DCE-MRI Assessment of Soft-Tissue Sarcoma Response to Preoperative Therapy

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Introduction: One strategy for treating patients with high-risk soft-tissue sarcoma is to use a combination of preoperative chemotherapy and radiation (1). In current standard-of-care, measurement of tumor size change is generally used to evaluate solid tumor response to treatment. As a noninvasive imaging method for functional characterization of tissue microvasculature, dynamic contrast-enhanced (DCE) MRI has been increasingly used in research settings and early-phase clinical trials to assess tumor response to targeted therapies, such as antiangiogenic therapies (2). In this prospective study, we sought to evaluate the utility of quantitative DCE-MRI for early prediction and assessment of soft-tissue sarcoma response to preoperative therapy, in comparison with imaging tumor size measurement.

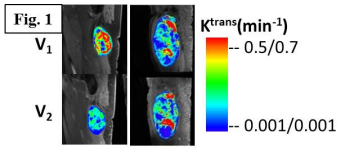
Table 1. MRI Metrics for Early Prediction of Response

Response	V1			V2			V21 (%)		
	K^{trans} (min^{-1})	k_{ep} (min^{-1})	RECIST (cm)	K^{trans} (min^{-1})	k_{ep} (min^{-1})	RECIST (cm)	K^{trans}	k_{ep}	RECIST
Optimal	0.091 ± 0.082*	0.314 ± 0.214#	10.1 ± 7.4	0.056 ± 0.030#	0.294 ± 0.267*	9.3 ± 7.3	-38.2 ± 24.9*	-18.4 ± 17.3	-0.4 ± 16.8
Sub-Optimal	0.211 ± 0.163	0.753 ± 0.432	11.9 ± 5.2	0.200 ± 0.134	0.744 ± 0.701	11.0 ± 5.0	-8.9 ± 33.0	-1.8 ± 47.2	-3.1 ± 8.4

Unpaired t test: *, P < 0.05; #, P < 0.01

Methods: Twenty patients with grade 2-3 soft-tissue sarcomas were enrolled in this research DCE-MRI study. Among them, 12 patients underwent a conventional preoperative chemoradiotherapy regimen with three cycles of chemotherapy plus one radiation session; the other 8 patients participated in a phase I clinical trial in which the vascular endothelial growth factor receptor (VEGFR) inhibitor, Sorafenib, was added to the conventional chemoradiotherapy regimen, with the patients taking Sorafenib only in the first two weeks and Sorafenib plus chemoradiotherapy in the next eight weeks. DCE-MRI studies were performed at visit 1 (V1) - before treatment, V2 - after two weeks of conventional chemotherapy (one cycle) or Sorafenib treatment, and V3 – after completion of therapy before definitive surgery. Several subjects dropped out of the MRI study at the V2 and V3 due to various reasons, resulting in 16 subjects (9 on conventional therapy and 7 on Sorafenib trial) at V2 and 12 subjects (7 on conventional therapy and 5 on Sorafenib trial) at V3. All studied tumors were located in the thigh, calf, or knee.

The DCE-MRI studies were performed using a 3T Siemens instrument and a 3D RF-spoiled gradient-echo sequence with 10^0 flip angle, TE/TR = 1.5/6.0 ms, 5 mm slice thickness, and 320x160 matrix size. A parallel imaging acceleration factor of 2 was used for DCE-MRI, resulting in 7-16 s temporal resolutions. 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 determination of pre-contrast T_1 value (3). An experienced radiologist drew tumor ROIs on post-contrast DCE-MRI images and measured tumor size according to the (one dimensional) RECIST (4) guidelines. Pharmacokinetic analyses of tumor ROI-averaged DCE-MRI data were performed using the two-compartment Shutter-Speed model (SSM) (5), which takes into account the effects of transcytolemmal water exchange kinetics. The arterial input function (AIF) was measured for each DCE-MRI study by placing a small ROI within the part of the femoral artery that was clearly visible and adjacent to the tumor. The derived pharmacokinetic parameters included K^{trans}, v_e, and k_{ep} ($=K^{trans}/v_e$). The mean parameter value of the whole tumor was calculated as the weighted (by ROI pixel number) average of the single-slice ROI values of the image slices covering the entire tumor.

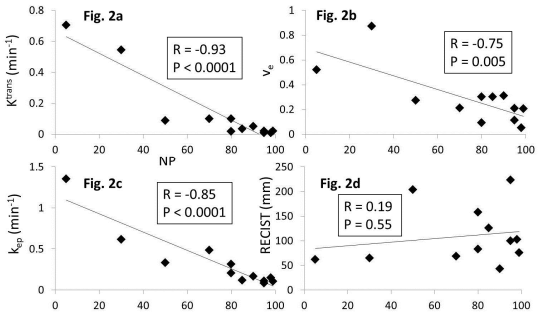


Results: Pathology review of the surgical specimens revealed that 9 sarcomas had optimal treatment responses to preoperative therapy with ≥95% necrosis, while the other 11 tumors had sub-optimal responses with <95% necrosis (6). There were no significant differences (P > 0.2) in RECIST and DCE-MRI parameters at V1, V2, and V3, or their percent changes at V2 and V3 (relative to V1) between the patients on conventional chemoradiotherapy and those on Sorafenib trial. Therefore, we combined the two groups of patients in assessing the utility of DCE-MRI for evaluation of sarcoma therapy response in comparison with RECIST measurement.

Table 2. Early Prediction of Response

MRI Metrics	ROC AUC
V2 K^{trans}	0.917
V21% K^{trans}	0.800
V1 k_{ep}	0.798
V2 k_{ep}	0.783
V21% RECIST	0.688

Table 1 lists the mean ± SD values of K^{trans}, k_{ep}, and RECIST at V1, V2, and the corresponding percent change (V21%: V2 relative to V1) for the optimal and sub-optimal responders. Compared to the sub-optimal responders, the optimal responders had significantly (P < 0.05) smaller K^{trans} and k_{ep} values at V1 and V2, as well as significantly (P < 0.05) larger percent decrease in K^{trans}. There was no significant difference between the two responder groups in RECIST tumor size at V1 and V2, and its percent change. **Fig. 1** shows the V1 (top) and V2 (bottom) tumor K^{trans} color maps of an optimal responder with 99% necrosis at surgery (left) and a sub-optimal responder with 50% necrosis (right) – both were on the Sorafenib trial. The two sets of color scale range correspond to the left and right panels, respectively. The substantial decrease in K^{trans} was clearly visible in the optimal responder compared to minimal change in the sub-optimal responder. Area-under-the-curve (AUC) values of Receiver Operating Characteristic (ROC) analysis (**Table 2**) show that, in contrast to V21% RECIST which was a poor early marker of response (AUC = 0.688), V1 k_{ep}, V2 k_{ep} and K^{trans}, and V21% K^{trans} were good to excellent early predictors of response. After completion of therapy, V3 tumor K^{trans}, v_e, and k_{ep} were found to have significantly strong ($P \leq 0.005$) negative correlations (**Fig. 2a-c**) with surgical specimen necrosis percentage (NP, labeled in Fig. 2a), while no significant correlation was observed between V3 RECIST and NP (Fig. 2d).



Discussion and Conclusion: The results suggest that quantitative DCE-MRI may be a useful imaging method for early prediction of soft-tissue sarcoma response to preoperative therapy, potentially enabling rapid adoption of alternative treatment for nonresponding patients – a step toward personalized care. The study findings imply that sarcoma with low perfusion and permeability at baseline, after one cycle of chemotherapy, or with large percent decrease may have less angiogenesis-induced abnormal vasculature, and therefore better drug delivery and response. However, RECIST imaging tumor size measurement was neither capable of providing early prediction of therapy response, nor assessing response after therapy completion. The strong correlations between DCE-MRI parameters and NP of surgical specimen suggest that, instead of anatomic imaging, a quantitative DCE-MRI study following preoperative therapy may be more beneficial if more accurate surgical staging is desired. The negative correlations of post-therapy K^{trans} and k_{ep} with NP are expected, as perfusion to the entire tumor decreases with increased necrosis. The similar relationship between post-therapy v_e and NP is interesting, however, with v_e expected to increase with increased cancer cell death and necrosis. The probable explanation is that, though defined as extravascular and extracellular volume fraction, v_e as measured by DCE-MRI is foremost the putative contrast agent distribution volume fraction, which is presumably reduced with increased necrosis and decreased viable perfused tumor area. Another interesting observation from this study is that the percent changes in K^{trans} and k_{ep} at V2 and V3 (relative to V1) were not significantly different between patients on the conventional chemoradiotherapy and those on the trial of Sorafenib plus chemoradiotherapy. This could be due to the small sample size in each subject group, or similar antiangiogenic effects whether indirectly by conventional chemotherapy or directly by Sorafenib, or both. Further investigation with a larger patient population is needed to validate the findings.

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