Breast Cancers Not Detected at MRI: Review of False-Negative Lesions

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OBJECTIVE. The objective of our study was to determine the sensitivity of cancer detection at breast MRI using current imaging techniques and to evaluate the characteristics of lesions with false-negative examinations.

MATERIALS AND METHODS. Two hundred seventeen patients with 222 newly diagnosed breast cancers or highly suspicious breast lesions that were subsequently shown to be malignant underwent breast MRI examinations for staging. Two breast imaging radiologists performed a consensus review of the breast MRI examinations. The absence of perceptible contrast enhancement at the expected site was considered to be a false-negative MRI. Histology of all lesions was reviewed by an experienced breast pathologist.

RESULTS. Enhancement was observed in 213 (95.9%) of the 222 cancer lesions. Of the nine lesions without visible enhancement, two lesions were excluded because the entire tumor had been excised at percutaneous biopsy performed before the MRI examination and no residual tumor was noted on the final histology. The overall sensitivity of MRI for the known cancers was 96.8% (213/220); for invasive cancer, 98.3% (176/179); and for ductal carcinoma in situ, 90.2% (37/41).

CONCLUSION. In a population of 220 sequentially diagnosed breast cancer lesions, we found seven (3.2%) MRI-occult cancers, fewer than seen in other published studies. Small tumor size and diffuse parenchymal enhancement were the principal reasons for these false-negative results. Although the overall sensitivity of cancer detection was high (96.8%), it should be emphasized that a negative MRI should not influence the management of a lesion that appears to be of concern on physical examination or on other imaging techniques.

Keywords: breast cancer, DCE-MRI, dynamic contrast-enhanced MRI

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Dynamic contrast-enhanced MRI (DCE-MRI) has clearly been shown to be a highly sensitive tool for the detection of breast cancer [1–14]. Reported high sensitivity (83–100%) [1–5] of MRI for breast cancer led imagers initially to presume that nonenhancing legions on MRI were benign and did not warrant biopsy [1, 15]. However, subsequently reported articles have shown that all malignant lesions do not show enhancement at DCE-MRI [2, 5, 16–20], with enhancement absent in up to 12% of known malignant lesions.

In a recent multiinstitutional study of 995 lesions in 854 women, Schnall et al. [20] reported that 16% of 77 ductal carcinoma in situ (DCIS) lesions and 3% of 422 invasive cancers showed no enhancement. Teifke et al. [18] found 28 (8.4%) of 334 invasive cancers and 13 (65%) of 20 noninvasive cancers were missed at MRI. The reasons given for lack of visualization of these missed lesions were technical difficulties, reader perception problems secondary to masking by intensely enhancing parenchyma, small lesion size (< 5 mm), and diffuse growth patterns. However, it remains uncertain which types of malignant lesions are likely to be missed at DCE-MRI using current techniques.

The purpose of this study was to evaluate the sensitivity of DCE-MRI in a cohort of patients with newly diagnosed breast cancer using modern breast MRI parallel imaging techniques at 1.5 T with high spatial and temporal resolution. In addition, we sought to evaluate the characteristics of the lesions with false-negative MRI examinations.

Materials and Methods

Study Population

This HIPAA-compliant retrospective study was approved by the institutional review board (IRB); the informed consent requirement was waived. Between January 2006 and April 2007, 261 sequential patients with 266 newly diagnosed cancers underwent breast MRI examinations for staging at our in-

stitution. Forty-four lesions in 44 patients were excluded because the final pathology at lumpectomy or mastectomy was performed at other institutions and was not available for review by our pathologists. The remaining 222 cancers in 217 patients were the subject of this retrospective review. The patients ranged in age from 28 to 85 years (median, 58 years). The spectrum of malignancy size and histology in these 217 patients is shown in Table 1.

Of the 222 cancers studied, 84 (37.8%) lesions were palpable, 80 (36.0%) lesions were nonpalpable, and clinical data as to palpability was not available for 57 (25.7%) lesions; 209 (94.1%) lesions were visible at mammography, 10 (4.5%) lesions were not visible at mammography, and mammograms were not available for three (1.4%) lesions. Additionally, 166 (74.8%) lesions were visible at sonography, 16 (7.2%) lesions were not visible at sonography, and ultrasound images were not available for 40 (18.0%) lesions. All index cancers, except 32 of 222 lesions, had been diagnosed by percutaneous biopsy or fine-needle aspiration (FNA) before MRI. The remaining 32 cancers underwent MRI because other imaging and clinical findings suggested a highly suspicious lesion and subsequent tissue sampling proved malignancy.

TABLE 1: Pathologic Diagnosis in 217 Patients With 222 Malignancies

Diagnosis	No. (%) of Malignant Lesions	No. (%) of Malignant Lesions by Size			
		< 2 cm	2–5 cm	> 5 cm	Not Available
Invasive ductal carcinoma	160 (72)	94 (80)	54 (76)	11 (55)	0 (0)
Invasive lobular carcinoma	19 (8)	8 (7)	9 (13)	2 (10)	0 (0)
Ductal carcinoma in situ	44 (20)	15 (13)	8 (11)	7 (35)	14 (100)
Total	222 (100)	117 (100)	71 (100)	20 (100)	14 (100)

Conventional Diagnostic Imaging

In all but three patients, mammograms (obtained with different equipment and films, many from different referral centers) were available and were reviewed at our institution by breast imaging specialist radiologists before MRI. Mammograms obtained at outside referral centers accounted for approximately 20% of the total 217 patients.

All patients with invasive cancer or extensive DCIS lesions (166 cases, 75%) underwent targeted ultrasound examination of the affected breast and the ipsilateral axillary region, using an ATL HDI 5000 unit (Philips Healthcare International) and a 5-12–MHz linear transducer, before MRI. These imaging examinations were performed by breast specialist radiologists at our institution. An additional ultrasound examination was not standard procedure for patients with a diagnosis of pure DCIS at our institution unless mammograms showed extensive disease suspicious for the presence of an invasive component.

MRI Protocol

MRI examinations were performed using two 1.5-T imaging units (Signa, GE Healthcare, for 116 patients; and Intera Achieva, Philips Healthcare, for 101 patients). All patients underwent MRI in the prone position using parallel imaging technique. A dedicated 8-channel breast coil was used for the Signa scanner, and a dedicated 7-channel breast coil was used for the Intera Achieva scanner. After obtaining bilateral non-fat-saturated T2-weighted images (TR/TE: Signa, 5,000/103.5; Intera Achieva, 16,907/120) of the breasts, a T1-weighted 3D gradient-echo sequence was performed before and 20 seconds after the injection of contrast material. For the Signa scanner, the imaging parameters were as follows: 4.6/2.2; flip angle, 10°; field of view (FOV), 34 × 34 cm; matrix, 320 × 320; section thickness, 2 mm; and acquisition time, 75 seconds. For the Intera Achieva scanner, the parameters were as follows: 7.9/3.9; flip angle, 10°; FOV, 48 × 48 cm; matrix, 352 × 352; section thickness, 2 mm; and acquisition time, 75 seconds. A dynamic study in the axial plane was performed six times after initiation of an IV injection of 0.1 mmol/kg of gadodiamide (Omniscan, GE Healthcare) at a rate of 2 mL/s, which was followed by a 20-mL saline flush at the rate of 2 mL/s. MRI examinations were processed by CADstream, version 4.1 (Confirma), and subtraction images, time course curves, and angiogenesis maps were obtained. The images were transferred to a workstation (Advantage Windows, software version 4.0, GE Healthcare) for analysis.

Image Analysis

IRB-approved retrospective review by consensus was performed by two radiologists with expertise in breast MRI, one with 15 years' experience and the other with 5 years. Images were interpreted with the benefit of a brief clinical history, knowledge of the histopathologic findings, and knowledge of the mammography and sonography results. In addition to the original images, maximum-intensity-projection and multiplanar reconstruction images were reviewed. The reviewers called findings positive even when there was no color on angiogenesis maps or when, for example, there was a persistent type of curve; they relied on morphology for diagnosis in these cases because

TABLE 2: False-Negative Lesions at Dynamic Contrast-Enhanced MRI

Case No.	Patient Age (y)	Pathology			Imaging			Reason for False-Negative MRI
		Type of Cancer	Nuclear Grade	Size (mm)	Mammography	Sonography	Size (mm)	
1	46	Extensive DCIS	2	NA	Pleomorphic and linear calcifications	NA	30	Diffuse parenchymal enhancement
2	43	DCIS	3	30	Pleomorphic calcifications	Negative	25	Diffuse parenchymal enhancement
3	54	Multifocal DCIS	3	NA	Punctate calcifications	NA	5	Unknown
4	79	DCIS	1	5	Pleomorphic calcifications	NA	5	Small size
5	53	IDC with DCIS	3	IDC, 0.8; DCIS, 10	Amorphous calcifications	NA	10	Unknown
6	49	IDC with extensive DCIS	2	IDC, 8; DCIS, NA	Pleomorphic and linear calcifications	Hypoechoic masses	65	Diffuse parenchymal enhancement
7	44	IDC with DCIS	2	IDC, 12; DCIS, NA	Negative	Mixed echogenic mass	10	Unknown; low-signal mass on T2-weighted images
Median	46						10	

Note—DCIS = ductal carcinoma in situ, IDC = invasive ductal carcinoma, NA = not applicable.

some malignant lesions especially DCIS and invasive lobular carcinoma (ILC) lesions can show slow uptake and perceptible kinetics [21, 22]. The absence of perceptive contrast enhancement at the expected site of the lesion was considered to be a false-negative MRI. Each study was also evaluated with bilateral breast parenchymal enhancement scores of minimal, mild, moderate, or marked enhancement by consensus opinion.

Technical factors such as patient motion, poor fat suppression, or susceptibility artifacts caused by percutaneously placed metallic clips did not compromise any of the study data sets.

Histopathologic Correlation

Of the 222 malignant cases, mastectomy was performed for 92 (41%) cases and breast-conserving surgery lumpectomy, with or without needle localization guidance, was performed for 130 cases (59%). Histology results of all lesions were reviewed by an experienced breast pathologist with 25 years of experience in breast pathology. Tumor type, grade, size, and histologic subtype were documented in the pathology reports. In general, in our pathology department, extensive DCIS is defined as a lesion larger than 5 cm. Correlation between imaging and pathology for each case with regard to location and size and treatment management decisions were discussed for each case at weekly internal multidisciplinary breast conference.

Results

Of the 222 cancerous lesions, enhancement was observed in 213 lesions (95.9%). There were nine examinations that showed no enhancement on MRI. All nine patients had undergone core biopsy or FNA before the MRI examination. Two of the nine lesions were excluded from our false-negative analysis, both presented with a cluster of calcifications, because the entire tumor had been excised by stereotactic core biopsy performed before the MRI examination. In these cases, no residual tumor was noted at histology on the subsequent excised breast specimens. Histology of both lesions indicated low-grade DCIS. The sensitivity of MRI for the known cancers was, therefore, 96.8% (213/220) for all cancer, 98.3% (176/179) for invasive cancer, and 90.2% (37/41) for DCIS.

Of the 217 patients, 35 patients (16.1%) were recalled for MRI-directed ultrasound, 22 patients (10.1%) underwent ultrasound biopsies with benign results, and nine patients (4.1%) underwent MRI biopsies with benign results.

The seven (3.2%) nonenhancing cancers included four cases of DCIS (one low-grade, one intermediate-grade, two high-grade), and three cases of invasive ductal carcinoma (IDC) (two intermediate-grade, one high-grade), as shown in Table 2. One of the two scanners was used for 116 patients (119 lesions), and four malignant lesions (3.4%) were missed. The other scanner was used for 101 patients (103 lesions), and three lesions (2.9%) were missed.

All of the false-negative lesions except one were detected at mammography. The mammographic features of these lesions were classified as pleomorphic and linear calcifications (2/6), pleomorphic calcifications (2/6), amorphous calcifications (1/6), and punctate calcifications (1/6). One lesion was detected as a palpable, tender mass in the retroareolar region and was visible at sonography but not at mammography. The overall

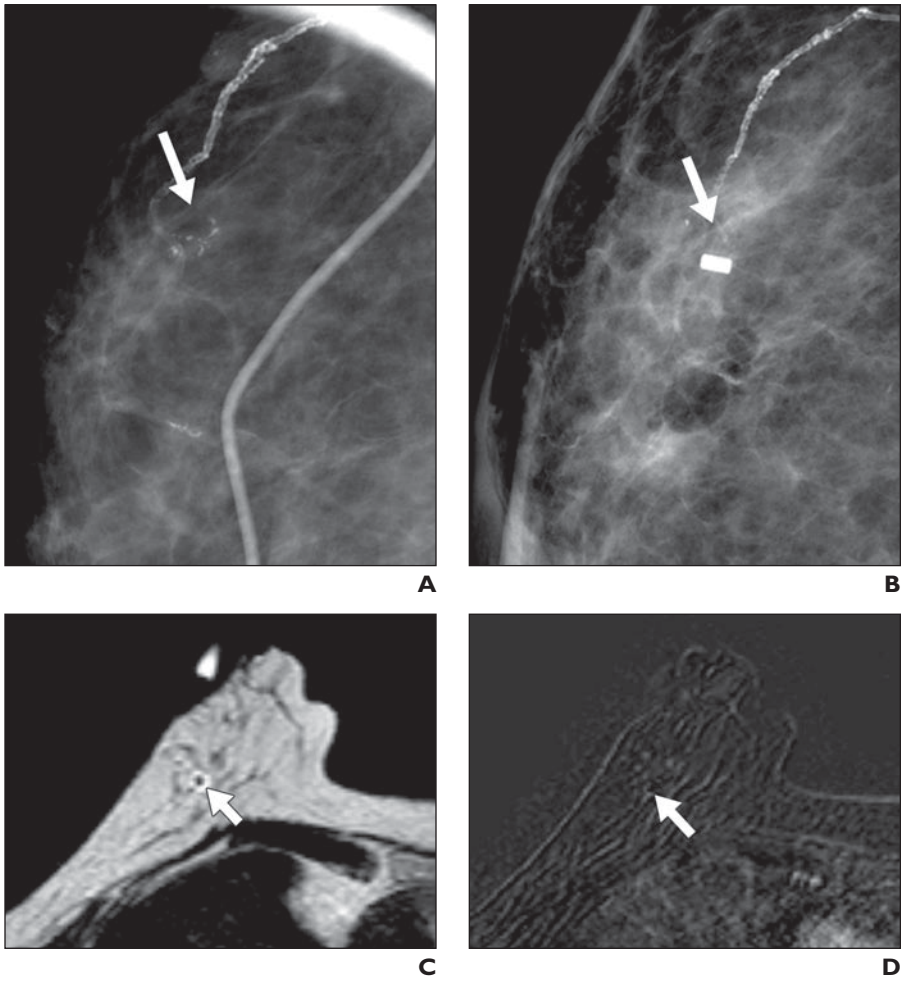

Fig. 1—79-year-old woman with history of right lumpectomy for ductal carcinoma in situ (DCIS) 10 years earlier (case 4 in Table 2).
A, Craniocaudal magnification view of right breast from routine follow-up mammography shows 5-mm cluster of pleomorphic calcifications (*arrow*) near lumpectomy scar. Stereotactic core biopsy revealed DCIS, grade 1.
B, Craniocaudal mammographic view of right breast obtained after biopsy shows metallic clip with a few residual calcifications (*arrow*) at site of biopsy.
C, T2-weighted image shows susceptibility artifact from metallic clip (*arrow*).
D, On early phase of dynamic contrast-enhanced study (subtraction, T1-weighted image), no enhancement is seen around clip (*arrow*). Subsequent right mastectomy revealed DCIS measuring 5 mm in vicinity of biopsy site.

median size of the false-negative lesions on final pathology evaluation was 10 mm.

There were four false-negative DCIS lesions, one of which was very small by pathology (5 mm) (Fig. 1). Two other DCIS lesions were obscured by diffusely enhancing surrounding parenchyma (Fig. 2) even at the early phase (75 seconds) of the dynamic study. The remaining multifocal DCIS lesion (grade 3) did not show enhancement in a background of minimal parenchymal enhancement for reasons that are not known.

There were three false-negative invasive carcinomas. One 8-mm IDC with extensive DCIS was obscured by diffusely enhancing surrounding parenchyma (Fig. 3). One very small (0.8 mm) IDC with DCIS did not show enhancement in a background of mild parenchymal enhancement for reasons that are not known. The remaining lesion, IDC with DCIS, was visible on T2-weighted images as a low-signal mass; however, no enhancement was noted after the administration of contrast medium.

TABLE 3: Data From Published Articles Compared With Data From This Study

Journal, Year of Publication	First Author [Reference No.]	Total No. of Lesions	No. of False-Negative Lesions			Sensitivity (%)		
			Total	Invasive Cancer	In Situ Cancer	Total	Invasive Cancer	In Situ Cancer
AJR, 2005	Ghai [19]	104	9	9	—	91.3	91.3	—
Radiology, 2002	Teifke [18]	354	41	28	13	88.4	91.6	35.0
Radiology, 2006	Schnall [20]	995	25	13	12	95.0	96.9	84.4
	This study	220	7	4	3	96.8	98.3	90.2

Note—Dash (—) indicates no ductal carcinoma in situ present in this population.

Discussion

In this study, DCE-MRI offered a high sensitivity in a cohort of patients with newly diagnosed breast cancer. Sensitivity for all breast carcinoma, invasive carcinoma, and in situ carcinoma was 96.8%, 98.3%, and 90.2%, respectively. These results are comparable or slightly superior to previously published results [18–20] (Table 3). This improvement could be explained by the more modern technical parameters used compared with those of prior studies—that is, higher field strength (1.5 T), higher temporal resolution (75 seconds), and higher spatial resolution (slice thickness, 2 mm; in-plane resolution, 1–1.5 mm). The percentage of palpable lesions in this study (84/164 lesions, 51%), when known, was similar to or lower than the percentage of palpable findings in previously reported studies [7, 20].

However, there are some differences in study methodology when this experience is compared with prior reports [18, 20]. Entry criteria in these prior studies include patients with histologically proven benign lesions and those with malignant lesions. In contrast, the reported sensitivity in this study and in the study by Ghai et al. [19], both retrospective studies, was achieved in cases in which readers knew malignancy was present before reading MRI studies. In the study by Schnall et al. [20], 13 (3.1%) of 422 invasive lesions and 12 (15.6%) of 77 DCIS lesions did not exhibit enhancement at MRI. Teifke et al. [18] found that 28 (8.4%) of 334 invasive lesions and 13 (65%) of 20 DCIS lesions were missed at MRI. In addition, unlike the cases presented in this report, the false-negative lesions described by Teifke et al. included malignancies that were not detected because of technical reasons. No technically inadequate examinations compromised this study and none were included in that of Ghai et al. Despite these differences in study design, the results of this study and all other studies show the existence of MRI-occult breast malignancies.

In this study, seven cancers (3.2%) showed no enhancement on MRI. Of the seven false-negative cases, four malignancies represented pure DCIS. Pure DCIS lesions often present as nonmass, clumped enhancement in a segmental or linear distribution [23] with plateau or washout curve types [22–25] but with lower peak enhancement values. Non-mass-like enhancement may be more difficult to perceive

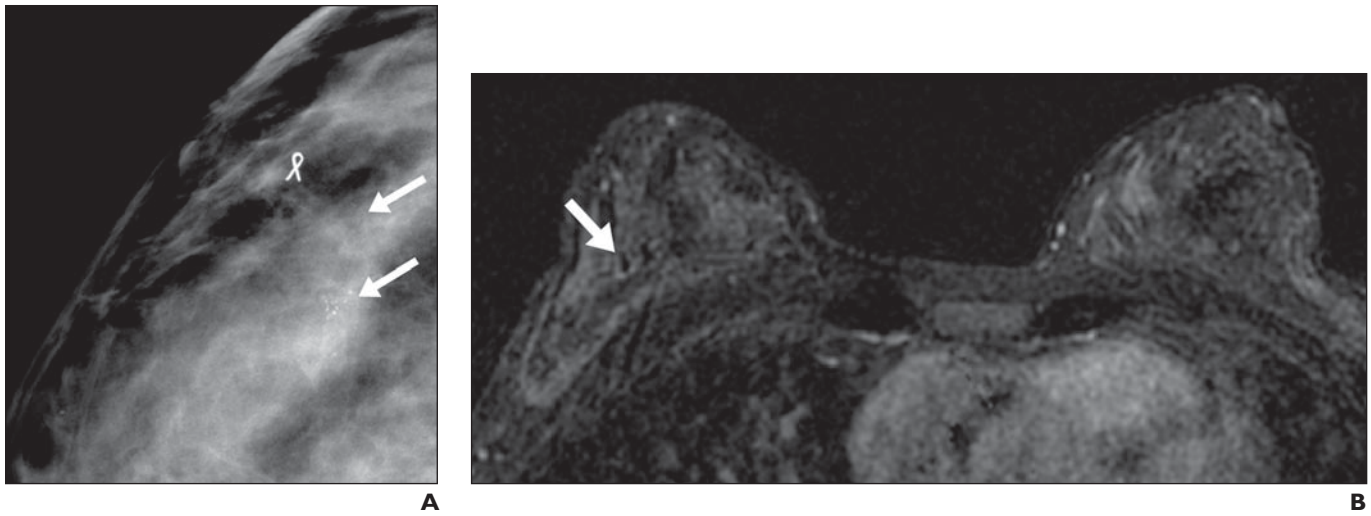

Fig. 2—43-year-old woman with screening-detected pleomorphic calcifications measuring 2.5 cm in right breast (case 2 in Table 2). Stereotactic core biopsy revealed ductal carcinoma in situ (DCIS), grade 3.
A, Craniocaudal mammographic view of right breast obtained after stereotactic core biopsy shows residual calcifications (*arrows*).
B, On early phase of dynamic contrast-enhanced study (subtraction, T1-weighted images), no abnormal enhancement is observed at area of susceptibility artifact from metallic clip placed after stereotactic core biopsy (*arrow*) because of diffuse parenchymal enhancement. Needle localization lumpectomy revealed DCIS, grade 3, measuring 3 cm.

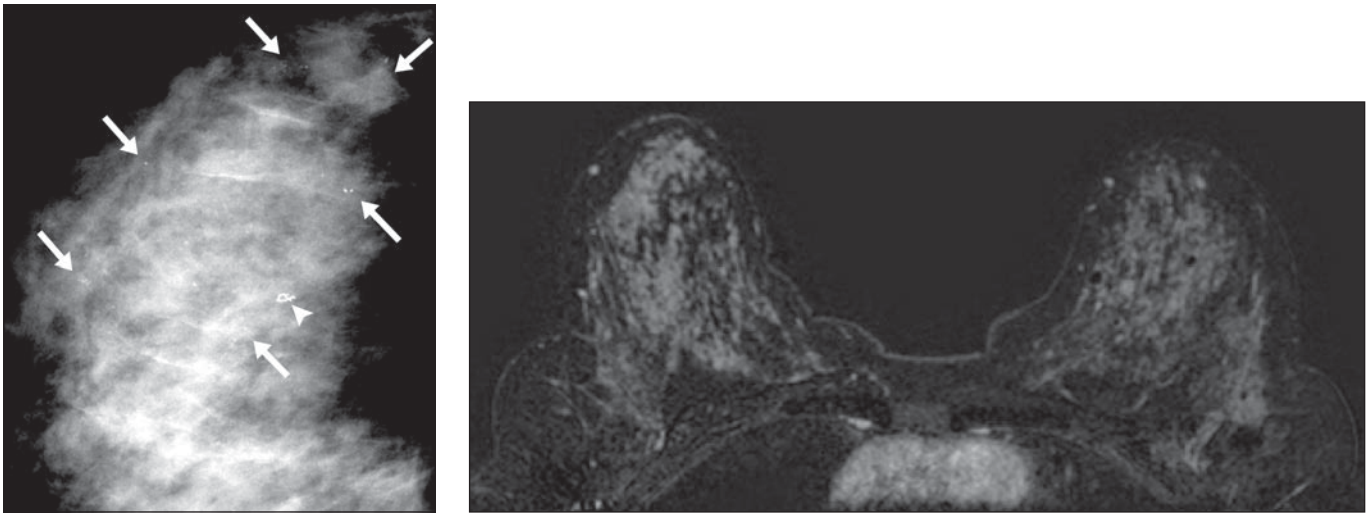

Fig. 3—49-year-old woman with diffuse pleomorphic and linear calcifications measuring 6.5 cm in right breast, proven to be DCIS, grade 2, by stereotactic core biopsy (case 6 in Table 2).
A, Mediolateral magnification view of right breast obtained after stereotactic core biopsy shows calcifications (*arrows*). Metallic clip (*arrowhead*) was placed in upper inner quadrant.
B, On early phase of dynamic contrast-enhanced study (subtraction, T1-weighted images), no abnormal enhancement is observed in upper outer quadrant of right breast because of diffuse parenchymal enhancement. Right simple mastectomy revealed 8-mm invasive ductal carcinoma, grade 2, with extensive ductal carcinoma in situ.

especially in the presence of enhancing breast parenchyma. This observation is supported by a report from the MRI Lexicon Committee indicating that reader agreement for the classification of linear enhancement distribution was poor [24].

There were three cases (two DCIS and one IDC with DCIS) in patients who were younger than the median age of the patient cohort with diffusely enhancing surrounding parenchyma, that could obscure an abnormal enhancing lesion. The median age of these three patients was 46 years, whereas the median age of newly diagnosed cancer patients overall was 58 years. One limitation of this study is that we did not take the hormonal status of our patients into account for scheduling the examinations. At our institution, scheduling patients for breast MRI to stage newly diagnosed cancer has not routinely been done according to the phase in the menstrual cycle for premenopausal women. Perhaps imaging in the second week or at least in the middle of the menstrual cycle, as advocated by Viehweg et al. [26] and Müller-Schimpfle et al. [27], might reduce the number of cases with false-negative MRI due to diffusely enhancing surrounding parenchyma. However, this type of scheduling can be psychologically stressful for patients and can present a perceived delay in care.

Of the remaining false-negative malignancies, one was a small (0.8 mm) IDC with DCIS. Teifke et al. [18] suggested that infiltrating cancers associated with DCIS might be difficult to detect on MRI. The sensitivity of MRI for DCIS reported by Teifke et al. was 35%, and those investigators concluded that MRI cannot reliably diagnose DCIS-positive cancers. Although there are some differences in the study methodologies in this study, the sensitivity for DCIS was 90.2%, which suggests that improvement in DCE-MRI technique may aid in achieving a higher sensitivity for DCIS. Further studies are required to prove a definitive association between false-negative MRI examinations and DCIS lesions.

Other invasive cancers may not be visualized readily because of very small size or because of diffuse pattern of spread. Prior studies have shown ILC to be MRI occult because of diffuse infiltration without mass formation [16, 17, 19]. However, in this study, all ILC lesions (8.6% of total malignancies) were detected at MRI. The relatively thicker slice thickness (range, 3–10 mm) used in prior reported studies could have negatively impacted the sensitivity of MRI for ILC.

A limitation of this study includes a possible bias because it is a retrospective review. At the time of the retrospective read for this study, reviewers were aware of both the initial and the final histologic findings. In routine practice, we may not be aware of all of the details concerning the histology for all cases, although we routinely have histology or cytology findings for most staging MRI cases at the time of the prospective read. However, this study has shown that improved technical parameters—that is, a higher field strength (1.5 T), higher temporal resolution, higher spatial resolution, and improved coil design—led to better results for the detection of small malignant lesions, particularly DCIS.

To summarize, in a population of 220 sequentially diagnosed known breast cancer lesions, we found seven (3.2%) MRI-occult cancers, which is fewer than reported in other published studies. Small tumor size and diffuse parenchymal enhancement were likely the principal reasons for these false-negative results. Although the overall sensitivity of breast MRI for cancer detection was high (96.8%), it should be emphasized that a negative MRI should not influence the management of a lesion that appears to be of concern on physical examination, mammography, or ultrasound. MRI is complementary to—but is not a replacement for—other breast imaging techniques and should not be used as the sole imaging study because, as this study shows, a small number of cancers may not be visible at MRI.

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