

Evaluation of Diffusion Anisotropy and Diffusion Shape in Grading of Glial Tumors

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ABSTRACT

Background: The most common primary tumors of brain are gliomas. Grading of tumor is vital for designing proper treatment plans. The gold standard choice to determine the grade of glial tumor is biopsy which is an invasive method.

Objective: In this study, we try to investigate the role of fractional anisotropy (diffusion anisotropy) and linear anisotropy coefficient (its shape) with the aim of Diffusion Tensor imaging (as a non-invasive method) in the grading of gliomas.

Methods: A group of 20 patients with histologically glial approved was evaluated. In this study, we used a 1.5-Tesla MR system (AVANTO; Siemens, Germany) with a standard head coil for scanning. Multi-directional diffusion weighted imaging (measured in 12 non-collinear directions) and T1 weighted non-enhanced were performed for all patients. We defined two Regions of Interest (ROIs); white matter adjacent to the tumor and the homologous fiber tracts to the first ROI in the contralateral hemisphere.

Results: Linear anisotropy coefficient (CL), fractional anisotropy (FA) values and ratios of low-grade peri-tumoral fiber tracts were higher than high-grade gliomas (P-value $CL_t=0.014$, P-value $CL_{t/n}=0.019$ and P-value $FA_t=0.006$, P-value $FA_{t/n}=0.024$). In addition, we perform ROC curve for each parameter (CL ratio-AUC = 0.82 and FA ratio-AUC = 0.868).

Conclusion: Our findings prove significant difference between diffusion anisotropy (FA) and diffusion shape (CI) between low grade and high grade glioma, based on which we find this evaluation helpful in the grading of glial tumors.

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Keywords

Diffusion Magnetic Resonance Imaging • Glioma • Anisotropy

Introduction

The most common primary tumors of the central nervous system are gliomas [1]. Glioma arises from the glial cells of the brain [2]. Despite improvements in prognosis for patients with low grade glioma, it is still poor for high grade glioma patients [3, 4]. Tumor grading is essential for designing proper treatment strategies [5, 6].

The gold standard method for grading of glial tumor is the biopsy which is an invasive method and has its own problems and risks. Biopsy can lead to swelling or bleeding on the brain, infections, seizures, stroke or coma. Sometimes, tests on the sampled tissue are inconclusive and

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the whole procedure must be repeated. The resulting problems of biopsy depend on many variables such as lesion properties (location, histology) or preoperative pharmacological therapy (corticosteroids, antiplatelet agents) [7]. Intracranial hemorrhage is the most common side effect of brain biopsy and has direct association with inpatient mortality [8].

In recent years, the results of various studies have shown that the use of MRI techniques has improved the detection and assessment of lesions. Routine magnetic resonance imaging (MRI) may underestimate tumor size, and that is not a reliable method in high-grade and low-grade glioma discrimination and grading of tumor, and that may cause mistakes in treatment strategy [9, 10].

Diffusion Tensor Imaging (DTI) is a totally non-invasive MRI method that allows the mapping of water molecules diffusion. Because of different obstacles (like fibers and membranes), water molecules cannot freely diffuse. Diffusion Tensor Imaging with the aim of water molecule diffusion patterns reveals the microscopic details about tissue architecture like fibers. Because of its ability in defining abnormalities in fiber architecture, DTI has become standard for white matter disorders [11]. DTI is mainly used for the study and treatment of neurological disorders.

In this study, we use fractional anisotropy (FA) and linear anisotropy coefficient (CL) in order to investigate anisotropic features of water molecules. Fractional anisotropy (FA) describes the degree of anisotropy of water molecules diffusion process. Several studies on FA and grading of glioma tumors have been done but results are controversial [12-16]. With the aim of linear anisotropy coefficient (CL), we study the linearity of water molecules diffusion. While sampling of pathology as a gold standard is an invasive way, we perform a prospective study to investigate the role of Diffusion Tensor Imaging (as a non-invasive method) by mean of FA and CL in grading of glioma tumors.

Material and Methods

Patient Population

The imaging data of 20 patients (mean age \pm standard deviation (S.D.), 45.9 years \pm 13.65) with biopsy-proven WHO Low grade (13 patients) and High grade (7 patients) gliomas were analyzed. 9 patients were female (age range, 15–68 years; mean age, 48.3 years \pm 15.9) and 11 were male (age range, 26–69 years; mean age, 43.9 years \pm 11.89).

MR Imaging

MRI scanning was performed using a 1.5-Tesla MR system (AVANTO; Siemens, Germany) equipped with a standard head coil. For DTI, a diffusion-weighted echo-planar imaging sequence was obtained (repetition time = 8600 ms; echo time = 107 ms; number of excitations = 1). Diffusion gradient encoding was performed in 12 non-collinear directions with a diffusion weighting factor (b) of $b = 1000 \text{ s/mm}^2$, as well as with $b = 0 \text{ s/mm}^2$ (no diffusion gradient).

Image Analysis

Data Processing

Spatial normalization and pre-processing on twenty DTI series and b_0 image series were performed using “Explore DTI” (“Leemans A, Jeurissen B, Sijbers J, and Jones DK. Explore DTI: a graphical toolbox for processing, analyzing and visualizing diffusion MR data. In: 17th Annual Meeting of Intl Soc Mag Reson Med, p. 3537, Hawaii, USA, 2009). Final processing was performed by DTI Studio version 3.0.3 (Processing Tools and Environment for Diffusion Tensor Imaging – H. Jiang and S. Mori, Radiology Department, Johns Hopkins University, Baltimore, MD, USA) to measure fractional anisotropy (FA) and linear anisotropy coefficient (CL).S

Fractional Anisotropy (FA) is between 0 and 1. This scalar parameter describes the degree of anisotropy of a diffusion process. In white matter, FA depends on fiber density, axonal di-

ameter, packing and myelin thickness. A value of one implies that diffusion occurs only along one axis and is fully restricted along all other directions. We observe high anisotropy in healthy fiber bundles. A value of zero means that diffusion is isotropic and there is no restriction for water molecules e.g. when fiber bundle is damaged, barriers for water molecules diffusion disappear and we can observe isotropic diffusion. Fractional Anisotropy was computed using the following standard algorithm:

$$FA = \sqrt{\frac{1}{2} \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_1 - \lambda_3)^2 + (\lambda_2 - \lambda_3)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

Although FA is a good indicator of diffusion anisotropy, it does not give us any information about the shape of diffusion ellipsoid [17]. In this case, we use diffusion contrast mechanisms to differentiate the tubular, planar and spherical types of diffusion anisotropy. The linear anisotropy coefficient (CL) becomes bright where diffusion is mainly along the direction corresponding to the largest Eigen value and tubular ellipsoid regions but remains dark for planar regions. CL value can be calculated using the following equation [18]:

$$CL : \frac{\lambda_1 - \lambda_2}{\lambda_1 + \lambda_2 + \lambda_3}$$

Determination of Region of Interest and Parameters

For each patient, two rectangular ROIs (10.10 pixels) were located at: 1- the white matter adjacent to the tumor and 2- the homologous fiber tracts to ROI 1 in the contralateral hemisphere (Figure 1). CL and FA values were obtained in each ROI. The ratios were then calculated by dividing the mean CL and FA values of ROI 1 by those of ROI 2.

Statistical Analysis

In this study, we use Statistical Package for Social Sciences version 16.0 (SPSS; Chicago, IL, USA) to analyze our data. A p-value of less than 0.05 was considered significant. We per-

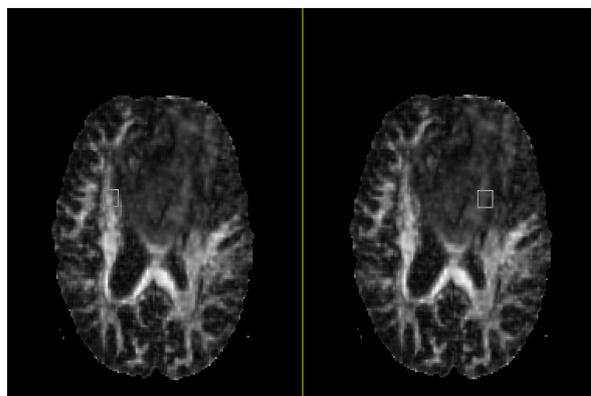


Figure 1: A 43 year-old man with high grade glioma: adjacent white matter and normal hemisphere ROI

form ROC (receiver operating characteristic) curve and use AUC (Area Under Curve) to evaluate the association between each parameter (CL and FA ratio) and glioma classification. Additionally, we performed t-test exam to investigate the correlation between our parameters and tumor grading.

Results

Tumor grade, FA and CL values and ratios can be seen in Table 1. In peri-tumoral fibers, the FA values (FA_t) and FA ratios ($FA_{t/n}$), CL values (CL_t) and CL ratios ($CL_{t/n}$) of the low-grade gliomas are higher than those of the high-grade gliomas (P-value $CL_t=0.014$, P-value $CL_{t/n}=0.019$ and P-value $FA_t=0.006$, P-value $FA_{t/n}=0.024$).

In addition, we performed ROC curve for each parameter (Figure 2). Results are reported in Table 2. We calculate $CL_{t/n}$ (0.25) and $FA_{t/n}$ (0.31) threshold between low grade and high grade gliomas in this study.

Table 1: FA and CL values and ratios for low grade and high grade gliomas

ROI	Low grade	High grade	P-value
CL_t	0.17 ± 0.05	0.11 ± 0.04	0.014
$CL_{t/n}$	0.48 ± 0.18	0.44 ± 0.64	0.019
FA_t	0.18 ± 0.036	0.12 ± 0.42	0.006
$FA_{t/n}$	0.45 ± 0.164	0.27 ± 0.153	0.024

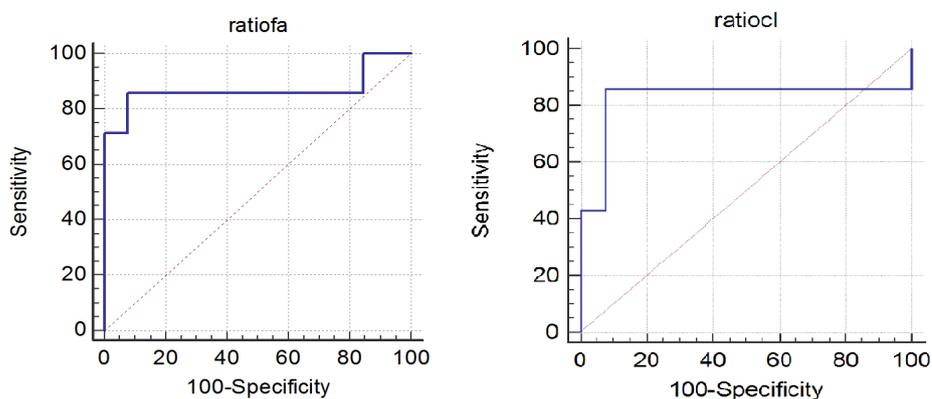


Figure 2: ROC curves for FA and CL

Table 2: Rock curve results for FA and CL ratio

Parameter	Cutoff value	sensitivity	specificity	AUC	P-value
CL _{v/n}	0.25	85.71	92.31	0.82	0.022
FA _{v/n}	0.31	85.71	92.31	0.86	0.0024

Discussions

Our finding suggested that FA and CL values and ratios are significantly higher in low-grade gliomas than in high-grade ones. Studies show that the difference between FA and CL is surprisingly big in human brain suggesting that most pixels consist of one dominant fiber [18]. CL (linear anisotropy coefficient) is mainly along the direction of the largest Eigen value hence when the contrast becomes bright, that means we have high anisotropy. As mentioned before, Fractional anisotropy in white matter indicates fiber integrity and significantly depends on fiber density, axonal diameter, myelin thickness, packing and organizations of neural fiber bundles. When fiber density or fiber packing and organizations damage and decrease, barriers for water molecule diffusion disappear, diffusion pattern becomes more isotropic and we can observe isotropic diffusion and the decrease of anisotropic diffusion of water molecules (FA value). Magnetic resonance imaging (MRI) basically depends on water molecules and in this advanced imaging (DTI) method we investigated diffusion of

water molecules. Because of different obstacle (e.g. fibers and membranes), water molecules cannot freely diffuse. In the presence and integrity of fibers (as an obstacle), water molecules diffusion pattern becomes more anisotropic. In this way, Diffusion Tensor Imaging (DTI) with the aim of water molecule diffusion patterns reveals the microscopic details about tissue architecture like fibers.

Based on that, our findings demonstrated that fiber tracts in the vicinity of low-grade gliomas are significantly preserved and well-organized (high FA); hence, diffusion shape becomes more tubular (high CL) while peritumoral fiber tracts in high grade gliomas are damaged, disorganized and miss their integrity (low FA), and diffusion shape is not tubular (low CL). Several studies on FA in low and high grade gliomas and their relationships have been done but results are not the same. This difference in results increases the importance of further research in this field.

Inoue et al. reported lower FA values for low grade gliomas than high grade ones. They proposed the relation between tumor cellularity

and vascularity, and FA values [13]. The same result was obtained in Liu et al. study. They examined the supra-tentorial gliomas and observed that the average FA values in low grade gliomas tended to be meaningfully lower than those of high grade gliomas [14]. Smitha reported significant decrease of FA value in high grade gliomas compared to peri-tumoral area and homologous fiber tracts in the contralateral hemisphere. They also reported that FA values are significantly lower in low grade gliomas [16]. On the other hand, some studies reported the opposite result (the same as our study) for example Goebell et al. reported higher FA values for low-grade peri-tumoral fiber tracks than high grade ones [12]. Andrés Server revealed that mean values of FA_t and FA_{v_n} present statistically significant difference between grades III and IV [15]. Yiyong Chen suggested that the peri-tumoral area of low-grade glioma has higher value of FA than high grade one and he concluded that the integrity of neural fiber bundle in low grade glioma is preserved more than high grade glioma. He found these results helpful in grading of glial tumors [1].

In order to describe the reason of variety in results, we agree with Yiyong Chen and we relate the main cause of variation to the placement of region of interest. Many studies used T2 or ADC images to place ROI. In this case, the location of second ROI (in normal cerebral hemisphere) is subjective. We used FA-map which can better define the anatomic relationship between tumor and adjacent fibers. So, we could better characterize peri-tumoral fiber and define them in contralateral hemisphere.

There are limited studies in grading of glial tumor with the aim of diffusion parameter shape. Lin Ma et al. used combined diffusion tensor imaging metrics to differentiate between low-grade and high-grade gliomas. They proposed the largest curve area (AUC = 0.81) and the best classification ability (86.7% sensitivity and 80% specificity) for the combination of FA, shape parameter and ADC of

immediate peri-tumoral area. They report that “diffusion tensor shape parameters” can offer further “spatial information” to improve glioma classification [4]. Kumar et al. had a study on brain abscess cavity and they reported the excellence of diffusion tensor shape parameters in discriminating true from pseudo-white matter fibers. Their results showed significant decrease of CL in the abscess cavity in comparison with normal white matter [7]. Sumei Wang et al. used diffusion tensor imaging in their study to differentiate between glioblastomas and solitary brain metastases. They found a combination of ADC, FA and shape parameters with a sensitivity of 92%, specificity of 100% and AUC 0.98; the best parameters for discrimination [8].

We cannot compare different fiber tracts with each other because there is normal variation between different fibers. As the saying goes, one must compare “apples to apples, not apples to oranges” [19]. Due to this fact, we calculated ratios of CL and FA in order to overcome this problem. We use fractional anisotropy map for drawing ROIs which is more standard than gray scale images (T1, T2...) for this purpose. One of our study limitations is the effect of edema and mass effect of the tumor which might impact our parameters.

Conclusion

In this study, we investigated the role of DTI tensor shape parameters including: linear coefficient (CL) and fractional anisotropy (FA) in glial tumor grading. Our study showed that these parameters were significantly different from low-grade gliomas and high-grade ones, which could be useful for pre-operative grading of glioma tumors.

Conflict of Interest

None

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