New Image Processing Technique for Evaluating Breast Microcalcifications

A Comparative Study

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Objectives—The purpose of this study was to evaluate a new commercial image processing technique (MicroPure; Toshiba America Medical Systems, Tustin, CA) for identifying breast microcalcifications compared to gray scale ultrasound imaging (US) using mammography as the reference standard.

Methods—Twenty women, with breast calcifications identified mammographically, underwent gray scale US and MicroPure examinations of the breast. Still images and digital clips of the target area were acquired using gray scale US and MicroPure (at 3 different sensitivity levels: 0, 1, and 2). The images were analyzed by 4 independent and blinded readers (2 radiologists and 2 physicists) to determine the number of calcifications as well as to score image quality and artifacts.

Results—For all 4 readers, there were significantly more calcifications seen with MicroPure (at the 2 highest sensitivity levels) compared to gray scale US ($P < .009$). Agreement between readers consistently increased from gray scale US to MicroPure imaging (gray scale intraclass correlation coefficient, 0.02–0.44; versus MicroPure intraclass correlation coefficient, 0.34–0.71). The agreement improved between mammography and MicroPure (13.2%–28.3%) when compared with mammography and gray scale US (1.7%–5.2%); the 2 radiologists saw a bigger improvement. Two readers preferred the MicroPure image quality over gray scale US ($P < .001$) and vice versa for the other 2 readers ($P < .001$). All 4 readers saw fewer artifacts with MicroPure (at level 2) than with gray scale US ($P < .02$).

Conclusions—MicroPure imaging identified significantly more breast microcalcifications than gray scale US.

Key Words—breast; image processing; microcalcifications; ultrasound imaging

Mammography is considered the reference standard for the evaluation of breast microcalcifications, including morphologic aspects, which helps differentiate possibly benign from suspicious microcalcifications.[1–12] Microcalcifications that are considered more suspicious are further analyzed with biopsy and/or surgical excision to determine their exact nature through histologic analysis. Mammography has high sensitivity and specificity for screening of breast cancer, varying from 63% to 96% for sensitivity[2,13–23] and 87% to 97% for specificity.[16,17,19,22] Mammography has been validated as a screening method for breast cancer, and microcalcifications are considered an important finding for the diagnosis of breast cancer.[5,9,11,12,14,24–31]

Clinical evaluation of breast microcalcifications by gray scale ultrasound imaging (US) is not usually performed, due to the limitations of this imaging technique in identifying microcalcifications. There have been some attempts by researchers to use gray scale US to identify microcalcifications, but even the most promising results from these studies/methods do not support the clinical use of gray scale US for the evaluation of microcalcifications.[4,5,7–9,11–13,15,26–29,32,33]

Research has shown that when microcalcifications lie within a mass, they are easier to visualize with gray scale US, since the mass in question works as an acoustic window. The microcalcifications appear on gray scale US as hyperechoic foci, which usually do not have an acoustic shadow.[1,3–5,7–9,11,12,29,33,34] However, the evaluation of isolated and/or clusters of microcalcifications that lie within normal breast tissue is considered to be more difficult to accomplish with gray scale US, due to the lack of contrast between normal parenchyma and the microcalcifications.[2–5,7–9,11–13,26–28,32,33]

Ultrasound is used to guide percutaneous core biopsies or wire localizations for surgical biopsies of breast masses. For the patients, there are many advantages to a US-guided procedure compared with a mammographically guided procedure. Besides the fact that a US study does not involve radiation,[35] making it a safer choice for pregnant and lactating women, a US-guided procedure permits the patient to stay in a comfortable and more physiologic position without compression of the breast. The real-time aspect of US provides an advantage for the radiologist, who can see the needle position in real time during the entire procedure.[8,9,11,28,29,33,34] Ultrasound imaging allows access to a greater number of lesions than does stereotactic biopsy. Therefore a US-guided approach for the evaluation of microcalcifications would enable more patients to undergo US procedures instead of mammographic ones.[4,8,9,11,28,29,33]

MicroPure (Toshiba America Medical Systems, Tustin, CA) is a new commercial US image processing technique that processes US images in order to improve the visualization of breast microcalcifications. MicroPure combines nonlinear imaging and speckle suppression to mark suspected calcifications as white spots in a blue overlay image. The purpose of this study was to determine if MicroPure can identify microcalcifications seen on mammography better than gray scale US, which might enable MicroPure to be used in the future as a diagnostic tool for guiding breast biopsies.

Materials and Methods

Patients

This study was a prospective clinical trial conducted from June to October 2010 involving 20 adult female patients who were approached when they went to the Breast Imaging Center at Thomas Jefferson University Hospital for their scheduled annual mammogram. The patients all had diffuse/scattered calcifications seen on mammography. The mean age of the patients participating in the study was 61.7 years (range, 41–83 years) and everyone provided written informed consent. The study was approved by the university's Institutional Review Board and was compliant with the Health Insurance Portability and Accountability Act.

This study was supported in part by Toshiba America Medical Systems. The sponsor provided an Aplio XG scanner. The authors of this article had sole control of the data generated by this trial and the information provided for publication.

Data Acquisition

MicroPure is integrated software on the Aplio XG scanner that uses a filter technique called the constant false alarm rate, which is known in the radar field.[36–38] For each pixel, the average brightness of the surrounding area is calculated, and the difference between the two is the filter output. Hence, a constant false alarm rate filter can detect locations where there is a characteristic change from the surrounding area.[36] As the focus of MicroPure imaging is to detect microcalcifications in breast tissue, the filter kernel is optimized in the horizontal direction to detect only isolated points with higher brightness compared to the surrounding breast tissue. This technique has the ability to differentiate microcalcifications from areas of the breast tissue that also appear with high brightness on the US image.[36]

MicroPure also uses a compounding technique on transmission that preprocesses the image to reduce speckle and separate true microcalcifications from artifacts in the normal breast tissue. In order to provide better visualization of the microcalcifications, MicroPure filters the microcalcifications as images in white that are superimposed on the original US image shown in blue hues.[36] MicroPure has the same size limitations for the identification of microcalcifications as gray scale US, around 100 μm; the difference is the way that MicroPure interprets the microcalcifications and the surrounding tissue for better identification of the microcalcifications.[36]

All enrolled patients underwent US of the area in the breast where calcifications were seen with mammography. The Aplio XG scanner with a 14-MHz broad-bandwidth linear array was used to perform gray scale US and MicroPure

imaging. MicroPure has 3 levels of sensitivity (display thresholds for which an echo level is designated as a microcalcification) implemented by the manufacturer, and the patients were scanned with all 3 levels (denoted as 0, 1, and 2, with 2 being the highest sensitivity) to allow for interlevel comparisons. For each anatomic location, the focal zone and scanning depth were adjusted (in the gray scale US mode) to optimize visualization of the target region and then kept constant. No compounding or other image processing techniques were applied. The time-gain compensation and 2-dimensional gain setting were optimized separately for each imaging technique. Sagittal and transverse still images as well as real-time digital video clips of the area with calcifications were obtained in all patients with all 4 imaging techniques (ie, gray scale US, MicroPure 0, MicroPure 1, and MicroPure 2). A total of 30 areas were scanned in the 20 patients, as 10 patients presented with 2 areas of microcalcifications. The number of still images acquired for each case varied from 5 to 25 depending on the size of the scanned area. Likewise, the acquisition of digital clips required 2 to 10 clips per area.

A radiologist at the Breast Imaging Center selected patients in whom microcalcifications were seen on mammography, without any diagnostic consideration; just the identification of microcalcifications on mammography was necessary. Mammographic images were acquired in 2 standard image planes: mediolateral oblique and craniocaudal (Figure 1). Additional views were not acquired for all patients; they were only acquired when the radiologists doing the diagnosis reading thought necessary (those were different radiologists than the one doing the selection). Mammography was performed using a Senographe Essential or Senographe DS system (GE Healthcare, Milwaukee, WI).

After the study was done, 2 blinded radiologists had access to the mammographic study to determined the number of microcalcifications seen on mammography. They counted the exact number of microcalcifications seen, and for that, they had access to the entire mammographic study; after that, their results in consensus were analyzed and used as the reference for the analyses of the agreement between methods.

Figure 1. Mammographic study of a right breast that shows diffuse microcalcifications on the upper outer quadrant of the breast (arrow); **A**, mediolateral oblique view; **B**, craniocaudal view.
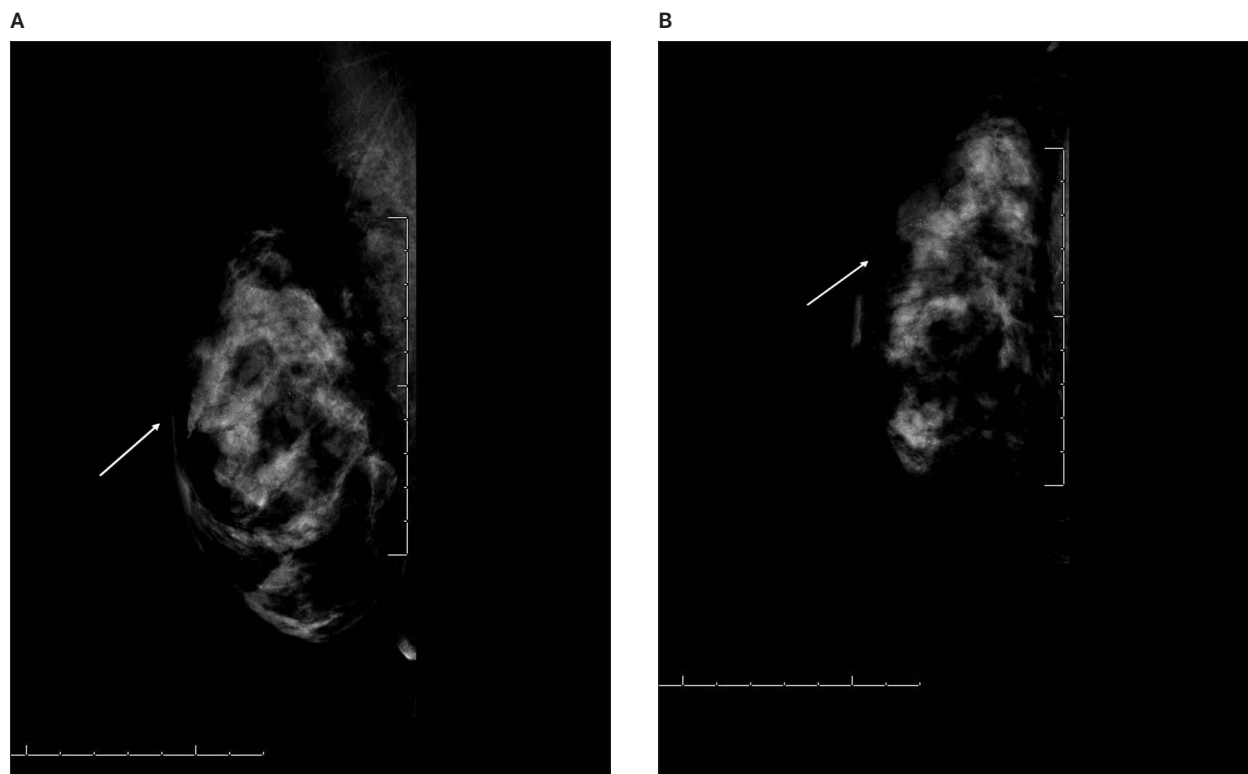
Data Analyses

The still gray scale US and MicroPure images acquired for each patient were assessed in randomized side-by-side comparisons, since the distinct blue color overlay of MicroPure prevented a randomization scheme based on individual images. Four independent and blinded readers, consisting of 2 radiologists and 2 physicists, compared 332 side-by-side images to determine the number of microcalcifications (as 0, 1, 2, 3, 4, and 5 or more) and scored image quality as well as artifacts on a visual analog scale from 1 (worst) to 10 (best). The digital clips were analyzed in 2 separated sets, 1 for the gray scale US and other for MicroPure (at sensitivity level 1). The same 4 independent and blinded readers analyzed 58 gray scale US clips and 53 MicroPure clips to determine the number of microcalcifications, classified as 1 to 5, 6 to 10, 11 to 20, and more than 20.

The qualitative scores (ie, for image quality and artifacts) were compared using a nonparametric Wilcoxon signed rank test, while the number of breast calcifications was compared with paired t tests and intraclass correlation coefficients (ICCs). All tests were performed using Stata 9.2 (StataCorp, College Station, TX) with $P < .05$ indicating statistical significance.

Results

Still Images

Figures 2 and 3 show examples of matching acquired still images obtained in gray scale US and MicroPure modes (at sensitivity levels 0, 1, and 2). Figure 2 shows a cyst with internal septations and microcalcifications (marked with an arrow). The microcalcifications within the cyst can be seen on gray scale US and MicroPure at all 3 levels of sensitivity; the difference is that in this example, the MicroPure images show microcalcifications that were not seen by gray scale US located at the left of the image; those microcalcifications are marked with a star. Figure 3 depicts breast tissue that on gray scale US would be considered

Figure 2. A, Gray scale ultrasound image; **B**, MicroPure at level 0; **C**, MicroPure at level 1; **D**, MicroPure at level 2. At the center of the cyst, there is a microcalcification (tip of the arrow), which can be seen on the gray scale image, but on MicroPure at all sensitivity levels, other microcalcifications can be seen located at the left (star).
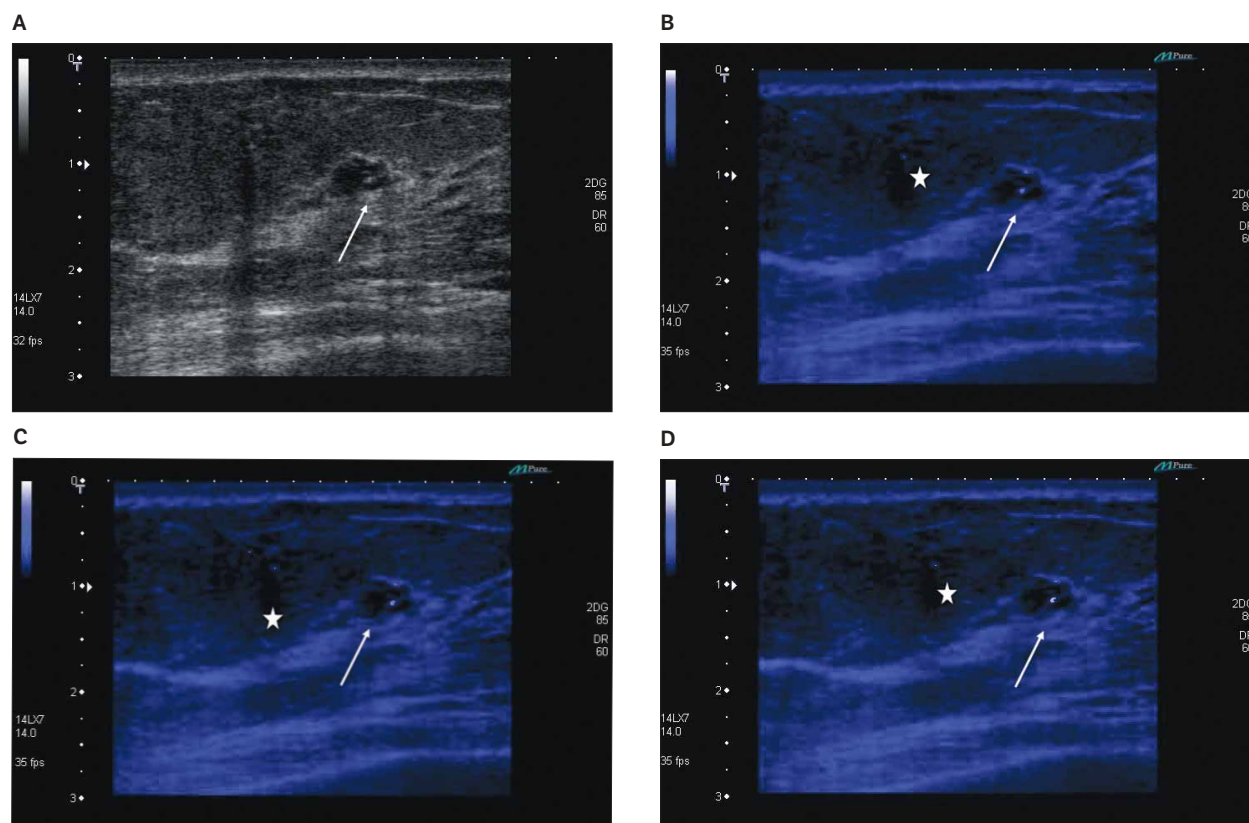
normal tissue. However, once MicroPure was activated, the microcalcifications became clear, making a more complete evaluation of the breast tissue; an arrow is used for a better view of the microcalcifications.

For all 4 readers, there were significantly more calcifications seen with MicroPure at the 2 highest sensitivity levels (levels 1 and 2) when compared to gray scale US ($P <$ .009). At the lowest MicroPure level (level 0), 1 reader saw no difference relative to gray scale US ($P = .52$), while the other 3 readers did ($P < 0.001$). The mean number of cal-

cifications ± SD seen among all 4 readers increased from 0.7 ± 1.10 for gray scale US to 1.9 ± 1.70 with MicroPure. The results for each reader and the totals are shown in Table 1.

The agreement between readers consistently increased from gray scale US to MicroPure. The ICC values from gray scale US ranged between 0.02 and 0.44; for MicroPure, the ICC values ranged between 0.34 and 0.71. The results are detailed in Figure 4A, where the gray scale results are in the gray rectangle and the MicroPure results are in the blue rectangle, with the latter showing the lowest

Figure 3. A, Gray scale ultrasound image; **B**, MicroPure at level 0; **C**, MicroPure at level 1; **D**, MicroPure at level 2. At the center of the image, there is a microcalcification (tip of the arrow in **A**) that cannot be clearly seen on the gray scale image, but it is visible on the MicroPure images at all 3 levels of sensitivity.
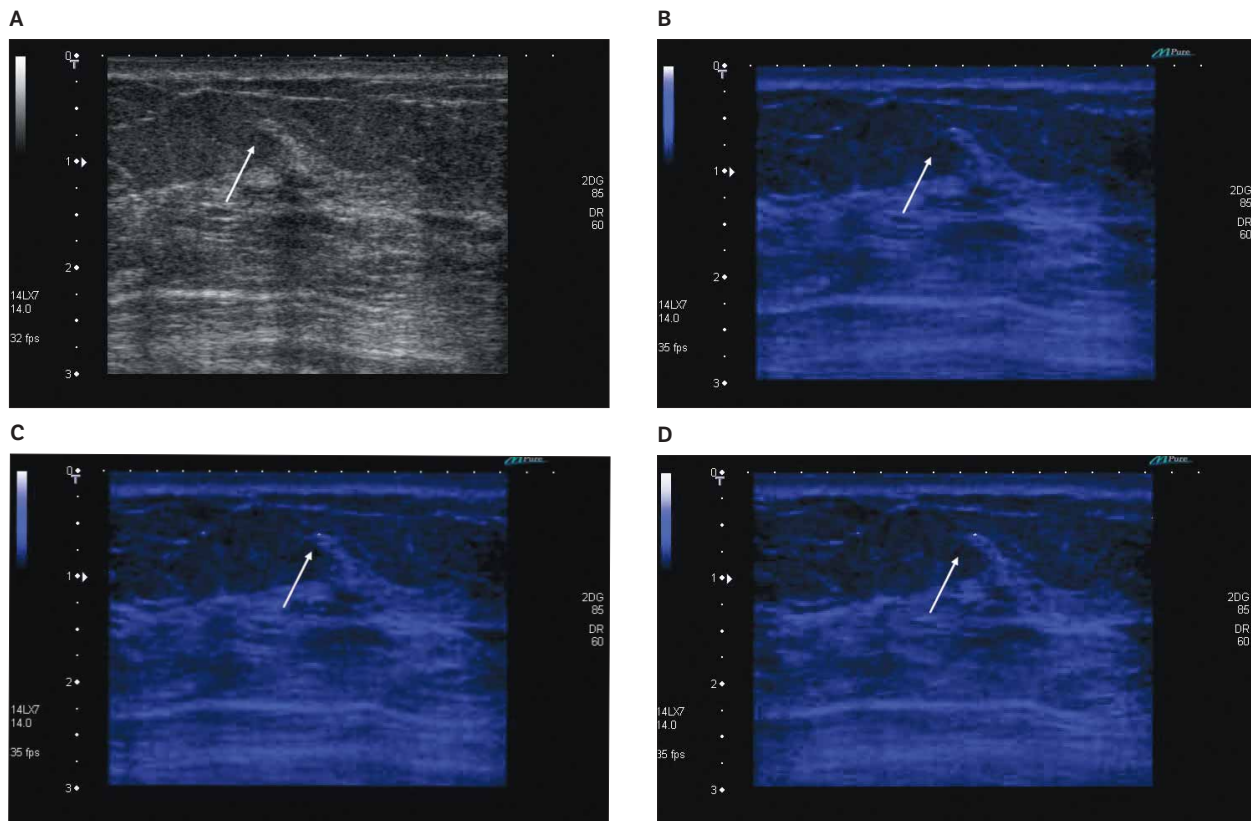
Table 1. Mean Number of Microcalcifications Seen on the Still Images

Reader	Ultrasound	MicroPure 0	MicroPure 1	MicroPure 2
1	0.8 ± 1.2	3.2 ± 1.8	3.4 ± 1.8	3.5 ± 1.8
2	1.1 ± 1.2	1.4 ± 2.0	1.7 ± 2.0	1.9 ± 2.0
3	0.7 ± 1.0	1.7 ± 2.0	2.2 ± 2.0	2.3 ± 2.0
4	0.5 ± 1.1	0.8 ± 1.3	1.0 ± 1.3	1.4 ± 1.3
Total	0.7 ± 1.1	1.7 ± 1.8	2.0 ± 1.8	2.2 ± 1.8

Values are mean ± SD.

Figure 4. **A**, Intraclass correlation coefficient values for the agreement between readers with regard to the mean number of microcalcifications seen on gray scale ultrasound imaging and MicroPure (at all sensitivity levels) on still images. **B**, Intraclass correlation coefficient values for the agreement between readers with regard to the mean number of microcalcifications seen on gray scale ultrasound imaging and MicroPure at sensitivity level 1 on digital clips. The gray scale values are in the gray rectangle, and the MicroPure values are in the blue rectangle.
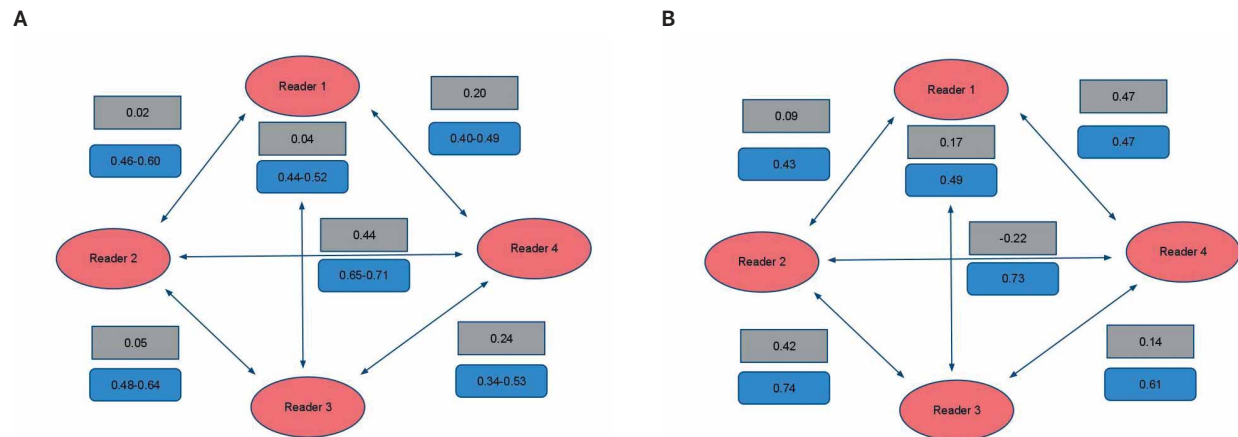
Figure 5. Examples of artifacts with MicroPure and how they change according to the transducer angle and position. **A** and **B**, Images of the same area, where **A** shows no artifacts, and **B** shows several artifacts. **C** and **D**, Images of the same area, where **C** shows no artifacts, and **D** shows several artifacts.
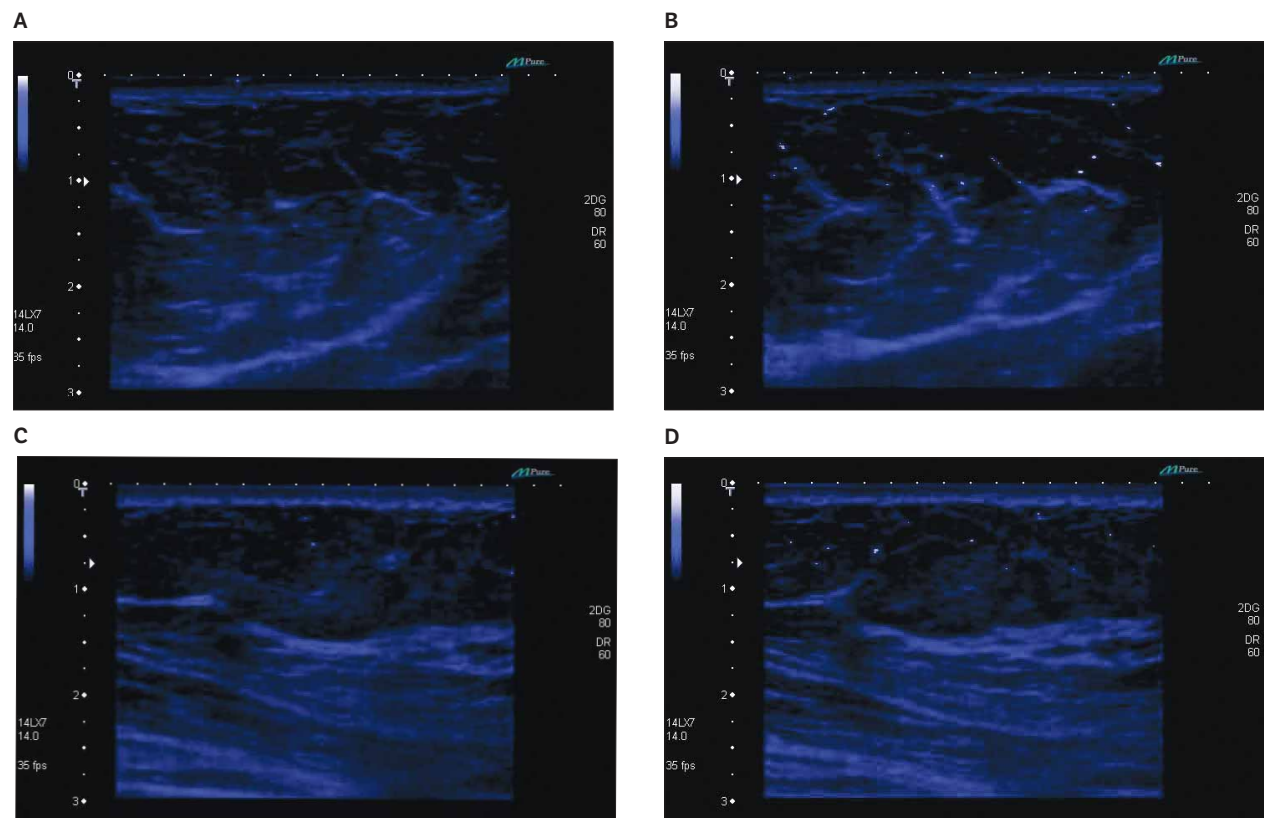
and highest values obtained for the 3 MicroPure sensitivity levels. When specifically comparing each level of sensitivity of MicroPure, there was a better agreement between readers on the number of calcifications seen with MicroPure at level 1 of sensitivity, with a range of 0.22, compared to the results achieved with MicroPure sensitivity levels 0 and 2. The ICC values for MicroPure at level 1 ranged from 0.44 to 0.66; for MicroPure at level 0, the ICC values ranged from 0.34 to 0.65; and for MicroPure at level 2, the values ranged from 0.38 to 0.71. These values show that MicroPure at level 2 had the highest ICC value but also the highest difference in agreement (0.33), which means that it was the level of sensitivity where the readers had a more variable opinion; when all results were analyzed, the agreement between readers at level 1 surpassed that at the other 2 levels (0 and 2).

Two of the readers, 1 radiologist and 1 physicist, preferred the MicroPure image quality over that of gray scale US ($P < .001$), although for the other 2 readers (also consisting of a radiologist and a physicist), the image quality of gray scale US was preferred over MicroPure ($P < .001$). When artifacts were evaluated, all 4 readers saw fewer artifacts with MicroPure at the highest level of sensitivity (level 2) compared to gray scale US ($P < .02$). For the 2 lowest sensitivity levels, there were no statistically significant differences between gray scale US and MicroPure ($P > .52$).

The analysis of the still images from this study showed that MicroPure artifacts, which can be confused with microcalcifications, are usually due to Cooper ligaments. Such artifacts can increase the mean number of microcalcifications seen and, therefore, have to be assessed more closely to better differentiate real microcalcifications from artifacts in order to avoid false-positive findings on the MicroPure examination. Calcifications can be differentiated from artifacts during real-time scanning by changing the angle of the transducer. Therefore, digital clips were used in addition to still images to differentiate Cooper ligaments from calcifications.

Table 2. Mean Percentage of Agreement Between Mammography and the Digital Clips of Gray Scale Ultrasound or MicroPure (at Sensitivity Level 1) With Regard to the Exact Number of Microcalcifications

	Agreement, %	
Reader	Mammography × Ultrasound	Mammography × MicroPure 1
1	3.5	18.9
2	5.2	17.0
3	5.2	13.2
4	1.7	28.3
Total	3.9	19.4

Figure 5 shows 2 examples of these artifacts; the same area is seen first without the artifacts (Figure 5, B and C) and with the artifacts that could be confused with microcalcifications (Figure 5, B and D).

Digital Clips

The digital clips were analyzed for the exact agreement between mammography and gray scale US as well as between mammography and MicroPure at sensitivity level 1, since analysis of the still images showed better agreement between readers at this level of sensitivity.

Mammography and gray scale US showed an average agreement of 3.9 %, varying between readers from 1.7% to 5.2 %. When mammography and MicroPure (at sensitivity level 1) were compared, the overall agreement was 19.4%, which varied between readers from 13.2% to 28.3%, as shown in Table 2. All readers had marked increases in agreement between mammography and MicroPure compared to their agreement between mammography and gray scale US. Both radiologists (readers 1 and 4 in Table 2) saw a bigger improvement in agreement between mammography and MicroPure, relative to the 2 physicists. The ICC values from gray scale US ranged between –0.22 and 0.47, while for MicroPure (at sensitivity level 1), the ICC values ranged between 0.43 and 0.74. These results are detailed in Figure 4b, where the gray scale results are in the gray rectangle and the MicroPure results are in the blue rectangle.

Discussion

Breast microcalcifications are considered an important finding for the diagnosis of breast cancer, making their correct visualization and analysis crucial for early detection.[5–9,11–13,24–31] Mammography is considered the only reliable method to identify and classify microcalcifications.[1–12]

Current US technology is not considered a reliable method for the detection or evaluation of microcalcifications. Microcalcifications are more likely to be seen on US when they are located inside hypoechoic solid masses, because the solid masses provide a hypoechoic background that improves the visualization of the bright microcalcifications echoes.[3,7–9,11,27,35] The evaluation of isolated microcalcifications within normal breast tissue is considered to be more difficult with US, due to the lack of contrast between normal parenchyma and the microcalcifications.[1,3–5,7,9,11,12,27,29,32,35] The visualization of microcalcifications on US is limited by factors such as speckle noise, phase aberration, system spatial resolution, and display parameters.[1,32] Research shows that the use of high-frequency transducers, above 7.5MHz, improves the

detection of microcalcifications by US, but even with that improvement, results still show US to be an unreliable method for clinical use.[1,3–5,7,11,12,27–29,32,35] Some studies have indicated that microcalcifications can be seen using gray scale US in around 50% to 100% of cases.[3,4,7,11,12,27,28] However, the majority of these findings correspond to masses with microcalcifications inside. In addition, these studies show that even when microcalcifications are seen, the number seen with US is smaller than the real number found by pathologic examination.[3,4,7,11,12,27,28]

This study focused on the evaluation of MicroPure, a new US image processing technique for the evaluation of microcalcifications. The results are promising, with an increase in the mean number of microcalcifications seen on MicroPure images (1.9 ± 1.70) at all 3 levels of sensitivity compared to gray scale US, where on average, 0.7 ± 1.10 microcalcifications were seen.

The MicroPure image quality produced divided opinions among readers, where 2 readers preferred MicroPure ($P < 0.001$) and 2 readers preferred gray scale US ($P < .001$) image quality . One factor that may have contributed to this difference was the experience of the readers with MicroPure images. Readers who had seen MicroPure images prior to the study seemed more comfortable with the blue overlay used in this mode, and this factor may have influenced their readings. The 2 readers who preferred the quality of gray scale US images had never seen MicroPure images prior to this study.

The major component of the artifacts that we observed in this study was due to Cooper ligaments; the problem is that such artifacts can increase the number of microcalcifications seen on the area scanned; to try to avoid that problem, the use of real-time scanning when the angle of transducer can be changed is recommended. There are still several questions to be answered that were not analyzed in this study, such as its use for the evaluation of clusters of microcalcifications and limitations due to hyperechoic glandular and fibrous tissue. Future studies will take those issues into consideration.

It should be noted that this work was a pilot study performed on only 20 patients. The sample size was small; therefore, more studies with a larger sample size are necessary to be able to determine the ability of MicroPure to identify microcalcifications in clinical practice.

In conclusion, MicroPure images showed more microcalcifications than gray scale US, but still less than mammography, and with markedly improved agreement between readers. Although all readers saw fewer artifacts in the MicroPure mode, artifacts that were seen can still be confused with microcalcifications. These shortcomings become especially prevalent when only still images are assessed, indicating that real-time imaging and/or review will be essential for physicians to maximize the benefits of this new image processing technique. While the results of this pilot study are promising, more studies are required to determine if MicroPure can be used to analyze the morphologic characteristics of microcalcifications. At the moment, there are no existing data to determine whether the characteristics of benign and malignant microcalcifications can be established with MicroPure, which will be an essential concept if this new mode is to be used for diagnosis and biopsy of suspicious microcalcifications.

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