Selective sensitivity of diffusion-weighted MRI to various length scales in tumors following treatment

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Target Audience: Investigators who are interested in the biophysical mechanism of water diffusion changes in tumors and their use to assess anti-cancer therapy.

Purpose: Diffusion-weighted MRI (DWI) has been widely used for detecting cancer, differentiating tumor stages, and monitoring tumor response to treatment (1). Most DWI measurements use the pulsed gradient spin echo (PGSE) method, which incorporates relatively long diffusion times. Such acquisitions are very sensitive to variations in tumor cell density but may not detect intracellular structural changes (2). However, many practical anti-cancer treatments induce tumor microstructural variations at both supra- and subcellular levels, and detecting changes across different length scales is likely to provide more comprehensive information about tumor status (3). In this study, we used histology-based simulations and imaging in vivo of mouse xenografts to demonstrate the importance of probing various length scales of tumors.

Methods: Histological images of pre- and post-treatment tumors (Fig.1.a and b) were obtained from SW620 (a human colon cancer) mouse xenografts treated with barasertib, a targeted therapy drug that causes tumor cells to develop polyploidy (i.e. multiple copies of DNA and organelle contents, which can increase hindrance to intracellular diffusion) and increase in cell size (i.e. cell density decreases which can reduce restriction to diffusion at cellular level). Details of the animal and treatment models and our in vivo imaging studies can be found in (3). The histological images were segmented to separately identify cell nuclei, cytoplasm and extracellular space using the k-means clustering method in ImageJ. Cell boundaries were obtained using the watershed method followed by manual adjustments. A finite-difference time-domain algorithm (4) was then used to simulate apparent diffusion coefficients (ADC) that would be obtained by the PGSE and OGSE (oscillating gradient spin echo) methods based on the segmented histological images. The simulations assumed TE=40ms, b=400s/mm^2 for OGSE and b=1000s/mm^2 for PGSE (except that b values were adjusted to lower values at very short diffusion times to avoid large computing errors caused by large diffusion gradients (4)). The intra-nuclear intrinsic diffusion coefficient was assumed to decrease from 2.0 to 1.6 μm^2/ms to reflect the polyploidy effect and the nuclear envelop was assumed to be perfectly permeable.

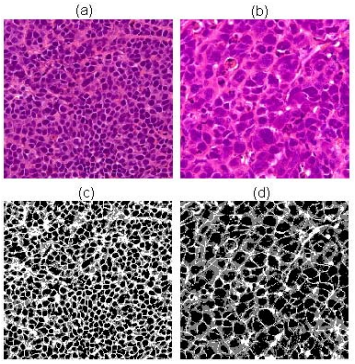

Fig.1 Histological images of pre-treatment (a) and post-treatment (b) SW620 xenografts using H&E staining. (c) and (d) are corresponding segmented images, respectively. Black regions are nuclei, gray are cytoplasm and white are extracellular space.

Results: Fig.2 estimated the ADC percentage changes after treatment. Because of the reduced restriction to water diffusion at cellular level, post-treatment ADCs of PGSE acquisitions showed significant increases for most diffusion times. However, at very short diffusion times (<1ms), decreased ADCs are found due to treatment-induced polyploidy that enhances hindrance to intracellular diffusion. Similarly, ADCs using OGSE showed a clear dependence on the gradient frequency (approximately proportional to the reciprocal of diffusion time), from a significant increase at 50 Hz to a decrease at frequencies > 200Hz. For comparison, in vivo OGSE results from mouse xenografts show a similar behavior as found by the simulations.

Discussion and Conclusion: Many studies have reported that ADCs of tumors using PGSE will increase after effective treatments. However, this work suggests that this may be a potentially misleading simplification. Practical anti-cancer treatments can cause complex tumor microstructural variations that are not limited to cell density changes alone, and such multi-level variations may affect water diffusion very differently at different length scales. In order to obtain comprehensive information about tumor status, diffusion measurements with a broad range of diffusion times may be necessary. However, due to hardware limitations, conventional PGSE methods have difficulty achieving very short diffusion times (<1ms) in practice, and OGSE instead may provide the feasibility to detect tumor microstructural changes at both supra- and subcellular length scales. In addition, Fig.2.a shows that the magnitudes of post-treatment ADC changes using PGSE depend on the diffusion times used, which suggests there is a need to optimize diffusion times in ADC measurements in order to maximum the sensitivity for monitoring tumor response to treatment.

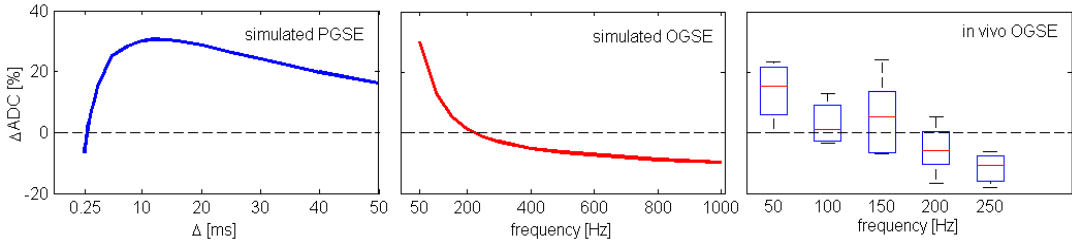

Fig.2 Simulated ADC percentage change post-treatment using PGSE (left) and OGSE (right). For comparison, in vivo OGSE results from mouse xenografts are provided (right).

References:

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