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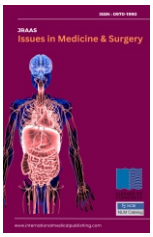

Research Article

Section: Radiodiagnosis

Diagnostic Value of Diffusion Weighted Imaging & MR Spectroscopy in Characterisation of Intracranial Neoplasms with Histopathological Correlation

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HIGHLIGHTS

- DWI improves tumor characterization
- MRS enhances diagnostic accuracy
- ADC correlates with grade
- Metabolic ratios aid differentiation
- Strong histopathological correlation

Key Words:
Diffusion-Weighted Imaging
Magnetic Resonance Spectroscopy
Intracranial Neoplasms
Magnetic Resonance Imaging
Apparent diffusion coefficient

ABSTRACT

Introduction: Intracranial neoplasms represent a heterogeneous group of lesions with varied biological behaviour, prognosis, and management strategies. Accurate preoperative characterization remains a diagnostic challenge, as conventional magnetic resonance imaging (MRI) often shows overlapping features among different tumor types. **Aim & Objective:** This study aimed to evaluate the diagnostic utility of diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) in the characterization of intracranial neoplasms, with histopathological examination as the reference standard. **Material & Methods:** A prospective observational study was conducted on 35 patients with suspected intracranial tumors. All patients underwent comprehensive MRI, including DWI with apparent diffusion coefficient (ADC) mapping and multivoxel MRS for metabolite analysis. **Results:** Quantitative parameters such as tumor and peritumoral ADC values, along with metabolite ratios (Cho/Cr, Cho/NAA, NAA/Cr), were analysed and correlated with histopathological findings. The mean tumor ADC value was $1.03 \pm 0.30 \times 10^{-3}$ mm²/s, with significantly lower values observed in high-grade tumors and lymphoma compared to low-grade tumors ($p < 0.001$). MRS demonstrated elevated choline and reduced NAA in neoplastic lesions, with higher Cho/Cr and Cho/NAA ratios in high-grade tumors. MRI showed high specificity (95.7%) and overall diagnostic accuracy of 85.7% in identifying high-grade gliomas, though sensitivity was moderate (66.7%). **Conclusion:** The combined use of DWI and MRS improved diagnostic confidence in tumor characterization, grading, and differentiation from other intracranial lesions. These advanced imaging techniques provide valuable non-invasive insights into tumor cellularity and metabolism, complementing conventional MRI and aiding in clinical decision-making. In conclusion, integration of DWI and MRS significantly enhances the diagnostic performance of MRI in intracranial neoplasms, with strong correlation to histopathology.

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INTRODUCTION

Intracranial neoplasms comprise a diverse group of benign and malignant tumors arising from the brain parenchyma, meninges, cranial nerves, or as metastatic lesions from systemic malignancies. These tumors remain a major cause of neurological morbidity, disability, and mortality worldwide, including in India. Owing to their varied biological behavior and clinical presentation, accurate preoperative characterization is essential for determining appropriate treatment strategies, surgical planning, and prognosis. Early diagnosis facilitates timely intervention, minimizes treatment-related complications, and improves overall patient outcomes. Consequently, reliable neuroimaging techniques play a pivotal role in the diagnostic evaluation and management of patients with intracranial tumors [1,2]. Magnetic Resonance Imaging (MRI) is the imaging modality of choice for evaluating intracranial neoplasms because of its excellent soft-tissue contrast and multiplanar capability. Conventional MRI sequences, including T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR), and contrast-enhanced imaging, provide detailed anatomical information regarding tumor location, size, morphology, surrounding edema, mass effect, and contrast enhancement. Despite these advantages, conventional MRI alone often cannot accurately distinguish tumors with similar imaging appearances but different histopathological characteristics. High-grade gliomas, metastatic lesions, lymphomas, & certain inflammatory or demyelinating conditions frequently demonstrate overlapping radiological features, thereby limiting diagnostic specificity and emphasizing the need for advanced functional imaging techniques [3].

Diffusion-weighted imaging (DWI) has emerged as an important functional MRI technique that evaluates the microscopic movement of water molecules within tissues. Quantitative assessment using the apparent diffusion coefficient (ADC) reflects tissue cellularity, membrane integrity, & microstructural organization. Highly cellular malignant tumors typically demonstrate restricted diffusion with low ADC values, whereas low-grade tumors, necrotic lesions, and cystic components exhibit relatively higher ADC values due to facilitated diffusion. These diffusion characteristics enable DWI to differentiate high-grade from low-grade tumors, distinguish neoplastic lesions from abscesses or infarcts, and identify the most cellular regions for biopsy. Furthermore, DWI offers rapid image acquisition without requiring intravenous contrast, making it particularly valuable in critically ill patients and those with contraindications to contrast administration [4].

Magnetic Resonance Spectroscopy (MRS) complements conventi-onal MRI and DWI by providing non-invasive metabolic information about intracranial lesions. It evaluates tissue biochemistry through metabolite concentrations, including choline (Cho), N-acetylaspartate (NAA), creatine (Cr), lactate, and lipid peaks. Increased choline levels indicate enhanced cellular proliferation and membrane turnover, while reduced NAA reflects neuronal loss or dysfunction. Elevated lipid-lactate peaks are commonly associated with tumor necrosis, anaerobic metabolism, and high-grade malignancies. In addition to tumor grading, MRS assists in differentiating neoplastic lesions from infectious, inflammatory, or demyelinating disorders and can identify metabolic abnormalities beyond morphologically abnormal regions visible on conventional MRI [5,6]. Although histopathological examination remains the definitive standard for tumor diagnosis and grading, tissue sampling may be affected by tumor heterogeneity, sampling errors, and limited accessibility of lesions located in eloquent or deep brain regions. Advanced MRI techniques such as DWI and MRS provide valuable physiological and metabolic information that complements histopathology by

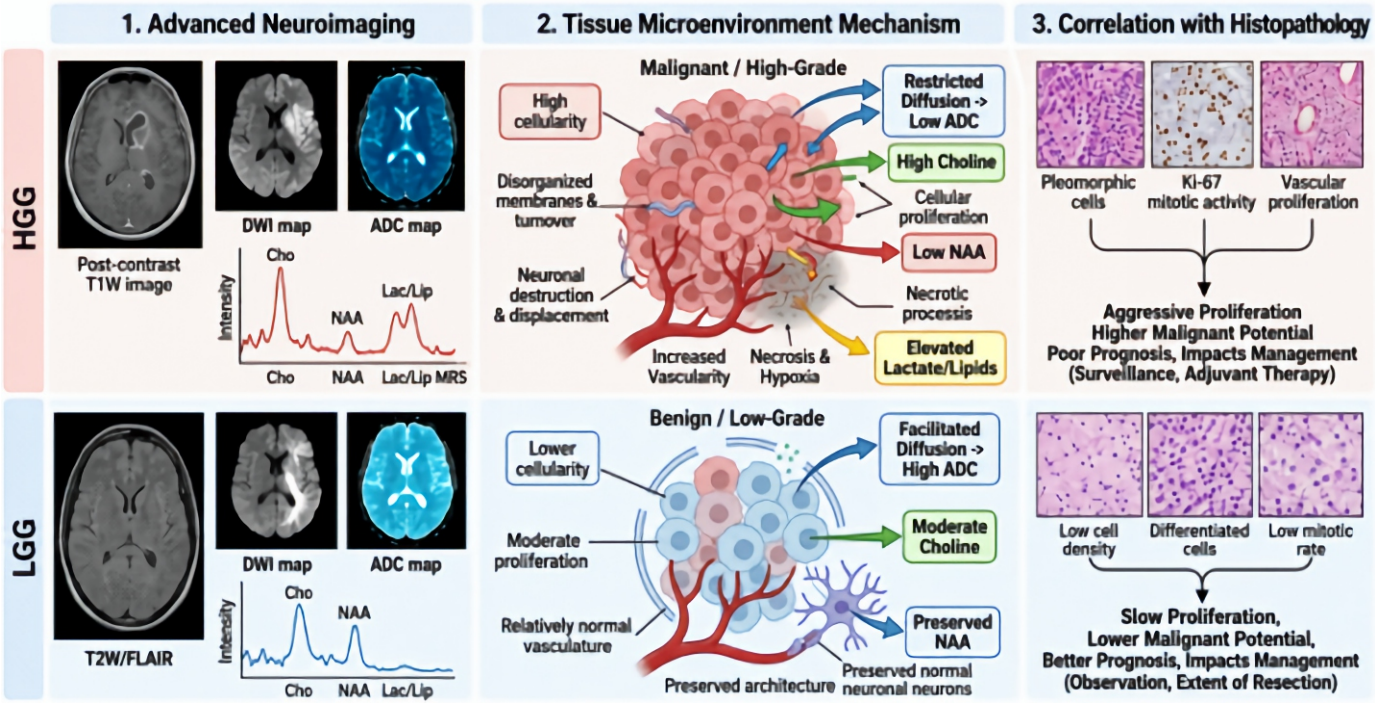

Figure 1: Diagnostic value of DWI & MRS in intracranial neoplasm characterization: Biological mechanisms driving HGG vs. differentiation with histopathological correlation.

improving biopsy targeting and increasing preoperative diagnostic confidence. Their combined application enhances the non-invasive assessment of tumor biology and facilitates more accurate characterization of intracranial neoplasms [7,8]. Accurate preoperative characterization significantly influences clinical management by guiding the extent of surgical resection, planning adjuvant therapy, & predicting patient prognosis. With the increasing burden of primary and metastatic brain tumors, particularly in developing countries such as India, incorporating advanced MRI techniques into routine neuroimaging protocols has become increasingly important. The integration of DWI and MRS with conventional MRI improves diagnostic accuracy without substantially increasing examination time or invasiveness, thereby supporting personalized treatment planning and improving overall patient care [9,10].

Thus, the integration of diffusion-weighted imaging and MR spectroscopy, in correlation with histopathology, represents a promising approach for improving the characterization and grading of intracranial neoplasms. The present study aims to evaluate the diagnostic utility of these advanced MRI techniques in differentiating intracranial tumors, with histopathological correlation serving as the reference standard

MATERIAL & METHODS

This prospective observational study was conducted at the Radiodiagnosis, Ramaiah Medical College Hospital, Bangalore from May 2024 to January 2026. Ethical approval has been obtained from the Ethical Approval Committee of Ramaiah Medical College Hospital, Bangalore.

Study Population

The study population comprised clinically diagnosed or suspected patients with intracranial tumours undergoing brain MRI who provided informed consent for participation. Patients were included only if intracranial lesions were identified on MRI. Cases without any intracranial mass, those with infective intracranial pathologies, and postoperative cases of brain tumours were excluded from data interpretation to maintain a homogeneous study population and ensure accurate evaluation of imaging findings and study outcomes.

Data Analysis

Data were entered into MS Excel and analysed using SPSS version 26.0. Quantitative variables were summarized as mean and standard deviation, while qualitative variables were expressed as proportions. Data normality was assessed using the Kolmogorov–Smirnov test. Differences in quantitative means among three or more groups were evaluated using one-way ANOVA. A p-value of less than 0.05 was considered statistically significant for all analyses conducted in the study.

RESULTS

A total of 35 participants were included in the study, with a mean age of 52.17 ± 15.93 years (median 54 years; range 24–82 years), indicating that the study population predominantly comprised middle-aged individuals with a moderately wide age distribution. Females constituted 54.3% of the participants, while males accounted for 45.7%, showing a slight female predominance. The mean tumor apparent diffusion coefficient (ADC) was 1.03 ± 0.30 × 10^{-3} mm^2/s (range 0.61–1.48 × 10^{-3} mm^2/s), whereas the mean peri-tumoral ADC was 0.95 ± 0.22 × 10^{-3} mm^2/s (range 0.59–1.57 × 10^{-3} mm^2/s), demonstrating moderate variability in diffusion characteristics among tumors. Magnetic resonance spectroscopy revealed a mean NAA/Creatine ratio of 0.62 ± 0.37 (range 0.02–1.40), a mean NAA/Choline ratio of 0.74 ± 1.53 (range 0.01–9.20), and a mean Choline/Creatine ratio of 2.36 ± 1.58 (range 0.62–8.00). The wide distribution of metabolite ratios reflects considerable biological heterogeneity among intracranial tumors and highlights the variability in metabolic profiles observed across different histopathological tumor types.

Among the 35 study participants, indeterminate neoplastic lesions were the most common MRI diagnosis (31.4%), followed by high-grade glial tumors (25.7%), other intra-axial non-glial tumors (17.1%), low-grade glial tumors (14.3%), and extra-axial tumors (11.4%), with high-grade glioma being the most frequently identified specific radiological subtype (14.3%) **(Table 1)**. Histopathological examination showed that low-grade/other glial tumors were the most common lesions (40.0%), followed by high-grade glial tumors (34.3%), with glioblastoma representing the single most frequent diagnosis (20.0%). Extra-axial tumors accounted for 11.4% of cases, while metastatic tumors and primary CNS lymphoma comprised 8.6% and 5.7% of the study population, respectively **(Figure 2)**. Comparison of MRI findings with histopathology demonstrated good concordance for extra-axial tumors, with all cases correctly identified radiologically. MRI accurately diagnosed most high-grade glial tumors, although some were misclassified or reported as indeterminate. Low-grade glial tumors showed greater diagnostic variability, while primary CNS lymphoma and metastatic tumors were frequently categorized as other intra-axial or indeterminate lesions. Overall, histopathology remained the reference standard, with discrepancies mainly observed in glioma grading and non-specific neoplastic diagnoses **(Table 2)**. MRI demonstrated an overall diagnostic accuracy of 85.7% for identifying high-grade gliomas, with high specificity (95.7%) and positive predictive value (88.9%), but moderate sensitivity (66.7%), indicating reliable confirmation of high-grade lesions while missing a small proportion of histopathologically proven cases **(Table 3)**.

Tumor ADC values were slightly higher than peritumoral ADC values, although the difference was not statistically significant ($p=0.089$). Tumor ADC varied significantly across histopathological groups ($p<0.001$), with lower values observed in high-grade glial tumors, primary CNS lymphoma, and metastatic tumors compared with low-grade glial tumors, whereas peritumoral ADC showed no significant variation among tumor types ($p=0.093$), despite a large effect size suggesting possible biological differences **(Table 4)**.

MR spectroscopy demonstrated no statistically significant differences in NAA/Cr ($p=0.797$) or Cho/Cr ($p=0.098$) ratios

across histopathological groups. However, the NAA/Cho ratio varied significantly (p=0.002), with primary CNS lymphoma showing markedly higher values than other tumor types, indicating its potential utility in differentiating specific intracranial neoplasms **(Table 5)**. Tumor ADC was lower in lymphoma than in glioblastoma, while peri-tumoral ADC values were comparable between the two groups; however, neither difference was statistically significant (tumor ADC p=0.062, peri-tumoral ADC p=0.652). Similarly, peri-tumoral ADC did not differ significantly between glioblastoma and metastatic tumors (p=0.580), indicating limited discriminatory value of peri-tumoral diffusion measurements in these comparisons **(Table 6)**.

Table 1: Spectrum of MR radiological diagnoses in study participants (N=35)

Category	Tumor Type	Frequency	Percentage
High-Grade Glial Tumors	Glioblastoma	2	5.7%
	High grade glioma	5	14.3%
	Gliomatosis cerebri	2	5.7%
Low-Grade Glial Tumors	Glioma	3	8.6%
	Low grade astrocytoma	1	2.9%
	Oligodendroglioma	1	2.9%
Extra-Axial Tumors	Meningioma	2	5.7%
	Schwannoma	2	5.7%
Other Intra-Axial Tumors (Non-Glial)	Lymphoma	3	8.6%
	Medulloblastoma	1	2.9%
	Ganglioglioma	1	2.9%
	Metastasis	1	2.9%
Indeterminate Neoplastic Lesions	Neoplastic etiology	11	31.4%
Total	**35**	**100%**	

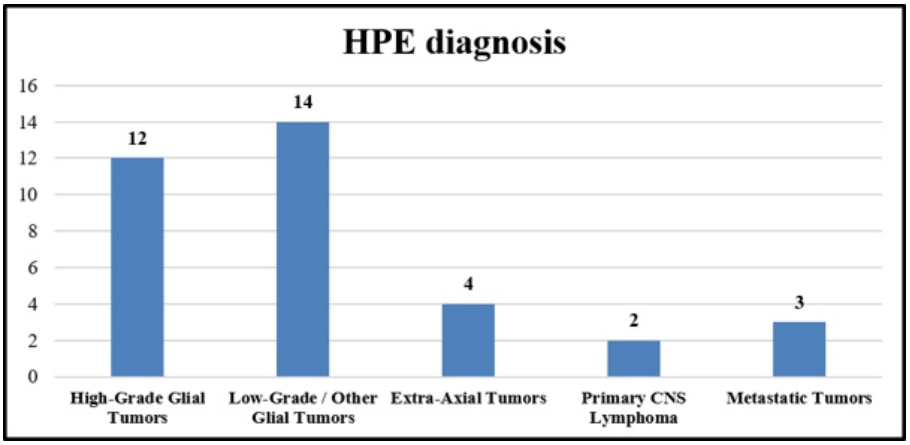

Figure 2: Spectrum of final histopathological diagnoses in study participants (N=35)

Table 2: Cross-tabulation of MR diagnosis vs HPE diagnosis in study participants (N=35)

MR Diagnosis ↓ / HPE Diagnosis →	High-Grade Glial	Low-Grade / Other Glial	Extra-Axial	CNS Lymphoma	Metastatic	Total
High-Grade Glial (n=9)	8	1	0	0	0	9
Low-Grade Glial (n=5)	1	4	0	0	0	5
Extra-Axial (n=4)	0	0	4	0	0	4
Other Intra-Axial (n=6)	1	2	0	2	1	6
Indeterminate Neoplastic (n=11)	2	7	0	0	2	11
Total	**12**	**14**	**4**	**2**	**3**	**35**

Table 3: Diagnostic performance of MRI impression vs HPE in study participants (N=35)

	HPE: HGG (Positive)	HPE: Non-HGG (Negative)
MRI: HGG (Positive)	8 (TP)	1 (FP)
MRI: Non-HGG (Negative)	4 (FN)	22 (TN)
Measure		**Value**
Sensitivity		66.7%
Specificity		95.7%
Positive Predictive Value (PPV)		88.9%
Negative Predictive Value (NPV)		84.6%
Overall Accuracy		85.7%

Table 4: Comparison of Tumor and Peritumoral ADC Values According to Histopathological Diagnosis in Study Participants (N = 35)

HPE Category	Tumor ADC Mean ± SD	Min–Max	Peritumoral ADC Mean ± SD	Min–Max
High-Grade Glial Tumors	0.83 ± 0.18	0.64–1.21	0.86 ± 0.13	0.59–1.02
Low-Grade / Other Glial Tumors	1.28 ± 0.19	0.85–1.48	1.03 ± 0.28	0.64–1.57
Extra -Axial Tumors	1.14 ± 0.21	0.93–1.32	1.11 ± 0.03	1.06–1.14
Primary CNS Lymphoma	0.67 ± 0.04	0.64–0.69	0.76 ± 0.19	0.62–0.89
Metastatic Tumors	0.74 ± 0.21	0.61–0.98	0.90 ± 0.11	0.78–0.98
Overall	**1.03 ± 0.30**	**0.61–1.48**	**0.95 ± 0.22**	**0.59–1.57**

Table 5: Comparison of MR Spectroscopy Metabolite Ratios According to Histopathological Diagnosis in Study Participants (N = 35)

HPE Category	NAA/Cr Mean ± SD	Min–Max	NAA/Cho Mean ± SD	Min–Max	Cho/Cr Mean ± SD	Min–Max
High-Grade Glial Tumors	0.57 ± 0.34	0.02–1.40	0.58 ± 0.42	0.01–1.70	2.29 ± 1.99	0.83–8.00
Low-Grade / Other Glial Tumors	0.61 ± 0.33	0.10–1.20	0.51 ± 0.48	0.05–1.92	2.07 ± 0.84	0.70–4.00
Extra -Axial Tumors	0.80 ± 0.57	0.03–1.25	0.16 ± 0.08	0.04–0.22	3.80 ± 2.18	0.80–5.60
Primary CNS Lymphoma	0.79 ± 0.81	0.22–1.36	4.68 ± 6.40	0.15–9.20	3.85 ± 0.21	3.70–4.00
Metastatic Tumors	0.52 ± 0.13	0.39–0.65	0.58 ± 0.26	0.38–0.87	1.05 ± 0.57	0.62–1.70
Overall	**0.62 ± 0.37**	**0.02–1.40**	**0.74 ± 1.53**	**0.01–9.20**	**2.36 ± 1.58**	**0.62–8.00**
One-way ANOVA						
p-value	0.797	-	0.002	-	0.098	-

Table 6: Comparison of Tumor and Peritumoral ADC Values Between Selected Intracranial Tumor Groups

ADC Parameter	Comparison	Group	Mean ± SD	p-value
Tumor ADC	Glioblastoma vs. Lymphoma (N = 9)	Glioblastoma	0.82 ± 0.18	0.062
		Lymphoma	0.67 ± 0.04	
Peritumoral ADC	Glioblastoma vs. Lymphoma (N = 9)	Glioblastoma	0.84 ± 0.14	0.652
		Lymphoma	0.76 ± 0.19	
Peritumoral ADC	Glioblastoma vs. Metastasis (N = 10)	Glioblastoma	0.83 ± 0.14	0.580
		Metastasis	0.90 ± 0.10	

DISCUSSION

The present study included 35 patients with intracranial neoplasms, with a mean age of 52.17 ± 15.93 years and a slight female predominance (54.3%). Histopathological evaluation revealed that glial tumors constituted the majority of cases, followed by extra-axial tumors, metastatic lesions, and primary central nervous system (CNS) lymphoma. Conventional MRI successfully detected intracranial lesions; however, a considerable proportion of cases remained radiologically indeterminate, highlighting the inherent limitations of morphology-based imaging. Similar imaging appearances among high-grade gliomas, metastases, lymphoma, and certain inflammatory lesions often reduce the specificity of routine MRI, emphasized the need for advanced functional imaging techniques such as diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) for improved tumor characterization [11,12].

In the present study, MRI demonstrated good overall diagnostic performance for identifying high-grade glial tumors, with high specificity and satisfactory overall accuracy, although sensitivity remained moderate. This indicated that MRI reliably identified high-grade tumors when characteristic imaging findings were present but failed to classify some histologically proven high-grade lesions because of overlapping radiological appearances. Such variability has been attributed to tumor heterogeneity, including differences in cellularity, necrosis, hemorrhage, and infiltrative growth patterns. **Weinberg BD, et. al; 2021,** reported that integrating advanced MRI sequences with conventional imaging significantly improves diagnostic confidence and preoperative tumor grading [13].

Diffusion-weighted imaging proved to be one of the most valuable imaging techniques in the present study. Tumor apparent diffusion coefficient (ADC) values differed significantly among histopathological categories, with high-grade gliomas, primary CNS lymphoma, and metastatic tumors demonstrating lower ADC values than low-grade gliomas. These findings supported the established biological principle that highly cellular tumors restrict water diffusion because of reduced extracellular space and increased nuclear density, resulting in lower ADC values. **Wang QP, et. al; 2020,** demonstrated significantly lower ADC values in glioblastomas than in low-grade astrocytomas, while **Zhang L, et. al; 2017,**

reported that minimum ADC measurements provide reliable discrimination between glioma grades. Furthermore, recent meta -analyses have confirmed the excellent diagnostic performance of ADC for differentiating high-grade from low-grade gliomas, reporting pooled sensitivities of approximately 81–82% and specificities ranging from 75% to 87%, thereby supporting the observations of the present study [14,15].

Primary CNS lymphoma exhibited the lowest mean ADC values among all tumor groups, reflecting its characteristic hypercellularity and densely packed tumor architecture. Although the present study demonstrated lower ADC values in lymphoma compared with glioblastoma, statistical significance was not achieved because of the limited number of lymphoma cases. **Kono K, et. al; 2001** and **Ko CC, et. al; 2016** and **Suh CH, et. al; 2018,** demonstrated significantly lower ADC values in lymphoma than in glioblastoma. Likewise, metastatic tumors also showed relatively low ADC values, although considerable overlap with high-grade gliomas was observed because diffusion characteristics vary according to the primary tumor type, degree of necrosis, hemorrhage, and region of interest selected during analysis [16-18]. Peritumoral ADC measurements did not demonstrate statistically significant differences among tumor categories in the present study. Although high-grade gliomas showed relatively lower peritumoral ADC values than low-grade gliomas and extra-axial tumors, the observed overlap limited their discriminatory value. Previous investigations have similarly reported inconsistent findings regarding peritumoral diffusion because measured values depend heavily on region-of-interest placement, diffusion gradients, and tumor infiltration patterns. **Suh CH, et. al; 2018** and **Guzman R, et. al; 2008,** suggested that diffusion gradients across peritumoral edema improve differentiation between glioblastoma and metastases, whereas systematic studies have concluded that peritumoral diffusion provides only moderate diagnostic accuracy owing to considerable methodological variability among studies [18-20].

Magnetic resonance spectroscopy provided complementary metabolic information in the present study. Although NAA/Cr and Cho/Cr ratios did not differ significantly among tumor groups, the NAA/Cho ratio demonstrated significant variation across histopathological categories. Conventionally, high-grade gliomas exhibit elevated choline levels with reduced N-acetylaspartate, reflecting increased membrane turnover and neuronal destruction. Meta-analytic evidence indicates that Cho/NAA provides the highest diagnostic accuracy among spectroscopic ratios for glioma grading.80 However, the absence of significant differences in Cho/Cr and NAA/Cr in the present study may be explained by tumor heterogeneity, variable voxel placement, partial-volume effects, mixed tumor composition, and relatively small subgroup sizes. Extra-axial tumors generally demonstrated metabolic profiles consistent with previous reports describing elevated choline and reduced neuronal metabolites, although minor deviations were likely related to adjacent brain tissue contamination during voxel placement [21].

The spectroscopic findings in primary CNS lymphoma showed considerable variability, particularly with respect to the NAA/Cho ratio, which differed from the characteristic metabolic profile reported in previous studies. Earlier investigations have consistently demonstrated elevated choline, reduced NAA, and prominent lipid-lactate peaks in lymphoma. The atypical observations in the present study are most likely attributable to the very small lymphoma sample size, partial-volume effects, voxel misregistration, or prior corticosteroid therapy, all of which are recognized factors influencing MRS interpretation [22].

Overall, the findings of the present study reinforced the value of multiparametric MRI for the characterization of intracranial neoplasms. Among all advanced imaging parameters, tumor ADC emerged as the most reliable biomarker for differentiating tumor grades and histological subtypes, while MRS provided valuable complementary metabolic information despite greater variability. These observations are consistent with current evidence supported the combined use of conventional MRI, DWI, and MRS to improve diagnostic accuracy, guide biopsy, facilitate treatment planning, and strengthen radiological-histopathological correlation in patients with intracranial tumors [18,22].

CONCLUSIONS

The present study demonstrates that combining diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS) with conventional MRI significantly improves the non-invasive characterization of intracranial neoplasms. Lower ADC values were associated with higher-grade tumors, supporting DWI as a reliable biomarker for tumor grading. MRS provided complementary metabolic information, with the NAA/Cho ratio showing significant variation across tumor types. The integrated approach enhanced diagnostic accuracy, improved differentiation of tumor categories, correlated well with histopathological findings, and contributed valuable information for preoperative assessment, treatment planning, and prognostic evaluation in clinical practice.

LIMITATIONS & FUTURE PERSPECTIVES

The study's limitations include a single-centre setting, a relatively small sample size, and a short study duration, which may limit the broader applicability of the results. Future studies should incorporate multicentre designs with larger populations to enhance validity, assess long-term outcomes, and investigate advanced diagnostic & management approaches. Such efforts will improve overall patient care & help minimize complications.

CLINICAL SIGNIFICANCE

The clinical significance of this study lies in its potential to bridge the gap between research findings and practical health-.care, diagnosis, and treatment outcomes. By highlighting real-care applications. It emphasizes the importance of translating scientific observations into meaningful improvements in patient world relevance, the study contributes to evidence based medical

practice and supports informed clinical decision making. Ultimately, the findings aim to enhance patient quality of life, optimize therapeutic strategies, and promote better disease management in clinical settings.

ABBREVIATIONS

MRI: Magnetic Resonance Imaging
DWI: Diffusion-Weighted Imaging
MRS: Magnetic Resonance Spectroscopy
ADC: Apparent Diffusion Coefficient
Cho: Choline
Cr: Creatine
NAA: N-Acetyl Aspartate
Cho/Cr: Choline-to-Creatine Ratio
Cho/NAA: Choline-to-N-Acetyl Aspartate Ratio
NAA/Cr: N-Acetyl Aspartate-to-Creatine Ratio
HPE: Histopathological Examination

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AUTHOR CONTRIBUTIONS

All authors significantly contributed to the study conception and design, data acquisition, or data analysis and interpretation. They participated in drafting the manuscript or critically revising it for important intellectual content, consented to its submission to the current journal, provided final approval for the version to be published, and accepted responsibility for all aspects of the work. Additionally, all authors meet the authorship criteria outlined by the International Committee of Medical Journal Editors (ICMJE) guidelines.

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CONFLICT OF INTEREST

Authors declared that there is no conflict of interest.

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ETHICAL APPROVAL & CONSENT TO PARTICIPATE

All necessary consent & approval was obtained by authors.

CONSENT FOR PUBLICATION

All necessary consent for publication was obtained by authors.

DATA AVAILABILITY

All data generated and analyzed are included within this research article. The datasets utilized and/or analyzed in this study can be obtained from the corresponding author upon a reasonable request.

USE OF ARTIFICIAL INTELLIGENCE (AI) & LARGE LANGUAGE MODEL (LLM)

The authors confirm that no AI & LLM tools were used in the writing or editing of the manuscript, and no images were altered or manipulated using AI & LLM.

AUTHOR'S NOTE

This article serves as an important educational tool for the scientific community, offering insights that may inspire future research diretions. However, they should not be relied upon independently when making treatment decisions or developing public health policies.

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