

MRS Imaging as Complement to MRI in the Post-treatment Follow-up of Glial Brain Tumors

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Abstract

Background/Aim: Central nervous system tumors have a very low incidence worldwide. However, they represent a significant cause of mortality and morbidity. Magnetic resonance imaging (MRI), magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopy imaging (MRSI) techniques provide metabolic information complementary to anatomical alterations. The aim of this study was to characterize different metabolic patterns and determine treatment outcomes in glial brain tumors.

Patients and Methods: Forty-four previously treated patients participated in this prospective study, including 20 cases of low-grade (LG) and 24 high-grade (HG), gliomas. All patients underwent conventional MRI combined with MRS and MRSI using a 1.5 Tesla (T) magnet.

Results: Distinct metabolic profiles were observed via MRS and MRSI compared to normal brain tissue. Among the LG tumors, 10 remained stable with mean choline (Cho)/ N-Acetyl Aspartate (NAA) and NAA/creatinine (Cr) ratios of

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1.49 ($p=0.036$) and 0.92 ($p=0.038$), respectively, while the other 10 progressed to HG, with Cho/NAA and Cho/Cr ratios of 2.24 ($p=0.026$) and 4.48 ($p=0.016$). Among HG tumors, 17 remained stable with similar metabolic profiles, while seven showed progression. Gliosis was identified in 21 cases, characterized by a Cho/NAA ratio of 1.57 ($p=0.028$) and NAA/Cr ratio of 1.36 ($p=0.026$). Radiation necrosis was observed in 14 tumors, with significant spectroscopic changes including Cho/Cr ratios of 2.14 ($p=0.02$) and 1.9 ($p=0.003$), and NAA/Cr ratios of 1.28 ($p=0.001$) and 0.49 ($p=0.001$) across SV-MRS and MV-MRSI modalities. Tumor recurrence was detected in 20 cases based on MRSI metabolic maps.

Conclusion: MRS and MRSI provide valuable metabolic information that complements MRI in the post-treatment evaluation of glial brain tumors. These techniques enhance the detection of tumor recurrence, progression, and radiation necrosis, thereby supporting clinical decision-making and optimizing patient management.

Keywords: Brain tumors of glial origin, magnetic resonance spectroscopy, magnetic resonance spectroscopy imaging.

Introduction

Tumors of the central nervous system have a very low incidence worldwide; however, they represent a significant cause of mortality and morbidity. Most primary intracranial tumors arise from glial cells, which include astrocytes, oligodendrocytes, microglia, and ependymal cells (1). Magnetic resonance spectroscopy (MRS) and magnetic resonance spectroscopic imaging (MRSI) are non-invasive techniques that provide metabolomic information complementary to anatomical brain alterations (1). Both have a crucial role in the clinical diagnosis and differentiation of brain tumors from other non-neoplastic pathologies, distinguishing tumor recurrences and assessing tumor grade post-treatment. Nowadays, a combination of advanced imaging technologies such as MRI, MRSI, perfusion-weighted imaging (PWI), positron emission tomography (PET), diffusion-weighted imaging (DWI), single photon emission computed tomography (SPECT) enhances the accuracy to improve differential diagnoses (2).

Treatment options for this category of tumors in adults may include surgery, radiosurgery, radiotherapy, chemotherapy, and targeted therapy. These therapeutic approaches induce alterations in the tumor's pathophysiology resulting in metabolic changes within the tumors, which subsequently affect its imaging characteristics (3), observable at various stages: at baseline, during or after

the course of treatment. These metabolic alterations can be assessed using techniques such as single voxel (SV) MRS and multivoxel (MV) MRSI (1, 3, 4). MRS has the capacity to measure the presence of macromolecules, including brain metabolites associated with cellular metabolism and proliferation, providing concentrations of choline (Cho), *N*-acetyl aspartate (NAA), creatine (Cr), lipids (lipid), lactate (lac), myoinositol (MI) and glutamine (Gln)-glutamate (Glu) (5-7). The MV-MRSI or chemical shift imaging configuration or modality is based on obtaining sequences of Magnetic Resonance Images that provide reference images of the area to be studied, which includes a specific volume "voxel" of interest as a spatial description and is represented as a three-dimensional matrix or metabolic map (1, 8-11). The extent of the mapped surface can be measured in reference to the size and/or depth to which the main tumor has grown into the surrounding tissues, allowing assessment of tumor progression and response to treatment. Both techniques allow for clear distinction between normal and abnormal brain tissue, characterization of metabolic alterations associated with tumor growth, assessment of the degree of malignancy, and monitoring of treatment responses (1, 5, 7).

The aim of the present study was to characterize the different metabolic patterns generated by treatment, to assess the potential spatial extent of the distribution of metabolic abnormalities and differentiate recurrent tumors from radiation necrosis in low-grade (LG) and

Table I. Acquisition parameters for each study.

Protocol	RT	ET	Average	Volume	AT	Bandwidth
Research spectroscopy						
SV SET MRS (T)	1,500	30 ms	128	20×20×20 mm	3.20 m	1,000 hz
SV SET MRS (N)	1,500	30 ms	128	20×20×20 mm	3.20 m	1,000 hz
SV LET MRS (T)	1,500	135 ms	128	20×20×20 mm	4.56 m	1,000 hz
SV LET MRS (N)	1,500	135 ms	128	20×20×20 mm	4.56 m	1,000 hz
MV MRSI	1,600	135 ms	4	10×10	7.41 m	1,000 hz
Study time					22.93 m	

RT: Relaxation time; ET: echo time; AT: acquisition time; SET: short echo time; LET: long echo time; T: tumor; N: normal; MRS: magnetic resonance spectroscopy; MRSI: magnetic resonance spectroscopy imaging.

high-grade (HG) glial brain tumors through MRI, SV-MRS and MV-MRSI.

Patients and Methods

This prospective study, conducted at the INC, Bogotá, Colombia, was approved by the Research Ethics Committee and was performed in accordance with the Declaration of Helsinki. This study included a group of 44 previously treated patients [27 female (average age 44 years) and 17 male (average age 43 years)] recruited between September 2018 to November 2020 having provided written informed consent to participate in the study. Of 44 patients, 20 cases were categorized as LG (astrocytomas grade 1 and 2, diffuse gliomas, ganglioma grade 2 and oligodendroglioma grade 2) and 24 as HG (astrocytomas grade 3, oligodendroglioma grade 3, glioblastomas grade 4, anaplastic astrocytomas grade 3 and anaplastic oligodendroglioma grade 3) according to their initial diagnosis (primary pathology). These 44 patients were treated with surgery (four LG and three HG), radiotherapy (seven LG and 12 HG), or chemoradiotherapy (four LG and 20 HG) and underwent the SV-MRS and MV-MRSI protocol. In the image analysis and magnetic resonance spectroscopy, data were acquired on a 1.5-T MR unit, Magnetom, Vision (Siemens, Erlangen, Germany), equipped with a 16-channel head/neck coil. Five spectroscopy sequences were incorporated prior to gadolinium administration: one for MV-MRSI and two pairs

for SV-MRS. These two pairs represent new sequences introduced in this study and are described in Table I, as well as the different parameters used in spectroscopy. Treatment metabolic characterization was achieved by measuring the concentration of Cho, Cr and NAA and the analysis of the relationships Cho/Cr, Cho/NAA, and NAA/Cr both in the lesion and in the contralateral control tissue. For spectral analysis, a sum of Gaussian fits associated with each metabolite was executed on a sixth-degree baseline. As part of the quality control process, it was essential that this baseline exhibited minimal variations in amplitude and maintained relatively stable behavior. To standardize the measurements, Cr was considered as a reference due to its relatively constant presence in the healthy and pathological tissues (5, 12). Consequently, the Cho/Cr and NAA/Cr ratios were calculated, and unlike the other two proportions, the Cho/NAA ratio was calculated as the proposed malignancy index.

The potential spatial extent of the distribution of metabolic abnormalities was analyzed and characterized through MRSI, which is performed after the precontrast MRI and before the administration of gadolinium contrast. The volume of interest includes the lesion (contrast enhancement on T1-weighted images or hyperintense area on T2-weighted FLAIR images) and the surrounding normal-appearing brain tissue. Applying the MRSI grid, images superimposed on the respective CE-T1W or T2W/FLAIR anatomical images were generated, thus estimating the Cho/NAA, Cho/Cr and NAA/Cr peak area

ratios and generating color maps to define the degree of metabolic abnormality in Cho/NAA, Cho/Cr and NAA/Cr according to Li X *et al.* (11).

Additionally, we measured and compared the two-dimensional tumor surface extent (extent and location) obtained by radiologic anatomic imaging and MV-MRSI extent in twenty-one cases and determined the variability between them.

Statistical analysis. The Cho/NAA, Cho/Cr, and NAA/Cr ratios in the detected abnormalities and in the contralateral control tissue were quantified using a *t*-test to determine whether these ratios were associated with tumor grade, treatment effects (e.g., radiation necrosis), and tumor recurrence. Furthermore, measurements of the two-dimensional extent of the tumor surface obtained by radiological anatomical images and MV-MRSI were compared using a scatter plot. The variability between two types of measurements was determined by means of Pearson, Lin and Intraclass correlation coefficients. SPSS v25.0 statistical package (IBM Corp., Armonk, NY, USA) was used for all statistical analyses and *p*-values <0.05 were considered statistically significant.

Results

Different spectroscopic patterns were observed in the malignancies of the 44 cases included in this study in comparison with the normal parenchyma (Figure 1). Among the 20 LG tumors, 10 progressed to HG (Figure 2) with significant increase in Cho and Lac, and decrease Cr and MI, while 10 who remained stable were confirmed as LG with SV-MRS long Echo Time (LET) sequences [mean Cho/NAA ratio of 1.49 ($p=0.036$) and NAA/Cr ratio of 0.92 ($p=0.038$)]. Among the 24 HG, 17 were characterized as HG with SV-MRS short ET (STE) sequences [mean Cho/NAA ratio of 2.24 ($p=0.026$) and mean Cho/Cr ratio of 4.48 ($p=0.016$)], seven progressed with significant increase in Cho and Lac and decrease in Cr and MI and the remaining nine remained stable. Gliosis was characterized in 21 tumors with LET SV-MRS sequences [mean Cho/NAA ratio of 1.57 ($p=0.028$) and mean NAA/Cr ratio

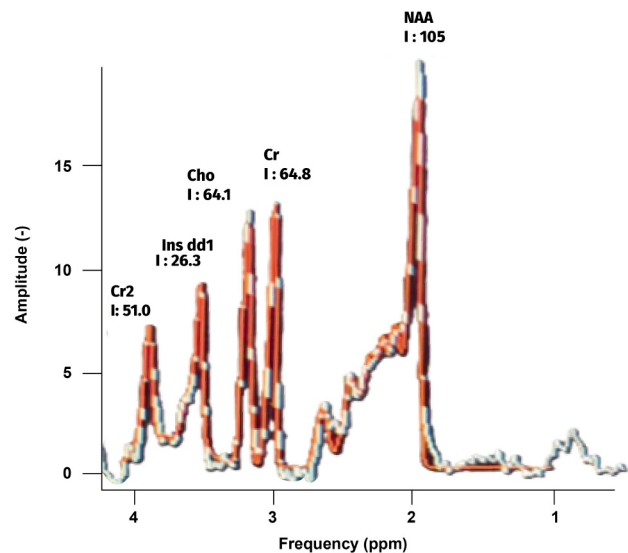


Figure 1. Single voxel-magnetic resonance spectroscopy in the normal brain parenchyma of case 54 (astrocytoma grade 2 that progressed to diffuse glioma grade 3).

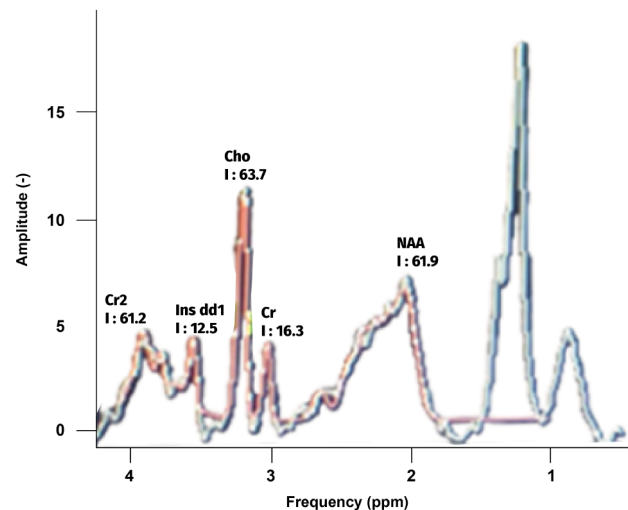


Figure 2. Long echo time single voxel-magnetic resonance spectroscopy pathological spectral. Metabolic changes consistent with progression, characterized by increased choline (Cho) and lactate (Lac), and decreased creatine (Cr) and MI in case 54.

of 1.36 ($p=0.026$)] (Figure 3) and with SET SV-MRS sequences a slight trend of association was observed [mean Cho/Cr ratio of 2.14 ($p=0.055$)]. Radiation necrosis was observed in 14 tumors with STE SV-MRS sequences

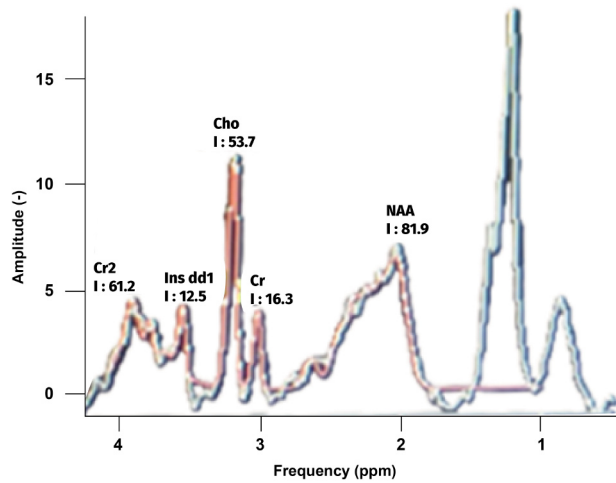


Figure 3. Long echo time single voxel-magnetic resonance spectroscopy metabolic changes consistent with gliosis, characterized by decreased N-Acetyl Aspartate (NAA) in Case 54.

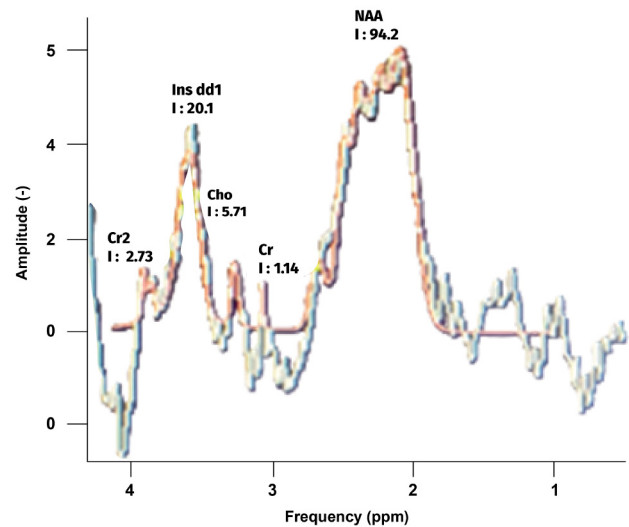


Figure 4. Short echo time single voxel-magnetic resonance spectroscopy metabolic changes consistent with radiation necrosis, characterized by decreased choline (Cho), creatine (Cr) and N-acetylaspartate (NAA) in case 54.

(mean Cho/Cr ratio of 2.14, $p=0.02$), and with LET SV-MRS sequences [mean Cho/Cr ratio of 1.25 ($p=0.005$) and mean NAA/Cr ratio of 1.28 ($p=0.001$)] (Figure 4), and with LET MV-MRSI sequences [(mean Cho/Cr ratio of 1.9 ($p=0.003$), mean Cho/NAA ratio of 3.48 ($p=0.01$) and mean NAA/Cr ratio of 0.49 ($p=0.001$)]. Furthermore, among the 44 cases, 20 were characterized as recurrent tumors with LET MV-MRSI [mean Cho/Cr ratio of 2.21 ($p=0.02$), mean Cho/NAA ratio of 4.49 ($p=0.01$) and mean NAA/Cr ratio of 1.73 ($p=0.06$)] (Figure 5). In the analysis of the spatial extent of metabolic abnormalities using MV-MRSI, the standard sequences used at the INC imaging service were applied. Spatial heterogeneity was observed within the T2 detected abnormalities in HG tumors and in the Cho/NAA and NAA/Cr abnormalities in LG tumors, as well as in volume in both LG and HG tumors (Figure 6A and B).

We also determined the extent of surface metabolic distribution in 21 cases with a tumor lesion after treatment analyzing the spatial distribution of specific metabolites such as Cho, Cr, NAA among others, quantifying and detecting them within both the tumor and the surrounding tissue. As result, a significant increase in Cho/NAA ratio, coupled with a slight decrease in Cho/Cr

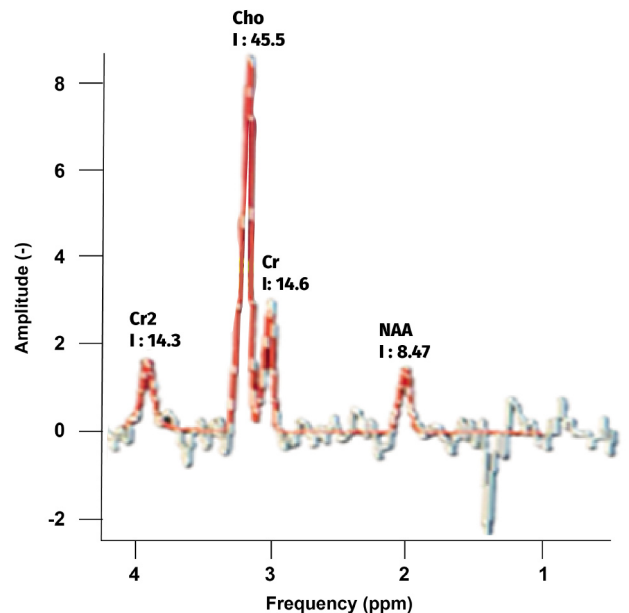


Figure 5. Long echo time multivoxel-magnetic resonance spectroscopy imaging pathological spectra. Metabolic changes consistent with tumor recurrence, characterized by increased choline (Cho)/creatine (Cr) ratio in case 54.

ratio were found. Moreover, MRSI showed a difference of 25% and 18% and 46% in LG, HG tumors and gliosis respectively, compared with MRS characterization.

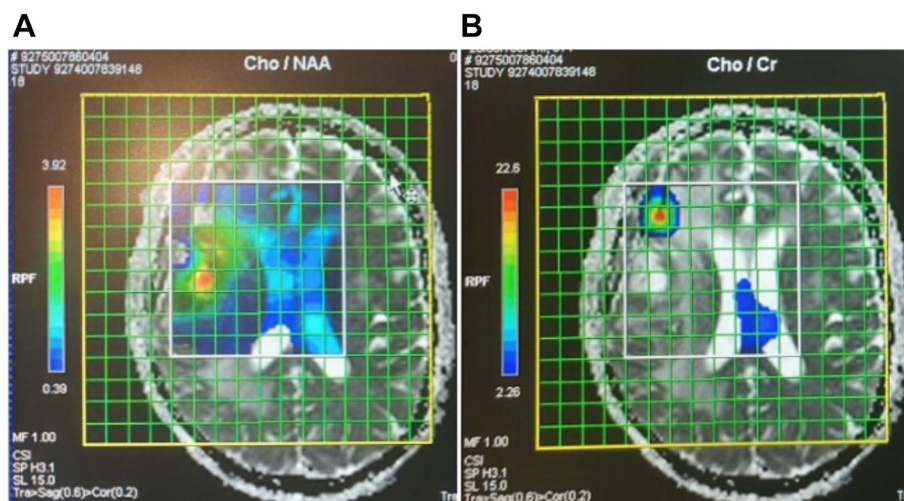


Figure 6. Patient with a diffuse astrocytoma grade 2. Magnetic resonance imaging and magnetic resonance spectroscopy imaging - Parametric map: increased choline (Cho)/N-Acetyl Aspartate (NAA) ratio of 6.0 (A) and Cho/creatine (Cr) ratio of 3.0 (B), indicative of tumor recurrence in case 19.

Furthermore, comparison of the two-dimensional extent of tumor surface measurement obtained by radiological anatomical imaging and by MV-MRSI, showed an increase in the two types of measurements, revealing a positive association (Figure 7). The analysis performed to evaluate the variability between the two types of measurements showed for instance that the Pearson coefficient was 0.74 ($p < 0.001$), which means there was a strong positive correlation between the data of the two measures. The Lin's correlation agreement coefficient was 0.43 [95% confidence interval (CI)=0.24-0.58], showing a moderate to good agreement between the data. Furthermore, the intraclass correlation coefficient was 0.44, indicating poor to moderate reliability.

Discussion

The results of this study showed that radiation-induced cell necrosis was the most distinct post-treatment effect when compared to gliosis. This observation was evidenced by LET SV-MRS sequences and with NAA/Cr ratios showing significant differences ($p = 0.001$ vs. 0.026). Using MRS, we assessed, progression and tumor recurrence of LG and HG tumors using both SV-MRS and MV-MRSI, as

has also previously reported (13). The use of MRS and MRSI allowed to separate disease progression from treatment-related tissue changes. MV-MRSI together with anatomical imaging allowed a clearer picture of the progression of LG gliomas, especially in situations of clinical uncertainty (14). Furthermore, when differentiating between recurrent tumors and radiation necrosis using MV-MRSI, the Cho/NAA and Cho/Cr ratios were higher in recurrent tumors than in tumors with radiation necrosis, whereas the NAA/Cr ratios showed a slight increase in recurrent tumors compared to those with radiation necrosis. Unlike a slight increase in NAA/Cr ratio, our results are in concordance with previous studies by Weybright *et al.* (13), Zeng *et al.* (15), and Chuang *et al.* (16). Aseel *et al.* (2) reports similar results in a systematic review and meta-analysis, showing that Cho/NAA, Cho/Cr, and NAA/Cr ratios are significantly better predictors of tumor recurrence and concluded that MV-MRSI plays a crucial role in distinguishing between recurrence and radiation necrosis, making it the main application. In the analysis to distinguish between tumor recurrence and radiation-induced necrosis, we observed some cases of tumor recurrence with a lower lipid peak. In contrast, those with radiation-induced necrosis showed a

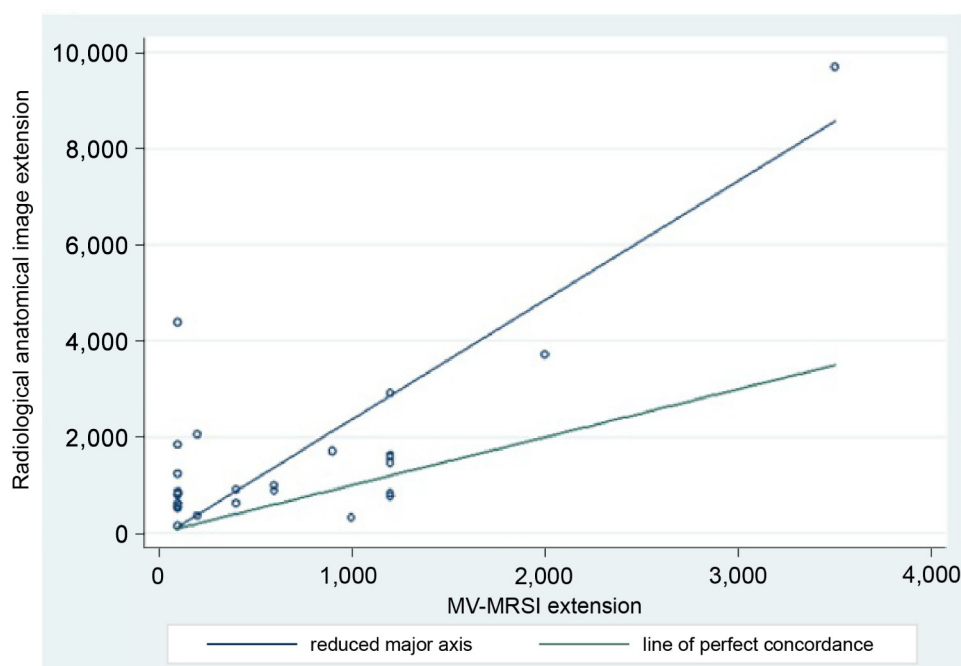


Figure 7. Measurement of the two-dimensional extent of the tumor surface: Behavior between radiological anatomical image extension and multivoxel-magnetic resonance spectroscopy imaging extension in twenty-one cases.

prominent lipid peak. This observation is in accordance with previous results by Anbarloui *et al.*, (17) who developed an algorithm using the Cho/NAA and Cho/lipid ratios to analyze spectroscopic changes and investigate their accuracy in discriminating between radiation-induced necrosis and tumor recurrence, showing that Cho/NAA and Cho/Lipids were significantly different between tumor recurrence and radiation-induced necrosis. Even more, techniques such as MV-MRSI allowed to spot abnormal tissue areas surrounded by local edema within the irradiated volume on the primary glioma. Thus, contributing to the differentiation between tumor recurrence and radiation necrosis, as observed in a grade 2 astrocytoma, which progressed to grade 3 anaplastic oligodendroglioma, case 54 of this study.

Evaluation of the spatial extent of the distribution of metabolic abnormalities in brain tumors using MV-MRSI provides a color map of metabolite concentrations in the tumor, normal parenchyma and surrounding brain tissue. This color map shows the spatial distribution of the tumor,

and differences in volume, allowing to evaluate the heterogeneity in areas adjacent to the tumor that are sometimes undetectable (1, 10, 11, 14). In the diffuse grade 2 astrocytomas included in this study, *e.g.*, case 19, color parametric mapping allows determination of metabolite concentrations in the normal parenchyma and surrounding brain tissue, as well as the increase in Cho/NAA and Cho/Cr concentrations within the tumor, which are indicative of tumor recurrence.

The concordance found between the radiological anatomical imaging and MV-MRSI measurement of the analysis of the two-dimensional extension of the tumor surface shows complementarity between the two types of measurements, contributing to an accurate determination of such measurement. In the case of the MV-MRSI, it helps to delineate the extent of tumor invasion, potentially revealing tumor borders or infiltrates in the surrounding tissue by examining metabolite gradients across the tumor and surrounding areas. In addition, it has demonstrated compelling and promising results related to grading,

prediction of treatment resistance patterns and prognosis in glioblastomas (18). MV-MRSI also allowed the identification and the quantification of brain metabolites in areas damaged by treatment such as recurrent lesion or tumor, radiation necrosis, and tumor persistence and progression using either single or multiple voxels. Thus, MRSI is a tool that can adequately complement anatomical MRI, allowing better determination of tumor burden and extent. Moreover, the use of both SV-MRS and MV-MRSI techniques offers additional benefits, as they enhance the characterization of treated brain tumors in terms of degree and extension. Currently a combination of advanced imaging technologies such as MRSI, PET, DWI, SPECT and PWI contribute to differential diagnosis. In fact, Jung JH and Ahn BC (19), reported in their review that PET is considered a highly accurate tool to differentiate radiation necrosis from brain tumor progression. The integration of these imaging technologies will improve metabolic spatial characterization and, consequently, management and treatment, while preserving relevant functional tissue (18, 20). In our study, it was observed that in some cases PWI, a type of MRI technique, was required in conjunction with MRSI to adequately characterize follow-up findings, thus contributing to determining prognosis and predicting treatment response. In developing countries like ours and within our institution, despite the availability of techniques such as PET, challenges persist related to the accessibility of tracers or amino acid analogs, crucial for distinguishing between recurrence and radiation necrosis. Under these circumstances, the use of MV-MRSI remains vital for differentiating between diagnoses, and SV-MRS and MV-MRSI contribute to decision-making regarding modifications or adaptations in treatment management.

Conclusion

MRS and MRSI play a significant role as complementary sequences to MRI to determine treatment outcomes, tumor extension, progression, recurrence or post-radiation necrosis. This synergy serves as a valuable tool

to support neuroradiologists, neurologists, neurosurgeons and radiation oncologists in the therapeutic management of patients.

Conflicts of Interest

All Authors declare no competing interests regarding this study.

Authors' Contributions

Conceptualization and design: Moreno Acosta, P., Gamboa, O., Malaver, G.; Methodology and statistical analysis: Gamboa, O., Moreno-Acosta, P., Malaver, G.; Reading and interpreting of MRI, MRS and MRSI: Rodriguez, C., Singh, C. All Authors commented on previous versions of the article and read and approved the final article.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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