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FULL PAPER

Superb microvascular imaging in diagnosis of breast lesions: a comparative study with contrast-enhanced ultrasonographic microvascular imaging

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Objective: To evaluate the diagnostic performance of superb microvascular imaging (SMI) in breast lesions, comparing with contrast-enhanced ultrasonographic microvascular imaging (MVI).

Methods: From April to November 2015, 132 patients (with 132 breast lesions) were enrolled in the retrospective study. All lesions were evaluated with colour Doppler flow imaging (CDFI), colour SMI (cSMI), monochrome SMI (mSMI) and contrast-enhanced ultrasonographic MVI. Receiver-operating characteristic curve analysis was performed to compare the diagnostic performance of SMI and MVI for discrimination between benign and malignant breast lesions.

Results: Histological analysis showed 58 malignant and 74 benign lesions. mSMI was more sensitive in detecting blood flow signals in breast lesions than CDFI ($p < 0.001$) and cSMI ($p < 0.001$). Differences of vessels inside breast

lesions and morphologic features of vessels between benign and malignant lesions were statistically significant on mSMI ($p < 0.001$). Using root hair-like and crab claw-like patterns as the criteria for malignant lesions, the sensitivity, specificity and accuracy for differentiation based on the microvascular architecture patterns were 77.6, 90.5 and 84.8% for mSMI and 89.6, 87.8 and 88.6% for MVI. Areas under curve of mSMI and MVI were not significantly different ($p = 0.129$).

Conclusion: mSMI can increase blood flow detection and depict the microvascular architecture of breast lesions. The diagnostic performance of mSMI was not significantly different from MVI. SMI has potential in the differential diagnosis of breast lesions.

Advances in knowledge: mSMI is a non-invasive technique for vascularity evaluation of breast tumours and it is beneficial for breast tumour differentiation.

INTRODUCTION

Breast cancer is one of the major causes of morbidity and mortality in females aged over 40 years.¹ Ultrasonography is a standard procedure for examining dense breast in females at high risk for breast cancer² and is widely used to assess palpable abnormalities.³ Angiogenesis plays an important role in local growth, invasion and distant metastasis of breast cancer.⁴ The vascular morphologic and distribution feature varies between benign and malignant breast tumours. Vessels of benign lesions are straight and natural, while vessels of malignant lesions are tortuous and irregular.^{5–7} Imaging tumour angiogenesis could be beneficial for breast tumour differentiation.

In the field of ultrasound, colour Doppler flow imaging (CDFI) and power Doppler imaging (PDI) are widely used

to assess the vascularity of breast lesions non-invasively. CDFI is proved to be an adjunct to B-mode ultrasound in the differential diagnosis of breast lesions.^{8–10} Compared with CDFI, PDI has limited value in solid breast mass evaluation, owing to significant overlaps in the vascularity of malignant and benign lesions.^{11–13} Another approach in ultrasound imaging of tumour angiogenesis is contrast-enhanced ultrasound (CEUS). Contrast agents with microbubbles are used to increase vascular signals in ultrasonography, which improves the assessment of the presence and morphology of tumour microvessels in the breast.^{14–16} Microvascular imaging (MVI) uses a maximum-holding technique. And a trace of microbubbles in a temporal dimension can be clearly depicted, which reflects the vascularity in the scanning area.^{17,18} However, CEUS is a relatively invasive method and contrast agents

may cause allergic reactions. Pregnancy and lactation are also contraindications to CEUS.

Superb microvascular imaging (SMI) is a new Doppler technique designed to improve the visualization of blood flow, especially slow flow signals, through a new adaptive algorithm which removes clutter dramatically while maintaining very high frame rates. It can operate in two modes: colour SMI (cSMI) and monochrome SMI (mSMI). The former simultaneously displays conventional greyscale ultrasound with colour-encoded Doppler signals, while mSMI displays only the vasculature by subtracting away the background signals. This technique was first reported to depict microvascular flow in thyroids,¹⁹ and another research proved that SMI could provide microvessel information in breast tumours.²⁰ However, the potential of using microvascular morphologic features detected by SMI to differentiate breast tumours still needs to be confirmed. And to the best of our knowledge, the ability of SMI to depict microvascular architecture of breast tumours has not yet been compared with CEUS.

Therefore, the aim of this study was to compare the detection ability of CDFI and SMI in evaluating breast tumour vascularity and to assess the tumour microvascular architecture by SMI comparing with MVI on CEUS, in order to study the potential of SMI in the differential diagnosis of breast tumours.

METHODS AND MATERIALS

Patients

From April 2015 to November 2015, 132 consecutive females (age range, 16–78 years; mean age, 44.06 years) who had ultrasound-visible solid breast masses were recruited. Patients were excluded if they were pregnant or lactating, had a previous needle biopsy or had any treatments of the same lesions. This study was approved by the ethics committee of our institution, and patient informed consents were obtained. Of these 132 patients, 113 patients had solitary lesions and 19 patients had multiple lesions. When multiple masses were present, the single mass that was most suggestive of malignancy was included from each female. Thus, 132 breast lesions of 132 patients comprised our study population. The maximum diameter of the lesions was 18.3 ± 9.2 mm (range 6.1–56.2 mm) and the maximum depth was 17.8 ± 6.2 mm (range 8.7–48.9 mm). All the lesions were then confirmed pathologically by ultrasound-guided core needle biopsy and/or surgery according to standard clinical protocols.

Ultrasonographic examination

Greyscale ultrasound, CDFI and SMI were performed with a high-frequency transducer (L14-5 Aplio™ 400; Toshiba Medical Systems Corporation, Tochigi, Japan). Greyscale ultrasound was first performed to scan the breasts thoroughly. Once a lesion was detected, the general characters of breast lesions were observed and the best tumour imaging in the maximum plane was selected. Lesion size (maximal diameter) and lesion depth (maximal vertical distance from the skin to the bottom of the mass) were recorded. Subsequently, CDFI and SMI were performed to evaluate the vascularity both in and around the lesions. At least two orthogonal planes containing the richest vasculature planes of each lesion were obtained. As for SMI,

10–15-s cine clips of sagittal and transverse planes were also obtained in all subjects.

The following settings were used for CDFI examination: colour velocity scale was adjusted at $<5 \text{ cm s}^{-1}$, wall filter was about 50–100 Hz and colour gain was adjusted adequately as the background colour was suppressed. The region of interest included the whole lesion and normal breast tissue at least 3 mm surrounding the lesion. For those large breast masses (>40 mm) that were not single-screen included, we observed the lesions in various planes overlapping to guarantee surrounding areas to be covered. Settings for SMI: colour velocity scale was adjusted to $1.0\text{--}2.0 \text{ cm s}^{-1}$ and frame rates were >50 Hz. Gain settings were optimized for each imaging. During the examinations, patients were asked to breathe quietly, and no pressure was applied through the transducer to prevent the vessels from collapsing.²⁰ The signal was considered real blood flow signal only if pulsed Doppler showed an arterial or venous flow pattern.

CEUS were performed with a linear transducer (L9-3, iU22; Philips Medical Systems, Bothell, WA). The plane of a lesion with rich blood was chosen as the target plane, and then various planes were observed dynamically in order to compare with SMI. The mechanical index was set at 0.06. Contrast agent used was SonoVue® (Bracco Imaging B.V., Geneva, Switzerland). A volume of 4.8-ml contrast agent was injected in a bolus fashion through a 20-gauge i.v. cannula within 1–2 s, followed by injection of 5–10 ml of saline water.²¹ Real-time images were recorded for up to 120–180 s for further analysis. MVI mode was initiated when the amount of microbubbles was adequate, and the cumulative images were captured. Digital cine clips of all ultrasonographic images and the whole CEUS process were stored on the hard disk for subsequent analysis.

All ultrasonographic examinations were performed by the same investigator, who had >15 years' experience in breast ultrasound and >8 years' experience in CEUS.

Imaging analysis

The imaging data were retrospectively analyzed by two investigators (with about 10 years' experience in breast ultrasound and 5 years' experience in CEUS), who were blinded to the pathologic findings. A third investigator (who performed all the examinations) evaluated the lesions in cases of disagreement.

The vascularity of all the lesions detected by CDFI, cSMI and mSMI was assessed according to Adler's grading, which was subjectively determined to be 4 grades.²² On mSMI, vessels whose courses could be recognized inside the breast lesions were counted. The morphologic and distribution features of vessels in and around the lesions were also observed on mSMI. The features for malignant lesions were as follows: (1) enlarged vessels and twisted vessels inside the lesions (Figure 1), (2) penetrating vessels and (3) spiculated vessels or radial vessels (Figure 2). The feature for benign lesions was peripheral annular vessels (Figure 3).

Based on the morphologic and distribution features observed on mSMI and other previous studies about microvessels of breast

Figure 1. (a) A 59-year-old female with a lesion in the upper outer quadrant of the right breast. (b, c) Colour Doppler flow imaging and colour superb microvascular imaging are showing vessels adjunct to the upper right of the lesion; (d) monochrome superb microvascular imaging (mSMI) is showing more detailed twisted vessels inside the lesion, especially in the upper right part, which has manifested as a root-hair like pattern; (e) contrast-enhanced ultrasound of the same lesion; (f) microvascular imaging is also showing the twisted vessels inside the lesions, but vessel courses are not seen as clearly as on mSMI. This lesion was pathologically proven to be invasive ductal carcinoma.

tumours on MVI,^{14,18} the microvascular architecture of breast lesions was divided into five patterns according to the shapes of vascular networks for both mSMI and MVI: (1) non-vascular pattern, which was lack of vessels; (2) a linear or curvilinear pattern, where single or few straight or slightly curved vessels without crossing were found inside the lesion; (3) a tree-like pattern, which consisted of proportioned microvessels branching within the lesions; (4) a root hair-like pattern, which was dominated by a twisted and chaotic arrangement and irregular vessels within the lesion with less than two enlarged and twisted vessels surrounding the lesion; and (5) a crab claw-like pattern, which was characterized by radial vessels, with small spiculated vessels commonly seen in the periphery region.

Statistical analysis

To compare the efficiency of CDFI, cSMI and mSMI in evaluating vascularity for the same breast lesion, Wilcoxon signed ranks test was applied. The differences of blood vessels inside breast lesions and morphologic features of vessels in and around the lesions were evaluated by χ^2 tests or Fisher's exact test, and

microvascular architecture patterns detected by mSMI and MVI were analyzed with marginal homogeneity test. A receiver-operating characteristic curve analysis was used to evaluate the diagnostic performance of mSMI and MVI. Kappa statistic was used to determine the interobserver agreement. $p < 0.05$ was considered statistically significant. SPSS® v. 16.0 (IBM Corp., New York, NY; formerly SPSS Inc., Chicago, IL) was used for all statistical analyses.

RESULTS

Pathology

Of all 132 breast lesions, 58 lesions were malignant and 74 lesions were benign. Malignant lesions included invasive ductal carcinomas ($n = 49$), ductal carcinomas *in situ* ($n = 5$), invasive lobular carcinomas ($n = 2$), an invasive papillary carcinoma ($n = 1$) and an invasive micropapillary carcinoma ($n = 1$). Benign lesions included fibroadenomas ($n = 50$), mammary adenosis ($n = 9$), intraductal papillomas ($n = 7$), mastitis ($n = 4$), a sclerosing adenosis ($n = 1$), a radial scar ($n = 1$), a complex sclerosing lesion ($n = 1$) and a benign phyllodes tumour ($n = 1$).

Figure 2. (a) A 50-year-old female with a lesion in the upper inner quadrant of the left breast. (b, c) Colour Doppler flow imaging and colour superb microvascular imaging are showing blood signals in the peripheral region of the lesion; (d) monochrome superb microvascular imaging (mSMI) is showing no vessels inside the lesion but radial vessels in the peripheral (arrows), which has manifested as a crab claw-like pattern; (e) contrast-enhanced ultrasound (CEUS) of the same lesion; (f) microvascular imaging (MVI) is also showing crab claw-like enhancement. Both CEUS and MVI are showing more radial vessels (arrowheads) than mSMI. This lesion was pathologically proven to be invasive ductal carcinoma.

Interobserver reproducibility

The interobserver reproducibility was assessed. The κ coefficients were 0.894, 0.886 and 0.824 for Adler's grading on CDFI, cSMI and mSMI. As for blood vessels inside the breast lesions and microvascular morphologic features of vessels on mSMI, the κ coefficients were 0.826. The κ coefficients for the microvascular architecture on mSMI and MVI were 0.865 and 0.791.

Adler's grading of breast lesions on CDFI, cSMI and mSMI

The degrees of blood flow in all the lesions were assessed according to Adler's method (Table 1). Wilcoxon analysis indicated that there was no significant difference between CDFI and cSMI ($p = 0.088$). However, the differences between mSMI and CDFI and between mSMI and cSMI were significantly different ($p < 0.001$).

Vessels inside breast lesions and morphologic features of vessels on monochrome superb microvascular imaging

The number of blood vessels observed inside benign and malignant lesions was significantly different (Table 2). There were often <3 vessels found in benign lesions, while >3 vessels were always found in malignant lesions. Differences in the morphologic

and distribution features of vessels between benign and malignant lesions were statistically significant (Table 2). More than one feature was found in some malignant lesions. Enlarged and twisted penetrating and radial vessels were found to be more common in malignant lesions, whereas annular vessels were mainly seen in benign lesions.

There were no vessels found inside the lesions in 15 cases, and only 1 (6.7%) lesion was malignant. However, this lesion had peripheral radial vessels (Figure 2). 38 cases had 1–2 vessels inside the lesions, 29 lesions were benign and 9 lesions were malignant. Only 1 (3.4%) of the 29 benign lesions had twisted vessels inside. Among the 9 malignant cases, enlarged and twisted vessels were found inside 3 (33.3%) lesions and radial vessels were found in 2 (22.2%) lesions. 38 cases had 3–4 vessels inside. Of them, 17 lesions were benign and 21 lesions were malignant. Only 2 (11.8%) of the 17 benign lesions manifested as enlarged and twisted vessels; 10 (58.8%) of them had annular vessels. However, no malignant features were found in 6 (28.6%) of the 21 malignant lesions. There were >4 vessels found in 14 benign lesions and 27 malignant lesions. No malignant features were found in only 1 (3.7%) malignant lesion. Annular vessels were found in 11 (78.6%) of these 14 benign lesions. 3 (21.4%) of the benign lesions had enlarged and twisted vessels with annular vessels.

Figure 3. (a) A 50-year-old female with a lesion in the lower inner quadrant of the left breast. (b, c) Colour Doppler flow imaging and colour superb microvascular imaging are showing blood signals around the lesion; (d) monochrome superb microvascular imaging is showing that the peripheral annular vessel was discontinuously observed; (e) contrast-enhanced ultrasound of the same lesion; (f) microvascular imaging is also showing peripheral annular vessel. This lesion was pathologically proved to be fibroadenoma.

Microvascular architecture of breast lesions on monochrome superb microvascular imaging and microvascular imaging

In this study, the microvascular architecture of all 132 lesions was clearly delineated on both mSMI and MVI (Tables 3 and 4). There were significant differences of microvascular architecture between benign and malignant lesions ($p < 0.001$). Non-vascular pattern, linear or curvilinear pattern and tree-like

pattern were set as the criteria for benign lesions, while root hair-like and crab claw-like patterns were set for malignant lesions. The sensitivity, specificity and accuracy were (45/58) 77.6%, (67/74) 90.5% and (112/132) 84.8% for mSMI and (52/58) 89.7%, (65/74) 87.8% and (117/132) 88.6% for MVI.

Receiver-operating characteristic curves were generated according to the microvascular architecture of breast lesions detected

Table 1. The amount of vascularity according to Adler's method, [n (%)]

All masses		Grade 0	Grade 1	Grade 2	Grade 3
CDFI	Benign	24 (32.4)	18 (24.3)	13 (17.6)	19 (25.7)
	Malignant	2 (3.4)	10 (17.5)	11 (19.0)	35 (60.3)
cSMI	Benign	24 (32.4)	20 (27.0)	12 (16.2)	18 (24.3)
	Malignant	3 (5.2)	11 (19.0)	13 (22.4)	31 (53.4)
mSMI	Benign	14 (18.9)	12 (16.2)	11 (14.9)	37 (50.0)
	Malignant	1 (1.7)	3 (5.2)	5 (8.6)	49 (84.5)

CDFI, colour Doppler flow imaging; cSMI, colour superb microvascular imaging; mSMI, monochrome superb microvascular imaging.

Table 2. Number of blood vessels inside breast lesions and morphologic features of vessels on monochrome superb microvascular imaging [*n* (%)]

	Benign (<i>n</i> = 74) (%)	Malignant (<i>n</i> = 58) (%)	<i>p</i> -value
Number of vessels in the lesion			
0	14 (18.9)	1 (1.7)	<0.001
1–2	29 (39.2)	9 (15.5)	
3–4	17 (23.0)	21 (36.2)	
≥5	14 (18.9)	27 (46.6)	
Morphology and distribution of the vessels			
Enlarged and twisted	7 (11.7)	41 (71.9)	<0.001
Penetrating	1 (1.4)	20 (34.5)	<0.001
Spiculated or radial	0 (0.0)	27 (46.6)	<0.001
Annular	33 (44.6)	1 (1.7)	<0.001

by mSMI and MVI (Figure 4). The areas under curve were 0.924 for MVI and 0.876 for mSMI. The difference between the areas under curve for MVI and for mSMI was not statistically significant ($p = 0.129$).

DISCUSSION

Angiogenesis is critical to tumour development and metastasis. CDFI and SMI are different Doppler techniques to detect blood flow inside breast tumours. Earlier studies figured out that benign lesions had either no or low colour signals, while moderate and marked signals were commonly seen in malignant lesions.^{9,10} Our study also confirmed this with CDFI. However, value in microvascular (vessels smaller than 100 μm in diameter) detection is limited by CDFI. Tumour vascularity could not be clearly delineated by CDFI, which made it hard to identify hypervascular benign lesions from malignant ones. SMI has two modes. In this study, mSMI was superior in gaining more details of internal small branches. This finding was consistent with Machado et al's experience.¹⁹ However, cSMI was reported to be better than CDFI in detecting blood flow according to Machado et al's study. Our study did not reach the same result. We found that background noises, which overlap with high-echo tissues inside the mammary gland, were obvious on cSMI. Detectable vessels decreased while the background noises were suppressed. Therefore, the capabilities of cSMI and CDFI in blood flow detection were not significantly different. Ma et al²⁰ suggested that the number of vessels detected by SMI but not by CDFI could improve the diagnostic performance of

ultrasound in differential diagnosis. In our study, marked blood signals were detected in half of the benign lesions and in most of the malignant lesions by mSMI, which suggested that semi-quantitative analyses were not enough to discriminate benign and malignant lesions independently.

Some authors used PDI to illustrate vessel morphology in breast tumours. They found that the presence of penetrating and branching disordered patterns were significant features of malignant lesions.^{11,23} CEUS is another technique focusing on blood vessel delineation. Morphologic and distribution features of breast lesions such as enlarged and twisted vessels inside breast lesions, peripheral radial vessels and penetrating vessels were supposed to be a good indicator for differential diagnosis.^{14–16} In this study, we also observed similar morphologic and distribution features in breast tumours. Malignant lesions more often showed enlarged and twisted vessels inside breast lesions, penetrating vessels and spiculated or radial vessels in the peripheral region, whereas benign lesions mainly showed peripheral annular vessels. If no <3 vessels inside breast lesions were defined to be malignant, (31/74) 41.9% benign lesions would be misdiagnosed and (10/58) 17.2% malignant lesions would be missed in this study. However, few of these benign lesions (5/31) were observed to be enlarged and twisted vessels disguised as malignant ones, and most of them (21/31) had peripheral annular vessels. As for the missed malignant lesions, more than half of them (6/10) were found to have at least one of the above morphologic and distribution features of malignant

Table 3. Microvascular architectural pattern on monochrome superb microvascular imaging (mSMI)

Pathology	<i>n</i>	mSMI pattern [<i>n</i> (%)]				
		Non-vascular	Linear or curvilinear	Tree-like	Root hair-like	Crab claw-like
Benign ^a	74	14 (18.9)	31 (41.9)	22 (29.7)	7 (9.5)	0 (0.0)
Malignant ^a	58	0 (0.0)	9 (15.5)	4 (6.9)	17 (29.3)	28 (48.3)
Total	132	14 (10.6)	40 (30.3)	26 (19.7)	24 (18.2)	28 (21.2)

^aStatistically significant difference between benign and malignant groups ($p < 0.001$, χ^2 test).

Table 4. Microvascular architectural pattern on microvascular imaging (MVI)

Pathology	n	MVI pattern [n (%)]				
		Non-vascular	Linear or curvilinear	Tree-like	Root hair-like	Crab claw-like
Benign ^a	74	9 (12.2)	13 (17.6)	43 (58.1)	5 (6.8)	4 (5.4)
Malignant ^a	58	0 (0.0)	0 (0.0)	6 (10.4)	9 (15.5)	43 (74.1)
Total	132	9 (6.8)	13 (9.8)	49 (37.1)	14 (10.6)	47 (35.6)

^aStatistically significant difference between benign and malignant groups ($p < 0.001$, χ^2 test).

tumours. Therefore, combining vessels observed inside breast lesions with morphologic and distribution features of vessels on SMI could, to an extent, provide more information in the differential diagnosis of breast tumours.

Contrast-enhanced ultrasonographic MVI was valid in depicting the microvascular architecture of breast tumours, owing to its ability to detect microvessels (7–10 μm in diameter). Previous

studies had reported on the evaluation of microvascular architecture of breast tumours using MVI. Du et al¹⁴ found that benign lesions mainly displayed the tree-like pattern while malignant lesions tended to display crab claw-like pattern. Root hair-like pattern was seen more in benign lesions than in malignant lesions. However, root hair-like pattern was found more in malignant lesions than in benign ones in our study. Two more types were raised in our study to describe the microvascular architecture, non-vascular and linear, and both were commonly found in benign lesions on MVI. Comparing with CEUS, SMI is a non-invasive method to detect small vessels with low velocity. As SMI did not use contrast agents it allowed enough time to finish whole-breast scanning and multiple-plane scanning of the lesions. In our study, the microvascular architecture of breast lesions on SMI divided into five types as well. Non-vascular, linear and tree-like patterns were mainly seen in benign lesions, whereas root hair-like and crab claw-like patterns were mainly seen in malignant lesions. Using root hair-like and crab claw-like patterns as the criteria for malignant lesions, diagnostic ability was not significantly different between mSMI and MVI.

Nevertheless, there were some differences between micro-vascular architecture illustrated by MVI and mSMI. First, MVI can detect more blood flow signals than mSMI. In this study, no blood vessels were detected inside 15 breast lesions by mSMI, and only 9 lesions displayed no enhancement on CEUS. Vessels in these lesions were difficult to detect on mSMI, probably because vascular calibre and velocity were lower than the threshold for to be detected by it. However, vessel path and distribution inside the lesions were more clearly observed on mSMI than on MVI (Figure 1). Secondly, peripheral radial vessels, a good indicator for malignant lesions,^{14,16,21} were more commonly seen on MVI than on mSMI (Figure 2). The reason might be the difficulty in distinguishing blood flows from noises generated when subtracting the high-echo tissues outside the lesions by mSMI. Therefore, radial vessels, especially those parallel to Cooper's ligament, were hard to figure out on mSMI. Moreover, for lesions or parts of lesions located at a depth deeper than 25–30 mm, vessels were hardly described by mSMI. But, we found enhancement on CEUS at the corresponding depth of the same lesions.

There were some limitations to this study. First, it is a preliminary study carried out in one centre with a small sample. Second, the time span was short, and the pathological categories collected were limited. Third, the volumes of malignant lesions in this study were relatively large. Therefore, most of them

Figure 4. The performances of monochrome superb microvascular imaging (mSMI) and microvascular imaging in the discrimination between benign and malignant breast lesions according to microvascular architecture are shown in the receiver-operating characteristic curve. CEUS, contrast-enhanced ultrasound.

displayed typical angiogenesis characters. Fourth, we did not compare SMI with microvascular density, which was found to correlate with tumour growth and metastasis. Fifth, only one sonologist performed all the examinations for image quality control, inter-operator differences were not compared.

In conclusion, SMI is more sensitive than CDFI in tumour blood detection. SMI can depict the microvascular architecture of breast lesions and has potential in the differential diagnosis of benign and malignant lesions. SMI is non-invasive but has a diagnostic performance parallel to CEUS.

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