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Detection of Intraductal Component around Invasive Breast Cancer Using Ultrasound: Correlation with MRI and Histopathological Findings

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Purpose: The purpose of this study was preoperatively to diagnose the intraductal component, which is indispensable in planning for breast conservation therapy, and also to minimize local recurrence. This study investigated the efficacy of ultrasound (US) in the detection of intraductal component in comparison with magnetic resonance imaging (MRI) and histopathological findings.

Patients and Methods: In 47 patients with invasive breast cancer, US features of the intraductal component were classified as (a) solid ductal dilatation radiating from the tumor, (b) presence of satellite lesion in the same segment without ductal dilatation, and (c) ductal dilatation between the main tumor and satellite lesion. MRI depicted intraductal extension as the most enhanced area during the first or second phase of the dynamic study. Other criteria for the detection of the intraductal component by MRI were as follows: (a) a satellite lesion around the main tumor, (b) bridging enhancement between the main tumor and satellite lesions. The extent of the intraductal component was measured and classified as mimimal (0-5 mm), moderate (6-15 mm) or wide (>15 mm).

Results: In 28 of 47 (60.0%) patients, a wide intraductal component of more than 15 mm was proved histopathologically. Of 28 patients, US and MRI could accurately detect wide intraductal components in 16 patients and 14 patients, respectively. Sensitivity, specificity, and accuracy were 57.1%, 84.2%, and 68.1% respectively for US and 50.0%, 89.5% and 65.9% for MRI, respectively. When both US and MRI results were combined, sensitivity, specificity, and accuracy were 75.0%, 84.2%, and 78.7%.

Conclusion: Current US examination depicted the intraductal component of breast cancer more accurately than MRI. Further, our study suggests that the use of both US and MRI together is complementary and offers more advantage than US alone.

Key words: breast neoplasm, intraductal component, ultrasound, magnetic resonance imaging

INTRODUCTION

MAMMOGRAPHY (MMG) AND ULTRASOUND (US) ARE THE standard imaging techniques for the detection and evaluation of breast diseases. US is extremely reliable in differentiating cystic from solid lesions and also benign from malignant solid nodules.[1] In certain patients, especially in young women with dense breasts, US can be a complementary technique to MMG.[2,3] However, it has some limitations owing to its dependency on the diagnostic ability, technique, and experience of the examiner. Recent advances in image quality have allowed the increasing use of US in the detection of intraductal diseases.[4,5]

Although breast magnetic resonance imaging (MRI) was developed in the late 1980s, it was not until the advent of gadolinium-enhanced dynamic MRI that its potential for detecting breast cancer became evident.[6] Breast MRI has advantages over other techniques for its ability to diagnose breast cancer with excellent sensitivity without the use of ionizing radiation.[7,8] The disadvantages of MRI include the cost, time needed to

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carry out the procedure, and inability to examine patients with pacemakers or metallic stents.

For the optimal local treatment of breast cancer, it is important to obtain precise information regarding the extent and distribution of the disease in the breast. In particular, the microscopic intraductal component is one of the factors that is usually unrecognized during surgery and can cause local recurrence after breast conservation therapy.[9,10] Consequently, accurate assessment of the extent of the intraductal component is essential for determining the feasibility of breast conservation therapy and the range of excision of the mammary gland. In this retrospective study, we compared the diagnostic capability of detecting the extent of the intraductal component by US and dynamic MRI with that of histopathological studies.

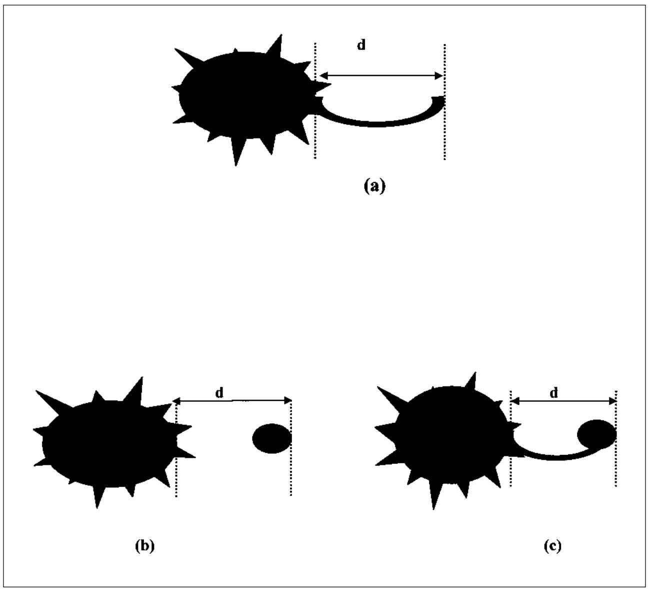


Fig. 1. Classification of US features for intraductal component of breast cancer.
a: Solid duct dilatation radiating from the primary lesion and distance (d mm) of intraductal component.
b: Presence of satellite lesion in the same segment without solid duct dilatation and distance (d mm) of intraductal component.
c: Ductal dilatation between main tumor and the satellite lesion and distance (d mm) of intraductal component.

Patients and Methods

Between January 2003 and March 2004 (15 months), 99 patients with 100 breast cancers, including one synchronous bilateral cancer, underwent surgery at the Department of Breast and Endocrine Surgery in Tsukuba University Hospital. Breast cancer was suspected in all of them, on the basis of clinical examination, MMG, US, fine-needle aspiration cytology, or core biopsy.

Patient demographics

Seventy-two of the total 99 patients underwent both US and MRI examinations. Of them, 25 patients (DCIS and non-mass-forming tumors in US) were excluded. Finally, 47 patients with 47 invasive breast cancers who had undergone a complete US examination for intraductal component and mass-forming tumors were chosen for this retrospective study. Patient age ranged from 29 years to 81 years (median age, 52 years). On the basis of the TNM classification of the International Union against Cancer (UICC), 27 patients were categorized as T1 and 20 patients as T2.

Ultrasound examination

US was performed using an HDI 5000 (Philips) equipped with a 12-5 MHz linear array transducer by a radiologist or a breast surgeon, both with more than 20 years of experience in breast ultrasound and board certified by the Japanese Society of Ultrasound in Medicine.

Special attention was focused on detecting and measuring the extent of intraductal component according to the following protocol[4]: (a) solid duct dilatation radiating from the tumors, (b) presence of satellite lesion in the same segment without ductal dilatation, (c) ductal dilatation between the main tumor and satellite lesion (Fig. 1).

The extent of the intraductal component of US was classified into three groups, namely 0-5 mm, 6-15 mm, and >15 mm as minimal (min), moderate (mod), and wide (wide) intraductal components, respectively.

MR examination

MR examinations of the involved breast were performed using a 1.5 Testla (Philips) Gyroscan NT Intera and PT 1000 (Philips) Gyroscan ACS NT Power Tract using a single breast coil in the prone position. Dynamic MRI was performed in coronal planes using a three-dimensional fast field echo sequence (3DFFE), and dynamic subtraction images were employed. Image parameters of 3DFFE were TR 42 m sec, TE 2.3 m sec, flip angle 30˚, field of view 250 mm, matrix 256×76.5, and slice thickness 3-5 mm, no slice gap, and an acquisition time of 1 min and 20 sec. After the pre-contrast images were acquired, a 10 ml bolus intravenous injection of Gd-DTPA (Isovist, Japan), followed by 15-20 ml of saline infusion was given. After infusion was completed, four enhanced studies were taken. The series of sagittal and axial fat-suppressed T1-weighted images (T1W) were obtained after the dynamic study. Maximum intensity projections (MIP) were reconstructed to obtain the 3D view of the main tumor mass and areas of intraductal component.

MRI results were read by the board-certified radiologist who performed the ultrasound, and the criteria for diagnosis were strictly followed. The radiologist was not aware of the pathological results when MRI was interpreted. Criteria for diagnosing intraductal component by MRI were defined as follows[5]: (1) a satellite lesion around the main tumor, (2) a strand-like enhancement on the margin of the main tumor, or bridging enhancement between the main tumor and the satellite lesion. The intraductal component was diagnosed and measured in the maximum contrast enhancement during the first or second phase (within a 2 min, 40 sec interval) of dynamic imaging.

Surgical resection methods

Breast conservation therapy has become the treatment of choice for early stage (T1 and T2) breast cancers. Breast conservation surgery (2×4 lumpectomy) is followed by radiation therapy in Tsukuba University Hospital. In 2×4 lumpectomy, the distances between the margin of the main tumor and surgical stumps were 40 mm towards the nipple and 20 mm of free margin on the other three sides.

According to the surgical point of view, an intraductal component of 15 mm measured by US and MRI preoperatively was taken as the borderline limit to decide whether or not breast conservation therapy should be performed for the patient. If a wide intraductal component (>15 mm) was diagnosed by US or MRI, wider resection, namely, quadrantectomy or modified radical mastectomy was performed by the surgeon, with the patient's consent.

Other contraindications for performing breast conservation therapy were multicentric tumors, tumors too close to the nipple, and tumors so large they could cause severe cosmetic dispropotionality. Of these patients, 22 of them underwent breast conservation therapy, and 25 patients underwent mastectomy.

Histopathological study

The surgical specimens were fixed by formalin infusion, and whole specimens were serially sliced at 5-7 mm intervals, perpendicular to the line connecting the nipple and the center of the tumor. The specimens were prepared as usual paraffin-embedded sections and stained with hematoxylin and eosin. Diagnoses of breast cancer were made by the breast pathologist according to the established criteria.[12,13] To precisely study the extent and direction of the intraductal component, serially sliced specimens of all cases were examined, and histopathological cancer mapping was done. The intraductal component around the main tumor was classified histologically into three groups, namely 0-5 mm, 6-15 mm and >15 mm, as minimal (min), moderate (mod), and wide (wide) intraductal components respectively.

Table 1. Histopathological classification (HP) of intraductal component and correlation with US and MRI

		HP		
		Wide	Mod	Min
US	Wide	**16**	0	3
	Mod	8	2	7
	Min	4	0	7

		HP		
		Wide	Mod	Min
MRI	Wide	**14**	0	2
	Mod	6	1	1
	Min	8	1	14

Statistical analysis

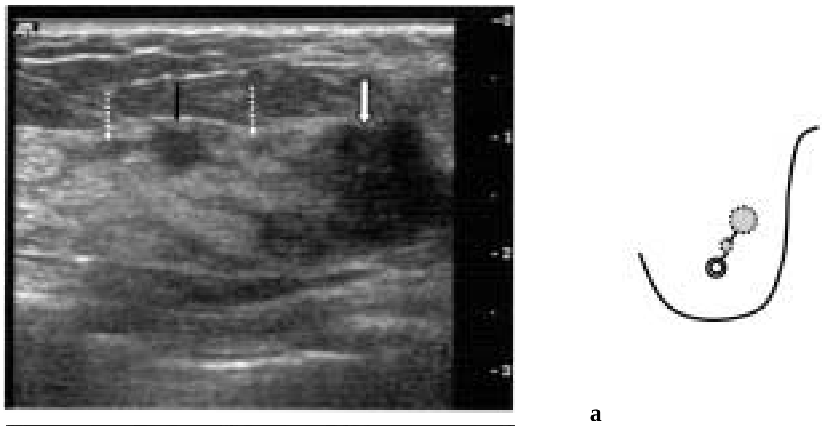
Interpretation of the intraductal component by both US and MRI was compared with the histological examination with regard to sensitivity, specificity, and accuracy. A result was classified as true positive (TP) when a wide intraductal component (greater than 15 mm) detected by US or MRI was histologically confirmed. The present study compared the performance of both diagnostic methods (US and MRI) individually, and their combination (US+MRI) using the results obtained from all patients. If any one modality could diagnose a wide intraductal component, it was considered as true positive.

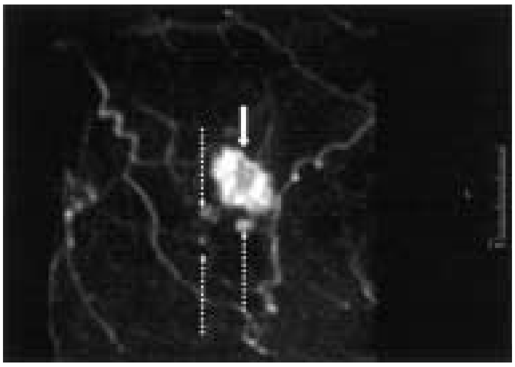
RESULTS

Table 1 summarizes the results of US and MRI in comparison with histopathology. The histopathological examination revealed the presence of a wide intraductal component in 28 (60.0%) of 47 invasive carcinoma patients. The remaining patients with minimal and moderate intraductal components were considered as wide intraductal component-negative in this study.

US examination could accurately detect 16 (true positive) of the 28 wide intraductal component-positive patients and 16 (true negative) of 19 wide intraductal component-negative patients. US underestimated the intraductal component in 12 patients (false negative) and overestimated (false positive) it in 3 patients. The sensitivity, specificity, and accuracy of US were 57.1%, 84.2%, and 68.1%, respectively.

MRI could detect 14 true positive patients out of 28 histopathologically proved wide intraductal component patients, and 17 true negative patients. However, US





a
b

Fig. 2. Invasive ductal carcinoma in a 63-year-old woman.
a: Ultrasound shows main tumor mass (*white arrow*) and satellite lesion (*black arrow*) with a ductal dilatation (*dotted arrows*) towards the nipple. The extent of intraductal component measured by US was 19 mm.
b: Contrast enhanced MRI study with MIP image shows main tumor (*solid arrow*) and satellite lesions (*dotted arrows*) in 3D coronal image. The extent of intraductal component measured by MRI was 18 mm. Histopathological studies diagnosed the invasive ductal carcinoma with satellite lesion and an intraductal component of 18 mm towards the nipple.

could detect more true positive patients but fewer true negative patients compared with MRI. MRI showed a higher number of underestimations (14 false negatives) compared with US. On the other hand, MRI overestimated only 2 patients, fewer than US. The sensitivity, specificity, and accuracy of MRI were 50.0%, 89.5%, and 65.9%, respectively.

Surgical margins were checked for the presence of cancer cells in all the patients. In 3 patients who underwent breast conservation therapy, surgical margins were positive. In all 3 patients, wide spread of intraductal cancer cells was seen towards the nipple area. In one of the 3 patients neither US nor MRI could detect a wide intraductal component. In the other two patients, US and MRI could detect the wide intraductal component, but underestimated the length by about 20 mm.

In only 9 of 28 true positive patients, could both US and MRI accurately determine the intraductal component in comparison with histopathology. One such true positive patient has been illustrated (Fig. 2). In this patient, the length of the intraductal component measured by both US and MRI was well correlated with histopathology.

The results of combined analysis of both US and MRI are illustrated in Table 2. Among the 28 histopathologically proved patients in whom the intraductal component was more than 15 mm, 21 patients had been detected either by one imaging modality or by both techniques. This brought down the underestimation to 7 patients, from 12 patients for US and 14 patients for MRI. Overestimation occurred in 3 patients, similar to the results of US alone.

Table 2. Histopathological classification (HP) of intraductal component and correlation with the results of US+MRI

		HP		
		Wide	Mod	Min
US+MRI	Wide	**21**	0	3
	Mod	5	2	7
	Min	2	0	7

When both the MRI and US results were combined and analyzed together, the results were as follows: 75.0% (sensitivity), 84.2% (specificity), and 78.7% (accuracy), and this yielded higher sensitivity and accuracy rates than each individual imaging modality.

Discussion

US and MMG have long been used for evaluating the extent of breast cancer, but both have limitations. MMG cannot identify a wide intraductal component that does not include minute calcifications, and it has been pre-

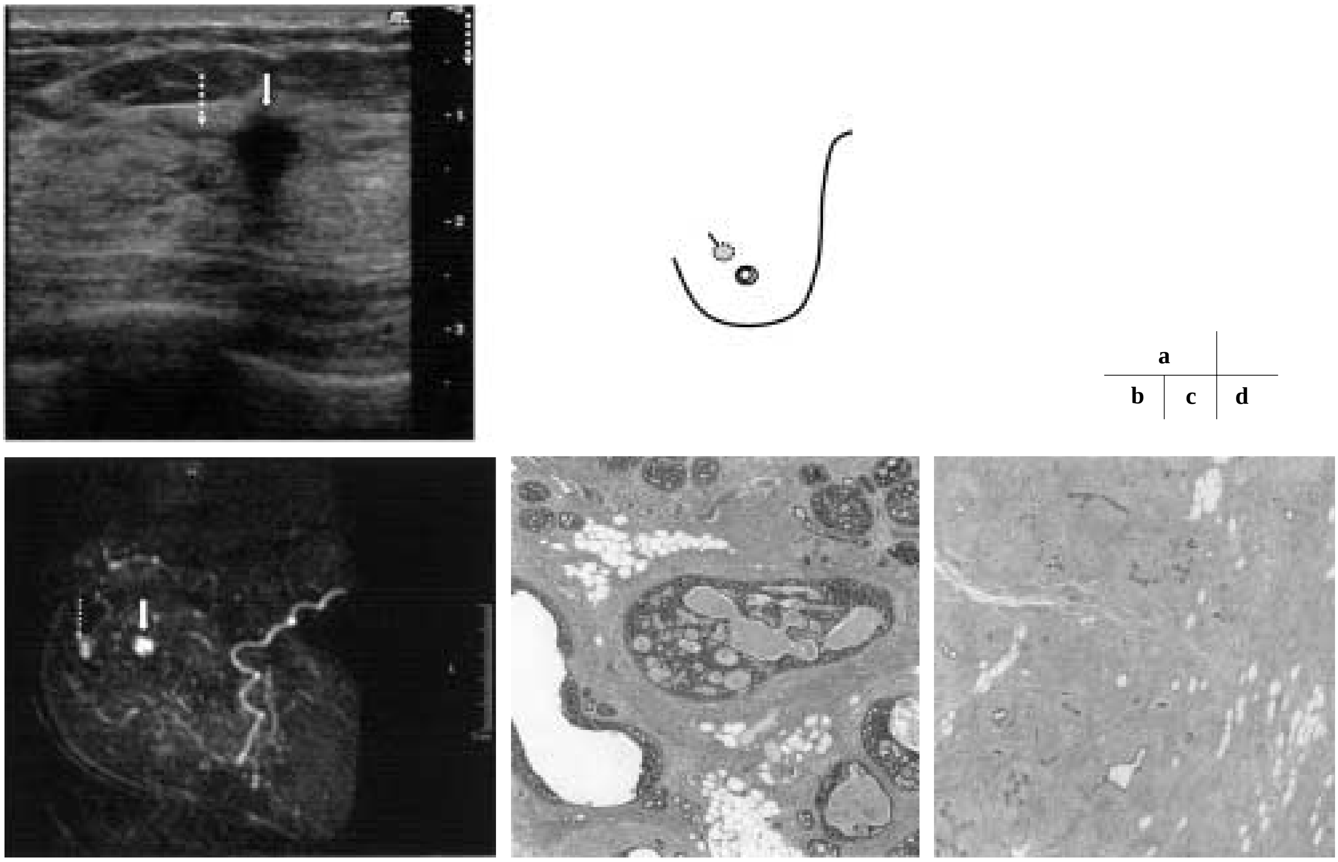


Fig. 3. Invasive ductal carcinoma in 52-year-old woman.
a: US shows the main tumor (*solid arrow*) is located at 11 o'clock position with moderate (7 mm) solid ductal dilatation towards periphery (*dotted arrows*).
b: Contrast enhanced MRI study shows a main tumor (*solid arrow*) and satellite lesion (*dotted arrow*) in coronal MIP images. Intraductal component was diagnosed as 20 mm towards the periphery.
c: Microscopic picture shows the presence of cancer cells lining the duct that are diagnosed as intraductal component.
d: Microscopic picture shows fibroadenomatosis change around the intraductal component.

viously reported that the sensitivity of MMG for detecting intraductal component is lower than that of MRI and US.[5,8] US can easily detect subtle changes due to an intraductal tumor itself or to necrosis. Satake *et al*.[5] reported that US can detect intraductal component more accurately than MRI, which correlates well with the results of the present investigation.

However, in our study, we have not included the carcinoma *in situ* cases (7 ductal carcinoma *in situ* patients and 2 lobular carcinoma *in situ* patients proved histopathologically) and non-mass forming tumors (2 patients) shown in the US examinations. The reason for excluding the above-mentioned patients is that diagnosing and measuring the exact extent of the intraductal component around the main tumor would be difficult in both US and histopathology. Further, our study did not include simple ductal dilatation and the distorted type of ductal dilatation for diagnosing the intraductal component by US. These were the differences in criteria compared with the study of Satake *et al*. Despite all the above differences, US showed a similar trend of higher sensitivity compared with MRI.

MRI was able to detect the intraductal component in fewer patients than US, resulting in lower sensitivity than US. According to the recent literature,[13,14] the rate of sensitivity for MRI in the diagnosis of intraductal component ranged from 55.0% to 100.0%. Recently, three-dimensional MRI has been used for the detection of intraductal spread, and its usefulness is superior to that of computed tomography.[15]

In three false-positive patients diagnosed by US examination, US overestimated the range of extension of the intraductal component, with a deviation of about 20 mm. In one of these three patients, periductal lymphocytic infiltration led to ductal dilatation and satellite lesion. MRI indicated intraductal component negative, and this was proved histologically. The remaining two patients were overestimated by both US and MRI.

Histologically atypical ductal hyperplasia was diagnosed around the intraductal component in one of the patients. Several investigations have found that benign lesions and normal glandular tissue are occasionally enhanced in the early phase and can appear similar to malignant tumors.[16,17] Evaluation of patients with rich parenchyma or severe mastopathy is also one of the chief limitations[18,19] in diagnosing the intraductal component.

Ultrasound underestimated 9 out of 28 wide intraductal component-positive patients. In one such patient, the reason for underestimation has been illustrated (Fig. 3) Fibroadenomatosis change near the main tumor, which lead to underestimation by US, was proved histopathologically. Similarly, when the breast shows a mottled pattern and fibrocystic change, underestimation by US has occurred.

Presence of the intraductal component on MRI was difficult to evaluate in one of our patients, because the gland was hypervascular and strongly enhanced after contrast administration. Histologically the breast was proved to have severe epithelial hyperplasia and proliferative disease.

Enhancement of the intraductal component in the late phase of MRI was considered negative according to our protocol; thus one patient resulted in underestimation, in which intraductal component enhancement was seen in the late phase. In two false-negative patients on both US and MRI, histopathological results showed the presence of an intraductal component more than 40-50 mm in length.

To reduce underestimation and to increase sensitivity for diagnosing the intraductal component, US and MRI results were assessed together. This increased sensitivity to 75.0% compared with the sensitivities of each individual modality. Specificity remained the same as that of US.

When both US and MRI were used to diagnose the intraductal component, the results correlated well with the pathological findings. Thus the surgeon more accurately could decide what type of surgery should be performed for the patient according to the presence or absence of wide intraductal extension of the tumor.

Of 22 patients who underwent lumpectomy, 14 patients were true negative and one was false positive for wide intraductal component by both US or MRI. Four patients were false negative and three patients were true positive by both US or MRI. Of these, two true-positive patients and one false-negative patient were diagnosed as surgical margin positive. These three patients were closely followed up by clinical and US examination after radiation therapy to check for recurrence.

Of 25 patients who underwent mastectomy, 18 patients were true positive and one patient was false positive. Four false-negative patients and one true-negative patient also underwent mastectomy. The reasons for performing mastectomies were the patient's wish or age and tumors located near the nipple.

One of the limitations of our study was that the direction of the intraductal component could not be diagnosed since it was a retrospective study. The prospective study that has been carried out recently has overcome this limitation.

Current US examination is useful in depicting the wide intraductal component of breast cancer more accurately than MRI. Further, our study suggests that US and MRI should be combined to diagnose wide intraductal component. In view of their particular advantages, both US and MRI appear to be indispensable for determining the appropriateness of breast conservation therapy and for planning the surgical approach to prevent postoperative local recurrence.

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