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Magnetic Resonance Spectroscopic (MRS) Correlation of Diffusely Infiltrating Astrocytomas with Histological Grading

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ABSTRACT

Background: *Diffusely infiltrating astrocytomas are common primary brain tumors with variable histopathological grades. Accurate preoperative grading is crucial for treatment planning. Magnetic resonance spectroscopy (MRS) provides a non-invasive means to evaluate tumor metabolism, potentially aiding in grading.* ***Objective:*** *To evaluate the correlation between MRS findings and histological grading in diffusely infiltrating astrocytomas.* ***Methods & Materials:*** *This observational cross-sectional study included 30 patients diagnosed with diffusely infiltrating astrocytomas at multiple tertiary centers in Dhaka, Bangladesh, from June 2010 to April 2012. MRS parameters—choline (Cho) peak, N-acetyl aspartate (NAA) peak, creatine (Cr) peak, and Choline/Creatine (Cho/Cr) ratio—were measured preoperatively. Tumor specimens were collected during surgery for histopathological grading according to WHO criteria. Data were analyzed using SPSS, and ANOVA was used to compare metabolite peaks across tumor grades.* ***Results:*** *The mean age was 37.77 ± 13.16 years, with male predominance (70%). Histopathology revealed 33.3% grade II, 20% grade III, and 46.7% grade IV astrocytomas. Cho peak increased from grade II to IV, NAA decreased from grade II to III but rose in grade IV, and Cr showed variable trends. The Cho/Cr ratio progressively increased with tumor grade (Grade II: 1.997 ± 0.42; Grade III: 2.312 ± 1.07; Grade IV: 2.961 ± 1.08) and demonstrated a significant correlation with histological grade ($F = 3.444$, $p = 0.047$). No significant correlation was observed for Cho, NAA, or Cr peaks individually.* ***Conclusion:*** *The Cho/Cr ratio is a reliable MRS biomarker for differentiating low- and high-grade diffusely infiltrating astrocytomas. Absolute metabolite peaks alone may be insufficient due to variability and overlap. MRS can aid in preoperative tumor grading, particularly for patients unfit for surgical intervention.*

Keywords: *Diffusely infiltrating astrocytomas, Magnetic resonance spectroscopy (MRS), Choline/Creatine ratio, Tumor grading, Brain tumors.*

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INTRODUCTION

Gliomas are the most common primary brain tumors and exhibit significant histological heterogeneity, characterized by varying degrees of cellular and nuclear pleomorphism, mitotic activity, vascular proliferation, and necrosis. They are classified as low- or high-grade malignancies, and despite aggressive treatment, malignant gliomas have a poor prognosis due to their infiltrative nature and high recurrence rate [1]. Diffusely infiltrating astrocytomas comprise a subset of astrocytic neoplasms, including diffuse astrocytomas (WHO grade II), anaplastic astrocytomas (WHO grade III), and glioblastoma multiforme (WHO grade IV) [2]. Treatment strategies differ substantially according to tumor grade, highlighting the importance of accurate, non-invasive techniques for preoperative grading to guide therapeutic decisions [1].

Magnetic resonance imaging (MRI) is the imaging modality of choice for brain tumors, providing excellent soft tissue contrast and pathophysiologic insight without ionizing radiation [3]. Beyond anatomical imaging, magnetic resonance spectroscopy (MRS) allows non-invasive assessment of tissue metabolism, offering information on biochemical changes associated with brain tumors [3]. Developed from nuclear magnetic resonance techniques in chemistry and physics, in vivo MRS evolved alongside MRI since the 1980s, combining anatomical and metabolic evaluation [4]. The brain is particularly well-suited for proton MRS (H-MRS) due to favorable spectroscopic properties [4].

H-MRS detects key brain metabolites at millimolar concentrations, including N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), lactate (Lac), myo-inositol, glutamine, glutamate, lipids, and amino acids [5]. NAA, a neuronal marker, decreases in tumors and neuronal injury (peak 2.0 ppm), while Cho, reflecting cell membrane turnover, increases in high-grade tumors and correlates with proliferation markers such as Ki-67 (peak 3.22 ppm). Creatine reflects energy reserves (peak 3.0 ppm), and lactate indicates anaerobic glycolysis or metabolic stress (peak 1.33 ppm) [5].

Gliomas typically demonstrate decreased NAA, elevated Cho, altered Cho/Cr and NAA/Cr ratios, and increased lactate, all of which correlate with tumor grade and cellular proliferation [1,6]. Quantitative MRS assessment can provide valuable information on tumor biology, grading, and prognosis before histological examination. Nevertheless, histopathological evaluation of nuclear features remains the gold standard for glioma classification according to WHO criteria [7]. This study aims to evaluate the correlation between magnetic resonance spectroscopic findings and histological grading in diffusely infiltrating astrocytomas, with the goal of assessing the potential of MRS as a non-invasive tool for preoperative tumor grading.

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METHODS & MATERIALS

This observational cross-sectional study was conducted from June 2010 to April 2012 in the Department of Neurosurgery at Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka Medical College Hospital (DMCH), Metropolitan Medical Centre, Popular Medical College Hospital, and Green Life Hospital, Dhaka, Bangladesh. The study population comprised all patients diagnosed with astrocytoma and admitted to these centers during the study period. Based on hospital records, approximately 600 patients were admitted with glioma over 18 months, 36 underwent surgery, and one-third of them underwent MRS, yielding an estimated sample size of 30 patients. Non-probability convenient sampling was employed. Patients diagnosed with glioma on MRI were included, while those unfit for surgery or biopsy or whose histopathology revealed lesions other than astrocytoma were excluded. Eligible patients were identified after screening, and previous imaging was reviewed: 10 patients with only CT scans underwent MRI and MRS, while 17 patients with prior MRI underwent MRS alone. Informed written consent was obtained from all participants or guardians. MRS parameters—including choline (Cho) peak, creatine (Cr) peak, Cho/Cr ratio, and N-acetyl aspartate (NAA) peak—were recorded, and tumor specimens were collected during surgery for histopathological examination. Histological grading of astrocytomas was compared with MRS findings. Data were collected using a structured sheet, including detailed history, general and neurological examination, MRS parameters, and histopathology reports. Ethical clearance was obtained from the Department of Neurosurgery and the Central Ethical Committee of BSMMU. Data analysis was performed using SPSS version 19, with continuous variables expressed as mean ± standard deviation, categorical variables as frequencies and percentages, and statistical significance set at $p < 0.05$.

RESULTS

The mean age of the study participants was 37.77 years (range: 19–70 years). About 43.33% of patients were aged ≤30 years, followed by 36.67% between 31–50 years and 20% above 50 years. Male patients predominated (70%) compared to females (30%), with a male-to-female ratio of 2.33:1 (*Table I*).

Table I: Distribution of respondents (*n* = 30) by age group and sex

Variable	Category	Frequency	Percent
Age (years)	≤30	13	43.33
	31–50	11	36.67
	>50	6	20.00
Sex	Male	21	70.00
	Female	9	30.00
Total		30	100.0

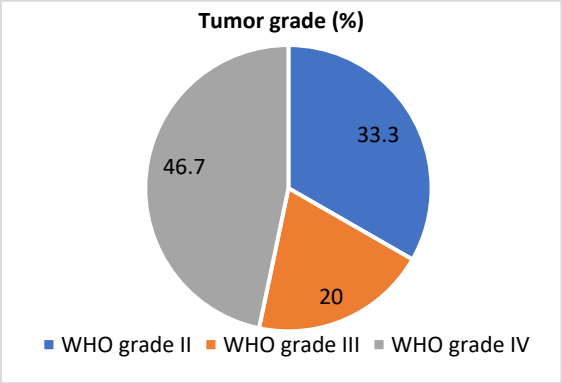

Figure 1: Distribution of the respondents by histopatho-logical grade of tumors (*n*=30)

Figure 1 shows that prevalence of grade IV astrocytoma was more, 46.7 % (14); followed by grade II astrocytoma, which was 33.3 % (10); then grade III astrocytoma, which was 20 % (6). Among the 30 patients, the majority had Grade IV astrocytoma (46.7%), followed by Grade II (33.3%) and Grade III (20.0%). The Choline peak increased progressively from Grade II to IV, while the NAA peak declined from Grade II to III but rose again in Grade IV. The Creatine peak increased slightly from Grade II to III and then declined in Grade IV. The Choline-Creatine (Cho/Cr) ratio showed a consistent increase with tumor grade, being highest in Grade IV, supporting its role as a potential metabolic marker for tumor aggressiveness (*Table II*).

Table II: Mean values of different MRS metabolites across histopathological grades of astrocytomas (*n* = 30)

Tumor Grade (WHO)	Frequency (%)	Choline Peak (Mean ± SD)	NAA Peak (Mean ± SD)	Creatine Peak (Mean ± SD)	Cho/Cr Ratio (Mean ± SD)
Grade II	10 (33.3)	95,681.40 ± 28,937.39	43,150.80 ± 28,629.14	50,765.00 ± 20,743.96	1.9970 ± 0.41945
Grade III	6 (20.0)	110,012.83 ± 35,996.05	36,380.00 ± 22,857.03	52,862.33 ± 21,386.09	2.3117 ± 1.06824
Grade IV	14 (46.7)	114,981.43 ± 55,179.82	49,547.14 ± 38,877.52	44,997.86 ± 26,032.61	2.9607 ± 1.07769
Total	30 (100)	—	—	—	—

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Table III shows ANOVA of MRS Peaks by Tumor Grade: Analysis of variance revealed no statistically significant differences in the mean values of Choline peak (F = 0.559, p = 0.578), NAA peak (F = 0.368, p = 0.696), or Creatine peak (F = 0.304, p = 0.740) across the different histopathological grades of astrocytomas. However, the Choline-Creatine (Cho/Cr) ratio demonstrated a statistically significant difference among the tumor grades (F = 3.444, p = 0.047). This finding suggests that while individual metabolite peaks did not vary significantly with histological grade, the Cho/Cr ratio may serve as a more sensitive parameter for distinguishing between low- and high-grade astrocytomas.

Table III: ANOVA for different MRS peaks in different histological grades of astrocytoma

Source of variables		Sum of squares	df	Mean square	F	Sig.(P)
Choline peak of astrocytomas	Between groups	2.218E9	2	1.109E9	.559	.578
	Within groups	5.360E10	27	1.985E9		
	Total	5.582E10	29			
NAA peak of astrocytomas	Between groups	7.681E8	2	3.840E8	.368	.696
	Within groups	2.817E10	27	1.043E9		
	Total	2.894E10	29			
Creatine peak of astrocytomas	Between groups	3.372E8	2	1.686E8	.304	.740
	Within groups	1.497E10	27	5.544E8		
	Total	1.531E10	29			
Choline-Creatine ratio	Between groups	5.712	2	2.856	3.444	.047
	Within groups	22.387	27	.829		
	Total	28.099	29			

DISCUSSION

Significant metabolic alterations in brain tumors have been reported using proton magnetic resonance spectroscopy (1H-MRS). In gliomas, particularly diffusely infiltrating astrocytomas, elevated Choline (Cho) peaks and reduced N-acetyl aspartate (NAA) peaks have been consistently documented, while Creatine (Cr) is considered relatively stable but may vary with tumor metabolism. These changes are attributed to increased cell membrane turnover (Cho), loss of neuronal integrity (NAA), and altered energy metabolism (Cr). In our study, the mean age of patients was 37.77 years (range: 19–70), consistent with prior reports. Guillamo et al. (2001) found a mean onset at 34 years [8], while Zulch reported 36.15 years and Dastur & Lalita found 31.15 years [9]. This suggests that diffusely infiltrating astrocytomas predominantly affect younger and middle-aged adults. About 80% of our patients were ≤50 years, reflecting a relatively early onset compared to other intracranial neoplasms. Regarding sex distribution, males were more commonly affected (70%) than females (30%), with a male-to-female ratio of 2.33:1. This aligns with previous literature where male predominance has been observed, such as Ramamurthi (3:1) [10], Guillamo et al. (2.2:1) [8], and Doran & Thorell (1.44:1) [11]. Thus, our findings are consistent with the global trend of male predominance in astrocytomas.

Concerning histopathological grading, most of our cases were WHO grade IV (46.7%), followed by grade II (33.3%) and grade III (20%). These proportions are in agreement with Nafe et al. (2003), who reported 63% grade IV, and Kaminogo et al. (1998), who found 64% grade IV [6,7]. This underscores the predominance of higher-grade astrocytomas among symptomatic cases.

Our MRS analysis revealed a progressive rise in Cho peak values from grade II to grade IV, though ANOVA did not demonstrate statistical significance (F = 0.559, p = 0.578). This is consistent with the biological rationale that higher-grade tumors exhibit elevated choline due to increased membrane synthesis and turnover. Similar findings of rising Cho with tumor grade were reported by Law et al. (2002) [12] and Bulakbasi et al. (2003) [13]. However, some studies (e.g., Tedeschi et al., 1995) noted substantial overlap in Cho values across grades, limiting its diagnostic precision [14]. The NAA peak was higher in grade II tumors, lower in grade III, but unexpectedly increased in grade IV in our cohort. While most studies (e.g., Nafe et al., 2003) [7] show progressive decline of NAA with grade, our finding of higher NAA in some grade IV cases may reflect residual neuronal tissue at tumor margins or sampling variability. This highlights the inherent complexity and heterogeneity of astrocytomas. Creatine peaks in our study showed no consistent trend, rising slightly from grade II to III and then declining in grade IV. Previous studies have shown both stability and reduction in Cr levels [7,14]. Thus, Cr remains an unreliable marker for grading.

The most significant observation in our study was the Cho/Cr ratio, which increased progressively with grade (Grade II: 1.99, Grade III: 2.31, Grade IV: 2.96) and showed statistical significance (F = 3.444, p = 0.047). This is consistent with multiple prior reports where Cho/Cr ratio was found to be the most sensitive spectroscopic parameter distinguishing low- from high-grade gliomas. For instance, Law et al. (2002) [12] and Usenius et al. (1994) [15] both reported that Cho/Cr ratio significantly correlates with glioma grade and may aid in non-invasive tumor grading.

Taken together, our findings suggest that while absolute metabolite peaks (Cho, NAA, Cr) show variability and overlap across tumor grades, the Cho/Cr ratio emerges as a more robust and reproducible biomarker for grading diffusely infiltrating astrocytomas. This supports its role in clinical decision-making, especially in differentiating low-grade from high-grade tumors preoperatively.

This study had several limitations, including a small sample size, short duration, and exclusion of Grade I gliomas. Some MRS variables, such as Lactate peak and NAA/Cr ratio, were not analyzed, and tissue specimens may not have exactly matched the MRS voxel locations; in cases with mixed histology, the highest tumor grade was recorded. Despite these limitations, the results suggest that the Choline/Creatine (Cho/Cr) ratio is a reliable MRS marker for differentiating low- and high-grade gliomas. We recommend that patients with radiologically suspected high-grade gliomas, especially those unfit for surgery, be further evaluated with MRS to guide palliative therapy, and that protocols be established to perform MRS in all suspected glioma cases during the same MRI session.

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CONCLUSION

Significant correlation was found between spectroscopic variables of choline/creatine ratio and grading of diffusely infiltrating astrocytomas. Correlation between the Choline, NAA, creatine peak and grading of astrocytoma from grade II to IV was not significant. Though there was a positive correlation between choline peak and grading of astrocytoma but ANOVA shows it non-significant, probably due to small sample size.

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