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# Role of magnetic resonance spectroscopy in adequately differentiating neoplastic from non-noplastic and low-grade from high-grade lesions in brain masses

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**Abstract**
**Objective:** The aim of this study was to provide objective data on the clinical utility of MRS in difference diagnosis of brain lesion and also to provide metabolite ratios neoplastic from non-neoplastic lesion and low-grade from high-grade neoplasms.
**Method:** A prospective study conducted at Sri Aurobindo Institute of Medical Sciences and PG Institute, Indore and Department of Radiology after approval from the ethical and research committee. The duration of this study was June 2018 to July 2020. A total of 102 patients (age range 21-60 years) Who were found to have cerebral mass lesion by computed tomography (CT) and convention MRI and from whom high quality MRS imaging data were obtained, were prospectively assessed and included in this study.
**Result:** The mean age was 53.5±3.15 (range 28-70 years). Majority of the patients in the study were males forming 70 (68.6%) and females 32 (31.3%). Various spectroscopy ratios like Cho/Cr, Cho/NAA, Cho+Cr/NAA, NAA/Cr were calculated with the help of MRS.
**Conclusion:** MRS gives information about the biochemical changes in tissues, which appear earlier than the structural changes, and so, in recent times, MRS has been used as a noninvasive method for the diagnosis and grading of brain tumors. All neoplastic lesion showed increase Cho and decreased NAA and this was more prominent in high-grade neoplasms. While we did not detect any LL peak in all 27 low-grade neoplasms, but 60 high-grade neoplasms showed an LL peak.

**Keywords:** computed tomography, magnetic resonance imaging

## Introduction
Magnetic Resonance Imaging (MRI) is considered to be the gold standard for preoperative diagnosis, local staging and posttherapeutic monitoring for brain tumor. In recent years, the advancement of MRI made it possible to make efficient diagnoses in a large number of diseases, including brain tumors with an accuracy that goes from 30 to 90% depending on the type of tumor [1, 2].
The classification and grading of glioma grading, ranging from 55.1% to 83.3% [3]. Conventional MRI provides evidence of contrast material enhancement which is often association with a higher tumor grade. MRS is an application of MRI that provides chemical information about tissue metabolites.
However, any pathological process associated with disruption of the blood-brain barrier can result in enhancement on MRI. Thus, there is a need for additional imaging modalities, such as proton magnetic resonance spectroscopy (MRS) which may aid in improving the diagnosis of unknown brain lesion. MRS has, however, been shown to differentiate between neoplastic and non-neoplastic lesions with a high sensitivity and specificity [4, 5]. MRS imaging is a non-invasive tool for investigation the spatial distribution of metabolic changes in brain lesions. MRS is also useful in the differential diagnosis of brain tumor and the characterization of metabolic changes associated with tumor progression, degree of malignancy, and response to treatment.
The aim of this study was to provide objective data on the clinical utility of MRS in difference diagnosis of brain lesion and also to provide metabolite ratiosneoplastic from non-neoplastic lesion and low-grade from high-grade neoplasms.

## Material and Method

A prospective study conducted at Sri Aurobindo Institute of Medical Sciences and PG Institute, Indore and Department of Radiodiagnosis after approval from the ethical and research committee. The duration of this study was June 2018 to July 2020. A total of 102 patients(age range 21-60 years)Who were found to have cerebral mass lesion by computed tomography (CT) and convention MRI and from whom high quality MRS imaging data were obtained, were prospectively assessed and included in this study. All the recruited patients were explained about the study and written consent was taken from every patient dually signed by her. The medical records were checked for a definitive diagnosis, valid at the time of the MRS. Al specimens were histologically examined by neuropethologist and grated according to the World Health Organization (WHO) classification. Histopathological results were compared with MRS results.

### Inclusion criteria

Patients ready to give consent for study. Space occupying lesion of brain evident on CT/MRI.

### Exclusion criteria

Cases in which good quality of spectrum was not obtained due to patients non-cooperation. Lesion containing larg amount of hemorrhage or air. Lesion near ventricles. Small leions less than a centimeter. Those lesions near to calvarium and paranasal sinuses (PNS).

### Technique

MRI and MRS imaging were performed by a 1.5T SIEMENS symphony Timtechnology (18 channel), clinical whole-body imager quipped with the standard head coil. Routine brain MRI was performed in three orthogonal planes, including at least T1, T2, fluid-attenuated inversion recovery (FLAIR) weighted images, diffusion weighted images and susceptibility weighted images (SWI). T1-weighted images after intravenous gadolinium based contrast material administration (0.1mmol/kg) were obtained in at least 2 planes. In all cases, 2 dimensional (2D) multivoxel MRS was performed regarding the numerical and volumetric features of the lesions after administration of gadolinium. Spectroscopic information was obtained from mainly contrast-enhanced areas of lesion by using a double-SE point- resolved spectroscopy (PRESS) sequence with1-pulse water signal suppression and with 1500/135 ms repetition time/echo time (TR/TE) an in few selected cases with TR/TE =1500/30ms. The volume of interest (VOI) was selected as the lesion identified on MRI, and compared with the contralateral hemisphere having a normal MRI appearance. The VOI was positioned to exclude lipids of the skull and subcutaneous fat. Appropriate automatic shimming and water suppression were achieved by automated software developed by the manufacture. Spectroscopic data from cubic volumes of $1x1x2x2x2cm^3$were obtained depending on the size of the lesion.

We fit the signals of choline (Cho), cretine(Cr), N-acetyl aspartate(NAA), and lactate-lipid (LL), to a Gaussian line shape using a simplex routine. The peak area ratios of Cho/Cr, Cho/NAA, Cho+Cr/NAA and NAA/Cr were calculated from the peak areas of the respective signals. To ensure quality control and acceptable quality of spectroscopic data, normal values for Cho/Cr, Cho/NAA, and NAA/Cr were obtained in normal-appearing parenchyma in the contralateral hemisphere. 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 and inverted at TE of 130 ms.

## Result

The mean age was 53.5±3.15 (range 28-70 years). Majority of the patients in the study were males forming 70 (68.6%) and females 32 (31.3%). Most common presenting complaint was headache, seen in 68 (66.6%) of the patients, followed by seizures 52 (50.9%). Symptoms of raised intracranial pressure, Projectile vomiting was seen in 30 (29.3%) of the patients. Weakness and hemiparesis was the major complaint in 18 (17.6%) of the patients. Fever 14 (13.7%) and Dementia 6 (5.8%) was seen in minority of patients.

Various spectroscopy ratios like Cho/Cr, Cho/NAA, Cho+Cr/NAA, NAA/Cr were calculated with the help of MRS. In all the cases, expect for 4 abscess, cases, Cho/Cr, Cho/NAA, NAA/Cr and Cho+Cr/NAA ratios obtained from the pathological and contralateral normal pearenchyma showed statistically significant difference. In abscess cases of NAA was recorded. Therefor Cho/NAA, Cho+Cr/NAA and NAA/Cr ratios could not be calculated. It was observed that Cho/Cr, Cho/NAA and Cho+Cr/NAA ratio intervals increased from non-neoplastic to low-grade neoplastic lesions and from low-grade neoplastic lesions to high-grade neoplastic lesions. (Table 1)

Various metabolite peak ratio intervalslike lowest and highest metabolite ratios that were observed for respective lesions after final diagnosis. It was observed that Cho/Cr, Cho/NAA and Cho+Cr/NAA ratio intervals increased from non-neoplastic to low-grade neoplastic lesions and from low-grade neolpastic lesions to high-grade neolpastic lesions this observation was near same when the lesions were distributed on the basis of MR morphology (provisional diagnosis) (Table 1).

Out of 21 non-neoplastic lesions, lipid-lactate was present in 18 (85.7%) patients and out of 30 low-grade neoplastic lesions, lipid-lactate was present in 8 (26.6%) patients. Out of 51 high-grade neoplatic lesions, lipid-lactate was present in 36 (70.5%) patients (Provisional diagnosis). (Table 2)

Out of 15 Non-neoplastic lesions lipid-lactate was present in 15 (100%) patients and out of 60 high-grade neoplastic lesions, lipid-lactate was present in 47 (78.3%) patients. Lipid-lactate peak was absent in all low-grade neoplastic lesions. (Table 2)

According to statistical results of ROC curve for neoplastic vs non-neoplastic differentiation of lesions, Cho/Cr ratio with cut-off value >1.98 were neoplastic with sensitivity of 74.4% (with 95% confidence interval) and specificity of 100% (with 95% confidence interval). Cho/NAA ratio with cut-off value >1.87 were neoplastic with high sensitivity of 89.7% (with 95% confidence interval)and high specificity of 100% (with 95% confidence interval). Cho+Cr/NAA ratio with cut-off value >2.99 were neoplastic with sensitivity of 84.6% (with 95% confidence interval) and specificity of 100% (with 95% confidence interval). Hence, Cho/NAA ratio with cut-off value >1.87 has high sensitivity and high specificity among all ratios for non-neoplastic vs neoplastic differentiation of brain lesion. (Table 3)

According to the statistical results of ROC curve for low-grade vs high-grade neoplastic differentiation on lesions, Cho/Cr ratio with cut-off value >2.18 were high-grade neoplasdtic with sensitivity of 96.2% (with 95% confidence interval) and specificity of 84.6% (with 95% confidence interval). Cho/NAA ratio of cut-off value>3.22 were high-grade neoplastic with high sensitivity of 84.6% (with 95% confidence interval) and high specificity of 100% (with 95% confidence interval). Cho+Cr/NAA ratio with cut-off value >5.12 were high-grade nepolasicwith sensitivity of 73.1% (with 95% confidence interval) and specificity of 100% (with 95% confidence interval). In the differentiation of low-grade vs high-grade neoplastic lesions, the sensitivity and specificity of LL were calculated as 69.6% (with 95% confidence interval) and 100% (with 95% confidence interval) respectively. (Table 3)

With help of ROC curve, AUC for ratio like Cho/Cr, Cho/NAA, NAA/Cr and Cho+Cr/NAA was calculated. AUC values >0.85 are assumed to be significant in statistical tests. AUC value for Cho/Cr, Cho/NAA, Cho+Cr/NAA ratios were >0.85, while AUC value for NAA/ Cr was <0.85. Hence, Cho/Cr, Cho/NAA and Cho+Cr/NAA ratio were significant while NAA/ Cr ratio was in significant for analysis of neoplastic vs non neaoplasic lesionsby ROC curve (Figure 1) and low-grade vs high-grade lesions. (Figure 2)

**Table 1:** Pre and post Metabolite peak ratio intervals (Lowest ration – Highest ratio)

| MRI morphology (Provisional Diagnosis) | No. of patients | Metabolite peak ratio intervals (Lowest ration – Highest ratio) | | | |
|---|---|---|---|---|---|
| | | Cho/Cr | Cho/NAA | NAA/Cr | Cho+Cr/NAA |
| Non-neoplastic | 21 (20.1%) | 0.66-6.22 | 0.44-7.65 | 0.59-1.50 | 1.10-8.97 |
| Low-grade (Neoplastic) | 30 (29.4%) | 0.69-4.84 | 0.49-8.65 | 0.38-1.50 | 1.2-10.44 |
| High-grade (Neoplastic) | 51 (50%) | 2.16-9.39 | 1.95-9.75 | 0.32-1.63 | 2.66-12.88 |
| **Histopathology Final Diagnosis** | | | | | |
| Non-neoplastic | 15 (14.7%) | 0.66-1.97 | 0.44-1.84 | 0.88-1.50 | 1.10-2.90 |
| Low-grade (Neoplastic) | 27 (26.4%) | 0.69-2.90 | 0.49-4.19 | 0.38-1.40 | 1.2-6.79 |
| High-grade (Neoplastic) | 60 (58.8%) | 1.03-9.3 | 1.06-9.75 | 0.30-1.63 | 2.09-12.88 |

**Table 2:** Pre and post morphology and Lipid-Lactate peak

| MRI morphology (Provisional Diagnosis) | No. of patients | Lipid-Lactate peak present | Lipid-Lactate peak Absent |
|---|---|---|---|
| Non-neoplastic | 21 | 18 (85.7%) | 3 (14.2%) |
| Low-grade (Neoplastic) | 30 | 8 (26.6%) | 22 (73.3%) |
| High-grade (Neoplastic) | 51 | 36 (70.5%) | 15 (29.4%) |
| **Histopathology Final Diagnosis** | | | |
| Non-neoplastic | 15 | 15 (100%) | 0 (0%) |
| Low-grade (Neoplastic) | 27 | 0 (0%) | 27 (100%) |
| High-grade (Neoplastic) | 60 | 47 (78.3%) | 13 (21.6%) |

**Table 3:** ROC curve analysis result for metabolite ratio in Neoplastic Vs Non-neoplastic and low-grade vs high-grade difference of neoplastic intracranial lesions.

| ROC curve analysis result for metabolite ratio in Neoplastic Vs Non-neoplastic | | | | |
|---|---|---|---|---|
| **Metabolite ratio** | **AUC** | **Cut-off** | **Sensitivity (%)** | **Specificity (%)** |
| Cho/Cr | 0.913* (0.829-0.996) | >1.98 | 74.4 | 100 |
| Cho/NAA | 0.954* (0.902.1-1.0) | >1.87 | 89.7 | 100 |
| NAA/Cr | 0.233 (0.108-0.358) | ** | ** | ** |
| Cho+Cr/NAA | 0.944* (0.877-1.0) | >2.99 | 84.6 | 100 |
| ROC curve analysis result for metabolite ratio in low-grade vs high-grade | | | | |
| Cho/Cr | 0.956* (0.892-1.0) | >2.18 | 96.2 | 84.6 |
| Cho/NAA | 0.932* (0.855-1.0) | >3.22 | 84.6 | 100 |
| NAA/Cr | 0.555 (0.399-0.711) | ** | ** | ** |
| Cho+Cr/NAA | 0.888* (0.789-0.987) | >5.12 | 73.1 | 100 |
| LL | *** | *** | 69.6 | 100 |

ROC: Receiver Operating Characteristic; AUC: Area Under Curve value greater than 0.85 are assumed to be significant in statistical tests; ** could be not calculated because of very low values of AUC, cut-off, sensitivity and specificity

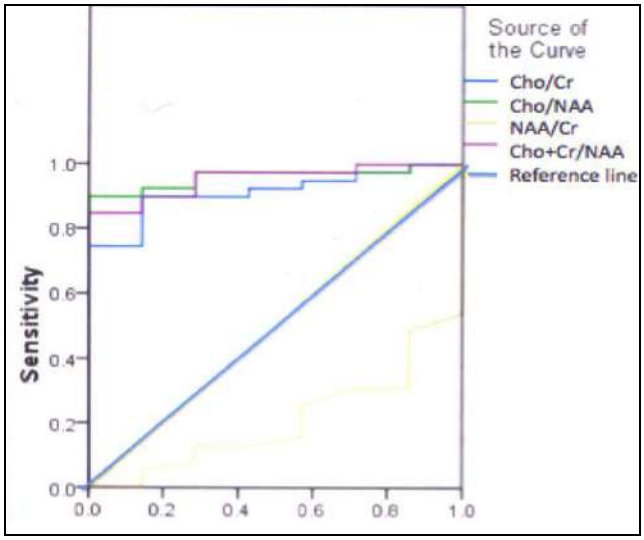


**Fig 1:** ROC neoplastic vs non neoplastic lesions

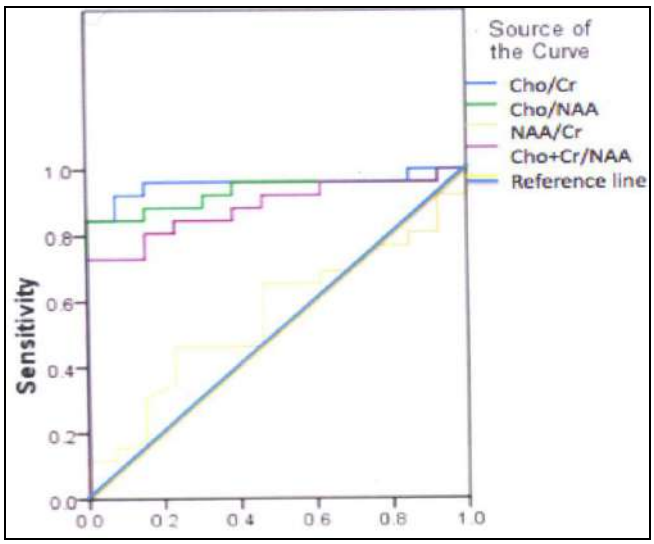


**Fig 2:** ROC curve Low-grade vs High-grade

## Discussion

In our study regarding gender distribution in intracranial lesions is 70 Males (68.6%) and 32 Females (31.3%). This is in agreement with the findings of Al-Okaili *et al*. [6], who found that the incidence of brain tumors among male is more than that in female patients. Irrespective of causes, the predominate presenting symptoms was headache seen in 66.6% and seizures 50.9%. Only a minority had fever as the presenting complaint. These observations were similar in previous study [7, 8]. Single- voxel and multivoxel proton MRS have been used for the assessment and grading of brain tumors [9]. Single volex proton MRS, using STEAM or PRESS, has been performed tow study brain lesions in clinical settings [7, 10, 11, 12, 13]. The utility of these sequences in the differentiation of lesion have been assessed by various workers in the past. Proton MRS is useful only when the voxel of interest is taken from well within the lesion. For very lesion, the possibility of partial averaging from surrounding tissues and hence obtaining a misleading spectrum is a limiting factor [7, 13]. Increased Cho has been observed in most brain tumors, attributed to the increased membrane turnover and cell proliferation [14]. Study by Poptani *et al*. [15] compared high-grade and low-grade neoplastic lesions and found that high-grade neoplastic lesions showed higher values of Cho/NAA and Cho/Cr rations than did low-grade lesions. These authors also reported that the LL peak is an indicator of a higher grade malignancy. As a consequence they explained that MRS helps the tissue characterization of lesions; the combination of neoplastic lesions. In this study all neoplastic lesion showed increase Cho and decreased NAA and this was more prominent in high-grade neoplasms. While we did not detect any LL peak in all 27 low-grade neoplasms, but 60 high-grade neoplasms showed an LL peak. Some reported state that increase Cho levels with an LL peak indicate high-grade malignancy [10, 16]. The Cho/NAA ration showed the most significant difference between high-grade and low-grade tumors. In present study we found that an increased Cho/Cr (>2.18) ratio associated with an LL peak together have a sensitivity and specificity of 100% (with 95% confidence interval) in the differentiation of high-grade vs low-grade neoplastic lesions. Early in the development of human brain proton MRS, it was realized that brain tumors exhibited markedly different spectra from normal brain tissue [17]. It was found that nearly all brain tumors have decreased N-acetyl aspartate (NAA) signals, and often also have increased levels of Choline (Cho), leading to increased Cho/NAA ratios. Control conventional MRI following radiotherapy did not show any significant difference, whereas MRS showed not decreased Cho, Cr and Cho/NAA ratios obtained from the sum tumor region. This decrease was evaluated as an indicator of regression. Thus the present study was shown that MRS can clearly distinguish the neoplastic intracranial lesions from the non-neoplastic lesions as well as diagnosed various lesions based on the metabolite spectrum and ratios. It complements the information obtained from conventional MR imaging and contrast studies, proving particularly useful when these studies are inconclusive. This study was also provided some quantitative guide line for distinguishing neoplastic from non-neoplastic lesions and low-grade from high-grade neoplasms. The small number of cases and the variety of intracranial lesions was the limitation of this study. We think that this was the main reason why these studies come to a conclusion with very high sensitivity and specificity values of different metabolite ratios. Further prospective studies with larger groups of patients including a large variety of non-neoplastic lesions in the control group and better statistical data obtained from similar types of lesions are desirable to support or contradict these results and to determine accuracy of MRS in differential diagnosis and grading of intracranial space occupying lesions.

## Conclusion

MRS gives information about the biochemical changes in tissues, which appear earlier than the structural changes, and so, in recent times, MRS has been used as a noninvasive method for the diagnosis and grading of brain tumors. MRS works on metabolic information and pick up the lesion in early stage even when MRI may be normal in certain condition.In this study all neoplastic lesion showed increase Cho and decreased NAA and this was more prominent in high-grade neoplasms. While we did not detect any LL peak in all 27 low-grade neoplasms, but 60 high-grade neoplasms showed an LL peak. Stereotactic biopsy and even reaction may reflect sampling errors of the tumor that can be removed. Histology is not always reflective of the actual tumor grade and there for MRS can be helpful. We believe

that MRS plays a critical role in pre-operative or pre-interventional differential diagnosis of cerebral mass lesions by distinguishing neoplatic from non-neoplastic lesions, by grading neoplatic lesions and by improving the accuracy and confidence level of neuroradiologists in their diagnoses. It is also an effective method complimenting conventional MRI in following response to therapy.

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