An empirical mathematical model for analysis of contrast agent uptake kinetics in breast lesions distinguishes benign from malignant breast lesions

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Introduction: The dynamic contrast enhanced magnetic resonance imaging (DCEMRI) is a promising tool for detection and diagnosis of cancer. Physiological parameters derived from the pharmacokinetic models, such as two compartment model, are often employed to analyze DCEMRI data. However, the arterial input function required by the two compartment model is hard to measure accurately or predict a priori. Even with an accurate input function, the simple pharmacokinetic model often does not accurately fit experimental contrast concentration v.s. time curves. Therefore, we analyzed DCEMRI data acquired from breast patients to distinguish between benign and malignant breast lesions using an EMM that was designed to fit this data using a small number of parameters.

Methods: DCEMRI of suspicious breast lesions were acquired at 1.5 Tesla. T_1-weighted (TR = 5 msec, pulse angle = 30 degrees) spoiled gradient echo images of 4 slices (thickness = 3 mm) through and around the suspicious lesion were acquired before and for 1.5 minutes after contrast media injection (Omniscan, 0.2 mM/kg). Subsequently, the same pulse sequence was used to sample contrast media washout at 5.5, 7.5, 13, and 30 min after injection. During the gaps between the rapid imaging sequences, routine clinical images were acquired. We analyzed a total 17 patients with 9 biopsy proven benign and 10 biopsy proven malignant lesions. Contrast media concentration as a function of time $C(t)$ was calculated from MRI data for the most enhancing portion of the tumors. $C(t)$ was fitted using the EMM to describe the contrast agent uptake and washout in tissue [1]:

$$C(t) = A \cdot \left(1 - e^{-\alpha t}\right)^{q} \cdot e^{-\beta t} \cdot \left(1 + e^{-\gamma t}\right) / 2 ,$$

where A (mM) is the upper limit of tracer concentration, α (min^{-1}) is the rate of contrast uptake, β (min^{-1}) is the overall rate of contrast washout, γ (min^{-1}) is the initial rate of contrast washout, and q is related to the curvature of $C(t)$ at the transition from first pass uptake to washout.

	A	α	β	γ	q	R^2	T_{peak}
Benign	3.5	0.29	0.006	0.0	0.8	0.92	21.2
Malignant	5.6	1.58	0.022	0.0	0.9	0.93	3.1
Liver	2.9	5.88	0.027	0.35	4.0	0.90	1.0
Heart	5.1	13.4	0.026	0.46	4.5	0.85	0.5
Vessel	5.0	10.9	0.029	0.03	4.8	0.86	1.4

Table 1. The average values of fitted parameters obtained from the EMM. R^2 – goodness of fit. T_{peak} (min) – time to peak enhancement.

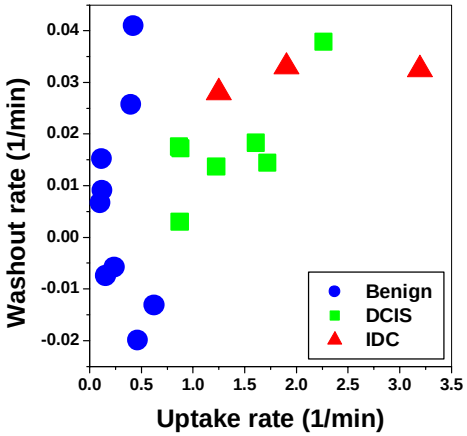

Figure 1. Uptake rate v.s. washout rate for all the lesions.

Results: Table 1 shows the average values of fitted parameters obtained from the EMM for small ROIs over the most enhanced region. The EMM provided accurate fits to the contrast concentration vs. time curves. Nine benign tumors had uptake and washout rates of 0.29±0.18 min^{-1} and 0.006±0.02 min^{-1}, respectively. Seven DCIS lesions had much larger uptake and washout rates of 1.35±0.54 min^{-1} and 0.017±0.01 min^{-1}, respectively. Three IDC tumors had uptake rate (2.12±0.99 min^{-1}) and washout rate (0.03±0.003 min^{-1}). The contrast uptake and washout rates are significantly larger for malignant tumors compared to benign tumors ($p < 0.0003$ for uptake and $p < 0.05$ for washout using two tailed unequal variance t-test). The time to peak enhancement was longer for benign lesions than for malignant lesions. A plot of contrast uptake rate vs. washout rate show in Fig. 1 shows a good separation between benign and malignant breast lesions.

Discussion: The present preliminary results suggest that the EMM provides excellent fits to experimental data, and that parameters derived from the EMM may increase diagnostic accuracy. Only the initial phase of contrast media uptake was required to distinguish cancer from normal tissue. However, extended temporal sampling – for example to 15 minutes after injection – may be important for discriminating among types of cancer. For example, the data in Fig. 1 suggest that some separation of DCIS and IDC is possible based on washout. Well defined physical models – such as the two compartment model – that are commonly used for fitting DCEMRI data have the important advantage that the fitting parameters have direct physiological correlates. However, they often do not work well for cancers, probably because of the heterogeneity of the tumor microenvironment. Poor fits to experimental data result in inaccurate diagnosis. The EMM offers practical advantages: it fits a wide variety of concentration vs. time curves accurately, and the data presented here suggest that these fits provide diagnostically relevant information.

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Reference: [1] Fan et al. MRM 51:487-494 (2004).