

Three-Dimensional Power Doppler Ultrasound and A Microbubble Contrast Agent in the Evaluation of Breast Tumor Vascularity

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Purpose: To evaluate the diagnostic value of three-dimensional (3D) power Doppler (PD) ultrasound (US) combined with a microbubble contrast agent in characterization of tumor vascularity in solid breast masses.

Materials and Methods: Sixty consecutive patients with solid breast masses visualized by gray-scale US were evaluated with two-dimensional (2D) and 3D PDUS before and after injection of the contrast agent SH U 508 A. The tumor size varied 0.5–3.2 cm (mean, 1.2 cm). At each US studies, lesion vascularity (avascular, hypovascular, hypervascular) and morphology (regular vs irregular) of vessels were prospectively assessed by two radiologists. Diagnostic accuracy was calculated at unenhanced 2D and contrast-enhanced 3D PDUS.

Results: At unenhanced 2D PDUS, 19 (70%) of 27 cancers were vascular whereas 12 (36%) of 33 benign lesions were vascular. At contrast-enhanced 3D PDUS, all cancers (100%) were vascular whereas 20 (61%) benign lesions were vascular ($p < .01$). Irregular vessels were seen in 7 cancers (26%) and 1 benign lesion (3%) at unenhanced 2D PDUS and 22 cancers (81%) and 3 benign lesions (9%) at contrast-enhanced 3D PDUS ($p < .001$). By using the presence of irregular vessels in the mass as the diagnostic criterion for malignancy, sensitivity, specificity, positive and negative predictive values were 26% (7/27), 97% (32/33), 88% (7/8), and 62% (32/52), respectively, at unenhanced 2D PDUS and 81% (22/27), 91% (30/33), 88% (22/25), and 73% (30/41), respectively, at contrast-enhanced 3D PDUS.

Conclusion: Contrast-enhanced 3D PDUS was superior to unenhanced 2D PDUS in the characterization of tumor vascularity in solid breast masses.

Index words: Breast neoplasms, US; US, contrast agent; US, power Doppler studies, Three-dimensional US

INTRODUCTION

Gray-scale ultrasonography (US) of the breast has been applied and found to be helpful for tumor charac-

terization (1–4). The additional contribution of color and power Doppler (PD) US for tumor characterization has been stressed by some reports (5, 6) but it is controversial (7). Specific to Doppler imaging is the assumption that neoangiogenesis within a malignant mass may enable differentiation from benign disease (8, 9). PDUS based on total integrated power of the Doppler spectrum is now considered superior to color Doppler US in the demonstration of vascular flow because of such advantages as high sensitivity to slow flow, no angle dependency, and no aliasing (10, 11). Recently developed

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microbubble US contrast agents also improve the detection of characteristic neovascular morphologic features by enhancing the signal strength in small vessels (12). Previous studies of Doppler US found that echo enhancement by a contrast agent could increase the diagnostic accuracy in breast tumors (13-15). In those studies, however, tumor vascularity was analyzed at two-dimensional (2D) PD US with the qualitative or quantitative methods. To our knowledge, the usefulness of a contrast agent in three-dimensional (3D) PDUS has not been evaluated in breast lesions.

We performed a prospective study to investigate the diagnostic value of 3D PDUS combined with a microbubble contrast agent in characterization of solid breast masses.

MATERIALS AND METHODS

Between December 2003 and June 2004, 60 consecutive patients (age range, 30-65 years; median age, 51 years) with solid breast masses visualized by gray-scale US were included in this study. At the time of examinations, 36 (60%) were nonpalpable lesions. Two patients had undergone previous breast surgery for malignant lesions.

On mammograms, the lesions were seen as a mass in 25 cases (41%), a mass with microcalcifications in 19 cases (32%), and were not seen in 16 cases (27%). According to American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) (17), the final assessment category based on mammography and gray-scale US was probably benign lesions (category 3) in five cases (8%), suspicious lesions (category 4) in 45 cases (75%), and highly suspicious lesions (category 5) in 10 cases (17%). Three cases of probably benign lesions were biopsied due to patient or referring clinician preference on the basis of clinical grounds.

The contrast agent was SH U 508 A (Levovist; Schring, Berlin, Germany), which is a suspension of monosaccharide microparticles (galactose) in sterile water. Microbubbles (2-8 μ m in average diameter) are stabilized in the microparticle suspension; they can transverse the pulmonary capillary bed and enhance the signal of blood. Before US, the agent was prepared for injection by shaking it with 5 mL of water for 5-10 sec-

onds. A milky suspension of galactose microparticles and microbubbles was created by disaggregation of the granules. After standing for 2 minutes for equilibration, 6.0 mL of 400 mg/mL suspension was injected manually at 1 mL/sec via 18-20-gauge cannula placed in an antecubital vein. An additional 10 mL of physiologic saline solution was then injected at the same rate to flush the cannula. The intravenous cannula was placed prior to the commencement of US examinations.

All US examinations were performed by one experienced radiologist with power map US equipment (HDI 3000 or 5000; Advanced Technology Laboratories, Bothell, Wash). A 10-5-MHz, 38-mm linear transducer was used in all cases, which automatically shift to 6 MHz when in color Doppler interrogation mode. The following settings were used: transmit power, low; mechanical index of 0.7; and log compression, 55 dB. The color box was enlarged to include the lesion and a margin of normal breast tissue. The scanning plane was selected for optimal visualization of vascularity. Color sensitivity was set at a level where background color was just suppressed and small vessel could be detected. The resultant PDUS gains ranged from 75-85%. Care was taken not to apply pressure with the probe as this had previously been found to obliterate the small, low-pressure vessels associated with breast lesions.

For 3D PDUS data acquisition, a free-hand technique was used. From the serial 2D images, 3D images were reconstructed and volume rendered images were displayed in a cine mode.

Dynamic PD US data were recorded on videotape and stored in the US unit until the signal enhancement had completely diminished. Static images were obtained before and 30, 60, 90, 120, 180, 210, 240, and 300 seconds after injection of the contrast agent. At each time frame, one or two representative hard-copy images were obtained in all cases.

Surgical excision or core needle biopsy revealed 27 cancers and 33 benign diseases (Table 1). Malignant lesions were 7 cases of ductal carcinoma in situ (DCIS) and 20 cases of invasive carcinoma. The histologic diameter of the lesions ranged from 5 to 30 mm (mean, 9.8 mm) for DCIS and 6 to 32 mm (mean, 13.1 mm) for invasive cancer. Benign lesions were five cases of non-proliferative fibrocystic disease, 20 cases of proliferative

fibrocystic disease, and eight cases of fibroadenomas. The histologic diameter of fibroadenomas ranged from 5 to 23 mm (mean, 10.9 mm).

At unenhanced 2D and contrast-enhanced 3D PDUS, lesion vascularity, and morphology of vessels were analyzed in consensus by two radiologists preoperatively, one who actually performed the examination and one who evaluated the video and static images. Morphologic analysis of tumor vessels was performed based on the US images obtained at the time of maximal enhancement. The lesion vascularity was quantified using a computer-assisted program (Sonic v10R). This software automatically quantified the color pixel density within the region of interest. The vascularity of the lesion determined by the number and the estimated amount of vessels within the mass was classified into three categories: avascular (without flow), hypovascular (one or two vessels and less than 10% color flow), and hypervascular (more than three vessels or greater than 10% color flow). The amount of enhancement after contrast agent injection was arbitrary classified into three categories: minimal (no or equivocal additional vessels), moderate (one or two additional vessels), and marked (more than three additional vessels). The shape of vessel was divided into regular or irregular. Irregular

vessels indicated blood vessels lack of normal tapering or vessels with tortuosity or penetrating the tumor in a radial fashion. If there is a penetrating vessel (16), it was reported.

The vascularity of the lesions and distribution and morphology of vessels before and after the contrast agent were correlated with histopathologic results. The findings with a *p* value less than .05 were considered as statistically significant. Using the presence of vascularity in the mass or irregular vessels as the diagnostic criterion for malignancy, a diagnostic accuracy including sensitivity, specificity, and positive and negative predictive values was calculated at unenhanced 2D and contrast-enhanced 3D PDUS.

RESULTS

PDUS findings of the breast masses before and after administration of the US contrast agent were summarized at Tables 1 and 2.

Malignant Lesions

At unenhanced 2D PDUS, 19 (70%) of the 27 cancers were vascular; hypovascular in ten and hypervascular in nine. Irregular vessels were seen in seven cases

Table 1. Vascularity of 60 Nonpalpable Breast Masses at Unenhanced 2D and Contrast-enhanced 3D Power Doppler US

Vascularity	Invasive Cancer (n = 20)	DCIS (n = 7)	Fibrocystic Disease (n = 25)	Fibroadenoma (n = 8)
Unenhanced 2D US				
avascular	5	3	17	4
hypovascular	7	3	6	2
hypervascular	8	1	2	2
Contrast-enhanced 3D US				
avascular	0	0	11	2
hypovascular	7	4	11	2
hypervascular	13	3	3	4

Table 2. Morphology of Tumor Vessels at Unenhanced 2D and Contrast-enhanced 3D Power Doppler US

Vessel Morphology	Invasive Cancer (n = 20)	DCIS (n = 7)	Fibrocystic Disease (n = 25)	Fibroadenoma (n = 8)
Unenhanced 2D US				
regular	15	5	24	8
irregular	5	2	1	0
Contrast-enhanced 3D US				
regular	3	2	23	7
irregular	17	5	2	1

(including two cases showing penetrating vessels).

At contrast-enhanced 3D PDUS, all cancers were vascular; hypovascular in 11 and hypervascular in 16. The increase in PD signal reached a maximum at 30 seconds after injection in 19 cases and 60 seconds after injection in nine cases. Irregular vessels were seen in 22 cases (including five cases showing penetrating vessels) (Fig. 1).

Benign Lesions

At unenhanced 2D PDUS, 12 (36%) of 33 benign lesions were vascular; hypovascular in eight and hypervascular in four. Irregular vessels were seen in one case. Penetrating vessel was not seen in any cases.

At contrast-enhanced 3D PDUS, 20 (61%) benign le-

sions were vascular; hypovascular in 13 and hypervascular in seven. The increase in PD signal reached a maximum at 60 seconds after injection in eight cases and 90 seconds after injection in 12 cases. Irregular vessels were seen in three (9%) lesions at contrast-enhanced 3D PDUS. Penetrating vessel was not seen in any cases.

Diagnostic Accuracy

By using the presence of vascularity in the mass as the diagnostic criterion for malignancy, sensitivity, specificity, positive and negative predictive values were 70% (19/27), 64% (21/33), 61% (19/31), and 72% (21/29), respectively, at unenhanced 2D PDUS and 100% (27/27), 39% (13/33), 57% (27/47), and 100%

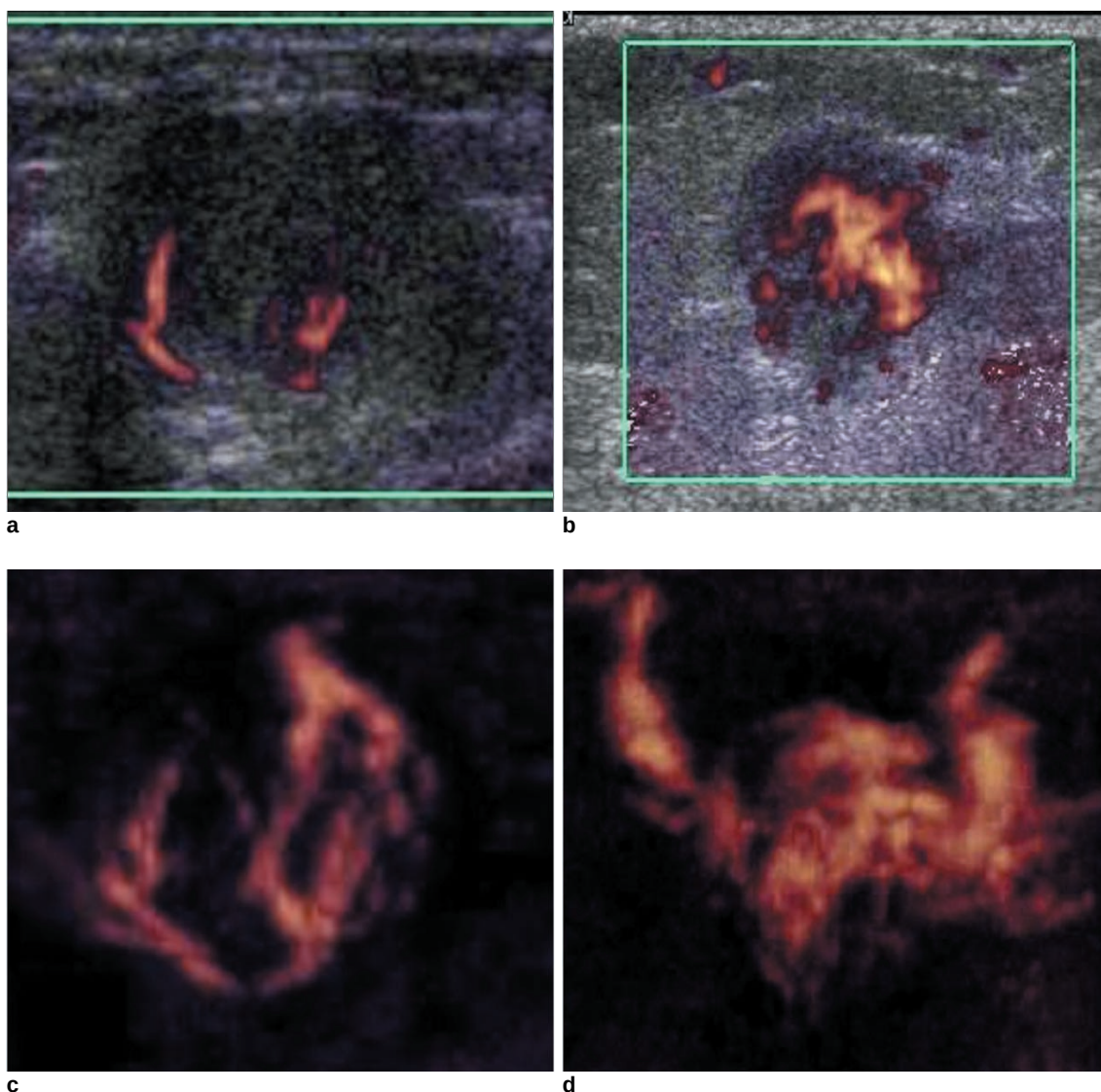


Fig. 1. Compared to unenhanced 2D power Doppler US (a, b), 3D power Doppler US (c, d) obtained 1 minute after injection of the contrast agent better depicts vessel morphology and the branching pattern of fibroadenoma (a, c) and breast cancer (b, d).

(13/13), respectively, at contrast-enhanced 3D PDUS.

By using the presence of irregular vessels in the mass as the diagnostic criterion for malignancy, sensitivity, specificity, positive and negative predictive values were 26% (7/27), 97% (32/33), 88% (7/8), and 62% (32/52), respectively, at unenhanced 2D PDUS and 81% (22/27), 91% (30/33), 88% (22/25), and 73% (30/41), respectively, at contrast-enhanced 3D PDUS.

DISCUSSION

Malignant breast tumors secrete angiogenesis factors to recruit new blood vessels (17). Experimental evidence indicates that the formation of new blood vessels is necessary for solid tumors to enlarge beyond a few millimeters in size. Abnormal neovascularity not only occurs in invasive or infiltrative breast tumors but also arises in DCIS (18, 19). Pathologic vessels typically show an irregular course without progressive diminution in caliber. In this study, PDUS rather than color Doppler US was used for the evaluation of tumor vascularity since more vessels are likely to be depicted and vessels are more likely to be displayed as contiguous structures, allowing vessel morphology and characteristics to be visualized with PDUS (11, 14, 20).

Our results show that Doppler enhancement can contribute to the differentiation between hypovascular carcinomas and benign tumors like fibroadenomas. Specific features of malignant neovascularity are a lack of the normal vessel tapering pattern, vessel tortuosity and radial penetration into the cancer from margins (6, 21). At contrast-enhanced 3D PDUS, these features could be distinguished from the circumferential, gently curved and tapering vessels typically associated with fibroadenomas.

The most important function of a US contrast agent is to enhance the power of the backscattered echo signal. Backscattering and sonic attenuation are interrelated and depend on the concentration of the contrast agent. Backscattering increases at a low concentration, whereas the sonic attenuation caused by backscattering increases at a high concentration (22). In addition to the concentration, the injection rate of the agent may influence the duration of vascular enhancement in the tumor and induction of color blooming artifact. Motion

and color blooming artifacts reported as limitations of contrast-enhanced PDUS in the abdomen (23) were not a significant problem in this study. Further studies are needed to establish an optimal injection protocol that is suitable for the purpose of each examination.

In breast masses, tumor vascularity has been assessed with MR imaging after injection of an extracellular contrast agent (24, 25). Comparative studies of contrast-enhanced MR imaging and contrast-enhanced 2D PDUS showed similar sensitivity and specificity in detection and characterization of breast cancers (26). The potential advantage of the MR imaging is the detection of multifocal disease. US is simple to perform, performed in real time, and relatively inexpensive. Microbubble contrast agent strictly confined to the vascular bed allows objective quantification of enhancement dynamics of tumors at PDUS that is analogous to time-activity curves of nuclear medicine isotope tracer studies (15). The assessment of vascularity with contrast-enhanced 3D PDUS may also be helpful in guiding therapy as some treatments specifically target the blood supplies of the tumors (27, 28).

In conclusion, contrast-enhanced 3D PDUS was superior to unenhanced 2D PDUS in the characterization of tumor vascularity in solid breast masses.

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