Differentiation between Recurrent Glioma and Radiation Injury by Magnetic Resonance Spectroscopy Combined with Diffusion-Weighted Imaging

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Abstract:

Background: The aim of this study was to investigate the diagnostic efficiency of magnetic resonance (MR) spectroscopy with diffusion-weighted imaging in the evaluation of the recurrent contrast-enhancing regions at the location of treated gliomas. Patients and Methods: In 49 patients who had new contrast-enhancing lesions at the vicinity of previously resected and irradiated high-grade gliomas, single-voxel MR spectroscopy and diffusion-weighted imaging were performed. Spectral data for N-acetylaspartate (NAA), creatine (Cr), choline (Cho), lipid (Lip), and lactate (Lac) were analyzed in combination with the apparent diffusion coefficient (ADC) in all patients. Diagnosis of these lesions was allocated by means of follow-up or histopathology. Results: The Cho/NAA and Cho/Cr ratios were significantly higher in recurrent tumor group than in radiation injury group (p < 0.001). The ADC values and ADC ratios (quotient of ADC of contrast-enhancing lesion and matching structure in the contralateral hemisphere) were significantly higher in radiation injury regions than in recurrent tumor (p< 0.001). With MR spectroscopy, two variables (Cho/NAA and Cho/Cr ratios) were proved to differentiate recurrent glioma from radiation injury, and 81.5% of total patients were classified into correct groups. Using discriminant analysis for MR spectroscopy with diffusion-weighted imaging, three independent variables (Cho/NAA, Cho/Cr, and ADC ratio) could classify 91% of total patients into their correct groups. There was a significant difference between the diagnostic accuracy of the two discriminant analyses (Chi-square=4.15, p=0.042). Conclusion: MR spectroscopy combined with ADC ratio can enhance the ability to differentiate recurrent glioma from radiation injury.

Keywords: Magnetic resonance spectroscopy, Radiotherapy, Radiation injury, Tumor recurrence

Introduction

Gliomas constitute over 90% of primary brain tumors in persons older than 20 years[1, 2]. In many cases, the extent of surgical excision is limited by the involvement of neoplasm in vital or functional anatomic parts of the brain[3]. For this reason postsurgical external-beam radiotherapy is a generally accepted and common procedure for the management of gliomas[4]. Enhancing lesions that arise on routine follow-up brain magnetic resonance imaging (MRI) at the site of a previously identified and treated primary intracranial neoplasm may present a significant diagnostic dilemma. Many of these lesions do not have specific imaging characteristics that enable the radiologist to

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discriminant tumor recurrence from inflammatory or necrotic changes that result from treatment with radiation and/or chemotherapy[5]. MR spectroscopy and diffusion-weighted (DW) imaging are noninvasive functional imaging methods that provide information complementary to that of anatomic imaging, these methods have been proposed as alternative modalities for differentiating tumor recurrence and radia-tion[6, 7].

Single-voxel MR spectroscopy used in earlier investigations showed interpretative difficulties with overlapping metabolic ratios as a result of partial volume contamination[8]. Multivoxel MR spectroscopy allows coverage of a larger volume and investigation of multiple regions of the lesion[7, 9]. Nonetheless, multivoxel MR spectroscopy could not correctly classify lesions in about 18% of cases[10, 11]**.** Diffusion-weighted (DW) imaging has been considered a mean to characterize and differentiate morphologic features such as edema, necrosis, and tumor tissue by measuring differences in the apparent diffusion coefficient (ADC)[12]. It was established that assessment of ADCs of enhanc-ing regions was useful in differentia-ting recurrent glioma and radiation injury[6, 13].

Both single-voxel MR spectroscopy and DW imaging could be carried out in our MR scanner. Both techniques were carried out on 49 patients as a try to differentiate recurrent glioma from radiation injury. The aim of this study was to investigate whether the addition of DW imaging parameters to MR spectroscopic data would improve the ability to differentiate the two groups.

Patients and Methods:

Forty-nine patients (27 male and 22 female; mean age, 35.77±16.88 years, range 10-69 years) who had been subjected to surgical resection of brain tumors with pathology proven high-grade gliomas (histology according to the classification schemes of the World Health Organization: grade III, n=34; grade IV, n=15) were enrolled in the study. All patients had undergone a full course of conventional fractionated radiotherapy after resection, and all patients had developed new contrast-enhancing lesions at or near the site of the original treated tumor; these lesions were seen on planned follow-up MR images. Written informed consents were obtained from all patients after explaining the background of the examinations. The Medical Ethical Committee of Suez Canal University, Faculty of Medicine, approved the study.

Follow-up MR Scans were performed 6 weeks after completion of radiotherapy and at 3-4 month intervals, depending on the clinical course. MR spectroscopy and DW imaging examinations were performed after initial identification of the recurrent contrast-enhancing lesion on follow-up MR images.

Histopathologic examination and follow-up MR imaging (after MR spectro-scopy and diffusion-weighted imaging) were used to ascertain the characteristics of the contrast-enhancing lesion. Lesions were considered tumor recurrence if they showed later histopathologic evidence of tumor (by biopsy or surgical resection) or if they showed mass effect and steady increase of enhancement at the follow-up MR images. Lesions were classified as radiation injury if they showed later histopathologic confirmation of radiation injury (by biopsy or surgical resection) or if they showed stable or resolving areas of contrast-enhancement on subsequent MR image.

Tissue specimens were obtained from 16 patients by biopsy, 5 by means of stereotactic biopsy, and 11 by means of surgi-

cal resection; biopsies were taken by neurosurgeons. Of the specimens, 12 were classified as tumor recurrence and 4 as radiation injury. The remaining 33 patients underwent additional conventional MR follow-up after the initial functional imaging; the follow-up time was 6.36 months (range, 3-12) where 8 patients were classified as tumor recurrence and 25 patients were classified as radiation injury.

MR and DW imaging

All examinations were performed on a 1.5T MRI system *(Achieva, Philips Medical Systems, Best, The Netherlands)*. The conventional MR images consisted of axial T1-weighted (500/11 ms [TR/ TE]) spin-echo (SE), T2-weighted (4000/100 ms) fast SE, and fluid-attenuated inversion-recovery (FLAIR) (9000/120/ 2250 ms [TR/TE/TI]) images obtained by using 6-mm section thickness, 240-mm field of view (FOV), and 320×224 matrix.

The DW images were obtained by using an axial echo-planar SE sequence (5000/65 ms [TR/TE]; one average; 6-mm thickness; diffusion gradient encoding in three orthogonal directions; b=100 s/mm^2; 240-mm FOV; 160 ×192 matrix) in 1 min. Contrast-enhanced T1-weighted SE images were then obtained in axial, coronal, and sagittal planes after intravenous administration of gadopen-tetate dimeglumine *(Magnevist, Schering, Berlin, Germany)* at a dose of 0.1 mmol/kg of body weight. Post processing of ADC maps was performed by using dedicated standard software on a workstation. Regions of interest (ROIs) were drawn manually onto the obtained ADC maps in the regions matching to the enhancing areas on contrast-enhanced T1-weighted images. The dedicated software calculated the ADC value automatically. The ADC ratio (normalized ADC value) was calculated as the quotient of the ADC value of the enhancing region and the matching structure of same-size ROI in the contralateral hemisphere.

MR spectroscopy

MR spectroscopy was performed after 1 hour from contrast-enhanced MR imaging to minimize the effect of gadolinium on MR spectroscopy. The following parameters were used for MR spectroscopy: a point-resolved spectroscopy sequence (PRESS), which included water and outer volume saturation pulses; 1500/144 ms [TR/TE]; 16-cm FOV; 16×16 matrix; 10-mm slice thickness; 1 average acquisition; scanning time, 4 min. The volume of interest (VOI) was placed on axial T1-weighted images matching to the contrast-enhancing area on contrast-enhanced axial T1-weighted mages. Automatic pre-scanning was performed before each spectroscopic scan to guarantee adequate water suppression. The full-width half-maxi-mum was kept at less than 15 Hz and water saturation between 95-99%.

Within the obtained VOI, separate 1×1×1 cm voxels were positioned in the area of enhancement. Metabolite peaks used were as follows: N- acetylaspartate (NAA) at 2.02-ppm, choline-containing compounds (Cho) at 3.22-ppm, (phospho-) creatine (Cr) at 3.02-ppm, lipid-containing compounds (Lip) in the range of 0.9–1.3 ppm, and lactate (Lac) at 1.33-ppm (inverted β-methyl doublet). Metabolite values were calculated automatically from the area under each metabolite peak by the dedicated software. The metabolite ratios (NAA/Cr, Cho/Cr, Lip/Cr and Lac/Cr) were calculated by the software and the Cho/NAA was manually calculated.

Statistical analysis

Statistical analysis was performed using SPSS for Windows software, release 11.5 (SPSS Inc., Chicago, IL). Metabolite ratios and ADC parameters (ADC value and ADC

ratio) between the recurrent tumor group (n=20) and radiation injury group (n=29) were compared using the unpaired, two-tailed Student **t** test. A forward stepwise discriminant analysis was carried out to evaluate the power of metabolite ratios and ADC parameters to distinguish tumor recurrence and radiation injury. Diagnostic accuracy was then compared between metabolite ratios alone and metabolite ratios besides ADC parameters for discriminating the two entities by using the Chi-square test. The level of significance was set at $p < 0.05$.

Results

Findings of MR spectroscopy

The Cho/Cr and Cho/NAA ratios of the contrast-enhancing lesions in the recurrent tumor group were significantly higher than those in the radiation injury group (p=0.001 and p=0.001 respectively), whereas the NAA/Cr, Lac/Cr and Lip/Cr ratios of the contrast-enhancing lesions in the recurrent tumor group were significantly lower than those in the radiation injury group (p=0.001, p=0.001 and p=0.001 respectively). The mean values of the metabolite ratios in relevant lesions are shown in Table 1**.** Representative MR images, MR spectroscopic images and diffusion-weighted ADC map images are shown in Figures 1 and 2.

Findings of DW imaging

The recurrent tumor group showed significantly lower ADC value (1.12±0.14 mm^2/s, mean ±SD) compared with the radiation injury group (1.44±0.11 mm^2/s); *p*=0.001. The normalized ADC (ADC ratio) was significantly lower in the recurrent tumor group (1.40±0.08) compared to that in the radiation injury group (1.68±0.1); *p*=0.001. A box-and-whisker diagram of the ADC values and ADC ratios was used to illustrate these results in Figures 3, 4.

Table 1: Calculated magnetic resonance spectroscopy ratios in various groups

Groups	Cho/Cr	Cho/NAA	Lac/Cr	Lip/Cr	NAA/Cr
Tumor recurrence (n=20)	2.7±0.68	3.07±0.71	1.04±0.16	0.31±0.10	0.87±0.23
Radiation injury (n=29)	1.81±0.64	1.78±0.63	1.81±0.64	0.64±0.18	1.31±0.31

Abbreviations: Cho=choline-containing compounds; Cr=(phospho-)creatine; Lac=lactate; Lip= lipid-containing compounds; NAA=N-acetyl-aspartate. Data are presented as Means ± SD

Findings of MR spectroscopy combined with DW imaging

To evaluate the power of correct classification, two discriminant analyses were carried out for metabolite ratios alone and for metabolite ratios combined with ADC parameters. In the first analysis, NAA/Cr, Cho/Cr, Lip/Cr, Lac/Cr, and Cho/NAA were used as independent variables. In the second analysis, all variables (metabolite ratios and ADC parameters) were used as independent variables. For both analyses, the findings of follow-up or histopathology provided the group variable. In the first analysis, two variables were significant. The Cho/NAA value appeared as the first variable to differentiate tumor recurrence from radiation injury. To settle the ability of other variables, Cho/ NAA was removed and Cho/Cr came out as the second variable. When Cho/Cr was expelled, other variables did not contribute significantly.

When both variables (Cho/NAA and Cho/Cr) were assembled together for classification, 81.5% of total subjects were classified correctly according to radiation injury (83%) versus tumor recurrence (80%) (Table 2).

In the second analysis, three significant variables were identified. The ADC value did not add significantly to differentiate tumor recurrence from radiation injury. When all the three variables (Cho/Cr, Cho/NAA, and ADC ratio) were introduced together for classification, 91% of total subjects were classified into correct groups (radiation injury, 97%; tumor recurrence, 85%) Compared with the first analysis, the second analysis could increase the accuracy of discriminant analysis for the assessment of the recurrent enhancing lesion (Chi-square=4.15, *p*=0.042). On the basis of discriminant analysis, two different equations were derived (Table 2). If D (tumor recurrence) was more than D (radiation injury), the lesion was classified as tumor recurrence. If D (radiation injury) was more than D (tumor recurrence), the lesion was classified as radiation injury.

Table 2: Results of stepwise discriminant analyses (SDA)

	Variable	Tumor recurrence	Radiation injury	Group	Classified (%)
SDA for metabolite ratios	Cho/NAA	2.87	0.72	Tumor recurrence	80
	Cho/Cr	7.25	5.12	Radiation injury	83
	Constant	–17.04	–5.43	Total	81.5
SDA for combined metabolite ratios and ADC parameters	Cho/NAA	6.55	5.23	Tumor recurrence	85
	Cho/Cr	8.16	6.30	Radiation injury	97
	ADC ratio	176.55	198.39	Total	91
	Constant	–149.68	–181.05		

Abbreviations: ADC ratio=quotient of apparent diffusion coefficient of contrast-enhancing lesion and matching structure in contralateral hemisphere; Cho=choline-containing compounds; Cr=(phospho-) creatine; Lac=lactate; Lip=lipid-containing compounds; NAA=N-acetyl-aspartate. Based on the discriminant analysis, the discriminant equation is: *For metabolite ratios:* D (tumor recurrence)= 2.87 (Cho/NAA) + 7.25 (Cho/Cr) – 17.04, D (radiation injury)= 0.72 (Cho/NAA) + 5.12 (Cho/Cr) – 5.43. *For combined metabolite ratios and ADC parameters:* D (tumor recurrence)= 6.55 (Cho/NAA) + 8.16 (Cho/Cr) + 176.55 (ADC ratio) – 149.68, D (radiation injury)= 5.23 (Cho/NAA) + 6.30 (Cho/Cr) + 198.39 (ADC ratio) – 181.05

Discussion

When encountering an indeterminate T1 enhancing lesion after radiation therapy for a high-grade tumor then we have common diagnostic dilemma; what is that focal lesion, "radiation injury", or "recurrent tumor"? Recurrent glioma and radiation injury are difficult to distinguish due to shared MR imaging characteristics such as areas of abnormal enhancement with surrounding edema[14-16]. The conventional MR imaging findings as clues to diagnose recurrent tumor and radiation injury have been disputed[14].

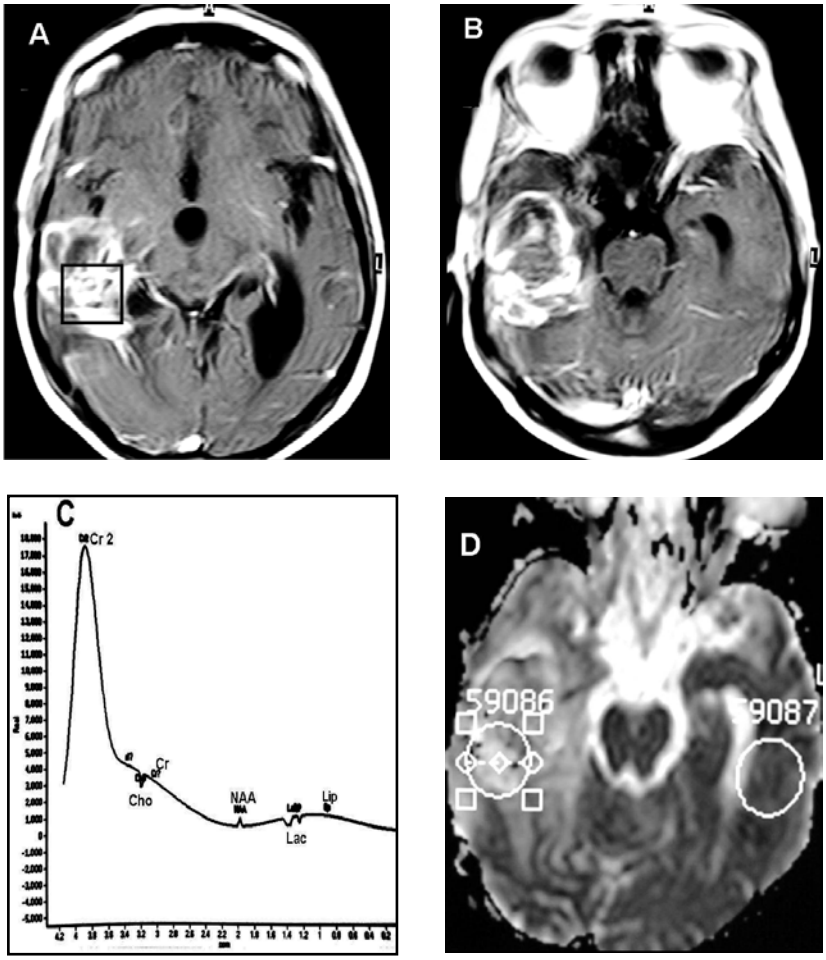

Figure 1 Radiation necrosis in a 58-year-old female who underwent surgery and radiotherapy for right temporal lobe anaplastic astrocytoma. (A) and (B) Contrast-enhanced T1-weighted axial images demonstrate large complex enhanced area with central necrosis. Volume of interest of magnetic resonance (MR) spectroscopy is shown in (A). (C) MR spectroscopic image shows markedly diminished metabolites except Lip and Cr2. Area under curve for Lip (0.9-1.3 ppm) is increased. (D) Apparent diffusion coefficient (ADC) map image (b = 1000 s/mm^2) shows no evidences of diffusion restriction with ROI is placed onto solid contrast-enhancing part of the lesion. Mean ADC value was 1.76 × 10^{-3} mm^2/s and ADC ratio was 1.88. Biopsy of this lesion revealed radiation necrosis.

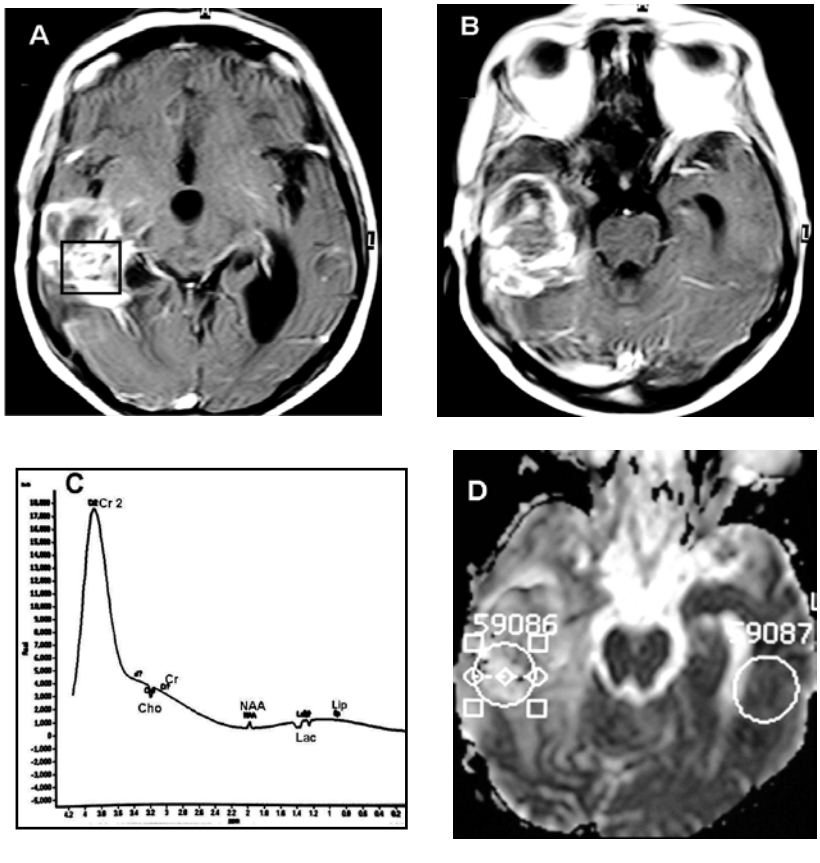

Figure 2: Tumor recurrence in a 69-year-old male who underwent surgery and radiotherapy for left parietal glioblastoma multiforme (A) & (B) Contrast-enhanced T1-weighted axial images demonstr-ate large enhanced area with irregular walls surrounded by edema with no midline shift. (C) MR spectroscopic image shows markedly increased Cho with increased Cho/Cr and Cho/NAA ratios (3.74 and 4.1 respectively). Small increase in Lac is also seen with Lac/Cr ratio = 0.6. Apparent diffusion coefficient (ADC) map image (b = 1000 s/mm^2) with ROI placed onto solid contrast-enhan-cing part of the lesion. Some diffusion restriction is seen as dark area within ROI. Statistics for ROIs showed mean ADC value in the contrast-enhancing lesion of 1.15 × 10^{-3} mm^2/s and ADC ratio of 1.36. Biopsy of this lesion revealed hypercellular glioblastoma multiforme with areas of radiation changes.

In an attempt to overcome this problem; we applied in our study a combination of two MR imaging modalities (MR spectroscopy and diffusion-weighted imaging) aiming to increase the accuracy of differentiation between these entities. Either MR spectroscopy or DW imaging has been used to distinguish tumor recurrence from radiation injury. These physiology based imaging methods (MRS and DWI) can direct neurosurgeon and pathologist to obtain biopsy from the appropriate sites and to provide appropriate histopathologic evaluation. Furthermore, any sequential therapeutic measures depend on the correct classification[17, 18].

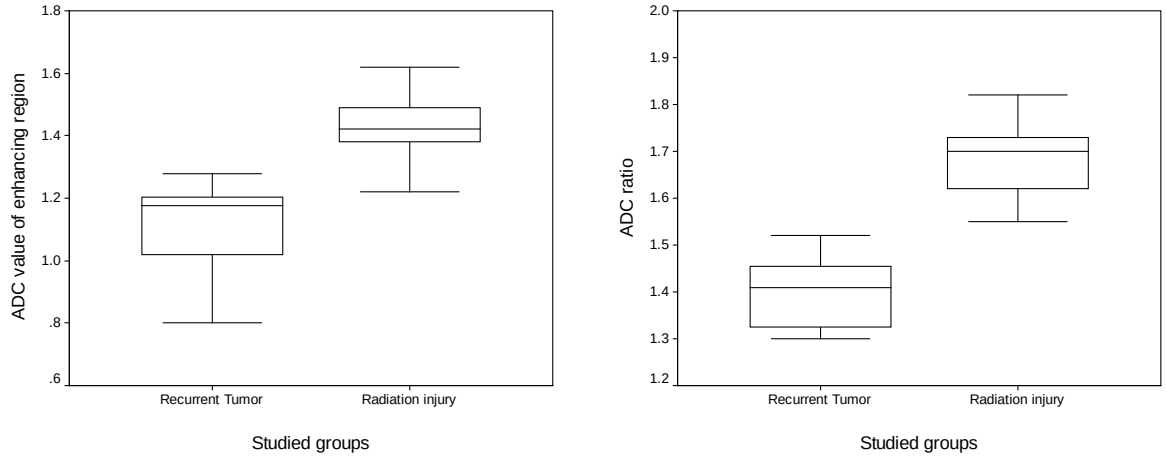

Figure 3: Comparison of apparent diffusion coefficient values ($\times 10^{-3}$ mm^2/s) between the recurrent tumor and radiation injury groups. Line indicates the range of data; boxes represent the distance between the first and third quartiles, with the median between them. **Figure 4** Comparison of apparent diffusion coefficient ratio between the recurrent tumor and radiation injury groups. Line indicates the range of data; boxes represent the distance between the first and third quartiles, with the median between them.

The main findings of the current study were: (1) Significant differences in the studied metabolite ratios (Cho/Cr, Cho/NAA, NAA/Cr, Lac/Cr and Lip/Cr) and ADC parameters (values and ratios) were found between the tumor recurrence and radiation injury groups. (2) With discriminant analysis, Cho/Cr, Cho/NAA, and ADC ratios were the main factors to distinguish recurrent tumor from radiation injury, and the addition of ADC ratios to MR spectroscopy ratios could increase the power of differentiation for the two entities. In our stepwise discriminant analysis, the first classification vector was correlated highly with Cho/NAA. The second classification vector concerned mainly Cho/Cr. According to the classification vectors we used in our study to differentiate between the two groups (radiation injury and tumor recurrence); 40 patients (81.5%) were classified into correct groups; 80% of recurrent tumor patients could be correctly classified (16 out of 20 patients); 83% of radiation injury patients could be correctly classified (24 out of 29 patients). These results are in close agreement with the previous studies[10, 11]. In the study of Lichy et al[11] using 2D MR spectroscopy, Cho/Cr and Cho/NAA ratios allowed a correct classification in more than 80% of the cases which is in excellent match with our results. A comparable result was found in the study of Zeng et al[19] who got an ac-

curacy of 85.5% for the combined Cho/Cr and Cho/NAA ratios in differentiating tumor recurrence from radiation injury. Matching of our results with that of Zeng might be explained on basis of near similarity in both the sample size (49 patients in our study versus 55 patients in his study) and the statistical methods used.

The apparent diffusion coefficient (ADC) values of biologic tissue reflect the Brownian movement of water molecules, which reveal potentially histopathologic characteristics of cellular structure[13]. Cellularity, is an important factor that influences ADC in brain tumors (after therapy). Previously, higher cellularity in recurrent neoplasm would contribute to lower ADC values[20]. Significant differences in ADC value were found between the two groups in our study, which is explained by the fact that recurrent growth of tumor determines to great extent the tissue ADC.

In our study; the function of discriminant analysis was interrelated highly with combined Cho/Cr, Cho/NAA and ADC ratio in the second analysis; the ADC value alone did not add through discriminant analysis to further discriminant tumor recurrence and radiation injury; this result is in excellent agreement with previous studies[19, 21]. In the study by Rock et al.[21] on 18 patients with malignant glioma previously treated with surgery and radiotherapy; the authors concluded that metabolite ratio analysis might allow for discrimination between specimens of tumor and necrosis. However, the direct addition of ADC value to MR spectroscopy did not add to the value of MR spectroscopy in distinguishing the two groups. In our study, a highly significant difference of the ADC ratio between the two entities was observed. Additionally, DW imaging could assess entire contrast-enhancing regions[22] which may defeat the shortcoming of 2D MR spectroscopy that only confines a limited region size. For these reasons, when the three variables (Cho/Cr, Cho/NAA, and ADC ratio) were concerned together for classification in the second discriminant analysis, 91% of the total patients were correctly-classified.

Biopsy is the only 'gold standard' reference test and is desired in all patients. Due to absence of histopathological verification of the final diagnosis; most of the current imaging modalities gave a low level of evidences when reviewing their accuracy in differentiating tumor recurrence from radiation necrosis[23]. Biopsy was not available in all of our patients; to overcome this problem clinical and imaging follow-up in our patients were an alternative which is accepted by Alexiou et al.[23]. In our study; histopathologic confirmation was in 32.6% of patients and follow-up imaging was applied for 67.4 % of patients. McGirt et al[24] reported that histopathologic confirmation is not always clinically practicable because of a high risk of morbidity and approximately 10% sampling error in biopsy cases[24]. Small tumor cell clusters may be missed by biopsy specimens, which are not necessarily representative for the whole, heterogeneous lesion[10]. Another limitation in our study is the short follow-up of these lesions after MR spectroscopy (6.36 months; range, 3-12 months). A prolonged follow-up imaging of contrast-enhancing lesions after MRS is desirable in all cases to minimize the possibility of misclassification. Additional limitation in our study is the variability in the timing of follow-up imaging, which is influenced by the distinctive clinical courses of the different patients.

Conclusion Our results suggest that MR spectroscopy allows a noninvasive differentiation of recurrent gliomas from radiation injury in patients with indeterminate

findings on routine follow-up MR images. Adding the ADC ratio to MR spectroscopy signify-cantly improves the ability to differentiate the two entities. The accuracy of differ-rentiation of MR spectroscopy in combination with ADC ratio is higher than that of MR spectroscopy alone.

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