Evaluation of Two Post-Processing Analysis Methods of Proton Magnetic Resonance Spectroscopy in Glioma Tumors

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ABSTRACT

Background: Magnetic resonance spectroscopy (MRS) is a non-invasive diagnostic and the neuroimaging method of choice for the noninvasive monitoring of brain metabolism in patients with glioma tumors. ^{1}H-MRS is a reliable and non-invasive tool used to study glioma. However, the metabolite spectra obtained by ^{1}H-MRS requires a specific quantification procedure for post-processing. According to our knowledge, no comparisons have yet been made between spectrum analysis software for quantification of gliomas metabolites.

Objective: Current study aims to evaluate the difference between this two common software in quantifying cerebral metabolites.

Material and Methods: In this analytical study, we evaluate two post-processing software packages, java-based graphical for MR user interface packages (jMRUI) and totally automatic robust quantitation in NMR (TARQUIN) software. ^{1}H-MRS spectrum from the brain of patients with gliomas tumors was collected for post-processing. AMARES algorithms were conducted to metabolite qualification on jMRUI software, and TARQUIN software were implemented with automated quantification algorithms. The study included a total of 30 subjects. For quantification, subjects were divided into a normal group (n=15) and group of gliomas (n=15).

Results: When calculated by TARQUIN, the mean metabolites ratio was typically lower than by jMRUI. While, the mean ratio of metabolites varied when quantified by jMRUI vs. TARQUIN, both methods apparent clinical associations.

Conclusion: TARQUIN and jMRUI are feasible choices for the post-processing of cerebral MRS data obtained from glioma tumors.

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Keywords

Proton Magnetic Resonance Spectroscopy; Glioma; Software Validation

Introduction

Glioma tumors are differently graded in terms of major malformations in adults [1]. Diagnosis and grading them with high accuracy in a non-invasive manner is very important to determine a correct treatment plan and, in some cases, to prevent aggressive surgical treatment [2, 3]. Grade histological information and tissue type in brain tumors are important for clinical management of patients, which have a close relationship with patients' survival probability. However, there are two major limitations in the grading and histologic diagnosis of brain tumors, especially in Glioma. Initially, the sampling error through Stereotactic method can be mentioned. In some cases, the sample cannot be considered as representative of the total volume of the tumor. Moreover, it is difficult to correctly

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evaluate the remaining tumor tissue after cytoreductive surgery [4]. Contrast-enhanced magnetic resonance imaging (MRI) is currently used as a gold standard method to guide the biopsy by neurosurgeons. However, the results of this technique are sometimes ambiguous [5]. MRI is recognized as the most common imaging modality in the evaluation of intracranial tumors [6]. MRI is an excellent method for structural and anatomic diagnosis of the brain, but it does not provide information on vascularity, metabolism, and cellularity that are important for tumor diagnosis and grading [7]. For this reason, the use of MRI advanced techniques such as MRS is important. Proton magnetic resonance spectroscopy (^{1}H-MRS) is a noninvasive method which can provide information about neuronal integrity, cell proliferation, cell degradation, and energy metabolism in brain tissue [8]. In the brain, ^{1}H-MRS can be used to calculate various metabolites like N-acetyl aspartate (NAA), choline compounds (Cho), creatine and phosphocreatine (Cr), lactate and lipid [9]. ^{1}H-MRS can play an important role in making brain tumor diagnosis more accurate, which can represent the metabolic changes before observing the structural change on MRI [10]. The ^{1}H-MRS range is expanding at the clinic [11], but using this method requires a proper post-processing process to properly quantify the spectrum obtained from the test [12]. Spectra of magnetic resonance spectroscopy are analyzing and quantifying to determine cerebral metabolites using two types of software packages: a java-based version of the MR user interface package (jMRUI v. 5.0) [13] and the totally automatic robust quantitation in nuclear MR (TARQUIN) algorithm [14]. JMRUI is a highly flexible software package that provides a wind range of algorithms for ^{1}H-MRS signal processing, and includes preprocessing tools and peak fitting. TARQUIN is a new algorithm, free to use and change under the general public license, accessible on computer platforms and designed to provide rapid and automatic metabolite quantitation. In a fully automated operation, baseline interference is minimized by point truncation and HSVD water removal [15], thus eliminating user variability. Point truncation removes the very early points of the free induction decay, which includes very large signals that are difficult to model and the last ones that only contain noise. However, studies have been conducted to assess the sensitivity of quantification approaches in certain diseases [16, 17], but no report evaluated the quantification models in the analysis of Glioma tumor metabolites according to available data. The purpose of this research was to compare two models of ^{1}H-MRS data analysis to identify changes in the metabolite in Glioma tumors.

Material and Methods

In this analytical study, the inclusion criterion was people whose Glioma tumor was confirmed by histologic information. Two post-processing methods of java-based graphics for MR user interface packages (JMRUI) and fully automated robust quantitation in NMR (TARQUIN) were used to quantify the H-MRS results. Data analysis was performed on 15 patients with glial brain tumor and 15 control cases. In this research, the differences in metabolism quantification were investigated using these two models in Glioma tumor. Each subject gave their written informed consent after the procedure was fully explained and understood.

^{1}H-MRS

^{1}H-MRS imaging was performed on a 1.5-T scanner (Siemens MAGNETOM Verio; Siemens Medical Systems, Erlangen, Germany) at Qaem Hospital, Mashhad, Iran. In order to ensure a precise location of the voxels, T1 weighted brain MR images were taken on the sagittal, coronal and axial planes and T2 weighted images were collected to remove any apparent cerebral pathology. A manual of procedures for MRS spectroscopy (MRS) was used to ensure that all MRS exams were carried out using similar operating settings. Voxels were put on areas of the brain that appeared anatomically abnormal in images T1 and T2 for glioma group and normal areas for control group. Subjects were told to lie down in a supine position. The Circular polarized (CP) head coil was then placed over the head for both image and ^{1}H-MRS acquisition. First, localiza-

tion images were obtained, then T2 weighted images were obtained in the coronal, axial and sagittal planes (Echo time (TE)=30 ms, repetition time (TR)=1500 ms, and slice thickness =6 mm) to ensure voxel localization. The automatic shimming protocol available on MRI was performed. Later, single-voxel ^{1}H-MRS acquisition for metabolites assessment was done with point resolved spectroscopy (PRESS) pulse sequence (TE=43 ms, TR=2000 ms, Number of signal averages =156, Data point =2048, and band width=2500 Hz) with water suppression. Voxel size of 20×20×20 mm^3 was carefully placed in glioma tumor. Cerebral metabolites N-acetyl aspartate (NAA), Myo-inositol (Mi), and Choline (Cho) have been measured and expressed as creatin ratios (Cr). All spectra were visually checked by an experienced physicist to ensure acquisition efficiency and the acquisition was repeated in cases with low signal-to-noise ratio.

Analysis models

In this study, an advanced method for accurate, robust, and efficient spectral fitting (AMARES algorithm) was applied for spectra fitting in time domain [18] in JMRUI software. JMRUI provides two-stage time domain analysis of in vivo MRS data. Pre-processing involves user interaction with the HLSVD / HLSVDPro filters to remove residual water molecules [18] and the Cadzow function is used to filter the signal [12]. This manual pre-processing step will impact model fitting results and hence affect the accuracy of the signal quantification. For all analyses in this report, the same prior knowledge of the approximate peaks was input, with peaks set at the following positions [19]; 2.0 parts per million (ppm) and 3.9 line width [LW (Hz)] for NAA, 3.01 ppm and 4.9 LW for Cr, 3.2 ppm and 4.9 LW for Cho and 3.54 ppm and 4.9 LW for mI. TARQUIN has more advantages than jMRUI since it enables automatic post processing for spectra metabolites, and wide ranges of ^{1}H-MRS data can be accepted. TARQUIN is an algorithm which suits a time domain by a least square projection used to determine signal amplitude. Notable features are that TARQUIN imposes soft constraints with basis in-vivo spectra data set that includes macromolecules, lipids, and metabolites to avoid possible over fitting of spectrum [14, 20]. This algorithm was found to be suitable for comparison with LC model using both clinical and simulated data [14]. These approaches quantified the cerebral metabolites N-acetyl aspartate (NAA), Myo-inositol (Mi) and Choline (Cho) and reported as ratios to Cr.

Statistical analysis

All data is expressed as mean±standard deviation (SD), unless state otherwise. All statistical analyzes were carried out on version 17.0 of SPSS (SPSS Inc., Chicago). Comparisons of metabolite ratio in normal tissue and glioma tumor were performed between each software package using a paired sample t-test. The relationship between signal intensity from each of the metabolites obtained by jMRUI and TARQUIN was assessed using a Pearson correlation. $P<0.05$ was considered as statistically significant.

Results

Comparing the quantitative models jMRUI and TARQUIN

The representative ^{1}H-MRS spectra from normal tissue and glioma tumor in both programs are shown in Figures 1 and 2. The water suppressed spectra show the peaks at the following chemical shifts: choline (3.2 ppm), creatine (3.01 ppm), NAA (2.0) and mI (3.54). Cho/Cr, NAA/Cr and mI/Cr signal intensities were calculated. The comparison of metabolites between normal group and glioma group has shown in Figure 3. Figure 3 reveals increasing choline in both algorithms as having a similar pattern, and this tendency was found to be statistically significant across the software packages and it is significantly higher in JMRUI. However, both methods could be able to recognize the differences between normal tissue and glioma tumor. Cerebral metabolite ratios (CMRs) for NAA/Cr and Cho/Cr were significantly higher when quantified using the jMRUI software. Table 1 displays variation coefficients (CoVs) and confidence intervals of 95 percent for each CMR by algorithm. In general, these were lower for

TARQUIN quantified NAA/Cr, Cho/Cr and mI/Cr. When quantified using jMRUI, mI/Cr displayed considerably more variation than the other two cerebral metabolite ratios (CMRs). Generally, both methods were able to detect Glioma metabolism changes compared to healthy tissues, which were specified by the significant ratios of NAA/Cr and Cho/Cr. However, the significant differences of metabolites in the comparison of both methods indicate a change in the results by performing a unique procedure, although the clinical goals for diagnosis of glioma will be achieved in both methods. Table 2 displays the Pearson correlation coefficients for CMR values.

Discussion

In this research, Glioma tumor data ^{1}H-MRS were analyzed using two metabolite quantification models namely jMRUI and TARQUIN. This is the first research to evaluate these two models in Glioma tumors. The difference of the quantified values of metabolites was observed by these two models in glioma tumors, which is generally shown as the difference in Cho/Cr ratio. Both models were able to identify the changes caused by Glioma tumor to normal tissue ratio, indicating that both models were able to identify tumors from normal tissue. The metabolites values in the TARQUIN model are estimated to be lower than jMRUI in a study that examined the differences between these two methods in the quantification of metabolites in HIV-infected patients [21]. In the present research, NAA/Cr and Cho/Cr ratios showed significant differences in quantification by these two models in glioma tumors. The observed differences can be attributed to the fully automated algorithm of the TARQUIN method because in this method the user's skill in quantification is eliminated. In the JMRUI technique, some steps are done manually for example Water peak suppression and noise removal of the MRS spectrum should be done manually and this user intervention can affect the final quantification of the spectrum, which will influence the test results. The results

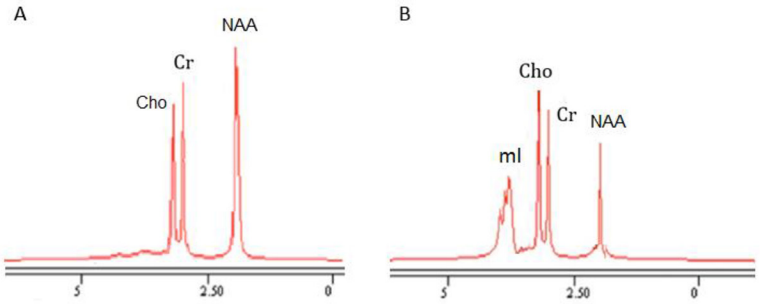

Figure 1: Examples of Magnetic Resonance Spectroscopy (MRS) spectra in java-based graphical for MR user interface packages (jMRUI) model. (A) Normal tissue (B) Glioma tumor.

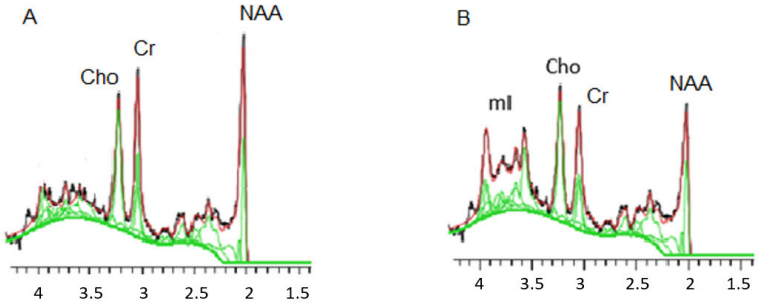

Figure 2: Examples of Magnetic Resonance Spectroscopy (MRS) spectra in totally automatic robust quantitation in NMR (TARQUIN) model (red) with providing individual peaks (green). (A) Normal tissue (B) Glioma tumor

indicated that the metabolite ratios in Glioma tumors would change using two different models. However, there was no significant change that affects clinical diagnosis and in other words, impairs the diagnosis of glioma tumors from healthy tissue. Further studies will ensure the accuracy and reproducibility of these results.

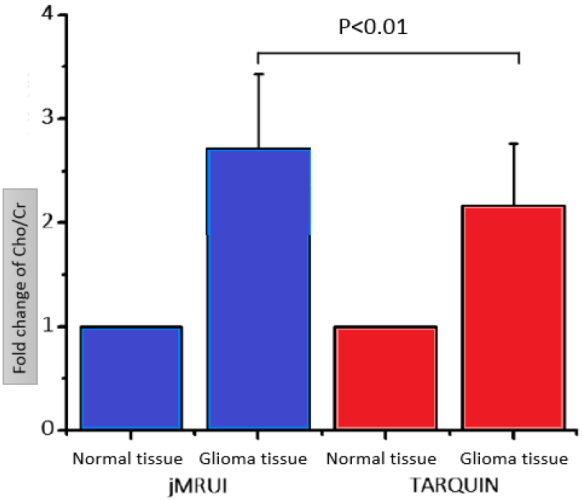

Figure 3: Changes of signal intensity of Choline/Creatine in java-based graphical for MR user interface packages (jMRUI) and totally automatic robust quantitation in NMR (TARQUIN) software packages in both group.

Conclusion

This study reveals the differentiation of metabolites results from Java-based graphical for MR user interface package (jMRUI) and totally automatic robust quantitation in NMR (TARQUIN) software packages. It can be asserted that both programs can be used for glioma tumor quantification study, but it should be considered that JMRUI software will show higher values in glioma tumor.

Authors' Contribution

E. Saatchian analyzed the data and wrote the article results, method and discussion. S. Ehsani gathered the magnetic resonance spectroscopy and MRI data and wrote the article introduction. A. Montazerabadi supervised the physique-based analysis of gathered data. All the authors read, modified, and approved the final version of the manuscript.

Table 1: Transitions in parameters of cerebral metabolite ratio by tissue and software.

Grade of glioma	Algorithm	Metabolite ratio			
		NAA/Cr	Cho/Cr	ml/Cr	NAA/Cho
Normal tissue	TARQUIN	1.8 (0.26)	0.6 (0.045)	0.045 (0.0032)	2.75 (0.31)
	jMRUI	2.01 (0.2)	0.85 (0.025)	0.086 (0.0042)	2.96 (0.35)
Glioma tumor	TARQUIN	1.19 (0.24)	2.03 (0.23)	1.12 (0.19)	0.83 (0.01)
	jMRUI	1.45(0.24)	2.59 (0.21)	1.62 (0.32)	1.01 (0.03)

NAA: N-acetyl aspartate (NAA), Cr: Creatine, Cho: Choline compounds, TARQUIN: Totally automatic robust quantitation in NMR, jMRUI:java-based graphical for MR user interface packages

Table 2: Pearson's correlations of cerebral metabolite ratios by normal tissue and glioma tumor.

Metabolite ratio	Normal tissue		Glioma	
	r	*P*-value	r	*P*-value
NAA/Cr	0.15	0.07	0.73	>0.01
Cho/Cr	0.35	0.26	0.62	>0.01
ml/Cr	0.12	0.66	0.19	0.32
NAA/Cho	0.41	0.38	0.35	0.11

NAA: N-acetyl aspartate (NAA), Cr: Creatine, Cho: Choline compounds

Ethical Approval

The Ethics Committee of the Faculty of Associated Medical Science at Mashhad University of Medical Science approved this report (Ethic cod: IR.MUMS.MEDICAL.REC.1398.599).

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Conflict of Interest

None

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