ORIGINAL ARTICLE

Diagnostic Accuracy (sensitivity and specificity) of Magnetic Resonance Spectroscopy as an imaging tool in the differentiation of benign vs malignant intracranial space occupying lesions

SARAH NISAR[1], MARYAM RAUF[2], LUBNA SARFRAZ[3]
[1]*Assistant Professor, Radiology, Quaid e Azam Medical College/ Bahawal Victoria hospital Bahawalpur.*
[2]*Consultant Radiologist, PESSI, Islamabad*
[3]*Associate Professor, Pathology Department, Quaid-e-Azam Medical College. Bahawalpur*
Correspondence to Dr. Sarah Nisar, E.mail:sarahawais@hotmail.com, Cell No:03212880224

ABSTRACT

Background: Accurate diagnosis is paramount in patients presenting with intracranial tumors for optimum clinical management. Brain tumor is one of the most common causes of cancer related deaths amongst young patients of less than 35 years age in the United States. The incidence rate of all primary central nervous system tumors (malignant or non-malignant) is 18.71 cases per 100,000 persons.
Aim: To determine the diagnostic accuracy (sensitivity and specificity) of MRS (Magnetic resonance spectroscopy) as an imaging tool in the differentiation of benign versus malignant tumors.
Study design: Cross-sectional (validation) study.
Settings: This study was conducted in department of Diagnostic radiology, Pakistan Institute of Medial Sciences, Islamabad from June 2018 to June 2019.
Method: Patients with clinical diagnosis or CT scan based diagnosis of an intra-cranial space occupying lesion and referred to the radiology department for MRI of brain were identified. Single voxel MR spectroscopy was performed along with MRI brain. Interpretation was made with evaluation of MR spectrum by consultant radiologists.
Results: Total 157 patients were included in the study. Mean age of patients was 47.52 years with a standard deviation of 12.32 years. 81 (51.59%) patients were male and 76 (48.41%) patients were female. Sensitivity of MR Spectroscopy was 72.20%, specificity of MR Spectroscopy was 83.67%, positive predictive value was 90.60%, negative predictive value was 57.70% and diagnostic accuracy of MR Spectroscopy was 75.70%.
Conclusion: MRS is an important, useful ,non -invasive technique in the distinction of inflammatory brain lesions and high-degree tumors when the Choline peak is greater than other peaks. It can be used as an additional tool for characterization of tumors, prior doing a biopsy which is highly specific and sensitive.
Keywords: MR Spectroscopy, MRI, intracranial space occupying lesion, Benign and malignant intracranial tumors

INTRODUCTION

Accurate and timely diagnosis is really important for clinical management of patients presenting with intracranial tumors. A tumor that is accessible, is surgically resected, but there is a balance between removing as much tumor tissue as possible while maintaining vital brain functions, followed by radiotherapy to treat the residual disease[1].

Brain cancer is the leading cause of cancer related deaths in patients younger than 35 years of age in United States, and the incidence rate of central nervous system tumors (malignant or non-malignant) is 18.71 cases per 100,000 persons. In United Kingdom the incidence rate of CNS tumors was found to be 9.21 per 100,000 persons, and the most common cause of cancer related deaths in age group 0-24 years[2].

Imaging is important for the clinical management of brain tumors, as it can accurately define tumor boundaries, infiltration and relation to adjacent brain structures. Recently, MRI and (MRS) Magnetic resonance spectroscopy have become key diagnostic modalities for this purpose. Although MRI provides excellent soft tissue contrast, the validity of this technique alone in defining tumor characteristics is however, limited. Integration of Proton MR spectroscopy (^{1}H-MR spectroscopy),which is a noninvasive MR technique along with routine MR imaging ,has shown great promise as an imaging tool, that identifies biochemical signature of the tumor on MRI[3].

Currently MRI is widely used in determining tumor extent for surgical planning or radiotherapy. It is also used for post-therapy monitoring to see any tumor residue, recurrence or progression to higher grade. MRI provides an initial diagnosis of an intracranial mass lesion with a success rate of 30–90% depending on tumor type[4] ·However biopsy is still considered the gold standard for determining the cancer type and degree of malignancy.[5] A sensitivity of 72.2% and specificity of 91.7% has been achieved in differentiating neoplastic tumors from non-neoplastic lesions MR Spectroscopy. A 1.7% mortality rate was reported with biopsy procedures, and in a study of 550 patients undergoing stereotactic biopsy: 8% had abscesses or inflammatory processes, 2.2% had other lesions, 3.4% were non-diagnostic; and 8% suffered complications.[6] A noninvasive prediction of lesion type can help in reducing unnecessary surgical biopsy procedures for tumors that are not or less accessible by surgery ,and can be treated by radio- or chemotherapy. MRS non-invasively provides information on biochemical status of tissue and is increasingly being used to classify brain tumors. Earlier MRS studies have clearly showed differences between the spectra of brain tumors versus normal brain tissue. Single voxel proton MR spectroscopy has been applied for characterizing the metabolic activity in brain tumors. It is a

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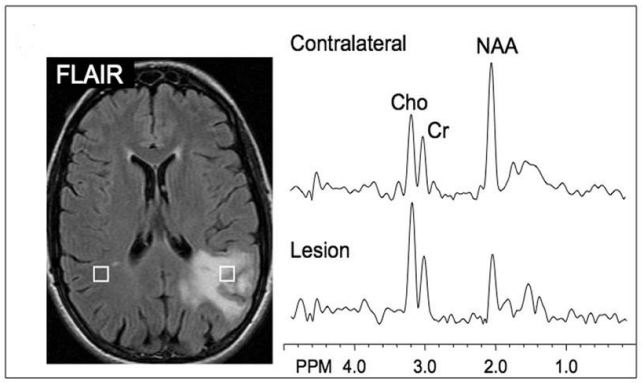
relatively rapid and non-invasive method for obtaining information about the metabolic events in a 4-8cc region within the lesion[7].

MRS allows us to measure major metabolites in defined are of tumor and delineate from surrounding brain parenchyma, that is choline containing compounds (Cho which is a rate limiting precursor to cell membrane, it is increased in tumors), N-acetyl aspartate **(NAA**, represents normal neuro metabolics), Lactate (produced in anaerobic metabolism in tumors necrosis), myo-inositol (astrocyte marker) and mobile lipid moieties (associated with necrosis).A reduction in NAA and increase in choline in tumor ,in comparison to the normal brain parenchyma has been shown in various studies with strong evidences[8].

Figure 1: Left Occipital primary brain tumors recorded using MRS



MATERIAL AND METHODS

This c oss-sectional (validation) study was conducted from June 2018 to June 2019 in the Department of Diagnostic Radiology, Pakistan Institute of Medial Sciences, Islamabad, in collaboration with Departments of Neurosurgery and Pathology of Federal government Services Hospital, Islamabad. Sample size calculated by using the WHO sample size calculator, taking sensitivity of 72% and specificity of 91%. The annual, global, age-standardized incidence of primary malignant Brain Tumors is ≈3.7 per 100,000 for men and 2.6 per 100,000 for women[8]. Consecutive non probability sampling technique was used.

Inclusion criteria: All patients with clinical diagnosis or CT scan based diagnosis of an intra-cranial SOL and undergoing magnetic resonance imaging of brain.

Exclusion criteria:

1. Patients who refuse to have an MRI scan
2. Any contra indication to MRI scan
3. Diagnosed cases who have undergone surgery.
4. Patients who refuse to undergo biopsy/surgery after radiological diagnosis.

Data collection procedure: After having permission from the ethical committee of hospital, patients with clinical diagnosis or CT scan based diagnosis of an intra-cranial space occupying lesion and referred to the radiology department for MRI of brain was identified. Taking into consideration patient's confidentiality, brief clinical history of the patient was obtained .Written consent was obtained from the patients after explaining the procedure. Philips 1.5 Tesla Achieva Nova was employed, and single voxel MR spectroscopy was performed in addition to the MRI of brain. Interpretation was made with evaluation of images by experienced radiologist of the department. The patient's course of management was followed in collaboration with neurosurgery department of PIMS, till he/ she underwent biopsy or was operated upon. Histopathology was performed in Federal government services hospital, Islamabad. Histopathological diagnosis (malignant/benign) was correlated with the findings of the magnetic resonance spectroscopy of the lesion. MRS findings and histopathological findings was recorded on the data collection performa.

The data was analyzed on SPSS version 23. A 2x2 table was used to determine sensitivity, specificity, positive and negative predictive value and diagnostic value. Mean and standard deviations was calculated for quantitative variables like age. Frequencies and percentages were calculated for qualitative variables like gender and malignancy of intracranial lesion on histopathology and MR Spectroscopy.

RESULTS

Total of 157 patients were included in the study. Mean age of patients was 47.52 years with standard deviation of 12.32 years. The minimum age of patients was 23 years; maximum age of patients was 69 years with range of 46 years. Out of 157, 81 (51.59%) patients were male and 76 (48.41%) were female .21 (13.38%) patients were in 15-30 years of age group, 41 (26.11%) patients were in 31-45 years of age group, 78 (49.68%) patients were in 46-60 years of age group and 17 (10.83%) patients were in 61-75 years of age group .

On histopathological diagnosis, 108 (68.79%) patients had malignant lesion while 49 (31.21%) patients had benign lesion .86 (54.78%) patients had choline peak while 71 (45.22%) patients had other peak on MR Spectroscopy . In histopathological diagnosis, 60 male and 48 female patients had malignant lesion while 21 male and 28 female patients had benign lesion . On MR Spectroscopy, 48 male patients and 38 female patients had choline peak while 33 male patients and 38 female patients had Other (NAA/Lactate/Myo-inositol) peak.

In15-30 years of age group, 14 patients had choline peak while 7 patients had other (NAA/Lactate/Myo-inositol) peak; in 31-45 years of age group, 28 had choline peak while 13 patients had other (NAA/Lactate/Myo-inositol) peak; in 46-60 years of age group, 40 patients had choline peak while 38 patients had other (NAA/Lactate/Myo-inositol) peak; in 61-75 years of age group, 4 patients had choline peak and 13 patients had other (NAA/Lactate/Myo-inositol) peak. In15-30 years of age group, 14 patients had malignant lesion while 7 patients had benign lesion; in 31-45 years of age group, 35 patients had malignant lesion while 6 patients had benign lesion; In 46-60 years of age group, 52 patients had malignant lesion while 26 patients had benign lesion; in61-75 years of age group, 07 patients had malignant lesion while 10 patients had benign lesion.

In our study 78 patients were true positive, 8 patients were false positive, 30 patients were false negative and 41 patients were true negative. In our study, sensitivity of MR

Spectroscopy was found 72.20%, specificity of MR Spectroscopy was found 83.67%, positive predictive value was recorded 90.60%, negative predictive value was noted 57.70% and diagnostic accuracy of MR Spectroscopy was 75.70% .

Table 1: Age Statistics of patients

Total number of patients	Valid	157
	Missing	0
Mean age of patients (years)		47.52
Median age of patients (years)		49.00
Mode		57
Std. Deviation age of patients (years)		12.328
Range of age of patients(years)		46
Minimum age of patients (years)		23
Maximum age of patients (years)`		69

Figure 2: Histopathological diagnosis

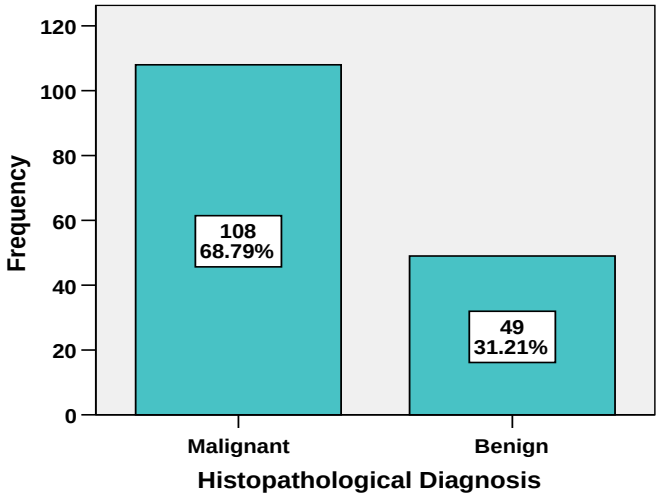


Figure 3: MR Spectroscopy Peak

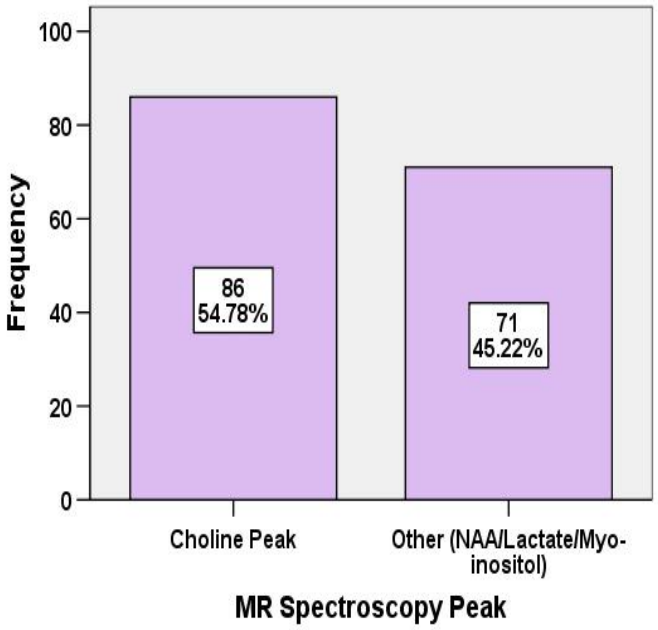
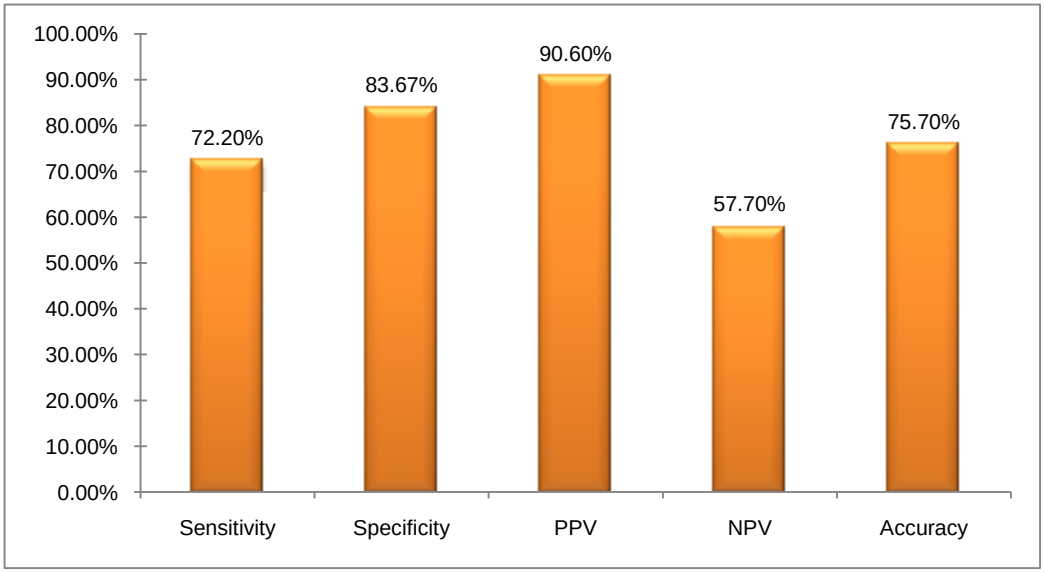


Table 2: Gender of patients in different age group of patients

Age group	Male	Female	Total
15-30 years of age	12(57.1%)	9(42.9%)	21
31-45 years of age	20(48.8%)	21(51.2%)	41
46-60 years of age	42(53.8%)	36(46.2%)	78
61-75 years of age	7(41.2%)	10(58.8%)	17
Total	81(51.6%)	76(48.4%)	157

P value 0.732

Figure 4: Sensitivity, specificity, PPV, NPV and diagnostic accuracy of MR Spectroscopy



Where PPV: positive predictive value, NPV: negative predictive value

DISCUSSION

MRI is a sensitive diagnostic tool being used for characterizing brain lesions, but most of the time it is not really possible to differentiate between benign and malignant nature due to overlapping features. Magnetic resonance spectroscopy can determine the chemical composition of the lesion non-invasively. MR Spectroscopy can help in differentiating neoplastic masses from other lesions. MR Spectrum is after placing an appropriate voxel on the focal lesion .[8] Lesions can evaluated on analyzing MR Spectrum, using criteria including Cho/Cr and Cho/ NAA ratio and choline and NAA peak.[9]

This study showed that MRS can very well discriminate high grade glial tumors from benign lesions ,where the choline peak (Cho/Cr ratio) is found to be higher. This raise in choline peak (Cho/Cr ratio) in the evaluation of neoplastic lesions has already been observed and studied in various researches. Choline is a constitutent of cell membranes and its peak increases when there is increase in cell synthesis and conversion to carcinogenic cells. NAA is found in normal brain cells and altered peak is seen in neuronal loss. The NAA/Cr ratio has a discriminatory value and upon analysis with the Cho/Cr ratio, it increase the specificity of the technique used.[10]

The important differentiation between inflammatory brain lesions and malignant tumors may help in the early planning of treatment therapy for better prognoses with cerebral lesions to avoid inappropriate treatment that may cause unnecessary surgeries, allergic reactions and intoxication in already debilitated sick patients.[11]

In Previous studies described in literature, the evaluation of a heterogeneous group of patients, some with known prior tumor or unknown new masses, variable diagnostic test characteristics for MRS with sensitivities ranging from 79% to 100% and specificity ranges from 74% to 100% was observed. The positive predictive values ranged from 92% to 100%, while the negative predictive values ranged from 60% to 100%.[12,13] These facts and figures resemble to our study in which MRS showed a sensitivity of 72.20% and a specificity of 83.67%. Positive predictive value was 90.60% and negative predictive value was 57.70%. Diagnostic accuracy was found to be 75.70%.

In studies, where MRS evaluated gliomas[14,] the usefulness of differentiation high- and low-degree glial tumors was reported, with the Cho/Cr ratio higher than 1.56 in high-degree tumors. These data are replicated in studies who demonstrated that a Cho/Cr ratio greater than 1.55 has a marked discriminatory ability to differentiate between high- and low-grade glial tumors[15].

To our knowledge ,MRS investigations comparing high-degree glial tumors and infectious lesions has not been studied yet and thus there are few published data to compare with the results of this study.[16] It was concluded in some of the studies that the Cho/Cr and NAA/Cr ratios are not useful in the differentiation of certain lesion; this was also supported by Simone et al[17], who studied 11 patients with cerebral toxoplasmosis and 8 with lymphomas, and did not utilize ratios between metabolites in their studies but ascertained that MRS is useful for differentiation, thus agreed with the conclusion of Harting et al[18] in which they studies many cases and found that MR Spectroscopy was helpful in differentiating malignant and benign lesion. The results of these studies are comparable to the results of our study in which we have found MR spectroscopy gave better results in analysis of space occupying lesion in brain to differentiate into malignant and benign lesion and helping the neurosurgeons for planning future treatment strategies. There was a high accuracy of (75.70%) observed in our results, however, there were significant false positive and false negative results. Various factors could be responsible for these false positives and negatives, one of them is voxel placement position. Voxel placement is critical in accuracy of MR spectroscopy findings. In an enhancing brain lesion ,placement at the leading edge appears to increase the likelihood of including viable proliferating tumor in the spectroscopy volume at the same reduces the chances of including microscopic necrosis. Another possible factor is due to lesions present in the periphery or base of the skull, where increased noise hinders accuracy of the spectrum obtained from the lesion near bones.[19]

Lipid as well as lactate peaks are considered relatively non-specific in discriminating neoplastic from non-neoplastic lesions .It can be found in both as described in results of this study and previous literature. [20]Few other studies described the presence of these in both pyogenic and tuberculous abscesses. Kumar et al[21] also described presence of lipid/lactate peak both in gliomas as well as tuberculous lesions. Kim et al also reported similar results. Magnetic resonance spectroscopy had helped to characterize a brain mass on the MRI as a neoplasm. Although on a routine MRI brain study, the mass demonstrated may have all of the MRI findings of a neoplasm, the MRS can provide objective chemical evidence of tumor and in children in whom the MRI findings are not unique to tumor, MRS can provide objective chemical evidence. Although MRS is extremely useful in evaluating patients with brain neoplasm, in less than 5%, there may be overlapping spectra of brain neoplasms with some forms of multiple sclerosis, acquired immunodeficiency syndrome (AIDS) masses and infarction. Therefore, MRS studies (spectra and quantification data) must be interpreted in conjunction with the MRI examination and the clinical history and symptoms of the patient[22]

Magnetic resonance spectroscopy can aid in differentiating residual tumor from postsurgical changes and scar formation. After recent surgery for the removal of a brain neoplasm, it may be difficult to determine if we are dealing with postsurgical changes or residual tumor in the surgical bed. Even with early postsurgical changes, the adjacent tissue may demonstrate enhancement due to surgical manipulation and swelling. The tumor bed with postsurgical changes and without residual tumor will demonstrate decreased metabolites, including choline. Magnetic resonance spectroscopy also allows for identification of inactive neoplasm. Residual neoplasm may become inactive or go into remission. In these patients, the choline decreases and then sequential MRS will demonstrate stable low levels of choline over several months, while the MRI shows no change in size, signal intensity, and enhancement. In most of our patients, we

were able to obtain diagnostic spectra on the first MRS examination. In the 5% of patients in whom an initial MRS spectrum could not be obtained or the initial MRS spectrum was non-diagnostic, the reasons were recent hemorrhage within the neoplasm-producing magnetic susceptibility interference; air, fat, or bone adjacent to or within the voxel preventing shimming of the gradients; and inadequate water suppression.[23]

Conclusion:

To conclude, MRS is considered an important tool that is useful in the distinction of inflammatory brain lesions and high-degree tumors where the Choline peak is greater than other peaks in the spectra. As diagnostic accuracy of MR Spectroscopy is low (75.70%) as compared to gold standard, it can be used as an additional tool prior to biopsy. This modality should be considered as an adjunct to conventional imaging rather than replacement for histopathological evaluation. Furthermore it can be helpful in the treatment and monitoring plan for better therapeutic strategies and avoiding unnecessary surgeries.

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