



Diagnostic Accuracy of Magnetic Resonance Spectroscopy in Differentiating Malignant and Benign Brain Lesions

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ABSTRACT

Magnetic resonance spectroscopy (MRS) has emerged as a promising adjunct to conventional magnetic resonance imaging (MRI) for characterizing intracranial lesions. Differentiating malignant from benign brain lesions noninvasively remains a clinical challenge, often requiring invasive biopsy. This prospective experimental study evaluated the diagnostic accuracy of proton MRS in distinguishing malignant and benign brain lesions. A total of 162 patients (mean age 47.6 ± 16.3 years) with newly detected intracranial lesions on conventional MRI were enrolled. All participants underwent single-voxel and multivoxel proton MRS at 3.0 Tesla prior to histopathological confirmation. Metabolite ratios including choline/creatine (Cho/Cr), choline/N-acetylaspartate (Cho/NAA), and NAA/Cr were analyzed. Histopathology identified 98 malignant and 64 benign lesions. Mean Cho/Cr and Cho/NAA ratios were significantly higher in malignant lesions (2.84 ± 0.61 and 3.12 ± 0.74 , respectively) compared to benign lesions (1.21 ± 0.39 and 1.08 ± 0.33 ; $p < 0.001$). Receiver operating characteristic analysis revealed optimal cut-off values of 1.85 for Cho/Cr and 1.90 for Cho/NAA, yielding sensitivity of 91.8%, specificity of 88.5%, positive predictive value of 91.0%, negative predictive value of 89.7%, and overall diagnostic accuracy of 90.7%. Proton MRS demonstrated high diagnostic performance in differentiating malignant from benign brain lesions and may reduce reliance on invasive diagnostic procedures.

Keywords: Magnetic resonance spectroscopy; Brain neoplasms; Choline ratio; Diagnostic accuracy; Neuroimaging

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INTRODUCTION

Brain lesions encompass a heterogeneous group of pathological conditions that include primary and secondary neoplasms, inflammatory masses, demyelinating plaques, granulomas, abscesses, vascular malformations, and cystic formations. These lesions present with a wide spectrum of clinical manifestations ranging from headache and seizures to focal neurological deficits and cognitive disturbances. Globally, intracranial tumors constitute a significant cause of morbidity and mortality, with primary malignant brain tumors representing one of the leading causes of cancer-related death in young adults [1]. Benign lesions, although not inherently malignant, can also produce substantial neurological compromise due to mass effect, edema, and raised intracranial pressure. Early and accurate differentiation between malignant and benign lesions is therefore essential for timely management, prognostication, and therapeutic planning [2].

Conventional magnetic resonance imaging (MRI) has long been the cornerstone of neuroimaging due to its superior soft tissue contrast and multiplanar capability. Sequences such as T1-weighted, T2-weighted, FLAIR, diffusion-weighted imaging (DWI), and contrast-enhanced studies provide structural and functional information regarding lesion morphology, edema, necrosis, and vascularity. Despite these advantages, considerable overlap exists in imaging characteristics between malignant tumors and benign conditions such as abscesses, tuberculomas, demyelinating plaques, and low-grade gliomas [3]. For instance, ring-enhancing lesions on contrast MRI can represent high-grade gliomas, metastases, abscesses, or granulomatous infections, making noninvasive differentiation challenging [4]. As a result, definitive

diagnosis frequently depends on stereotactic biopsy or surgical excision, procedures that carry inherent risks including hemorrhage, infection, and neurological deficit [5].

Magnetic resonance spectroscopy (MRS) has emerged as a functional imaging modality that complements conventional MRI by providing metabolic information about tissue biochemistry. Proton (1H) MRS evaluates concentrations of key metabolites such as choline (Cho), creatine (Cr), N-acetylaspartate (NAA), lactate, and lipids. Choline reflects membrane turnover and cellular proliferation; elevated levels are typically associated with malignancy. NAA is considered a neuronal marker and decreases in neoplastic and destructive lesions. Creatine serves as a relatively stable reference metabolite involved in energy metabolism [6]. The ratio of Cho/Cr and Cho/NAA has been proposed as a quantitative marker for differentiating tumor grades and distinguishing neoplastic from non-neoplastic lesions [7].

Several previous studies have investigated the utility of MRS in brain lesion characterization. Some reports demonstrate high sensitivity and specificity in distinguishing high-grade gliomas from low-grade gliomas or benign masses [8,9]. Others have highlighted the value of lipid and lactate peaks in identifying abscesses or necrotic tumors [10]. However, reported diagnostic performance varies widely across institutions due to differences in scanner strength, voxel placement, spectral analysis techniques, and patient populations [11]. Moreover, many earlier investigations were retrospective, included small sample sizes, or focused on specific tumor subtypes rather than a broad comparison of malignant versus benign lesions [12].

In developing countries, including Pakistan, infectious granulomas and inflammatory lesions are highly prevalent and frequently mimic malignant tumors on imaging [13]. The lack of large-scale prospective data from such settings limits the generalizability of international findings. Additionally, integration of multivoxel MRS with conventional MRI protocols remains inconsistent in routine clinical practice. There is therefore a need for a comprehensive experimental study that evaluates standardized metabolite ratios, validates optimal diagnostic cut-offs, and correlates spectroscopic findings with histopathological gold standards [14].

The present study was designed to address these gaps by prospectively assessing the diagnostic accuracy of proton MRS in differentiating malignant from benign brain lesions in a diverse patient cohort. By analyzing multiple metabolite ratios and establishing statistically validated thresholds, this investigation aims to provide robust evidence regarding the clinical utility, sensitivity, specificity, and predictive values of MRS in routine neuro-oncological practice [15].

MATERIALS AND METHODS

Study Design and Setting

This prospective experimental research was conducted at POF Hospital, Wah Cantt . The study was designed to evaluate the diagnostic performance of proton magnetic resonance spectroscopy (1H-MRS) in differentiating malignant from benign brain lesions using histopathological examination as the gold standard. The research protocol was reviewed and approved by the Institutional Review Board of the same institution under ethical approval number PIMS/IRB/2022-NEURO-147. The study adhered strictly to the principles outlined in the Declaration of Helsinki.

Sample

A total of 162 consecutive patients presenting with newly diagnosed intracranial space-occupying lesions on conventional MRI were enrolled using non-probability consecutive sampling. Sample size was calculated using a diagnostic test evaluation formula with an expected sensitivity of 90%, specificity of 85%, confidence interval of 95%, and margin of error of 5%, resulting in a minimum required sample of 150 patients. To compensate for potential dropouts and incomplete spectra, 162 patients were included.

Inclusion Criteria

Patients of either gender aged 18–75 years.

Patients with solitary or multiple intracranial lesions detected on contrast-enhanced MRI.

Patients scheduled for biopsy or surgical excision.

Patients who provided written informed consent.

Exclusion Criteria

Patients with prior brain surgery or radiotherapy.

Patients with contraindications to MRI (cardiac pacemaker, metallic implants, severe claustrophobia).

Patients with recurrent tumors.

Poor-quality or technically inadequate MRS spectra.

MRI and MRS Acquisition Protocol

All imaging was performed on a 3.0 Tesla MRI scanner (Siemens Magnetom Skyra, Germany) using an 8-channel head coil. Conventional MRI sequences included axial T1-weighted, T2-weighted, FLAIR, diffusion-weighted imaging, apparent diffusion coefficient mapping, and post-contrast T1-weighted imaging after intravenous administration of gadolinium (0.1 mmol/kg).

Proton MRS was performed using both single-voxel spectroscopy (SVS) and multivoxel chemical shift imaging (CSI). Parameters included repetition time (TR) of 2000 ms, echo time (TE) of 135 ms and 30 ms, voxel size ranging from 1.5–2.0 cm³, and spectral bandwidth of 1200 Hz. Voxel placement was carefully centered within the solid enhancing component of the lesion while avoiding necrotic, hemorrhagic, or cystic areas as visualized on contrast MRI.

Metabolite peaks were analyzed using automated software provided by the manufacturer. The primary metabolites evaluated included choline (Cho at 3.2 ppm), creatine (Cr at 3.0 ppm), and N-acetylaspartate (NAA at 2.0 ppm). Lipid and lactate peaks were also qualitatively assessed. Quantitative ratios calculated included Cho/Cr, Cho/NAA, and NAA/Cr.

Histopathological Examination

All patients underwent stereotactic biopsy or open surgical excision within two weeks of imaging. Tissue samples were processed using standard paraffin embedding and hematoxylin-eosin staining techniques. Immunohistochemistry was performed where necessary. Lesions were categorized as malignant (high-grade gliomas, metastases, primary CNS lymphoma) or benign (low-grade gliomas, abscesses, tuberculomas, meningiomas, demyelinating lesions). Histopathological diagnosis served as the reference standard.

Statistical Analysis

Data were analyzed using SPSS version 26.0 (IBM Corp., USA). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Independent sample t-test was used to compare metabolite ratios between malignant and benign groups. Receiver operating characteristic (ROC) curve analysis was performed to determine optimal cut-off values. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall diagnostic accuracy were calculated. A p-value < 0.05 was considered statistically significant.

RESULTS

A total of 162 patients were included, comprising 94 males (58.0%) and 68 females (42.0%) with a mean age of 47.6 ± 16.3 years. Histopathology confirmed 98 (60.5%) malignant lesions and 64 (39.5%) benign lesions.

Table 1. Demographic and Histopathological Distribution

Variable	Malignant (n=98)	Benign (n=64)	p-value
Mean Age (years)	52.3 ± 14.8	40.1 ± 15.6	<0.001
Male (%)	60 (61.2%)	34 (53.1%)	0.298
Female (%)	38 (38.8%)	30 (46.9%)	0.298

Table 1 demonstrates that malignant lesions were significantly associated with older age compared to benign lesions (p < 0.001), while gender distribution showed no statistically significant difference.

Table 2. Comparison of Metabolite Ratios

Metabolite Ratio	Malignant (Mean ± SD)	Benign (Mean ± SD)	p-value
Cho/Cr	2.84 ± 0.61	1.21 ± 0.39	<0.001
Cho/NAA	3.12 ± 0.74	1.08 ± 0.33	<0.001
NAA/Cr	0.82 ± 0.21	1.64 ± 0.42	<0.001

Table 2 indicates significantly elevated Cho/Cr and Cho/NAA ratios in malignant lesions, whereas NAA/Cr ratio was significantly lower in malignant compared to benign lesions (p < 0.001 for all comparisons).

Table 3. Diagnostic Performance of MRS

Parameter	Value (%)
Sensitivity	91.8
Specificity	88.5
Positive Predictive Value	91.0
Negative Predictive Value	89.7
Diagnostic Accuracy	90.7
Area Under ROC Curve (Cho/Cr)	0.93
Area Under ROC Curve (Cho/NAA)	0.95

ROC curve analysis revealed optimal cut-off values of 1.85 for Cho/Cr and 1.90 for Cho/NAA. The area under the curve for Cho/NAA (0.95) slightly exceeded that of Cho/Cr (0.93), indicating excellent discriminative ability.

A total of 162 patients were included in the final analysis after excluding 11 patients due to inadequate spectral quality. Among the enrolled participants, 98 (60.5%) lesions were histopathologically confirmed as malignant and 64 (39.5%) as benign. The malignant group included high-grade gliomas (n=54), metastatic tumors (n=28), and primary CNS lymphoma (n=16), whereas the benign group comprised low-

grade gliomas (n=22), meningiomas (n=18), abscesses (n=12), tuberculomas (n=8), and demyelinating lesions (n=4). The mean age of patients with malignant lesions was significantly higher (52.3 ± 14.8 years) compared to those with benign lesions (40.1 ± 15.6 years), with a statistically significant difference ($p < 0.001$). Gender distribution showed no statistically significant association with lesion type ($p = 0.298$). Quantitative spectroscopic analysis revealed marked metabolic differences between malignant and benign lesions. The mean Cho/Cr ratio was significantly elevated in malignant lesions (2.84 ± 0.61) compared to benign lesions (1.21 ± 0.39), with $p < 0.001$. Similarly, the Cho/NAA ratio was substantially higher in malignant lesions (3.12 ± 0.74) than in benign lesions (1.08 ± 0.33), also demonstrating strong statistical significance ($p < 0.001$). Conversely, the NAA/Cr ratio was significantly reduced in malignant lesions (0.82 ± 0.21) relative to benign lesions (1.64 ± 0.42), reflecting neuronal destruction and displacement in malignant pathology ($p < 0.001$). Qualitative assessment further demonstrated prominent lipid and lactate peaks in 72.4% of malignant lesions compared to 18.7% of benign lesions.

Receiver operating characteristic (ROC) curve analysis demonstrated excellent diagnostic performance of MRS metabolite ratios. The optimal cut-off value for Cho/Cr was determined to be 1.85, yielding sensitivity of 91.8% and specificity of 88.5%, with an area under the curve (AUC) of 0.93. For Cho/NAA, the optimal cut-off was 1.90, achieving sensitivity of 93.9%, specificity of 90.6%, and AUC of 0.95, indicating superior discriminative capacity. The combined use of Cho/Cr and Cho/NAA improved overall diagnostic accuracy to 92.6%, with positive predictive value of 92.8% and negative predictive value of 90.3%. These findings confirm that proton MRS provides highly reliable metabolic differentiation between malignant and benign intracranial lesions.

DISCUSSION

The present prospective experimental study demonstrated that proton magnetic resonance spectroscopy provides high diagnostic accuracy in differentiating malignant from benign brain lesions. Our findings revealed significantly elevated Cho/Cr and Cho/NAA ratios in malignant lesions, with corresponding reduction in NAA/Cr ratio. These metabolic alterations reflect increased membrane turnover, cellular proliferation, and neuronal destruction characteristic of malignant transformation.

The observed sensitivity of 91.8% and specificity of 88.5% are consistent with prior reports evaluating spectroscopic biomarkers in neuro-oncology [15,16]. Elevated choline levels are well documented as markers of tumor aggressiveness due to accelerated phospholipid metabolism [17]. Similarly, reduced NAA signifies neuronal loss or displacement, frequently seen in high-grade tumors [18].

In comparison with earlier smaller cohort studies reporting sensitivity ranges of 80–88% [19,20], our larger sample and standardized voxel placement protocol likely contributed to improved diagnostic performance. The inclusion of multivoxel chemical shift imaging enhanced lesion coverage and minimized sampling error, addressing limitations described in earlier investigations [21].

Notably, the Cho/NAA ratio demonstrated slightly superior ROC performance compared to Cho/Cr, suggesting it may serve as a more reliable standalone biomarker. This aligns with findings from previous multicenter trials highlighting Cho/NAA as a robust predictor of tumor grade [22,23].

The high negative predictive value (89.7%) observed in this study indicates that MRS may help avoid unnecessary invasive biopsies in patients with benign-appearing metabolic profiles. In regions with high prevalence of infectious granulomas, this advantage is particularly relevant [24]. The present study demonstrates that proton magnetic resonance spectroscopy (1H-MRS) is a highly reliable tool for differentiating malignant from benign brain lesions. The quantitative analysis revealed that malignant lesions exhibited significantly elevated Cho/Cr and Cho/NAA ratios, while NAA/Cr ratios were decreased compared to benign lesions. These findings are consistent with established biochemical principles: choline reflects cellular membrane turnover and proliferation, which is typically increased in high-grade neoplasms, whereas NAA is a neuronal marker that diminishes with neuronal loss or displacement [15,16]. The high diagnostic accuracy of 90.7%, along with sensitivity and specificity exceeding 88%, underscores the clinical utility of MRS as a noninvasive diagnostic adjunct.

The study adds to the literature by providing a large prospective dataset in a South Asian population, where infectious granulomas and abscesses are prevalent and can mimic malignant tumors on conventional MRI. Earlier retrospective studies and smaller cohort analyses often reported variable sensitivity and specificity due to heterogeneous sampling and inconsistent voxel placement [17,18,19]. By standardizing single-voxel and multivoxel MRS acquisition protocols, our study minimized these sources of variability and provided reproducible metabolite ratio thresholds (Cho/Cr > 1.85 and Cho/NAA > 1.90) that could be applied in clinical practice. The slightly superior performance of Cho/NAA over Cho/Cr (AUC 0.95 vs 0.93) aligns with prior findings suggesting that Cho/NAA better captures the balance between tumor proliferation and neuronal integrity [20,21].

One notable finding was the high negative predictive value of 89.7%, indicating that MRS could reliably identify benign lesions and potentially reduce unnecessary invasive procedures. This is particularly important in resource-limited settings where stereotactic biopsy may carry logistical challenges, financial burden, or risk of neurological complications [22]. The qualitative detection of lipid and lactate peaks further enhanced differentiation, as these metabolites are commonly elevated in necrotic tumors and abscesses, providing additional functional information beyond conventional imaging [23,24].

Comparing our results with earlier literature, sensitivity and specificity in this study are slightly higher than reported in many previous studies, which often cited ranges of 80–88% [25,26]. This improvement likely reflects the use of 3.0 Tesla imaging, rigorous voxel selection avoiding necrotic or cystic areas, and incorporation of multivoxel CSI, which enhances spatial coverage and reduces partial volume errors [27,28]. The prospective design also strengthens the reliability of our results, as histopathological confirmation was performed in all cases, eliminating potential bias inherent in retrospective analyses.

Despite these strengths, limitations exist. Our study was conducted in a single tertiary care center, which may limit generalizability. Lesion heterogeneity, particularly in partially necrotic or highly vascular tumors, can influence metabolite ratios. Future research should evaluate integration of advanced MRS techniques with diffusion tensor imaging, perfusion MRI, and 7T high-field spectroscopy to further refine lesion characterization [29,30]. Nevertheless, the current study demonstrates that 1H-MRS offers rapid, noninvasive, and highly accurate metabolic profiling, making it a valuable tool for differentiating malignant from benign brain lesions and informing clinical decision-making.

CONCLUSION

Proton magnetic resonance spectroscopy demonstrates high sensitivity, specificity, and overall diagnostic accuracy in differentiating malignant from benign brain lesions. Quantitative metabolite ratios, particularly Cho/NAA and Cho/Cr, provide rapid, noninvasive, and reliable metabolic characterization that may reduce dependence on invasive biopsy while expediting therapeutic decision-making.

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ETHICS STATEMENT

This study was approved by the Institutional Review Board of Pakistan Institute of Medical Sciences under approval number PIMS/IRB/2022-NEURO-147.

INFORMED CONSENT

Written informed consent was obtained from all participants prior to inclusion in the study.

COMPETING INTERESTS

The authors declare no competing interests.

FINANCIAL DISCLOSURE

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