

Unenhanced breast magnetic resonance imaging: detection of breast cancer

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Abstract. – **OBJECTIVE:** To evaluate the diagnostic performance of unenhanced MRI (UE-MRI) for malignant breast lesions and its reproducibility.

PATIENTS AND METHODS: We retrospectively included 118 patients who had breast MRI. DWI and STIR images were read in combination and referred to as UE-MRI; the presence or absence of the malignant lesion was noted by two observers. Their results were compared with those of final histopathology or with a two-year negative follow-up for diagnostic performance assessment; ROC curves were built. Diagnostic performance was stratified according to lesion site and size. Interobserver agreement was evaluated through the Cohen's κ statistic.

RESULTS: Specificity of STIR and DWI was 99.3% and 95.7% for Reader 1; 99.3% and 96.4% for Reader 2. Sensitivity was 76.5% and 76.5% for Reader 1; 77.5% and 77.6% for Reader 2. The ROC AUC (Reader 1) was 0.869 and 0.844 for STIR and DWI, respectively ($p < 0.001$ both); for Reader 2, values were 0.874 and 0.853 respectively ($p < 0.001$ both). Lesion dimension ≤ 10 mm was associated with lower AUC values. Lesion site didn't influence the diagnostic performance. Interobserver agreement was very good for STIR and DWI ($\kappa = 0.887$, $p < 0.001$, and $\kappa = 0.867$, $p < 0.001$).

DISCUSSION: UE-MRI has a good overall diagnostic performance in the detection of breast cancer and a very good specificity for both STIR and DWI sequences. We observed reduced diagnostic performance for lesions ≤ 10 mm in size. Lesion's site isn't associated with a significantly decreased diagnostic performance of UE-MRI. There's a good interobserver agreement for both sequences (STIR and DWI).

CONCLUSIONS: UE-MRI may be employed in patients with contraindication to gadolinium. It has considerable specificity and positive predictive value and good reproducibility.

Key Words:

Unenhanced MRI, Breast cancer, DWI, STIR.

Introduction

MR imaging has gained a major role in the detection and characterization of primary and recurrent breast cancer, and in the evaluation of the response to therapy^{1,2}, in addition to the conventional techniques (mammography, ultrasonography). Enhancement through intravenous administration of gadolinium-based contrast agent allows the acquisition of pre-contrast and post-contrast sequences; it relies on the differential enhancement between normal and malignant tissue to improve lesion characterization. Increased neoangiogenesis and tissue permeability to contrast agent within malignant lesions is believed to be the underlying mechanism. The pattern of time-to-intensity curves, together with morphological criteria, are therefore key elements in the discrimination among benign or malignant lesions. Nonetheless, the intravenous administration of contrast agent (CA) during breast MRI examination increases the acquisition time and costs, and it is associated with potential toxicity³ (such as allergic reactions or the rare nephrogenic systemic fibrosis in patients with impaired renal function^{4,5}). Diffusion-weighted imaging (DWI) is also frequently employed in breast MRI, and has good diagnostic performance in the detection of breast lesions⁶⁻²⁰ and the differentiation between benign and malignant tumours²¹⁻²³. DWI measures the mobility of water molecules *in vivo*; it reflects cell density and organization as well as the membrane integrity²⁴. The apparent diffusion coefficient (ADC) offers a comprehensive quantification of these parameters²⁵.

Some exploratory investigations have been conducted about the performance of unenhanced MRI (UE-MRI) in the detection of breast cancer and compared with dynamic contrast-enhanced MRI (DCE-MRI), alone or with mammography²⁶⁻²⁹. These studies offered encouraging results about the potential role of UE-MRI, sug-

gesting its superior diagnostic performance compared to mammography and comparable performance with DCE-MRI in some series of mass lesions. Nonetheless, the debate over the potential role of UE-MRI in clinical protocols requires the confirmation of its reproducibility and the collection of further data about its performance according to the lesion features.

Our purpose was to evaluate the diagnostic performance of UE-MRI in the detection of malignant breast lesions and its reproducibility (interobserver agreement). We also aimed at clarifying whether the size and localization of breast lesions may influence the diagnostic performance of UE-MRI.

Patients and Methods

Patients' Selection

We reviewed our institutional database and we selected 118 female patients who underwent MRI in our Department between June and December 2012. We included in our study either patients with histopathologically proven lesions (core-needle biopsy) or with 2-years imaging follow-up at our Department. We evaluated both advanced tumours and small lesions in asymptomatic patients; we included cases with previous breast surgery and/or radiation therapy. The present series also comprised patients who underwent MRI because of equivocal findings at conventional breast imaging, in order to evaluate the specificity of UE-MRI. Conversely, we excluded patients who underwent breast MRI to evaluate the response to neo-adjuvant chemotherapy, patients receiving chemotherapy and those who underwent a bilateral mastectomy.

MRI Protocol

Since all data were managed retrospectively and analyzed anonymously, and since the present study did not entail any additional diagnostic or therapeutic protocol than state-of-the-art clinical care, patients' consent to enter the study was waived.

MRI was performed with a 1.5T unit with 23 mT/m gradient intensity (Signa Excite; GE Medical System, Milwaukee, WI, USA) using a dedicated breast coil, the patient being in the prone position.

The following sequences were acquired:

1. STIR axial sequence (short time inversion recovery; repetition time [TR] = 5900, echo time [TE] = 68, echo train length [ETL] = 17, band-

width 41-67, 512 · 512 matrix, thickness = 4 mm, 0 interval, field-of-view [FOV] = 32-34 cm, Number of Excitation [NEX] = 1-2).

2. DWI axial sequence (TR = 5150, TE = min, frequency-phase 96 · 96, 256 · 256 matrix, thickness = 4 mm, 0 interval, FOV = 32-34 cm, NEX = 2).

DWI was acquired before dynamic sequences with a spin echo EPI sequence in the axial plane. Sensitizing diffusion gradients were applied sequentially in the x-, y-, and z-directions. The b values were 0 and 1,000 seconds/mm², according to the current literature^{11,24,25,32}. The dynamic study was carried out after having completed the DWI and STIR sequences.

3. Three-dimensional (3D) fast spoiled gradient echo (FSPGR) fat saturation (fat sat) coronal sequence (flip angle [FA] 15 degrees, TR 30 ms, TE 5 ms, NEX 0.5, thickness 2-3 mm, 0 interval, 512*512 matrix, FOV 34-38 cm, scan time for each sequence: 43 seconds, total scan time: 3 minutes 52 seconds) was performed before and 5 times after intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine. Contrast medium was injected with a 10-second delay into the antecubital vein with an 18- to 20-gauge needle at a flow rate of 2 mL/s followed by a flush of 20 mL saline solution.
4. 3D FSPGR sagittal postcontrast fat-suppressed sequence (TR 30, TE5, FA15 degrees, 512512 matrix, thickness = 2-3 mm, 0 interval, FOV = 22-26 cm, NEX2, scan time = 3 minutes 29 seconds).
5. 3D FSPGR axial post-contrast fat-suppressed sequence (TR30, TE 5, FA 30 degrees, 512 FORMTEXT 512 matrix, thickness 2-3 mm, 0 interval, FOV 34-38 cm, NEX 2, scan time 3 minutes 51 seconds). The acquisition time for this complete MRI protocol went from 18 to 20 minutes.

Postprocessing and Data Analysis

We evaluated the signal intensity and the morphological features on STIR images and the apparent diffusion coefficient (ADC). STIR and DWI sequences were individually assessed using a dedicated workstation (GE Healthcare FORMTEXT, Advantage Windows 4.1) by two radiologists (PB and EB) experienced in breast imaging. For each target lesion, we evaluated the DWI sequence and measured the ADC values according to the following relation: $ADC = (\ln S_0 \ln S) / b$ (where S_0 is signal intensity obtained at $b = 0$ and S is signal intensity obtained at $b = 1000$). A sin-

gle ROI was positioned on the slice corresponding to the maximum diameter of the lesion ("Single ROI" method³³). DWI images were read in combination with STIR images, and referred to as UE-MRI. The visibility of the lesions on DWI and STIR sequence was initially assessed. Lesion margins on STIR images were rated as: 1= regular, 2= irregular margins. Signal intensity on STIR images in comparison with fibroglandular tissue was rated on a nominal scale as 1= hyperintense, 2= isointense or 3=hypointense. The lesion size was assessed in a transversal plane on STIR images. Each observer independently rated the UE-MRI for both the STIR and DWI sequences. Concerning STIR sequence, the ordinal BIRADS classification was employed (1= no lesion, 2= benign, 3= probably benign, 4= suspicious, 5= clearly malignant); type of margins and signal intensity were used as diagnostic criteria. All the lesions were categorized as either malignant or benign independently by each reader. For DWI sequences, the lesion status (either malignant or benign) was similarly attributed by each reader, who had worked independently. To such purpose, diagnostic criteria for malignant lesion were: low ADC value ($<1.4 \times 10^{-3} \text{ mm}^2/\text{s}$ as based on previous data³⁴), high signal intensity and spiculated or irregular lesion borders. Lesion status attributed by each reader was noted for subsequent analysis. To the purposes of the current investigation, the results of UE-MRI were compared to those of final histopathology as the reference to estimate the diagnostic performance indexes and to verify the lesion type (malignant or benign). We hypothesized that lesions located in the retroareolar position or in the inferior quadrants could present lesser visibility at UE-MRI (due to artifacts associated with either the areolar tissue or the chest wall).

Statistical Analysis

Continuous data are presented as mean $\pm$ standard deviation and categorical variables as percentages. The mean comparison was performed through the two-tailed Student's *t*-test. Interobserver agreement among Reader 1 and Reader 2 was evaluated through the Cohen's *k* test, and performed separately for lesion status according to the STIR and DWI sequences. Sensitivity, specificity, positive/negative predictive values and diagnostic accuracy were calculated separately for the STIR and DWI sequences, and for the data provided by each reader. Diagnostic performance was also evaluated through the

construction of Receiver Operating Characteristic (ROC) curves and the calculation of the area under the curve (AUC). In order to identify the lesion features potentially associated with sub-optimal diagnostic performance of UE-MRI, stratified diagnostic performance evaluation was conducted according to lesion size (cutoff value: 10 mm maximum diameter) and to lesion site (Retro-areolar and Inferior-quadrants localization vs. the remainders). The alpha value was set at 0.05. Analyses were performed through SPSS ver. 11.0 for Windows.

Results

118 women were ultimately included in the study. Since 3 patients had previous history of mastectomy, 233 breasts were studied. The interpretation of the DWI sequence was flawed by artifacts in 3 out of 118 patients; therefore, the STIR sequence alone was evaluated in these patients.

Reader 1 identified 86 malignant lesions at UE-MRI; histopathology demonstrated that 4 of these were actually benign lesions (false positive observations). These included one case of borderline phyllodes tumor, one case of granuloma, one case of sclerosing adenosis and one case of fibro-fatty nodule. No alterations were observed in 147 breasts, among which 22 were proven to be false negative observations. These last included 14 cases of invasive ductal carcinoma, 5 cases of invasive lobular carcinoma, 3 cases of DCIS (ductal carcinoma in situ), as revealed by the histologic examination.

Reader 2 correspondingly identified 86 malignant lesions at UE-MRI. Three of them were false positive observations (one case of borderline phyllodes tumor, one case of granuloma and one case of sclerosing adenosis). No lesion was detected among the remaining 147 cases; among these, 21 were false negative observations (13 cases of invasive ductal carcinomas, 4 cases of invasive lobular carcinoma, 4 cases of DCIS). Histology revealed 104 carcinomas in 101 patients (74 invasive ductal carcinomas, 12 invasive lobular carcinomas, 5 ductal carcinomas in situ and 13 other forms of invasive cancer), with 3 bilateral cancers. Average lesion size was 38.3 mm (range 7-100 mm). Seventy-three out of 104 tumours (70%) were greater than 2 cm in size; additional clinical signs (such as lymph node involvement, oedema, skin or areolar retraction)

Table I. Diagnostic performance analysis of UE-MRI in the detection of breast cancer for STIR and DWI sequences, and for Reader 1 and Reader 2.

Characteristic	Reader 1		Reader 2	
	STIR	DWI	STIR	DWI
Sensitivity	76.5%	76.5%	77.5%	77.6%
Specificity	99.3%	95.7%	99.3%	96.4%
Positive predictive value	98.7%	92.6%	98.8%	93.8%
Negative predictive value	84.7%	85.2%	85.3%	85.8%
Accuracy	89.4%	87.7%	89.8%	88.6%

were detected in 54 cases (52%). Table I summarizes the sensitivity, specificity, positive/negative predictive values, and accuracy for UE-MRI in the detection of breast cancer; the data are stratified according to sequence (STIR and DWI) and according to Reader (1 and 2). For both Readers, the STIR and DWI sequences showed very good specificity (99.3% and 95.7% for Reader 1; 99.3% and 96.4% for Reader 2), indicating good performance in identifying true negative cases. On the other hand, sensitivity was adequate though slightly lower for both sequences and both Readers (76.5% and 76.5% for Reader 1; 77.5% and 77.6% for Reader 2), suggesting the existence of several false negative cases. Accuracy was good (Reader 1: 89.4% for STIR and 87.7% for DWI; Reader 2: 89.8% for STIR and 88.6% for DWI). There was a very good interobserver

agreement for the detection of breast cancer for both the STIR (Cohen's kappa = 0.887, $p < 0.001$) and the DWI sequences (Cohen's $k = 0.867$, $p < 0.001$). The noted average ADC value was not significantly different among the two readers ($1.02 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.19$ for Reader 1 vs. $1.05 \times 10^{-3} \text{ mm}^2/\text{s} \pm 0.17$ for Reader 2, $p = 0.21$). Figure 1 displays the ROC curves for the detection of breast cancer by UE-MRI using either the STIR or DWI sequence in the overall population. For Reader 1, the ROC AUC was 0.869 and 0.844 for STIR and DWI, respectively ($p < 0.001$ both). Reader 2 scored similar values of ROC AUC (0.874 and 0.853 for STIR and DWI, respectively, $p < 0.001$ both). After the stratification of breast lesions, according to the size measured on final UE-MRI, diagnostic performance analysis was conducted in the subgroup of patients with lesion

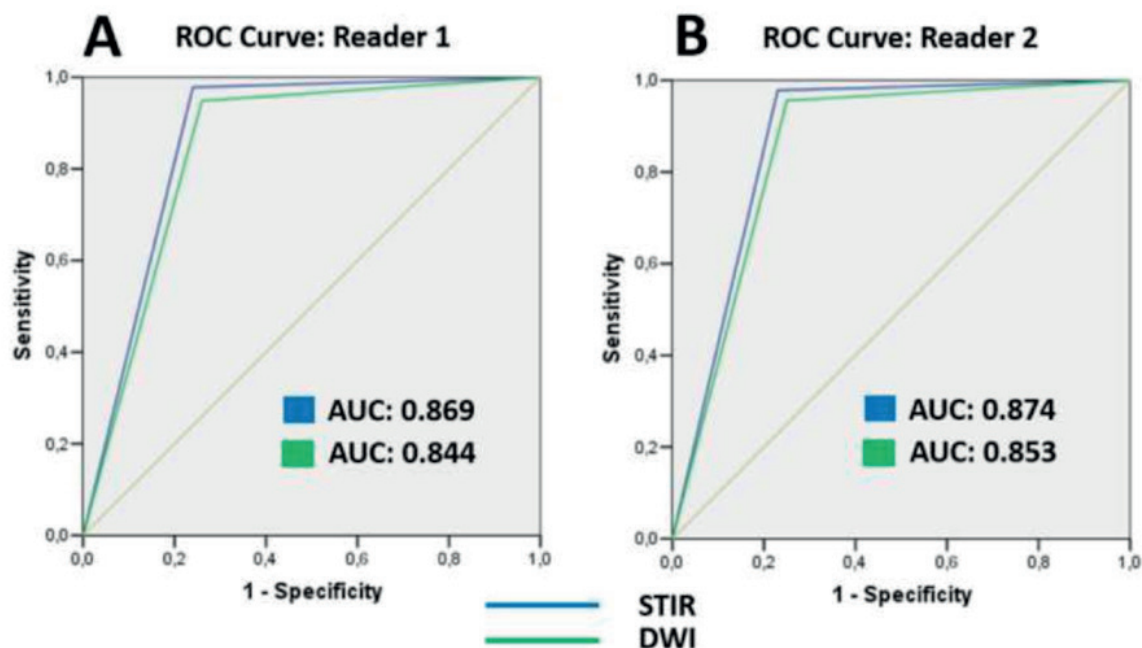


Figure 1. ROC curves for detection of breast cancer by UE-MRI using either the STIR (blue line) or the DWI sequence (green line) for Reader 1 (panel A) and Reader 2 (panel B).

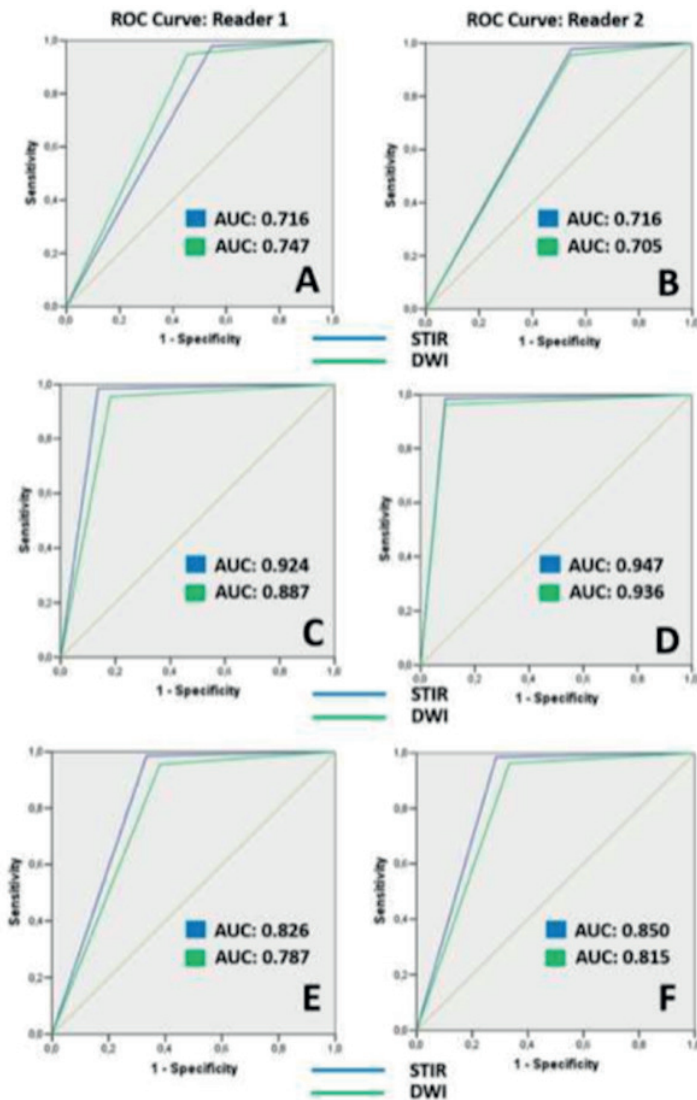


Figure 2. ROC curves for detection of breast cancer by UE-MRI using either the STIR (blue line) or the DWI sequence (green line). Panels A and B (Readers 1 and 2, respectively): lesions having diameter ≤ 10 mm only. Panels C and D (Readers 1 and 2, respectively): lesions localized in the retroareolar region only. Panels E and F (Readers 1 and 2, respectively): lesions localized in the inferior quadrants only.

diameter ≤ 10 mm (21.1% of the total). Both Readers showed again a comparable overall performance; nonetheless, ROC AUC in these patients was remarkably smaller than in the overall population: 0.716 and 0.747 (STIR and DWI; $p=0.017$ and $p=0.007$) for Reader 1; 0.716 and 0.705 (STIR and DWI; $p=0.017$ and $p=0.024$) for Reader 2 (Figure 2 A and B). Figure 2 (C and D) displays the ROC curves only for retroareolar lesions. Interestingly, diagnostic performance was better than the one conducted on the overall population (Reader 1: AUC = 0.924 and 0.887 for STIR and DWI, $p<0.001$ both; Reader 2: AUC = 0.947 and 0.936 for STIR and DWI, $p<0.001$ both). The diagnostic performance for the lesions located within the inferior breast quadrants was slightly lower than the one for the general population, al-

though remaining consistent (Reader 1: AUC = 0.826 and 0.787 for STIR and DWI, $p<0.001$ both; Reader 2: AUC = 0.850 and 0.815 for STIR and DWI, $p<0.001$ both) (Figure 2 E and F). The DWI sequence was particularly useful for the detection of non-mass lesions. Among 13 lesions, which could be detected on DWI better than on STIR, 9 cases (69%) could be characterized as non-mass, being not evident on STIR sequence (Figure 3).

Discussion

MRI is accepted as an invaluable diagnostic tool for the assessment of breast disease. Diffusion imaging has proven reliable and effective for the detection and characterization of breast ma-

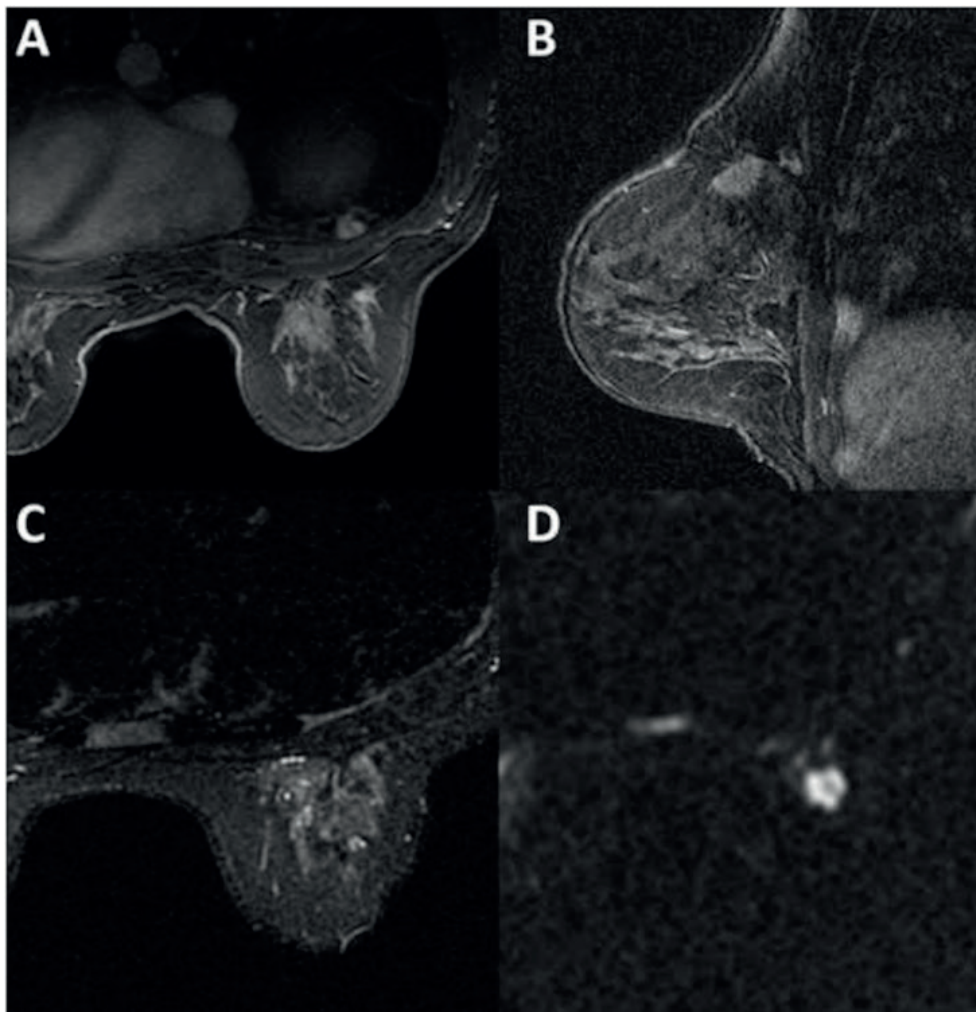


Figure 3. 3D-FSPGR axial and sagittal post contrast fat-suppressed sequences, showing an area of focal and irregular enhancement within the right breast, about 26 mm maximum size (Panels A and B). The lesion is not clearly appreciated on the unenhanced STIR sequence (C), but visible on the DWI sequence (D).

lignancies²⁸⁻³². Nonetheless, the use of contrast agent represents a limit for a larger employment of this technique, due to concerns for allergic reaction, contrast-induced systemic fibrosis, increased costs and examination time. Up to now, the role of UE-MRI in the evaluation of breast lesions was addressed by a limited number of studies. A previous study by Baltzer et al²⁷ evaluated 81 mass lesions by UE-MRI without prior biopsy, being the majority larger than 20 mm. Kuroki et al¹² reported the sensitivity of DWI and STIR sequences in a series of 70 women, but specificity was not addressed. Yabuuchi et al²⁶ reported a series of 42 non-palpable breast lesions in asymptomatic women. Overall, these studies suggested that the diagnostic performance of UE-MRI is greater than that of mammography; none-

theless, the potential role of UE-MRI in clinical protocols is still to be determined. In order to contribute to such debate, in this study we present the largest currently available patients' database of UE-MRI in breast cancer assessment. Sample size allowed stratification according to lesion diameter and localization, in order to identify lesion-related factors potentially associated with reduced diagnostic performance of UE-MRI with respect to the standard CE-MRI.

In our work, we evaluated both advanced tumours and small lesions in asymptomatic patients; we included cases with previous breast surgery and/or radiation therapy. The present series also comprised patients who underwent MRI because of equivocal findings at conventional breast imaging, in order to evaluate the

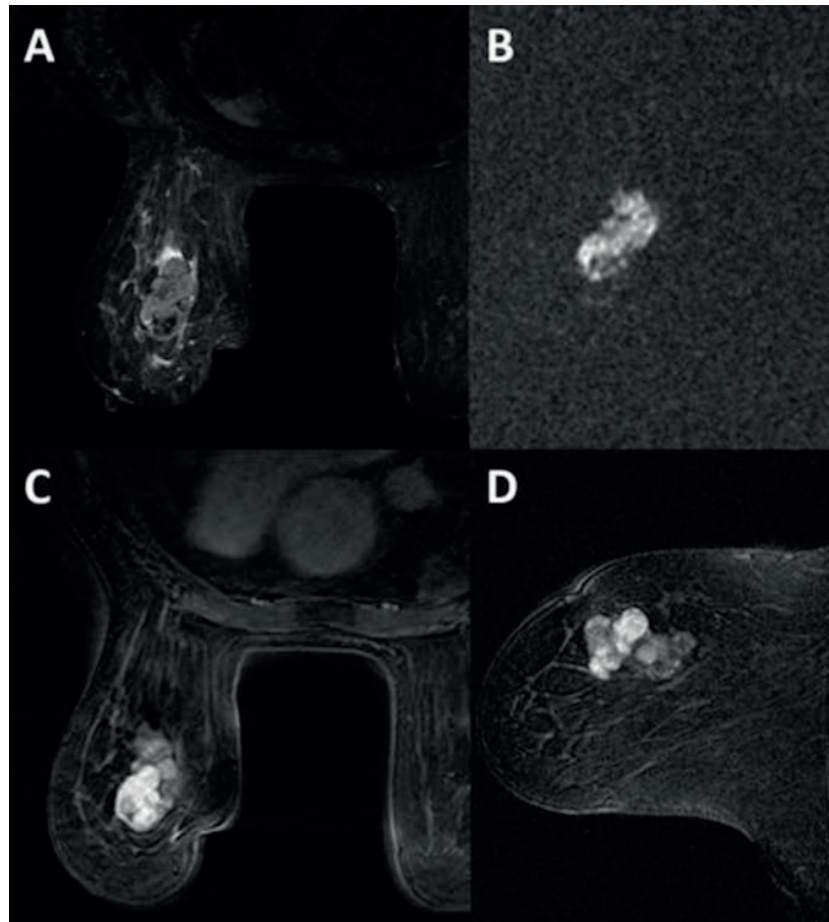


Figure 4. False positive finding at UE-MRI (borderline phyllodes tumor). STIR and DWI axial sequences show a mass lesion within the retroareolar region of the left breast. The lesion has polycyclic morphology and regular margins (Panels A and B). In 3D-FSPGR axial and sagittal post contrast fat-suppressed sequences, the lesion shows increased and heterogeneous enhancement after contrast medium injection (Panels C and D).

specificity of UE-MRI. Conversely, we excluded patients who underwent breast MRI to evaluate the response to neo-adjuvant chemotherapy. The first main finding consists of the good overall diagnostic performance of UE-MRI in the detection of breast cancer. In a separate analysis of STIR and DWI sequences, we observed comparable performance in the global population, thus suggesting that DWI cannot offer a diagnostic advantage in this context with respect to lesion detection. DWI has been reported to be mainly useful in lesion characterisation⁶; under such perspective, it could be employed during UE-MRI in order to retrieve additional useful data for decision-making. DWI has the potential to predict tumour aggressiveness and phenotype^{23,35}. STIR and DWI remain nonetheless two complementary methods which should be coupled in any UE-MRI examination

in order to maximize the chances of lesion detection (Figure 3). The second main finding consists in the observation of very good specificity for both STIR and DWI sequences. Our 99.3% specificity rate for the STIR sequence and both Readers well compares with the 90% and 91% specificity-rates previously reported in literature^{24,36}. In the present series, no more than 4 and 3 false positive results were observed for Reader 1 and 2, respectively. These were represented by one borderline phyllodes tumor, one granuloma, one sclerosing adenosis and one fibrofatty lump. Artifacts at the fat-parenchyma interface may determine false enhancement in fibrofatty lump³⁴ and false positive result. Phyllodes tumours and benign lesions such as sclerosing adenosis may also present marked enhancement, especially in premenopausal women (Figure 4). If these drawbacks are consid-

ered, UE-MRI may nonetheless represent a valid alternative to mammography in patients at lower risk of presenting breast cancer. On the other hand, sensitivity seems to represent the weak spot of this approach. Sensitivity-rate for the STIR sequence was 76.5% and 77.5% for the two Readers, without evidence of gain through analysis of DWI sequences. Nonetheless, lower sensitivity rates have been previously reported for smaller experiences (50%²⁶), potentially limited by sample bias. In the present series, except for 4 instances, either small lesion size or worse quality of examination determined cases of undetected breast cancer at UE-MRI (artifacts due to inhomogeneity of magnetic field). Under such circumstances, assessment through DWI is particularly hindered, owing to the difficult identification of hyperintense areas for ROI placement. We observed reduced diagnostic performance for lesions ≤ 10 mm in size. In these cases, additional findings such as lymph node alterations, oedema and skin retraction can be helpful to establish the diagnosis. Our data also suggest that lesion's site is not associated with a significantly decreased diagnostic performance of UE-MRI. In particular, retro-areolar position and localization within the inferior breast quadrants did not hinder the lesions' detectability. In the present series, only 2 out of 20 lesions located in the retro-areolar or near-nipple areolar complex were not correctly identified. Another major finding of the present investigation is the demonstration of good inter-observer agreement for both sequences (STIR and DWI). To this respect, our work confirms and extends previous evidence^{24,27} about the reproducibility of UE-MRI results among two independent observers. Such findings corroborate the reliability of this technique, which application should anyway remain limited to referral centers with consolidated experience in breast MRI. The use of a 1.5T device and without parallel imaging are among the limitations of the present study. Nonetheless, one can reasonably expect improved results obtained with a 3T equipment, and this hypothesis deserves confirmation in further studies. In addition, herein about 70% of breast tumours were greater than 2 cm in size and showed additional signs of disease. Although sample bias might influence the reliability of subgroup analysis, herein we present the largest series so far evaluating the diagnostic performance of UE-MRI for breast cancer.

Conclusions

UE-MRI is a useful tool for the diagnosis of breast cancer. It showed considerable specificity and positive predictive value; reproducibility among different readers was excellent. This strategy may be employed in patients with renal failure, gadolinium intolerance or who refuse contrast-enhanced MRI. Reduced accuracy is observed in the case of smaller breast lesions; such issue needs to be considered when evaluating these patients and further investigations are required to better clarify the role of UE-MRI in earlier disease stages. Lesions' detectability does not seem to be influenced by their location.

Conflicts of interest

The authors declare no conflicts of interest.

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