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Diffusion-Weighted Imaging: Effects of Intravascular Contrast Agents on Apparent Diffusion Coefficient Measures of Breast Malignancies at 3T

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Abstract

Purpose—To determine whether apparent diffusion coefficient (ADC) measures of breast lesions at 3 tesla (T) are affected by gadolinium administration.

Materials and Methods—The study included 19 patients who underwent 3T MRI. Diffusion-weighted imaging (DWI) was acquired with $b=0, 100$, and 800 s/mm^2 before and after a dynamic contrast-enhanced (DCE) sequence. ADC values were measured for each lesion and normal fibroglandular tissue. Pre and post-contrast ADC measures were compared by Wilcoxon signed-rank test, and differences between groups were compared by Mann-Whitney U test; $p<0.05$ was considered statistically significant.

Results—There was no significant difference in pre and post-contrast ADC measured at $b=0, 100, 800 \text{ s/mm}^2$ for malignancies (median change: -0.4% , $-0.01 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.40$), but there was a slight increase in post-contrast ADC in normal tissue ($+1.6\%$, $+0.04 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.0006$). Findings were similar for both lesions (-0.4% , $-0.01 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.54$) and normal tissue ($+1.5\%$, $+0.03 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.002$) with ADC measured at $b=0, 800$ and also at $b=100, 800 \text{ s/mm}^2$ (lesions: $+0.9\%$, $+0.01 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.71$; normal tissue: $+1.8\%$, $+0.03 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.005$). For lesions, results were not affected by lesion size, type (mass vs. non-mass enhancement), mean initial enhancement, late enhancement, or delayed enhancement rate on DCE-MRI ($p>0.05$ for all). Normal tissue showed some trends with greater progressive enhancement rates and higher late enhancement levels correlating with greater increase in post-contrast ADC ($p=0.09$ for both).

Conclusions—Our results show that breast lesion ADC measures using our approach were not significantly altered following DCE-MRI at 3T, suggesting DWI and DCE-MRI can be performed in any order without affecting diagnostic criteria. However, influences of contrast on ADC measures in normal breast tissue were observed and require further investigation.

Keywords

magnetic resonance imaging; diffusion-weighted imaging; apparent diffusion coefficient; gadolinium; breast cancer

INTRODUCTION

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is widely used to characterize and delineate the extent of breast malignancies. Malignancies are distinguishable on DCE-MRI due to alterations in microvasculature characteristics, and can be detected with high sensitivity. In a meta-analysis across 44 breast MRI studies, sensitivity ranged from 89 to 100% for invasive cancers (1). However, specificity was more variable, ranging widely from 21% to 100%, with an overall specificity of 72% (1). Diffusion-weighted imaging (DWI) is a non-contrast-enhanced MRI technique that has shown promise for improving upon the specificity of DCE-MRI (2–4). DWI assesses molecular water motion in tissue and complements DCE-MRI because it is sensitive to tissue microstructural features, including cell density and membrane integrity (5). Multiple studies have indicated that apparent diffusion coefficient (ADC) values measured by DWI are useful for characterizing breast lesions on MRI (5–8). Typically, malignant breast lesions demonstrate lower ADC values than benign breast tissue, reflecting higher cell density (5).

DWI is increasingly performed as an adjunct sequence to the routine diagnostic DCE-MRI. Some centers, including our institution, prefer to have the DWI after contrast administration, following the DCE-MRI sequence rather than before, in case the patient is not able to tolerate the full exam. However, the effect of gadolinium contrast agents on ADC measurements is not well understood, and previous studies have shown mixed results (7,9–15).

Several mechanisms have been suggested by which the presence of contrast agent could alter ADC measurements. Both intravascular and extravascular water motion contribute to ADC measures on DWI. Gadolinium-based contrast agents work by decreasing the T1 and (to a lesser extent) T2 relaxation times of nearby water protons. Multiple researchers have proposed that a contrast agent may selectively suppress signal from the intravascular compartment, where concentration of contrast material is highest, thereby eliminating so-called pseudodiffusion contributions and reducing observed ADC values post contrast (9,10,13,14). Others have questioned this theory, citing the fact that very high intravascular concentrations of contrast agent would be required to cause such an effect (16). Chen et al. investigated the influence of contrast at different concentrations and found no changes in ADC measures following contrast agent dosages of 0.2 mmol/kg or 0.4 mmol/kg in mouse mammary carcinomas (15). It has also been theorized that gadolinium within tissue compartments can cause local magnetic field susceptibilities, which can then couple with diffusion-sensitizing gradients on DWI and alter T2* and measured ADC values (16–18).

Early work by Yamada et al. found statistically significant reductions in ADC values after gadolinium contrast agent administration in normal brain tissue (mean, –1.3%) and brain infarcts (mean, –3.5%) (10). In known breast carcinomas at 1.5T, Yuen et al reported

dramatic ADC reductions (mean, -23%) after gadolinium administration (9). A more recent study by Janka et al. also found a decrease in ADC after contrast in breast lesions (19), although the changes were smaller than reported by Yuen et al (mean, -11%). However, a number of other prior studies found no statistically significant change in ADC values after contrast in multiple organ systems including breast, brain, and liver as well as in mouse mammary carcinomas (7,12,14,15).

Given the mixed results in the current literature, more information is needed to optimize breast MRI protocols by determining whether performing DWI prior to or after DCE-MRI makes a difference for evaluation of breast lesions. Therefore, the purpose of our study was to compare ADC values obtained from malignant lesions and normal breast tissue before and after DCE-MRI to determine the effect of contrast agents on ADC values.

MATERIALS AND METHODS

This study was approved by our Institutional Review Board and was Health Insurance Portability and Accountability Act compliant. The standard breast MRI protocol at our institution includes a DCE-MRI sequence and a post-contrast DWI sequence. From October 2011 to July 2012, an additional diffusion sequence was performed prior to contrast agent injection when time permitted for clinical protocol optimization purposes. Women who underwent this extra pre-gadolinium DWI scan as part of their breast MRI examination were eligible for this study. Informed consent was waived due to the retrospective nature of the study.

Subjects and Lesions

Our study included women with biopsy-proven malignancies who underwent a clinical breast MRI examination to evaluate the extent of disease, which included the additional pre-contrast DWI sequence. Subjects were required to be 18 years or older, and not undergoing neoadjuvant chemotherapy within 6 months prior to the MRI. Twenty-three patients with 25 lesions met the study eligibility criteria. Three lesions measuring less than 1.5 cm in diameter were excluded due to their small size and potential for slice misregistration. Two lesions were excluded because of obscuration caused by a prior breast biopsy. Another lesion was excluded due to difficulty in identifying the lesion on DWI. The final cohort included 19 women with 19 malignant lesions.

Control Data

For comparison, six normal healthy volunteers underwent the same MRI protocol as the patients, but without injection of the contrast agent. All volunteers gave informed consent to participate in the study.

MRI Acquisition

Breast MRI was performed with a Philips Achieva Tx 3 tesla (T) scanner using a dedicated bilateral 16-channel breast coil (MammoTrak). All breast MRIs included a T2-weighted fast spin echo sequence, T1-weighted non-fat-suppressed sequence, T1 weighted fat-suppressed DCE-MRI sequences, and DWI sequences before and after the DCE-MRI (Figure 1).

Patients were imaged in the prone position with free-breathing for all sequences, and images were acquired in the axial orientation.

DCE-MRI was performed using a T1-weighted fat suppressed 3D Fast Gradient Echo (eTHRIVE) sequence with parallel imaging (SENSE). The following parameters were used: repetition time/echo time: 5.96 ms/3.09 ms, flip angle: 10°, matrix size: 440×660, field of view: 22×33 cm, number of slices: 280, slice thickness: 1.3 mm, in plane voxel size: 0.5 mm. The contrast agent administered was 0.1 mmol/kg-body weight gadoteridol (ProHance, Bracco Diagnostics) delivered at 2 cc/sec followed by a 20 mL saline flush. One pre-contrast and three post-contrast sequences were acquired, with the first post-contrast sequence started at initiation of contrast agent injection. DCE-MRI acquisition time was 2 minutes 57 seconds per sequence (center k space acquired at 114 seconds); total post-contrast scan time was 8 minutes 51 seconds.

DWI was performed prior to and immediately following the DCE-MRI acquisition (approximately 9 minutes post-contrast injection). DWI was acquired using a diffusion-weighted spin echo echo-planar imaging sequence with parallel imaging. The same imaging parameters were used for both DWI sequences, including: repetition time/echo time: 5336 ms/61 ms; reduction factor: 3; averages: 2; matrix size: 240×240; field of view: 36×36 cm; number of slices: 30; slice thickness: 5 mm; gap: 0. Diffusion gradients were applied in six directions with b values of 0, 100, and 800 s/mm²; the acquisition time was 3 minutes 28 seconds. These b values are used for the clinical breast MRI scans at our institution and were selected for optimal performance at 3T, to maximize conspicuity of breast lesions and differentiation between benign and malignant lesions (20). For this study, ADC calculations were performed using both zero and nonzero (b=100 s/mm²) minimum b-values to evaluate whether any differences in ADC pre versus post-contrast were attributable to the perfusion or microvascular component in ADC, which has been suggested previously (9).

Image Analysis

A commercially available 3D affine transformation algorithm (Diffusion Registration tool, Philips Healthcare, Best, The Netherlands) was used for image registration. This algorithm has previously been shown to reduce misregistration of breast DWI images due to motion and eddy-current based distortion effects (21,22). Any cases observed to have residual misalignment between the b=0, b=100 and b=800 s/mm² DW images that is not corrected by the registration algorithm are typically excluded from analyses. However, this was not identified to be an issue for the 19 lesions in the study. DWI was analyzed with in-house software written in Java language and incorporating open source image analysis tools (ImageJ, National Institutes of Health). Pixel-based ADC maps were calculated for three b-value combinations: 0, 100, and 800 s/mm² (ADC_{0,100,800}); 0 and 800 s/mm² (ADC_{0,800}); and 100 and 800 s/mm² (ADC_{100,800}) by fitting the monoexponential function

$$S = S_0 \times e^{-b \times ADC} \quad (1)$$

where S is the signal intensity after application of the diffusion gradient and S_0 is the signal intensity on the DW image acquired at $b = 0$ s/mm².

DWI measures were performed by a radiology resident, who was blinded to the order of the DWI scans (pre or post contrast). Clinical radiology reports were used to identify each malignant lesion on the DCE-MRI images. The corresponding location of each lesion was then identified on the $b=800 \text{ sec/mm}^2$ diffusion-weighted images. A region of interest (ROI) was drawn freehand on the DW image to include the largest area of hyperintensity corresponding to the lesion (Figure 2), referencing the T2-weighted images to avoid including areas of T2 shine through that may represent cyst and necrosis rather than viable tumor. For measurement of the contralateral normal breast tissue, an ROI was drawn freehand around the largest area of normal fibroglandular breast tissue while minimizing inclusion of fat pixels (Figure 3), referencing the T2-weighted images to avoid areas of tissue with high T2 signal such as cysts and fibroadenomas. If the patient did not have normal contralateral breast tissue, normal tissue was measured in the ipsilateral breast as distant from the lesion as possible. Lesion and normal breast tissue ROIs were propagated to the multiple corresponding ADC maps, and the mean of the pixel values within the ROIs were calculated from each map. The same ROIs were also propagated to the second set of DW images (Figures 2 and 3). On some scans, there was a small amount of patient motion between the two DWI sequences during the MRI examination. If needed, the ROI position was adjusted to compensate for misregistration.

For the control group, a representative slice was selected on DWI with the largest area of fibroglandular breast tissue, generally at the level of the nipple. The same ROI method as described above was used to measure normal fibroglandular breast tissue in each breast, and the ROIs were propagated to the second set of DW images.

DCE-MRI scans were prospectively interpreted by one of four fellowship-trained radiologists specializing in breast imaging, all with breast MRI experience. Lesion characteristics including size and location, morphologic type (focus, mass or non-mass enhancement), and kinetic features assessed according to the American College of Radiology (ACR) BI-RADS Breast MRI Lexicon (23), were recorded into a clinical database at the time of interpretation and later extracted for the purposes of this study. Contrast enhancement levels in breast lesions and normal tissue were further quantified offline for the study using custom software developed with MATLAB (The Mathworks, Natick, MA). In each case, ROIs were defined on DCE-MRI images at corresponding locations and size to those defined for the DWI measures and mean signal intensity was calculated at each DCE-MRI time point. Enhancement (%) at each post-contrast time point was calculated as the percent change in signal intensity from pre-contrast measures $[100 \times (\text{post} - \text{pre}) / \text{pre}]$. Delayed enhancement rate (%/min) was calculated as change in enhancement/time between the initial and late post-contrast DCE-MRI time points (approximately six minutes apart).

We hypothesized that lesion characteristics could potentially influence the vascular contributions to ADC calculations, including lesion size (larger lesions may be more highly vascularized than smaller lesions), morphologic type (masses and non-mass enhancement may exhibit differences in vascularity), and initial and late enhancement on DCE-MRI (at 114 sec and 7 min 48 sec after contrast agent injection, respectively; reflecting perfusion and contrast agent uptake/washout in the lesion). Lesions were therefore stratified based on these

characteristics for sub-analyses. Normal tissue findings were also stratified by DCE-MRI enhancement characteristics.

Statistical Analysis

Pre and post-contrast ADC measures were compared separately for lesions and normal tissue by Spearman rank-order correlation and Wilcoxon signed-rank test. Lesions were further classified based on size, type (mass vs. non-mass enhancement), and enhancement curve characteristics (initial enhancement, late enhancement, and delayed enhancement rate) on DCE-MRI, with size and enhancement cutoffs defined as the median values. Normal tissue was also further classified by enhancement curve characteristics using median values as cutoffs. Differences between groups were compared by Mann-Whitney U test. Correlations between change in ADC and delayed enhancement rate on DCE-MRI were determined by Spearman's rank-order correlation. All analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC); $p < 0.05$ was considered statistically significant.

RESULTS

The study included 19 patients, median age of 52 (range: 29 – 74) years, with 19 malignancies (15 invasive carcinomas and four DCIS lesions). On DCE-MRI, 14 lesions presented as masses and five as non-mass enhancement; the median size by longest dimension was 34 mm; the median initial enhancement was 146%. Lesion characteristics are reported in Table 1. Normal breast tissue was measured in the contralateral breast to the malignancy for 18/19 subjects and in the ipsilateral breast for one subject due to a contralateral mastectomy. Normal tissue enhancement characteristics are also given in Table 1.

Comparison of Pre and Post-contrast ADC Measures

Pre- and post-contrast $ADC_{0,100,800}$ measures demonstrated strong correlation for both lesions ($\rho=0.94$) and normal tissue ($\rho=0.98$) in patients (Figure 4). Comparison of pre and post-contrast measures are given in Table 2. Malignancies showed no significant difference in $ADC_{0,100,800}$ in post-contrast compared to pre-contrast DWI scans ($p=0.40$). However, the normal breast tissue in the same patients showed a small but statistically significant increase in $ADC_{0,100,800}$ (median change: +1.6%, $0.04 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.0006$) after contrast administration. Individual breast lesion and normal tissue ADC comparisons are illustrated using Bland-Altman plots in Figure 5. Increases in normal tissue ADC tended to be greater in subjects with lower mean tissue ADC.

Similar results were obtained for ADC calculations using two b-values, with a zero and a nonzero ($b=100 \text{ s/mm}^2$) minimum b. Malignancies showed no difference in $ADC_{0,800}$ ($p=0.54$) or $ADC_{100,800}$ ($p=0.71$) and normal tissue showed a small but statistically significant increase in $ADC_{0,800}$ (median change: +1.5%, $0.03 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.002$) and $ADC_{100,800}$ (median change: +1.8%, $0.03 \times 10^{-3} \text{ mm}^2/\text{s}$, $p=0.005$) after contrast administration, with greater changes in subjects with lower tissue ADC.

Association with DCE-MRI Characteristics

Mean DCE-MRI enhancement curves are shown for both lesions and normal tissue, Figure 6. Breast lesions exhibited much higher contrast uptake than normal tissue across all DCE-MRI time points. While breast lesions tended to increase rapidly and then wash out, there was relatively wide variability in enhancement levels and delayed enhancement behavior across individuals, with some lesions (7/19) continuing to increase in mean signal intensity by the final time point. Normal tissue demonstrated less variability across individuals and progressively enhanced over the approximately nine minute DCE-MRI sampling period in all subjects.

Stratifying lesions by size, type (mass vs. non-mass enhancement), and enhancement characteristics on DCE-MRI (with median values as cutoffs) did not affect the observed findings; Differences in ADC change between groups were not significant ($p > 0.05$), Table 3. On the other hand, post-contrast change in ADC of normal tissue showed some trends of association with DCE-MRI kinetics, with greater increases in ADC observed for tissue regions with higher late enhancement ($p = 0.09$) and greater delayed enhancement rate from initial to late DCE-MRI time points ($p = 0.09$), Table 4. Correlations between change in ADC and delayed enhancement rate for both lesions and normal tissue are shown in Figure 7. Of note, the delayed enhancement rate was highly correlated with the late enhancement level in normal tissue ($\rho = 0.85$), but not in breast lesions ($\rho = 0.25$).

Normal Non-contrast Controls

Six normal healthy volunteers who did not receive any contrast agent were evaluated as controls, ranging in age from 30 to 45 years (median, 35 years). Across the group, ADC differences between repeated DWI scans were very small, $0.1 \text{ mm}^2/\text{s}$ or less, and varied in positive and negative directions. No significant difference in ADC was found in this control group for the right, left, or bilateral repeated breast measures for any of the b-value combinations (Table 5).

DISCUSSION

DWI is increasingly being incorporated into breast MRI protocols due to its potential for improving characterization of breast lesions. However, controversy still exists regarding the effects of gadolinium-based contrast agents on DWI measures. In our study, ADC values were not significantly different after the DCE-MRI sequence in breast lesions, which is in agreement with the majority of the prior studies that found no statistically significant change in ADC values after contrast administration (7,12,14,15).

On the other hand, the normal contralateral breast tissue in our patients showed a slight but statistically significant increase in ADC values in post-contrast scans. Normal tissue comparisons in our control group of healthy volunteers (who underwent the same scan protocol but did not receive any contrast agent) showed no such change in ADC values. The reason for the post-contrast increase in normal tissue ADC is not clear. We observed that the changes in normal tissue ADC tended to be greater in subjects with lower fibroglandular tissue ADC values. The increase persisted even when ADC was calculated with a nonzero

minimum b-value of 100 s/mm² (to minimize contributions from the microvasculature), suggesting the effect is not directly related to microvasculature effects. One possible explanation for the small increase in ADC post-contrast normal breast could be related to contrast agent kinetics. Change in T2 due to contrast agent wash in or wash out over the course of the post-contrast DWI scan (with approximately 2 minutes between the b=0 s/mm² and b=800 s/mm² acquisitions) would produce an inherent change in calculated ADC. In our case, a continuing increase in normal tissue gadolinium concentration could reduce T2 and signal intensity of the b=800 s/mm² versus b=0 s/mm² and/or b=100 s/mm² images, thereby increasing ADC, as suggested in Figure 7. This could also explain why the effect was not seen in breast lesions, despite the substantially higher uptake of gadolinium, if contrast agent concentration reaches more of a plateau by this time. However, our scan protocol with limited DCE-MRI time points did not allow us to fully verify this theory. Higher DCE-MRI temporal resolution and additional T1-weighted scans after the post-contrast DWI would have been helpful to more accurately characterize the delayed enhancement kinetics of lesions versus normal tissue. Change in normal breast tissue ADC after contrast has not been previously reported, and further work is needed to better understand the ADC elevation in the normal tissue observed in these patients. Regardless, the effect of contrast agent on normal tissue may impact the utility of normalized lesion ADC values (lesion ADC divided by tissue ADC), which have been proposed for characterizing breast lesions (2).

Several factors of our study design may explain why breast lesion ADC values were not significantly affected by contrast, while the prior Yuen (9) and Janka (19) studies reported contrast-induced decreases in breast lesion ADC. These include field strength (3T versus 1.5T), contrast agent type, and repetition time (TR). Our study was performed at 3T, while the prior studies were performed at 1.5T. Differences in relaxivity between field strengths can affect the contrast-induced change in ADC for a given dosage of contrast agent. Based on their research in animal tumor models with 7T MRI, Chen et al. suggested that a higher magnetic field may reduce the contrast-induced effect on ADC due to a theoretical relative decrease in contrast-induced shortening of intrinsic T1 and T2 at higher field (15). Furthermore, relaxivity also varies with the contrast agent itself, with lower r1 and r2 reported for gadoteridol (ProHance, Bracco Diagnostics) used in our study than for either gadopentetate dimeglumine (Magnevist, Bayer Schering Pharma AG) or gadobutrol (Gadovist, Bayer Schering Pharma) used in the Yuen and Janka studies, respectively (24). Thus, the difference in contrast material relaxivities along with different field strengths may explain the variation in findings amongst the studies.

Another important difference between our study and the Yuen study in particular was related to TR. Yuen et al. used a relatively short TR (1270 msec), which may have contributed to the large post-contrast ADC changes they observed (9). Such a short TR does not allow for complete longitudinal relaxation of the breast tissue between excitations, which leads to T1 saturation effects and SNR reductions in the DWI signal, and could increase sensitivity to the T1 and T2 shortening effects of the contrast agent. In the same study, they also reported that the relative change in ADC after contrast was reduced and no longer significant using a longer TR of 3000 msec, which they attributed to increased T2* effects at longer TR (9) but may also be related to lessened T1 saturation effects.

The late timing of the post-contrast DWI acquisition, approximately 9 minutes after injection, may also explain why our study did not identify significant alterations in lesion ADC. At this timing, much of the contrast has leaked from the microvasculature to the extracellular space (and perhaps even washed out of the tumor region). Firat et al. compared ADC measures of brain lesions prior to contrast administration, immediately following contrast agent injection, and 5–10 minutes after contrast delivery (13). They reported ADC values significantly decreased (–3%) on early post-contrast DWI but then normalized and were no different from pre-contrast ADC values at the later time point 5–10 minutes after contrast delivery. However, this does not explain the difference in our results with the Yuen study, as they reported post-contrast DWI was obtained 8 minutes after injection (9), comparable to our study.

Our study had several limitations. We investigated only a single delayed post-contrast DWI time point of 9 minutes after injection; we did not assess acute influences of contrast agents on lesion ADC. We also investigated only one type of contrast agent (gadoteridol; ProHance, Bracco Diagnostics). Other agents may produce different findings. Furthermore, the number of b values was limited due to scan time restrictions and compatibility with our clinical breast DWI protocol. Exploring a greater number and/or range of b values may provide further insights as to underlying physical and physiological mechanisms of contrast agent effects on ADC measures. Gadolinium is known to reduce signal-to-noise (SNR) on EPI images (25). As a result, the diffusion-weighted images may have a lower SNR, closer to the noise floor, and result in an artificially increased (or decreased, at higher b values) ADC calculation (26). However, we could not accurately measure tissue SNR to evaluate this influence on our findings because the image-based shimming and parallel imaging techniques used in our study masked out all air signal and caused non-uniform noise across tissue regions in the images. The total number of lesions evaluated was small, and our findings require validation in a larger study. Finally, our study also excluded very small lesions and benign lesions, which both warrant further investigation.

In conclusion, we found that ADC measures using our approach were not significantly changed after contrast administration for malignant breast lesions at 3T. Acquisition considerations to minimize contrast effects on breast ADC measures include use of higher field strength (3T), late post-contrast DWI timing (>9 minutes after injection), adequate TR (> 4secs), adequate SNR (2 or more averages), and short total DWI scan (time between low and high b value acquisitions). Our findings support the possibility that DWI optimized based on these factors may be obtained before or after DCE-MRI without compromising important clinical information.

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Figure 1.

Diagram summarizing the breast MRI protocol used in the study. After the localizer sequence and preparatory calibrations, a pre-contrast T1-weighted non-fat suppressed sequence (scan time 1 min 42 sec), T2-weighted fast spin echo sequence (scan time 5 min 15 sec), and the pre-contrast diffusion-weighted imaging sequence (scan time 3 min 28 sec) were obtained. Next, DCE-MRI was performed and consisted of four sequential sequences, each with scan time of 2 min 57 sec (center of k-space obtained at 114 sec). Gadolinium contrast agent (0.1mmol/kg body-weight gadoteridol, with 20mL saline flush) was injected into the patient after the first DCE-MRI sequence. Finally, the post-contrast diffusion-weighted imaging sequence was acquired (scan time 3 min 28 sec), at approximately 9 minutes after the contrast injection.

Figure 2.

A 52-year-old female with biopsy-proven invasive lobular carcinoma in the right breast. (a) DCE-MRI of the right breast at 114 seconds post-contrast injection (initial time point) demonstrates an enhancing 34 mm malignant mass, with initial enhancement of 167%. (b) DCE-MRI of the right breast at 7 min 48 sec post-contrast injection (late time point) redemonstrates the mass, with late enhancement of 138%. The calculated delayed enhancement rate for the lesion is $-4.9\%/min$. (c) Pre-contrast diffusion weighted image ($b=800$ s/mm²) of the right breast demonstrates high signal intensity in the region of known

malignancy. An ROI is drawn containing the lesion. (d) Pre-contrast $ADC_{0,800}$ map of the right breast shows low ADC values in the region of the known malignancy, with mean $ADC_{0,800} = 0.89 \times 10^{-3} \text{ mm}^2/\text{s}$ calculated for pixels in the ROI. (e) Post-contrast DWI ($b=800 \text{ s/mm}^2$) of the right breast demonstrates the same ROI as seen in (c) propagated onto the high signal intensity of the known malignancy. (f) Post-contrast $ADC_{0,800}$ map of right breast shows low ADC values in region of the known malignancy, with mean $ADC_{0,800} = 0.94 \times 10^{-3} \text{ mm}^2/\text{s}$ calculated for pixels in the ROI.

Figure 3.

The contralateral normal left breast in the 52-year-old woman shown in Figure 2.

(a) DCE-MRI of the left breast at 114 seconds post-contrast injection (initial time point) demonstrates normal fibroglandular breast tissue, initial enhancement of 15%. (b) DCE-MRI of the left breast at 7 min 48 sec post-contrast injection (late time point) redemonstrates the normal fibroglandular breast tissue, with late enhancement of 24%. The calculated delayed enhancement rate for the normal breast tissue is +1.5%/min. (c) Pre-contrast diffusion weighted image ($b=800 \text{ s/mm}^2$) of contralateral left breast demonstrates normal

fibroglandular breast tissue. An ROI is drawn within the confines of the normal breast tissue. (d) Pre-contrast $ADC_{0,800}$ map of left breast, with mean $ADC_{0,800} = 2.21 \times 10^{-3} \text{ mm}^2/\text{s}$ calculated for pixels in the ROI. (e) Post-contrast DWI ($b=800 \text{ s/mm}^2$) of left breast demonstrates the same ROI as seen in (c) propagated onto the normal breast tissue. (f) Post-contrast $ADC_{0,800}$ map of left breast, with mean $ADC_{0,800} = 2.25 \times 10^{-3} \text{ mm}^2/\text{s}$ calculated for pixels in the ROI.

Figure 4. Scatterplots comparing ADC measures at $b=0, 100, 800 \text{ s/mm}^2$ before and after contrast agent administration in (a) breast lesions and (b) normal breast tissue in patients showed highly significant correlations ($p < 0.0001$ for both).

Figure 5. Bland-Altman plots illustrate individual breast lesion and normal tissue ADC comparisons. Plotted are the differences versus the mean of pre and post-contrast ADC values for each subject, (units = $\times 10^{-3}$ mm²/s, mean difference = solid red line, 95% confidence interval = dotted red line). For ADC calculated with $b=0, 100, 800$ s/mm²: (a) no significant difference was observed in lesion ADC comparing pre to post-contrast DWI scans (mean difference, +0.02 mm²/s, $p=0.40$, Wilcoxon signed-rank test), while (b) a slight but significant increase in ADC (mean difference, +0.09 mm²/s, $p=0.006$) was observed in normal breast tissue. The

increase in ADC tended to be greater in patients with lower fibroglandular breast tissue ADC values. Results were similar for ADC calculated with $b=0, 800 \text{ s/mm}^2$ in both (c) lesions (mean difference, $+0.02 \text{ mm}^2/\text{s}$, $p=0.54$) and (d) normal tissue (mean difference, $+0.08 \text{ mm}^2/\text{s}$, $p=0.002$); and with ADC calculated at $b=100,800 \text{ s/mm}^2$ in both (e) lesions (mean difference, $0.00 \text{ mm}^2/\text{s}$, $p=0.71$) and (f) normal tissue (mean difference, $+0.06 \text{ mm}^2/\text{s}$, $p=0.005$).

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Figure 6. DCE-MRI signal enhancement curves for breast lesions and contralateral normal fibroglandular tissue in 19 patients. Plotted are mean percent changes in signal intensity from precontrast values at each of three post-contrast acquisition timings (with k-space centered approximately 2, 5, and 8 minutes after contrast injection), error bars represent standard deviation across patients. Breast lesions enhanced much more rapidly than normal tissue, with most exhibiting contrast washout after the first two minutes (mean delayed enhancement rate = -1.8 ± 3.3 %/min). Normal tissue uniformly exhibited progressive enhancement across all subjects (mean delayed enhancement rate = $+2.2 \pm 1.4$ %/min).

Figure 7. Association between post-contrast change in $\text{ADC}_{0,100,800}$ and DCE-MRI delayed enhancement rate (%/min) in (a) breast lesions and (b) normal fibroglandular tissue. There was no significant correlation in lesions ($p=0.3$). In normal tissue, greater progressive DCE-MRI enhancement was weakly associated with greater increases in post-contrast ADC ($p=0.05$).

Table 1

Lesion and Normal Tissue Characteristics (N = 19 Malignancies)

Characteristic	N (%) or Median (Range)
Histology	
Invasive ductal carcinoma	13 (68%)
Grade 1	1
Grade 2	4
Grade 3	8
Invasive lobular carcinoma *	2 (11%)
Grade 1	0
Grade 2	1
Grade 3	1
Ductal carcinoma in situ *	4 (21%)
Low/Intermediate Grade	0
High Grade	4
Morphologic Type	
Mass	14 (74%)
Non-Mass Enhancement	5 (26%)
Size (mm)	34 (15 – 106)
Lesion DCE-MRI Kinetics	
Initial Enhancement (%)	146 (44 – 185)
Late Enhancement (%)	134 (74 – 179)
Delayed Enhancement Rate (%/min)	–3.6 (–5.6 – 5.1)
Normal Tissue DCE-MRI Kinetics	
Initial Enhancement (%)	21 (12 – 55)
Late Enhancement (%)	34 (12 – 88)
Delayed Enhancement Rate (%/min)	1.8 (0.1 – 5.4)

* Grade reported as Nottingham grade (1, 2 or 3) for invasive cancers and nuclear grade (low, intermediate, or high) for ductal carcinoma in situ lesions.

Table 2

Comparison of pre- and post-contrast breast ADC measures.

Tissue Type	n	Pre-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	Post-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	ADC Difference Post-Pre Median (range) [$\times 10^{-3}$ mm ² /s] (%)	p-value*
b=0,100,800 s/mm²					
Lesion	19	1.10 (0.52 – 1.82)	1.10 (0.63 – 1.78)	–0.01 (–0.11 – 0.26) (–0.4%)	0.40
Normal Tissue	19	1.73 (0.74 – 2.29)	1.84 (1.02 – 2.33)	0.04 (–0.05 – 0.29) (1.6%)	0.0006
b=0,800 s/mm²					
Lesion	19	1.14 (0.50 – 1.87)	1.09 (0.63 – 1.84)	–0.01 (–0.10 – 0.26) (–0.4%)	0.54
Normal Tissue	19	1.86 (0.88 – 2.31)	1.92 (1.07 – 2.34)	0.03 (–0.10 – 0.26) (1.5%)	0.002
b=100,800 s/mm²					
Lesion	19	0.92 (0.53 – 1.51)	0.87 (0.55 – 1.48)	0.01 (–0.10 – 0.07) (0.9%)	0.71
Normal Tissue	19	1.57 (0.65 – 1.98)	1.60 (0.83 – 2.02)	0.03 (–0.04 – 0.20) (1.8%)	0.005

* Wilcoxon signed-rank test p-value comparing pre and post ADC measures

Abbreviations: ADC = apparent diffusion coefficient

Table 3

Comparison of pre and post-contrast lesion ADC measures at b=0,100,800 s/mm² stratified by lesion size, type, and DCE-MRI enhancement characteristics.

Lesion Characteristic	n	Pre-Contrast ADC Median (range) [×10 ⁻³ mm ² /s]	Post-Contrast ADC Median (range) [×10 ⁻³ mm ² /s]	ADC Difference Post-Pre Median (range) [×10 ⁻³ mm ² /s] (%)	p-value*
Size					
34 mm	10	0.96 (0.73 – 1.82)	1.05 (0.77 – 1.78)	0.07 (–0.11 – 0.17) (4.2%)	0.60
> 34mm	9	1.12 (0.52 – 1.57)	1.10 (0.63 – 1.75)	–0.01 (–0.11 – 0.26) (–1.2%)	
Type					
Mass	14	0.96 (0.52 – 1.67)	1.02 (0.63 – 1.61)	–0.01 (–0.11 – 0.17) (–0.9%)	0.38
Non-Mass Enhancement	5	1.50 (0.91 – 1.82)	1.70 (0.98 – 1.78)	0.06 (–0.04 – 0.26) (3.9%)	
Initial Enhancement					
146%	10	1.04 (0.52 – 1.82)	1.05 (0.63 – 1.78)	0.02 (–0.11 – 0.26) (1.8%)	0.78
> 146%	9	1.11 (0.86 – 1.67)	1.10 (0.90 – 1.61)	–0.02 (–0.11 – 0.17) (–1.2%)	
Late Enhancement					
134%	10	0.96 (0.52 – 1.64)	0.98 (0.63 – 1.75)	0.04 (–0.11 – 0.26) (4.1%)	0.39
> 134%	9	1.11 (0.86 – 1.82)	1.13 (0.90 – 1.78)	–0.02 (–0.11 – 0.17) (–1.2%)	
Delayed Enhancement Rate					
–3.6 %/min	9	0.95 (0.52 – 1.57)	0.99 (0.63 – 1.47)	–0.01 (–0.11 – 0.11) (–0.4%)	0.78

Lesion Characteristic	n	Pre-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	Post-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	ADC Difference Post-Pre Median (range) [$\times 10^{-3}$ mm ² /s] (%)	p-value*
> -3.6 %/min	10	1.18 (0.73 – 1.82)	1.18 (0.77 – 1.78)	0.02 (-0.11 – 0.26) (1.7%)	

* Mann-Whitney U test p-value comparing differences in ADC change between groups.
Abbreviations: ADC = apparent diffusion coefficient

Table 4

Comparison of pre and post-contrast normal tissue ADC measures at b=0,100,800 s/mm² stratified by DCE-MRI enhancement characteristics.

Normal Tissue Characteristic	n	Pre-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	Post-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	ADC Difference Post-Pre Median (range) [$\times 10^{-3}$ mm ² /s] (%)	p-value*
Initial Enhancement					
21%	10	1.94 (1.03 – 2.29)	1.96 (1.23 – 2.33)	0.04 (–0.05 – 0.21) (1.5%)	0.39
> 21%	9	1.66 (0.74 – 2.16)	1.84 (1.02 – 2.18)	0.11 (–0.01 – 0.29) (5.9%)	
Late Enhancement					
34%	10	2.05 (1.18 – 2.29)	2.07 (1.29 – 2.33)	0.03 (–0.05 – 0.15) (1.2%)	0.09
> 34%	9	1.56 (0.74 – 2.16)	1.66 (1.02 – 2.18)	0.19 (–0.01 – 0.29) (15.3%)	
Delayed Enhancement Rate					
1.8%/min	10	1.96 (1.18 – 2.29)	1.96 (1.29 – 2.33)	0.03 (–0.05 – 0.28) (1.2%)	0.09
> 1.8%/min	9	1.50 (0.74 – 2.16)	1.66 (1.02 – 2.19)	0.15 (0 – 0.29) (10.3%)	

* Mann-Whitney U test p-value comparing differences in ADC change between groups.

Abbreviations: ADC = apparent diffusion coefficient

Table 5

Comparison of pre- and post-contrast ADC measures for normal healthy volunteers.

Side	n	Pre-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	Post-Contrast ADC Median (range) [$\times 10^{-3}$ mm ² /s]	ADC Difference Median (range) [$\times 10^{-3}$ mm ² /s] (%)	p-value*
b=0, 100, 800 s/mm²					
Right	6	2.06 (1.31 – 2.26)	2.03 (1.28 – 2.28)	-0.01 (-0.03 – 0.06) (-0.7%)	0.69
Left	6	2.06 (1.55 – 2.34)	2.04 (1.44 – 2.41)	0.00 (-0.10 – 0.10) (0.2%)	1.0
Bilateral	6	2.06 (1.43 – 2.29)	2.04 (1.36 – 2.34)	-0.01 (-0.10 – 0.06) (-0.4%)	0.84
b=0, 800 s/mm²					
Right	6	2.08 (1.35 – 2.29)	2.02 (1.30 – 2.28)	-0.01 (-0.10 – 0.08) (-0.6%)	0.56
Left	6	2.12 (1.53 – 2.39)	2.08 (1.48 – 2.42)	0.00 (-0.10 – 0.06) (-0.1%)	1.0
Bilateral	6	2.11 (1.44 – 2.34)	2.05 (1.39 – 2.35)	-0.01 (-0.10 – 0.07) (-0.3%)	0.84
b=100, 800 s/mm²					
Right	6	2.02 (1.25 – 2.23)	2.00 (1.20 – 2.26)	-0.02 (-0.10 – 0.05) (-0.8%)	0.69
Left	6	2.02 (1.54 – 2.33)	2.01 (1.41 – 2.42)	0.00 (-0.10 – 0.09) (0.0%)	0.84
Bilateral	6	2.02 (1.40 – 2.28)	2.00 (1.30 – 2.34)	-0.01 (-0.10 – 0.06) (-0.4%)	0.84

* Wilcoxon signed-rank test p-value comparing pre and post ADC measures

Abbreviations: ADC = apparent diffusion coefficient.