Early prediction of tumor responses to therapy by MR diffusion and magnetization transfer methods

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Introduction: The diversity of chemotherapy or radiation therapy treatments available in some tumor types forces the physician to choose one treatment based on its statistical success. However, validation of positive response to treatment might take several months and in many cases, the initial treatment, given at earlier stages of the tumor, dictate treatment outcome since the effect of an initial 'incorrect' treatment is often irreversible. For that reason any method to shorten the treatment evaluation period is of major importance. In this study we intend to test our hypothesis, namely that non-invasive diffusion weighted (DW) and magnetization transfer (MT) MRI measurements (i) give a reliable estimator for tumor response in an early stage of treatment and (ii) allow defining of an 'intermediate' region between live and necrotic regions. The logic of using DW and/or MT measurements to monitor tumor development and treatment progress is based on the assumption that changes in the vascular bed, the extra-cellular architecture and/or the intra-cellular composition caused by the treatment are measurable by these methods. This is due to the sensitivity of these methods to the permeability and mobility of the water within the tumor

Animal and tumor: Malignant rat sarcoma cells ($20x10^4$/200µl) were injected to one leg of control (N=5) and treated (N=5) Fischer rats. Rats were treated with drug, when tumor reaches 0.5ml volume, by intra-tumor injection of 50µl of slow release polymer containing 1.5% of cis-Pt while the control group received the polymer alone.

MRI: DW MRI was obtained by stimulated-echo sequences with 'b' between 0 to 4500 s/mm^2. Apparent diffusion coefficient (ADC) was calculated using a single exponential fitting procedure for each image voxel. MT measurements were obtained by the FLASH sequence (TE=6ms, TR=300ms) using off-resonance radiation of 50µT, 3000Hz off resonance. MT contrast (MTC) for each voxel was defined as the difference signal (without minus with the irradiation) normalized to the former.

Analysis: In DW and MT studies we segment the data according to histology. Namely, we have defined the range of ADC and MTC values contained in a pathologist's defined necrotic region (named hereafter as 'fast-like' diffusion and low-MTC) and in a pathologist's defined live cell region (named hereafter as 'slow-like' diffusion and high-MTC). The fractional volume of each segment was measured with time for the whole tumor.

Results: From the third day after polymer injection until day 14 (which correlates with the amount of drug within the tumor as measured by atomic absorption – see figure 1), there is a significant difference of the 'fast-like' and 'slow-like' diffusion volumes between control and treated groups, whereas significant volume-changes were observed only after the sixth day from injection. Of particular importance is the fact that during that time, the ratio between fast-like to slow-like diffusion volumes was reversed between the groups with higher slow-like fraction in the control group. However, the MT results do not show any differences between the two groups. Most importantly, our data shows that diffusion measurements when separated into its 'fast-like' and 'slow-like' compartments can be used to validate drug effectiveness. Specifically, by calculating the volume difference between the fast and slow diffusion compartments normalized to the total tumor volume at each time point, we can estimate treatment efficiency. Namely, when this ratio is positive or close to zero, our hypothesis suggests that the treatment works, while, for negative ratios, the treatment does not work (**Figure 1**).

Inspection of the data of all the animals (treated and untreated) through all measurements reveals the following observations: (i) Volume characterized by fast diffusion was always larger than the volume characterized by 'low-like' MTC and (ii) volume characterized by 'high-like' MTC was always larger than the volume characterized by 'slow-like' diffusion. This suggests the existence of three distinct regions. One that is defined by low MTC; second that is defined by the 'slow-like' ADC and third that is defined by combining both methods. Low MTC is predictable in regions with high density of free liquids as expected in necrotic like regions. Hence we hypothesize that the region of low MTC represents the 'pure' necrotic regions. Slow ADC values are predictable in volumes with limited motion as expected in dense tissue, thus we hypothesize that slow diffusion is characterized by growing tumor tissue. "Intermediate" on the other hand is characterized by high MTC and fast ADC. We believe that "intermediate" represents the transition stage between the live and the necrotic regions. This region therefore, can point to early detection of tumor response to treatment.

Figure 2. Shows two sets of images taken two days after polymer injection; in one set (left images-A1-D1), the polymer contained 1.5% cis-Pt while in the second set (right images – A2-D2) pure polymer was injected as a control. The figure shows the anatomical T2-weighted images (A1, A2), the ADC map (B1, B2), the MTC map (C1, C2) and color maps representing the volumes of "necrotic", "live" and the "intermediate" regions as defined above. Inspection of images D1 and D2 show clear differences that must to be attributed to the drug: Whereas there is almost no intermediate region in the D2 image, the intermediate region occupied large portions of the D1 image particularly around the "necrotic" region. This suggests a positive correlation between location of the drug and the intermediate volumes.

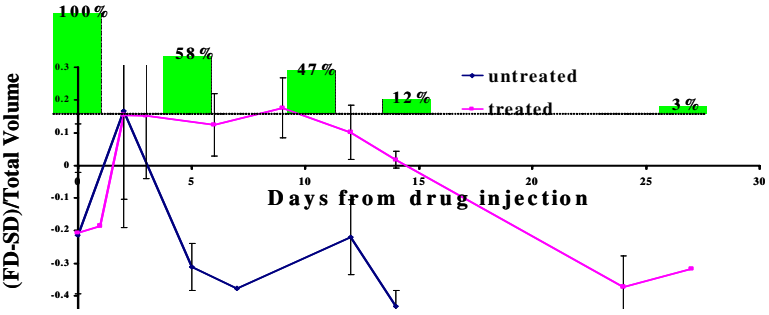

Figure 1. Predictor criterion based on diffusion measurements with positive values indicating successful treatment. Note that it predicts that the treatment stops being effective at day 15 in agreement with total tumor growth. The average Platinum level (in percentage with respect to the injection day) in the tumor, as measured by atomic absorption at different times from injection, is shown as green bars above the curves. It shows good correlation with the suggested criterion.

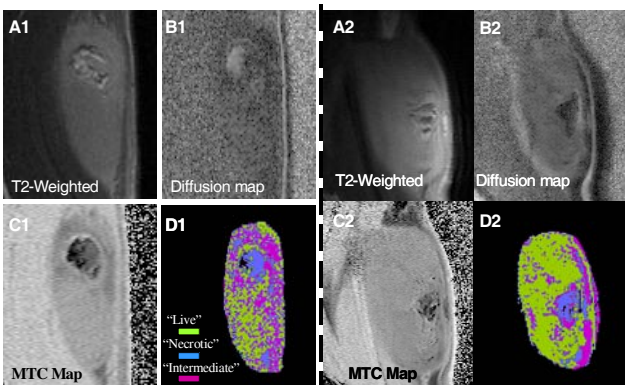

Figure 2. T2-weighted, diffusion, MTC and color map representing the "necrotic", "intermediate" and "live" regions of two rats, two days after polymer injection. On the left, polymer contained Cis-Pt 1.5% while on the right polymer control without drug.

Conclusions: A. A predictor criterion, based on diffusion measurements with positive values, was found to indicate successful treatment.
B. An "intermediate" region was defined by combination of DW and MT MRI, that can be assessed for early response to drug treatment.