Differentiation of Low-Grade and High-Grade Gliomas Using A Non-Gaussian Diffusion Imaging Model

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PURPOSE: Accurately grading gliomas using MRI prior to treatment has been challenging despite development of a number of advanced neuroimaging techniques [1]. Conventional diffusion MRI, for example, lacks specificity likely because of its reliance on apparent diffusion coefficient (ADC) derived from a Gaussian diffusion model [1,2]. This simple model assumes a uniform diffusion process in a voxel, which is rarely the case for heterogeneous tumor tissues. To address this problem, a number of non-Gaussian diffusion models have been developed. Recently, one of the non-Gaussian diffusion models, known as the fractional order calculus (FROC) model [3,4], has been used to successfully differentiate pediatric brain tumors and demonstrated improved performance over using ADC values [5]. The goal of this study is to investigate the feasibility of extending FROC model to differentiating between high-grade and low-grade gliomas in adult patients.

METHODS: ***Patients***: Twenty-seven (27) glioma patients (18 – 64 years old) were enrolled in this study with IRB approval and written informed consent. According to the WHO classification [6], 13 patients had histologically proven low-grade (I or II) gliomas and 14 had high-grade (III or IV) gliomas. ***Imaging:*** MR images were acquired on a 3T MRI scanner (GE MR750; GE Healthcare, Milwaukee, WI) with a 32-channel phased-array head coil. The imaging protocol included pre-contrast T1W with FLAIR, T2W PROPELLER, and diffusion-weighted (DW) sequence with multiple b-values needed for FROC model analysis, followed by post-contrast T1W imaging. Diffusion-weighted images were produced using an EPI sequence with 17 b-values up to 4000 s/mm^2 (TR/TE = 3025/110.7 ms, NEX = 1, FOV = 24 × 24 cm^2, matrix size = 160 × 160, slice thickness = 5 mm). ***FROC Model Fitting:*** The multi-*b*-value diffusion data were fitted to FROC model pixel-by-pixel using the following equation: $S/S_0 = \exp\{-D\mu^{2(\beta-1)}(\gamma G_d \delta)^{2\beta}[\Delta-(2\beta-1)\delta/(2\beta+1)]\}$, where D is diffusion coefficient (similar to ADC); β, the spatial fractional order, is related to the degree of intravoxel tissue heterogeneity; and μ, a spatial quantity in units of μm, is related to the diffusion mean free length [3]. ROIs were placed both on the normal appearing gray matter (NAGM) (i.e., contralateral thalamus) as an internal control and on the solid part of tumors on each slice of the T2W EPI images (b = 0), guided by the T1W and T2W images. The same ROIs were propagated to the corresponding D, β, and μ maps for statistical analysis. All image processing and fitting were performed using Matlab (Mathworks Inc, MA). ***Statistical Analysis:*** Mean values of D, β, and μ were calculated from the NAGM and the tumor ROIs for each patient. Based on these values, the low-grade and high-grade brain tumor groups were compared using Mann-Whitney U-test setting $p < 0.05$. ROC analysis was performed to determine the area under the curve (AUC) for assessing the performance of tumor differentiation using individual FROC parameters. All statistical analyses were carried out using SPSS software (SPSS, Inc., Chicago, IL).

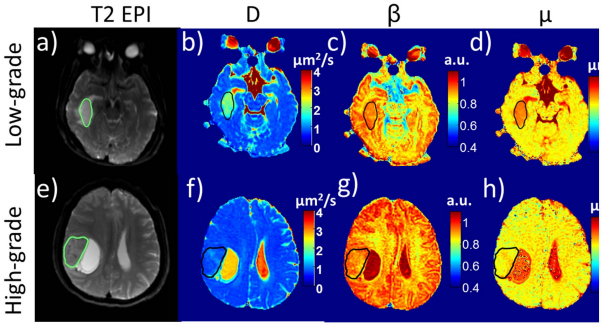

Figure 1. A set of images from representative patients with low- (top row) and high-grade (bottom row) gliomas. Tumor ROIs (in green) were defined on T2W EPI images (Figs. 1a, e). The FROC parameters D, β, and μ in tumors (black ROIs, Figs. 1b-d, respectively) were considerably higher in the low-grade than those in the high-grade patient (Figs. 1f-h).

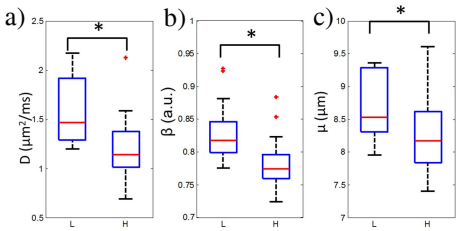

Fig. 2 Box plots of FROC parameters D (a), β (b), and μ (c) between low-grade (L) and high-grade (H) gliomas. * indicates significant differences ($p < 0.05$) between the low- and high-grade tumors.

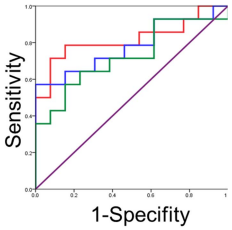

Fig. 3 ROC curves for D (blue), β (red), and μ (green) with the dialog reference line for differentiating between high- and low-grade gliomas.

RESULTS: Figure 1 shows a set of images from representative patients of low- (top row) and high-grade (bottom row) gliomas. Tumor ROIs were outlined in green on T2W (b=0) EPI images (Figs. 1a, e). The FROC maps of D, β, and μ in this low-grade glioma (Figs. 1b-d, respectively) presented higher signal than those in the high-grade tumor (Figs. 1f-h), leading to a distinct difference between low- and high-grade tumors. Group analysis showed that the D, β and μ values of NAGM (the internal control) showed no significant difference between the two groups as expected ($p > 0.67$). Significant differences between the low and high grade gliomas were found in D (1.58±0.34 μm^2/ms vs 1.23±0.36 μm^2/ms, $p = 0.012$), β (0.83±0.05 vs 0.79±0.04, $p = 0.004$), and μ (8.66±0.51μm vs 8.23±0.57μm, $p = 0.048$), as shown in the box plot (Fig. 2). In the ROC curves (Fig. 3), the AUC value of β (AUC=0.82) is higher than that of D (AUC = 0.78) and μ (AUC=0.73), suggesting that individually β was the best indicator for differentiating low- from high-grade gliomas.

DISCUSSION AND CONCLUSION: The FROC diffusion model produced a new set of parameters for differentiating low- and high-grade gliomas. Compared with diffusion coefficient D, the new parameter β, which has been shown to be sensitive to tissue heterogeneity, exhibited better performance in differentiating the two groups. Although a larger number of patients is helpful to further validate the findings, our results suggested that FROC model using high b-values may become be a strong candidate for an MR-based grading of glioma.

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