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Diffusion tensor imaging and proton magnetic resonance spectroscopy in brain tumor

Correlation between structure and metabolism☆

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Abstract

Proton magnetic resonance spectroscopy and diffusion tensor imaging are non-invasive techniques used to detect metabolites and water diffusion *in vivo*. Previous studies have confirmed a positive correlation of individual fractional anisotropy values with N-acetylaspartate/creatine and N-acetylaspartate/choline ratios in tumors, edema, and normal white matter. This study divided the brain parenchyma into tumor, peritumoral edema, and normal-appearing white matter according to MRI data, and analyzed the correlation of metabolites with water molecular diffusion. Results demonstrated that in normal-appearing white matter, N-acetylaspartate/creatine ratios were positively correlated with fractional anisotropy values, negatively correlated with radial diffusivities, and positively correlated with maximum eigenvalues. Maximum eigenvalues and radial diffusivities in peritumoral edema showed a negative correlation with choline, N-acetylaspartate, and creatine. Radial diffusivities in tumor demonstrated a negative correlation with choline. These data suggest that the relationship between metabolism and structure is markedly changed from normal white matter to peritumoral edema and tumor. Neural metabolism in the peritumoral edema area decreased with expanding extracellular space. The normal relationship of neural function and microstructure disappeared in the tumor region.

Key Words

neural regeneration; neuroimaging; brain neoplasms; magnetic resonance spectroscopy; diffusion tensor imaging; metabolism; diffusion; anisotropy; edema; nerve fiber; extracellular space; correlation analysis; grants-supported paper; neuroregeneration

Research Highlights

(1) In normal-appearing white matter, N-acetylaspartate/creatine ratios were positively correlated with fractional anisotropy values, negatively correlated with radial diffusivities, and positively correlated with maximum eigenvalues. Maximum eigenvalues and radial diffusivities in peritumoral edema showed a negative correlation with choline, N-acetylaspartate, and creatine. Radial diffusivities in tumors were negatively correlated with choline.
(2) Neural metabolism in the peritumoral edema area decreased with expanding extracellular space. The normal relationship of neural function and microstructure disappeared in the tumor region.

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INTRODUCTION

Proton magnetic resonance spectroscopy and diffusion tensor imaging are used to detect metabolites and image white matter structure *in vivo*. These techniques have been widely used in large numbers of neurological disorders, including brain tumors[1-4]. Pathological changes in neurons are often associated with changes of water diffusion and metabolites. Correlation analysis may provide further insights into neuronal pathology. Numerous studies have examined the relationship of cerebral metabolites and structure in a number of diseases using combined magnetic resonance spectroscopy and diffusion tensor imaging[5-11]. A positive correlation of fractional anisotropy and N-acetylaspartate was found in cerebral small vessel disease and X-linked adrenoleukodystrophy[5, 9]. Ding *et al* [6] also reported a positive correlation between fractional anisotropy and myoinositol/creatine ratio in patients with Alzheimer's disease, and a positive correlation between fractional anisotropy and N-acetylaspartate/creatine in normal controls. However, a positive correlation of fractional anisotropy and N-acetylaspartate/creatine was also observed in cerebral small vessel disease[10]. Furthermore, in a study of normal, appearing corpus callosum related to multiple sclerosis, the N-acetylaspartate/creatine ratio was negatively correlated with radial diffusivity[8]. In patients with glioma, N-acetylaspartate/creatine was also correlated with fractional anisotropy, although the regions of tumor and peritumoral areas were combined[11]. Recent studies have reported a similar relationship in normal brain tissue[12-13]. For example, Irwan *et al* [12] showed that fractional anisotropy was positively correlated with choline and N-acetylaspartate, and negatively correlated with creatine, as previously reported[13].

Nevertheless, the majority of these correlative studies only examined fractional anisotropy. Fractional anisotropy, a commonly used parameter of diffusion tensor imaging, is calculated from three eigenvalues and describes the directionality of water diffusion. Fractional anisotropy is believed to be determined by the dense packing of axons and their inherent axonal membranes that significantly hinder water diffusion perpendicular to the long axis of fibers. In normal white matter, many factors contribute to the formation of fractional anisotropy, and it cannot be used as a specific marker as it is altered in various pathologies[14-17]. In the present study, we explored whether analysis of metabolism with proton magnetic resonance spectroscopy may have an additional role in exploring the anisotropy of white matter. The correlation analysis of metabolites and more fundamental parameters of diffusivity, such as radial diffusivity, may improve our understanding of the relationship between brain structure and metabolism.

Magnetic resonance spectroscopy and diffusion tensor imaging have been widely used in the study of brain tumors, and significant changes of metabolism and structures in patients with brain tumors have been revealed separately by magnetic resonance spectroscopy and diffusion tensor imaging. In general, magnetic resonance spectroscopy of tumors showed increased choline and decreased creatine and N-acetylaspartate[18]. These changes are related to active proliferation of tumor cells and damage of normal neural structures. By diffusion tensor imaging, decreased fractional anisotropy values are commonly observed in tumor areas[19], which is believed to result from the disordered tumor tissue replacing the regular arranged neural fibers. Nevertheless, little is known about the relationship between metabolism and structure in patients with brain tumors. A significant correlation of median fractional anisotropy values and N-acetylaspartate ratios in patients with glioma was previously reported, and the individual fractional anisotropy values were found to have moderate positive correlation with the N-acetylaspartate/creatine and N-acetylaspartate/choline ratios[11]. However, the correlation analysis in that study was performed by combining areas of tumor, edema, and normal white matter. It is well known that metabolism and structure are very different between tumor, peritumoral areas, and normal white matter. Thus, it remains unclear whether there is a correlation between metabolites and fractional anisotropy in normal white matter in areas of tumor or peritumoral edema, and whether there are relationships between metabolites and structures reflected by diffusion tensor imaging in tumor regions. Thus, in the present study, we examined the hypothesis that there are different correlations of DIT parameters, including fractional anisotropy, with different brain tissues including normal white matter, edema and tumors.

RESULTS

Quantitative analysis of subjects

A total of 24 patients with brain tumors were enrolled in this study, including 14 males and 10 females, aged 18–67 years, with a mean age of 44 years. All lesions were confirmed histologically after surgery. Of 24

patients, six were diagnosed with high grade glioma (World Health Organization (WHO) grade III and IV), 10 with low grade glioma (WHO grade II), four with meningioma, and four with brain metastasis. Brain regions were divided into groups of tumor, peritumoral edema, and normal-appearing white matter. A total of 24 patients were included in the final analysis.

In regions of tumor, a total of 68 square regions of interest of approximately 56 mm^2 were selected for analysis. In peritumoral edema and normal-appearing white matter, 21 and 69 regions of interest were selected, respectively. Values of diffusion tensor imaging and magnetic resonance spectroscopy parameters of tumor, peritumoral edema, and normal-appearing white matter are shown in Table 1. Choline increased in the tumor regions and decreased in the peritumoral edema. Creatine, N-acetylaspartate, and fractional anisotropy all decreased in the peritumoral edema and tumor, and were lowest in the tumor. Maximum eigenvalues and radial diffusivity were highest in peritumoral edema and lowest in normal-appearing white matter. Metabolites in the three groups were all significantly different from each other (P < 0.001), except choline between the peritumoral edema and normal-appearing white matter, and creatine between the tumor and peritumoral edema. The metabolite ratios of the tumor were significantly different from the peritumoral edema and normal-appearing white matter (P < 0.001), but no difference was found between the peritumoral edema and normal-appearing white matter. Significant differences in fractional anisotropy, maximum eigenvalues, and radial diffusivity were detected between the tumor and normal-appearing white matter, the peritumoral edema, and normal-appearing white matter (P < 0.001), but not between the tumor and peritumoral edema.

Characteristics of magnetic resonance spectroscopy and diffusion tensor imaging in brain tumor patients

Fractional anisotropy, maximum eigenvalues, and radial diffusivity in normal-appearing white matter showed a moderate correlation with N-acetylaspartate/creatine ratio; the correlation coefficients were 0.65 (P < 0.001), 0.53 (P < 0.001), and –0.65 (P < 0.001), respectively (Figure 1).

In normal-appearing white matter, fractional anisotropy also showed a weak negative correlation with N-acetylaspartate (r = 0.25, P = 0.043) and choline/ N-acetylaspartate (r = –0.34, P = 0.005), maximum eigenvalues showed a weak correlation with creatine (r = –0.26, P = 0.034), and radial diffusivity showed a weak negative correlation with N-acetylaspartate (r = –0.31, P = 0.010) and a moderate correlation with choline/ N-acetylaspartate (r = 0.46, P < 0.001). In peritumoral edema, maximum eigenvalues and radial diffusivity, but not fractional anisotropy, had a moderate or strong negative correlation with choline, creatine, and N-acetylaspartate; the correlation coefficients were –0.62 (P = 0.003), –0.78 (P < 0.001), and –0.68 (P = 0.001), respectively, for maximum eigenvalues, and –0.58 (P = 0.006), –0.67 (P = 0.001), and –0.62 (P = 0.003), respectively, for radial diffusivity (Figure 2). In tumors, radial diffusivity demonstrated a moderate correlation with choline (r = –0.414, P < 0.001), and a weak correlation between fractional anisotropy and creatine (r = 0.34, P = 0.004), maximum eigenvalues and choline (r = –0.37, P = 0.002), maximum eigenvalues and creatine (r = -0.27, P = 0.029), and radial diffusivity and creatine (r = –0.34, P = 0.005).

DISCUSSION

In the present study, we found that various metabolites and their ratios showed significant changes between normal-appearing white matter, peritumoral edema, and tumors.

Table 1 Magnetic resonance spectroscopy and diffusion tensor imaging parameters of tumor, peritumoral edema, and normal-appearing white matter

Brain region	*n*	Cho (×10^4)	Cr (×10^4)	NAA (×10^4)	Cho/Cr	Cho/NAA	NAA/Cr	FA	λ3 (×$10^{-4}$$mm^2$/s)	RD (×$10^{-4}$$mm^2$/s)
Tumor	68	12.56±5.12	4.63±2.83	4.87±2.84	3.66±2.32	3.50±2.40	1.32±0.98	0.13±0.06	5.13±0.47	4.87±0.49
Peritumoral edema	21	6.40±3.64	5.28±3.14	8.48±4.39	1.26±0.39	0.83±0.40	1.72±0.58	0.16±0.05	5.27±0.21	4.91±0.22
Normal-appearing white matter	69	8.19±3.09	7.48±2.44	14.08±3.98	1.12±0.35	0.60±0.23	1.95±0.44	0.43±0.14	4.71±0.17	4.09±0.11

Contents of Cho, Cr and NAA were measured as areas of peak. Cho increased in the tumor regions and decreased in the peritumoral edema. Cr, NAA, and FA all decreased in the peritumoral edema and tumor, and were lowest in the tumor. λ3 and RD were highest in the peritumoral edema, and were lowest in the normal-appearing white matter. Cho: Choline; Cr: creatine; NAA: N-acetylaspartate; FA: fractional anisotropy; λ3: maximum eigenvalues; RD: radial diffusivity. Data are expressed as mean ± SD. *n*: Number of regions of interest.

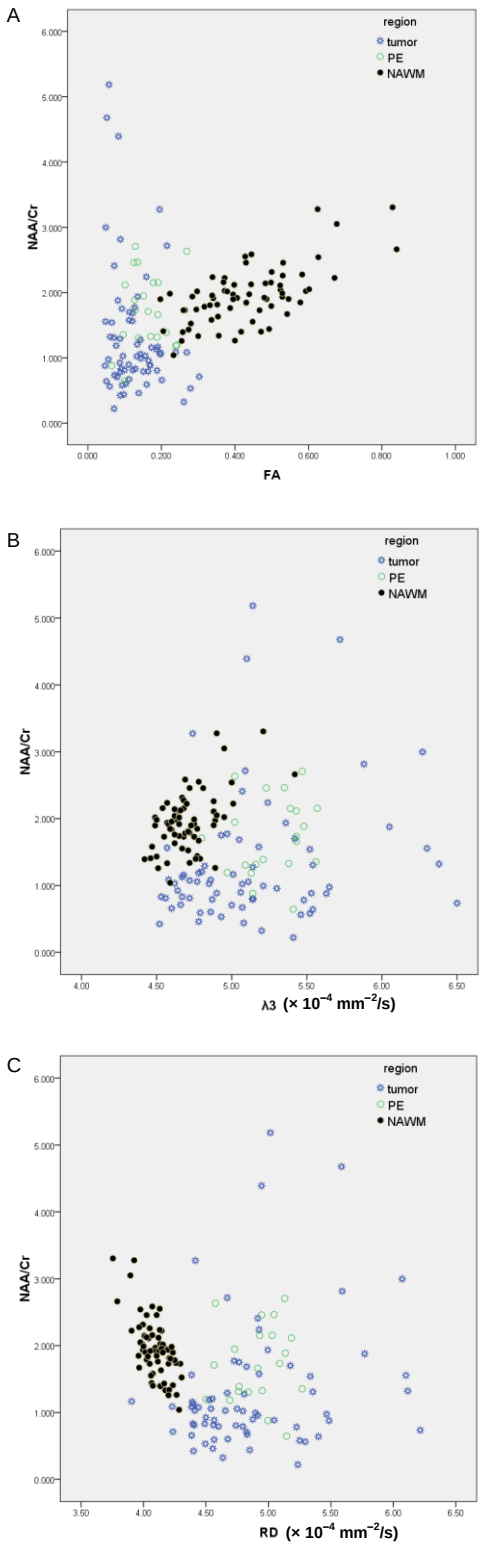

Figure 1 Scatter plot showing negative correlation between N-acetylaspartate/creatine (NAA/Cr) and fractional anisotropy (FA) (A), between NAA/Cr and maximum eigenvalues (λ3) (B), and between NAA/Cr and radial diffusivity (RD) (C) in the tumor (n = 68), peritumoral edema (PE) (n = 21), and normal-appearing white matter (NAWM) (n = 69; Pearson's correlation analysis).

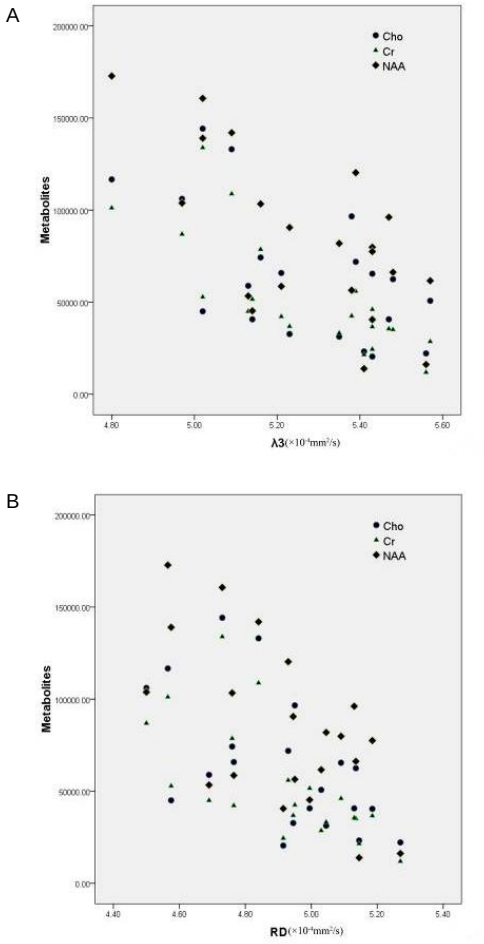

Figure 2 Scatter plots showing negative correlation between choline (Cho), creatine (Cr), and N-acetylaspartate (NAA) and maximum eigenvalues (λ3) in the peritumoral edema (PE, n = 21; A) and between metabolites and radial diffusivity (RD) in the PE (n = 21; B) (Pearson's correlation analysis).

The most obvious change was the elevated choline and its ratios in the tumor regions, and the decrease of metabolites in edema compared with normal-appearing white matter (although choline did not reach statistical significance). For the diffusion tensor imaging parameters, fractional anisotropy of the tumor and peritumoral edema all decreased, while maximum eigenvalues and radial diffusivity increased. Fractional anisotropy, maximum eigenvalues, and radial diffusivity showed no statistical difference between tumor and edema. The results observed for glioma and peritumoral edema are different from those previously reported, which may be due to differences in the types of tumors used in our study. In general, disordered structures such as new vessels in proliferating regions and cystic changes can decrease the directionality of water diffusion. However, some areas with regular

arrangement of cells may allow water molecules to move with directionality, especially in meningiomas[20], which will lead to an increase of fractional anisotropy in tumors.

In this study, the N-acetylaspartate/creatine ratio had a stronger correlation with fractional anisotropy, maximum eigenvalues, and radial diffusivity in normal-appearing white matter than for N-acetylaspartate. Goebell *et al* [11] also detected a positive correlation between fractional anisotropy values and N-acetylaspartate/creatine ratios in patients with gliomas. However, the regions of interest in that study combined areas of tumor with normal-appearing white matter. By analyzing these different regions separately, we found that the correlation between fractional anisotropy and N-acetylaspartate/creatine was weakened in areas of peritumoral edema and tumor. Similar trends were also found for the relationships of maximum eigenvalues, radial diffusivity, and N-acetylaspartate/creatine.

Previous studies have reported a positive correlation between fractional anisotropy and N-acetylaspartate in normal or normal-appearing white matter; the linear correlation coefficients of fractional anisotropy and N-acetylaspartate were 0.41, 0.69, and 0.71, and the logarithmic relationship was 0.64[9, 12-13]. The weaker correlation in our study may be attributed to differences in the various white matter regions selected. N-acetylaspartate is the only metabolite involved in nervous system metabolism, and is commonly used as a neuronal density index[13, 21]. However, the role of N-acetylaspartate in the nervous system remains controversial, but is thought to include synthesis of fatty acid and steroids, including myelination of neural fibers, as well as osmoregulation[22]. Myelination facilitates the molecular diffusion parallel to axons and decreases the perpendicular diffusivity[17], causing an increase in the anisotropy of neural fibers. Osmosis can also contribute to white matter anisotropy. Therefore, in normal white matter, N-acetylaspartate may have relationship with molecular diffusion by regulation of osmosis and myelin thickness. It is also possible that an increase of fiber density in the white matter leads to an enhanced longitudinal diffusion coefficient and a decreased transverse diffusion coefficient, causing an increase in fractional anisotropy[23-24]. The creatine peak predominantly consists of creatine and phospho-creatine, which are involved in energy metabolism, and is considered a measure of cellular density of astrocytes[11, 25-26]. Steen *et al* [26] also showed that creatine kinase B activity was reduced in patients with multiple sclerosis, which may lead to a defective phospho-creatine metabolism in astrocytes. This was speculated to be responsible for the degeneration of oligodendrocytes and axons in multiple sclerosis. In an animal study of neuroAIDS, Ratai *et al* [25] found a decrease of N-acetylaspartate/creatine levels consistent with increased neuronal injury. The increases in creatine were believed to be related to increased energy usage due to astrocytosis and glial activation. This may explain why N-acetylaspartate/creatine has a stronger relationship with diffusion tensor imaging parameters than N-acetylaspartate alone, and suggests that energy metabolism or cellular density may contribute to anisotropic diffusion in white matter[27]. However, the effect of creatine on anisotropy in normal white matter requires further research. The N-acetylaspartate/creatine ratio was reported to be decreased and have a moderate correlation with radial diffusivity in patients with multiple sclerosis, which was considered evidence of demyelination and Wallerian degeneration[8]. However, based on our results, this negative correlation may exist in diseases with demyelination as well as normal-appearing whiter matter. This correlation should be considered in future studies examining brain diseases.

In previous studies, no correlation analysis of metabolites and diffusion tensor imaging parameters was performed in areas of peritumoral edema. In the present study, we found that diffusivity in the peritumoral edema had a significant negative correlation with various metabolites. In contrast to normal-appearing white matter, N-acetylaspartate/creatine ratios and diffusion coefficients in the edema area showed no significant relationship. The increase of extracellular fluid can cause dilution and result in a decrease of metabolite concentrations[28]. Furthermore, enlargement of the extracellular space can lead to an increase in diffusivity[29]. We confirmed these changes in the present study. This negative correlation appeared in peritumoral edema, suggesting that the characteristic changes of diffusion and metabolism are largely determined by changes in the extracellular space.

In tumor regions, only choline and radial diffusivity showed a moderate negative correlation. Choline is a marker for tumor cell proliferation[30-31]. Radial diffusivity is the average of the minimum and middle eigenvalues, and is often used to represent diffusivity perpendicular to the fiber bundle in normal structures. The increase of radial diffusivity is associated with demyelination, destruction, or edema of neural fibers. However, it is difficult to explain the changes of radial diffusivity in

tumors with a normal model as most neural fibers are destroyed within tumors. The negative correlation between radial diffusivity and choline demonstrated a reduction in space between cells associated with cellular proliferation, suggesting that cell density may have greater contribution to diffusion characteristics of tumors. Other relationships between metabolites and parameters derived from diffusion tensor imaging showed a weak correlation or disappeared in tumor tissues, indicating that normal white matter structure was damaged and metabolism was disordered.

This study has a number of limitations: First, the plane thickness of diffusion tensor imaging and magnetic resonance spectroscopy was different, where the measurements of diffusion tensor imaging were only limited to the center of the magnetic resonance spectroscopy plane. This leads to measurement variation. However, the correlation analysis of diffusion tensor imaging and magnetic resonance spectroscopy was still meaningful here, as they had a fixed positional relationship. Second, regions of interest drawn manually in diffusion tensor imaging may differ somewhat with regions of interest selected in magnetic resonance spectroscopy. We attempted to avoid this variation by identifying anatomical structures. Our results may be also limited by the sample size, and the different tumor types included may reduce the correlation coefficient in tumors. However, this influence is unlikely to appear in peritumoral edema and normal-appearing white matter. Finally, there is potential for gray matter voxels to be included in regions of interest because of the partial volume effect.

In summary, this study revealed that the relationships between diffusion characteristics and metabolites are very different between normal-appearing white matter, peritumoral edema and the tumor itself. Neural metabolism in the peritumoral edema area decreased with expanding extracellular space, while the most common relationship of neural function and microstructure disappeared in the tumor region.

SUBJECTS AND METHODS

Design

A case-control study.

Time and setting

Experiments were performed at the Medical Imaging Center of the First Affiliated Hospital of Xi'an Jiaotong University, China from March 2011 to March 2012.

Subjects

A total of 24 patients with brain tumors enrolled in this study.

Inclusion criteria: (1) tumors located above the tentorium; (2) diagnosis was confirmed by histopathological results; (3) a combined imaging protocol comprising MRI diffusion tensor imaging and magnetic resonance spectroscopy sequences should be committed.

Exclusion criteria: (1) patients with non-tumorous disease; (2) images with motion artifacts.

Patients were informed of the scan protocol and risk in accordance with the *Administrative Regulations on Medical Institution*, formulated by the State Council of China[32]. Written informed consent was obtained from all of subjects before the study.

Methods

MRI

All images were acquired using a 3.0 T whole body scanner (GE Signa HDXT, Milwaukee, WI, USA) equipped with an 8-channel head receiver coil. For diffusion tensor imaging, a total of 28 consecutive slices were acquired in 5 mm thickness and 0 gaps; repetition time and echo time were 8 000 ms and 86 ms, respectively. Thirty direction, *b* values of 0/1 000 s/mm^2 were employed. The in-plane resolution was 128 × 128, and was interpolated to an image matrix of 256 × 256. The total acquisition time was 4 minutes 14 seconds. Proton magnetic resonance spectroscopy was performed with 2D PROBE-SI imaging with automated shimming to reduce field inhomogeneity. All magnetic resonance spectroscopy parameters were set up by PROBE-SI autoprescan, which was run to optimize water suppression, radiofrequency power, and shimming over the region of interest. Typically 99% water suppression and a line-width of 7–10 Hz were obtained.

The scan plan of the magnetic resonance spectroscopy was placed based on axial T_2-weighted images, which had the same planes as diffusion tensor imaging. The volume of interest was placed in the center of the tumor including the peritumoral edema and normal-appearing white matter. The voxel size was 56 mm^2 × 15 mm.

Data processing

All data were processed with Functool software provided in a GE workstation AW4.4 (GE Healthcare, Milwaukee, WI, USA). During metabolites spectrum data analysis, one to three volumes of interest were chosen in the solid

area of the tumor (according to tumor size and avoiding cystic areas where possible), the peritumoral edema, and the normal-appearing white matter, and key metabolites including total choline, N-acetylaspartate, and creatine were assessed. The ratios of choline/creatine, choline/ N-acetylaspartate, and N-acetylaspartate/creatine were then calculated. Tumor, peritumoral edema, and normal normal-appearing white matter were distinguished on the basis of T1W-contrast enhanced and T2W images, as described previously[33-34].

On diffusion tensor imaging, the region of interest with a square of 56 mm^2 was placed on the same volume of interest of magnetic resonance spectroscopy (Figure 3) based on anatomical characteristics. Minimum eigenvalues (λ1), middle eigenvalues (λ2), maximum eigenvalues, and fractional anisotropy were then measured. Radial diffusivity was calculated as (λ1+λ2)/2.

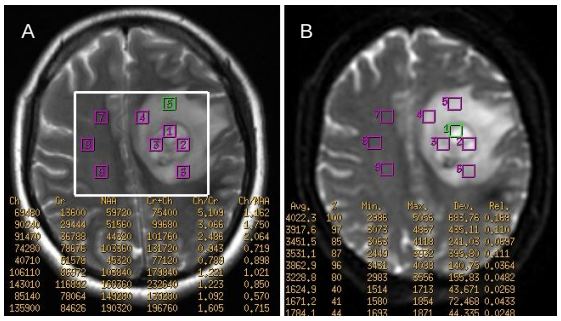

Figure 3 Measurement of magnetic resonance spectroscopy (MRS) and diffusion tensor imaging (DTI) parameters of a female patient aged 45 years (headache and right side numbness) with anaplastic astrocytoma.

The scanning region of MRS (white rectangle) covered tumor, peritumoral edema, and normal appearing whiter matter. Volumes of interest (little squares 1–9) of MRS were selected on T_2 weighted imaging (A). Regions of interest of DTI were manually drawn on images with a *b* value = 0 (B), as for volumes of interest selected in MRS based on anatomical structure.

Statistical analysis

Continuous data were expressed as mean ± SD. The linear correlation between parameters derived from diffusion tensor imaging and magnetic resonance spectroscopy were analyzed with Pearson's correlation coefficient using SPSS 16.0 software (SPSS, Chicago, IL, USA). A value of $P < 0.05$ was considered statistically significant. Correlation coefficients (*r*) greater than 0.7 were defined as a strong correlation, 0.4–0.7 as a moderate correlation, and less than 0.4 as a weak correlation.

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Author contributions: Zhigang Min was responsible for the data collection, data analysis, manuscript writing, the study concept and design, and obtained the funding. Chen Niu participated in data collection. Netra Rana participated in manuscript writing. Huanmei Ji and Ming Zhang participated in study design. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Ethical approval: This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, China.

Author statements: The manuscript is original, has not been submitted to or is not under consideration by another publication, has not been previously published in any language or any form, including electronic, and contains no disclosure of confidential information or authorship/patent application/funding source disputations.

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