Contrast-Enhanced Power Doppler Sonography in Breast Lesions

Effect on Differential Diagnosis After Mammography and Gray Scale Sonography

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Objective. To evaluate the efficacy of contrast-enhanced power Doppler sonography in the differential diagnosis of breast lesions after a mammography–gray scale sonography combination. ***Methods.*** Sixty-eight patients with 69 breast masses underwent power Doppler sonography before and after intravenous injection of a contrast agent. The lesions were diagnosed as "highly suggestive of malignancy" (category 5; n = 32), "suspicious" (category 4; n = 21), and "probably benign" (category 3; n = 16) by mammography and gray scale sonography, modeled on the American College of Radiology Breast Imaging Reporting and Data System classification. Power Doppler findings did not affect patient treatment. The authors subjectively evaluated the estimated area of vascularity, degree of enhancement following contrast agent administration, morphologic features, and distribution of vessels within the lesions. ***Results.*** The final diagnoses were malignant in 28 lesions and benign in 41. Significant enhancement after contrast agent injection was detected in both the malignant and benign groups. Only 2 criteria, estimated area of vascularity and degree of enhancement following contrast agent administration, proved to be significant diagnostic determinants for contrast-enhanced power Doppler sonography ($P < .001$; interobserver agreements, 74.4 and 77.8, respectively). Contrast-enhanced power Doppler sonography provided a higher specificity, positive predictive value, and negative predictive value than power Doppler sonography but a lower sensitivity and negative predictive value than mammography–gray scale sonography. Only in the category 4 lesions could the combination of mammography–gray scale sonography and contrast-enhanced power Doppler sonography accomplish a higher specificity (71%) and positive predictive value (70%) than mammography–gray scale sonography (39% and 53%, respectively). ***Conclusions.*** Power Doppler and contrast-enhanced power Doppler sonography cannot be recommended as confirmatory tests in Breast Imaging Reporting and Data System category 3 and category 5 lesions. Although contrast-enhanced power Doppler sonography may help reduce unnecessary biopsies in Breast Imaging Reporting and Data System category 4 lesions, recommendation of its use has many drawbacks, such as imperfectly established criteria, lack of absolute certainty, and high cost. ***Key words:*** breast neoplasms, diagnosis; breast neoplasms, sonography; sonography, contrast media; sonography, power Doppler studies.

Abbreviations
BI-RADS, Breast Imaging Reporting and Data System; CE-PD, contrast-enhanced power Doppler sonography; DEFC, degree of enhancement following contrast agent administration; EAV, estimated area of vessels; FPR, false-positive ratio; MG, mammography; PD, power Doppler sonography; PPV, positive predictive value; NPV, negative predictive value

Received August 12, 2003, from the Department of Radiology, University Hospital of Gazi, Ankara, Turkey (A.Ö., K.K., H.Ö., C.Y., Ş.A.); and Department of Healthcare Management, Faculty of Health Sciences, University of Başkent, Ankara, Turkey (M.Ç.). Revision requested September 5, 2003. Revised manuscript accepted for publication September 30, 2003.

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The combined use of mammography (MG) and gray scale sonography has a proven efficiency in increasing diagnostic sensitivity compared with MG alone.[1–4] By combining MG and sonography, sensitivities as high as 91% and 94.2% have been obtained.[1,2]

However, despite some favorable results,[5] improved sensitivity by combining these modalities has usually been at the expense of reduced specificity.[2,6] In one such study, sensitivity increased from 78.9% to 94.2%, whereas the specificity reduced from 82.7% to 67.9%.[2] Color and power Doppler studies without and recently with intravenous contrast agent use may be expected to increase the specificity obtained with the MG-sonography combination. In a recent noncontrast study for the evaluation of Doppler parameters in breast tumors, the morphologic characteristics of the tumoral vessels (form, location, and color tone) was found to be the most sensitive (91.2%) parameter in diagnosing the malignant lesions.[7] Although not sufficiently specific when used alone (45.5%), this parameter improved the diagnostic specificity of MG-sonography significantly (from 76.2% to 92.7%).[7] In a contrast-enhanced Doppler study in which vessel morphologic analysis with similar criteria was applied, Stuhrmann et al[8] reported not only a high sensitivity (90%) but also a higher specificity (81%) than obtained in the former study.[7] These findings suggested that it might be possible to attain even higher specificities by combining the morphologic criteria based on the contrast-enhanced Doppler studies and the information obtained from MG-sonography.

Therefore, the aim of this study was to evaluate the usefulness of contrast-enhanced power Doppler sonography (CE-PD) after MG-sonography and power Doppler sonography (PD) in differentiating between benign and malignant breast lesions, in other words, improving the diagnostic specificity without loss of sensitivity. Lesions in American College of Radiology Breast Imaging Reporting and Data System (BI-RADS)[9] categories 3, 4, and 5, namely, "probably benign," "suspicious," and "highly suggestive of malignancy," were also separately evaluated to determine guidelines for everyday practice.

Materials and Methods

Clinical Procedures

Between December 1999 and June 2001, sonographically visible breast masses found in women who had been examined with routine MG and sonography for screening or diagnostic purposes were consecutively evaluated for further investigation with power PD before and after intravenous bolus injection of Levovist (SH U 508A; Schering AG, Berlin, Germany). The study was approved by our Institutional Review Board. The goals of the study were explained to the patients, and written informed consent was obtained. Types of lesions other than masses and characteristically benign (BI-RADS category 2) masses on mammograms, such as radiolucent ones and calcified fibroadenomas, were eliminated at the very beginning. After the sonographic examination, cysts and other sonographically characteristic benign solid masses, such as markedly hyperechoic ones, were further eliminated. Finally, patients who did not consent for the study, patients who underwent biopsy before any of the particular examinations, and those for whom pathologic examination reports or interval sonographic follow-up might have been unavailable (because they lived in rural areas or other cities) were excluded. The remaining 81 breast masses in 80 women, which met the inclusion criteria, were examined with PD before and after contrast agent application.

At the end of the study, 12 lesions were excluded from the analysis: 1 from a patient who refused biopsy and 11 from patients who were lost to follow-up. The usefulness of CE-PD was analyzed in the remaining 69 solid lesions (size range, 6–44 mm; mean ± SD, 16.1 ± 7.29 mm) in 68 women after the routine breast imaging (MG and sonography) and PD evaluations. Twenty-two (32%) of the lesions were palpable, and 47 (68%) were nonpalpable. The patients' ages ranged from 19 to 75 years (mean age, 47.28 ± 13.16 years).

Mammography was performed for both breasts and in standard positions (mediolateral oblique and craniocaudal). Additional imaging including the use of spot compression, magnification, and supplementary views was performed when necessary. The same MG unit (Senographe DMR; GE Medical Systems, Milwaukee, WI) and film-screen systems (Kodak Min-R M film [Eastman Kodak Company, Rochester, NY] and Fuji UM-MA HC film [FUJIFILM Medical Systems, Inc, Stamford, CT] with Kodak Min-R screens) were used in all patients.

After the MG, lesion-targeted sonography in fatty breasts (Wolfe patterns N1 and P1) and

whole-breast sonography in dense breasts (Wolfe patterns P2 and DY), including both axilla, were performed with a 6- to 13-MHz transducer (LOGIQ 500; GE Medical Systems). Whole-breast sonography has been our routine practice in dense breasts as part of a screening study design. Sixty women were evaluated with both MG and sonography, whereas 8 women who were younger than 30 years were evaluated with sonography alone. The same faculty radiologist (A.Ö.), who is specialized in breast imaging, evaluated all the mammograms and performed all the sonographic examinations. The patients' clinical histories and prior mammograms and sonographic records, if there were any, were available to this examiner. One of the 2 assistant radiologists (K.K. and Ş.A.) attended these examinations to ensure that the lesions found by the first examiner would be the ones examined on PD by the second examiner. The assistant radiologists did not take part in the evaluation or diagnosis.

Lesion characterization on mammograms was based on the evaluations of standard criteria, including size, shape, margins, presence of architectural distortion, and presence of microcalcifications, and a final assessment category according to the American College of Radiology BI-RADS was assigned for each lesion.[9]

Lesion characterization on sonograms was performed in real time and was based on the previously published criteria, including shape, margin, sagittal- or transverse-anteroposterior dimension ratio, edge refraction, echo texture, echogenicity, posterior echo intensity, and pseudocapsule.[10,11] Among these, shape, margin, and sagittal- or transverse-anteroposterior dimension ratio, which proved to be the most predictive, most frequent, and least variable sonographic criteria according to a recent report[11] and which were in concordance with our own unpublished data, were used to provide the probably benign (category 3), suspicious (category 4), and highly suggestive of malignancy (category 5) final assessment categories modeled on the BI-RADS. According to these criteria, an ellipsoid shape with no or mild (≤3) lobulations, greater sagittal or transverse dimensions than the anteroposterior dimension, and circumscribed margins were considered individual benign characteristics, whereas an irregular shape, spiculated or microlobulated (many small [1- to 2-mm] surface lobulations) margins, and smaller sagittal or transverse dimensions than the anteroposterior dimension were considered individual malignant characteristics. The presence of a single malignant feature was sufficient to classify a lesion in BI-RADS category 5, and lack of any malignant findings plus the presence of all the benign features was necessary to classify a lesion in BI-RADS category 3. When all benign features were not present but none of the malignant features were found, the lesion was classified as sonographically "indeterminate," corresponding to the BI-RADS category 4 (suspicious finding). A multilobulated (>3 lobulations) shape and poorly defined margins were the 2 additional features that in the absence of any malignant findings represented the "suspicious" lesions.

After the mammographic and sonographic evaluation, a final BI-RADS assessment category was assigned for each lesion by the first examiner (A.Ö.) by taking into account the findings of each modality. The higher category assigned by either modality was accepted as the final assessment category. Thus, 32 of our lesions were assigned as category 5, 21 as category 4, and 16 as category 3. Lesions in categories 4 and 5 were classified together as positive, and biopsy was proposed; category 3 lesions were classified as negative, and periodic sonographic follow-up of at least 2 years was proposed. Precontrast and postcontrast power Doppler findings were not available to this examiner at the time of decision making; thus PD evaluations did not affect the diagnosis or treatment.

Power Doppler examinations were performed within a week after the MG and sonography by a second examiner (H.Ö.), a faculty radiologist who is specialized in Doppler and contrast studies. The same Doppler sonography equipment (HDI 5000; Philips Medical Systems, Bothell, WA) with a 5- to 12-MHz transducer was used in all cases. The power gain was set to a level high enough to eliminate the background noise while achieving the maximal Doppler sensitivity to low-velocity flow. Particular attention was paid not to apply pressure with the probe to avoid flow signal obliteration by small-vessel compression. System settings were as follows: pulse repetition frequency, 700; persistence, medium; frame rate, low; dynamic range, 150 dB; and wall filter, medium. The second examiner was blinded to the patients' clinical histories, mammograms, and the interpretations of the first examiner but was informed of the existence of a

solid mass in the particular site of the breast. This lesion was indicated and confirmed by an attending assistant radiologist (K.K. or Ş.A.) for being the one initially evaluated by the first radiologist. Power Doppler evaluations were confined to the lesion and the surrounding breast tissue only. After localizing the lesion with sonography, power Doppler examination was performed in transverse and longitudinal planes across the lesion. The slices best representing the tumor's vessel content, distribution, and morphologic characteristics were first evaluated and then considered for the next analysis with the contrast agent use.

The attending assistant (K.K. or Ş.A.) prepared and injected the contrast medium during the power Doppler evaluations performed by the second examiner (H.Ö.). Four grams of sterile granules of Levovist were dissolved in 7 mL of distilled water to obtain a suspension of 8.5 mL with a 300-mg/mL concentration. This suspension was left 2 minutes for stabilization. After completion of the baseline PD evaluations and while the examiner held the transducer on the lesion, Levovist was manually injected at approximately 2 mL/s into an antecubital vein through an 18-gauge needle and flushed through with a bolus of 5 mL of saline. After the contrast agent injection, PD examination was repeated without changing the previously selected system settings. The slices best representing the tumor's vessels on the precontrast examination were particularly evaluated during the maximal contrast enhancement and with the same criteria for comparison, although the CE-PD evaluations were not confined to these slices and included all parts of the tumor. Static images, which best represented the vessel content and vessel characteristics of the lesions before contrast enhancement, during maximal enhancement, and after contrast enhancement were obtained by the second examiner during this evaluation. Image recording was continued until the intensity of the flow signals was subjectively judged to have returned to the baseline level. Five to 11 images sufficiently represented the lesions' precontrast and postcontrast vascular characteristics. These images were saved for evaluation collectively at the end of the whole study period.

At the end of the study period, the same sets of power Doppler images were interpreted by the second (H.Ö.) and the third (C.Y.) examiners, unaware of each other's and the first examiner's interpretations. The second and the third examiners were equally experienced in PD and CE-PD applications. Statistical significances of the criteria used and interobserver agreements from the comparisons of the second and the third examiners' evaluations were calculated. Although both examiners' evaluations were used in determining the significances of differences between the precontrast and postcontrast evaluations and the interobserver agreements, the final PD and CE-PD diagnoses were based only on the second examiner's interpretations.

Criteria used in the PD and CE-PD evaluations were as follows:

1. Presence and estimated area of vessels (EAV) within the lesion, as suggested by Moon et al[12]: (A) avascular, no vessels; (B) hypovascular, defined as 1 or 2 vessels or EAV less than 20%; and (C) hypervascular, defined as more than 3 vessels or EAV is 20% or greater. Small dots of color that did not follow a linear course were not considered vessels but artifacts.
2. Degree of enhancement following contrast agent administration (DEFC), based on the change in the rough number of vessels after contrast agent administration and graded on a scale of 0 to 4 as suggested by Kedar et al,[13] with 0 representing none and 4 representing a marked enhancement (better delineation of the tumor vessels alone, when the contrast agent was applied, was not considered sufficient as a diagnostic determinant).
3. Distribution of tumor vessels before and after contrast agent application: (A) intratumoral, defined as flow signals detected within the lesion, extending or not extending to the margin; and (B) peripheral, defined as flow signals at the edge or within 2 mm of the margin of the lesion.
4. Morphologic features of the individual vessels before and after contrast agent application: (A) regular, uniform in caliber and course; and (B) irregular, caliber irregularities and tortuous course.

Analysis of Data

The statistical analysis of the PD findings was performed with SPSS software (release 11.0; SPSS Inc, Chicago, IL) by a biostatistician (M.Ç.) expe-

rienced in imaging research. In the selection of the most useful PD criteria, the significances of the differences between each observer's precontrast and postcontrast evaluations, as well as the highest interobserver agreement rates both in the precontrast and postcontrast stages, were considered. A marginal homogeneity test was used to determine the statistical significance of the differences in the precontrast and postcontrast evaluations for each parameter in the benign and malignant groups. This test is an extension of the McNemar test from a binary response to a multinominal response. It tests for changes in response with the use of the χ^2 distribution and is useful for collecting response changes in before-and-after designs.[14] Interobserver agreements were measured for each characteristic with κ statistics, which were considered excellent when the κ coefficient was greater than 0.8. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for the single and combined modalities. In this study, sensitivity was used to mean the number of positive interpretations that were truly malignant at tissue diagnosis, and specificity was used to mean the number of negative interpretations that were truly benign at tissue diagnosis or follow-up. Positive predictive value was defined as the percentage of all cases recommended for biopsy (BI-RADS categories 4 and 5) that resulted in the diagnosis of cancer, and NPV was defined as the percentage of all cases recommended for follow-up (BI-RADS category 3) that resulted in the diagnosis of benign breast disease.

The interobserver agreement rates and the statistical significance of the changes between the postcontrast and precontrast phases were calculated for each power Doppler criterion (Table 1). The EAV and DEFC, which were shown to be the most reliable criteria by statistical analysis, were used in retrospect to determine our benign and malignant calls in the precontrast and postcontrast stages: in the precontrast stage, hypervascularity and hypovascularity indicated the malignant, whereas avascularity indicated the benign; in the postcontrast stage, either hypervascularity or enhancement grades 3 and 4 within a lesion indicated the malignant, whereas either avascularity and hypovascularity or enhancement grades 0 to 2 within a lesion indicated the benign. The other 2 criteria, distribution and morphologic features of the vessels, were excluded from further analysis.

Table 1. Interobserver Agreements in the Precontrast and Postcontrast Evaluations (κ Coefficient) and the Statistical Significance of the Changes Between the Postcontrast and Precontrast Phases for the PD Criteria Used

	κ Coefficient		
PD Criteria	**Precontrast**	**Postcontrast**	***P****
EAV	0.535	0.744	<.05
DEFC	NS	0.778	<.05
Distribution	0.489	0.563	>.05
Morphologic features	0.374	NS	>.05

NS indicates not suitable for calculation.
**P* value for the marginal homogeneity test (*P* < .05 is significant).

The theoretical adjunctive roles of PD and CE-PD to MG-sonography were calculated first in the whole study group and later in the mammographically and sonographically suspicious (BI-RADS category 4) subgroup. When the whole group was studied, a malignant call in either of the 2 tests (MG-sonography and PD or MG-sonography and CE-PD) was sufficient for a lesion to be diagnosed as malignant, whereas a benign diagnosis necessitated benign calls in both tests. When the category 4 subgroup was studied, the diagnosis suggested by the adjunctive test (either PD or CE-PD) was accepted as the final diagnosis.

Results

Biopsy was performed in all cases within the BI-RADS 4 and 5 categories and in 8 cases within the BI-RADS 3 category (n = 61). Biopsies in the last group were due to the physician or patient preference. The biopsy method was either excision (58 lesions) or core 14 gauge under sonographic guidance (3 lesions). The histopathologic results obtained in these 61 lesions revealed infiltrating ductal carcinomas in 26, ductal carcinoma in situ in 1, mucinous carcinoma in 1, fibroadenoma in 12, fibrocystic changes in 12, adenosis in 3, intraductal papilloma in 2, and fat necrosis in 4. The remaining 8 lesions were followed at 3- to 6-month intervals for at least 2 years (completed in May 2002), and were accepted as benign for no change in size or appearance within the follow-up period. The final diagnoses, determined either by biopsy or follow-up, revealed 28 malignant and 41 benign lesions.

The overall sensitivity and specificity of MG-sonography were 100% and 39%, respectively (Table 2). Twenty-six (81%) of 32 category 5 lesions proved to be malignant, whereas only 2 (9.5%) of 21 category 4 lesions proved to be (PPV, 53%). All category 3 lesions came up as benign (NPV, 100%; Tables 2 and 3). The false-positive ratio (FPR) for MG-sonography was 61% (25 of 41). Among the false-positive lesions, 6 were category 5 (24%) and 19 were category 4 (76%).

The sensitivity and specificity of PD were 82% and 37%, respectively (Table 2). Detection of 1 or more vessels in 26 of 41 benign lesions resulted in an FPR of 63%, whereas the absence of vessels in 5 of 28 malignant lesions led to a false-negative ratio of 18% (Table 3). Four of the false-negative lesions were category 5 on MG-sonography, and 1 was category 4. Conversely, PD truly diagnosed 2 (33%) of 6 lesions that were false-positive on MG-sonography in category 5 and 7 (37%) of 19 that were false-positive on MG-sonography in category 4. Among its 26 false-positive lesions, 6 (23%) were smaller than 10 mm (range, 6–9 mm; mean, 7.3 mm).

The sensitivity and specificity of CE-PD were 82% and 66%, respectively (Table 2). Enhancement after contrast agent administration was shown in 22 (54%) of 41 benign and 24 (86%) of 28 malignant lesions (Table 4). According to the marginal homogeneity test, frequency of the postcontrast enhancement was statistically significant in both the benign and malignant groups ($P < .001$ each). Most of the enhancement (81.8% in the benign and 62.5% in the malignant groups) was of grade 1 or 2 (Table 4), which caused misdiagnosis of 5 cancers, all in category 5 on MG-sonography (size range, 8–22 mm; mean, 12.8 mm; Figure 1). Three of these cancers were also misdiagnosed at PD. Conversely, CE-PD truly diagnosed 4 (66%) of 6 lesions that were false-positive on MG-sonography in category 5 and 13 (68%) of 19 that were false-positive on MG-sonography in category 4 (Figure 2). Among its 14 false-positive lesions, the smallest was a fat necrosis of 6 mm.

Contrast-enhanced power Doppler sonography achieved higher specificity, PPV, and NPV than PD did (Table 2). Two cancers that were avascular on PD showed grade 4 enhancement on CE-PD. One of them was an infiltrating ductal carcinoma of 7 mm, and the other was a mucinous carcinoma of 33 mm (Figure 3).

Contrast-enhanced power Doppler sonography could differentiate fat necrosis from malignancy in some cases. At MG-sonography, 3 cases of fat necrosis were diagnosed as category 4, and 1 was diagnosed as category 5 (FPR, 100%). The PD diagnosis was malignant in 3 (FPR, 75%), and the CE-PD diagnosis was malignant in 2 of those (FPR, 50%; Figure 4).

We found that combining MG-sonography with PD or CE-PD in the whole group resulted in lower specificities and positive predictions than obtained with MG-sonography. This is unacceptable because our goal in combining the modalities was to increase the specificity. Only in the BI-RADS category 4 subgroup could PD (more specifically, CE-PD) accomplish a higher specificity and PPV than obtained with MG-sonography (Table 2). With CE-PD, the increase in the specificity was from 39% to 71%, and the increase in the PPV was from 53% to 70%. Importantly, increases in the specificity and PPV were without any loss in the sensitivity and NPV.

Discussion

In some malignant breast lesions, blood flow signals are difficult to detect on color and power Doppler systems because of either small vessel size or inadequate equipment. Intravenous contrast agents give rise to stronger color encoding during a color or power Doppler evaluation by providing enhancement of the ultrasound signal as high as 25 dB (>300-fold increase).[15]

Table 2. Diagnostic Values of the Single and Combined Modalities in 69 Breast Lesions

Diagnostic Test	Sensitivity, %	Specificity, %	PPV, %	NPV, %
MG-sonography	100	39	53	100
PD	82	37	47	75
CE-PD	82	66	62	84
MG-sonography + PD	100 (96)	15 (56)	44 (60)	100 (96)
MG-sonography + CE-PD	100 (100)	24 (71)	47 (70)	100 (100)

Numbers in parentheses are the percentages that could be obtained when the diagnosis suggested by the additional test (either PD or CE-PD) was accepted as the final diagnosis in BI-RADS category 4 lesions.

The utility of contrast-enhanced color and power Doppler sonography in the detection and differentiation of benign and malignant breast tumors has been evaluated in recent studies.[8,12,13,15–21] Those studies showed that demonstration and characterization of breast tumor vessels on color and power Doppler sonography has been improved with the use of contrast agents. By showing increased blood flow signals in malignant breast tumors, contrast-enhanced color and power Doppler studies were able to increase the sensitivity to as high as 34% to 60%.[12,20] Conversely, differentiation of benign tumors on color and power Doppler sonography became further complicated with contrast agent use because many of them showed postcontrast enhancement in addition to vascularization patterns similar to those of malignant tumors.[12,20] A substantially high frequency of postcontrast enhancement in the benign lesions (54%) as well as the malignant lesions (86%) in our series supports the general opinion that, after contrast agent administration, the mere presence of vessels in a breast tumor cannot be considered a criterion of malignancy.

While evaluating the PD and CE-PD as single tests, we found that the diagnostic specificities of PD and CE-PD obtained in our study (37% and 66%, respectively) were within the wide range of previously reported rates: 35% to 89% for PD[12,13,17,18] and 5.6% to 100% for CE-PD.[8,12,13,16,17,20] The sensitivities of PD and CE-PD in our study (82%, each) were also within the wide range of previously reported rates: 36% to 89% for PD[12,13,17,18] and 55% to 100% for CE-PD.[8,12,13,16,17,20] These wide ranges of sensitivities and specificities suggest the unreliability of single PD and CE-PD examinations in the breast.

To our knowledge, combined effects of PD and CE-PD with MG-sonography have not been evaluated extensively before. Our study compared the usefulness of individual and combined modalities. Each modality was practiced alone and blinded to the others so that it would not influence the diagnoses made by the other modalities (although patient treatment was based on the MG-sonography decisions only). So that the roles of individual modalities were not obscured, the efficiency of combinations of modalities was evaluated only theoretically. Because MG-sonography is highly sensitive, our primary concern in combining multiple techniques was to increase the diagnostic specificity.

Table 3. Benign and Malignant Calls in Each Diagnostic Test in Comparison With the Reference Values

Diagnostic Test	Reference Test*		
	Benign	Malignant	Total
MG-sonography			
Benign	16	0	16
Malignant	25	28	53
Total	41	28	69
PD			
Benign	15	5	20
Malignant	26	23	49
Total	41	28	69
CE-PD			
Benign	27	5	32
Malignant	14	23	37
Total	41	28	69
MG-sonography + PD			
Benign	6 (23)	0 (1)	6 (24)
Malignant	35 (18)	28 (27)	63 (45)
Total	41	28	69
MG-sonography + CE-PD			
Benign	10 (29)	0 (0)	59 (40)
Malignant	31 (12)	28 (28)	10 (29)
Total	41	28	69

Numbers in parentheses are the percentages that can be obtained when the diagnosis suggested by the additional test (either PD or CE-PD) was accepted as the final diagnosis in BI-RADS category 4 lesions.
*Histopathologic or follow-up results.

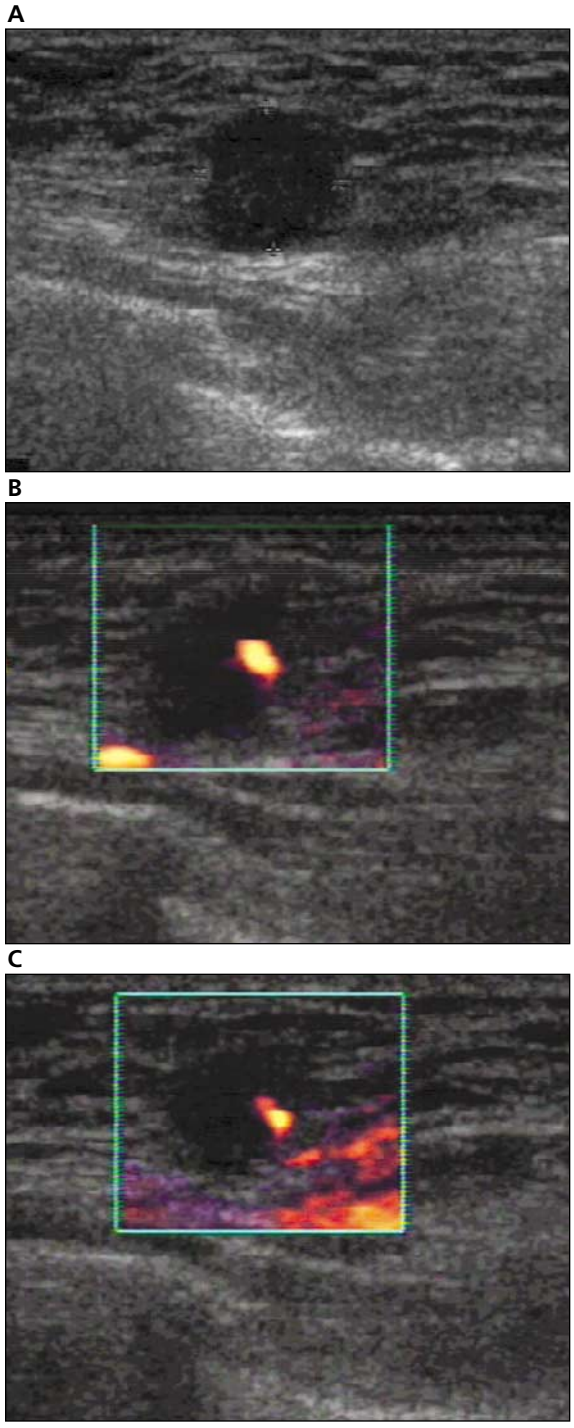
Ideally, this should be done without causing a decrease in the sensitivity. In this study, that was achieved by considering lesion suspicion in combining the diagnostic information. Our results indicate that both PD and CE-PD (particularly CE-PD) are capable of increasing the specificity and PPV of MG-sonography in category 4 and 5 lesions. The specificity increase was more pronounced in the category 4 lesions. If CE-PD had been used as the determinant test selectively in the category 4 lesions in our series, 13 (68%) of 19 benign lesions would have been downgraded into category 3, the follow-up category, and thus would have been saved from

Table 4. Degree of Postcontrast Enhancement in 46 Contrast-Enhanced Lesions

Pathologic Finding	n	Degree of Enhancement		
		Grades 1 and 2	Grade 3	Grade 4
Benign	22	18 (81.8)	4 (18.2)	0 (0.0)
Malignant	24	15 (62.5)	7 (29.2)	2 (8.3)
Total	46	33 (74.0)	11 (24.0)	2 (2.0)

Numbers in parentheses are row percentages.

Figure 1. Infiltrating ductal carcinoma in the right breast of a 42-year-old woman. The too-lateral location of the lesion did not allow its depiction on MG. **A**, Gray scale sonogram showing an 8.0 × 8.5-mm hypoechoic round mass with circumscribed margins and a large (>1) anteroposterior-to-transverse diameter ratio (diagnosis: BI-RADS category 5). **B**, Nonenhanced power Doppler sonogram showing a hypovascular mass containing 1 intratumoral vessel (diagnosis: malignant). **C**, Contrast-enhanced power Doppler sonogram showing no additional intratumoral vessels (grade 0, no enhancement; diagnosis: benign).



unnecessary biopsy, without compromising the 100% sensitivity and NPV achieved with MG-sonography.

We think that, in category 5 lesions, a negative PD or CE-PD finding should not delay the decision to perform a biopsy because of the higher sensitivity of MG-sonography in this group (100% compared with 85% and 81%, respectively). In 2 cases with shared false-negative findings on PD and CE-PD (infiltrating ductal carcinomas sized 10 and 14 mm), no intratumoral vessels were detected. The inability to show vessels in these lesions on PD or CE-PD cannot be explained only by small lesion size because we were able to detect flow signals on PD in 6 benign lesions smaller than 10 mm; 2 of them also showed grade 3 enhancement on CE-PD. Therefore, the potential usefulness of the newer and more sensitive contrast agents in the breast seems questionable.

The MG-sonography combination provides high specificity (100%) in category 3 lesions. Application of PD or CE-PD would cause unnecessary biopsies in this group because of the high false-positive diagnosis rate. Therefore, we can confidently say that PD and CE-PD have no place in this group, and these lesions should be followed-up traditionally.

Four of the 12 fibroadenomas, including the 2 of myxoid type, received false-positive diagnoses on CE-PD in this study. Difficulty in determining the benign nature of fibroadenomas was also reported recently by Alamo and Fischer[20] in a strictly selected group of lesions consisting only of invasive carcinomas and fibroadenomas. We think that the misleading CE-PD findings in fibroadenomas, particularly the myxoid type, may be related to similar factors that cause confusing enhancement properties on dynamic magnetic resonance imaging. This starting point may lead to an idea that comparisons with equivalent dynamic magnetic resonance imaging findings may help in determining an efficient way of using the enhancement-related information. However, a fundamental difference, existing in the distribution patterns of sonographic and magnetic resonance contrast media, makes a direct comparison impossible: after intravenous application, Levovist remains confined to the vessels and does not diffuse across the endothelium, whereas gadolinium diethylenetriaminepentaacetic acid diffuses into the extravascular space.[15,20] Confusing pre-

contrast and postcontrast power Doppler properties observed in 4 cases of fat necrosis in our series are also noteworthy and need further research.

The main difficulty of this study was the setup of the evaluation criteria. The criteria used in previous studies have varied extensively. Among them are the demonstration of blood flow signals,[12,19,20] number of vessels,[8,13,20,21] distribution of vessels,[12,20,21] number of shunts,[13] multiple morphologic features of tumor vessels,[8,13,17,18] degree of enhancement,[8,13] washout pattern,[16,17] measurement of the spectral indices,[18] and dynamic quantitative measures such as duration of enhancement,[13,17,20,21] time to peak enhancement,[8,13,16,17,20,21] and intensity at peak.[16,17] All these criteria have some restrictions.

Determining the number, course, and interrelations of vessels, as done in some studies,[8,13,20,21] is not easy, particularly in very small lesions, at least until the evolution and widespread use of real-time 3-dimensional sonography takes place. Low interobserver agreements in the distribution and morphologic features of tumoral vessels found in our study may be partly related to this difficulty. With current technology, vessels lying close together can be visualized as a single vessel; a tortuous vessel running through several sections could be counted twice; and neighboring vessels can be misinterpreted as intervascu-

Figure 2. Intraductal papilloma in the left breast of a 75-year-old woman. **A**, Focal mammogram in the mediolateral oblique projection showing a dense mass with a somewhat hazy and microlobulated appearance in parts of the inferior and posterior margins (arrows). **B**, Gray scale sonogram showing an 11 × 7-mm (transverse × anteroposterior) hypoechoic mass with circumscribed margins corresponding to the mammographic density (MG-sonographic diagnosis: BI-RADS category 4). **C**, Nonenhanced power Doppler sonogram showing a hypovascular mass containing 2 intratumoral vessels (diagnosis: malignant). **D**, Contrast-enhanced power Doppler sonogram showing no additional intratumoral vessels (grade 0, no enhancement; diagnosis: benign).

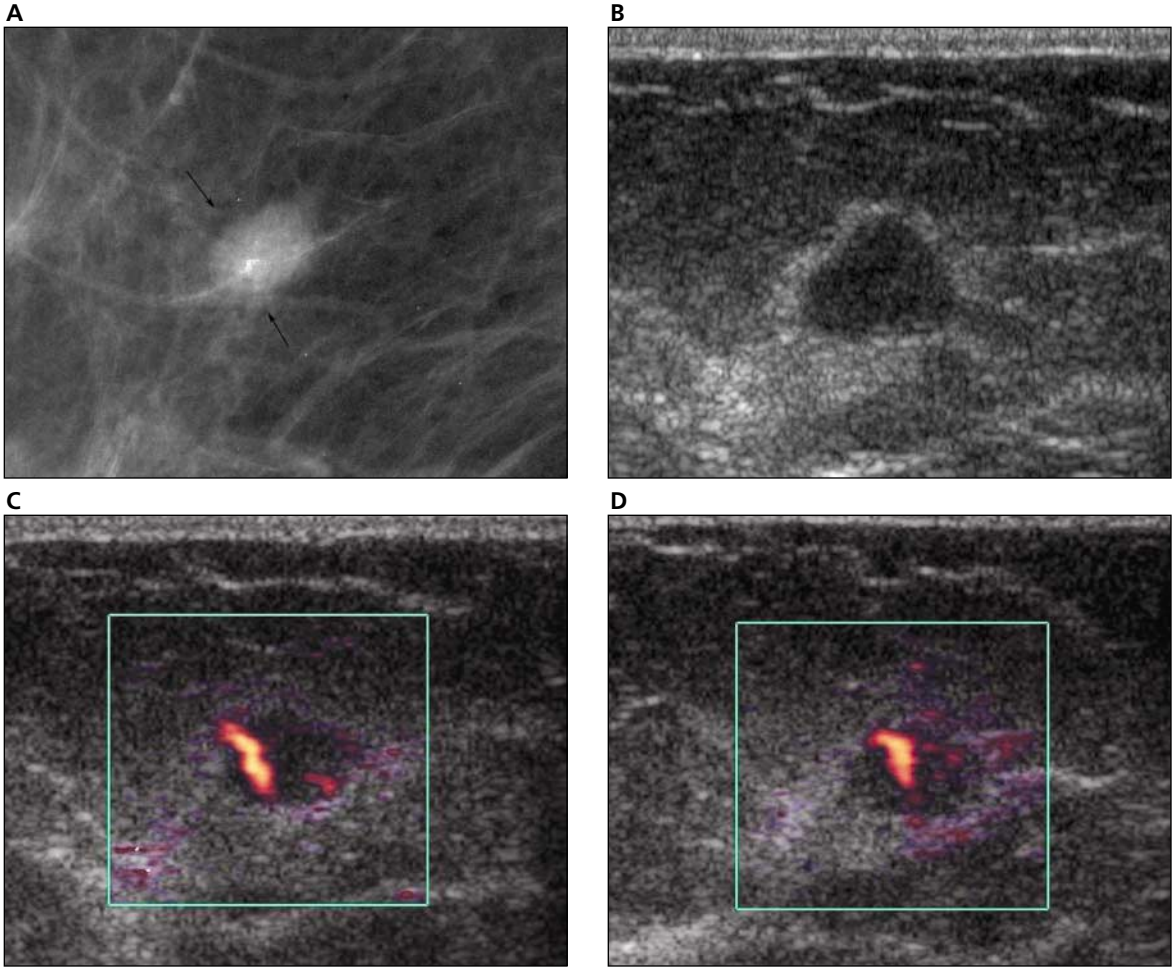
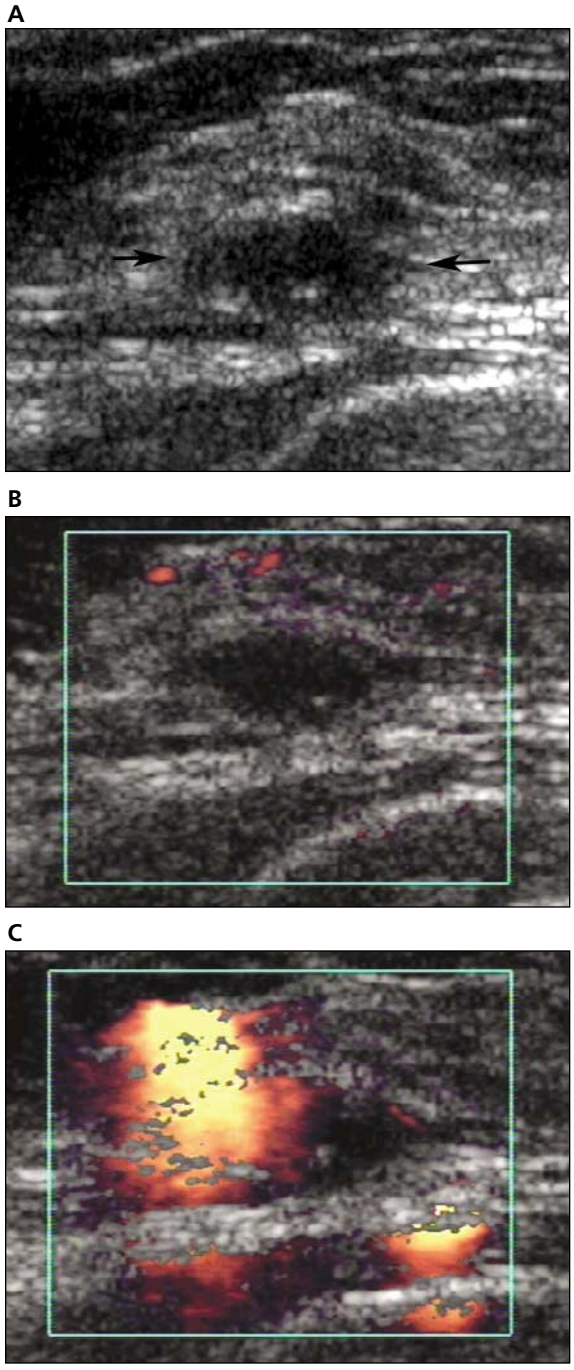


Figure 3. Infiltrating ductal carcinoma in the right breast of a 48-year-old woman. Dense breast parenchyma surrounding the lesion did not allow its depiction on MG. **A**, Gray scale sonogram showing a 7 × 4-mm (transverse × anteroposterior) hypoechoic mass with poorly defined margins (arrows; MG-sonographic diagnosis: BI-RADS category 4). **B**, Nonenhanced power Doppler sonogram showing the absence of vascular signals in the mass (PD diagnosis: benign). **C**, Contrast-enhanced power Doppler sonogram showing a hypervascular mass with grade 4 enhancement and with an EAV of greater than 20% (CE-PD diagnosis: malignant).



lar shunts.[8] Despite increased sensitivities provided with the demonstration of blood flow signals,[19,20] the number of vessels has been found to be an unreliable diagnostic criterion.[8,13,20] The EAV and DEFC seem to be more reliable assessments than only the number of vessels. The interobserver agreement rate for the DEFC found by Kedar et al[13] (78.0%) was similar to ours, which may indicate that the DEFC may be a better reproducible criterion among the others. To our knowledge, the EAV was used previously in only 1 study, by Moon et al.[12] In that study, hypervascular and hypovascular lesions were defined as malignant, in contrast to avascular lesions, which were defined as benign, to provide an increase in the sensitivity (from 36% before contrast to 95% after contrast).[10] Conversely, our intent was to improve the specificity. Because many benign lesions appeared to be vascular to some degree, we used the EAV and DEFC together in the postcontrast evaluation and defined the hypervascular lesions or DEFC grades 3 and 4 as malignant and the hypovascular and avascular lesions or DEFC grades 0 through 2 as benign. With this definition, we provided an increase in the specificity from 37% in the precontrast examinations to 66% in the postcontrast examinations. It has to be noted that determining the EAV and DEFC in very small lesions was difficult, and the use of both criteria together possibly increased the reliability of the final evaluations.

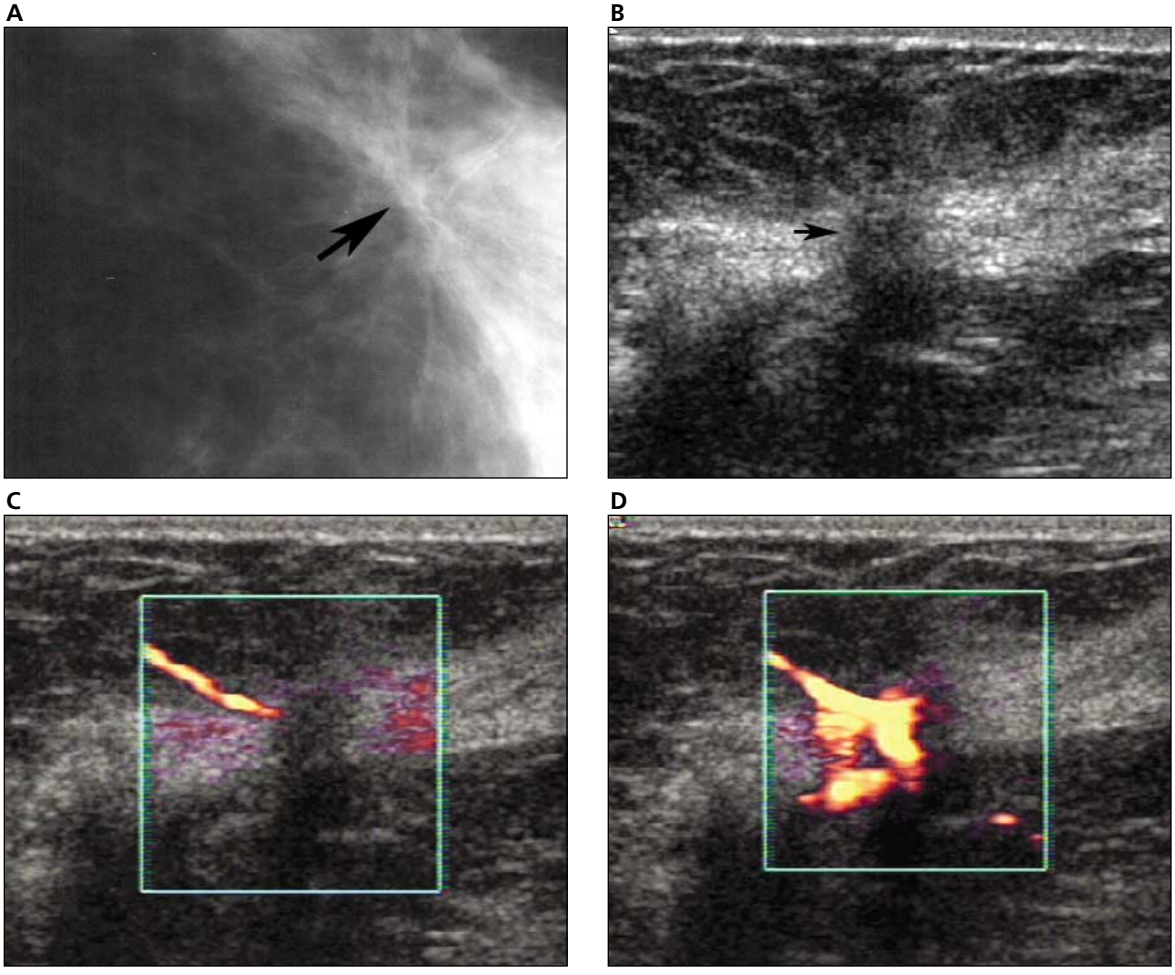
In this study, we did not analyze the dynamic properties of the contrast enhancement in relation to the malignant and benign lesions. In one of the first studies that made use of a sonographic contrast agent in the breast, Kedar et al[13] reported greater and longer enhancement in cancers than in benign lesions, with 100% sensitivity and specificity. However, others did not confirm their findings, either in subjective or quantitative studies.[8,16,17,20,21] Evaluation of the enhancement kinetics through subjective assessment of tape-recorded examinations, as Kedar et al[13] and most others did, is not quantitative and is hardly reproducible. Estimation of the time to peak enhancement and its duration may differ among different readers by as much as 60 seconds.[16] Image-based, computer-assisted analysis was expected to provide an objective assessment. In such a study, after injection of the contrast agent, the peak color pixel density was found to be higher; the peak was reached earlier; and the decline in color pixel density (directly

after the peak) began earlier in carcinomas than in benign lesions.[16] However, differential diagnosis of a lesion, based on the time and the color pixel density relationships, was not found to be reliable with the computerized-quantitative technique used in that study (55% sensitivity and 79% specificity).[16]

Other quantitative measurements such as the resistive and pulsatility indices and the maximal systolic frequency shift also proved not to be helpful.[18] The washout pattern in the time-intensity curves was investigated for its contribution to the differential diagnosis in 2 studies.[16,17] It was shown in both studies that, in carcinomas, there was typically early and marked enhancement, followed by a marked decline.[16,17] Albrecht et al[17] defined monophasic and multiphasic declines in benign and malignant tumors, respectively. However, overlapping results in the benign and malignant lesions limit the use of this parameter.

It is also important to note that the enhancement kinetics are determined by many factors other than just the degree of tumoral vascularization, such as the circulatory differences of patients; selection method of lesions; properties, concentration, volume, and injection rate of the contrast agent; sensitivity of the instrument; type of assessment (subjective or computerized); presence of arteriovenous shunts in the lesion;

Figure 4. Fat necrosis in the right breast of a 66-year-old woman. **A**, Magnification mammogram in the craniocaudal projection showing an area of parenchymal distortion (arrow). **B**, Gray scale sonogram showing a 6-mm round, irregularly marginated hypoechoic mass (arrow) in the area corresponding to the mammographic abnormality (MG-sonographic diagnosis: BI-RADS category 5). **C**, Nonenhanced power Doppler sonogram showing a penetrating vessel in the mass (PD diagnosis: malignant). **D**, Contrast-enhanced power Doppler sonogram showing hypervascularity (EAV >20%) and grade 4 enhancement within the lesion (CE-PD diagnosis: malignant).



and even blooming artifacts (excessive broadening of color areas due to the initial arrival of the contrast agent, contributing to the early peak).[8,16] Multiplicity of the influential factors and the inability to control most of them limit the reliability of evaluations based on enhancement kinetics.

Expectedly, discordance among the results of subjective studies is particularly evident. For example, Stuhrmann et al[8] reported a clearly different vascular distribution, morphologic structure, and course in benign and malignant breast tumors, which afforded the best differential diagnosis on CE-PD, with a sensitivity of 90% and a specificity of 81%. Using the same parameter, Albrecht et al[17] found 100% sensitivity and 56% specificity, whereas Schroeder et al[18] found 100% sensitivity and 95% specificity. Contrary to our expectations, we did not find significant differences in the precontrast and postcontrast evaluations of the vascular distribution and vascular morphologic features of the benign and malignant lesions, and this finding was in concordance with another report by Alamo and Fischer.[20] Low to moderate interobserver agreements (56.3%) obtained for vascular distribution and vascular morphologic features in our study are also meaningful as a way of indicating high levels of subjectivity, thus raising questions about the reliability of these criteria. Interobserver agreement rates reported by Kedar et al[13] for demonstration of vessel tortuosity and intervascular shunts were high, 79% and 88%, respectively. The discrepancy between the interobserver agreement rates of that study and ours may, again, be due to the subjectivity in the evaluations, although the definitions of the evaluation parameters were similar in both studies.

Concentration, volume, injection rate, size of the injection needle, and amount of postinjection saline flush differed extensively in previous studies performed with the same contrast agent (Levovist).[13,16,18–21] These factors may contribute to the discordance in the findings, and their standardization may be useful in lessening the confusion.

Our findings relied on descriptive criteria defined by the investigator and a subjective scoring system. We did not perform quantitative and dynamic evaluations because of their abovementioned limitations. Also, we think that subjective evaluation has an advantage of being easily attained and practical. To overcome the limitations of the subjectivity, we considered the interobserver agreement rates in determining the reliable parameters. The finally selected parameters (DEFC and EAV) had the highest reproducibility, apart from showing substantial changes between the precontrast and postcontrast evaluations. However, these parameters, too, along with those previously studied, are still imperfectly established.

The cost of the tests is also important in the selection of treatment. They vary in different territories of the world. In this country, CE-PD, including the Levovist contrast agent, costs around $120, whereas sonographically guided core needle biopsy, including the needle and the pathologic tests, costs around $80. The higher cost of CE-PD, together with its lack of absolute certainty, invasiveness, and impracticality, is worth reconsideration of its use.

In conclusion, the highest accuracy in the diagnosis of breast lesions on the basis of PD and CE-PD can be accomplished only when these tests are used together with a complete mammographic and sonographic evaluation. It is certain that PD and CE-PD cannot be recommended as confirmatory tests in BI-RADS category 3 and category 5 lesions, and although CE-PD may help reduce the number of unnecessary biopsies in BI-RADS category 4 lesions, recommendation of its use has many drawbacks. A better understanding of the enhancement kinetics and improvements in ultrasound technology may change the current indications for contrast agent use in the breast.

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