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POTENTIAL OF MR SPECTROSCOPY IN DIFFERENTIATING BETWEEN LOW GRADE AND HIGH GRADE CEREBRAL GLIOMAS KEEPING HISTOPATHOLOGY AS GOLD STANDARD

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Abstract

Objective: *To determine the diagnostic accuracy of magnetic resonance spectroscopy (MRS) using choline-creatine (Cho/Cr) ratio for preoperative grading of gliomas, taking histopathology as the gold standard.*

Study design: *Cross-sectional study.*

Place and Duration of study: *Radiology department, Armed Forces Institute of Radiology, Rawalpindi, Pakistan from Oct 2023 to April 2025.*

Methodology: *Thirty-two patients with MRI-detected supratentorial gliomas underwent proton MR spectroscopy (^{1}H-MRS) using a 1.5 T MRI scanner. The Cho/Cr ratio was measured from the solid, enhancing component of the tumour. A ratio > 1.2 was considered suggestive of high-grade glioma, while ≤ 1.2 indicated low-grade. Findings were compared with histopathological grading. Diagnostic parameters including sensitivity, specificity, predictive values, accuracy, and p-value were calculated.*

Results: *Of 32 patients, 29 were male and 3 females (mean age = 44.1 ± 12.7 years; range 17–65 years). Based on MRS, 23 were labelled high-grade (Cho/Cr > 1.2) and 9 low-grade (≤ 1.2). Histopathology confirmed 25 high-grade and 7 low-grade gliomas. True positives = 21, false positives = 2, false negatives = 4, true negatives = 5. Sensitivity = 84.0%, specificity = 71.4%, PPV = 91.3%, NPV = 55.6%, accuracy = 81.3%. The Chi-square test value was 6.22 (p = 0.013).*

Conclusion*: MRS is a reliable, non invasive, radiological investigation for differentiating between high-grade and low-grade gliomas. The MRS parameter Cho/Cr ratio serves as a reliable metabolic parameter in determining the tumor grade and shows comparable results with histopathological diagnosis.*

INTRODUCTION

Cerebral gliomas account for a vast majority of brain neoplasms , with an incidence of approximately 2–3 cases annually per 100,000 population.[1] As with other cerebral neoplasms, gliomas consist of a wide range of histological subtypes which are broadly classified into low grade benign cerebral gliomas and high grade infiltrative/aggressive lesions. Accurate histological classification of these cerebral gliomas

is essential for further management and for determining prognosis.[2]

Based on available literature, incidence of these cerebral gliomas within the Pakistani population is significantly high having an estimated prevalence of over 10,000 cases. It is pertinent to note that high grade glioblastoma multiforme (butterfly glioma) accounts for one third of these cases.[3] [4]

Conventional magnetic resonance imaging (MRI) is the primary radiological investigation for assessment of cerebral gliomas however, its ability to accurately differentiate between low grade high-grade tumors is limited due to overlapping imaging features.[5] An adjunct to conventional MRI is magnetic resonance spectroscopy (MRS) that uses various metabolic markers (choline, creatine, NAA and lactate being the primary ones) to determine the tumor behaviour and hence its grade. Among various parameters, the choline-to-creatine (Cho/Cr) ratio has been found to be strongly associated with cellular turnover of these neoplasms and when combined with conventional MRI, can greatly improve its diagnostic accuracy. [6] [7]

This study was conducted to determine the diagnostic accuracy of the Cho/Cr ratio obtained using single-voxel 1.5 Tesla MRS in the preoperative grading of gliomas, using histopathology as the gold standard, at AFIRI, Rawalpindi.

METHODOLOGY

This prospective cross-sectional study was conducted at Armed Forces Institute of Radiology and Imaging (AFIRI), Rawalpindi, from Oct 2023 to April 2025 after approval from the Institutional Ethical Review Board (ERB No: 00024).

Inclusion Criteria

Patients of either gender, aged 16–65 years, with magnetic resonance imaging (MRI) findings suggestive of supratentorial glioma and planned for histopathological evaluation were included.

Exclusion Criteria

Patients with prior brain surgery, chemotherapy or radiotherapy, recurrent tumors, contraindications to MRI, or lesions with predominant necrosis/hemorrhage limiting adequate spectroscopic voxel placement were excluded.

Non-probability consecutive sampling was employed.

A sample size of thirty-two patients was used in this study. This was based on the number of cerebral gliomas referred to our setup for MR spectroscopy within a two year period. Using previously published data by Alam *et al.* [8] where the sensitivity of the Cho/Cr ratio in differentiating high from low-grade gliomas ranged between 80% and 90%, the minimum required sample size was calculated through the formula for proportions in diagnostic studies, which came out to be 30. Similar sample sizes ranging from 25 to 50 patients have been documented in literature as well.[9]

Hence a concise sample of 32 patients was considered sufficient as the emphasis of this study was to correlate and determine accuracy of metabolic MRS parameters rather than epidemiology of the tumor.[10]

Although there are multiple metabolic parameters employed in MRS including NAA, lactate peak etc, the choline-to-creatine (Cho/Cr) ratio was selected as the primary variable to be assessed and compared with histopathology results. This is because choline reflects glioma infiltration secondary to increased membrane turnover, while creatine represents tissue metabolism; hence their ratio effectively highlights the histological nature of neoplastic tissue.[11] [12] Ratios involving N-acetylaspartate (NAA), though also informative, are more susceptible to voxel placement errors and partial-volume effects, particularly in peritumoral or necrotic regions.[13] Therefore, Cho/Cr was considered a much more reliable parameter of tumor behaviour.

The cutoff value of 1.2 for the Cho/Cr ratio was adopted after reviewing previously published literature. Javed *et al.*[14] conducted a study on Pakistani population and demonstrated that a threshold of 1.2 effectively distinguished high-grade from low-grade gliomas. Hence we used a cut off value of 1.2 as well.

All patients underwent MRI on a 1.5 Tesla scanner. Conventional sequences included T1-weighted, T2-weighted, fluid-attenuated inversion

recovery (FLAIR), and post-contrast T1-weighted imaging.

Single-voxel proton magnetic resonance spectroscopy (^{1}H-MRS) was performed using point-resolved spectroscopy (PRESS) with repetition time (TR) 1500–2000 ms, echo time (TE) 135 ms, voxel size 1–2 cm^3, and 128 acquisitions. The voxel was placed in the solid enhancing tumor component, avoiding necrosis and hemorrhage.

The choline-to-creatine (Cho/Cr) ratio was calculated. A cutoff value of >1.2 was considered high-grade glioma and < 1.2 was considered low grade.

All patients then underwent biopsy or surgical resection. Histopathological grading was performed according to the World Health Organization 2021 classification.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26. Continuous variables were expressed as mean ± standard deviation. Independent sample t-test was used to compare Cho/Cr ratios between groups.

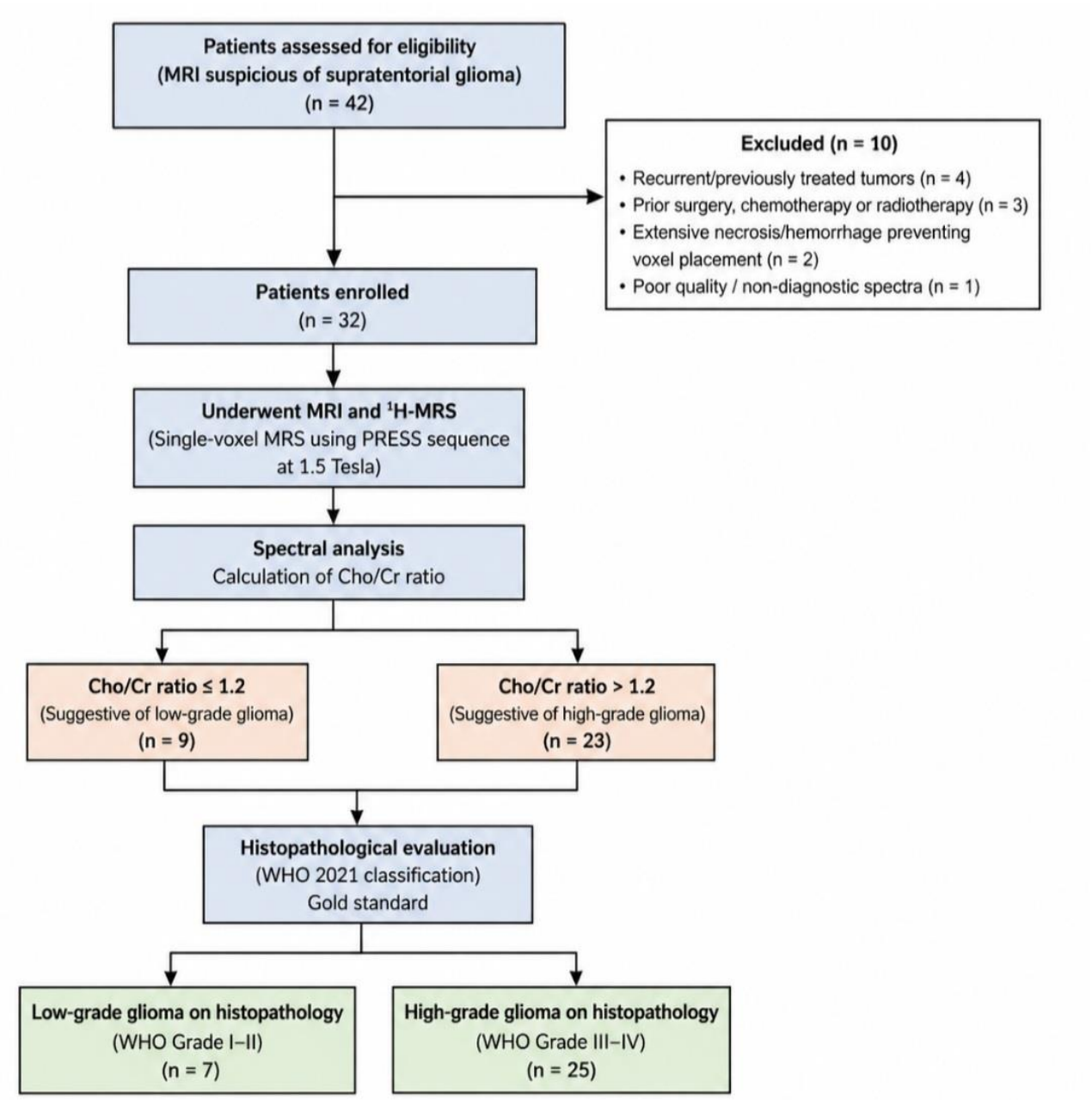

Figure-1: Patient flow diagram

Abbreviations: MRI = Magnetic Resonance Imaging; MRS = Magnetic Resonance Spectroscopy; ¹H-MRS = Proton Magnetic Resonance Spectroscopy; PRESS = Point RESolved Spectroscopy; Cho/Cr = Choline-to-Creatine ratio; WHO = World Health Organization.

Diagnostic accuracy parameters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated. Receiver operating characteristic (ROC) curve analysis was used to determine diagnostic performance. A p-value ≤0.05 was considered statistically significant.

RESULTS

Of 32 patients, 3 (9.4%) were female and 29 (90.6%) male, ages 17–65 years (mean 44.1 ± 12.7 years. Table-I showed the basic characteristics of individuals recruited for this study. Based on MRS, 23 were labeled high-grade (Cho/Cr > 1.2) and 9 low-grade (≤ 1.2).

Table-II showed the MR Spectroscopic and histopathological correlation. Histopathology confirmed confirmed 25 high-grade and 7 low-grade gliomas.

Our findings demonstrated a sensitivity of 84%, specificity of 71.4%, positive predictive value (PPV) of 91.3%, and overall accuracy of 81.3%, with a statistically significant p-value of 0.013 and AUC of 0.82. These findings reaffirm the role of MRS as a reliable non-invasive adjunct to conventional MRI in the preoperative evaluation of gliomas.

Table-I: Characteristics of Patients (n= 32)

Study Parameters	n (%)
Age (years) Mean + SD	(44.1 ± 12.7 years).
Gender Female Male	3 (9.4%) 29 (90.6%)

Table-II: Spectroscopic and Histopathological Correlation: (n= 32)

MRS finding (Cho/Cr)	Histopathology High Grade	Histopathology Low Grade	Total
> 1.2 (High grade)	21	2	23
≤ 1.2 (Low grade)	4	5	09
Total	25	7	32

Table-III: Diagnostic Performance (n= 32)

Study Parameters	Values
Sensitivity	84.0 %
Specificity	71.4%
Positive Predictive Value	91.3%
Negative Predictive Value	55.6%
Accuracy	81.3%
False Positive Rate	28.6%
False Negative Rate	16.0%
χ^2 (p-value)	6.22 (p = 0.013)

DISCUSSION

Aim of this study was to assess the diagnostic accuracy of magnetic resonance spectroscopy (MRS) in differentiating between low and high grade cerebral gliomas using the choline-to-creatine (Cho/Cr) ratio, while keeping a threshold

of 1.2 as a standard and comparing our results with histopathological diagnosis, thus establishing the significance of non-invasive radiological investigations in the grading and management of cerebral gliomas.

The findings of our study are more or less similar to the study perfomed by Law *et al.*,[15] They also used Cho/Cr ratio as their primary parameter, comparing MRS findings of 36 patients conducted on 1.5 T machine (sample size nearly similar to ours) with histopathological diagnosis. Using a threshold of 1.2 as well, their results gave a diagnostic accuracy of approximately 89%. Our study, also conducted on a 1.5 T using single-voxel spectroscopy, achieved comparable accuracy (81.3%), validating the effectiveness of Cho/Cr ratio as a reliable metabolic marker for tumor aggressiveness even in single-voxel settings. Although Law *et al*. Used both perfusion and spectroscopic parameters, our study utilised only the Cho/Cr ratio, and yielded comparable results. Similarly, another study using Cho/Cr was done by Majós *et al.*[16] which showed a sensitivity of 83 % and a specificity of 75 %. They however used a cut off of 1.6 which was slightly higher than ours. A study conducted on 38 patients by Fathi Kazerooni *et al.*[17] showed that Cho/Cr ratio has a sensitivity of 85% and a specificity of 79%, in differentiating between high and low grade gliomas further establishing and supporting its diagnostic utility. Likewise, another study published by Cai *et al.*[18] showed that ^{1}H-MRS demonstrated an AUC of 0.86 for glioma grading, which is nearly the same as our AUC (0.82).

Comparable results demonstrating significant correlation between MRS parameters and histopathological grading of cerebral gliomas were reported by Aydin *et al.* [19] as well.

Our study's slightly lower specificity (71.4%) compared to some western literature (typically 75–85%) can be attributed to small sample size and the inherent overlap of metabolic spectra between low-grade gliomas with focal proliferation and high-grade lesions with necrosis. The false positives (n = 2) in our series likely represented low-grade tumors with elevated choline due to inflammation or atypical cellular activity, while false negatives (n = 4) may have resulted from sampling error or intratumoral heterogeneity—issues previously discussed by Patel *et al.*[20]

Overall, our study shows that MRS, even with a single parameter of Cho/Cr, plays a vital role in differentiating low vs high grade cerebral gliomas. Hence its inclusion in preoperative glioma assessment protocols can greatly influence optimal patient management.

LIMITATIONS

Our study was limited to the use of a single yet reliable metabolic parameter i.e the Cho/Cr ratio, hence metabolic significance of other MRS parameters like NAA, lipid and lactate peaks were not assessed. The relatively small sample size, available during the study period, also may have contributed to a restricted outcome. Therefore further studies should incorporate a larger sample size and multiple MRS ratios and parameters to further support the diagnostic value of MRS in pre-operative glioma grading.

CONCLUSION

Magnetic resonance spectroscopy is a reliable, non-invasive radiological investigation that can be used as an adjunct for differentiating between high and low grade gliomas. The Choline/Creatine ratio, particularly using a threshold of 1.2, shows strong concordance with histopathological grading. Given its non-invasive nature, MRS could reduce the need for biopsy in selected cases where surgical risk is high. Future directions may include integrating MRS with diffusion and perfusion imaging to improve specificity and reduce overlap between grades.

Conflict of interest: None
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