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Diagnostic value of Magnetic Resonance Spectroscopy (MRS) for detection of Brain Tumors in patients

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ABSTRACT

Objective: In the present research, the sensitivity and specificity of MRS in the diagnosis of brain tumors were investigated in patients with brain tumors. *Materials and Methods:* Patients visiting the Kashani Hospital and Sepahan Clinic of Isfahan in 2017, who met the inclusion criteria, were enrolled in this cross-sectional study. The 35 patients included in the study were examined by an experienced radiologist through MRI with and without contrast. Patients with a brain tumor diagnosed by the radiologist were enrolled in the study and evaluated through MRS. A part of the brain tumor was removed by a neurosurgeon and examined by a pathologist to determine the degree of malignancy. The pathologist was blinded to the MRS results, and the radiologist was blinded to the biopsy results. *Findings:* In the present study, the measured variables in terms of the area under the ROC curve (AUC), sensitivity, and specificity showed a high accuracy for the diagnosis of brain tumors (AUC=0.917, 95%CI=80%-100%). The cutoff point was determined as 1.5 (p =0.002 <0.05) which had the highest sensitivity (0.667) and specificity (0.955) in comparison with other cutoff points. *Conclusion:* In this study, the measured variables in terms of the area under the ROC curve, sensitivity, and specificity showed a high accuracy for the diagnosis of brain tumors by MRS.

Keywords: magnetic resonance spectroscopy (MRS), brain tumor, diagnostic value

1. INTRODUCTION

Brain tumors are associated with the highest mortality rate and prevalence among all tumor groups and require new methods to improve clinical management (Horská and Barker, 2010). Magnetic resonance imaging (MRI) and other biomedical imaging techniques only allow ambiguous detection and positioning of tumors, therefore, biopsies are typically needed for tumor detection. Unfortunately, many tumors may not be available for biopsy. Tumors type, grade, and volume are the most important factors in evaluating their prognosis (Zimm et al., 1981 and Kleihues et al., 1993). Despite the proper contrast of MRI for soft tissues, it has limited sensitivity and specificity for determining the tumor type and degree. This is partly due to tumor necrosis that can be mistaken with the tumor and, to a lesser extent, due to its low ability to differentiate tumors, edema, and the effects of non-specific therapies in the area of signal enhancement in T2 images.

Magnetic resonance spectroscopy (MRS) has been used in some cases to characterize the metabolic properties of brain tumors (Horská and Barker, 2010 and Fitzek et al., 1999 and Johnson et al ., 2017 and Zimm et al., 1981 and Kleihues et al., 1993 and Dean et al., 1990 and Earnest et al., 1988 and Mabray et al., 2015 and Janus et al., 1993 and Kim et al., 1992 and Brunberg et al., 1995 and Sugahara et al., 1999 and Tien et al., 1994 and Heesters et al., 1993 and Negendank et al., 1996 and Brandão and Castillo, 2016). Various studies have shown that the amount of N-acetyl-aspartate (NAA) is decreased and choline-containing compounds are increased in tumors compared with brain parenchyma (Chang et al., 1995 and Carrera et al., 2016). In addition, lactate and fat related resonance can be observed in some metastatic lesions and highly malignant gliomas (Usenius et al., 1994). Early studies on the role of MRS in determining the brain tumors malignancy grade in various institutions have reported different results with a high diversity of data quality. Introduction of automated packages for performing MRS in clinical scanners improved the quality and repeatability of information. With the addition of multivariate statistical analyzes, certain schemas were developed which helped identify the type and grade of tumors (Shimizu et al., 1996). Recent studies have shown that differentiation of various types of brain lesions can be improved by measuring the levels of glutamine and glutamate through MRS and analyzing the results (Preul et al., 1996). Although MRS is a quick method for obtaining information about metabolism at 4-8 cm of brain damages, it does not provide researchers with information on spatial heterogeneity and cannot determine the spatial size of the lesion. This inability gains importance regarding determination of focal therapy modalities such as radiotherapy, surgery, and follow-up. However, there is little information about the sensitivity of this test. Every method has advantages and disadvantages, and their correct selection is important for any particular purpose to improve the quality of the results. Given the conditions and facilities, the present study examined the sensitivity and specificity of MRS in the diagnosis of brain tumors.

2. MATERIALS AND METHODS

The study population in this cross-sectional research consisted of patients with brain mass who visited the neurosurgery clinic of Kashani Hospital and the Sepahan private clinic in Esfahan in 2017.

The inclusion criteria were patients with brain tumors who were candidate for MRS and the exclusion criteria were history of brain surgery, brain biopsy, contrast contraindication (pregnancy, renal dysfunction), MRI contraindication (metal objects in the body

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and claustrophobia), and reluctance to continue the cooperation. The participants were selected in this study through non-random convenience sampling method until reaching the sample size of 35 patients.

Procedure

The research was first approved by the Research Council of Esfahan University of Medical Sciences and launched after receiving the code of ethics. Patients visiting the Kashani Hospital and Sepahan clinic in Esfahan in 2017 and had the inclusion criteria were enrolled in the study. Based on the sample size, 35 patients were examined. Patients with exclusion criteria or unwilling to perform the study were excluded.

All patients were undergone MRI with and without contrast by an experienced radiologist, and those diagnosed with a brain tumor were included in the study and examined with MRS. MRS information is presented as a spectrum that is obtained from Fourier transformation of spectroscopic studies. It appears as a series of peaks in the longitudinal axis designated by frequency (Hz) or in parts per million (ppm). Therefore, instead of the image, a spectrum of MR signals amplitude in terms of their resonance frequency will be seen in MRS. The spectrum horizontal axis indicates the amount of chemical shifts of each of these materials and the vertical axis presents the amount of this chemical shift, which is the amplification signal obtained from magnetic resonance. In this spectrum, the amplitude and frequency of amplification peaks represent the relative amount of different metabolites in the study area. After corrections of peak overlapping, the area under the curve of each peak will be proportional to the concentration of that peak metabolite. Proton magnetic resonance spectroscopy, like any spectroscopy, utilizes a physical characteristic to identify, differentiate, and detect various compounds. This physical characteristic arises from the resonance of different materials' protons in an external magnetic field. Difference in these frequencies is due to the chemical shift phenomenon. According to their type, brain cells have their own different metabolites which can be distinguished by MRS. Numerous studies have reported these specific metabolic profiles for primary brain tumors and various grades of tumors of the same cellular origin. Brain metastasis is more common than primary brain tumors. In this regard, measurement of choline is an appropriate indicator of differentiation of high-grade gliomas and brain metastases. The level of choline in metastases is low compared to gliomas. Lipid peaks can also be used to differentiate high grade gliomas and metastases. Differentiation of 14GC and 15LGG in an anatomical context is usually difficult, but the use of MRS variables can solve this problem. The level of creatinine (Cr) is lower in GC than LGG. Primary brain tumors, regardless of their grade, have low levels of NAA and Cr and high levels of choline-containing compounds. The level of lactate is lower in glioma than meningioma and neuroma, and meningioma usually has a high level of alanine. In this study, the levels of NAA, choline, and Cr, and the ratios of NAA to Cr and choline to Cr were measured and reported as MRS results.

A part of the brain tumor was excised by the neurosurgeon and its malignancy grade was assessed by the pathologist. The pathologist was blinded to the results of MRS and the radiologist was blinded to the results of biopsy. Information about the tumor benignancy or malignancy and the malignancy grade were recorded in a checklist. Patients whose pathological results were uncertain or undetermined were excluded.

Then, based on the positive and negative results of MRS and pathology, statistical analyzes were performed to determine the sensitivity, specificity, positive and negative likelihood, and AUC.

AUC (area under the ROC curve) indicates the system prediction value through describing its ability to accurately estimate and not estimate the events occurring.

Sensitivity = True Positive / (True Positive + False Negative)

Specificity = True Negative / (True Negative + False Positive)

Positive Likelihood Ratio = Sensitivity / (1 − Specificity)

Negative Likelihood Ratio = (1 − Sensitivity) / Specificity

Data were entered into SPSS 20 and analyzed in two sections of descriptive and analytic by the statistician. In the descriptive section, the quantitative variables were reported as the mean and standard deviation and the qualitative variables as percent (number). Sensitivity, specificity, positive likelihood, and area under ROC curve (AUC) were investigated for the predictive role of the two assessment methods. All analyzes were performed at a 5% error level.

Ethical committee approval code

This study was approved by ethical committee of Isfahan University of Medical Sciences with code 397195 2018 April.

3. RESULTS

Regarding the gender distribution, 27 patients (77.3%) were male and 8 patients (22.7%) were female (Table 1).

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Table 1 Gender distribution

Gender[a]	Male	22 (77.3%)
	Female	8 (22.7%)

[a] Frequency (%)

Table 2 shows that 6 patients diagnosed with a tumor grade 1 by the pathologist received the same diagnosis in MRS. Similarly, 7, 2, and 7 patients were correctly diagnosed with tumor grades 2, 3, and 4 by MRS, respectively. Two patients were diagnosed with malignancy grade 1 by the pathologist, while the MRS incorrectly diagnosed them with grade 2. In addition, 5 patients diagnosed with tumor grade 2 by the pathologist were incorrectly diagnosed with grade 3 by MRS. One patient was diagnosed with grade 1 by MRS and with grade 3 by the pathologist. Two patients were diagnosed with grade 2 by MRS and with grade 3 by the pathologist. In addition, 2 patients were diagnosed with grade 3 by MRS and with grade 4 by the pathologist.

Table 2 The agreement table of diagnosis through pathology versus MRS

Pathology MRS		Pathology				Total
		Grade 1	Grade 2	Grade 3	Grade 4	
	grade1	6	0	1	0	7
	grade2	2	7	2	0	11
	grade 3	0	5	2	2	9
	grade 4	0	0	1	7	8
Total		8	12	6	9	35

Continuous quantitative variables included the levels of NAA, Cr, and choline, and the ratios of NAA/Cr, and choline/Cr, choline/NAA, and NAA/choline which are reported in Table 3 as mean ± SD.

As can be seen, the area under the ROC curve has an upward trend (Figure 1), indicating the high diagnostic value of MRS in diagnosing brain tumors.

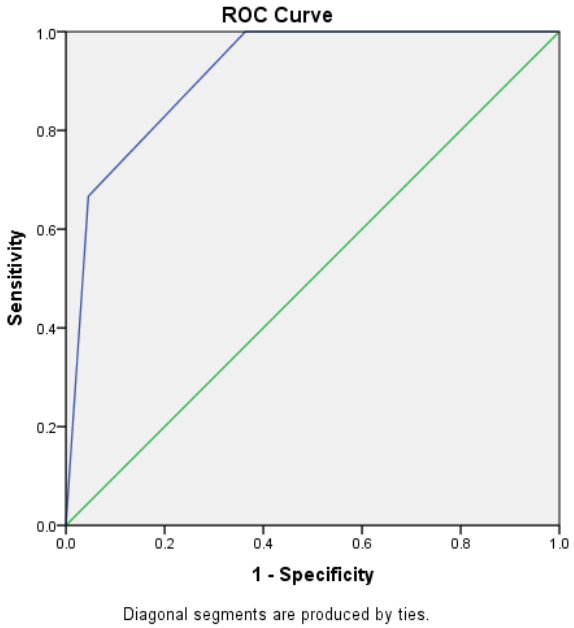

Figure 1 ROC curve and AUC for MRS

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Table 3 Continuous quantitative variables distribution

	NAA	Cr	Choline	NAA/Cr	Choline/Cr	Choline/NAA	MI/Cr	NAA/Choline
Mean ± SD	0.15±0.04	0.25±0.04	0.35±0.07	0.51±0.13	3.23±0.86	4.87±1.24	0.75±0.10	0.03±0.00
Minimum	0.02	0.16	0.20	0.04	1.30	1.20	0.60	0.03
Maximum	0.45	0.62	0.90	1.30	98.02	20.00	0.95	0.04

In Table 4, the significance level (p-value <0.05) shows that MRS has a positive significant diagnostic value for detection of brain tumors. The above confidence interval shows that AUC is between 80.5% and 100% with a confidence interval of 95%. In other words, if the selected patients represent a larger community, the prediction power of MRS to detect brain tumors is minimally 80.5% and maximally 100%, with 95% confidence.

Table 4 Area under the ROC curve (AUC)

AUC	Standard error	p-value	95% confidence interval	
			Lower limit	Upper limit
0.917	0.057	0.002	0.805	1.000

According to specificity and sensitivity values, the appropriate cut-off point is 1.5 with a sensitivity of 0.667 and a specificity of 0.955. This point has the highest sensitivity and specificity. Sensitivity of MRS for diagnosing brain tumors is 0.667. In other words, MRS can correctly detect 66.7% of patients with brain tumors. Specificity of MRS for diagnosis brain tumors is 0.955. The positive likelihood at this point is 14.82 and the negative likelihood is 0.348 (Table 5).

Table 5 Characteristics of studied points

Points	Sensitivity	Specificity	LR^+	LR^-
0.00	0.000	1.000	0.000	1.000
1.50	0.667	0.955	14.82	0.348
2.50	1.000	0.636	2.747	0.000
3.50	1.000	0.273	1.375	0.000
5.00	1.000	0.000	1.000	0.000

4. DISCUSSION

The results of this study showed that the levels of NAA, Cr, and choline were 0.15±0.04 (from 0.02 to 0.45), 0.25±0.04 (from 0.16 to 0.62), and 0.35±0.07 (from 0.20 to 0.90), respectively. The ratios of Choline/NAA and Choline/Cr increased in the brain tumors from 1.20 to 4.87 (with an average of 4.87±1.24) and from 1.30 to 0.92 (with an average of 3.33±0.86), respectively. Evaluation of the levels of metabolites in the present study showed the increase of choline peak in the tumors center. This increase is associated with cell density and indicates that the cells are moving towards tumorization. Since gliomas are infiltrative or penetrating in nature, they can destroy nerve cells and reduce NAA. According to Cohen et al. (2005), reduced NAA in the whole brain of patients with glial tumors beyond the main tumor is a sign of penetration. This significant reduction of NAA in the whole brain possibly shows the spread of tumor in the apparently healthy brain in MRI (Heesters et al., 1993). Soares and Law found that the pure level of NAA decreases with the penetration rate of tumor, while the choline pure level and the NAA/choline ratio increase with the penetration rate of tumor (Brandão and Castillo, 2016). Changizi et al. (2017) also proved that a significant decrease in NAA levels indicates the presence of high grade gliomas in these individuals. In a review article by Wang Q et al. in 2017 into the role of MRS as a diagnostic method of metastatic glioma, 17 studies with a total of 261 patients were evaluated. They showed that MRS can be used as a moderately precise instrument for differentiating highly malignant gliomas from metastases, and that the choline/NAA ratio has a high specificity for differentiation (Wang et al., 2017).

Therefore, grading of tumors with MRS, as a non-invasive diagnostic method, is an additional advantage. MRS is an important method for assessing the type and grade of tumors, and for targeting and evaluating response to treatment (Zimm et al., 1981). MRS is increasingly used to evaluate the brain neoplasms. This method demonstrates the biochemical composition and metabolism of various types of brain tumors (Kleihues et al., 1993), and not only can reveal abnormal findings in about 100% of brain tumors,

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but also can distinguish brain tumors and identify metabolic changes associated with tumor growth, malignancy grade, and treatment response (Dean et al., 1990). Findings of MRS from brain tumors show elevated levels of choline and reduced levels of NAA compared to the normal brain, indicating the increase in cellular tissue (Earnest et al., 1988 and Mabray et al., 2015). Since the tumors are heterogeneous and have necrotic nucleus and invasive margins of the brain surrounding tissue, the spectra are very diverse depending on the area examined by MRS (Janus et al., 1993). However, due to lesions diversity and heterogeneity, overlap between different tumor types, and analytical methods, it is often difficult for the physician to use only MRS for diagnosis; therefore, it should be used as a diagnostic assisting method.

In a study by Cheng et al. to investigate the role of MRS in the diagnosis of brain tumors, brain tumors were studied, 20 were lower-grade astrocytoma, one was anaplastic astrocytoma, 8 were glioblastoma, 6 were meningioma, and 2 were schwannoma. They used metabolites and tumor functions through MRS to examine tumors and concluded that MRS can be used to determine brain tumors and examine normal brain (Cheng et al., 1998). It is important to understand that MRS is highly sensitive to changes in metabolite levels, and recent studies have shown that MRS can detect tumors through evaluating the function and metabolites.

In the present study, the ROC (receiver operating characteristic) curve, AUC (the area under the ROC curve), and high sensitivity and specificity showed that brain tumors can be diagnosed through MRS.

5. CONCLUSION

Therefore, we can state that MRS is able to evaluate and grade brain tumors and should be a part of clinical diagnosis; however, further studies with larger sample sizes are necessary to achieve more conclusive results.

Conflicts of interest

There are no conflicts of interest between authors.

Financial resources

There are no financial resources.

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