Fusion of MRI and Sonography Image for Breast Cancer Evaluation Using Real-time Virtual Sonography with Magnetic Navigation: First Experience

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Objective: We recently developed a real-time virtual sonography (RVS) system that enables simultaneous display of both sonography and magnetic resonance imaging (MRI) cutaway images of the same site in real time. The aim of this study was to evaluate the role of RVS in the management of enhancing lesions visualized with MRI.

Methods: Between June 2006 and April 2007, 65 patients underwent MRI for staging of known breast cancer at our hospital. All patients were examined using mammography, sonography, MRI and RVS before surgical resection. Results were correlated with histopathologic findings. MRI was obtained on a 1.5 T imager, with the patient in the supine position using a flexible body surface coil. Detection rate was determined for index tumors and incidental enhancing lesions (IELs), with or without RVS.

Results: Overall sensitivity for detecting index tumors was 85% (55/65) for mammography, 91% (59/65) for sonography, 97% (63/65) for MRI and 98% (64/65) for RVS. Notably, in one instance in which the cancer was not seen on MRI, RVS detected it with the supplementation of sonography. IELs were found in 26% (17/65) of the patients. Of 23 IELs that were detected by MRI, 30% (7/23) of IELs could be identified on repeated sonography alone, but 83% (19/23) of them were identified using the RVS system (P = 0.001). The RVS system was able to correctly project enhanced MRI information onto a body surface, as we checked sonography form images.

Conclusions: Our results suggest that the RVS system can identify enhancing breast lesions with excellent accuracy.

Key words: real-time virtual sonography – MRI – sonography – breast cancer – incidental enhancing lesion

INTRODUCTION
Breast magnetic resonance imaging (MRI) is one of the most sensitive diagnostic imaging techniques for breast cancer, with sensitivity ranging from 94% to 100%. Its specificity, however, ranges from 20% to 100%, depending on the technique and patient selection (1–5). There is a large overlap in the MRI findings of enhancing lesions, which often makes decisions regarding patient management difficult.

Incidental enhancing lesions (IELs) that were initially identified by MRI, but not by conventional imaging, are found in 16–29% of the patient upon performing breast MRI (6,7). When these morphologic evaluation and dynamic
patterns suggest malignancy, a breast biopsy needs to be done immediately. To localize IELs, MRI-guided biopsies have recently started to be performed with high reports of success (8). Nevertheless, this technique is costly and time-consuming, and therefore can only be performed in a limited number of facilities. For this reason, in many facilities, IELs are often only identified upon second-look sonography, followed by a biopsy (9–12). However, the success of the examination depends on the experience and technique of the operator; in many cases, sonographic identification is difficult, because the patient’s body is positioned differently than it is during MRI. Furthermore, IELs found in separate quadrants from the index tumor are clinically more important than those in the same quadrant.

Recently, we have developed a real-time virtual sonography (RVS) system, in which a position tracking system is coordinated with a magnetic sensor. RVS can synchronize a sonography image and the MR image with multi-planar reconstruction (MPR) of the same section in real time. The effectiveness of RVS in liver tumor treatment has been reported (13); however, few studies have investigated the utility of RVS in breast imaging (14,15).

The purpose of this study was to evaluate the usefulness of RVS for detection of index tumors and IELs. In addition, we compared the detection rates across different techniques for index tumors and IELs.

PATIENTS AND METHODS

PATIENTS

From June 2006 through April 2007, 65 patients (age range, 31–72 years; mean, 47 years) with operable breast cancer, Stages 0–III A, were enrolled in this study at our hospital. Among the 65 patients, 52 (80%) complained of the presence of a self-palpable mass, 2 (3%) complained of nipple discharge and 11 (17%) had lesions that were detected during screening. Core needle biopsy was performed for all index tumors.

All patients underwent breast MRI and RVS in addition to conventional assessment, physical examination, mammography and sonography. If MRI detected an additional lesion that was not identified upon prior imaging in the separate quadrants from the index tumor, the patient underwent RVS after a second-look sonography. If the lesions were detected by sonography, an image-guided biopsy was performed. If the lesions were detected only by RVS, but not detected by sonography, excisional biopsy was performed after MRI information was marked onto the body surface using the RVS system. The results were correlated with histopathologic findings. All patients gave written informed consent prior to undergoing the MRI. Patients with inflammatory breast cancer, bilateral breast cancer and metastatic disease were excluded. Furthermore, patients were excluded if MRI was deemed unnecessary. We also excluded patients with pregnancy, presenting with history of breast cancer and patients who had MRI performed at an outside institution.

A quadrantectomy or wide local excision was initially performed for 42 patients, and mastectomy was performed for 23 patients. Of the 42 patients, 9 required re-excision because of positive margins. Four of those nine patients underwent complete mastectomy.

IMAGING EXAMINATION TECHNIQUE

MAMMOGRAPHY EXAMINATION

A standard bilateral mammogram, with additional views as necessary, was obtained using conventional mammography units (Lorad M-IV, Hologic).

SONOGRAPHY EXAMINATION

All sonography was performed by one experienced surgeon (S.N.). A 13 MHz linear-array probe was used in all patients (EUB-8500, Hitachi Medical Corporation, Japan). Sonography was performed with patients lying in the supine position with the arm raised. Scanning was performed in the radial and anti-radial planes, as well as in the longitudinal and transverse planes. Sonography examination took ~8 min (range, 5–13 min).

MRI EXAMINATION

MRI were obtained on a Magnetom 1.5 T imager (Siemens Medical Systems, Germany) using a flexible body surface coil. All patients were examined in the supine position with the arm raised, in order to achieve the same position as in sonography. The MRI scan protocol parameters included diffusion-weighted imaging; both non-enhanced and contrast-enhanced images were acquired using a coronal T1-weighted three-dimensional fast low-angle shot (FLASH) gradient-echo sequence (TR/TE, 4.8/2.4; flip angle, 18°; matrix, 256 × 256; section thickness, 1.5–2.0 mm without intersection gap; acquisition time, 19 s). Gadodiamide (Omniscan; Daiichi Pharmaceutical Co., Ltd, Tokyo, Japan), 0.2 ml/kg body weight, was injected at a rate of 2.0 ml/s into the antecubital vein, followed by a 20 ml saline flush. After examination, unenhanced images were subtracted from the corresponding contrast-enhancing images on a pixel-by-pixel basis, and maximum intensity projections were generated from these subtraction images.

Any suspicious enhancing lesions were described with regard to lesion shape, borders, distribution, internal architecture and kinetic analysis by two experienced radiologists (K.O. and J.K.).

RVS EXAMINATION

The RVS system comprised a sonography scanner using a 13 MHz linear-array probe, magnetic field generator, magnetic sensor and workstation with built-in RVS software (Hitachi Medical Corporation) (Fig. 1). The breast MRI
volume data of each enhancing phase were transferred to the RVS system as digital imaging and communications in medicine (DICOM) data before the RVS system launched. The magnetic sensor installed on the tip of the probe sensed the magnetic field and detected the position and motion of the probe while it was scanning. The orientation of the probe was transmitted to the workstation that stores patient MRI volume data. The workstation computed the positional information and displayed an MPR image corresponding to the sonography image at a rate exceeding 10 frames/s, in real time. Up to four different MPR images corresponding to the sonography image could be displayed on the monitor (Fig. 2). Because two modalities operate simultaneously in RVS, a reference point is necessary. Therefore, we defined the nipple of the examined side, which can be easily identified by both sonography and MRI, as the reference point for synchronization.

When either image (sonography image or virtual image) caused a discrepancy, due to respiratory movement or disturbance of the magnetic field by a nearby metal object, we undertook re-synchronization using the ‘adjust’ function. We resumed the RVS system after the almost identical sonography image that re-adjusted the position and inclination of the probe was fitted to the frozen virtual image, where the nipple or tumor itself was demonstrated clearly.

**ANALYSIS**

For mammograms, malignancy was defined as microcalcification, architectural distortion and characteristic mass, as defined in the BI-RADS MMG lexicon. For sonography images, malignancy was defined a mass or ductal extension as defined in the BI-RADS US lexicon. For MR images, malignancy was defined by the presence of foci, characteristic mass and no-mass enhancement as defined in the BI-RADS MR lexicon (16).

Statistical analysis was performed using Fisher’s exact test and Mann–Whitney U-test, using SPSS 11.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was inferred for P-values < 0.05.

**RESULTS**

**DETECTION OF INDEX TUMOR**

On histopathologic examination, the index tumors of 65 patients were found to have a malignant tumor (Table 1). Upon pathologic examination, 56 of the index tumors were found to have invasive ductal carcinoma, 1 had mucinous carcinoma and 8 had ductal carcinoma *in situ*. The median MRI lesion size of the index tumor was 17 mm (range, 5–56 mm). Of the index tumors, the histologic staging was T1 in 43 (66%) patients, T2 in 11 (17%) patients and T3 in 3 (5%) patients. Of the 65 patients, 14 patients displayed one
or more additional malignant lesions that had been detected by conventional examination.

Abnormal mammographic findings were seen in 55 of the 65 patients, including 3 of 55 (5%) asymmetric densities, 4 (7%) architectural distortions, 10 (18%) microcalcifications and 29 (53%) masses. Mammographic findings were negative in 10 cancers. The sensitivity of mammography for the detection of the index tumors was 85%. The 55 index tumors identified with mammography included 49 of the 56 (88%) invasive ductal carcinomas detected by pathologic examination, 1 of 1 (100%) mucinous carcinoma and 5 of 8 (63%) ductal carcinomas in situ.

In the 65 patients who underwent sonography, 59 focal hypoechoic areas were detected. Six patients had negative initial sonography examination. The sensitivity of sonography for the detection of the index tumors was 91%. The 59 index tumors identified with sonography included 54 of 56 (96%) invasive ductal carcinomas, 1 of 1 (100%) mucinous carcinoma and 4 of 8 (50%) ductal carcinomas in situ.

Six-five patients had MRI examination, with 63 of 65 index tumors enhancing after injection of gadolinium, including nine lesions that were not visualized on mammography and five lesions that were not visualized on sonography. Fifty-five lesions were described as mass enhancement and eight were described as no-mass enhancement. The sensitivity of MRI for the detection of the index tumors was 97%. The 63 index tumors identified with MRI included 56 of 56 (100%) invasive ductal carcinomas, 1 of 1 (100%) mucinous carcinomas and 6 of 8 (75%) ductal carcinomas in situ.

In the 65 patients who underwent RVS, 64 of 65 index tumors were detected. Of the two lesions not visualized on MRI, one that both sonography and MRI missed was also missed on RVS, whereas the other lesions missed on MRI alone was found on RVS. All enhancing lesions on MRI, and all sonography-detected lesions, were detectable by RVS. A virtual MRI–MPR image of the target tumor was displayed, showing good correspondence with the sonography image, in 64 patients whose tumor was detectable by MRI or sonography (Fig. 3). The sensitivity of RVS for detection of the index tumor was 98%. The 64 index tumors identified with MRI included 56 of 56 (100%) invasive ductal carcinomas, 1 of 1 (100%) mucinous carcinoma and 7 of 8 (88%) ductal carcinomas in situ.

### Table 1. The sensitivity of breast index tumors by each breast imaging method

<table>
<thead>
<tr>
<th></th>
<th>MMG</th>
<th>US</th>
<th>MRI</th>
<th>RVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index tumors (n = 65)</td>
<td>55 (85%)</td>
<td>59 (91%)</td>
<td>63 (97%)</td>
<td>64 (98%)</td>
</tr>
<tr>
<td>IDC (n = 56)</td>
<td>49</td>
<td>54</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Mucinous carcinoma (n = 1)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DCIS (n = 8)</td>
<td>5</td>
<td>4</td>
<td>6</td>
<td>7</td>
</tr>
</tbody>
</table>

MMG, mammography; US, sonography; MRI, magnetic resonance imaging; RVS, real-time virtual sonography; IDC, invasive ductal carcinoma; DCIS, ductal carcinoma in situ.

### Figure 3. A 55-year-old woman with a palpable mass in the left breast upper inner quadrant. Coronal, T1-weighted, contrast-enhanced MRI shows an irregular, heterogeneously enhancing mass consistent with biopsy-proven invasive ductal carcinoma (arrow) (A). Sonography shows a hypoechoic mass correlating with the MRI findings (arrowheads). RVS (B) allows for the display of the pre-contrast MRI–multi-planar reconstruction (MPR) image (b), the early-phase MRI–MPR image with rim enhancement (c) and the late-phase MRI–MPR image (d), all of which correspond to the sonography cutaway image (a). By visualizing each enhancement phase, we can observe and compare imaging dynamics directly. A color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org.
with MRI, 3 of 11 (27%) were identified without RVS, and 9 of 11 (82%) were identified with RVS.

Mean size of IELs was not significantly associated with detection rate using the various techniques ($P = 0.65$).

Among 7 IELs without RVS, there were 2 focus/foci and 5 masses, whereas there were 8 focus/foci, 10 masses and 1 no-mass in 19 IELs with RVS.

Twelve IELs could be identified by RVS, but not by repeated sonography. Of these, six were benign and six were malignant. Among the 6 benign lesions, there were four focus/foci and two masses, whereas among the malignant lesions, there were two focus/foci, three masses and one no-mass lesion.

Table 2. Detection rate of incidental enhancing lesions (IELs) and histopathologic characteristics with and without RVS at second-look sonography

<table>
<thead>
<tr>
<th>IELs detection rate ($n = 23$)</th>
<th>Without RVS</th>
<th>RVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant ($n = 12$)</td>
<td>7 (30%)</td>
<td>19  (83%)</td>
</tr>
<tr>
<td>Invasive ductal carcinoma ($n = 7$)</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>DCIS ($n = 5$)</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Benign ($n = 11$)</td>
<td>3 (27%)</td>
<td>9 (82%)</td>
</tr>
<tr>
<td>Fibrocystic disease ($n = 6$)</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Fibroadenoma ($n = 2$)</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Intraductal papilloma ($n = 1$)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Intramammary lymph node ($n = 1$)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hemangioma ($n = 1$)</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Mean size (mm)</td>
<td>6.0</td>
<td>6.6</td>
</tr>
<tr>
<td>MRI type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focus/foci ($n = 9$)</td>
<td>2 (22%)</td>
<td>8 (89%)</td>
</tr>
<tr>
<td>Mass ($n = 12$)</td>
<td>5 (42%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>No mass ($n = 2$)</td>
<td>0 (0%)</td>
<td>1 (50%)</td>
</tr>
</tbody>
</table>

Eighteen (95%) of these 19 lesions subsequently underwent sonography-guided biopsy. Although 1 (5%) of 19 lesions was not detected by sonography, excisional biopsy could be performed after MRI information was marked onto the body surface using RVS.

**DISCUSSION**

Many studies have documented the utility of breast MRI to detect breast cancer that is occult to physical examination and conventional imaging. In 10–34% of patients (17), additional foci of mammographically occult cancer are found by MRI. Because about half of these additional foci are in separate quadrants from the index tumor, attempts must be made to identify these foci, in order to decide the indication for breast conservation surgery. The use of targeted sonography to detect suspicious breast MRI lesions varies among practice sites (7,9–11).

We directly compared the morphology of lesions in MRI with that of sonography images of any section, using the RVS system. The results of our study show that RVS has the greatest sensitivity (98%) for detecting index tumor of breast cancer, followed by MRI (97%), sonography (91%) and mammography (85%). Notably, in one instance in which the cancer was not seen on MRI, RVS detected the index tumor (intracystic papillary carcinoma), with the supplementation of sonography. This is the first study, to our knowledge, to compare the sensitivity of four different breast imaging techniques for breast cancer diagnosis. Nevertheless, the determination of whether RVS has a sensitivity that is equal to or greater than that of MRI for the detection of breast cancer awaits additional larger trials. Causer et al. (18) reported that an MRI–sonography co-registration system, with the patient in the prone position, was found to be an accurate means for targeting sonography to MRI of the same breast lesions.

Our study was performed to clarify the usefulness of RVS in the evaluation of IELs. The detection rate of IELs was

![Figure 4](http://www.jjco.oxfordjournals.org).
83% for RVS, which is significantly better than repeated sonography alone (30%). Compared with the use of sonography alone, RVS is useful in identifying lesions in patients whose diagnostic images exhibited smaller differences in echogenicity between the interior and exterior of the tumors, and who exhibited non-tumor low-echo regions in the background. Suspicious lesions detected by breast MRI require tissue sampling for definitive diagnosis. MRI-guided breast biopsy is used with increasing frequency, particularly for biopsy of lesions that are visible only on MRI but are occult to conventional imaging (8,19,20). Nevertheless, these techniques are not widely available and require costly use of MR magnet time and personnel. Furthermore, the sampling is not performed under real-time visualization, as with sonography or RVS; it is not currently practical to image the sample with MRI to confirm retrieval of the targeted lesion, as with stereotactic biopsy of calcifications. Prior studies that included relatively small numbers of patients have found MRI-guided biopsy to be very accurate, with false-negative rates of 2–4% in vivo (19–22). If sonographic correlates are found, the lesions should be sampled under sonographic guidance, which have several advantages over MRI-guided procedures. RVS is one of the procedures that allow a prompt and evidence-based approach to IELs. Accurate assessment of IELs using RVS might avoid unnecessary mastectomy or wider excisions with resultant poorer cosmetic outcomes.

RVS does not require any cumbersome preparation or extra time; RVS can be started within 5 min after setting up sonography equipment (data not shown). Furthermore, the RVS system is relatively simple; we are currently performing RVS on outpatient basis. The technique neither requires large equipment nor poses risk of exposure to radiation. It is clear that MRI-guided biopsy is an indispensable tool for detecting index tumors and IELs; however, we believe that RVS is useful for narrowing down and identifying the patients who truly need MRI-guided biopsy.

Because any DICOM data can be transferred to the RVS system, some RVS studies have reported using CT–DICOM data for detection or treatments for hepatocellular carcinoma (13,23–27) and renal cell carcinoma (28). This study is the first, to our knowledge, to transfer MRI–DICOM data to an RVS system for breast imaging.

Our study has several limitations. The RVS system synchronizes the images obtained by different imaging techniques used while a patient assumes the same physical position. Therefore, in order to synchronize the images obtained RVS with sonographic images, we imaged patients in the supine position. MRIs obtained in the prone position enable more detailed observations, because the mammary gland morphology is straightened. Furthermore, it is not easy to simulate the position of lesions, because the body position is not the same between operation and sonography. Some authors have reported the usefulness of pre-operative MRI taken in the supine position (29–31). However, this approach yields a lower-quality image, because MRIs obtained in a supine position can be blurred by respiratory movements or heartbeats. In addition, the MR coil that was used was produced for another purpose. Supine MRI has not been established as a diagnostic imaging technique; therefore, taking MRI in this position is not generally recommended. For this reason, upon MRI imaging a patient in the supine position, Nakamura et al. (30) suggested also obtaining MRI images of the same patient in the prone position, in order to compare these images with standard MRI. In this study, we performed RVS while monitoring supine MRI, by using multidetector-row computed tomography (MDCT) in the supine position, an imaging technique established for diagnosis of the extent of breast cancer before or after neoadjuvant chemotherapy (32), on the same patient (data not shown). MDCT is known to have a sensitivity equivalent to MRI in identifying invasive ductal carcinoma, and a...
sensitivity slightly inferior to MRI in the identification of ductal carcinoma in situ (33,34).

Because of its softness, it is inevitable that the breast will change shape; however, when the probe operation is conducted gently, these shape changes do not adversely affect synchronization between the two imaging techniques. Respiratory movement hardly affects either one. The gap between the true sonography image and the virtual image in the index tumor was within ~7 mm (data not shown), which is acceptable for practical application without any problems.

In conclusion, RVS can synchronize sonography image and the MRI image in the same section in real time. By using RVS, we can accurately project enhancing MRI information onto the body surface, as we are checking sonographic morphology. Our study suggests that the two different forms of diagnostic imaging can be integrated in real time, and thereby complement each other using RVS. RVS is a diagnostic imaging system that can overlay high-resolution structural images taken by sonography with functional images reflecting the amount of imaging agent due to vascular hyperpermeability taken by MRI. Therefore, we believe that in the future, the RVS system may become a useful tool for mammary diagnostics, especially at second-look sonography. To verify its utility, larger scale multi-institutional studies should be conducted in order to evaluate the RVS system for diagnostic imaging for breast cancer.

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Conflict of interest statement

None declared.

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