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 1, I. A. Tudorica 1, E. S. Venkatraman 1, Y. Wang 1, J. Xu 1, and C. S. Springer 1,6

1Medical Physics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, 2Radiology, Memorial Sloan Kettering Cancer Center, New York, NY, United States, 3Advanced Imaging Research Center, Oregon Health & Science University, Portland, Oregon, United States, 4Radiology, State University of New York, Stony Brook, NY, United States, 5Epidemiology-Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, United States, 6Cancer 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: $K_{\text{trans}}$, 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 intercompartamental 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 $K_{\text{trans}}$ 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 $K_{\text{trans}}$ underestimation is greater the longer the transcytoplasmic water exchange system departs the FXL during the CR passage. This occurs disproportionately in the loci of $K_{\text{trans}}$ 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 BI-RADS (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° 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 sets 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 $K_{\text{trans}}$ 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 (ICDs), 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 $K_{\text{trans}}$ and $v_e$ scatter plots (each patient’s values are connected). The SM $K_{\text{trans}}$ value [0.85 (min)] of one IDC is off the top of the chart. Under the condition of retaining the clinical MRI 100% sensitivity, SM achieves complete separation of malignant and benign lesions (100% PPV) with a threshold $K_{\text{trans}}$ value between 0.12 and 0.14 (min) (Fig. 1a $K_{\text{trans}}$ 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 $K_{\text{trans}}$ value that cannot be greater than 0.048 (min) 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 $K_{\text{trans}}$ cases. Fig. 1b shows the SM and SSM $K_{\text{trans}}$ ROC curves ($v_e$ analogs not shown). The SM and SSM $K_{\text{trans}}$ 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 $K_{\text{trans}}$ diagnostic marker provides significantly better discrimination of malignant and benign breast lesions compared to SM. The pixel-by-pixel SSM $K_{\text{trans}}$ 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 $K_{\text{trans}}$ threshold. Unless extremely accurate, a “benign” $K_{\text{trans}}$ 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 $K_{\text{trans}}$ been part of the clinical MRI interpretation. Though $v_e$ is a poor diagnostic marker, both $v_e$ (direct measure of cellularity) and $K_{\text{trans}}$ (directly related to perfusion and vessel permeability) may be important biomarkers for monitoring cancer therapies.

REFERENCES