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The Radiological Response Rate Pattern Is Associated With Recurrence Free Survival in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy

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ABSTRACT

Purpose: The aim of this study was to evaluate the radiological response rate patterns during neoadjuvant chemotherapy (NAC) in patients with breast cancer.
Methods: Patients who underwent NAC with two specific chemotherapy regimens (doxorubicin with cyclophosphamide or doxorubicin with docetaxel) and who underwent a response evaluation every two cycles were included in the study. The initial response ratio was defined as the ratio of the largest tumor diameter at diagnosis to that after two cycles of NAC. The latter response ratio was defined as the ratio between the tumor size after two cycles and that after four cycles of NAC. The radiological response rate pattern was divided into three groups: the fast-to-slow response group (F–S group, initial response ratio > latter response ratio + 20%), slow-to-fast response group (S–F group, latter response ratio > initial response ratio + 20%), and constant response group (less than 20% difference between the initial and latter response ratios).
Results: In total, 177 patients were included in the analysis. Forty-two (23.9%) patients were categorized into the F–S group, 26 (14.8%) into the S–F group, and 108 (61.2%) into the constant group. Clinicopathologic factors did not differ according to radiologic response rate patterns. The median follow-up period was 50 months (range, 3–112) months. In the univariate analysis, the F–S group had a significantly worse recurrence-free survival than the S–F and constant groups (hazard ratio [HR], 3.63; 95% confidence interval [CI], 1.05–12.46; $p = 0.041$). The F–S group also presented with significantly worse survival than the S–F group in the multivariate analysis (HR, 3.45; 95% CI, 1.00–11.89; $p = 0.049$).
Conclusion: The F–S group had a poorer survival rate than the S–F group. Radiological response rate patterns may be useful for accurate prognostic assessments, especially when considering post-neoadjuvant therapy.

Keywords: Breast Neoplasms; Magnetic Resonance Imaging; Neoadjuvant Therapy; Recurrence; Response Rate

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Ahn J, Park WC, Yoo TK; Data curation: Ahn J, Yoo TK; Investigation: Ahn J; Methodology: Ahn J; Supervision: Park WC, Yoon CI, Paik PS, Cho MK, Yoo TK; Visualization: Ahn J; Writing - original draft: Ahn J; Writing - review & editing: Ahn J, Yoo TK.

INTRODUCTION

Neoadjuvant chemotherapy (NAC) is the standard treatment for locally advanced breast cancer and is increasingly being used in the treatment of early breast cancer. The primary advantage of NAC is improved surgical outcomes by improving the rate of breast-conserving surgery [1]. Randomized clinical trials have demonstrated no significant differences in the overall survival (OS) or disease progression between patients who underwent adjuvant chemotherapy and NAC [2, 3]. However, response to NAC provides important prognostic information, such as pathologic complete response (pCR), which is related to favorable long-term disease-free survival (DFS) and OS [4]. The frequency of pCR was relatively low; a frequency of 18% was found for ypT0/is ypN0 in a previous meta-analysis [5]. Recent studies have shown higher response rates in human epidermal growth factor receptor 2 (HER2)-positive tumors owing to the development of new targeted therapies [6,7].

A large proportion of patients with residual disease still lacks surrogate markers for survival. This has become increasingly relevant as adjuvant therapy is currently commonly recommended in patients with residual disease after NAC, especially in triple-negative and HER2-positive breast cancers [8,9]. Several studies have attempted to develop models to predict the prognosis of patients with post-NAC residual lesions. The yp-stage from the American Joint Committee on Cancer (AJCC) and residual cancer burden (RCB) are the two main methods used to evaluate residual disease in pathologic resection specimens [10,11]. The preoperative endocrine prognostic index score also uses post-treatment pathology results for the individualization of adjuvant therapy in patients undergoing neoadjuvant endocrine therapy [12].

Breast magnetic resonance imaging (MRI) is the most accurate imaging modality for the assessment of tumor response to NAC [13,14]. Several studies have demonstrated that an early change in tumor size, observed via MRI, during NAC is an effective tool for predicting tumor response [15-17]. Yu et al. [15] evaluated magnetic resonance images of patients who underwent NAC with doxorubicin and cyclophosphamide (AC), followed by a taxane regimen after the first cycle. They found that an early change in tumor size observed on MRI was highly predictive of the final response. A small study by Padhani et al. [17] also demonstrated that tumor size reduction was the best early predictor of tumor response.

Here, we investigated whether the pattern of tumor size reduction on breast MRI was related to NAC response and patient survival.

METHODS

Breast cancer patients who underwent NAC at Seoul St. Mary's Hospital between 2010 and 2017 were retrospectively reviewed. The inclusion criteria were as follows: 1) patients who were treated with two specific chemotherapeutic regimens (doxorubicin and docetaxel [AT] or AC) were included to assess the temporal change in tumor response without change in chemotherapeutic agents; and 2) patients who underwent a response evaluation using breast MRI every two cycles were included to accurately assess the tumor size. Patients with metastatic breast cancer, occult breast cancer, or those who had undergone incomplete NAC treatment for any cause were excluded (**Figure 1**). HER2-targeted therapy was only administered as adjuvant therapy to patients with HER2-positive tumors.

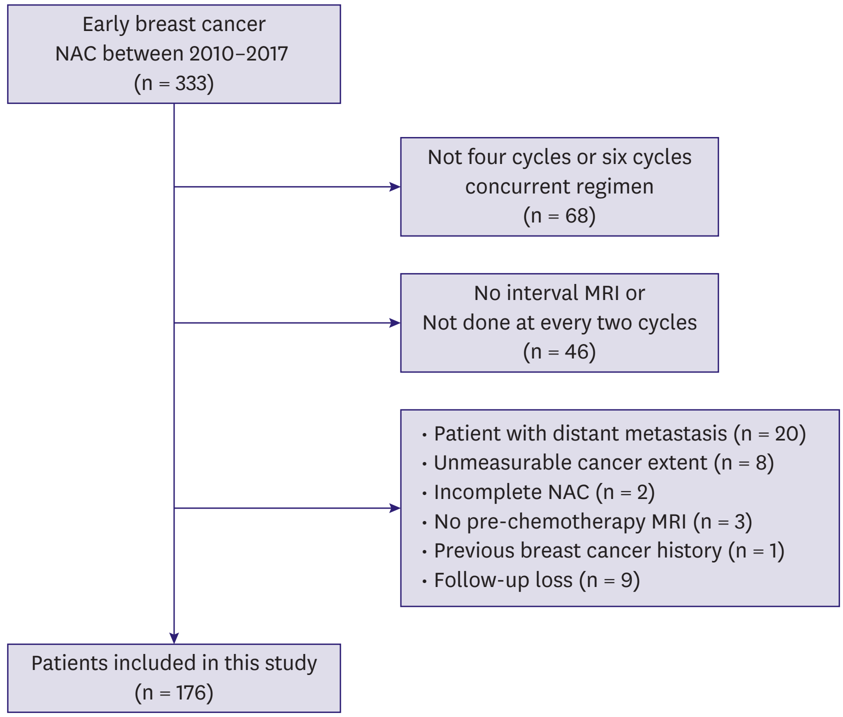

Figure 1. Flow diagram of patient inclusion.
MRI = magnetic resonance imaging; NAC = neoadjuvant chemotherapy.

The tumor shrinkage rate was calculated using the change in the largest tumor diameter between the two cycles observed via breast MRI. The initial response ratio was calculated by comparing the tumor size at diagnosis with that after two cycles of chemotherapy. The latter response ratio was calculated by comparing the tumor size after two cycles to that after four cycles of chemotherapy.

$$\text{Initial Response Ratio} = \frac{\text{Pre-NAC Tumor Size - Post 2 NAC Tumor Size}}{\text{Pre NAC Tumor Size}} \times 100$$

$$\text{Latter Response Ratio} = \frac{\text{Post 2 NAC Tumor Size - Post 4 NAC Tumor Size}}{\text{Post 2 NAC Tumor Size}} \times 100$$

The radiologic response rate was classified into three groups using the initial and latter response ratios. A patient was classified into the fast-to-slow response group (F–S group) when the initial response ratio was greater than 20% compared with the latter response ratio, indicating that the tumor size decreased more in the first two cycles. On the other hand, patients were classified into the slow-to-fast response group (S–F group) when the tumor size decreased more in the latter two cycles, with a difference of more than 20%. Patients with less than a 20% difference between the two ratios were assigned to the constant group (**Figures 2** and **3**).

Pathologic factors such as histologic type, grade, hormone receptor status, HER2 status, and Ki-67 were primarily extracted from core needle biopsy pathology reports. When these factors were missing, data were obtained from surgical specimen pathology reports. Tumor, Node, Metastasis (TNM) staging was performed according to the 7th edition of the AJCC on Cancer staging system.

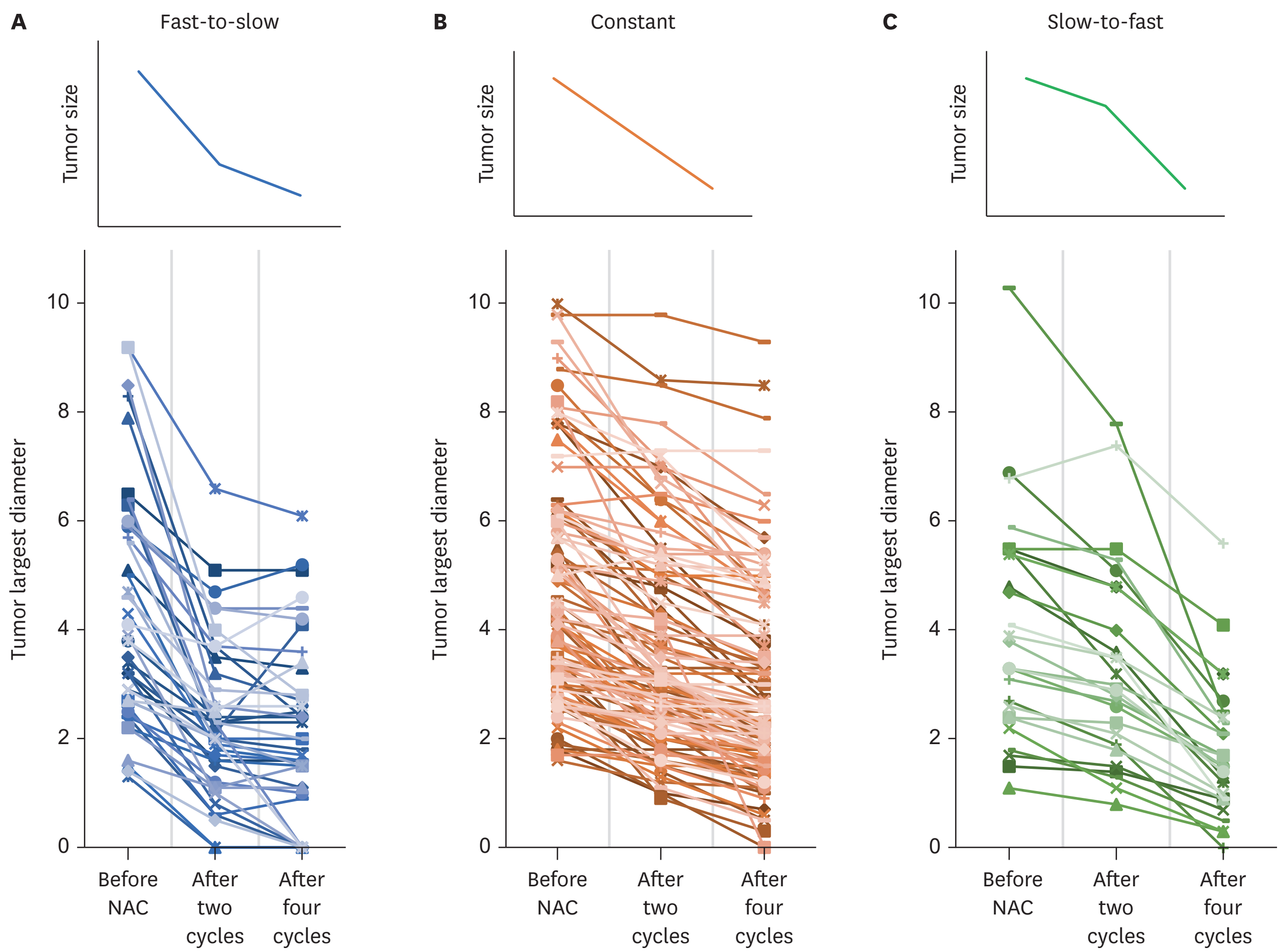

Figure 2. The three groups of radiologic response rate patterns.
(A) Fast-to-slow group, (B) Constant group, and (C) Slow-to-fast group.

Recurrence-free survival (RFS) and OS were estimated using the Kaplan–Meier test, with statistical significance based on the log-rank test. The RFS was calculated from the date of breast cancer diagnosis to locoregional recurrence, contralateral breast recurrence, or distant metastasis. OS was defined as the time from diagnosis to death due to any cause. Cox regression analysis of the association between RFS and radiologic response groups was performed using univariate and multivariate analyses, including prognostic pathologic factors. All analyses were performed using Statistical Package for the Social Sciences version 24 (IBM Corporation, Armonk, USA).

This study was approved by the Institutional Review Board of Seoul St. Mary's Hospital (IRB No. KC20RISI0684). The requirement for informed consent was waived.

RESULTS

Between 2010 and 2017, 396 patients with breast cancer underwent NAC at Seoul St. Mary's Hospital. Among them, 176 (44.4%) patients treated with concurrent chemotherapy (AC or AT) and who were evaluated every two cycles using breast MRI were included. A total of 114

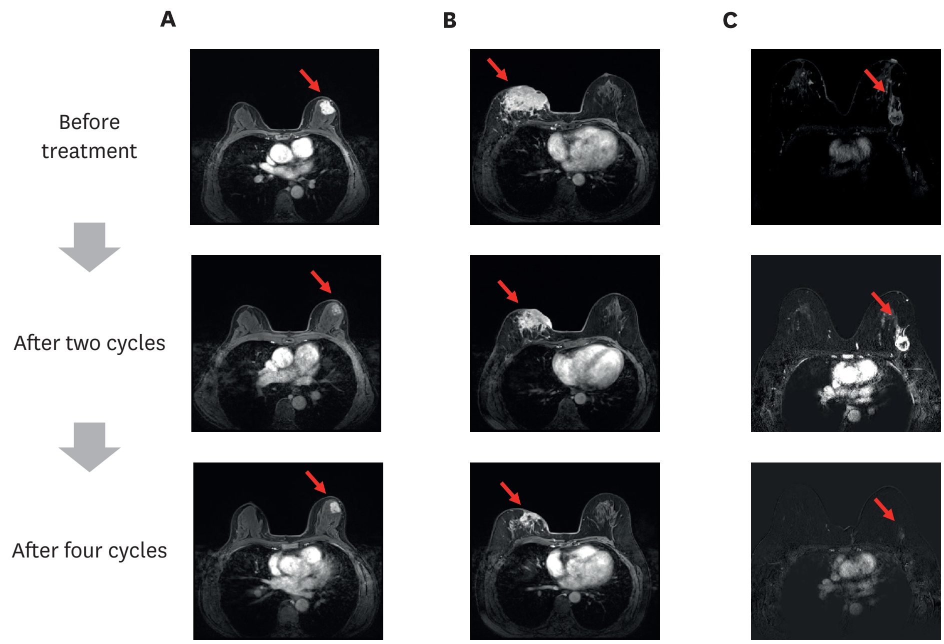

Figure 3. MRI images from cases of the three radiologic response rate patterns. The red arrows indicate the cancer lesion.
(A) Fast-to-slow group, (B) Constant group, and (C) Slow-to-fast group.
MRI = magnetic resonance imaging.

(64.8%) patients received four cycles of chemotherapy, and 62 (35.2%) patients received six cycles. Clinicopathological factors according to radiologic response rates are shown in **Table 1**. Among the 176 patients, 42 (23.9%) showed a fast-to-slow response, 26 (14.8%) presented with a slow-to-fast response, and 108 (61.2%) were categorized into the constant group. The mean age of the patients was 47 years (range, 21–69). Of these patients, 83 (47.2%) had stage 2 tumors and 93 (52.8%) had stage 3 tumors. The hormone receptor status was positive in 111 patients (63.1%). The NAC responses were as follows: pCR, 18 (10.2%) patients; partial response, 118 (67.0%) patients; stable disease, 38 (21.6%) patients; and progressive disease, 2 (1.1%) patients. The radiologic response rate pattern was not related to the pCR rate ($p = 0.160$). Additionally, no significant differences were observed in the clinicopathological factors according to the radiologic response rate. However, a non-significant but higher Ki-67 index was found in the F–S group than in the constant or S–F groups ($p = 0.056$).

The median follow-up period was 50 months (range, 3–112). The five-year OS and RFS rates were 93.2% and 76.7%, respectively. RFS was significantly worse in the F–S response group than in the constant and S–F groups (log-rank test, $p = 0.044$; hazard ratio [HR], 3.63; 95% confidence interval [CI], 1.05–12.46; **Figure 4A** and **Table 2**). However, the OS did not differ between the groups ($p = 0.368$; **Figure 4B**). After adjusting for prognostic factors that were significant for RFS in the univariate analysis, the F–S response group still presented with worse outcomes than the constant and S–F groups (HR, 3.45; 95% CI, 1.00–11.89; $p = 0.049$; **Table 2**). However, significance was only seen between the S and F and F–S groups, whereas the S–F and constant groups showed no significant difference (HR, 1.92; 95% CI, 0.57–6.42; $p = 0.289$).

Table 1. Clinicopathologic characteristics according to radiologic response pattern groups

Characteristics	Fast-to-Slow	Constant	Slow-to-Fast	*p*-value
No. of patients	42 (23.9)	108 (61.4)	26 (14.8)	
Age (yr)				0.443
< 50	27 (64.3)	59 (54.6)	13 (50.0)	
≥ 50	15 (35.7)	49 (45.4)	13 (50.0)	
Breast surgery				0.986
BCS	17 (40.5)	43 (39.8)	10 (38.5)	
TM	25 (59.5)	65 (60.2)	16 (61.5)	
Axillary surgery				0.080
SLNB	5 (11.9)	31 (28.7)	5 (19.2)	
ALND	37 (88.1)	77 (71.3)	21 (80.8)	
Clinical T stage				0.481
cT1-2	29 (69.0)	67 (62.0)	19 (73.1)	
cT3-4	13 (31.0)	41 (38.0)	7 (26.9)	
Clinical N stage				0.142
cN0-1	26 (61.9)	83 (76.9)	17 (65.4)	
cN2-3	16 (38.1)	25 (23.1)	9 (34.6)	
TNM Stage				0.944
II	19 (45.2)	52 (48.1)	12 (46.2)	
III	23 (54.8)	56 (51.9)	14 (53.8)	
ypTNM stage				0.189
I	8 (19.0)	25 (23.1)	6 (23.1)	
II	17 (40.5)	56 (51.9)	10 (38.5)	
III	11 (26.2)	23 (21.3)	7 (26.9)	
Histologic subtype				0.025
IDCa	31 (73.8)	96 (88.9)	26 (100)	
ILCa	3 (7.1)	5 (4.6)	0 (0.0)	
Others	8 (19.0)	7 (6.5)	0 (0.0)	
Histologic grade				0.147
1–2	26 (61.9)	76 (70.4)	22 (84.6)	
3	16 (38.1)	32 (29.6)	4 (15.4)	
Subtype				0.131
Luminal	19 (45.2)	73 (67.6)	19 (73.1)	
HER2	11 (26.2)	14 (13.0)	3 (11.5)	
TNBC	16 (38.1)	32 (29.6)	4 (15.4)	
Unknown	0 (0.0)	1 (0.9)	0 (0.0)	
Ki-67 (%)				0.056
< 20	17 (40.5)	61 (56.5)	18 (69.2)	
≥ 20	25 (59.5)	47 (43.5)	8 (30.8)	
Unknown	1 (2.4)	2 (1.9)	2 (7.7)	
Pathological response				0.160
pCR	4 (9.5)	4 (3.7)	3 (11.5)	
Non pCR	38 (90.5)	104 (96.3)	23 (88.5)	
Clinical response				0.014
CR	8 (19.0)	8 (7.4)	2 (7.7)	
PR	25 (59.5)	70 (64.8)	22 (84.6)	
SD	7 (16.7)	30 (27.8)	2 (7.7)	
PD	2 (4.8)	0 (0.0)	0 (0.0)	
Neoadjuvant chemotherapy regimen				0.044
AC	7 (16.7)	40 (37.0)	7 (26.9)	
AT	35 (83.3)	68 (63.0)	19 (73.1)	

Values are presented as number of patients (%).
BCS = breast-conserving surgery; TM = total mastectomy; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; IDCa = infiltrative ductal carcinoma; ILCa = invasive lobular carcinoma; HER2 = human epidermal growth factor receptor 2; TNBC = triple-negative breast cancer; pCR = pathological complete response; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NAC = neoadjuvant chemotherapy; AC = doxorubicin and cyclophosphamide; AT = doxorubicin and taxane.

Table 2. Univariate and multivariate analyses of clinicopathologic factors and recurrence-free survival

Clinicopathologic factors	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*p*-value	Hazard ratio	95% CI	*p*-value
Age (yr)						
< 50	1 (reference)					
≥ 50	1.64	0.89–3.04	0.113			
cT stage						
1–2	1 (reference)			1 (reference)		
3–4	2.15	1.15–4.02	0.016	2.19	1.17–4.11	0.014
cN stage						
0	1 (reference)			1 (reference)		
1–3	8.61	1.18–62.85	0.034	2.26	1.20–4.26	0.011
Histologic grade						
1–2	1 (reference)					
3	1.84	0.99–3.44	0.053			
Hormone receptor						
Positive	1 (reference)					
Negative	1.47	0.80–2.73	0.219			
HER2						
Positive	1 (reference)					
Negative	0.74	0.41–1.36	0.333			
Ki-67 (%)						
< 20	1 (reference)					
≥ 20	1.52	0.86–2.10	0.153			
Radiologic response group						
S-F group	1 (reference)		0.047	1 (reference)		0.085
F-S group	3.63	1.05–12.46	0.041	3.45	1.00–11.89	0.049
Constant group	1.92	0.57–6.42	0.289	2.02	0.60–6.82	0.255
Chemotherapy clinical response						
CR	1 (reference)					
PR	0.92	0.32–2.66	0.888			
SD	1.14	0.35–3.66	0.821			
PD	5.02	0.55–45.43	0.151			

CI = confidence interval; HER2 = human epidermal growth factor receptor 2; S-F = slow-to-fast; F-S = fast-to-slow; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

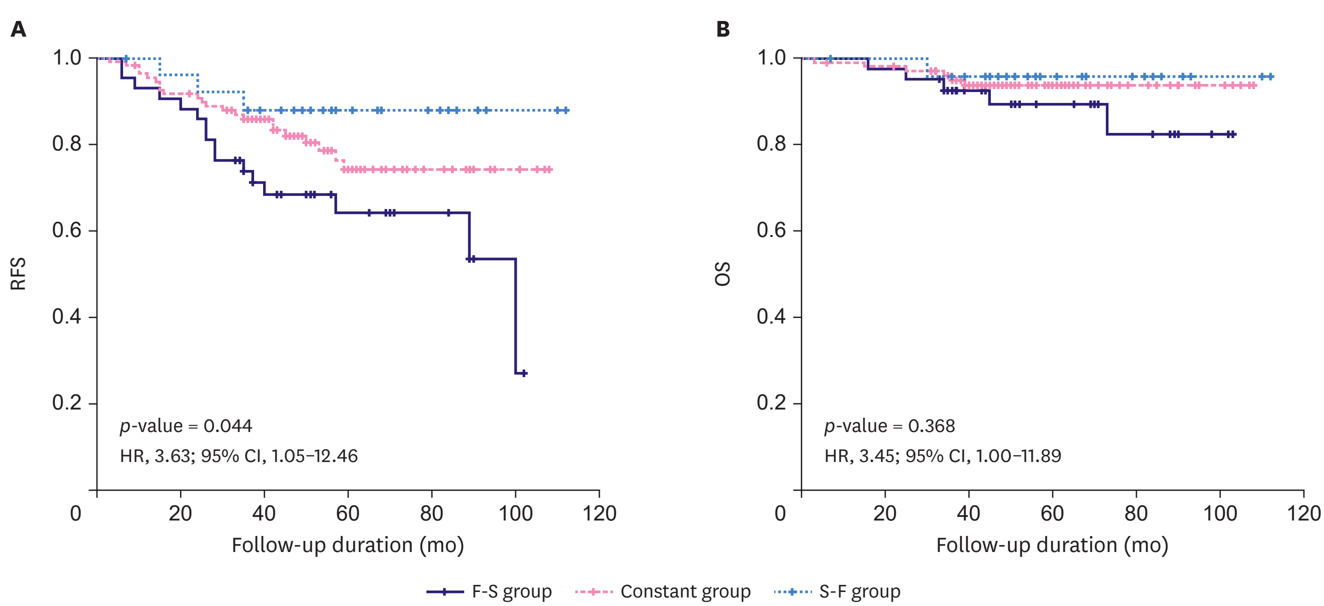

Figure 4. Kaplan–Meier curve of RFS and OS by radiologic response rate pattern group.
(A) RFS by radiologic response rate pattern group. (B) OS by radiologic response rate pattern group.
RFS = recurrence-free survival; OS = overall survival; HR = hazard ratio; CI = confidence interval.

DISCUSSION

In this study, we evaluated the pattern of tumor shrinkage during NAC in patients with breast cancer and investigated the association between size reduction rate and patient outcome. The radiologic response rate pattern showed no association with the pCR rate. However, the recurrence rate was higher in the F–S group than that in the S–F group. This means that a tumor with a slower size reduction rate during the latter cycles of neoadjuvant therapy has a higher recurrence rate than tumors that reduce consistently or faster during treatment.

Our study is the first to explore the significance of radiologic response rate patterns based on tumor size observed on MRI in breast cancer patients undergoing NAC. A tumor that reduces more slowly as therapy proceeds may indicate that tumor resistance develops during treatment, leading to a higher recurrence rate. This assumption is relevant, as all patients included in this study received two specific regimens (AT or AC) that did not change chemotherapy agents during the treatment period. Molecular studies on breast cancer have demonstrated the presence of molecular heterogeneity not only between subtypes but also within each subtype at the individual tumor level [18,19]. These results imply that even the same cancer subtype can elicit different responses to therapy. At the intratumor level, some tumor cells die, but others repopulate during treatment.

Our results can be partly explained by tumor heterogeneity and selective pressure. When selective pressure, such as chemotherapy, is administered, the treatment-sensitive portion of a tumor is eliminated, while the resistant portion survives and expands [20]. Chemotherapy also induces new genomic, transcriptomic, and epigenetic aberrations at the subclonal level, which leads to resistance. The reduced tumor shrinkage rate in the F–S group can be interpreted as treatment resistance, which leads to a higher recurrence rate.

The response to NAC varied among individuals. Molecular subtype, clinical stage, and treatment regimen can affect the response to NAC [21,22]. Currently, the classification by breast cancer stage after NAC is based on the AJCC on Cancer classification system. The system is based on the size of the tumor (T), number of positive lymph nodes (N), and existence of distant metastases (M). This system only applies to the final tumor size and has no specific correlation with prognosis. However, a more accurate prediction of the prognosis of NAC-treated patients can lead to an appropriate adjuvant therapy plan, avoiding overtreatment, which may cause harm to patients and unnecessary medical costs. Our study suggests that radiologic response rate patterns can contribute to the prediction of the prognosis of residual lesions.

The need for an additional prognostic factor to predict residual disease after NAC has been acknowledged by other groups who have presented various evaluation methods. The RCB index was developed to quantify residual disease and consists of the primary tumor bed diameter, ratio between the size of the primary tumor and that in residual invasive cancer, number of positive lymph nodes, and size of the largest metastatic lymph node [10]. The RCB index is a prognostic factor for long-term survival after NAC and has been used in clinical trials to evaluate the outcomes of residual disease after NAC [23]. Matsubara et al. [24] reported that a high reduction in Ki-67 after NAC is related to a favorable prognosis, similar to that of patients with pCR. Additionally, the tumor response ratio, calculated from the tumor size on pre-NAC imaging and residual tumor size, has been demonstrated to be a more accurate assessment of prognosis than pathologic staging [25].

However, the cut-off value for each radiologic response rate group is controversial. The difference between the initial and latter response ratios is a critical value in this study, and we suggest 20% as the standard cut-off value. No specific reference for the optimal cut-off value currently exists. We additionally analyzed the cases using different cutoff values, such as 15% and 30%, but the 20% cutoff value provided the best significance, which was the reason we adopted this value. To the best of our knowledge, no previous study has assessed the relationship between tumor size reduction patterns and prognosis. Further studies with larger sample sizes might set a standard and provide better support for certain cutoff values.

This study has some limitations. First, this was a retrospective, single-center study with a small sample size. Second, the duration of NAC was relatively short and consisted of only four or six cycles of chemotherapy. Additionally, even for patients who underwent six cycles of chemotherapy, the MRI images obtained after two and four cycles were used to evaluate tumor response. This was chosen so that we could compare the tumor response at identical time points for patients who underwent four cycles. However, assessing tumor response before the completion of NAC is a limitation. Third, HER2-targeted therapies were not used in the patients with HER2-amplified breast cancer. The lack of long-term follow-up data is also a limitation as breast cancer has a chance of late recurrence. Multivariate analysis showed no significant correlation between radiologic response pattern groups and RFS, but the F–S group tended to have a worse prognosis. Our small sample size may be one reason for this tendency. Therefore, further studies with larger populations are needed to provide statistically significant results before generalizing the trends observed in our study.

In conclusion, we demonstrated that certain patterns can be observed for reduction in tumor size during NAC in breast cancer. A slower reduction in tumor size as treatment proceeds presents with a poorer prognosis than consistent or faster reductions in tumor size during treatment. Further studies should be conducted with larger cohorts and longer follow-up periods to reproduce these results, which may help in the proper management of post-NAC residual lesions.

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