

The DCE-MRI ΔK^{trans} Biomarker Provides Early Prediction of Soft-Tissue Sarcoma Response to Anti-Angiogenic Therapy

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Introduction: By measuring changes in tumor vascular properties, dynamic contrast-enhanced (DCE) MRI is a powerful noninvasive imaging method for evaluation of cancer response to therapy. Analysis of the DCE-MRI time-course data using pharmacokinetic models allows for determination and mapping of quantitative properties of cancer biology *in vivo*. The Standard model (SM) (1) assumes effectively infinitely fast intercompartmental water exchange kinetics, while the Shutter-Speed model (SSM) (2,3) accounts for the finite water exchange kinetics. When a DCE-MRI data set is analyzed twice - once with the SM and once with the SSM, a new DCE-MRI biomarker, ΔK^{trans} , can be generated, defined as $[K^{trans}(\text{SSM}) - K^{trans}(\text{SM})]$, where K^{trans} is a rate constant for contrast agent plasma/interstitium transfer. ΔK^{trans} is a measure of the exchange effect on K^{trans} estimation and has been shown to be a very sensitive measure of vascular compromise and an accurate diagnostic marker for breast cancer (2-4). In this study, we sought to evaluate the effectiveness of the ΔK^{trans} parameter, in comparison with other MRI metrics, for prediction of soft tissue sarcoma response to antiangiogenic treatment.

Method: Patients with biopsy-proven, grade 2-3, deep, and > 5 cm soft tissue sarcomas participated in a phase I clinical trial in which the vascular endothelial growth factor receptor (VEGFR) inhibitor, Sorafenib, was added to a preoperative chemoradiotherapy regimen. Research MRI studies were performed at time-point zero (TP_0) - before therapy, TP_1 - after two weeks of Sorafenib only treatment, and TP_2 - after eight more weeks of treatment with Sorafenib plus chemoradiation therapy, followed by surgery and pathology review including estimation of tumor histologic necrosis. A total of eleven patients consented to the research MRI scans, with 9 of them having at least two DCE-MRI studies (at TP_0 and TP_1). In these 9 patients, five masses were located in the thigh, two in the calf, one in the knee, and one in the shoulder.

The MRI studies were performed using a 3T Siemens instrument with the body transmit and phased-array body matrix (combined with a spine matrix) receive RF coils. Following scout and axial T₂-weighted MRI, sagittal diffusion-weighted imaging (DWI) was performed (in seven of the 9 patients) using a spin-echo single-shot EPI sequence with TE/TR = 104/8000 ms, 24-36 cm FOV, 5 mm slice thickness with zero gap, 192x192 matrix size, and b values of 0, 500, and 1000 s/mm² applied in three orthogonal directions. Subsequently, a 3D RF-spoiled gradient-echo sequence was used to acquire sagittal DCE-MRI data with 10° flip angle, TE/TR = 1.5/6.0 ms, and 320x160 matrix size. The image FOV, slice number, location, and thickness matched those of the DWI scan. A parallel imaging acceleration factor of 2 was used for DCE-MRI, resulting in 7-16 s temporal resolutions depending on tumor size. The total DCE acquisition time was approximately 10 min with Gd contrast agent (Prohance®) IV injection (0.1 mmol/kg at 2 mL/s) carried out following acquisition of five baseline image volumes. Prior to DCE-MRI, proton density images were acquired with matching spatial coordinates - for pre-contrast T₁ determination.

ADC trace maps were generated with manufacturer's DWI data processing software. The DCE-MRI images were processed off-line using the SM and SSM pharmacokinetic models to fit both tumor ROI and pixel-by-pixel (within the ROI) time-course data (2-4). The arterial input functions (AIFs) used for the quantitative analyses were directly measured from ROIs placed in a femoral artery (for thigh, knee, and calf tumors) and an axillary artery (for the shoulder mass). The whole tumor ROI DWI/DCE-MRI parameter values were calculated by averaging the ROI values from each of the image slices covering the entire tumor, weighted by the pixel numbers within the image slice ROIs. Pixel parameter values were analyzed with histograms and the amplitude and median values were obtained. The post-contrast DCE images at or near signal intensity time-course maxima were used to measure tumor size according to the well-established (one dimensional) RECIST (5) guidelines.

Results: Pathology review of the surgical specimen revealed that three of the 9 sarcomas had optimal treatment responses to the preoperative therapy with ≥95% necrosis, while the other 6 tumors had sub-optimal responses with <95% necrosis (6). The baseline (TP_0) MRI metrics, including tumor size, ADC, and DCE-MRI parameter values (whole tumor ROI or histographic measures), were not predictive of response to the treatment regimen. **Fig. 1** shows $K^{trans}(\text{SM})$, $K^{trans}(\text{SSM})$, and ΔK^{trans} maps at TP_0 and TP_1 of a tumor with 95% necrosis (right thigh mass, Fig. 1a) and one with 50% necrosis (left thigh mass, Fig. 1b) at surgery (after TP_2). The optimal responder mass (1a) had considerable decreases in each of the three biomarkers at TP_1 with changes in ΔK^{trans} being the most dramatic, while no substantial

$K^{trans}/\Delta K^{trans}$ changes were observed in the sub-optimal responder tumor (1b).

Fig. 2 shows a column graph of the whole tumor ROI MRI biomarker % changes at TP_1 (relative to TP_0). The black columns represent three optimal responders, and the gray columns the other 6 sub-optimal responders. The changes in tumor size (RECIST) and ADC were small and indiscriminate for the two groups of responders. Among ROI $K^{trans}(\text{SM})$, $K^{trans}(\text{SSM})$, and ΔK^{trans} , only % change in ΔK^{trans} was able to completely separate the optimal and sub-optimal responders. Six of the 9 patients (two optimal and four sub-optimal responders) had MRI at TP_2 . Though the changes in RECIST and ADC were much smaller compared to those in K^{trans} and ΔK^{trans} at TP_2 (relative to TP_0), all MRI metrics provided discrimination of optimal/sub-optimal responders after completion of the entire treatment course (data not shown). However, it is the 2 wk. TP_1 biomarker changes that are crucial for early prediction and represent the effect of the VEGFR inhibitor alone. **Fig. 3** shows a scatter plot of % changes at TP_1 in RECIST, ROI ADC, ROI and histogram median ΔK^{trans} values vs. % necrosis at surgery for all 9 patients. There were significant linear correlations between % necrosis and % changes in ROI ΔK^{trans} ($R = -0.93$, $P = 0.0003$; Spearman's correlation), and histogram median ΔK^{trans} ($R = -0.71$, $P = 0.03$). No such relationships were observed for changes in either $K^{trans}(\text{SM})$ or $K^{trans}(\text{SSM})$.

Discussion: Our results suggest that the DCE-MRI biomarkers are more effective than tumor size and ADC measures for early prediction of sarcoma response to antiangiogenic treatment. This is probably because the tumor vascular shut-down induced by Sorafenib preceded cell death and tumor shrinkage. A recent study using DWI to assess sarcoma response to therapy (7) showed that significant ADC changes were detected only when there were substantial changes in tumor volume. This may elucidate why ADC was not a good predictor of response at TP_1 in this study, as the tumor size changes were minuscule. The results imply that ΔK^{trans} is more sensitive to therapy-induced tumor vascular changes than K^{trans} itself, and thus is an excellent early predictor of soft-tissue sarcoma pathologic response. Early identification of patients not responding to therapy may allow for prompt alternative treatments, sparing them from ineffective and potentially toxic therapies. As an additional benefit, the ΔK^{trans} calculation may mitigate or eliminate many common systematic DCE-MRI parameter errors, for example, from AIF uncertainty – since the SM and SSM analyses use the same AIF (8). Such systematic errors have long been principal challenges in using quantitative DCE-MRI for therapy monitoring.

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