Pharmacokinetic Parametric Mapping and Pixel Histogram Analysis for Benign and Malignant Breast Lesion Discrimination: A Preliminary Shutter-Speed DCE-MRI Study

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Introduction For pharmacokinetic modeling of dynamic contrast-enhanced (DCE) MRI time-course data, the standard model (SM) (1) implies effectively infinitely fast equilibrium transcytolemmal water exchange kinetics during the contrast reagent (CR) passage through tissue, while the more general shutter-speed model (SSM) (2) allows for effects of finite water exchange kinetics. In recent DCE-MRI studies of patients with suspicious breast lesions (3, 4), it was shown that the SM underestimates the rate constant for passive CR plasma/interstitium transfer, K^{trans}, significantly in only the malignant tumors. This allows the difference in K^{trans} extracted from the two model analyses, ΔK^{trans} (SSM K^{trans} – SM K^{trans}), to separate the benign and malignant lesions with extremely high accuracy (3, 4). ΔK^{trans} measures the exchange (shutter-speed) effect. Integration of SSM DCE-MRI into clinical practice could potentially reduce most if not all unnecessary biopsy procedures that yield benign results.

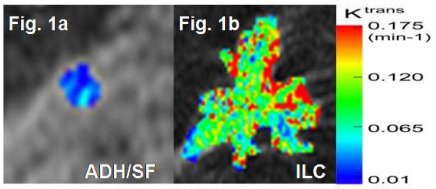
However, mostly tumor region-of-interest (ROI) analytical results were reported in those studies (3, 4). With the unavoidable partial volume averaging effect in ROI parametric analysis, it is expected that "borderline" benign and malignant breast lesions will be hard to distinguish. In this preliminary study, we explore the potential for parametric mapping and pixel histogram analyses of pharmacokinetic parameters to further improve DCE-MRI breast cancer diagnostic accuracy.

Methods The patients recruited for this IRB-approved research DCE-MRI study had undergone the institutional clinical breast MRI protocol and been referred for biopsies based on radiologic interpretation scores of the CR-enhanced lesions presented: BIRADS (Breast Imaging Reporting and Data System) 4 (suspicious) or BIRADS 5 (highly suggestive of malignancy).

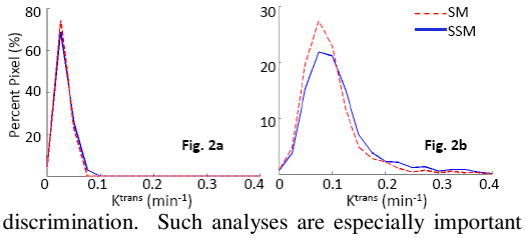
Using a 1.5T MR system, a body transmit and a four- or seven-channel phased-array bilateral breast receive RF coils, the DCE-MRI data were acquired during the patients' clinically scheduled MRI-guided preoperative needle localization or core biopsy procedures, just before needle insertions. A 3D SPGR pulse sequence with fat saturation was used to acquire 12-20 serial sagittal image volume sets continually, spatially covering the whole breast with the suspicious lesion to be biopsied. Other parameters included 10^{o} flip angle, 2-5 ms TE, 6-8 ms TR, 3 mm section thickness, 20-24 cm FOV, and 256x 128 matrix size. Depending on the breast size, 18-32 image sections were acquired for each set, resulting in an intersampling interval range of 16-29 s. At the start of the second volume set acquisition, $GdDTPA^{2-}$ was delivered intravenously [0.1 mmol/kg at 2 mL/s]. Reliable individual arterial input functions (AIFs) were measured from ROIs placed within axillary arteries of three patients. These were interpolated with a seven parameter empirical expression (2) and averaged to generate a mean AIF. The tumor signal time-courses, from both the ROI circumscribing the enhanced lesion and each ROI pixel, were then subjected with the mean AIF to both SM and (fast-exchange-regime-allowed) SSM analyses to extract ROI and pixel pharmacokinetic parameters, such as K^{trans} and v_e (the interstitial space volume fraction) (3, 4). These analyses were blinded from the pathology.

With adequate signal-to-noise ratio (SNR), reliable curve fittings of pixel signal time-courses were accomplished for data sets from 16 patients. Parametric maps within the enhanced ROIs were generated and overlaid onto the anatomical images. Histogram analyses were performed for the pixel pharmacokinetic parameters, to obtain peak probability (amplitude) and median biomarker values. The ROI parameter and histogram differences between the two analyses (SSM-SM) were calculated, and statistical discrimination analysis was carried out for separation of the benign and malignant lesions, to be validated by the subsequent gold standard pathology results.

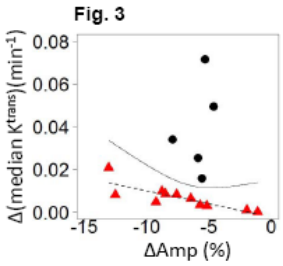
Results Of this group, pathology analyses revealed 11 benign and 5 malignant lesions. Constrained to 100% sensitivity for breast cancer diagnosis, none of the ROI analyses achieves complete separation of the benign and malignant groups, though the specificity of the ROI ΔK^{trans} biomarker (92%) is greater than for either ROI SSM or SM K^{trans} (each 85%). Fig. 1 shows the magnified SSM K^{trans} color maps in the CR-enhanced lesion ROIs of a benign (1a) and a malignant (1b) lesion: atypical ductal hyperplasia/stromal fibrosis (ADH/SF) and invasive lobular carcinoma (ILC), respectively. Note the hot spots (K^{trans}>0.18 min^{-1}) at the posterior rim of the very large (5 cm in the greatest enhanced ROI dimension) ILC lesion and their absence in the ADH/SF lesion. Fig. 2 plots the SM and SSM K^{trans} histograms for the same benign (2a) and malignant (2b) lesion pair. The histogram is slightly shifted and broadened by the SSM analysis, but noticeably for only the already broad malignant tumor histogram.



In Fig. 3, the median K^{trans} difference, Δ(median K^{trans}) [SSM median K^{trans} – SM median K^{trans}], is plotted (ordinate) *vs.* the change in maximum histographic probability (amplitude) (abscissa), ΔAmp [SSM amplitude – SM amplitude]. There is significant negative linear correlation (dashed line, Pearson correlation = -0.82, p = 0.0018) for the eleven benign lesions (red triangles), while the five malignant lesions (black circles) exhibit an almost orthogonal correlation. The lowest black circle represents the ILC (Fig. 1b), which cannot be distinguished from the benign group with simple ROI ΔK^{trans} analyses. However, using quadratic discrimination analysis (5), the benign and malignant lesions can be completely separated (100% sensitivity and 100% specificity) by the solid partition curve with no misclassification under leave-one-out cross validation (5).



Discussion Though the ROI ΔK^{trans} biomarker can achieve high specificity for benign/malignant breast lesion discrimination (3,4), the partial volume averaging effects of ROI analyses can cause overlap in ROI pharmacokinetic parameter values, and thus prevent clearer separation of the two groups. The results from this preliminary study suggest that pharmacokinetic parametric mapping and histogram analyses could further improve discrimination. Such analyses are especially important when the lesion ROI biomarker value falls in the vicinity of a binary classifier cut-off value (3, 4). Thus, it is important to acquire DCE-MRI data with sufficient SNR, since this is crucial for reliable pixel signal time-course curve fitting. The negative linear correlation of the benign lesions and the orthogonal behavior of the malignant lesions in Fig. 3 are quite interesting. Compared to malignant lesions that can have noticeable median K^{trans} increases (shutter-speed (SS) histographic shifts) without significant histographic maximum probability changes (SS broadening), the areas in benign lesions where increased blood vessel CR permeability incurs SS effects, if any, are smaller. Considerable SS histographic broadening is associated with even minuscule SS histographic shifting.



References **1.** Tofts PS, *et al. JMRI* 1999; 10:223-232. **2.** Yankeelov TE, *et al. Magn Reson Med* 2003; 50:1151-1169. **3.** Li X, *et al. Proc Natl Acad Sci* 2008; 105:17937-17942. **4.** Huang W, *et al. Proc Natl Acad Sci* 2008; 105:17943-17948. **5.** Johnson RA, *et al.* Applied multivariate statistical analysis. 5th Ed. 2002.