a considerable rate of false positives, where a significant proportion of Grade 1 tumors may be misclassified as Grade 2/3.

Interpretation of Relative Cerebral Blood Flow (rCBF) Cut-off Analysis

Receiver Operating Characteristic (ROC) analysis of relative cerebral blood flow (rCBF), conducted to differentiate Grade 2/3 meningiomas from Grade 1 tumors, yielded an area under the curve (AUC) of 0.692. This value indicates a moderate and clinically acceptable diagnostic performance for rCBF in this context. Although the associated P-value of 0.103 did not reach the conventional threshold for statistical significance, the AUC value exceeding 0.65, together with its 95% confidence interval (0.475–0.910), suggests that the diagnostic performance of rCBF may be considered promising. Using the Youden Index, which identifies the optimal balance between sensitivity and specificity, the most appropriate cut-off value for distinguishing Grade 1 from Grade 2/3 tumors was determined to be 6.94 ml/100 g/min.

Table 2- Comparison of cerebral perfusion parameters in different histopathological types of meningiomas

	Type								
	Anaplastic		Atypical		meningothelioma		transitional		
Variable	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Probability Value
rCBV	29.00	2.00	8.01	0.83	6.92	2.25	5.16	3.21	<0.001
rCBF	44.67	6.03	20.00	26.32	5.05	1.26	3.86	2.37	0.005
MTT (Sec)	23.67	4.04	14.90	5.92	13.63	7.83	26.53	12.74	0.091

Table 3- Determining the cut-off ofrCBV for tumor grade detection

Index	Value
area under the curve (AUC)	0.731
P-value for AUC	0.050
Cut-off based on Youden index	7.5500
Sensivity at thecut-off point	0.833
specifityat the cut-off point	0.308

Table 4- Results of determining the rCBF cut-off for tumor grade differentiation

Index	Value
Cut-off based on Youden index	6.49 ml/100g/min
Sensitivity	٪50
Specificity	٪100
AUC	0.692
P-value for AUC	0.103

At this threshold, specificity reached 100%, indicating that all Grade 1 tumors were correctly classified. However, sensitivity was 50%, meaning that only half of the Grade 2/3 tumors were correctly identified. Accordingly, this cut-off may be particularly useful in settings where minimizing false-positive results is essential, such as preliminary screening or excluding the presence of Grade 2/3 disease.

Overall, these findings suggest that rCBF may serve as a useful adjunctive marker for differentiating meningioma grades, particularly when interpreted alongside other diagnostic parameters. Detailed results are presented in Table 4. The Receiver Operating Characteristic (ROC) curves for rCBV and rCBF are shown in Figures 3 and 4, respectively.

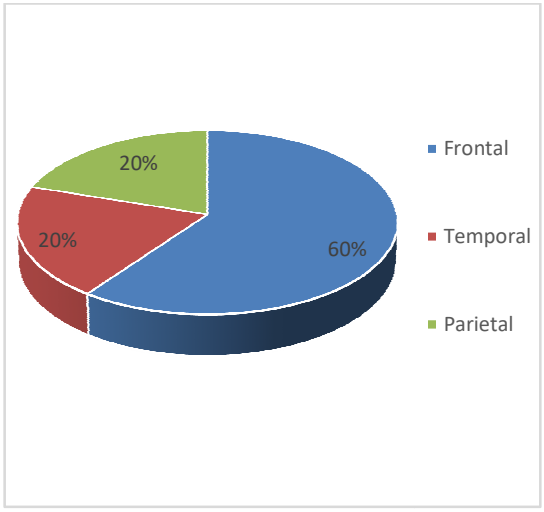

Diagram 2- Tumor location in the studied patients

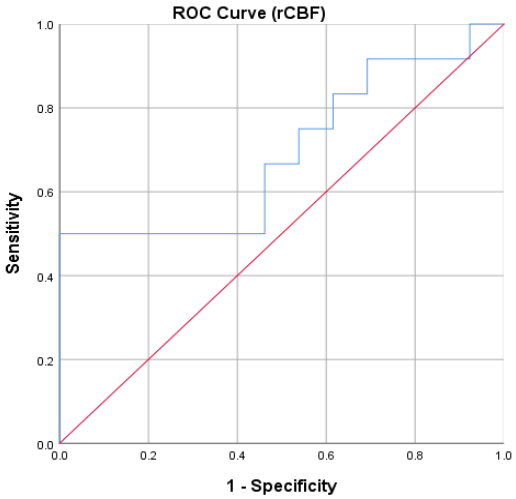

Diagram 4- ROC diagram for rCBF

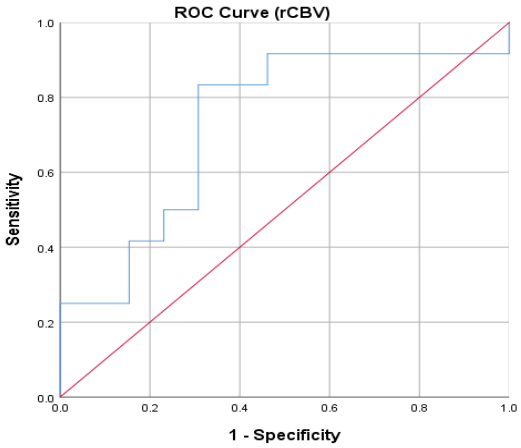

Diagram 3- ROC diagram for rCBV

Discussion

This study evaluated 25 patients, with a mean age of 55.08 ± 12.07 years, of which 17 patients (68%) were female. The mean Ki67 was 0.06 ± 0.04, and headaches were the most common symptom, reported by 76% of participants. Grade 1 tumors were most frequently operated on, comprising 52% of the cases. rCBV and rCBF significantly increased with higher tumor grades, with anaplastic meningiomas exhibiting the highest values.

The study identified cut-off values for differentiating grade 1 from grade 2/3 meningiomas, with rCBV at 7.55 (sensitivity: 83.3%, specificity: 30.8%, P-value: 0.05) and rCBF at 6.94 (sensitivity: 50%, specificity: 100%, P-value: 0.1). However, neither cut-off achieved statistical significance, likely due to the small sample size. A significant association was found between rCBV and rCBF with Ki67 levels, indicating that higher Ki67 levels were associated with higherrCBV and rCBF.

MRI is an important imaging modality for evaluating pathophysiological processes. Specifically, the characterization of brain tumors has significantly benefited from advancements in techniques such as diffusion-weighted imaging (DWI) and perfusion imaging. Nevertheless, despite the numerous computational methods that have been proposed, a comprehensive analysis of meningiomas remains insufficient. Furthermore, it has been suggested that MR perfusion parameters may serve as promising biomarkers for tumor staging.[11,12]

In a study examining the role of MR perfusion utilizing arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) in the grading of skull base meningiomas, Eissa et al. concluded that MR perfusion is effective in distinguishing between low-grade and high-grade meningiomas.[13] The findings of the present study corroborate the effectiveness of MR perfusion in diagnosing meningiomas. Our investigation revealed a significant association between meningioma grading and MR perfusion parameters, with the rCBV and rCBF exhibiting higher values in higher tumor grades compared to lower grades. Furthermore, the current study demonstrated that different grades of meningiomas could be differentiated based on established cutoff values. However, it is important to note that the cutoffs for rCBV and rCBF did not achieve statistical significance, which may be attributed to the limited sample size. This concern necessitates further studies with larger populations to validate the proposed cutoffs.

Qiao et al. investigated the effectiveness of MRperfusion with ASL in differentiating benign from malignant meningiomas. They identified three perfusion patterns: Pattern 1 showed homogeneous hyperperfusion, associated with grade I meningiomas; Pattern 2 exhibited heterogeneous hyperperfusion; and Pattern 3 revealed no significant hyperperfusion, correlating with grade II and III meningiomas. The study concluded that qualitative assessment of cerebral blood flow (CBF) maps could aid in distinguishing benign from higher-grade tumors, potentially influencing treatment strategies.[14]

The current study found that rCBVand rCBFwere positively and significantly associated with increasing tumor grade. Although the mean transit time (MTT) was different between the groups, it was not statistically significant, possibly due to the small sample size.

The study conducted by Rohilla et al. assessed the grading of meningiomas by analyzing rCBV. The findings indicated that the maximum rCBV within the tumor did not significantly aid in distinguishing benign meningiomas from malignant ones. Notably, an rCBV threshold of 2.5 mL/100 g in peritumoral edema demonstrated a sensitivity of 75%, specificity of 84.6%, and an accuracy of 83.3% for differentiating between benign and malignant meningiomas. Consequently, it was concluded that benign and malignant meningiomas can be effectively differentiated based on the maximum rCBV in peritumoral edema. Nevertheless, intratumoralrCBV values may provide valuable insights into the subtyping of meningiomas, particularly in the assessment of transitional and meningothelialtypes.[15]

In the current study, rCBV values were found to exhibit a statistically significant association with the grading of meningiomas, with elevated rCBV values associated with higher tumor grades. Both studies corroborated the notion that rCBV may serve as a potential indicator of meningioma grading, albeit employing differing methodologies. Despite these methodological difference, existing research appears to substantiate the diagnostic utility of MRperfusion in assessing meningioma status. In our study, the diagnostic cutoff established for differentiating meningioma grades based on rCBV was identified as 7.55, yielding a sensitivity of 83.3% and a specificity of 30.8%. The discrepancies observed between our findings and those reported by Rohilla et al. may be attributable to differences in the target sites for rCBV measurement; our study focused on the tumor itself, whereas Rohilla et al.

concentrated on the peritumoral edema. Previous research has indicated that the evaluation site, the type of imaging device, and the software utilized can significantly influence the values of MR perfusion parameters, which may explain the difference in results observed across studies.[16,17]

Pond et al. investigated preoperative magnetic resonance imaging (MRI) features of intracranial chordoid meningiomas (WHO Grade II) to identify distinctive characteristics that could distinguish this subtype from other meningioma variants. Their findings demonstrated that chordoid meningiomas exhibited significantly elevated apparent diffusion coefficient (ADC) and normalized ADC values compared with other meningioma grades (I, II, and III), thereby enabling reliable preoperative prediction of this atypical histopathological diagnosis.[18] A key distinction between the present study and that of Pond et al. is that ADC measurements were not included in our analysis. Nevertheless, our study included all meningioma subtypes, which provides a broader analytical scope. Despite these methodological differences, our findings are consistent with prior evidence supporting the diagnostic value of MRI in meningioma evaluation. Perfusion MRI and ADC are complementary MRI techniques that assess different tissue characteristics. Perfusion MRI evaluates blood flow and microvascularity, whereas ADC reflects the diffusion of water molecules and provides information regarding tissue microstructure and cellularity.[19-21] Future studies should therefore aim to compare the relative diagnostic and grading performance of these modalities in meningioma assessment.

Lum et al.'s study aimed to evaluate the efficacy of Intra-Arterial (IA) MR perfusion in characterizing the vascular supply of meningiomas. The findings indicated that Full Width at Half Maximum (FWHM), rCBV, and rCBFshowed statistically significant differences between Regions of Interest (ROIs) for IA MR perfusion. Moreover, rCBV and MTTwere significantly lower for IA perfusion in the Dural External Carotid Artery (ECA) compared to intravenous (IV) perfusion, while rCBF was notably higher in the Internal Carotid Artery (ICA) region for IA MR.[22]

The current study demonstrates that MR perfusion can effectively differentiate different grades of meningioma, highlighting its diagnostic utility for preoperative assessments. Although MTT did not show significant differences among grades, the parameters of rCBV and rCBF proved valuable due to their sensitivity and specificity. This comparison suggests that MR perfusion is a promising imaging technique for grade differentiation in meningiomas, but further studies are necessary to confirm its diagnostic value. Regarding the utility of MR perfusion parameters, some other studies were performed, but they didn't evaluate our parameters. In this respect, our study was similar to the previous study regarding the importance of MR perfusion relationships with meningioma's pathologic features.

In our study, the expression of Ki67 was observed to increase with escalating tumor grades from 1 to 2 and 3, particularly noted in grades 2 and 3, where a higher proportion of patients exhibited elevated Ki67 levels. However, it is important to note that the small sample size precluded the establishment of statistical significance. Numerous studies have indicated that Ki67 serves as an independent prognostic indicator for meningioma.[23-25] Nevertheless, the prognostic implications of Ki67 in meningioma remain inconclusive. Some research has identified a negative correlation between Ki67 expression levels and meningioma prognosis, while other investigations have reported findings that lack significance. This discripencies may be attributed to the substantial differences in cut-off values used for Ki67 analysis, the definition of these cut-off values, and the tumor grades considered across studies.[26-28] Our findings indicate a statistically significant association between rCBF and Ki-67. This observation aligns with the study conducted by Ginat et al., which reported a positive and statistically significant relationship between

maximum rCBV and Ki-67. Notably, our investigation reveals that no existing studies have assessed the association between Ki-67 and rCBF, underscoring the necessity for further research in this area and highlighting the novelty of this evaluation in the current study.

Implementation Constraints and Mitigation Strategies

A small sample size was one of the important limitations of the study, and this limitation occurred due to the low prevalence of meningioma. On the other hand, our center is a referral center, and most referred patients are complicated. Most of our tumorwere falx and parasagital meningioma, and the high percentage of grades 1 and 2 could be due to this issue. Other molecular and genetic tests could be associated with MR perfusion parameters. However, we could not investigate other molecular and genetic factors because they were inaccessible and costly.

Conclusion

The values of MR perfusion parameters, including rCBV and rCBF, demonstrate statistically significant differences between different grades of meningioma. These parameters may be potential as preoperative diagnostic tools that may enhance the management of patients presenting with these tumors. According to our findings, the established differential cutoffs for rCBV and rCBF were 7.55 and 6.94, respectively. While these cutoffs exhibited commendable sensitivity and specificity for the diagnosis of meningioma grades, were not statistically significant, possibly attributable to the small sample size utilized in this study.

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