Diffusion MRI study of slowly growing human glioma models in mice at 14.1T

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Introduction: Implanting human glioma cell xenografts into the brain of immunodeficient mice can be used to study tumor development. Depending on the condition of glioma cells, they can produce a rapidly growing bulk tumor visible after several weeks or a slowly growing diffuse one, which appears after about 3 months. The slowly growing tumors are invisible in T2-weighted MRI in early stages of their development and shows very little Gd(DTPA) enhancement (1). The aim of this study was to investigate feasibility of diffusion weighted and diffusion tensor imaging techniques for early detection of these tumors and to compare diffusion properties of the tumors grown in two different glioma models.

Materials and Methods: Both tumor cell models were cultured under stem cell condition. In Model 1, human glioblastoma-derived spheres (10^5 cells) were injected into the right striatum of female athymic nude mice (2,3). The Model 2 used $8 \cdot 10^4$ human glioma-initiating cells, which were injected into the left striatum of 7-9 week old female immunodeficient NOD/Scid mice (4).

The injected mice were repeatedly measured on a 14.1T/26cm scanner (Varian/Magnex Scientific) using a home-built 14mm×21mm quadrature coil as a transceiver. MRI-protocol included T2-weighted turbo-spin-echo images, diffusion-weighted imaging (DWI), and diffusion tensor imaging (DTI). Diffusion-weighted images were acquired using a pulse-gradient-stimulated-echo (PGSTE) sequence (TR/TE=3920/22ms, Δ=80 ms, δ=4ms, in-plane resolution=156×156μm^2). Eight *b* values ranging from 294 to 2688 s/mm^2 were used and the diffusion gradient was applied along the read direction. DTI was carried out by collecting images using diffusion gradients applied along six non-collinear directions at *b*=1352s/mm^2. Apparent diffusion coefficient (ADC), mean diffusivity (MD) and fractional anisotropy (FA) maps were computed using FSL software. Healthy (control) mice for each model were also investigated using the same MRI protocol. Mean ADC values, FA and MD indices in selected ROIs were calculated using a homemade MATLAB script. Statistical analysis was performed using two-tailed, unpaired Student's *t*-test. Finally, mice were sacrificed and brains underwent histopathological assessment.

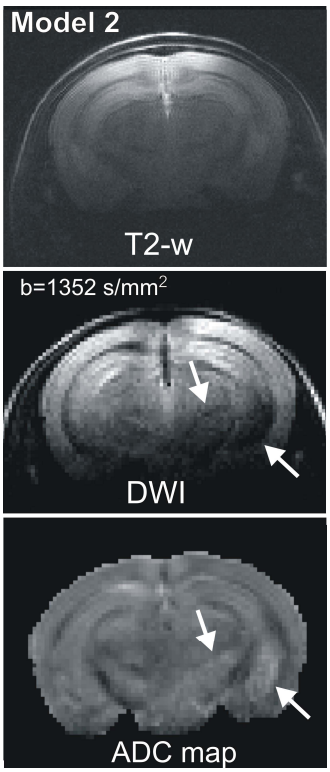

Fig. 1. T2-w and DWI images, and ADC map of a coronal slice from a Model 2 mouse with a tumor, 6 months after cell injection. DWI image and ADC map show a lesion (arrowheads).

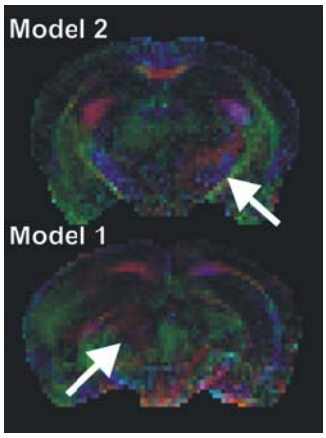

Fig. 2. Direction encoded FA maps of tumor regions in Model 1 and 2 mice.

Results: A hypointense region indicating tumor is seen in DWI of Model 2, which corresponds to a hyperintense area in the ADC map (Fig. 1). No lesion is visible in the T2-weighted image. The tumors in Model 1 were also seen in DW images and in ADC maps. The direction encoded FA maps of the same region of the Model 2 mouse brain shown in Fig. 1, and of the tumor region in a Model 1 mouse are given in Fig. 2. The mean ADC, MD and FA values in tumors, in the corresponding contralateral areas, and in the same brain regions (in both hemispheres) of controls are summarized in Table 1. Compared to the contralateral regions and to the values obtained in controls, a stronger increase in ADC and MD was observed in tumors of Model 1 than in Model 2, whereas FA decreased in Model 1 and increased in Model 2. Tumor size and location seen by histology agreed with MRI findings.

Table 1. ADC values, FA and MD indices of tumors (T) and contralateral (CL) areas for two xenograft models, and for the same brain regions in control animals in both hemispheres. Values are mean ± 1 s.e.m.

	Model 1		Model 1 control	Model 2		Model 2 control
	T	CL		T	CL	
ADC [10^{-3} mm^2/s]	0.69 ± 0.05$^{¶¥#}$	0.55 ± 0.06	0.54 ± 0.02	0.58 ± 0.02$^{¶¥}$	0.53 ± 0.02	0.52 ± 0.02
FA	0.17 ± 0.03$^{¶#}$	0.20 ± 0.02	0.20 ± 0.01	0.28 ± 0.03$^{¶¥}$	0.26 ± 0.02	0.26 ± 0.02
MD [10^{-3}mm^2/s]	0.70 ± 0.05$^{¶¥#}$	0.57 ± 0.02	0.56 ± 0.03	0.59 ± 0.01$^{¶¥}$	0.55 ± 0.01	0.55 ± 0.03

Statistics: ¶significantly different from CL area in the same group (unpaired two-tailed *t*-test, p<0.01); $^{¥}$significantly different from the related brain regions in the controls (unpaired two-tailed *t*-test, p<0.01); $^{#}$significantly different from the corresponding value in Model 2.

Discussion: Our measurements showed that the MRI techniques based on diffusion properties can be more successful than T2-weighted MRI in early detection of slowly growing tumors in mouse brain. Differences in diffusion properties of tumors indicate that the microstructure of the Model 1 tumors is looser and less anisotropic than that of Model 2.

Acknowledgments
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