

Second-Look Ultrasound

When Things Are Not Always as They Seem

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Abstract: The purpose of this study was to compare size, morphologic features, and degree of suspicion between findings at second-look ultrasound (SL-US) and additional lesions with histological confirmation detected on breast magnetic resonance imaging (MRI). We performed an observational retrospective study including women who underwent SL-US between January 2021 and August 2022. Size, morphology according to Breast Imaging Reporting and Data System (BI-RADS) lexicon, and BI-RADS categories were analyzed for MRI and US findings. Two hundred twenty-four consecutive patients (aged 29–88 years; mean, 59.2 years) underwent SL-US to identify 235 additional lesions detected on MRI. US identified 173 (73.6%) findings. US-guided biopsy was performed in 148 (85.5%) of the detected lesions, proving 56 (37.8%) malignant and 92 (62.2%) benign. Mean size was 15.2 mm on MRI and 9.4 mm on US. Foci and masses showed good correlation, whereas nonmass enhancements tended to appear larger on MRI, and this difference was statistically significant ($P = 0.0001$). Morphology showed a higher agreement in the case of foci and masses than with nonmass enhancements. BI-RADS categories agreed in 66 cases (44.6%), whereas in 61 cases (41.2%), the degree of suspicion was higher for MRI, and in only 21 cases (14.2%) were lesions more suspicious on US than on MRI. In conclusion, lesions detected at SL-US show a higher agreement in size and morphologic features for foci and masses than with nonmass enhancements and similar or lower degree of suspicion than on MRI; therefore, decision to perform a biopsy should be based primarily on MRI findings.

Key Words: magnetic resonance imaging, second-look ultrasound, breast cancer, biopsy.

Abbreviations: MRI = magnetic resonance imaging, SL-US = second-look ultrasound, US = ultrasound, BI-RADS = Breast Imaging Reporting and Data System, BC = breast cancer, DWI = diffusion-weighted imaging, IDC = invasive ductal carcinoma, ILC = invasive lobular carcinoma.

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Key Points

- Second-look ultrasound (US) is a useful test for assessment of additional breast lesions detected with magnetic resonance imaging (MRI).
- Lesions detected at second-look US show a smaller size than on MRI, especially nonmass enhancements, which show less correlation in size and morphology with MRI findings.
- Findings at second-look US generally appear with a similar or lower degree of suspicion than on MRI; therefore, a lower threshold for biopsy should be applied than on routine US.

Breast magnetic resonance imaging (MRI) is the most sensitive diagnostic tool for detection of breast cancer (BC) and for the detection of multifocal and multicentric cancers.^{1–3} In cases where MRI was performed to confirm extension of a diagnosed BC, a change in the initial prescribed treatment has been reported in 12% to 32% of patients⁴ due to additional MRI findings. However, MRI has shown a moderate specificity, with a large number of false-positive findings; for this reason, histological confirmation of additional MRI-detected suspicious lesions is required before changing the surgical plan to reduce the number of unnecessary mastectomies. MRI-guided biopsy is not widely available and is associated with high operating costs and procedure time.⁵ Furthermore, the positive predictive value of MR-guided biopsy has been reported as relatively low due to the high benignity rate found at pathology,⁶ thus leading to a high number of unnecessary biopsies. On the other hand, ultrasound (US) has several advantages over MRI to guide percutaneous biopsies because sonographically guided biopsy is more broadly available and less time-consuming and costly and allows better accessibility to certain areas of the breast and greater comfort for the patient.

Second-look US (SL-US) is an additional targeted breast imaging examination directed to locate a correlative US lesion of an MRI-detected lesion and obtain histological verification with US-guided instead of MRI-guided biopsy. Detecting target lesions at SL-US and correlating images between the 2 modalities may be challenging because of difficulties in location of the lesions due to differences in positioning and differences in presentation at US and MRI.

Several studies have evaluated the accuracy of SL-US,^{7–9} reporting different detection rates, sensitivities, and specificities. Other groups studied the US-detection rate according to MRI lesion characteristics,^{10,11} but there are scarce references describing

the features of these US-detected lesions¹² and their correlation with the final pathological results.

The aim of this study was to assess correlation between SL-US lesion characteristics and grade of suspicion of the MRI findings and the final pathology result of the biopsies, to provide evidence and improve lesion detection at SL-US.

MATERIALS AND METHODS

Design and Subjects

An observational retrospective study was performed in a tertiary referral center including women who underwent SL-US after contrast-enhanced breast MRI. The study was approved by the ethics committee of the hospital, and requirement for informed consent was waived. However, written informed consent was obtained from all patients before core-needle biopsy.

Between January 2021 and August 2022, 837 women underwent contrast-enhanced breast MRI at our institution. Patient selection flowchart is shown in Figure 1. Two hundred twenty-four consecutive patients (aged 29–88 years; mean, 59.2 [SD, 13.37] years) underwent SL-US to identify 235 additional lesions detected on MRI. All patients had mammography and US examination performed before the MR study. Overall, 173 lesions (73.6%) were identified on US, whereas 62 (26.4%) did not have a US correlate. US-guided core-needle biopsy was performed in 148 (85.5%) of the detected lesions. In 25 patients, biopsy was not performed either for clearly benign findings (19 cases), confirmation with fine-needle aspiration cytology (4 cases), or extended surgery (2 cases). Histopathological analysis yielded 92 benign and 56 malignant lesions.

Procedures

MRI Technique

Dynamic contrast-enhanced breast MRI was performed on two 1.5-T MRI units: a 1.5-T MRI (Signa; GE Medical Systems, Milwaukee, Wisconsin) and a 1.5-T MRI (Aera; Siemens,

Erlangen, Germany). All patients were examined in the prone position with a dedicated bilateral breast coil using standard technique with intravenous contrast material and axial imaging with 2-mm-thick contiguous slices. The protocol included an axial 2-dimensional (2D) T2-weighted image without fat suppression, a diffusion-weighted imaging (DWI), and a 3-dimensional (3D) fat-suppressed T1-weighted gradient echo image, which were all obtained before and 5 times after a rapid bolus of contrast injection (gadobutrol 0.1 mmol/kg by weight). For DWI, 2 *b* values according to recommendations optimized for a magnetic field strength of 1.5 T were used (0 and 700 s/mm² for the GE system and 50 and 700 s/mm² for the Siemens system). The detailed imaging parameters are shown in Table 1.

US Technique

US examination was performed by 1 of 4 radiologists with 5 to 28 years of experience in breast imaging. A Canon Ultrasound Diagnostic System Aplio1800 (Canon Medical Systems, Tochigi, Japan) attached to a 50-mm array transducer (PLT-1005BT; center frequency 10 MHz) was used for US examinations. US scanning was performed focusing the attention on the anatomical area of the detected lesion using MRI scans as a guide. The difference in the position of the patients for the 2 techniques was considered; patients were in the prone position for MRI and in a supine or supine oblique position for US. When MRI-detected lesions were visible on SL-US, the lesions were evaluated according to the US Breast Imaging Reporting and Data System (BI-RADS) lexicon. US-guided biopsies were performed using a 14-gauge core needle. A titanium clip was placed at the biopsy site for better imaging correlation.

Image Interpretation

Lesion size, morphology, and BI-RADS assessment were analyzed on MRI scans by 1 of 3 radiologists with more than 15 years of experience in breast MRI. Suspicious enhancing lesions included any lesion apart from the index lesion that could

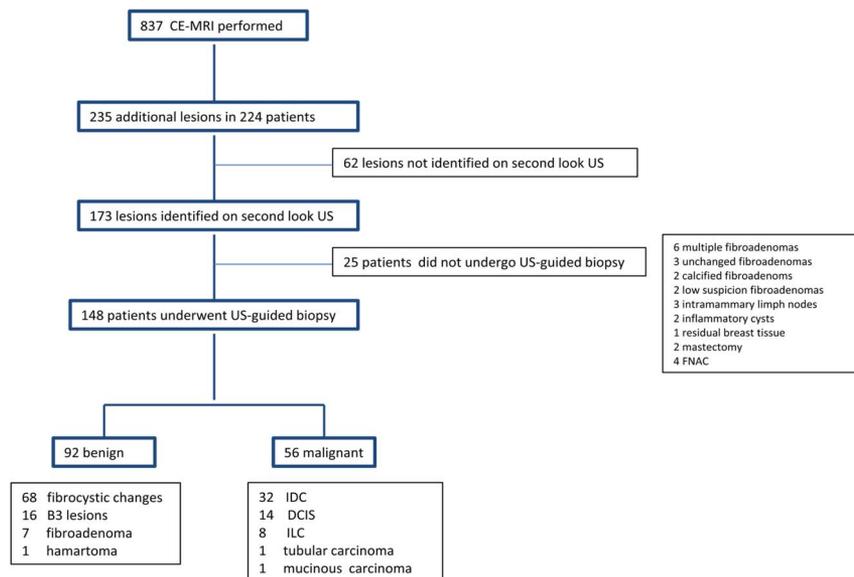


FIGURE 1. Patient selection flowchart.

TABLE 1. MRI Parameters

	Signa (GE)	Aera (Siemens)
2D T2-Weighted Imaging Fast Spin Echo Sequence		
Repetition time (ms)	3800	1200
Time to echo (ms)	120	253
Slice thickness (mm)	2	2
Field of view (mm)	330 × 330	340 × 340
Matrix (mm)	416 × 416	512 × 476
3D T1-Weighted Imaging Gradient Echo Sequence		
Flip angle	15°	10°
Repetition time (ms)	4.7	4.65
Time to echo (ms)	2.3	1.78
Slice thickness (mm)	2	2
Field of view (mm)	330 × 330	340 × 340
Matrix (mm)	416 × 416	416 × 416
In-plane resolution (mm)	0.8 × 0.8	0.8 × 0.8
Acquisition time (s)	72	75
DWI Sequence		
Repetition time (ms)	8000	6500
Time to echo (ms)	65	66
Slice thickness (mm)	4	4
Field of view (mm)	320 × 320	360 × 270
Matrix (mm)	132 × 132	192 × 115
<i>b</i> Values (s/mm ²)	0/700	50/700

potentially alter the treatment. Size, morphology, and BI-RADS categories were recorded. MRI and US lesions were evaluated according to the lexicon from the fifth BI-RADS edition.¹³ Morphological patterns for MRI included focus, mass, and nonmass enhancement. On US, mass and nonmass lesions were considered. Although nonmass lesions are not described at the current BI-RADS fifth edition, they are expected to be included in the forthcoming sixth edition. MRI BI-RADS 4 lesions were also subdivided in a, b, and c subcategories for comparison purposes.

Careful anatomic and radiopathological correlation was carried out. A clip was placed at the biopsy site, and mammography was performed for correlation. No postbiopsy MRI confirmation

was performed. Benign concordant results in which biopsy was considered unnecessarily were not included in the study and had no specific follow-up. In histologically benign concordant lesions, usual protocols for benign lesion follow-up were applied. In selected cases, 6-month follow-up MRI was also performed.

Statistical Analysis

Statistical analysis was performed with the Software for Statistics and Data Science release 15.1 (Stata; StataCorp LLC, College Station, TX). A χ^2 test, Fisher exact test, and analysis of variance (ANOVA) test were used for analysis of dichotomous variables in both modalities and to compare differences in size. $P < 0.05$ was considered statistically significant.

RESULTS

Of the 148 lesions considered in this study, 56 (37.8%) proved to be malignant, and 92 (62.2%) were benign. Malignant lesions included 32 invasive ductal carcinoma (IDC), 14 ductal carcinoma in situ, 8 invasive lobular carcinoma (ILC), 1 tubular carcinoma, and 1 mucinous carcinoma. Benign lesions included 68 fibrocystic changes, 16 B3 lesions, 7 fibroadenomas, and 1 hamartoma.

Mean lesion size on MRI was 15.2 mm (range, 4–90 [SD, 17.8] mm) and 9.4 mm on US (range, 3–50 [SD, 5.93] mm). Whereas foci and masses showed good correlation between MRI and SL-US, nonmass enhancements tended to appear larger on MRI than on US, and this difference was statistically significant for both benign and malignant lesions ($P = 0.0001$) (Table 2).

Regarding lesion morphology, on MRI, 67 lesions (45.3%) were described as mass-like lesions, 43 (29%) as non-mass-like lesions, and 38 (25.7%) were foci. On US, 113 lesions appeared as mass-like lesions (76.4%), 29 (19.6%) as nonmass lesions, and 6 (4%) as other types (clustered microcysts and complex cystic lesions). Table 3 shows correlation between morphology findings on MRI and US. Thirty-one of 38 foci (81.6%) appeared as small masses on US, most MRI masses (59/67 [88%]) showed an agreement with their US correlate (Fig. 2), whereas MRI nonmass enhancements corresponded to masses in 23 cases (53.5%) (Fig. 3) and nonmass lesions in 19 (44.2%), such as ill-defined hypoechoic areas ($n = 7$), tubular images or dilated

TABLE 2. Correlation of Lesion Size at MRI and US for Malignant and Benign Lesions

	Total				Lesion	n	Malignant				Lesion	n	Benign			
	Mean	SD	Min	Max			Mean	SD	Min	Max			Mean	SD	Min	Max
Focus	38				Focus	11				Focus	27					
MR size (mm)		5.29	1.56	4	11		5	1.09	4	7			5.41	1.71	4	11
US size (mm)		5.71	1.74	3	10		5.45	1.8	3	9			5.81	1.73	4	10
Mass	67				Mass	30				Mass	37					
MR size (mm)		9.55	3.96	4	23		10.8	4.63	5	23			8.54	3.02	4	17
US size (mm)		9.22	4.15	3	25		9.67	4.66	5	25			8.86	3.71	3	19
Nonmass	43				Nonmass	15				Nonmass	28					
MR size (mm)		32.79	25.04	6	90		40.6	25.34	10	90			28.61	24.29	6	80
US size (mm)		13	8.22	5	50		15.4	11.39	5	50			11.71	5.73	5	28
Total	148				Total	56				Total	92					
MR size (mm)		15.21	17.81	4	90		17.64	19.4	4	90			13.73	16.71	4	80
US size (mm)		9.41	5.93	3	50		10.37	7.56	3	50			8.84	4.62	3	28
ANOVA					$P = 0.0001$	ANOVA				$P = 0.0007$	ANOVA				$P = 0.0593$	

ducts with echogenic contents (n = 6), subtle heterogeneous areas (n = 5), and distortion (n = 1). Although foci and masses showed higher agreement than nonmass enhancements, this difference did not reach statistical significance in the case of malignant lesions (P = 0.081).

Distribution of BI-RADS categories is displayed in Table 4. BI-RADS categories for MRI findings were 3 (n = 38), 4a (n = 33), 4b (n = 42), 4c (n = 34), and 5 (n = 1). On US, lesions were categorized as 2 (n = 11), 3 (n = 48), 4a (n = 37), 4b (n = 30), 4c (n = 20), and 5 (n = 2). Agreement between MRI and US categories occurred in 66 cases (44.6%), whereas in 61 cases (41.2%), the degree of suspicion was higher for MRI than for US, and in only 21 cases (14.2%) were lesions more suspicious on US than on MRI (Table 5).

DISCUSSION

SL-US is an additional targeted US examination directed to identify a correlative US lesion of an MRI suspicious finding. Lesion detection rate at SL-US is markedly heterogeneous. In a meta-analysis by Spick and Baltzer⁷ including 17 studies, lesion detection rate ranged between 22.6% and 82.1%, with a pooled detection rate of 57.5%. In our study, 73.6% of lesions were identified on US, which is higher than the average published data. Thorough breast examination and close correlation made by experienced breast radiologist may have been the key to obtain such a high rate of detection. We compared imaging features such as size, morphology, and BI-RADS final assessment score between lesions detected on MRI and those detected on SL-US. Overall, lesion size was larger on MRI than on US (15.2 vs 9.4 mm), but although foci and masses showed good correlation, nonmass enhancements tended to look larger on MRI than on US, and this difference was statistically significant, for both benign and malignant lesions. Regarding lesion morphology, most foci and masses showed an agreement with their US correlate, whereas nonmass enhancements corresponded equally to masses and nonmass lesions. In our series, nonmass enhancements appeared on US as a mass in 53.5% of cases and as nonmass lesions in 44.2% (Fig. 4). Some authors have reported that non-mass-like enhancing lesions detected on breast MRI are less likely than a mass or focus to have a US correlate and that US correlates for nonmass enhancement include masses or nonmass patterns, often subtle or not apparent at all.^{14,15} Additional techniques, including power Doppler imaging or elastography, can be used to increase the conspicuity of lesions that would otherwise be difficult to detect (Fig. 5).

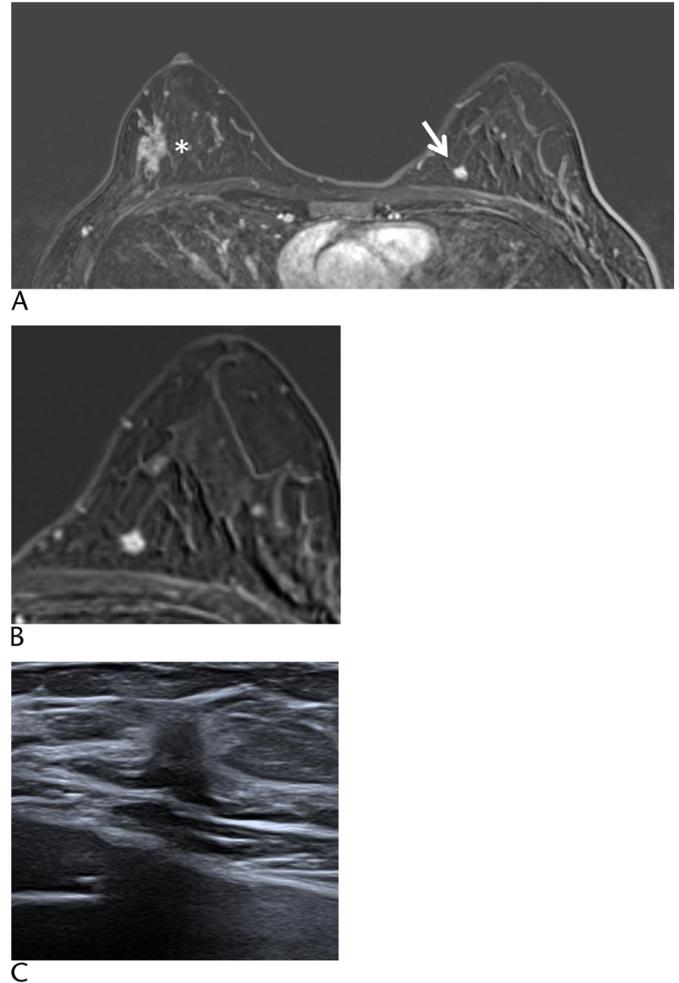


FIGURE 2. A 50-year-old woman underwent breast MRI for local staging of a BC. Axial fat-saturated postcontrast subtracted images (A, B) show the index lesion in the right upper outer quadrant of the right breast (asterisk) and a suspicious mass-enhancing lesion at the left breast (arrow). SL-US (C) identified a small ill-defined mass with an echogenic halo. US-guided biopsy confirmed IDC. Agreement was found in size, morphologic features, and BI-RADS categories.

Detecting target lesions at SL-US and correlating images between the 2 modalities may be challenging because differences in body positioning can cause considerable variability in

TABLE 3. Correlation of Morphology Findings at MRI and US for Malignant and Benign Lesions

MR	Total			MR	Malignant				MR	Benign				
	US				US					US				
	Mass	Nonmass	Other	Total	Mass	Nonmass	Other	Total		Mass	Nonmass	Other	Total	
Focus	31	4	3	38	Focus	9	1	1	11	Focus	22	3	2	27
Mass	59	6	2	67	Mass	26	4	0	30	Mass	33	2	2	37
Nonmass	23	19	1	43	Nonmass	8	6	1	15	Nonmass	15	13	0	28
Total	113	29	6	148	Total				56	Total				92
Pearson χ^2				P = 0.000	Pearson χ^2				P = 0.081	Pearson χ^2				P = 0.001
Fisher exact				P = 0.000	Fisher exact				P = 0.043	Fisher exact				P = 0.000

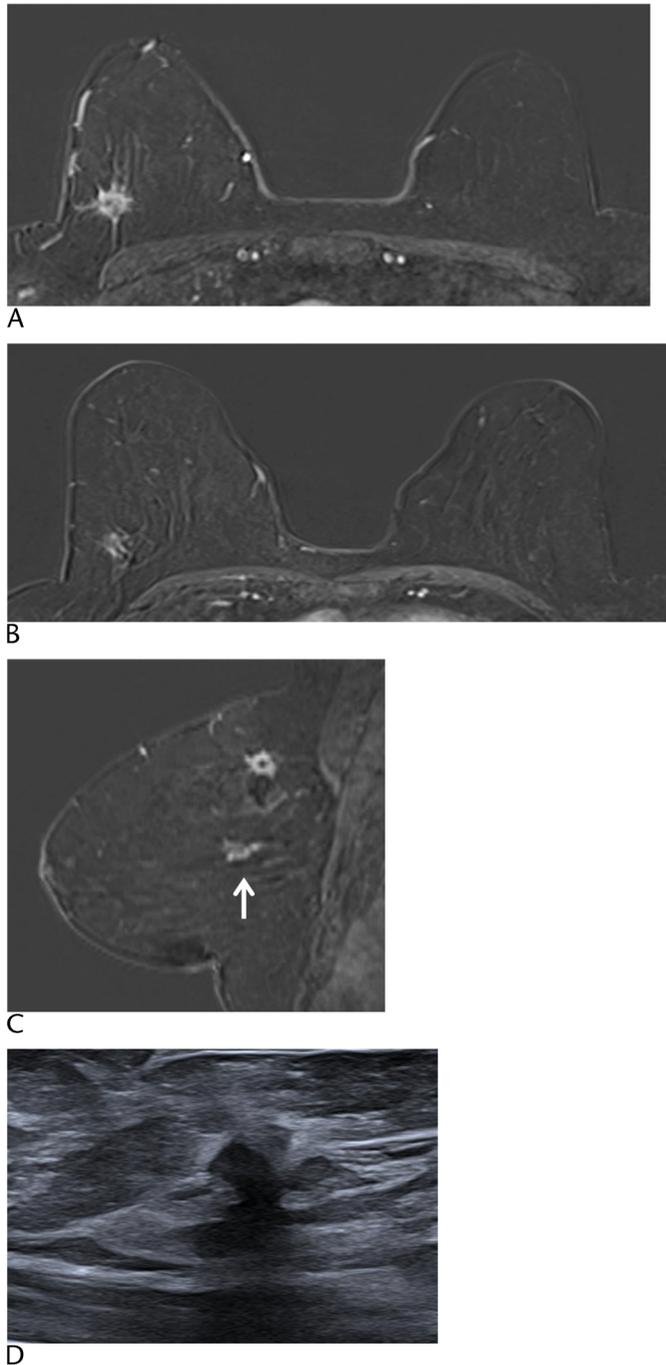


FIGURE 3. A 72-year-old woman presented with BC in the right breast. Axial (A, B) and sagittal (C) subtracted MR images show a spiculated mass at the upper outer quadrant of the right breast (asterisk) and an additional small enhancing nonmass 15-mm lesion at the 9-o'clock position of the right breast (arrow). D, A corresponding ill-defined irregular hypoechoic 10-mm mass was detected on SL-US. US-guided biopsy yielded IDC. In this case of a nonmass lesion, size and shape on US were not identical to MRI features.

TABLE 4. Correlation of BI-RADS Categories on MRI and SL-US

		US					
Benign		2	3	4a	4b	4c	5
MRI	2	2	3	4a	4b	4c	5
3	2	23	7				32
4a	3	8	8	5			24
4b	3	8	9	7			27
4c		1	2		6		9
Total	8	40	26	12	6		92
Malignant		US					
MRI		2	3	4a	4b	4c	5
3	1	1	2	2			6
4a	1	4	3	1			9
4b		2	4	6	3		15
4c	1	1	2	9	11	1	25
5						1	1
Total	3	8	11	18	14	2	56
Total		US					
MRI		2	3	4a	4b	4c	5
3	3	24	9	2			38
4a	4	12	11	6			33
4b	3	10	13	13	3		42
4c	1	2	4	9	17	1	34
5						1	1
Total	11	48	37	30	20	2	148

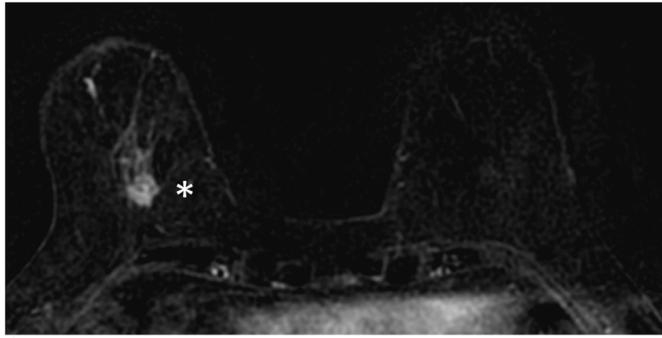
the apparent position of the corresponding lesions. Lesion depth, distance to the nipple, and anatomical landmarks should be considered to improve the accuracy of SL-US.^{16,17}

For clinical decision-making, it is important to know which lesions detected at MRI are most likely to be detected at SL-US, and therefore several studies have focused on which variables influence the SL-US detection rate. In the meta-analysis by Spick and Baltzer,⁷ the highest SL-US detection rates were observed for mass lesions (as opposed to nonmass lesions) and for malignant (vs benign) lesions, whereas lesion size was not a significant predictor of SL-US detection rate. They concluded that, on the basis of their data, a lesion visible at SL-US was more likely to be malignant, thus prompting US-guided biopsy. However, the lack of detection of a lesion with SL-US did not exclude malignancy. Other studies^{8,9,11,18,19} have shown that larger lesions, masses, and IDC are generally more likely to be identified at US than are smaller lesions, non-mass-like enhancement, and ILC or ductal carcinoma in situ.

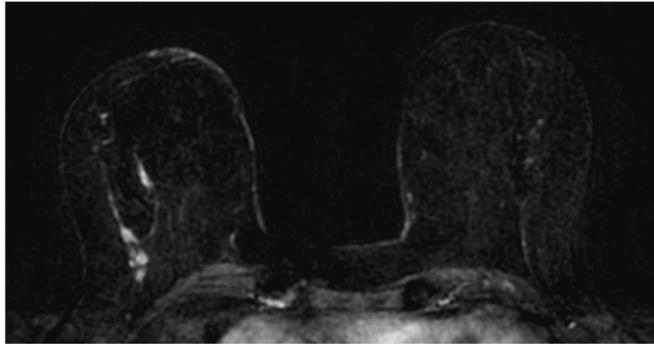
TABLE 5. US and MRI BI-RADS Correlation

	Benign		Malignant		Total	
	n	%	n	%	n	%
Agreement	44	47.8	22	39.3	66	44.6
MRI > US	36	39.1	25	44.6	61	41.2
US > MRI	12	13.1	9	16.1	21	14.2

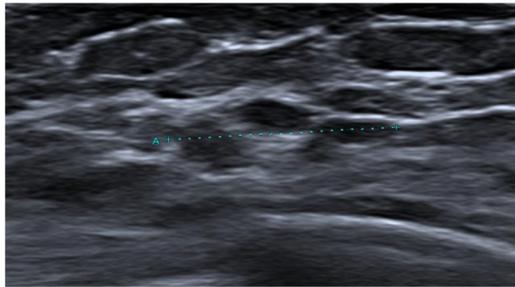
Agreement: MRI and US categories agree. MRI > US: the degree of suspicion is higher for MRI than for US. US > MRI: the degree of suspicion is higher for US.



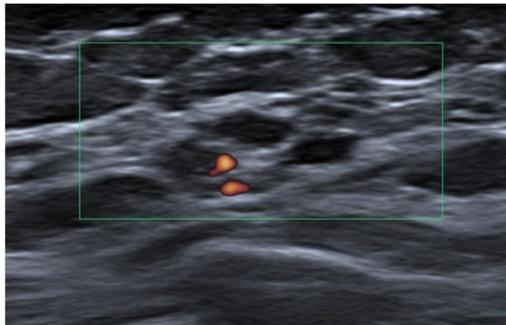
A



B



C



D

FIGURE 4. A 74-year-old woman presented with right BC. Axial T1-weighted postcontrast subtraction MR images (A, B) show an irregular mass at the 6-o'clock position (asterisk) and an additional linear 60-mm nonmass enhancement (arrow) in the 8-o'clock position of the same breast. SL-US (C) identified at the corresponding location a heterogeneous nonmass 14-mm area similar to the surrounding parenchyma. D, The vascularity of the lesion appreciated with power Doppler imaging confirmed correlation with the MRI finding. Despite the subtlety of the image and disagreement in size, biopsy was performed and confirmed IDC.

The findings identified at SL-US have been reported to be subtle. Few published articles, among the most recently reviewed literature, include features of the targeted US lesions. Abe et al¹⁸ found that malignant breast lesions initially detected at MRI tended to be subtle at US, and classic malignant US findings often were absent, with 33% of lesions showing no suspicious US features. Laguna et al¹² reviewed the SL-US characteristics of 26 documented additional malignant lesions with sonographic correlation. Approximately 60% to 70% of the findings were classified as BI-RADS 2 and BI-RADS 3 when assessing the final US category. In these studies, most lesions were small in size (<10 mm). The authors, however, did not specifically correlate US and MRI features of the detected lesions. Comparison of lesion size and shape is one of the most basic methods of lesion correlation, although these are not always identical at MRI and US, especially for non-mass-like enhancements.¹⁶ Our results support the lack of agreement in size and morphology of nonmass lesions compared with foci and mass lesions.

Because carcinomas detected using SL-US may appear nonspecific or present with benign features, some authors^{12,18,20} suggest that a lower threshold for biopsy decision must be applied for these lesions than for those found at routine US. We analyzed BI-RADS assessment categories for MRI and US findings and subdivided MRI BI-RADS 4 lesions in a, b, and c subcategories for comparison purposes. Our results showed agreement between MRI and US categories occurred in 44.6% of cases, whereas in 41.2% of cases, the degree of suspicion was higher for MRI than for US, and in only 14.2% of cases were lesions more suspicious on US than on MRI. Most findings detected on SL-US appear with a lower or equal degree of suspicion than on MRI, and this occurs equally for both benign and malignant lesions, and therefore, US-BIRADS classification of lesions should not affect the indication for histological confirmation. The decision of performing a biopsy at SL-US should be based primarily on MRI findings.

Strengths and Limitations

The strengths of this study include a detection rate of SL-US higher than the average reported in previous studies. US features of pathologically confirmed both malignant and benign lesions were reviewed. Although postbiopsy MRI was not performed, a clip was placed at the biopsy site, and mammography was performed to warrant the certainty of the MRI-US correlation.

Limitations of our study include its retrospective design, although only consecutive patients were included and that there may have been a selection bias because MRI-directed US examinations were recommended at the discretion of the interpreting radiologist, with no standardized protocol to define the indications for SL-US. Another limitation is that US imaging is an operator-dependent modality, and therefore US findings cannot confidently be retrospectively reviewed, as can the MRI examinations, and interpretations of US features are made on the basis of the images obtained.

CONCLUSIONS

Size, location, and morphologic features must be considered when correlating MRI findings at SL-US performance. For accurate correlation of findings between MRI and US, it is

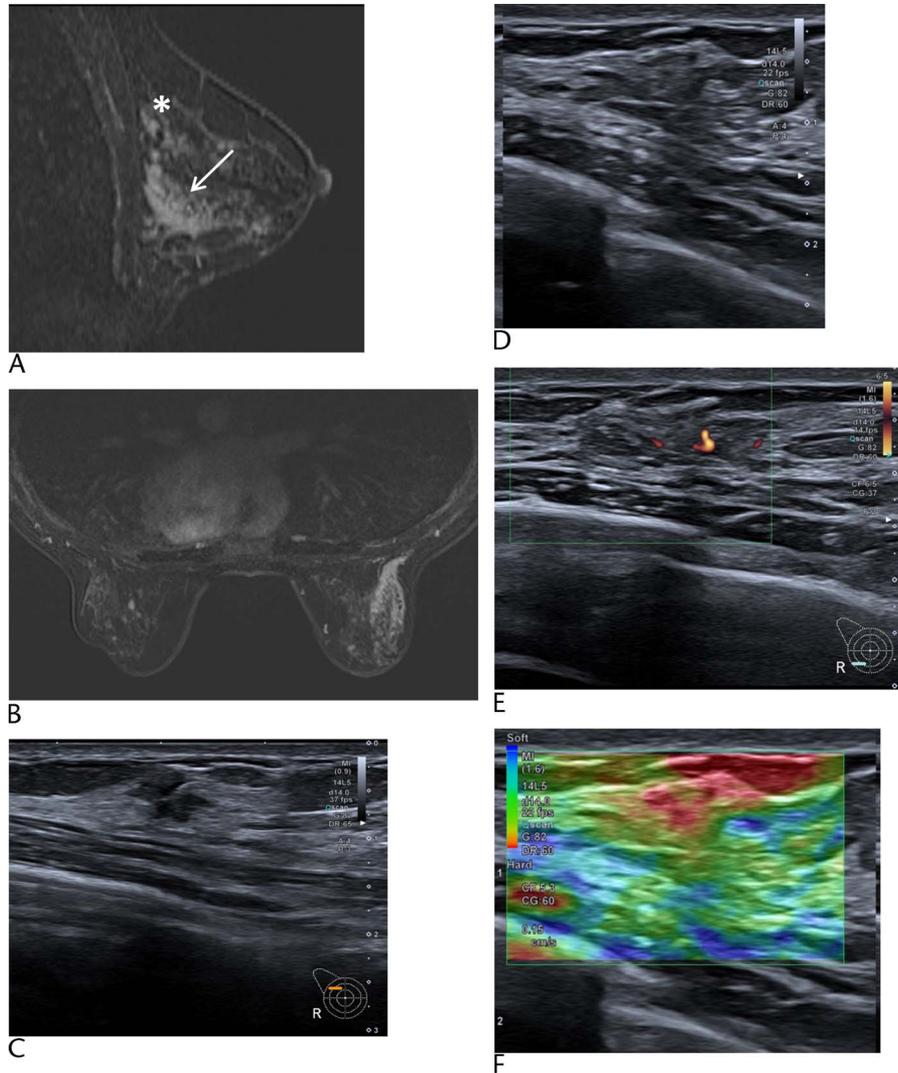


FIGURE 5. A 44-year-old woman with biopsy-proven left breast ILC. Sagittal fat-saturated postcontrast T1-weighted image (A) shows the 7-mm index lesion at the upper outer quadrant of the right breast (asterisk). Extensive segmental nonmass enhancement is seen at the lower outer quadrant of the same breast (arrow) on sagittal (A) and axial (B) images. US images show the index lesion (C) and a subtle heterogeneous nonmass lesion at the lower outer quadrant of a smaller size than the MRI finding (D). Increased vascularity on power Doppler images (E) and tissue hardness on elastography (F) prompted biopsy that yielded ILC.

essential to understand the differences in breast position in each modality. Comparison of lesion size and shape is one of the most basic methods of lesion correlation. However, our results show that lesion size and shape are not always identical at MRI and US, especially for non-mass-like enhancements. Findings identified at SL-US have been reported to be subtle, often appearing on US with a lower degree of suspicion than on MRI; therefore, decision to perform a biopsy should be based primarily on MRI findings, applying a lower threshold for biopsy than for those on routine US.

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