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ROLE OF DIFFUSION WEIGHTED IMAGING IN DIAGNOSIS OF MENINGIOMA

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		KEVWORDS

INTRODUCTION

Abbreviations & Keywords: ADC- Apparent Diffusion Coefficient, DWI-Diffusion Weighted Imaging

Introduction: Meningiomas are dural based tumors, which arise from meningothelial cells or arachnoid cap. Meningiomas account for approximately 1/3 of primary intracranial tumors in adults. Despite their higher incidence, there have not been as many advances in understanding and managing meningiomas.

DIAGNOSIS OF MENINGIOMA

Imaging characteristics; advanced imaging technology; and radiomics are playing an increasingly important role in tumor diagnosis, prognosis, and treatment response. Diffusion-weighted magnetic resonance imaging (DW-MRI), diffusor tensor imaging, and PET imaging have been studied for preoperative prediction of biological behavior of meningiomas. But, their clinical utility is not yet established. Peritumoral edema around meningiomas is associated with higher proliferation index and irregular tumor margins, which may be a marker for more aggressive phenotype. Increased VEGF secretion and associated angiogenesis may also be associated with peritumoral edema. Comprehensive risk stratification models deploying imaging features, like preoperative ADC t MRI sequences, along with Simpson grade of classification, have shown superiority in envisaging which patients will experience progression or recurrence over standard histopathological grading and histopathological in combination with Simpson grading. Studies by Amer ME et al, and Di Ieva A et al, showed that preoperative fractal analysis of MRIs, a software method which better describes complexity of an image, may play a role in identifying non-BMs."

Octreotide scintigraphy has been demonstrated as an effective method to image meningiomas since 1990s. More contemporary imaging techniques, like PET imaging, have added a new dimension in the diagnosis and grading of meningiomas. Gadolinium DOTA-octreotate PET has been shown to be a reliable predictor of tumor growth in the BM and AM. Tumors with fast growth rate and transosseous expansion have the highest binding of the radionuclide, which indicates the potential for DOTATATE-based therapy.

According to the literature, DWI provides information regarding tissue microstructure. Therefore, the purpose of this study was to compare the findings diffusion-weighted MR imaging and histopathology in patients with meningiomas.

DIFFUSION-WEIGHTED MRI

It is possible using MRI to sensitize the image appearance to the extent to which water can freely diffuse in any volume element (voxel). When the motion of water molecules within a voxel is restricted there is greater magnetization coherence and that voxel will appear bright. This technique is referred to as diffusion weighted imaging (DWI). Reduced water diffusivity has been correlated with more aggressive tumor behavior and is sometimes seen with atypical/ malignant meningiomas, high cellular density, and recurrence.³³

The diffusion weighting in DWI acquisitions is encoded on top of the usual T1 and T2 properties of the underlying sequence. It is possible to create images that are insensitive to those underlying T1 and T2 values by performing multiple DWI acquisitions and extracting from them a map of the diffusion effect alone, referred to as an apparent diffusion coefficient (ADC) map. A decrease in ADC values at follow up of a benign meningioma should raise suspicion for dedifferentiation to higher tumor grade.³² Although diffusion-weighted imaging provides an added tool in the approach to defining meningioma grade a recent report calls into question the predictive ability of DWI methods in grading meningiomas or identifying histological sub-types.

ROLE OF DW-MRI IN DIAGNOSIS OF MENINGIOMAS

Meningiomas are the most common extra-axial brain tumors. Meningiomas are the third most common intracranial tumors in adults following gliomas and metastases. Based on the WHO classification they are classified as benign (WHO type I, 80% cases), atypical (WHO type II, 15–20%) and malignant (WHO type III, 1–3%). Meningiomas show characteristic findings on conventional MRI; thus, their differentiation from intra-axial tumors is easy.

Meningiomas are readily diagnosed by MR imaging, and most are asymptomatic. Meningiomas comprise approximately 14% to 20% of all intracranial tumors. Atypical meningiomas account for 7.2% of all meningiomas, whereas malignant meningiomas are rare and constitute approximately 2.4%. Malignant and atypical meningiomas are more prone to recurrence and aggressive growth, which increases patient morbidity and mortality. It would be useful to distinguish among benign, malignant, and atypical meningiomas before resection, because this would aid in surgical and treatment planning. This distinction between benign and malignant or atypical meningioma is neither easily nor reliably accomplished to date when assessing the imaging features of meningiomas on routine MR images.

Diffusion-weighted MR imaging has been used to investigate primary brain neoplasms. Correlations between apparent diffusion coefficient (ADC) values, tumor cellularity, and tumor grade have been made, and the use of diffusion-weighted imaging to monitor treatment response has been evaluated.

Hakyemez et al,³² evaluated the contribution of DWI to differentiation of atypical/malignant and typical meningiomas. They demonstrated that atypical/malignant meningiomas had lower ADC values than typical meningiomas.

Although meningiomas are easily diagnosed by conventional MRI, differentiation of histological types is usually not possible. Type II and III meningiomas are more aggressive and have a higher recurrence rate. The recurrence rate of atypical and malignant meningiomas is about 40% and 50–80%, respectively at 5 years of follow up. Patients

Thus, there are several studies describing features of meningiomas on DWI. But, the provided data were inconsistent. Some authors found an association between ADC and histological parameters of meningiomas, whereas others did not.

AIMAND OBJECTIVES:

Aim:

 To compare the findings of diffusion-weighted MR imaging and histopathology in patients with meningiomas.

OBJECTIVES:

- To list the findings of diffusion weighted MRI among patients with meningiomas
- To assess the histopathologic findings of meningiomas.
- To compare and measure the agreement in findings between diffusion weighted MRI and histopathology of meningiomas.

MATERIALAND METHODS

- 1. Study Setting: The present study will be carried out in a tertiary care teaching hospital in North India.
- Study design: The present study was undertaken as a cross sectional analytical study.
- **3. Study period**: The study was undertaken for a period of two years from Jun 2017 to Jun 2019.
- 4. Study Population: Patients who were referred from Medicine and Neurology department to the Department of Radiodiagnosis; and were diagnosed to have meningiomas on radiographic imaging were enrolled for the study based on the following criteria.
- a. Inclusion Criteria: Patients who are radiologically diagnosed to have meningioma.

b. Exclusion Criteria:

- Patients with MRI findings of abundant calcification, necrosis and cyst.
- Patients with previous radiotherapy or radiosurgery,
- · Patients with Preoperative transarterial embolization
- Patients with incomplete or uninterpretable preoperative MRI studies.
- Patients with metallic implants, cardiac pacemakers, cochlear implants
- Patients who are claustrophobic.
- Patient who are unwilling for imaging.

5. Sample Size:

The study of Christopher G. Filippi, et al⁴¹ observed that meningiomas comprise 14% to 20% of all intracranial tumors. Taking this value as reference, the minimum required sample size with 10.5% margin of error and 5% level of significance is 56 patients. To reduce margin of error, total sample size taken is 60.

Formula used is:- $N \ge ((p(1-p))/(ME/z\alpha)2)$

Where $Z\alpha$ is value of Z at two sided alpha error of 5%, ME is margin of error and p is proportion of meningiomas in intracranial tumors.

Calculations:

1) Taking p as 14%

- $n \ge ((.14*(1-.14))/(.105/1.96)) = 41.95 = 42(approx.)$
- 2) Taking p as 20%
- n>=((.20*(1-.20))/(.105/1.96)2=55.75=56(approx.)

Sampling technique: Universal sampling, since the study includes all the reporting eligible patients.

6. Data collection:

Patients who had a preoperative MR imaging with DW imaging between during the data collection period and a final histopathological diagnosis of meningioma were included in the study. Detailed information about the study was given to the patients and an informed

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consent was obtained for the same. The detailed demographic profile of the patients were recorded in the study proforma and the MRI findings were correlated with histopathology findings of the prostate lesions.(Annexure) Tumor grading of the meningiomas were made based on the World Health Organization (WHO) classification (2007). Radiologist evaluation of the findings of DW MR images were blinded to the histopathology findings, if already available. All the DW MR were evaluated by a single senior radiologist and for research purpose. DW images were visually inspected and classified as hyperintense, isointense and hypointense as compared with normal white matter.

7. Brief Procedure

Preoperative MRI was available for each patient and was performed using a GE 1.5-T MR unit (SIGNA 1.5 T WIPRO GE). The MRI protocol was TR 2140 msec, TE 30 msec, TI 420 msec, matrix size 256 × 256, section thickness 3 mm, and intersection gap 0.21 mm. Routine images of the whole brain, including spin echo T1-weighted images, spin echo T2-weighted images, and fluid-attenuated inversion recovery (FLAIR) images were obtained. Spin echo contrastenhanced T1-weighted images were obtained in the coronal, sagittal, and axial planes after intravenous Gd administration (0.1 mmol/kg body weight). Diffusion-weighted imaging (DWI) was acquired in the axial plane using a single-shot, spin echo, echo planar imaging sequence. ADC will be measured with a manual placement of region of interests (ROIs) in the solid part of the lesion.

The solid part of the lesion was identified on the basis of a detailed analysis of T1-weighted images after contrast administration and T2-weighted images, including FLAIR sequence. In case of enhancing tumors, ROIs will be placed in the enhanced region, while in case of non-enhancing tumors; ROIs will be placed in the solid part of the lesion, identified on the basis of a FLAIR image. Capsular enhancement was defined as the entire enhanced layer at the tumorbrain interface and was categorized as positive or negative. The presence of brain edema was judged as a hyperintense extension adjacent to tumors on T2-weighted imaging and was judged as positive or negative.

8. Statistical Analysis:

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean \pm SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used.

Statistical tests were applied as follows-

- 1. Quantitative variables were compared using Independent t test (as the data sets were normally distributed) between the two groups.
- 2. Qualitative variables were correlated using Fisher's Exact test.
- 3. Receiver operating characteristic curve was used to find out cut off point of ADC for predicting malignancy.
- 4. Inter-rater kappa agreement was used to find out the strength of agreement between ADC and histopathological grade.

Ap value of <0.05 was considered statistically significant.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

9. Ethical Considerations:

Informed written consent was obtained from all the eligible patients before including them in the study. Procedures involved and the implication of the study were explained to the patients in the language that they can understand before obtaining consent. Institute ethical committee clearance and certification was obtained for the study.

10. Outcome measures

- a. Histopathological diagnosis and grading distribution of meningiomas cases included in the study
- b. Diffusion weighted MRI findings for the meningiomas cases.
- c. Mean ADC values and cut off values to differentiate histopathologically diagnosed Grade I meningiomas from Grade II/III.
- d. Sn, Sp, PPV, NPV of mean ADC value cut-off to diagnose and differentiate Grade I meningiomas from Grade II/III.
- e. Kappa agreement of mean ADC value of DWMRI with histopathology grade of meningiomas.

International Journal of Scientific Research

69

RESULTS AND OBSERVATIONS

This cross-sectional comparative study was conducted in a tertiary care teaching hospital in North India (Base Hospital Delhi Cantt) from June 2017 to Jun 2019. Patients diagnosed with meningiomas on radiographic imaging (MRI and DW imaging) were included in the study. Tumor grading of the meningiomas was based on the WHO classification (2007). Radiologist evaluation of the findings of DW MR Images were blinded to the histopathology findings. Following results were obtained relating to the study:

Table/Fig 1:-Distribution of age of study subjects.

Age distribution	Frequency	Percentage	
<=30	2	3.33%	
31-40	10	16.67%	
41-50	16	26.67%	
51-60	14	23.33%	
>60	18	30.00%	
Total	60	100.00%	
Mean ± Stdev	52.57 ± 13.12		
Median(IQR)	52(44.500 - 62)		

The mean age of the patients in our study was 52.57 years. Majority of the patients i.e. 18 (30%), were in the age group >60 years; followed by 16(26.67%) in the age group 41-50 years.



In our study, histopathology was available for only 59 patients. 1 of the biopsy reports was not available. There were 50(83.33%) patients with Grade 1; 6(10%) patients with Grade 2 and 3(5%) with Grade 3. In Grade 1, most common variant was Meningothelial variant as seen in 35(58.33%) patients; followed by Fibroblastic variant which was seen in 5(8.33%) patients. Other variants were Angiomatous, Microcystic, Mixed, Psammomatous and Transitional. In Grade 2, there were 3 cases of atypical and clear cell variant each. In Grade 3, a single case of mixed phenotypic variant was see.





Table/Fig 4: - Right frontal meningioma with sinus invasion, ADC-0.72×10–3mm2s–1, histopathology findings revealed A GR II clear cell type meningioma.

70



;/Fig 5: - Left parafalcine meningioma with ADC value of 0.95×10–3mm2z-1, histopath revealed a benign menigotheliomatous meningioma-grade I.

Table/Fig 6: - Distribution of DWI of study subjects.

DWI	Frequency	Percentage			
No	38	63.33%			
Not done	2	3.33%			
Yes	20	33.33%			
Total	60	100.00%			
DWI was present in 20 (33.33%) cases and was absent in 38					

(63.33%) cases. It was not done in 2 cases.

Table/ Fig 7 :- Descriptive statistics of mean ADC value of study subjects.

Mean ADC value(X 10 ⁻³ mm ² s ⁻¹)	Mean ± SD	Median(IQR)
	0.88 ± 0.1	0.9 (0.820 - 0.955)



Table/ Fig 8 :- Box whisker plot of mean ADC value of study subjects.



Table/ Fig 8 :- Planum sphenoidale meningioma, ADC-0.88×10-3mm2s-1, meningothelial meningioma grade I on histopathology.

Fable	/ Fig 9 :	-Association of	DWI and	histopatho	logical grade.
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DWI	Histopatholo	gical grade	Total	P value
	Grade	Grade		
	I(II-30)	II/III(II-7)		



There was no association of DWI and histopathological grade of the meningiomas. (P>0.05).



Table/ Fig 10 :- Right parieto-temporal meningioma, ADC OF 0.68×10-3mm2s-1, atypical grade II on HPE.

Table/ Fig 11 :	Association	of contrast :	and hist	opatholo	ogical	
grade.				_		
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Contrast	Histopathol	ogical grade	Total	P value
	Grade	Grade		
	I(N=50)	11/111(n= 9)		
Hetero/intense	25 (55.56%)	5 (55.56%)	30 (55.56%)	1.000
Yes	20 (44.44%)	4 (44.44%)	24 (44.44%)	
Total	45 (100.00%)	9 (100.00%)	54 (100.00%)	

Table/ Fig 13 :- Receiver operating characteristic curve to find out cut off point of ADC value for predicting malignancy.

For predicting malignancy	AUC (95% CI)	Standard Error	P value	Cut off	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
Mean ADC Value(X 10 ⁻³ mm ² s ⁻¹)	1(0.939 to 1.000)	0	< 0.0001	≤0.76	100%(66.4 - 100.0)	100%(92.9 - 100.0)	100%(66.4 - 100.0)	100%(92.9 - 100.0)
Conclusion:	The ROC curve for mean ADC values showed that a cut off value of 0.76 had the 100% Sn, Sp, PPV and NPV. (AUC=1, P<0.0001)							



Table/ Fig 14 :- Inter-rater kappa agreement between ADC value and histopathological grade.

Mean ADC	Histopathological		Total	P value	Kappa
value(X	grade				
10^{-3} mm ² s ⁻¹)	Benign Malignant				
	Grade	Grade			
	I(n=50)	II/III(n=9)			
>0.76	50 (84.75%)	0 (0.00%)	50 (84.75%)	<.0001	1.000
<=0.76	0 (0.00%)	9 (15.25%)	9 (15.25%)		
Total	50 (84.75%)	9 (15.25%)	59 (100.00%)		



Table/ Fig 11 :- Right parafalcine meningioma, ADC VALUE-0.69×10-3mm2s-1, atypical grade II on HPE

Table/ Fig 12 :- Association of ADC value and histopathological grade.

Mean ADC value (X 10 ⁻³ mm ² s ⁻¹)	Grade I(n=50)	Grade II/III(n=9)	P value
Mean ± SD	0.92 ± 0.07	0.7 ± 0.04	<.001
Median(IQR)	0.9(0.870 - 0.970)	0.69(0.680 - 0.722)	



Association of ADC value and histopathological grade: The mean ADC values in Grade II/III cases were 0.7 ± 0.04 which was significantly less than the mean ADC values of Grade 1 cases (0.92 ± 0.07). There was a significant association of mean ADC values and histopathological grade of the meningiomas. (P<0.001).

 Conclusion:
 The mean ADC cut off value of 0.76 showed an excellent agreement with histopathological grading of meningiomas. (K=1, P<0.0001). All cases of Grade 1 meningiomas had ADC values more than 0.76 and all cases of Grade II/III meningiomas had mean ADC values of <=0.76.</td>

DISCUSSION

Meningiomas are mainly benign, however, 20% of these tumors have aggressive clinical and histopathological behaviors. Clinical prognosis is affected by a histological grade of meningioma and the extent of surgical resection. Preoperative knowledge regarding the histological grade of meningioma leads to better tumor resection and even dura substitution in advanced tumors.

The atypical/malignant tumors are associated with higher recurrence rates, which increase morbidity and mortality Reliable distinction between benign and atypical/malignant meningioma, based on the imaging features of the tumor on conventional MR images, is not possible.¹⁰⁹

Because of the fact that meningioma is the most frequent intracranial tumor and is often an incidental finding on magnetic resonance imaging (MRI), it is important to correctly estimate tumor grade and proliferation potential on imaging.

As per the published literature, diffusion-weighted imaging (DWI)

International Journal of Scientific Research

71

provides information related to tissue microstructure. It has been shown that DWI can be used in distinguishing malignant tumors from benign tumors. As reported in previous studies, malignant tumors showed lower values of apparent diffusion coefficient (ADC) as compared to benign lesions.

Along with this, as suggested by previous studies, ADC values under $1.00 \times 10^{-3} \text{ mm}^2 \text{s}^{-1}$ were suspicious for a malignancy. But, according to the published literature, some of the benign lesions had also very low ADC values and they can mimic malignancies. As reported previously, ADC values correlated well with cell count of the investigated lesions. According to the literature, ADC can be used as a marker to predict response to therapy in different malignant diseases.¹⁴

There were several reports describing features of meningiomas on DWI; however, the provided data were inconsistent. Whereas some authors found an association between ADC and histological parameters of meningiomas, others did not.

Thus we conducted this study to findings of diffusion weighted MRI among patients with meningiomas and analyze to assess the histopathologic findings of meningiomas. We also aimed to compare the findings of diffusion-weighted MR imaging and histopathology in patients with meningiomas.

We found that Sensitivity, Specificity, PPV, and NPV of mean ADC values to diagnose Grade 1 meningiomas were 100% with a cut off of more than 0.76; and for Grade II/III tumors were 100% with a cut off of \leq 0.76. There was a significant correlation between DWMRI and histopathology (K=1, P<0.0001).

DEMOGRAPHY

The incidence increases with age and there is a notable increase after the age of 65. They are nearly twice as common in females than in males and are estimated to be three times more common in females within the age range of 35 to 54 years.

The mean age of the patients in our study was 52.57 years. Majority of the patients, i.e. 18(30%) were in the age group >60 years; followed by 16(26.67%) in the age group 41-50 years.

In our study, there were 42(70%) females and 18(30%) males.

Histopathology characteristics

Histopathological examination and grading of meningiomas gives valuable prognostic information. In clinical practice, however, the diagnosis is based on light microscopy of routinely stained haematoxylin-eosin sections with criteria given by World Health Organization (WHO). This classification scheme provides guidelines for tumour grading and subtypes. As per WHO classification, grade I meningiomas (benign) are recognised by their histologic subtype and lack of anaplastic features.

In our study, there were 83.33% cases of Grade 1; 10% of Grade 2 and 5% of Grade 3. In Grade 1, most common variant was Meningothelial variant as seen in 35(58.33%) patients; followed by Fibroblastic variant which was seen in 5(8.33%) patients. Other variants were Angiomatous, Microcystic, Mixed, Psammomatous and Transitional. In Grade 2, there were 3 cases of atypical and clear cell variant each. In Grade 3, a single case of mixed phenotypic variant was see.

The World Health Organization (WHO) classification for meningiomas is based solely on histopathological characterizations of mitotic rate, cellular features of atypia, and local invasion. About 80% are WHO grade I (also referred to as BM), 17% are WHO grade II (AM), and 2% are WHO grade III (anaplastic meningioma/MM). The WHO classification has prognostic value but has limitations because of a lack of reliable molecular markers for aggressive and recurrence-prone tumors.¹¹⁰

Correlation of DWMRI and Histopathology

72

In our study, among all the Grade II/III cases where DWMRI was done, the edema was mild/moderate in 66.67% cases and extensive in 33.33% cases and among the Grade 1 cases, the edema was mild/moderate in 95.74% cases and extensive in 4.26% cases. There was a significant association of peritumoral edema and histopathological grade of the meningiomas. (P<0.05)

Abdel-Kerima A et al,¹⁰⁸ mentioned that peri-tumoural edema was not

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distinctive imaging features in the study. Nagar et al,³³ couldn't show a significant diagnostic value of peritumoral edema as it was not unique for the malignant counterpart and could be identified in the benign neoplasms equally. In contrast, Liu et al,³⁹ considered peritumoral edema to be at least an indicator of the high-grade tumors.

DWI and apparent diffusion coefficient (ADC) measurements helps in preoperative evaluation and planning of treatment of different brain tumors reliably in a noninvasive manner. Atypical and anaplastic meningiomas show lower ADC values as compared to low-grade tumors. But, the results reported in the literature are controversial about the effectiveness of ADC values in distinguishing low-grade versus high-grade meningioma.¹⁰⁹

• In our study, the mean ADC of the study patients were $0.88 \times 10^{-3} \text{ mm}^2 \text{s}^{-1}$ The mean ADC of Grade I tumors was $0.92 \pm 0.07^{-3} \text{ mm}^2 \text{s}^{-1}$ and for Grade II/III tumors was $0.7 \pm 0.04^{-3} \text{ mm}^2 \text{s}^{-1}$.

The ROC curve for mean ADC values showed that a cut off value of 0.76 had the 100% Sn, Sp, PPV and NPV. (AUC=1, P<0.0001).

Association of ADC value and histopathological grade

In our study, the mean ADC values in Grade II/III cases were significantly less as compared to mean ADC values of Grade 1 cases $(0.7 \pm 0.04 \text{ vs} 0.92 \pm 0.07)$. There was a significant association of mean ADC values and histopathological grade of the meningiomas. (P<0.001). The mean ADC cut off value of 0.76 showed an excellent agreement with histopathological grading of meningiomas. (K=1, P<0.0001). All cases of Grade 1 meningiomas had ADC values more than 0.76 and all cases of Grade II/III meningiomas had mean ADC values of <=0.76.

We observed a significantly lowered ADC value among grade II tumors. This could be explained by their higher cellularity and mitotic activity, high nucleo-cytoplasmic ratio and steady growth pattern; resulting in reduced diffusion and lower ADC values.

In our study, the mean ADC values had Sensitivity 100%, specificity 100%, PPV 100% and NPV 100% (AUC=1, P<0.0001).

Thus, diffusion-weighted MR imaging findings of atypical and typical meningiomas differ. Atypical meningiomas have lower intratumoral ADC values than typical meningiomas. The use of ADC ratios while helpful in eliminating interscanner variability is capable of differentiating between typical and atypical meningiomas.

CONCLUSION

Our study included majority i.e. 83.33% patients with Grade 1 meningiomas; and few with Grade II/III; most common variant being Meningothelial variant. Atypical and malignant meningiomas tend to be markedly hyperintense on diffusion-weighted MR images. There was no association of T1W, T2W, FLAIR image intensity; GRE; DWI; contrast MRI; and Dural tail with histopathological grade of the meningiomas. However, a significant association existed among peritumoral edema and histopathological grade of the meningiomas.

The mean ADC values in Grade II/III cases were statistically significant lower than the mean ADC values of Grade 1 cases. The cut-off ADC value was more than 0.76 for Grade 1 meningiomas and \leq 0.76 for Grade II/III meningiomas. Thus, there was an inverse relation between ADC values and histopathological grade of tumor. The mean ADC values showed that cut off value of 0.76 with 100% Sensitivity, 100% Specificity, 100% PPV, and 100% NPV. The mean ADC cut off value showed an excellent agreement with histopathological grading of meningiomas. (K=1, P<0.0001).

In conclusion, our analysis showed significant associations between different DWI findings and histopathological parameters. DWI-MRI provides a valuable information, improving the capability of the radiologist to distinguish between grade I and II/III.

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