Predicting the response of neoadjuvant chemotherapy in hormone receptor-positive and HER2-negative breast cancer with axillary lymph node metastasis by a multigene assay (GenesWell™ BCT)

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Abstract

The GenesWell™ BCT (BCT score) is a recently developed multigene assay that predicts the risk of distant recurrence in patients with hormone receptor-positive (HR+) and HER2 negative (HER2-) early breast cancer (BC). The ability of the assay to predict the response to neoadjuvant chemotherapy (NACT) has not been established to date. Biopsy specimens of HR+/HER2- BC patients with axillary lymph node (LN) metastasis who underwent NACT were analyzed using the BCT score. The modified breast cancer test (BCT) score was developed and classified into high-and low-response groups. A total of 88 patients were available for the BCT score among 108 eligible patients. The median follow-up duration was 35.9 (7.8-128.5) months. Among these, 61 (65.1%) had cN1 and 53 (60.2%) had cT1 or T2. The BCT score was low in 25 (28.4%) patients and high in 63 (71.6%) patients. Among 50 patients with pathologic complete response or partial response, 41 (82.0%) were in the high-response group, and 9 (18.0%) were in the low-response group. Among 38 patients with stable disease or progressive disease, 22 (57.9%) patients were in the high-response group, and 16 (42.1%) were in the low-response group ($p = 0.025$). Ki-67 before NACT was a significant factor for predicting tumor response ($p = 0.006$; 3.81 [1.50-10.16]). The BCT score showed a significant response to NACT ($p = 0.016$; 4.18 [1.34–14.28]). A significant difference was found in distant metastasis-free survival between the high and low response groups ($p = 0.004$). We demonstrated that the BCT score predicts NACT responsiveness of HR+/HER2- BC with LN metastasis and might help determine whether to undergo NACT or not. Further studies are warranted to validate these findings.

Introduction

Over the decades, neoadjuvant chemotherapy (NACT) has become the standard treatment for locally advanced breast cancer (BC) and a treatment option for many patients with human epidermal growth factor-2 positive (HER2+), triple negative early BC[1]. NACT can render previously inoperable BC amenable to surgical resection and has the potential to increase surgical de-escalation to the breast and axilla by downstaging both breast tumors and axillary lymph nodes (LNs)[2]. Pathologic complete response (pCR) is a surrogate marker for improved survival of patients with the HER2+, triple-negative, or luminal B subtype after NACT for BC[3,4]. In addition, NACT enables the assessment of sensitivity to specific drugs *in vivo* and allows additional therapeutic strategies according to the NACT response.

In contrast, the benefits of NACT for patients with hormone receptor-positive (HR+)/HER2- BC are limited because of the substantial rates of pCR[4,5]. Furthermore, the HR+/HER2- subtype is the most common subtype, which comprises 60%-70% of all BC cases, unresponsive to NACT; patients have a high risk of delay in surgery for the primary tumor, progression of cancer, and the increasing possibility of tumor cell dissemination. Consequently, appropriate patient selection for NACT is necessary.

Multigene assays using breast tumor RNA expression profiles have been highly successful as prognostic markers to aid decision-making for adjuvant chemotherapy. RNA expression signatures from formalin-fixed, paraffin-embedded (FFPE) surgical specimens are now commercially available to assess prognosis in estrogen receptor positive (ER+) in early and pN1 BC patients. Furthermore, pT1-2N0M0 with ER+/HER2- BC combined with a low risk of multigene panels are expected to be categorized as stage IA according to the National Comprehensive Cancer Network guidelines. Therefore, many clinicians are interested in the ability of the NACT response in patients using FFPE breast biopsy specimens. Several studies have evaluated the ability of various multigene assays to predict the response of NACT using FFPE biopsy specimens before surgery. However, few studies have predicted the response to NACT using a multigene assay with FFPE breast biopsy specimens[6–10]. Here, we analyzed GenesWell™ BCT (BCT score), a recently developed multigene assay that predicts the risk of distant recurrence in patients with HR+/HER2- early BC and ability to predict the response to NACT in BC with axillary LN metastasis using FFPE breast biopsy specimens.

Results

Patient selection. A total of 88 patients were available for the BCT scores among the 108 eligible patients (Table 1). The median follow-up duration was 35.9 months (7.8-128.5). Accordingly, 63 (71.6%) patients were assigned to the BCT score as a high-response group, and 25 (28.4%) patients were assigned to the low-response group. Among these, 61 (65.1%) had cN1, and 53 (60.2%) had cT1 or cT2. Among the 50 patients who responded to pCR or PR, 41 (82.0%) were in the high-response group and 9 (18.0%) were in the low-response group. Among 38 patients with SD or PD, 22 (57.9%) patients were in the high-response group, and 16 (42.1%) were in the low-response group; there were significant differences between the two groups ($p = 0.025$). Ki-67, a proliferative marker, is well divided into high and low response groups of the BCT score based on the 1 + score ($p = 0.030$). No significant differences were observed in clinical and ypT and N stages and grades after NACT between the high and low BCT score groups.

Table 1
Demographics and baseline characteristics of all patients.

	All patients	BCT score		p-value
		High	Low	
N	88	63	25	
cT				0.788
1 or 2	53 (60.2%)	39 (61.9%)	14 (56.0%)	
3 or 4	35 (39.8%)	24 (38.1%)	11 (44.0%)	
cN				0.308
1	61 (69.3%)	41 (65.1%)	20 (80.0%)	
2 or 3	26 (29.5%)	21 (33.3%)	5 (20.0%)	
NA	1 (1.1%)	1 (1.6%)	0 (0.0%)	
Response				**0.025**
pCR or PR	50 (56.8%)	41 (65.1%)	9 (36.0%)	
SD or PD	38 (43.2%)	22 (34.9%)	16 (64.0%)	
RCB Class				1.000
0 or I	15 (17.0%)	11 (17.5%)	4 (16.0%)	
II or III	73 (83.0%)	52 (82.5%)	21 (84.0%)	
Ki-67†				**0.030**
1+	33 (37.5%)	19 (30.2%)	14 (56.0%)	
> 1+	54 (61.4%)	44 (69.8%)	10 (40.0%)	
NA	1 (1.1%)	0 (0.0%)	1 (4.0%)	
Grade after NACT				0.238
0 or 1	18 (20.5%)	11 (17.5%)	7 (28.0%)	
2 or 3	67 (76.1%)	51 (80.9%)	16 (64.0%)	
NA	3 (3.4%)	1 (1.6%)	2 (8.0%)	
pT after NACT				0.160
0–2	67 (76.1%)	51 (81.0%)	16 (64.0%)	
3 or 4	21 (23.9%)	12 (19.0%)	9 (36.0%)	
pN after NACT				0.636
0	20 (22.7%)	16 (25.4%)	4 (16.0%)	
1	32 (36.4%)	22 (34.9%)	10 (40.0%)	
2 or 3	36 (40.9%)	25 (39.7%)	11 (44.0%)	

† Ki-67 index measurement methods are as follows. 1 + were divided on the basis of 25% of nuclear expression in the ratio of stained and unstained cells quantitatively. See “Data collection” in the article for details.

cT, clinical T staging; cN, clinical N staging; pCR, pathologic complete response; PR, partial response; SD, stable disease; PD, progressive disease; RCB, residual cancer burden; NACT, neoadjuvant chemotherapy; pT, pathologic T staging; pN, pathologic N staging

Except for weakly ER + patients, we divided subgroups into strongly ER + patients with an Allred score of > 5 and analyzed the same clinicopathologic parameters (Table 2). The BCT score showed significant differences in tumor response and Ki-67, similar to the analysis of all patients. When plotting the BCT score distribution as a histogram, no difference was found in the distribution of the BCT score between the two groups, and the distribution of pCR or PR was high with a BCT score of ≥ 4 (Fig. 1).

Table 2
Demographics and baseline characteristics of strongly ER-positive patients (ER > 5)

	Strongly ER + patients	BCT score		p-value
		High	Low	
n	79	57	22	
cT				0.610
1 or 2	45 (57.0%)	34 (59.6%)	11 (50.0%)	
3 or 4	34 (43.0%)	23 (40.4%)	11 (50.0%)	
cN				0.182
1	58 (73.4%)	39 (68.4%)	19 (86.4%)	
2 or 3	21 (26.6%)	18 (31.6%)	3 (13.6%)	
NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Response				0.004
pCR or PR	44 (55.7%)	38 (66.7%)	6 (27.3%)	
SD or PD	35 (44.3%)	19 (33.3%)	16 (72.7%)	
RCB Class				0.169
0 or I	11 (13.9%)	10 (17.5%)	1 (4.5%)	
II or III	68 (86.1%)	47 (82.5%)	21 (95.5%)	
Ki-67†				0.044
1+	32 (40.5%)	19 (33.3%)	13 (59.1%)	
> 1+	46 (58.2%)	38 (66.7%)	8 (36.4%)	
NA	1 (1.3%)	0 (0.0%)	1 (4.5%)	
Grade after NAC				0.543
0 or 1	17 (21.5%)	11 (19.3%)	6 (27.3%)	
2 or 3	62 (78.5%)	46 (80.7%)	16 (72.7%)	
NA	0 (0.0%)	0 (0.0%)	0 (0.0%)	
pT after NAC				0.132
0–2	58 (73.4%)	45 (78.9%)	13 (59.1%)	
3 or 4	21 (26.6%)	12 (21.1%)	9 (40.9%)	
pN after NAC				0.162
0	14 (17.7%)	13 (22.8%)	1 (4.5%)	
1	30 (38.0%)	20 (35.1%)	10 (45.5%)	
2 or 3	35 (44.3%)	24 (42.1%)	11 (50.0%)	

† Ki-67 index measurement methods are as follows. 1 + were divided on the basis of 25% of nuclear expression in the ratio of stained and unstained cells quantitatively. See “Data collection” in the article for details.

cT, clinical T staging; cN, clinical N staging; pCR, pathologic complete response; PR, partial response; SD, stable disease; PD, progressive disease; RCB, residual cancer burden; NACT, neoadjuvant chemotherapy; pT, pathologic T staging; pN, pathologic N staging.

The predictive value of the BCT score in NACT was indicated for all patients, especially in strongly ER + patients (Table 3). The sensitivity and specificity were higher in the strongly ER + group than in the all-patient group (sensitivity: 86.4% vs. 82.0%, specificity: 45.7% vs. 42.1%). The positive predictive value (PPV) and negative predictive value (NPV) were also higher in the strongly ER + group than in the all-patient group (PPV, 66.7% vs. 65.1%; NPV, 72.7% vs. 64.0%). This result demonstrates that the BCT score predicts tumor response in strongly ER + patients.

Table 3
Predictive value of the BCT score with all and strongly ER-positive (ER > 5) in each patient.

All patients (n = 88)	pCR or PR	SD or PD	
Low	9	16	Negative Predictive Value (NPV) 64.0% (42.5–82.0%)
High	41	22	Positive Predictive Value (PPV) 65.1% (52.0-76.7%)
	Sensitivity 82.0% (68.6–91.4%)	Specificity 42.1% (26.3–59.2%)	

The BCT score and clinicopathological parameters were analyzed using univariate and multivariate logistic regression analyses to identify factors related to tumor response (Table 4). cT1/2 and cN1 did not show a significant NACT response (p = 0.090; odds ratio [OR] (95% confidence interval [CI]), 0.47 [0.19–1.12] and p = 0.617; 1.27 [0.50–3.32]). A high molecular score and more than 1 + score of Ki-67 showed a significantly positive correlation with tumor response (p = 0.015; 3.31 [1.28–9.02] and p = 0.009; 3.35 [1.38–8.46]) in all patient groups and strongly ER + group (p = 0.003; 5.33 [1.87–16.96], p = 0.006; 3.81 [1.50-10.16]). The BCT score was the only significant factor related to tumor response in the multivariate analysis (p = 0.016; 4.18 [1.34–14.28]).

Table 4
Univariate and Multivariate Logistic Regression Analyses with the BCT score and clinicopathologic parameters with all and strongly ER-positive (ER > 5) in each patient.

Strongly ER + patients (n = 79)	pCR/PR	SD/PD		
Low	6	16	Negative Predictive Value (NPV) 72.7% (49.8–89.3%)	
High	38	19	Positive Predictive Value (PPV) 66.7% (52.9–78.6%)	
	Sensitivity 86.4% (72.7–94.8%)	Specificity 45.7% (28.8–63.4%)		
All patients (n = 88)	**Univariate**		**Multivariate**	
Parameter	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**
BCT score (low versus high)	3.31 (1.28–9.02)	0.015	2.62 (0.93–7.65)	0.070
cT stage (cT1 or 2 versus cT3 or 4)	0.47 (0.19–1.12)	0.090	0.54 (0.20–1.45)	0.223
cN stage (cN1 versus cN2 or 3)	1.27 (0.50–3.32)	0.617	1.19 (0.42–3.46)	0.743
Ki-67 (1 + versus > 1+)	3.35 (1.38–8.46)	0.009	2.60 (0.99 – 0.97)	0.054

Discussion

This study investigated the predictive responsiveness of NACT to tumors and identified factors related to NACT using the BCT score in HR+/HER2- BC with metastatic LN. We demonstrated that the high-response group could predict pCR and PR for NACT in HR+/HER2- BC with metastatic LN.

Although NACT has been established as a standard treatment option for HER2 + and triple-negative BC (TNBC) subtypes, many oncologists still have difficulty determining NACT in HR + BC because of the low rate of pCR and limited benefit of NACT for HR + BC[4]. As the application of ACOSOG Z0011 and AMAROS to axillary treatment has expanded and pCR rate has increased in the HER2 and TNBC subtypes in NACT, axillary de-escalation is increasing in patients with positive axillary LN[11–13]. Ironically, although luminal type breast cancers show favorable biologic characteristics compared with HER2 and TNBC subtypes, axillary LN dissection continues in terms of axillary treatment in the luminal subtype[14]. Therefore, many efforts are being made to predict the responsiveness of NACT in HR + BC using various modalities such as multigene assay and clinicopathologic scale.

Recently, attempts have been made to predict the responsiveness of NACT using multigene assays in HR+/HER2- BC. The BCT score was developed to predict the risk of distant metastasis and responsiveness of chemotherapy using five proliferation-related genes, one immune response-related gene, and clinical information such as tumor size and nodal status[15,16]. Through this study, it was shown that concordant results were obtained when comparing the predictive power of pCR with existing gene tests in predicting NACT responsiveness (Table 5)[8,9,17–22].

Table 5
Comparison table of multigene assay for predicting NACT responsiveness in hormone receptor-positive breast cancer.

Strongly ER + patients (n = 79)	Univariate		Multivariate	
Parameter	**OR (95% C.I.)**	**p-value**	**OR (95% C.I.)**	**p-value**
BCT score (low versus high)	5.33 (1.87–16.96)	0.003	4.18 (1.34–14.28)	0.016
cT stage (cT1 or 2 versus cT3 or 4)	0.44 (0.17–1.07)	0.074	0.58 (0.20–1.65)	0.303
cN stage (cN1 versus cN2 or 3)	1.08 (0.40–3.03)	0.876	0.89 (0.28–2.93)	0.847
Ki-67 (1 + versus > 1+)	3.81 (1.50-10.16)	0.006	2.74 (0.99–7.79)	0.054

	Multigene assay	Sample (no.)	pCR (%)	pCR or PR (%)	Age (mean)	cT1 or 2 (%)	cT3+ (%)	cN0 (%)	cN+ (%)	Tumor grade 1 (%)	Tumor grade 2/3 (%)	Ki-67 > 1+	Odds Ratio
A.M.Pease et al. (2019)	Oncotype Dx®	989	42 (4.3)	N/A	54.6	882 (89.2)	107 (10.8)	757 (76.5)	232 (23.5)	123 (12.4)	866 (87.6)	N/A	4.87 [2.01–11.82]
H. Iwata et al. (2019)	Oncotype Dx®	295	N/A	133 (45.1)	63.0	295 (100)	0 (0)	295 (100)	0 (0)	195 (66.1)	86 (29.2)	184 (62.4)	0.06 [0.01–0.18]
J.A.Pardo et al. (2021)	Oncotype Dx®	158	10 (6.3)	N/A	N/A	158 (100)	0 (0)	0 (0)	158 (100)	105 (66.5)	53 (33.5)	N/A	3.16 [1.06–9.45]
T. Sella et al. (2021)	Oncotype Dx®	76	10 (13.2)	N/A	35.9	51 (67.1)	25 (32.9)	20 (26.3)	56 (73.7)	4 (5.3)	71 (93.4)	N/A	4.80 [0.95–24.34]
A.M.Ohara (2019)	Prosigna™ (PAM50)	124	12 (9.7)	N/A	51.3	98 (79.0)	26 (21.0)	41 (33.1)	83 (66.9)	25 (20.2)	99 (79.8)	59 (47.6)	6.98 [1.17-133.97]
F.Bertucci et al.(2014)	EndoPredict®	553	64 (11.6)	N/A	49.0	40 (7.2)	512 (92.6)	183 (33.1)	336 (60.8)	47 (8.50)	464 (83.9)	N/A	1.13 [1.04–1.24]
P.C.Dubsky et al.(2020)	EndoPredict®	134	N/A	N/A	N/A	116 (86.6)	18 (13.4)	69 (51.5)	63 (47.0)	1 (0.7)	121 (90.3)	N/A	1.44 [1.20–1.74]
M.C.Mathieu, el al. (2012)	Breast Cancer Index^{SM}	150	22 (14.7)	N/A	51.0	97 (64.7)	53 (35.3)	70 (46.7)	76 (50.7)	16 (10.7)	132 (88.0)	N/A	26.25 [3.19-216.24]
Present study	GenesWell™ BCT	88	6 (6.8)	50 (56.8)	N/A	53 (60.2)	35 (39.8)	0 (0)	87 (98.9)	18 (20.5)	67 (76.1)	54 (61.4)	4.18 [1.34–14.28]

According to the latest ASCO/CAP guidelines, only 1%-10% of ER expression by IHC is divided by low positive ER[23]. Low ER has a property similar to basal-like gene expression profiles as shown in the TNBC subtype; thus, it is emerging as an important prognostic factor for consideration of NACT[24,25]. Moreover, in the case of the strongly ER + group in this study, the predictive power of pCR and PR was higher in the BCT high response group than in the all-patient group. In other words, the response to NACT was high even in the BCT low-response group in the case of the weakly ER + group. Therefore, our results demonstrate that the BCT score clearly predicts tumor response and is an independent factor for predicting tumor response in NACT, especially in strongly ER + patients.

Although this study is a retrospective, single-center study with a small sample size, it is significant as it predicted the NACT response from the core biopsy sample for the first time using the BCT score. In addition, efforts have also been made to predict the responsiveness of neoadjuvant endocrine therapy (NET) by multigene assay[21,26]. Further studies are needed to prove the predictive potential of the BCT score response to NET in Asian patients with BC

because many multigene assays have been developed with a focus on the Western population[27,28]. Although the number of patients with pCR was so small that we could not show the BCT score as a tool to determine surgical de-escalation, the BCT score might be a helpful gene test for determining the surgical treatment plan after NACT if larger populations are included.

In conclusion, we demonstrated that the BCT score predicts NACT responsiveness in HR+/HER2- BC with LN metastasis. The BCT score might be an early surrogate of prognostic signatures for predicting the response of NACT in HR+/HER2- BC with LN metastasis. Therefore, the BCT score might be a helpful tool for predicting NACT responsiveness in HR+/HER2- BC with LN metastasis. Further validation using the BCT score and prospective studies is needed to increase the accuracy of the prediction of the NACT response.

Materials And Methods

Patient selection. A retrospective review was conducted among cytology-proven HR+/HER2- BC patients with axillary LN metastasis who underwent NACT followed by surgery at Samsung Medical Center (SMC) between January 2008 and December 2018. We excluded the following: distant metastasis at presentation, lack of immunohistochemistry (IHC) data for ER, progesterone receptor (PR), and HER2, lack of biopsy slides, insufficient RNA concentration or tumor volume, and inadequate the BCT score test (Fig. 2).

Data collection. We collected the following variables: age at operation, clinical stage, and pathologic stage according to the 8th edition of the American Joint Committee on Cancer classification[10], histopathology, nuclear grade, histologic grade, lymphovascular invasion, Ki-67 (pre-NACT and post-NACT), ER, PR, HER2 status, and type of adjuvant treatment such as chemotherapy, radiotherapy, and hormonal therapy. Ki-67 labeling index was calculated in the following way. Nuclear expression was analyzed quantitatively and at least 1,000 cells were assessed to calculate labeling index. Pathologists identify the ratio of stained and unstained cells, 1 + were divided on the basis of 25%. Tumor volume was calculated as the tumor tissue/total tissue. Tumor response was analyzed using the Response Evaluation Criteria in Solid Tumors[29]. pCR was defined as breast Tis/T0 and N0, partial response (PR) as ≥ 50% decrease in total tumor lesions by two observations not less than 4 weeks apart, stable disease (SD) as neither PR nor progressive disease, and progressive disease (PD) as ≥ 25% increase in the size of one or more measurable lesions or the appearance of new lesions[30]. According to the tumor response to NACT, we set pCR and PR as endpoints because there were only six patients with pCR. The dates of recurrence and death were collected by reviewing the electronic medical charts.

BCT score assay. The BCT score criteria were referenced from a previous study. The modified BCT score was developed as follows and classified as high or low according to the NACT response (Fig. 3). Some modifications were made to the existing algorithm because clinical information on tumor size and nodal status is applied, which is not suitable for the NACT setting. The cut-off of the BCT score was set to 4, the same as the previous paper as the point where the sum of sensitivity and specificity becomes maximum.

Statistical analyses. Patient characteristics were compared using independent t-tests for continuous variables and the chi-square or Fisher's exact test for categorical variables. Values are reported as the mean ± standard deviation or median with ranges. Patients with missing or unknown data were excluded from analysis using the Cox model. All tests were two-sided, and statistical significance was set at $p < 0.05$. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.4.0 (Vienna, Austria; http://www.R-proje ct.org).

Ethics. The requirement for informed consent was waived because of the low risk posed by this study. This study adhered to the ethical tenets of the Declaration of Helsinki. The present study was approved by the Institutional Review Board (IRB) of Samsung Medical Center in South Korea (IRB No.: 2018-12-096).

Declarations

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Conflicts of Interest

The authors declare no competing interests.

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Figures

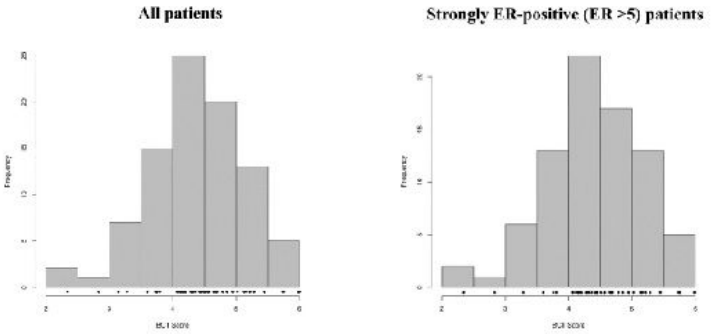

Figure 1

Distribution of the BCT score in the histogram with the all patients and strongly ER-positive patient groups

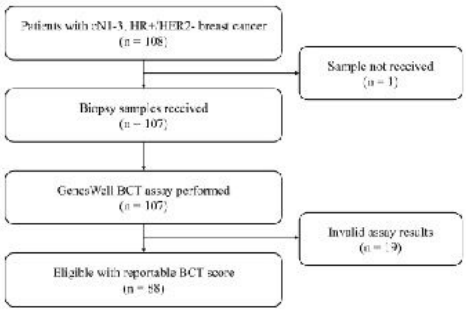

Figure 2

Consort flow diagram of eligible patient selection for the BCT score analysis

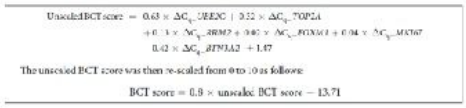

Figure 3

Development of modified BCT score model using molecular data