Shutter-Speed DCE-MRI Pharmacokinetic Analyses Facilitate the Discrimination of Malignant and Benign Breast Disease

W. Huang[1,2], X. Li[3], E. A. Morris[2], L. A. Tudorica[4], E. S. Venkatraman[5], Y. Wang[1], J. Xu[3], and C. S. Springer[3,6]

[1]Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [2]Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [3]Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, [4]Radiology, State University of New York, Stony Brook, NY, United States, [5]Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, [6]Cancer Institute, Oregon Health & Science University, Portland, Oregon, United States

INTRODUCTION There has been increasing interest in the Dynamic-Contrast-Enhanced (DCE) MRI method for the study of many different tumor types, using the approved monomolecular Gd(III) chelate contrast reagents (CRs) [1]. At the most sophisticated, DCE-MRI time-course data are analytically modeled to extract important pharmacokinetic parameters. These are usually variants of: K^{trans}, a rate constant for CR plasma/interstitium transfer, and v_e, the interstitial space volume fraction (the putative CR distribution volume). These can be obtained for ROI data or mapped on a pixel-by-pixel basis. Unfortunately so far, this quantitative DCE-MRI approach has been disappointing in its promised ability to increase cancer diagnostic selectivity [2].

The common Standard pharmacokinetic Model (SM) embeds the assumption that all tissue equilibrium intercompartmental water exchange MR systems remain in their fast-exchange-limit (FXL) conditions. The alternative Shutter-Speed Model (SSM) [3] does not assume this. For a limited cohort of (six) patients, it was recently shown that SSM K^{trans} maps significantly improved malignant and benign breast lesion discrimination. The positive predictive value (PPV) results for a clinical MRI protocol, SM, and SSM DCE-MRI analyses were 50%, 75%, and 100%, respectively [4]. The SM K^{trans} underestimation is greater the longer the transcytolemmal water exchange system departs the FXL during the CR passage. This occurs disproportionately in the *loci* of K^{trans} hot spots, where there is greater vascularization and/or CR extravasation, and particularly in malignant tumors [4]. The current study determines the clinical MRI, SM, and SSM PPV results for a population of 22 patients.

METHODS All 22 patients had undergone a clinical MRI protocol prior to the research DCE-MRI study. All had contrast-enhanced lesions radiologically classified in the BIRADS (Breast Imaging Reporting and Data System) 4 (B-4, suspicious, n = 17) or 5 (B-5, highly suggestive of malignancy, n = 5) categories based on lesion morphology and qualitative assessment of enhancement kinetics (persistent, plateau, or washout). These results led to biopsy recommendations. The research DCE-MRI data acquisitions were performed under IRB-approved protocols. The data from six patients were collected as part of a combined MRI/MRS protocol prior to excisional or core biopsy. Those from the other 16 patients were acquired during the 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 transmitter RF coil and a four- or seven-channel phased-array bilateral breast receiver coil. A three dimensional (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 30^o flip angle, 3-4 ms TE, 6-9 ms TR, 3 mm section thickness, 20-24 cm field of view (FOV). Depending on the size of the breast, 16-32 image sections were acquired for each set, resulting in a temporal resolution range of 13-26 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. The latter was interpolated with a seven parameter empirical expression [3]. The time-course pairs were then subjected to both SM and SSM analyses [4]. Receiver-operating-characteristic (ROC) curves evaluated the diagnostic accuracy of the SM and SSM K^{trans} and v_e parameters.

RESULTS Upon pathology, 13 of the B-4 and two of the B-5 lesions were found benign (fibroadenoma, fibrocystic changes, lobular carcinoma *in situ*, stromal fibrosis, atypical ductal hyperplasia, and sclerosing adenosis). The other seven lesions were found malignant [five invasive ductal carcinomas (IDCs), one ductal carcinoma *in situ* (DCIS), and one IDC/DCIS mixture]. Though the sensitivity of the clinical MRI protocol is 100% (no false negative reading), its PPV is only 32%.

Fig. 1a shows the SM and SSM K^{trans} and v_e scatter plots (each patient's values are connected). The SM K^{trans} value [0.85 $(min)^{-1}$] of one IDC is off the top of the chart. Under the condition of retaining the clinical MRI 100% sensitivity, SSM achieves complete separation of malignant and benign lesions (100% PPV) with a threshold K^{trans} value between 0.12 and 0.14 $(min)^{-1}$ (Fig. 1a K^{trans} plot black horizontal line). On the other hand, SM can achieve at best 58% PPV (five false positives and seven true positives) with a threshold K^{trans} value that cannot be greater than 0.048 $(min)^{-1}$ and avoid false negatives. In the v_e dimension, there is no apparent SM and SSM difference in separating malignant and benign lesions. These results are quite consistent with those from a smaller population [4]: the SSM significantly increases parameter values except in the benign K^{trans} cases. **Fig. 1b** shows the SM and SSM K^{trans} ROC curves (v_e analogs not shown). The SM and SSM K^{trans} ROC areas under the curve (AUCs) are 0.878 and 1.0, respectively. The permutation test to compare ROC curves from paired continuous markers gives a statistically significant p-value of 0.017. The SM and SSM v_e ROC curve AUCs are 0.52 and 0.55, respectively, suggesting that v_e is a poor diagnostic marker when used in this way.

DISCUSSION Even with ROI analysis, this preliminary study shows that the SSM DCE-MRI K^{trans} diagnostic marker provides significantly better discrimination of malignant and benign breast lesions compared to SM. The pixel-by-pixel SSM K^{trans} map, which reveals the nature of tumor heterogeneity [4], may perform the task even better. Incorporation of SSM DCE-MRI into clinical MRI protocols may help to reduce the number of possibly unnecessary (benign) biopsies. Recruitment of a larger population, including more pathology types, is warranted to refine the statistically significant K^{trans} threshold. Unless extremely accurate, a "benign" K^{trans} value is unlikely to counterindicate biopsy of a spiculated lesion. Thus, the population that may benefit the most from the SSM method might be that in the B-4 category, where the lesions have suspicious, but not compelling, features. In this study, 13 B-4 patients could have been spared biopsies had the SSM K^{trans} been part of the clinical MRI interpretation. Though v_e is a poor diagnostic marker, both v_e (direct measure of cellularity) and K^{trans} (directly related to perfusion and vessel permeability) may be important biomarkers for monitoring cancer therapies.

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