Evidence for Caution in DCE-MRI Assessment of Response to Antiangiogenic Therapy Using the Reference Tissue Method

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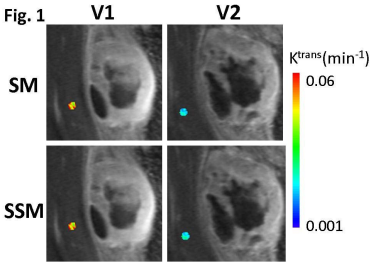
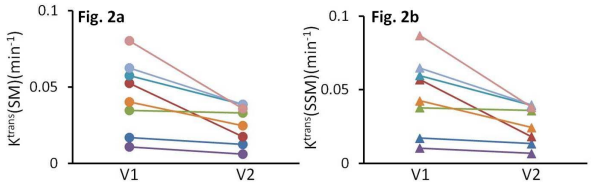
Introduction: As a noninvasively imaging method for characterization of tissue microvasculature, dynamic contrast-enhanced (DCE) MRI has been widely used in research settings and early-phase clinical trials to evaluate tumor response to targeted therapies, especially antiangiogenic therapies (1). However, performing quantitative pharmacokinetic analysis of DCE-MRI data with high reproducibility and reliability remains a significant challenge in a longitudinal study to assess tumor therapy response. There are many errors or uncertainties in the processes of data acquisition and analysis, such as determination of arterial input function (AIF), quantification of pre-contrast T_1, scanner hardware drifting, etc., that can affect accuracy and precision of the derived DCE-MRI parameters.

One approach that has been suggested to ameliorate the problem is the reference tissue method with the assumption that the microvascular properties of normal appearing (or reference) tissue will remain stable over the course of therapy. The reference tissue method allows not only derivation of AIF (2,3) when it cannot be reliably measured from a feeding artery but also normalization of DCE-MRI biomarkers (such as K^{trans}) of the tumor to that of the reference tissue and comparison of the normalized values over the treatment course. However, the assumption for the reference tissue method might not be valid. Hypertension is a common side effect of antiangiogenic therapeutics (4), and impaired tissue perfusion could be a downstream consequence of hypertension (5,6), suggesting that antiangiogenic treatment of tumor may affect perfusion in normal tissue. In this study, we retrospectively examined the changes of DCE-MRI parameters in normal appearing muscle regions in soft-tissue sarcoma patients receiving antiangiogenic treatment.

Methods: 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 DCE-MRI studies were performed at visit 1 (V1) - before therapy, V2 - after two weeks of Sorafenib only treatment, and V3 – after eight more weeks of treatment with Sorafenib plus chemoradiation therapy, followed by definitive surgery. A total of eight patients consented to the MRI studies, with 2 of them failing to undergo the last DCE-MRI study (at V3). In these 8 patients, five masses were located in the thigh, two in the calf, and one in the knee.



The MRI scans 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 T_2-weighted MRI, a 3D RF-spoiled gradient-echo sequence was used to acquire sagittal DCE-MRI data with 10^0 flip angle, TE/TR = 1.5/6.0 ms, and 320x160 matrix size. 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 T_1 determination (7).



Pharmacokinetic analyses of tumor ROI-averaged and pixel-by-pixel (within the ROI) DCE-MRI time-course data were performed using the Standard (Tofts) Model (SM) and Shutter-Speed Model (SSM) (7) – the latter takes into account the intercompartmental water exchange kinetics. For this study, a circular ROI (50-60 pixels) was drawn on an image slice in the normal appearing muscle region adjacent to the tumor, and the corresponding DCE data were analyzed in the same fashion. The derived kinetic parameters included K^{trans}, v_e, and k_{ep} (=K^{trans}/v_e). To assess the effects of antiangiogenic treatment on DCE-MRI parameters of the normal muscle tissue, the muscle ROI was placed in the same anatomic location with the best visual estimation and its size was kept the same throughout the longitudinal MRI studies of each patient. The AIF used for quantitative analysis was measured directly from a ROI placed in a femoral artery clearly visible within the image FOV.

Results: We have previously reported that percent change in sarcoma K^{trans} at V2 (relative to V1) provides early prediction of optimal *vs.* suboptimal therapy response determined by pathology review of the surgical specimens (7) – all 3 optimal responders exhibited substantial decreases in tumor K^{trans}. Interestingly, the decrease in K^{trans} was also observed in the normal appearing muscle regions adjacent to the tumor in both optimal and suboptimal responders. **Fig. 1** shows the color SM (top) and SSM (bottom) K^{trans} maps at V1 (left) and V2 (right) of a muscle ROI anterior to an upper thigh sarcoma that had optimal therapy response. The decrease in muscle K^{trans} after 2 weeks Sorafenib-only treatment is visually noticeable. **Fig. 2** shows the scatter plots of muscle ROI K^{trans}(SM) (Fig. 2a) and K^{trans}(SSM) (Fig. 2b) values from the eight patients at V1 and V2 with the straight lines connecting data points from the same patient, demonstrating the general trend of K^{trans} decrease from V1 to V2. The mean muscle ROI K^{trans}(SM) and K^{trans}(SSM) values at V1, V2, and V3 are listed in the **Table**. Paired t tests revealed statistically significant decreases in muscle K^{trans} obtained by either the SM (P = 0.011) or the SSM (P = 0.013) analysis. The same pattern was observed for muscle k_{ep} (P = 0.015 for the SM; P = 0.020 for the SSM) (mean values not shown here). There were no significant changes in muscle v_e at V2 *vs.* V1. Furthermore, no statistically significant differences were found in all three DCE-MRI parameters when comparing V3 *vs.* V1 or V3 *vs.* V2.

Table. Normal Appearing Muscle ROI Mean K^{trans} Values

DCE-MRI Time Point	K^{trans}(SM) (min^{-1})	K^{trans}(SSM) (min^{-1})
Visit 1 (n=8)	0.044*	0.047#
Visit 2 (n=8)	0.026	0.027
Visit 3 (n=6)	0.064	0.067

Paired t test (Visit 1 *vs.* Visit 2): *P = 0.011, #P = 0.013

Discussion and Conclusion: Our findings of K^{trans} (or k_{ep}) decrease in normal appearing muscle region following treatment of soft-tissue sarcoma patients with the antiangiogenic agent Sorafenib are consistent with those of a recent preclinical study where reduction of muscle K^{trans} was observed following Sorafenib treatment of a murine model of colorectal cancer (8). It appears that the antiangiogenic effects exerted by Sorafenib occur not only in the tumor but also in normal muscle tissue. Though Sorafenib continued to be administered between V2 and V3, the fact that we did not observe significant K^{trans} decrease in the muscle at V3 (relative to V1 or V2) may be due to several reasons or a combination of them: a) insufficient number of subjects (n = 6) had V3 MRI studies; b) the conventional chemoradiation given along with Sorafenib between V2 and V3 might have neutralized Sorafenib's effects on the muscle; and c) recovery of muscle perfusion from the initial effects by Sorafenib. The exact mechanism underlying muscle K^{trans} decrease in response to antiangiogenic treatment is unclear. Reduced tissue perfusion (5,6) as a results of the common side effect of antiangiogenic drugs, hypertension, may provide a plausible explanation. Nonetheless, the results from this study serve the evidence that DCE-MRI parameters of normal tissue could be altered following administration of anticancer drugs, and caution must be taken when reference tissue method is used in DCE-MRI assessment of cancer therapy response.

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