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Surgery Outcome and Adjuvant Chemo-Radiotherapy Response Evaluation in High-grade Glioma with Magnetic Resonance Spectroscopy (MRS)

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ABSTRACT

Introduction: Accurately identifying the remaining tumor extent following glioma near-total or subtotal resection is crucial for determining appropriate treatment options. We aimed to evaluate the surgery outcome and responses to chemoradiation therapy (CRT) in glioma patients with multiparametric magnetic resonance imaging (MRI).

Material and Methods: This prospective study involved 12 patients diagnosed with High-grade glioma. Magnetic resonance spectroscopy (MRS) parameters (Cho/Cr and Cho/NAA) and structural parameters (enhanced lesion volume, non-enhanced lesion volume) were measured to evaluate the surgery outcome with the residual tumor and response to CRT. The imaging process was performed in two stages: once after surgery, before radiotherapy, and once one month after radiotherapy.

Results: The study found that the ROI centers of the Cho/NAA > 1.7 regions had the highest level of agreement and the least separation from the structural ROI. In the case of Cho/Cr, the most significant similarity was seen at a value above 1.5. In the second stage of the study, by comparing metabolic and structural data before and after chemo-radiotherapy treatment, no significant changes in metabolites were observed alongside a substantial decrease in structural parameters in the group with high conformity of structural ROI and metabolic ROI. Still, a significant increase in metabolic ratios was observed in the group with low conformity.

Conclusion: The study's results suggest that employing MRS mapping is a suitable approach for detecting residual tumors and predicting the effectiveness of chemoradiation therapy in glioma patients, in contrast to relying exclusively on conventional MR imaging features.

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Introduction

Gliomas, the most frequently occurring brain tumors, are identified by specific cell types and include glioblastoma, a malignant form of glioma [1]. The primary treatment for high-grade gliomas is typically maximum surgical resection. Complete removal of the entire tumor is often not feasible due to factors such as tumor size, location, and proximity to critical areas of the brain. The presence of any remaining tumor after surgery is associated with a patient's survival [2-3]. As a result, it impacts the decision-making process for post-operative re-resection or the development of an effective treatment plan [4]. Furthermore, chemoradiation therapy is a commonly used treatment for brain tumors, and evaluating how tumor cells react to radiation is an essential consideration in the treatment plan, necessitating post-treatment care for all patients [5]. Despite progress in diagnosing and treating gliomas, evaluating treatment effectiveness is inadequate and requires additional research [6].

Utilizing imaging for tumor measurement and evaluation offers the advantage of streamlining assessment time and reducing costs [7]. The response evaluation criteria initially proposed by Macdonald et al. in 1990 and later refined by the Response Assessment in Neuro-Oncology (RANO) working group were established as radiological assessment techniques for managing high-grade gliomas through magnetic resonance imaging (MRI). This criterion, incorporating volumetric measurement, has evolved

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into the prevailing neuroimaging method, as revised in 2010 [8]. Structural MRI is frequently utilized to identify the extent of tumor growth. Among various imaging characteristics, contrast-enhanced lesions highly indicate high-grade gliomas, as they strongly correlate with the tumor [9].

Conventional MR imaging features are unreliable for indicating any remaining tumor. Therefore, it is necessary to utilize advanced imaging techniques such as molecular spectroscopic imaging, which is crucial for evaluating tumors following surgery. Magnetic resonance (MR) spectroscopy is a non-invasive diagnostic examination used to detect biochemical alterations in the brain, particularly the existence of tumors [10]. Studies have shown that changes in metabolite concentration ratios, such as Cho/Cr and Cho/NAA, are closely associated with the characteristics of the tumor, and it is used as a marker to indicate the extent of the tumor [11,12].

This study aimed to compare the identification of any remaining tumor using various thresholds in MRS parameters with MR imaging features of T1-weighted contrast enhancement after tumor removal to determine the differences between the metabolic-based and MRI-based definitions of the tumor. Additionally, the study aimed to find a suitable method to assess the response of high-grade glioma cells to radiation therapy using MRS indices and the RANO criteria.

Materials and Methods

Study design

All procedures were performed under a protocol approved by the Institutional Review Board of Baqiyatallah University of Medical Sciences. Written informed consent for participation and the subsequent use of imaging data was obtained from the entire patient cohort. The research involved individuals who were referred to Emam Reza Hospital's oncology department between May 2023 and June 2024 with suspected glioma cell-type tumors. Twelve adult patients with glioma, with an average age of 40 years (mean ± SD), who had undergone near-total or subtotal tumor resection, were enrolled in the study. Five of the patients had undergone a stereotactic biopsy. All participants had been newly diagnosed with glioma and had not previously undergone head surgery, radiotherapy, or chemotherapy. The imaging process was performed in two stages: after surgery and one month after radiotherapy.

Stage One: One Week After Surgery

MRS peaks were measured, which included choline (Cho), creatine (Cr), and N-Acetyl Aspartate (NAA). Furthermore, the Enhanced Lesion Volume (ELV) and Non-Enhanced Lesion Volume (NELV) were calculated for all patients. A metabolic map was created for particular metabolite ratios. Postcontrast T1 or T2-weighted images were utilized to outline the region of interest (ROI) and measure the volume of enhanced and non-enhanced lesions. The metabolic ROI was determined using two different thresholds for Cho/NAA (> 1.7 and 2) and Cho/Cr (> 1.5 and 2). (Figure 1)

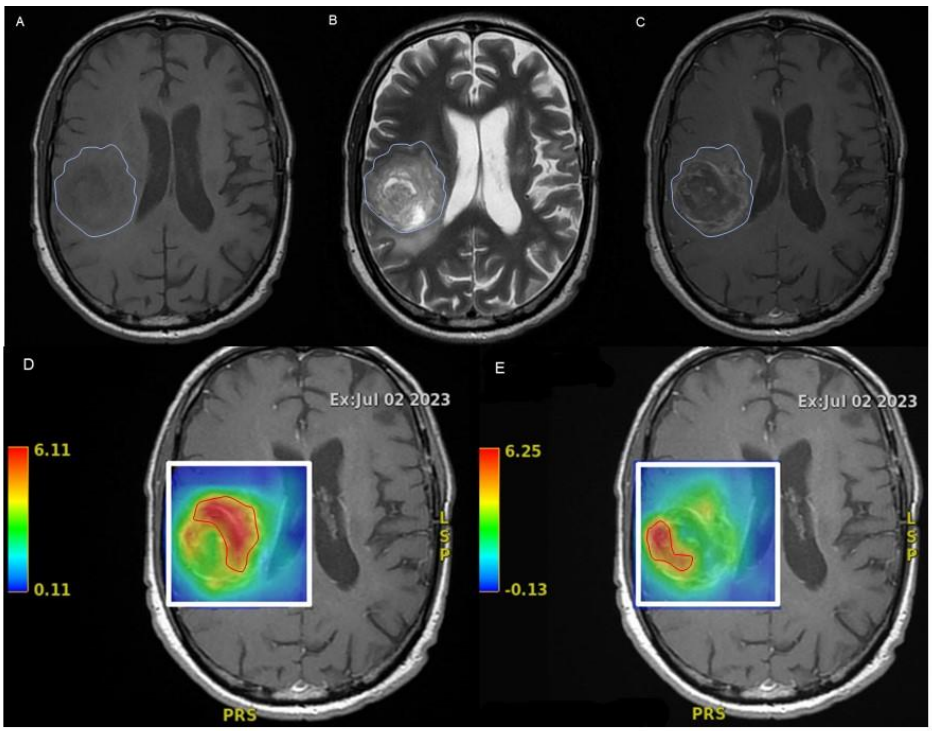

Figure 1. Structural magnetic resonance imaging of the brain in patients and structural contouring of ROIs on A) T1-weighted image, B) T2-weighted image, C) T1 post-Gd image (blue lines). Metabolic ROIs D) Cho/Cr, C) Cho/NAA with different thresholds (red lines).

Stage Two: One Month after Radiation Therapy

All protocols executed in stage one were repeated in stage two to generate comparable values, and parameters related to magnetic resonance spectroscopy techniques and structural parameters were calculated. These parameters were used to evaluate the response to radiotherapy in individuals with different matches of metabolic and structural regions of interest.

Imaging Protocol

The tests were conducted in two stages with a 1.5T MRI machine (Siemens Healthcare, Erlangen, Germany) outfitted with a 20-channel head coil. Traditional brain MRI sequences included axial T2 (TR/TE = 3000/100, FOV =256x2256x256 mm^3) and post-gadolinium axial T1 (TR/TE = 500/15 ms, FOV = 256x256x256 mm^3) as baseline images for the MRS Protocol.

MRS protocol and analysis

Before contrast injection, multi-voxel 3D MRS imaging (5×5×5 mm^3) was carried out on three reference images using a point-resolved spectroscopy pulse sequence (PRESS) over the volume of interest (VOI). To minimize spectral contamination from extracerebral lipids, the voxel of interest (VOI) was positioned to exclude the skull and subcutaneous fat, a strategy augmented by outer-volume saturation bands. Water suppression was achieved using a chemical shift selective (CHESS) technique. Spectra were acquired with a repetition time (TR) of 3000 ms, an echo time (TE) of 250 ms, a 150 × 150 mm^2 field of view (FOV), 10 signal averages, and a 10 mm slice thickness, for a total scan time of 12.6 minutes. Post-processing was performed in TARQUIN (v4.3.10) [13], where raw data were fitted to a basis set containing N-acetylaspartate (NAA), creatine (Cr), and choline (Cho). From the resulting signal amplitudes, key metabolic ratios (Cho/NAA, Cho/Cr, and NAA/Cr) were calculated for each voxel.

Radiation Therapy Protocol

All GBM patients selected for the study were treated with an average total dose of 60 Gy, administered in 2 Gy fractions, along with TMZ (75 mg per body weight area orally daily), followed by adjuvant TMZ (150–200 mg/m2 orally for five days during each 28-day cycle).

Statistical Analysis

After acquiring the first imaging data, the statistical Dice test was performed to examine the level of concordance between metabolic and structural central areas. Then, a threshold for high and low concordance was defined. Following the acquisition of the second phase imaging data, the Wilcoxon statistical test was used to assess the impact of concordance on metabolic and structural changes. The data was analyzed using SPSS Version 22 (IBM, Portsmouth, UK) software, and a significance level of $p < 0.05$ was applied to all tests.

Results

Surgery outcome

The average dice coefficient values for comparing the structural ROI and metabolic ROI of Cho/NAA and Cho/Cr, as well as the calculated distance between the centers of the structural ROI and metabolic ROIs, are presented in Table 1. Additionally, we computed the size of the structural ROI and all metabolic ROIs. The area of Cho/NAA in six patients exceeded the structural ROI. (Figure 2)

Table 1. The average Dice coefficients between various metabolic and structural regions of interest and the mean distance in millimeters (mm) between the center of the structural ROI and the metabolic ROIs

Metabolic Ratios	Cho/NAA		Cho/Cr	
Threshold	1.7	2	1.5	2
Dice coefficient	0.55 ± 0.22	0.48 ± 0.19	0.40 ± 0.18	0.34 ± 0.21
Distance from structural ROI (mm)	9.51 ± 3.2	9.83 ± 3.6	12.2 ± 4.6	10.81 ± 3.8

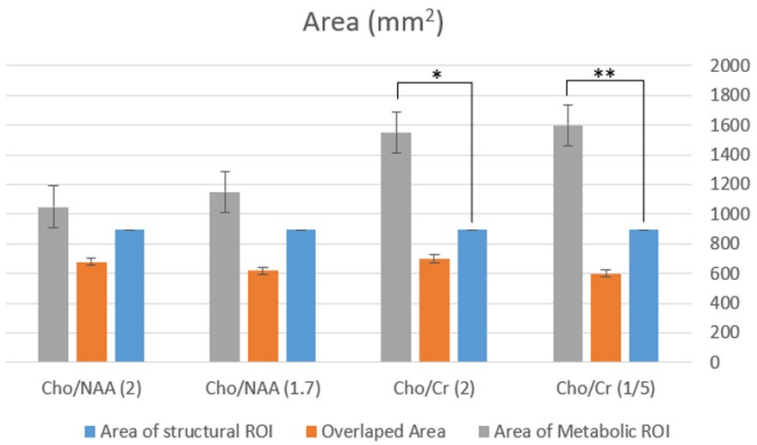

Figure 2. The plot illustrates the average values along with the standard error for the area of metabolic ROIs, the area of structural ROIs, and the overlapping area between different thresholds of metabolic ROI and imaging structural ROIs. Significance levels are denoted by * for p < 0.01 and ** for p < 0.001.

Table 2. Metabolic ratio and mean volume of the tumor evaluation pre- (after surgery) and one month after chemo-radiation therapy.

Patient Group	Parameters	After Surgery and before CRT (Mean±SD)	After CRT (Mean±SD)	P-value
HC	Cho/Cr	1.74 ± 0.3	1.93 ± 0.1	0.153
	Cho/NAA	1.88 ± 0.2	2.12 ± 0.3	0.265
	ELV (cm^3)	59.6 ± 1.5	42.3 ± 1.2	0.021*
	NELV (cm^3)	48.7 ± 1.6	37.5 ± 1.4	0.041*
LC	Cho/Cr	1.69 ± 0.4	2.61 ± 0.1	0.001**
	Cho/NAA	1.92 ± 0.5	2.75 ± 0.3	0.001**
	ELV (cm^3)	61.5 ± 1.3	58.3 ± 1.3	0.241
	NELV (cm^3)	49.1 ± 1.7	45.9 ± 1.5	0.352

* P-value < 0.05 ** P-value < 0.001
HC: Patients with High Conformity between structural and metabolic ROI
LC: Patients with Low Conformity between structural and metabolic ROI

Chemo-Radiation Response Evaluation

Based on the data obtained in the previous stage, a criterion was defined to assess the level of alignment between the metabolic and structural regions. For this purpose, the patients were divided into two groups: those with high alignment and those with low alignment. Individuals with a dice coefficient above 0.5, displacement of fewer than 10 millimeters, and significant differences between the choline and creatine areas were placed in the high conformity (HC) group. In contrast, those with lower values were placed in the low conformity (LC) group. After conducting statistical tests between the pre-and post-radiotherapy imaging values, the treatment response in these two groups was examined.

Table 2 summarizes the information from this comparison. This table depicts the ratios of Cho/Cr and Cho/NAA and the significant assessments for ELV and NELV patients before and one month after CRT in high-grade glioma types.

Discussion

This research aimed to assess the effectiveness of quantitative MRI techniques alongside RANO criteria to evaluate the outcome and response to CRT in high-grade glioma. As a result, quantitative assessments, including ELV, NELV, and MRS metabolite ratios, were computed both before (post-surgery) and one month after CRT. Initially and post-surgery, the study findings indicated that conventional MRI features were unsuitable for tumor detection. However, MRS imaging findings through metabolic mapping of Cho/NAA and Cho/Cr could provide a different assessment of tumor burden based on location. The existence of residual tumors after surgery is an undeniable reality, and it is associated with the location and the misinterpretation of tumor burden due to inadequate imaging findings [14,15]. Indeed, the volume of the remaining tumor is linked to the treatment outcome and the survival of the patient [16]. Our findings in MRS imaging on glioma patients after tumor removal are consistent with the aforementioned studies [17,18], demonstrating differences in the location of the metabolic region of interest compared to the imaging region of interest. In the first phase of our current study, we have determined that there are disparities in the positioning of metabolic and structural ROIs. Cho/NAA and Cho/Cr are the most relevant metabolic ratios for identifying tumor location [19]. Previous MRS studies examining the association between histopathological findings of glioma have highlighted differences in the positioning of metabolic and imaging features [20,21]. A comparative analysis was conducted between metabolically-defined tumor volumes, derived from established Cho/NAA and Cho/Cr thresholds, and their anatomical counterparts delineated on conventional MRI. A significant spatial discrepancy between these volumes was quantified, evidenced by low Dice similarity coefficients and a notable displacement between their respective geometric centers. An investigation of multiple Cho/NAA thresholds revealed a direct relationship between the stringency of the metabolic criterion and the degree of spatial divergence. As the Cho/NAA ratio threshold was elevated, the centroid-to-centroid distance increased from 9.51 mm to 9.83 mm, while the area of the metabolic ROI concurrently decreased. This spatial incongruity suggests that the region of highest metabolic activity, indicative of aggressive tumor biology, does not necessarily coincide with areas of contrast enhancement or T2 hyperintensity. This observation is consistent with prior studies that have identified metabolically active, high-choline regions extending beyond the boundaries of anatomically defined lesions [20]. The Cho/Cr map results also demonstrated the displacement in location between structural ROI and the metabolically defined ROI, aligning with the findings from the Cho/NAA map, with the most significant similarity observed for Cho/Cr > 1.5. One of the critical points is the significant difference in the metabolic choline to creatinine ratio and the structural area in both thresholds, confirming the distinction and difference between these two areas.

Therefore, by obtaining information in the first stage and setting a threshold for matching the metabolic area and the structural area of patients, two groups, high conformity (HC) and low conformity (LC), were divided, and we sought to find therapeutic efficacy differences in these two groups by obtaining post-radiotherapy treatment data. Six patients were placed in the HC group, and six were placed in the LC group. In

the high conformity group, although ELV and NELV have significantly decreased (P-values: 0.021 and 0.041, respectively), there has been no significant change in the metabolites, which could indicate the effectiveness of radiotherapy treatment after surgery with high efficacy and conformity. On the other hand, in the LC group, we did not observe a significant decrease in structural volumes, but we also noticed a significant increase in metabolic ratios. This indicates the impact of surgical procedures on the outcome of radiotherapy treatment. In other words, when there is a significant difference between the metabolic and structural areas after surgery, the efficacy of subsequent radiotherapy treatment is also affected.

One limitation of this study is the lack of a 6-month follow-up, which could play an important role in confirming the results. Due to the low spatial resolution of MRS imaging, it is not possible to accurately determine a threshold for metabolic ratios for tumor delineation. However, based on our findings, we can suggest that a metabolic ratio can be a determining parameter in assessing the efficacy of surgery and radiotherapy treatment.

Conclusion

Using metabolic ratios obtained through the MRS technique can be an effective method for assessing the results of surgical procedures. In the evaluation of adjuvant treatment with chemo-radiation, cases where there is high conformity between metabolic and structural mapping in post-surgical evaluation, higher efficacy of radiotherapy treatment is expected, and In cases of low conformity between the metabolic and structural maps, incomplete response to radiotherapy, and increased metabolic ratios arising from tumor area activity were observed. According to the study's findings, utilizing MRS mapping is an effective method for identifying any remaining tumor and predicting the success of chemoradiation therapy in glioma patients, as opposed to relying solely on conventional MR imaging features.

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