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Changes in Automated Mammographic Breast Density Can Predict Pathological Response After Neoadjuvant Chemotherapy in Breast Cancer

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Objective: Mammographic density is an independent risk factor for breast cancer that can change after neoadjuvant chemotherapy (NCT). This study aimed to evaluate percent changes in volumetric breast density (ΔVbd%) before and after NCT measured automatically and determine its value as a predictive marker of pathological response to NCT.

Materials and Methods: A total of 357 patients with breast cancer treated between January 2014 and December 2016 were included. An automated volumetric breast density (Vbd) measurement method was used to calculate Vbd on mammography before and after NCT. Patients were divided into three groups according to ΔVbd%, calculated as follows: Vbd (post-NCT – pre-NCT)/pre-NCT Vbd x 100 (%). The stable, decreased, and increased groups were defined as -20% ≤ ΔVbd% ≤ 20%, ΔVbd% < -20%, and ΔVbd% > 20%, respectively. Pathological complete response (pCR) was considered to be achieved after NCT if there was no evidence of invasive carcinoma in the breast or metastatic tumors in the axillary and regional lymph nodes on surgical pathology. The association between ΔVbd% grouping and pCR was analyzed using univariable and multivariable logistic regression analyses.

Results: The interval between the pre-NCT and post-NCT mammograms ranged from 79 to 250 days (median, 170 days). In the multivariable analysis, ΔVbd% grouping (odds ratio for pCR of 0.420 [95% confidence interval, 0.195–0.905; $P = 0.027$] for the decreased group compared with the stable group), N stage at diagnosis, histologic grade, and breast cancer subtype were significantly associated with pCR. This tendency was more evident in the luminal B-like and triple-negative subtypes.

Conclusion: ΔVbd% was associated with pCR in breast cancer after NCT, with the decreased group showing a lower rate of pCR than the stable group. Automated measurement of ΔVbd% may help predict the NCT response and prognosis in breast cancer.

Keywords: Mammography; Breast density; Breast neoplasm; Neoadjuvant therapy; Biomarkers; Predictive value of tests

INTRODUCTION

Neoadjuvant chemotherapy (NCT) is now accepted as a valuable treatment option for breast cancer that enables patients with stage 2–3 disease or particular breast cancer subtypes to improve treatment outcomes and quality of life [1]. Pathological responsiveness to NCT can be a prognostic marker for improved survival, and achievement of ypT0 or ypTis and ypN0 is closely linked to better event-free survival and overall survival [2]. Many researchers have attempted to identify clinical, radiological, and pathological factors to accurately predict pathological complete response (pCR)

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after NCT. Clinically, several parameters, including age, stage, histologic grade, estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), Ki-67, and molecular subtype, have been determined as predictive factors of pCR in patients with breast cancer receiving NCT [3-5]. However, persistent efforts must be made to identify other effective predictive factors associated with pCR after NCT.

Breast density can be qualitatively or quantitatively estimated using mammography, three-dimensional digital tomosynthesis, breast magnetic resonance imaging, and computed tomography [6,7]. Mammographic density (MD) is a well-known independent risk factor for breast cancer, and the dynamics of MD using sequential data have been regarded as potential biomarkers for prognosis, especially in patients with breast cancer treated with adjuvant tamoxifen [8,9]. However, research on the association between MD and chemotherapy in patients with breast cancer is limited. Previous studies have suggested that NCT or adjuvant chemotherapy could reduce MD, probably as a secondary effect of chemotherapy-induced amenorrhea [10,11]. Regarding the predictive role of MD scored according to the Breast Imaging-Reporting and Data System (BI-RADS) in patients who underwent NCT, a recent report associated a higher MD at pre-NCT that was visually assessed by an experienced specialist in radiology with failure to achieve pCR, with this relationship being more pronounced in premenopausal patients with breast cancer [12]. In clinical practice, mammography is performed twice, before and after the completion of NCT, to evaluate response, and changes in MD also need to be considered. In addition, automated methods are more popular for volumetric breast density (Vbd) measurements because they increase objectivity and reproducibility. The commercially available Volpara (Matakina Technology Ltd) and Quantra (Hologic Inc.) software perform automated measurements of Vbd and grade them similarly to the BI-RADS categories. Of the two, the Quantra software measures the total breast and fibroglandular tissue volumes by physical modeling, after which the percentage Vbd is calculated as a percentage of fibroglandular tissue and total breast volumes [13]. It generates four density categories by rounding off an estimate of the overall breast composition relative to the reference population.

In this study, we calculated the percent changes in volumetric breast density (ΔVbd%) serially measured automatically using the Quantra software. ΔVbd% was cross-tabulated with various clinicopathological characteristics of patients with breast cancer treated with NCT, and its association with pCR was analyzed to determine the clinical feasibility of ΔVbd% as a predictive marker of pathological responsiveness to NCT.

MATERIALS AND METHODS

Patient Enrollment

A total of 684 patients who were treated with NCT and subsequently underwent breast and axillary surgery between January 2014 and December 2016 were retrospectively screened. The entire study population was evaluated for MD before and after NCT. A total of 357 patients were excluded with the following criteria: stage IV at diagnosis, non-epithelial origin tumor, occult breast cancer with node metastasis, simultaneous bilateral breast cancer, age of < 40 years at diagnosis, male breast cancer, past history of contralateral breast cancer surgery, incomplete administration of planned NCT at diagnosis, inability to undergo examinations for MD both prior to or after receiving NCT, or examinations for which the software failed to obtain quantitative values (Fig. 1). Finally, 357 patients were included in the analysis. This study was approved by the Institutional Review Board of Severance Hospital, Seoul,

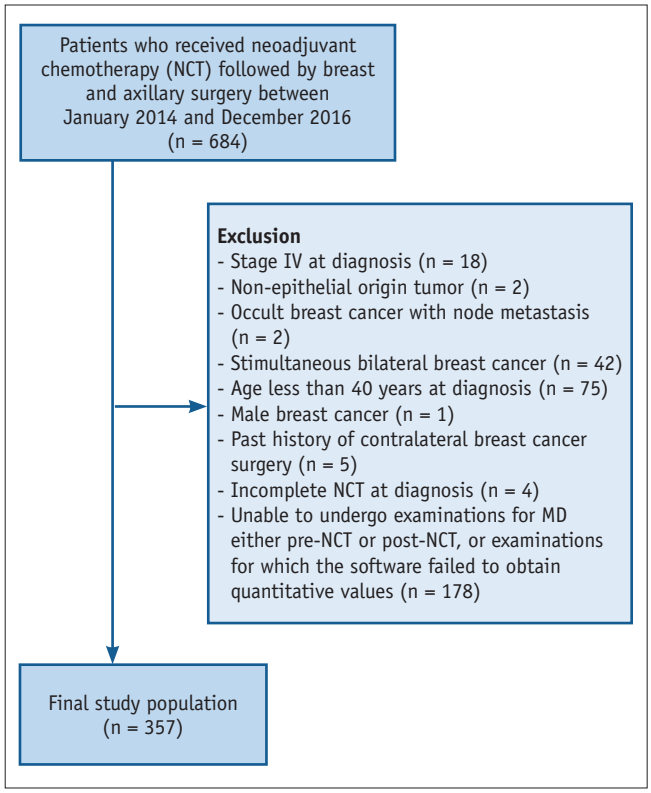

Fig. 1. Diagram of patient selection. MD = mammographic density

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Republic of Korea (No. 4-2019-1109), and the need for written informed consent was waived.

MD Assessment

Mammograms were obtained using a full-field digital mammography unit (Lorad Selenia; Hologic). Standard mediolateral oblique and craniocaudal views of the bilateral breasts were obtained for all patients at the time of diagnosis (pre-NCT value) and after the completion of NCT (post-NCT value). Vbd was automatically calculated using the Quantra software (version 2.0; Hologic), which provided the volumes of the total breast tissue (Vb, cm^3), fibroglandular tissue (Vfg, cm^3), Vbd (%), and quantized density (Qabd). The pre-NCT and post-NCT values of the non-diseased breast were used for analysis. To focus on the changes in volumetric density during NCT, ΔVbd was calculated as post-NCT Vbd minus pre-NCT Vbd. ΔVbd% was calculated using the following formula: (ΔVbd/pre-NCT Vbd) x 100 (%). As the 25 and 75 percentiles of ΔVbd% in our study population were -18.9% and 16.7%, respectively, we used similar but arbitrarily chosen cutoff values for ΔVbd (-20% and 20%) to divide patients into the decreased, stable, and increased groups (ΔVbd% < -20%, -20% ≤ ΔVbd% ≤ 20%, and ΔVbd% > 20%, respectively) (Fig. 2).

Clinicopathological Factors

Clinicopathological characteristics were retrospectively collected from electronic medical records. Age, menopausal status, body mass index (BMI = weight/$height^2$) at diagnosis, age at menarche, marital status, number of full-term deliveries, breastfeeding history, oral contraceptive use, hormone replacement therapy history, clinical stage at diagnosis, NCT regimen, histologic type, histologic grade, subtype, postoperative pathology, and type of breast surgery were compiled. The absence of in situ and invasive carcinomas or residual in situ carcinoma alone, without invasive carcinoma in the breast, and no evidence of metastatic tumors in the axillary and regional lymph nodes on surgical pathology were considered to indicate the achievement of pCR after NCT. Tumors with ≥ 1% nuclear-stained cells on immunohistochemistry were considered positive for ER or progesterone receptor (PR) expression according to the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines [14]. HER2 immunostaining was scored from 0 to 3+, and HER2 equivocal cases were performed using an in situ hybridization test following the ASCO/CAP guidelines for HER2 testing [15]. Ki-67 labeling indices were scored by counting the number of positively stained nuclei and expressed as the percentage of total tumor cells. Ki-67 of > 15% was used as the cutoff for high expression. Breast cancer subtypes were categorized into four subgroups: luminal A-like (ER- and/or PR-positive, HER2-negative, and Ki-67 of ≤ 15%), luminal B-like (ER- and/or PR-positive, HER2-negative, and Ki-67 of > 15%, or ER- and/or PR-positive and HER2-positive, irrespective of Ki-67), HER2-

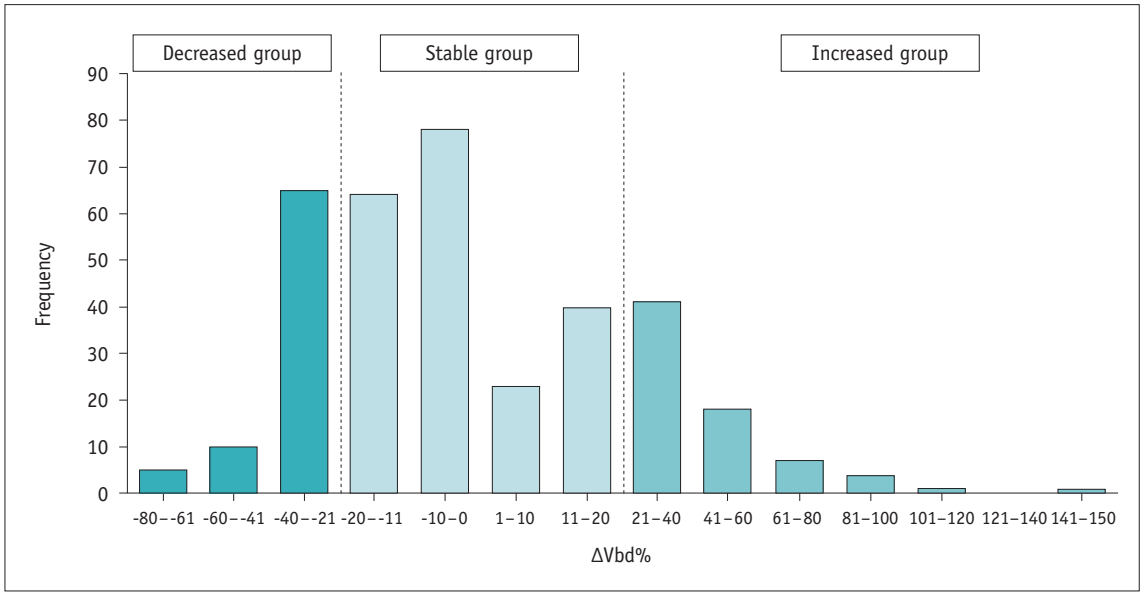

Fig. 2. Distribution of changes in volumetric breast density (ΔVbd%) before and after neoadjuvant chemotherapy. The decreased, stable, and increased groups are defined as ΔVbd% < -20%, -20% ≤ ΔVbd% ≤ 20%, and ΔVbd% > 20%, respectively.

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positive (ER-negative, PR-negative, and HER2-positive), and triple-negative breast cancer (TNBC; ER-negative, PR-negative, and HER2-negative). In luminal subtypes that did not have Ki-67 results, histologic grade III was considered high proliferation, and histologic grade I or II was considered low proliferation [16].

Statistical Analysis

Differences in clinicopathological parameters among the ΔVbd% groups were evaluated using the chi-square test, Fisher's exact test, and one-way analysis of variance with Bonferroni correction according to the data types. Univariable and multivariable logistic regression analyses were used to identify variables that were significantly associated with pCR after NCT. Variables that were statistically significant for pCR in the univariable analysis or those considered clinically important albeit statistically insignificant in the univariable analysis were included in the multivariable analysis. All statistical tests were two-sided, and *P*-values of < 0.05 were considered statistically significant. SPSS version 25.0 (IBM Inc.) was used for all analyses.

RESULTS

Mammographic Characteristics

The interval between the pre-NCT and post-NCT mammograms ranged from 79 to 250 days (median, 170 days). Breast and axillary surgery was performed a median of 185 days after pre-NCT mammography and a median of 14 days after post-NCT mammography. The mean Vbd values were 15.8% ± 9.3% (range, 3%–64%) at pre-NCT and 15.0% ± 8.6% (range, 2%–65%) before surgery (paired *t*-test; *P*-value = 0.003). The parameters of the pre- and post-NCT mammograms are presented according to the ΔVbd% in Table 1. At pre-NCT, the decreased ΔVbd% group showed significantly lower Vb and higher Vbd values than the increased group. The Vfg was significantly lower in the increased ΔVbd% group than in the stable group. The decreased ΔVbd% group demonstrated a higher proportion

Table 1. Mammographic Characteristics according to the ΔVbd% Grouping

	All (n = 357)	Decreased ΔVbd% (n = 80)	Stable ΔVbd% (n = 205)	Increased ΔVbd% (n = 72)	*P**
Pre-NCT					
Vb, cm^3	615.7 ± 326.3	530.5 ± 283.4	629.3 ± 317.0	671.5 ± 379.3	0.019
Vfg, cm^3	87.8 ± 61.8	90.9 ± 72.7	95.6 ± 62.4	61.9 ± 35.2	< 0.001
Vbd, %	15.8 ± 9.3	19.0 ± 10.3	16.4 ± 8.9	10.5 ± 6.4	< 0.001
Qabd‡					< 0.001†
Q1	31 (8.7)	4 (5.0)	15 (7.3)	12 (16.7)	
Q2	129 (36.1)	21 (26.3)	68 (33.2)	40 (55.6)	
Q3	152 (42.6)	42 (52.5)	92 (44.9)	18 (25.0)	
Q4	45 (12.6)	13 (16.3)	30 (14.6)	2 (2.8)	
Post-NCT					
Vb, cm^3	589.3 ± 325.4	534.6 ± 271.1	595.8 ± 296.8	631.2 ± 436.8	0.171
Vfg, cm^3	80.7 ± 54.6	65.8 ± 54.5	86.6 ± 54.7	80.6 ± 51.7	0.015
Vbd, %	15.0 ± 8.6	12.5 ± 6.5	15.9 ± 8.7	15.0 ± 9.9	0.010
Qabd‡					0.216†
Q1	18 (5.0)	6 (7.5)	9 (4.4)	3 (4.2)	
Q2	152 (42.6)	39 (48.8)	77 (37.6)	36 (50.0)	
Q3	147 (41.2)	30 (37.5)	91 (44.4)	26 (36.1)	
Q4	40 (11.2)	5 (6.3)	28 (13.7)	7 (9.7)	
Between pre-NCT and post-NCT					
ΔVbd	-0.8 ± 5.2	-6.5 ± 6.2	-0.5 ± 2.0	4.6 ± 4.0	< 0.001
ΔVbd%	0.5 ± 30.0	-32.9 ± 13.5	-2.1 ± 11.6	44.9 ± 25.0	< 0.001

Values are presented as mean ± standard deviation or patient number (%). ΔVbd was calculated as post-NCT Vbd minus pre-NCT Vbd. ΔVbd% was calculated with the following formula: (ΔVbd/pre-NCT Vbd) x 100. The decreased group was defined with ΔVbd% < -20%, the stable group with -20% ≤ ΔVbd% ≤ 20%, and the increased group with ΔVbd% > 20%. *Analysis of variance (ANOVA) test, †Chi-square test, ‡The number of patients (%). Vb = total breast volume, Vfg = fibroglandular tissue volume, Vbd = volumetric breast density, Qabd = quantized density, NCT = neoadjuvant chemotherapy

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of dense Q3 and Q4 in the Qabd. After NCT, the Vb and Qabd did not differ among the three ΔVbd% groups. The decreased ΔVbd% group showed significantly lower Vfg and Vbd values than the stable group. The mean ΔVbd% values were -32.9%, -2.1%, and 44.9% for the decreased, stable, and increased groups, respectively.

Clinicopathological Characteristics

The median age at diagnosis was 52 (range, 40–79) years for the total study population. The NCT regimens consisted of anthracycline- or taxane-based agents in 12 (3.4%) patients, anthracycline plus cyclophosphamide followed by taxane in 243 (68.1%) patients, anthracycline plus cyclophosphamide followed by taxane plus targeted agents in 76 (21.3%) patients, and taxane-based agents plus targeted agents in 26 (7.3%) patients.

The clinicopathological characteristics are summarized in Table 2. The decreased ΔVbd% group included younger age, premenopausal women, no history of full-term delivery, and larger tumor size. This group was significantly less likely to achieve pCR after NCT. There were no differences in BMI, age at menarche, marital status, breastfeeding history, oral contraceptive use, hormone replacement therapy use, nodal status, NCT regimen, histologic type, histologic grade, or breast cancer subtype. Patients with a decreased ΔVbd% were more likely to undergo total mastectomy with borderline statistical significance.

Analyses of the Association with pCR

After NCT, breast pCR, irrespective of nodal status, was achieved in 137 (38.4%) patients. Eighty-nine patients did not have residual invasive and in situ carcinomas, whereas 48 patients only had residual in situ disease. Axillary pCR, irrespective of the primary tumor status, was detected in 225 (63.0%) patients. Overall, tumor and nodal pCR after NCT were achieved in 128 (35.9%) patients. Images of pCR and non-pCR associated with breast density assessment using Quantra are shown in Figures 3 and 4.

The predictive factors that were significantly associated with pCR after NCT are shown in Table 3. In the univariable logistic regression analysis, the decreased ΔVbd% group had a significantly lower probability of pCR than the stable group. These findings were noticeable in premenopausal patients; the pCR rates were 18.5% in 54 premenopausal women with decreased ΔVbd% and 26.9% in 26 postmenopausal patients with decreased ΔVbd%. When the pre-NCT and post-NCT Qabd values were analyzed, pre-

Table 2. Clinicopathological Characteristics according to the ΔVbd% Grouping

	Decreased ΔVbd%	Stable ΔVbd%	Increased ΔVbd%	*P*
Age at diagnosis, yr				< 0.001*
Mean ± standard deviation	49.2 ± 7.0	52.5 ± 7.6	56.4 ± 8.3	
Menopausal status				< 0.001
Premenopause	54 (67.5)	91 (44.4)	17 (23.6)	
Postmenopause	26 (32.5)	114 (55.6)	55 (76.4)	
BMI, kg/m^2				0.689
< 23	38 (47.5)	101 (49.3)	31 (43.1)	
23– < 27	31 (38.8)	75 (36.6)	26 (36.1)	
≥ 27	11 (13.8)	29 (14.1)	15 (20.8)	
Age at menarche, yr				0.230
≤ 13	25 (31.3)	43 (21.0)	11 (15.3)	
14–15	32 (40.0)	88 (42.9)	30 (41.7)	
≥ 16	18 (22.5)	65 (31.7)	27 (37.5)	
Unknown	5 (6.3)	9 (4.4)	4 (5.6)	
Marital status				0.711†
Unmarried	6 (7.5)	12 (5.9)	3 (4.2)	
Married/divorced	74 (92.5)	193 (94.1)	69 (95.8)	
No. of full-term deliveries				0.025
0 child	12 (15.0)	15 (7.3)	4 (5.6)	
1 child	15 (18.8)	36 (17.6)	19 (26.4)	
2 children	36 (45.0)	127 (62.0)	34 (47.2)	
≥ 3 children	17 (21.3)	27 (13.2)	15 (20.8)	
Breast feeding history				0.308†
No	24 (30.0)	59 (28.8)	14 (19.4)	
Yes	54 (67.5)	135 (65.9)	52 (72.2)	
Unknown	2 (2.5)	11 (5.4)	6 (8.3)	
Oral contraceptives use				0.932†
No	64 (80.0)	167 (81.5)	57 (79.2)	
Yes	16 (20.0)	36 (17.6)	15 (20.8)	
Unknown	0 (0.0)	2 (1.0)	0 (0.0)	
HRT history				0.137†
No	75 (93.8)	182 (88.8)	59 (81.9)	
Yes	5 (6.3)	21 (10.2)	13 (18.1)	
Unknown	0 (0.0)	2 (1.0)	0 (0.0)	
T stage at diagnosis				0.048
cT1	10 (12.5)	23 (11.2)	10 (13.9)	
cT2	41 (51.2)	136 (66.3)	50 (69.4)	
cT3-4	29 (36.3)	46 (22.4)	12 (16.7)	
N stage at diagnosis				0.892
cN0	15 (18.8)	47 (22.9)	14 (19.4)	
cN1	46 (57.5)	115 (56.1)	40 (55.6)	
cN2-3	19 (23.8)	43 (21.0)	18 (25.0)	
NCT regimen				0.331
A or Taxane-based alone	5 (6.3)	5 (2.4)	2 (2.8)	

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Table 2. Clinicopathological Characteristics according to the ΔVbd% Grouping (continued)

	Decreased ΔVbd%	Stable ΔVbd%	Increased ΔVbd%	*P*
A → Taxane	60 (75.0)	135 (65.9)	48 (66.7)	
A → Taxane + anti-HER2 agent	11 (13.8)	49 (23.9)	16 (22.2)	
Taxane + anti-HER2 agent	4 (5.0)	16 (7.8)	6 (8.3)	
Histology type				0.878†
Ductal	73 (91.3)	188 (91.7)	67 (93.1)	
Lobular	2 (2.5)	7 (3.4)	3 (4.2)	
Others	5 (6.3)	10 (4.9)	2 (2.8)	
Histologic grade				0.321
I	14 (17.5)	24 (11.7)	6 (8.3)	
II	50 (62.5)	124 (60.5)	49 (68.1)	
III	16 (20.0)	57 (27.8)	17 (23.6)	
Breast cancer subtype				0.089
Luminal A-like	30 (37.5)	60 (29.3)	19 (26.4)	
Luminal B-like	22 (27.5)	44 (21.5)	11 (15.3)	
HER2-positive	8 (10.0)	44 (21.5)	15 (20.8)	
TNBC	20 (25.0)	57 (27.8)	27 (37.5)	
Postoperative pathology				0.008
pCR	17 (21.3)	82 (40.0)	29 (40.3)	
Non-pCR	63 (78.8)	123 (60.0)	43 (59.7)	
Type of breast surgery				0.058
BCS	39 (48.8)	107 (52.2)	48 (66.7)	
Total mastectomy	41 (51.2)	98 (47.8)	24 (33.3)	

Data are number of patients (%), unless specified otherwise. *Analysis of variance (ANOVA) test, †Fisher's exact test. BMI = body mass index, No. = number, HRT = hormone replacement therapy, NCT = neoadjuvant chemotherapy, A = anthracycline, HER2 = human epidermal growth factor receptor 2, TNBC = triple-negative breast cancer, pCR = pathological complete response, BCS = breast conservation surgery, Vbd = volumetric breast density

NCT Q4 alone was associated with a significantly lower probability of pCR (odds ratio, 0.305; 95% confidence interval, 0.113–0.824; *P*-value = 0.019). However, post-NCT Q2, Q3, and Q4 were less likely to achieve pCR (Table 3); therefore, the post-NCT Qabd was selected for the multivariable model because the pre-NCT Qabd was closely related to the post-NCT Qabd. Menopausal status, clinical node stage at diagnosis, NCT regimen, histologic grade, and breast cancer subtype were also statistically associated with pCR. The remaining clinical variables were not associated with pCR (data not shown).

In the multivariable analysis, the breast cancer subtype was the most powerful predictor of pCR. Node staging at diagnosis, histologic grade III, and a combination of anti-HER2 agents were also significantly associated with pCR. Vbd measurements were statistically significant. Patients with preoperatively dense breast Q3 and Q4 after completion of NCT were less likely to achieve pCR, and the decreased ΔVbd% group also had a lower probability of pCR after NCT independently.

When a subgroup analysis stratified by breast cancer subtype was performed (Table 4), the decreased ΔVbd% group had significantly lower pCR rates in patients with the luminal B-like and TNBC subtypes. Changes in the Vbd were not related to pCR achievement in luminal A-like and HER2-positive breast cancers.

DISCUSSION

In the early 2000s, quantitative methods were developed, and automated volume measurement was implemented to overcome the subjectivity of radiology specialists, to compensate for the difference in X-ray exposure according to the degree of mammography pressure, and in response to the need for three-dimensional area measurements for breast density [17].

In this study, we objectively measured the MD using automated density assessments. We focused on the individual effects of chemotherapy on breast density during a relatively short treatment course and calculated the changes in the Vbd before and after NCT. We eventually revealed that a decrease in the Vbd difference that grew larger after NCT was a poor predictive factor of pCR, especially in patients with luminal B-like breast cancer and TNBC.

According to Skarping et al. [18], three-quarters of patients who received NCT prospectively showed that the post-NCT MD was lower than the pre-NCT MD. Patients with pCR did not show significant changes in the volumetric MD between pre- and post-NCT examinations despite adjustment for other clinicopathological variables. However, half of the patients in our cohort showing decreased absolute Vbd values after NCT were young and premenopausal and had dense breasts at diagnosis compared with the other patients. Importantly, patients with decreased ΔVbd% were less likely to achieve pCR on multivariable analysis, suggesting that the degree of change in the volumetric MD was a valuable predictive factor of chemotherapeutic effects, namely, the achievement of pCR. In addition, this association was more pronounced in luminal B-like breast cancer and TNBC than in luminal A-like or HER2-positive breast cancers.

Both adjuvant tamoxifen and NCT were associated

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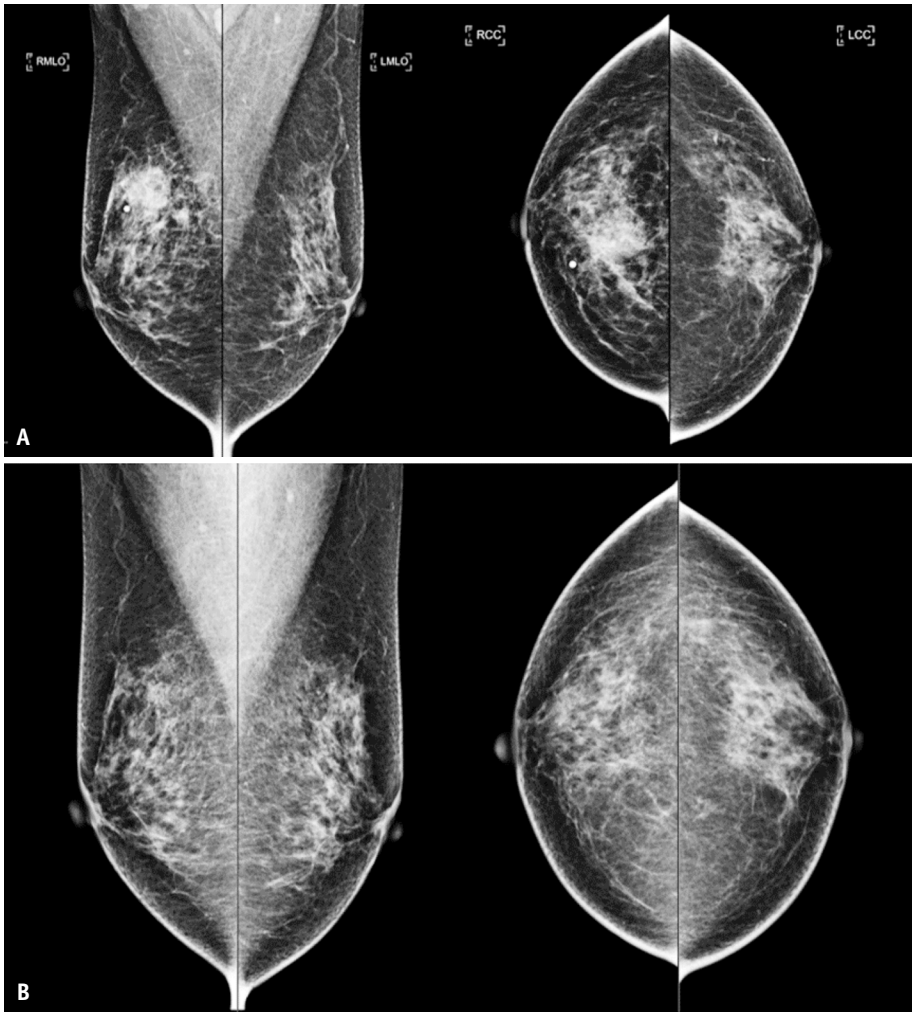

Fig. 3. A case of pathological complete response (pCR) associated with breast density assessment using Quantra. The pre-neoadjuvant chemotherapy **(A)** and post-neoadjuvant chemotherapy **(B)** images of a patient with increased percent changes in volumetric breast density (ΔVbd%) of left breast and pCR of right breast are shown. The Vbd (%) increases from 6 to 13.

with reduced MD in the treatment of ER-positive breast cancer. Several studies have shown improved prognosis in 30%–60% of patients treated with adjuvant tamoxifen who also showed reduced MD [19,20]. Kim et al. [21] reported that in patients who had MD that decreased to < 5% or increased after 1 year of adjuvant endocrine therapy, the risk of recurrence approximately doubled or was greater than in those who had MD that decreased to > 10%. They also suggested that a decrease in circulating estrogen due to adjuvant endocrine therapy could lead to a decrease in MD; however, this has not yet been proven.

Aktepe et al. [22] showed that NCT can induce lobular atrophy and alter the composition of dense breast parenchymal regions forming MD to fibrosis and hyalinization. These studies have shown that MD or Vbd decreases after NCT and is associated with higher MD at diagnosis with a lower pCR rate [10,23].

Recently, Swedish researchers analyzed the association between pCR after NCT and MD using visual assessment with BI-RADS in 495 patients with breast cancer [12]. In a model adjusted for patient age, BMI, and menopausal status, the pCR rates were significantly lower in premenopausal women classified as BI-RADS D, which represents extremely dense breasts [12]. Consistently, our multivariable analysis confirmed that higher Qabd categories and decreased ΔVbd% were significantly independently associated with lower pCR rates, whereas aggressive breast cancer subtype, high-grade tumor, and use of anti-HER2 agents with chemotherapy were significantly associated with increased pCR rates after NCT.

Currently, there are two commercial programs available for automated Vbd measurements: Quantra and Volpara. Breast

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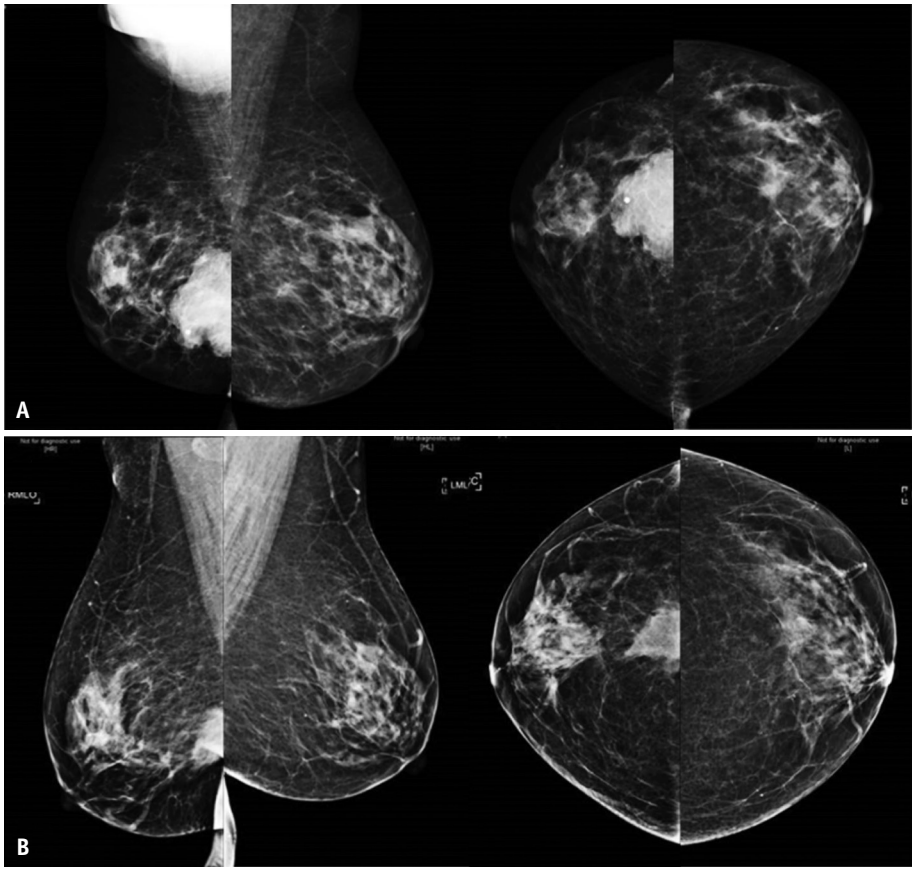

Fig. 4. A case of non-pathological complete response (non-pCR) associated with breast density assessment using Quantra. The pre-neoadjuvant chemotherapy **(A)** and post-neoadjuvant chemotherapy **(B)** images of a non-pCR patient with decreased percent changes in volumetric breast density (ΔVbd%) of left breast are shown. The Vbd (%) decreases from 14 to 7, and residual cancer is visible.

thickness is measured by accumulating X-rays, and patients undergo additional processes to classify the breast into dense and nondense tissues [24]. In previous publications, the automated density method differed by up to 14% from visual assessment and was associated with a risk measure for developing breast cancer. Differences were also observed in the capabilities of the two automated programs for volumetric density measurements. Youk et al. [25] reported that Quantra is more useful for classifying nondense breast tissue, and Volpara can classify more images of denser breast tissue than visual assessment. Compared with visual evaluation, Quantra and Volpara were correlated with MD (γ = 0.79–0.99, P < 0.001), although the regions studied by the Volpara and Quantra software were reported to be different.

Although pCR-related chemosensitivity is unclear in obese patients receiving NCT, patients with a high BMI (≥ 25 kg/m^2) and high visceral fat are generally known to show poor prognosis [26,27]. Obesity causes changes that alter the body's physiological environment, making it resistant to insulin, causing sustained chronic inflammation, and increasing the secretion of endogenous steroids associated with carcinogenesis and cancer progression [28]. Approximately 15% of the patients in our study population were obese; however, a higher BMI was not associated with responsiveness to NCT. Future studies with larger sample sizes should be conducted.

The current study has some limitations. First, we retrospectively ran a single automated volumetric program at one institution to collect data, and the number of study subjects was too small to reflect the entire population. It was also difficult to specifically reflect the differences in each NCT regimen according to the type of breast cancer. More importantly, the degree of ΔVbd% was classified into decreased or increased levels with arbitrary cutoff values, which means that the results need to be interpreted with caution. A larger study that would enable the exploration of different grouping methods and cutoffs or analysis of ΔVbd% as a continuous variable would be needed. Second, changes in body weight during NCT could not be incorporated directly, and dynamic BMI changes could not be

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Table 3. Univariable and Multivariable Logistic Regression Analysis for the Achievement of Pathological Complete Response after Neoadjuvant Chemotherapy

Variables	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
ΔVbd%						
Stable	Ref			Ref		
Decreased	0.405	0.221–0.741	0.003	0.420	0.195–0.905	0.027
Increased	1.012	0.585–1.749	0.967	1.043	0.525–2.070	0.905
Post-NCT Qabd						
Q1	Ref			Ref		
Q2	0.284	0.101–0.798	0.017	0.222	0.058–0.854	0.029
Q3	0.235	0.083–0.665	0.006	0.151	0.037–0.618	0.008
Q4	0.269	0.083–0.873	0.029	0.199	0.040–1.002	0.050
Menopausal status						
Premenopause	Ref			Ref		
Postmenopause	1.571	1.011–2.440	0.045	0.903	0.475–1.720	0.757
BMI, kg/m^2						
< 23	Ref			Ref		
23– < 27	0.985	0.617–1.573	0.950	1.154	0.626–2.129	0.646
≥ 27	0.500	0.250–1.002	0.051	0.769	0.316–1.872	0.563
N stage at diagnosis						
cN0	Ref			Ref		
cN1	0.314	0.181–0.543	< 0.001	0.345	0.170–0.700	0.003
cN2-3	0.599	0.318–1.130	0.113	0.408	0.185–0.898	0.026
NCT regimen						
A, Taxane or combined	Ref			Ref		
A → Taxane + anti-HER2 agent	3.265	1.923–5.542	< 0.001	3.557	1.250–10.123	0.017
Taxane + anti-HER2 agent	4.229	1.832–9.762	0.001	3.157	0.858–11.616	0.084
Histologic grade						
I/II	Ref			Ref		
III	6.744	3.986–11.409	< 0.001	3.986	2.065–7.696	< 0.001
Breast cancer subtype						
Luminal A-like	Ref			Ref		
Luminal B-like	7.774	2.994–20.180	< 0.001	2.742	0.838–8.971	0.095
HER2-positive	30.757	11.744–80.551	< 0.001	7.150	1.715–29.800	0.007
TNBC	19.269	7.776–47.809	< 0.001	6.533	2.327–18.340	< 0.001
ΔVbd% x Breast cancer subtype						0.002
Decreased x Luminal B-like				0.199	0.045–0.871	0.032
Decreased x HER2-positive				5.965	1.179–30.182	0.031
Decreased x TNBC				0.852	0.316–2.296	0.752
Increased x Luminal B-like				1.136	0.324–3.989	0.842
Increased x HER2-positive				1.740	0.610–4.958	0.300
Increased x TNBC				3.976	1.714–9.225	0.001

OR = odds ratio, CI = confidence interval, Vbd = volumetric breast density, NCT = neoadjuvant chemotherapy, Qabd = quantized density, BMI = body mass index, Ref = reference category, A = anthracycline, HER2 = human epidermal growth factor receptor 2, TNBC = triple-negative breast cancer

adjusted for the analysis. Third, even if the same inspectors perform examinations on the same patient using the same equipment at a single institution, imaging parameters may differ between examinations because the machine runs automatically with settings decided by the patient's present condition. NCT can change the tumor status of the breast, and such changes may be more pronounced in patients with pCR. Finally, patients who could not be assessed for MD were

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Table 4. Association between ΔVbd% and pCR Stratified by Breast Cancer Subtype

	Decreased ΔVbd%	Stable ΔVbd%	Increased ΔVbd%	*P*
Luminal A-like				0.451
pCR	3 (10.0)	3 (5.0)	0 (0.0)	
Non-pCR	27 (90.0)	57 (95.0)	19 (100)	
Luminal B-like				0.030
pCR	2 (9.1)	18 (40.9)	4 (36.4)	
Non-pCR	20 (90.9)	26 (59.1)	7 (63.6)	
HER2-positive				0.282
pCR	6 (75.0)	30 (68.2)	7 (46.7)	
Non-pCR	2 (25.0)	14 (31.8)	8 (53.3)	
TNBC				0.042
pCR	6 (30.0)	31 (54.4)	18 (66.7)	
Non-pCR	14 (70.0)	26 (45.6)	9 (33.3)	

Data are number of patients (%). Vbd = volumetric breast density, pCR = pathological complete response, HER2 = human epidermal growth factor receptor 2, TNBC = triple-negative breast cancer

excluded from this analysis, and the potential for selection bias remained.

In conclusion, chemotherapy with or without anti-HER2 therapy decreased the breast density, and ΔVbd% was associated with the likelihood of achieving pCR after NCT in patients with breast cancer. A decreased ΔVbd% after NCT may be an unfavorable factor for pCR, especially for the luminal B-like or TNBC subtypes. Automated measurement of ΔVbd% can be considered when predicting treatment response to NCT and cancer prognosis. A larger study is required to validate our results.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due their containing information that could compromise the privacy of research participants but are available from the corresponding author on reasonable request.

Conflicts of Interest

Min Jung Kim, a contributing editor of the *Korean Journal of Radiology*, was not involved in the editorial evaluation or decision to publish this article. All remaining authors have declared no conflicts of interest.

Author Contributions

Conceptualization: Min Jung Kim, Seho Park. Data curation: Seho Park, Jee Hyun Ahn. Formal analysis: Seho Park, Jee Hyun Ahn. Funding acquisition: Min Jung Kim. Investigation: Seho Park, Jee Hyun Ahn, Jieon Go, Suk Jun Lee. Methodology: Seho Park, Min Jung Kim. Project administration: Seho Park, Min Jung Kim. Resources: Byeong-Woo Park, Seung Il Kim, Seho Park, Hyung Seok Park, Jee Ye Kim, Min Jung Kim, Jung Hyun Yoon, Vivian Youngjean Park. Software: Seho Park, Jee Hyun Ahn. Supervision: Seho Park, Min Jung Kim. Validation: Seho Park, Jee Hyun Ahn. Visualization: Seho Park, Jee Hyun Ahn. Writing—original draft: Seho Park, Jee Hyun Ahn. Writing—review & editing: Min Jung Kim, Seho Park, Jee Hyun Ahn.

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