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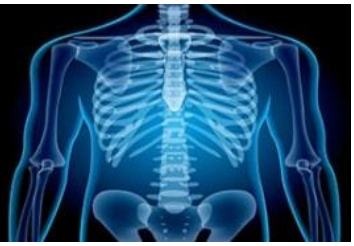

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Role of diffusion tensor imaging and diffusion metrics in primary, secondary brain tumours and tumour mimics

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Abstract
Background and Aim: Diffusion Tensor Imaging studies provide a valuable information regarding the status of white matter tracts adjacent to the intracranial brain lesions. The quantitative nature of Diffusion Tensor Imaging will play a role in assessing the outcome of clinical trials, as an additional surrogate marker in monitoring the therapeutic response. The aim of our study were to determine the Mean Diffusivity and Fractional Anisotropy coefficients in the affected white matter tracts and thereby to compare the Fractional Anisotropy and Mean Diffusivity of the affected white matter tracts in primary, secondary brain tumours and tumour like lesions.
Materials and Methods: From December 2018 to September 2019, 49 patients were included in the study who were referred to the department for conventional Magnetic Resonance Imaging. The histopathological diagnosis was obtained and confirmed in patients who have undergone surgical resection.
Results: Diffusion Tensor Imaging studies provide a valuable information regarding the status of white matter tracts adjacent to the intra cranial brain lesions. Fractional Anisotropy depends on the orientation and density of white matter fibres and Mean Diffusivity depends on the degree of perilesional edema. Gliomas present with white matter fibre destruction and less vasogenic edema when compared to tumour like lesions, and a higher perilesional Apparent Diffusion Coefficient favours a non-neoplastic etiology. Thus, the Diffusion Tensor Imaging sequences may help in differentiating the brain lesions of different aetiologies.
Conclusion: The quantitative nature of Diffusion Tensor Imaging will play a role in assessing the outcome of clinical trials, as an additional surrogate marker in monitoring the therapeutic response. Careful studies to validate Diffusion Tensor Imaging and its metrics will allow it to become more applicable clinically and can affect therapeutic decision-making, choosing appropriate treatment and eventually patient outcome.

Keywords: diffusion tensor imaging, fractional anisotropy, mean diffusivity

Introduction
Diffusion Tensor Imaging studies provide a valuable information regarding the status of white matter tracts adjacent to the intracranial brain lesions. Fractional anisotropy depends on the orientation and density of white matter fibres and Mean diffusivity depends on the degree of perilesional edema [1]. The altered states of white matter resulting from cerebral neoplasm might be expected to influence the measurement of diffusion tensor anisotropy and orientation in various ways, resulting in several possible patterns on Diffusion Tensor Imaging color maps [2].
Involvement of the eloquent cortex and functional white matter tracts in the brain is not demonstrated by the conventional MRI [3]. Diffusion tensor imaging has become a cornerstone in the resection of gliomas in or near eloquent areas [4, 10].

Objectives
The objectives of our study were to determine the Mean diffusivity and Fractional Anisotropy coefficients in the affected white matter tracts and thereby to compare the Fractional Anisotropy and Mean Diffusivity of the affected white matter tracts in primary and secondary brain tumours. The diffusion metrics of peritumoral edema was compared with that of centre of the tumour. To determine whether the Mean Diffusivity (MD) and

Fractional Anisotropy (FA) can distinguish tumour infiltrated edema of high and low grade gliomas from edema of metastases and meningiomas.

Materials and Methods

The study was prospective study and conducted in radiology department at Coimbatore Medical College Hospital, Coimbatore. The study was conducted between the period December 2018 and September 2019. The study group consisted of 49 patients with intra cranial mass lesions who have come to the department for conventional MRI. The histopathological diagnosis was obtained and confirmed in patients who have undergone surgical resection.

Inclusion criteria

The study group included patients with high and low grade gliomas, metastatic brain tumours, meningothelial tumours and tumour like lesions.

Exclusion criteria

The patients with previous history of cranial surgery or radiotherapy and contraindications for MRI (Pacemakers, Head and Neck Metallic Prosthesis) were excluded from the study.

Imaging technique and data-analysis

MR imaging was performed using a 1.5 tesla scanner (Siemens) using Head Neck 20 channel coil, the T1(TR/TE, 620/20ms), T2(TR/TE, 5430/95ms) and FLAIR (TR/TE/TI, 10500/120/2800 ms) sequences with matrix 80 x80, FOV 230 x 177 mm2 and slice thickness about 5 mm were obtained. The contrast gadolinium DTPA was given intravenously at a dose of 0.5mL/kg (0.1 mmol/kg) body weight and a flow rate of approximately 2 mL/s with maximum dose of 10mL.

Table 1: MRI protocol

MRI Sequences	Non contrast scans			Contrast scan	DTI
	TI W FSE	T2 W FSE	FLAIR	FST1W FSE	SS EPI
Imaging Plane	Axial and sagittal	Axial and sagittal	Coronal	Axial	Axial
TR/TE (m sec)	620/20	5430/95	10500/120 TI -2800	620/20	3500/83
Section thickness	5mm	5mm	5mm	5mm	5mm
Matrix	320 x 256	420 x270	244 x 152	256 x256	128 X 128

Statistical analysis

The FA and MD values between the two groups (neoplastic and non-neoplastic) were compared using Independent t test. A "*p* value" <0.05 was considered statistically significant. Comparison of categorical variables (age) was done by Chi -square test based on the number of observations.

Results and Discussion

A total of 49 patients with intracranial brain tumours were analysed and classified based on location, tumour grade, tumour type, histopathology and clinical diagnosis. The lesions were categorised into 5 groups for statistical comparison as follows:

Group 1: High grade glioma -12 patients
Group 2: Low grade glioma - 18patients
Group 3: Non glial tumour - 9 patients
Group 4: Metastasis - 6 patients
Group 5: Tumour like lesions – 4 patients

Of these, Group 1 included 12 patients (25%), 18 patients in Group 2 (37%),
9 patients in Group 3 (18%), 6 patients in Group 4 (12%), 4 patients in Group 5 (8%).

DTI patterns in white matter tracts altered by the tumour

In our study, gliomas and other high grade brain tumours disrupts and distorts the white matter fiber tracts by invasion or vasogenic edema, resulting in lowering of the Fractional anisotropy (FA) value.

Pattern 1 - (Deviated white matter tracts) was associated with normal Fractional anisotropic value and it was the most common pattern noted in non-glial tumours.

Pattern 2 - (white matter fiber tracts appear edematous) was the most common pattern in 49% of the study population and this pattern was most commonly associated with low grade gliomas.

Pattern 3 - (Infiltration of the white matter tracts) was associated with abnormal fractional anisotropic value and it was most commonly associated with high grade gliomas. It was also associated with low grade neoplasms.

Pattern 4 - (Destruction of white matter tracts) wasthe least common one, seen in 2 % of the study population and this pattern was commonly associated with WHO grade IV gliomas and Metastasis. Fractional anisotropic value was decreased indicating the destruction of white matter tracts.

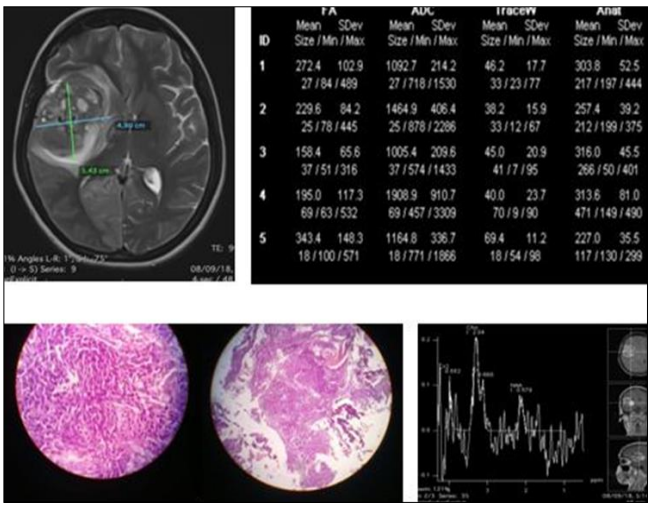
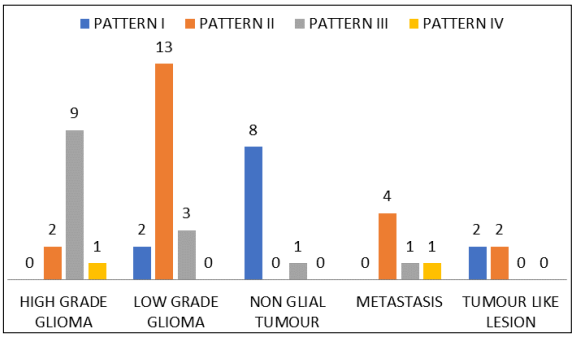


Fig 1: A case of *Glioblastoma multiforme* -grade IV

Table 2: Diagnosis vs DTI pattern

Diagnosis	Pattern I	Pattern II	Pattern III	Pattern IV
High grade glioma	0	2	9	1
Low grade glioma	2	13	3	0
Non glial tumour	8	0	1	0
Metastasis	0	4	1	1
Tumour like lesion	2	2	0	0

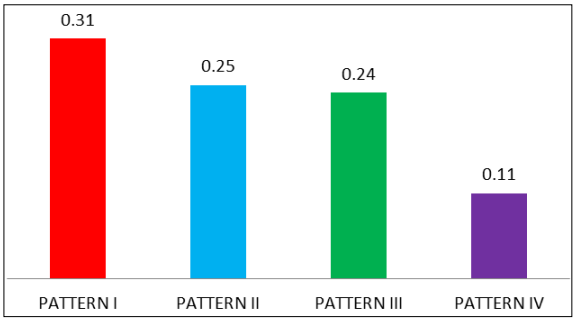


Graph 1: Diagnosis vs pattern

Kruskal Wallis Test -Statistical comparison between the groups for each of the DTI pattern, shows a "*p* value" of 0.218, indicating that the difference was statistically not significant.

Table 3 & Graph 2: DTI pattern vs mean peritumoural FA

DTI Pattern	Peritumoral – FA	
	Mean	SD
Pattern I	0.31	0.08
Pattern II	0.25	0.15
Pattern III	0.24	0.08
Pattern IV	0.11	0.01



Graph 2: DTI pattern vs mean peritumoural FA

ANOVA test -Comparison of DTI pattern and mean peritumoural diffusivity with a *p* value of 0.127 which was statistically not significant.

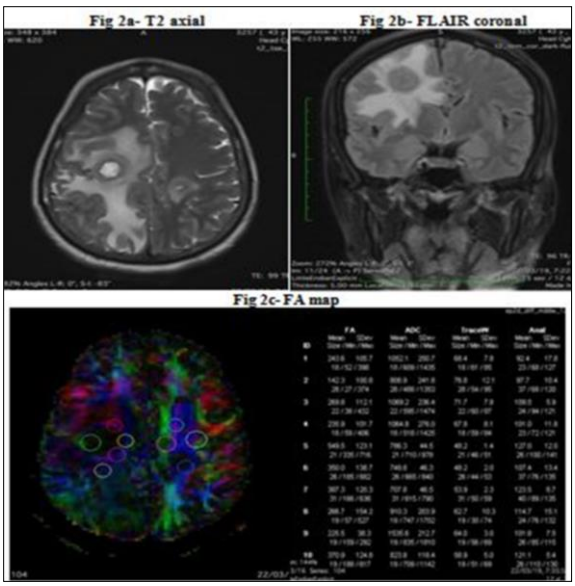


Fig 2: A case of metastasis

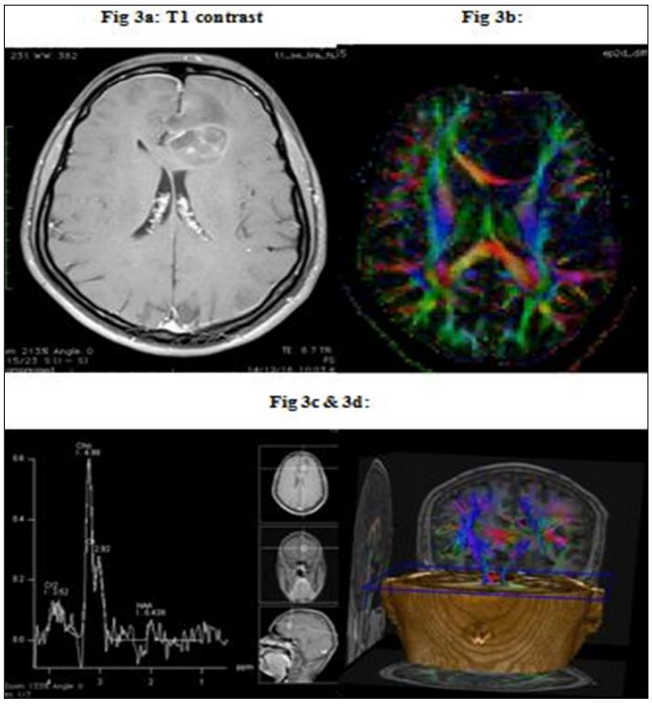
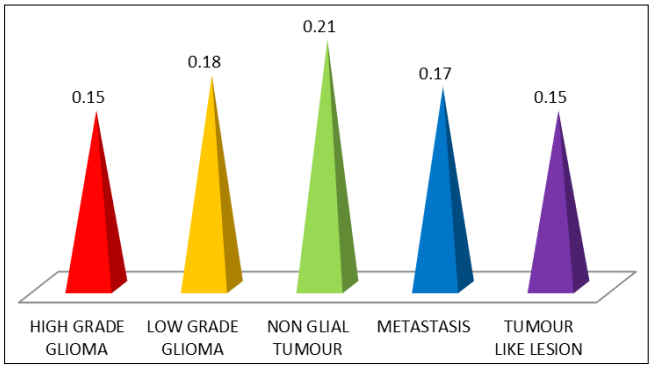


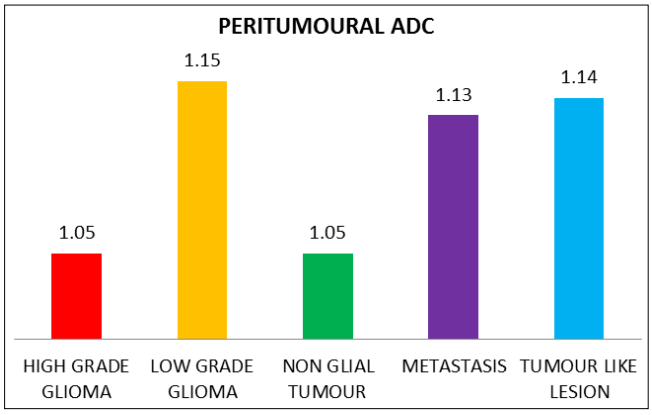
Fig 3: A case of Ependymoma



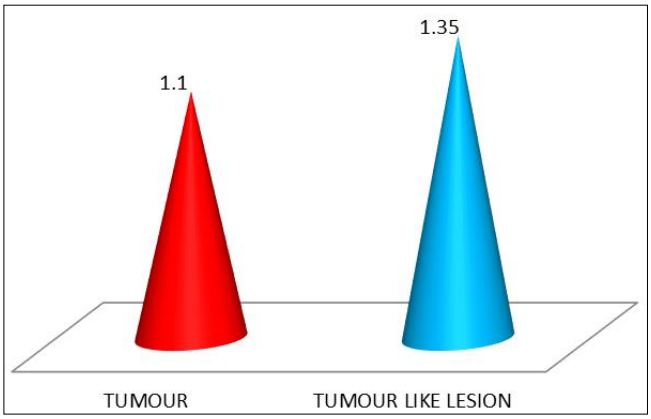
Graph 3: central FA

Table 4: Diagnosis vs peritumoural ADC

Diagnosis	Peritumoural ADC	
	Mean	SD
High grade glioma	1.05	0.21
Low grade glioma	1.15	0.21
Non glial tumour	1.05	0.15
Metastasis	1.13	0.26
Tumour like lesion	1.14	0.06



Graph 4: Peritumoral ADC



Graph 5: Tumour Vs Non Tumour – Peritumoural ADC

Table 5: Peritumoural ADC

Type	Peritumoural ADC	
	Mean	SD
Tumour	1.1	0.2
Tumour like lesion	1.35	0.06

Unpaired t test -Comparison of tumour vs tumour like lesion and mean peritumoural ADC with a *p* value of 0.031 which was statistically significant.

In our study, the tumoural mean diffusivity was increased in all the primary and secondary tumours.

However the central Fractional anisotropy (FA) value was decreased in both the primary and secondary brain tumours. Most of the glial tumours, tumour like lesions show decreased central Fractional anisotropy and in non-glial tumours the central FA value was normal. There was no significant difference in peritumoural FA, central and peritumoural ADC in Glial and Non-glial tumours. There was also increase in peritumoural mean diffusivity in tumour like lesions and non-glial tumours, when compared to glial tumours.

In our study, the Fractional anisotropy and mean diffusivity of primary brain tumours were compared to metastases the perilesional FA was higher in high grade gliomas, while the perilesional ADC was higher in metastases.

Central Fractional anisotropy and mean diffusivity were higher in high grade gliomas compared to metastases; however, these results were statistically insignificant (*P* =0.895; *P* =0.652).

The perilesional mean diffusivity (MD) was higher for the tumour like lesions (non-neoplastic group) compared to the primary brain tumours, which was statistically significant (*P* value = 0.031); while the difference in central MD between neoplastic and non-neoplastic group was statistically insignificant (*P* = 0.278).

The mean FA of perilesional edema was higher in the primary and secondary brain tumours compared to the non-neoplastic group; however the difference was statistically insignificant (*P* =0.418).

The Fractional anisotropy values in the centre of the lesion were higher in the primary and secondary brain tumours compared to the tumour like lesions and it was statistically insignificant(*P*=0.774).

Majority of the benign lesions have vasogenic perilesional edema, while gliomas have infiltrating cells along with vasogenic edema. Subtle differences in the DTI parameters were evaluated in our study. On comparing, it was found that the mean perilesional MD values were significantly higher in tumour like lesions (*P* value = 0.031) compared to the primary and secondary brain tumours, while the differences in central MD, FA and perilesional FA values were not statistically significant.

On further subgroup analysis of primary brain tumours and metastasis, the mean perilesional FA was higher in primary brain tumours, while the Perilesional MD was found to be higher in secondaries (*P* value 0.750), and the differences in central FA and central MD were statistically insignificant.

Mean Diffusivity is determined by an increased extracellular water, and metastatic lesions have a high expression of vascular endothelial growth factor, which increases the vascular permeability. The later factor is responsible for a higher perilesional ADC in metastases than in high grade gliomas, however it was found to be statistically insignificant.

DTI is used for characterisation of T2-signal changes surrounding high grade gliomas, have compared measurements from high grade gliomas with those from nonglial tumours and sometimes metastases. The perilesional edema in neoplastic and non-neoplastic brain lesions differs in composition. Capillaries of metastatic brain lesion resemble the organ of origin which do not possess the unique blood brain barrier function. The blood brain barrier is highly leaky resulting only in perilesional vasogenic edema [5].

The results are conflicting: one study found a difference between high grade gliomas and meningiomas in peritumoural ADC and FA; a second study found a difference between tumour types in peritumoural ADC, but not in peritumoural FA ; and a third study found no difference between tumour types in peritumoural ADC or FA. ADC and especially FA are known to vary substantially within the brain [6-9].

Conclusion

FA depends on the overall orientation and density of WM fibres and MD depends on the degree of vasogenic edema. High grade tumours present with more WM fibre destruction and less vasogenic edema in comparison to tumour like lesions, and a higher perilesional MD favours a non-neoplastic pathology.

Limitation of the study

Factors such as cellularity, viscosity, permeability, and histology can affect the diffusivity of water. The values of parameters measured with DTI are the summation effect of all these micro structural barriers. Because *in vivo* quantification of the individual effect of each factor is currently impossible, we could not definitely state that the changes of tensor metrics were directly related to the differences in histological features alone thus explaining the limitation of the study.

Conflicts of interest

Authors have no conflicts of interest with anyone.

Funding sources

Nil

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