A High Specificity Biomarker for Breast Cancer Diagnosis: Shutter-Speed DCE-MRI Discrimination among Seventy Seven Suspicious Lesions

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INTRODUCTION   Current clinical breast MRI examination protocols have quite limited specificity. This often leads to possibly unnecessary biopsy procedures (yielding benign results). Thus, there is genuine need to improve breast MRI diagnostic accuracy. Dynamic contrast-enhanced (DCE) MRI is an important component in a breast exam. Compared to qualitative or semi-quantitative analysis, it is more desirable to perform analytical modeling of the DCE-MRI signal time-course data to extract pharmacokinetic parameters independent of image acquisition schemes, contrast reagent (CR) dose, injection rate, field strength, etc. These parameters are usually variants of: K^{trans}, a rate constant for passive CR plasma/interstitium transfer, and v_e, the interstitial space volume fraction (the putative CR distribution volume). The commonly used standard model (SM) (1) embeds the assumption that equilibrium transcytolemmal water exchange is effectively infinitely fast. Unfortunately the SM DCE-MRI approach has been inadequate in improving breast cancer diagnostic specificity (2).

The more general shutter-speed model (SSM) (3) allows effects of finite water exchange kinetics during CR passage through tissue. It was recently shown in a cohort of 22 patients with suspicious breast lesions that using the tumor region-of-interest (ROI) K^{trans} biomarker, the positive predictive value (PPV) for malignancy was 78% for SSM DCE-MRI, significantly higher than those from the SM analysis and the qualitative clinical interpretations (58% and 32%, respectively) (4, 5). Further, it is apparent that the SM K^{trans} underestimation occurs significantly only in malignant breast tumors. Therefore, the K^{trans} difference, ΔK^{trans} (SSM K^{trans} – SM K^{trans}), allowed complete separation of the benign and malignant lesions, or 100% PPV in that population (4, 5). The increased permeability of malignant tumor blood vessels exceeds a threshold above which exchange kinetics become influential. This amplification is measured by the ΔK^{trans} biomarker, and accounts for the high SSM specificity (4, 5). This current study of an expanded population evaluates and statistically compares ROI SM and SSM pharmacokinetic biomarkers for discrimination of benign and malignant breast tumors.

METHODS   A total of 74 patients underwent clinical breast MRI protocols and had 77 contrast-enhanced lesions (3 patients presented 2 lesions each) radiologically classified in the BIRADS (Breast Imaging Reporting and Data System) 4 (B-4, suspicious, n = 67) or 5 (B-5, highly suggestive of malignancy, n = 10) categories based on lesion morphology and qualitative enhancement kinetics assessment. These clinical interpretations led to biopsy referrals. The research DCE-MRI data acquisitions were IRB-approved. The data from 6 patients were collected as part of a combined MRI/MRS protocol prior to excisional or core biopsy. Those from the other 68 patients (71 lesions) were acquired during clinically scheduled MRI-guided preoperative needle localization or core biopsy procedures, just before needle insertions.

The study was conducted at 1.5T using a body transmit and a four- or seven-channel phased-array bilateral breast receive RF coils. A 3D SPGR pulse sequence 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° or 30° (for the 6 patients) flip angle, 2-5 ms TE, 6-9 ms TR, 3 mm section thickness, 20-24 cm FOV. Depending on the breast size, 16-36 image sections were acquired for each set, resulting in inter-sampling intervals of 13-42 s. At the start of the second volume set acquisition, Gd CR was delivered intravenously [0.1 mmol/kg at 2 mL/s]. ROIs circumscribing the enhanced lesion and within an axillary artery produced the tumor signal intensity and arterial input function (AIF) time-courses, respectively. Three reliable individual AIFs were measured, which were interpolated with an empirical expression (3) and averaged to generate a mean AIF. The tumor ROI and mean AIF signal time-courses were then subjected to both SM and (fast-exchange-regime-allowed) SSM analyses, which were blinded from the pathology (4, 5). Receiver-operating-characteristic (ROC) curves were used to evaluate pharmacokinetic parameter diagnostic accuracies, and the areas under the curve (AUCs) were compared using a Bootstrap nonparametric test.

RESULTS   Upon pathology, only 18 lesions (10 B-4 and 8 B-5) were found malignant and the other 59 (57 B-4 and 2 B-5) benign. Though the clinical MRI protocol sensitivity is 100% (no false negatives), its PPV is only 23%. The SSM K^{trans} ROC AUC (0.973) is significantly (p = 0.032) greater than that for the SM K^{trans} (0.929). Similar results were obtained for other strong biomarkers: k_{ep} (=K^{trans}/v_e, the unidirectional CR intravasation rate constant) [SSM AUC = 0.960, SM AUC = 0.861, p = 0.006] and $[(K^{trans})^2 + k_{ep}^2]^{1/2}$ (5) [SSM AUC = 0.970, SM AUC = 0.887, p = 0.009]. Maintaining 100% sensitivity, the diagnostic specificities of the SM ROI K^{trans}, k_{ep}, and $[(K^{trans})^2 + k_{ep}^2]^{1/2}$ are 47%, 42%, and 51%, while those for the corresponding SSM parameters are 76%, 61%, and 75%, respectively; each biomarker used as a binary classifier. The SM and SSM v_e ROC curve AUCs are 0.555 and 0.615, respectively, suggesting that v_e is a poor diagnostic marker.

Fig.1 plots ROI ΔK^{trans} for all lesions. Note the ordinate scale break. Each column represents one pathology category (from left to right): 1) invasive ductal carcinoma (IDC)/ductal carcinoma *in situ* (DCIS) mixture, 2) IDC/invasive lobular carcinoma (ILC) mixture, 3) IDC, 4) DCIS, 6) IDC/lobular carcinoma *in situ* (LCIS) mixture, and 9) ILC, for the malignant group (circles); 5) tubular adenoma, 7) LCIS, 8) atypical lobular hyperplasia, 10) atypical ductal hyperplasia, 11) stromal fibrosis, 12) benign parenchyma, 13) fibrocystic changes, 14) papillary lesions, 15) miscellaneous benign conditions, 16) fibroadenomatoid changes, and 17) fibroadenoma, for the benign group (triangles). The categories are ranked roughly in order of decreasing mean ΔK^{trans} from left to right. Consistent with the previous smaller population study (4, 5), the ΔK^{trans} biomarker represents the strongest binary classifier for benign and malignant group separation, with its ROC AUC = 0.990, and 88% specificity for 100% sensitivity.

DISCUSSION   The SSM DCE-MRI ROI pharmacokinetic parameters consistently perform better than those from SM DCE-MRI and the commonly used clinical MRI protocols for benign and malignant discrimination within this group of 77 suspicious breast lesions. If the simple ROI ΔK^{trans} analyses had been integrated into clinical practice, as many as 52 benign lesions (68% of the total population) could have been spared the biopsy procedures. As expected from the earlier study (4, 5), the malignant lesions cluster almost exclusively on the left of Fig. 1, while the benign lesions are almost all to the right – the axes are independent. The solid cut-off line value, ΔK^{trans} = 0.028 min^{-1}, is very close to that for 100% specificity in the smaller population (4, 5). Remarkably, it yields only one false positive (the sole tubular adenoma) and one false negative (the sole ILC) lesion. A more lenient, dashed cut-off line can be drawn at ΔK^{trans} = 0.012 min^{-1} to avoid any false negative and still incur only 14 benign biopsies. But, even these might be avoided. The likely reason for a malignant lesion ROI ΔK^{trans} to fall between the solid and dashed cut-off lines is only because of partial volume averaging in the ROI analyses (4, 5). Consistent with this, the ILC had the very large value of 5 cm as the greatest enhanced ROI dimension. Its pixel-by-pixel SSM K^{trans} map (not shown) features hot spots (K^{trans} > 0.18 min^{-1}) only in the posterior rim region. Though these are diluted by a very large area of small K^{trans} values in the ROI, they confirm the lesion as malignant. This suggests that ΔK^{trans} or SSM K^{trans} maps should be made when an ROI ΔK^{trans} falls between the solid and dashed lines. In conclusion, incorporation of SSM DCE-MRI into clinical MRI protocols may help to greatly reduce the number of possibly unnecessary (benign) biopsies.

REFERENCES   **1.** Tofts PS, *et al. JMRI* 1999; 10:223-232. **2.** Port RE, *et al. JMRI* 1999; 10:233-241. **3.** Yankeelov TE, *et al. Magn Reson Med* 2003; 50:1151-1169. **4.** Li X, *et al. Proc Natl Acad Sci* 2008; 105:17937-17942. **5.** Huang W, *et al. Proc Natl Acad Sci* 2008; 105:17943-17948.