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ORIGINAL RESEARCH

Magnetic resonance spectroscopy and diffusion contrast imaging in differentiating recurrence of primary brain tumors

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Abstract

Objective: Differentiation of brain tumor recurrence from necrosis caused by radiation after radiotherapy is often considered a radiological ambiguity. The purpose of this study is to investigate the effectiveness of magnetic resonance spectroscopy in differentiating the recurrence of primary brain tumors (glioma) from necrosis caused by radiation.
Materials and Methods: 15 patients (with an average age of 40.07, 8 men and seven women) were examined in this study. The samples of this study were selected from patients who have already been confirmed to have a glioma brain tumor and requested radiotherapy. 12 weeks (or three months) after radiotherapy, MRS imaging sequences with CSI technique and DWI imaging sequence with b-value=1000 s/mm2 were performed for all patients, and metabolic coefficients and quantitative ADC maps were also obtained. Then, the average ADC value and metabolic ratios were calculated for all patients.
Results: The pathological and clinical results of the patients were compared with the results of MRS and DWI. By analyzing the ROC curve on the data obtained from the two techniques implemented in this study, it shows that the area under the ROC curve for ADC maps was higher than that of the MRS technique, which shows that the results of DWI can reliably diagnose and differentiate tumor recurrence from radiotherapy necrosis. Also, the result of this study showed that tumor recurrence has a significantly lower ADC compared to radiotherapy necrosis (p=0.035).
Conclusion: The results of MRS indicates that the metabolic ratios of Cho/NAA and Cho/Cr are higher in people who have had tumor recurrence than in people in whom necrosis from radiotherapy has been reported. DWI images obtained with b-value = 1000 s/mm2 provide more reliable results than MRS images with the CSI technique and are considered a valuable tool in differentiating tumor recurrence from radiotherapy necrosis; the reliability of both imaging results increases, and the ability to detect tumor recurrence from necrosis caused by radiotherapy.
Keywords: Diffusion contrast imaging, Magnetic resonance spectroscopy, Glial brain tumors, Radiotherapy tumor necrosis recurrence

Introduction

Gliomas are the most common primary brain tumors in the central nervous system in adults [1, 2]. Surgery and radiotherapy are the main methods of treatment in patients with glioma. Radiotherapy after surgery improves treatment results for these patients. However, the use of radiotherapy has a series of side effects on the brain of patients, among which radio necrosis is considered as the goal of the worst radiotherapy injuries [3]. The diagnosis of radio necrosis can be evaluated in the case of recurrence within 24-18 months after the end of treatment, and these changes happen 12 weeks after the end of treatment and even much earlier. Radiotherapy necrotic tumor recurrence may cause changes near the main tumor location, which include contrast enhancement following the injection of contrast material, due to the destruction of the blood-brain barrier, mass effect and the surrounding air, so they look similar on normal imaging [4, 5]. Based on the studies conducted, the use of conventional MRI techniques such as T1W Gd has limitations in distinguishing tumor recurrence from radiotherapy necrosis, and to achieve a correct diagnosis in this field, it is recommended to use other methods such as MRS, DWI, PWI, etc.

The aim of this study is to evaluate, diagnose, and distinguish the recurrence of tumor necrosis with radiotherapy with both DWI imaging sequences. b value = 1000 s/mm2 and the calculation of quantitative ADC maps as an effective method and the images obtained from the MRS sequence of the CSI technique. In addition, the calculation of metabolic ratios at an earlier time when there is still time to treat the patient.

Materials and Methods

In this study, 15 patients (eight men and seven women, with an average age of 40.07) were selected from people in whom the intracerebral glioma tumor was confirmed. The samples for this research were selected from people whose doctors requested radiotherapy to continue their treatment. The selected patients were referred to the imaging center for tumor evaluation three months (12 weeks) after the completion of radiotherapy. The imaging was done with a Siemens AVANTO 5.1 Tesla MRI machine. DWI imaging was done with b = 1000 s/mm2 for all patients. Quantitative ADC maps were also obtained based on DWI images. Two-sequence DWI and MRS parameters are summarized in Tables I and II.

After obtaining the quantitative ADC maps, the radiologist quantitatively considered the ADC value by drawing a specific region (ROI) in the central and peripheral parts of the lesion. Then he reported the average of the two values for the desired lesion. This style of ROI drawing includes relevant information. It helps to calculate different parts of the lesion accurately. Then, the MRS Battechnik CSI-SE imaging sequence with two long and short TEs (135 and 30 milliseconds) was also performed on all patients. After MRS imaging, the metabolites were measured by the software and the metabolite ratios were also calculated for comparison.

Fig.

TABLE I DWI SEQUENCE PARAMETERS WITH BAB-VAUE=1000 IN SIEMENS DEVICE (SIEMENS AVANTO 1.5T)

Base-Sequence	SE-EPI
FOV	230
ADC matrix size	192×192
Slice thickness	5mm
EPI-factor	144
Parallel imaging	GRAPPA
FA	90
Gap	1mm
TR	3400ms
TE	94ms

TABLE II PARAMETERS OF MRS SEQUENCE WITH CSI SE TECHNIQUE IN SIEMENS DEVICE (SIEMENS AVANTO 1.5T)

	TR	TE
TE Long	1300 ms	135 ms
TE Short	1300 ms	30 ms

Requesting the radiologist to state the severity of the confidence level of his assessment regarding the type of lesion in the imaging sequence using one of the following ratings.

1- Recurrence

2- Radiotherapy necrosis

The radiologist expresses the confidence level of his assessment of the DWI images with one of the two ratings mentioned above so that the decrease in intensity. The signal in DWI images with b value=1000 corresponds to the increase in ADC in quantitative ADC maps.

A tumoral lesion is considered a tumor recurrence if it appears with high signal intensity in DWI images with b value=1000 s/mm2, and in quantitative ADC maps, it has significantly less ADC than the surrounding tissues, and if it is necrotic, this lesion is DWI images with b value = 1000 s/mm2 appear as low signal and in quantitative maps, the ADC will have a higher ADC compared to the surrounding tissues.

The same comparison was made for MRS images. This time, the radiologist gave a high

rating by evaluating the change in metabolite levels.

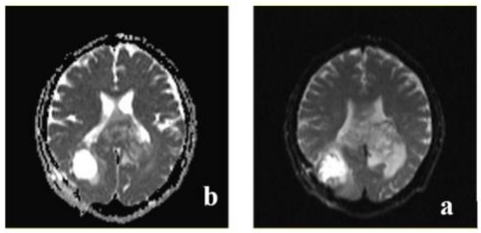

Fig. 1 Example of DWI (a) and ADC (b) images of a patient with glioma

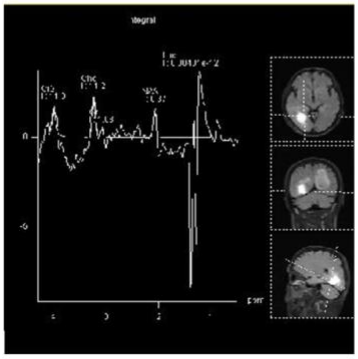

Fig. 2 MRS image sample with TE=135 msec in a patient with glioma

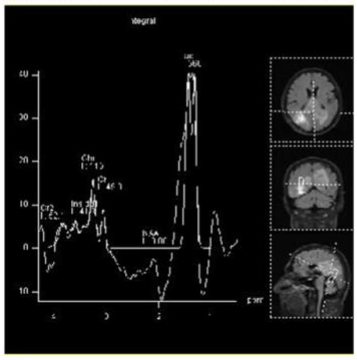

Fig. 3 MRS image sample with TE=30 msec in a patient with glioma

If the change in the level of metabolites is in the form of an increase in Cho and a decrease in NAA and Cr, it ultimately leads to an increase in the ratios of Cho/NAA and Cho/Cr and causes the diagnosis of recurrence in the corresponding tumor. But when the change in metabolites is such that Cho decreases and NAA increases, it causes the metabolic ratios to change in such a way that Cho/NAA and Cho/Cr decrease and the radiologist's diagnosis will be necrosis, of course, at such a time on the spot. Lactate and fat are observed in the tumor.
In the stages of statistical analysis, the lesions were first classified into two groups of recurrence of venous necrosis. The statistical tests were performed in order using SPSS 16 software. A comparison of mean metabolic coefficients in two groups of venous necrosis tumor recurrence was done with a t-test. The difference in ADC value and Cho/NAA and Cho/Cr metabolic ratios in two groups of venous necrosis tumor recurrence was investigated by a t-test. The difference between the metabolic coefficients of Lip or/and Lac in two groups of recurrent tumor necrosis was investigated by the ChiSquare test. The degree of agreement between DWI and MRS methods with the actual condition of the patients (final result) was checked with the Kappa coefficient of agreement. The degree of agreement between the imaging techniques and the final result was investigated and compared by drawing the ROC curve and examining the area under the ROC curve.

Results

There was no significant difference in comparing the average metabolic coefficient in the radiotherapy tumor necrosis recurrence groups.
($p > 0.05$): Examining ADC values and metabolic ratios in recurrence and necrosis groups with the t-test showed a statistically significant difference only in ADC.
($P=0.035$): The average was higher in the necrosis group than in the tumor recurrence. Still, no significant difference was observed between the two groups regarding the Cho/Cr and Cho/NAA metabolite ratios. The relationship between the metabolic coefficients of Lip or/and Lac in the two groups of odonnecrosis was investigated with the Chi-Square test. The result of Fisher's exact test showed the significance of the test.
($p=0.026$): The degree of agreement of two DWI and MRS sequences with the actual condition of patients was done with the Kappa statistic, and the degree of understanding of the DWI and MRS methods with the actual state of patients was 0.57 and 0.44, respectively, which indicates a relatively good agreement in both cases. Then the prediction power of the two methods was assessed by drawing the ROC curve and checking the area under the curve.
DWI predictive power was calculated with ADC 0.84 and MRS with Cho/Cr metabolite ratio 0.75 and Cho/NAA 0.57 (Table 3).

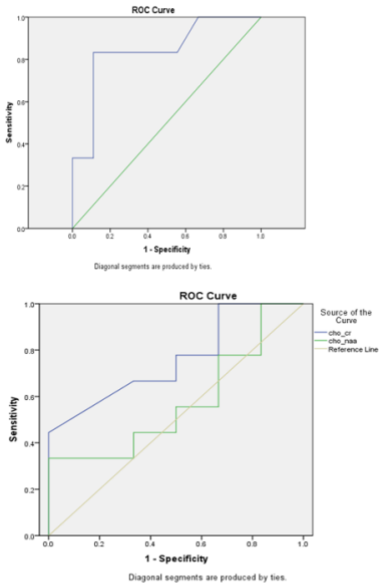

Fig. 4 Comparison of the ROC curve of MRS and DWI techniques with the actual condition of patients

TABLE III THE TESTED TECHNIQUES OF THE SURFACE UNDER THE CURVE

The tested techniques	The surface under the curve ROC
DWI quantitative maps ADC	0.84
MRS with evaluation Cho/Cr	0.75
MRS evaluated Cho/NAA	0.57

The order was 0.57 and 0.44, which indicates agreement in both cases. It is relatively acceptable. Then the ability to predict two methods was checked by drawing the ROC curve and the area under the curve (Figure 4).

Discussion

Histological findings can differentiate benign tumors (with a low malignancy grade) from malignant tumors (with a high malignancy grade). Pathology is grading and differentiating these tumors from other lesions and then planning treatment and evaluating the progress of the disease. And finally, checking the response to the treatment of tumors plays an important role [6].

Surgery and radiotherapy are the main methods of treatment in patients with glioma. Radiotherapy after surgery improves treatment results for these patients. However, radiotherapy has a series of side effects on the patients' brains, among which radionecrosis as the ultimate goal is considered the worst injury of radiotherapy [3]. In general, radiotherapy causes damage to the target tissue. These injuries are divided into three-time stages based on the time created.

- Acute refers to injuries that occur during radiotherapy.
- Subacute injuries that appear up to 12 months after the end of radiotherapy.
- Late injuries that appear months or years after radiotherapy.

The injuries that are diagnosed at these three-time stages are somewhat different. Vasodilation and edema are common effects of radiotherapy in acute and sub-acute conditions. The imaging differences between these injuries are discussed below. In the acute stage, there will be no change in the enhancement of the area with the contrast material. In the sub-acute phase, it increases the enhancement rate of the site, and this process is caused by edema necrosis in that area.

In the late stage, the degree of enhancement increases due to the formation of necrosis, but this time it is caused by secondary ischemia due to damage to the blood vessels. In this stage, cerebral edema is caused due to the increase in capillary permeability. Pseudo-progression is a term that has been enhanced in the form of an increase in the area, but this term is an imitation of progress, which is why this name calls it. This process in sub-acute time in patients with glioma brain tumor with a high degree of malignancy results from tissue reaction to radiotherapy. The reaction is seen with inflammation, edema and normalization of vascular permeability. This pseudo-progression is an active inflammation as a tumor response to radiotherapy. These changes are detected in the follow-up imaging as a decrease in the enhancement area [7].

In the radiological findings of necrosis after radiotherapy, they are usually seen around the ventricles, the white matter of the brain, the corpus callosum and away from the primary tumor and in the form of a soap bubble or Swiss cheese. However, it is still impossible to distinguish between radiotherapy necrosis and tumor recurrence based on normal MRI [8]. While planning treatment and timely diagnosis, this radionecrosis should be distinguished from tumor recurrence. Recurrence of a necrotic tumor after radiotherapy may cause changes near the leading site of the tumor, which include contrast enhancement following the injection of contrast material due to the destruction of the blood-brain barrier, mass effect and surrounding edema, so they look similar in routine imaging [4].

Conventional MRI techniques such as T2W and T1W with contrast have limitations in detecting tumor recurrence from radiotherapy necrosis [5]. Patients can be biopsied for the final

diagnosis of radiotherapy necrosis from tumor recurrence, and a definitive diagnosis can be made. Still, besides this method as an invasive method, there are other methods for diagnosis [4]. With the advancement of MRI imaging techniques, it is possible to use methods such as DWI, MRS, etc. Non-invasively, Wyman distinguished tumor recurrence from radiotherapy necrosis. In fact, with DWI and MRS, it is possible to perform physiological and metabolic evaluations of lesions and improve the process of diagnosing tumor recurrence from necrosis caused by radiotherapy.

DWI imaging is based on detecting random movement changes of water protons, and this technique can perform tissue characteristics and pathology examinations at the microscopic level (8). During the research conducted, due to the presence of a limiting factor in the movement of water molecules in tumor recurrence, these areas appear with high density in DWI images and low signal in ADC, which is probably due to the increase in cell density in tumor recurrence, which is caused due to the restriction created. ADC decreases [9].

In the conducted studies, the average ADC in the tumor recurrence group is significantly lower than in the group of changes after radiotherapy. ADC reduction in tumor recurrence results from high cell density [10].

MRS is a new and valuable method for the early diagnosis of many diseases. In this method, it is possible to observe the chemical environment to investigate the metabolism of the target areas. This evaluation provides us with information about the biochemical conditions of the living tissue environment, which helps diagnose tumor recurrence from radiotherapy necrosis. During the studies conducted based on this technique, Cho NAA Cr metabolites have been measured, and the calculation of Cho/NAA and Cho/Cr ratios has been introduced as the best marker for detecting the recurrence of necrosis. An increase in Cho/Cr ratio, with an increase in Cho, indicates cell change, brain tumor metastasis, and tumor return; It is a sign of tumor regrowth or recurrence [11].

An increase in the ratio of Cho/NAA, which is the result of an increase in Cho and a decrease in NAA; this decrease indicates the involvement of neurons and damage to the nervous system; It is a sign of tumor recurrence; as a result, the increase of Cho/Cr and Cho/NAA can be a sign of tumor recurrence [11, 12]. This is even though when the tumor undergoes necrosis after radiotherapy, these ratios are reduced, and fat is seen in the necrotic part [13, 15].In another study, the use of DWI and the calculation of quantitative ADC maps have been introduced as an increase in the ability to detect the recurrence of radiotherapy necrosis, and the addition of the MRS technique and the calculation of metabolites have been considered to increase its diagnostic accuracy [14].

In this study, we tried to use both imaging methods to detect tumor recurrence and radiotherapy necrosis in three months (12 weeks) after radiotherapy. This study, like many studies, faced obstacles and problems, such as the short life span of the patients and the difficulty communicating with them, the lack of cooperation of patients and the limitation of the research budget, which led to the reduction of the number of samples in this study.

To get a better result, it is necessary to take both images, increasing accuracy. Based on the study and statistical analysis, it can be said that by using DWI imaging and ADC calculation, along with MRS and measuring metabolites, it is possible to distinguish tumor recurrence from changes after radiotherapy. The result of our study, which was carried out using DWI and MRS imaging techniques, like previous studies, is a confirmation in this matter that the decrease in the average and coefficient of ADC, along with the increase in the metabolic coefficients of Cho and Cr and the reduction in NAA can indicate tumor recurrence. In contrast, the increase in ADC and the decrease in coefficients of high metabolism can indicate necrosis after radiotherapy. According to the calculations, the ratio of Cho/Cr and Cho/NAA coefficients in tumor recurrence is higher than in the necrosis group after radiotherapy. On the other hand, the ADC value in the tumor recurrence group decreases due to the diffusion limitation caused by the tumor recurrence, but the same factor in the necrosis group after radiotherapy due to the lack of new restrictions and the more unrestrained movement of water molecules, the phase difference is more

significant, and the ADC is higher. The ROC curve analysis for both imaging methods performed in this study shows that the DWI images obtained with b value = 1000 s/mm2 provide more reliable results than the images derived from MRS with the CSI technique and are considered valuable in differentiating tumor recurrence from radiotherapy necrosis. Also, the ROC threshold level for quantitative ADC maps was higher than that of the MRS technique. This shows that ADC maps help detect and differentiate the recurrence of necrosis more reliably.

Conflict of interest

Author declares no conflict of interest.

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