Magnetic Resonance Imaging Combined With Second-look Ultrasonography in Predicting Pathologic Complete Response After Neoadjuvant Chemotherapy in Primary Breast Cancer Patients

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Abstract

Magnetic resonance imaging (MRI) or ultrasonography (US) alone is limited in the ability to predict the pathologic complete response (pCR) accurately after neoadjuvant chemotherapy. We found that MRI combined with second-look US for predicting pCR was useful compared with MRI alone, especially for estrogen receptor-negative/human epidermal growth factor receptor-positive tumors. However, it was difficult to predict the residual in situ component.

Background: Magnetic resonance imaging (MRI) or ultrasonography (US) alone is limited in the ability to predict the pathologic complete response (pCR) accurately after neoadjuvant chemotherapy (NAC). The aim of the present study was to predict the pCR using MRI combined with second-look US in primary breast cancer patients. **Materials and Methods:** A total of 1274 consecutive primary breast cancer patients who were examined by MRI and second-look US before and after NAC and had undergone breast-conserving surgery from 2004 to 2014 were included. The positive predictive value (PPV) of a clinical complete response (cCR) by MRI alone and MRI plus US was assessed. A CR was defined as no residual invasive carcinoma. The presence of a residual in situ component was also assessed (ypTis). **Results:** Of the 1274 patients, 333 (26.1%) had a pCR (ypT0/is), and 102 (8.0%) had a residual in situ component (ypTis). A cCR was found in 247 patients (19.4%) using MRI alone and in 182 patients (14.3%) using MRI plus US. The PPV for a cCR using MRI alone was 79.4% and the PPV for MRI plus US was 86.8%. The PPV for a cCR by MRI plus US was the greatest at 98.1% in the estrogen receptor-negative (ER^-)/human epidermal growth factor receptor-positive ($HER2^+$) group (86.5% in the $ER^+/HER2^+$, 83.0% in the $ER^-/HER2^-$, and 64.7% in the $ER^+/HER2^-$ groups). The PPV for residual in situ component was as low as 72.2%. **Conclusion:** Our results have shown that MRI combined with second-look US in predicting for a pCR was useful compared with MRI alone, especially for $ER^-/HER2^+$. However, it was difficult to predict for the presence of a residual in situ component. Our ongoing prospective multi-institutional study has shown that adding vacuum-assisted biopsy to MRI plus second-look US is warranted to improve the prediction of pCR for omitting breast surgery.

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Introduction

Neoadjuvant chemotherapy (NAC) is 1 of the standard treatments for primary breast cancer patients. The benefits of using NAC include decreasing the tumor size and increasing the rate of breast-conserving surgery.[1] Recent advances in NAC, especially the addition of an anti-human epidermal growth factor receptor (HER2) agent for $HER2^+$ breast cancer, have increased the rate of the pathologic complete response (pCR).[2] Several studies have shown that patients who achieved a pCR after NAC had a significantly more favorable prognosis.[3-5] However, it has been revealed that the response to NAC and the prognostic effects on pCR depends on the breast cancer subtype.[2,4,6-8]

Patients who achieved a clinical complete response (cCR) with NAC must still undergo surgical treatment in current clinical practice because the radiologic findings cannot confirm the presence of pCR. The response to NAC is radiologically assessed using mammography, magnetic resonance imaging (MRI), ultrasonography (US), or computed tomography. However, the best method to use to predict for a pCR has not been established. Several studies have reported that MRI alone was limited in the ability to predict pCR.[9] Recently, the utility of second-look US with consideration of the MRI findings has been revealed.[10] We hypothesized that breast surgery could be omitted if pCR of primary breast cancer could be accurately predicted after NAC. Thus, as a first step, the aim of the present study was to predict the pCR after NAC using MRI combined with second-look US compared with MRI alone in patients with primary breast cancer.

Materials and Methods

Patients

A total of 1274 consecutive patients with stage I to III primary breast cancer who had been examined using both MRI and second-look US before and after NAC and had undergone breast-conserving surgery from 2004 to 2014 were included in the present study. Those patients who had been assessed by MRI or US alone, who had bilateral breast cancer, and/or who had had an initial diagnosis of stage IV breast cancer were excluded. Lymph node metastases were not considered in the present study because the axillary lymph node status after NAC might confer a different prognostic effect than the presence of residual primary breast cancer.[8] Also, no breast surgery after achieving pCR of primary breast cancer might improve patients' cosmetic, economic, mental, and physical issues rather than the prognosis.

The patients received an anthracycline and taxane regimen in NAC setting. All data for the present study were retrospectively collected from a single-institution database. Our institutional review board approved the present study, which had waived the need for written informed consent because of the retrospective nature of the study.

Radiologic Assessment

The MRI and US findings were assessed by 2 board-certified breast imaging radiologists with $>$ 15 years of experience. US was performed by radiologists with $>$ 15 years of experience. A cCR determined from radiologic findings was defined as no invasive carcinoma regardless of the presence of a residual in situ component (ycT0/is). The presence of a residual in situ component was also assessed (ypTis). The radiologic findings were assessed prospectively in clinical practice. We excluded the use of mammography to assess the response to NAC from the present study, because we performed mammography after NAC only for patients with tumor with microcalcifications on mammography before NAC during the study period.

MRI examinations were performed as described in a previous study.[9] In brief, we used a 1.5T to 3.0T MRI unit (GE Health Care, Chicago, IL; Siemens Healthineers, Erlangen, Germany) with dedicated 4- or 8-channel (GE Health Care) and 32-channel (Siemens Healthineers) breast array coils. Patients underwent MRI in the prone position. The imaging protocol consisted of high-resolution precontrast imaging and dynamic contrast-enhanced imaging in the axial plane before and 60, 180, 300, and 420 seconds after starting an intravenous injection of meglumine gadopentetate. A cCR by MRI was diagnosed if the lack of gadolinium enhancement or any enhancement was observed in any phase of the MRI study (ycT0). Spotted, linear, or trabecular lesions that enhanced on the late phase with loss of vascularity on MRI findings were suspected to indicate residual in situ carcinoma (ycTis).

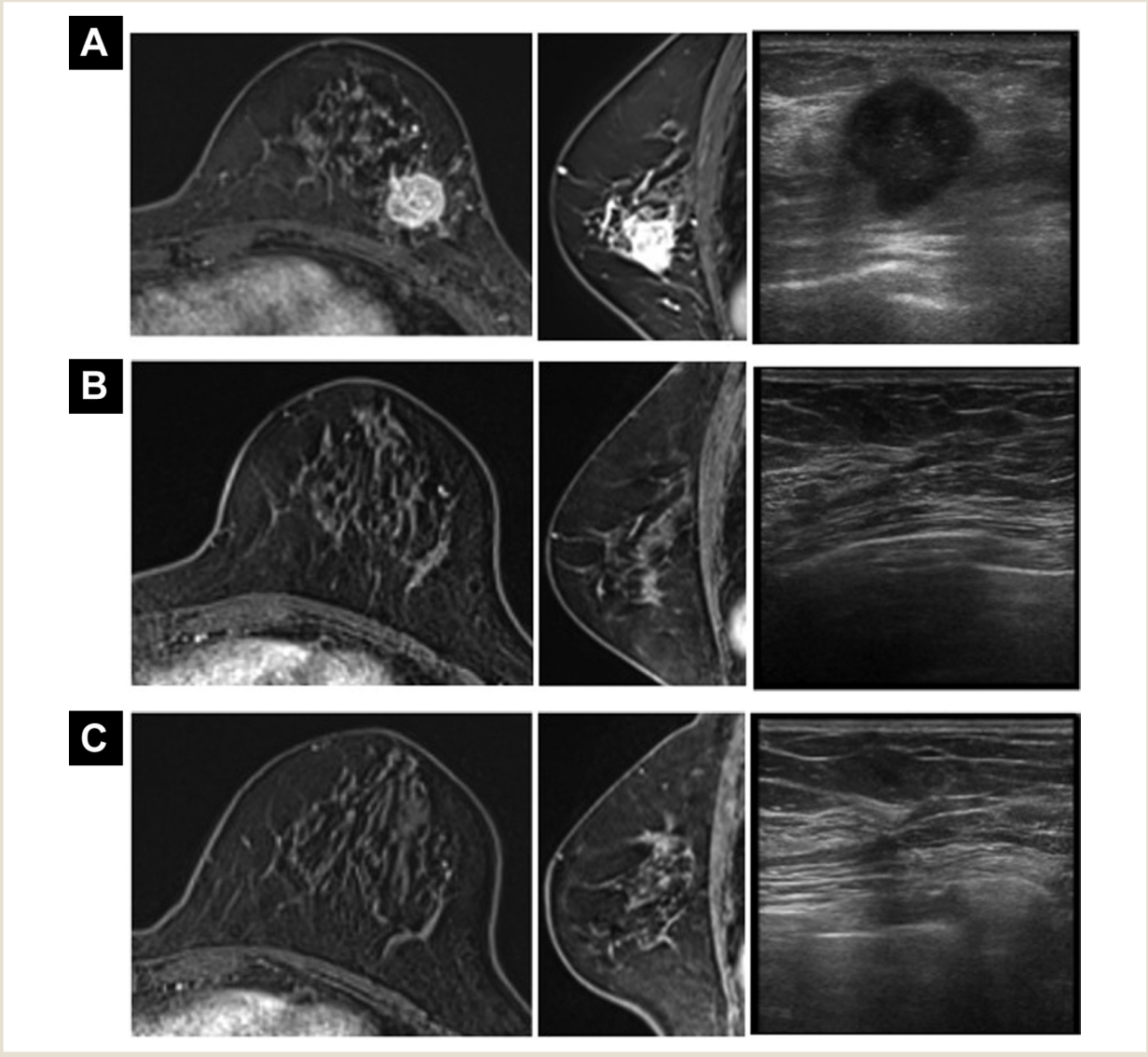
Second-look US with consideration of the MRI findings was also performed as described in previous studies.[10,11] Breast US was performed using LOGIQ 7 (probe frequency, 10 MHz; GE), HDI 5000 (probe frequency, 12 MHz; Phillips), SSA 790A (probe frequency, 12 MHz; Toshiba Medical Systems), and EUB 7500 (probe frequency, 14 MHz; Hitachi Medical). A cCR by US was diagnosed if a collapse of a low echoic lesion with the loss of vascularity, high compressibility, and changes in the tumor regions of interest were observed[11] (Figure 1). Low echoic lesions without the loss of vascularity detected by US were suspected to be residual in situ carcinoma (ycTis).

Pathologic Assessment

Invasive breast cancer was histologically confirmed on biopsy specimens before NAC, and the nuclear grade and estrogen receptor (ER) and progesterone receptor (PR) status were determined using immunohistochemistry (IHC). ER/PR status was considered positive if the Allred score was ≥ 3 or if the cutoff of $\geq$ 10% of the cells had nuclear staining for the receptor on immunohistochemical analysis.[12] HER2 status was determined using IHC and/or fluorescent in situ hybridization assays. HER2 positivity was defined as a receptor overexpression staining score of 3+ on IHC or as gene amplification using fluorescent in situ hybridization with a CEP-17 ratio $>$ 2.0. Patients were categorized into the following 4 subtypes according to the ER and HER2 status: $ER^+/HER2^-$ tumors, $ER^-/HER2^-$ tumors, $ER^+/HER2^+$ tumors, and $ER^-/HER2^+$ tumors.

The presence of a pCR in the primary tumor of the breast was defined as no residual invasive carcinoma, regardless of the presence of ductal carcinoma in situ and lymph node status. In addition, for the pCR patients, the presence of a residual in situ component was also assessed (ypT0/is). Immunohistochemical stains (cytokeratin AE1/AE3) were used to identify the presence of residual tumor cells, if necessary.

Figure 1 Magnetic Resonance Imaging and Ultrasound Scans (A) Before, (B) During, and (C) After Neoadjuvant Chemotherapy (NAC) in Primary Estrogen Receptor-Negative (ER^-)/Human Epidermal Growth Factor Receptor-Positive ($HER2^+$) Primary Breast Cancer Patients Who Had Received Weekly Paclitaxel for 12 Cycles With Trastuzumab, Followed by FEC (5-Fluorouracil, Epirubicin, Cyclophosphamide) for 4 Cycles in the NAC Setting and Achieved ycT0/ypT0



Statistical Analysis

The positive predictive value (PPV), sensitivity, and specificity of a cCR using MRI alone and MRI combined with US were assessed according to the breast cancer subtype. Each parameter was correlated with a pCR (ycT0/is) using a 2-sided Fisher's exact test. All statistical analyses were performed using SPSS software, version 23 (IBM, Armonk, NY). *P* values $< .05$ were considered statistically significant.

Results

Patient Characteristics

The clinicopathologic characteristics of the patients are summarized in Table 1. The median age was 49 years (range, 23-80 years). The breast cancer subtype was $ER^+/HER2^-$ in 719 patients (56.4%), $ER^+/HER2^+$ tumor in 132 patients (10.4%), $ER^-/HER2^+$ in 129 patients (10.1%), and $ER^-/HER2^-$ in 272 patients (21.4%). Of the 161 HER2 patients, 110 (68.3%) had received trastuzumab in the NAC setting. Of the 1274 patients, 333 (26.1%) had pCR (ypT0/is), and 102 (8.0%) had a residual in situ component (ypTis). The median maximum size of the residual tumor was 1.7 cm (range, 0.01-8.0 cm).

cCR by MRI Alone and MRI Combined With Second-look US

A cCR (ycT0/is) was found in 247 patients (19.4%) using MRI alone and 182 patients (14.3%) using MRI plus US (Figure 2).

Table 1 Patient and Clinicopathologic Characteristics Total (n = 1274)

Characteristic	n (%)
Age, y	
Median	49
Range	23-80
Clinical tumor size	
cT1	209 (16.4)
cT2	897 (70.4)
cT3	120 (9.4)
cT4	46 (3.6)
NA	2 (0.2)
Clinical stage	
I	75 (5.9)
IIA	472 (37.0)
IIB	478 (37.5)
IIIA	144 (11.3)
IIIB	31 (2.4)
IIIC	72 (5.7)
NA	2 (0.2)
Clinical response	
cCR	182 (14.3)
In situ negative	97 (7.6)
In situ positive	85 (6.7)
Non-cCR	1092 (85.7)
Pathologic response	
pCR	333 (26.1)
In situ negative	231 (18.1)
In situ positive	102 (8.0)
Non-pCR	941 (73.9)
Subtype	
$ER^+/HER2^-$	719 (56.4)
$ER^+/HER2^+$	132 (10.4)
$ER^-/HER2^+$	129 (10.1)
$ER^-/HER2^-$	272 (21.4)
NA	22 (1.7)
Chemotherapy regimen	
Anthracycline + taxane	1123 (88.1)
Anthracycline only	11 (0.9)
Taxane only	90 (7.1)
Other	50 (3.9)
Trastuzumab	110 (8.6)

Abbreviations: cCR = clinical complete response; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; NA = not assessed; pCR = pathologic complete response; PPV = positive predictive value.

Of the 247 patients with a cCR using MRI alone, 196 patients (79.4%) had a pCR. Of the 182 patients with a cCR using MRI plus US, 154 (84.6%) had a pCR. The PPV for MRI plus US was 86.8% and the PPV for MRI alone was 79.4% (Table 2). Because of these results, further assessment of the response to NAC according to breast cancer subtype was performed using MRI plus US. A cCR was found in 34 of 719 patients (4.7%) with $ER^+/HER2^-$ cancer (PPV, 64.7%), 37 of 132 patients (28.0%) with $ER^+/HER2^+$ cancer (PPV, 86.5%), 52 of 129 patients (40.3%) with $ER^-/HER2^+$ cancer (PPV, 98.1%), and 59 of 272 patients (21.7%) with $ER^-/HER2^-$ cancer (PPV, 83.0%; Table 3).

Prediction of Residual In Situ Component

In terms of the prediction of a residual in situ component using MRI plus US, of the 97 patients with ycT0, 70 (72.2%) had ypT0, 13 (13.4%) had ypTis, and 14 (14.4%) had residual invasive carcinoma. Of the 85 patients with ycTis, 23 (27.1%) had ypT0 and 48 (56.5%) had ypTis (Table 4). The PPV of ypTis was 72.2%.

Discussion

Our results showed that MRI combined with second-look US in predicting the pCR after NAC in primary breast cancer patients had a high PPV compared with MRI alone. The PPV was the greatest for $ER^-/HER2^+$ tumors.

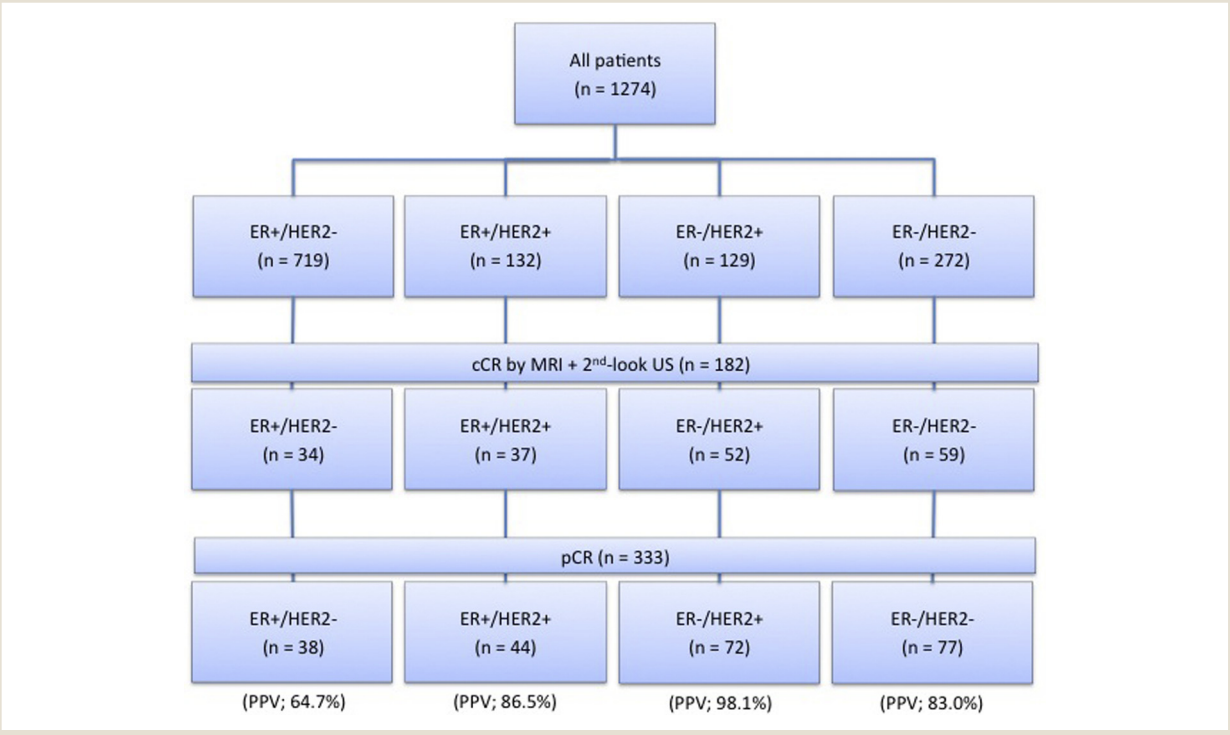
Previous studies have shown the accuracy of each imaging modality (MRI, US, mammography) for the prediction of pCR.[9,13-20] Namura et al[9] reported that MRI alone was insufficient to predict the pCR, regardless of the breast cancer subtype. A meta-analysis of 25 studies with a total of 1212 patients showed the difficulty of predicting for pCR using contrast-enhanced MRI alone, with 91% specificity for breast cancer and 63% sensitivity for predicting pCR.[21] Lesions with a loss of vascularity on MRI findings were considered negative for residual tumor because of the complete absence of contrast uptake.[22]

US was not considered suitable for assessing the response to NAC in terms of reproducibility and objectivity.[23,24] Recently, MRI and US were found to be similar but limited in their ability to accurately measure the size of the residual tumor after NAC.[25] In addition, a systematic review and meta-analysis has revealed the utility of second-look US with consideration of the MRI findings.[10] The loss of blood flow, fibrosis, or tissue necrosis after NAC has been reported to lead to under- or overestimation of the radiologic findings.[17,26] Furthermore, an assessment of the response to NAC is difficult owing to the various patterns of tumor shrinkage and complexity of invasive carcinoma and the in situ component even in the same breast cancer subtype.[27]

Several novel techniques to predict the response to NAC have been reported. Evans et al[28] found a significant relationship between the pretreatment tumor stiffness measured using shear wave elastography and the pathologic response to NAC. Contrast-enhanced US is also a promising method to assess the response to NAC.[29] Conventional radiologic findings, combined with these methods, might improve the accuracy of the prediction of pCR.

As numerous previous studies have reported, the accuracy of predicting pCR using the radiologic diagnosis from a single modality is insufficient to omit the need for breast surgery.[9,13-20] Therefore, in the present study, a combination of 2 modalities with different principles of image formation, MRI and US, was used to assess the response to NAC. To the best of our knowledge, no other study has assessed the residual in situ component after NAC using MRI combined with second-look US in patients who had achieved a pCR. However, differentiating the residual in situ component from invasive cancer using these conventional radiologic findings is difficult owing to the biologic and morphologic changes.

Figure 2 CONSORT (Consolidated Standards of Reporting Trials) Diagram Showing Patients Who Achieved Clinical Complete Response (cCR) Using Magnetic Resonance Imaging (MRI) Plus Second-Look Ultrasonography (US) After Neoadjuvant Chemotherapy (NAC) and Pathologic Complete Response (pCR) on Surgical Specimen for Each Subtype



These results suggest that pathologic intervention, in addition to MRI combined with second-look US, is needed to predict the complete pCR (ypT0) more accurately.

The definition for pCR has been not standardized in clinical trials. Some studies defined pCR to include residual noninvasive cancer.[30,31] However, another group defined pCR as no residual invasive or noninvasive cancer,[32] and the prognostic effect of the residual in situ component remains controversial.[33] However, the association between the prognosis and the presence of a residual in situ component has been discussed in these studies after complete surgical resection of the tumor. For our purpose of omitting breast surgery, the accurate diagnosis of the residual in situ component would be fundamental because of the risk of local recurrence with tumor invasiveness. In addition, we conducted and validated a model to predict for locoregional recurrence in patients without a pCR after NAC.[34] In that study, locoregional recurrence after NAC indicated a poor prognosis. Therefore, complete resection is mandatory if any residual tumor is present after NAC, and absence of a residual in situ component must be confirmed to be able to omit breast surgery.

For the purpose of omitting breast surgery, the priority is not to increase the pCR rate among patients who have received NAC but to improve the accuracy of the prediction of pCR among patients who have achieved a cCR. Therefore, we assessed the PPV to predict the pCR rather than the sensitivity of pCR using the radiologic findings.

Table 2 Prediction of Pathologic Complete Response Using MRI Alone or Combined With Second-Look US

Clinical Response	Pathologic Response, n			PPV, %	Sensitivity, %	Specificity, %
	pCR	Non-pCR	Total			
MRI alone				79.4	84.8	95.1
cCR	196	51	247			
Non-cCR	35	992	1027			
MRI + US				86.8	66.6	97.3
cCR	154	28	182			
Non-cCR	77	1015	1092			

Abbreviations: cCR = clinical complete response; MRI = magnetic resonance imaging; pCR = pathologic complete response; PPV = positive predictive value; US = ultrasonography.

Table 3 Prediction of Pathologic Complete Response Using MRI and Second-Look US Stratified by Breast Cancer Subtype

Clinical Response	Pathologic Response, n			PPV, %	Sensitivity, %	Specificity, %
	pCR	Non-pCR	Total			
$ER^+/HER2^-$ (n = 719)				64.7	57.9	85.6
cCR	22	12	34			
Non-cCR	16	669	685			
$ER^+/HER2^+$ (n = 132)				86.5	72.7	94.3
cCR	32	5	37			
Non-cCR	12	83	95			
$ER^-/HER2^+$ (n = 129)				98.1	70.8	98.2
cCR	51	1	52			
Non-cCR	21	56	77			
$ER^-/HER2^-$ (n = 272)				83.0	63.6	94.9
cCR	49	10	59			
Non-cCR	28	185	213			

Abbreviations: cCR = clinical complete response; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; pCR = pathologic complete response; PPV = positive predictive value.

Next, with consideration of the size of residual tumor, we hypothesized that pathologic intervention using vacuum-assisted breast biopsy (VAB), in addition to radiologic findings, would improve the accuracy of predicting pCR. Based on the results from the present study, a multicenter prospective trial to confirm the accuracy of cCR using MRI combined with second-look US and to assess the predictive value of adding VAB to the radiologic findings is ongoing.

The present study had some limitations. These included a retrospective study design, a single-institution study, the objectivity of the radiologic findings, and the nonstandardization of the modalities used to assess the response to NAC. Therefore, radiologic and pathologic central reviews have been included in our ongoing prospective study to enhance the objectivity. It is challenging to standardize the protocols for MRI and US. However, in the present study, the imaging studies were performed using the same definition of cCR and several types of MRI and US equipment owing to the long study period. Therefore, the definition of cCR might be acceptable for universal use, regardless of the modalities in multi-institution studies. These findings will be also confirmed in our prospective study. Also, the use of trastuzumab for primary breast cancer became available in 2008 in Japan. Therefore, only 110 of 261 of $HER2^+$ patients (42.1%) had received trastuzumab in the present study. This might have affected the relatively low pCR rate compared with the current standard.

Table 4 Prediction of Residual In Situ Component Using MRI and Second-Look US

cCR	Pathologic Response			
	pCR/In Situ Negative	pCR/In Situ Positive	IDC Positive	Total
In situ negative	70	13	14	97
In situ positive	23	48	14	85

Abbreviations: cCR = clinical complete response; IDC = invasive ductal carcinoma; pCR = pathologic complete response.

Regarding our hypothesis, an accurate assessment of the pCR is required to omit breast surgery for patients achieving a cCR. The next step is to predict pCR more accurately. Thus, in addition to our phase II prospective study using VAB based on the radiologic MRI findings combined with second-look US, several prospective clinical trials using VAB, core needle biopsy, or MRI-guided biopsy are ongoing (ClinicalTrials.gov identifiers, NCT03188393, NCT03289195, NCT03273426, NCT03289195, and NCT03273426).

Conclusion

Our results have indicated that MRI combined with second-look US could be useful in predicting pCR after NAC in primary breast cancer patients, especially $ER^-/HER2^+$ patients. However, it remained difficult to predict the presence of residual in situ carcinoma. Our ongoing prospective multi-institutional study with the addition of VAB is warranted to improve the prediction of pCR.

Clinical Practice Points

- NAC is 1 of the standard treatments for primary breast cancer patients.
- It has been revealed that the response to NAC depends on the breast cancer subtype.
- Patients with a cCR to NAC must undergo surgical treatment in current clinical practice because the radiologic findings cannot confirm a pCR.
- We hypothesized that breast surgery could be omitted if the pCR of primary breast cancer could be accurately predicted after NAC; however, MRI and US alone have limited ability to predict the pCR after NAC.
- The aim of the present study was to predict the pCR after NAC using MRI combined with second-look US compared with MRI alone in primary breast cancer patients.
- The presence of a residual in situ component was also assessed (ypTis).
- To the best of our knowledge, no other study has assessed the residual in situ component after NAC using MRI combined with

second-look US in patients with a pCR stratified by breast cancer subtype.

- We found that MRI combined with second-look US for the prediction of pCR after NAC in primary breast cancer patients showed a high PPV compared with MRI alone.
- The PPV was the greatest for $ER^{-}/HER2^{+}$ tumors (98.1%); however, it was difficult to identify the residual in situ component using these conventional radiologic findings (PPV for ypTis, 72.2 %).
- Our ongoing prospective multi-institutional study with the addition of VAB is warranted to confirm these results and improve the prediction of pCR.

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Disclosure

The authors declare that they have no competing interests.

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