Quantitative characterization of tumor microstructural variations in response to chemotherapy using temporal diffusion spectroscopy

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Target audience: Investigators who are interested in diffusion MRI and its application in cancer.

Purpose: We show that temporal diffusion spectroscopy, which measures the variation of apparent diffusion coefficient (ADC) over a range of effective diffusion times, can quantitatively and specifically characterize tumor microstructural variations in response to chemotherapy, and hence may provide more specific and potentially earlier imaging biomarkers of tumor response than conventional diffusion imaging. Pulse gradient spin echo methods that are usually used to assess ADC incorporate relatively long diffusion times. Consequently, measured ADC values are increased when cell densities decrease, but are insensitive to changes that occur at subcellular scales[1]. Although ADC has been found to be correlated with tumor cellularity in many studies, others have reported contradictory observations[2]. Presumably, this is because ADC is actually influenced by several microstructural features, such as cell size, density and membrane permeability, and all these features combined can change in complex ways in tumor response to therapy[3]. Oscillating gradient spin echo measurements allow interrogation of structure at shorter distances and thus may be more specific for detecting changes before cell density changes arise.

Methods: The human breast cancer cell line MDA-MBA-231 is positively responsive to nab-paclitaxel (Abraxane), an FDA-approved mitotic inhibitor which interrupts cell division and causes G2/M arrest. For *in vitro* experiments, cultured MDA-MBA-231 cells were treated with 200 nM of either Abraxane or PBS (drug vehicle) for 24 hours. Cell samples were then collected, fixed, transferred to a tube, and centrifuged to form cell pellets for DWI experiments. For the *in vivo* experiments, MDA-MBA-231 tumor-bearing mice were treated with either Abraxane (n=10) or PBS (n=8) for 8 days (10 mg/kg, every other day). DWIs were collected before and after treatments. ADCs were obtained with two b-values (0 and 400 sec/mm^2) using oscillating gradient spin echo (OGSE) for 50-350 Hz and pulsed gradient spin echo (PGSE) methods (δ/Δ = 4/48 ms) to approximate 0 Hz. The entire ADC spectra were then fit to the equation: $ADC(f)=ADC_{res}(d, D_{in}\text{-}D_0)+D_0$, where ADC_{res} is modeled as the ADC of diffusion inside impermeable spherical cells of diameter d, and D_{in} and D_0 are the ADC values for the intra/extra-cellular compartments respectively. For comparison, ADC values obtained using PGSE sequences (ADC_{PGSE}) were also measured.

Results: The *in vitro* results are tabulated in Table 1. The fitted apparent mean cell sizes of control and treatment groups were consistent with results from light microscopy, indicating the accuracy of our method in quantifying cell size. Interestingly, there were no significant differences in the other fitted microstructural parameters (D_{in} and D_0) and ADC_{PGSE}, suggesting these parameters did not change at early stages after treatments. Figure 1 summarizes the percentage changes in the fitted parameters and ADC_{PGSE} for the PBS- and Abraxane-treated, tumor-bearing mice. Similar to the *in vitro* results, the apparent cell size d was the only parameter that changed significantly ($p = 0.04$) after Abraxane treatment. By contrast, all other parameters, including ADC_{PGSE}, did not show significant changes in the treatment group. D_0 and ADC_{PGSE} values increased significantly in the control group, possibly because of the large volume of extracellular fluid generated in the development of tumor.

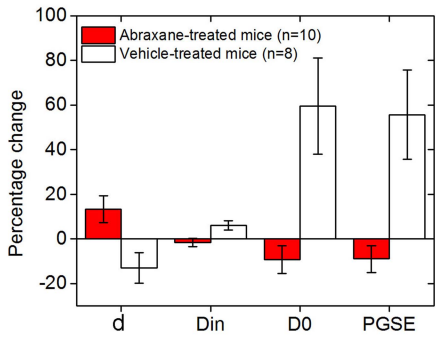

Figure 1. Percentage changes in ADC measured by PGSE, and three fitted parameters, i.e. D_0, D_{in}, and d (apparent cell size), of control and treated mice.

Conclusion: Temporal diffusion spectroscopy provides a means to quantitatively characterize specific tumor microstructural features, e.g. cell size. These specific features may change earlier in the response of tumors to therapy, and hence may be more accurate indicators of tumor state.

References: 1. Gore JC, et al. NMR Biomed 2010;23:745–756.
2. Squillaci E, et al. Anticancer Res 2004;24:4175–9.
3. Xu J, et al. Magn Reson Imaging 2011;29:380–390.

	Apparent cell size (μm)	D_{in} (μm^2/ms)	D_0 (μm^2/ms)	ADC_{PGSE} (μm^2/ms)	Cell size (microscopy) (μm)
control	14.24±0.72	1.15±0.07	0.50±0.02	0.48±0.01	15.72±1.84
treated	16.82±0.44	1.11±0.02	0.52±0.01	0.49±0.01	22.48±0.90

Table 1. *In vitro* MR and microscopy results for PBS- (control), and Abraxane-treated MDA-MBA-231 cells.