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Original contributions

Diagnosis of suspicious breast lesions using an empirical mathematical model for dynamic contrast-enhanced MRI

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Abstract

The purpose of this study was to test whether an empirical mathematical model (EMM) of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) can distinguish between benign and malignant breast lesions. A modified clinical protocol was used to improve the sampling of contrast medium uptake and washout. T_1-weighted DCE magnetic resonance images were acquired at 1.5 T for 22 patients before and after injection of Gd-DTPA. Contrast medium concentration as a function of time was calculated over a small region of interest containing the most rapidly enhancing pixels. Then the curves were fitted with the EMM, which accurately described contrast agent uptake and washout. Results demonstrate that benign lesions had uptake ($P<2.0\times10^{-5}$) and washout ($P<.01$) rates of contrast agent significantly slower than those of malignant lesions. In addition, secondary diagnostic parameters, such as time to peak of enhancement, enhancement slope at the peak and curvature at the peak of enhancement, were derived mathematically from the EMM and expressed in terms of primary parameters. These diagnostic parameters also effectively differentiated benign from malignant lesions ($P<.03$). Conventional analysis of contrast medium dynamics, using a subjective classification of contrast medium kinetics in lesions as 'washout,' 'plateau' or 'persistent' (sensitivity=83%, specificity=50% and diagnostic accuracy=72%), was less effective than the EMM (sensitivity=100%, specificity=83% and diagnostic accuracy=94%) for the separation of benign and malignant lesions. In summary, the present research suggests that the EMM is a promising alternative method for evaluating DCE-MRI data with improved diagnostic accuracy.

Keywords: Breast lesion; DCE-MRI; Gd-DTPA; Pharmacokinetic modeling

1. Introduction

Magnetic resonance imaging (MRI) of the breast has demonstrated advantages over other imaging modalities. These include improved staging and treatment planning, enhanced evaluation of the augmented breast, better detection of recurrence and improved screening of high-risk patients [1,2]. Dynamic contrast-enhanced (DCE) MRI is a promising method for detecting and diagnosing breast cancer. This is because the rates of contrast medium uptake and washout are related to tumor blood flow — an important indicator of malignancy [3]. Extraction of hemodynamic parameters from DCE-MRI data requires the calculation of contrast medium concentration as a function of time ($C(t)$) either in each image voxel or in regions of interest (ROI). $C(t)$ is analyzed based on various pharmacokinetic models from which hemodynamic parameters, such as perfusion rate, blood volume and capillary permeability, are extracted. However, the accuracy of such parameters depends on an appropriate theoretical model and related assumptions used to interpret data. With current approaches to data analysis and interpretation, DCE-MRI has high sensitivity for the detection of invasive breast cancer, but variable specificity is a major limitation [4,5]. Therefore, improvements in specificity are highly desirable. In addition, while sensitivity is high, further improvements would be helpful for reliable detection of early noninvasive cancers such as ductal carcinoma in situ (DCIS).

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Generally, breast DCE-MRI data are analyzed using a two-compartment model approach [6–11] or a modified two-compartment model [12]. This allows determination of the transfer constant (K^{trans}) and the extracellular extravascular space fraction (v_e). However, the two-compartment model requires that the rates of contrast uptake and washout be closely related [10]. This is not the case for many tumors; as a result, this model sometimes does not provide a good fit to experimental data, thereby limiting its diagnostic utility. Models with three or more compartments are more realistic [13], but due to the complexity of these algorithms, meaningful fits to experimental data can only be obtained when raw images have a very high signal-to-noise ratio (SNR). In addition, physiological models require knowledge of contrast medium concentration in the blood as a function of time and, thus, the measurement of arterial input function (AIF). Measuring the AIF is often very difficult, and errors in the AIF translate into errors in measurements of tracer kinetics.

To overcome problems associated with limited SNR, semiquantitative analysis of DCE-MRI data can be performed. Most commonly in clinical practice, contrast medium uptake and washout are analyzed by simply classifying contrast medium kinetics without fitting $C(t)$. Some common diagnostic parameters include the 'initial area under the curve' [14,15], 'signal enhancement ratio' [16], 'maximum slope' [15,17], 'time to peak of enhancement' [18], 'washout ratio' [19] and so on. The most widely used clinical approach is the system proposed by Kuhl et al. [20], which classifies $C(t)$ curves as either 'washout,' 'plateau' or 'persistent.'

As an alternative to these approaches, empirical functions can be used to fit $C(t)$ accurately, without making assumptions about tumor physiology. Diagnostic parameters are derived from these functions, rather than from raw $C(t)$, which reduces the effect of noise. Unfortunately, the mathematical functions with limited parameters employed so far — for instance, Gamma functions [21] — do not have the flexibility to accurately describe contrast uptake and washout for long periods of time in a number of different types of tissue. Some functions accurately fit the concentration-versus-time curve or the signal-intensity-versus-time curve, but only for short periods after contrast medium injection. Recently, we developed an empirical mathematical model (EMM) with five parameters to describe contrast uptake and washout behavior [22]. The EMM has been tested on transplanted rodent prostate tumors and accurately fits data for both low-molecular-weight and high-molecular-weight contrast agents, even at times long after contrast agent injection. Previous work [22,23] demonstrated that parameters derived from the EMM distinguish between metastatic and nonmetastatic rodent prostate tumors more reliably than the 'two-compartment model' approach. This is likely due to improved fits to experimental data obtained with the EMM.

In the present study, we employed the EMM to fit DCE-MRI data from suspicious breast lesions acquired with a clinical 1.5-T scanner. Three useful secondary diagnostic parameters — time to peak of enhancement, enhancement slope at the peak and curvature at the peak of enhancement — were also derived from the EMM after fits to experimental data had been performed. The use of the EMM to distinguish between benign and malignant lesions was compared to the standard classification of $C(t)$ performed by experienced radiologists using the aforementioned 'Kuhl method'. Finally, the sensitivity of the EMM to various phases of contrast medium uptake and washout kinetics was evaluated.

2. Materials and methods

2.1. Patients and imaging protocol

Women with suspicious breast lesions detected by mammography or physical exams frequently undergo DCE-MRI scans before biopsy as part of normal clinical care at the University of Chicago Hospital. We analyzed MRI data from 22 female patients aged 34–79 years (mean age=59±11 years) using a protocol approved by the Institutional Review Board after the patients had given informed consent. Based on the pathologist's (W.R.) analysis of biopsy samples, six patients had benign lesions, nine had DCIS, two had infiltrative ductal carcinoma (IDC) and one had infiltrative lobular carcinoma (ILC). In addition, four patients had lesions missed by DCE-MRI (because slices were not properly positioned) or had no lesions.

MRI exams were performed with a 1.5-T Signa scanner (General Electrical Medical System, Milwaukee, WI, USA). T_1-weighted spoiled gradient-echo images of four slices (T_R/T_E=8.9/4.2 ms, field of view=24 cm, slice thickness=6 mm, acquisition matrix size=256×160, reconstruction matrix size=256×256, flip angle=30°, bandwidth=31.25 kHz, number of acquisitions=1) containing the suspicious lesion and surrounding tissues were acquired with high temporal resolution (7 s) before and for 1.5 min after contrast medium injection. Subsequently, the same pulse sequence was used to sample contrast medium washout at approximately 8.5, 20 and 30 min after injection during gaps in routine clinical imaging sequences. The same gain and shim settings were used for all of these scans. Omniscan was injected at a dose of 0.1 mM kg^{-1} and at a rate of 2 ml s^{-1}. About 200 images were collected for each patient.

2.2. Contrast concentration calculations

Contrast agent concentration as a function of time $C(t)$ after contrast medium injection was estimated by comparing the signal intensity $S(t)$ from selected ROI to the control signal intensity $S(0)$ (i.e., before contrast injection) in a reference tissue with known T_1 [24]. A uniform fat region was selected as a reference tissue in this study. Since $T_R \ll T_1$, we can approximate signal intensity