Observational Study

Clinical significance of interval changes in breast lesions initially categorized as probably benign on breast ultrasound

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Abstract

The aims of this study were to determine the malignancy rate of probably benign lesions that show an interval change on follow-up ultrasound and to evaluate the differences seen on imaging between benign and malignant lesions initially categorized as probably benign but with interval change on follow-up breast ultrasound.

We retrospectively reviewed 11,323 lesions from ultrasound-guided core-biopsies performed between June 2004 and December 2014 and identified 289 lesions (266 patients) with an interval change from probably benign (Breast Imaging Reporting and Data System [BI-RADS] category 3) in the previous 2 years. Malignancy rates were compared according to the ultrasound findings and the characteristics of the interval changes, including changes in morphology and/or diameter.

The malignancy rate for probably benign lesions that showed an interval change on follow-up ultrasound was 6.9% (20/289). The malignancy rate was higher for clustered cysts (33.3%) and irregular or noncircumscribed masses (12.7%) than for circumscribed oval masses (5%) or complicated cysts (5%) seen on initial ultrasound (P = 0.043). Fifty-five percent of the malignancies were found to be ductal carcinoma in situ and there was 1 case of lymph node metastasis among the patients with invasive disease in whom biopsy was delayed by 6 to 15 months. The extent of invasiveness was greater in missed cases. There was a significant difference in the maximal diameter change between the 20 malignant lesions and the 269 benign lesions (4.0 mm vs 2.7 mm, P = 0.002). The cutoff value for maximal diameter change per initial diameter was 39.0% for predicting malignancy (sensitivity 95%, specificity 53.5%). The malignancy rate for morphologically changed lesions was significantly higher than for morphologically stable lesions (13.6% vs 4.9%; P = 0.024)

Our 6.9% of probably benign lesions that showed an interval change finally turned out to be malignancy was mostly DCIS. The sonographic features, interval changes in sonographic features, and lesion size might help in the recategorization of these lesions.

Abbreviations: AUROC = area under the receiver-operating characteristic curve, BI-RADS = Breast Imaging Reporting and Data System, DCIS = ductal carcinoma in situ, LN = lymph node, US = ultrasound, US-CNB = ultrasound-guided core-needle biopsy, US-VAE = ultrasound-guided vacuum-assisted excision.

Keywords: benign, breast, follow-upneoplasm, ultrasonography

1. Introduction

Classification of a breast lesion as Breast Imaging Reporting and Data System (BI-RADS) category 3 indicates that it is probably benign and that the likelihood of malignancy is less than 2%.[1]

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Solid masses with a circumscribed margin, oval shape and parallel orientation, isolated complicated cysts, and clustered microcysts are usually assessed as probably benign lesions.[1] The recommended management for a probably benign lesion is short-term follow-up rather than an immediate biopsy because of the low probability of malignancy and to avoid a negative biopsy result.[2,3] Short-term follow-up consists of repeat examinations at 6 and 12 months.[1,3] If the lesion appears stable, the recommended follow-up interval is extended to 1 year. If the lesion remains stable for 24 months, the final assessment is changed to category 2.

A lesion that shows changes on follow-up mammography requires prompt biopsy.[1] The malignancy rates reported for probably benign lesions that show interval change range from 10% to 56% on follow-up mammography [4–6] and from 0% to 33% on follow-up ultrasound (US) examination.[7–11] Therefore, prompt biopsy has been recommended for probably benign lesions that have increased in size by more than 10% or have developed features suspicious for malignancy on follow-up US examination.[2] However, this increases the number of unnecessary biopsies and lowers the positive predictive value. Because of the lack of long-term follow-up results for probably benign breast lesions that show interval change on US examination, appropriate management remains controversial.

The aims of this study were to determine the malignancy rate in probably benign lesions with interval change on follow-up US and to identify any differences that can be seen on imaging

between benign and malignant breast lesions initially categorized as probably benign but found to show interval change on follow-up US.

2. Materials and methods

2.1. Study design and inclusion criteria

Approval to conduct this research was obtained from the institutional review board of the Seoul National University Bundang Hospital. The need for informed patient consent was waived because of the retrospective nature of the study. Between June 2004 and December 2014, 84,753 breast US examinations were performed at our hospital and 38,905 (45.9%) lesions were categorized as probably benign lesions. During the same period, 11,323 US-guided core-needle biopsies (US-CNBs) were performed for suspicious lesions found on breast US examination. These included suspicious lesions that showed interval change when compared with previous benign findings, newly appeared suspicious lesions on routine follow-up US examination, and lesions that were suspicious on initial US examination. Among these, we identified 329 suspicious lesions in 305 patients that showed an interval change after having been categorized as probably benign (category 3) in the previous 2 years. Eight of the 305 patients were excluded because of a previous history of breast cancer and 32 patients with benign results on US-CNB were excluded because of loss to follow-up, leaving 289 lesions (266 patients) available for inclusion in the study (Fig. 1). These included lesions confirmed to be malignant on US-CNB (n = 20), benign on US-CNB with follow-up of more than 12 months (n = 174), and considered benign on US-CNB and confirmed as benign by US-guided vacuum-assisted excision (US-VAE; n = 61) or surgical excision (n = 49).

2.2. US imaging and biopsy methods

Each US examination was performed by one of 13 breast-dedicated radiologists (with 1–15 years of experience) using either of 2 machines (iU22 or HDI 5000, Advanced Technology Laboratories, Philips, Bothell, WA); either a 5 to 12 or a 7 to 12 MHz linear array transducer was used. In each case, the examining radiologist reviewed all available medical and imaging records before performing the US examination. Masses were examined in the transverse and longitudinal planes, and the number, side, location (clock position), distance from the nipple, and size of the lesion(s) were recorded. A lesion-to-lesion comparison was performed during follow-up.

US-CNB was performed using 14-gauge dual-action semiautomatic core biopsy needles (Stericut with a coaxial needle; TSK Laboratory, Tochigi, Japan), and US-VAE was performed using an 11-gauge or 8-gauge vacuum-assisted device (Mammotome: Devicor Medical Products, Cincinnati, OH). When a malignancy was detected, surgical excision was performed according to the decision of the clinician and/or patient.

2.3. Interpretation of US images

Two radiologists (BLY and SMK, with 7 and 13 years of breast imaging experience, respectively) retrospectively reviewed all US examinations without the pathologic information at hand and together reached a consensus on lesion descriptors and final assessments for the masses. The three-dimensional diameter (transverse, longitudinal, height) and morphologic change (shape, margin, echo pattern, orientation) in the lesions were recorded using the American College of Radiology BI-RADS lexicon.[1] Of the three-dimensional diameters, the longest diameter and maximal diameter change were recorded for comparison. The maximal diameter change, maximal diameter change per month, percentage of maximal diameter change from initial diameter, and percentage of maximal diameter change from initial diameter per month were calculated. The shape was described as oval, round, or irregular. The margin was classified as circumscribed, indistinct, angular, microlobulated, or spiculated. The echogenicity of the mass was compared with that of normal fat tissue and classified as hypoechoic, isoechoic, hyperechoic, complex cystic and solid, or heterogeneous. The orientation was classified as parallel if the long axis of the mass ran parallel to the skin line. The final diagnosis was based on the radiology reports from more than 12 months of follow-up after US-CNB and histopathology reports for US-CNB, US-VAE, or surgery.
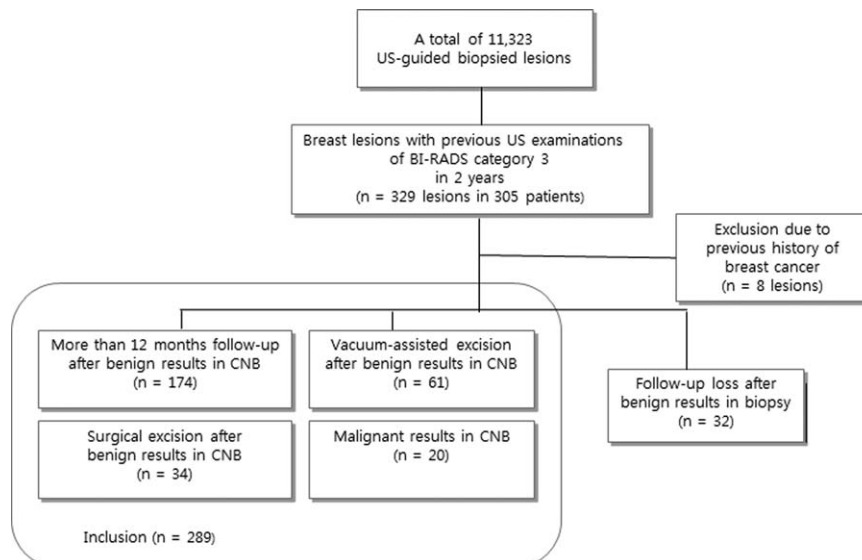

Figure 1. Patient selection.

Table 1

Final histopathologic diagnosis of probably benign lesions on follow-up ultrasound (n=289).

Histologic diagnosis	n (%)
Malignant	20 (6.9)
Ductal carcinoma in situ	11 (55)
Invasive ductal carcinoma	7 (35)
Mixed invasive ductal and lobular carcinoma	1 (5)
Invasive lobular carcinoma	1 (5)
Borderline	12 (4.2)
Radial scar	5 (41.7)
Phyllodes tumor, borderline malignancy	3 (25.0)
Flat epithelial atypia	2 (16.7)
Atypical ductal hyperplasia	1 (8.3)
Lobular carcinoma in situ	1 (8.3)
Benign	257 (88.9)
Fibroadenoma	100 (38.9)
Fibrocystic change	68 (26.5)
Intraductal papilloma	31 (12.1)
Phyllodes tumor, benign	8 (3.1)
Duct ectasia	7 (2.7)
Fibroepithelial neoplasm	6 (2.3)
Sclerosing adenosis	5 (1.9)
Pseudoangiomatous stromal hyperplasia	4 (1.6)
Tubular adenoma	4 (1.6%)
Benign mammopathy	3 (1.2%)
Columnar cell change	3 (1.2%)
Usual duct hyperplasia	3 (1.2%)
Adenosis	2 (<0.1%)
Adenosis tumor	2 (<0.1%)
Epidermal cyst	2 (<0.1%)
Others	9 (3.5%)
Total	289

Table 2

Malignancy rates according to ultrasound findings and whether masses were single or multiple.

Ultrasound finding	Malignant	Benign	Malignancy rate (%)	Total
Largest of more than 3 masses	10	165	5.71	175
Circumscribed oval	7	135	4.93	142
Irregular or not circumscribed	3	30	10.34	33
Single mass	10	104	8.77	114
Circumscribed oval	4	54	6.9	58
Irregular or not circumscribed	3	19	13.64	22
Complicated cyst	1	19	5.0	20
Intraductal	0	8	0.00	8
Clustered cyst	2	4	33.3	6

Of the 269 nonmalignant lesions, 12 (4.2%) were high-risk lesions and 257 (88.9%) were benign lesions.

One hundred seventy-five (60.6%) of the 289 masses coexisted with more than 3 masses (mean 5.05, range 3–12) in both breasts, 80 were single solid masses, 20 were complicated cysts, 8 were intraductal lesions, and 6 were clustered cysts. The malignancy rate according to US findings and whether the masses were single or multiple are summarized in Table 2. The malignancy rate was higher for clustered cysts (33.3%) and irregular or noncircumscribed masses (12.7%) than for circumscribed oval masses (5%) or complicated cysts (5%) on initial US ($P=0.043$).

Of the 289 lesions initially categorized as probably benign, 230 (79.6%) were true circumscribed oval parallel masses and included 18 complicated cysts, 4 clustered cysts, and 8 intraductal lesions. The remaining 59 lesions were noncircumscribed or irregular masses, and included 2 complicated cysts, 2 clustered cysts, and 55 misclassified irregular or noncircumscribed masses (Table 2). Of the 55 misclassified masses, 22 of 114 were single masses and 33 of 175 were 1 of more than 3 masses ($P=0.13$). Six of the 55 misclassified masses were confirmed as malignant, which was not a statistically significant finding, and there were no missed cases (10 of 199 single masses or 1 of more than 3 masses; $P=0.12$). The rate of invasive cancer was higher in the missed cases (6/7 vs 3/13; $P=0.016$). Lymph node (LN) metastasis was found in 1 of 9 patients who underwent LN biopsy. The final invasive histologic size was larger in the missed group (mean 0.33 cm vs 1.6 cm; $P=0.01$).

The patients with malignant lesions were significantly older (mean age 46 years in the group with malignant lesions vs 43 years in the group with benign lesions; $P=0.0036$, Table 3). There was no significant difference in the mean follow-up interval between the group with malignant lesions and the group with benign lesions (7.1 months vs 6.7 months; $P=0.31$, Table 3). Menopausal status was known in 229 patients; there was no significant difference in the malignancy rate between the premenopausal and postmenopausal groups (2/52 vs 12/177; $P=0.74$). The family history of breast cancer was known in 204 patients; the malignancy rate was not significantly different between women who did and those who did not have a positive family history (1/14 vs 16/190; $P=1$). Malignancy was found in 15 of 233 asymptomatic patients, in 5 of 25 patients with a palpable lump, in 3 patients with breast pain, and in 8 with nipple discharge ($P=0.16$).

2.4. Statistical analysis

The statistical analysis was performed using MedCalc software (MedCalc, Mariakerke, Belgium). The Mann–Whitney rank sum test was used to compare patient age, follow-up interval, longest diameter of the lesion, maximal diameter change (transverse, longitudinal, height), maximal diameter change per month, and percentage of maximal diameter change from the initial diameter between malignant and benign lesions. Receiver-operating characteristic curve analysis was used to compare the accuracy of the above values and cut-off values for predicting malignancy. Accuracies are reported as the area under the receiver-operating characteristic curve (AUROC) with the 95% confidence interval. Fisher exact test was used to evaluate the statistical significance of morphologic change, hormonal status, family history, and missed cases. P values <0.05 were considered to be statistically significant.

3. Results

3.1. Clinical and lesion characteristics

The study included 266 patients with 289 lesions. The median patient age was 43 (16–66) years. Of the 289 lesions, 20 (6.9%) were confirmed as malignant and 269 (93.1%) were confirmed as nonmalignant. Eleven (55%) of the malignant masses were ductal carcinoma in situ (DCIS), 7 (35%) were invasive ductal carcinoma, 1 (5%) was mixed invasive ductal and lobular carcinoma, and 1 (5%) was invasive lobular carcinoma (Table 1).

Table 3

Comparison of clinical and lesion characteristics.

	Malignant (n = 19)	Benign (n = 269)	P value
Median patient age, y	46 (36–66)	43 (16–66)	0.0036
Median interval, mo*	7.1 (5.9–20.0)	6.7 (5.13–23.9)	0.31
Median longest diameter, mm	11.05 (7.1–27.6)	11.4 (4.0–52.0)	0.56
Mean D, mm	4.0 (0–39.8)	2.7 (0–19.9)	0.002
Mean D per month, mm	0.6 (0–6.6)	0.4 (0–3.2)	0.018
Mean P, %	85.3 (43.0–109.8)	36.0 (32.8–42.4)	0.0001
Mean P per month, %	8.6 (5.6–15.2)	4.9 (4.2–5.3)	0.001

For median patient age, interval, and longest diameter, the numbers in parentheses indicate the range. For the mean D, D per months, P, and P per month, the numbers in parentheses are the 95% confidence intervals for the median.

D = maximal diameter change, P = maximal diameter change per initial diameter.

*Interval from initial probably benign assessment to detection of morphology or diameter change.

3.2. Diameter change

There was no statistically significant difference in the mean longest diameter between the malignant and benign lesions (11.05 mm vs 11.4 mm; P = 0.56, Table 3). The mean change in maximal diameter for the malignant lesions was greater than that for the benign lesions (4.0 mm vs 2.7 mm; P = 0.002). The mean change in maximal diameter per month was also greater for the malignant lesions than for the benign lesions (0.6 mm/month vs 0.4 mm/mo; P = 0.018), as was the mean percentage change in maximal diameter per initial diameter (85.3% vs 36.0%; P = 0.0001) and mean percentage change in maximal diameter per initial diameter per month (8.6% vs 4.9%; P = 0.001). When the AUROC values were compared to determine the parameter that was the most accurate in predicting malignancy, the highest value was the percentage change in maximal diameter per initial diameter (0.762, Table 4); the sensitivity and specificity values for predicting malignancy were 95% and 53.5%, respectively.

3.3. Morphologic change

Of the 289 lesions, 223 (77.2%) showed only a diameter change. Sixty-six lesions (22.8%) showed morphologic changes in shape, margin, echogenicity, or orientation; 64 (97%) of these lesions showed changes in both morphology and diameter, and 2 (3%) showed only a morphologic change (Fig. 2).

Nine (45%) of the 20 malignant lesions showed changes in both morphology and diameter (Fig. 3) and 11 (55%) showed only a change in diameter (Fig. 4). Of the 269 benign lesions, 57 (21.2%) showed a change in morphology and 212 (78.8%) showed a change in diameter only (Fig. 5). The malignancy rate of

lesions showing a change in morphology was significantly higher than that of morphologically stable lesions (13.6 vs 4.9%; P = 0.024). Seven (35%) of the 20 malignant lesions still appeared as circumscribed oval parallel masses on follow-up US examination; 2 of these were invasive ductal carcinoma and 5 were DCIS.

In the 9 malignant lesions that showed a change in morphology, the margin showed the highest rate of change (7/9, 77.8%) followed by shape (4/9, 44.4%). Seven lesions had a circumscribed margin at the initial US examination; of these, 6 changed to indistinct and 1 changed to microlobulated. All 9 lesions appeared oval at the initial US examination, but 4 underwent an interval change to irregular. One lesion showed a change in internal echogenicity from anechoic to solid and cystic. The echogenicity and orientation remained unchanged in all 9 malignant lesions that showed an interval change.

4. Discussion

Our present findings show a malignancy rate of 6.9% in probably benign lesions that show an interval change, which is consistent with previous reports.[2,11] The diagnosis was DCIS in more than 50% of the malignant lesions and one of the patients with invasive disease had a LN metastasis, biopsy of which was delayed by 6 to 15 months. Moon et al[12] reported a 10.3% malignancy rate in 214 lesions initially categorized as probably benign lesions but showed interval growth on follow-up US examination. The mean age of the patients in our study was similar to that of patients in the study by Moon et al, but our malignancy rate was slightly lower (6.9% vs 10.3%). The mean change in diameter per month was significantly greater for malignant lesions than for benign lesions (1.8 mm vs 0.5 mm) in the study reported by Moon et al; the respective values in our study were 0.6 and 0.4 mm, indicating less interval change in the malignancy group than that observed by Moon et al.[11] These conflicting results may reflect the fact that the mean interval follow-up period was longer in the study by Moon et al (8.5 months for patients with malignant disease and 12.5 months for those with benign disease) than in our study. Our finding that the malignancy rate of morphologically changed lesions was significantly higher than that of morphologically stable lesions (13.6% vs 4.9%; P = 0.024) is comparable with the finding of 38.5% versus 4.0% reported by Moon et al.[11]

Shape and margin have been reported to be the most important morphologic features for differentiating benign and malignant masses.[13–15] Although BI-RADS restrictively recommends a category 3 classification for a solid mass with a circumscribed margin, oval shape, and parallel orientation and for complicated cysts and clustered cysts, other studies have recommended a more generous category 3 classification for other breast lesions.[14–16] The reported detectability of BI-RADS category 3 is higher on

Table 4

Receiver-operating characteristic curve analysis of interval size on ultrasonographic follow-up (n = 289).

	AUROC (95% CI)	Cutoff	Sensitivity (95% CI)	Specificity (95% CI)
Mean D	0.707 (0.650–0.758)	2.6 mm	90 (68.3–98.8)	48.3 (42.2–54.5)
Mean D per month, mm	0.658 (0.600–0.713)	0.3 mm	80 (56.3–94.3)	37.9 (32.1–44.0)
Mean P, %	0.762 (0.710–0.810)	39.0%	95 (75.1–99.9)	53.5 (47.4–59.6)
Mean P per month, %	0.721 (0.680–0.785)	5.2%	85 (62.1–96.8)	54.6 (48.5–60.7)

AUROC = area under the receiver-operating characteristic curve, CI = confidence interval, D = maximal increased diameter, P = maximal diameter change per initial diameter.
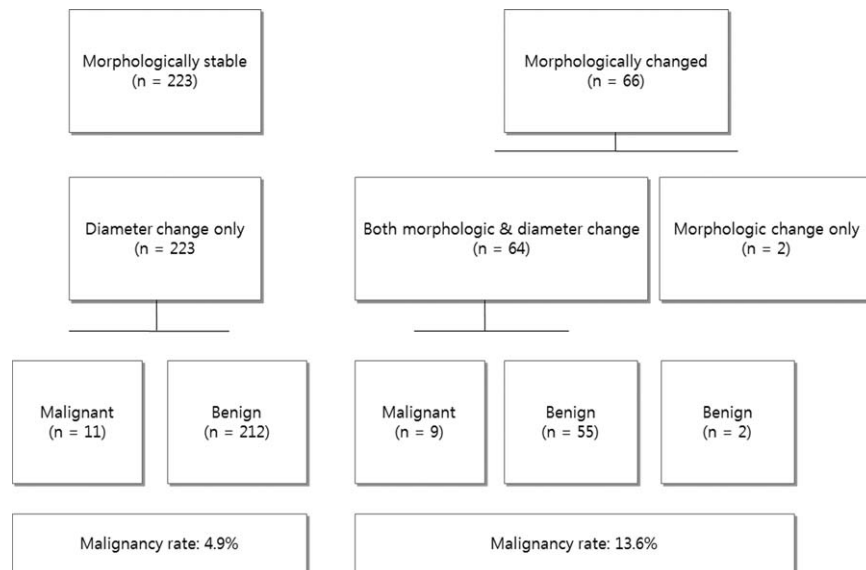
Figure 2. Morphologic changes in 289 lesions.

screening US than on screening mammography (25% vs 2.4%).[17] Our high rate of BI-RADS category 3 lesions may be explained by the fact that our institution is a referral hospital, so most of the patients in our study were referred for an abnormality detected in primary care and are not representative of the whole population screened.

In our study, 230 (79.6%) of the 289 probably benign lesions that showed interval change had the appearance of a circumscribed oval mass at initial US examination, whereas 59 (20.4%) did not. These 59 lesions comprised complicated cysts or clustered cysts with variable shapes and margins, 55 of which were misclassified as irregular or noncircumscribed masses. The malignancy rate among the circumscribed oval masses with interval change on follow-up US examination was 4.8% (11/ 230), which is lower than the rate of 10.9% found for noncircumscribed oval solid masses with interval change (6/ 55); however, the difference was not statistically significant ($P =$ 0.1). The size of the invasive tumors was larger in the missed
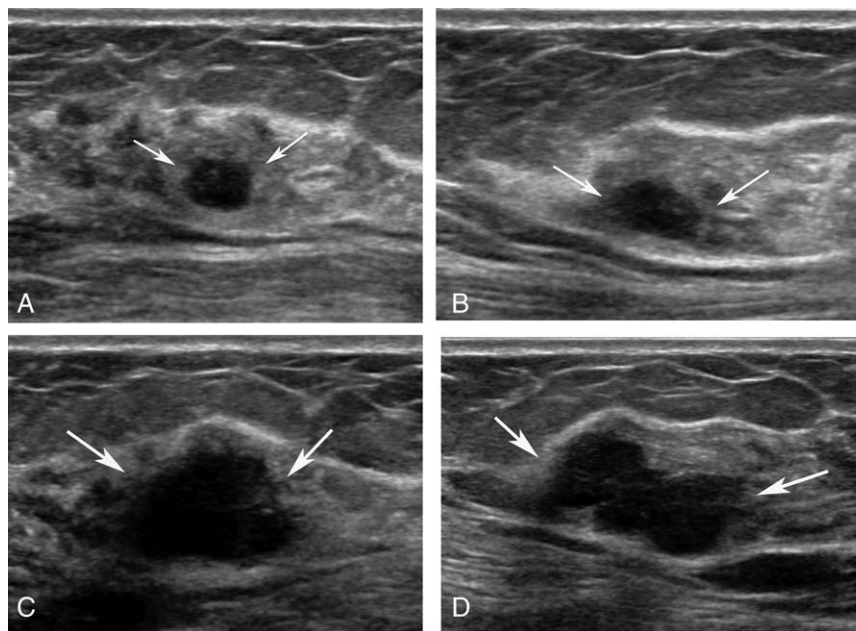

Figure 3. Breast ultrasound images for a 46-year-old woman with an invasive ductal carcinoma. Transverse (A) and longitudinal (B) ultrasound images show a hypoechoic solid mass (arrows) with an oval shape and circumscribed margin in the right breast. The mass was initially categorized as a probably benign lesion. After 9 months, the mass (arrows) showed an increase in diameter from 7.4 × 6.7 × 4.5 to 20.2 × 16.6 × 10.5 mm and had developed morphologic changes on ultrasound (C, transverse image; D, longitudinal image). Ultrasound-guided core-needle biopsy was performed and invasive ductal carcinoma was diagnosed. The maximal diameter change, diameter change per month, diameter change per initial diameter, and diameter change per initial diameter per month were 12.8 mm, 1.46 mm, 173.0%, and 19.7%, respectively.
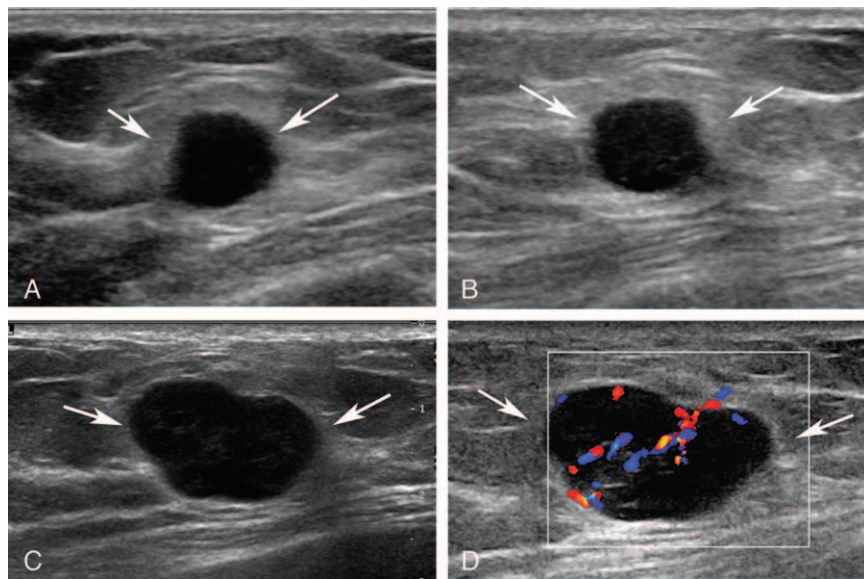
Figure 4. Breast ultrasound images for a 63-year-old woman with an invasive ductal carcinoma. Transverse (A) and longitudinal (B) ultrasound images show a hypoechoic solid mass (arrows) with an oval shape and angulated margin in the right breast. The mass was initially categorized as a probably benign lesion. After 6 months, the mass (arrows) showed an increase in diameter from $12 \times 10 \times 14$ to $22 \times 14 \times 19$ mm (C, longitudinal image; D, Doppler image). Ultrasound-guided core-needle biopsy was performed and invasive ductal carcinoma was diagnosed. The greatest diameter change, diameter change per month, diameter change per initial diameter, and diameter change per initial diameter per month were 10 mm, 1.7 mm, 82.0%, and 13.9%.

group. Moon et al[12] reassessed 32 malignancies initially categorized as probably benign lesions and found that 28 (87.5%) were either misclassified or not recognized as having suspicious features. A noncircumscribed margin was the suspicious feature most often missed on US, as in a previous study.[12] The lesions that the radiologist believes, through personal experience, require a watchful-waiting approach, preferably involving observation of a sufficient number of cases of additional sonographic findings to suggest a likelihood of malignancy within the defined ($\leq 2\%$) probably benign range.[1]
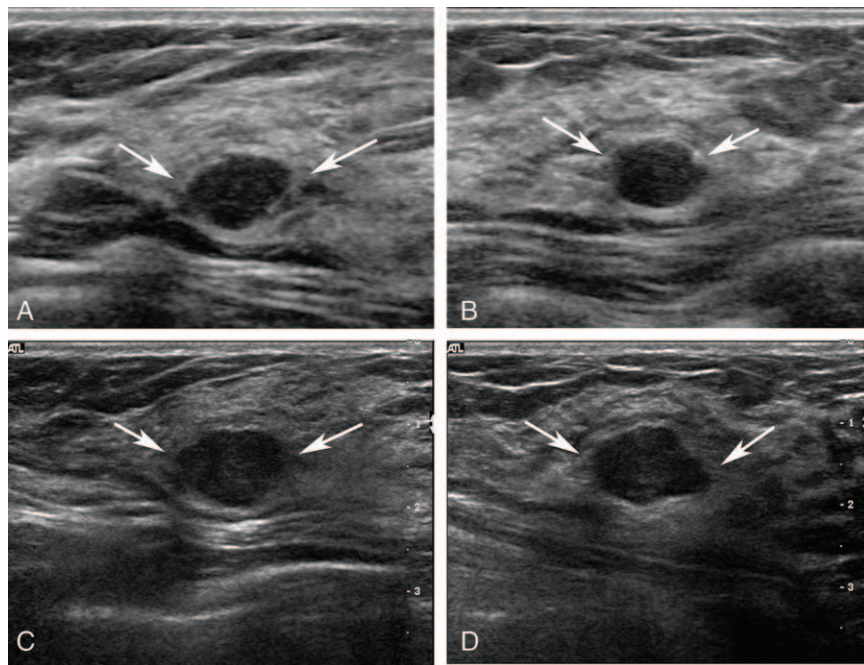

Figure 5. Breast ultrasound images for an 18-year-old woman with a fibroadenoma. Transverse (A) and longitudinal (B) ultrasound images show a hypoechoic solid mass (arrows) with an oval shape and circumscribed margin in the right breast. The mass was initially categorized as a probably benign lesion. After 6 months, the mass (arrows) showed an increase in diameter from $9.8 \times 6.5 \times 9.1$ to $15.7 \times 13.9 \times 10.1$ mm without morphologic changes (C, transverse image; D longitudinal image). The patient underwent ultrasound-guided vacuum-assisted excision and fibroadenoma was diagnosed. The maximal diameter change, diameter change per month, diameter change per initial diameter, and diameter change per initial diameter per month were 5.9 mm, 1.0 mm, 60.2%, and 10.2%, respectively.

Thus, more caution is needed in the management of probably benign lesions with interval change that appear as noncircumscribed oval solid masses at the initial US examination.

This study has some limitations. First, it was retrospective in nature and the malignancy rate of the lesions showing an interval change was already known. Therefore, a degree of observer bias was inevitable. Second, the status of the patients with regard to menopause and hormonal treatment could not be determined in some cases; fibroadenomas can progress, especially in premenopausal women but also in postmenopausal women on hormone replacement therapy. However, given that the median age was 46 years in the patients with malignant lesions and 43 years in those with benign lesions, any difference in menopause status between the 2 groups is unlikely to have been critical. Third, 174 (60.2%) of the benign lesions were not pathologically confirmed by US-VAE or surgical excision, and the inclusion criterion for these lesions was 12 months of follow-up after US-CNB, which is not as long as 24 months. Therefore, some slowly progressing cancers may have been missed in this study.

Our 6.9% of probably benign lesions that showed an interval change finally turned out to be malignancy was mostly DCIS. The sonographic features, interval changes in sonographic features, and lesion size might help recategorization. The likelihood of invasiveness was greater in patients with irregular or noncircumscribed masses. Thus, more caution is needed when categorizing a lesion as probably benign at the initial US examination.

Acknowledgments

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