Intra-Voxel Distribution of DWI Decay Rates Reveals C6 Glioma Invasion in Rat Brain

K. M. Bennett[1], J. S. Hyde[2], S. D. Rand[3], R. Bennett[4], K. J. Rebro[1], H. G. Krouwer[5], K. M. Schmainda[2,3]

[1]Medical College of Wisconsin, Milwaukee, WI, United States, [2]Biophysics, Medical College of Wisconsin, Milwaukee, WI, United States, [3]Radiology, Medical College of Wisconsin, Milwaukee, WI, United States, [4]GE Medical Systems, Waukesha, WI, United States, [5]Neurology and Neurosurgery, Medical College of Wisconsin, Milwaukee, WI, United States

Introduction: A noninvasive method for detecting the invasion of malignant gliomas is critical, because invasion is blamed for the dismal prognosis of glioma patients (1). One frequent observation in gliomas is the high degree of heterogeneity present in the main tumor mass, which is reflected in parmeters measured by MRI (2). It is therefore hypothesized here that intravoxel heterogeneity, as measured by stretched-exponential measurements of DWI decay curves (α-DWI), is a marker of tumor invasion (3). In α-DWI, the heterogeneity index α and the distributed diffusion coefficient (DDC) are obtained. These parameters provide a new type of contrast that may enable non-invasive detection of brain tumor cells.

Methods: Eight male Sprague-Dawley rats were inoculated with 10^5 (10μl) human C6 glioma cells. Cells were injected at a depth of 3 mm from the dural surface. Rats were imaged 14-15 days after tumor inoculation. In three of the rats, glioma cells were labeled with the PKH26 red fluorescent dye. Five healthy Sprague-Dawley rats were imaged as a control. The rats were anesthetized using urethane (1.2 g/kg), and were immobilized with a fiberglass bite bar. Rats were imaged on a Bruker 3T/60 scanner using a Stejskal-Tanner pulse sequence with a 64×64 matrix, a FOV of 6.4 cm, an axial slice thickness of 1.0 mm, and a TE of 46 ms. The b-value was varied from 0 to 6500 s/mm^2 in increments of 500 s/mm^2, with a diffusion time of 27 ms, and b-values were applied in a random order in the read-gradient direction. Rats were given an injection of gadopentate (Magnevist) following the DWI, and T_1-weighted images were acquired. The DWI data were fitted with the stretched-exponential model on a voxel-wise basis. Fluorescence microscopy was performed using a Nikon fluorescence microscope. The intensity of fluorescence was calculated using Metamorph image analysis software (Universal Imaging Corp, PA).

Results: Histograms of α in white matter, peri-tumor and gray matter ROIs are shown in Fig. 1. The value of α was significantly ($p<0.05$) lower in the peri-tumor ROI than in gray matter, and was significantly higher than in white matter. The value of DDC was significantly lower than in white matter and was not significantly different from gray matter. Labeled tumor cells visible in the tumor and peri-tumor regions by fluorescence microscopy seen in Fig 2. There was no fluorescence in ipsiliateral or contralateral gray matter. There was no observed increase in T2-weighted or proton-density images, suggesting that peri-tumor edema did not cause the local decrease in α. When used in combination, α and DDC allowed the tumor, white-matter, and gray-matter ROIs to be distinguished, as seen in Fig. 3.

Conclusions: Using α-DWI, changes in intra-voxel heterogeneity were observed in the tumor and peri-tumor ROIs, where the presence of invading tumor cells was confirmed using fluorescence microscopy. This supports the hypothesis that intra-voxel heterogeneity is a marker of glioma invasion in rat brain.

References:

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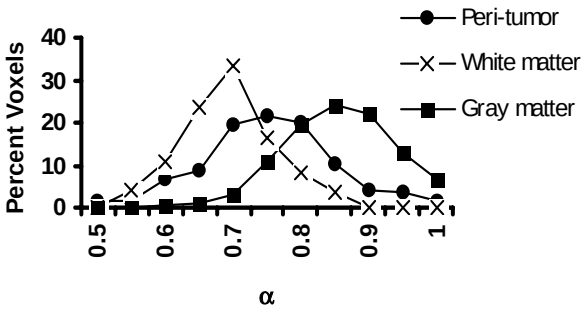

Figure 1 (Above): Pooled results of α-DWI for five tumor-inoculated and five normal control rats showing separation in α between peri-tumor, normal white matter, and normal gray matter ROIs. The differences were statistically significant ($p < 0.05$) between each of the groups, though there was visible overlap between the ROIs.

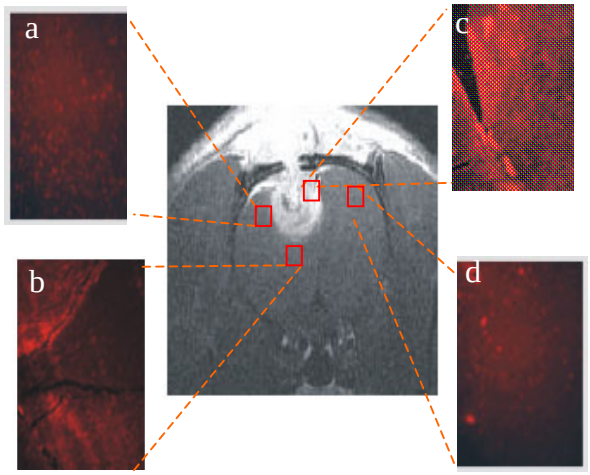

Figure 2 (Above): Fluorescence microscopic image (10×) of rats inoculated with C6 glioma cells. The cells were labeled with a red fluorescent dye. Fluorescent images are shown relative to the post-contrast MRI. ROIs are a) Ipsiliateral, b) Peri-tumor, c) Tumor, and d) Contralateral regions. Tumor and peri-tumor changes in α were observed using α-DWI.

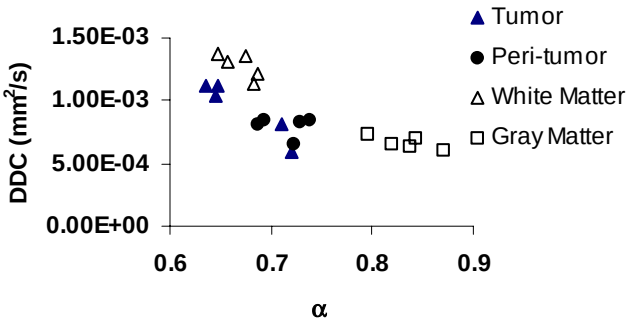

Figure 3 (Left): A scatterplot of α-DWI results showing the average values of α and DDC in each rat, in tumor, peri-tumor, white matter, and gray matter ROI$_S$. A clear separation was made between tumor, white matter, and gray matter in the inter-rat comparison that is statistically significant.