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Original Research Article

Accuracy of magnetic resonance imaging diagnosis and grading of gliomas

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ABSTRACT

Background: Low- and high-grade gliomas differ in clinical presentation, natural history, treatment outcome, prognosis, survival pattern, histopathological, immunohistochemical and biomolecular profiles. Accurate pre-operative prediction of histopathological grade of gliomas remains challenging, and is critical for making optimum management plan and prognosticating the disease beforehand to determine the most cost-effective therapeutic choice with the best patient outcome. This prospective observational study on 54 patients aims to determine accuracy of pre-operative magnetic resonance imaging (MRI) in diagnosing and grading gliomas.
Methods: Pre-operative grading of MRI-suspected gliomas was done by assigning scores of 0-2 to 9 criteria – midline crossing, perilesional edema, signal heterogeneity, intra-tumoral hemorrhage, tumor border definition, cystic/necrotic changes, mass effect, contrast enhancement and diffusion restriction. Total scores of 0-5, 6-9 and 10-18 were considered radiologically low, intermediate and high grades respectively and correlation with World Health Organization (WHO) grades I+II, III and IV respectively was determined.
Results: MRI diagnosed 85.18% gliomas correctly. Pre-operative MR grading was 76-89% sensitive and 86-96% specific in predicting the histopathological grade of the gliomas. Signal heterogeneity and contrast enhancement had the highest whereas midline crossing and mass effect had the lowest correlation with histopathological grade.
Conclusions: Pre-operative MRI is highly specific and somewhat less sensitive tool for grading gliomas pre-operatively. The diagnostic yield is higher for LGGs and GBMs, compared to anaplastic gliomas, probably due to their mixed or intermediate features.

Keywords: Pre-operative MRI, Gliomas, Histopathological correlation, Sensitivity, Specificity, Diagnostic accuracy, Prediction

INTRODUCTION

Gliomas constitute about 25-30% of all primary brain tumors and almost 80% of primary malignant brain tumors, and they cause loss of more years of life than any other tumor.[1,2] Biological behavior of a central nervous system (CNS) neoplasm, and hence therapeutic choices for it can be predicted by its histological grade arranged into a "malignancy scale" from grade I to IV. Grade I lesions have low proliferative potential and surgical resection alone cures most of the m. Grade II tumors are generally infiltrative and despite low-level proliferative activity, generally recur or progress to higher grades of malignancy. Grade III lesions are definitely malignant and are characterized by nuclear atypia and brisk mitotic activity and require adjuvant radiation and/or chemotherapy. Grade IV lesions are rapidly progressive, almost uniformly fatal, cytologically malignant, mitotically active, prone to

necrosis, infiltrate the surrounding tissue widely and some of these tumors have a propensity for craniospinal dissemination.[3] Among the grade IV neoplasms, glioblastoma is the most frequent (65%) and most malignant histological type.[4]

Conventional magnetic resonance (MR) imaging with gadolinium-based contrast agents is a time-tested tool in the characterization of cerebral tumors. It provides important information about size, shape, anatomical location and extent, perilesional edema, contrast enhancement, multifocality, hemorrhage, necrosis and mass effect which help in predicting tumor grade.[5,6] But, it does not provide reliable information on many parameters of tumor physiology like microvascularity, angiogenesis, metabolism, micronecrosis, or cellularity, which can be obtained by inclusion of advanced MRI techniques like fluid attenuated inversion recovery (FLAIR), diffusion-weighted MRI (DWI), perfusion scans and magnetic resonance spectroscopy.[7-9]

Pre-operative accurate prediction of the histological nature of gliomas and their histological grading remains a challenge. It is also critical for making optimum plan of management and for prognosticating the disease beforehand, so that most cost-effective therapeutic choice with the best patient outcome can be determined. This prospective observational study analyses the accuracy of pre-operative MRI in predicting the diagnosis and histological grade of gliomas.

METHODS

This is a prospective observational study done on 54 patients who underwent tumor decompression between 01-04-2018 to 31-03-2020 with diagnosis of MRI-suspected glioma. All such patients except those with recurrent gliomas, metastatic lesions and those found unfit for surgery due to co-morbidities or moribund state were included in the study after written informed consent and approval from the institutional scientific committee and ethical committee.

Pre-operative MRI was done with 1.5 Tesla machine. T1 (TR/TE/acquisition=650/15/1) and T2-weighted fast spin echo (TR/TE/acquisition=2500/80/1) images in axial, sagittal, and coronal cuts were taken, supplemented by FLAIR (TR/TE/acquisition=9000/119/2106/1) and DWI sequences. Post-contrast (gadolinium) sequences were taken. The images were assessed for 9 criteria as given in Table 1 and a tentative diagnosis and grading of the tumor was noted. The pre-operative grading was adopted from the criteria described by Dean et al and modified to add degree of contrast enhancement and diffusion restriction on DWI as additional criteria, keeping the same scoring system ranging from 0-2 for each individual MR criterion.[10] A total score of 0-5 on MR criteria was considered radiologically low grade, corresponding histopathologically to World Health Organization (WHO) grade I and II, score of 6-10 was considered radiologically intermediate grade, corresponding histopathologically to WHO grade III and a score of 11 or above was considered radiologically high grade, corresponding histopathologically to WHO grade IV.

Histopathological and immunohistochemical findings on formalin-fixed, paraffin blocks were studied for cellularity, nuclear atypia, mitosis, vascular proliferation, necrosis and immune-histochemical markers. WHO grading was assigned to the histopathological finding of the tumor.

Table 1: MR scoring system of 9 characteristics of gliomas used in the study.

Criteria	Point 0	Point 1	Point 2
Crossing midline	No crossing	Equivocal	Crossed midline
Surrounding edema	Mild	Moderate	Severe
Signal heterogeneity	Mild	Moderate	Severe
Tumor hemorrhage	No	Equivocal	Definitive
Tumor border definition	Well circumscribed	Poorly circumscribed	Diffuse infiltration
Cystic/necrotic changes	No	Equivocal	Definitive
Mass effect of tumor	Mild	Moderate	Severe
Contrast enhancement	No or equivocal	Mild to moderate	Significant
Diffusion restriction	No or equivocal	Mild to moderate	Significant

Statistical package for the social sciences (SPSS) 24.0, primer of biostatistics and medcalc.org softwares were used to analyse the data and sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of MRI in determining the grades of gliomas were calculated. The following tests were applied for determining statistical significance – one sample proportion test for single discrete variables like age, sex; Chi square test, Pearson's linear regression and correlation test and Spearman's rank order correlation test to determine the correlation between the MR characteristics and the histopathological grade; and in each case, a confidence interval of 95%, i.e. a cut-off value of 0.05 for p was taken as a measure of statistical significance.

RESULTS

Out of 54 MRI-suspected gliomas studied, 8 turned out to be false positive on histopathological examination. PPV of MRI in diagnosing gliomas was 85.18%. Of the 8 glioma

mimickers, the distribution was as follows - 2 atypical meningiomas and 1 each of arterio-venous malformation, brain abscess (nocardial), choriocarcinoma and hemangioblastoma.

29 (63.04%) patients were male and 17 (36.96%) were female. No patient identified as transgender. 5 (10.87%) patients were in 0–14-year age group, 11 (23.91%) were in 15–34-year age group, 26 (56.52%) were in 35–64-year age group and 4 (8.70%) were in >65-year age group. The youngest patient was of 3 years, while the eldest was 72-year-old. The mean age was 40.91 years while the median was 43.5 years, with standard deviation of 17.44 and standard error of 2.572 years.

Applying the one sample proportion test for gender and age distributions, p value in either was found to be <0.05, hence the null hypothesis was rejected and a significant difference in the proportions was accepted. All the results have been summarized in tabular and diagram form (Tables 2-10 and Figures 1 and 2).

Table 2: Frequency distribution of sex in gliomas (n=54).

Sex	Number	Proportion (%)	Z value	Significance level (p value)	95% CI of observed proportion
Male	29	63.04	9.946	<0.0001	47.54-76.79
Female	17	36.96	18.062	<0.0001	23.21-52.46
Total	46	100	Taking null hypothesis value at 95%		

Table 3: Frequency distribution of sex in gliomas (n=54).

Age group (years)	Number	Proportion (%)	Z value	Significance level (p value)	95% CI of observed proportion
0-14	5	10.87	26.181	<0.0001	3.63-23.57
15-34	11	23.91	22.123	<0.0001	12.58-38.76
35-64	26	56.52	11.975	<0.0001	41.11-71.06
>64	4	8.70	26.856	<0.0001	2.42-20.80
Total	46	100	Taking null hypothesis value at 95%		

Table 4: Frequency distribution of the histopathological diagnosis and grading of all the cases in the study.

Histopathological grade (WHO)	Number	Percentage
Grade I (pilocytic astrocytoma)	2	4.35
Grade II		
Diffuse astrocytoma	10	21.73
Diffuse oligoastrocytoma	3	6.52
Ependymoma	2	4.35
All grade II	15	32.6
Grade III		
Anaplastic astrocytoma	7	15.21
Anaplastic oligodendroglioma	2	4.35
Anaplastic ependymoma	1	2.17
All grade III	10	21.73
Grade IV (glioblastoma multiformed)	19	41.32
Total	46	100

Table 5: Frequency distribution of each of the 9 MR criteria across the study sample.

Criteria and score	Grade I	Grade II	Grade III	Grade IV	Total
Midline crossing					
0	1 (2.17)	9 (19.57)	3 (6.52)	9 (19.57)	22 (47.83)
1	0	2 (4.35)	2 (4.35)	6 (13.04)	10 (21.74)
2	1 (2.17)	4 (8.70)	5 (10.87)	4 (8.70)	14 (30.43)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Peri-lesional edema					
0	1 (2.17)	5 (10.87)	1 (2.17)	0	7 (15.22)
1	1 (2.17)	10 (21.74)	8 (17.39)	9 (19.57)	28 (60.87)

Continued.

Criteria and score	Grade I	Grade II	Grade III	Grade IV	Total
2	0	0	1 (2.17)	10 (21.74)	11 (23.91)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Signal hetero-geneity					
0	2 (4.35)	11 (23.91)	1 (2.17)	0	14 (30.43)
1	0	4 (8.70)	8 (17.39)	8 (17.39)	20 (43.48)
2	0	0	1 (2.17)	11 (23.91)	12 (26.09)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Tumor bleeding					
0	2 (4.35)	10 (21.74)	7 (15.22)	2 (4.35)	21 (45.65)
1	0	5 (10.87)	2 (4.35)	9 (19.57)	16 (34.78)
2	0	0	1 (2.17)	8 (17.39)	9 (19.57)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Tumor border definition					
0	2 (4.35)	8 (17.39)	6 (13.04)	0	16 (34.78)
1	0	7 (15.22)	4 (8.70)	8 (17.39)	19 (41.30)
2	0	0	0	11 (23.91)	11 (23.91)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Cystic/necrotic changes					
0	2 (4.35)	13 (28.26)	7 (15.22)	2 (4.35)	24 (52.17)
1	0	1 (2.17)	2 (4.35)	3 (6.52)	6 (13.05)
2	0	1 (2.17)	1 (2.17)	14 (30.43)	16 (34.78)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Mass effect					
0	0	2 (4.35)	0	0	2 (4.35)
1	1 (2.17)	10 (21.74)	4 (8.70)	7 (15.22)	22 (47.83)
2	1 (2.17)	3 (6.52)	6 (13.05)	12 (26.09)	22 (47.83)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Contrast uptake					
0	0	2 (4.35)	0	0	2 (4.35)
1	1 (2.17)	10 (21.74)	4 (8.70)	7 (15.22)	22 (47.83)
2	1 (2.17)	3 (6.52)	6 (13.05)	12 (26.09)	22 (47.83)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)
Diffusion restriction					
0	2 (4.35)	7 (15.22)	1 (2.17)	0	10 (21.74)
1	0	7 (15.22)	8 (17.39)	6 (13.05)	21 (45.65)
2	0	1 (2.17)	1 (2.17)	13 (28.26)	15 (32.61)
Total	2 (4.35)	15 (32.61)	10 (21.74)	19 (41.30)	46 (100)

Table 6: Total scores of different MRI criteria in different grades of tumor across the study population.

Grade of tumor	n	Minimum score	Maximum score	Median	Mean	Standard deviation	Standard error
I	2	2	4	3	3	1.414	1
II	15	2	9	4	4.667	1.952	0.504
III	10	3	13	8.5	8.2	2.486	0.786
IV	19	8	18	13	13.42	2.714	0.6227

Table 7: Statistical parameters of predictive accuracy of pre-operative MR characteristics in different grades of gliomas in the study.

Grade	Grade I and II		Grade III		Grade IV	
Parameter	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**	**Value (%)**	**95% CI**
Sensitivity	76.47	50.10-93.19	80.00	44.39-97.48	89.47	66.86-98.70
Specificity	96.55	82.24-99.91	86.11	70.50-95.33	96.30	81.03-99.91
PPV	92.86	65.05-98.91	61.54	40.12-79.26	94.44	71.17-99.15

Continued.

Grade	Grade I and II		Grade III		Grade IV	
NPV	87.50	74.77-94.30	93.94	81.67-98.18	92.86	77.76-97.97
PLR	22.18	3.17-154.92	5.76	2.41-13.75	24.16	3.51-166.36
NLR	0.24	0.10-0.58	0.23	0.07-0.81	0.11	0.03-0.41
Accuracy	89.13	76.43-96.38	84.78	71.13-93.66	93.48	82.10-98.63

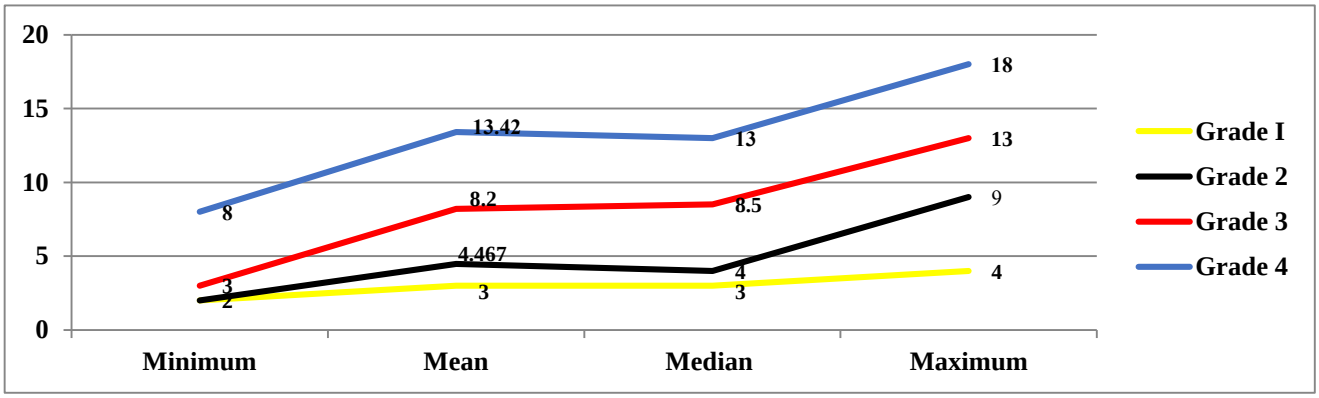

Figure 1: Line diagram showing the relation between minimum score, mean, median and maximum score of MR characteristics of each grade of gliomas.

Table 8: Results of statistical tests of significance applied to all MR criteria individually and taken together.

Criteria	Spearman rank-order correlation test		Pearson's Linear regression & correlation test			Chi-square test	
	r_s	P	r	P	Equation	χ^2	P
Crossing midline	0.141	0.35	0	1	$y = 3.000 + 0.000x$	5.043	0.283
Surrounding edema	0.714	0.001	0.6466	0	$y = 1.855 + 1.033x$	20.615	0.000
Signal heterogeneity	0.818	0.001	0.7881	0	$y = 2.04 + 1.003x$	37.121	0.000
Tumor hemorrhage	0.657	0.001	0.5954	0	$y = 2.45 + 0.7443x$	20.104	0.000
Tumor border definition	0.736	0.001	0.69	0	$y = 2.225 + 0.8694x$	26.569	0.000
Cystic/necrotic changes	0.756	0.001	0.6953	0	$y = 2.401 + 0.7252x$	26.569	0.000
Mass effect of the tumor	0.460	0.001	0.355	0.01549	$y = 2.156 + 0.5881x$	9.530	0.049
Contrast enhancement	0.797	0.001	0.7651	0	$y = 2.01 + 0.9106x$	31.537	0.000
Diffusion restriction	0.752	0.001	0.7176	0	$y = 1.957 + 0.9404x$	31.800	0.000
Total	0.876	0.001	0.8549	0	$y = 1.407 + 0.1774x$		

r=correlation co-efficient in Pearson's linear regression and correlation test; rs=correlation co-efficient in Spearman rank-order correlation test; for each MR criterion, 3 scores (0,1,2) and 4 WHO histopathological grades of the gliomas were used. So, power of the Chi-square test stands at (3-1) x (4-1) = 6; and for a power of 6, if confidence interval is taken at 95%, i.e. p value <0.05, the calculated value of $\chi 2$ is 12.592. If the observed value is >12.592, the null hypothesis remains rejected and vice versa.

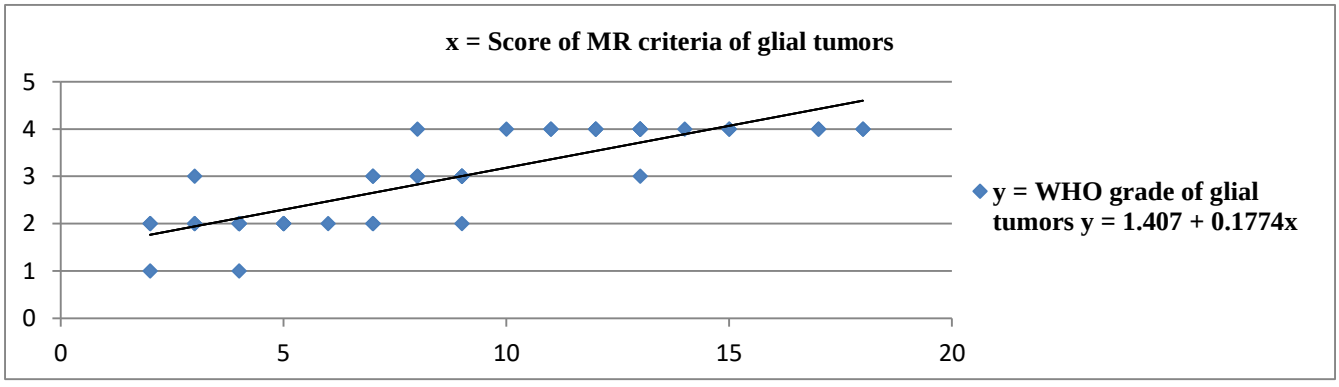

Figure 2: XY scatter diagram of linear regression and correlation graph of total score of MR criteria versus WHO grade of gliomas included in this study, $y = 1.407 + 0.1774x$.

Table 9: Frequency distribution of gliomas in children and adolescents (0-19 years) in various population and hospital-based registries of The National Cancer Registry Programme of The National Centre for Disease Informatics and Research, Bengalooru.[17]

Gliomas	Boys		Girls	
	Percentage of CNS tumors	Percentage of all tumors	Percentage of CNS tumors	Percentage of all tumors
Ependymoma	12.0	0.7	14.4	0.9
Astrocytoma	22.7	1.3	26.0	1.6
Other gliomas	20.0	1.2	19.0	1.2
Total	54.7	3.4	59.4	3.7

Table 10: Frequency distribution of gliomas in adult men and women in various population and hospital-based registries of The National Cancer Registry Programme of The National Centre for Disease Informatics and Research, Bengalooru.[14]

Gliomas	Men					Women				
	Percentage of CNS tumors					Percentage of CNS tumors				
	Mum	Beng	Che	Thi	Dib	Mum	Beng	Che	Thi	Dib
Astrocytoma	45.8	32.0	43.5	33.8	50.0	40.0	27.9	41.8	30.9	71.4
ODGs	3.3	11.9	3.3	4.8	5.6	10.3	9.8	3.6	2.9	0.0
Glioblastoma	22.9	32.0	27.2	21.1	11.1	21.1	33.0	29.1	20.6	0.0
Ependymoma	6.5	3.1	3.3	2.0	5.6	4.6	5.6	1.8	4.1	0.0
Other gliomas	5.8	6.7	7.6	28.2	5.6	6.3	5.6	7.3	21.8	0.0
Total	84.3	85.7	84.9	89.9	77.9	82.3	81.9	83.6	80.3	71.4

Mum–Mumbai; Beng–Bengalooru; Che–Chennai; Thi–Thiruvananthapuram; Dib-Dibrugarh.

DISCUSSION

Positive predictive value of MRI in diagnosing gliomas

In this study, conventional MRI with T1 and T2 weighted images with contrast enhancement with gadolinium and DWI sequences predicted gliomas with a PPV of 85.18%. Chishty et al in their study on 53 patients found that MRI could correctly diagnose the cases as glioma on 50 occasions, with a sensitivity of 94%.[11] Suárez-García et al in their study modelled on analysis of texture analysis in conventional brain MRI found sensitivity, specificity and accuracy of 94.12%, 88.24% and 91.18% respectively in diagnosing gliomas.[12]

Epidemiology of gliomas: age, sex and histopathology

Many different organizations i.e. state-wide or country-wide cancer registries track the incidence of gliomas. Data can also be collected from government cancer surveillance and health system records. Incidence rates of glioma vary significantly by histologic type, age at diagnosis, gender, race, and country, making a comprehensive global data compilation difficult.[13] The age groups in this study have been adopted from consolidated report of hospital based cancer registries 2004-2006: National cancer registry programme (ICMR), Bangalore, 2009.[14] Looking at the global picture, overall age-adjusted incidence rates (adjusted to the national population of each respective study) for all gliomas (ICD-O-3 morphologycodes 9380–9480) range from 4.67 to 5.73 per 100,000 persons. Age-adjusted incidence of glioblastoma (ICD-O-3 morphology codes 9440–9442, WHO grade IV), the most common and most deadly glioma subtype in adults, ranges from 0.59 to 3.69 per 100,000 persons. Anaplastic astrocytoma and glioblastoma increase in incidence with age, peaking in the 75–84-year age group. Oligodendrogliomas and oligoastrocytomas are most common in the 35–44-year age group. Older persons are less likely to have microscopically confirmed diagnoses of glioma, which may affect age-related incidence rates. In general, gliomas are more common in men than women, with the exception of pilocytic astrocytoma, which occurs at similar rates in men and women.[13]

Talking of the Indian scenario, in the absence of centralized cancer registration system in India, the various population and hospital-based cancer registries are the prime sources of epidemiological data on gliomas.[15,16] Tables 7 and 8 describe the age and gender wise epidemiology of gliomas in India.[14,17]

Value of individual MR criteria in grading of gliomas

Midline crossing of the tumor

Among the 4 grades, there is no clear pattern of correlation between the histopathological grade of the tumor and its propensity to cross the midline. While 4 out of 19 GBMs, the most aggressive tumor crossed the midline definitely and another 6 abutted the midline, the other lower grade tumors also had a fair share of this property e.g. 1 of the 2 cases of pilocytic astrocytoma was a butterfly glioma, and hence for obvious reasons, it crossed the midline.

Similarly, 4 out of 15 grade II and 5 out of 10 grade III gliomas definitely crossed midline. These included all the ependymomas (2 of grade II and 1 of grade III) which were inherently midline and some diffuse and anaplastic gliomas, which have the propensity of crossing the midline if they originate near the midline, e.g. a WHO grade III brain stem astrocytoma in a 3 year old girl and a WHO grade II astrocytoma in the brain stem of a 28 year old male.

A glial tumor's propensity to cross the midline is not a function of its histopathological grade. Other factors like position of the tumor near the midline, differential growth of various parts and infiltration along the commissural white matter tracts may play more significant roles.

Surrounding edema

Of the 11 tumors showing severe edema, barring 1 which was a grade III tumor, all the cases were GBMs. 3 in every 5 tumors showed moderate edema, which included 1 grade I tumor and quiet closely placed distribution of all other grades. There was no GBM and only 1 grade III tumor (anaplastic ODG) with mild edema. Mild edema was a feature found mostly in low grade gliomas. One-third of all grade II and half of all grade I tumors had mild edema.

That there was no glial tumor without any surrounding edema shows that surrounding vasogenic edema is an important and integral part of the spectrum of MR features of a glioma. With increasing grade, there is more neoangiogenesis and surrounding edema and hence can be a useful marker to pre-operatively predict the grade of a glial tumor.

Signal heterogeneity

Among 12 cases of severe signal heterogeneity, 11 were GBMs and 1 was an anaplastic astrocytoma. All grade I tumors were fairly homogenous, with only occasional signal changes if any. Similarly, among the grade 2 tumors, majority (n=11) had only mild signal heterogeneity, while 4 had moderate heterogeneity. There was a dramatic increase in signal heterogeneity as the study proceeded to analyse the signal heterogeneity in grade III tumors with only 10% of such tumors confined to mild signal heterogeneity. 80% showed moderate and another 10% showed severe signal heterogeneity. The tendency of severity of signal heterogeneity with increasing grade of the glial tumor continued with the analysis of grade IV tumors, among which there was no sample that showed mild signal heterogeneity. 8 out of 19 had moderate, while 11 had severe signal heterogeneity.

Signal heterogeneity which is a function of variance among different components of the tumor and signifies the level of differentiation of the neoplastic tissue tends to increase as the grade of the tumor increases and can be a useful marker to pre-operatively grade the tumor.

Tumor hemorrhage

Among the 9 cases showing definitive hemorrhage, 8 were GBMs and 1 was an anaplastic astrocytoma, showing that intratumoral hemorrhage was a feature, predominantly of grade IV tumors. This inference gets strengthened with the observation that no grade I tumor showed any hemorrhage, 2 out of every 3 grade II tumors had no hemorrhage, while the other one-third had equivocal hemorrhage only. Among the grade III tumors, 70% had no hemorrhage at all and 20% had equivocal hemorrhage.

Tumor hemorrhage increases as the grade of tumor increases and can be a useful predictor of the histopathological grade of a glioma.

Tumor border definition

All tumors showing diffuse infiltration were grade IV tumors. No grade IV tumor was well circumscribed. On the other hand, all grade I tumors were well-circumscribed. The features among the other grades were mixed. Among grade II tumors, 8 were well circumscribed and other 7 had breach of the tumor border. Within the grade III tumors, this proportion was reversed with about 2 in every 3 tumors showing features of poorly circumscribed tumor border.

Tumor border definition is a function of tumor aggressiveness and malignant potential. It changes according to the grade of a glioma and hence can act as a good marker for pre-operatively predicting the grade of a glioma.

Cystic/necrotic changes

14 out of 16gliomas exhibiting definitive cystic/necrotic changes were GBMS, denoting strong correlation between the two. All grade I, most of grade II (13 out of 15) and 70% of grade III tumors had no cystic/necrotic changes at all.

Statistical analysis indicated progressively stronger probability of cystic/necrotic changes in gliomas as the grades become higher.

Mass effect of the tumor

All gliomas barring 2 cases produced mass effect, making it an important criterion of most of the gliomas. Even the grade I tumors represented moderate and severe mass effect in 1 case each. Among the grade II tumors, two-third of gliomas had moderate mass effect and 3 even had severe mass effect. These were the ependymomas and other midline tumors. 60% of grade III tumors had severe and the rest had moderate mass effect. 12 out of 19 grade IV tumors had severe and the rest had moderate edema.

The statistical tests implied a positive, albeit weaker correlation between the 2 variables, when compared with

other MR criteria and a correlation between the set of these 2 variables did not get established. Mass effect does not seem to have a direct correlation with the grade of the tumor as even low-grade tumors can grow to large sizes undetected and create mass effect or if situated around midline, may compress the ventricular system of the brain and cause obstructive hydrocephalus. Higher grade tumors having aggressive course have higher chances of causing mass effect but the difference in this study was of equivocal statistical significance.

Contrast enhancement

Most of GBMs (15 out of 19) showed significant contrast uptake, while no grade 1 or grade II tumor showed significant contrast enhancement. Grade III tumors had mixed findings, mostly mild to moderate enhancement in 70% of the cases.

There is a strong correlation between histopathological grade of the tumor and contrast uptake, which is a function of the angioneogenesis and hence the aggressiveness of the tumor.

Diffusion restriction

Most of the gliomas (13 out of 15) showing significant diffusion restriction on DWI, were GBM. Of the 10 tumors having no restriction of diffusion at all, 90% were LGGs. With increasing grade and the ensuing hypercellularity, a tumor tends to show more restriction of diffusion.

Overall correlation of all criteria combined together

The minimum score, median, mode and maximum score in each grade show an upward trend underscoring the usefulness of the scoring system. Moreover, the scoring system yielded high values of different parameters of diagnostic accuracy (sensitivity, specificity, PPV, NPV, PLR, NLR and accuracy) for each grade of the glioma. It goes on to show that pre-operative MRI can be a very highly specific and somewhat less sensitive tool for grading gliomas pre-operatively. The diagnostic yield is highest for LGGs and GBMs, compared to anaplastic gliomas, probably due to mixed or intermediate features in this grade of gliomas.

Dean et al in 1990 first tried to objectively grade gliomas based on MR criteria and found that MRI is capable of predicting these grades with mass effect and cystic/necrotic changes showing the highest statistical yield.[10] Chishty et al reported necrosis, mass effect and irregular margins as the best predictors of grades of gliomas.[11] With the use of gadolinium contrasts, the predictive accuracy made a giant leap.[18,19]

While conventional MRI protocols provide high resolution multiplanar structural information, and substantially improved tissue characterization when compared with CT, it has certain limitations, which were pinpointed by other authors soon. Upto one-third of the high-grade tumors do not enhance on post contrast T1 weighted images, which may lead to a false radiological impression of low grade.[20] The MRI signal lacks biological specificity, e.g. T2-weighteddependent signal abnormality is dominated by tissue water content, and contrast enhancement reflects a non-specific increase in blood-brain barrier permeability. This limits diagnosis of non-invasive gliomas and characterization, therapeutic planning and assessment of active tumor load may be confounded by treatment-related effects. The complex features of glioma morphology and often subtle changes between MRI examinations are also frequently difficult to detect reliably by visual inspection of the images, even by an experienced radiologist. Moreover, the most widely used response criteria in clinical practice and therapeutic trials rely on linear measurements of enhancing tumor and are further challenged by the irregular shape and heterogeneous composition of gliomas. This contributes to the poor correlation of these criteria with hard clinical endpoints. The lack of pathology-specific biomarkers available from standard MRI sequences and methods of image analysis limit overall diagnostic and prognostic efficacy of the examination.[21] Earnest et al pointed the inability of contrast enhanced conventional MRI in detecting the tumor seedings within the intact white matter and in distinguishing the contrast enhancement due to gliomas and that due to radiation necrosis.[22] Upadhyay et al attributed these limitations to the complexity of glioma morphology ad the non-specificity of MR criteria, including the contrast enhancement.[21]

Other authors advocated the use of advanced sequences of MRIs like DWI, perfusion scans, DTIs and MRS to grade gliomas. Tien et al, Kono et al and Guo et al in separate studies reported the added value of DWI in diagnosing and grading gliomas. Hypercellularity and high nucleus: cytoplasm ratios of high-grade gliomas are associated with restricted diffusion (hyperintense signal) and low ADC. The low-grade gliomas have, accordingly, increased diffusion and higher ADC. Within the tumor, contrast enhancing parts have more restricted diffusion and lower ADC than the non-enhancing parts. The necrotic/cystic part has the highest signal suppression on DWI and the highest ADC. The peritumoral edema can be distinguished from the non-enhancing part of the tumor by its relatively more marked signal suppression on DWI and a higher ADC. In ring enhancing lesions with perilesional edema and mass effect, DWI can help distinguish an abscess from a high-grade necrotic glioma as pus shows extremely high diffusion restriction, unlike the necrotic centre of a high-grade glioma.[23-25]

Law et al and Hakyemez et al in separate studies found perfusion MRI useful in differentiating between low and high grade gliomas by demonstrating statistically significant difference in relative CBV and CBF ratios between the 2 groups, the hyperperfusion in higher grade attributed to neoangiogenesis.[7,26] Similarly, Zidan et al concluded that measurement of relative CBV can

accurately differentiate between grade III and IV gliomas.[27] Aronen et al concluded that high CBV was associated with mitotic activity and vascularity, but not with cellular atypia, endothelial proliferation, necrosis, or cellularity.[28] MR perfusion scans are also helpful in differentiating gliomas from other mimickers, like mets, radiation necrosis, non-glial lesions like lymphoma and extra-axial lesions like meningiomas.[20,29] Law et al reported that gliomas with high perfusion progressed rapidly and showed marked reduction in prognosis and survival, thus underscoring the role of perfusion scans in predicting the progression of gliomas to higher grades.[30]

But Zhang et al in their review pointed out the limitations of the perfusion scans e.g. propensity to get influenced by various hemodynamic factors, types of contrast agents and total acquisition time or overlapping features between glial tumors and radiation necrosis or among different grades of gliomas.[31] Guzmán-De-Villoria et al noted that perfusion scans were of very little value in adding to the predictive accuracy of conventional MRI.[32]

Goebell et al and Geneidi et al advocated the use of DTI in grading gliomas, documenting the differential peritumoral DTI features in low-and high-grade gliomas.[33,34]

Hall et al have advocated the use of MR spectroscopy for biopsy guidance from the most metabolically active area of the tumor.[35] Senft et al found that difference between maximum choline values represented high chance of differentiating high from low grade tumors.[36] But Howe et al reported overlapping findings, probably due to extensive necrosis and ensuing sampling bias.[37] Non-specificity and poor spatial resolution may limit the use of MRS in grading glial tumors.[20]

The inconclusive debate on whether the addition of individual advanced MRI sequences add to the predictive accuracy of MRI has prompted authors like Caulo et al to study quantitative data-driven multi-parametric MRI and they have reported very high improvement in the diagnostic accuracy, with very high sensitivity (84.2%), specificity (100%) and AUC (0.959).[38] But such studies are resource-intense and pose a challenge in cost-constrained setups.

Big data analytical tools are coming up to the rescue for such centres with low cost with highly accurate prediction being reported in studies of machine learning and radiomic analysis. Suárez-García et al from texture features obtained from the gray level size zone matrix calculated that the best model reached a sensitivity, specificity and accuracy of 94.12%, 88.24% and 91.18% respectively, providing a simple, low cost, easy to implement, reproducible and highly accurate glioma classifier, accessible to populations with reduced economic and scientific resources.[12] Similarly, Nakamoto et al concluded that the grade III and IV glioma scan be accurately and easily predicted by radiomic analysis of contrast-enhanced T1 and T2 weighted images.[39]

Addition of advanced sequences would have enriched this study by allowing assessment of their impact on the predictive accuracy of conventional MRI, but cost constraints limited it to conventional sequences of MRI only.

Limitations

This study found a strong correlation between degrees of most of the MR criteria and the grades of glial tumors, but had a few limitations which if worked upon by subsequent investigators can yield useful insights on this issue.

This was a hospital-based study. A population-based study would have had a broader scope and more chance of representing the true picture in the population.

This study was done a sample size well above what is required for such one-group analytical studies. But larger studies with a bigger sample size would have ironed the statistical convolutions even more properly.

Advanced MRI sequences were not used in this study, due to cost constraints. Inclusion of those sequences would have enriched the findings and inference of the study.

Use of big data analytical logarithms and machine learning programmes and comparing them with the analysis done by human experts can point out the accuracy, effectiveness and efficacy of such state-of-the-art yet cost effective tools and have the potential of opening new horizons in this field. Such concepts deserve more intense scientific investigation.

CONCLUSION

In this prospective observational study, the predictive accuracy of MRI in diagnosing and grading glial tumors was studied on 54 patients. Glial tumors remain a heterogenous entity with low grade tumors differing radically from high grade tumors in their histopathology, genetic and molecular profile, clinical course, and hence in their management options, prognosis and chance of survival. Surgical resection of gliomas comes at the price of significant complications. Rate of perioperative complications in patients undergoing 1st craniotomy is about 24% and those undergoing surgery for recurrent tumors is 33%.[40] Similarly, adjuvant chemoradiation of tumors come with adverse effects of their own. This has aroused the interest of investigators in finding out ways of accurate pre-operative confirmation of the diagnosis and prediction of the histological grade of gliomas so that the best course of management can be tailored out without under or overdoing things.

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