Molecular Aspects of NMR Shutter-Speed Discrimination of Malignant and Benign Breast Tumors

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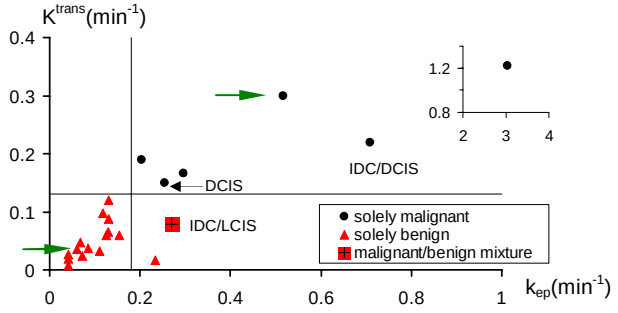
INTRODUCTION Recent reports suggest that quantitative analyses of (Dynamic-Contrast-Enhanced) DCE-MRI pharmacokinetic data using the Shutter-Speed Model (SSM) can yield very high breast cancer screening specificity [1,2]. The SSM differs from the Standard Model (SM) normally used only by allowing that equilibrium intercompartmental water exchange processes have finite kinetics [1-3]. The SM intrinsically assumes that these are effectively infinitely fast: the MR systems are in the fast-exchange-limit (FXL). However, during the peak of the contrast reagent (CR) bolus passage through the tumor tissue, the equilibrium transcytolemmal water exchange (CWX) system departs the FXL. This happens for both benign and malignant breast tumors and, consequently, the SM underestimates the extracellular extravascular volume fraction (v_e) pharmacokinetic parameter values by similar factors for each group [1,2]. However, the volume-weighted CR extravasation rate constant (K^{trans}) parameter values are greater for angiogenic malignant tissues than for benign lesions. As a consequence, the FXL departure is greater for the malignant tumors, and this causes the SM to underestimate K^{trans} values for these – but *not* for benign lesions. This affords the SSM near perfect discrimination of benign and malignant breast lesions [1,2]. Here, we explore the molecular basis for this.

METHODS A 22 patient cohort had already undergone a clinical MRI protocol prior to the research DCE-MRI study. All had contrast-enhanced lesions radiologically classified in the BIRADS 4 (B-4, n = 17) or 5 (B-5, n = 5) categories based on lesion morphology and qualitative enhancement kinetics assessment (persistent, plateau, or washout), and were referred for biopsy. The research DCE-MRI data acquisitions were IRB-approved. 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 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 4- or 7-channel phased-array bilateral breast receive RF coil. A 3D SPGR pulse sequence was used to acquire 12-20 serial sagittal image volume sets continually, spatially covering the entire breast with the suspicious lesion to be biopsied. Other parameters included: 10° or 30° flip angle, 3-4 ms TE, 6-9 ms TR, 3 mm section thickness, 18-24 cm FOV. Depending on the breast size, 16-32 image sections were acquired for each set, yielding a 13-26 s temporal resolution. 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) signal intensity time-courses, respectively. The latter was interpolated with a seven parameter empirical expression [4]. The time-course pairs were subjected to both SM and SSM analyses [1-3].

RESULTS As above, the SSM increases the v_e values from the SM analysis by substantial, but similar, factors for both the malignant and benign lesions, and thus do not serve to discriminate these. However, the K^{trans} values are underestimated by the SM for only the malignant tumors. In the pharmacokinetic model, K^{trans}/v_e is equal to k_{ep}, the unidirectional CR intravasation rate constant [5], which is independent of K^{trans} or v_e (but not both). A 2D (K^{trans} *vs.* k_{ep}) parametric scatter plot provides a useful display [6]. In the **Figure**, the lesion ROI SSM values are plotted for each of the 22 patients. For 21 of these, gold standard pathology analyses yielded 15 solely benign [red triangles] and six solely malignant [black circles] lesions. Though some points are near the K^{trans} or the k_{ep} cut-off lines - 0.13 and 0.18 min^{-1}, respectively, none are very near their intersection. All but one of the triangles are clustered in the lower left quadrant, and all of the circles are found in the diagonally opposite quadrant [one so far out, it is plotted in an inset]. This near complete separation is not found for SM-returned parameter values [2,6]. Most of the malignant tumors are invasive ductal carcinomas (IDCs). The only ductal carcinoma *in situ* (DCIS) and the only IDC/DCIS mixture are marked. There are several types of benign lesions. One of the B-4 ROIs is shown with the black cross on red square symbol. Though it is above the k_{ep} cut-off value, it is below the K^{trans} cut-off line. This is the only ROI pathologically proven to be a malignant/benign mixture: a moderately differentiated IDC embedded within a larger benign lobular carcinoma *in situ* (LCIS). It is in the lower right quadrant only because of the averaging effects of ROI analysis. Though the institutional positive-predictive-value (PPV) of the clinical breast MRI protocol for this population is only 32% [7/22], the criterion of falling outside of the lower left SSM quadrant yields a PPV of 88% [7/8].



DISCUSSION Apparently, in the vascular beds of only malignant breast tumors does the interstitial ("outside") CR concentration, $[CR_o]$, transiently rise sufficiently during the bolus passage that the equilibrium CWX system transiently departs the FXL to sufficient extent and/or for sufficient duration to substantially invalidate the SM K^{trans} determination. The SSM interpretation is that, during the bolus passage through lesions, the relaxographic shutter-speed (τ^{-1}) value for the CWX process, $|R_{1o} - R_{1i}|$, transiently approaches or exceeds that for the unchanging exchange rate constant, $\tau_i^{-1} + \tau_o^{-1}$, (*in vivo* studies are isothermal) sufficiently for the system to enter at least the fast-exchange-*regime* (FXR) [4,7]. The quantities R_{1o}, R_{1i}, τ_i^{-1} and τ_o^{-1} represent the longitudinal relaxation rate constants for the interstitial and intracellular ^1H_2O signals (in the absence of exchange) and the unidirectional rate constants for cellular water efflux and influx, respectively. R_{1o} increases with $[CR_o]$, while R_{1i} remains constant. This is a manifestation of the varying equilibrium competition for interstitial water molecules between diamagnetic cytoplasmic spaces and paramagnetic interstitial CR molecules. Informative estimates can be made by comparison of a sample benign and malignant lesion pair (green arrows in the Figure). For these, the SSM (v_e,τ_i) coordinates are similar: (0.60,0.40 s), and (0.69,0.39 s) for benign and malignant, respectively. Thus, the unidirectional rate constants for water cellular entry $[\tau_o^{-1} \equiv (v_e^{-1} - 1)\tau_i^{-1}]$ are similar: 1.7 and 1.2 s^{-1}, respectively. These are constant, and not infinitely large. However, before the arrival of interstitial CR_o, the CWX appears infinitely fast in the NMR signal because τ^{-1} is almost negligible. The interstitial water molecules encounter no paramagnetic CR_o molecules before entering a diamagnetic cytoplasm. However, as $[CR_o]$ increases, the interstitial water CR encounter rate constant, $([CR_o]/[H_2O_o])\tau_M^{-1}$, also increases. While, for the benign lesion $[CR_o]$ maximizes at 0.52 mM (at ~7.5 min of the DCE acquisition time scale), for the malignant tumor this is 1.6 mM (at ~3.5 min). Thus, $([CR_o]_{max}/[H_2O_o])\tau_M^{-1}$ values are 104 and 313 s^{-1} for the benign and malignant lesions, respectively [taking the interstitial water concentration, $[H_2O_o]$ as 50 M, and the mean water lifetime on the CR, τ_M, as 10^{-7} s]. At maximum CR_o, an interstitial water molecule in the benign lesion encounters a paramagnetic CR molecule on average 60 times (104/1.7) before it enters a diamagnetic cell [sufficient, apparently, for the SM 40% underestimation of v_e for this particular benign lesion, but not for K^{trans} underestimation], while in the malignant tumor, this happens 260 times (313/1.2) on average; more than four times as often. This appears to be sufficient to cause significant K^{trans} underestimations in malignant tumors if it is neglected. Allowing for this effect provides for very high diagnostic specificity.

$$\mathbf{H_2OCR_o} \underset{([CR_o]/[H_2O_o])\tau_M^{-1}}{\rightleftharpoons} \mathbf{CR_o} + \mathbf{H_2O_o} \underset{(v_e^{-1}-1)\tau_i^{-1}}{\rightleftharpoons} \mathbf{H_2O_i}$$

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