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EARLY PREDICTION OF RESPONSE TO NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER USING MRI

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ABSTRACT

Neoadjuvant chemotherapy (NAC) is the favored treatment of choice among locally advanced breast cancer patients because it significantly increases the possibility of breast-conserving surgery. However, for non-responders, an early prediction of response to NAC is essential. The purpose of this study was to determine whether an early prediction of response to NAC is possible using MRI. Eleven breast cancer patients (12 lesions) scheduled to receive NAC were recruited for this study. The patients were examined by MRI prior to and after the first and fourth courses of anthracycline-containing chemotherapy and after subsequent taxane-containing chemotherapy. Lesions were divided into 2 types (mass type and non-mass type) based on contrast MRI prior to chemotherapy. Among 8 mass types, 6 were responders (R) and 2 were non-responders (NR). R cases showed either an increased apparent diffusion coefficient (ADC) or volume reduction after the first course of NAC, whereas NR cases showed neither ($p<0.005$). Of the 4 non-mass types, 2 were R and 2 were NR. Changes in ADC or volume after the first course of NAC may indicate chemo-sensitivity for mass-type breast cancer. However, the same method cannot be used to predict the response to NAC for non-mass types.

Key Words: Breast cancer, Neoadjuvant chemotherapy, MRI, Response prediction

INTRODUCTION

Neoadjuvant chemotherapy (NAC) is the favored treatment of choice among locally advanced breast cancer patients because it significantly increases the possibility of breast-conserving surgery.[1-3] The European Organization for Research and Treatment of Cancer Trial (EORTC) Study 10902, a large randomized trial, reported that up to 23% of patients who were primarily unable to have breast-conserving surgery became capable of doing so by undergoing NAC.[2] However, considering the high toxicity and cost of chemotherapeutic drugs, an early assessment of the tumor's response to therapy is essential, especially for non-responders. In addition, if such non-responders could be predicted early in the NAC course, further increases in breast-conserving surgery rates may be possible by switching to an alternative regimen. Another advantage of NAC is its capability of monitoring chemo-sensitivity. Though large randomized studies, such

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as the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocols B-18 and B-27, suggest that pathological complete remission (pCR) is the only predictor of prognosis,[1,3] there are some reports of a correlation between the chemo-response for non-pCR and recurrence.[4,5] If the response rate relates to recurrence, an early prediction of chemo-response would be very informative in terms of prognosis as well.

The conventional technique for monitoring response to treatment in oncology is to measure tumor size. For breast cancer, physical palpation and ultrasonography are often used to monitor the response during NAC. However, recent studies have shown magnetic resonance imaging (MRI) to be superior to physical examination and ultrasonography for revealing the extent of breast cancer and for assessing residual disease after NAC.[6-8] Thus, MRI is widely chosen to diagnose residual disease after chemotherapy. When considering an early prediction of chemo-sensitivity, it is known that functional properties such as metabolism, vascularity, and cellularity change before structural changes become evident. From this perspective, MRI is superior to other examinations because of its potential to characterize the functional and biochemical properties of tumors with various techniques. In breast cancer, qualitative monitoring to detect early response to NAC is performed using 3 major techniques: dynamic contrast-enhanced MRI (DCE-MRI), MR spectroscopy (MRS), and diffusion-weighted imaging (DWI). DCE-MRI reveals drug-induced changes in tumor vascularity,[9-12] while MRS shows changes in the water/fat ratio and concentrations of choline-containing compounds in tumors.[13,14] DWI shows *in vivo* images of biological tissues weighted with the local microstructural characteristics of water diffusion. The apparent diffusion coefficient (ADC) is used to quantify the water diffusion, so that changes in ADC values may represent changes in the cellular density of tumors. Pickels et al. and Sharma et al. have reported that changes in the ADC value precede morphological changes.[15,16] However, Nilsen et al. have reported that ADC increases observed during NAC do not correlate with chemo-response.[17] This disagreement concerning the change in the ADC value and its correlation to chemo-sensitivity may derive from the pathological diversity of breast cancer. In this study, breast cancer was classified into mass and non-mass types prior to NAC based on the definition of the Breast Imaging Reporting and Data System MRI (BI-RADS-MRI) Guidelines.[18] The shrinkage pattern, ADC values, and volumetric changes were then observed to determine if an early prediction of clinical response is possible for patients with these 2 types of tumors.

MATERIALS AND METHODS

Patients and chemotherapy

From July 2008 to December 2009, female patients aged 38–69 years (mean 54 years) with stage II or III breast cancer, a tumor greater than 2 cm in diameter and/or with at least one tumor-positive lymph node, who were scheduled to receive NAC, were invited to participate in this study. All had invasive breast cancer diagnosed by core biopsy or fine needle aspiration before chemotherapy, and none of the patients had been treated with hormone therapy, chemotherapy, or radiotherapy before the first MR examination. MRI was performed prior to and after the first, fourth, and final scheduled courses of NAC to allow for an evaluation of DWI and DCE-MRI. Chemotherapy consisted of 4 courses of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) administered at 3-week intervals. Following FEC, a taxane-containing treatment of 12 courses of weekly paclitaxel (80–100 mg/m^2) or 4 courses of docetaxel (70–75 mg/m^2) at 3-week intervals, were administered. An institutional review board approved this prospective study to assess the capability of MRI for predicting response to treatment, all patients gave their written informed consent.

MRI examination

Patients were scanned in the prone position on a 3.0-T scanner (MAGNETOM Trio; Siemens Medical Solutions, Erlangen, Germany) with a dedicated 4-channel, phased-array, bilateral breast coil. Before the administration of contrast media, axial bilateral DWI images were acquired. DWI images were obtained using spin-echo single-shot EPI imaging with the following parameters: TR/TE 7500/71 ms; FOV 385×289 mm; matrix 128×96; thickness 3.0 mm; gap 0.6 mm; acquisition time 158 seconds. Spectral attenuated with inversion recovery (SPAIR) was used for fat suppression. Motion-probing gradients (MPGs) in 3 orthogonal orientations were applied with b values of 50, 800, and 1500 s/mm^2. Isotopic diffusion-weighted (trace) images were reconstructed for each b-factor. ADC maps were automatically created on the workstation from diffusion-weighted images with b values of 50, 850, and 1500 s/mm^2. Dynamic axial bilateral breast images of fat-suppressed high-resolution T1-weighted 3-dimensional fast-gradient echo images (VIEWS) were sequentially acquired before and 75, 185, and 295 seconds after the administration of contrast medium. For a dynamic study, *gadopentetate* dimeglumine (Magnevist; Bayer Schering, Osaka, Japan) was administered intravenously using a power injector at a dose of 0.1 mmol/kg body weight at a flow rate of 2 ml/s, followed by flushing with 20 ml saline. The parameters of the VIEWS sequence were: TR/TE 4.2/1.6 ms, flip angle 15, FOV 340×340 mm, matrix 512×410, thickness 0.9 mm, acquisitions 1, acquisition time 106 seconds. SPAIR for fat suppression was applied. With this parameter setting, the spatial voxel size was 0.7×0.8×0.9 mm.

MRI analyses

Each tumor was categorized as a mass or non-mass type from the DCE-MRI prior to NAC. According to the Breast Imaging Reporting and Data System MRI (BI-RADS-MRI) Guidelines,[18] a mass type was defined as a 3-dimensional space-occupying lesion with definable margins from surrounding glandular tissue. A non-mass type was defined as lesions without mass formation. The ADC for each tumor was calibrated using the following procedure: A region of interest (ROI) was drawn in all slices within the tumor on the ADC map. In each slice, an ROI was drawn to be as large as possible within the tumor by referring to the post-contrast enhanced images and DWI images to verify the tumor boundaries. Care was taken to exclude areas of necrosis given that they have a high ADC. Areas of enhancement deficit or high signal intensity within the tumor demonstrated on the T2 images were taken to represent tumor necrosis. To calibrate the average ADC of all slices, the weighted average of ADC based on the ROI area was used instead of simple averaging by the number of ROIs. For each MRI examination, patients were scanned on the same MRI using the same protocol. The volume of a tumor in the mass-type group was calculated by a summation of tumor areas in all slices and multiplied by the slice thickness. Due to the difficulty of drawing the lesion boundaries, a measurement of the largest diameter on the post-contrast image was used to define the standard size for a non-mass type. The shrinkage pattern was noted according to the classification proposed by Tozaki et al.[19] as concentric shrinkage or shrinkage with residual multi-nodular lesions with reference to the information from the post-contrast images.

According to the RECIST criteria and the report by Partridge et al.,[5] responders (R) were patients with a percentage of tumor volume reduction greater than 65% and the largest diameter reduction greater than 30%. Patients with a percentage of tumor size reduction less than R were classified as non-responders (NR). The response was classified after a full course of NAC, and all patients had either a mastectomy or breast-conservation surgery after NAC. The largest histopathological diameter was reported to represent the final tumor size and was compared with the largest diameter of the tumor measured by contrast MRI at the end of chemotherapy to assess the reliability of the MRI measurement.

Data and statistical analysis

Reduction rates of the lesion volume after the first, fourth, and last courses of chemotherapy for the mass type were calculated as follows:

Δvolume = {(tumor volume at baseline – tumor volume after first, fourth, and last chemotherapy) / tumor volume at baseline} × 100(%)

The reduction rates of the largest diameter were calculated using the same procedure to measure the reduction rates of lesion volume. The change in ADC from baseline to after the first course of chemotherapy was defined as follows:

ΔADC = {(ADC after the first course – ADC at baseline) / ADC at baseline} × 100(%)

The changes in volume and ADC after the first course of FEC in the R/NR groups were tested for statistical significance using Fisher's exact test. Correlations between early volume reduction and volume reduction after 4 courses of FEC and after the full course of chemotherapy was tested using Pearson's correlation coefficient. For all analyses, a p value of less than 0.05 was defined as statistically significant.

RESULTS

Of the 11 patients examined, 1 failed after the first NAC cycle due to severe hepatic damage. A second patient received only FEC since she did not reveal metastatic lymph nodes. One patient did not receive fluorouracil. The remaining patients received the FEC and taxane-containing treatment. The time interval between imaging acquisition and the first, fourth, and last treatment courses ranged from 17 to 20 days. Based on pretreatment DCE-MRI, 4 lesions were categorized as a non-mass type and 8 as a mass type. In 1 bilateral breast cancer patient, one side was a non-mass type while the other was a mass type.

Table 1 shows the patients' characteristics, ADC and volume changes after the first course of FEC, response after all NAC courses and surgery type for the mass type lesions. All mass type lesions showed concentric shrinkage on DCE-MRI. Among the 8 mass types, 6 cases were R and 2 were NR. After the first course of FEC, 4 lesions (patients 5-8L) showed noticeable shrinkage, and their respective volume reduction rates were 67%, 44%, 75%, and 37%. The other 4 lesions showed no noticeable shrinkage after the first course of FEC (patients 1-4). However, 2 lesions (patients 3, 4) had increased ADC with ΔADC of 19.7% and 14.3%, respectively, and they became R after subsequent taxane treatment (Fig. 1). On the other hand, 2 lesions (patients 1, 2) with neither increased ADC nor reduction in volume after the first course of FEC were NR after the full course of NAC. Figure 2 shows the volume reduction rate during NAC for mass type patients who achieved R. Patients 3 and 4 showed no shrinkage after the first course of FEC but had ADC increases. As seen from this figure, they showed less volume reduction after 4 courses of FEC compared to the other 4 patients, but exhibited greater shrinkage during taxane-containing treatment. A significant correlation was observed in volume reduction after 1 course of FEC and after 4 courses of FEC (r = 0.95, 95% CI = 0.69–0.99). However, the correlation in volume reductions after the first course of FEC and after the full course of chemotherapy were not significant (r = 0.53, 95% CI = –0.49–0.94). On the other hand, all cPR cases (patients 3-8L) showed either a noticeable volume reduction or ADC increases after the first treatment course of FEC, while SD cases exhibited neither (Fisher's exact test, $p<0.005$).

Table 1 Patient characteristics, early change during NAC[a], overall response and surgery type for mass type lesions

Patient	Age	TNM stage	ER/PgR	HER2	After 1 course of FEC[b]		Response after full course of NAC	Surgery
					ΔADC[c] (%)	ΔVolume[d] (%)		
1	58	IIIB	+/+	-	3.1	6	NR	BC[f]
2	64	IIA	-/-	-	-5.2	-8	NR	M[g]
3	38	IIIA	+/-	+	19.7	4	R	BC
4	44	IIB	+/+	-	14.3	6	R	M
5	64	IIB	-/-	-	-5.6	67	R	BC
6	40	IIB	+/-	-	6	44	R	BC
7	50	IIB	-/-	-	15.9	75	R	BC
8L[e]	65	IIA	+/+	-	23.5	37	R	BC

[a] NAC, neoadjuvant chemotherapy; [b] FEC, fluorouracil+epirubicin+cyclophosphamide;
[c]ΔADC, change in ADC (apparent diffusion coefficient) value after first course of FEC;
[d]ΔVolume, change in volume after first course of FEC; [e]8L, patient with bilateral breast cancer, left breast; [f]BC, breast-conserving surgery; [g]M, mastectomy

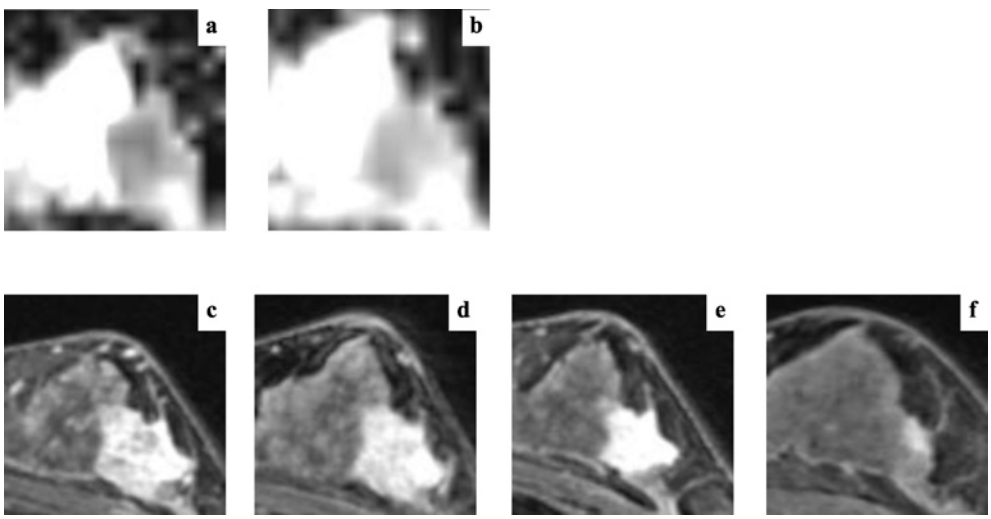

Fig. 1 Chemo-response during neoadjuvant chemotherapy (NAC) in patient 4. ADC map before NAC (a) and after first course of FEC (b). Dynamic contrast-enhanced MRI before NAC (c), after first course of FEC (d), after 4 courses of FEC (e), and after additional taxane treatment (f). Volume reduction is not seen after first course of FEC, but ADC value has increased with ΔADC of 14.3%. By the end of NAC, the patient achieved a good response.

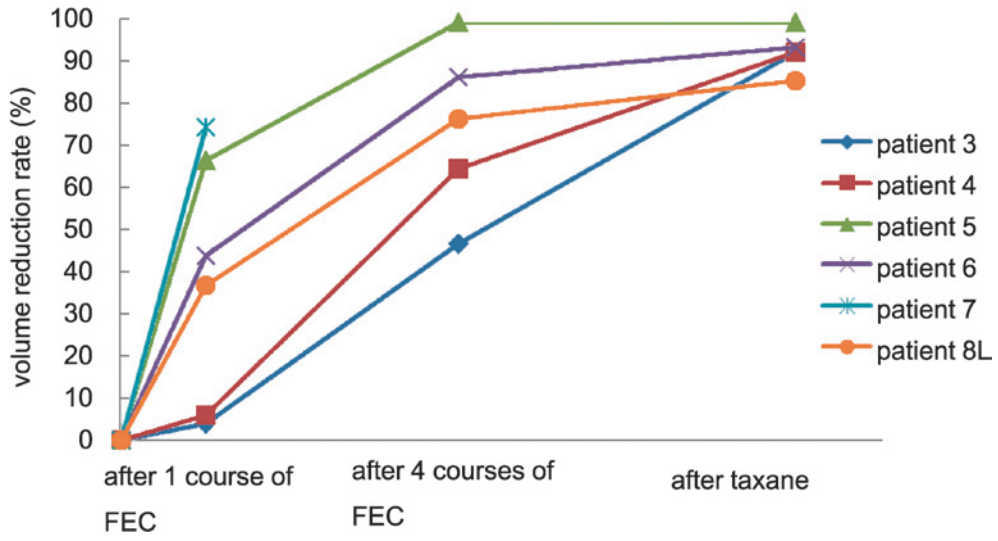

Fig. 2 Volume reduction rate in mass type lesions during NAC

Table 2 Patient characteristics, early change during NAC[a], overall response and surgery type for non-mass type lesions

[a] NAC, neoadjuvant chemotherapy; [b] FEC, fluorouracil+epirubicin+cyclophosphamide;

Patient	Age	TNM stage	ER/PgR	HER2	After 1 course of FEC[b]		Response after full course of NAC	Surgery
					ΔADC[c] (%)	Δdiameter[d] (%)		
8R[e]	65	IIIB	+/+	-	11	-2	NR	M[f]
9	69	IIIB	+/+	-	10	0	NR	M
10	49	IIB	+/+	-	-11	18	R	M
11	50	IIIA	+/+	-	22	36	R	M

[c]ΔADC, change in ADC (apparent diffusion coefficient) value after first cycle of FEC;
[d]Δdiameter, change in largest diameter captured one-dimensionally after first course of FEC; [e]8R, patient with bilateral breast cancer, right breast; [f]M, mastectomy

Table 2 shows the patients' characteristics, changes in ADC and the largest diameter after the first course of FEC, the response after the full course of NAC, and surgery type for the non-mass type lesions. The non-mass type showed both concentric shrinkage and shrinkage with residual multi-nodular lesions on DCE-MRI. However, pathologically, all cases were seen to have multiple foci. Of the 4 non-mass types, 2 were NR. After the first course of FEC, 2 cases (patients 10, 11) showed noticeable shrinkage in the largest diameter on DCE-MRI, with reduction rates of 36% and 18%, respectively. These 2 cases were both R after the full course of NAC. ADC increases occurred in both R and NR cases (patients 8R, 9, 11). The reduction rates of the largest diameter during NAC for the non-mass type were shown in Fig. 3. Two non-mass

type lesions (patients 8R, 11) enlarged during taxane-containing treatment. One case (patient 9) achieved a major reduction in the largest diameter after the full course of NAC. However, in a pathological study, this case showed a residual tumor extent greater than the contrasted area on MRI, and was thus categorized as NR after surgery. In addition, all non-mass type lesions, including R cases, could not have breast-conserving surgery because of the difficulty of correctly drawing the boundaries of the lesions for surgery.

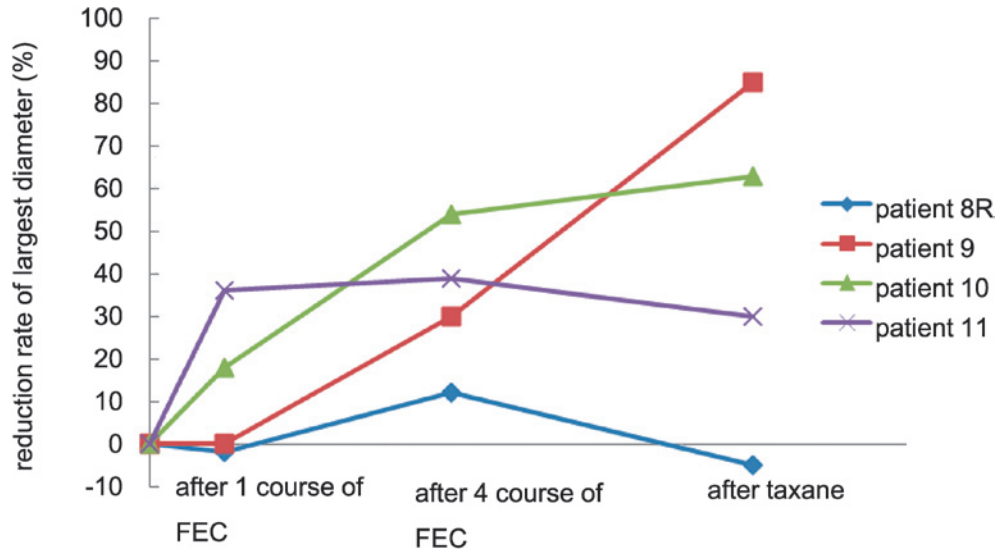

Fig. 3 Reduction rate of the largest diameter for non-mass type lesions during NAC

DISCUSSION

An early prediction of chemo-sensitivity is essential to maximizing patient benefit and minimizing the harm from NAC. Though our study contained a small number of patients, to the best of the authors' knowledge, this study is the first published trial using MRI to differentiate mass type from non-mass type prior to NAC, and to evaluate the early response to chemotherapy for locally advanced breast cancer. Sharma et al. and Pickles et al. have reported that ADC increases preceded volume reduction in NAC, because biochemical or functional changes precede morphological changes.[15,16] Yu et al. have reported that the most reliable tool to predict chemo-response after one course of NAC is the change in tumor size.[10] Our results show that 2 different MRI patterns of response to chemotherapy were observed for mass-type responders after the first course of treatment. One response was a shrinkage of the contrasted area on DCE-MRI, and the other was an increase in the ADC. The chemotherapy regimen of Yu et al. consisted of 4 courses of anthracycline and cyclophosphamide. Our results agreed with theirs in that the 4 cases with noticeable shrinkage in the contrasted lesion after the first course of FEC became R within 4 FEC courses. However, the 2 cases with ADC increase without shrinkage after the first course

of FEC also became R after an additional taxane regimen. Since a change during additional taxane treatment may include the effect from FEC, it is very difficult to interpret whether this later shrinkage was caused by taxane or whether the volume reduction rate was simply slow. Although the NSABP protocol B-27 suggests that additional docetaxel increases pCR, this study failed to increase the breast conservation rate by adding docetaxel. The authors concluded that because 85% of the tumors achieved clinical responses with the administration of 4 courses of anthracycline containing chemotherapy and only an additional 6% of patients became clinical responders with the addition of docetaxel, thus failing to achieve statistical significance.[3] From our results, ADC increases after first FEC course without noticeable shrinkage might represent the cases that benefit from additional chemotherapy. Thus it might prove worthwhile to investigate further.

The present study included 4 non-mass type breast cancers. Based on the results, shrinkage of the largest diameter on DCE-MRI captured after the first course of treatment appears to represent chemo-sensitivity. However, since our result includes only 2 responders out of 4 patients, no statistically valid conclusions can be drawn. ADC increases were seen in both chemo-sensitive and resistant cases after the first course of NAC. Thus, ADC values may not prove reliable in predicting chemo-response for non-mass type lesions. Furthermore, as Tozaki et al. and many other researchers have reported, non-mass type breast cancer is likely to show shrinkage with residual multi-nodular lesions.[19-22] In the present study, all cases revealed multiple residual foci on pathology, with 2 cases showing concentric shrinkage on DCE-MRI. We agree with other researchers that non-mass type lesions may not be promising candidates for NAC if the aim of treatment is to perform breast-conserving surgery. In addition, if a tumor showed shrinkage with residual multi-nodular lesions after NAC, it is very difficult to diagnose the extent of it. Thus, the use of NAC for non-mass type lesions should be carefully chosen. Moreover, a higher response of NAC is observed in patients with HER2-positive breast cancer than in those with HER2-negative. Our result contained only one HER2-positive breast cancer, while the rest were HER2-negative. A change in MRI during NAC might be less predictive of a pathology such as HER2-negative breast cancer. Thus, further studies will be necessary to evaluate the change in MRI during NAC in patients with HER2-positive breast cancer.

In summary, this study demonstrated that classifying breast cancer morphologically into mass and non-mass types prior to NAC is very important in terms of an early prediction of chemo-response, as well as in performing breast-conserving surgery. Early predictions of chemo-response using MRI may be possible for mass-type lesions. Such an early response consists of 2 different patterns: one is a change in size measured on contrast MRI, and the other is an increase in the ADCs. If neither change is observed after the first course of NAC, the patient may be chemo-resistant. This method of predicting the early response to NAC should not be used for the non-mass type of breast cancer. In addition, the non-mass type may be unsuitable for NAC if the aim of treatment is to perform breast-conserving surgery. However, a major limitation of the study is its small number of cases, indicating that further investigation is clearly warranted.

REFERENCES

1) Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monographs*, 2001; 30: 96–102.
2) van der Hage JA, van de Velde CJ, Julien JP, Tubiana-Hulin M, Vandervelden C, Duchateau L. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer Trial 10902. *J Clin Oncol*, 2001; 19(22): 4224–4237.

3) Bear HD, Anderson S, Brown A, Smith R, Mamounas EP, Fisher B, Margolese R, Theoret H, Soran A, Wickerham DL, Wolmark N. The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide: preliminary results from National Surgical Adjuvant Breast and Bowel Project B-27. *J Clin Oncol*, 2003; 21: 4165–4174.
4) Nagashima T, Sakakibara M, Sangai T, Kazama T, Nakatani Y, Miyazaki M. Tumor reduction rate predicts early recurrence in patients with breast cancer failing to achieve complete response to primary chemotherapy. *Breast Cancer*, 2010; 17(2): 125–130.
5) Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Tripathy D, Wolverton DS, Rugo HS, Hwang ES, Ewing CA, Hylton NM. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. *AJR Am J Roentgeno*l, 2005; 184: 1774–1781.
6) Prati R, Minami CA, Gornbein JA, Debruhl N, Chung D, Chang HR. Accuracy of clinical evaluation of locally advanced breast cancer in patients receiving neoadjuvant chemotherapy. *Cancer*, 2009; 115(6): 1194–1202.
7) Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Sudilovsky D, Hylton NM. Accuracy of MR imaging for revealing residual breast cancer in patients who have undergone neoadjuvant chemotherapy. *AJR Am J Roentgenol*, 2002; 179: 1193–1199.
8) Yeh E, Slanetz P, Kopans DB, Rafferty E, Georgian-Smith D, Moy L, Halpern E, Moore R, Kuter I, Taghian A. Prospective comparison of mammography, sonography and MRI in patients undergoing neoadjuvant chemotherapy for palpable breast cancer. *AJR Am J Roentgenol*, 2005; 184: 868–877.
9) Padhani AR, Hayes C, Assesohn L, Powles T, Makris A, Suckling J, Leach MO, Husband JE. Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: initial clinical results. *Radiology*, 2006; 239: 361–374.
10) Yu HJ, Chen JH, Mehta RS, Nalcioglu O, Su MY. MRI measurements of tumor size and pharmacokinetic parameters as early predictors of response in breast cancer patients undergoing neoadjuvant anthracycline chemotherapy. *J Magn Reson Imaging*, 2007; 26: 615–623.
11) Loo CE, Teertstra HJ, Rodenhuis S, van de Vijver MJ, Hannemann J, Muller SH, Peeter MJV, Gilhuijs KGA. Dynamic contrast-enhanced MRI for prediction of breast cancer response to neoadjuvant chemotherapy: initial results. *AJR Am J Roentgenol*, 2008; 191: 1331–1338.
12) Johansen R, Jensen LR, Rydland J, Goa PE, Kvistad KA, Bathen TF, Axelson DE, Lundgren S, Gribbestad IS. Predicting survival and early clinical response to primary chemotherapy for patients with locally advanced breast cancer using DCE-MRI. *J Magn Reson Imaging*, 2009; 29: 1300–1307.
13) Beak HM, Chen JH, Nie K, Yu HJ, Bahri S, Mehta RS, Nalcioglu O, Su MY. Predicting pathologic response to neoadjuvant chemotherapy in breast cancer by using MR imaging and quantitative ^{1}H MR Spectroscopy. *Radiology*, 2009; 251(3): 653–662.
14) Tozaki M, Oyama Y, Fukuma E. Preliminary study of early response to neoadjuvant chemotherapy after the first cycle in breast cancer: comparison of 1H magnetic resonance spectroscopy with diffusion magnetic resonance imaging. *Jpn J Radiol*, 2010; 28: 101–109.
15) Pickles MD, Gibbs P, Lowry M, Turnbull LW. Diffusion changes precede size reduction in neoadjuvant treatment of breast cancer. *Magn Reson Imaging*, 2006; 24: 843–847.
16) Sharma U, Danishad KK, Seenu V, Jagannathan NR. Longitudinal study of the assessment by MRI and diffusion-weighted imaging of tumor response in patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. *NMR Biomed*, 2009; 22: 104–113.
17) Nilsen L, Fangberget A, Geier O, Olsen DR, Seierstad T. Diffusion-weighted magnetic resonance imaging for pretreatment prediction and monitoring of treatment response of patients with locally advanced breast cancer undergoing neoadjuvant chemotherapy. *Acta Oncol*, 2010; 49(3): 354–360.
18) American College of Radiology: Breast imaging reporting and data system. BI-RADS (Reston VA ed), 4th ed, American College of Radiology, 2003.
19) Tozaki M, Kobayashi T, Uno S, Aiba K, Takeyama H, Shinoya H, Tabei I, Toriumi Y, Suzuki M, Fukuda K. Breast-conserving surgery after chemotherapy: value of MDCT for determining tumor distribution and shrinkage pattern. *AJR Am J Roentgenol*, 2006; 186: 431–439.
20) Murata Y, Ogawa Y, Yoshida S, Kubota K, Itoh S, Fukumoto M, Nishioka A, Moriki T, Maeda H, Tanaka Y. Utility of initial MRI for predicting extent of residual disease after neoadjuvant chemotherapy: analysis of 70 breast cancer patients. *Oncol Rep*, 2004; 12(6): 1257–1262.
21) Kim HJ, Im YH, Han BK, Choi N, Lee J, Kim JH, Choi YL, Ahn JS, Nam SJ, Park YS, Choe YH, Ko YH, Yang JH. Accuracy of MRI for estimating residual tumor size after neoadjuvant chemotherapy in locally advanced breast cancer: relation to response patterns on MRI. *Acta Oncol*, 2007; 46(7): 996–1003.
22) Bahri S, Chen JH, Mehta RS, Carpenter PM, Nie K, Kwon SY, Yu HJ, Nalcioglu O Su MY. Residual breast

cancer diagnosed by MRI in patients receiving neoadjuvant chemotherapy with and without bevacizumab. *Ann Surg Oncol*, 2009; 16(6): 1619–1628.