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Separation of benign and malignant breast lesions using dynamic contrast enhanced MRI, in a biopsy cohort

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Abstract

PURPOSE—To assess the diagnostic utility of contrast kinetic analysis for breast lesions and background parenchyma of women undergoing MRI-guided biopsies, for whom standard clinical analysis had failed to separate benign and malignant lesions.

METHOD—This study included 115 women who had indeterminate lesions based on routine diagnostic breast MRI exams and underwent an MRI(3T)-guided biopsy of one or more lesions suspicious for breast cancer. Breast DCE-MRI was performed using a radial stack-of-stars 3D spoiled gradient echo pulse sequence and modified k-space weighted image contrast (KWIC) image reconstruction. Contrast kinetic model analysis was conducted to characterize the contrast enhancement patterns measured in lesions and background parenchyma (BP). The transfer rate (K^{trans}), interstitial volume fraction (v_e), and vascular volume fraction (v_p) estimated from the lesion and BP were used to separate malignant from benign lesions.

RESULTS—The patients with malignant lesions had significantly ($p < 0.05$) higher median lesion- K^{trans} (0.081 min^{-1}), higher median BP- K^{trans} (0.032 min^{-1}), and BP- v_p (0.020) than those without malignant lesions (0.056 min^{-1} , 0.017 min^{-1} and 0.012 , respectively). The area under the receiver operating characteristic curve (AUC) of the BP- K^{trans} (0.687) was highest among the single parameters and higher than that of the lesion- K^{trans} (0.664). The combined logistic regression model of lesion- K^{trans} , lesion- v_e , BP- K^{trans} , BP- v_e and BP- v_p had the highest AUC of 0.730 .

CONCLUSION—Our results suggest that the contrast kinetic analysis of DCE-MRI data can be used to differentiate the malignant lesions from the benign and high-risk lesions among the indeterminate breast lesions recommended for MRI-guided biopsy exams.

Keywords

breast cancer; dynamic contrast enhanced MRI; biopsy; contrast kinetic analysis; breast compression

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INTRODUCTION

Dynamic contrast-enhanced (DCE) MRI is a highly sensitivity tool for breast cancer screening and is currently recommended by the American Cancer Society for this indication in high-risk patients (1). Previous studies, as reviewed by Warner *et al.* (2), have shown that DCE-MRI has higher sensitivity than mammography, particularly in young women with high lifetime risk for breast cancer. Contrast enhancement kinetics is particularly helpful if the lesion has a benign morphologic appearance (3). In the case of a well-defined mass that might be benign, enhancement kinetic data may help one decide whether biopsy is required or whether it is safe to recommend follow-up of the lesion (3,4).

However, DCE-MRI suffers from low and variable specificity (26–97%) (2,5–9). The clinical dilemma results from the overlap of the morphologic and kinetic characteristics between benign and malignant lesions (10–13), which often leads to MRI-guided biopsies. It has been reported that the rate of detecting malignant lesions in the patients who undergo MRI-guided breast biopsy is between 20% and 60% (14–18). While there are multiple studies using DCE-MRI for breast cancer diagnosis, most studies did not focused on the patients with indeterminate lesions from diagnostic imaging studies (2,5,7–9,15,19). Hence, the ultimate potential of DCE-MRI to differentiate malignant lesions from benign ones in the MRI-guided biopsy cohort has not yet been fully studied.

Quantitative analysis of DCE-MRI data remains nontrivial, particularly to incorporate it into clinical practice. Model-based contrast kinetic analysis of contrast agent uptake curves of suspicious lesions has been applied to temporal DCE-MRI data in an attempt to improve its diagnostic accuracy (19–21). In addition to the lesion, background parenchymal enhancement (BPE) has also been reported as related to breast cancer risk (22). However, to our knowledge, quantitative kinetic analysis of BPE has not been utilized in improving diagnostic accuracy of breast lesions.

In this study, we investigated the utility of DCE-MRI in patients recommended for MRI-guided biopsy exams since standard clinical analysis has already failed to separate benign and malignant lesions in this cohort. The purpose of this study was to assess the diagnostic utility of contrast kinetic analysis for the lesions and breast background parenchyma of women undergoing MRI-guided biopsies.

METHODS

Patients

This retrospective study was Health Insurance Portability and Accountability Act compliant and was approved by our institutional review board. Informed consent was waived. This study included 115 women (age: 51+/- 11 years; 26–76 years) who had MRI-guided biopsy of one or more lesions suspicious for breast cancer at our institution between November 2011 and February 2013 and whose MRI protocol included dynamic contrast enhanced (DCE) MRI using a radial stack-of-stars 3D spoiled gradient echo pulse sequence. The radial pulse sequence was used when the radiologists who performed the biopsy exams preferred to use it instead of the conventional Cartesian pulse sequence, such as VIBE. This

study includes all cases with the radial pulse sequence collected during the period. There were 139 lesions biopsied. Based on the pathology evaluation of the biopsy specimens, lesions were divided into benign (n= 81 (58%)), high risk (n=33 (24%); 12 papillary, 11 atypia, 6 radial scar and 4 lobular carcinoma in situ), and malignant (n=25 (18%); 7 with ductal carcinoma in situ, 15 with invasive ductal carcinoma, and 3 invasive lobular carcinoma) categories.

Data Acquisition

Breast DCE-MRI was performed on the patients who underwent MRI-guided biopsy scans on a whole-body 3T scanner (MAGNETOM TimTrio, Siemens Healthcare, Erlangen, Germany) equipped with a seven element breast coil array (InVivo, FL). Mild breast compression was used as in routine MRI-guided biopsy scans. A radial stack-of-stars 3D spoiled gradient echo pulse sequence with golden-angle spoke ordering was used for continuous data acquisition (20,23) with these imaging parameters: sagittal slab orientation, FOV=280 × 280 × 144 mm³, FA = 12 degrees, TE/TR = 1.47/3.6 ms, and BW = 710 Hz/pixel. A total of 2280 spokes were acquired for each of the 35 partitions during free breathing to cover one breast planned for biopsy. The reconstructed image matrix size per frame was 256×256×72 with zero padding along the slice direction. Two-fold readout oversampling (512 sample points/spoke) was used to minimize spurious aliasing along each spoke. All partitions in the slice direction corresponding to one radial angle were acquired sequentially before rotating to the next angle. Frequency-selective fat suppression was used after each partition loop. System-dependent gradient-delay errors were estimated using 60 initial calibration lines (24). The total acquisition time was 5 min 40 s. After baseline acquisition of 57 s, a single dose of Gd-DTPA (Magnevist, Bayer Healthcare, Leverkusen, Germany) at 0.1 mM/kg body weight was injected at 2 ml/sec into an antecubital vein while the scan continued for another 4 min 43 s.

Image Reconstruction

A modified version of the k-space weighted image contrast (KWIC) algorithm with golden-angle (GA) view-ordering (25) was used to reconstruct the dynamic images. KWIC is a radial data-based image reconstruction method to achieve a high temporal resolution by sharing the k-space data at high frequencies (26). Reconstructed images were produced from the series of radial views by selecting a continuous set of 610 radial views and then applying. We used six circular regions (one circle in the middle and five donut shape areas as moving to the outer k-space). A Fibonacci number of views were used for all annuli, in order to minimize streaking artifacts. Each image was reconstructed using 610 total radial views with annuli consisting of 21, 34, 55, 89, 144, 233, 377, and 610 views. The radius of each annulus was chosen to satisfy the Nyquist criterion. A modified ramp filter was used to compensate for sampling distribution. Radial k-space data were interpolated onto a Cartesian grid before cropping by half and performing a 2D inverse fast Fourier transform to generate the reconstructed images. This was achieved using a 2D Kaiser-Bessel kernel on a 6×6 voxel grid (27). The selection of consecutive 610 radial views for image reconstruction was shifted by 21 spokes to generate a series of 3D images at a temporal resolution of 3.2 s/frame. The temporal resolution is defined as the time to collect the data for the central part (3.2 s). But as in most view sharing methods, GA-KWIC images may have some temporal and/or spatial

blurring. The effect of temporal and/or spatial blurring was studied in our earlier study (25) that found the temporal/spatial blurring in GA-KWIC method does not reduce diagnostic accuracies. In addition to the high-temporal resolution data using the GA-KWIC method, we also used the images generated by the scanner using conventional gridding method with 380 spokes/frame (57 s/frame) for comparison.

Data Analysis

Regions of interest (ROI) for the lesions were manually selected by the two readers (with 7 (A.K.L.) and 15 (L.M.) years of experience), to draw one ROI per lesion in consensus, after review of the MRI images and associated reports. With the conventional gridding images (57 s/frame), the contrast enhancement curve based on the average value of the lesion ROI was characterized in terms of two parameters: initial enhancement ratio (IER) defined as the percent difference between the first ($t = 0$ s) and third ($t = 114$ s) time points and delayed enhancement ratio (DER) defined as the percent difference between the first and fifth ($t = 228$ s) images with respect to the signal strength of the first point.

For contrast kinetic model analysis, we used the extended Tofts model with a plasma compartment, in which the contrast-agent concentration in a voxel ($C_t(t)$) is described by (28):

$$C_t(t) = v_p C_p(t) + K^{trans} \int_0^t C_p(u) \exp\left(-\frac{K^{trans}(u-t)}{v_e}\right) du,$$

where K^{trans} is the volume transfer constant between blood plasma and interstitial space, v_e denotes the extravascular extracellular space volume fraction, v_p the volume fraction of the plasma space, and C_p the contrast agent concentration in plasma. C_p was measured from the axial artery in the same reconstructed images for evaluation. The pre-contrast T_1 relaxation value of the lesion and the contrast agent relaxivity were assumed to be 1.5 s and 4.3 $\text{mM}^{-1}\text{s}^{-1}$, respectively, based on literature data (29,30). Parameter estimation was performed using the Simplex algorithm (31) provided in IDL (Exelis VIS, Boulder, CO).

Quantitative analysis of dynamic signal enhancement in the background parenchyma (BP) was performed using a mask of the fibroglandular tissue generated using the principal component analysis (PCA) method that was introduced in our previous studies to investigate the hormonal influence in BPE (32,33), where a full description of the method can be found. The PCA method decomposes conventional gridding DCE-MRI images into eigenvalues, eigenvectors, and projection coefficient maps. It was assumed that the primary principal component represents the contrast enhancement kinetics of the BP, and the projection coefficient map for the primary principal component was used to generate the mask of the fibroglandular tissue by selecting voxels with coefficients larger than 0.9 (Fig. 1A). Note that the PCA-based segmentation was developed only for the fibroglandular tissue, not the lesion. The PCA method was applied to three representative, randomly-selected sagittal slices without any benign or suspicious lesion. The slices were chosen from both the lateral and medial aspects of the breast. It was demonstrated in our earlier study that the BPE measured using the PCA method with the randomly selected three slices was robust and

reproducible when comparing with different sets of three slices selected by a different operator or the same operator with some time interval (32). The mean time-intensity curve of the voxels included in the fibroglandular tissue masks of the three slices was converted to the time concentration curve (Fig. 1B) that was used for the same quantitative analysis as the lesions using the extended Tofts model.

Statistical Analysis

Median K^{trans} , v_e and v_p values of malignant and non-malignant groups were compared using the Mann Whitney U test. Chi-square test was used for categorical variables. The diagnostic accuracies of lesion as well as BP parameters were evaluated in terms of the area under receiver operating characteristic (ROC) curve (AUC) with the standard error estimated under the nonparametric assumption. A univariate logistic regression analysis was used to evaluate the predictive power of individual parameters. A multivariate logistic regression analysis was also performed to determine an optimal logistic regression model for differentiation of two groups; malignant group vs non-malignant group (high-risk and benign combined). All statistical tests were conducted at the two-sided 5% significance level. The p values presented in this study were not adjusted for multiple comparisons. Data analysis was performed by using the IBM SPSS Statistics, Version 20 (IBM Corp., Armonk, NY).

RESULTS

Figure 2 shows IER and DER values measured using the images reconstructed with conventional gridding method. The data are grouped in three lesion types - benign, high risk and malignant -based on the pathology. There is no significant difference between lesion types for these parameters.

The extended Tofts model parameters, K^{trans} , v_e and v_p measured in the biopsied lesions are shown in Figure 3A–C. The median lesion K^{trans} of the malignant group (0.081 min^{-1} , interquartile range (IQR): $0.045\text{--}0.140$) is significantly ($p = 0.037$) higher than that of the patients without a malignant lesion (0.056 min^{-1} , IQR: $0.034\text{--}0.097$), which includes both benign and high-risk groups. The median lesion v_p of the malignant group (0.10 , IQR: $0.04\text{--}0.13$) is also higher than that of non-malignant lesions (0.06 , IQR: $0.03\text{--}0.10$), but does not reach a statistical significance ($p = 0.051$).

Figure 3 also shows the extended Tofts model parameters measured in the background parenchyma selected using the fibroglandular tissue mask generated using the PCA method. Overall lesion K^{trans} values (Fig. 3A) are at least one order of magnitude higher than those of the fibroglandular tissue (Fig. 3D). The median BP K^{trans} of the malignant group (0.032 min^{-1} , IQR: $0.019\text{--}0.038$) is significantly ($p = 0.021$) higher than that of the patients without a malignant lesion (0.017 min^{-1} , IQR: $0.009\text{--}0.029$), which includes both benign and high-risk groups. The median BP v_p of the malignant group (0.020 , IQR: $0.011\text{--}0.025$) is also significantly higher ($p = 0.007$) than that of high-risk group (0.012 , IQR: $0.006\text{--}0.023$).

Figure 4 shows the benign case with the highest K^{trans} value of 0.35 min^{-1} among the women in the benign group, and the malignant case with the with the highest K^{trans} value of

0.23 min⁻¹ among the women in the malignant group. These two examples demonstrate the difficulty of separating the lesion types based on the contrast enhancement curves in this biopsy cohort.

Diagnostic accuracies of the estimated contrast kinetic parameters for detection of malignant lesions from non-malignant cases (high risk and benign cases combined) are compared in terms of the area under the receiver operating characteristic curve (AUC) as shown in Figure 5 and Table 2. The AUC of the BP K^{trans} (0.687 ± 0.068) is highest among the single parameters and higher than that of the lesion K^{trans} (0.664 ± 0.076). The combined model of lesion K^{trans} , lesion v_e , BP K^{trans} , BP v_e , and BP v_p has the highest AUC of 0.730 ± 0.069 (Fig. 5B).

DISCUSSION

Patients referred for biopsy of breast lesions represent the most difficult cases, since standard clinical analysis could not confidently separate benign from malignant lesions. For the biopsy cohort used in this study, we found simple measures, such as IER and DER are inadequate for separation of lesion types in this population. Application of contrast kinetic model technique to this cohort in the present study shows that there are significant differences in median K^{trans} and v_p values between the malignant and non-malignant groups, suggesting a possible role of quantitative data analysis in improving the specificity of breast DCE-MRI. Given that only about 20 – 25% of current MRI-guided biopsy exams found cancer (14–18), DCE-MRI combined with a proper contrast kinetic analysis may help to reduce unnecessary follow up procedures, such as biopsy exams.

Recently, El Khoully et al (34) have evaluated the effects of breast compression on breast DCE-MRI exams. They found that the percentage enhancement was higher in noncompressed-versus compressed-breast studies by about 50% in early and delayed phase. More importantly, their contrast enhancement curve type analysis (persistent, plateau, and washout) for identifying invasive cancer decreased significantly from AUC = 0.71 to AUC=0.53 after compression. Our study was conducted with typical compression required for biopsy scans. However, we found that AUC of K^{trans} (0.664) was higher. This observation suggests that the contrast kinetic model analysis can be more accurate than the simple curve type analysis despite the breast compression. In addition, this also suggests that the accuracy of K^{trans} for detecting could have been higher if the breast compression is reduced.

One of the key challenges in performing breast DCE-MRI has been to achieve high temporal resolution while keeping the high spatial resolution required for bilateral breast imaging with a large field of view (35). Because of this difficulty, tumor morphological assessment has been the main tool in breast cancer diagnosis, and the potential benefit of using contrast kinetics information has not been fully assessed in the setting of clinical exams. Recent development of fast MRI methods provides an opportunity to utilize both morphological and contrast kinetic information in DCE-MRI data (36). K-space weighted image contrast (KWIC) has been proposed as a view sharing method to utilize the temporal redundancy in a radial k-space acquisition with a bi-sectional view ordering (26) or golden-angle view

ordering (25,37). The golden-angle radial MRI data can also be used for an iterative reconstruction using compressed sensing and parallel imaging, known as Golden-angle RAdial Sparse Parallel (GRASP) technique (20,23) to improve the image quality, particularly when the image matrix size is substantially larger as in bilateral diagnostic breast MRI. Future studies are warranted to assess the diagnostic accuracy of breast DCE-MRI using GRASP image reconstruction.

The present study also found that the K^{trans} measured in the normal-appearing fibroglandular tissue showed a significant difference between the malignant and non-malignant groups. Furthermore, the AUC of BP K^{trans} is as high as that of lesion K^{trans} . Background parenchymal enhancement (BPE) has been indicated as a possible biomarker for breast cancer risk (22). However, BPE quantification is complicated by the difficulty of selecting normal fibroglandular tissue embedded in the surrounding adipose tissue, even at the highest spatial resolution of 3D MRI. The conventional assessment of BPE is based on *qualitative* categorical classification of enhancement as none/minimal, mild, moderate, and marked (22,38). While many studies underscore the importance of BPE in breast MRI, there is little consensus on how to *quantify* BPE. It is also not clearly understood how BPE is associated with the other characteristics of fibroglandular and adipose tissues in the breast, or whether BPE is a truly independent biomarker. A semi-automatic segmentation method based on principal component analysis was used in a recent study (32) to extract a representative time-intensity curve for the fibroglandular tissue and measure the percent enhancement at 1 min post injection. The study showed that the women with benign lesions showed a characteristic pattern of BPE change depending on the menstrual cycle, whereas the women with malignant lesions did not show such pattern. This observation of the previous study and the result of the current study regarding the increased K^{trans} in BP of the malignant group suggest that the vascular properties of the background parenchyma may be associated with the presence of a malignant lesion in the breast.

It is interesting to note that the BP v_p of the benign group is as high as that of the malignant group. The relatively high level of BP v_p in the benign group may be related to the fibroglandular tissue characteristic of the patients in the benign group of this study. The patient characteristics in Table 1 shows that the patients with benign lesions in this study have more cases with marked BPE, dense FGT and mammography density than the high-risk or malignant group. Further study with a larger cohort is warranted to assess the relationship of BP v_p and the fibroglandular tissue characteristics, such as BPE and density.

Limitations of our study included its retrospective design and relatively small sample size. It has been reported that the contrast kinetic parameter estimation can be affected by pre-contrast T1 and radiofrequency (RF) coil sensitivity (39). However, due to the limited scan time available during the biopsy exam, the measurement of pre-contrast T1 and RF coil transmit field sensitivity B1 is not included in our clinical MRI-guided biopsy protocol as in many other institutions. Instead, we used a fixed T1 for the lesions and arterial blood, along with the assumption of the homogeneous transmit coil sensitivity. Since we have the limited accuracy in measuring the contrast agent concentration due to the lack of T1 and B1 information, we did not include the effect of inter-compartmental water exchange in our data analysis which can also be an important factor to determine the malignancy of the lesion

(19,40,41). Future studies are warranted to perform the study in a prospective way to include the T1 and B1 measurements for more quantitative analysis of DCE-MRI data.

In conclusion, our results suggest that the contrast kinetic analysis of DCE-MRI data can be used to differentiate the malignant lesions from the benign and high-risk lesions among the indeterminate breast lesions recommended for MRI-guided biopsy exams. Our results also suggest that BP enhancement kinetic properties may be associated with the presence of the malignant lesion. Further evaluation of the lesion and BP contrast kinetic properties is required to determine if the contrast kinetic parameters can be used to select patients who may not need biopsy.

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Figure 1. Selection of voxels for measurement of background parenchymal enhancement. **A.** Voxels within the red lines were selected based on the principal component analysis method that identifies voxels strongly associated with the background parenchymal enhancement. **B.** Plotted is the time concentration curve of the breast background parenchyma that was calculated from the average time intensity curve of the selected voxels in A.

Figure 2.

Comparisons of patients with benign, high-risk (HR) or malignant lesions in terms of initial enhancement ratio (A) and delayed enhancement ratio (B) using conventional breast DCE-MRI data. Neither IER nor DER shows a significant difference among patient groups with different lesion types.

Figure 3.

Comparison of patients groups with different lesion types in terms of contrast kinetic model parameters estimated using the high-temporal resolution images. The boxes for individual groups represent the interquartile ranges between the first and third quartiles, along with the lines in the middle for the median values. The entire ranges of the data are shown by the whiskers. The pairs of groups with a significant difference between their median values are noted.

Figure 4.

Examples of lesions (**A**, **C**) and their contrast enhancement curves (**B**, **D**) acquired during MRI-guided biopsy exams. The first example shown in **A** and **B** is a 40-year-old woman with a benign lesion that had the highest K^{trans} value in the benign group. This case could not be classified as a benign case using any of the kinetic model parameters or their combinations. The second example shown in **C** and **D** is a 49-year-old woman with invasive ductal carcinoma that had the highest K^{trans} value in the malignant group. These examples demonstrate the challenges in diagnosing these lesions.

Figure 5.

A. Comparison of diagnostic accuracies of contrast kinetic model parameters estimated in lesions (L) and background parenchyma (B). The combined model with the highest AUC value was comprised of lesion K^{trans} , lesion v_e , BP K^{trans} , and BP v_p . **B.** The receiver operating characteristic curve of the combined model.

Table 1

Patient Characteristics

						P Value		
						B vs. M	H vs. M	B vs. H
No. of patients	81	33	25					
Age (years)	47.0 ± 10.1	55.7 ± 9.5	52.0 ± 10.1			0.001	0.716	< 0.001
Lesion size (average in cm)	1.6 ± 1.5	1.9 ± 1.6	1.2 ± 0.9			0.119	0.057	0.423
BPE						0.287	0.771	0.110
Non/minimal	14 (17)	7 (21)	6 (24)					
Mild	26 (32)	10 (30)	10 (40)					
Moderate	25 (31)	15 (45)	8 (32)					
Marked	16 (20)	1 (3)	1 (4)					
FGT density						0.771	0.231	0.039
Predominantly fatty	11 (14)	5 (15)	4 (16)					
Scattered FGT	16 (20)	12 (36)	7 (28)					
Heterogeneously dense	14 (17)	9 (27)	3 (12)					
Dense	40 (49)	7 (21)	11 (44)					
Mammographic density						0.158	0.016	0.009
Predominantly fatty	7 (9)	4 (12)	3 (12)					
Scattered FGT	12 (15)	8 (24)	8 (32)					
Heterogeneously dense	22 (27)	16 (48)	3 (12)					
Dense	40 (49)	5 (15)	11 (44)					
Lesion kinetic curve						0.036	0.412	0.215
Type I	55 (68)	17 (52)	10 (40)					
Type II	21 (26)	14 (42)	11 (44)					
Type III	5 (6)	2 (6)	4 (16)					
BI-RADS score						0.001	0.258	0.040
4	68 (84)	22 (67)	13 (52)					
5	13 (16)	11 (33)	12 (48)					

Note: Unless otherwise indicated, data are number of patients, with percentages in parentheses. Data may not add to 100% because of rounding.

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Diagnostic characteristics of contrast kinetic parameters to classify malignant lesions from non-malignant lesions. The cut-off values were determined by maximizing the sum of sensitivity and specificity, i.e., Youden index. * the combined model is a logistic regression model with all parameters except lesion V_p .

Table 2

	Parameter	Cut-off value	Sensitivity	Specificity	AUC
Lesion	K^{trans}	0.088 min^{-1}	62.5 %	71.0 %	0.664
	V_e	0.352	60.9 %	68.8 %	0.625
	V_p	0.065	75.0 %	63.8 %	0.659
BPE	K^{trans}	0.028 min^{-1}	62.5 %	72.5 %	0.687
	V_e	0.217	43.5 %	81.3 %	0.544
	V_p	0.011	93.8 %	47.8 %	0.648
Combined model*		0.433	87.5 %	58.0 %	0.730