



# Real-Time MRI Navigated Ultrasound for Preoperative Tumor Evaluation in Breast Cancer Patients: Technique and Clinical Implementation

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Real-time magnetic resonance imaging (MRI) navigated ultrasound is an image fusion technique to display the results of both MRI and ultrasonography on the same monitor. This system is a promising technique to improve lesion detection and analysis, to maximize advantages of each imaging modality, and to compensate the disadvantages of both MRI and ultrasound. In evaluating breast cancer stage preoperatively, MRI and ultrasound are the most representative imaging modalities. However, sometimes difficulties arise in interpreting and correlating the radiological features between these two different modalities. This pictorial essay demonstrates the technical principles of the real-time MRI navigated ultrasound, and clinical implementation of the system in preoperative evaluation of tumor extent, multiplicity, and nodal status in breast cancer patients.

**Keywords:** Breast neoplasm; Magnetic resonance imaging; Ultrasonography; Navigation; Image correlation

## INTRODUCTION

The image fusion technique is classically defined as overlaying images from the same or different imaging modalities. The practical method of image fusion covers the side-by-side display of both images and co-registration on the same position and orientation (1, 2). Ultrasound is the most widely used imaging modality for medical image fusion, because it is a real-time technique which enables image-guided intervention, is easy to fuse with other static imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/CT, and has no radiation harm (1).

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Real-time image fusion has been widely applied to liver diseases (3). Several investigations reported that fusion imaging of real-time ultrasound and CT/MRI was superior to conventional ultrasound in detection of hepatic nodules, especially for small hepatocellular carcinoma or metastasis (4-6). By extension, CT/MRI navigated ultrasound was useful to guide radiofrequency ablation for hepatocellular carcinomas that are poorly defined on conventional ultrasound (7-9).

Recently, the utility of real-time image fusion also has been investigated in the field of breast. Yamamoto et al. (10) reported that fusion imaging of real-time ultrasound and CT-lymphography improved the preoperative detection of sentinel lymph nodes, and its accuracy for predicting metastasis was 81%. Breast MRI and ultrasound are the most popular imaging modalities for the assessment of preoperative stages of breast cancer. Breast MRI is a sensitive imaging technique for detection of breast cancer; however, it has a wide range of specificity and high false positive rates (10-14). Breast ultrasound is a very convenient way to evaluate breast and lymph nodes, but is dependent on the doctors' experience and equipment. We often face difficulties in interpreting and correlating the

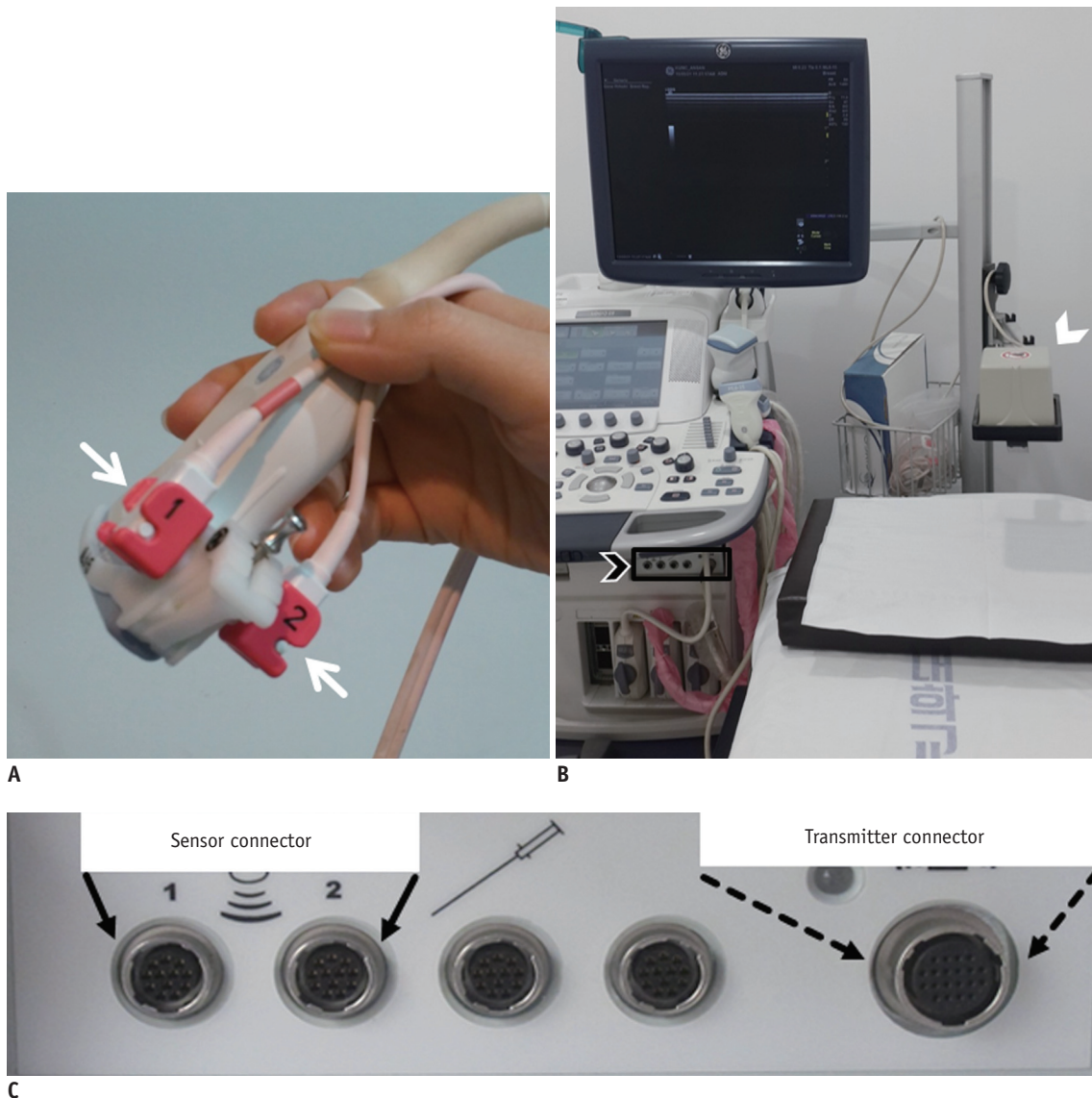
radiological features between these two imaging modalities in preoperative evaluation of breast cancer patients. Therefore, a combination technique of MRI and real-time ultrasound imaging, namely “real-time MRI navigated ultrasound” could be more objective, and can enhance the sensitivity of conventional ultrasound for initially detected breast lesions on MRI during the second-look ultrasound evaluation (15-18). Consequently, real-time MRI navigated ultrasound and biopsy could replace the MRI-guided biopsy for MRI-detected lesions.

The purpose of the current pictorial essay is to illustrate the technical principles of real-time MRI navigated

ultrasound, and to demonstrate the clinical implementation of the system in preoperative evaluation of breast cancer patients.

### Technical Principles of Real-Time MRI Navigated Ultrasound

The following ultrasound navigation systems are commercially available: Volume Navigation (GE Healthcare, Ltd., Chalfont St. Giles, England); Real-time Virtual Sonography (Hitachi Medical Corporation, Tokyo, Japan); Virtual Navigator (Esaote SpA, Genoa, Italy); PercuNav



**Fig. 1. Equipment of MRI navigated ultrasound.**

**A.** Two electromagnetic sensors (arrows) are attached to tip of transducer. **B, C.** Portable electromagnetic transmitter (white arrowhead) is positioned near patient undergoing examination. Position-sensing unit (black arrowhead) connects electromagnetic sensors and transmitter, which allows tracking probe position and orientation within electromagnetic field.

(Philips Healthcare, Best, the Netherlands); eSie Fusion (Siemens Healthcare, Erlangen, Germany); and Smart Fusion (Toshiba Medical Systems Corporation, Tochigi, Japan). These systems operate on the basis of similar equipment components and technical principles. The equipment is composed of two electromagnetic sensors attached to the tip of a transducer, a portable electromagnetic transmitter that is positioned near the patient under examination, and a position-sensing unit that connects the electromagnetic sensors and transmitter (Fig. 1). It allows the tracking probe position and orientation within the electromagnetic field.

After setting the equipment, the following process is followed: upload the acquired digital imaging and communications in medicine (DICOM) images of MRI to ultrasound system; side-by-side display of a MRI image and a real-time ultrasound image on a monitor; co-registration of both images on the same position and orientation. To fuse the imaging information obtained from breast MRI and ultrasound, a co-registration is required to ensure that pixels from the datasets represent approximately the same volume. For a precise co-registration, image registration and data reslicing are implemented.

The methods of co-registration include 'parallel plane registration' and 'point registration'. At the beginning of the image fusion, the axial plane at the nipple level of each breast on MRI and ultrasound are registered. After this plane registration, additional point registration is carried out to enable a more precise adaptation. For point registration, either external (fiducially placed on the patient) or internal (anatomic structures or pathologic lesions) landmarks can be used (1, 18). When either image causes a discrepancy, re-synchronization is needed by additional point registration.

### Clinical Researches about the Use of Real-Time MRI Navigated Ultrasound in Breast

There are several studies in the use of real-time MRI navigated ultrasound in evaluation of breast lesions. Real-time MRI navigated ultrasound is mostly applied as an adjunctive modality for second-look ultrasound examination in breast cancer patients (15-18). Second-look ultrasound is the targeted ultrasound examination for identification of a breast lesion which is detected on MRI, but not seen on initial ultrasound examination. It allows ultrasound-guided biopsy or ultrasound follow-up for the additional breast lesion, consequently substituting for MRI-guided

interventions. However, a recent review article reported that second-look ultrasound could find the MRI-detected lesions in 64% of cases, ranging from 23% to 89% (19, 20). Therefore, it was suggested that real-time MRI navigated ultrasound could enhance the detection of lesions, as compared to conventional second-look ultrasound. Nakano et al. (15) compared the sensitivity between conventional second-look ultrasound and MRI navigated ultrasound in 67 MRI-detected lesions, and reported that MRI navigated ultrasound identified more breast lesions with statistical significance in comparison to conventional ultrasound (90% vs. 30%,  $p < 0.001$ ). They also reported that MRI navigated ultrasound improved the detection of lesions around mammary fascia rather than within mammary gland ( $p = 0.023$ ) (15). In another similar investigation, Pons et al. (18) reported that the detection rate of MRI navigated ultrasound and conventional ultrasound was 91 and 43%, respectively, and the diagnostic performance of MRI navigated ultrasound in identifying malignancy was 96.3% in sensitivity, 18.8% in specificity, 66.7% in positive predictive value, and 75% in negative predictive value.

Another study showed that real-time MRI navigated ultrasound could measure the cancer size more accurately in comparison with conventional ultrasound. Chang et al. (21) presented that the tumor size estimated with MRI navigated ultrasound correlated better with the histologic tumor size, than conventional ultrasound ( $r = 0.688$  vs.  $r = 0.540$ ). In addition, MRI navigated ultrasound was also useful in detecting deeply located axillary lymph nodes. Pons et al. (18) identified two suspicious axillary lymph nodes located near the chest wall through MRI navigated ultrasound, and ultrasound-guided biopsy revealed the metastasis from known breast carcinoma.

### Clinical Implementation of Real-Time MRI Navigated Ultrasound in Breast Cancer Patients

Our institution has been conducting real-time MRI navigated ultrasound during second-look ultrasound examination in breast cancer patients since October 2013. Ultrasound examinations were performed using LOGIQ E9 (GE, Milwaukee, WI, USA) that contains a magnetic tracking system and a special software for real-time volume navigation. Second-look ultrasound examination was performed in supine position in the following two steps: first, we performed the conventional B-mode ultrasound, followed by real-time MRI navigated ultrasound. MRI

examinations were performed using 3T scanner (Achieva 3T TX, Philips Healthcare, Best, the Netherlands) with a dedicated phased-array breast coil in prone position. A contrast-enhanced fat-suppressed 3D fast spoiled gradient echo sequence (repetition time/echo time, 3/1; flip angle, 10°; image matrix, 360 x 360; field of view, 217 x 217 mm; section thickness, 3 mm) was used for dynamic imaging every 60, 120, 180, 240, and 300 seconds, which included one pre-contrast and five post-contrast dynamic series. The last post-contrast axial DICOM image was uploaded to ultrasound system for MRI navigation ultrasound examination. For co-registration of both real-time ultrasound and uploaded MRI images, axial plane registration on the nipple line was done first, and then additional point registrations were done using known pathologic lesions or anatomic structures such as vessels, fat lobules, or Cooper's ligament. The average time for equipment installation and examination was less than 10

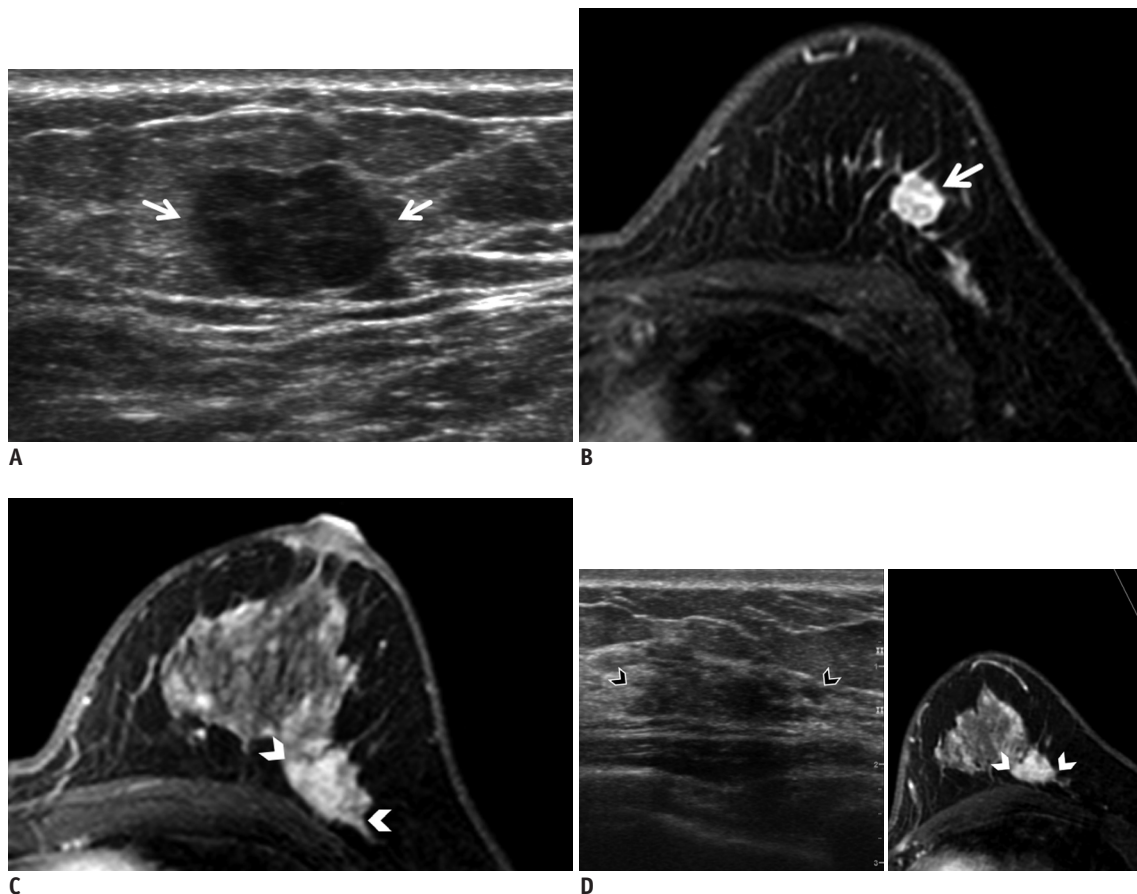
minutes.

Real-time MRI navigated ultrasound is useful to assess tumor extent and lymph nodal status in breast cancer patients, and leads to optimal preoperative tumor staging and treatment plan in breast cancer patients.

### Assessment of Tumor Extent

Breast MRI is performed for staging in most breast cancer patients. In a patient who has additional suspicious enhancing lesions on breast MRI, real-time MRI navigated ultrasound is valuable during second look ultrasound examination. This system displays the interesting site simultaneously, and the MRI and ultrasound features for each breast lesion can be correlated. In addition, it allows performing prompt ultrasound-guided biopsy instead of inconvenient MRI-guide biopsy, and enhances the detection of multiple synchronous cancers or high-risk lesions.

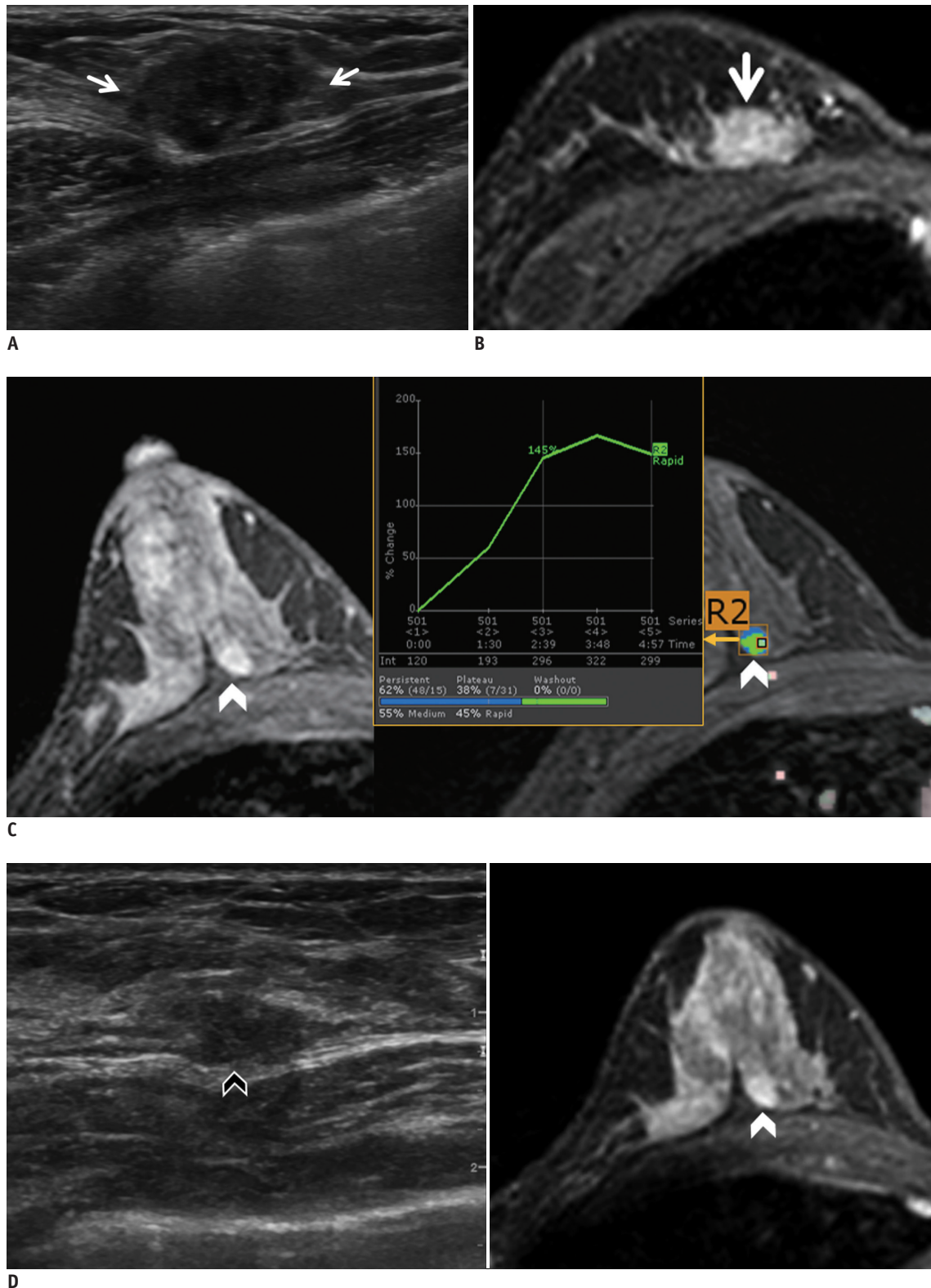
Figures 2 and 3 demonstrate real-time MRI navigated



**Fig. 2. 43-year-old female with multiple cancers in ipsilateral breast.**

Breast ultrasound (A) and contrast-enhanced axial T1-weighted MRI (B) images show biopsy-proven invasive ductal carcinoma (arrows) in 1 o'clock direction on left breast. MRI image (C) depicts another 19 mm-sized heterogeneous non-mass enhancement (white arrowheads) in 3 o'clock direction on left breast. Real-time MRI navigated ultrasound (D) identified indistinct irregular isoechoic mass (arrowheads). Mass was diagnosed as invasive ductal carcinoma, and patient underwent breast conserving surgery for multifocal breast cancers.





**Fig. 3.** 37-year-old female with multiple cancers in ipsilateral breast.

Breast ultrasound (A) and contrast-enhanced axial T1-weighted MRI (B) images show biopsy-proven invasive ductal carcinoma (arrows) in 1 o'clock direction on right breast. MRI and computer-aided detection images (C) depict another 6 mm-sized circumscribed oval mass (white arrowhead) with early fast and delayed plateau enhancement pattern in right subareolar area. Real-time MRI navigated ultrasound (D) identified microlobulated oval isoechoic mass (arrowheads) in right subareolar area. Ultrasound-guided core needle biopsy verified this mass as ductal carcinoma *in situ*, and patient underwent modified radical mastectomy. Final pathologic result was multiple invasive ductal carcinomas.

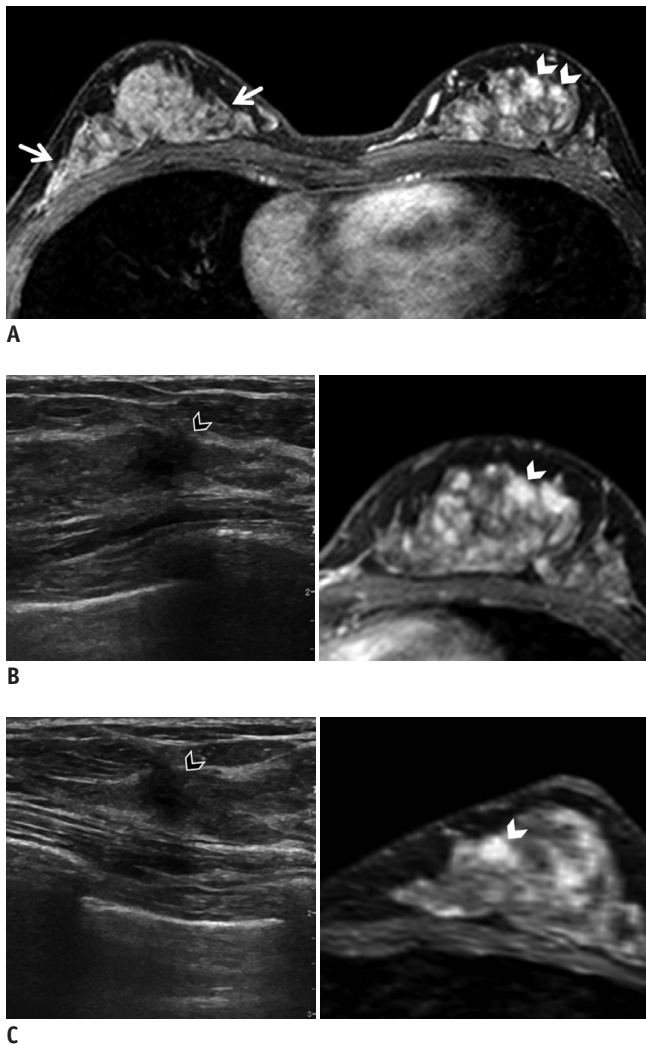
ultrasound examinations detect multiple cancers in the ipsilateral breast. A 43-year-old woman had an invasive ductal carcinoma in the 1 o'clock direction in the left breast (Fig. 2). On dynamic MRI, we found an additional 19 mm-sized heterogeneous non-mass enhancement in the mid outer portion on the left breast. We performed real-time MRI navigated ultrasound to evaluate the additional non-mass enhancement on the same breast, and found a suspicious mass in the 3 o'clock direction, which corresponded with the non-mass enhancement on MRI. The mass was pathologically verified as invasive ductal

carcinoma with ultrasound-guided core needle biopsy. The patient underwent breast conserving surgery for multifocal breast cancers. In another case, a 37-year-old woman had an invasive ductal carcinoma in the 1 o'clock direction, 5 cm from the nipple site on the right breast (Fig. 3). Dynamic MRI revealed another 6 mm-sized oval mass in the right subareolar area. The mass had early fast and delayed plateau enhancement. We performed real-time MRI navigated ultrasound to figure out the additional mass on MRI, and detected a suspicious mass in the right subareolar area. Ultrasound-guided core needle biopsy was performed, and the mass was diagnosed as ductal carcinoma *in situ*. The patient underwent modified radical mastectomy, and the final pathologic result was multiple invasive ductal carcinomas.

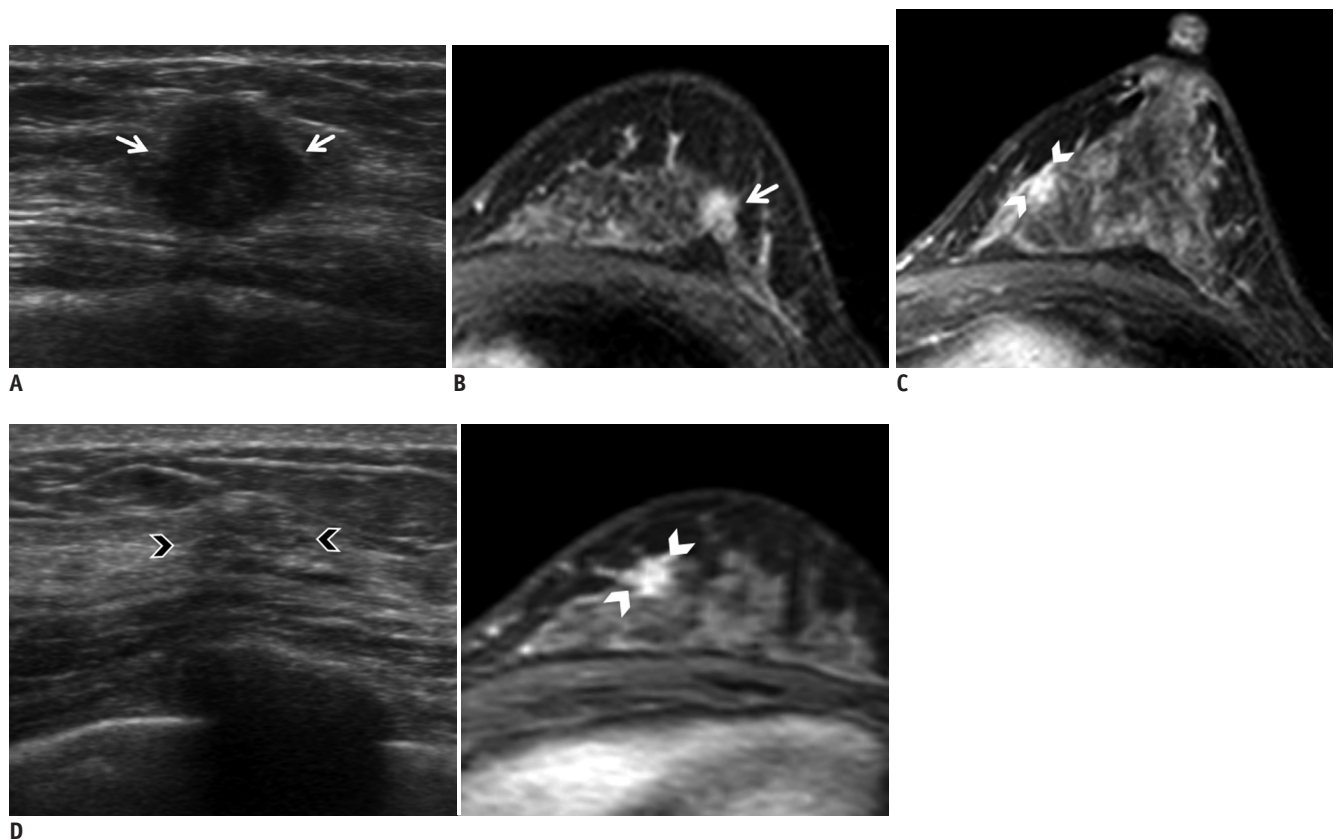
Figure 4 demonstrates that real-time MRI navigated ultrasound is useful to detect bilateral synchronous cancers. A 49-year-old woman had multicentric invasive ductal carcinomas on the right breast. Dynamic MRI showed multiple enhancing masses in the left breast. Real-time MRI navigated ultrasound was performed to assess these masses in the contralateral breast. An irregular hypoechoic mass was detected in the left breast at the 2 o'clock direction, and was confirmed as invasive ductal carcinoma with ultrasound-guided core needle biopsy. Finally, the patient underwent bilateral modified radical mastectomy.

Figure 5 is a case where real-time MRI navigated ultrasound detected a high-risk lesion in the ipsilateral breast. A 40-year-old woman had an invasive ductal carcinoma in the 2 o'clock direction on the left breast. Dynamic MRI revealed another 10 mm-sized focal non-mass enhancement in the 9 o'clock direction on the same breast. Real-time MRI navigated ultrasound detected an irregular isoechoic mass in the 9 o'clock direction. This was pathologically confirmed as atypical ductal hyperplasia with ultrasound-guided biopsy. The patient underwent breast conserving surgery for the cancer mass in the 2 o'clock direction, and excisional biopsy for the atypical ductal hyperplasia in the 9 o'clock direction on the left breast.

Real-time MRI navigated ultrasound is helpful to evaluate the tumor size (Fig. 6). Sometimes, the measured tumor size on multimodal breast imaging are discrepant. A 46-year-old woman had grouped fine pleomorphic calcifications in the right mid outer breast on mammography. Ultrasound revealed focal ductal change with microcalcifications in the 9 o'clock direction on the right breast. The measured tumor size was 9 mm on mammography and 12 mm on ultrasound,



**Fig. 4. 49-year-old female with bilateral synchronous cancers.** Contrast-enhanced axial T1-weighted MRI image (A) shows diffuse heterogeneous non-mass enhancement (arrows) in right breast, biopsy-proven invasive ductal carcinoma, and multiple enhancing masses (arrowheads) in left breast. Real-time MRI navigated ultrasound transverse (B) and longitudinal (C) images depict irregular indistinct hypoechoic mass (arrowheads) in left breast 2 o'clock direction. Mass was diagnosed as invasive ductal carcinoma, and patient underwent bilateral modified radical mastectomy.



**Fig. 5. 40-year-old female with concurrent high-risk lesion in ipsilateral breast.**

Breast ultrasound (A) and contrast-enhanced T1-weighted MRI (B) images show biopsy-proven invasive ductal carcinoma (arrows) in 2 o'clock direction on left breast. MRI (C) depicts another 10 mm-sized focal non-mass enhancement (white arrowheads) in left inner mid portion. Real-time MRI navigated ultrasound (D) identified irregular isoechoic mass (arrowheads) in left 9 o'clock direction. Lesion was diagnosed as atypical ductal hyperplasia. Patient underwent breast conserving surgery for invasive ductal carcinoma, and excisional biopsy for atypical ductal hyperplasia.

respectively. Ultrasound-guided biopsy was performed, and this was confirmed as ductal carcinoma *in situ*. For tumor staging, dynamic MRI was undertaken. There was a 50 mm-sized segmental non-mass enhancement in the right 9 o'clock position. For precise assessment of tumor size, real-time MRI navigated ultrasound was performed. A 45 mm-sized ductal change and calcifications were identified in the 9 o'clock direction on the right breast, which corresponded with the segmental non-mass enhancement on dynamic MRI. Ultrasound-guided wire localization was performed at proximal and distal ends of the lesion, after which breast conserving surgery was done. On the pathological examination, the tumor size was 40 mm.

#### Assessment of Lymph Node

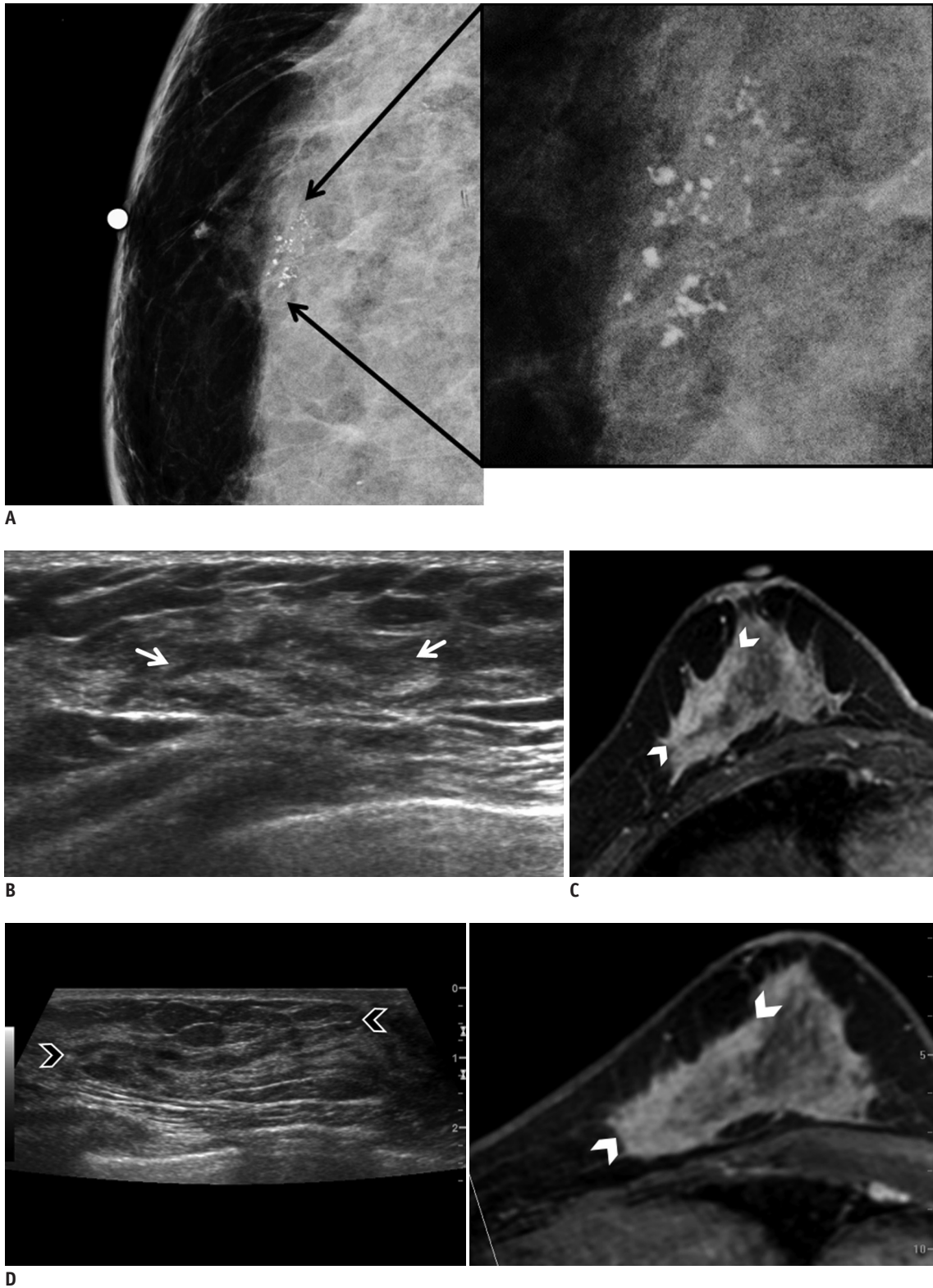
We often overlook metastatic axillary lymph nodes on preoperative breast ultrasound because of borderline findings in diagnosing metastasis, or deep or peripheral locations within the axilla. Real-time MRI navigated

ultrasound can be helpful to detect suspicious lymph nodes and perform the ultrasound-guided biopsy for accurate nodal staging (Fig. 7). A 30-year-old woman had an invasive ductal carcinoma on the right breast. On MRI, there was an ill-defined lymph node in the right axilla, which was not detected on initial ultrasound examination. We performed real-time MRI navigated ultrasound and found a 11 mm-sized lymph node with cortical thickening. Ultrasound-guided core needle biopsy was performed, and the node was pathologically verified as metastasis.

#### Limitations and Counterplans of Real-Time MRI Navigated Ultrasound in Breast

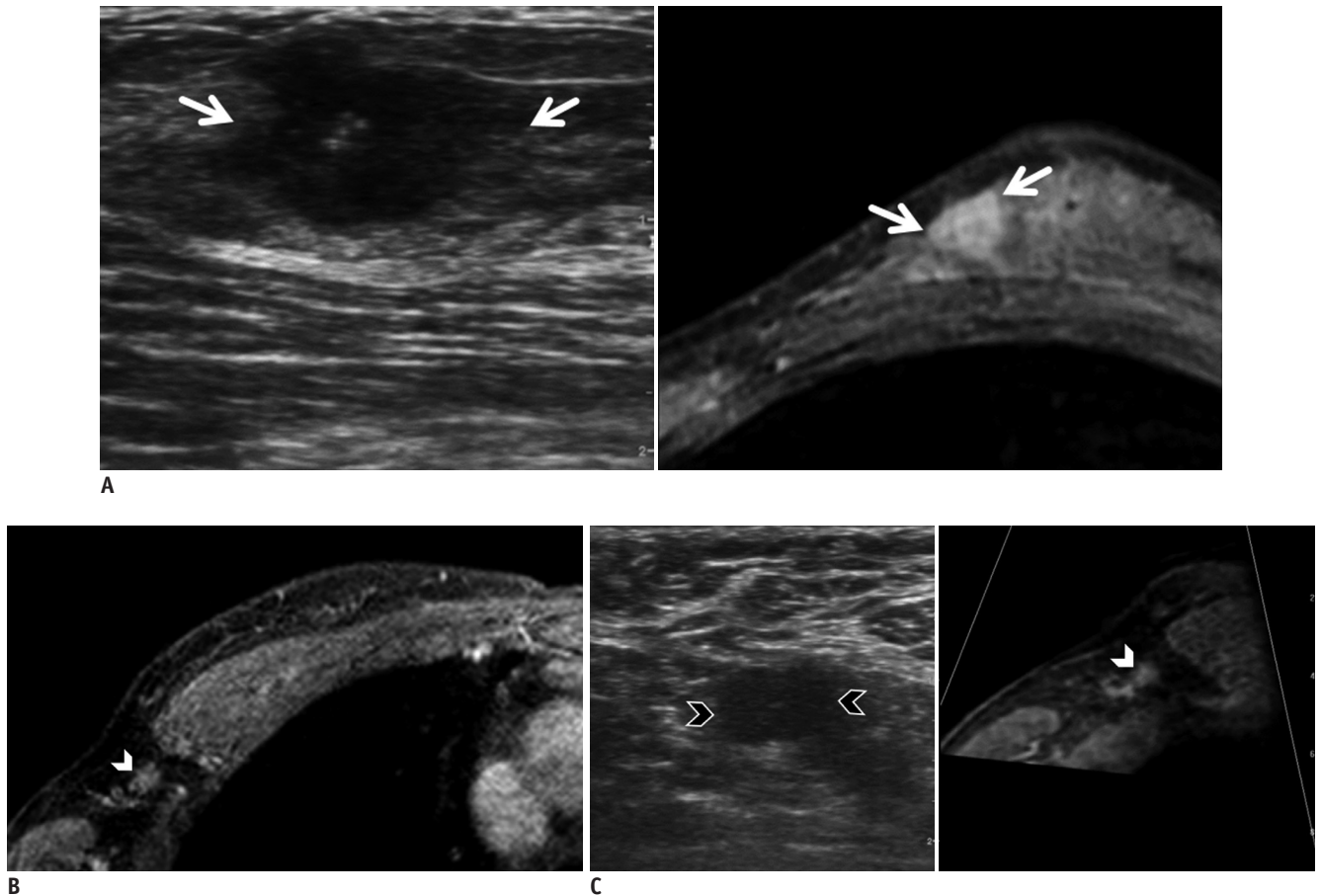
The major limitation in application of MRI navigated ultrasound for breast lesions is the difficulty in accurate co-registration between real-time ultrasound images and uploaded MRI data. The breast tissues are highly mobile, and thus the position difference during both ultrasound and





**Fig. 6.** 46-year-old female with ductal carcinoma *in situ* showing discordant tumor extent on mammography, ultrasound, and MRI. Magnification mammography (A) shows grouped fine pleomorphic calcifications in right breast. Ultrasound image (B) shows 12 mm-sized focal ductal change with microcalcifications (arrows) in 9 o'clock direction on right breast. Contrast-enhanced T1-weighted MRI image (C) shows 50 mm-sized segmental non-mass-enhancement (white arrowheads) in right mid outer breast, which was not well correlated with mammographic or ultrasound features. Real-time MRI navigated ultrasound (D) identified 45 mm-sized ductal change (arrowheads) in right 9 o'clock direction. Patient underwent ultrasound-guided wire localization at proximal and distal ends of lesion, and breast conserving surgery. Pathological tumor size was 40 mm.





**Fig. 7. 30-year-old female with invasive ductal carcinoma on right breast and ipsilateral axillary lymph node metastasis.** Real-time MRI navigated ultrasound image (A) shows biopsy-proven invasive ductal carcinoma (arrows) in 11 o'clock direction on right breast. MRI (B) depicts ill-defined lymph node (white arrowhead) in right axilla, which was not detected on initial ultrasound examination. Real-time MRI navigated ultrasound (C) identified 11 mm-sized lymph node with cortical thickening (arrowheads). Ultrasound-guided core needle biopsy for this lymph node verified metastasis.

MRI examinations (supine vs. prone) can cause difficulty in co-registration between two images. In addition, breast parenchyma is changeable in composition according to the individual hormonal status, such as menstrual cycle (20). These factors can finally affect the detection rate and cause misdiagnosis of breast lesions on second-look ultrasound. Therefore, Rizzatto and Fausto (22) recommended the additional MRI examination with supine position, and the immediate MRI navigated ultrasound examination for breast lesions that were not detected on conventional second-look ultrasound examination. Actually, Fausto et al. (23) proved the accuracy and reproducibility of MRI navigated ultrasound when both MRI and ultrasound scans were performed in supine position for five healthy volunteers. For point co-registration, five points of interest were used: three skin markers (vitamin E capsules) positioned at 9, 12, and 3 o'clock direction, the nipple, and the internal mammary artery. The distance on the skin surface between transducer

real position when point of interest was displayed on the MRI image and its expected position visually detected was minimal, and showed no inter-observer difference between two radiologists (the first measurement,  $0.42 \pm 0.32$  and  $0.58 \pm 0.41$  cm,  $p = 0.161$ ; the second,  $0.50 \pm 0.32$  and  $0.56 \pm 0.52$  cm,  $p = 0.928$ ) (23).

However, additional MRI examination in supine position only for MRI navigated ultrasound or use of external body markers could be practically time-consuming or unavailable. Therefore, we recommend doing multiple and repeated point-registrations using internal landmarks before and during the examination for the targeted area of breast. The available internal landmarks include anatomic structures such as nipple, vessel, fat lobule, or Cooper's ligament, and breast lesions. In addition, as previous investigators suggested, the area of targeted ultrasound examination may be a least a quadrant's worth of tissue on either side of the clock position of the lesion identified on MRI (24). Also,

it would be better that the radiologist who interpretes the MRI images perform the real-time MRI navigated ultrasound (24, 25).

## CONCLUSION

The real-time MRI navigated ultrasound is a promising imaging fusion technique in breast evaluations. This is an easy and convenient technique to correlate two different image modalities, MRI and ultrasound. It is recommended as a second-look evaluation tool for decision of tumor extent, multiplicity, and lymph nodal status in breast cancer patients. Finally, it could lead to accurate tumor staging and optimal therapeutic decisions.

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