

Changes in background parenchymal enhancement in HER2-positive breast cancer before and after neoadjuvant chemotherapy

Association with pathologic complete response

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Abstract

This study aimed to analyze the relationship between pathologic complete response (pCR) and changes in background parenchymal enhancement (BPE) levels in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer and who received neoadjuvant chemotherapy (NAC).

The pre- and post-NAC magnetic resonance imaging results of 51 patients with confirmed unilateral HER2-positive breast cancer were retrospectively analyzed by 2 experienced radiologists. Pre- and post-NAC of contralateral BPE levels were classified into 4 categories (1 = minimal, 2 = mild, 3 = moderate, and 4 = marked). The 4 categories of BPE were defined by the visually estimated enhancement of fibroglandular tissue of the breast. Changes in BPE before and after NAC were compared between the premenopausal and postmenopausal groups and between the pCR and non-pCR groups. The associations between BPE and pCR and between BPE and tumor size were analyzed before and after NAC.

Twenty-three patients achieved pCR, and 28 patients achieved non-pCR. Premenopausal patients had significantly higher baseline BPE levels than postmenopausal women ($P = .023$). The post-NAC BPE levels of premenopausal patients significantly decreased relative to those of postmenopausal patients ($P = .027$). The baseline BPE levels of the pCR group were not significantly different from those of the non-pCR group ($P = .892$). However, the decrease in BPE levels in the pCR group was more drastic than that in the non-pCR group ($P < .001$). Decreased BPE levels were directly associated with pCR and tumor size reduction ($P < .05$). Women with hormone receptor (HR)-negative tumors were more likely to exhibit pCR than those with HR-positive tumors ($P = .007$).

Decreased BPE of patients with HER2-positive breast cancer may serve as an indicator of NAC effectiveness. Furthermore, women with HR-negative tumors were more likely to exhibit pCR than women with HR-positive tumors.

Abbreviations: BPE = background parenchymal enhancement, DCE-MRI = dynamic contrast-enhanced magnetic resonance imaging, ER = estrogen, FISH = fluorescence in situ hybridization, HER2 = human epidermal growth factor receptor 2, HR = hormone receptor, HRT = hormone replacement therapy, IDC = invasive ductal cancer, IHC = immunohistochemical, NAC = neoadjuvant chemotherapy, NME = nonmass enhancement, pCR = pathologic complete response, PR = progesterone.

Keywords: background parenchymal enhancement, breast cancer, HER2-positive, MRI, neoadjuvant chemotherapy, pathologic complete response

1. Introduction

Breast cancer seriously affects the health of women worldwide and is the commonly reported malignant tumor among women.

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The prevalence of breast cancer has gradually increased in recent years. Human epidermal growth factor receptor 2 (HER2)-positive breast cancer has been shown to be 20% to 25% of all breast cancer cases.^[1]

Neoadjuvant chemotherapy (NAC) is a treatment for operable breast cancer.^[2] This method can induce pathologic complete response (pCR) and improve long-term prognosis among patients with HER2-positive breast cancer.^[3,4] An accurate assessment of tumor response to NAC is important to determine and manage follow-up treatment. Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is used to monitor the post-NAC response of patients with breast cancer.^[5,6] A breast MRI report should first describe the amount of fibroglandular tissues, and background parenchymal enhancement (BPE) is defined as the enhancement of normal breast tissues after contrast injection in DCE-MRI.^[7] Research has shown that BPE does not decrease the cancer detection rate but increases the call-back rate, and it is recommended by breast imaging and reporting data system.^[8]

BPE levels can be affected by age, menopausal status, menstrual cycle, and hormone therapy.^[9–11] For example, the BPE levels of patients aged more than 50 years tend to be lower than those of patients aged less than 50 years.^[12] The BPE levels of postmenopausal women are significantly lower than those of

premenopausal women.^[13] BPE is the lowest at the second week of the menstrual cycle.^[10] The BPE level decreases following tamoxifen treatment and is increased by hormone replacement therapy (HRT) in postmenopausal women.^[9,14] NAC can affect the BPE levels of normal breast and breast cancer tissues; thus, BPE levels may reflect the therapeutic response or prognosis of patients with cancer.^[15–17] Patients with higher pre-NAC BPE levels have been shown to have poor recurrence-free survival.^[16] The higher degree of BPE reduction after NAC is associated with good tumor response (Response Evaluation Criteria in Solid Tumors 1.1 criteria).^[17] The reduction in the BPE levels during the early stage of NAC is positively associated with pCR, particularly in patients with hormone receptor (HR)-negative cancer.^[18]

Previous studies mostly focused on the relationship between tumor size or pCR and change in BPE for various phenotypes of breast cancers.^[19,20] Different phenotypes and pathological types of breast cancer may result in alteration in BPE. HER2-positive breast cancer is associated with higher metastases and mortality rates, shorter disease-free survival, and lower overall survival rate.^[21] Thus, the effect of NAC is crucial to HER2-positive breast cancer. We studied unilateral invasive ductal breast cancer of HER2-positive breast cancer to develop a novel approach to BPE for predicting pCR.

This study aimed to analyze changes in the BPE levels of contralateral normal breast with HER2-positive breast cancer during NAC and investigate whether the change in BPE could serve as an indicator of NAC effectiveness.

2. Materials and methods

2.1. Study subjects and treatments

Our retrospective study was approved by the Ethics Committee at the Affiliated Hospital of Binzhou Medical University. The

review of medical records or images does not require the consent of patient.

Patients who met the following inclusion criteria from August 2013 to February 2018 were retrospectively analyzed: underwent unilateral invasive ductal cancer (IDC) with HER2-positive tumor confirmed by preoperative core-needle biopsy and postoperative pathology of NAC; subjected to MRI examinations before and after NAC; and treated with neoadjuvant trastuzumab-based chemotherapy. The exclusion criteria are as follows: patients who did not undergo surgical treatment after NAC; patients with insufficient MRI data; and patients who had incomplete chemotherapy.

One hundred forty-five patients with breast cancer were treated with NAC and considered for the study. Of these, 8 patients were excluded; 3 patients did not undergo surgical treatment after NAC, 3 patients had insufficient MRI data, and 2 patients had incomplete chemotherapy. Of the remaining 137 patients, 89 patients had unilateral IDC with HER2-positive tumor, 59 patients were treated with neoadjuvant trastuzumab-based chemotherapy, and 51 patients underwent MRI examinations before and after NAC. Finally, 51 patients were included in the analysis. Our study sample included 51 patients with a mean age of 46.24 ± 8.79 years and an age range of 27 to 63 years (Fig. 1).

The chemotherapy protocols were standardized as follows: docetaxel, carboplatin, and trastuzumab ($n=29$); and doxorubicin, cyclophosphamide, docetaxel, and trastuzumab ($n=22$). These patients received at least 6 or 8 cycles of NAC followed by surgical operation. No patients received HRT or radiation therapy prior to surgery.

2.2. Breast MRI

Breast MRI was performed with patients in the prone position by using a 3.0 T MRI (Skyra, Siemens, Munich, Germany) with a 4-

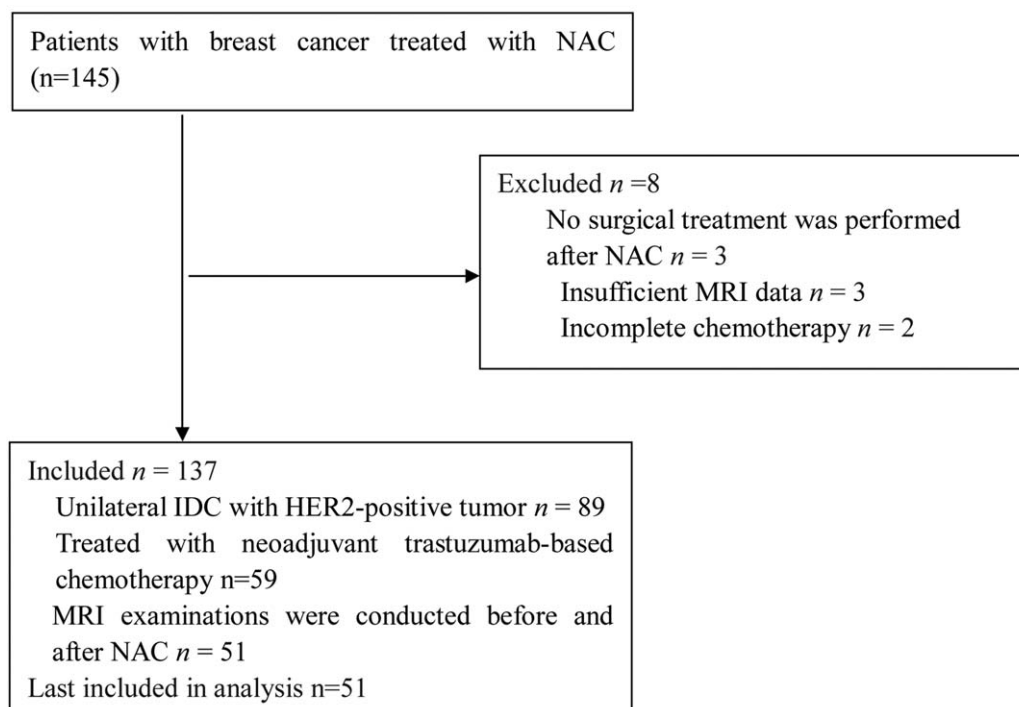


Figure 1. Patient selection.

channel dedicated breast coil. All patients underwent routine MRI sequences and DCE-MRI before and after NAC. The routine MRI sequences consisted of T1 gradient echo sequence (repetition time of 169.0 ms, echo time of 2.61 ms, field of view of 340 mm, matrix of 352 × 246, slice thickness of 4 mm, flip angle of 70°, and 2D SPGR) and T2-weighted fat-suppressed sequence (repetition time of 3630 ms, echo time of 68 ms, field of view of 340 mm, matrix of 320 × 240, slice thickness of 4 mm, and flip angle of 80°). DCE-MRI consisting of 1 phase before enhancement and 7 phases after enhancement was performed by using volumetric interpolated breath-hold examination sequence (repetition time of 4.49 ms, echo time of 1.68 ms, field of view of 340 mm, matrix of 352 × 260, slice thickness of 1.2 mm, and flip angle of 10°). At 12 s after the first phase, 0.2 mL/kg gadopentetate dimeglumine (Germany, Berlin, Schering Co, Ltd (SCHERING)) was injected at a rate of 2.5 mL/s into the median cubital vein by using an antecubital vein pressure injector. The injection was followed by a 20 mL saline flush. The enhancement parameters of the 5 phases after enhancement were identical to those of the first sequence. Subtraction and maximum intensity projection images were obtained. All images were acquired with bilateral axial views. Tumor size was measured at the first phase after injecting the contrast material. BPE was assessed using subtraction images, and the time point was the first phase after contrast material injection. To prevent treatment delay, cycle status was not taken into account when scheduling MRI; thus, we did not analyze the effect of the menstrual cycle on BPE levels.^[17]

2.3. Data collection

The baseline characteristics of the patients were noted; the following data were obtained: age, largest tumor diameter, menopausal status, HR status (estrogen (ER), progesterone (PR)), clinical T stage, clinical N stage, and histologic grade (Table 1). HR-positive status was defined as ≥10% ER and/or PR expression; otherwise, the status is negative.^[22]

A mass is 3D and occupies space structure. Nonmass enhancement (NME) is the enhancement of an area that is not a mass and may extend over small or large regions, whose internal enhancement characteristics can be described as a pattern discrete from the normal surrounding breast parenchyma.^[7] The largest tumor diameter of mass and NME was measured. Post-NAC reduction in tumor size on MRI was calculated as follows: $\Delta\text{size} = (\text{tumor size}_{\text{post-NAC}} - \text{tumor size}_{\text{pre-NAC}}) / \text{tumor size}_{\text{pre-NAC}} \times 100\%$.

All images were reviewed by 2 radiologists who were blinded to the patients' information. The 2 radiologists had 6 and 7 years of experience in assessing breast images. When opinions differed between the 2 radiologists, a consensus was reached on the overall assessment. The 4 categories of BPE are defined by the visually estimated enhancement of the fibroglandular tissue of the breast.^[7] BPE levels were categorized as 1=minimal, 2=mild, 3=moderate, and 4=marked before and after NAC. The 2 radiologists evaluated the BPE categories of the contralateral breast before and after NAC and in premenopausal and postmenopausal women. After NAC, the BPE levels were divided into 2 groups: unchanged and decreased BPE (no BPE levels increased). According to the BPE levels before and after NAC, the decreased BPE levels were further divided into 3 categories: 1 level, 2 levels, and 3 levels (For example, the BPE level was 4=marked before NAC and 1=minimal after NAC, the decreased BPE levels should be 3 levels).

Table 1

Patient baseline characteristics in pCR and non-pCR groups.

Characteristics	Total (n=51)	pCR (n=23)	Non-pCR (n=28)	P value
Age, y				
>50	21	10	11	.762
≤50	30	13	17	
Largest tumor diameter, mm	49.51 ± 12.61	44.30 ± 11.52	53.79 ± 12.02	.006
Menopausal status				
Premenopausal	27	14	13	.304
Postmenopausal	24	9	15	
HR status				
HR-positive	14	2	12	.007
HR-negative	37	21	16	
Clinical T stage				
T1	1	0	1	.340
T2	25	13	12	
T3	16	5	11	
T4	9	5	4	
Clinical N stage				
N0	4	1	3	.526
N1	33	17	16	
N2	10	3	7	
N3	4	2	2	
Histologic grade				
Grade I	1	1	0	.438
Grade II	38	17	21	
Grade III	12	5	7	

pCR = pathologic complete response.

2.4. Pathologic assessment

The final surgical specimen (lumpectomy versus mastectomy) was used to assess pCR, which was defined as no residual tumor or only ductal carcinoma in situ.^[23] HER2-positive was defined as standard immunohistochemical (IHC) 3+ or positive fluorescence in situ hybridization (FISH). If the IHC test of the patient was 3+, then the cancer was directly diagnosed as HER2-positive; if the IHC test result was 2+, then the result was confirmed through FISH. If the IHC test result was 1+ or 0, then the cancer was defined as HER2-negative.^[24] The assessment was performed by 2 experienced pathologists.

2.5. Statistical analysis

Statistical Package for Social Sciences 19.0 software (IBM Company, Illinois) was used for data analysis. The baseline characteristics of pCR and non-pCR groups were compared using Pearson χ^2 test and independent sample *t* test. Wilcoxon test was used to evaluate changes in BPE levels before and after NAC. Mann-Whitney *U* test was used to identify differences in BPE levels between premenopausal and postmenopausal groups and between pCR and non-pCR groups. Spearman rank correlation test was used to describe the correlation between changes in BPE levels and pCR, changes in BPE levels and tumor size, and tumor size reduction and pCR. All statistical tests were 2-sided, and *P* < .05 was considered statistically significant.

2.6. Interreader agreement

K-coefficient was used to evaluate the agreement between the 2 radiologists. The strength range of κ agreement was categorized as poor for < 0.00, slight for 0.00 to 0.20, fair for 0.21 to 0.40,

moderate for 0.41 to 0.60, substantial for 0.61 to 0.81, and almost perfect for 0.81 to 1.00.^[25]

3. Results

3.1. Patient characteristics

All the patients in the study were assigned to either the pCR group (n=23) or the non-pCR group (n=28). The largest tumor diameter observed in the pCR group was lower than that in the non-pCR group ($t=-2.856$, $P=.006$). Patients with HR-negative status were more likely to exhibit pCR than those with HR-positive status ($\chi^2=7.399$, $P=.007$). The remaining baseline characteristics of the 2 groups were not statistically significant ($P>.05$) (Table 1).

3.2. BPE levels in premenopausal and postmenopausal groups

Premenopausal (n=27) patients had higher baseline BPE levels ($Z=-2.279$, $P=.023$) than postmenopausal women (n=24). The post-NAC BPE level decreased in 81.48% (21 out of 27) of premenopausal patients ($Z=-4.289$, $P<.001$) and in 50% (12 out of 24) of postmenopausal patients ($Z=-3.276$, $P=.001$). The post-NAC BPE levels of premenopausal patients significantly

Table 2

Changes in BPE for premenopausal and postmenopausal status after NAC.

Baseline level of BPE	Unchanged	Decreased		
		1 level	2 levels	3 levels
Premenopausal				
Minimal (n=3)	3 (100)	0 (0)	0 (0)	0 (0)
Mild (n=12)	1 (8)	11 (92)	0 (0)	0 (0)
Moderate (n=8)	2 (25)	3 (37.5)	3 (37.5)	0 (0)
Marked (n=4)	0 (0)	1 (25)	1 (25)	2 (50)
Postmenopausal				
Minimal (n=5)	5 (100)	0 (0)	0 (0)	0 (0)
Mild (n=16)	7 (44)	9 (56)	0 (0)	0 (0)
Moderate (n=2)	0 (0)	1 (50)	1 (50)	0 (0)
Marked (n=1)	0 (0)	0 (0)	1 (100)	0 (0)

Numbers in parentheses () are percentages.

BPE = background parenchymal enhancement, NAC = neoadjuvant chemotherapy.

decreased relative to those of postmenopausal patients ($Z=-2.207$, $P=.027$) (Table 2).

3.3. BPE levels in pCR and non-pCR groups

Twenty-three patients achieved pCR, and 28 patients achieved non-pCR. There was no significant difference in the baseline BPE

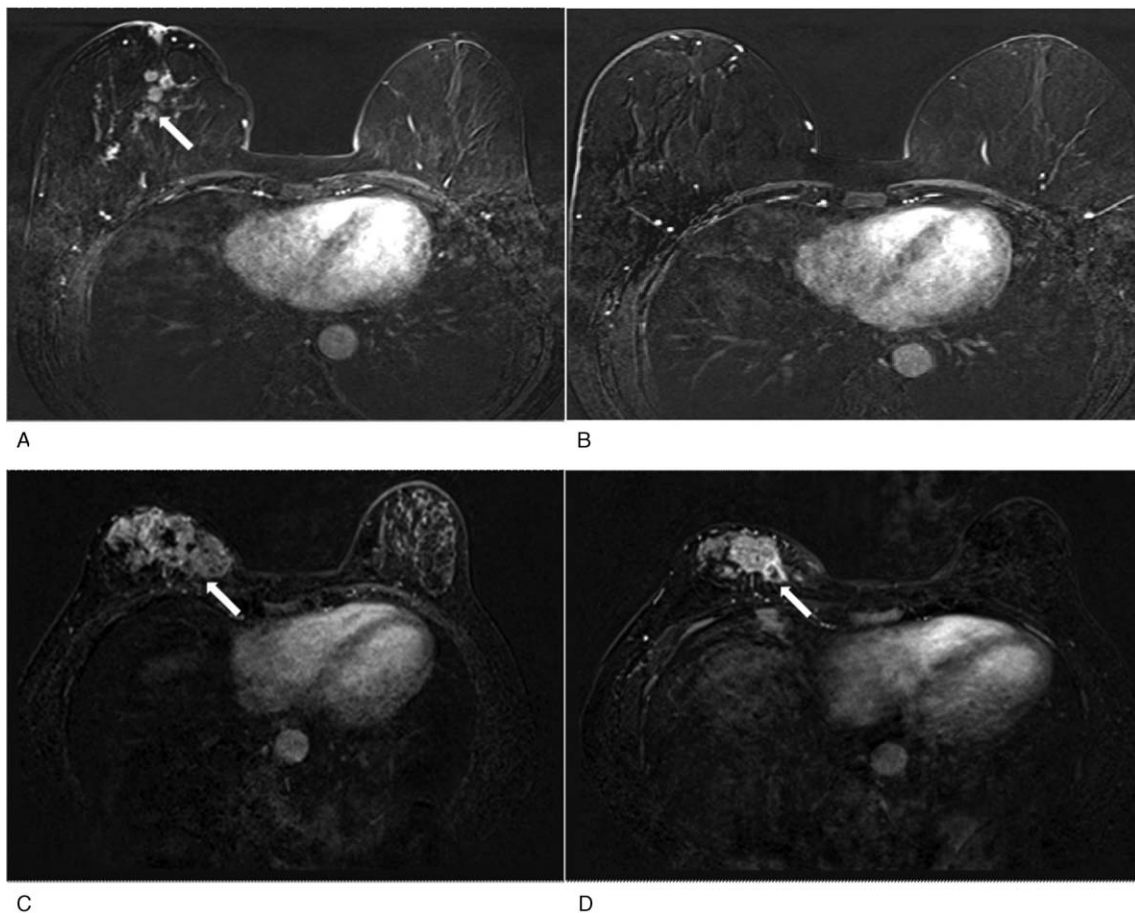


Figure 2. A 59-year-old woman with pCR after NAC. Before NAC, a 3.5 cm IDC in the right breast was noted (arrow). Subtraction image with minimal BPE before (A) and after (B) NAC. The mass completed MRI response to NAC. A 40-year-old patient with non-pCR after NAC, a 7.7 cm IDC in the right breast and 6.5 cm after NAC was noted (arrow). Subtraction image with mild BPE before (C) and minimal BPE after (D) NAC. IDC = invasive ductal cancer, NAC = neoadjuvant chemotherapy, pCR = pathologic complete response.

Table 3
Changes in BPE levels before and after NAC in pCR and non-pCR groups.

Baseline level of BPE	Unchanged	Decreased		
		1 level	2 levels	3 levels
pCR group				
Minimal (n=2)	2 (100)	0 (0)	0 (0)	0 (0)
Mild (n=16)	1 (6)	15 (94)	0 (0)	0 (0)
Moderate (n=3)	0 (0)	2 (67)	1 (33)	0 (0)
Marked (n=2)	0 (0)	0 (0)	1 (50)	1 (50)
Non-pCR group				
Minimal (n=6)	6 (100)	0 (0)	0 (0)	0 (0)
Mild (n=12)	4 (33)	8 (67)	0 (0)	0 (0)
Moderate (n=7)	1 (14)	5 (71)	1 (14)	0 (0)
Marked (n=3)	0 (0)	2 (67)	1 (33)	0 (0)

Numbers in parentheses () are percentages.

BPE = background parenchymal enhancement, NAC = neoadjuvant chemotherapy.

of the pCR and non pCR groups ($Z = -0.136$, $P = .892$). The post-NAC BPE levels decreased in 86.96% (20 out of 23) of the patients in the pCR group ($Z = -4.347$, $P < .001$) and in 60.71% (17 out of 28) of the patients in the non-pCR group ($Z = -3.900$, $P < .001$). The BPE level did not increase in any patient after NAC. Additionally, the decrease in the BPE level was more dramatic in the pCR group than in the non-pCR group (Fig. 2) ($Z = -2.013$, $P = .044$) (Table 3).

3.4. Correlation analysis

Baseline BPE levels and pCR were not significantly correlated ($r = 0.019$, $P = .894$). However, post-NAC BPE levels and pCR were significantly correlated ($r = 0.322$, $P = .021$). Specifically, the post-NAC decrease in the BPE level was correlated with pCR ($r = -0.285$, $P = .043$).

Baseline BPE levels and tumor size were not significantly correlated ($r = 0.066$, $P = .644$) but were significantly correlated after NAC ($r = 0.389$, $P = .005$). The decrease in the BPE level and the reduction in tumor size after NAC were significantly correlated ($r = 0.333$, $P = .017$). Tumor size reduction and pCR were also significantly correlated ($r = 0.692$, $P < .001$).

3.5. Interreader agreement

A substantial interreader agreement regarding BPE level was observed ($\kappa = 0.773$ at baseline; $\kappa = 0.706$ after NAC).

4. Discussion

We demonstrated that the decrease in the BPE levels after NAC is significantly related to pCR in 51 patients with HER2-positive breast cancer. Studies using qualitative analysis have demonstrated that the degree of change in BPE after NAC may predict tumor response.^[17] Thus, the change in BPE could influence treatment protocols, adjusting NAC regimens, and surgical approach. However, whether the changes in BPE before and after NAC can be used to predict pCR in HER2-positive breast cancer remains unclear.

BPE does not decrease the cancer detection rate, but moderate and marked BPE levels are associated with inaccurate MRI-based estimation of tumor size.^[26] Therefore, we evaluated BPE levels in the contralateral breasts of patients with HER2-positive breast

cancer. However, given that our study is a retrospective study, we could not determine the menstrual cycle stage of the patients at the time of MRI and menstruation may affect the higher decrease in the premenopausal group. Although we were unable to analyze the effects of the menstrual cycle on BPE level, we considered the effect of menopausal status. The low baseline BPE levels in the postmenopausal group may be attributed to the low estrogen levels of the women. After NAC, the BPE levels of premenopausal and postmenopausal women decreased, and the decrease was more drastic in premenopausal women than in postmenopausal women. These results may be attributed to decreased hormone levels due to ovarian suppression induced by NAC.^[27]

In a previous study, decreased BPE in breast MRI was correlated with pCR to NAC in patients with breast cancer, but no significant difference in post-NAC BPE and change in BPE were observed with molecular subtypes.^[28] The present study focused on HER2-positive breast cancer and analyzed the relationship between pCR and baseline and post-NAC BPE levels. We did not find any correlation between baseline BPE level and pCR. The baseline BPE levels in the contralateral breasts of patients with pCR are not significantly higher than those in the non-pCR groups.^[29] After NAC, however, the BPE levels in the pCR group significantly decreased, and the decreased BPE level was associated with pCR. A pathological study found that after 24 hours of NAC, the apoptosis of tumor cells increases and the proliferation of cells decreases.^[30] Studies using qualitative analysis demonstrated that the degree of change in BPE after NAC may be a predictor of tumor response; however, baseline pre-NAC BPE levels cannot predict tumor response.^[27] Therefore, the decrease in the BPE level may be a predictor of pCR. The association between decreased post-NAC BPE levels and pCR may be attributed to the following mechanism: chemotherapy via perfusion delivery increases breast vascular perfusion, enabling high amounts of drugs to reach the tumor and normal breast parenchyma. The drugs kill tumor cells and cause normal vascular injury, thereby decreasing the BPE level. Decrease in HER2-positive tumor size was associated with decreased BPE and with pCR. Tumor size on MRI could be used to predict pathological tumor response during NAC.^[18] The decrease in the BPE level could be used to predict tumor outcome with NAC.^[17,29] Hence, the change in tumor size may reflect the change in BPE levels during NAC.

We found that women with HR-negative tumors of HER2-positive breast cancer are more likely to attain pCR than those with HR-positive tumors. A possible explanation for this result is that HR status may be an important mechanism that mediates chemoresistance in HER2-positive breast cancer.^[31] Therefore, future research should focus on HR status.

Our present study has some limitations. First, we qualitatively analyzed BPE. This method is easily influenced by the subjectivity of the readers even if the 2 readers provide concurrent qualitative analytical results for BPE. Thus, in future studies, the conclusions should be validated through quantitative analyses. Second, this retrospective study involves a small population. Studies with a large number of patients are needed to further investigate the changes in BPE during NAC. Third, the MRI was not timed in the premenopausal patients, and this could influence the BPE categories determined.

In conclusion, the post-NAC decrement in the BPE levels in the contralateral breast of patients with HER2-positive breast cancer may be a predictor of pCR. In addition, patients with HR-negative tumors are more likely to attain pCR than those with HR-positive tumors. The association between the decrease in the

BPE level after NAC and the survival outcome of patients with HER2-positive breast cancer requires future investigation.

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