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Application of Multivoxel 1H-Magnetic Resonance Spectroscopy in the Grading of Cerebral Glioma

Farnoosh Musavi[1], Sina Ehsani[1], Erfan Saatchian[1*]

1. Department of Medical Imaging, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Department of Medical Physics, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran.

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ABSTRACT

Introduction: Gliomas represent a considerable percentage of all diagnosed primary central nervous system tumors. A non-invasive access method, like magnetic resonance spectroscopy (MRS), is required for preoperative evaluation. So, the present study aimed to evaluate the application of Multivoxel 1H-MR Spectroscopy in the differentiation of high-grade from low-grade gliomas.

Material and Methods: 13 patients suspected of Cerebral Glioma, which already had been selected for brain surgery or biopsy, underwent a Multivoxel 1H-MR Spectroscopy. After the MRS exam, the pathology tests on specimens confirmed the grade of tumors. Then results were compared and represented as receiver operating characteristic (ROC) curves to show their sensitivity and specificity as well.

Results: Choline to creatine (Cho/Cr) and choline to N-acetyl-aspartate (Cho/NAA) were statistically lower in the low-grade group than in high-grade (p=0.007 and p=0.027, respectively) and N-acetyl-aspartate to creatine (NAA/Cr) was statistically higher in the high-grade group (p=0.037). But in border regions, only Cho/Cr and Cho/NAA were significant (P values= 0.19 and 0.22, respectively). With receiver operating characteristic (ROC) curves analysis, Cho/Cr had the best sensitivity and specificity in the differentiation of high-grade from low-grade gliomas in tumor area (92.86% sensitivity and 85.71% specificity) and this ratio had the best sensitivity and specificity in border regions of tumor (92.86% sensitivity and 78.43% specificity).

Conclusion: Metabolite ratios of low and high-grade gliomas (HGG) were significantly different from each other. Cho/Cr and Cho/NAA ratios can use as an internal reference for grading the glioma non-invasively in the tumor area and the border area of the tumor.

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Introduction

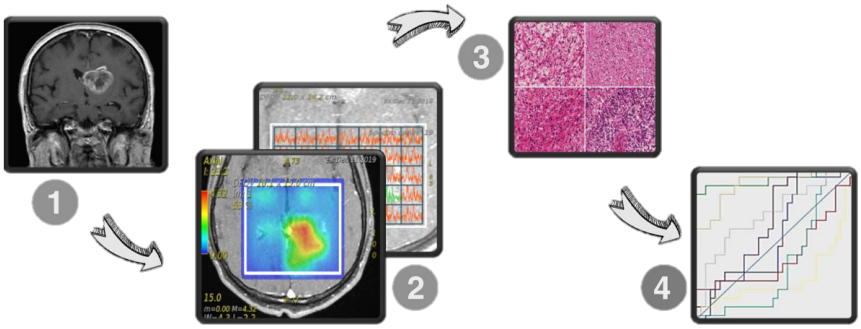
According to the tumor registry data, the incidence of brain tumors is remarkable worldwide [1] and tumors with glial sources are the most common primary brain malignancy [2]. A glioma is a type of brain tumor that arises from glial cells and as we know, glial cells support neurons with nutrients and help to maintain the blood-brain barrier. But in the case of pathology, they turn cancerous. However, different therapies exist, such as surgery which is usually flowed by radiotherapy or chemotherapy, and selecting the optimum treatment is crucial for achieving the best possible outcome [3]. Treatment planning and their prognosis are highly dependent on tumor grade [4] because every high or low-grade tumor has a different invasion and aggression [5]. For example, in higher grades, the survival is just limited to 14 months [6], because of their infiltrative growth nature and recurrence.

Glioma is graded by cell activity and its aggressions on a scale of I to IV, based on the World Health Organization (WHO) classification [7]. These consist of grade I – pilocytic astrocytoma, grade II – low-grade glioma (includes astrocytoma, oligodendroglioma, and mixed oligoastrocytomas), grade III – malignant glioma (includes anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic mixed oligoastrocytoma), and grade IV – glioblastoma multiform (GBM); high-grade glioma.

Currently, tumor grading has been done by histopathological tests like a biopsy, which is the golden standard of diagnosis. Despite its high accuracy and sensitivity, suffers from some disadvantages. For instant, because of the heterogeneity of tumors, sampling may not be enough. Also, it is limited in coverage [8] and accounts for an invasive technique that is hard to repeat. For all of these reasons, an adjacent procedure is required. Albeit magnetic resonance imaging (MRI) has excellent soft-tissue contrast, may cause mistakes, because it just relies on the enhancement of the tumor. Unfortunately, 10 % of GBMs and 30% of anaplastic astrocytoma show no enhancement in contrast enhancement (CE) MRI [9].

*Corresponding Author: Tel: +98-9157130137; Email: erfan.saatchian@yahoo.com

Graphical abstract



Study workflow;1) structural magnetic resonance imaging 2) multivoxel spectroscopy and making color map 3) histopathological tests 4) ROC analysis

Also, the enhancement of some lesions (like multiple sclerosis or abscess) in post-contrast images so resembles GBM and leads to misclassifications [10-12]. So, to access a high sensitivity and specificity in tumor grading a non-invasive evaluation requires. Multi-voxel spectroscopy can show the concentrations of the metabolites within the tumor and help to distinguish high-grade glioma (HGG) from low-grade glioma (LGG) for preoperative assessments. Also represents a color code map of tumor spatial spreading which helps to see the area of invasions. The majority of former studies used SVS (single-voxel spectroscopy), which was limited in coverage.

So, the present study aimed to evaluate the application of 1H-multivoxel spectroscopy in the grading of cerebral glioma as a quantitative and noninvasive approach. Histopathological specimen derived by biopsy is used as proof for MRS results.

Materials and Methods

Subjects

We conducted this study prospectively, from October 2019 to January 2020 at Emdadgaran medical imaging center, Tehran, Iran. Based on the specialist's prescription, 13 Patients who had been candidates for brain surgery or biopsy (Stereotactic) in the case of cerebral glioma (supratentorial glioma), undergone the 1H-multivoxel spectroscopy (also known as chemical shift imaging (CSI)) scan before any treatments like chemo/radiotherapy. No cost was imposed on patients for their CSI exam and a written informed consent form was given to all participants. Also, the right to leave the study whenever they want was given to them. Patients who had already experienced any brain surgery were excluded from the study. This study was approved by the ethics committee of Mashhad University of Medical Sciences (MUMS) and all patients signed a written consent to participate in the study.

Magnetic resonance spectroscopy

The 1.5 Tesla GE Signa Explorer (General Electric Medical Systems, Milwaukee, WI) scanner and quadrature (brain array 2) head coil was used in this study. CSI exam was a single slice multivoxel performed as a point-resolved spectroscopy sequence (PRESS - PROBE in GE), with the following parameters; TR/TE=8000/135 ms, FOV=20*20 cm, voxel box=5-7 * 7-10 depending on lesion size, slice thickness=5 mm). Outer volume saturation (OVS) bands were placed around the voxels too. Voxels placement was performed on axial T1-weighted post-contrast images (DOTAREM®-gadoterate meglumine). Each PRESS BOX, included both suspected and normal contralateral sides to ensure spectral accuracy. To minimize the susceptibility artifact and signal contamination from subcutaneous lipids, box positioning was done with caution.

Histopathological tests

Biopsy as the gold standard for diagnosis of glioma was done for all participants during complete tumor resection or Stereotactic biopsy. Then all specimens were categorized into 2 main groups according to the *WHO II criteria*; LGG (grade I & II) and HGG (grade III & IV).

Statistical analysis

The analysis was performed in SPSS software (SPSS, Inc., Chicago, IL, USA). P values of less than 0.05 were considered statistically significant. Mean±SD of each metabolite and their ratios were calculated for both tumoral and normal contralateral sides then the non-parametric Mann–Whitney U test was used to evaluate the significant difference in metabolites between low-grade and high-grade tumors. It should also be noted that to measure the ability of this modality in grading in the border areas of tumors, the values of metabolites at the tumor boundaries were also examined. Diagnostic value of Multivoxel 1H-MR Spectroscopy in comparison to histopathology tests determined by ROC curves. So, the area under the curve is considered as the overall accuracy of each metabolite ratio. Also, high-grade and low-grade were regarded as true positive (TP) and true negative (TN) respectively. Then the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were obtained for each metabolite ratio.

Results

As a whole, 13 patients (7 males and 6 females; 5-61 years old; mean age 31.38±16.5 years) were enrolled in the study. The result of tumor grading based on histopathology reports was; 6 high-grade (Grade III, n=3 – Grade IV, n=3) and 7 low-grade (Grade I, n=1 – Grade II, n=6). The main metabolites derived from the spectrum were; NAA, Cho, Cr, and MI. also, the sum of lactate and lipid peak (0.9-1.3 ppm) is considered LL. The Mean±SD of their concentrations and ratios are represented in Tables 1 and 2.

As represented in table 1, some metabolite ratios such as Cho/Cr and Cho/NAA were significantly higher in tumor sites in comparison to the normal-appearing contralateral side. Likewise, the NAA/Cr ratios of the tumoral area were significantly lower than those of the normal sides. In the same way, the comparison between high-grade and low-grade metabolites ratios showed remarkable results (Table 2). As expected, the Cho/Cr and Cho/NAA ratios were significantly higher in HGG and NAA/Cr ratios were seen significantly lower in high-grade only in the tumoral area while in the border area, there is no significant difference in this ratio between the two groups. Color code maps of metabolite ratios were also obtained and demonstrated as an example in figure 1.

Table 1. Metabolite ratios of glioma and normal-appearing contralateral brain parenchyma

	Glioma(n=13)	Normal	P values
	Tumor site (Mean±SD)	Contralateral brain parenchyma (Mean±SD)	
Cho/Cr	2.86±0.69	0.65±0.12	0.001*
Cho/NAA	2.38±0.45	0.41±0.06	0.009*
NAA/Cr	1.44±0.14	1.73±0.21	0.021*

* Statistical significance

Table 2. Metabolite ratios according to glioma grade and area

	Tumor			Borders			Normal		
	Cho/Cr (Mean±SD)	Cho/NAA (Mean±SD)	NAA/Cr (Mean±SD)	Cho/Cr (Mean±SD)	Cho/NAA (Mean±SD)	NAA/Cr (Mean±SD)	Cho/Cr (Mean±SD)	Cho/NAA (Mean±SD)	NAA/Cr (Mean±SD)
Low-grade	1.72±0.49	1.47±0.35	1.89±0.15	1.17±0.62	0.77±0.12	1.85±0.08	0.91±0.17	0.51±0.07	1.56±0.13
High-grade	4.01±1.32	3.29±1.12	1.80±0.19	1.97±0.52	1.71±0.41	1.69±0.11	0.75±0.09	0.28±0.05	1.37±0.08
P values	0.007*	0.027*	0.037*	0.019*	0.022*	0.523	0.802	0.623	0.754

* Statistical significance

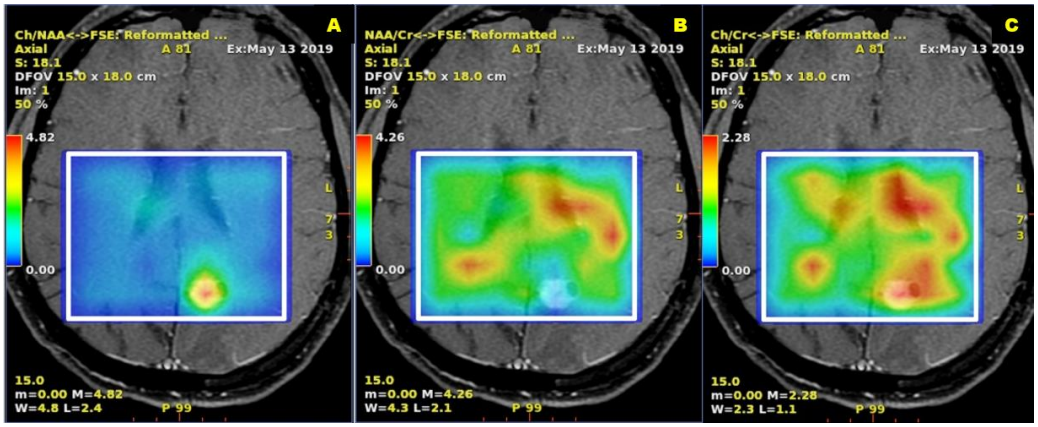


Figure 1. A 54-year-old man with glioblastoma multiforme. Color code maps of metabolites ratios (A) show Cho/NAA (B) NAA/Cr (C) Cho/Cr. The colors used in this spectral map indicate that the higher the level of metabolites, the redder will prevail.

Table 3. Different metabolite ratio's sensitivity, specificity, PPV, and NPV in predicting tumor grade

Metabolites ratio	region	Cutoff	Sensitivity	Specificity	PPV	NPV	AUC ± SE
Cho/Cr	tumor	1.82	92.86	85.71	0.94	0.67	0.882±0.06
Cho/NAA		1.5	85.71	64.29	0.89	0.33	0.862±0.07
NAA/Cr		0.7	40.32	57.14	0.89	0.33	0.561±0.11
Cho/Cr	border	1.49	92.86	78.43	0.94	0.67	0.918±0.05
Cho/NAA		0.96	64.29	71.43	0.94	0.55	0.729±0.10
NAA/Cr		0.56	45.82	64.29	0.89	0.33	0.505±0.11

PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; SE: standard error

It's clear that as we move from the central area of the tumor to the margins, the gradients of color changes and invasion of the tumor are predictable. Using this blue-to-red color scale, by increasing the value of metabolites, the voxel color of that area will be displayed with a color closer to red, and also by decreasing the concentration of metabolites, this area will be displayed with a color closer to blue.

The ROC curves analysis revealed that Cho/Cr and Cho/NAA are significantly powerful in predicting tumor grading in tumoral and marginal areas but NAA/Cr had poor sensitivity in this matter (Table 3).

Discussion

Before performing an effective treatment, it is necessary to differentiate the glioma's grade which can be very helpful in the determination of treatment planning. Also, could be interpreted as a predictor for the outcome. a non-invasive and quantitative method like Magnetic resonance spectroscopy can play an important role in determining the grade of glioma before treatment [13]. In HGG, especially grade IV, the image on the weight of T2 has special signs like central hyperintense core, peripheral edema, and lateral region with normal or intensified signal intensity, or in the image on the weight of T1, irregular intensification of the tumor area with an injection of contrast agent can be seen [14]. However, the determination of glioma grade using MRI images is not reliable. In many cases contradictory results have been reported and, in some conditions, can lead to incorrect grading [15]. Advanced techniques of magnetic resonance imaging such as magnetic resonance spectroscopy (MRS) can play an important role in improving the diagnostic accuracy of glioma grade [16]. Proton magnetic resonance spectroscopy, which non-invasively provides biochemical information in the tumor area, in some cases, has been used to determine the grade of glioma, although its accuracy has been controversial [17]. In general, MRS cannot replace biopsy and histopathological confirmation. However, in cases where biopsy is not possible, MRS can provide biochemical information on changes in tumor tissue metabolites [18]. Using the multi-voxel technique makes it possible to obtain spectra simultaneously from several areas, including the tumor area, the tumor border, and the surrounding healthy tissue, this is important in cases where there is no sign of a tumor in conventional imaging images. In some cases, perfusion and diffusion MRI have been reported as effective techniques in determining the grade of glioma, which can be combined with these techniques to achieve higher accuracy and precision in diagnosis [19]. In previous studies in this field, mainly single-voxel MRS has been used [20]. Using the single-voxel technique due to the limited use of small voxel size, it is difficult to obtain information with high accuracy, especially in the border areas of the tumor. To overcome this limitation, the use of the multi-voxel technique can be useful. The main findings in this study were these cases: 1) Significant differences in choline to creatinine ratios, and choline to N-acetyl aspartate between the high-grade and LGG groups, this difference was also observed at the tumor boundaries 2) Using ROC curve analysis, cut-off values were calculated and the sensitivity and specificity of metabolic ratios such as choline to creatine by magnetic resonance multiplexing technique in differentiating glioma grades, especially in border areas, were obtained 3) The diagnostic accuracy of the ratio of choline to creatine was higher than the ratio of choline to N-acetyl-aspartate and N-acetyl-aspartate to creatine.

Based on our findings in the present study, couples of metabolite differences such as *Cho*, *Cr*, and *NAA* were seen as significant in low and high-grade tumors. For Choline we ought to infer, Cho as a pointer for cell membrane turnover and in relationship with the cellular thickness of tumors can hoist in neoplasms, and inflammation and display around 3.2 ppm and 3.52 ppm. [13-14]; Creatine is presented at 3.0 ppm chemical shift and is found in tissues that are metabolically active where it is imperative in capacity and exchange of energy and is transcendently utilized as a helpful inner reference, in spite of the fact that it diminishes in HGG. Of note, it isn't noticeable in cerebral metastases and nonattendance of a creatine peak in an upgrading cerebral mass proposes metastasis over glioblastoma. [15-16]. the resonance of NAA is 2.0 ppm with 8-10 mM concentration in a normal situation [17]. NAA is found in high concentrations in neurons and could be a marker of neuronal viability. It is in this manner decreased in any prepare that annihilates neurons, such as high-grade tumors. [18].

In the present study, the capability of the multi-voxel magnetic resonance spectroscopy technique in determining the glioma grade was observed. Tumor boundary values also confirmed this ability, and Cho/Cr ratio was a reliable measure of glioma grade. The diagnostic quality of 95.37% was obtained in the multi-voxel magnetic resonance spectroscopy technique in all patients which indicates the correct position of saturated bands, the correct position of voxels, and proper shimming. Ensuring the standard level of metabolites in the tissue is one of the challenges in MRS. To obtain reliable and reportable information, normal metabolic levels in the normal parenchymal region of the brain were measured. In the present study, no significant change was observed in the level of normal tissue metabolites in HGG and LGG. The ratios of choline to creatine, n-acetyl aspartate to creatine, and choline to n-acetyl aspartate in the parenchymal area were normal for low grades 0.91, 1.56, and 0.51, and for high grades were 0.75, 1.37, and 0.28 which are considered insignificant like in previous studies [21-27]. ROC analysis was performed to obtain the optimal cutoff values [28]. In the present study, using statistical methods, the optimal cutoff was determined for each metabolic ratio to distinguish the high grade from the low grade in the tumor area and the border area. These results were similar to previous studies [29]. At cutoff 1.82 for choline to creatine ratio, AUC values for tumor

and border region were 0.882±0.06 and 0.918±0.05, and sensitivity and specificity for tumor and border regions were 92.86, 85.71, 92.86, and 78.43, respectively. A study reported lower AUC in the tumor (0.772±0.11) and higher AUC in the normal area (0.991±0.12) as reported in several studies, there is a statistically significant relationship between magnetic resonance spectroscopy and biopsy specimens [30, 33]. However, Tomas et al. reported the highest sensitivity and specificity in the ratio of choline to N-acetyl-aspartate in recurrence glioblastoma (95.23% sensitivity and 89.52% specificity). Besides, they have reported low sensitivity and specificity for the ratio of choline to creatine (86.21% sensitivity and 71.28% specificity) [31]. In contrast, our results showed that the ratio of choline to creatine is the best criterion for distinguishing between HGG and LGG (92.86% sensitivity and 85.71% specificity) nevertheless Ando et al reported sensitivity and specificity of 71.23 and 83.52) in CUTOFF 1.5 (despite observing an increase in the ratio of choline to creatine in high-grade samples. This difference in sensitivity and specificity is probably due to differences in the details of the imaging technique and differences in the number of samples. In the present study, by using the appropriate voxel volume, the system's ability to identify differences in grades in the border area was also examined and the ratio Cho/Cr had the appropriate sensitivity and specificity to differentiate glioma grades (92.86% sensitivity and 78.43% specificity).

Conclusion

The present study aimed to evaluate the application of Multivoxel 1H-MR Spectroscopy in the differentiation of HGG from LGG. With ROC curves analysis, Cho/Cr had the best sensitivity and specificity in the differentiation of HGG from LGG in the tumor area (92.86% sensitivity and 85.71% specificity) and this ratio had the best sensitivity and specificity in border regions of tumor (92.86% sensitivity and 78.43% specificity). These biomarkers can be perfectly used in preoperative tumor assessments of glioma grading, especially in borders of tumors which is a controversial topic. The color code map of each metabolite's ratios gives insight through the monitoring of the area under invasion, which helps to predict the next level of involvement.

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