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ORIGINAL ARTICLE

# Magnetic resonance spectroscopy of enhancing cerebral lesions: Analysis of 78 histopathology proven cases

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## Abstract

**Objectives:** To investigate the efficacy of magnetic resonance spectroscopy in differentiating various types of neoplastic and non-neoplastic enhancing cerebral lesions.

**Methods:** The prospective study was conducted from January 2007 to December 2009 at the Department of Radiology, Aga Khan University Hospital, Karachi. All patients with enhancing brain lesions on magnetic resonance imaging who underwent magnetic resonance spectroscopy and a biopsy with histopathological analysis were included in study. The lesions were categorised into neoplastic and non-neoplastic lesions on the basis of spectroscopy findings. The sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of magnetic resonance spectroscopy were calculated. Predicted probabilities were computed and comparison of median values of metabolites and their ratios was analysed using non-parametric Mann Whitney U test to differentiate between neoplastic and non-neoplastic lesions.

**Results:** Of the 102 patients enrolled, 78(76.5%) comprised the final study sample. There were 53(68%) male and 25(32%) female patients with an overall mean age of 40.21±17.69 years (range: 4-76 years). The mean overall size of the lesion was 4.01±1.79cm, and 61(78%) lesions were neoplastic and 17(22%) were non-neoplastic. The sensitivity, specificity, positive predictive value and negative predictive value and diagnostic accuracy of magnetic resonance spectroscopy in differentiating neoplastic and non-neoplastic lesions were 90.16%, 64.70%, 90.16%, 64.70% and 78.20% respectively. A cut-off value of 2.55 of Choline/N-Acetyl Aspartate ratio depicted sensitivity of 70% in differentiating the lesions.

**Conclusion:** Magnetic resonance spectroscopy is a highly sensitive technique in addition to conventional magnetic resonance imaging in characterising and differentiating between neoplastic and non-neoplastic cerebral lesions.

**Keywords:** Spectroscopy, Functional imaging, Cancer, Neoplasm, Infections, Tuberculoma. (JPMA 64: 1141; 2014)

## Introduction

Enhancing brain lesions are one of the most commonly encountered abnormalities in routine conventional brain scanning. These can be due to a variety of neoplastic, infectious and vascular pathologies.[1-3] In the West, after excluding multiple sclerosis, these are mostly neoplastic in aetiology. However, in developing countries, the spectrum of aetiologies of multiple enhancing lesions of the brain is likely to be different as infective pathologies are more frequently encountered.[4-6] These lesions most of the time have similar appearances on routine non-invasive conventional imaging techniques like Computed Tomography (CT) scanning and Magnetic Resonance Imaging (MRI). It is imperative to differentiate neoplastic mass lesions from infective pathologies as management and further treatment plan is entirely different in these cases. Newer MRI techniques like spectroscopy and diffusion-weighted imaging further help in reaching the more likely diagnosis. MR spectroscopy (MRS) has the potential for discerning the presence and relative amount of various chemical metabolites in the brain and is therefore a useful technique to further assess various intracranial diseases.[7,8]

Initial in vivo brain MRS studies were done in the early 1980s and then its clinical effectiveness was further recognised. MRS extends the diagnostic utility of the MR brain examination beyond the typical structural images of anatomy and provides another molecular dimension based on biochemical information.[9,10] The major brain metabolites detected are Choline (Cho), Creatine (Cr), N-acetyl aspartate (NAA), lactate, myo-inositol, glutamine, glutamate, lipids, and the amino acids leucine and alanine. Major differentials of enhancing cerebral lesions are primary neoplastic lesion versus inflammatory and infective lesions. Infective lesions like brain abscess usually show reduced level of all major metabolites, including Cho, Cr and NAA, while neoplastic lesions show increased Cho peak with reduced NAA levels. Lipid/lactate peak can be observed in both types of lesions, but more commonly in necrotic lesions and abscess cavities.

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Literature shows MRS is increasingly useful in studying brain tumours, infections and various types of inflammatory lesions.[7-11] Recent reports regarding MRS support its use as a powerful tool in grading of glioma and also in distinguishing it from metastasis.[12-16] Similarly, tumour infiltration can occur in non-enhancing regions at the periphery of the tumour and that these areas are most of the time, sites of tumour recurrence after surgical removal. MRS can show increased metabolism along with loss of neuronal activity at these sites and can help in diagnosing tumour recurrence. MRS is also being used to avoid sampling errors and guide the most appropriate site for obtaining a biopsy when residual tumour is suspected.[17,18] Radiation-induced necrosis versus recurrent or residual tumour is yet another diagnostic dilemma where MRS may be helpful.[19] MRS also complements conventional MR imaging in characterising infectious lesions and being used to differentiate between brain abscess and high-grade glioma. Similarly, this tool can also be used to discriminate tuberculous from pyogenic brain abscesses.[20,21]

The utility of MRS in various types of brain lesions has been extensively studied all over the world. Very few centres in Pakistan have the options of MRS in their MR scanners and most of the cases are diagnosed on conventional MR sequences, and the available resources are very costly and not affordable or reachable for most of the population. The current study was planned as the first large-scale investigation in Pakistan. It aimed at looking for the pattern of metabolites in enhancing brain lesions in patients presenting at a tertiary care center and to differentiate between various types of infective lesions on the basis of the quantitative values and ratio of metabolites, especially tuberculous versus non-tuberculous or fungal infections.

## Patients and Methods

The prospective study was conducted from January 2007 to December 2009 at the Department of Radiology, Aga Khan University Hospital (AKUH), Karachi, after getting approval from the institutional ethics review committee.

All patients with enhancing brain lesions on MRI who underwent MRS and a biopsy with histopathological analysis were included in study.

Those included came from inpatient wards, clinics and as outpatient referrals. Those who were found to have enhancing brain lesions on MRI were initially included. Their history was taken on prescribed proforma. Informed consent was taken from all the patients. Gadolinium was used as intravenous contrast. All images were interpreted on Leonardo software by two trained neuro-radiologists.

All scans were done on Siemens 1.5 Tesla MR Scanner using head coil. Axial T1, T2, Sagittal T2, coronal Fluid Attenuated Inversion Recovery (FLAIR) and post-contrast axial, coronal and sagittal images were acquired. MRS was performed through single and multi-voxel technique. After water suppression, a point-resolved spectroscopy (PRESS) technique was used for localisation and the studies were obtained with TE and TR of 135 and 1500 respectively.

Metabolites were plotted on the X axis on the MR Spectrum in parts per million (ppm). The height of peak on the Y axis indicated their relative concentrations.

Major metabolites were NAA which appears at 2.01ppm, Cho at 3.22ppm, Cr at 3.02, lipid at 0.8 to 1.3ppm and lactate at 1.32 to 1.33ppm.

All the images were interpreted by two consultant radiologists having experience in MRI interpretation, including MRS. Final diagnosis was made on histopathology results. On the basis of MRS findings, lesions were categorised into neoplastic and non-neoplastic lesions.

After routine evaluation of the lesions on conventional sequences, MR spectra were evaluated for presence and integral values of metabolites, notably including NAA, Cho, Cr and lipid/lactate.

On MRS, lesions were categorised as neoplastic if there was increased Cho and decreased NAA levels, and increased Cho/Cr and Cho/NAA ratio. They were considered non-neoplastic if there was decreased Cho, Cr and NAA levels.[8-11]

Data was analysed using SPSS 19.0. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of MRS was calculated. Median values of major metabolites and their ratio were also calculated and comparisons of median values of neoplastic and non-neoplastic enhancing lesions were evaluated using Mann-Whitney U test to test for significance at $p<0.05$.

Sensitivity and specificity were also calculated for Cho, Cho/Cr and Cho/NAA values to differentiate between neoplastic and non-neoplastic lesions by computing predicted probabilities.

## Results

Of the 102 patients initially enrolled, 24(23.5%) were excluded due to non-availability of biopsy reports or histopathology. As such, the final study sample comprised

78(76.4%) cases. There were 53(68%) male and 25(32%)

female patients with an overall mean age of 40.21±17.69 years (range: 4-76 years). The mean overall size of the lesion was 4.01±1.79cm, and 61(78%) lesions were neoplastic and 17(22%) were non-neoplastic on the basis of MRS. Histopathological evaluation also showed 61(78%) neoplastic and 17(22%) non-neoplastic lesions, but 55(90.1%) of 61 neoplastic lesions on MRS turned out to be neoplastic on histopathology. Similarly 11(64.7) of the 17 non-neoplastic lesions on MRS were diagnosed as non-neoplastic on histopathology. Overall sensitivity, specificity, PPV and NPV were 90.16%, 64.70%, 90.16%, 64.70% and diagnostic accuracy was 78.20%.

Neoplastic lesions included various grades and types of astrocytoma [35; 57.37%], metastatic lesions [6; 9.84%], lymphoma [5; 8.19%], meningioma [7; 11.47%], medulloblastoma [2; 3.27%], acoustic neuroma [2; 3.27%], anaplastic ependymoma [2; 3.27%], Primitive Neuroectodermal tumour (PNET) [1; 1.63%] and haemangioblastoma [1; 1.63%].

Non-neoplastic infective/inflammatory lesions included tuberculous granulamotous inflammation [10; 58.82%], reactive glial tissue [4; 23.52%], fungal [2; 11.76%] and pyogenic abscess [1; 5.88%].

False positive were granulomatous inflammation [2; 33.33%], reactive glial tissue [2; 33.33%], necrotic tissue [1; 16.66%] and fungal infection [1; 16.66%] on histopathology. Similarly, false negative cases diagnosed on histopathology as various types of astrocytoma [3; 50%], metastatic lesion [2; 33.33%] and anaplastic ependymoma [1; 16.66%].

**Table:** Cut-off values of Cho/Cr, Cho/NAA and NAA/Cr ratios in differentiating neoplastic and non-neoplastic lesions.

| Positive if ≥ | Sensitivity | [1- Specificity] |
|---|---|---|
| **§Cho/Cr** | | |
| 1.2350 | 0.900 | 0.778 |
| 1.6400 | 0.800 | 0.667 |
| 1.96560 | 0.717 | 0.500 |
| 2.4350 | 0.617 | 0.444 |
| **^Cho/ NAA** | | |
| 1.3400 | 0.900 | 0.778 |
| 1.3800 | 0.900 | 0.722 |
| 1.4750 | 0.900 | 0.667 |
| 2.0150 | 0.800 | 0.556 |
| 2.0950 | 0.800 | 0.500 |
| 2.5150 | 0.700 | 0.444 |
| 2.5550 | 0.700 | 0.389 |
| **¤NAA/Cr** | | |
| 0.1000 | 0.967 | 0.944 |
| 0.4050 | 0.800 | 0.778 |
| 0.4900 | 0.700 | 0.722 |

§Cho/Cr: Choline to Creatine ratio
^Cho/ NAA: Choline to N-acetyl aspartate ratio
¤NAA/Cr: N-acetyl aspartate to Creatine ratio.

Median NAA value of neoplastic lesions was 0.39 and non-neoplastic lesions of 0.54 (p<0.160). Cho level 2.15 was significantly increased in neoplastic lesions compared to non-neoplastic lesions of 1.03 (p<0.0001). Cr value in neoplastic lesions was 0.58 compared to 0.55 in non-neoplastic lesions (p<0.799).

Cho/Cr ratio in neoplastic lesions was 3.44 and 1.89 in non-neoplastic lesion (p<0.003). Similarly, Cho/NAA ratio was 4.28 compared to 1.67 in non-neoplastic lesions (p<0.0001). NAA/Cr ratio was 0.73 in neoplastic lesions compared to 0.91 in non-neoplastic lesions (p=0.289).

Out of 10 tuberculous lesions on histopathology, 6 (60%) were diagnosed as non-neoplastic lesions on MRS, while 4 (40%) were interpreted as neoplastic lesion. Similarly, 5 out of 7 (70%) non-tuberculous non-neoplastic lesions were identified as non-neoplastic on MRS.

There were 24 cases of high grade gliomas and 11 low grade gliomas. Mean Cho value in high-grade astrocytoma was 2.36±1.15 compared to 1.65±1.03 in low-grade gliomas. Mean Cho value in 6 metastatic lesions was 1.67±1.47. NAA in high-grade astrocytoma was 0.74±0.53 compared to 0.47±0.33 in low-grade gliomas. NAA in metastatic lesions was 0.51±0.25. Cho/Cr ratio in high-grade gliomas was 3.93±3.93 and 2.98±2.73 in low-grade gliomas. Cho/NAA and Cho/Cr ratio was 3.28±2.35 and 3.74±4.76 respectively in metastatic lesions. A characteristic pattern for tuberculous lesions on MRS could not be found.

Predicted probabilities were computed to look for the best relationship between sensitivity and specificity. Cho/NAA ratio of 2.55 and sensitivity of 70% was significant (p<0.019). Mean Cho value of 1.44 and sensitivity and specificity of 69% and 65% respectively was also significant (p<0.002). Lipid/lactate peaks were observed in 37 lesions. Out of these, 28(45.90%) were identified in 61 lesions and 9(52.94%) in 17 non-neoplastic lesions. Cut-off values of Cho/Cr, Cho/NAA and NAA/Cr ratios in differentiating between neoplastic and non-neoplastic lesions were also worked out (Table).

## Discussion

MRS provides a chemical profile of the cerebral lesions that may facilitate the determination of the type of the lesion. Radiologically detected brain lesions are classified as neoplastic and non-neoplastic on the basis of certain MRS criteria. MR Spectrum was obtained from the lesion after placing an appropriate voxel over the area of

interest. Previous studies have extensively described the role of MRS in differentiating various types of brain lesions.[7-21] The present study revalidates this technique as highly sensitive in differentiating between neoplastic and non-neoplastic brain lesions although it was not very specific. Cho level was significantly increased in brain tumours due to an increase in mitotic activity which is not present in non-neoplastic lesions. Our study showed median Cho levels of 2.15 in neoplastic lesions compared to non-neoplastic lesions of 1.03 which makes it single best marker to differentiate between thr two types of brain lesions. Previous studies have also described the mean Cho values in neoplastic and non-neoplastic lesions.[22,23] Similarly, significant increase in Cho/Cr and Cho/NAA ratio were observed in neoplastic lesions which were also reported in previous studies. The most frequently studied chemical ratios used to distinguish tumours from other brain lesions with MRS are Cho/Cr, Cho/NAA and Lactate/Cr. Specifically, a Cho/NAA ratio greater than 1 is considered to indicate a neoplasm.[24]

In our study, absolute NAA and Cr values did not show statistical significance in differentiating neoplastic and non-neoplastic brain lesions. Similarly, variance in NAA/Cr ratio in neoplastic and non-neoplastic lesions was not statistically significant. However, a study described sensitivity and specificity of 64% and 69% in detecting neoplastic lesion using NAA/Cr with a significant p value.[23]

Mean Cho value in high-grade astrocytoma was 2.36±1.15 compared to 1.65±1.03 in low-grade gliomas in our study. Similarly Cho/Cr ratio in high-grade gliomas was 3.93±3.33 and 2.98±2.73 in low-grade gliomas. Literature review also showed that mean Cho values and Cho/Cr and Cho/NAA can also help in differentiating low-grade gliomas and high-grade astrocytoma. One study reported mean Cho/Cr ratio of 2.11±0.93 and 1.26±0.38 in high-grade and low-grade gliomas.[25] A study described mean Cho/Cr ratio in high-grade gliomas and metastasis as 3.92±3.31 and 1.84±1.22 respectively.[11] Another reported that this method is useful in the differentiation of high- and low-degree glial tumours with the Cho/Cr ratio being higher than 1.56 in high-degree malignant tumours.[26] Our study also showed increased level of Cho and Cho/Cr in high-grade glial tumours. No significant difference was noted in mean values of Cho in high-grade glial tumours and metastasis.

A study described Cho/Cr ratio of 1.55 or larger predicted a malignant tumour with 93% sensitivity and 80% specificity.[25] In our study, Cho/NAA ratio of 2.55 and above showed sensitivity of 70% in differentiating between neoplastic and non-neoplastic lesions which is in contrast with the earlier study. Our mean Cho value was 1.44 and sensitivity and specificity were 69% and 65% respectively. An earlier study also reported the sensitivity and specificity of the Cho/Cr ratio in detecting neoplasm was 77% and 79% when the ratio was 1.97 or above to differentiate between inflammatory lesions and tumours.[23] There is little consensus in literature regarding actual integral value of Cho and Cho/Cr and Cho/NAA ratio in reliably differentiating between neoplastic and non-neoplastic lesions, and further studies need to be done on larger scale.

Lipid/lactate peaks were observed in both neoplastic and non-neoplastic lesions and was relatively non-specific in differentiating between these entities. Similar results have been reported in previous studies.[20-22]

We had 6 false positive and 6 false negative cases. Possible explanation for this is site of the lesion and the placement of voxel which can result in false analysis of the metabolites.[27] Lesions located near the base of the skull or bone can result in increased noise which again leads to incorrect results.[11] The content of the lesion can also result in false interpretation. High-grade necrotic tumour can have metabolite contents similar to non-neoplastic lesions with reduced Cho, Cr and NAA levels with high levels of lipid/lactate peak. Similarly, invasive fungal infection due to increased mitotic activity can produce high levels of Cho with reduced NAA and Cr levels.[28]

There are a few limitations in our study. The sample size was relatively small with only 17 cases of non-neoplastic lesions with histopathological analysis not available in a large number of patients who had to be excluded. This could be due to the fact that non-neoplastic lesions were usually medically treated rather than surgically and usual follow-up was done in these types of cases rather than invasive procedures. Although histological confirmation is the gold standard, but the change in size and number of lesions or stability over a period of a year is also a useful alternative.

## Conclusion

MRS is highly sensitive but relatively less specific technique in differentiating between neoplastic and non-neoplastic brain lesions. MRS is useful adjunct in problematic cases and Cho, Cho/Cr and Cho/NAA ratios are the best indicators in MRS for differentiating between lesions, although no established demarcating values of these metabolites and their ratios have been established and further larger-scale studies are needed in this regard.

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