DCEMRI of breast lesions: Is kinetic analysis equally effective for both mass and nonmass-like enhancement?

Sanaz A. Jansen, Xiaobing Fan, Gregory S. Karczmar, Hiroyuki Abe, Robert A. Schmidt, Maryellen Giger, and Gillian M. Newstead^{a)}

Department of Radiology, The University of Chicago, 5841 South Maryland Avenue MC2026 Chicago, Illinois 60637

(Received 5 December 2007; revised 24 March 2008; accepted for publication 24 April 2008; published 13 June 2008)

To perform a pilot study investigating whether the sensitivity and specificity of kinetic parameters can be improved by considering mass and nonmass breast lesions separately. The contrast media uptake and washout kinetics in benign and malignant breast lesions were analyzed using an empirical mathematical model (EMM), and model parameters were compared in lesions with mass-like and nonmass-like enhancement characteristics. 34 benign and 78 malignant breast lesions were selected for review. Dynamic MR protocol: 1 pre and 5 postcontrast images acquired in the coronal plane using a 3D T1-weighted SPGR with 68 s timing resolution. An experienced radiologist classified the type of enhancement as mass, nonmass, or focus, according to the BI-RADS® lexicon. The kinetic curve obtained from a radiologist-drawn region within the lesion was analyzed quantitatively using a three parameter EMM. Several kinetic parameters were then derived from the EMM parameters: the initial slope ($\text{Slope}_{\text{ini}}$), curvature at the peak (κ_{peak}), time to peak (T_{peak}), initial area under the curve at 30 s (iAUC_{30}), and the signal enhancement ratio (SER). The BI-RADS classification of the lesions yielded: 70 mass lesions, 38 nonmass, 4 focus. For mass lesions, the contrast uptake rate (α), contrast washout rate (β), iAUC_{30} , SER, $\text{Slope}_{\text{ini}}$, T_{peak} and κ_{peak} differed substantially between benign and malignant lesions, and after correcting for multiple tests of significance SER and T_{peak} demonstrated significance ($p < 0.007$). For nonmass lesions, we did not find statistically significant differences in any of the parameters for benign vs. malignant lesions ($p > 0.5$). Kinetic parameters could distinguish benign and malignant mass lesions effectively, but were not quite as useful in discriminating benign from malignant nonmass lesions. If the results of this pilot study are validated in a larger trial, we expect that to maximize diagnostic utility, it will be better to classify lesion morphology as mass or nonmass-like enhancement prior to kinetic analysis. © 2008 American Association of Physicists in Medicine. [DOI: [10.1118/1.2936220](https://doi.org/10.1118/1.2936220)]

Key words: nonmass lesions, malignant, DCEMRI, sensitivity, specificity

I. INTRODUCTION

Dynamic contrast enhanced magnetic resonance imaging (DCEMRI) is being used in breast imaging for several purposes, including determining extent of malignant disease and post-treatment evaluation.^{1,2} When analyzing lesion presentation on breast DCEMRI, the radiologists assesses the morphology as well as the contrast media uptake and washout—or kinetics—of the lesion following the breast imaging reporting and data system (BI-RADS®) lexicon.

According to the BI-RADS® lexicon, the first step in assessing lesion morphology is to classify the type of enhancement as mass, nonmass, focus (Fig. 1). Then, subsequent descriptors of other lesion features (such as shape, distribution, margins, enhancement pattern) are selected, which differ depending on the type of enhancement. The BI-RADS® lexicon also classifies the initial rise of the kinetic curve, and the delayed phase as persistent, plateau, or washout.

The level of suspicion for malignancy is determined by assessing both the morphologic as well as the kinetic characteristics of the lesion. Invasive cancers often present as heterogeneously enhancing masses with irregular or spiculated margins, and kinetic curves that typically rise rapidly

and subsequently wash out over time. Benign lesions, on the other hand, often present as homogeneously enhancing masses with smooth margins and tend to enhance more slowly and persistently take up contrast over time.³ To move beyond the qualitative BI-RADS® description of kinetics, many prior studies have calculated quantitative parameters from the kinetic curve data. Chen *et al.* used automated and fuzzy *c*-means clustering to extract the most enhancing voxels within a lesion and then calculated empirical parameters, such as maximum enhancement percentage, time to peak enhancement, uptake rate, and washout rate.⁴ Others have applied mathematical models to DCEMRI kinetic data, such as the two-compartment model, to extract diagnostically useful parameters.^{5–10} Early work by Hayton and Brady combined both breast segmentation and registration with pharmacokinetic modeling to produce color kinetic parameter maps that were shown to be useful for cancerous lesion localization and characterization.¹¹ However, for low time resolution 3D DCEMRI data, the accuracy of physiological parameters obtained from compartmental models is questionable. In addition these models require an arterial input function (AIF),

FIG. 1. Examples of four breast lesions with measured and EMM fitted kinetic curves. For each kinetic curve, the measured signal intensity values are indicated with triangles, and the fitted EMM curve with solid lines. From the top to bottom: Benign mass lesion, malignant mass lesion, benign nonmass lesion, and malignant nonmass lesion. The lesions are indicated by a white arrow.

which is difficult to estimate accurately. As an alternative to these approaches, mathematical equations can be used to fit the kinetic curves.^{10,12}

The majority of preinvasive ductal carcinoma *in situ* (DCIS) lesions and some invasive cancers present as nonmass-like enhancement in a segmental distribution with a clumped enhancement pattern.^{13–17} Benign lesions, such as atypical ductal hyperplasia, can also present with nonmass-like enhancement, as can normal parenchyma. DCIS is con-

sidered to be a nonobligate precursor of invasive cancer, and if treated has dramatically higher survival than invasive cancers.^{18,19} Yet the sensitivity and specificity of DCEMRI for detection of DCIS needs improvement,^{15,16,20–27} particularly given recent American Cancer Society guidelines recommending breast MRI in the screening of women at high risk of developing breast cancer.²⁸ It is likely that mass-like and nonmass-like enhancement patterns reflect differences in the underlying physiology and vasculature of these lesions,

which may in turn affect the kinetic characteristics. The kinetic parameters that can distinguish benign and malignant mass lesions may not work well with nonmass lesions, and vice versa. However, while there have been several studies on nonmass lesions such as DCIS, the efficacy of kinetic analysis in mass-like vs. nonmass-like enhancement has not been well characterized.^{29–33}

We have performed a pilot study to investigate whether kinetic analysis is more diagnostically useful in mass lesions compared with nonmass lesions. In addition to using conventional BI-RADS® descriptors of kinetics, we have also applied a mathematical model to the kinetic data. The limited temporal resolution in conventional 3D bilateral DCEMRI implies that complex mathematical models cannot be directly applied to kinetic curves to obtain a unique solution. In this study, a three parameter empirical mathematical model (EMM) was used to analyze 3D bilateral DCEMRI breast data. Thus, using both qualitative and quantitative means, we evaluated kinetic patterns of enhancement separately in (i) benign vs. malignant mass lesions, and (ii) benign vs. malignant nonmass lesions.

II. METHODS

II.A. Patients

At our institution, it is a routine protocol to obtain breast MR imaging for evaluation of extent of malignant disease, for post-treatment evaluation of the cancer patient, and for high-risk screening. The institutional review board approved our HIPAA compliant retrospective study with waiver of informed consent. Bilateral 3D DCEMRI data from 100 female patients acquired between May 2002 and June 2003 were reviewed for study. The age range of the subjects was 24–81 years (mean age = 56.2 ± 13.3 years). Based on the consensus opinion of two experienced pathologists, there were a total of 112 lesions of which 35 were benign and 77 malignant.

II.B. MRI analysis

MR imaging was performed on a 1.5 T GE Signa scanner (GE Healthcare, Milwaukee, WI) using a dedicated four-channel breast coil (Invivo, Orlando, FL) with the patient in the prone position. One pre and five postcontrast images were acquired in the coronal plane using a 3D T_1 -weighted spoiled grass sequence (TR/TE = 7.7/4.2 ms, flip angle = 30°, slice thickness = 3 mm, and in plane resolution = 1.4 mm), without fat suppression. The first postcontrast acquisition was started 20 s after contrast injection and the remaining images were acquired every 68 s; 20 ml of 0.5 M Gadodiamide (Omniscan; Nycomed-Amersham, Princeton, NJ) was injected intravenously followed by a 20 ml saline flush at the rate of 2.0 ml/s.

One experienced radiologist retrospectively reviewed the images and classified lesion morphology and kinetics. The lesions were assessed according to the BI-RADS® lexicon as mass, nonmass, or focus. To generate the kinetic curve, the radiologist traced a small region of interest (ROI) around

what was perceived to be the most enhancing part of the lesion on the first postcontrast image. The plot of signal intensity vs. time for this ROI was assessed by the radiologist according to the BI-RADS® lexicon, which describes the “initial rise” (rapid, medium, slow) and “delayed phase” (persistent, plateau, washout) of the kinetic curve.

II.C. Simplified empirical mathematical model

The kinetic curve obtained above was analyzed quantitatively using a simplified empirical mathematical model (EMM). To implement the model, the average signal intensity as a function of time ($S(t)$) was first calculated in the selected ROI. Next, the relative signal changes after contrast injection were calculated: $\Delta S = (S_n - S_0)/S_0$, where S_0 is the average signal intensity in the precontrast scan, and S_n is the signal intensity at the n th postcontrast time point. Then $\Delta S(t)$ was fit to

$$\Delta S(t) = A \cdot (1 - e^{-\alpha t}) \cdot e^{-\beta t}, \quad (1)$$

where A is the upper limit of the signal intensity, α (min^{-1}) is the rate of signal increase, and β (min^{-1}) is the rate of the signal decrease during washout. This is a modified version of a more complicated five-parameter empirical mathematical model that has proven to be diagnostically useful.¹²

The 3D bilateral DCEMRI data were processed using software written in IDL (Research Systems, Inc., Boulder, CO). From the primary EMM parameters A , α and β , we derived kinetic parameters that are commonly used in the literature: iAUC_{30} , $\text{Slope}_{\text{ini}}$, T_{peak} , SER , κ_{peak} ^{9,34–38} which are described in Table I.

II.D. Data analysis and statistical evaluation

We compared the kinetic characteristics of benign and malignant lesions as evaluated by the BI-RADS® lexicon as well as the EMM. The kinetic characteristics of benign and malignant lesions within mass and nonmass lesions were compared: (i) benign vs. malignant mass lesions, and (ii) benign vs. malignant nonmass lesions. In addition, we also compared the kinetic characteristics of malignant mass vs. malignant nonmass lesions.

To compare the proportion of washout vs. plateau and persistent (or rapid vs. medium and slow) curves between benign and malignant lesions overall, as well as stratified by type of enhancement, we used the Pearson's χ^2 test for significance, with a p value of <0.05 indicating statistical significance.

After fitting the kinetic curve to the EMM the goodness of fit parameter R^2 was calculated for each lesion. Two-tailed unequal variance student's t -tests were performed to evaluate which EMM parameters showed significant differences between the benign and malignant breast lesions overall, as well as the subpopulations of mass and nonmass lesions. The Holm–Bonferroni correction method was applied to test for the multiple tests of significance.³⁹

Receiver operating characteristic (ROC) analysis was performed to compare the diagnostic performance of the EMM parameters on mass lesions vs. nonmass lesions. ROCKIT

TABLE I. A list and description of the EMM parameters derived from the primary parameters A , α , and β .

Description	Equation
$iAUC_{30}$: Initial area under the kinetic curve at 30 s ^{a,b}	$iAUC_{\tau} = A \cdot [(1 - e^{-\beta\tau}) / \beta + (e^{-(\alpha+\beta)\tau} - 1) / (\alpha + \beta)]$ Here we used $\tau = 30$ s.
$Slope_{ini}(\text{min}^{-1})$: Initial slope of the kinetic curve ^{a,c,d}	$Slope_{ini} \approx A\alpha$
T_{peak} (min): Time to peak enhancement ^c	$T_{peak} = 1 / \alpha \log(1 + \alpha / \beta)$ Note that when $\beta \leq 0$, the curves did not reach the peak within the duration of the experiment. In these cases, we used the last time point as T_{peak} .
κ_{peak} : Curvature at the peak of enhancement T_{peak} ^c	$\kappa_{peak} \approx -A\alpha\beta$
SER: Signal enhancement ratio ^e	$SER = \Delta S_1 / \Delta S_L = e^{(t_L - t_1)\beta} \cdot (1 - e^{-\alpha t_1}) / (1 - e^{-\alpha t_L})$ Here, $t_1 = 60$ s and $t_L = 300$ s used in this study. A SER value greater than 1.1 indicates the signal intensity decreases with respect to its value at 60 s; SER less than 0.9 indicates that signal intensity continues to rise; and SER between 0.9 and 1.1 represents a plateau relative to intensity at 60 s.

^aReference 34.^bReference 35.^cReference 36.^dReference 37.^eReference 38.

software (ROCKIT 0.9B Beta Version, Charles E. Metz, University of Chicago) was used to generate the ROC curves.

III. RESULTS

III.A. Qualitative (BI-RADS) kinetic findings

Of the 112 lesions, 70 were classified by the expert breast radiologist based on the BI-RADS lexicon as mass lesions, 44 of which were malignant and 26 benign; 38 were classified as nonmass lesions, with 31 malignant and seven benign. Of the remaining four focus lesions, two were benign and two malignant. In the subsequent analyses, focus lesions were excluded. The distribution of the BI-RADS® assessments of initial uptake and delayed phase for all malignant and benign lesions is shown in Table II. Overall, malignant lesions exhibited a substantially higher proportion of curves showing “rapid” initial rise, at 90% (69/77), compared with benign lesions, at 74% (26/35). Malignant and benign lesions

also differed in delayed phase distribution with 65% (50/77) and 40% (14/35) classified as “washout” curves, respectively ($p = 0.023$).

The classification of initial rise and delayed phase for mass and nonmass lesions is also shown in Table II. The kinetic curves of 77% (34/44) of mass-like malignant lesions were classified as “washout,” compared with 38% (10/26) of mass-like benign lesions ($p = 0.001$). Seventy three percent (19/26) of benign mass lesions showed “rapid” initial rise compared with 93% (41/44) of malignant mass lesions. However, we did not find a significant difference in the distribution of initial rise or delayed phase classification of non-mass malignant and nonmass benign lesions ($p > 0.65$).

III.B. Quantitative (EMM) kinetic findings

The EMM was able to accurately fit the curves, with a goodness of fit parameter R^2 greater than 0.90 for all lesions studied. Some examples of benign and malignant mass and

TABLE II. Distributions of BI-RADS® categories for the qualitative assessment of the initial rise and delayed phased of kinetic curves for benign and malignant lesions, as well as the subtypes of benign and malignant lesions considered here. There were two benign and two malignant lesions classified as focus type enhancement, which do not appear in the table below.

		Benign			Malignant		
		All ($n=35$)	Mass ($n=26$)	Nonmass ($n=7$)	All ($n=77$)	Mass ($n=44$)	Nonmass ($n=31$)
BIRADS® Initial rise	<i>Rapid</i>	26	19	5	69	41	27
	<i>Medium</i>	8	6	2	6	3	3
	<i>Slow</i>	1	1	0	2	0	1
BIRADS® Delayed phase	<i>Washout</i>	14	10	2	50	34	16
	<i>Plateau</i>	15	12	3	19	9	9
	<i>Persistent</i>	6	4	2	8	1	6

TABLE III. The primary and derived diagnostic parameters calculated from the EMM in malignant and benign lesions. Reported values are mean $\pm$ standard deviation of the sample for all cases. The p value after Student t -test is shown for each parameter, along with the required p value for significance according to the Holm–Bonferroni correction for multiple tests of significance. Numbers in bold indicate that there was a statistically significant difference between benign and malignant lesions, according to the Student's t -test and after using the Holm–Bonferroni correction for multiple comparisons.

EMM parameter	All Benign ($n=35$)	All Malignant ($n=77$)	p values	Required p value
A	4.2 ± 2.2	4.1 ± 2.2	$p=0.703$	$p=0.05$
α (min^{-1})	1.6 ± 1.1	2.1 ± 1.1	$p=0.047$	$p=0.01$
β (min^{-1})	0.045 ± 0.047	0.059 ± 0.061	$p=0.24$	$p=0.025$
iAUC_{30}	0.55 ± 0.34	0.71 ± 0.54	$p=0.07$	$p=0.013$
$\text{Slope}_{\text{ini}}$ (min^{-1})	6.1 ± 4.6	8.8 ± 8.4	$p=0.04$	$p=0.008$
$^aT_{\text{peak}}$ (min)	3.4 ± 1.8	2.7 ± 1.8	$p=0.12$	$p=0.017$
κ_{peak}	-0.30 ± 0.48	-0.68 ± 1.19	$p=0.02$	$p=0.007$
SER	0.88 ± 0.31	1.14 ± 0.49	$p=0.001$	$p=0.006$

^aFor those curves which did not reach a peak within the duration of the experiment, we assumed a time to peak of 5 min.

nonmass lesions, along with the fitted kinetic curves, are shown in Fig. 1. After fitting the kinetic curves, the five derived parameters were calculated using the equations in Table I. The average values of all primary and derived parameters are displayed in Table III. T -test comparisons demonstrated a trend that malignant lesions had substantially faster contrast uptake (α) steeper initial slope ($\text{Slope}_{\text{ini}}$), larger enhancement ratio (SER) and sharper curvature (κ_{peak}) than benign lesions. However, after applying the Holm–Bonferroni correction for multiple comparisons,³⁹ only the parameter SER was significant, probably due to our database size.

All of the primary and derived EMM parameters α , β , T_{peak} , iAUC_{30} , SER, $\text{Slope}_{\text{ini}}$, and κ_{peak} except for A differed substantially between benign and malignant mass lesions (Fig. 2). That is, kinetic curves of malignant mass lesions, exhibited stronger contrast uptake (α , iAUC_{30} , $\text{Slope}_{\text{ini}}$), earlier peak enhancement (T_{peak}), and sharper, stronger washout (SER, κ_{peak} , β) compared with benign mass lesions. After applying the Holm–Bonferroni correction for multiple tests of significance only the parameters SER and T_{peak} were significant, likely due to our database size. However, for nonmass lesions, we found no statistical differences in any of the primary or derived EMM parameters for benign vs. malignant lesions ($p > 0.51$ for all, Fig. 2). Considering malignant lesions only, those with mass-like enhancement had substantially larger A , β , iAUC_{30} , and $\text{Slope}_{\text{ini}}$ compared with malignant nonmass lesions, and after the Holm–Bonferroni correction only the parameter A remained significant ($p = 0.004$).

ROC analysis was used to evaluate the diagnostic accuracy of the primary and derived EMM parameters. ROC curves were generated for each parameter separately among mass and nonmass lesions. The A_z values in mass lesions ranged from 0.54 (A) to 0.72 (SER), and in nonmass lesions

from 0.52 (α) to 0.60 (A). For all parameters except for A , the A_z values were higher in mass lesions, but this was not significant ($p > 0.19$), likely due to the small number of benign nonmass lesions considered. The ROC curves for these parameters are shown in Fig. 3.

IV. DISCUSSION

We have found that kinetic parameters have the potential to distinguish benign and malignant mass lesions more effectively, but failed to demonstrate usefulness in discriminating benign from malignant nonmass lesions. This trend was found both for the qualitative BI-RADS® and quantitative EMM measures of kinetics. Malignant mass lesions exhibited a higher proportion of washout type curves as well as a higher initial uptake (α , iAUC_{30} , $\text{Slope}_{\text{ini}}$) and faster, stronger washout (β , T_{peak} , SER, κ_{peak}) compared with benign mass lesions, although after accounting for multiple tests of significance only the differences in SER and T_{peak} were significant. Conversely, the kinetic characteristics of malignant and benign nonmass lesions appeared not to differ according to either the BI-RADS® lexicon or EMM. These results translated into diagnostic performance: the A_z values derived from ROC curves also demonstrated that the diagnostic performance of all EMM parameters except one (A) was improved in mass lesions. Among malignant lesions, the parameters A , β , iAUC_{30} and $\text{Slope}_{\text{ini}}$ differed between mass and nonmass lesions, and the parameter A was significant after correcting for multiple comparisons.

Kinetic curve shape is related to the perfusion, capillary permeability, and diffusion of contrast media from blood vessels to the extracellular space—these biological properties ultimately explain the differences between mass and nonmass lesions noted above. One important class of malignant lesions that most often displays nonmass-like enhancement is *in situ* lesions, in which neoplastic ductal epithelial cells remain confined to mammary ducts. The growth of vasculature associated with DCIS is not well understood. Guidi *et al.* showed an increase in vessel density around ducts with DCIS, although with variable patterns.⁴⁰ Heffelfinger found that the expression of angiogenic growth factors (such as VEGF) increases from hyperplasia to DCIS.^{41,42} The physiology of DCIS is distinct from invasive ductal carcinoma (IDC), in which cancer cells have invaded the surrounding stroma with well-defined but infiltrative margins. The vasculature associated with IDC lesions is dense and leaky.^{43,44} These physiological differences of DCIS and IDC lesions are likely related to the corresponding differences in MR presentation, in which IDC predominantly presents as a mass lesion on MRI.¹⁷

Although most DCIS lesions display a distinctive nonmass-like enhancement at MR imaging, they do not exhibit a consistent kinetic pattern. Unlike invasive cancers, the kinetic curves of DCIS lesions can often exhibit persistent signal increase, or signal intensity that plateaus over time.^{13,14,16} Because of the variable kinetic pattern of DCIS lesions, some have suggested that kinetic information—specifically, the BI-RADS® qualitative assessment of de-

FIG. 2. The average value $\pm$ standard deviation for each EMM parameter in benign (white bars) and malignant (gray bars) lesions, stratified by type of enhancement as mass or nonmass. After correcting for multiple tests of significance, the parameters SER and T_{peak} demonstrated significant differences among malignant and benign mass lesions.

layed phase—is not useful in diagnosing DCIS lesions and instead, morphologic analysis should be favored.⁴⁵ Our results support this prior work, in that we have found large overlap in the kinetic characteristics of benign and malignant nonmass lesions. However, given that the physiological basis of enhancement is likely different in nonmass vs. mass lesions, it may be that more quantitative kinetic parameters need to be developed that are tailored for nonmass lesions. We found that malignant nonmass lesions exhibited significantly lower contrast uptake compared with malignant mass lesions; this underscores the importance of early imaging to distinguish nonmass lesions from enhancing normal parenchyma which has a similar nonmass morphology. Perhaps other imaging techniques may be important; recent work by Bartella *et al.* suggested that using proton spectroscopy to measure choline peaks yielded high sensitivity and specificity to malignant nonmass lesions.²⁹

There are several limitations to this study.

- While the total number of lesions studied was relatively

large, there were only seven nonmass-like benign lesions, which may be too small to perform reliable comparisons of the subtypes of benign and malignant lesions presented here. It is important to verify the results of this pilot study in a larger number of patients. In particular, because of the multiple parameters calculated in this study, the Holm–Bonferroni correction reduced the statistical significance of our findings. With larger numbers of lesions, this may no longer be the case.

- 40% of benign lesion kinetic curves were classified as washout, which is higher than many reports. The benign lesions considered were suspicious enough to warrant biopsy. Since most obviously benign lesions exhibit persistent type kinetic curves and would not be sent to biopsy, this may skew the delayed phase distribution in this study away from the persistent curve type. However, in other studies, where only histologically proven benign lesions were considered, comparable values were found.³⁶

FIG. 3. Fitted binormal ROC curves generated by the ROCKIT software are shown for the EMM parameters with the highest, and lowest, A_z values in mass and nonmass lesions. SER (solid blue line) and A (solid red line) had the highest A_z values in mass and nonmass lesions, respectively. A (dashed blue line) and α (dashed red line) had the lowest A_z values in mass and nonmass lesions, respectively.

- The placement and size of the ROI was determined manually, and only one small ROI was used to characterize the whole lesion. This single ROI may not capture the heterogeneity of kinetic enhancement patterns in the lesion. In addition, partial volume effects may compromise the accuracy of the kinetic curve, especially in lesions with nonmass-like enhancement. It is possible that partial volume effects produce the observed differences between mass and nonmass lesion. Furthermore, in our study the ROI was selected by one single radiologist. It is likely that other radiologists may select slightly different ROIs, which in turn would affect the kinetic curve of the lesion. Future studies should be performed to test the results of this pilot study both with increased numbers of lesions and more observers.
- Although the EMM fit the curves very well, sparse sampling of the kinetic curve may result in more fitting errors in the uptake phase. In addition, preclinical studies suggest that specificity of the EMM is improved when the tail of the washout curve is sampled for at least 15 min; the curves studied here were truncated at approximately 6 min.^{9,12}

Despite these shortcomings, as a pilot study our results suggest that current kinetic analysis may not be effective in nonmass lesions, while it may be effective in mass lesions, and that the enhancement kinetics of malignant nonmass and mass lesions are different. If the results of this study are validated in a larger trial, we expect that it may be useful in computer aided detection and diagnosis (CAD) algorithms. By training classifiers on mass and nonmass lesions separately, it may be that (i) detection of nonmass lesions could be improved by choosing accurate thresholds, (ii) the probability of malignancy in mass lesions may be improved, and

(iii) new kinetic parameters that are diagnostically effective in cases of nonmass-like enhancement may be discovered. Future work will focus on a larger group of lesions with detailed pathology analysis, to investigate new parameters targeted at nonmass lesions. In addition, pixel by pixel analysis, acquiring high spatial/temporal resolution of MR images, or following the later phase of the kinetic curves for a longer time, could be used to help improve the differentiation of nonmass malignant from nonmass benign lesions.

ACKNOWLEDGMENTS

The authors would like to thank the Segal Foundation, the Biological Sciences Division at the University of Chicago, DOD Grant No. W81XWH-06-1-0329 and NIH Grant No. R21 CA104774-01 A2 and 2 R01 CA078803-05A2 for financial support.

^{a)} Author to whom correspondence should be addressed; electronic mail: gnewstead@radiology.bsd.uchicago.edu

¹D. C. Abraham, R. C. Jones, S. E. Jones, J. H. Cheek, G. N. Peters, S. M. Knox, M. D. Grant, D. W. Hampe, D. A. Savino, and S. E. Harms, "Evaluation of neoadjuvant chemotherapeutic response of locally advanced breast cancer by magnetic resonance imaging," *Cancer* **78**, 91–100 (1996).

²C. Boetes, R. D. Mus, R. Holland, J. O. Barentsz, S. P. Strijk, T. Wobbes, J. H. Hendriks, and S. H. Ruys, "Breast tumors: Comparative accuracy of MR imaging relative to mammography and US for demonstrating extent," *Radiology* **197**, 743–747 (1995).

³C. K. Kuhl and H. H. Schild, "Dynamic image interpretation of MRI of the breast," *J. Magn. Reson. Imaging* **12**, 965–974 (2000).

⁴W. Chen, M. L. Giger, U. Bick, and G. M. Newstead, "Automatic identification and classification of characteristic kinetic curves of breast lesions on DCE-MRI," *Med. Phys.* **33**, 2878–2887 (2006).

⁵G. O. Cron, F. Kelcz, and G. E. Santyr, "Improvement in breast lesion characterization with dynamic contrast-enhanced MRI using pharmacokinetic modeling and bookend T(1) measurements," *Magn. Reson. Med.* **51**, 1066–1070 (2004).

⁶P. Armitage, C. Behrenbruch, M. Brady, and N. Moore, "Extracting and visualizing physiological parameters using dynamic contrast-enhanced magnetic resonance imaging of the breast," *Med. Image Anal.* **9**, 315–329 (2005).

⁷E. Furman-Haran, E. Schechtman, F. Kelcz, K. Kirshenbaum, and H. Degani, "Magnetic resonance imaging reveals functional diversity of the vasculature in benign and malignant breast lesions," *Cancer* **104**, 708–718 (2005).

⁸P. S. Tofts, B. Berkowitz, and M. D. Schnall, "Quantitative analysis of dynamic Gd-DTPA enhancement in breast tumors using a permeability model," *Magn. Reson. Med.* **33**, 564–568 (1995).

⁹X. Fan, M. Medved, G. S. Karczmar, C. Yang, S. Foxley, S. Arkani, W. Recant, M. A. Zamora, H. Abe, and G. M. Newstead, "Diagnosis of suspicious breast lesions using an empirical mathematical model for dynamic contrast-enhanced MRI," *Magn. Reson. Imaging* **25**, 593–603 (2007).

¹⁰E. V. Heiberg, W. H. Perman, V. M. Herrmann, and C. G. Janney, "Dynamic sequential 3D gadolinium-enhanced MRI of the whole breast," *Magn. Reson. Imaging* **14**, 337–348 (1996).

¹¹P. Hayton, M. Brady, L. Tarassenko, and N. Moore, "Analysis of dynamic MR breast images using a model of contrast enhancement," *Med. Image Anal.* **1**, 207–224 (1997).

¹²X. Fan, M. Medved, J. N. River, M. Zamora, C. Corot, P. Robert, P. Bourrinet, M. Lipton, R. M. Culp, and G. S. Karczmar, "New model for analysis of dynamic contrast-enhanced MRI data distinguishes metastatic from nonmetastatic transplanted rodent prostate tumors," *Magn. Reson. Med.* **51**, 487–494 (2004).

¹³S. A. Jansen, G. Newstead, H. Abe, A. Shimauchi, R. Schmidt, and G. S. Karczmar, "MR imaging of pure ductal carcinoma in situ: Kinetics, morphology and comparison with mammographic presentation and nuclear grade," *Radiology* **245**, 684–691 (2007).

- ¹⁴H. Neubauer, M. Li, R. Kuehne-Heid, A. Schneider, and W. A. Kaiser, "High grade and non-high grade ductal carcinoma in situ on dynamic MR mammography: Characteristic findings for signal increase and morphological pattern of enhancement," *Br. J. Radiol.* **76**, 3–12 (2003).
- ¹⁵J. H. Menell, E. A. Morris, D. D. Dershaw, A. F. Abramson, E. Brogi, and L. Liberman, "Determination of the presence and extent of pure ductal carcinoma in situ by mammography and magnetic resonance imaging," *Breast J.* **11**, 382–390 (2005).
- ¹⁶M. Van Goethem, K. Schelfout, E. Kersschot, C. Colpaert, J. Weyler, I. Verslegers, I. Biltjes, A. De Schepper, and P. M. Parizel, "Comparison of MRI features of different grades of DCIS and invasive carcinoma of the breast," *Jbr-Btr* **88**, 225–232 (2005).
- ¹⁷C. Kuhl, "The current status of breast MR imaging. Part I. Choice of technique, image interpretation, diagnostic accuracy, and transfer to clinical practice," *Radiology* **244**, 356–378 (2007).
- ¹⁸A. Recht, E. J. Rutgers, I. S. Fentiman, J. M. Kurtz, R. E. Mansel, and J. P. Sloane, "The fourth EORTC DCIS Consensus meeting (Chateau Marquette, Heemskerk, The Netherlands, 23–24 January 1998)—conference report," *Eur. J. Cancer* **34**, 1664–1669 (1998).
- ¹⁹T. Suzuki, M. Toi, S. Saji, K. Horiguchi, T. Aruga, E. Suzuki, S. Horiguchi, N. Funata, K. Karasawa, and N. Kamata, "Early breast cancer," *Int. J. Clin. Oncol.* **11**, 108–119 (2006).
- ²⁰C. K. Kuhl, S. Schrading, H. B. Bieling, E. Wardelmann, C. C. Leutner, R. Koenig, W. Kuhn, and H. H. Schild, "MRI for diagnosis of pure ductal carcinoma in situ: A prospective observational study," *Lancet* **370**, 485–492 (2007).
- ²¹P. Viehweg, D. Lampe, J. Buchmann, and S. H. Heywang-Kobrunner, "In situ and minimally invasive breast cancer: Morphologic and kinetic features on contrast-enhanced MR imaging," *Magn. Reson. Mater. Phys., Biol., Med.* **11**, 129–137 (2000).
- ²²R. Gilles, B. Zafrani, J. M. Guinebreteire, M. Meunier, O. Lucidarme, A. A. Tardivon, F. Rochard, D. Vanel, S. Neuenschwander, and R. Arriagada, "Ductal carcinoma in situ: MR imaging-histopathologic correlation," *Radiology* **196**, 415–419 (1995).
- ²³A. Shiraishi, Y. Kurosaki, T. Maehara, M. Suzuki, and M. Kurosumi, "Extension of ductal carcinoma in situ: Histopathological association with MR imaging and mammography," *Magn. Reson. Med. Sci.* **2**, 159–163 (2003).
- ²⁴A. P. Schouten van der Velden, C. Boetes, P. Bult, and T. Wobbes, "The value of magnetic resonance imaging in diagnosis and size assessment of in situ and small invasive breast carcinoma," *Am. J. Surg.* **192**, 172–178 (2006).
- ²⁵S. G. Orel, "MR imaging of the breast," *Radiol. Clin. North Am.* **38**, 899–913 (2000).
- ²⁶J. M. Lee, J. B. Kaplan, M. P. Murray, M. Mazur-Grbec, T. Tadic, D. Stimac, and L. Liberman, "Underestimation of DCIS at MRI-guided vacuum-assisted breast biopsy," *AJR, Am. J. Roentgenol.* **189**, 468–474 (2007).
- ²⁷K. J. Macura, R. Ouwerkerk, M. A. Jacobs, and D. A. Bluemke, "Patterns of enhancement on breast MR images: Interpretation and imaging pitfalls," *Radiographics* **26**, 1719–1734; quiz 1719 (2006).
- ²⁸D. Saslow, C. Boetes, W. Burke, S. Harms, M. O. Leach, C. D. Lehman, E. Morris, E. Pisano, M. Schnall, S. Sener, R. A. Smith, E. Warner, M. Yaffe, K. S. Andrews, and C. A. Russell, "American Cancer Society guidelines for breast screening with MRI as an adjunct to mammography," *Ca-Cancer J. Clin.* **57**, 75–89 (2007).
- ²⁹L. Bartella, S. B. Thakur, E. A. Morris, D. D. Dershaw, W. Huang, E. Chough, M. C. Cruz, and L. Liberman, "Enhancing nonmass lesions in the breast: Evaluation with proton (1H) MR spectroscopy," *Radiology* **245**, 80–87 (2007).
- ³⁰L. Bartella, L. Liberman, E. A. Morris, and D. D. Dershaw, "Nonpalpable mammographically occult invasive breast cancers detected by MRI," *AJR, Am. J. Roentgenol.* **186**, 865–870 (2006).
- ³¹M. A. van den Bosch, B. L. Daniel, M. N. Mariano, K. N. Nowels, R. L. Birdwell, K. J. Fong, P. S. Desmond, S. Plevritis, L. A. Stables, M. Zakhour, R. J. Herfkens, and D. M. Ikeda, "Magnetic resonance imaging characteristics of fibrocystic change of the breast," *Invest. Radiol.* **40**, 436–441 (2005).
- ³²L. Liberman, E. A. Morris, D. D. Dershaw, A. F. Abramson, and L. K. Tan, "Ductal enhancement on MR imaging of the breast," *AJR, Am. J. Roentgenol.* **181**, 519–525 (2003).
- ³³L. Liberman, E. A. Morris, M. J. Lee, J. B. Kaplan, L. R. LaTrenta, J. H. Menell, A. F. Abramson, S. M. Dashnaw, D. J. Ballon, and D. D. Dershaw, "Breast lesions detected on MR imaging: Features and positive predictive value," *AJR, Am. J. Roentgenol.* **179**, 171–178 (2002).
- ³⁴P. J. Moate, L. Dougherty, M. D. Schnall, R. J. Landis, and R. C. Boston, "A modified logistic model to describe gadolinium kinetics in breast tumors," *Magn. Reson. Imaging* **22**, 467–473 (2004).
- ³⁵J. L. Evelhoch, "Key factors in the acquisition of contrast kinetic data for oncology," *J. Magn. Reson. Imaging* **10**, 254–259 (1999).
- ³⁶B. K. Szabo, P. Aspelin, M. K. Wiberg, and B. Bone, "Dynamic MR imaging of the breast. Analysis of kinetic and morphologic diagnostic criteria," *Acta Radiol.* **44**, 379–386 (2003).
- ³⁷L. D. Buadu, J. Murakami, S. Murayama, N. Hashiguchi, S. Sakai, K. Masuda, S. Toyoshima, S. Kuroki, and S. Ohno, "Breast lesions: Correlation of contrast medium enhancement patterns on MR images with histopathologic findings and tumor angiogenesis," *Radiology* **200**, 639–649 (1996).
- ³⁸L. Esserman, N. Hylton, T. George, and N. Weidner, "Contrast-enhanced magnetic resonance imaging to assess tumor histopathology and angiogenesis in breast carcinoma," *Breast J.* **5**, 13–21 (1999).
- ³⁹S. Holm, "A simple sequentially rejective multiple test procedure," *Scand. J. Stat.* **6**, 65–70 (1979).
- ⁴⁰A. J. Guidi, L. Fischer, J. R. Harris, and S. J. Schnitt, "Microvessel density and distribution in ductal carcinoma in situ of the breast," *J. Natl. Cancer Inst.* **86**, 614–619 (1994).
- ⁴¹S. C. Heffelfinger, M. A. Miller, R. Yassin, and R. Gear, "Angiogenic growth factors in preinvasive breast disease," *Clin. Cancer Res.* **5**, 2867–2876 (1999).
- ⁴²S. C. Heffelfinger, R. Yassin, M. A. Miller, and E. Lower, "Vascularity of proliferative breast disease and carcinoma in situ correlates with histological features," *Clin. Cancer Res.* **2**, 1873–1878 (1996).
- ⁴³A. Rice and C. M. Quinn, "Angiogenesis, thrombospondin, and ductal carcinoma in situ of the breast," *J. Clin. Pathol.* **55**, 569–574 (2002).
- ⁴⁴E. Furman-Haran, F. Kelcz, and H. Degani, "Magnetic resonance imaging of breast cancer angiogenesis: A review," *J. Eval Clin. Pract.* **21**, 47–54 (2002).
- ⁴⁵S. E. Harms, "The use of breast magnetic resonance imaging in ductal carcinoma in situ," *Breast J.* **11**, 379–381 (2005).