Meta-Population Breast Cancer Screening with the ΔK^{trans} DCE-MRI Parameter

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Introduction: The new DCE-MRI pharmacokinetic parameter (ΔK^{trans}) shows remarkable breast cancer screening effectiveness (1-3). It results from analyzing a DCE-MRI data set twice, once with the Standard Model (SM) and once with the Shutter-Speed Model (SSM). ΔK^{trans} is defined as [K^{trans}(SSM) - K^{trans}(SM)], where K^{trans} is a contrast reagent (CR) extravasation rate constant. Thus, it appraises precisely the only SM/SSM difference - their treatments of inter-compartmental water exchange kinetics. The SM assumes the exchange kinetics are always effectively infinitely fast; all exchange MR systems remain in their fast-exchange-limit [FXL] conditions. The SSM admits these systems can transiently depart their FXLs during bolus CR passage through the tissue ROI or voxel (1,2). Since ΔK^{trans} seems a very sensitive vascular compromise measure, we tested its consistency across three disparate patient sub-populations at three different institutions.

Methods: The first sub-population [U. at Stony Brook (USB)] comprises 6 mammography-positive (M+) women (1 lesion each): DCE-MRI details have been reported (1,2,4). The challenging second cohort [Mem. Sloan Kettering Can. Cen. (MSKCC)] consists of 92 mammography-negative (M-) women. Since they are in the high-risk category (family history and/or BRCA1/2 mutations), they were also screened by clinical MRI and received positive diagnoses (95 lesions): DCE-MRI details for the first 16 (1,2) and the first 92 (3) have been reported. The third sub-population [Ore. Health & Science U. (OHSU)] comprises 31 M+ women (36 lesions). In all, the meta-population comprises 137 suspicious lesions in 129 patients [8 presented 2 tumors each]. They were radiologically rated as BIRADS 4 (suspicious; n = 124) or BIRADS 5 (highly suggestive of malignancy; n = 13) and referred for biopsies as standard care. The research DCE-MRI data were acquired prior to biopsies, and were analyzed with the FXR-a [fast-exchange-regime-allowed] SSM version (1,2). The USB, MSKCC, and OHSU DCE-MRI data were acquired with Philips/Marconi (Picker) 1.5T, GE 1.5T, and Siemens 3T instruments, respectively. Different 3D DCE-MRI acquisitions (with similar exchange-sensitivities) were employed: conventional sagittal unilateral gradient echo (GRE) (USB/MSKCC) and axial bilateral TWIST (OHSU) sequences. The latter is a new k-space undersampling and data sharing GRE method (5), delivering near isotropic 1 mm voxels at 18 s temporal resolution.

Results: **Figure 1** is a scatter-plot of lesion ROI ΔK^{trans} value [ordinate] *vs.* population or pathology [abscissa]. The 6 M+ USB results occupy the 1st column [m, malignant; t, total]. The 95 M- (but MRI-visible) MSKCC cohort points comprise the 2nd and 3rd columns. The 36 M+ OHSU cohort pathology types are indicated in the right columns. The meta-population entailed 32 malignant [11 invasive ductal carcinomas (IDCs), 11 IDC/(ductal carcinomas *in situ*)DCISs, 6 DCISs, 2 invasive lobular carcinomas (ILCs), and 2 invasive mammary carcinomas (IMCs)], and 105 benign [12 atypical ductal hyperplasias (ADHs), 10 lobular carcinomas *in situ* (LCISs), 1 atypical lobular hyperplasia (ALH), 1 tubular adenoma (TA), 24 fibrocystic changes (FCs), 17 fibroadenomas (FAs), 11 benign parenchymas (BPs), 5 papillary lesions (PLs), 8 stromal fibroses (SFs), and 16 others] tumors. If excisional biopsies followed core needle biopsies (CNBs) as standard care, the former pathology results were used to correlate with the MRI results. The ROI drawing and SM and SSM analyses were accomplished by pathology-blinded investigators: the vertical (MRI) and horizontal (pathology) axes are independent.

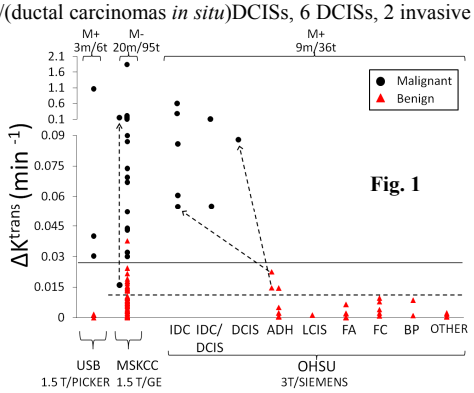

Fig. 1

Remarkably, the "training" binary classifier value obtained from the 6 USB and first 16 MSKCC lesions (2), [ROI-averaged] ΔK^{trans} = 0.028 min^{-1} (solid horizontal line), separates all but 1 of the 105 benign lesions from all but 3 of the 32 malignant tumors in the meta-population: 19 of the 20 malignancies missed by mammography in the high risk cohort are discriminated. In principle, the biopsies for 104 of 105 benign lesions [screening false positives (FPs)] could have been precluded: the only SSM FP is the only TA. But, one would not want to miss the 3 malignancies (points at the beginnings of 3 dashed arrows). To maintain 100% sensitivity, the binary classifier value could be reduced to 0.012 min^{-1} (dashed horizontal line) at the cost of 14 more FPs. However, these 3 false negatives (FNs; based on the solid cut-off line) are each anomalous, and refined SSM analyses resolve them. Voxel-by-voxel pharmacokinetic analyses yield parametric maps (2-4) and histograms. Consider the single FN in the MSKCC cohort [1 of that cohort's 2 ILCs] for which all other lesions were very small [8.6 (±5.7) mm]. This ILC was extremely large (4.5 cm) - an outlying >2X the next largest MSKCC lesion. Its ΔK^{trans} map features hot spots (>0.10 min^{-1}) mainly in the posterior rim (3). The ROI ΔK^{trans} value is greatly "diluted" by partial volume averaging. The median of the ΔK^{trans} histogram upper quartile distribution is >9X the solid cut-off line value. Thus, one can draw a vertical dashed arrow moving the point to a median hot spot value of 0.25 min^{-1}.

The 2 (from one patient; oblique dashed arrows) of the 8 OHSU ADH lesions are even more interesting. ADH is a high-risk benign atypical breast lesion (ABL), as are LCIS, ALH, and PL. Most CNB-proven ABLs are further referred for surgical excisions as standard care, because of possible malignancy miss-estimation due to poor CNB sampling. Malignancies are found in 15-38% of these (6). For the 2 ADH points with dashed arrows, follow-up excisional biopsies revealed 1 IDC and 1 DCIS. Dashed arrow horizontal components indicate revised pathology diagnoses from second biopsies. The 26 other MSKCC/OHSU CNB-proven ABLs were not upgraded to cancers. The ΔK^{trans} histographic median hot spot values provide dashed arrow vertical components for the 2 ADHs with focal malignancies. **Figure 2** shows the ΔK^{trans} map (overlaid on a post-contrast DCE image) of the ADH subsequently upgraded to IDC. The tiny, focal hot spot area might have been missed by CNB. Combined ROI and mapping ΔK^{trans} analyses yield 98% specificity, at 100% sensitivity, in breast cancer detection for the entire meta-population.

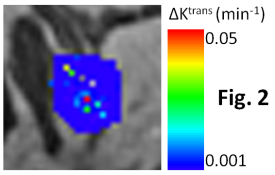

Fig. 2

Discussion: The malignant tumor ΔK^{trans} values are almost uniformly larger, suggesting their DCE-MRI shutter-speed (exchange) effects are significant (the almost negligible ΔK^{trans} for many benign lesions means no detectable shutter-speed effect). Note the Fig. 1 ordinate scale break. In fitting DCE time-courses, the SM problem lies *less* with fitting goodness than with systematic parameter miss-estimations. Though the SM comes close to the SSM in matching benign lesion data, it clearly fails for the malignant tumor (1,2,4) – just when most needed. The larger the K^{trans}, the greater the SM underestimation. A molecular basis of this observation has been described and explanatory competitive chemical reactions written (2). The finding that K^{trans}(SSM) > K^{trans}(SM) mostly for malignant tumors is maintained for the meta-population. This might be expected if malignant lesion capillaries are more angiogenic, and argues that K^{trans}(SSM) is closer to "truth." If we changed the plot from ROI-averaged to hot-spot ΔK^{trans} (map) based - using histographic analyses - all points would certainly move up. However, a reasonable expectation is that the malignant points would move up further than the benign points, leading to increased separation. All malignant breast tumor K^{trans}(SSM) or ΔK^{trans} maps so far reported (2,3,4) show distinct hot spots; as small as 1 mm in diameter. It appears that transient FXL-departures (*i.e.*, increased ΔK^{trans}) are often *focal*, and that these can be very diagnostic for breast malignancy. In some ways, ΔK^{trans} mapping behaves as a form of *in vivo* histological analysis of tissue microvasculature, with a larger FOV. Though the ΔK^{trans} map scale (mm) is not as fine as that of histology (μm), the removal of tissue from the body is not required.

The remarkable independence from cohort screening background, scanner vendor (platform/software), acquisition, CR, and magnetic field strength is gratifying, and suggests SSM robustness. It also argues that the ΔK^{trans} subtraction minimizes/eliminates many other systematic DCE-MRI quantification errors (*e.g.*, from Arterial Input Function (AIF) uncertainty: the same AIF is used for both analyses). SSM DCE-MRI can potentially reduce unnecessary benign breast biopsies and spare many ABL patients from not only CNB procedures but also subsequent unnecessary surgeries. The latter are usually more invasive, deforming, and costly.

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References: **1.** Li *et al. PNAS* **105**:17937-17942 (2008). **2.** Huang *et al. PNAS* **105**:17943-17948 (2008). **3.** Huang *et al. PISMRM* **18**:368 (2010). **4.** Li *et al. Magn Reson Med* **53**:724-729 (2005). **5.** Song *et al. Magn Reson Med* **61**:1242-8 (2009). **6.** Eby *et al. Am J Roentgenol* **192**: 229-34 (2009).