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ORIGINAL ARTICLE

Homogeneously enhancing breast lesions on contrast enhanced US: differential diagnosis by conventional and contrast enhanced US findings

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Abstract
Objective To clarify the details of homogeneously enhancing lesions on contrast-enhanced ultrasonography (CEUS) and also to elucidate whether their differential diagnosis is possible.
Methods Seventy-three homogeneously enhancing lesions on CEUS were retrospectively selected. Two radiologists first assessed conventional US findings alone in consensus to differentiate malignant vs. benign lesions. Then, qualitative and quantitative CEUS findings were analyzed to determine the useful findings for the differential diagnosis. Determined CEUS findings were applied to the indeterminate lesions based on conventional US findings to see whether CEUS can improve the diagnostic performance.
Results There were 42 cancers (58 %) out of 73. Sensitivity and specificity using conventional US findings alone were 91 and 55 %, respectively. Among the CEUS findings tested, multivariate analysis revealed only the type 3 enhancement pattern, which indicates a larger enhancing area than the precontrast hypoechoic lesion, was related to malignancy ($p < 0.05$). By adding this information, however, no improvement was achieved in the diagnostic performance as determined by conventional US findings.
Conclusions Approximately half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulous assessment of the conventional US rather than CEUS findings.

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Introduction

Since the advent of contrast agents for ultrasonography, several researchers have applied this technique, namely contrast-enhanced ultrasonography (CEUS), to breast imaging, and not a few promising data have been published in terms of malignancy vs. benignity differentiation [1–4]. Generally, it has been reported that irregularly or peripherally enhancing lesions are malignant, whereas homogeneously enhancing ones are benign [1–3]. However, we encounter a considerable number of "exceptional" cases in daily practice, which are against the above-mentioned rules, particularly for the latter [4–6]. To our knowledge, little has been investigated specifically focused on the differential diagnosis of homogeneously enhancing lesions on CEUS.

This study was conducted, therefore, to clarify the clinicopathological details of "homogeneously enhancing lesions" on CEUS and to elucidate whether differentiation between malignant and benign lesions in this particular cohort is possible.

Materials and methods

Between October 2012 and August 2015, 134 patients with 161 suspected breast lesions underwent CEUS in our institute. Among these, the lesions that showed homogeneous enhancement at their peaks, and also for which final pathological diagnoses were obtained, were retrospectively recruited. In our institute, CEUS is routinely performed as

Table 1 Criteria for malignancy and benignity of the lesions based on conventional sonographic findings before contrast enhancement

	Benign	Indeterminate	Malignant
Mass lesion [7][a]			
Shape	Oval	Round	Irregular
Orientation	Parallel to the skin		Not parallel to the skin
Margin	Circumscribed	Microlobulated	Angular, indistinct, spiculated
Internal echo	Aechoic, hyperechoic	Isoechoic, hypoechoic	Complex
Posterior acoustic features		Enhancement, None	Shadowing, combined
Calcification			In mass, intraductal
Architectural distortion			Yes
Duct change			Yes
Non-mass lesion [8][b]			
Types		Type Ia, type IIa, type III, type IV	Type Ib, type IIb

[a] Original [7] includes other factors including skin appearances, Doppler or elastography information. However, in our patients, none showed skin thickening, skin retraction or edema: Doppler sonography and elastography were obtained in a limited number of cases. These findings were therefore omitted in the table

[b] Type I ductal non-mass-like (NML) pattern: parallel orientation of multiple duct-like structures without calcifications (type Ia) or with associated calcifications (type Ib). Type II nonductal NML pattern: a geographic or mottled area that does not give a discrete mass and may present without calcifications (type IIa) or with associated calcifications (type IIb). Type III NML pattern: associated with architectural distortion; type IV NML pattern: associated with posterior acoustic shadowing [8]

a presurgical procedure or for patients whose diagnosis is indeterminate or questionable based on the conventional radiological workup. Our institutional review board waved obtaining informed consent because of the study's retrospective nature.

CEUS was performed with a clinical ultrasound unit (LOGIQ E9, GE HealthCare, Milwaukee, WI). Conventional and contrast-enhanced US images were obtained with an ML 6–15 and SL 9-MHz linear probe, respectively. The mechanical index was set at 0.2–0.21. After confirming that the target lesions were well visualized at the center of the field of view, bolus injection of contrast medium (Sonazoid, Daiichi Sankyo, Tokyo, Japan) of 0.015 ml/kg was performed from the antecubital vein, followed by a 10-ml saline flush. The target lesions were then continuously observed for 90 s using real-time grayscale harmonic imaging, the whole process of which was video-recorded.

All sonographic images and videos were reviewed by two experienced radiologists (RF and MS) who were experienced in breast sonographic imaging and blinded to the pathological results. First, the conventional US images alone were evaluated, and the confidence level of diagnosing malignancy was determined using a 5-point scale in consensus, with scores of 1, 2, 3, 4 and 5 indicating definitely benign, possibly benign, indeterminate, possibly malignant and definitely malignant, respectively, according to the previously reported criteria, namely, the Breast Imaging Reporting and Data System (BI-RADS) 2013 [7] for mass lesions and those defined by Ko et al. [8] for non-mass-like lesions. As for mass lesions, the final score of a certain patient was determined based on the total balance of the assessment for each finding of BI-RADS 2013 (Table 1); more specifically, all findings listed in Table 1 were checked for each lesion, and if findings favoring malignancy or benignity were dominant, scores of 4–5 or 1–2 were given, respectively; if these were similar in number, a score of 3 was given. As for non-mass lesions, types Ib and IIb were considered malignant, whereas the rest were benign or indeterminate (Table 1). Scores of 4 and 5 were regarded as suggesting malignancy, respectively, and the sensitivity and specificity were calculated.

Then, the enhancement patterns of the lesions on CEUS were reviewed and divided into the following three groups: type 1, in which the degree of enhancement of the lesions was almost equal to the surrounding breast tissue; type 2, where the degree of enhancement was greater than that of surrounding tissue with the area of enhancement being approximately the same as the precontrast hypoechoic lesion in size; type 3, in which the degree of enhancement was greater than that of the surrounding tissue, and the area of enhancement was larger than the hypoechoic lesion on the precontrast images. On the dynamic phase of contrast enhancement, one radiologist (RF) manually placed the region of interest to cover the whole lesion as visualized on the initial images before contrast arrival, and a time-intensity curve (TIC) was created. The following indices were semi-automatically calculated: the Axk value was defined as the slope of the tangent at the beginning of the TIC; the time to peak (TTP) was defined as the time period in seconds between the beginning point to the peak of TIC: the

Table 2 Correlation between contrast-enhanced US findings and histology

CEUS findings	Benign	Malignant	*P* values	Disease entities					*P* values	
				Benign			Malignant			
				FA/Phyl	IP	NSBL	IDC	DCIS	Uni	Mul
Ehn.pattern Type 1/2/3	14/17/0	23/11/8	0.004	3/7/0	4/8/0	7/2/0	11/4/8	12/7/0	0.01	0.0005
Axk	6.5 ± 3.2	7.1 ± 3.5	NS	6.8 ± 2.5	8.2 ± 3.3	4.1 ± 2.0	7.4 ± 4.2	6.8 ± 2.6	0.044*	NS
TTP	9.6 ± 3.0	9.7 ± 4.8	NS	9.3 ± 2.2	8.9 ± 1.4	10.1 ± 5.8	10.8 ± 4.6	8.9 ± 4.5	NS	
AS	2.2 ± 0.8	2.2 ± 1.0	NS	2.3 ± 0.7	2.4 ± 0.5	1.9 ± 1.1	2.2 ± 1.1	2.2 ± 0.9	NS	

CEUS contrast-enhanced ultrasonography, *Enh.pattern*.enhancement pattern, *Axk* the slope of the tangent at the beginning of time-intensity curve, *TTP* time to peak, *AS* ascending slope

FA fibroadenoma, *Phyl* phyllodes tumor, *IP* intraductal papilloma, *NSBL* non-specific benign lesion, *IDC* invasice ductal carcinoma, *DCIS* ductal carcinoma in situ, *Uni* univariate analysis, *Mul* multivaraiate analysis

* NSBL vs. IP

ascending slope (AS) was defined as the slope between the beginning point to the peak of the TIC.

The correlation between these CEUS parameters (enhancement patterns, Axk, TTP and AS) and malignancy vs. benignity was assessed, and significant factors for differentiation were sought. Significant factors, if present, were applied to the above-mentioned score 3 groups, namely, indeterminate lesions when assessed solely with conventional US image findings, and the sensitivity and specificity were again calculated to check whether adding CEUS information might improve the diagnostic capability.

For statistical analyses, the Wilcoxon Kruskal-Wallis test, Fisher's exact probability test and χ^2 test were used for univariate analyses, and the logistic regression test was used for multivariate analysis. *P* values <0.05 were considered significant. The statistical software used was JMP version 11 (SAS Corp., Cary, USA).

Results

There were 73 patients with 73 lesions, with ages ranging from 34 to 80 years old (mean 53.2), including 10 fibroadenoma/phyllodes tumors, 12 intraductal papillomas, 19 ductal adenocarcinomas in situ (DCIS), 23 invasive ductal adenocarcinomas (IDC) and 9 other non-specific benign lesions (NSBLs). Namely, 58 % (42/73) of homogeneously enhancing lesions were malignant in our patient population. All NSBLs showed fibrocystic changes or adenosis with or without slight inflammatory cell infiltration. The lesion sizes ranged from 4 to 85 mm in their maximum dimension, with malignant lesions (19.5 ± 15.1 mm) being larger than benign ones (10.5 ± 6.3 mm). Among these, histological diagnoses were made by surgical resection, percutaneous needle biopsy and cytology for 50, 19 and 4 lesions, respectively.

Diagnosis solely based on conventional US findings

For mass lesions, 2, 1, 12, 27 and 7 lesions were given scores of 1, 2, 3, 4 and 5, respectively; for non-mass lesions, these were 0, 0, 6, 10 and 8. In total, 2, 1, 18, 37 and 15 lesions were graded as scores 1, 2, 3, 4 and 5, respectively, by the two reviewers. The three lesions given scores 1 or 2 were all benign, and 15 lesions given scores of 5 were all malignant. Those scored as 3 (indeterminate lesions) included 14 benign and 4 malignant lesions. Those scored as 4 (probably malignant) included 14 benign and 23 malignant lesions. Thus, when scores of 4 and 5 were considered to suggest malignancy, the sensitivity, specificity and accuracy were 90.5 % (38/42), 54.8 % (17/31) and 75.3 % (55/73), respectively.

CEUS findings

The details of the CEUS findings vs. histological classification are shown in Table 2. When histology was simply divided into benign vs. malignant, the enhancement pattern was the only significant factor, suggesting the type 3 enhancement pattern was significantly related to malignancy. When each disease entity was separately considered, univariate analysis suggested the enhancement pattern and Axk were significant factors, with the type 3 enhancement pattern being associated with IDC and Axk of NSBL being smaller than those of IP (Table 1). No other indices were significantly different among the disease entities.

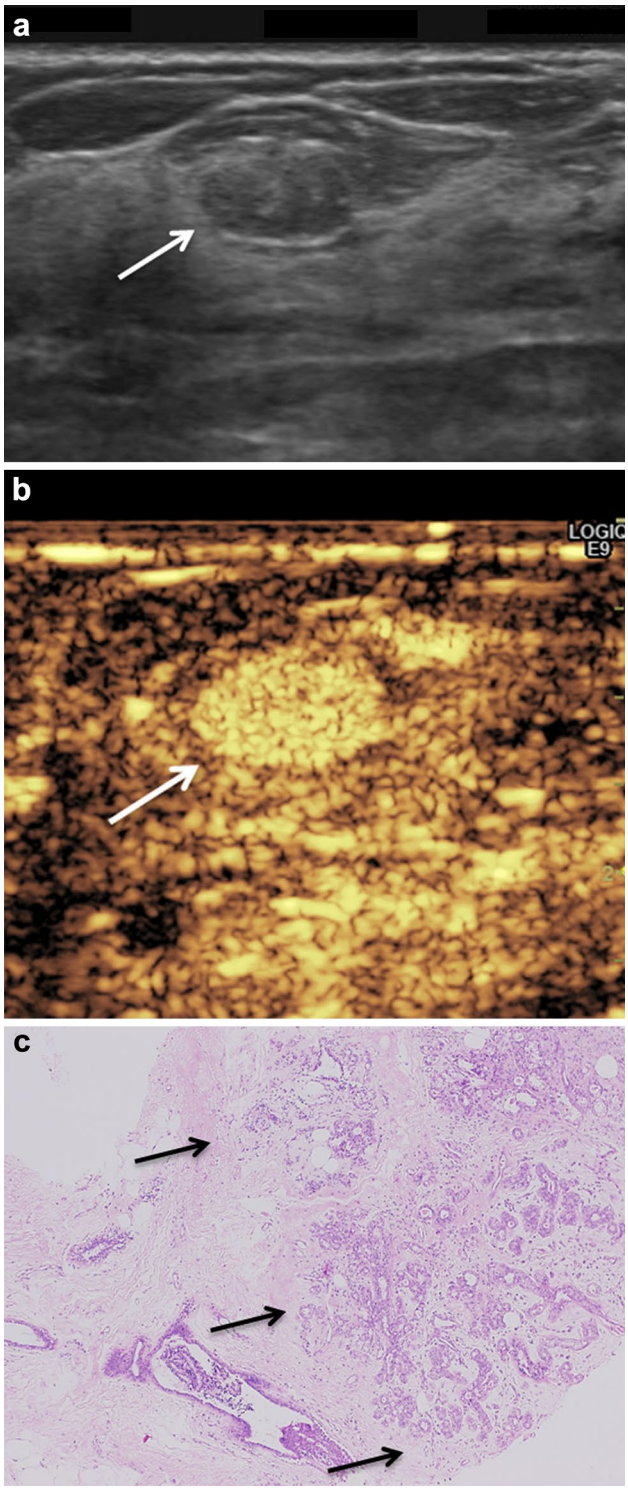


Fig. 1 Pathologically proven fibroadenoma in a 65-year-old female. **a** Conventional sonography revealed an oval-shaped, well-circumscribed mass of 10 mm in its greatest dimension, with an internal echogenicity similar to that of the adjacent adipose tissue, associated with slight posterior acoustic enhancement (*arrows*). **b** Contrast-enhanced sonography showed homogeneous enhancement of the lesion, corresponding to a type 2 enhancement pattern (*arrows*). The Axk value was semi-automatically calculated to be 3.82 (time-intensity curve not shown). **c** Microscopic appearance of the lesion (H&E ×100). *Arrow* indicates the boundary of the lesion

Multivariate analysis revealed that only the enhancement pattern was independently significant with the likelihood ratio χ^2 (chi-square) values of 13.1.

Diagnosis using both conventional US and CEUS findings

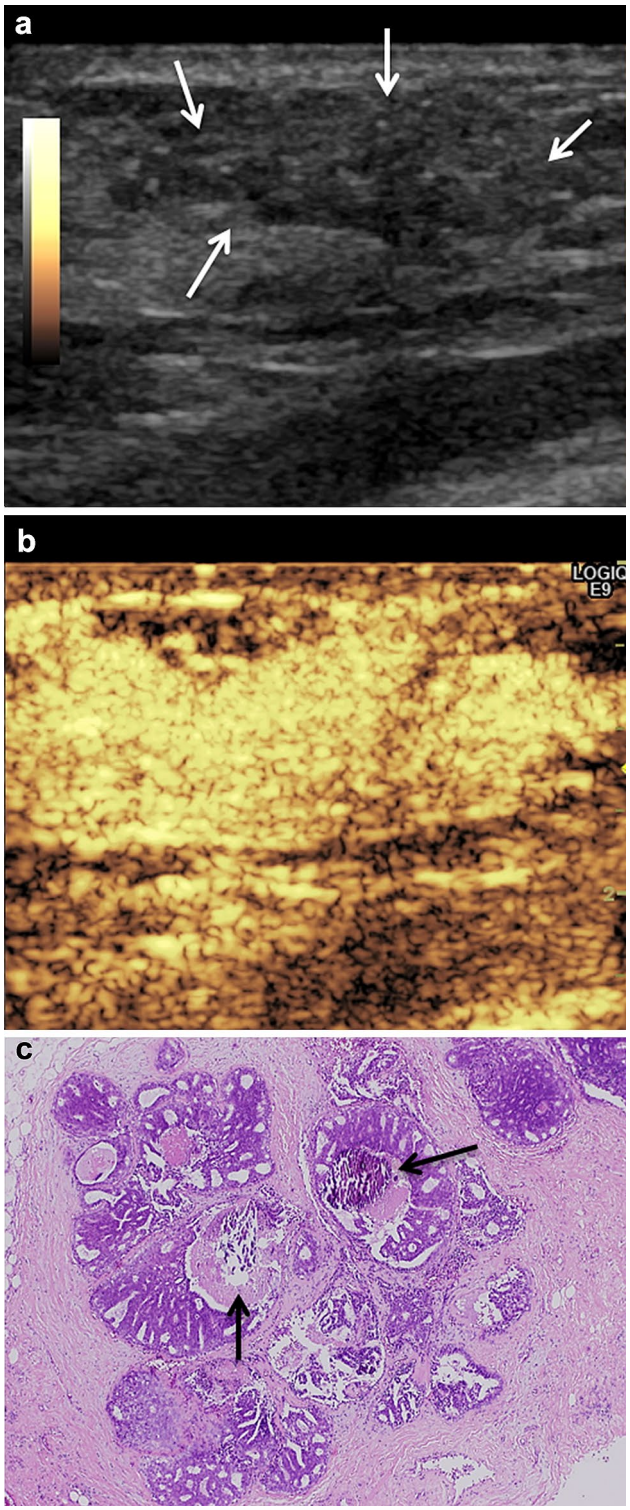
Incorporating the significant parameter in CEUS findings, namely the enhancement pattern, into the diagnosis was attempted using the conventional US findings; however, all eight lesions showing a type 3 enhancement pattern had already been diagnosed as malignant by conventional US findings (two and six lesions were scored as 5 and 4, respectively). Thus, incorporating CEUS findings into conventional US findings did not improve the diagnostic performance in terms of malignant vs. benign differentiation. Representative cases are shown in Figs. 1, 2 and 3.

Discussion

Our results suggested homogeneously enhancing lesions are not necessarily benign, but a considerable number of malignancies (approximately 60 % in our cohort) can be included in this group of lesions. Among these, approximately 75 % of lesions can be correctly diagnosed as benign or malignant by conventional US findings alone, but one quarter of them (18/73) remain indeterminate.

As for CEUS findings, our factor analysis revealed an enhancement pattern, and Axk values were significantly related to the final diagnoses of the lesions.

Actually, all eight lesions showing a type 3 enhancement pattern (the degree of enhancement was greater than that of the surrounding tissue, and the area of enhancement was larger than the hypoechoic lesion on the precontrast images) were IDCs. Histopathological correlation revealed two of these lesions showed strong lymphocytic infiltration around the marginal areas of the lesions (Fig. 3). A similar observation, namely peritumoral enhancement around the IDC, has already been reported, which was attributed to the DCIS component around the IDC, adenosis with lobular hyperplasia or inflammatory cell infiltration around the IDC [5, 9, 10]. A "crab claw-like microvascular architecture" or increased microvessel density or vascular endothelial growth factor expression may be related to these findings [5, 10–12].

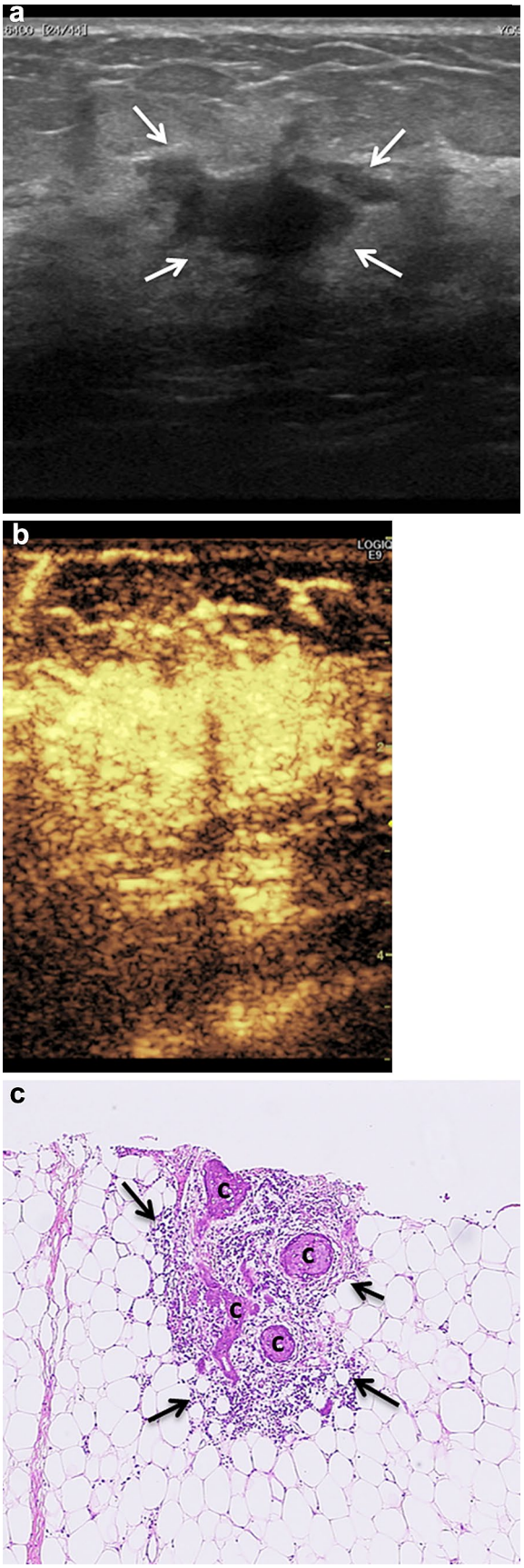


◀**Fig. 2** Ductal carcinoma in situ in a 41-year-old female. **a** Conventional sonography reveals a well-demarcated hypoechoic lesion without mass formation, measuring 30 mm in its greatest dimension (*arrows*). **b** Contrast-enhanced sonography showed homogeneous enhancement of the whole lesion, which is indistinguishable from the background tissue, in keeping with a type 1 enhancement pattern. The Axk value was semi-automatically calculated to be 8.22 (time-intensity curve not shown). **c** Microscopic appearance of the lesion (H&E ×200). *Arrow* indicates the calcification within the lesion

In contrast to the previous reports [1, 6, 9], quantitative indices derived from TIC did not serve to make the differential diagnosis, except for the Axk values, which were useful only in differentiating NSBL from IP. NSBL and IP tended to show lower and higher Axk values, respectively, among the disease entities included in this study. NSBL in our population consisted of fibrocystic changes or adenosis with or without slight inflammatory cell infiltration, possibly representing mastopathy or chronic mastitis. We presume angiogenic features may be similar regardless of their benignity or malignancy in this particular cohort. In addition, multivariate analysis revealed that only the enhancement pattern, not Axk, was the independently significant factor in the differential diagnosis.

Adding the significant factors derived from CEUS, namely the enhancement pattern, however, did not improve diagnostic performance solely based on conventional US findings. All lesions showing a type 3 enhancement pattern had readily been diagnosed as malignant using conventional US findings (Table 1). Thus, CEUS findings, either qualitative or quantitative, added little to the differential diagnosis of homogeneously enhancing lesions on CEUS. We therefore recommend reviewing the conventional US findings meticulously when dealing with the lesions in this particular cohort.

There are several limitations to this study, in addition to the retrospective nature. First, although the total number of subjects was over 70, there were both benign and malignant lesions including various entities of limited number, and therefore our result may not be applicable to different cohorts of different disease configurations. Ideally, our results should have been tested in another cohort consisting of homogeneously enhancing lesions. Second, because the enhancement pattern of the lesions was assessed as compared to that of the background breast tissue, the results would have been affected by the condition of the background tissue, for example, because of the menstrual cycle or age-related fatty changes, in addition to that of the lesions themselves. Third, placement of the ROI to create the TIC and subsequent quantitative index measurements were performed by one radiologist, which may have caused some bias in the results. Fourth, the qualitative assessment was made by two radiologists in consensus, not by independent interpretation, which also may have resulted in some bias. Further prospective study with a larger population and meticulous design is needed to solve these problems.



◀**Fig. 3** Invasive ductal carcinoma in a 49-year-old female. **a** Conventional sonography reveals an irregularly shaped hypoechoic mass of 24 mm in its greatest dimension, showing a spiculated margin and slight posterior shadowing (*arrows*). **b** Contrast-enhanced sonography showed homogeneous enhancement, the size of which was larger than the hypoechoic area as observed on the precontrast image, in keeping with the type 3 enhancement pattern. The Axk value was 3.08 (time-intensity curve not shown). **c** Pathological specimen reveals prominent lymphocytic infiltration (*arrows*) around the margin of the lesion (**c**), which may explain the extensive peritumoral enhancement (H&E ×200)

In conclusion, radiologists should be aware that almost half of the homogeneously enhancing lesions on CEUS are malignant, and differentiation of malignant from benign lesions may be possible, at least to some extent, by meticulously referring to the conventional US findings, not to the CEUS findings.

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Compliance with ethical standard

Conflict of interest The authors have no conflicts of interest to declare.

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