Separation of benign and malignant breast lesions using pharmacokinetic analysis for a biopsy cohort

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INTRODUCTION: Dynamic contrast-enhanced (DCE) MRI is a high sensitivity tool for breast cancer screening and is currently recommended by the American Cancer Society for this indication in high-risk patients [1]. However, this technique suffers from a low and variable specificity (26-97%; Refs [2-4]), which leads to unnecessary biopsies. Clinical evaluation of the kinetic enhancement of indeterminate lesions relies on the time-signal intensity curves that also have significant overlap between benign and malignant lesions. Model-based pharmacokinetic analysis of contrast agent uptake curves in suspicious lesions is one method that has been applied to temporal DCE-MRI data in an attempt to improve its diagnostic accuracy. In this study, we investigate the utility of pharmacokinetic analysis of lesion kinetic data for patients that have been referred for biopsy. This is a uniquely problematic patient population since standard clinical analysis has already failed to separate benign and malignant lesions in this cohort.

Fig 1. Comparison of initial enhancement ratio and delayed enhancement ratio for three lesion types (benign, high-risk benign, and malignant).

METHODS: *Patient Data.* Unilateral DCE-MRI data were acquired at the NYU Cancer Center between November 2011 and October 2012 for 69 women undergoing MRI-guided biopsy of one or more lesions suspicious for breast cancer. The data were acquired on a 3T Tim Trio system (Siemens, Germany) using a dedicated 7 channel breast coil (Invivo). The DCE-MRI protocol used a 3D gradient-echo imaging sequence with fat-suppression and radial k-space sampling (radial VIBE; TR/TE=3.57/1.72 ms, FA=10 deg, FOV=280 mm, resolution 1.4 x 0.9 x 1.5 mm, 380 radial views/frame, 5-6 frames/scan) with a "stack-of-stars" scheme and golden-angle view ordering [5]. Contrast agent (Magnevist, Bayer) was administered approximately 60 seconds after the beginning of data acquisition. For each lesion, a core biopsy was obtained and the lesion type was determined via histology by a trained pathologist.
Data Analysis. High temporal resolution (5.5 sec) data were reconstructed using modified k-Space Weighted Image Contrast (KWIC) view-sharing [6] (10 subapertures, 38 spokes per subaperture) and regridding to a Cartesian grid. Regions-of-interest (ROIs) for each lesion as well as the internal mammary artery (IMA) were selected manually by a breast radiologist. The 25% most enhancing voxels in the manual ROIs for the lesion and the IMA were averaged to create kinetic MR signal curves for both the lesion and arterial input function (AIF), respectively. MRI signal was converted to contrast agent concentration using the spoiled gradient-echo signal equation and assuming a linear relationship between the contrast agent concentration and the longitudinal relaxation rate [7]. The pre-contrast T_1 relaxation values of the lesion and the AIF were assumed to be 1.5 s. The generalized kinetic model [8] with vascular volume fraction (GKM) was fitted to the MR signal curves for the lesion and background parenchymal tissue. For comparison with the pharmacokinetic model results, initial and delayed enhancement ratios (IER and DER) for each lesion were calculated from the clinical data (55 sec temporal resolution) by subtracting the pre-contrast MR signal from the MR signal for the third and fifth time points, respectively, and normalizing by the pre-contrast MR signal.

Fig 2. (left) Example breast images reconstructed with the clinical temporal resolution (55 sec) and at high temporal resolution (5.5 sec) with KWIC. The manual lesion ROI is shown in red. (right) Lesion and AIF kinetic curves and pharmacokinetic model fit for example benign breast lesion. The AIF is shown as blue dots, the lesion as red dots, and the pharmacokinetic model fit as a black line (Ktrans=0.14 min^{-1}, v_e=0.56, v_p=0.15).

RESULTS: Eighty lesions were identified in 69 women. Forty-five were benign (56%), 14 were high-risk benign (18%), and 21 were malignant (26%). Initial and delayed enhancement ratios as well as the model parameters for the GKM model (transfer constant (K_{trans}), volume fraction of extracellular/extravascular space (v_e), and volume fraction of blood plasma (v_p)) were calculated for each lesion and grouped by lesion type (benign, high-risk benign, and malignant). Fig. 1 shows the comparison of IER and DER for the lesion types. There is no significant difference between lesion types for these parameters. Breast images, lesion and AIF kinetic curves, and the pharmacokinetic model fit are shown in Fig. 2 for an example benign lesion. Fig 3. shows a comparison of the fit parameters K_{trans}, v_e, and v_p for the lesion types. There is no significant difference between the lesion types for any of the model parameters, however a promising trend is noted between all three lesion types for K_{trans} and between benign and the high-risk benign and malignant groups for v_e.

Fig 3. Comparison of GKM model parameters for lesion types (benign, high-risk benign, and malignant). The difference between benign and high-risk benign and benign and malignant lesions is significant for vp only.

DISCUSSION: Patients referred for biopsy of breast lesions represent the most difficult cases since standard clinical analysis has already failed to separate benign and malignant lesions. Simple measures, such as IER and DER are inadequate for separation of lesion types in this population. Application of pharmacokinetic model techniques to this cohort shows that, although the results are not statistically significant, there are noticeable differences in median K_{trans} and v_e values between the lesion types. More detailed pharmacokinetic analysis may enhance these differences and provide a significant result. We will continue to accrue additional patient cases as well as expand the pharmacokinetic analysis to include more detailed models, such as the shutter-speed model, and T_1 and B_1 measurements. Methods appropriate for diagnosis of screening populations may not be adequate for discrimination of challenging cases as represented by the biopsy population considered in this study. More detailed analysis of these cases is necessary to reduce the number of biopsies performed in the clinic.

REFERENCES: [1] Saslow et al., CA Cancer J Clin, 57, 75, 2007 [2] Berg et al., Radiology, 233, 830, 2004 [3] Heywang-Köbrunner et al., Eur J Radiol, 24, 94, 1997 [4] Heywang-Köbrunner et al., Eur Radiol, 11, 531, 2001 [5] Winkelmann et al., IEEE TMI, 26, 68, 2007 [6] Song and Dougherty, MRM, 44, 825, 2000 [7] Tofts et al., MRM, 33, 564, 1995 [8] Tof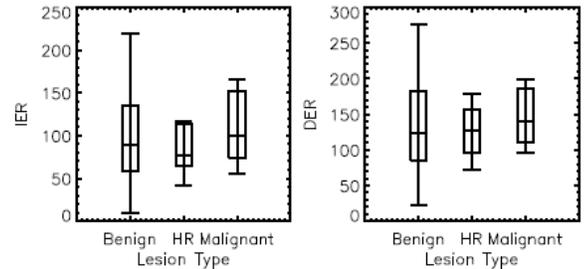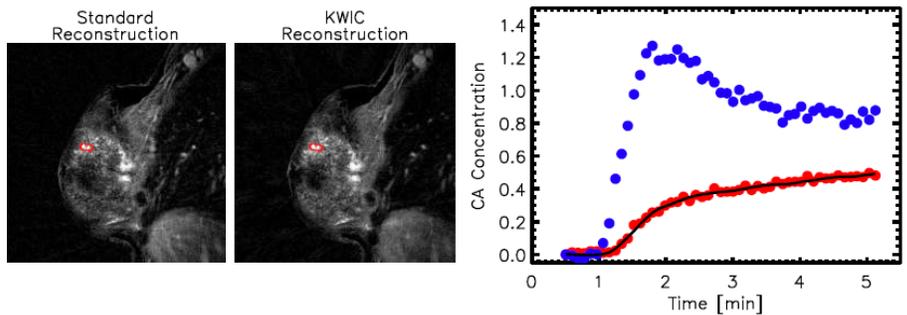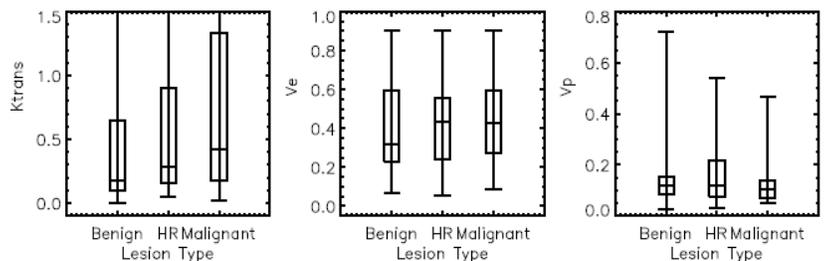ts et al., JMRI, 10, 223, 1999.