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14. ABSTRACT We developed novel calibration phantoms that when placed in a breast coil during a routine dynamic contrast enhanced MRI of the breast allow for the acquisition of quantitative images displaying the concentration of contrast media as well as MRI-detectable proton density. To date 21 patients have been scanned with the phantoms. Preliminary results suggest a differentiation between benign and malignant lesion by peak concentration of contrast media. A study is under way to determine whether these methods eliminate any variability seen across two different field strengths, 1.5T and 3T. These methods also allow for pharmacokinetic modeling, which will lead to physiological parameters that have been shown to be diagnostically useful.					
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Introduction

We propose to develop methods that allow for the acquisition of truly quantitative images of a dynamic contrast-enhanced (DCE) MRI of the breast. To achieve this we have developed novel calibration phantoms consisting of compartments with varying amounts of contrast agent. The phantoms provide a reference signal that can be used to convert signal enhancement to a measure of the concentration of the contrast media in tissue, as well as quantitative proton density images of the breast. These quantitative images allow for standardized analysis of the DCE-MRI data, leading to diagnostically useful parameters derived from pharmacokinetic modeling of the data. We are investigating whether these parameters will aid in determining malignancy. We will also determine whether our methods reduce variability in the enhancement patterns seen across different scanners and field strengths, providing a way to standardize clinical DCE-MRI data, which would allow for inter-institutional comparisons and comparisons of different scans of the same patient. Finally, we believe MRI-detectable proton density may prove to be a useful biomarker for the detection of breast cancer.

Body

The calibration phantoms described in the proposal, which provide the reference signals that allow for the acquisition of concentration of contrast media and proton density images, were re-designed from the original model. These phantoms originally consisted of a mixture of distilled water, a small amount of dye (for visual differentiation of the compartments) and varying amounts (0.0 – 0.5mM) of the gadolinium based contrast agent Omniscan (Gd-DTPA GE Healthcare). However, during the initial scans with the clinical protocol, the high signal from the water in the phantom compartments led to bright ghosting artifacts, which could sometimes be seen in the breast tissue. In order to eliminate this issue we decided to modify the composition of the solution in the phantom compartments, this time using deuterated water (D2O) in order to reduce the signal from the calibration phantoms. We scanned different mixtures of H2O and D2O and determined that 70% D2O 30% H2O was adequate for our purposes. The new version of the phantoms consists of 70% D2O, 0.05, 0.1, 0.2, 0.3, 0.4, and 0.5mM Omniscan and a minute amount of dye.

The new phantoms were then scanned at 1.5T and 3T using an inversion recovery sequence with varying inversion delays in order to obtain the ‘gold standard’ T1’s for each phantom compartment. The phantoms have been scanned every few months to ensure stability of the T1’s, and proton density relative to water.

Since December 2010, 21 patients have been scanned with the calibration phantoms inserted in the breast coil. These patients have come from the following cohorts: patients called back from a screening mammogram due to a suspicious finding, patients newly diagnosed with some form of breast cancer, patients presenting with high risk lesions, or patients enrolled in the high risk screening program. In addition to the standard clinical protocol for breast MRI used at our institution, we have added a few scans to the examination. These include: low resolution images with the body and breast coils, a

variable flip angle gradient echo sequence, and a B1 or transmit field map. The low-resolution scans are used to correct our images for coil sensitivity, under the assumption that the quadrature body coil gives a uniform image. The variable flip angle series is used to find pre contrast T1 and proton density maps. Our acquisition protocol has been adjusted in order to minimize the time added to the clinical scan while at the same time providing adequate signal and resolution for our purposes. The protocol we arrived at for the calibration scans is:

Variable flip angle sequence: 3D FFE, TR = 10ms, TE = 2.4ms, FA = 5,10,15,20°, voxel size 1x1x1mm, NSA = 1

Low-resolution images for coil sensitivity correction: 3D FFE, TR = 15ms, TE = 2.4ms, FA = 12°, voxel size 4x4x2mm, NSA = 1, repeat with QBC and breast coil.

The B1 maps have been acquired with a dual TR method, however the noise level in the resulting maps has been too high. We are currently exploring ways to obtain useful B1 maps.

The software used to analyze the data acquired and generate the concentration of contrast media and proton density images, was written in Matlab (Mathworks, Natick, MA). The software loads the variable flip angle series and uses the low-resolution images to generate a ratio image which is applied to the VFA series in order to correct for the sensitivity of the coil. The signal from these images is then fit to the gradient echo signal model in order to find T1 and proton density. Using the 'gold standard' T1's in each compartment it is possible to correct for any deviations in the prescribed flip angle [1]. After the flip angle correction the data are fit again to generate the final T1 and PD maps. The software then takes the data from the dynamic contrast enhanced MRI and converts the subtraction images to images displaying concentration of contrast media, using the signal from the compartment models and the proton density map. The software still requires some manual guidance; we are currently exploring ways to automatize some of the steps in order to speed up the analysis. The analysis performed to date does not include a correction for inhomogeneities in the B1 field, due to the fact that the B1 maps acquired thus far have had high noise levels, as discussed earlier. Once the protocol is modified and usable B1 maps are acquired, we will include that information in the analysis, both in future scans and retrospectively.

Representative peak concentration values, measured for ROIs in lesions, are in Table 1. These preliminary results suggest that peak concentration may prove useful in differentiating benign and malignant lesions. Figure 1 compares a difference image with a concentration image at the time of peak enhancement. Although the two images are similar - there are significant differences in contrast - some examples are indicated by arrows. The plot of enhancement vs. concentration (Fig. 2) shows that a single value of enhancement corresponds to a range of concentrations - suggesting that signal enhancement alone does not provide an accurate measure of contrast media concentrations, and therefore cannot produce accurate measures of pharmacokinetic parameters. The ratio of MRI-detectable proton density in tissue to that of water has been measured in the range of 0.20-0.31. The fact that this value is so low suggests a large, broad component of the water signal.

Lesion Type	Peak Concentration (mM)
Ductal Carcinoma in-situ (DCIS)	0.64
Mucinous Cancer	0.59
DCIS	0.47
Invasive Ductal Carcinoma (IDC)	0.45
Benign enhancing focus	0.41
Fibroadenoma	0.39
Atypical Ductal Hyperplasia (ADH) biopsy site enhancement	0.32
Fibroadenoma	0.30

Table 1. Peak concentration values for enhancing lesions

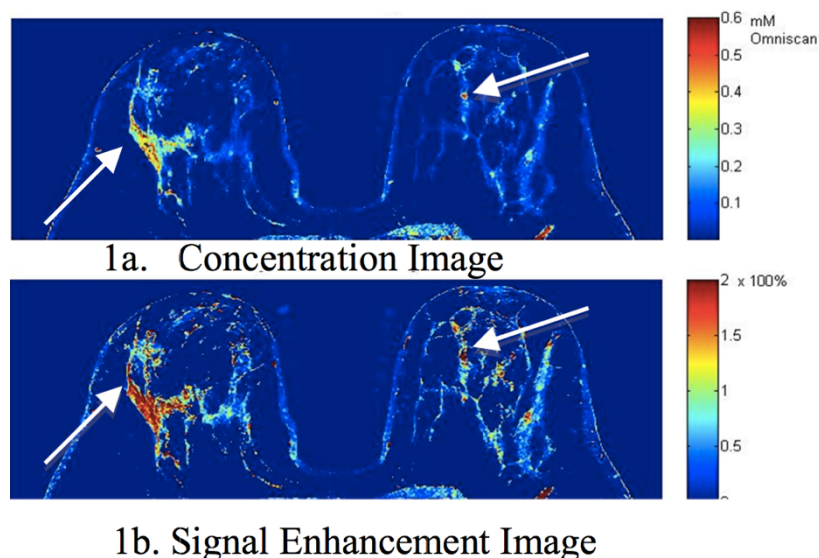


Figure 1. Concentration and signal enhancement images for patient presenting with DCIS in the right breast, arrows highlight areas of difference between the two images

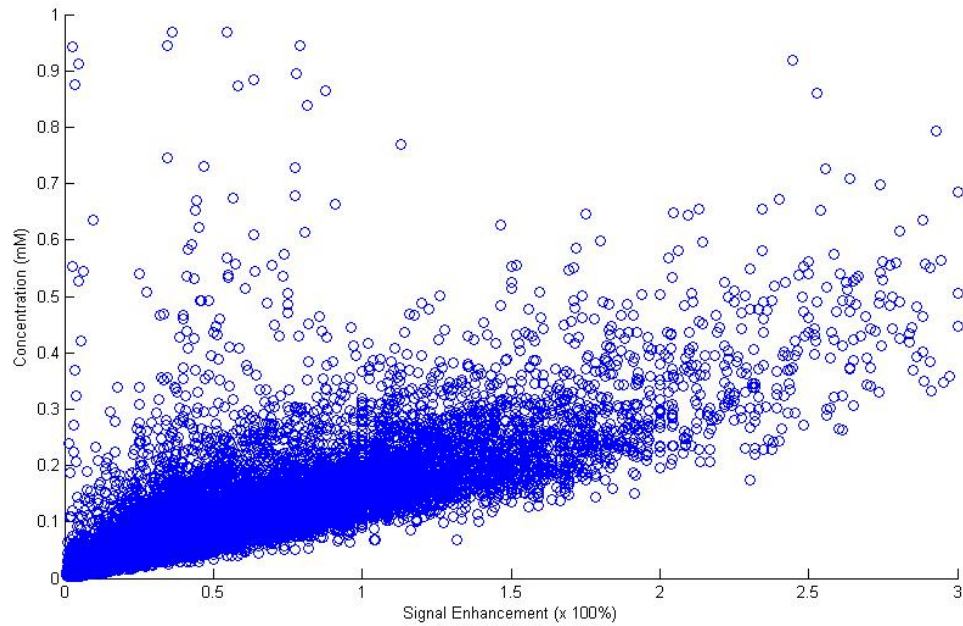


Figure 2. Example plot of concentration vs signal enhancement for patient presenting with ADH

The next component of this research involves pharmacokinetic analysis of the concentration of contrast media in the breast as a function of time, by fitting the data to the widely used Tofts two compartment model (TCM), with the goal of finding physiological parameters such as the volume transfer constant K^{trans} . However, clinical images are acquired with too low a temporal resolution for such analysis to be accurate. In order to overcome this, the low temporal resolution data are fit to an empirical mathematical model (EMM), which contains parameters descriptive of the uptake and washout of the contrast media [2]. This EMM has been shown to accurately describe the contrast media kinetic curves in previous work from our group.

The existing software that performed this analysis on pre-clinical data has been modified to perform the analysis on our clinical concentration images. After inputting the concentration images we acquire, the software fits the concentration time curves to the EMM. Once this step is done it is possible to create parameter maps for the rate of uptake and washout of contrast media as well as the initial area under the concentration curve (Fig. 3), the diagnostic usefulness of these maps will be assessed in the future. With the EMM parameters, it is possible to simulate high temporal resolution data. In the next step the arterial input function (AIF) is derived for each patient. To find the AIF, the software employs the artery plus reference tissue method [3]. First, an ROI is drawn in the muscle (e.g. chest wall or shoulder), the data from this ROI is fit to the EMM to generate high resolution muscle data. With this we begin by approximating that the TCM holds in muscle with the literature values for the K^{trans} and v_e parameters, with these it is possible to derive the AIF. Because this AIF is derived from literature values it is not specific to each patient.

In order to address this issue, a second ROI is drawn in the aorta, giving us arterial values of concentration over time. The physiological parameters of muscle are varied slightly so that the derived AIF passes through the values found in the aorta. Once this is completed the derived AIF is used to apply the TCM to the entire breast and the parameters K^{trans} , v_e , and v_p can be found for each voxel.

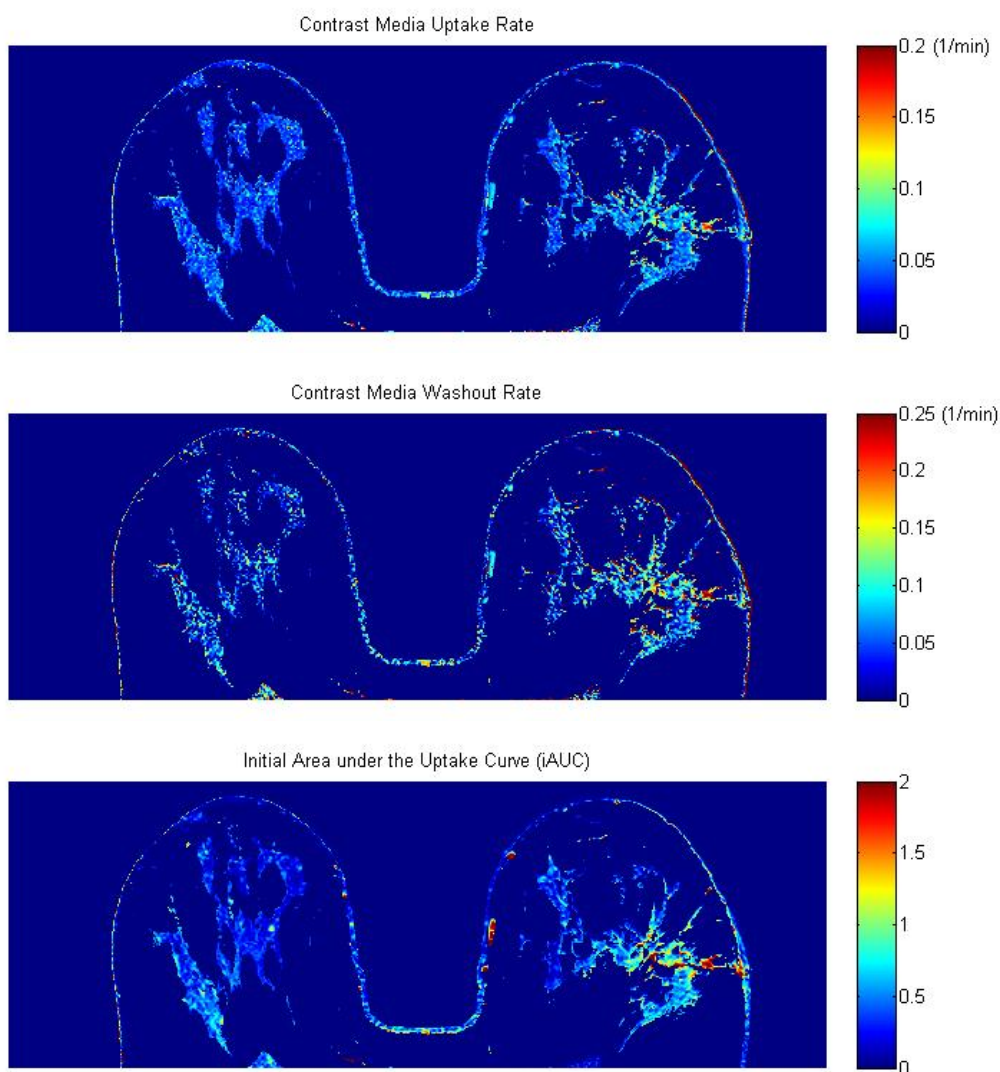


Figure 3. Images generated by fitting data to the EMM, displaying contrast media uptake (top), washout (middle) rates as well as initial area under the curve.

At this point the pharmacokinetic modeling software has been written and is able to handle the clinical data, however, we have had issues when selecting the reference muscle for the derivation of the AIF, due in part to low signal in the muscle. We are currently exploring different options to obtain an acceptable AIF. The code is also being optimized for calculation time, seeing as how it presently takes several minutes per slice.

A subset of patients has been scanned at two field strengths, 1.5T and 3T (Philips Achieva 1.5T and Philips Achieva 3T-TX). To date 7 patients have been scanned at both fields. We have attempted to minimize the time between the scans in order to eliminate variations in parenchymal enhancement during the menstrual cycle [4]. When it has not been possible to scan the same patient within a few days they have been asked to return at a time when they are in the same phase of the menstrual cycle as the initial scan. We are in the planning phase of a study to compare the 3T and 1.5T images. After consulting with the radiologists who routinely read breast MRIs we have come up with a questionnaire that will be used to evaluate the images at both fields. Radiologists will be asked to rate: lesion conspicuity, noise level, fat saturation quality, artifact level, and sharpness of the margins and internal lesion. Quantitative and semi-quantitative parameters will also be used in the comparison, including signal-to-noise ratio, lesion uptake and washout rates (from fitting to the EMM), peak concentration in the lesion, as well as physiological parameters from the pharmacokinetic analysis.

Key Research Accomplishments

- Calibration phantoms were re-designed with deuterated water to reduce intensity of ghosting artifacts
- 21 patients have been scanned with the calibration phantoms, and additional scans required to obtain concentration and proton density images
- Software which processes the data and converts dynamic contrast enhanced sequence to concentration images has been written
- We have begun pharmacokinetic modeling of the concentration data to obtain physiological parameters for each case
- Recruitment for the 1.5T vs. 3T comparison study has begun, 7 patients have been scanned at both fields

Reportable Outcomes

Presentations:

F. Pineda, M. Heisen, A. Wood, D. Mustafi, S. Lobregt, B. Peng, G. Newstead, J. Buurman, G. Karczmar. "Moving towards quantitative breast MRI: dynamic contrast media concentration images", presented at the 53rd Annual Meeting of the AAPM, Vancouver, BC, July 31-August 4, 2011.

F. Pineda. "Quantitative DCE-MRI of the breast using calibration phantoms", presented at the First Annual University of Chicago Medical Physics Retreat, Chicago, IL, October 13, 2011.

Abstract (under review):

F. Pineda, M. Ivancevic, G. Newstead, H. Abe, J. Buurman, G. Karczmar. "Quantitative contrast media concentration and proton density images", submitted to the 20th ISMRM Annual Meeting and Exhibition, Melbourne, Australia, May 5-11, 2012.

Conclusions

The calibration phantoms were re-designed with 70% D₂O, which reduced the signal intensity of the ghosting artifacts seen in clinical images with the previous prototype of these phantoms.

We have scanned 21 patients with the phantoms and adding a few calibration scans to the clinical breast MRI examination. For these patients, our methods allow the acquisition of quantitative images displaying concentration of contrast media, and MRI-detectable proton density. Preliminary results suggest that peak concentration of contrast agent may provide to be a useful differentiator of benign and malignant enhancing lesions. MRI-detectable proton density measured thus far was low, suggesting a large, broad component of the water signal. This may prove to be a novel source of diagnostically useful information. 7 patients have been scanned at both 1.5T and 3T with the same acquisition protocol. Analysis of these scans will determine whether our methods eliminate variability across different scanners, which would prove that these methods can provide a reliable calibration of MRI of the breast.

The concentration images found can be analyzed with a pharmacokinetic model to obtain physiological parameters, which have been shown in previous research to be diagnostically useful. A reference tissue plus artery model is being used to determine the arterial input function. This analysis is currently being refined.

References

- [1] Yang C, Wolf GL, Karczmar G, and Stadler WM. Improved T1 estimation with spoiled gradient recalled echo (SPGR) images using a modified variable flip angle method. ISMRM 14, Seattle, USA, 2006
- [2] Fan X, Medved M, River JN, Zamora M, Corot C, Robert P, Bourrinet P, Lipton M, Culp RM, Karczmar GS. New Model for Analysis of Dynamic Contrast-Enhanced MRI Data Distinguishes Metastatic from Nonmetastatic Transplanted Rodent Prostate Tumors. MRM 2004; 51:487-494
- [3] Fan X, Haney CR, Mustafi D, Yang C, Zamora M, Markiewicz EJ, Karczmar GS. Use of a reference tissue and blood vessel to measure the arterial input function in DCEMRI. Magn Reson Med. 2010; 64:1821-6.
- [4] Delille JP, Slanetz PJ, Yeh ED, Kopans DB, Garrido L. Physiologic Changes in Breast Magnetic Resonance Imaging during the Menstrual Cycle: Perfusion Imaging Signal Enhancement, and Influence of the T1 Relaxation Time of Breast Tissue. The Breast Journal 2005; 11:236-241

Appendix A

Abstract presented at the 53rd Annual Meeting of the AAPM

Abstract ID: 15824

Moving Towards Quantitative Breast MRI: Dynamic Contrast Media Concentration Images

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Purpose: To develop methods for the acquisition of dynamic contrast media concentration images during routine clinical DCE-MRI.

Methods: We designed calibration phantoms consisting of color-coded tubes filled with gadodiamide solutions (0.0-0.5mM Omniscan), which were placed into a 16-channel bilateral breast coil. Three patients (ages a. 55, b. 50, and c. 41) were scanned at 1.5T (a, b) and 3T (c) with IRB approval. We acquired one variable flip angle gradient echo series, and a T₁-weighted dynamic series (3D turbo field echo) before and after a gadodiamide injection (0.1mmol/kg). Under the present experimental conditions 1/T₁ is approximately proportional to signal intensity. Allowing us to convert signal intensity to concentration of contrast media, by determining the factor of proportionality from the known T₁ values in the phantom. This relation is corrected using the phantom-to-tissue proton density ratio to make it applicable to breast tissue. Concentration images for the different time points in the series were produced, using the signal from the standard dynamic series.

Results: After conversion from signal intensity to concentration, peak contrast media concentration in the parenchyma was measured in the range of 0.26-0.32mM. For patient 'c' a mucinous cancer was present in the left breast and had a peak concentration of 0.59mM. The phantom-to-tissue apparent proton density ratios were in the range of 3.75-3.90, and 2.25 for the cancer.

Conclusions: The results of this pilot study demonstrate the possibility of performing quantitative measurements on standard clinical data. The pulse sequence used for the present study is not easy to model accurately; the 'spoiled gradient echo' model isn't appropriate. However, this approach demonstrates that subtraction images can be converted into quantitative concentration images, even if a good mathematical model is not available. The concentration images could facilitate inter-institutional comparisons, as they allow for the standardization of DCE-MRI across different scanners.

Appendix B

Abstract submitted to the 20th ISMRM Annual Meeting and Exhibition (under review)

Quantitative contrast media concentration and proton density images

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Introduction: Development of quantitative, reproducible methods for dynamic contrast enhanced MRI (DCEMRI) would greatly improve diagnostic accuracy. Here we demonstrate the use of phantoms to increase the accuracy of contrast media concentration measurements. Phantoms were inserted in a breast coil to calibrate and standardize breast MRI measurements. Signal from the phantoms was analyzed to produce images of contrast media concentration as well as MRI-detectable proton density.

Methods: We designed calibration phantoms, consisting of color-coded tubes filled with gadodiamide solutions (0.05, 0.1, 0.2, 0.3, 0.4, 0.5 mM, Omniscan) and 70% deuterated water, that were placed into a breast coil. 23 patients were scanned in a 16-channel bilateral breast coil at either 1.5 T or 3T (Philips Achieva 1.5T and 3T-TX) under an IRB approved protocol. We acquired a variable flip angle (VFA) gradient echo series (3D spoiled gradient echo, flip angles = 5,10,15,20°, TR/TE = 10/2.4ms), and a T1-weighted dynamic series (3D turbo field echo with fat-sat) before and after a gadodiamide injection (0.1mmol/kg).

The VFA data were fit to find T1 and proton density values for each voxel. Using the known T1 values in the phantom we corrected the nominal flip angles and created a proton density map. Under the experimental conditions, 1/T1 is approximately proportional to signal intensity. This allows us to convert signal intensity to concentration of contrast media using the following¹

$$C(t) = \frac{PD_{phantom}}{PD_{tissue}} \cdot \frac{1}{F \cdot r_1} \cdot (S_{tissue}(t) - S_{tissue}(0)) \quad \text{Eqn. 1}$$

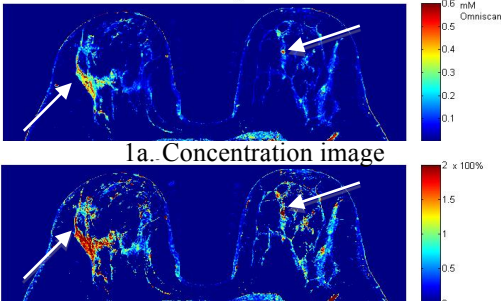
Where 'C(t)' is contrast media concentration as a function of time, 'F' is determined from the calibration phantom, using the known T1 values in the phantom compartments and their measured signal; $S_{tissue}(t)$ and $S_{tissue}(0)$ are the signals at each time point and before contrast injection respectively; and 'r1' is the relaxivity of the contrast agent. A correction for the tissue-to-phantom proton density (PD) ratio is applied.

Results: Representative peak concentration values, measured for ROIs in lesions, are in Table 1. The ratio of proton density in the tissue to that of pure water was 0.20 - 0.31. Figure 1 compares a difference image with a concentration image at the time of peak enhancement. Although the two images are similar - there are significant differences in contrast - some examples are indicated by arrows. The plot of enhancement vs. concentration (Fig. 2) shows that a single value of enhancement corresponds to a range of concentrations - suggesting that signal enhancement alone does not provide an accurate measure of contrast media concentrations.

Discussion: The pulse sequence used for the present study is not easy to model accurately due to effects of spectrally selective fat saturation. Yet, the present approach can convert subtraction images into concentration images. Due to the use of the calibration phantoms, acquisition of quantitative images required only the addition of a VFA series to the clinical examination; adding less than 10 minutes to the scan time, which means this method can easily be implemented in a clinical environment. The MRI-detectable proton density in tissue was low and highly variable, suggesting a large, broad component of the water signal; this may be a novel source of diagnostically useful information. Peak concentration values found thus far suggest a correlation with malignancy.

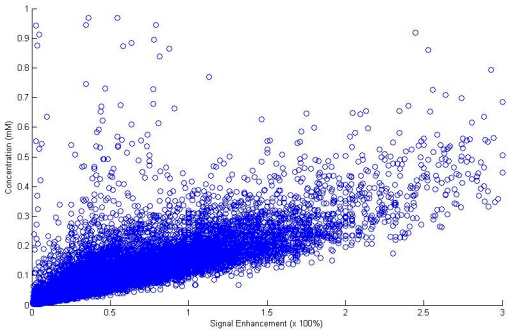
Conclusions: The present approach can convert subtraction images into quantitative concentration images, even if a good mathematical model is not available. The concentration images have the potential to provide standardized, quantitative information that is independent of acquisition parameters, allowing for standardization across different scanners and institutions. The method additionally provides MR-detectable proton density, potentially a novel source of diagnostic information, and native T1 maps.

Lesion Type	Concentration
DCIS	0.64mM
Mucinous Cancer	0.59mM
DCIS	0.47mM
IDC	0.45mM
Benign enhancing focus	0.41mM
Fibroadenoma	0.39mM
ADH Biopsy site enhancement	0.32mM
Fibroadenoma	0.30mM



1a. Concentration image

1b. Sig. enhancement image



2. Concentration vs Signal Enhancement

¹ Medved, M., et al. JMRI, 20: 122–128, 2004