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Visibility of Mammographically Occult Breast Cancer on Diffusion-Weighted MRI versus Ultrasound

N Amornsiripanitch, MD¹, H Rahbar, MD², AE Kitsch, BS², DL Lam, MD², B Weitzel, MD², and SC Partridge, PhD²

¹Breast Imaging, University of Massachusetts Memorial Medical Center, Seattle, WA

²Department of Radiology, University of Washington, Seattle, WA

Abstract

Purpose—To investigate the visibility of mammographically occult breast cancers on diffusion-weighted MRI (DWI) versus ultrasound.

Materials and Methods—Mammographically occult breast cancers (n=60) initially detected on contrast-enhanced MRI that underwent pre-biopsy targeted ultrasound were retrospectively evaluated for visibility on DWI and ultrasound..

Results—More cancers were visible on DWI than ultrasound (78% vs. 63%; p=0.049), with 32 (53%) visible on both and 7 (12%) not visible on either. Visibility differences were more significant in larger lesions (92% vs. 68%, p=0.006).

Conclusion—DWI may detect more mammographically occult cancers than ultrasound, warranting further investigation as an alternative supplemental screening technique.

Keywords

breast cancer; supplemental screening; diffusion-weighted MRI (DWI); ultrasound; dynamic contrast-enhanced MRI (DCE-MRI)

1. Introduction

Since the 1970's, multiple randomized controlled trials have demonstrated that screening mammography reduces breast cancer-related mortality (1–9). However, additional scientific research has demonstrated that mammography alone performs inadequately for some patient populations, particularly those at an elevated lifetime risk of breast cancer and women with dense breasts. High-risk women—defined as those with an estimated lifetime breast cancer risk > 20%—are recommended by the American Cancer Society to receive screening dynamic contrast-enhanced MRI (DCE-MRI) in addition to annual mammography (10).

Corresponding Author: Savannah C. Partridge, PhD, 825 Eastlake Ave E, G3-200, Seattle, WA 98109, Tel: (206) 606-1306, Fax: (206) 606-6556, scp3@uw.edu.

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Unfortunately, this criteria represents a relatively small fraction of women who will be diagnosed with a mammographically occult breast cancer. It thus remains unclear whether contrast-enhanced MRI approaches are appropriate as a supplemental screening test for women who are of intermediate risk, such as those with 15–20% lifetime risk, previous history of breast malignancy, high-risk lesions, or dense breasts, all of whom are also at increased risk of developing a mammographically occult breast cancer (11).

Many screening methods have been proposed for intermediate risk women, including DCE-MRI and screening whole breast ultrasound. Despite DCE-MRI's high sensitivity (12–17), the associated high cost, while justifiable for women at highest risk, may be less so for women at lower risk. Abbreviated MRI protocols may be a solution to reducing scan time and cost, but are still associated with potential risks of repeated use of intravenous contrast. On the other hand, whole breast ultrasound is relatively low in cost, widely accessible, and has been shown to increase diagnostic yield of cancer in high-risk population when combined with mammography (18). However, results from the American College of Radiology Imaging Network (ACRIN) 6666 trial and subsequent single center trials suggest low specificity of supplemental handheld whole breast ultrasound for women with dense breasts with and without elevated risk (18–23). The expected high false positive biopsy rate from the addition of screening ultrasound to mammography, as suggested by Sprague *et al*, may render the method cost-ineffective (24).

Diffusion-weighted imaging (DWI) is a rapid MRI technique that does not require administration of a contrast agent. DWI measures movement of water molecules within imaged tissue, reflecting the cellular microenvironment. Early studies supported the hypothesis that breast tumors have restricted diffusion compared to surrounding tissue, presumably due to high cellularity (25,26). Subsequently, multiple studies demonstrated DWI's ability to differentiate breast malignancy from benign lesions, as summarized by two meta-analyses demonstrating pooled sensitivities/specificities of 84%/79% and 86%/76% respectively (27,28). Perhaps most importantly, DWI has also been shown to identify mammographically occult disease (29–32). However, while there have been a number of studies comparing the sensitivities of DWI versus DCE-MRI, there are few data comparing DWI and ultrasound for breast cancer detection. The goal of this study was to explore the role of DWI as a possible supplemental screening modality to mammography by specifically investigating the relative visibility of mammographically occult cancers on DWI versus ultrasound.

2. Materials and Methods

This study was approved by our Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act. Informed consent was prospectively obtained for this study.

2.1. Subjects and Lesions

From October 2010 through December 2013, women with American College of Radiology Breast Imaging-Reporting and Data System (BI-RADS) category 4 or 5 breast lesions detected on DCE-MRI at our institution were prospectively enrolled prior to biopsy in a

large trial to investigate the diagnostic value of lesion DWI measures. All patients underwent clinical 3T breast MRI at our institution, which included both DCE-MRI and DWI sequences. Patient clinical factors (age, clinical indication, menopausal status, breast density) were collected at time of enrollment. For this secondary retrospective analysis, the study only included lesions with malignant pathology outcome (DCIS or invasive carcinoma) determined by results of MRI-guided or ultrasound-guided needle biopsy, performed based on recommendation of the DCE-MRI interpretation, or subsequent final surgical pathology. In cases where pathology of the core needle biopsy specimen and final surgical specimen differed, the worst pathology result was used for analysis. To restrict the analysis to mammographically occult cancers, prior mammogram reports were reviewed and mammographically visible lesions were excluded, as well as those patients without a prior mammogram within 12 months of DCE-MRI. This study included only lesions that underwent pre-biopsy targeted ultrasound. Lastly, one patient was excluded from our study due to a technical failure resulting in inadequate DWI signal to noise ratio for interpretation.

2.2. MRI Acquisition

All breast MR examinations were performed on a Philips Achieva Tx 3T scanner using a dedicated bilateral 16-channel breast coil (MammoTrak, Philips Healthcare). The MRI sequences were acquired in the axial orientation and included T2-weighted fast spin echo, T1-weighted non-fat-suppressed, T1-weighted fat-suppressed DCE-MRI, and DWI.

DCE-MRI included one pre- and three post-contrast T1-weighted fat suppressed three-dimensional fast gradient echo (eTHRIVE) sequences, acquired with parallel imaging technique (SENSitivity Encoding; SENSE). The following imaging parameters were utilized: 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/s followed by a 20 mL saline flush. DCE-MRI acquisition time was 2 minutes 57 seconds per sequence, with center k-space acquired at 2 minutes; total post-contrast scan time was 8 minutes 51 seconds.

DWI was performed immediately following the DCE-MRI acquisition (typically 9 minutes post-contrast injection), and was acquired using a diffusion-weighted echo-planar imaging sequence with parallel imaging and fat suppression (Spectral Attenuated Inversion Recovery; SPAIR). The following imaging parameters were utilized: 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. Total DWI acquisition time was 3 minutes 28 seconds.

2.3. Image Analysis

Each DCE-MRI scan was prospectively interpreted by a fellowship-trained radiologist specialized in breast imaging. Lesion characteristics including lesion type (mass, non-mass enhancement, focus), size, location, and BI-RADS assessment were recorded at the time of interpretation.

Lesion visibility on DWI was scored visually on a scale of 1–5 by three independent readers based on signal strength and focality of the signal, as described in prior studies (32,33) and detailed in Table 1. Examples are shown in Figure 1. At the time of scoring, the first reader was a fellowship trained breast imager with 3 years of experience (D.L.), the second reader was radiology board eligible and a current fellow in breast imaging (N.A.), and the third reader was a researcher with 2 years of experience in breast DCE-MRI and DWI analysis (A.K). Readers were not blinded to DCE-MRI in order to ensure that the correct pathologically proven malignant BIRADS 4 and 5 lesions were evaluated on DWI. DWI visibility was defined as a mean score of ≥ 2.5 . Ultrasound visibility was retrospectively determined from imaging reports.

DWI was quantitatively analyzed using custom in-house software to calculate apparent diffusion coefficient (ADC maps) and perform lesion measurements, as previously described (34,35). Lesion locations were identified from clinical radiology reports and DCE-MR images. Regions of interest (ROIs) were defined on the $b = 800 \text{ s/mm}^2$ diffusion-weighted images for the lesion and normal non-adipose fibroglandular breast tissue in the contralateral breast, referencing T2-weighted images in order to avoid including areas of T2 shine-through that may represent cyst and necrosis rather than viable tumor or tissue. The mean ADC pixel value (ADCmean) was calculated for each lesion ROI. Additionally, the contrast-to-noise ratio (CNR) of lesion-to-normal tissue signal intensity on DWI ($b = 800 \text{ s/mm}^2$) was calculated as previously described (36):

$$\text{CNR} = (\mu_{\text{lesion}} - \mu_{\text{tissue}}) / \sqrt{(\sigma_{\text{lesion}}^2 + \sigma_{\text{tissue}}^2)}$$

where μ_{lesion} and μ_{tissue} are the mean DWI signal intensities for lesion and normal tissue ROIs, respectively, and σ_{lesion} and σ_{tissue} are the corresponding ROI standard deviations. A $\text{CNR} > 0$ indicates higher signal intensity in a lesion compared to normal tissue.

2.4. Statistical Analysis

Inter-reader agreement for scoring DWI visibility (scale 1–5) was evaluated by weighted Cohen's kappa (37) between each pair of readers, where a kappa coefficient κ of 0 represents no agreement and 1 perfect agreement. DWI and ultrasound lesion visibility were compared using McNemar's test (equal to Bowker's test of symmetry). Exploratory subanalyses comparing DWI and ultrasound lesion visibility within subgroups, including: age (<50 years old, ≥ 50 years old), mammographic breast density ('not dense'-BI-RADS breast composition A or B, 'dense' – BI-RADS C or D), clinical indication (evaluation for extent of disease, high-risk screening), lesion size (<1 cm, ≥ 1 cm), morphology (mass, non-mass enhancement, focus), and histology (invasive, DCIS) were also performed using McNemar's test. Comparison of CNR and ADCmean between DWI visible versus not visible lesions was performed with Wilcoxon Rank Sum Test. All analyses were performed using SAS statistical software, version 9.3 (SAS Institute, Cary, NC) with a p value <0.05 considered statistically significant.

3. Results

During the study period, 222 women with BI-RADS 4 or 5 lesions detected on DCE MRI in clinical 3T breast MRI examinations (that also included a DWI sequence) were enrolled in the study. Pathologic diagnosis was obtained by subsequent MRI-guided or ultrasound-guided biopsy or excision for 250 lesions in 202 women, of which 104 (42%) lesions were found to be malignant. Eighteen lesions that were visible on concurrent mammography or did not have mammograms available to determine mammographic visibility were excluded. Of the remaining 86 mammographically occult cancers detected by DCE-MRI, 60 lesions (53 invasive; 7 ductal carcinoma in situ [DCIS]) in 52 women (median age 53 years, range 23–75 years) were imaged by ultrasound prior to biopsy and were evaluated for this study. Patient and lesion characteristics are summarized in Table 2. Patients were predominantly postmenopausal (62%) with dense breasts (63%), who underwent breast MRI for evaluation of extent of disease (72%). Lesions ranged in size from 4 to 102 mm (median, 12 mm) and included 39 masses, 20 non-masses, and 1 focus.

3.1. Multi-reader lesion DWI visibility assessments

Inter-reader comparisons of DWI visibility scores (1 to 5) showed moderate agreement between the 3 readers, with kappa values ranging from 0.57 to 0.64 between reader pairs. Of the 60 mammographically occult lesions detected by DCE-MRI, the number assessed as DWI visible (score ≥ 2.5) by each reader were 50 (83%), 35 (58%), and 44 (73%). Further, 31 (52%) lesions were scored as visible on DWI by all three readers, 13 (22%) by 2 readers, 10 (16%) by one reader, and 6 (10%) by none.

3.2. Relative lesion visibility: DWI versus ultrasound

Overall, 47/60 (78%) DCE-MRI detected lesions were visible on DWI after averaging reader DWI assessments, and 38/60 (63%) were visible on ultrasound. By direct comparison, 32 (53%) lesions were visible by both modalities, 15 (25%) by DWI only, 6 (10%) by ultrasound only, and 7 (12%) by neither (Table 3). Nine more malignancies were visible by DWI (9/60, 15%) than ultrasound ($p=0.049$). Examples of lesions with varying DWI and US visibility are illustrated in Figures 2 to 4.

Analysis by subgroups demonstrated that larger malignancies (≥ 1 cm), which included a higher proportion of non-mass enhancements (51% vs. 8%), were more likely seen on DWI than by ultrasound (91% vs. 69%, $p=0.006$). In the subset of women undergoing MRI for clinical indication to evaluate extent of disease, incidental cancers were more likely to be seen on DWI than US (84% vs. 64%, $p=0.018$). Cancers in younger women (<50 years) were also more likely seen on DWI than ultrasound, although the difference did not reach statistical significance (74% vs. 56%, $p=0.058$). There were no significant associations identified between DWI visibility and other factors of menopausal status, breast density, lesion type, or pathology (Table 3).

3.3. Quantitative lesion DWI characteristics

ADCmean and CNR were compared for DWI visible versus not-visible lesions, Figure 5. CNR could not be calculated for two DWI visible lesions due to lack of sufficient areas of

normal reference tissue. DWI visibility was not associated with lesion ADC, with similar ADCmean for DWI visible and not visible lesions (median, 1.30; range 0.90 – 2.22 versus 1.24; range 0.69 – 2.00, $p=0.524$). DWI visible lesions exhibited higher CNR than that of not visible lesions (median, 2.8; range –2.7 – 7.8 versus 1.4; range –1.8 – 4.7), although the difference did not reach statistical significance ($p = 0.078$).

4. Discussion

While mammography remains the only screening modality proven in randomized controlled trials to reduce mortality, its breast cancer detection performance is lower for women at above average lifetime risk and/or with dense breasts. As a result, there is a need to identify practical supplemental screening tests that can improve breast cancer detection for these important subpopulations. In this era of increasing breast density legislation, many centers in the U.S. have begun to use screening ultrasound as a supplemental screening tool even though the evidence for such an approach is relatively limited (38). Accordingly, we sought to explore the DWI visibility of mammographically occult breast cancers identified on DCE-MRI, which has been established as the gold-standard supplemental screening examination. In this retrospective study of 60 mammographically occult breast malignancies identified on DCE-MRI, we found that nearly four in five breast cancers were visible on DWI, and that DWI detection performance has the potential to exceed that of ultrasound.

Multiple prospective trials have demonstrated that DCE-MRI is an effective supplemental screening tool for the detection of breast cancer in high-risk women, proven to detect on average an additional 31 cancers per 1000 women screened (39). However, high cost and lengthy exam time contributes to limited DCE-MRI utilization, even among women who meet criteria for high-risk screening (40,41). To decrease scan time, abbreviated MRI protocols have been explored with promising preliminary results (42,43). However, both DCE and abbreviated MRI protocols are dependent on the use of intravenous gadolinium, which accounts for additional cost and time associated with obtaining intravenous access and the gadolinium agent itself. Furthermore, gadolinium is contraindicated in patients with renal impairment, gadolinium allergy, and women who are pregnant. Finally, recent reports of intracranial gadolinium deposition (44,45), though of unclear clinical significance, have also heightened concerns regarding long-term consequences of repeated use of DCE-MRI in an asymptomatic population.

DWI is a short scan that does not require a contrast agent, which may render the modality more comparable in cost and exam length to handheld whole breast ultrasound. However, despite promising data comparing DWI sensitivity and specificity to that of DCE-MRI (27,28), little is known of DWI's performance as a stand-alone screening tool compared to that of ultrasound.

Our study suggests that DWI may detect more mammographically occult malignancies than ultrasound. These findings may be partially explained by the fact that ultrasound has limited sensitivity in detecting non-mass enhancement (46,47). Indeed, our data also showed that DWI was superior to ultrasound in detecting larger lesions, which were more likely to be non-mass enhancement in our studied population. However, likely due to small sample size,

there was no statistical significance in subanalysis comparing DWI and ultrasound in detection of non-mass enhancement. Of note, suspicious findings detected on DWI that are not visible on ultrasound will necessitate an MRI-guided biopsy, which is costlier than an ultrasound-guided biopsy. However, this proposed workflow does not differ from that of current clinical routine practice where suspicious findings detected on DCE-MRI that are not visible on MRI-directed targeted ultrasound must undergo MRI-guided biopsy.

Limitations of our study include small sample size, which is in part due to exclusions of malignant lesions that were not evaluated under targeted ultrasound (30/90, 33%). To facilitate timely diagnosis and for patients' convenience, it is routine at our institution to bypass pre-biopsy targeted ultrasound and directly recommend MRI-guided biopsy for lesions that are likely to be difficult to visualize under ultrasound. Although no strict criteria exist, and decisions vary on a case-by-case basis, these lesions often include small lesions and non-mass enhancement. Inclusion of these lesions may further strengthen the relative performance of DWI. Moderate agreement between readers as to lesion DWI visibility suggests need for further improvements in interpretation algorithms and/or reader training, which may further increase cancer detectability on DWI. Our readers were also not blinded to DCE-MRI images for DWI or targeted ultrasound interpretations. Future studies where DWI and screening whole breast ultrasound examinations are independently assessed by readers blinded to DCE-MRI are needed to better ascertain their relative performance for supplemental screening. Lastly, our study excluded benign and negative cases, preventing direct comparison of ultrasound versus DWI specificity. Evaluation of specificity is of interest because a major concern of whole breast ultrasound screening is its low specificity, and, therefore, high false positive biopsy rate (18–24,48). However, DWI specificity was reported by a prior blinded reader study as 91% (32), which is higher than that reported for whole breast screening ultrasound (84%) (18).

In conclusion, our study suggests that DWI may detect more mammographically occult breast cancers than ultrasound, supporting the potential role of DWI as a safer and more cost-effective supplemental screening tool as an alternate to DCE-MRI that warrants further investigation.

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Highlights

- Many mammographically occult breast cancers are visible on non-contrast DWI.
- As a supplemental screening technique to mammography, DWI may detect more additional breast cancers than ultrasound.
- DWI may better detect larger cancers and those in younger women versus ultrasound.
- DWI continues to show promise as an effective supplemental breast screening tool.

Figure 1.
Examples of lesions with DWI visibility scores of 1 to 5.

Figure 2.

Lesion visible on both DWI and ultrasound, identified in a 44 year-old female who underwent bilateral breast MRI for evaluation of extent of disease for a grade 2 invasive ductal carcinoma in the left breast (not shown). a) DCE-MRI detected an additional irregular mass (arrow) with spiculated margins in the left breast at 8 o'clock, anterior depth, 36 mm from the nipple measuring $13 \times 9 \times 10$ mm (AP $\times$ ML $\times$ SI). b) On DWI, lesion visibility was scored 5/5 by all readers (mean score = 5). CNR measured 2.8. c) ADC measured 0.84×10^{-3} mm²/s. d) Subsequent targeted ultrasound demonstrated a solid mass measuring 7×7 mm at 8 o'clock, 3 cm from the nipple. Ultrasound guided biopsy revealed invasive ductal carcinoma (grade 2).

Figure 3.

Lesion not visible on DWI or ultrasound, identified in a 55 year-old female who underwent bilateral breast MRI for high-risk screening. a) DCE-MRI detected a lobulated mass (arrow) with smooth margins in the right breast at 8 o'clock, posterior depth, 10 cm from the nipple measuring $6 \times 4 \times 3$ mm (AP $\times$ ML $\times$ SI). b) On DWI, lesion visibility was scored 2/5 by reader 1, 1/5 by reader 2, and 1/5 by reader 3 (mean score = 1.33). CNR measured -0.7 . c) ADC measured 1.30×10^{-3} mm²/s. d) Subsequent targeted ultrasound demonstrated no correlate. MRI guided biopsy revealed invasive lobular carcinoma (grade 2).

Figure 4.

Lesion visible on DWI but not visible on ultrasound, identified in a 75 year-old female who underwent bilateral breast MRI for high-risk screening. a) DCE-MRI detected an oval mass (arrow) with irregular margins in the left breast at 9 o'clock, middle depth, 47 mm from the nipple measuring $7 \times 6 \times 11$ mm (AP $\times$ ML $\times$ SI). b) On DWI, lesion visibility was scored 4/5 by reader 1, 5/5 by reader 2, and 5/5 by reader 3 (mean score = 4.67). CNR measured 2.8. c) ADC measured 0.83×10^{-3} mm²/s. d) Subsequent targeted ultrasound demonstrated no correlate. MRI guided biopsy revealed invasive ductal carcinoma (grade 1).

Figure 5.

Comparison of ADCmean and CNR between cancers that were and were not visible on DWI. a) There was no difference in ADCmean between DWI visible lesions (median, $1.30 \times 10^{-3} \text{ mm}^2/\text{s}$) and not visible lesions (median, $1.24 \times 10^{-3} \text{ mm}^2/\text{s}$), $p = 0.524$. b) CNR of DWI visible lesions tended to be higher than that of not visible lesions (median, 2.8 versus 1.0; $p = 0.078$).

Table 1**DWI Visibility Score and Definition**

Score	Definition
1	Isointense to normal fibroglandular tissue
2	Non-localized with mild-to-moderate signal intensity and an indistinct margin
3	Localized with mild-to-moderate signal intensity
4	Non-localized with strong signal intensity and an indistinct margin
5	Localized with strong signal intensity

Table 2

Patient and Lesion Characteristics

	Median (Range) or Number (%)
Patient Characteristics (n = 52):	
Age (years)	54 (23–75)
Menopausal Status	
Premenopausal	20 (38)
Postmenopausal	32 (62)
Breast density on mammography	
Almost entirely fatty	3 (6)
Scattered fibroglandular density	17 (33)
Heterogeneously dense	27 (52)
Extremely dense	5 (10)
Clinical Indication	
Evaluate Extent of Disease	42 (81)
High Risk Screening	10 (19)
Lesion Characteristics (n = 60):	
Size (mm)	12 (4 – 102)
Type	
Mass	39 (65)
Non-mass enhancement	20 (33)
Focus	1 (2)
Pathology	
DCIS	7 (12)
Invasive carcinoma	53 (88)

Table 3

Visibility of mammographically occult malignancies on DWI versus targeted ultrasound.

	n	Lesion Visibility			Visibility Rate			P *
		Both	DWI only	US only	Neither	DWI	US	
All Lesions	60	32	15	6	7	78%	63%	0.049
Patient Age								
Age < 50	27	14	6	1	6	74%	56%	0.058
Age ≥ 50	33	18	9	5	1	82%	70%	0.285
Menopausal Status								
Premenopausal	23	10	5	2	6	65%	52%	0.256
Postmenopausal	37	22	10	4	1	86%	70%	0.108
Breast Density								
Not Dense	22	14	5	2	1	86%	73%	0.256
Dense	38	18	10	4	6	74%	58%	0.108
Clinical Indication								
Evaluate Extent of Disease	50	28	14	4	4	84%	64%	0.018
High Risk Screening	10	4	1	2	3	50%	60%	0.564
Lesion Type								
Mass	39	21	10	4	4	79%	64%	0.108
NME	20	11	5	2	2	80%	65%	0.256
Focus	1	0	0	0	1	0	0	-
Lesion Size								
Size ≥ 1 cm	37	24	10	1	2	92%	68%	0.006
Size < 1 cm	23	8	5	5	5	57%	57%	1.000
Lesion Pathology								
DCIS	7	3	2	0	2	71%	43%	0.157
Invasive	53	29	13	6	5	79%	66%	0.108

Abbreviations: NME = non mass enhancement, DCIS = ductal carcinoma in situ, US = ultrasound

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By McNemar's test comparing percentage of lesions visible on DWI versus ultrasound; not evaluable for focus type subgroup (n=1 lesion)
*