High Order Diffusion Tensor Imaging in Human Glioblastoma

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Rationale and Objectives: Diffusion tensor imaging has been used to characterize tumor heterogeneity and invasion in human glioblastoma. Recently, higher order diffusion tensors have been proposed as solutions to errors associated with diffusion tensor imaging estimates of complex microstructures. The purpose of the current study was to examine higher order diffusion characteristics in human glioblastoma prior to surgical resection using the fourth-order diffusion tensor model.

Materials and Methods: Twenty-five patients with newly diagnosed glioblastoma participated in the study. Diffusion-weighted images were collected in 21 directions. The second-order (traditional) and fourth-order diffusion tensors were calculated and compared in regions of contrast enhancement, T2 signal abnormality, and normal-appearing white matter.

Results: Orientation distribution functions were strikingly different between the two tensor models, particularly in regions with tumor heterogeneity and/or regions of suspected tumor invasion. Image contrast was significantly higher in fourth-order scalar measures compared to second-order scalars. Results of particular eigenvalues and scalars using the fourth-order tensor showed differences between T2 abnormal regions and contrast enhancement, whereas second-order eigenvalues and scalars did not show differences. This suggests that higher order diffusion images could potentially be more sensitive to tumor invasion.

Conclusions: These results suggest that the fourth-order diffusion tensor has the ability to add value to second-order (traditional) diffusion tensor imaging in the evaluation of glioblastoma.

Key Words: DTI; diffusion MRI; fourth-order tensor; GBM; glioblastoma; brain tumor.

Diffusion-weighted magnetic resonance imaging (MRI) techniques are highly sensitive to the underlying microstructural characteristics of biologic tissues. This sensitivity to subvoxel, microscopic features has helped provide insight into many physiologic changes that occur as a result of brain tumor growth and invasion, such as cerebral edema (1), hypoxia (2), the increase in diffusion observed after successful radiotherapy due to cell breakdown (3), and the change in diffusion characteristics resulting from increasing tumor cellularity (4) and invasion (5,6). Additionally, diffusion magnetic resonance characteristics have been shown to be predictive (7,8) and prognostic (6,9) biomarkers in new brain tumor therapeutics and have shown utility in histopathologic grading of gliomas (10).

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Diffusion tensor imaging (DTI) involves the addition of directional encoding to diffusion measurements, allowing novel structural information about the microenvironment to be acquired. For example, in normal tissues, DTI typically shows high diffusion anisotropy within tightly packed white matter fiber bundles because of diffusion restriction perpendicular to axon fibers. This high degree of diffusion anisotropy within white matter regions provides the basis for DTI tractography (11), in which pseudoaxonal tracts are "grown" from seed regions placed within white matter tracts. For relatively simple tissue structures, such as the thick white matter bundle within the corpus callosum, the "traditional" diffusion tensor model may be an adequate representation of the general tissue architecture. For more complex tissues, "nontraditional" diffusion models may be beneficial.

Primary human brain tumors, such as the highly aggressive and malignant glioblastoma, have an extremely complex and heterogeneous microenvironment consisting of pallisading necrosis, edema, leaky neovasculature, and cells of various sizes excreting numerous signaling molecules and proteins. Traditional DTI techniques have shown tremendous utility in the diagnosis (12,13), prognosis (14), and surgical planning of adult primary brain tumors (15,16). Traditional DTI involves collecting multiple diffusion-weighted images, encoded for specific directional sensitivities, and then fitting these data to a 3 × 3, second-order diffusion tensor field

(17). Higher order diffusion tensors, such as the fourth-order 9 × 9 covariance diffusion tensor proposed by Basser and Pajevic (18), offer an alternative model to the simple 3 × 3 diffusion tensor with significantly less complexity and acquisition requirements compared to other advanced techniques, including diffusion spectral imaging or q-space imaging (19). Additionally, the fourth-order tensor has demonstrated superiority over the second-order diffusion tensor when describing complex structures such as white matter tract crossing (20), which suggests that this technique may be potentially useful in highly heterogeneous neoplasms.

On the basis of promising initial results in complex neural structures and the known benefits of traditional DTI in human brain tumor imaging, we hypothesized that application of fourth-order DTI may provide additional insight into the complexity of the tumor microenvironment in human glioblastoma. In the current pilot study, we report fourth-order DTI characteristics in 25 patients with newly diagnosed glioblastoma.

MATERIALS AND METHODS

Patients

A total of 25 patients with newly diagnosed, histologically confirmed glioblastoma were included in the current study. For all patients, the average ± standard error of the mean contrast-enhancing tumor volume was 33.4 ± 4.0 mL, the average volume of necrotic tissue was 5.25 ± 1.1 mL, and the average volume of T2 signal abnormality was 131.2 ± 8.2 mL. Fourteen patients were male and 11 were female. Seven of the patients had frontal lobe tumors, 10 patients had parietal lobe tumors, five had temporal lobe tumors, and two had occipital lobe tumors. All patients received maximal tumor resection and radiotherapy (typically 6000 cGy) after presurgical MRI and DTI scans. All patients in this study provided institutional review board–approved informed consent. Data acquisition was performed in compliance with all applicable Health Insurance Portability and Accountability Act regulations.

MRI

Data were collected using a 3.0-T magnetic resonance system (Magnetom Trio; Siemens Medical Systems, Erlangen, Germany) using pulse sequences supplied by the scanner manufacturer. Standard anatomic MRI sequences included axial T1-weighted (echo time [TE], 2.5 ms; repetition time [TR], 375 ms; slice thickness, 3 mm; no slice gap; number of signals acquired, 2; matrix size, 320 × 261, flip angle, 60°; field of view [FOV], 24 cm), T2-weighted fast spin-echo (TE, 92 ms; TR, 3800 ms; slice thickness, 3 mm; no slice gap; number of signals acquired, 2; matrix size, 256 × 256; FOV, 24 cm), and gadopentetate dimeglumine–enhanced (Magnevist 0.1 mmol/kg; Berlex Laboratories, Wayne, NJ) three-dimensional magnetization-prepared rapid gradient-echo T1-weighted images (TE, 3.52 ms; TR, 1900 ms; inversion time, 1900 ms; slice thickness, 1 mm; number of signals acquired, 2; matrix size, 256 × 256; FOV, 24 cm) acquired after contrast injection.

Diffusion MRI Data

Diffusion-weighted images were collected (TE, 100 ms; TR, 10,600 ms; number of signals acquired, 1; slice thickness, 2 mm; no slice gap [collected interleaved]; matrix size, 128 × 128; FOV, 24 cm) using a twice-refocused spin-echo echo-planar imaging preparation (21) in a total of 20 diffusion-sensitizing directions with b = 1000 s/mm^2 and a single b = 0 s/mm^2 image with the same image parameters.

Conventional Second-order DTI and Scalar Metrics

The traditional second-order diffusion tensor (17) was constructed using Analysis of Functional Neuroimages commands (http://afni.nimh.nih.gov/afni). The traditional 3 × 3 second-order diffusion tensor is defined as

$$\mathbf{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}. \quad (1)$$

Fractional anisotropy (FA) (22) and the three eigenvalues associated with the 3 × 3 second-order diffusion tensor (λ_1, λ_2, and λ_3) were used for subsequent analysis.

Fourth-order DTI and Scalar Metrics

The symmetric, positive-definite fourth-order diffusion tensor field was constructed using methods described in previous publications (23,24). Briefly, the 9 × 9 fourth-order diffusion tensor field is defined as (18,20)

$$\mathbf{\Delta} = \begin{bmatrix} D_{xxxx} & D_{xxxy} & D_{xxxz} & D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxxz} & D_{xxyz} & D_{xxzz} \\ D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xxyz} & D_{xyyz} & D_{xyzz} \\ D_{xxxz} & D_{xxyz} & D_{xxzz} & D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xxzz} & D_{xyzz} & D_{xzzz} \\ D_{xxxy} & D_{xxyy} & D_{xxyz} & D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xxyz} & D_{xyyz} & D_{xyzz} \\ D_{xxyy} & D_{xyyy} & D_{xyyz} & D_{xyyy} & D_{yyyy} & D_{yyyz} & D_{xyyz} & D_{yyyz} & D_{yyzz} \\ D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xyyz} & D_{yyyz} & D_{yyzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} \\ D_{xxxz} & D_{xxyz} & D_{xxzz} & D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xxzz} & D_{xyzz} & D_{xzzz} \\ D_{xxyz} & D_{xyyz} & D_{xyzz} & D_{xyyz} & D_{yyyz} & D_{yyzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} \\ D_{xxzz} & D_{xyzz} & D_{xzzz} & D_{xyzz} & D_{yyzz} & D_{yzzz} & D_{xzzz} & D_{yzzz} & D_{zzzz} \end{bmatrix} \quad (2)$$

Similar to the second-order tensor field, common scalars can be extracted from the fourth-order diffusion tensor for additional visualization and analysis. These scalars include the generalized variance (GVar) (25) and the six independent eigenvalues (18) associated with the fourth-order tensor (β_1–β_6). Note that the symbols $\mathbf{\Delta}$ and β were used only to separate fourth-order DTI terms from second-order DTI terms. Implementation of the fourth-order, regularized, positive-definite 9 × 9 diffusion tensor field was performed for each voxel using MATLAB scripts courtesy of Angelos Barmpoutis, PhD, as described in other publications involving higher order DTI (23,24).