

Original Research Article

Role of magnetic resonance spectroscopy in grading of gliomas- a tertiary care centre study

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ABSTRACT

Background: Grading of gliomas is important for the determination of appropriate treatment strategies. MR spectroscopy has found increasing utility in grading of gliomas.

Methods: MR spectroscopic imaging was done for the referred patients to obtain Cho/NAA and Cho/Cr ratios. After analyzing histopathology reports, gliomas were classified into low grade and high grade. Histologically proven 54 low grade and 54 high grade gliomas were included in the study. The mean and standard deviation of these variables were obtained and compared between two groups. ROC curve analyses were performed in order to identify the optimal cut-off value for metabolite ratios for prediction purposes of high grade versus low grade gliomas.

Results: The mean and SD of Cho/NAA ratio in low grade glioma was 1.93 ± 1.19 . The mean and SD of Cho/NAA ratio in high grade glioma was 3.16 ± 1.73 was significantly higher. The optimal cut-off for differentiating low grade and high grade gliomas was 2.15 with a sensitivity of 74.07% and specificity of 66.67%. The mean and SD of Cho/Cr in low grade glioma was 2.05 ± 0.76 . The mean and SD of Cho/NAA in high grade glioma was 2.87 ± 1.65 was significantly higher. The optimal cut-off for differentiating low grade and high grade gliomas was 1.98 with a sensitivity of 64.8% and specificity of 64.1%.

Conclusions: MR spectroscopy imaging plays a pivotal role in prediction of glioma grade preoperatively and helps in deciding appropriate treatment strategies.

Keywords: Cho/Cr, Cho/NAA, Glioma grading, MR spectroscopy

INTRODUCTION

Gliomas are the most common primary neoplasms of the central nervous system. Grading of gliomas is important for the determination of appropriate treatment strategies and in the assessment of prognosis.¹ Conventional MR imaging with gadolinium-based contrast agents is an established and useful tool in the characterization of cerebral tumors.^{2,3}

However, despite optimization of sequences and protocols, the classification and grading of gliomas with conventional MR imaging is sometimes unreliable. Advanced MR imaging techniques such as MR

spectroscopy have found increasing utility in studying brain tumors.⁴ Recent reports regarding MR spectroscopy support its use as a powerful tool in tumor grading as well.¹ The metabolite ratios of Cho/creatine (Cr), NAA/Cr, and myo-inositol/Cr and the presence of lipids and lactate are useful in grading tumors and predicting tumor malignancy.⁵ Specifically, elevation in choline (Cho) with depression of N-acetyl aspartate (NAA) is a reliable indicator of tumor.

The main purpose of this study was to compare, Cho/NAA and Cho/Cr ratios obtained in MR spectroscopic imaging in low grade and high-grade gliomas.

Aims and objectives

Primary objective

To compare the means of choline/creatine and choline/N-acetyl aspartate ratios obtained in magnetic resonance spectroscopic imaging in low grade and high grade gliomas.

Secondary objective

To identify logical cut off values of choline/creatine ratio and choline/N-acetyl aspartate ratio using ROC curve for differentiating low grade from high grade gliomas.

METHODS

Research protocol was submitted to Human Ethical Committee, Medical College, Thiruvananthapuram. Study was initiated after getting clearance from both the Human Ethical Committee and Research committee.

It was a cross sectional study conducted at the Department of Radiodiagnosis, Government Medical College, Thiruvananthapuram for a period of 18 months February 2018 to July 2019.

Study population

All patients referred to the Department of Radiodiagnosis for evaluation of brain tumours with conventional MRI diagnosis of gliomas.

Sample size

Sample size was calculated from the formula:

$$n = \frac{(SD_1^2 + SD_2^2) (Z_{\alpha/2} + Z_{\beta})^2}{(d_1 - d_2)^2}$$

Where SD_1 and SD_2 are the standard deviations and d_1 and d_2 the means of two groups; $(Z_{\alpha/2} + Z_{\beta})^2 = \text{constant} = 7.9$

From the study by Law et al, the mean and standard deviation of rCBV, cho/cr and cho/NAA were obtained.⁶

Substituting this,

$$n = \frac{(2.79 + 10.82)(7.9)}{(1.42)^2}$$

$= 53.22 \approx 54$. So, each group contains 54 subjects

Sampling technique

All consecutive study participant satisfying the inclusion/exclusion criteria will be recruited for the study until the sample size is obtained.

Data collection

Based on interview using structured proforma, MRI examination and histopathological results. Study tools were written informed consent form, structured proforma, MRI.

Inclusion criteria

Patients referred to the Department of Radiodiagnosis, Government Medical College, Thiruvananthapuram, for MRI evaluation of brain tumours with conventional MRI diagnosis of gliomas.

Exclusion criteria

Patients not willing to participate in the study. Patients with pacemakers, cochlear implants, metallic clips or metallic foreign bodies. Patients with histopathological diagnosis other than gliomas.

Study procedure

Patients were selected according to selection criteria and consent obtained. MR examinations were performed on a 1.5T SIEMENS MAGNETOM system. MR imaging of all the cases are performed using the protocol followed in the Department of Radiodiagnosis for brain tumours.

This includes sequences like axial T_1 -weighted spin-echo, axial fluid attenuated inversion recovery (FLAIR) sequences, sagittal, axial and coronal T_2W_1 and diffusion weighted axial and SW_1 sequence before contrast study.

Intra venous gadolinium based contrast is administered after ensuring that the renal parameters are within normal range. T_2^* -weighted dynamic susceptibility contrast-enhanced perfusion MR imaging was performed 5 seconds after the beginning of the injection using a gradient-echo echoplanar sequence.

A volume selective 2D CSI sequence with 1500/144 was used for MR spectroscopic imaging. The hybrid multivoxel CSI technique uses a point-resolved spectroscopy (PRESS) double spin-echo sequence for preselection of a VOI that was usually defined to include the abnormality as well as normal-appearing brain tissue when possible. To prevent strong contribution to the spectra from subcutaneous fat signals, the VOI was completely enclosed within the brain and positioned at the center. Methodology 25 of the phase-encoded field of view, which was large enough to prevent wraparound artifact. The metabolite peaks were assigned as follows: Cho, 3.22 ppm; Cr, 3.02 ppm; NAA, 2.02 ppm; mobile lipids, 0.5-1.5 ppm. Lactate was identified at 1.33 ppm by its characteristic doublet that is caused by J modulation and inverted at TE of 144 ms. Maximal Cho/Cr and Cho/NAA ratios are obtained from spectral maps. To ensure quality control and acceptable quality of spectroscopic data, normal values for Cho/Cr and

Cho/NAA were obtained in normal-appearing white matter in the contralateral hemisphere. Histopathology reports were analysed. The gliomas were graded into high grade (WHO Grade 3 and 4) and low grade (WHO Grade 1 and 2) based on histopathology findings. Cho/Cr ratio, Cho/NAA ratio in low grade and high-grade gliomas were compared.

Definition of variables

Cho/NAA-Choline to N-acetyl aspartate ratio in tumor parenchyma (measured at echo time of 144 ms).

Cho/Cr-Choline to creatine ratio in tumor parenchyma (measured at echo time of 144 ms).

Data analysis

Data was entered into Microsoft Excel sheet. Analysis of data was done using appropriate statistical software. The values were expressed as mean±standard deviation. The differences between the means of low grade and high-grade brain tumors were compared using an independent-student t-test. P values less than 0.05 indicated a statistically significant difference. Receiver operating characteristic (ROC) curve analyses based on logistic regression models were performed in order to identify the optimal cut-off value for metabolite ratios for prediction purposes of high-grade gliomas versus low grade gliomas.

RESULTS

Magnetic resonance imaging with spectroscopic imaging was done for patients to image gliomas. Over a period of 18 months (from February 2018 to July 2019) total of 108 patients were included in the study which included 54 low grade and 54 high grade gliomas based on the post-operative histopathological report. WHO grade I and II gliomas were included in low grade and WHO grade III and IV were included in high grade groups for comparison of Choline/Creatine ratio (Cho/Cr) and Choline/N-Acetyl Aspartate ratio (Cho/NAA) values. Following observations were made after the study.

Table 1: Age distribution of study population.

Age	Count	Percent
≤ 40	6	5.6
41-50	34	31.5
51-60	37	34.3
61-70	28	25.9
≥70	3	2.8
Mean±SD	54.5±8.7	

Among the 108 patients included in the study, most of them were in the age group 51-60 immediately followed by patients in the age group 41-50. There were 3 patients over the age of 70.

Table 2: Gender distribution of study population.

Sex	Count	Percent
Male	64	59.3
Female	44	40.7

Table 3: Gender distribution of low and high grade glioma.

Outcome	Male		Female	
	Count	Percent	Count	Percent
High grade	48	75	6	13.6
Low grade	16	25	38	86.4

Out of the 64 males, 48 were having high grade gliomas (75%) and 16 were having low grade gliomas (25%). Among 44 females, 38 had low grade gliomas (86.4%) and 6 had high grade gliomas (13.6%)

The mean and SD of CHO/NAA in low grade glioma was 1.93 ± 1.19 , and in high grade glioma the mean CHO/NAA was 3.16 ± 1.73 was significantly higher ($p=0.028$).

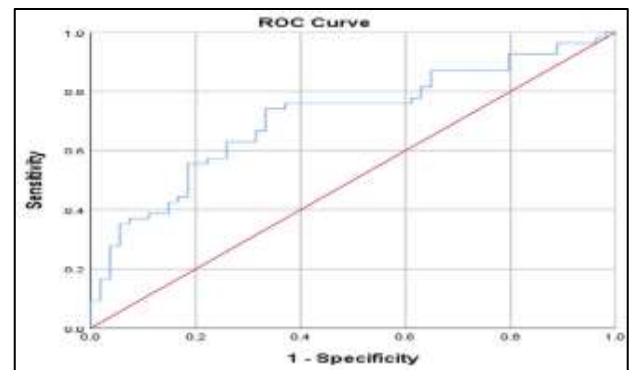


Figure 1: ROC curve for predicting cut off for CHO/NAA.

Area under the curve = 0.712. From the graph, a cut off value of 2.15 was derived. This cut off has a sensitivity of 74.07% and specificity of 66.67%.

Evaluation of CHO/cr values of gliomas

The mean and SD of CHO/NAA in low grade glioma was 2.05 ± 0.76 , and in high grade glioma the mean Cho/NAA was 2.87 ± 1.65 was significantly higher ($p=0.001$).

Table 4: Statistical analysis of CHO/Cr values of gliomas.

Outcome	N	rCBV	P value
Low grade	54	2.05 0.76	0.001
High grade	54	2.87 1.65	

Area under the curve = 0.636. From the graph, a cut off value of 1.98 was derived. This cut off has a sensitivity of 64.8% and specificity of 61.1%.

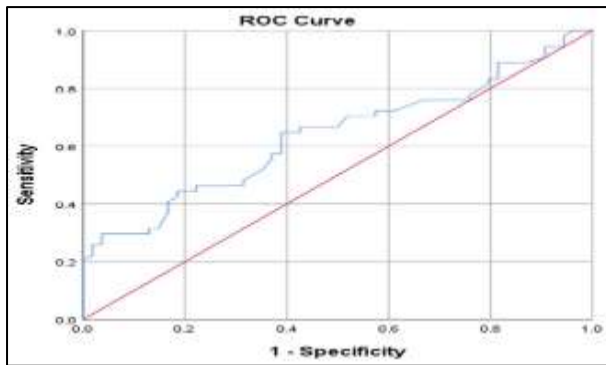


Figure 2: ROC curve for predicting cut off for CHO/Cr.

DISCUSSION

‘Tumours of neuroepithelial tissue’ form the largest group of primary CNS neoplasms. This category is divided into several tumour subtypes.

Classification of glial neoplasms.²

Astrocytomas

Astrocytomas are the most common subtype of glial neoplasm. Different types are, a) Low-grade diffuse astrocytoma, b) Anaplastic astrocytoma, c) Glioblastoma multiforme.

Nonastrocytic gliomas

These tumours include oligodendrogliomas, ependymomas, mixed gliomas and choroid plexus tumours. 1) Oligodendroglial tumours MR and perfusion imaging is helpful in differentiating grade II and III oligodendroglial tumours.³ 2) Ependymal tumours. 3) Choroid plexus tumours. 4) Other neuroepithelial tumours include astroblastoma, angiocentric glioma and chordoid glioma of the 3rd ventricle. 5) Neuronal and mixed neuronal-glial tumours. This group includes neuroepithelial tumours with ganglion-like cells differentiated neurocytes or poorly differentiated neuroblastic cells.

MR spectroscopic imaging

The mean and SD of CHO/NAA in low grade glioma was 1.93 ± 1.19 . The mean and SD of CHO/NAA in high grade glioma was 3.16 ± 1.73 was significantly higher ($p=0.028$). The optimal cut-off for differentiating low grade and high-grade gliomas was 2.15 with a sensitivity of 74.07% and specificity of 66.67%.

The mean and SD of CHO/Cr in low grade glioma was 2.05 ± 0.76 . The mean and SD of CHO/NAA in high grade glioma was 2.87 ± 1.65 was significantly higher ($p=0.001$). The optimal cut-off for differentiating low grade and high

grade gliomas was 1.98 with a sensitivity of 64.8% and specificity of 64.1%.

Many previous studies show elevated choline in high grade gliomas compared to low grade gliomas.⁴ Histopathologically, the linear correlation of Cho with cellular proliferative activity suggests that Cho may be a strong predictor of tumor grade.⁵ A statistically significant difference was noted in the metabolite ratios in low grade and high gliomas. The mean values obtained for Cho/NAA and Cho/Cr in our study are comparable to study by Law et al.⁶

MR spectrum

Number of metabolites depicted in cerebral MR spectroscopy is limited even with the development of higher field strengths such as 3T, 7T and 9.4T.⁷ Quality of spectra depends on magnetic field homogeneity, however high field MRS gives more signal separation.⁸ The echo time (TE) also influences the metabolites in the spectrum. Commonly used TEs are 20-30 ms, 135-145 ms and 270 ms. Only peaks of major brain metabolites like choline, creatine, NAA and lactate are depicted in long TE. Shorter TEs are used for detection of lipid, glutamate, glutamine, GABA and inositol peaks.

Table 5: Important metabolites of central nervous system.

Ppm	Metabolite	Properties
0.9-1.4	Lipids	Products of brain destruction
1.3	Lactate	Product of anaerobic glycolysis
2.0	NAA	Neuronal marker
2.2-2.4	Glutamine/GABA	Neurotransmitters
3.0	Creatine	Energy of metabolism
3.2	Choline	Cell membrane marker
3.5	Myo-inositol	Glial cell marker, osmolite hormone receptor mechanisms

Brain tumors exhibit different spectra compared with the brain tissue. Most of the tumors demonstrate decreased NAA (N-acetyl aspartate), creatine and elevated choline. Loss and dysfunction of normal neuronal tissue is responsible for depletion of NAA as it is considered as a marker of neuronal tissue.⁹ Metabolic activity of tumors results in depletion of energy stores resulting in reduced creatine. In MR spectroscopy creatine is utilized as reference standard for characterizing other peaks due to its high levels and relative comparability in different tissue types of brain.¹⁰ Increase in choline is attributed to increased membrane turn-over in neoplasms since various choline containing molecules are involved in membrane generation.¹¹ Choline elevation is proportionate to cellularity and is helpful in identifying tumor margins in

planning treatment Other changes include elevation of lipid and lactate and sometimes myoinositol. The increase in lactate is due to anaerobic glycolysis and elevated lipids is associated with necrosis. Elevated myoinositol reflects the increased glial cells which are supposed to have high myoinositol. Grade II gliomas are associated with high myoinositol.¹²

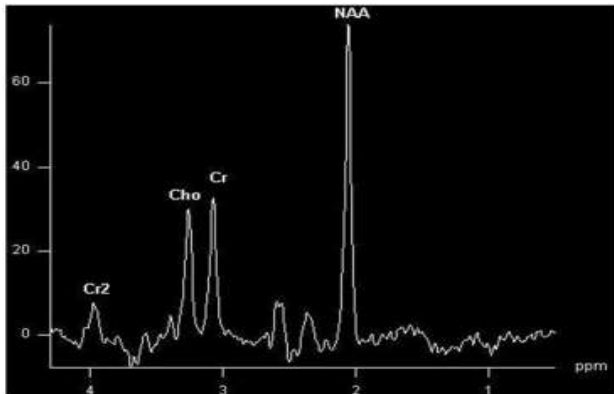


Figure 3: Intermediate TE acquisition (TE=135ms) in a normal patient showing prominent NAA, Cr and Cho peaks.¹³

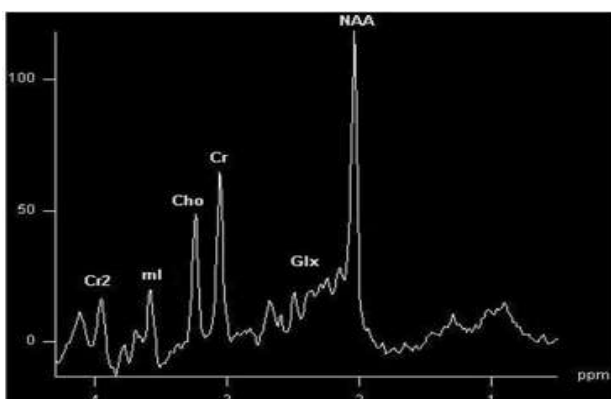


Figure 4: Short TE acquisition (TE=30ms) in a normal patient showing the same NAA, Cr, Cr2 and Cho peaks, and additional ml and Glx peaks, in normal ranges.¹³

Demographics

Age distribution of study population

In our study group of 108 patients with glioma, the age group ranged from 35 to 72 years. The maximum number of cases were in the age group 51-60 years followed by 41-50.

Sex distribution

In our study population, 64 were males (59.3%) and 44 were females (40.7%). Among 64 males, 48 males (75%) were having high grade gliomas. Among 44 females, 6 females (13.6%) had high grade gliomas.

Histopathology distribution

54 low grade and 54 high grade tumours were included in the study.

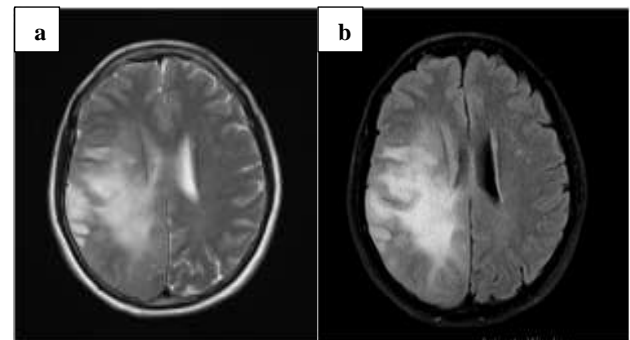


Figure 5: a) T2WI of HPR-WHO grade-II glioma in right temporoparietal region; b) FLAIR image of HPR-WHO grade-II glioma in right temporoparietal region.

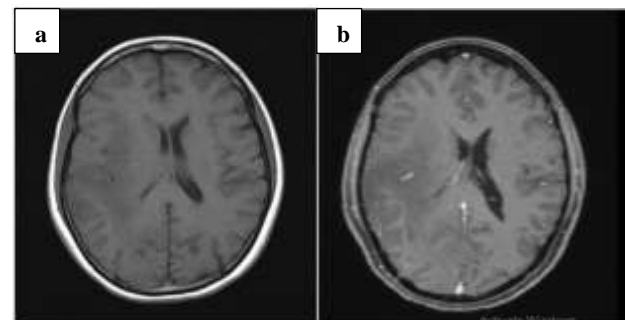


Figure 6: a) T1WI of HPR-WHO grade-II glioma in right temporoparietal region; b) T1 postcontrast image of HPR-WHO grade-II glioma in right temporoparietal region.

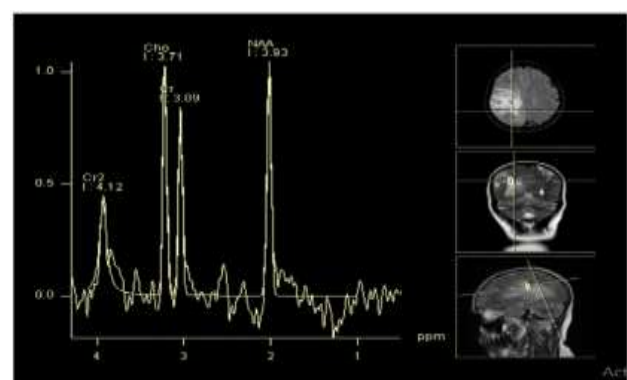


Figure 7: MR spectroscopy of WHO grade II glioma.

Conventional MRI alone is insufficient in accurately detecting low grade and high grade gliomas.¹⁴ Hence advanced MR imaging techniques have been used for preoperative grading of gliomas. Cut-off values can be used as important adjunct data in the noninvasive, neuroradiologic grading of gliomas.

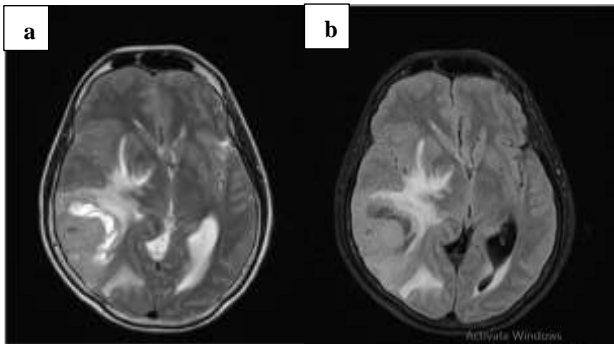


Figure 8: a) T2WI of HPR-WHO grade-IV glioma in right parietooccipital region; b) FLAIR image of HPR-WHO grade-IV glioma in right parietooccipital region.

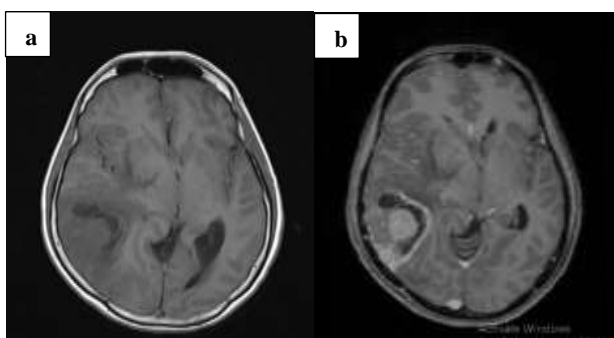


Figure 9: a) T1WI of HPR-WHO grade-IV glioma in right parietooccipital region; b) T1 postcontrast image of HPR-WHO grade-IV glioma in right parietooccipital region.

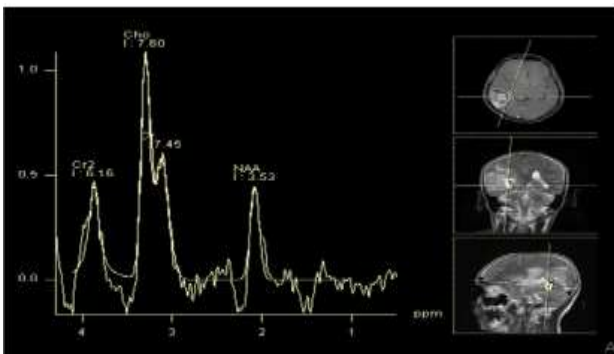


Figure 10: MR spectroscopy of WHO grade IV glioma.

Limitations of the study were the study sample might not be true representative of the real world due to “sampling errors” and spectrum bias. Inoperable cases of gliomas were omitted from the study.

CONCLUSION

MR spectroscopy can reliably differentiate low grade from high grade gliomas. Among the metabolite ratios, Cho/NAA and Cho/Cr ratios were studied. Significant difference in means of these ratios was present between

low grade and high grade gliomas. Cut-off of 2.15 for Cho/NAA had a sensitivity of 74.07% and specificity of 66.67% in differentiating low grade and high grade gliomas. Cut-off of 1.98 for Cho/Cr had a sensitivity of 64.8% and specificity of 64.1% in differentiating low grade and high grade gliomas.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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