

RESEARCH ARTICLE

Intratumoral and Peritumoral Apparent Diffusion Coefficient and MGMT mRNA Expression in Different Meningioma Histopathological Grade

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Abstract

BACKGROUND: Histopathological examination is the gold standard for diagnosing meningioma and determining the treatments. However, it is invasive in nature. This study was conducted to identify intratumoral and peritumoral apparent diffusion coefficient (ADC) value and mRNA O6-methylguanine-DNA methyltransferase (MGMT) expression in meningioma.

METHODS: Data were collected from 39 patients who were clinically diagnosed with meningioma. However, only 37 patients met the inclusion criteria. These subjects then underwent examinations and received treatment from October 2017 to September 2018. Magnetic resonance imaging (MRI) data with diffusion-weighted imaging-apparent diffusion coefficient (DWI-ADC) sequence, histopathological diagnosis of meningioma, and results of MGMT mRNA expression were obtained.

RESULTS: The most frequent type of low-grade and overall tumor was meningioma not otherwise specified (56.8%).

For high-grade tumor, there were two atypical cases: atypical meningioma (2.7%) and rhabdoid meningioma (2.7%). Meningothelial meningioma had the highest mean value of minimum intratumoral ADC at $864.57 \pm 219 \times 10^{-3} \text{ mm}^2/\text{s}$, whereas rhabdoid meningioma had the lowest at $417 \times 10^{-3} \text{ mm}^2/\text{s}$. For minimum peritumoral ADC, rhabdoid meningioma had the highest mean value at $1,651 \times 10^{-3} \text{ mm}^2/\text{s}$, while atypical meningioma has the lowest at $1,281 \times 10^{-3} \text{ mm}^2/\text{s}$. For MGMT mRNA, meningothelial meningioma had the highest mean value at 10 ± 1.2 fold change, whereas rhabdoid meningioma had the lowest mean at 6.18 fold change.

CONCLUSION: WHO grade I meningiomas had higher minimum intratumoral ADC values and higher MGMT mRNA expression than the high-grade tumors. Minimum peritumoral ADC values differed across the histopathological grades.

KEYWORDS: meningioma, RNA, messenger, MRI, methyltransferases, RT-PCR, ADC, MGMT mRNA

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Introduction

Meningioma is a tumor that arises from arachnoid cap cells which are attached to arachnoid villi in every location. Most meningiomas are located in the skull vault and the skull base. In addition, meningiomas can be found in the spinal cord. Most cases of meningiomas are classified as World Health Organization (WHO) grade I based on histopathology examination. The prevalence of meningioma is between 50.4 and 70.7 per 100,000 population.(1) According to the statistical report from the Central Brain Tumor Registry of the United States (CBTRUS), meningioma was the most common type of brain tumor (37.1%) in 2011-2015.(2) Meningioma is found twice as often in women than in men.(3)

Histopathological examination is still the gold standard for diagnosing brain tumor and determining subsequent treatments. However, this examination is invasive because a biopsy is needed. To obtain a preoperative diagnosis of brain tumor, radiological examination is the best modality. (4) Magnetic resonance imaging (MRI) is the modality of choice for diagnosing meningioma. With MRI, contrast differentiation and differences between intra-axial and extra-axial lesions can be shown.(3) Moreover, structural, cellular, vascular, metabolic, and functional characteristics of the tumor can be seen.(4)

To evaluate the differences between benign, atypical, and malignant meningioma, the use of conventional MRI is not sufficient.(3) Using one particular type of MRI, multiparametric MRI, the physiology and molecular properties of the brain can be shown with apparent diffusion coefficient (ADC) measurement.(5) Several studies reported that there was a decrease of ADC in high-grade tumors. A decrease in ADC value is caused by the reduction of extracellular free water diffusion and the high nuclear-to-cytoplasmic ratio in high-grade tumors. As a result, the free movement of intracellular water is reduced.(3)

To determine the tumor grade, another important modality is molecular biology examination. There are numerous publications regarding the potency of molecular biomarkers as a tumor predictive factor. However, only a few of those markers are relevant in clinical settings. For instance, Co-deletion 1p/19q in oligodendroglioma and O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status in glioblastoma.(6) Several studies found that in malignant tumors, MGMT expression was closely related to chemotherapy resistance.(7) MGMT gene promoter hypermethylation is a predictor of response

to temozolomide (TMZ) in glioblastoma patients. One meta-analysis reported that glioblastoma patients who had MGMT promoter methylation had better survival than those who had not when they were treated using TMZ.(8) One study showed that MGMT mRNA expression played a direct role for mediating tumor sensitivity to alkylating agents. Here are three methods for detecting MGMT methylation: methylation-specific polymerase chain reaction (MSP), quantitative real-time polymerase chain reaction (PCR) or MethyLight methylation-specific quantitative real-time PCR (MethyLight qMSP), and pyrosequencing.(9) So far, eight studies regarding methylation status of MGMT promoter region have been conducted. In 6 of these 8 studies, only few meningiomas (up to 6%) had methylated MGMT promoter. In two other studies, methylated MGMT promoter was found in 16% and 34% meningioma cases, respectively. Another study that determined MGMT promoter methylation status in 61 meningioma cases using pyrosequencing analysis, only found that 2 out of 61 tumors (3%) had higher mean value of methylation.(8)

In Indonesia, ADC value and MGMT mRNA measurement are not routinely done in meningioma patients in daily practice. The limitations in using ADC value are caused by the differences between results of studies regarding the efficacy of using ADC for determining brain tumor grade and type. Many previous studies investigating MGMT have examined its role in glial tumors. However, studies on the use of MGMT promoter methylation in meningiomas are still limited. For these reasons, this study was conducted to identify the characteristics of intratumoral ADC value, peritumoral ADC value, and MGMT mRNA expression in different types of meningioma based on the histopathological results.

Methods

Study Design and Subjects Selection

This was an observational descriptive study with cross-sectional design, conducted between October 2017 and September 2018. This study was approved by the Health Research Ethics Committee Faculty of Medicine, Universitas Indonesia (No. 950/UN2.F1/ETIK/2017), the Health Research Ethics Committee Faculty of Medicine, Universitas Hasanuddin (No. 863/H4.8.4.5.31/PP36-KOMETIK/2017), the Health Research Ethics Committee RSUPN Dr. Cipto Mangunkusumo (No. LB.02.01/X.2/984/2017), and the Research Ethics Committee Dharmas Cancer Hospital (No. 091/KEPK/XI/2017).

Thirty-nine patients were diagnosed meningioma clinically, underwent examinations, and received treatment in Cipto Mangunkusumo National General Hospital and Dharmais Cancer Hospital. However, only 37 patients met the inclusion criteria. The inclusion criteria of subjects for this study were patients diagnosed with meningioma according to histopathological results using ICD-WHO classification and had head MRI data with intratumoral and peritumoral diffusion-weighted imaging-apparent diffusion coefficient (DWI-ADC) sequences. The subjects were examined for MGMT mRNA expression using quantitative real-time polymerase chain reaction (qRT-PCR). Subjects who had incomplete examination results or incomplete medical records were excluded. All subjects had signed informed consent for participating in this study prior to examinations based on the study protocol.

Histopathology Data Acquisition

The diagnosis of meningioma was obtained from histopathological results which were categorized according to the WHO Classification of Tumors of the Central Nervous System 2016. Meningiomas were graded as WHO grade I, II, and III. The morphology codes for malignancy are based on the International Classification of Diseases for Oncology (ICD-O) [742A]. For statistical purposes, WHO grade I tumors were grouped as low-grade tumors, while WHO grade II and III tumors were grouped as high-grade tumors.(10)

MRI Measurement

All subjects underwent MRI using 1.5 Tesla Siemens Avanto. MRI images include: T2 weighted image (T2WI) = (time repetition (TR) /time echo (TE) 5160/112 ms; section thickness 5 mm; intersection gap 1 mm; matrix 269 x 384; field of view (FOV) 20.1 x 23.0 cm) and T1 weighted image (T1WI) = (TR/TE 500/9.4 ms; section thickness 5 mm; intersection gap 1 mm; matrix 256 x 256 ; FOV 23.0 x 23.0 cm). T1WI was performed in all subjects. T2 fluid-attenuation inversion recovery (FLAIR) = (TR/TE 7000/92 ms; inversion time 2214.1 ms; section thickness 5 mm; intersection gap 1 mm; matrix 230 x 256; FOV 23.0 x 23.0 cm). DWI was obtained in axial plane (TR/TE 4000/97; section thickness 5 mm; intersection gap 1 mm; matrix 128 x 128; FOV 23.0 x 23.0 cm). DWI was obtained with b values 0, 500, and 1000 mm²/s. Minimum intratumoral and peritumoral ADC value was determined by placing the region of interest (ROI) using the workstation (Syngo MR Workplace); the placement of 5 ROI spots was done by one researcher. For DWI identification, tumor with hyperintense

lesion was chosen, whereas tumor with hypointense lesion was identified for ADC measurement. ROI placement was done carefully with regard to the visual image of the tumor with an area of 1.6-1.7 mm². After that, the lowest value for ADC in mm²/s was obtained.

qRT-PCR AnalysisThe qRT-PCR was done to measure MGMT mRNA gene promoter. The following primers were used : MGMT Forward: 5'-GTGATTTCTTACCAGCAATTAGCA-3', MGMT Reverse: 5'-CTGCTGCAGACCACTCTGTG-3, human TATA-box binding Protein (TBP) (Forward: 5'-GAACATCATGGATCAGAACAACA-3',

The human TBP (hTBP) Reverse: 5'-ATAGGGATTCCGGGAGTCAT-3'. The qRT-PCR was conducted at 95°C for 10 seconds and at 60°C for 30 seconds, in 45 cycles. RNA sample was obtained and extracted with Guanidium thiocyanate (GuSCn) (Cat #820613, Sigma-Aldrich, Darmstadt, Germany) with Boom method RNA extraction.(11) Quantitative real-time PCR was done in triplicates using a Bio-Rad CFX Connect PCR (Biorad, Hercules, CA, USA) machine. PCR Mastermix (22.5 µL) and SYBR Green QRT were mixed and prepared. The PCR results were analyzed by Bio-Rad CFX Manager 3.1 software (Biorad) using an algorithm that corrected the standard curve with material for generating is normalized gene references to hTBP.(12)

Statistical Analysis

Patients' age, gender, brain tumor diagnosis from medical records, MRI DWI-ADC results, histopathological results, and qRT-PCR results were collected. Data were analyzed descriptively using Statistical Package for the Social Sciences (SPSS) version 20 (IBM Cooperation, Armonk, NY, USA). Data included frequencies and percentages for categorical variables or mean±standard deviation, median, and range for numerical variables.

Results

Subjects Characteristics

From 39 subjects participated in this study, only 37 of them had complete data. Based on the selection criteria, two subjects were excluded because of incomplete examination results or incomplete medical records.

The majority of the subjects in this study were females (91.9%) and aged 36-60 years (83.8%) (Table 1). Low-grade tumors were more common (94.6%) than high-grade tumors. In this study, meningioma not otherwise

Table 1. Subjects' characteristics.

Characteristics	n (%) (n=37)
Age (years old)	
1 – 5	1 (2.7)
6 – 10	0 (0)
11 – 18	1 (2.7)
19 – 35	1 (2.7)
36 – 60	31 (83.8)
61 – 81	3 (8.1)
Gender	
Male	3 (8.1)
Female	34 (91.9)

specified accounted for the largest percentage of low-grade and overall tumors at 56.8%. There were only two high-grade tumor cases, which were atypical meningioma (2.7%) and rhabdoid meningioma (2.7%) (Table 2). Due to the small amount and unequal distribution of data, the statistics could not be performed with confidence interval. Lower grade meningioma tends to have a higher minimum intratumoral ADC value and mRNA expression. Minimum intratumoral ADC value and mRNA expression were more likely to increase in meningothelial meningioma (WHO grade I, ICD-O 9531/0) and meningioma, not otherwise specified (WHO grade I, ICD-O 9530/0) than higher grade meningiomas (atypical meningioma (WHO grade II, ICD-O 9539/1) and rhabdoid meningioma (WHO grade III, ICD-O 9538/3)).

ADC value and MGMT mRNA Expression

According to Table 2, The highest value of minimum intratumoral ADC was found in meningothelial meningioma ($864.57 \pm 219 \times 10^{-3} \text{ mm}^2/\text{s}$), and the lowest minimum intratumoral ADC value was found in rhabdoid meningioma ($417 \times 10^{-3} \text{ mm}^2/\text{s}$). For minimum peritumoral ADC, the highest value of minimum peritumoral ADC was found in rhabdoid meningioma at $1,651 \times 10^{-3} \text{ mm}^2/\text{s}$, whereas the lowest mean value was found in atypical meningioma at $1,281 \times 10^{-3} \text{ mm}^2/\text{s}$. With regard to the highest and the lowest mean value of MGMT mRNA expression, the former was meningothelial meningioma at 10 ± 1.2 fold change, while the latter was rhabdoid meningioma at 6.18 fold change.

The median and range for each variable based on histopathological results were shown in Table 3. For peritumoral minimum ADC, the data were only obtained in 19 subjects because not all tumors showed this feature, 17 of which had low-grade tumors and only 2 subjects had high-grade tumors according to histopathological results.

As shown in Figure 1 there was a case of grade I meningioma that showed noticeable edema. It was revealed that minimum intratumoral ADC value was $806 \times 10^{-3} \text{ mm}^2/\text{s}$ and peritumoral one was $1,333 \times 10^{-3} \text{ mm}^2/\text{s}$. In one case of atypical meningioma (WHO Grade II), there were also similar MRI findings to grade I meningioma, which were noticeable peritumoral edema and midline shifting. However, it was revealed that minimum intratumoral ADC quantification was lower than the grade I, which was

Table 2. Histopathological and morphological characteristics of subjects.

Variables	Frequency (Percentage) [n (%)]	Mean±SD		
		Minimum Intratumoral ADC [x 10 ⁻³ mm ² /s]	Minimum Peritumoral ADC [x 10 ⁻³ mm ² /s]	MGMT mRNA [fold change]
Histopathological group				
Low-grade	35 (94.6)	807.45±183.00	1,537.70±289.20	9.55±1.33
High-grade	2 (5.4)	540.00±173.00	1,466.00±261.60	7.95±2.50
Tumor grade and morphology				
Meningioma, not otherwise specified (WHO grade I, ICD-O 9530/0)	21 (56.8)	769.38±148.00	1,336.00±313.00	9.19±1.30
Meningothelial meningioma (WHO grade I, ICD-O 9531/0)	14 (37.8)	864.57±219.00	1,428.25±210.00	10.00±1.20
Atypical meningioma (WHO grade II, ICD-O 9539/1)	1 (2.7)	663.00	1281.00	9.73
Rhabdoid meningioma (WHO grade III, ICD-O 9538/3)	1 (2.7)	417.00	1651.00	6.18
Total	37 (100)	793.00±190.00	1,369.11±282.00	9.46±1.40

Table 3. Median and range value of ADC and MGMT mRNA according to histopathological results.

Marker	Low-grade		High-grade	
	Median	Range	Median	Range
Minimum intratumoral ADC (n= 37)	806	487-1,259	540	417-663
Minimum peritumoral ADC (n= 19)	1,333	713-1,816	1,466	1,281-1,651
MGMT mRNA (n= 37)	9.62	6.15-11.62	7.95	6.18-9.73

Low grade : WHO Grade I; High-grade: WHO Grade II and WHO Grade III.

663 $\times 10^{-3}$ mm²/s, whereas peritumoral one was 1,281 $\times 10^{-3}$ mm²/s (Figure 2). In a more malignant type, rhabdoid meningioma, conventional MRI finding showed more aggressive features, such as infiltrative growth pattern, signal heterogeneity, contrast enhancement, and midline shifting. Minimum intratumoral ADC value was revealed to be 417 $\times 10^{-3}$ mm²/s according to DWI (Figure 3). These findings were confirmed with the histopathological examination. In grade I meningioma, it showed mixed type of meningothelial and transitional variants. In atypical one, it was found that mitoses index was high (5-7/10 high power field) (Figure 4).

Discussion

The gender distribution in meningioma was similar to previous studies which state that meningiomas are more frequent in women. This study found that meningioma was

diagnosed before the age of 60, especially 36-60 age group, in contrast to previous studies.(13-15)

The MRI results showed that the higher the tumor grade, the lower the ADC value. In general, minimum intratumoral ADC was higher in low-grade tumors than high-grade ones. However, different values were found. As stated in a multicenter analysis regarding ADC in meningiomas to predict tumor grade and the potency of proliferation, the mean intratumoral ADC value in WHO grade I meningiomas (1.05 \pm 0.39 $\times 10^{-3}$ mm²/s) was significantly higher than grade II (0.77 \pm 0.15 $\times 10^{-3}$ mm²/s) and grade III (0.79 \pm 0.21 $\times 10^{-3}$ mm²/s) ones with $p=0.001$.(16) In addition, several studies stated that the ADC value of meningioma was inversely correlated with its histopathological grade. (17,18) Similar results were also relatively comparable, in which the ADC mean value was significantly lower in WHO grade II meningiomas (0.72 \pm 0.09 $\times 10^{-3}$ mm²/s) compared with the one of WHO grade I ones (1.02 \pm 0.16 $\times 10^{-3}$ mm²/s) with $p<0.001$.(19) Despite these reports, a study found that

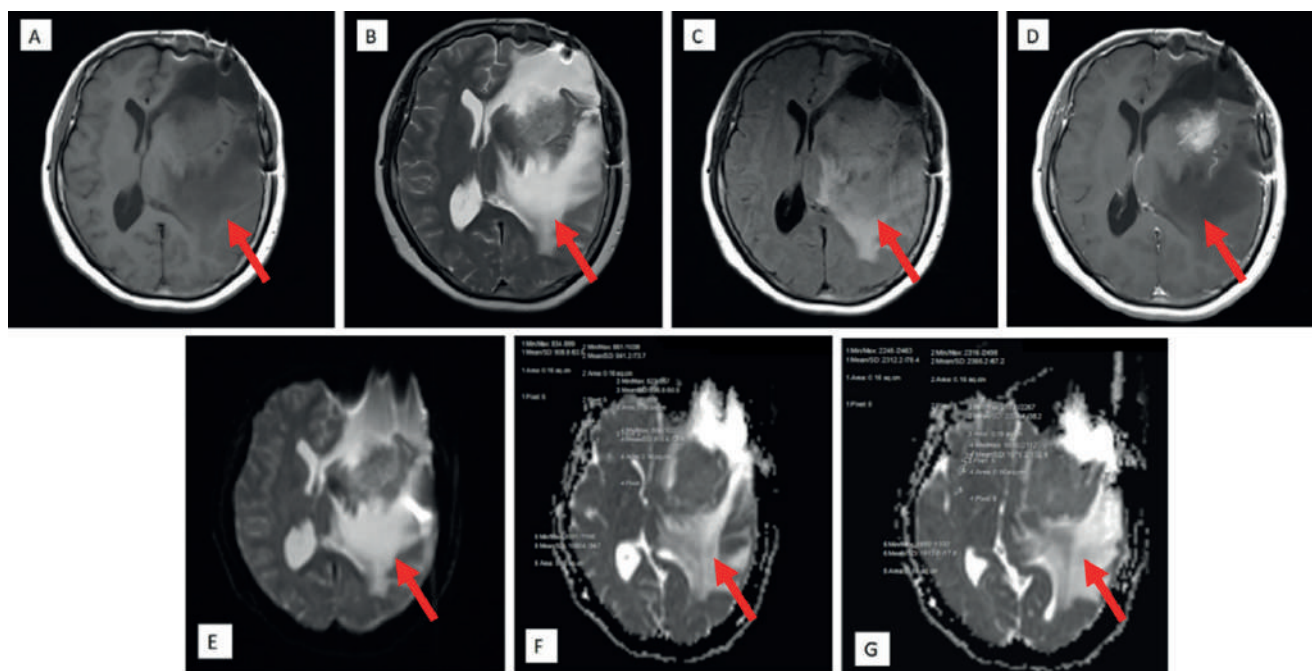


Figure 1. Meningioma, not otherwise specified case (WHO grade I, ICD 9350/0). A: T1WI; B: T2WI; C: FLAIR; D: Post-contrast T1WI; E: DWI; F: Tumoral ADC quantification; G: Peritumoral ADC quantification. Edema is shown with red arrow.

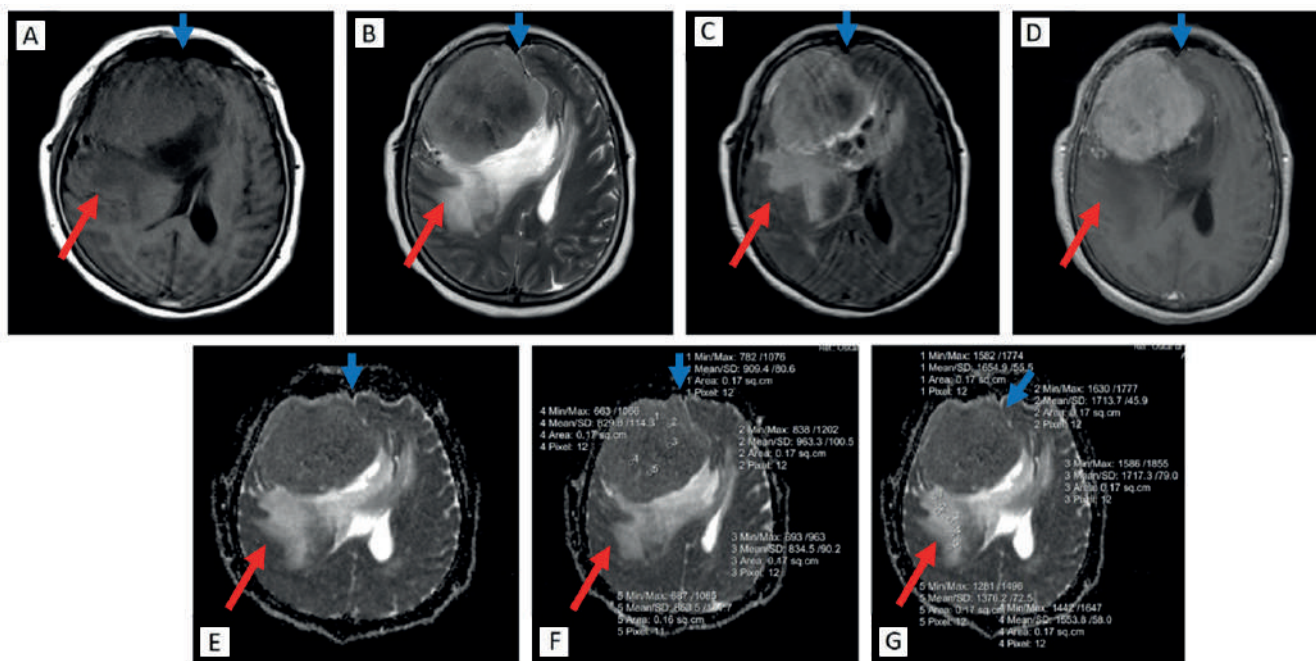


Figure 2. Atypical meningioma (WHO grade II, ICD 9359/1). A: T1WI; B: T2WI; C: FLAIR; D: Post-contrast T1WI; E: DWI; F: Tumoral ADC quantification; G: Peritumoral ADC quantification. Atypical meningioma showing peritumoral edema (red arrow) and midline shift (blue arrow).

distinguishing the histopathological grades of meningioma was not possible solely by using the ADC value.(20) Two published studies reported that DWI and ADC values were not useful in determining neither meningioma grades nor distinguishing histological subtypes.(21,22)

There were some cases of meningioma that did not show peritumoral edema. However, in meningioma that exhibited peritumoral edema, higher grade meningioma showed a higher minimum peritumoral ADC value. The result was slightly higher than in a previous study

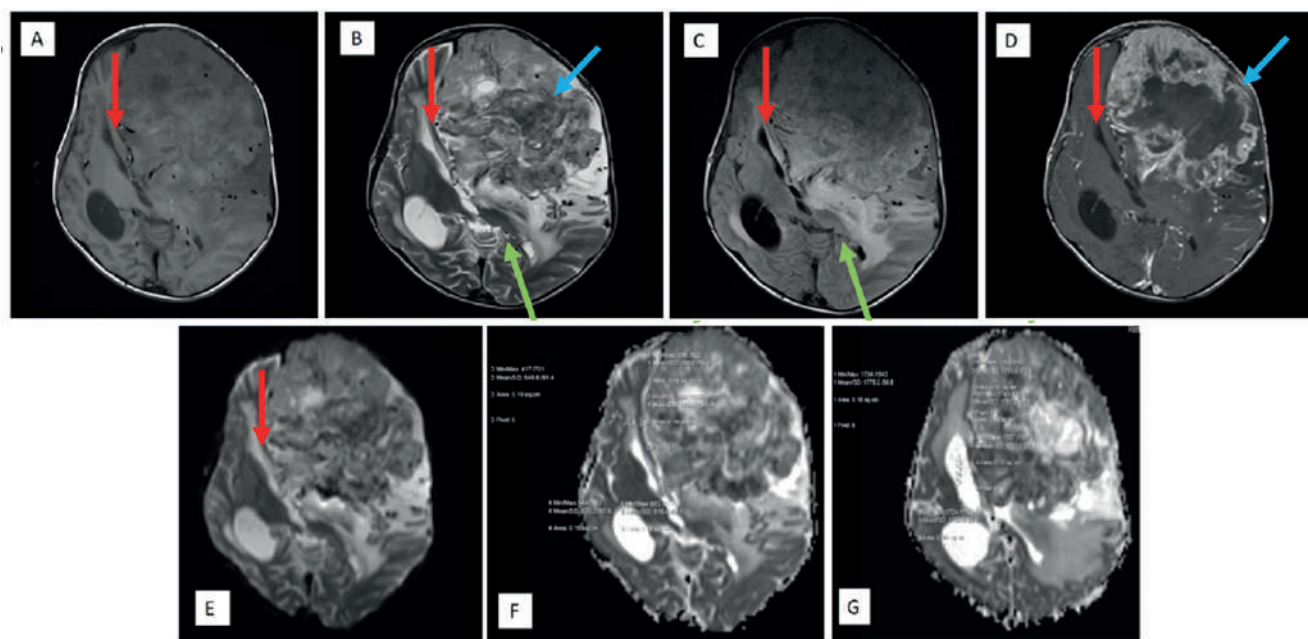


Figure 3. Rhabdoid meningioma (WHO grade III, ICD 9358/3). A: T1WI; B: T2WI; C: FLAIR; D: Post-contrast T1WI; E: DWI; F: Tumoral ADC quantification; G: Peritumoral ADC quantification. Rhabdoid meningioma shows infiltrative growth pattern (green arrow), signal heterogeneity (blue arrow), and midline shifting (red arrow) on conventional MRI.

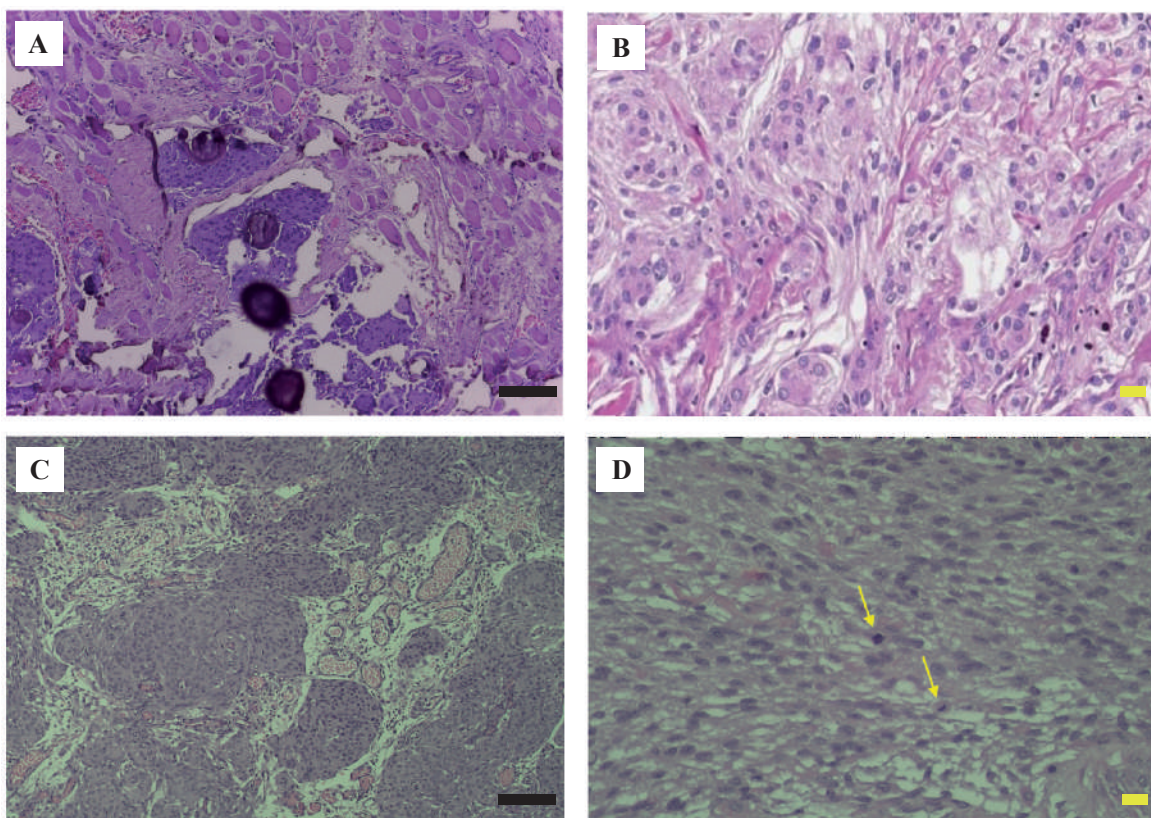


Figure 4. Histopathology of low-grade and high-grade meningioma. A and C: Mixed type transitional and meningothelial meningioma showing tumor cells in lobules and whorls with intranuclear pseudoinclusions, Black bar: 100 μm ; B and D: Atypical meningioma showing tumor cells with increased mitotic activity (total 6/10 HPF in this case, two of them are pointed by the yellow arrows), Yellow bar: 10 μm .

that showed the mean value of ADC in high-grade meningiomas in hyperintense regions to be $1,427 \times 10^{-3} \text{ mm}^2/\text{s}$, while in normal-appearing white-matter regions it was $0.743 \times 10^{-3} \text{ mm}^2/\text{s}$.(23) Our results were in accordance to another published report which found that ADC, high peritumoral edema, and the absence of calcification were prognostic of advanced histopathological meningioma grade.(24)

Another variable, MGMT mRNA expression, showed that lower tumor grade tends to have higher expression. However, at the present time, there is one study regarding the expression of MGMT protein. One study found MGMT protein expression in 55% of examined meningiomas. (25) Another study found that it was beneficial to examine MGMT protein expression status in meningeal hemangiopericytoma to predict the clinical outcome.(26) In one published research, fifteen MSP was done to examine meningiomas and found 13% of their grade I meningiomas to have their MGMT promoter methylated, and 33% and 15% of grades II and III, respectively.(27) By utilizing the same method, similar study found 2.8%, 5.6%, and 2.8% of 36 examined grade I, II, and III meningiomas have

methylated MGMT promoter.(28) A different research used quantitative MSP (qMSP) and found 0% of their examined meningiomas exhibiting MGMT promoter methylation.(13) A recent study used pyrosequencing in 61 meningiomas and found MGMT promoter methylation in 2% of grade I, 14% of grade II, and none of grade III tumors.(8) Furthermore, several studies have demonstrated an association between methylation status and various imaging features. Additionally, methylation status was more strongly linked with brain tumor prognosis.(29-31) Relationship between MGMT promoter methylation and radiological features of MRI showed that there was no significant difference ($p=0.14$ to $p=0.97$) between MGMT promoter methylation status and malignant tumor features in conventional MRI using Chi-Square test.(32)

There are several limitations to this study. First, there were only a few subjects who were enrolled. Second, the proportion of low-grade and high-grade tumors was unequal. Further study of the relationship between intratumoral ADC, peritumoral ADC, and MGMT mRNA in meningioma is needed, specifically with a larger sample size and more equal proportions of tumor grades.

Conclusion

From our study, low grade meningiomas had higher minimum intratumoral ADC values as well as higher MGMT mRNA expression than the high-grade ones. Minimum peritumoral ADC values vary across the histopathological grades. This could be useful for identifying meningioma grades as well as its corresponding biomolecular features.

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Authors Contribution

RM designed the study, performed radiological examinations, conducted statistical analysis, and wrote the manuscript. AAI, BM, and JT contributed to the development of idea, study design, and supervised the study. MH performed the molecular biology experiments and supervised the findings of this study. MF performed the surgery and collected the post-surgical findings. ES performed the histopathological examination and analyzed the results. JP contributed to the development of the statistical analysis. All authors read and approved the final manuscript.

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