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Improvements in Diagnostic Accuracy with Quantitative Dynamic Contrast Enhanced MRI

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14. ABSTRACT

We have continued scanning patients with the calibration phantoms and a research scanning protocol that allows us to acquire quantitative images of the breast displaying concentration of contrast media. These data can be used to generate maps displaying different parameters descriptive of contrast uptake, and pharmacokinetics, which are diagnostically useful. A subset of patients has been scanned at two field strengths (1.5T and 3T). Analysis of these data indicates a reduction in the variation across the scans with the quantitative methods proposed. By analyzing the sources of variability in the quantitative results, we aim to reduce differences across different fields even more. To date, 32 patients have been scanned with the calibration phantoms, 11 of them at two field strengths. Recruitment is ongoing, as well as refinement of our methods in order to increase their reliability.

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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 novel and useful biomarker for the detection of breast cancer.

Body

No further changes have been made to the calibration phantoms described in the previous report, we have continued to use solutions consisting of 70% deuterated water, 30% distilled water, and 0.05, 0.1, 0.2, 0.3, 0.4, 0.5 mM Omniscan (Gd-DTPA GE Healthcare).

We discovered large variations in proton density values found by fitting variable flip angle (VFA) data to the gradient echo signal model. We believe that voxels with longer T1 values may be leading to this variation. To address this we have added additional scans with a longer TR, in order to refine proton density estimates. First we acquire a VFA series as described in previous reports, a spoiled gradient echo acquisition with a TR of 10ms and four different flip angles (5, 10, 15, and 20^0). We have added two acquisitions with a TR of 25ms, and flip angles of 5 and 15 degrees. The reason we do not add more flip angles at TR=25ms is due to time constraints. We are currently exploring an iterative fitting method which includes the 10 and 25ms data with hopes of increasing the reliability of proton density measurements; we are still in the testing phase for this approach.

Since December 2011, we have scanned 10 patients with the calibration phantoms and the full research acquisition protocol, bringing the total number of patients scanned to 32. The number of patients which have been scanned at both 1.5T and 3T is now at 11. Recruitment was stopped for a period of time while the IRB reviewed our protocol, partly accounting for the lower number of patients scanned. In the last year, a collaboration between our group at the University of Chicago and NorthShore University Healthsystem (Evanston, IL) has begun, investigating whether certain high risk breast lesions could be safely managed with periodic MRI's. For scans at the University of Chicago we are including the phantoms and the additional calibration scans. Scans at NotrthShore also have the calibration scans added to the acquisition, but do not include the phantoms. It is our hope that we may include our phantoms in some of those scans in the future. Meanwhile, we are able to test our quantitative methods on these scans even though the signal-T1 factor of proportionality may not be as reliable.

The code used to generate the concentration of contrast media images was described in a previous report. The analysis does not correct for inhomogeneities in the transmit or B1 field due to our inability to acquire reliable, low noise maps of the B1 field (a problem which has been confirmed by another colleague in our group working on a separate project). Once the series of concentration images for the dynamic portion of the scan have been generated, these data are fit to an empirical mathematical model (EMM) which has been shown to model contrast uptake curves accurately in previous work [1]. The formula for this EMM is:

$$C(t) = A \cdot (1 - \exp(-\alpha t))^q \cdot \exp(-\beta t) \cdot \frac{(1 + \exp(-\gamma t))}{2} \qquad (1)$$

where A denotes upper limit of the concentration of contrast media, α (min^{-1}) is the uptake rate, β (min^{-1}) is the overall washout rate, γ (min^{-1}) is the initial washout rate and q is related to the slope of contrast media uptake. Fitting the data to this model yields values for each of these parameters, which first allow us to numerically compare the uptake and washout rates for each voxel; and secondly, can be used to simulate higher temporal resolution data, since the dynamic series are acquired at a relatively low temporal resolution (roughly 1 minute 15 seconds per acquisition). The higher temporal resolution data is necessary for pharmacokinetic modeling of the data.

In order to extract the pharmacokinetic parameters from the two-compartment model (TCM), knowledge of the arterial input function (AIF) is necessary [2]. We proposed to determine the AIF for each patient using a reference tissue plus heart chamber (or artery if possible) method, described as the reference tissue plus vessel (RTPV) method in [3]. To achieve this, we fit the decaying concentration of contrast media in the heart chamber to a bi-exponential model. This, in turn, allowed us to generate high temporal resolution data for the concentration of contrast media in blood. As a reference tissue we selected chest wall muscle. This method starts with known values of the volume transfer constant (K^{trans}) and the contrast media distribution volume (v_e) for muscle, and adjusts them until the differences between the resulting AIF from the TCM fit to the reference tissue and the concentration in the heart chamber are minimized. The region of interest in the heart chamber was selected by looking for regions which satisfied the following criteria: maximum concentration occurred in the first time-point after injection (shortly after 1 minute), and concentration dropped for every subsequent acquisition. This allowed us to eliminate voxels which, due to noise or perhaps varying stages of the cardiac cycle when the image was acquired, led to concentration curves that do not fit what is known to be the general pattern of concentration in blood. The ROI in the reference muscle was selected in an area with high signal and a pattern of uptake and some washout of the contrast media.

Unfortunately, AIFs found using the methods described above did not fit the pattern expected (i.e. the population based AIF), the RTPV AIFs often peaked at relatively late times, and had concentration values significantly lower to those in the population AIF published by Parker et al. (Fig. 1) [4]. We believe this could be due to the low signal-to-noise seen in the heart, as the images are acquired with a 16-channel bilateral breast coil, meaning signal drops off sharply in regions posterior of the breast. One possible solution to this issue could be adding

a surface coil on the patient's back, however the scanners used for this study (Phlips Achieva 1.5T and 3T-TX) cannot use more than the 16 acquisition channels that the breast coil utilizes. Furthermore, colleagues in our group working on MRI of the pelvic area have been presented with a similar impossibility of determining the AIF using the same method. We are planning on investigating whether changes to the acquisition protocol may allow us to overcome the issues we have encountered.
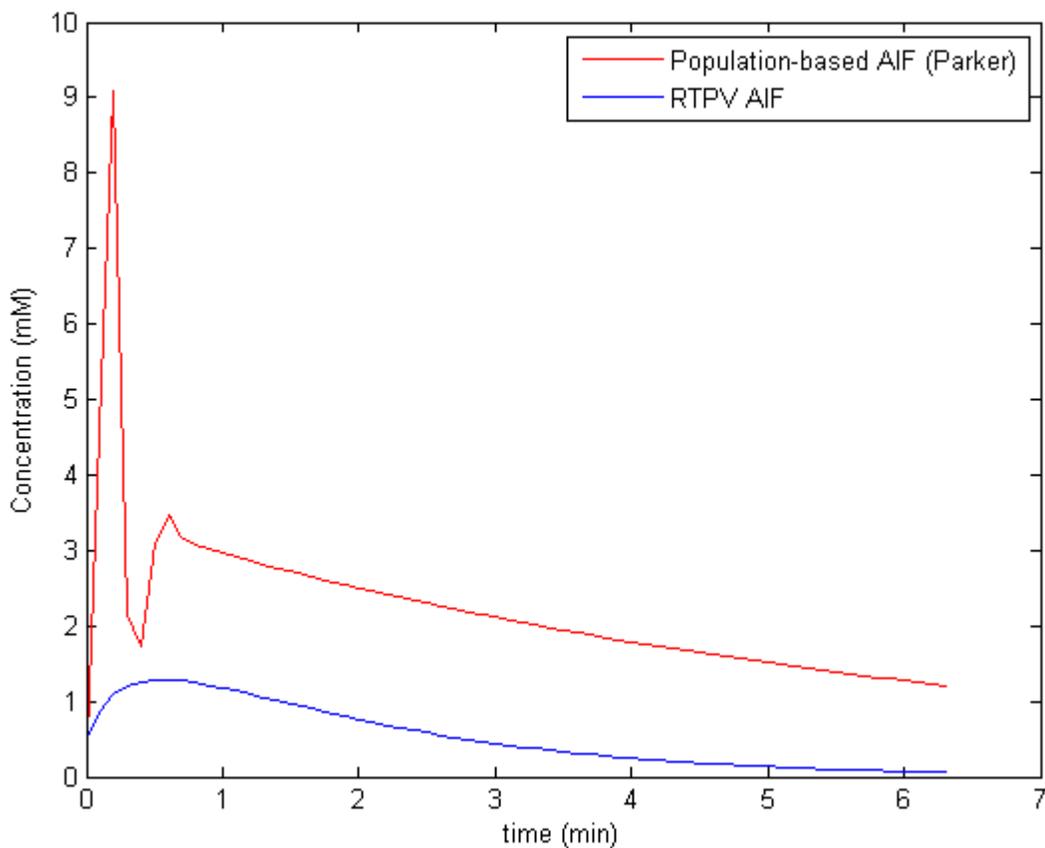
Fig. 1. Population-based AIF and AIF found using the reference tissue plus vessel (in this case heart chamber) method.

Due to the issues we have been presented with while attempting to determine the AIF for each patient, we have decided to move forward, for now, using the Parker population AIF, to determine the TCM pharmacokinetic parameters for the cases acquired. We realize this is not an ideal solution, as it does not allow for intra-patient variability due to physiological differences. We are currently exploring different approaches to scale or modify the population AIF, including scaling the magnitude of the AIF to the maximum concentration measured in the heart chamber, or using it as a starting point and modifying v_e or K^{trans} in a reference tissue, if an adequate one is determined.

A total of 11 patients have been scanned at both 1.5T and 3T to date. We have attempted to minimize the time between scans in order to eliminate variations in parenchymal enhancement during the menstrual cycle, for pre-menopausal patients [5]. When it has not been possible to scan them within a few days, their second scan was planned for a time when they were in the same phase of the menstrual cycle as in the first scan. The following tables summarize the results obtained so far from analysis of the 1.5T vs 3T comparison study, data from 2 cases are not included due to issues in the scan geometry which are currently being addressed.

	Top 10% Signal Enhancement Average		Top 10% Concentration Average		% difference between field strengths	
Lesion	1.5T	3T	1.5T	3T	SE	Concentration
Benign Focus	196%	133%	0.425	0.268	32%	37%
DCIS	163%	319%	0.471	0.575	96%	22%
IDC	116%	175%	0.352	0.449	51%	27%
IDC	195%	251%	0.258	0.321	29%	24%
FA	176%	229%	0.232	0.434	30%	87%
ADH	113%	465%	0.403	0.441	312%	10%
ADH	165%	243%	0.297	0.299	47%	1%
LCIS	154%	127%	0.238	0.291	17%	22%
Fibroepithelial	273%	401%	0.427	0.692	47%	62%
Mean					**73%**	**32%**

Table 1. Comparison between signal enhancement (SE) and concentration averages for the top 10% enhancing voxels in lesions.

	Ktrans (1/min)		ve		% difference between field strengths	
Lesion	1.5T	3T	1.5T	3T	Ktrans	ve
Benign Focus	0.021	0.020	0.795	0.755	4%	5%
DCIS	0.072	0.091	0.241	0.324	26%	34%
IDC	0.044	0.056	0.192	0.264	28%	38%
IDC	0.062	0.085	0.065	0.077	38%	18%
FA	0.033	0.049	0.150	0.199	51%	32%
ADH	0.021	0.045	0.573	0.264	112%	54%
ADH	0.028	0.022	0.271	0.333	21%	23%
LCIS	0.024	0.035	0.249	0.186	50%	26%
Fibroepithelial	0.056	0.167	0.193	0.307	198%	59%
Mean					**59%**	**32%**

Table 2. Two-compartment model pharmacokinetic parameters (using population- based AIF), average across lesion ROIs.

Lesion	Percentage difference between 1.5T and 3T EMM concentration parameters				
	Concentration Limit	Uptake rate	Uptake slope	Overall washout rate	Initial washout rate
Benign Focus	71%	84%	8%	92%	89%
DCIS	12%	6%	9%	79%	197%
IDC	33%	4%	6%	177%	41%
IDC	27%	2%	42%	35%	22%
FA	29%	14%	11%	75%	65%
ADH	9%	12%	27%	63%	45%
ADH	14%	34%	38%	100%	85%
LCIS	22%	22%	9%	78%	2%
Fibroepithelial	66%	42%	28%	50%	89%
Mean	**31%**	**24%**	**20%**	**83%**	**71%**

Table 3. Difference in empirical mathematical model (EMM) parameters for average across lesion ROIs

It can be seen in Table 1, that concentration measurements reduce the variability in signal enhancement in lesions, when looking at the top 10% enhancing voxels within a lesion ROI (a measure which is used by some computer aided visualization software when determining probability of malignancy). Even when one leaves out the ADH case which has a very large difference in signal enhancement between 1.5T and 3T, concentration measurements still reduce variability across field strengths (leaving this case out, signal enhancement leads to an average difference of 44% vs. 35% for concentration). We suspect that a major source of variability between scans for the quantitative parameters is uncertainty in the measurement of proton density, the approach outlined above may reduce this uncertainty and possibly reduce the variation across fields even smaller for quantitative measures. Table 2 summarizes the results of the TCM parameters found in the lesions when using a population-based AIF. We aim to reduce variability in these parameters by adjusting the AIF used as outlined above. Table 3 includes the results of fitting the concentration time-curves to the EMM described previously. It is interesting to note that the parameters descriptive of contrast uptake show lower variability compared to the washout rate parameters. One factor could be the number of acquisitions post contrast injection. It is possible that with shorter acquisitions not enough of the washout phase is sampled, leading to more inaccurate measures of contrast media washout. Recent acquisitions include longer sampling of the post contrast phase in the dynamic portion of the study (going out to roughly 10 minutes post contrast injection). The low variability in uptake rate is very promising and suggests that our current approach to data acquisition and analysis is probably not optimal. Our results indicate that we should be focusing on uptake rate as a primary diagnostic variable.

We are encouraged by the preliminary results that indicate a trend of quantitative methods reducing variability observed in data gathered on different scanners and different field strengths. Furthermore, by identifying the major sources of variability in our analysis, we may decrease variability in quantitative measurements even more. In addition to this analysis, Radiologists, experienced in breast MRI, are currently evaluating the images for all the cases acquired, and giving scores for factors relating to image quality and lesion conspicuity (see Appendix A).

Key Research Accomplishments

- A total of 32 patients have been scanned with the phantoms placed in the coil and the full calibration scan, 11 of them have been scanned at both 1.5T and 3T.
- We have begun using our quantitative methods on scans of women with high risk breast lesions both at the U of C and NorthShore, while scans at NorthShore (12 to date) do not include the phantoms, they do have the calibration scans added to their protocol.
- Determining the AIF on a patient-by-patient basis has been challenging, we are still working on refining our approach, including potentially scaling the population based AIF.
- Analysis on the dual field study has shown that the quantitative methods proposed reduce the variability observed across different field strengths when comparing with the conventional 'signal enhancement' data. By analyzing the sources of variability in our analysis and addressing them we aim to further reduce the variability seen in the quantitative results.
- Scanning protocols have been modified to include longer TR variable flip angle scans, in order to increase the accuracy of proton density measurements, and the DCE portion of the scan has been lengthened to better sample the contrast media washout.

Reportable Outcomes

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

F. Pineda, K. Yao, I. Koktzoglou, W. Weiss, G. Spear, J. Ecanow, B. Martz, S. Harris, M. Ivancevic, E. Dunkle, C. Sennett, H. Abe, G. Karczmar, G. Newstead. "Quantitative MRI evaluation of high risk breast lesions", presented at the University of Chicago and NorthShore University HealthSystem 2nd Joint Institutional Symposium, Chicago, IL, September 11, 2012

Conclusions

We have continued to scan patients with the calibration phantoms and minimal changes to the acquisition protocol. To date a total of 32 patients have been scanned with the full research protocol, 11 of them at both 1.5T and 3T on separate visits. This allows us to test whether the quantitative methods we propose eliminate variability across different scanners and field strengths. Results thus far indicate smaller variations in concentration measurements, further analysis is under way that may reduce the differences even further. The lower variability

observed in uptake rate (as measured by the empirical mathematical model used) indicates that uptake rate should be considered a primary diagnostic variable.

Pharmacokinetic analysis thus far has been carried out utilizing a population based arterial input function (AIF), due to challenges when determining an AIF on an individual basis. We realize this is not ideal, as it does not allow for variability across different subjects. For this reason we will continue to refine our methods in an effort to get the best possible AIF with the data we acquired, and then compare our results to those found with the population AIF.

A collaboration with NorthShore University Healthsystem will allow us to test our methods on data from a different site (and vendor), through a study aimed at investigating the potential of management of high risk breast lesions with MRI. We will also investigate whether parameters from the quantitative analysis are helpful for this task.

Recruitment continues both for the high risk lesion project, and for patients presenting with enhancing lesions in general.

References

[1] 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

[2] Tofts P, Modeling Tracer Kinetics in Dynamic Gd-DTPA Imaging. JMRI 2005; 7:91-101

[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] Parker GJ, Roberts C, Macdonald A, Buonaccorsi GA, Cheung S., Buckley DL, Jackson A, Watson Y, Davies K, Javson GC. Experimentally-derived functional form for a population-averaged high-temporal-resolution arterial input function for dynamic contrast-enhanced MRI. Magn Reson Med. 2006; 56(5):993-1000

[5] Delille JP, Slanetz PJ, Yeh ED, Kopans DB, Garrido L. Physiologic Changes in Breast Magnetic Resonance Imaging during the Menstrual Cylce: Perfusion Imaging Signal Enhanceent, and Influence of the T1 Relaxation Time of Breast Tissue. The Breast Journal 2005; 11:236-241

Appendix A

<div align="center">1.5T/3T Comparison Study</div>

Case #_____   Scan_____   Observer_____

Breast Volume
<25%   25%-50%   51%-75%   >75%
1   2   3   4

Parenchymal enhancement
None   Minimal   Mild   Moderate   Marked
1   2   3   4   5

Sharpness of the margins (how well can margins be delineated)
Low   High
1   2   3   4   5   N/A

Sharpness of internal lesion (how well can internal enhancement be read)
Low   High
1   2   3   4   5   N/A

Lesion conspicuity (how well can the lesion be seen)
Low   High
1   2   3   4   5   N/A

Fat sat quality (how well fat is saturated)
Poor   Very good
1   2   3   4   5

Artifact level (how much noise/artifacts are present in the images)
High noise   Low noise/artifacts
1   2   3   4   5

Lymph node conspicuity (how well can the axillary lymph node be seen)
Low   High
1   2   3   4   5

Conspicuity of other findings (edema, cyst, metallic clip, etc)
Low   High
1   2   3   4   5   Specify finding: _____

Appendix B (presented at the ISMRM 20th Annual Meeting and Exhibition, Melbourne, Australia, May 5-11, 2012)

Quantitative contrast media concentration and proton density images

Federico Pineda[1], Marko Ivancevic[2], Gillian Newstead[1], Hiroyuki Abe[1], and Gregory Karczmar[1]

[1]University of Chicago, Chicago, IL, United States, [2]Philips Healthcare, Best, Netherlands

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 T_1-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 T_1 and proton density values for each voxel. Using the known T_1 values in the phantom we corrected the nominal flip angles and created a proton density map. Under the experimental conditions, $1/T_1$ is approximately proportional to signal intensity. This allows us to convert signal intensity to concentration of contrast media using the following[1]

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

Where 'C(t)' is contrast media concentration as a function of time, 'F' is determined from the calibration phantom, using the known T_1 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 'r_1' 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 T_1 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. Signal Enhancement Image
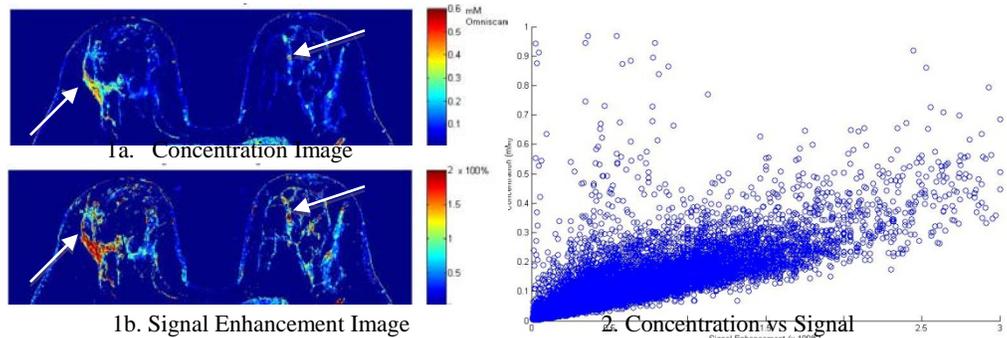
2. Concentration vs Signal Enhancement

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

Appendix C (presented at the University of Chicago and NorthShore University HealthSystem 2nd Joint Institutional Symposium, Chicago, IL, September 11, 2012)

Quantitative MRI Evaluation of High Risk Breast Lesions

Pineda F, Yao K, Koktzoglou I, Weiss W, Spear G, Ecanow J, Martz B, Harris S, Ivancevic M, Dunkle E, Sennett C, Abe H, Karczmar G, Newstead G.

Departments of Radiology and Surgery, NorthShore University HealthSystem and University of Chicago

Introduction: High risk breast lesions are associated with an increased risk of breast cancer. The current standard of care for these lesions is surgical excision after a high risk lesion has been identified by biopsy. The aim of this research is to determine whether quantitative MRI of high risk breast lesions yields enough information to rule out future malignancies associated with these lesions, with the ultimate goal of bypassing surgery if the breast MRI is negative.

In addition to a standard breast MRI protocol, calibration scans were added to allow measurement of concentration of contrast media in the breast as a function of time during the dynamic contrast enhanced (DCE) portion of the MRI examination. For a portion of these scans, novel calibration phantoms are placed in the breast coil. These phantoms consist of compartments with different concentrations of contrast media. Since the T_1 of each of these compartments is known, it is possible to calibrate the relationship between signal and T1 for each patient's scan, allowing us to convert the signal intensity differences in the DCE-MRI to an absolute measure of contrast media concentration. While other methods exist to convert signal intensity to concentration, such as the use of a reference tissue, our approach has the advantage of being patient independent and reproducible.

Methods: Patients with biopsy proven high risk breast lesions presented for a research MRI prior to surgery under an IRB approved protocol. Patients were scanned in either a Philips Achieva 1.5T or 3T-TX (University of Chicago) or a Siemens Verio 3T (NorthShore University HealthSystem), in a 16-channel bilateral breast coil. Acquisition protocols were standardized across all scanners and both sites. We acquired a variable flip angle (VFA) gradient echo series (3D spoiled gradient echo, flip angles = 5,10,15,20^O, TR/TE = 10/2.4ms), and a T_1-weighted dynamic series (3D turbo field echo with fat-sat) before and after a gadodiamide injection (0.1mmol/kg Omniscan). To date 17 patients have been scanned with this protocol. Patients at The University of Chicago were scanned with the calibration phantoms, consisting of color-coded tubes filled with gadodiamide solutions (0.05,0.1,0.2,0.3,0.4,0.5mM Omniscan) and 70% deuterated water, placed in the breast coil.

The VFA data were fit to find T_1 and proton density values in each voxel; in scans with the calibration phantoms the nominal flip angles were corrected using the known T_1 values in the phantom compartments. Contrast concentration images were used as the basis for pharmacokinetic analysis to find diagnostically useful parameters (i.e. V_e and K_{trans}). Radiologists at UC and NorthShore used standard forms to evaluate the MRIs.

Results: Plots of concentration vs. signal enhancement show 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. Information from the Radiologist's evaluation forms is being gathered for analysis, and pharmacokinetic analysis is under way.

Discussion: The present approach can convert subtraction images into quantitative concentration images, even if a good mathematical signal model for the DCE-MRI 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. Once a large number of cases have been acquired we will determine whether a negative MRI of a high risk breast lesion is sufficient to recommend active surveillance as an alternative to surgery.