Original Research Article

Role of magnetic resonance spectroscopy in brain space occupying lesions for detection of malignancy and grading of malignant lesions

Rajsekar Chandrasekharan*, Ramaiah Rajesh Kannan, Chinmay Kulkarni, Srikanth Moorthy

Department of Radiology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

*Correspondence:
Dr. Rajsekar Chandrasekharan,
E-mail: raj462750@gmail.com

ABSTRACT

Background: Magnetic resonance (MR) spectroscopy is a non-invasive technique that enables tissue characterization on a biochemical level using radio frequency signals emitted by the nuclei in the tissue. Primary aim is at determining the utility of MR spectroscopy to differentiate malignant from benign lesions and to assess its role in grading of gliomas as secondary objectives.

Methods: MR system with proton spectroscopic capability using standard head coils and quantum gradients used in a sample size of 50 patients with intracranial space occupying lesions in conventional MRI. The diagnostic accuracy of the spectroscopic data based on the Cho/Naa ratios was used to detect the malignant lesions and distinguish them from the benign lesions.

Results: The lesion characterization using the MR spectroscopic data in distinguishing malignant lesions from benign was statistically compared with the histopathological data using chi square tests proved to be significant with p value of less than 0.05. Grading of the malignant space occupying lesion with the available spectroscopic data was done with the corresponding histopathology that proved statistically not significant.

Conclusions: Statistical data proves utility of MR spectroscopic data in differentiating malignant occupying lesions from benign. Role of spectroscopic data in grading the malignant lesion to differentiate to low and high grade could not be determined statistically which may be attributed to low sample size in the secondary objective.

Keywords: Choline levels/N acetyl aspartate level, Magnetic resonance

INTRODUCTION

Magnetic resonance (MR) spectroscopy is a non-invasive technique that enables tissue characterization on a biochemical level surpassing that of conventional MRI. It works on the same physical principles as MRI, the difference being that the radio frequency signals emitted by nuclei in tissues are used to determine the concentration of different metabolites in the tissue instead of creating grey scale images. It can perform in 10-15 minutes and combined with conventional imaging protocols. Thus MRS offers the possibility of not just visualization of the lesion but also biochemical characterization simultaneously.[1]

Primary aim was to evaluate the diagnostic accuracy MR spectroscopy (based on Cho/Naa ratios) in differentiating benign from malignant intracranial space occupying lesions. Secondary role was to evaluate the accuracy of MR spectroscopy data in the grading of malignant lesions.

METHODS

This is retrospective observational clinical study is to assess the diagnostic accuracy of Spectroscopic data to

detect the malignant lesions and grading them. Magnetic resonance imaging was performed on a 1.5 tesla whole body symphony MR system (Siemens, Erlangen), and 1.5 T HDXT (GE Milwaukee) with proton spectroscopic capability using standard head coils (circularly polarized phased array head coil) and quantum gradients. Patients selected for the study were those referred with suspected intracranial space occupying lesions. After eliciting a detailed history and performing clinical examination. Conventional magnetic resonance imaging preceded MR spectroscopy that helped in better localization and planning the spectroscopy. The study was carried out in the Department of Radiodiagnosis, Amrita Institute of Medical Sciences, Kochi from 2016 to 2018. Institution based ethical approval AIMS IRB 2019 was obtained.

Inclusion criteria

Patient undergoing MR brain with space occupying lesions.

Exclusion criteria

Cases of secondaries in brain (known primary elsewhere in the body).

Space occupying lesions within the ventricle, small periventricular lesions and lesions in close proximity with the bony calvarium.

Based on these criteria 50 patients with intracranial space occupying lesions detected on conventional MR imaging were subjected to Magnetic Resonance Spectroscopy. As control for the spectroscopic data the normal spectrum was obtained from the corresponding contra lateral or normal parts of the brain.

Procedure and parameters

Initially, each patient was scanned for conventional imaging sequence.

1. T 1 weighted images {TR/TE (repetition time/ time to echo)-330/11}

2. T2 WI(TR/TE-4500/97)

3. Diffusion weighted imaging (b value 1000)

4. Contrast enhanced TIW (axial) images.

Contrast enhanced T1w axial images were used for localization for the multivoxel spectroscopic study .The portion of the space occupying lesion in the periventricular region, close to the CSF cleft space and close to the bony calvarium /skull base were exempted as they cause poor shimming and inhomogenicities that lead to poor spectroscopic data. Homogenously enhancing areas were selected preferentially to get a better spectroscopic spectrum.[2]

The area under the curve of a metabolite was considered as relative concentration (integral values) and was measured in terms of ratios. Measuring metabolite peak area ratios has the advantage of cancelling out the effect of general reduction in measured metabolite concentrations due to variations in cellular density. Figure 1 showing normal spectrum. NAA peak at 1.80 ppm and cho peak at 3.01 ppm.[2]
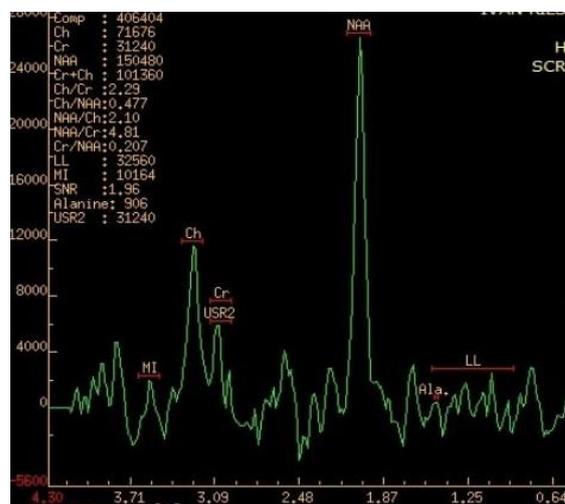

Figure 1: Normal spectrum.

The metabolites assessed were choline peak, NAA peak, and lipid lactate peak along with calculated Cho/NAA ratios.

Based on the Cho/NAA ratios the lesions were characterized as benign and malignant.

All lesions characterized as malignant were further categorised to high or low grade.

Statistical analysis

The MR spectroscopic data in our study was assumed to follow normal distribution. For the comparison of MRS with histopathology was considered the most important parameter. Based on the available figures (96% sensitivity based on Mc Knight et al) and with a confidence interval of 95%; precession of 15%, the sample space was computed to be 25.

In our study MR spectroscopic data of 48 patients were studied as two of the spectral data was poor for interpretation. Chi square test was done to compare the spectroscopic data with the clinic histopathological results to find the ability to distinguish benign from malignant and to assess the grade of tumor

RESULTS

Total of 50 patients were included in the study. On MR spectroscopy, reliable diagnosis spectrum was obtained in

48 patients (96%). In the remaining, spectrum obtained was non interpretable due to interference from hemorrhage within the lesion (in 1 case) and due to peripheral location close to bony calvarium (in the remaining 1 case) (Table 1).

Table 1: Sample distribution based on age.

Age group	No. of patients	Percentage
24-34	9	18.75
35-45	22	45.83
46-56	6	12.5
57-67	8	16.66
68-76	2	4.17
Total	48	100

Table 2: Gender distribution of the patient under study.

Gender	No. of cases	Percentage
Male	24	50
Female	24	50
Total	48	100

Table 3: Age distribution of patients with tumors.

Age group	No of patients
20-30	3
31-40	7
41-50	12
51-60	5
61-70	5
71-80	1
Total	33

Majority of patients in the study were in 35-45 years of age (45%). Both males and females in the study were 50% (Table 2 and Table 3).

Table 4: Location of mass lesions.

Location	No. of cases	Percentage
Frontal	17	35.4
Temporal	17	35.4
Parietal	9	26.47
Occipital	1	2.08
Others	4	8.3
Total	48	100

Even though majority of patient in the study belong to 35-45 yrs of age group, age distribution of patients with malignant space occupying lesions peaks at 41-50 yrs age group.

Majority of the space occupying lesions are at the frontotemporal regions.

Table 5: Composition of the MR spectroscopic data with that of the histopathological results.

Spectroscopy data	Histopathology		
	Malignant	Benign	Total
Malignant	27 (TP)	5 (FP)	32
Benign	7 (FN)	9 (TN)	16
Total	34	14	48

Pearson chi square value shows a 1-sided exact significance of 0.05, Sensitivity of the test= 79.4%, Specificity = 64.2%, Positive predictive value =84.37%, Negative predictive value = 56.25%

MR spectroscopy results were grouped into malignant and benign based on the Cho/ NAA level. Results were compared with histopatholgial results comprised of post operative histopathology.

The MRS results was seen to be statistically significant, (0.05<p) proving the ability of MR spectroscopy to distinguish benign and malignant disease.

Table 6: Grading of tumors by MR spectroscopy compared with histopathlogical results among malignant tumours.

Spectroscopic data(grading)	Histopathology results (grading)		
	Low	High	Total
High	4	19	23
Low	3	2	5
Total — No. of patients	7	21	28

Pearson chi square value shows one sided exact significance >0.05, Sensitivity of the test =90%, Specificity of the test= 42%, Positive predictive value =82 .6%, Negative predictive value= 60%

MR spectroscopy grading of the brain tumors is based on the Cho/NAA levels. Results were compared with histopathological microscopic results. However, chi square test could not prove the significance of MR spectroscopy in grading the neoplastic lesions.

DISCUSSION

Magnetic resonance spectroscopy is an emerging tool modality which offers information for tissue characterization that can potentially match histological diagnosis. Since its introduction, various studies have been done to determine its role and accuracy, especially in neuro imaging.

In our study , patients presenting with intracranial space occupying lesions ranged from 20 to 70 years of age of which majority of patients belonged to 35-45 yrs of age group. Males constitute 50%, of the study population. Predominant etiology of intracranial space occupying lesions encountered in the study was tumors (constitute 75%), in which gliomas (constitute 70%) being the most prevalent. The predominant presenting symptom was headache, seen in 44% of the patients, followed by seizures

(27%). These observations were in concordance with the findings of few studies including Harada.[3]

Single voxel proton MRS, using STEAM or PRESS has been performed to study brain lesions in several studies.[4] The utility of these sequences in the differentiation of lesions have been assessed by various researchers in the past. Proton MRS is useful only when voxel of interest is taken from well within the lesion. For very small lesions, the possibility of partial volume averaging from surrounding tissues and hence obtaining a misleading spectrum is a limiting factor.[4,5] The presence of prominent areas of hemorrhage, calcification or sometimes necrosis , or the peripheral location of the lesion close to calvarium or CSF also result in poor spectrum which does not serve any diagnostic purpose. In the present study, of the 50 patients with intracranial space occupying lesions, interpretable diagnostic spectrum was obtained in 48, i.e. in 96% of the cases. The study was done from the most homogenous part of the lesion in case of predominantly solid lesions.
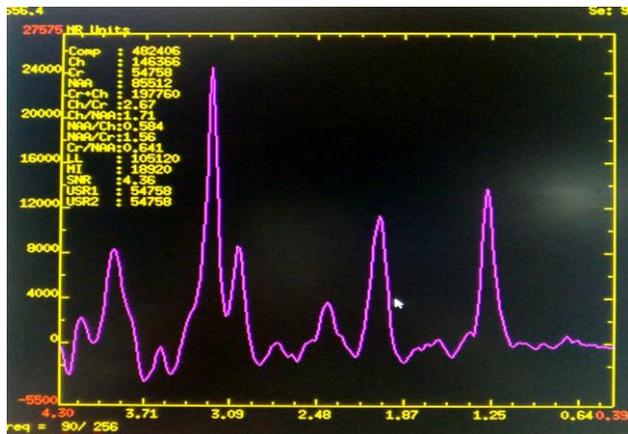

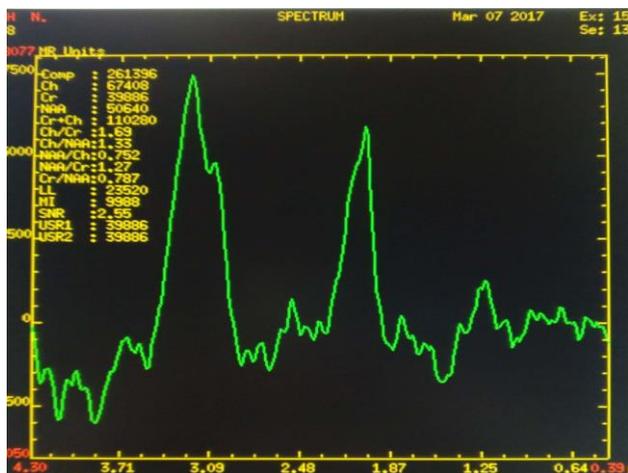**Figure 2: High Cho /NAA ratio that represents malignant pattern.**

Figure 3: Peaking of both the NAA and Cho that represents benign pattern.

Cho/NAA and Cho/Cr ratios were the main parameters used for spectroscopic assessment. This is similar to studies including Kugel and Sutton et al.[5,6] One of the parameters that can largely influence the spectrum is TE. A long TE allows the observation of a reduced number of metabolites and has less baseline distortion, yielding a spectrum that is easy to process, analyze, and interpret (Figure 1). A TE of 135 the alanine and lactate are inverted so that it is easier to differentiate its resonance from lipid and other macromolecules.[7,8]

This study was conducted on 50 cases with brain lesions, the spectroscopic data of 48 was considered interpretable by employing a long TE of 135ms from which Cho/Naa ratio were derived.

All primary neoplastic tumors, and metastasis are characterized by increased Cho, decreased NAA and creatinine (Cr) along with few cases showing the presence of, lactate and lipid (LL) peak. Increased Cho has been observed in most brain tumors, attributed to the increased membrane turnover and cell proliferation.[9] Figure 2 and Figure 3 shows MRS spectra pattern of malignant and benign lesions respectively.

NAA is predominantly located in neurons.[10] It has been shown that NMR visible NAA peak at 2.02 ppm arises mainly from N-acetyl aspartate and only a small component of it is from other N-acetyl containing compounds. Presence of NAA as seen in most of the tumors has been attributed to the difference in the cellular composition and nature of the tumor. Higher grade tumors, especially with tissue necrosis, naturally have lower NAA levels due to neuronal loss or replacement.

The correlation between the tumor grade and prognosis is well established.[11] Histological classification from biopsy specimens is the reliable and standard method for this purpose. However biopsies are associated with considerable morbidity especially the risk irreversible neurological deficit. Proton MRS, with its potential to differentiate lesions, can provide a preoperative diagnosis, obviating the need for surgical biopsy.

Grading of gliomas is this study has been done on the based on the Cho/Cr ratios similar to Howe et al.[12] NAA/Cr and Cho/Cr ratios have shown a consistency in predicting tumor grade based on Sutton et al. However Kugel did not find any significant difference in the metabolite ratios between various grades of tumors. In the present study statistical data analysis shows grading of tumour with MR spectroscopy data based on Cho/NAA ratio is found not significant.

A common clinical problem is distinguishing tumor recurrence from radiation effects several months following radiotherapy. Elevated choline is a marker for recurrent tumor.[13] Radiation change generally exhibits low NAA, creatine and choline on spectroscopy. If radiation necrosis is present, the spectrum may reveal elevated lipids and

lactate. In the present study 28 patients were imaged post radiotherapy and followed up. Chi square test done comparing the spectroscopic data with the histopathology.

This study has several limitations. Spectroscopic data obtained from the intraventricular lesions, skull-based lesions and lesions near the skull vault are often unreliable due to poor magnetic field in homogenities. Motion aretefacts may often lead poorly interpretable spectroscopic curves which we overcame with anesthetic procedures.

CONCLUSION

Our study shows that MRS can reliably distinguish the malignant intracranial lesions from the benign lesions, though its role in tumour recurrence is often questionable. Advance in knowledge is that MRS is an additional tool in diagnosing malignant lesion that complements the information obtained from conventional MR imaging and contrast studies, and helps to increase the overall diagnostic capability.

REFERENCES

1. Ross B, Bluml S. Magnetic resonance spectroscopy of the human brain. Anat Rec. 2001;265:54–84.
2. Scheau C, Preda EM, Popa GA, Ghergus AE, Capsa RA, Lupescu IG. Magnetic Resonance Spectroscopy–a non-invasive method in evaluating focal and diffuse central nervous system disease. J Med Life. 2012 Dec 15;5(4):423.
3. Harada M, Tanouchi M, Miyoshi H, Nishitani H, Kannuki S. Brain abscess observed by localized proton magnetic resonance spectroscopy. Mag Res Imag. 1994;12(8):1269-74.
4. Ott D, Hennig J, Ernst TH. Human brain tumors: assessment with in vivo proton MR spectroscopy. Radiology. 1993;186(3):745-52.
5. Kugel H, Heindel W, Ernestus RI, Bunke J, Du Mesnil R, Friedmann G. Human brain tumors: spectral patterns detected with localized H-1 MR spectroscopy. Radiol. 1992;183(3):701-9.
6. Sutton LN, Wang Z, Gusnard D, Lange B, Perilongo G, Bogdan AR, et al. Proton magnetic resonance spectroscopy of pediatric brain tumors. Neurosurg. 1992;31(2):195-202.
7. Safriel Y, Pol-Rodriguez M, Novotny EJ, Rothman DL, Fulbright RK. Reference values for long echo time MR spectroscopy in healthy adults. Am J Neuroradiol. 2005;26(6):1439-45.
8. Majós C, Julià-Sapé M, Alonso J, Serrallonga M, Aguilera C, Acebes JJ, et al. Brain tumor classification by proton MR spectroscopy: comparison of diagnostic accuracy at short and long TE. Am J Neur. 2004;25(10):1696-704.
9. Bruhn H, Frahm J, Gyngell ML, Merboldt KD, Hänicke W, Sauter R, et al. Noninvasive differentiation of tumors with use of localized H-1 MR spectroscopy in vivo: initial experience in patients with cerebral tumors. Radiol. 1989;172(2):541-8.
10. Miller BL. A review of chemical issues in 1H NMR spectroscopy: N-acetyl-L-aspartate, creatine and choline. NMR Biomed. 1991; 4(2):47-52.
11. Adamson AJ, Rand SD, Prost RW, Kim TA, Schultz C, Haughton VM. Focal brain lesions: effect of single-voxel proton MR spectroscopic findings on treatment decisions. Radiol. 1998;209(1):73-8.
12. Howe FA, Barton SJ, Cudlip SA, Stubbs M, Saunders DE, Murphy M, Wilkins P, Opstad KS, Doyle VL, McLean MA, Bell BA. Metabolic profiles of human brain tumors using quantitative in vivo 1H magnetic resonance spectroscopy. Magnetic Resonance in Medicine: J Inter Soci Mag Res Med. 2003;49(2):223-32.
13. Taylor JS, Langston JW, Reddick WE, Kingsley PB, Ogg RJ, Pui MH, et al. Clinical value of proton magnetic resonance spectroscopy for differentiating recurrent or residual brain tumor from delayed cerebral necrosis. Inter J Rad Oncol Biol Phy. 1996;36(5):1251-61.