Quantitative DCE-MRI Assessment of Breast Cancer Response to Neoadjuvant Chemotherapy

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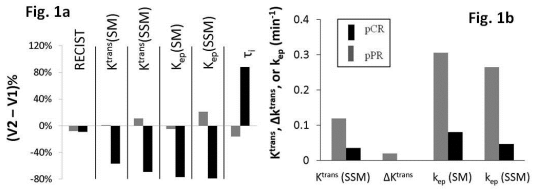
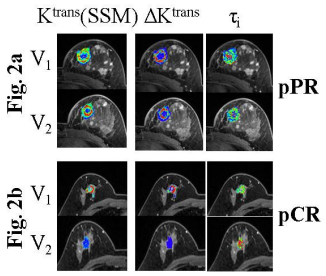
Introduction: Tumor size measurement by breast imaging is the current standard of care for evaluating breast cancer response to neoadjuvant chemotherapy (NACT). However, tumor size changes often lag behind functional changes during treatment (1,2) and fail to provide early prediction of therapy response, which is an important prerequisite for achieving personalized treatment of cancer patients. In addition, breast tumor size measured by imaging after NACT may over- or under-estimate residual disease (3), causing inappropriate surgical decision making of breast conservation *vs.* mastectomy. By measuring tumor microvascular properties, quantitative dynamic contrast-enhanced (DCE) MRI has been shown to be capable of providing early prediction of breast cancer response to NACT (1,4). Taking into account the finite intercompartmental water exchange kinetics, the Shutter-Speed model (SSM) pharmacokinetic analysis of DCE-MRI data (5) has been demonstrated to provide a more sensitive measure of tumor vasculature changes compared to the Standard (Tofts) model (SM). Furthermore, the SSM analysis quantifies a unique parameter, the mean intracellular water lifetime τ_i, which has been found to be inversely related to cellular energy metabolic activity (6). Here we report preliminary results of SSM and SM DCE-MRI assessments of breast cancer response to NACT.



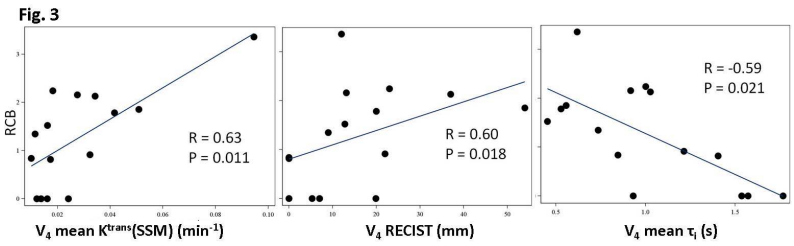
Methods: Fifteen consecutive women with locally advanced breast cancer who underwent NACT consented to research DCE-MRI studies performed at Visit 1 (V_1) - before NACT, V_2 - after first NACT cycle, V_3 – midpoint of NACT (usually after three NACT cycles), and V_4 - after NACT completion. Axial bilateral DCE-MRI images with fat-saturation and full breast coverage were acquired with a 3D gradient echo-based TWIST sequence (7) using a 3T Siemens scanner. DCE-MRI acquisition parameters included 10° flip angle, 2.9/6.2 ms TE/TR, a parallel imaging acceleration factor of two, 30-34 cm FOV, 320x320 matrix size, and 1.4 mm slice thickness. The total acquisition time was ~ 10 min for 32-34 image volume sets with 18-20 s temporal resolution. Gd contrast agent (Prohance®) IV injection (0.1 mmol/kg at 2 mL/s) was timed to start following acquisitions of two baseline image volumes. Tumor ROIs were drawn by experienced radiologists who also measured tumor size according to the (one dimensional) RECIST (8) guidelines. The ROI-averaged and pixel-by-pixel (within the ROI) DCE time-course data were subjected to both the SM and SSM pharmacokinetic analyses to extract K^{trans}, v_e, k_{ep} (= K^{trans}/v_e), and τ_i (SSM only) parameters. The ΔK^{trans} parameter [= K^{trans}(SSM) - K^{trans}(SM)], a measure of water exchange effects on K^{trans} quantification (5,7), was also calculated. The whole tumor mean parameter values were calculated as the weighted (by ROI pixel number) averages of the single-slice ROI values from the image slices covering the entire tumor.



Pathologic response to NACT and residual cancer burden (RCB) for each patient were determined by pathological analysis of post-therapy resection specimens and comparison with pre-therapy core biopsy specimens using previously published methods (9,10). The pathology endpoints were correlated with the MRI metrics using the univariate logistic regression (ULR) analysis and the Spearman's correlation (SC) to identify imaging biomarkers for early prediction of response and/or accurate assessment of residual disease following NACT.

Table. Predicting the RCB Rank	
V4 MRI Metrics	**ULR c Value**
V4 mean τ_i	0.833
V4 mean K^{trans}(SSM)	0.769
V4 mean K^{trans}(SM)	0.756
V4 mean ΔK^{trans}	0.750
V4 RECIST	0.731

Results: Pathological analyses revealed that 4 patients were pathologic complete responders (pCR) – no invasive cancer cell found in resection specimens, while the other 11 were pathologic partial responders (pPR) – reduced cancer cell density in resection specimens compared to biopsy specimens. The ULR analysis found that the % changes in tumor mean K^{trans} (SM and SSM), k_{ep} (SM and SSM), and pixel τ_i histogram median values after the first NACT cycle (at V_2 relative to V_1) were excellent discriminators of the pCRs from the pPRs with ULR c statistics values = 0.98, 0.98, 0.98, 0.95, and 1 (c=1 means complete separation), respectively; while the early RECIST % change was a poor predictor of response with c = 0.60. **Fig. 1a** shows a column graph of the mean % changes of these MRI metrics for the pCR (black) and pPR (gray) groups. In addition, the absolute values of V_2 tumor mean K^{trans}(SSM), ΔK^{trans}, and k_{ep} (SM and SSM) (**Fig. 1b**) were also excellent (c > 0.9) early predictors of response. The ΔK^{trans} column for the pCR group is almost invisible in Fig. 1b because its mean value was near zero. **Fig. 2** shows tumor K^{trans}(SSM), ΔK^{trans}, and τ_i maps (in color) of a pPR (2a) and a pCR (2b) at V_1 and V_2. Compared to the pPR, the K^{trans}(SSM) and ΔK^{trans} decreases and τ_i increase from V_1 to V_2 were dramatic for the pCR. The RCB can be described in numerical values or stratified in ranks (such as I, II, III, *etc.*) with RCB = 0 for pCR (9,10). ULR and SC analyses were used to correlate V_4 (after NACT completion) MRI metrics with RCB ranks and actual values, respectively. The **Table** shows that the V_4 tumor mean τ_i was a good (c = 0.8 - 0.9) marker of RCB rank, while K^{trans} (SM and SSM), ΔK^{trans}, and RECIST measures were fair (c = 0.7 – 0.8) markers. The SC analysis (**Fig. 3**) revealed that V_4 τ_i was inversely, while K^{trans} and RECIST were positively, correlated with RCB. These correlations were statistically significant (P < 0.05) for all three metrics.



Discussion and Conclusion: Consistent with previous studies (1,4), our preliminary results suggest that changes in breast tumor microvasculature as measured by DCE-MRI precede size changes in response to NACT. After only one cycle of NACT, the % changes (relative to baseline) or actual values of quantitative DCE-MRI biomarkers can provide excellent predictions of eventual pathologic response, while the RECIST measure of tumor size is a poor predictor of response at that early time point or even the midpoint of NACT (results not shown here). Both SM and SSM K^{trans} and k_{ep} parameters are excellent early predictors. However, the changes in the SSM parameters generally create larger separations of the two response groups (see Fig. 1a), and thus may be more sensitive markers of therapeutic response. Furthermore, the SSM-unique τ_i parameter may add a metabolic dimension (6) in DCE-MRI evaluation of therapy response and its potential is demonstrated in early prediction of response and accurate assessment of residual disease. The synergistic aspect of combining this cellular information with K^{trans}, v_e, and k_{ep} characterizations of microenvironment (11) has great promise. Continued patient enrollment is planned to validate the initial findings with a larger data set.

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References: **1.** Marinovich *et al. The Breast* 2012;21:669-677. **2.** Tan *et al. Magn Reson Imaging* 2008;26:26-34. **3.** Partridge *et al. AJR* 2002;179:1193-9. **4.** Ah-See *et al. Clin Cancer Res* 2008;14: 6580-9. **5.** Huang *et al. Radiology* 2011;261: 394-403. **6.** Zhang *et al. Biophys J* 2011;101:2833-42. **7.** Tudorica *et al. Magn Reson Imaging* 2012;30:1257-67. **8.** Therasse *et al. J Natl Cancer Inst* 2000;92:205-16. **9.** Symmans *et al. J Clin Oncol* 2007;25:4414-22. **10.** Rajan *et al. Cancer* 2004;100:1365-73. **11.** Pike *et al. PISMRM* 2013;21:3067.