Mean Intracellular Water Molecule Lifetime: Another Useful Breast DCE-MRI Biomarker?

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Introduction: The use of the Shutter-Speed Model (SSM) for DCE-MRI pharmacokinetic analysis shows significantly improved diagnostic accuracy in breast cancer detection, compared to the Standard Model (SM) (1-3). This is accomplished because the underestimate of \( K^{\text{trans}} \) (plasma to interstitium contrast agent (CA) transfer rate constant) by the SM (relative to the SSM) is substantially greater for malignant than benign lesions. The SM assumes that the inter-compartmental water exchange kinetics are always effectively infinitely fast: all exchange MR systems remain in their fast-exchange-limit [FXL] conditions (4). The SSM admits these systems can transiently depart their FXL conditions during CA bolus passage through tissue – due to the greater CA extravasation (3,5).

In addition to the conventional \( K^{\text{trans}} \) and \( v_i \) (interstitial volume fraction) parameters, an SSM fitting of DCE time-course data can also return a third parameter, the mean intracellular water molecule lifetime, \( \tau_i \), which accounts for the transcytoplasmal exchange effects. A recent yeast cell suspension study (6) that \( \tau_i \) is inversely correlated with cell membrane ion ATPase kinetics, a measure of metabolism. In this study, the characteristics of the \( \tau_i \) parameter for malignant and benign breast lesions are explored, as well as \( \tau_i \) relationships with other DCE-MRI parameters.

Methods: 157 patients with 172 suspicious breast lesions [89 patients with 92 lesions at institution A (IA); 68 patients with 80 lesions at institution B (IB)] consented to research DCE-MRI studies prior to standard care biopsy procedures. The 92 lesions at IA were mammographically negative, but referred for biopsies following positive mammography and/or ultrasound diagnoses. The research DCE-MRI acquisitions were performed using 1.5T GE MRI systems at uniform 18 s temporal resolution. The DCE-MRI acquisition time was ~8 (IA) or ~10 (IB) min with gadolinium CA (Magnevist® at IA and Prohance® at IB) IV injection through an antecubital vein (0.1 mmol/kg at 2 mL/s) carried out following acquisition of one (IA) or two (IB) baseline image volumes. The lesion ROI and pixel-by-pixel (within ROI) DCE time-course data were subjected to both the SM and the FXL conditions (4) to acquire bilateral high spatial resolution breast DCE-MRI at uniform 18 s temporal resolution. Receiver Operating Characteristic (ROC) curve analyses were conducted to assess the diagnostic accuracies of the DCE-MRI biomarkers, while Spearman’s correlation analyses were performed to evaluate relationships between \( \tau_i \) and other biomarkers.

Results: Biopsy pathology analyses revealed that 46 of the 172 lesions were malignant. The Table lists the mean±SD lesion ROI DCE-MRI biomarker values for the malignant and benign lesions, as well as the ROC area under the curve (AUC) values with unity indicating perfect diagnostic accuracy. For both SM and SSM analyses, the malignant lesion group has significantly (\( P < 0.0001 \)) higher \( K^{\text{trans}} \) and \( k_{ep} \) values than the benign group, while the SSM-only \( \tau_i \) biomarker is significantly (\( P = 0.02 \)) smaller for the malignant group compared to the benign group. There is no statistically significant difference in SM or SSM \( v_i \) values between the two groups. Based on ROC AUC values, \( K^{\text{trans}} \) and \( k_{ep} \) obtained from either model are good diagnostic markers with the SSM parameters having higher diagnostic accuracies than their SM counterparts. The difference in ROC AUC between SM and SSM \( K^{\text{trans}} \) is statistically significant (\( P = 0.0013 \), nonparametric test). The \( v_i \) and \( \tau_i \) parameters are poor diagnostic markers.

Discussion: Consistent with previous studies of smaller cohorts (1-3), substantial SM underestimation (relative to SSM) of \( K^{\text{trans}} \) occurred in only malignant lesions in this larger population. Since the FXL condition assumes \( \tau_i \to 0 \), the fact that malignant lesions have smaller \( \tau_i \) values than benign lesions suggests that the greater increase of malignant lesion \( K^{\text{trans}} \) value by the SSM is not simply because it includes an additional variable \( \tau_i \), but because of genuine exchange effects. The significant \( K^{\text{trans}} \), \( k_{ep} \) correlation is not due to intra-model parameter co-variance because \( \tau_i \) is a SSM-only parameter and it correlates with SM \( K^{\text{trans}} \), which has been shown to be inversely correlated with cellular metabolic activity (6). The smaller \( \tau_i \) values for malignant lesions suggest that they are more metabolically active (as expected), but the \( \tau_i \) hot spots areas within a malignant lesion may indicate regions of hypoxia/necrosis. This would be of tremendous clinical utility. \( K^{\text{trans}} \) has been shown to be a useful biomarker for prediction of breast cancer therapy response (8). The slope of the \( K^{\text{trans}}/\tau_i \) linear regression is -0.13 for the malignant lesions (Fig. 1, right), indicating that a small, therapy-induced \( K^{\text{trans}} \) change may be reflected by a larger \( \tau_i \) change. Thus, as potential measures of both tumor metabolism and perfusion/permeability, \( \tau_i \) may be a very sensitive DCE-MRI biomarker for evaluation of breast cancer therapeutic response.

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