Evaluating Treatment Response of Tumors with Temporal Diffusion Spectroscopy: Preliminary Results

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Introduction

Diffusion-weighted MRI is commonly used to depict variations in the rate of water diffusion within cancerous tissue. The apparent diffusion coefficient (ADC), is influenced by the presence of cell membranes and subcellular organelles, which serve to restrict the motion of self-diffusing water molecules. Microstructural alterations in the tissue alter the value of the measured ADC, so changes in ADC may be used to evaluate pathophysiological changes, including the response of tumors to treatment (1-2).

The degree to which the ADC varies depends upon the number of barriers a molecule encounters during an imaging experiment, so the time interval over which the ADC is measured determines the spatial scale over which structural variations have an influence. Conventional techniques employing the pulsed-gradient spin-echo (PGSE) method typically measure this process over tens of milliseconds, thereby allowing water molecules to diffuse distances greater than a cell diameter, so they encounter a variety of intra- and extracellular environments and mainly depict tissue cellularity. Structural variations occurring on scales smaller than a single cell are obscured. Oscillating Gradient Spin-Echo (OGSE) techniques at high gradient frequency are capable of examining diffusion over much shorter time scales, thereby probing variations in tissue structure occurring on spatial scales much smaller than a single cell (3-4). Here we begin to evaluate whether OGSE methods can provide a more sensitive method of evaluating treatment response in tumors.

Methods and Results

Both OGSE and PGSE methods were implemented at 9.4T to measure ADC in male Wistar rats inoculated intracranially with C6 gliosarcoma cells, before and after treatment with the chemotherapeutic drug Sunitinib (International Laboratory USA, San Bruno, CA). Approximately 14-16 days following inoculation with the tumor cells, PGSE images were obtained with δ = 5 ms, Δ = 30 ms, and b = 400 s/mm^2, while OGSE images were collected, at the same b-value, at gradient oscillation frequencies of 120Hz and 240Hz (corresponding to effective diffusion times of 2.1 ms and 1.0 ms, respectively). Other imaging parameters were TR/TE = 2000/76 ms, FOV = 48mm x 34mm, matrix = 96x64, slice thickness = 2mm, NEX = 4. Following imaging, animals were treated with 40 mg/kg Sunitinib (i.p. injection) and scanned 24 hours later using the same imaging protocol. Tumor bearing animals not treated with Sunitinib were imaged, at the same time points, as a control.

Representative ADC maps from both techniques, prior to and following treatment, are shown in Figure 1. The parametric maps from the PGSE technique show some increase in ADC between the two time points, consistent with expectations of a treatment effect. The OGSE data at high frequencies both before and after treatment provide much greater contrast and reveal details of tissue heterogeneity not seen in the PGSE images. Moreover, the change in ADC at high frequency (short diffusion time) caused by treatment is much greater in some areas of tumor. These initial data suggest that OGSE techniques, which are capable of assessing diffusion effects over much shorter spatial scales, reveal a greater range of spatial features within the tumor microenvironment, and may be more sensitive as early indicators of treatment response than conventional methods.

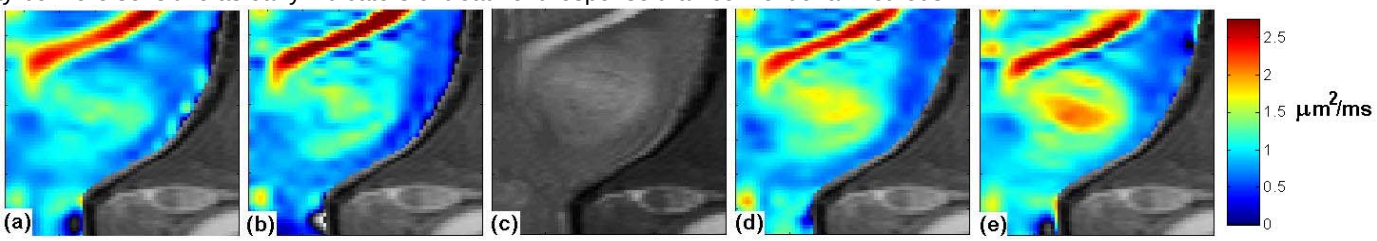

Figure 1. ADC maps of intracranial C6 tumor using PGSE methods (a) prior to and (b) 24 hours following treatment with Sunitinib (SU11248). (c) T2-weighted image. Panels (d) and (e) show the corresponding ADC maps created using OGSE methods at 240 Hz prior to and 24 hours following treatment, respectively.

Discussion

There is a continuing need for sensitive and reliable biomarkers of the response of tumors to treatment, and PGSE measurements of ADC are already in use for such purposes. While the PGSE technique has proven capable of detecting changes in tumor cellularity, it is not able to distinguish macroscopic changes from sub-cellular variations. OGSE methods, on the other hand, are able to measure water displacements over much smaller scales, and thus may be sensitive to structural changes occuring on an intracellular scale. These techniques may provide an improved method for evaluating the response of tumor cells to therapy, and may provide an earlier indication of treatment efficacy.

References

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