Radiology

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Downgrading of Breast Masses Suspicious for Cancer by Using Optoacoustic Breast Imaging[1]

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Conflicts of interest are listed at the end of this article.

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Purpose: To assess the ability of optoacoustic (OA) ultrasonography (US) to help correctly downgrade benign masses classified as Breast Imaging Reporting and Data System (BI-RADS) 4a and 4b to BI-RADS 3 or 2.

Materials and Methods: OA/US technology uses laser light to detect relative amounts of oxygenated and deoxygenated hemoglobin in and around suspicious breast masses. In this prospective, multicenter study, results of 209 patients with 215 breast masses classified as BI-RADS 4a or 4b at US are reported. Patients were enrolled between 2015 and 2016. Masses were first evaluated with US with knowledge of previous clinical information and imaging results, and from this information a US imaging–based probability of malignancy (POM) and BI-RADS category were assigned to each mass. The same masses were then re-evaluated at OA/US. During the OA/US evaluation, radiologists scored five OA/US features, and then reassigned an OA/US-based POM and BI-RADS category for each mass. BI-RADS downgrade and upgrade percentages at OA/US were assessed by using a weighted sum of the five OA feature scores.

Results: At OA/US, 47.9% (57 of 119; 95% CI: 0.39, 0.57) of benign masses classified as BI-RADS 4a and 11.1% (three of 27; 95% CI: 0.03, 0.28) of masses classified as BI-RADS 4b were correctly downgraded to BI-RADS 3 or 2. Two of seven malignant masses classified as BI-RADS 4a at US were incorrectly downgraded, and one of 60 malignant masses classified as BI-RADS 4b at US was incorrectly downgraded for a total of 4.5% (three of 67; 95% CI: 0.01, 0.13) false-negative findings.

Conclusion: At OA/US, benign masses classified as BI-RADS 4a could be downgraded in BI-RADS category, which would potentially decrease biopsies negative for cancer and short-interval follow-up examinations, with the limitation that a few masses may be inappropriately downgraded.

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Breast cancer is the most common malignant disease and the most common cause of death among women worldwide, and is associated with a substantial medical need and economic burden (1). Nevertheless, the survival rate has improved during the last 2 decades because of a combination of improvement of imaging tools that enabled earlier detection, more effective treatments, and better supportive care (2–4).

The three most important imaging modalities for detection and evaluation of breast abnormalities are mammography, magnetic resonance (MR) imaging, and conventional diagnostic ultrasonography (US) (5). Although breast imaging modalities have a substantial role in early detection of breast cancer, it is challenging to correctly diagnose a malignant mass without performing a biopsy (6,7). This is because of the histopathologic heterogeneity of these tumors, which have variable molecular profiles and growth patterns, contributing to the extensive variability in their morphologic manifestations at imaging. Moreover, breast cancer may go undetected at imaging because both benign and malignant lesions can be obscured by the surrounding normal breast tissue (8–10).

US imaging has a major role in guided breast biopsies. However, the reported rates of US-guided biopsies with results positive for cancer are low, varying from 7.9% to 17.0%, which results in many biopsies of benign masses (9,11–17). In retrospect, many of these biopsies negative for cancer might be considered unnecessary because they result in increased emotional distress for patients and higher overall costs related to interventional procedures and short-interval follow-up imaging studies. Among the greatest challenges in US breast imaging are to improve the differentiation between benign and malignant lesions,

Abbreviations

BI-RADS = Breast Imaging Reporting and Data System, CI = confidence interval, OA = optoacoustic, POM = probability of malignancy

Summary

Of benign masses classified as Breast Imaging Reporting and Data System (BI-RADS) 4a, 47.9% were downgraded to BI-RADS 3 or BI-RADS 2, potentially decreasing both biopsies negative for cancer and the need for short interval follow-up imaging examinations; additional research may be helpful in further minimizing the low (4.5%) rate of false-negative findings.

Implications for Patient Care

- Optoacoustic (OA) US may improve the distinction between benign and malignant masses compared with US alone.
- With OA/US, many benign masses classified as Breast Imaging Reporting and Data System (BI-RADS) 4a (ie, suspicious for cancer) at US could be downgraded to BI-RADS 3 or 2.
- OA/US has the potential to downgrade benign breast masses that are suspicious at US, which could decrease the number of biopsies negative for cancer and short interval follow-up imaging examinations.

to concurrently maximize sensitivity and specificity, to decrease false-positive findings while minimizing false-negative findings, and to decrease the number of biopsies negative for cancer.

Optoacoustic (OA) imaging combined with conventional US is a fusion diagnostic imaging technology that could address these challenges. OA/US fuses laser light with US, showing the morphologic structure together with functional information given by laser light. At OA/US imaging, laser light is transmitted into the breast from a hand-held duplex probe (OA and US) at two different wavelengths. The energy from laser light is absorbed by hemoglobin, which becomes warmer and briefly thermoelastically expands, producing a pressure wave that subsequently can be received as a US wave by the transducer within the duplex probe. The shorter of the two wavelengths (757 nm) is absorbed relatively more by deoxygenated hemoglobin, whereas the longer wavelength (1064 nm) is absorbed relatively more by oxygenated hemoglobin. The OA signals are coregistered (fused) with gray-scale US images, colorized for relative degrees of oxygenation and deoxygenation, and are interleaved with nonfused gray-scale US frames in real time. OA/US essentially creates a fused real-time hemoglobin map that shows presence or absence of blood vessels (including tumor angiogenic vessels), morphologic structure of vessels, and relative degrees of oxygenation or deoxygenation. Gray-scale US and OA/US demonstration of blood vessels represent morphologic features, whereas the relative degree of oxygenation or deoxygenation of the vessels represents functional information. The addition of functional information to morphologic information may help the radiologist to better differentiate between benign and malignant masses, potentially reducing false-positive findings and biopsies negative for cancer particularly in patients with Breast Imaging Reporting and Data System (BI-RADS) 4a- and 4b-classified masses that have low to intermediate risk of malignancy.

Therefore, the aim of this study was to assess the ability of OA/US to help correctly downgrade benign masses classified as BI-RADS 4a and 4b to BI-RADS 3 or 2.

Materials and Methods

This prospective, controlled, and multicenter study took place in five centers in the Netherlands between March 2015 and February 2016. The study was approved by the ethical boards of the participating hospitals and written informed consent was obtained from all patients. Seno Medical Instruments (San Antonio, Tex) provided equipment and financial support for this study. P.T.L. works for Boston Biostatistics Research Foundation, which has a research contract with Seno Medical Instruments to provide study design and analysis services. The remaining authors have no conflicts of interest and have control of inclusion of any data and information that might present a conflict of interest for P.T.L. All investigators (R.M.P., C.M., R.B., J.V., and R.M.) are dedicated breast radiologists with a minimum of 5 years of experience and underwent formal training in the performance and interpretation of OA/US examinations (Appendix E1 [online]). All investigators were familiar with the use of BI-RADS subcategories.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: women 18 years or older with at least one mass classified as BI-RADS 4a or 4b (and a corresponding probability of malignancy ranging from >2% to 50%) according to US imaging performed previously by using conventional site US equipment. All selected participants underwent an OA/US evaluation after conventional US, following consent and before biopsy. The investigators evaluated all patients in a nonblinded manner with access to all participant data and background clinical information (except histopathologic results). Histopathologic results were the reference standard with which OA/US results were compared. All masses underwent an image-guided core-needle biopsy, directional vacuum-assisted biopsy, and/or excisional biopsy of the same mass within 30 days of enrollment and after the OA procedure had been performed and interpreted. The exclusion criteria were as follows: patients with a condition that could interfere with the intended field of view (within one probe length or 4 cm of the mass), such as tattoos, skin rash, hematoma, or ecchymosis; patients with a condition such as porphyria, lupus erythematosus, or any kind of photosensitivity; patients who had previous biopsy or surgery in the mass of interest; patients who had previous biopsy or surgery within the same quadrant or quadrants as the mass or masses to be biopsied; patients with mastitis; pregnant or lactating women; patients who received neoadjuvant chemotherapy within the last 90 days before the examination; and patients in whom the mass to be biopsied was bigger than 3.0 cm in maximum diameter (Appendix E1 [online]). Patients with more than three lesions were excluded. Depth of lesion was not an exclusion criterion.

Scan Protocol and Estimator

After undergoing a conventional US examination, patients underwent an investigator-performed hand-held OA/US evaluation (Imagio; Seno Medical Instruments). We used four conventional US diagnostic devices (Acuson S2000, 18 L6 HD transducer, Siemens Medical Solutions, Mountain View, Calif; Aplio 500, 12 L5 and 18 L7 transducers, Toshiba, Tokyo,

Table 1: Optoacoustic US Feature Scoring and the Positive Predictive Values for Each Score

Score	Explanation	PPV
Internal features score		
OA/US internal vascularity and deoxygenation (vessel score)		
0	No internal vessels	26.7 (4/15)
1	Normal internal vessels without branches, red or green	14.0 (7/50)
2	Normal internal vessels with branches, mostly green	34.0 (33/97)
3	Internal speckle; green = red in amount and less red than background	35.7 (10/28)
4	Internal speckle or signal; red > green and red > background	43.5 (7/16)
5	Multiple internal red vessels	85.7 (6/7)
OA/US internal tumor blush and deoxygenation (blush score)		
0	No internal vessels	14.3 (2/14)
1	Minimal internal speckle, all green	29.7 (19/64)
2	Mild internal speckle; red = green and red + green < background	24.1 (21/87)
3	Mild internal speckle; red > green and both < background	48.1 (13/27)
4	Moderate internal speckle; red > green and red also > background	57.1 (8/14)
5	Red blush almost fills lesion	57.1 (4/7)
OA/US relative internal Hgb (Hgb Score)		
0	No internal Hgb	22.2 (2/9)
1	Minimal internal Hgb, less Hgb than background	30.9 (25/81)
2	Minimal internal Hgb in discrete vessels, Hgb = background	29.1 (16/55)
3	Moderate internal Hgb in discrete vessels, Hgb = background	28.2 (11/39)
4	Many large internal vessels containing Hgb amount > background	42.9 (9/21)
5	Many large Hgb filled vessels almost fill central nidus of mass	50.0 (4/8)
	OA/US External BZ Vascularity and Deoxygenation (BZ Score)	
OA/US capsular/BZ vessels		21.7 (5/23)
1	Normal capsular/BZ vessel(s) without branches (long, curved, parallel to capsule, not perpendicular to capsule)	15.0 (9/60)
2	Normal capsular/BZ vessel(s) with normal tapering acutely angled branches, mostly green	13.0 (6/46)
3	Capsular/BZ speckle; green = red; red < background red	37.5 (9/24)
4	Capsular/BZ speckle; red > green; red > background red	55.9 (19/34)
5	≥3 capsular/BZ red vessels, some perpendicular	73.9 (17/23)
6	Boundary zone deoxygenated blush (complete or partial)	66.7 (2/3)
OA/US peripheral zone radiating vessels score (peripheral zone score)		
0	No peripheral zone peritumoral vessels	19.2 (5/26)
1	1 or 2 peripheral zone feeding or draining vessels, at least one green, not in a radiating pattern	16.7 (12/72)
2	> 2 peripheral zone vessels, but random orientation, not radiating perpendicular to the surface of the mass	20.3 (12/59)
3	1 or 2 peripheral zone radiating vessels	73.7 (14/19)
4	> 2 peripheral zone radiating vessels on one side of the mass	61.5 (8/13)
5	> 2 peripheral zone radiating vessels on more than one side of the mass	66.7 (16/24)

Note.—Data are percentages and data in parentheses are numerator/denominator. There were a total of 215 lesions. Two high-risk lesions were excluded from this table. The reference keys for scoring each of the optoacoustic US features displayed in this table can be seen in Appendix E1 (online). BZ = boundary zone, Hgb = hemoglobin, PPV = positive predictive value, OA = optoacoustic.

Japan; Acuson 300, VF10–5 transducer, Siemens; and Prosound ×6, UST-5546 transducer, Hitachi Medical Systems Europe Holding AG, Zurich, Switzerland). After OA/US evaluation, patients were asked to complete a patient satisfaction survey.

On the basis of images obtained at OA/US, investigators estimated the probability of malignancy (POM) on a scale from 0% to 100% and, when appropriate, adjusted the previously conventional US-assigned BI-RADS classification (18,19). Five OA/US features were scored (19). Table 1 shows the scoring system used by investigators. For more details regarding the imaging protocol, POM adjustment, estimators, OA/US feature scoring, and reference keys for OA/US scoring, see Appendix E1 (online).

Biopsy and Histopathologic Analysis

Regardless of the outcome at OA/US, a biopsy was performed after the OA/US examination solely on the basis of findings at conventional imaging (BI-RADS 4a or 4b). All biopsied masses (and surgical specimens when available) underwent central pathologic review by an independent histopathologist. The central histopathologic diagnosis was considered the reference standard for OA/US comparison. In malignant masses inappropriately downgraded to BI-RADS 2 and 3, a comparison was made between the central pathologic review and the OA images to clarify possible reasons for a downgrade of false-negative findings. For more information regarding histopathologic analysis, see Appendix E1 (online).

Statistical Methods

With 210 qualifying masses expected among 200 eligible participants, approximately 140 benign and 70 malignant masses were projected. Benign mass downgrades and malignant mass upgrades were evaluated by using a one-sided binomial test with overall 2% type I error and greater than 80% power ($P <$ .05). Benign mass downgrades and malignant mass upgrades were also evaluated. Downgrade and upgrade percentages were analyzed at the mass level. The rates of true-positive, true-negative, false-positive, and false-negative findings were recorded. On the basis of the rates of false-negative, true-negative, true-positive, and false-positive findings, likelihood ratios were also calculated. The 95% confidence interval (CI) of all ratios was calculated. The decision about whether to upgrade or downgrade the POM and BI-RADS category of a mass from its US-assigned POM and BI-RADS category with OA/US was made by investigators on the basis of their OA/US feature scoring and OA/US feature scoring-based estimators. The same calculations performed by Neuschler et al (19) (ie, regression models) were performed in our study to show how estimators help to distinguish benign versus malignant masses. Wilcoxon rank-sum test was used to compute the two-sided *P* values and two-sided 99% CIs for the difference between benign versus malignant masses (for the three internal OA/US and two external OA/US features). Bland-Altman plots with 96% CI were calculated to show the mean differences between OA/US POM and US POM regarding benign and malignant masses. OA/US scores for the malignant and benign masses in different OA/US categories were also calculated (including the positive predictive value, the means, and the 99% CIs for external OA/US-feature scores vs internal OA/US feature scores). Mean sizes of benign and malignant lesions ± standard deviation were also calculated.

The 10-subject satisfaction scores were evaluated by using a 1–5 ordinal scale. Outcomes were evaluated as means. Data were analyzed by using statistical software (SPSS version 20.0; IBM, Armonk, NY).

Results

We enrolled 217 patients with 223 mass lesions. Three patients were excluded because of technical failure (not exposed to OA), two patients were excluded because of the absence of histologic analysis (no biopsy or only cytology was performed), two patients were excluded because of missing OA/US scores, and one patient was excluded because of a major protocol deviation (age, <18 years). Therefore, 209 patients with 215 lesions were included in the intention-to-diagnose population. The mean age of these patients was 49.2 years ± 14.7 (patients with benign masses: mean age, 45.9 years ± 14.4; patients with malignant masses: mean age, 56.7 years ± 12.6). The mean size of the 215 masses was 1.41 cm ± 0.78 (95% CI: 1.30, 1.51; mean size for benign masses and for malignant masses, 1.43 cm ± 0.85 and 1.36 cm ± 0.60, respectively). A study flow diagram from participants prescreened to the intention-to-diagnose population is shown in Appendix E1 (online). Scan time took on average 15:42 minutes ± 6:57 minutes (range, 4–54 minutes). Tables 2 and 3 show OA/US true-negative, true-positive, false-negative, and false-positive findings according to the participant characteristics and histopathologic results, respectively.

Of 215 masses, 68.0% (146 of 215; 95% CI: 61.0%, 74.0%) were benign, 31.1% (67 of 215; 95% CI: 25.0%, 38.0%) were malignant, and 0.9% (two of 215; 95% CI: 0%, 3.0%) were high-risk lesions.

Among the 146 benign lesions, 81.5% (119 of 146; 95% CI: 74.0%, 87.0%) were classified as BI-RADS 4a and 18.5% (27 of 146; 95% CI: 13.0%, 26.0%) were classified as BI-RADS 4b at conventional US. Sixty benign masses were correctly downgraded from BI-RADS 4a or 4b to BI-RADS 3 or 2 ($P <$ .0001) by using OA/US. From the benign masses classified as BI-RADS 4a, 47.9% (57 of 119; 95% CI: 39.0%, 57.0%) were downgraded to BI-RADS 3 or 2 and 12.3% (18 of 146; 95% CI: 7.0%, 19.0%) were upgraded from BI-RADS 4a to 4b. Of 27 benign masses classified as 4b, 11.1% (three of 27; 95% CI: 3.0%, 29.0%) were downgraded to BI-RADS 3, 6.1% (nine of 146; 95% CI: 3.0%, 11.0%) were upgraded to BI-RADS 4c, and 0.6% (one of 146; 95% CI: 0%, 4.0%) was upgraded from 4b to 5. Figure 1 shows an example of benign mass downgraded with OA/US.

Of malignant masses, seven were classified at conventional US as BI-RADS 4a and 60 were classified as BI-RADS 4b. Among the 67 malignant masses, 1.4% (one of 67; 95% CI: 0%, 8.0%) was upgraded from BI-RADS 4a to 4b, 44.7% (30 of 67; 95% CI: 33.0%, 57.0%) were upgraded from BI-RADS 4b to 4c, and 3.0% (two of 67; 95% CI: 0%, 10.0%) were upgraded from 4b to 5 (gross, 49.5% true-positive upgrades).

Among BI-RADS 4a and 4b masses, the rate of true-negative findings for OA/US was 41.1% (60 of 146; 95% CI: 33.0%, 50.0%), and the rate of false-positive findings was 58.9% (86 of 146; 95% CI: 50.0%, 67.0%). Figures 2 and 3 show malignant masses upgraded at OA/US. The rate of true-positive findings at OA/US was 95.5% (64 of 67; 95% CI: 87.0%, 99.0%) and it was 4.5% (three of 67; 95% CI: 1.0%, 13.0%) for false-negative findings. These three false-negative masses represented two invasive ductal carcinomas and one invasive lobular carcinoma. All false-negative findings were in the first 50 patients included in the study. None of the false-negative masses were because of inadequate depth penetration of laser light. The depth to the middle of the mass was less than 1.0 cm in two masses and 1.52 cm in the third mass. In two

Table 2: Optoacoustic US Findings according to the Participant Characteristics

Parameter	TN Findings that Affected Biopsy	TP Findings that Affected Biopsy	Findings that Affected Biopsy	FP Findings that Affected Biopsy	TN Findings that Did Not Affect Biopsy*	Findings that Did Not Affect Biopsy†	FN Findings that Did Not Affect Biopsy‡	FP Findings that Did Not Affect Biopsy§	No Change in Classification	Total No. of Participants
Group with 209 participants										
Postmenopausal (No)‖	13 (19.7)	0	1 (1.6)	0	2 (3.0)	20 (30.3)	2 (3.0)	14 (21.2)	14 (21.2)	66
Premenopausal (Yes)‖	38 (34.5)	0	2 (1.8)	0	1 (0.9)	9 (8.1)	3 (2.7)	11 (10.0)	46 (42.0)	110
Perimenopausal‖	7 (38.8)	0	0	0	0	2 (11.2)	0	2 (11.2)	7 (38.8)	18
Age <50 y	38 (34.3)	0	1 (0.9)	0	1 (0.9)	10 (9.0)	1 (0.9)	12 (10.8)	48 (43.2)	111
Age 50–59 y	17 (32.8)	0	1 (1.9)	0	0	8 (15.4)	5 (9.6)	6 (11.5)	15 (28.8)	52
Age 60–69 y	3 (11.1)	0	0	0	2 (7.5)	5 (18.5)	0	6 (22.2)	11 (40.7)	27
Age ≥70 y	2 (10.6)	0	1 (5.3)	0	0	9 (47.4)	0	4 (21.0)	3 (15.7)	19
Group with 215 participants										
Mass size < 1 cm	23 (32.0)	0	1 (1.4)	0	1 (1.4)	7 (9.8)	3 (4.2)	11 (15.2)	26 (36.0)	72
Mass size 1–2 cm	26 (27.4)	0	1 (1.0)	0	1 (1.0)	17 (18.0)	1 (1.0)	7 (7.4)	42 (44.2)	95
Mass size ≥ 2 cm	11 (23.0)	0	1 (2.0)	0	1 (2.0)	9 (18.8)	2 (4.1)	10 (21.0)	14 (29.1)	48
Breast density A#	4 (20.0)	0	1 (5.0)	0	0	4 (20.0)	1 (5.0)	0	10 (50.0)	20
Breast density B#	12 (19.7)	0	0	0	3 (5.0)	15 (25.0)	1 (1.1)	10 (16.4)	20 (32.8)	61
Breast density C#	19 (29.2)	0	0	0	0	10 (15.4)	3 (4.6)	9 (13.8)	24 (37.0)	65
Breast density D#	22 (40.8)	0	2 (3.7)	0	0	3 (5.5)	1 (1.8)	7 (13.0)	19 (35.2)	54
Not palpable**	24 (29.6)	0	1 (1.2)	0	0	9 (11.1)	3 (3.7)	15 (18.6)	29 (35.8)	81
Palpable**	33 (26.7)	0	2 (1.6)	0	3 (2.4)	22 (17.7)	3 (2.4)	11 (8.9)	50 (40.3)	124
Distance from nipple <3 cm††	17 (37.0)	0	0	0	1 (2.2)	7 (15.2)	2 (4.4)	6 (13.0)	13 (28.2)	46
Distance from nipple ≥3 cm††	42 (25.0)	0	3 (1.8)	0	2 (1.2)	26 (15.5)	4 (2.4)	22 (13.1)	69 (41.0)	168
Depth to middle mass <1 cm‡‡	30 (36.1)	0	2 (2.4)	0	1 (1.2)	12 (14.5)	1 (1.2)	11 (13.3)	26 (31.3)	83
Depth to middle mass 1 to <2 cm‡‡	24 (20.8)	0	1 (0.9)	0	2 (1.8)	21 (18.2)	3 (2.7)	17 (14.8)	47 (40.8)	115
Depth to middle mass ≥2 cm‡‡	5 (31.2)	0	0	0	0	0	2 (12.5)	0	9 (56.2)	16
Overall	60 (28.0)	0	3 (1.4)	0	3 (1.4)	33 (15.3)	6 (2.8)	28 (13.0)	82 (38.1)	215

Note.—Data are number of participants unless otherwise indicated; data in parentheses are percentages. There were 215 lesions included for mass size, breast density, palpability, distance from the nipple, and depth, and the two high-risk lesions were included in this table. They were neither downgraded nor upgraded at optoacoustic US, but remained with the same Breast Imaging Reporting and Data System (BI-RADS) classification (ie, no change in classification). There were 209 lesions included for menopausal status and age. The breast densities A, B, C, and D indicate breasts with less than 25% fibroglandular tissue, between 25% and 50% fibroglandular tissue, 50%–75% fibroglandular tissue, and more than 75% fibroglandular tissue, respectively. FN = false negative, FP = false positive, OA = optoacoustic, TN = true negative, TP = true positive.

* BI-RADS category 4b lesions downgraded to BI-RADS 4a. This would have no impact in biopsy as all masses classified as BI-RADS 4a or higher should undergo biopsy.

† BI-RADS 4a masses upgraded to 4b or higher and BI-RADS 4b masses upgraded to 4c or higher. This would have no impact in biopsy as all masses classified as BI-RADS 4a or higher should undergo biopsy6

‡ BI-RADS 4b downgraded to BI-RADS 4a. This would have no impact in biopsy as all masses classified as BI-RADS 4a or higher should undergo biopsy.

§ BI-RADS 4a and 4b upgraded to a higher BI-RADS category. This would have no impact in biopsy as all masses classified as BI-RADS 4a or higher should undergo biopsy.

‖ Fifteen patients underwent hysterectomy/oophorectomy or it was not possible to determine the menopausal status.

Breast density was not available for 15 masses.

** In 10 masses, data were missing whether the mass was palpable or not.

†† In one lesion distance from the nipple was not recorded.

‡‡ In one lesion depth was not reported.

Table 3: Optoacoustic US Findings according to Histopathologic Results

Parameter	TN Findings with Effect at Biopsy	TP Findings with Effect at Biopsy	FN Findings with Effect at Biopsy	FP Findings with Effect at Biopsy	TN Findings without Effect at Biopsy*	TP Findings without Effect at Biopsy†	FN Findings without Effect at Biopsy‡	FP Findings without Effect at Biopsy§	No change in Classification	Total
Benign lesions										
Fibroadenoma	35 (46.7)	0	0	0	1 (1.3)	0	0	10 (13.3)	29 (38.7)	75
Papilomas	1 (16.7)	0	0	0	0	0	0	3 (50.0)	2 (33.3)	6
Benign phyllodes tumor	0	0	0	0	0	0	0	0	1	1
Microcystic change	7 (43.7)	0	0	0	0	0	0	3 (18.7)	6 (37.6)	16
Other benign lesions	17 (35.4)	0	0	0	2 (4.2)	0	0	12 (25.0)	17 (35.4)	48
Malignant lesions										
Invasive breast cancer ductal NOS	0	0	2 (4.2)	0	0	24 (51.0)	0	4 (8.5)	17 (36.3)	47
Invasive breast cancer lobular	0	0	1 (12.5)	0	0	3 (37.5)	1 (12.5)	0	3 (37.5)	8
Encapsulated papillary carcinoma	0	0	0	0	0	3 (100.0)	0	0	0	3
DCIS	0	0	0	0	0	1 (50.0)	0	0	1 (50.0)	2
Others	0	0	0	0	0	2 (28.6)	1 (14.3)	0	4 (57.1)	7
High-risk lesions										
LCIS									1 (100)	1
Radial scar									1 (100)	1
Overall	60 (28.0)	0	3 (1.4)	0	3 (1.4)	34 (15.8)	2 (0.8)	30 (14.0)	83 (38.6)	215

Note.—Data are lesions; data in parentheses are percentages. There were 215 lesions. The two high-risk lesions were included in this table. They were neither downgraded nor upgraded at optoacoustic US, but remained with the same Breast Imaging Reporting and Data System (BI-RADS) classification (no change in classification). DCIS = ductal carcinoma in situ, FP = false-positive, FN = false-negative, LCIS = lobular carcinoma in situ, NOS = not otherwise specified, TN = true-negative, TP = true-positive.

* BI-RADS 4b lesions downgraded to BI-RADS 4a. This would have no effect on biopsy because all masses classified as BI-RADS 4a or higher should undergo biopsy.

† BI-RADS 4a masses upgraded to 4b or higher and BI-RADS 4b masses upgraded to 4c or higher. This would have no effect on biopsy because all masses classified as BI-RADS 4a or higher should undergo biopsy.

‡ BI-RADS 4b downgraded to BI-RADS 4a. This would have no effect on biopsy because all masses classified as BI-RADS 4a or higher should undergo biopsy.

§ BI-RADS 4a and 4b upgraded to a higher BI-RADS category. This would have no effect on biopsy because all masses classified as BI-RADS 4a or higher should undergo biopsy.

false-negative masses, a careful review of OA/US video sweeps showed suspicious findings that could have given the masses (in both situations) a higher OA/US BI-RADS classification, and could have prevented these masses from being incorrectly downgraded. Figure 4 shows an example of a mass that was downgraded from BI-RADS 4a to BI-RADS 2. A careful analysis of the boundary zone shows many short radiating boundary zone vessels with morphologic structures suspicious for cancer, which would result in an OA/US boundary zone score of 5. Therefore, this mass should have been upgraded to BI-RADS 4b (rather than downgraded). In one of the false-negative findings, neither mammography nor conventional US and OA/US could clearly depict suspicious characteristics. The mass was small (0.8 cm), ovoid, and well-circumscribed at mammography and conventional US, and was not palpable. At conventional US it was also hypoechoic, wider than it was tall, and had regular margins. This lesion was classified as BI-RADS 4a by considering the patient's wish to proceed with the investigation and because the lesion had a partial thin hyperechoic capsule. The mass was diagnosed as a rare subtype of lobular carcinoma (an alveolar subtype). The positive likelihood ratio at OA/US was 1.62 (95.5 of 58.9) and the negative likelihood ratio was 0.11 (4.5 of 41.1).

The two high-risk masses were excluded from the downgrade and upgrade analysis because they could not be clearly classified as benign or malignant by the independent histopathologist. Table 4 shows the classification of benign and malignant masses both at conventional US and OA/US. Table E1 (online) shows the OA/US scores for the malignant and benign masses in different OA/US categories. Table E2 (online) shows the histopathologic classification of the lesions found in our study.

The participant satisfaction survey showed that OA/US is acceptable to patients (Table E3 [online]). Approximately 95% of the patients agreed that OA/US had an acceptable level of comfort and 84% agreed that OA/US scan time was acceptable. There were no safety issues related to OA/US.

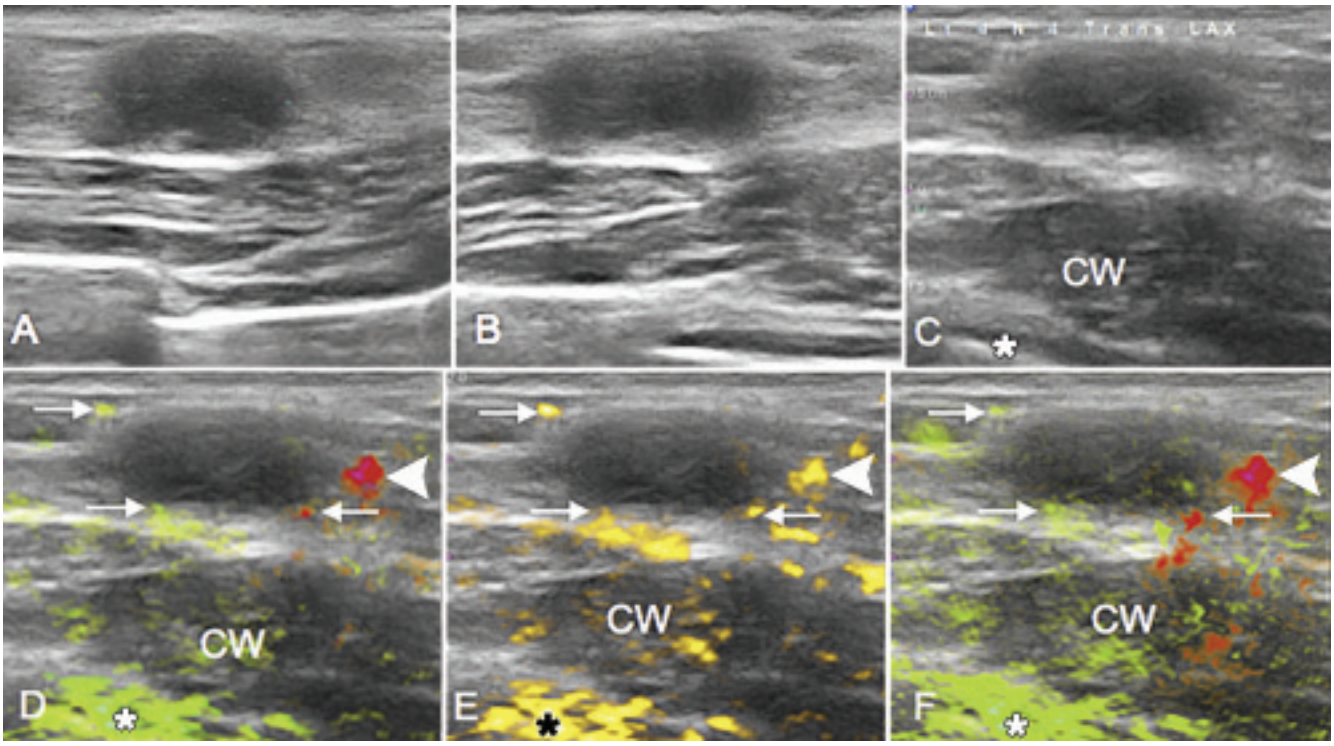

Figure 1: Benign fibroadenoma downgraded with optoacoustic US. A, Longitudinal and, B, transverse US images show an ovoid shaped mass that is parallel in orientation but not well-circumscribed, particularly along the lateral edges of the mass. It was classified Breast Imaging Recording and Data System (BI-RADS) 4a at US. Gray-scale US, C, on the optoacoustic US image shows findings similar to those seen with US on, A and B. D, Optoacoustic US–combined map shows no internal optoacoustic US signal and small round green and red capsular vessels (arrows). There is a large vessel that was noted to be passing by the mass on the real-time short-axis video sweep (arrowheads on D, E, and F). There are some vessels in the chest wall (CW) and artifact reflection signal at the lung-chest wall interface (* on C, D, E, and F). There were no internal or external findings suspicious for cancer. E, The optoacoustic US total hemoglobin map shows no internal hemoglobin and hemoglobin within normal appearing capsular vessels (arrows). F, The optoacoustic US relative map shows more background signal, but no additional findings. All three internal features scores were rated as 0, the boundary and capsular zone was scored as 1, and the peripheral zone vessels were scored as 1. The summed internal scores were 0 and the summed external scores were 2. The estimated probability of malignancy was 1.4% and the mass was correctly downgraded from BI-RADS 4a (at US) to BI-RADS 3 at optoacoustic US.

Discussion

The goal of our study was to determine if OA/US could potentially decrease the number of false-positive findings and lessen both the need for biopsy and short-interval follow-up by downgrading the BI-RADS category of benign breast masses to BI-RADS 3 or 2. Importantly, in this study, 60 benign masses were correctly downgraded from BI-RADS 4a or 4b to BI-RADS 3 at OA/US, highlighting the potential decrease in the number of biopsies with negative findings.

We observed three false-negative findings in our study. Review of the OA/US images of these masses showed that two of the three had interpretive errors. Had the positive OA findings been recognized in these two masses, the true-positive rate would have increased from 95.5% to 98.5%. One of the cases was a category 4a mass downgraded to BI-RADS 2. Such a downgrade may have a negative clinical effect, but it could have been prevented if the radiating vessels observed along the boundary zone on both sides of the mass had been noticed (these are signs that are strongly suggestive of malignancy). These three false-negative cases were among the first 50 included patients, and the investigators were still not completely familiar with the new technique. As with any new procedure, there is a learning curve, and the investigators' lack of experience might have affected these false-negative results. One of the false-negative cases would have been more difficult to prevent because neither mammography, US, nor OA/US could clearly depict characteristics suspicious for cancer. Naturally, there is always an overlap between the features of benign and malignant lesions, which makes absolute distinction difficult.

The negative likelihood ratio of 0.11 found in our study allows a pretest POM of 15.6% to be downgraded to a posttest probability of disease of 2%. Thus, with a negative likelihood ratio of 0.11, masses throughout the entire range of positive predictive values of BI-RADS 4a (>2% to ≤10%) can be downgraded to a posttest probability of 2% or less (BI-RADS 3). A downgrade to BI-RADS 2 is more challenging. With a negative likelihood ratio of 0.11, the lower end of BI-RADS 4a (approximately 3%) can be reduced to posttest POM of approximately 0.33%, and although it is not 0%, it might be low enough to allow a category 4a mass to be downgraded to BI-RADS 2. In our study, eight benign masses were successfully downgraded from BI-RADS 4a to BI-RADS 2 at OA/US. Because the range of positive predictive values of BI-RADS 4b lesions extends from greater than 10% and

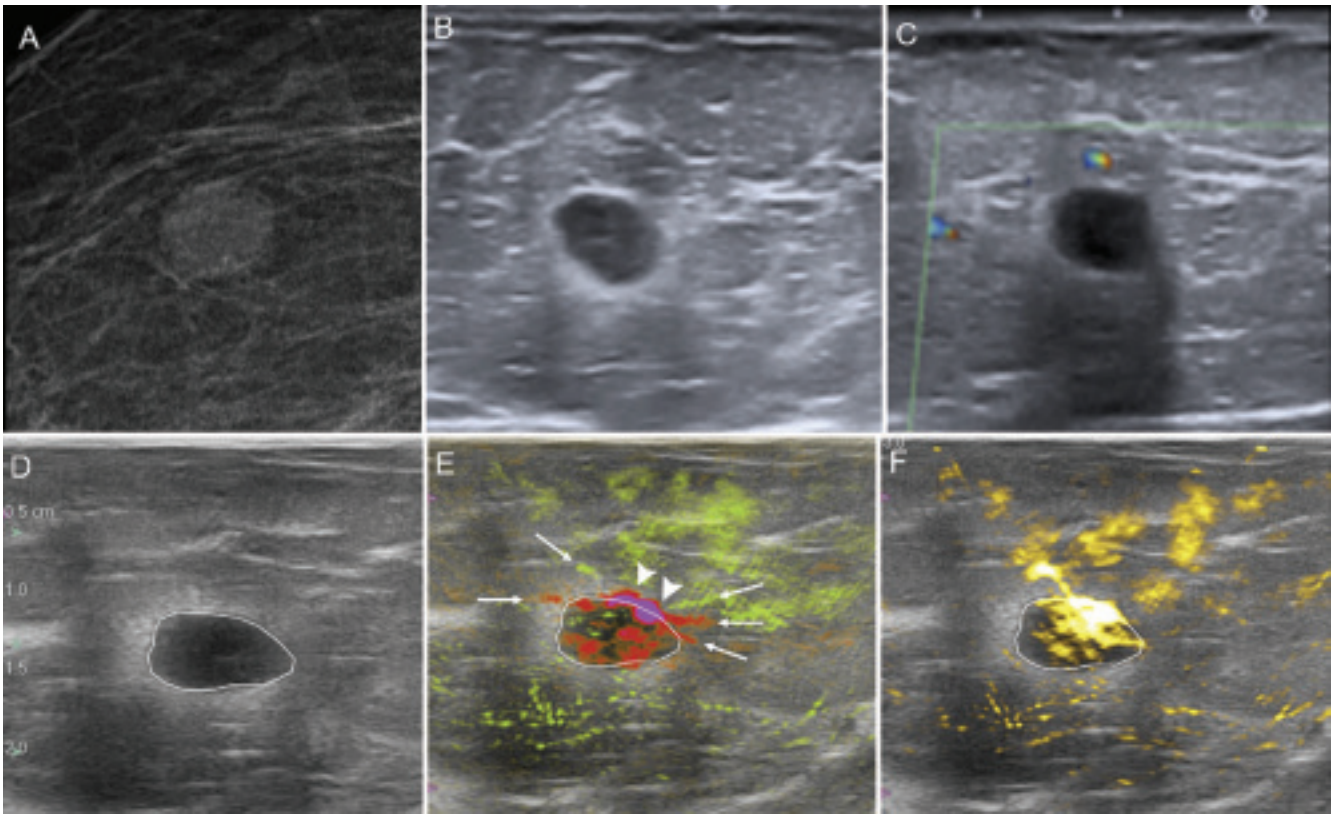

Figure 2: A grade II invasive ductal carcinoma that was upgraded at optoacoustic US. A, Mammography shows a partially circumscribed oval shaped medium density mass in the upper outer quadrant. B, US shows an oval-shaped circumscribed and parallel-oriented hypoechoic mass that has a thin capsule anteriorly but a thick halo posteriorly. Because of the indistinct posterior border with thick halo, the mass was classified as Breast Imaging Recording and Data System (BI-RADS) category 4a. C, Color Doppler shows no internal or capsular vessels. There are normal-appearing small vessels in the surrounding tissue. D, Optoacoustic US shows findings (white segmentation line) similar to those showed at US in B. E, Optoacoustic US combined map shows multiple internal pleomorphic vessels that vary in size, shape, and orientation. Deoxygenated red vessels are seen within the white segmentation line. There is an intense deoxygenated anterior boundary zone blush (arrowheads). There are also multiple short perpendicularly oriented oxygenated and deoxygenated boundary zone neovessels on both sides of the mass (arrows). F, The optoacoustic US total hemoglobin map shows markedly increased hemoglobin within the central tumor nidus (the white segmentation line). The optoacoustic US internal vessel score is 5. The internal hemoglobin score is 5, the boundary zone deoxygenated blush score is 6, and peripheral radiating vessel is 3. The estimator-derived probability of malignancy is 93%. The mass was upgraded from BI-RADS 4a at gray-scale US and Doppler to BI-RADS 4c at optoacoustic US.

50% or less, most lesions included in this category cannot be downgraded without increasing the false-negative rates. For daily clinical practice, the important conclusion is that BI-RADS 4a lesions can potentially be downgraded to BI-RADS 3. Further studies may confirm whether it is reasonable to not follow lesions that could potentially be downgraded to BI-RADS 2.

Previously published studies (20–25) on negative likelihood ratios of current breast diagnostic imaging modalities showed that only masses classified as BI-RADS 4a and 4b have pretest probabilities low enough to be downgraded to BI-RADS 3 or 2 without excessive false-negative findings. Therefore, only BI-RADS 4a and 4b were included in our study. Although BI-RADS 3 masses were not included, it is possible that future work will demonstrate that masses with a negative likelihood ratio of 0.11 classified as BI-RADS 3 (POM, ≤2%) might be downgraded to BI-RADS 2 with a posttest probability of 0.22% or less. Whereas the need for biopsy of malignant masses might not be affected by the 49.2% of masses that were upgraded at OA/US, upgrades of malignant masses at OA/US could increase diagnostic confidence. The potential effects of OA/US on masses originally classified as BI-RADS 2 or 3 that could possibly be wrongly upgraded to BI-RADS 3 or 4 have not been studied; this study evaluated only masses with low to moderate probability of malignancy (BI-RADS 4a or 4b). A multinational registry study including BI-RADS 0, 1, 2, 3, 4, 5, and 6 is now being designed by C.M. and J.V., and the results may help to clarify this question.

This study simulated a real-world clinical situation. The site investigators who performed the OA/US examinations were also able to immediately interpret the results. They had full access to clinical, mammographic, and conventional US information, which is consistent with everyday clinical practice.

In our study all investigators were familiar with the use of BI-RADS 4 subcategories, but radiologists who are not familiar with these same subcategories might have some initial difficulty with this categorization (26). Additionally, the investigators knew that their findings would not alter patient care, and this could have led to differences in willingness to

downgrade lesions. Finally, the investigators were familiar with the use of BI-RADS categories, but possibly were not as comfortable assigning a POM score. This could have affected results because POMs were used in both the conventional US and OA/US assessments. Another limitation of this technique is the fact that penetration of laser light decreases with depth (however, by fusing laser light with US, better penetration can be achieved). In breast tissue, OA can penetrate to approximately 3 cm of depth and, if the breast is 3 cm or more thick, the evaluation of the breast lesions by using OA/US might be more difficult. This study was also limited by the three false-negative masses. Two of these false-negative findings could have been prevented if signs suggestive of malignancy had been observed at OA/US. Additional studies and analyses may help to improve the scoring system used at OA/US, prevent eventual false-negative findings, and improve the technique.

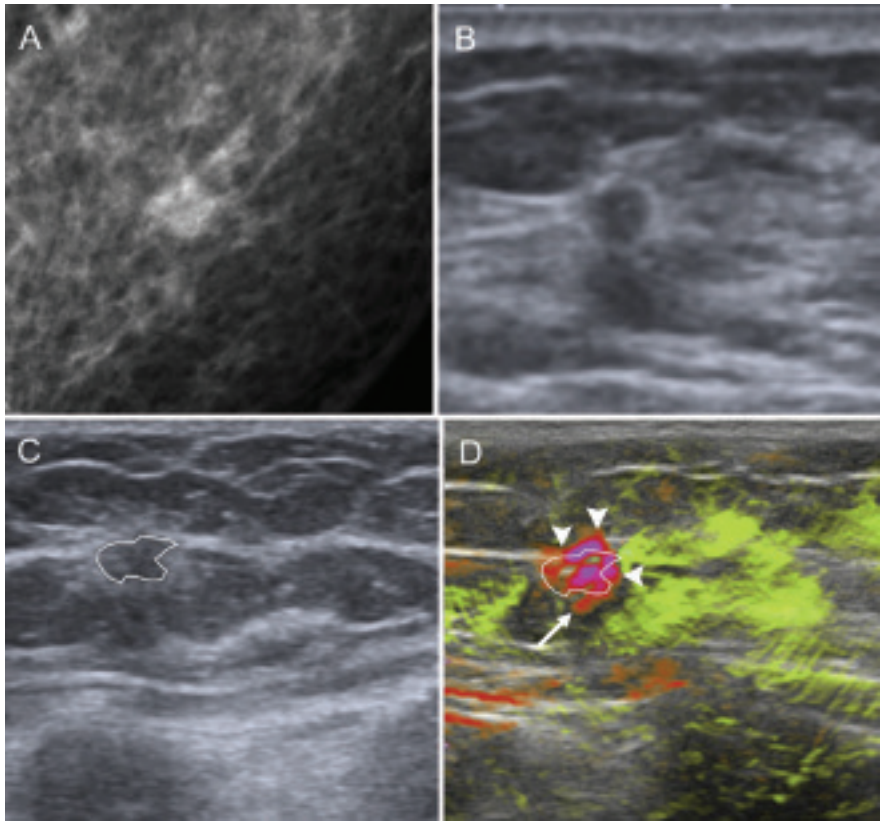

Figure 3: A grade II invasive ductal carcinoma upgraded at optoacoustic US. A, Mammography shows a mildly irregular small indistinct medium density mass. B, US shows a corresponding small round mass with a thick echogenic halo that was classified as Breast Imaging Recording and Data System (BI-RADS) category 4b with a probability of malignancy of 45%. C, Internal US on the optoacoustic US image confirms the mass to be irregular with angles and to have a thick halo (segmentation line). D, The optoacoustic US relative image shows intense deoxygenated blush both within the mass (inside the segmentation line), within the boundary zone (arrowheads), and a single posterior boundary zone deoxygenated vessel (arrow). No peripheral radiating vessels were observed. Together with other maps, internal vessel score was 5, the internal blush score was 5, the internal total hemoglobin score was 5, the boundary zone blush score was 6, and the peripheral zone score was 1. A probability of malignancy of 82% was given and the mass was correctly upgraded to a BI-RADS category 4c.

Previously published studies (27–31) with OA/US have only been performed with small numbers of patients and were mostly preclinical studies focused in description of patient cases. Our study investigated the use of breast OA/US in clinical practice with a relatively high number of patients. Our findings show that OA/US facilitates the distinction between benign and malignant masses. Of benign masses classified as BI-RADS 4a, 47.9% were downgraded to BI-RADS 3 or BI-RADS 2, potentially decreasing both biopsies negative for cancer and the need for short-interval follow-up imaging examinations. From the three false-negative masses found in our study, two masses could have been prevented if OA/US signs suggestive of malignancy had been observed at OA/US. Future analysis and studies performed to improve the scoring system used at OA/US may help to decrease the number of false-negative findings and may help us to unfold the full potential of this technology.

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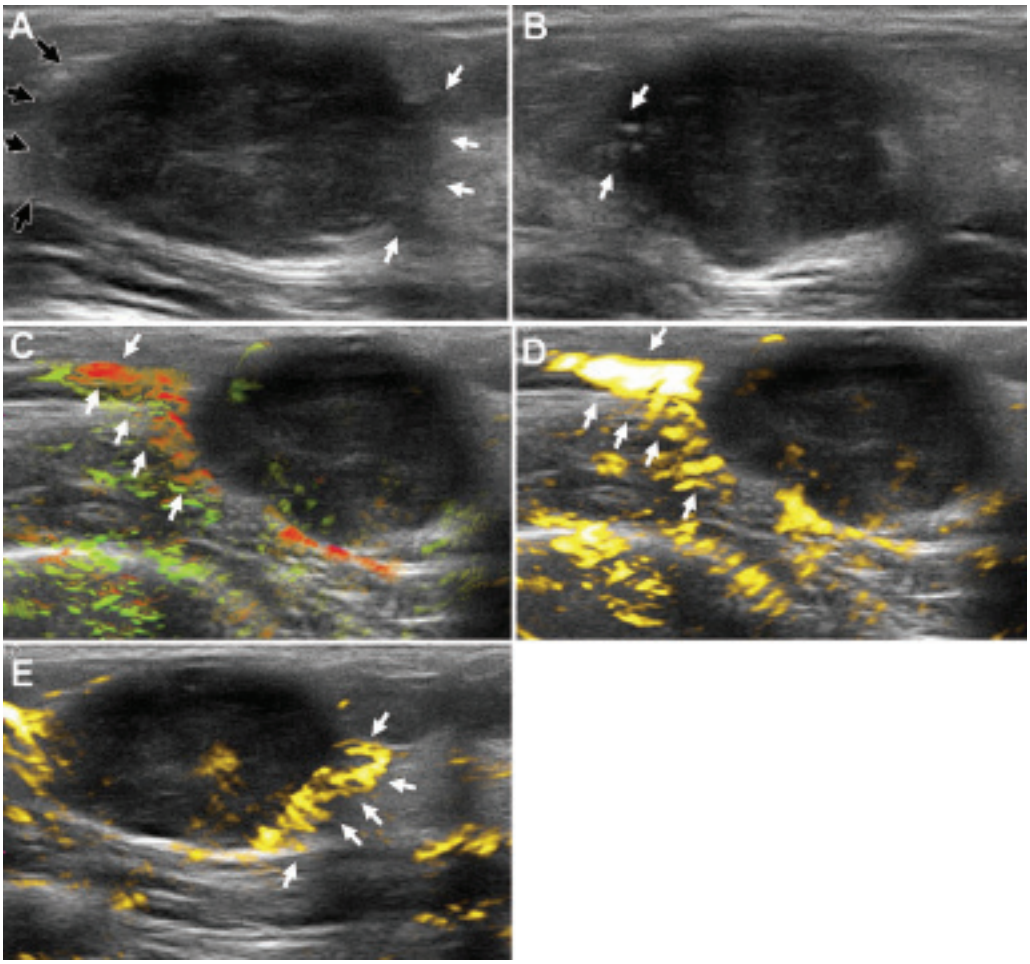

Figure 4: An example of a false-negative mass (an invasive ductal carcinoma grade 3) that was downgraded from Breast Imaging Recording and Data System (BI-RADS) category 4a to BI-RADS 2. A, Irregular (white arrows) and microlobulated (black arrows) margins observed on video sweeps are suggestive of malignancy (these characteristics were not clearly seen on still images). B, Linear and punctate calcifications (arrows) are observed on the side of the lesion. C–E, Many boundary zone vessels that are oriented perpendicular to the surface of the mass, boundary zone whiskers (arrows) are seen along both sides of the lesion, which is strongly suggestive of malignancy. Although optoacoustic US internal and peripheral zone scores are low (all scored 1), these boundary zone whiskers would merit a boundary zone vessel score of 5. Because of the importance of boundary zone findings, even in the absence of other findings suspicious for cancer, a boundary zone score of 5 yields a probability of malignancy of 47% and a high BI-RADS 4b classification. This examination and interpretation was among the first performed in the study and the boundary zone whiskers were not appreciated.

Table 4: Breast Imaging Reporting and Data System Classification of Pathologic Analysis–proven Benign and Malignant Lesions according to US and Optoacoustic US

	Benign Lesions at US		Malignant Lesions at US	
BI-RADS Category at OA/US	Category 4a (*n* = 119)	Category 4b (*n* = 27)	Category 4a (*n* = 7)	Category 4b (*n* = 60)
2	8 (6.7)	0	1 (14.3)	0
3	49 (41.2)	3 (11.1)	1 (14.3)	1 (1.7)
4a	44 (37.0)	3 (11.1)	4 (57.1)	6 (10.0)
4b	18 (15.1)	11 (40.7)	1 (14.3)	21 (35.0)
4c	0	9 (33.3)	0	30 (50.0)
5	0	1 (3.7)	0	2 (3.3)

Note.—Data are lesions; data in parentheses are percentages. High-risk lesions were excluded from this table. Lesions were found to be benign or malignant according to the Breast Imaging Reporting and Data System (BI-RADS) scoring. OA = optoacoustic.

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