Assesing the response of pre-clinical tumor models to anti-neoplastic therapies using functional diffusion mapping (fDM)

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Introduction: Functional diffusion mapping has recently (1,2) been shown to be an effective early biomarker of clinical brain tumor therapeutic efficacy. The approach uses MRI to map and quantify therapeutic induced changes in tumor water diffusion values which are sensitive to changes in tumor cell density/cell membrane function and micro-environment. This study was designed to investigate whether changes detected by fDM could be correlated with therapeutic dose and outcome measures in a pre-clinical tumor model. The dose dependency and correlation with outcome is critical for validating diffusion MRI/fDM as a biomarker for therapeutic efficacy. To test this hypothesis, serial T2 weighted and diffusion MRI was carried out on rodents with orthotopically implanted 9L gliosarcomas receiving 3 doses of BCNU (6.65, 13.3 and 26.6 mg/kg, i.p.). All images were co-registered to baseline T2 weighted images for fDM analysis. The relative volume of the responding tumor portion detected using fDM analysis was correlated with chemotherapy dose, and independent biomarkers of therapeutic efficacy including log cell kill and animal survival.

Methods:

Fischer 344 rodents bearing 9L gliosarcomas were treated with 6.6 (n=5, Fig.1c,d), 13.3 (n=12, Fig.1e,f) and 26.6 (n=6, Fig.1g,h) mg/kg BCNU 14 days after implantation. A control group (n=5, Fig.1a,b) receiving 0.01 mls of 100%EtOH was also evaluated. ADC images were acquired on a 7T MRI system as previously described (3) before and 7 days post therapy. MR images were spatially co-registered to the pre-treatment T_2-weighted images using a mutual information (MIAMI Fuse©) algorithm (4). For this study, tumor tissue was defined as that tissue which was hyper-intense on T_2 weighted images.

ADC values of each voxel within the tumor ADC map at 4 days post-therapy were plotted as a function of their pre-therapy ADC. All tumor voxels were then objectively segmented into 3 different categories: Red voxels (V_R) for which the ADC increased significantly ($p<0.05$); Blue voxels (V_B) for which the ADC decreased significantly ($p<0.05$); Green voxels (V_G) for which the ADC did not change significantly ($p>0.05$). The total volume of the voxels within each category was calculated for each animal, and normalized against the total tumor volume to give three normalized tumor volume segments (V_R, V_B, and V_G).

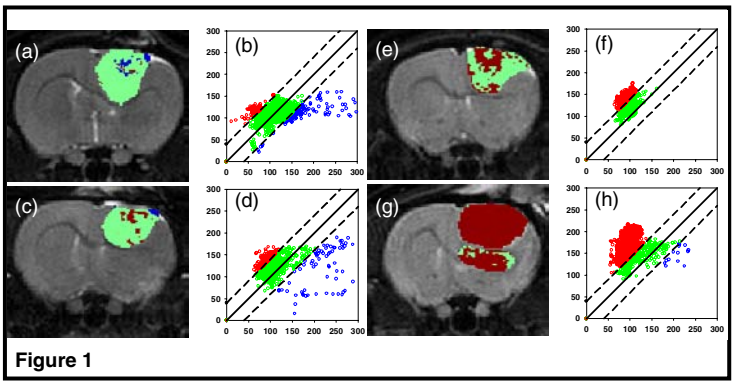

Figure 1

Results: Figure 1 shows examples of the fDM results for a control (Fig.1a,b), 6.6 mg/kg (Fig.1c,d), 13.3 mg/kg (Fig.1e,f) and 26.6 mg/kg (Fig.1c,d) treated animal. The scatter plots are ADC values for each voxel at 4 days post therapy as a function of the pre-treatment ADC value. The spatial distribution of these is shown as color overlays on anatomical T_2-weighted images from 4 animals receiving the different doses of BCNU. The 4-day FDM maps in Figure 1 are shown as color overlays on the anatomical images representing the 3 different categories of diffusion changes. It was found the that the V_R volumes correlated significantly (slope p value < 0.0001) with dose (Fig. 2a) and animal survival post therapy (Fig. 2b, slope p value = 0.002)

Discussion: The approach presented here provides a simple visual display of regions that exhibit response and resistance to treatment, as well as offers the potential of a quantitative response grade via the scatter plot. Spatial maps of regional response/resistance have the added potential to adaptively guide spatially-directed therapies (e.g. conformal radiation) over the treatment course. Although diffusion changes have previously been shown to correlate with changes in tumor cellularity (5), these results are the first to show that changes in tumor water diffusion (analyzed by fDM) are quantitatively dose dependent and correlate with survival in an animal model. These results are essential for validating diffusion MRI as an early predictive imaging biomarker of treatment efficacy in pre-clinical models. Such a biomarker has a great potential for use in the drug development process and in the future, clinical management of tumor therapeutic regimens. Early and accurate prediction of treatment response using alterations in MRI tumor diffusion values may provide an opportunity to switch to a more efficacious therapy in unresponsive patients thereby minimizing the morbitity associated with prolonged and ineffective treatment. Early modification of futile treatment regimens may also prove advantageous by reducing tumor resistance and provide for improved patient function thus enhancing clinical outcome in poor prognosis subgroups.

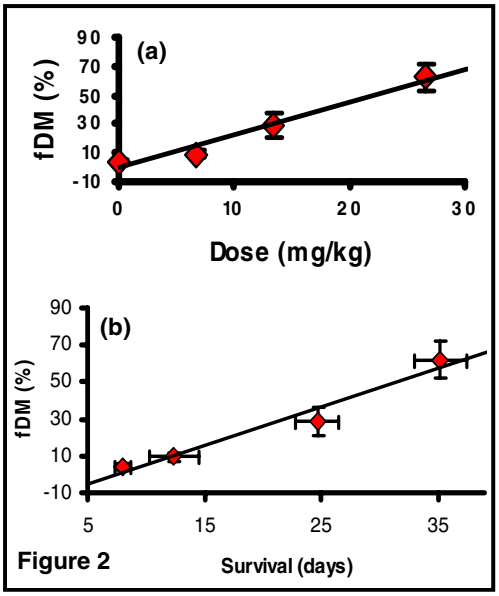

Figure 2

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