Grading Gliomas - Role of Diffusion Weighted Magnetic Resonance Imaging and Apparent Diffusion Coefficient (ADC) Values in Grading Gliomas

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ABSTRACT

BACKGROUND

The central nervous system is a common site of tumorigenesis, where gliomas constitute ~80% of primary malignant brain neoplasms. CNS neoplasms are first classified into specific tumour types and then further graded as a measure of malignancy. We wanted to evaluate the diffusion characteristics in high - and low - grade gliomas and correlate the ADC values of brain gliomas with the WHO histopathological grades.

METHODS

The study group included 35 patients during the period of June 2017 to July 2018, who had histopathologically proven gliomas of varying grades. The MRI images of the patients (performed using a Siemens Magnetom Avanto 1.5T MRI machine at Victoria Hospital, Bangalore Medical College and Research Institute, Bangalore) were reviewed retrospectively. MRI detected cases of Gliomas without HPE reports and patients with postoperative recurrent tumours, were excluded from the study group.

RESULTS

The most common age group was found to be 40 to 59 years, with a distinct male predilection. MR images revealed diffusion restriction in cases of glioma, differing only in the amount of restriction as assessed by the corresponding mean and minimum ADC values. It was noted that the mean and minimum ADC values were relatively higher for cases of low grade gliomas, when compared to that obtained from high grade gliomas. The average minimum ADC values were 1.11 (grade I tumour), 0.96 (grade II tumour), 0.92 (grade III tumour) and 0.74 (grade IV tumour). The average mean ADC values were 1.19 (grade I tumour), 1.05 (grade II tumour), 0.98 (grade III tumour) and 0.86 (grade IV tumour). Statistical significance was found between the calculated ADC values and the histopathological tumour grade (p value was <0.001 for both values).

CONCLUSIONS

Our study confirmed that diffusion weighted MR imaging with ADC (both mean and minimum) value measurements, can be used to differentiate high - and low - grade gliomas in a non-invasive method for approximating tumour grade. We demonstrated that as the tumour cellularity and the grade increases, both the mean and minimum ADC values decrease.

KEYWORDS

Grading, Gliomas, WHO, Diffusion Weighted Imaging, Apparent Coefficient Values, ADC

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BACKGROUND

The central nervous system is a common site of tumorigenesis and the brain hosts a large spectrum of the same. Gliomas refer to neoplasms arising from neuronal glial cells of the central nervous system, and constitute ~80% of primary malignant brain neoplasms.[1] The need to classify and grade these brain tumours has always been the need of the hour. In India the incidence of CNS neoplasms in the year 2016 alone was 23,334 and the percentage change in age - standardised rates between 1990 and 2016 was up by 3.3%. A similar alarming trend was noted on the global stage with regards to the incidence, with the percentage change in the age standardised rates between 1990 and 2016 increasing by a staggering 17.3%.[2] CNS neoplasms are first classified (into specific tumour types) and then graded (a measure of malignancy). WHO has published a 4 grade histopathological classification system. As opposed to the histological 2007 grading, the latest 2016 grading system also takes into account molecular parameters.[3] Magnetic resonance imaging has always been in the forefront of diagnosis of CNS neoplasms. With the latest advances and better software applications, it is now possible to grade gliomas. Numerous studies of the same have been conducted with encouraging results, especially with diffusion weighted imaging and ADC (apparent diffusion co - efficient) values.

Diffusion - weighted imaging (DWI) has greatly enabled the possibility to grade gliomas, where the ADC values inversely correlated with the tumour grade. We aim to further add to the pre - existing literature about this well known, but less reported aspect of gliomas. This study was carried out with two main objectives in mind–

- To evaluate the diffusion characteristics in high and low grade gliomas
- To correlate the ADC values of brain gliomas with the WHO histopathological grades.

METHODS

A retrospective study was conducted on a study group of 40 patients between the period of June 2017 to July 2018, who had biopsy proven brain parenchymal gliomatous neoplasms. The MRI images of these patients were performed using our Siemens Magnetom Avanto 1.5T MRI machine at Victoria Hospital, Bangalore Medical College and Research Institute, Bangalore. Imaging protocols included routine MRI sequences such as T1, T2, FLAIR, DWI, SWI, post contrast T1FS and post contrast T1 MPRAGE (after a bolus injection of 0.1 mmol per kilogram of body weight gadopentetate dimeglumine (Teslaview)]. DW MR imaging was acquired in the axial plane by using a single shot, spin echo planar imaging sequence with diffusion - gradient encoding in three orthogonal directions. The parameters for DW images were as follows: TR – 4000 msec, TE – 107 msec, 220 - mm field of view, 128 x 128 - pixel matrix size, 5 mm section thickness, 1 mm intersection gap, one acquisition, and b values of 0, 500, and 1000 sec/ mm^2. The corresponding mean and minimum ADC values of the lesions were calculated on a pixel - by - pixel basis with software incorporated in the MR imaging unit.

Inclusion Criteria

1. Patients of all age groups with HPE proven WHO graded gliomas
2. Patients with absence of other previous or concurrent brain diseases
3. The availability of review of digital data from pre - treatment MR imaging examinations including DW images

Exclusion Criteria

1. MRI detected cases of Gliomas without HPE reports.
2. Patients with post - operative recurrent tumours.

Out of the 40 patients, 3 cases were not included in the study because the DWI images had excessive motion artefacts. Two other cases were not included as their biopsy reports did not mention the exact WHO grade of the gliomatous tumour. This led to a total sample estimate of 35 patients.

ADC Calculation Technique

DW images and ADC maps were visually inspected and classified as (i). Restricted and (ii) Free diffusion, compared with normal white matter. Minimum and mean ADC values were calculated on the ADC maps using manually constructed ROIs (Region of interests) of ~ $0.3\mathrm{cm}^2$ area, ensuring uniformity. The ROIs were placed over the region of maximum hypointensity on the ADC map, corresponding to highest diffusion restriction of the solid portion of the tumour. The ROIs were carefully placed so as to avoid areas of calcifications as well as cystic, necrotic and haemorrhagic regions that might influence ADC values. The mean and minimum ADC values (expressed in multiples of $10^{-3}\ \mathrm{mm}^2/\mathrm{sec}$) were calculated on a pixel - by - pixel basis with software incorporated in the MR imaging unit, using the formula ADC = - (ln (Sb / S0)] / b, where Sb is the signal intensity of the ROI obtained through three orthogonally oriented DW images, S0 is the signal intensity of the ROI acquired through reference T2 - weighted images, and b is the gradient b factor with a value of 1000 sec/mm^2.

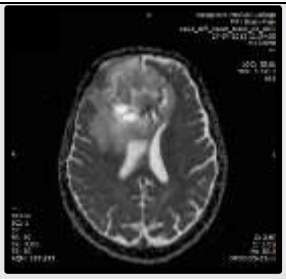


Figure 1. Calculation of ADC Values by Drawing a Suitable ROI

Statistical Analysis

The data thus obtained was tabulated and analysed using descriptive statistics and were presented as numbers, proportions and percentages. ANOVA and Kruskal Wallis test was applied to check the association of ADC values with the Histopathological WHO grades, and the results were presented in graphs, figures and tables as applicable.

RESULTS

Age Group (in Years)	No. (%)
0 - 19	9 (25.71%)
20 - 39	10 (28.57%)
40 - 59	12 (34.29%)
60 - 79	4 (11.43%)
Grand Total	35 (100.00%)

Table 1. Age Distribution

Sex	Tumour Grade (n=35)			
	Grade I (n=8)	Grade II (n=6)	Grade III (n=10)	Grade IV (n=11)
	No (%)	No. (%)	No. (%)	No. (%)
F	2 (25.00%)	2 (33.33%)	4 (40.00%)	3 (27.27%)
M	6 (75.00%)	4 (66.67%)	6 (60.00%)	8 (72.73%)

Table 2. Gender Distribution among Different Tumour Grades

ADC Parameter	Tumour			
	Grade I (mean ± SD)	Grade II (mean ± SD)	Grade III (mean ± SD)	Grade IV (mean ± SD)
Min ADC*	1.11 ± 0.01 (1.09 - 1.12)	0.96 ± 0.1 (0.79 - 1.08)	0.92 ± 0.08 (0.79 - 1.06)	0.74 ± 0.07 (0.61 - 0.85)
Mean ADC*	1.19 ± 0.04 (1.12 - 1.25)	1.05 ± 0.13 (0.85 - 1.25)	0.98 ± 0.09 (0.81 - 1.11)	0.86 ± 0.1 (0.67 - 0.96)

Table 3. Distribution of ADC Parameters amongst Different Tumour Grades

*ADC measurements are expressed in x 10^{-3} square millimetres per second.
*Numbers in parentheses are ranges of the ADC measurements.

Parameter	Tumour WHO Grade				
	I	II	III	IV	p Value
Min ADC	1.11 (1.1,1.12)	0.96 (0.85,1.07)	0.92 (0.86,0.97)	0.74 (0.69,0.79)	<0.001#
Mean ADC	1.19 (1.15,1.22)	1.05 (0.91,1.19)	0.98 (0.92,1.05)	0.86 (0.79,0.92)	<0.001^

Table 4. Association between WHO Tumour Grading and the Minimum and Mean ADC Values

The value outside parentheses represents mean values.
Values within parentheses are upper and lower limits of 95% confidence intervals.
#Kruskal Wallis test ^ANOVA

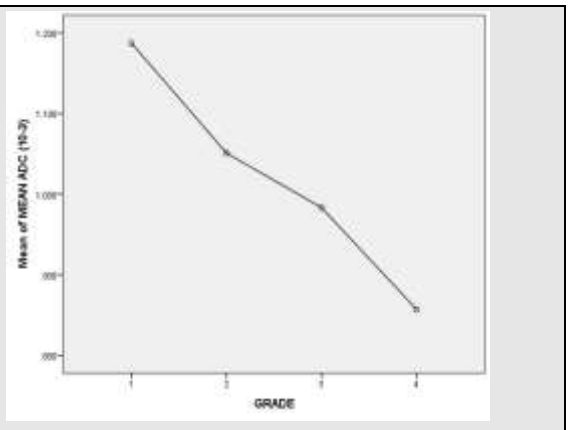


Figure 2. Variation of Mean ADC Values with Tumour Grade

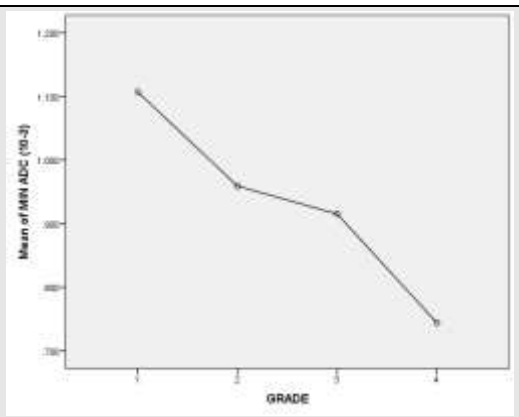
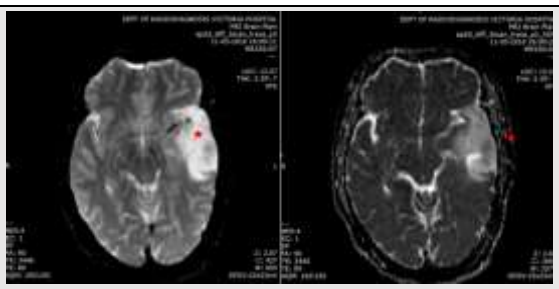
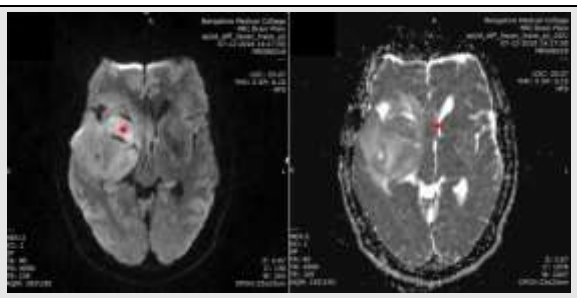


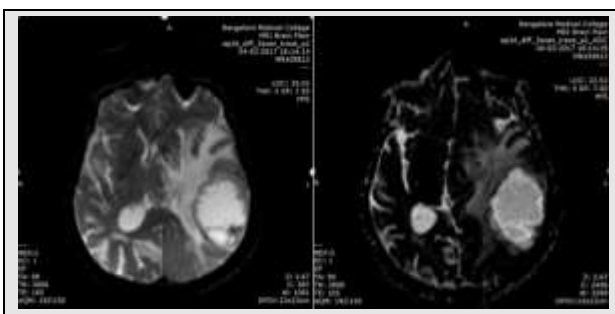
Figure 3. Variation of Minimum ADC Values with Tumour Grade



Figures 4a and 4b. DWI and Corresponding ADC Map of a Biopsy Proven Case of Pilocytic Astrocytoma (WHO Grade I Tumour). The Red Star Represents the Area of Maximal Restriction and the Corresponding Area of Hypointensity on the ADC Map



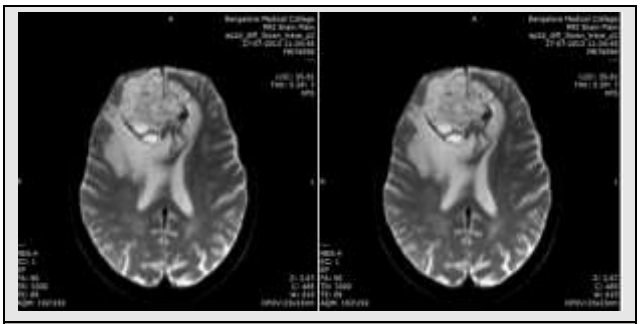
Figures 5a and 5b. DWI and Corresponding ADC Map of a Biopsy Proven Case of Diffuse Astrocytoma (WHO Grade II Tumour). The Red Star Represents the Area of Maximal Restriction and the Corresponding Area of Hypointensity on the ADC Map



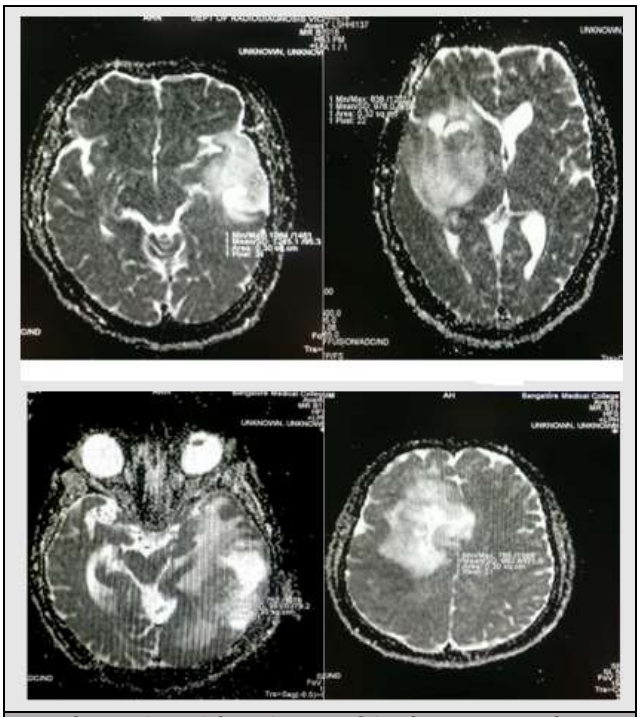
Figures 6a and 6b. DWI and Corresponding ADC Map of a Biopsy Proven Case of Anaplastic Astrocytoma (WHO Grade III Tumour)

Out of the total 35 patients, the most common age group was found to be between 40 - 59 years of age (34.29% of total study size population) and the least common age group

was 60 - 79 years (11.43% of study size population). It was found that gliomatous tumours in the study population was more common in male patients (24/35) than the female patients (11/35), with a ratio of 2.1:1. Majority of female patients (36.3%) presented with WHO grade III tumours, whilst majority of male patients (33.3%) presented with WHO grade IV tumours.



Figures 7a and 7b. DWI and Corresponding ADC Map of a Biopsy Proven Case of Glioblastoma Multiforme (WHO Grade IV Tumour)



Figures 8a to 8d. ADC Maps of Grade I, II, III and IV Gliomas Demonstrating the ROI's with the Calculated Mean and Minimum ADC Values

Minimum ADC values of the grade I tumours was 1.11 ± 0.01, grade II tumours was 0.96 ± 0.1, grade III tumours was 0.92 ± 0.08 and that of grade IV tumours was 0.74 ± 0.07. Mean ADC values of grade I tumours was 1.19 ± 0.04, grade II tumours was 1.05 ± 0.13, grade III tumours was 0.98 ± 0.09 and that of grade IV tumours was 0.86 ± 0.1. Both the mean and minimum ADC values showed a decreasing trend as we progressed from low grade to high grade tumours. MR images revealed diffusion restriction in all cases of gliomas, differing only in the amount of restriction as assessed by the corresponding mean and minimum ADC values. The mean and minimum ADC values were relatively higher for cases of low grade gliomas, when compared to that obtained from high grade gliomas. Statistical significance was found between the calculated ADC values (both mean and minimum) and the histopathological tumour grade.

DISCUSSION

Gliomas refer to neoplasms arising from neuronal glial cells of the central nervous system, and constitute ~80% of primary malignant brain neoplasms.[1] In India the incidence of CNS neoplasms in the year 2016 alone was 23,334 and the percentage change in age - standardised rates between 1990 and 2016 was up by 3.3%. A similar alarming trend was noted on the global stage with regards to the incidence, with the percentage change in the age standardised rates between 1990 and 2016 increasing by a staggering 17.3%.[2] Gliomas are traditionally classified according to their microscopic similarities. Principal groups include diffuse gliomas, characterized by extensive infiltrative growth into the surrounding parenchyma, and more circumscribed ('non - diffuse') gliomas.[4] The WHO grading system assigns gliomas from grades I to grade IV as depicted in table 1.

HPE Diagnosis	Assigned 'WHO' Grade	Description
1. Pilocytic astrocytoma 2. Sub ependymal giant cell astrocytoma	I	- Low proliferative potential - Long progression free survival
1. Diffuse astrocytoma, IDH - mutant 2. Oligodendroglioma, IDH mutant & 1p/ 19q - codeleted 3. Pleomorphic xanthoastrocytoma	II	- Tumours with cytological atypia alone
1. Anaplastic astrocytoma, IDH mutant 2. Anaplastic oligodendroglioma, IDH - mutant & 1p/ 19q - codeleted 3. Anaplastic pleomorphic xanthoastrocytoma	III	- Anaplasia and mitotic activity also present
1. Glioblastoma, IDH - wildtype 2. Glioblastoma, IDH - mutant 3. Diffuse midline glioma, H3 K27M - mutant	IV	- Additionally, demonstrate microvascular proliferation and/or necrosis

Table 5. WHO Grading of Gliomas[4]

MRI imaging adds a spectrum of information when it comes to the identification, characterization and sometimes even on the grading of tumours. Of the multitude of sequences available on hands, here we choose to deal with a basic yet quintessential sequence, 'DWI (Diffusion weighted Imaging)' and how it can go the extra mile in assisting modern day radiologists in grading gliomas and add a whole new dimension to the management of these neoplasms. In areas of restricted diffusion, the ADC is low because the extracellular space is small.[5] Tumours with high cellularity show increased signal on the DW images and a marked reduction in the ADC values. Likewise, low grade gliomas, because of their low cellularity, have significantly higher ADC values compared to high grade gliomas. Measurement of ADC values should be done from the maximally restricted diffusion areas, because histologically the actual grade of the tumour is determined from the areas with the highest grade.[5,6,7]

rade IV Gliomas	Min ADC	0.74 (0.69 - 0.79)	0.81 (0.52 - 1.17)	1.63 (0.80 - 2.46)	-	0.70 (0.55 - 0.85)	0.83 (0.61–1.07)	-
	Mean ADC	0.86 (0.79 - 0.92)	1.05 (0.68 - 1.35)	1.2 (0.80 - 1.60)	0.82 (0.69 - 0.95)	-	-	1.07 (1.04 - 1.16)
Grade III Gliomas	Min ADC	0.92 (0.86 - 0.97)	1.17 (0.77 - 1.62)	-	-	0.77 (0.56 - 0.98)	1.06 (0.72–1.40)	-
	Mean ADC	0.98 (0.92 - 1.05)	1.38 (1.03 - 1.94)	-	-	-	-	1.24 (1.22 - 1.28)
Grade II Gliomas	Min ADC	0.96 (0.85 - 1.07)	1.25 (1.09 - 1.58)	-	-	1.09 (0.89 - 1.29)	-	-
	Mean ADC	1.05 (0.91 - 1.19)	1.45 (1.21 - 1.72)	-	1.14 (0.96 - 1.32)	-	-	1.53 (1.49 - 1.65)
Grade I Gliomas	Min ADC	1.11 (1.10 - 1.12)	1.70 (1.52 - 1.90)	2.6 (1.94 - 3.30)	-	-	-	-
	Mean ADC	1.19 (1.15 - 1.22)	1.81 (1.57 - 2.04)	2.7 (2.00 - 3.40)	-	-	-	1.65 (1.57 - 1.74)
Study Name#		Our study (4 grades)	R. Murakami et al[18] (4 grades)	Sugahara T et al (Low vs High grade)	Kono K et al (Grade II and IV)	Kitis O et al (Grade II, III and IV)	Shuichi Higano et al (Grade III and IV)	Yamasaki F et al (4 grades)

Table 6. Study Wise Comparison of Mean and Minimum ADC Values in Grading Gliomas

*The number outside the parentheses represent the average value, and numbers within the parentheses represent the range; All values of ADC are expressed in x 10 - 3 mm^2/ sec. #The various studies represented in the table compared ADC values of different grades of gliomas. The actual grades of gliomas compared have been mentioned in the parentheses.

The reason as to why different grades of gliomas expressed different levels of restriction is an intriguing thought. The reason for this has been extensively looked in a study by Sadeghi N et al, who conducted a study to review the effect of hydrophilic components of the extracellular matrix on quantifiable diffusion weighted imaging of human gliomas, and compared the preliminary results of correlating apparent diffusion coefficient values and hyaluronan expression level. They suggested that decreased expression of hydrophilic glycosaminoglycans (for example, hyaluronan) in the extracellular spaces of high - grade tumours may lead to less of an increase in ADC in these tumours.[8] Some differences in conflicting findings from different studies may be due to whether areas of necrosis are carefully excluded from the analyses of tumour ADCs. Such necrotic regions are more common in high - grade tumours and would be expected to contribute highly elevated ADCs that would raise the mean values for the tumour.[8] Some studies[9 - 12] have indeed shown lower water diffusibility in high - grade gliomas than in lower grade gliomas.

Multiple studies in the past have mentioned about a correlation between the cellularity of gliomas and their ADC values. They stated that the lower the ADC values, higher was the tumour grade. They concluded that utilizing ADC values can be instrumental in determining the grade of gliomas. For example, in 2001, Kono K et al examined 56 patients with histologically verified or clinically diagnosed brain tumours. They evaluated the correlation between ADC values and tumour cellularity in both gliomas and meningiomas. They found that among astrocytic tumours, ADCs were higher in grade II astrocytomas (1.14 ± 0.18 x 10^{-3} mm^2/ sec) than in glioblastomas (0.82 ± 0.13 x 10^{-3} mm^2/ sec). They went on to concluded that ADC values may predict the degree of malignancy of astrocytic tumours.[13] Also, in 2005 Yamasaki F et al conducted a retrospective study on 275 patients with brain tumours, to determine if ADC can be used to differentiate brain tumours at MRI. The mean ADC values of each histological sub type under every WHO grade was calculated in this study. In their study the ADC of WHO grade 2 gliomas was significantly higher than that of WHO grade 3 and grade IV tumours ($P < 0.01$), and hence they concluded that the higher the astrocytic tumour WHO grade, the lower the ADC.[14] Although the mean and minimum ADC values were slightly different between this study and our present study, there was significant similarity in the terms of the decreasing trend of both the ADC values from grade I to grade IV tumours.

Our present study is also in agreement with the study conducted by Sugahara T et al, done in 1999 to evaluate the utility of DW - MRI in depicting the tumour cellularity and grading of gliomas. The minimum ADC of the low - grade gliomas was significantly higher than that of the high - grade gliomas.[15] The mean and minimum ADC values for low grade gliomas were 2.00 - 3.40 x 10^{-3} mm^2/ sec and 1.94 - 3.30 x 10^{-3} mm^2/ sec respectively, while those for high grade gliomas were 0.80 - 1.60 x 10^{-3} mm^2/ sec and 0.82 – 2.46 x 10^{-3} mm^2/ sec respectively. This is in correlation to our study where the mean and minimum ADC values for low grade gliomas (grade I and II) were significantly higher than those of the higher grades (grade III and IV).

We also found that in few studies where only minimum ADC values had been evaluated, like the study by Higano[16] and Kitis O et al.[17] They found that the minimum ADC values of low - grade gliomas were significantly higher than those of other tumours.[17] The average minimum ADC values of grade II gliomas were 1.09 ± 0.20 x 10^{-3} mm^2/ sec, grade III were 0.77 ± 0.21 x 10^{-3} mm^2/ sec and that of grade IV were 0.70 ± 0.15 x 10^{-3} mm^2/ sec.[17] These values are in close correlation to the minimum ADC values obtained in our study for grade II gliomas (0.96 ± 0.10 x 10^{-3} mm^2/ sec), grade III gliomas (0.92 ± 0.08 x 10^{-3} mm^2/ sec) and grade IV gliomas (0.74 ± 0.07 x 10^{-3} mm^2/ sec In the current study, we examined MR images of 4 grades of gliomas, and we measured the mean and minimum ADC values of these tumours. After statistical analysis we concluded that both the mean and minimum ADC values had an inverse correlation with the tumor grade. There were three limitations in our study, the first one being the small sample size. This led to reduced external validity, and sensitivity and specificity could not be commented upon. The assessment of reliability was also not performed in the present study.

CONCLUSIONS

Our study confirmed that Diffusion weighted MR imaging with ADC (both mean and minimum) value measurements, can be used to differentiate high- and low-grade gliomas in a non-invasive method for approximating tumour grade. We demonstrated that as the tumour cellularity and the grade increases, both the mean and minimum ADC values

decrease. We believe, that by providing extra information about the possible grade of such tumours we can be of more assistance to operating neurosurgeons in decision making on treatment options.

Limitations

1. Small sample size led to reduced external validity and sensitivity and specificity could not be commented upon.
2. Assessment of reliability.
3. Subjective measuring of ADC values – No interobserver variability assessment was done.

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