Early detection of treatment response to antiangiogenic therapy using IVIM-DWI in mouse model of breast cancer

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Introduction:
Abnormal tumor blood vessels can be normalized by direct or indirect anti-angiogenic drugs, which can provide a crucial window of opportunity to effectively deliver cytotoxic drugs (1, 2). However, it is not straightforward to apply such therapeutic strategies in clinical practice, mainly due to the absence of appropriate methods that can detect the tumor vascular normalization window noninvasively. The purpose of this study was to investigate the feasibility of using Intra-Voxel-Incoherent-Motion (IVIM) diffusion weighted imaging (DWI)(3) to detect the early onset of tumor vascular normalization induced by an antiangiogenic therapy.

Materials and Methods: Six- to eight-wk-old BALB/c mice (n = 5) were given a subcutaneous injection in the right flank with 1 x 10^6 4T1 mouse mammary tumor cells suspended in 0.1 ml of PBS. All mice were scanned when the longest diameter of the tumor was about 10 mm. Following the scan, the mice were given an intraperitoneal injection of 0.1 ml of 1mg/ml Avastin (Genentech, CA) and were scanned approximately 24 hours later. Four mice were sacrificed to collect the tumor tissue for histology on post-treatment day 1. The remaining one mouse received two additional treatments on post-treatment days 3 and 6 and was scanned on post-treatment days 4 and 7. Its tumor was also harvested following the last scan.
MRI was performed using a 7T horizontal bore magnet with a volume transmit and receive coil. General anesthesia was induced by 1.5% isoflurane in air. The animal was mounted on a cradle with respiratory and temperature monitoring probes. The animal body temperature was maintained at 32 ± 2 ºC during the scan. A T2-weighted rapid acquisition with relaxation enhancement (RARE) sequence was used to image the entire tumor (TR = 2s, TE = 35ms, FA=180º, res = 0.18 x 0.18 x 1.5 mm, 10 slices), and to select two slices near the tumor center. A pulsed gradient spin echo (PGSE) diffusion measurement (δ = 7ms, Δ = 14 ms) was performed with single-short spin echo imaging sequence (TR = 1 s, TE = 34 ms, resolution = 0.36 x 0.36 x 1.5 mm, 2 slices). The diffusion weighting gradient was varied from 0 to 28 G/cm to have diffusion weighting of b = 0, 30, 60, 100, 150, 200, 300, 500, and 750 s/mm^2. In addition to estimating apparent diffusion coefficient (ADC) by fitting a monoexponential model to the data, the following biexponential model was also used:

$$S/S(b=0) = f_p \cdot \exp\left(-b \cdot D_p\right) + \left(1 - f_p\right) \cdot \exp\left(-b \cdot D_t\right)$$

where S is the MR signal intensity, f_p perfusion fraction, D_p pseudodiffusivity, and D_t tissue diffusivity. The performance of the two models were compared in terms of the Bayesian information criterion (BIC) (4) which is one of the commonly used statistical criteria for model selection in order to take into account the difference in the degree of freedom. The BIC for a model with k parameters, m observations and average residual sums-of-squares χ^2 was defined as the following: $BIC = \ln\left(\chi^2\right) + \left(k \ln m\right)/m \cdot$

This study was approved by the institutional animal care and use committee.

Results and Discussion: Fig.1a and 1c show a 4T1 tumor before and after an antiangiogenic therapy. Fig.2 shows that the average ADC from the entire tumor did not change noticeably by post-treatment day 1. Red voxels in Fig.1b and 1d indicate where the BIC of the biexponential model was lower than that of the monoexponential model. Increase of red voxels in Fig.1d, compared with Fig.1b, indicates that, after the treatment, the biexponential model was found to be more adequate for more voxels. Fig.3a shows that, within the first 24 hours post treatment, there was a substantial increase of V_p (volume fraction of tumor that the BIC of the biexponential fit was lower than that of the monoexponential fit). Similar increase was also seen by f_p*D_p (Fig.3b) and V_p*f_p*D_p (Fig.3c) which we assert are related to regional blood flow and total blood flow, respectively (5). The trend of D_t (Fig.3d) was similar to that of ADC, which may originate from a secondary reduction of tumor cellularity. This preliminary result suggests a high potential of IVIM-DWI parameters as surrogate markers for early onset of tumor vascular normalization induced by antiangiogenic therapies. Future study will include a larger sample size with histological cross-validation.

Reference: **1**. Jain, Science 2005; 307:58-62,. **2**. Batchelor et al., Cancer Cell, 2007; 11:83-95. **3**. LeBihan et al., Radiology 1988;168(2):497-505. **4**. Schwarz. Annals of Statistics 1978; 6(2):461-464. **5**. LeBihan and Turner, MRM 1992; 27(1):171-178

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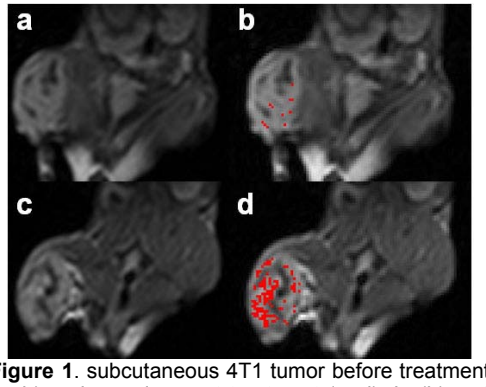

Figure 1. subcutaneous 4T1 tumor before treatment (a, b) and one day post treatment (c, d). In (b) and (d), the voxels with lower BIC are shown red.

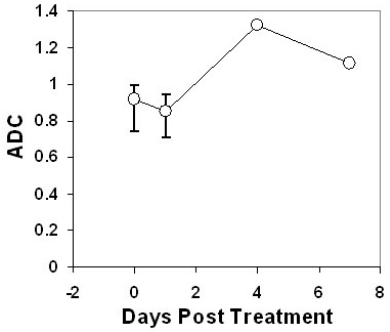

Figure 2. ADC measured from the entire tumor during therapy.

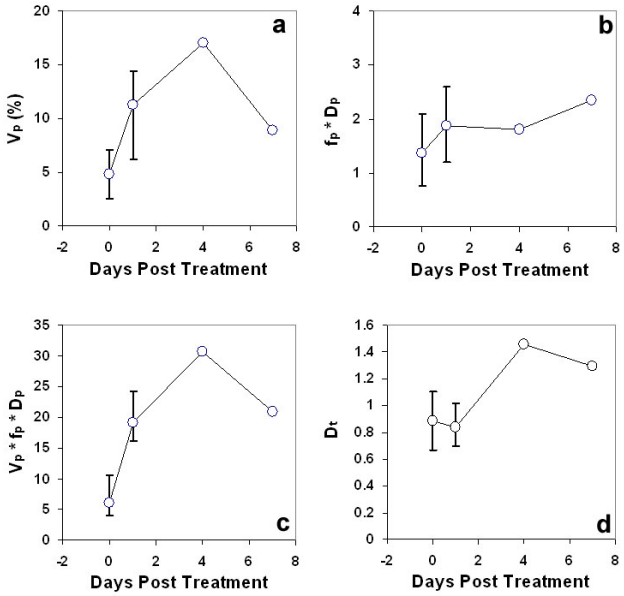

Figure 3. Therapeutic changes measured by IVIM-DWI. (a) volume fraction with lower BIC by the biexponential model than by the monoexponential model. (b-d) treatment response measured by biexponential parameters.check axis label in panel 3c.