The ΔK^{trans} DCE-MRI Parameter Provides Early Prediction of Soft-Tissue Sarcoma Therapy Response: Initial Experience

S. Hemmingson[1], K. Perlewitz[2], M. Holtorf[2], I. Tagge[1], W. Woodward[1], C. Ryan[2], C. Springer[1], and W. Huang[1]
[1]Advanced Imaging Research Center, Oregon Health & Science University, Portland, OR, United States, [2]Medicine, Oregon Health & Science University, Portland, OR, United States

Introduction: One of the major goals for (Dynamic-Contrast-Enhanced) DCE-MRI is the early assessment of therapeutic outcome - particularly for cancer. A new DCE-MRI pharmacokinetic parameter (ΔK^{trans}) has shown remarkable breast cancer screening effectiveness (1,2). It results from analyzing a DCE-MRI data set twice, once with the Standard Model (SM) (3) and once with the Shutter-Speed Model (SSM) (4). Thus, ΔK^{trans} is defined as [K^{trans}(SSM) - K^{trans}(SM)], where K^{trans} is a rate constant for contrast reagent (CR) extravasation. The ΔK^{trans} parameter appraises precisely the SM/SSM difference - their treatments of inter-compartmental water exchange kinetics, which seems to be significant in only malignant tumors (1,2). In fact, SM and SSM are really one model: the SM is a special limiting case of the SSM. The SM assumes that the exchange kinetics are always effectively infinitely fast: all exchange MR systems remain in their fast-exchange-limit [FXL] conditions. The SSM admits these systems can transiently depart their FXLs during the bolus CR passage through the tissue ROI or voxel (1). Since ΔK^{trans} seems a very sensitive measure of vascular compromise (1,2), we sought to test it for prediction of cancer therapy response. Here, we report on our first three studies of antiangiogenic potentiation of preoperative chemoradiotherapy of high risk extremity soft-tissue sarcoma.

Method: Three patients with biopsy-proven, high-grade, deep, and > 5 cm soft tissue sarcomas participated in a phase I clinical trial adding the vascular endothelial growth factor receptor (VEGFR) inhibitor Sorafenib to a preoperative chemoradiotherapy regimen. The masses were located in the right thigh (subj. 1), left thigh (subj. 2), and right shoulder (subj. 3). The patients consented for research MRI exams, including DCE-MRI, at time-point zero (TP_0) - before therapy, at TP_1 - after two weeks of Sorafenib treatment only, and at 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.

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. A 3D RF-spoiled gradient-echo sequence was used to acquire T_1-weighted DCE-MRI data, with 10^0 flip angle, 1.5 ms TE, 6 ms TR, 32-36 cm FOV, and 5 mm slice thickness. A parallel imaging acceleration factor of 2 was used, resulting in 9-16 s temporal resolution. The total DCE acquisition time was approximately 10 min with Gd CR (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 at the same spatial locations - for pre-CR T_1 determination. AIFs were measured from ROIs placed in a femoral artery (for thigh tumors) and an axillary artery (for the shoulder mass). The SM and SSM were used for pharmacokinetic modeling of ROI and voxel DCE-MRI time-course data. The whole tumor ROI parameter values were calculated by averaging the ROI values from each of the image slices covering the entire tumor, weighted by the ROI voxel numbers. The post-contrast DCE images at or near signal intensity time-course maxima were used to measure tumor size according to well-established RECIST (1D) (5) and WHO (2D) (6) guidelines.

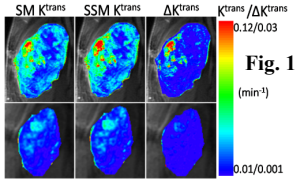

Fig. 1

Results: Sagittal pixel-by-pixel parametric maps (from one image slice) of the subj. 1 tumor are shown in **Figure 1**. The three **top** row maps were obtained at TP_0; the **bottom** row at TP_2. The three columns (l. to r.) show K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans} maps: the dual K^{trans}, ΔK^{trans} color scale bar is displayed. The maps show significant decreases in each biomarker after therapy completion (TP_2 *vs.* TP_0), with changes in ΔK^{trans} being the most dramatic. Pathology review of the surgical specimen revealed >95% necrosis, suggestive of an optimal treatment response to preoperative therapy (7).

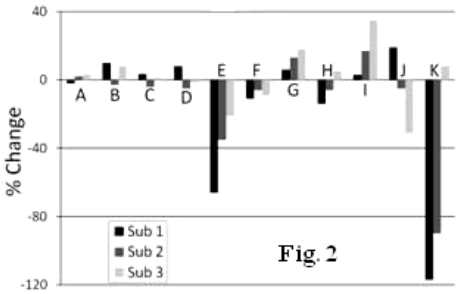

Fig. 2

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. **Figure 2** shows bar graphs of the TP_1 % changes (relative to TP_0) in many biomarkers for the three subjects. The 11 biomarkers (l. to r.) are: **A**, RECIST; **B**, WHO; **C-E**, whole tumor ROI K^{trans}(SM), K^{trans}(SSM), and ΔK^{trans}, respectively; **F** and **G**, K^{trans}(SM) histographic amplitude and median; **H** and **I**, K^{trans}(SSM) histographic amplitude and median; **J** and **K**, ΔK^{trans} histographic amplitude and median. Pathology analyses of the surgical specimens from subjs. 2 and 3 showed 80% and 20% necrosis, respectively, indicating sub-optimal responses (7). ROI and histographic ΔK^{trans} changes (columns E, J, and K) at TP_1 clearly provide much superior early predictions of responses compared with changes in tumor size and K^{trans}(SM). After therapy completion (at TP_2), the % changes (relative to TP_0) of all 11 imaging biomarkers give good discriminations between the responses. **Figure 3** shows the plot of % change in the median ΔK^{trans} value at 2 wks. (TP_1) *vs.* % necrosis after 10 wks. (TP_2) for all three patients. It is remarkably linear. [The pathology report for subj. 1 stated > 95% necrosis: we plotted it as 97.5 %.] The horizontal line at 95% necrosis is the current pathology binary classifier for sarcoma therapy response. [A >100% decrease in median ΔK^{trans} (subj. 1) means that the median ΔK^{trans} became negative. By definition K^{trans} must be positive, but ΔK^{trans} can be negative (8).]

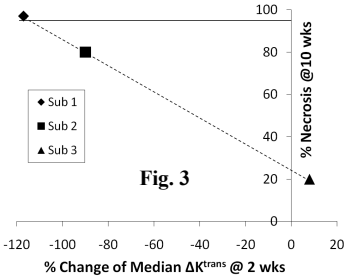

Fig. 3

Discussion: This initial experience suggests that the ΔK^{trans} biomarker is more sensitive to therapy-induced tumor vascular changes compared with tumor size and K^{trans}(SM), and can provide an early prediction of soft-tissue sarcoma pathologic response. As a bonus, the ΔK^{trans} calculation may mitigate or eliminate many common systematic DCE-MRI parameter errors from, for example, AIF uncertainty: the same AIF is used for both the SM and SSM analyses. These types of systematic errors have long posed tremendous challenges to longitudinal DCE-MRI studies monitoring therapy response. Early identification of patients not responding to therapy would allow prompt alternative treatments, sparing them from ineffective and potentially toxic therapies. This is the case for subject 3. The median ΔK^{trans} change at TP_1 was also encouraging for subject 2. Perhaps this result could have suggested a longer treatment period that might have yielded better outcome for this patient.

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References: **1.** Huang *et al. PNAS* **105**:17943-48 (2008). **2.** Huang *et al. PISMRM* **18**:368 (2010). **3.** Tofts *et al. JMRI* **10**:223-32 (1999). **4.** Li *et al. Magn Reson Med* **54**:1351-9 (2005). **5.** Therasse *et al. J Natl Cancer Inst* **92**:205-16 (2000). **6.** Miller *et al. Cancer* 47:207-14 (1981). **7.** Ryan *et al. Cancer* **112**:2432-9 (2008). **8.** Li *et al. JMR* **206**:190-199 (2010).