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Original Article

Relationship Between Breast and Axillary Pathologic Complete Response According to Clinical Nodal Stage: A Nationwide Study From Korean Breast Cancer Society

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ABSTRACT

Purpose: We evaluated the relationship between breast pathologic complete response (BpCR) and axillary pathologic complete response (ApCR) after neoadjuvant chemotherapy (NACT) according to nodal burden at presentation. As the indications for NACT have expanded, clinicians have started clinical trials for the omission of surgery from the treatment plan in patients with excellent responses to NACT. However, the appropriate indications for axillary surgery omission after excellent NACT response remain unclear.
Methods: Data were collected from patients in the Korean Breast Cancer Society Registry who underwent NACT followed by surgery between 2010 and 2020. We analyzed pathologic axillary nodal positivity after NACT according to BpCR stratified by tumor subtype in patients with cT1-3/N0-2 disease at diagnosis.
Results: A total of 6,597 patients were identified. Regarding cT stage, 528 (9.5%), 3,778 (67.8%), and 1,268 (22.7%) patients had cT1, cT2, and cT3 disease, respectively. Regarding cN stage, 1,539 (27.7%), 2,976 (53.6%), and 1,036 (18.7%) patients had cN0, cN1, and cN2 disease, respectively. BpCR occurred in 21.6% (n = 1,427) of patients, while ApCR and pathologic complete response (ypCR) occurred in 59.7% (n = 3,929) and ypCR 19.4% (n = 1,285) of patients, respectively. The distribution of biologic subtypes included 2,329 (39.3%) patients with hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative disease, 1,122 (18.9%) with HR-positive/HER2-positive disease, 405 (6.8%) with HR-negative/HER2-positive disease, and 2,072 (35.0%) with triple-negative breast cancer . Among the patients with BpCR, 89.6% (1,122/1,252) had ApCR. Of those with cN0 disease, most (99.0%, 301/304) showed ApCR. Among patients with cN1-2 disease, 86.6% (821/948) had ApCR.

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Conflict of Interest

The authors declared that have no competing interests.

Author Contributions

Conceptualization: Lee JE; Data curation: Park EH, Kim JY, Lee YJ, Park S, Lee J, Park HK; Supervision: Nam SJ, Kim SW; Visualization: Lee JH; Writing - original draft: Ryu JM, Choi HJ.

Conclusion: BpCR was highly correlated with ApCR after NACT. In patients with cN0 and BpCR, the risk of missing axillary nodal metastasis was low after NACT. Further research on axillary surgery omission in patients with cN0 disease is needed.

Keywords: Breast Neoplasms; Complete Response; Neoadjuvant Therapy

INTRODUCTION

One application of neoadjuvant chemotherapy (NACT) for breast cancer (BC) is the downstaging of inoperable tumors into operable tumors [1-3]. Over several decades, the response patterns to NACT have been used to design tailored treatments. An excellent response to NACT could allow the de-escalation of breast and axillary surgeries, including breast-conserving surgery (BCS) or sentinel lymph node biopsy (SLNB) in patients who are candidates for total mastectomy or axillary lymph node dissection (ALND) before NACT [4-6].

Studies that evaluated the addition of dual human epidermal growth factor-2 (HER2) blockage in HER2-positive BC and carboplatin in triple-negative breast cancer (TNBC) revealed pathologic complete response (ypCR) rates of up to 68% and 80%, respectively [7-9]. Accordingly, the indications for NACT have expanded to early BC and the expected ypCR rate has increased. Thus, it may be reasonable to consider omitting surgery in cases with excellent responses to NACT. Several recent retrospective studies and pilot prospective studies have reported on the possibility of breast surgery omission; however, the findings were controversial and many clinicians were reluctant to omit breast surgery [10,11]. In contrast, patients with an excellent response to NACT on imaging may only require minimal BCS. Oncoplastic surgery techniques are highly developed, and minimal breast deformities are expected. However, although SLNB is minimally invasive, some patients still experience complications such as lymphedema.

A prospective cohort study from the MD Anderson Cancer Center (MDACC) reported pathologic node negativity (pN0) in 100% of 527 patients with clinically node-negative (cN0) cT1/cT2 TNBC or HER-positive breast cancer who underwent NACT who achieved breast pathologic complete response (BpCR). Moreover, Barron et al. reported a nodal positivity rate of < 2.0% in the same patient group using the National Cancer Database (NCDB) [12,13]. A retrospective study from the Samsung Medical Center (SMC) in Korea reported that 96.4% of cT1-T3/cN0 patients with BpCR showed pN0 after NACT [14]. Although the findings of this study were concordant with those of the NCDB and MDACC studies, few results regarding the relationship between BpCR and pN0 after NACT were reported.

Using a clinical trial design, we evaluated the relationship between BpCR and pN0 after NACT using nationwide data from the Korea Breast Cancer Society Registry (KBCSR) to identify the optimal candidates for axillary surgery omission after NACT.

METHODS

We identified 11,064 patients who underwent NACT followed by surgery. We excluded the following cases: cT4 or cN3, ypT4 or ypN3, distant metastasis at presentation or after NACT, pregnancy-associated BC, and no axillary surgery. Patients with clinical and pathologic T4 or

N3 disease and distant metastasis were excluded because they were judged to be errors in the effectiveness of NACT as they very advanced stages of BC.

Data collection

Data from an online BC registration program collected by the KBCSR for patients who underwent NACT followed by surgery between January 2010 and March 2020 were retrospectively reviewed. The KBCSR is a nationwide BC database of the KBCS. Detailed information about the KBCSR has been provided previously [15].

Clinicopathologic data

We collected data on age at diagnosis; sex; clinical TN stage; family history of breast cancer; type of breast and axillary surgery; pathologic stage; nuclear grade (NG); histological grade (HG); and estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67, BpCR, and ypN0 statuses. Tumors were classified into four subtypes: hormone receptor (HR)-positive/HER2-negative; HR-positive/HER2-positive; HR-negative/HER2-positive; and TNBC (HR-negative/HER2-negative). ER, PR, and HER2 statuses were assessed in surgical specimens at each center using routine immunohistochemistry protocols. We analyzed pathologic axillary nodal positivity after NACT (ypN positivity) according to BpCR (vs. residual breast disease) stratified by tumor subtype in patients with cN0, cN1, and cN2 disease at diagnosis. cN0-2 was defined as the clinical axillary stage before NACT. The KBCSR collected clinical staging data before NACT, and the pathologic staging after surgery was based on the 8th edition of the American Joint Committee on Cancer TNM Staging System. BpCR was defined as no invasive disease (ypT0 or ypTis) on permanent pathologic results.

Statistical analysis

Patient characteristics were compared using independent *t*-tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Values are reported as means ± standard deviation (SD) or medians with ranges. All tests were two-sided, and $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R3.6.1 (Vienna, Austria; http://www.R-proje ct.org).

Ethics

This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of SMC (IRB number: 2020-03-022). The need for informed consent was waived due to the low risk posed by this study.

RESULTS

We identified 6,597 patients with cT1-3N0-2M0 BC who underwent NACT followed by surgery. A schematic of patient selection is shown in **Figure 1**. The mean age at operation was 47.9 ± 9.9 years. Most patients (n = 6,594, 99.9%) were women. Their clinicopathological characteristics are summarized in **Table 1**. At axillary surgery, 3,101 (47.0%) patients were treated with SLNB only and 3,495 (53.0%) were treated with ALND. According to the clinical T stage, 528 (9.5%), 3,778 (67.8%), and 1,268 (22.7%) patients had cT1, cT2, and cT3 disease, respectively. Regarding the clinical N stage, 1,539 (27.7%), 2,976 (53.6%), and 1,036 (18.7%) patients had cN0, cN1, and cN2 disease, respectively. The BpCR was 21.6% (n = 1,427), axillary pathologic complete response (ApCR) was 59.7% (n = 3,929), and ypCR was 19.4% (n = 1,285). The distribution of biologic subtypes included 2,329 (39.3%) patients with HR-

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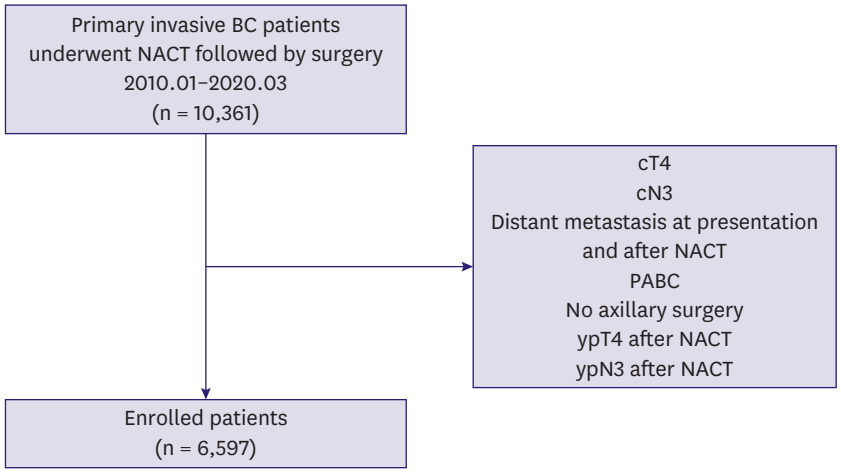

Figure 1. Schematic diagram of patient selection.
NACT = neoadjuvant chemotherapy; PABC = pregnancy-associated breast cancer; BC = breast cancer.

Table 1. Patient characteristics (n = 6,597)

Characteristics	Number	%
Age at operation (yr)		
< 40	1,285	19.5
40–49	2,540	38.5
50–59	1,977	30.0
≥ 60	795	12.0
Sex		
Male	3	0.1
Female	6,594	99.9
Clinical T stage		
cT1	528	9.5
cT2	3,778	67.8
cT3	1,268	22.7
Unknown	1,023	NA
Clinical N stage		
cN0	1,539	27.7
cN1	2,976	53.6
cN2	1,036	18.7
Unknown	1,046	NA
Breast operation		
BCS	3,538	53.6
TM	3,059	46.4
Axillary operation		
SLNB	3,101	47.0
ALND	3,495	53.0
Unknown	1	NA
Nuclear grade		
Low	299	6.1
Intermediate	2,321	47.5
High	2,233	46.4
Unknown	1,744	NA
Histologic grade		
Well differentiated	587	11.4
Moderate differentiated	2,846	55.3
Poorly differentiated	1,711	33.3
Unknown	1,453	NA

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Table 1. (Continued) Patient characteristics (n = 6,597)

Characteristics	Number	%
Pathologic T stage		
ypT0 (No residual tumor)	915	13.9
ypTis	512	7.8
ypT1	2,912	44.3
ypT2	1,875	28.5
ypT3	360	5.5
Unknown	23	NA
Pathologic N stage		
ypN0	3,929	59.6
ypN1	1,986	30.2
ypN2	662	10.2
Unknown	20	NA
ER status		
Negative	2,591	40.5
Positive	3,806	59.5
Unknown	200	NA
PR status		
Negative	3,395	56.7
Positive	2,595	43.3
Unknown	607	NA
HER2 status		
Negative	4,268	71.8
Positive	1,527	25.7
Equivocal	153	2.5
Unknown	649	NA
Subtype		
HR-positive/HER2-negative	2,329	39.3
HR-positive/HER2-positive	1,122	18.9
HR-negative/HER2-positive	405	6.8
HR-negative/HER2-negative	2,072	35.0
Unknown	669	NA
Breast response		
BpCR	1,427	21.6
Non-BpCR	5,147	79.0
Unknown	23	NA
Axillary response		
ApCR	3,929	59.7
Non-ApCR	2,648	40.3
Unknown	20	NA
ypCR		
ypCR	1,285	19.4
Non-ypCR	5,289	80.6
Unknown	23	NA

NA = not available; BCS = breast-conserving surgery; TM = total mastectomy; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection; ER = estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor-2; HR = hormone receptor; BpCR = breast pathologic complete response; ApCR = axillary pathologic complete response; ypCR = pathologic complete response.

positive/HER2-negative disease, 1,122 (18.9%) with HR-positive/HER2-positive disease, 405 (6.8%) with HR-negative/HER2-positive disease, and 2,072 (35.0%) with TNBC.

BpCR and ApCR according to biologic subtype

BpCR and ApCR according to biological subtype are shown in **Table 2**. BpCR and ApCR differed significantly according to the BC biological subtype ($p < 0.001$).

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Table 2. BpCR and ApCR according to biologic subtype

Subtype	BpCR	Non-BpCR	ApCR	Non-ApCR	ypCR	Non-ypCR	*p*-value*	*p*-value†	*p*-value‡
HR positive/HER2 negative	388 (16.6)	1,935 (83.4)	1,403 (60.1)	920 (39.9)	334 (14.3)	1,999 (85.7)	< 0.0001	< 0.0001	< 0.0001
HR positive/HER2 positive	321 (28.8)	794 (71.2)	724 (64.9)	392 (35.1)	289 (25.9)	988 (74.1)			
HR negative/HER2 positive	55 (13.7)	347 (86.3)	210 (52.2)	192 (47.8)	47 (11.7)	430 (88.3)			
HR negative/HER2 negative	174 (8.4)	1,895 (91.6)	1,027 (49.6)	1,042 (50.4)	154 (7.4)	2,219 (92.6)			
Total	938 (18.9)	4,971 (82.1)	3,664 (57.0)	2,546 (41.0)	824 (12.8)	5,636 (87.2)			

BpCR = breast pathologic complete response; ApCR = axillary pathologic complete response; ypCR = pathologic complete response; HR = hormone receptor; HER2 = human epidermal growth factor-2.
*p-value for BpCR vs. non-BpCR; †p-value for ApCR vs. non-ApCR; ‡p-value for ypCR vs. non-ypCR.

Pathologic ApCR according to BpCR

Among the patients with BpCR, 89.6% (1,122/1,252) had ApCR. Among those with cN0 disease, most (99.0%, 301/304) showed ApCR, while 86.6% (821/948) of patients with cN1-2 disease had ApCR. In contrast, among patients with residual breast disease, 47.4% (2,001/4,219) had ApCR, while 79.2% (970/1,235) and 34.1% (1,031/3,024) of patients with cN0 and cN1-2 disease, respectively, showed ApCR (**Table 3**).

Regarding patients with BpCR and residual axillary disease, among those with cN0 disease, only three (1.0%) showed ypN1 disease. Among patients with cN1 disease, 79 (11.4%) showed ypN1 and 10 (1.4%) showed ypN. Among patients with cN2 disease, 36 (13.0%) showed ypN1 and 7 (3.9%) showed ypN2 (**Table 4**). Among patients with BpCR and clinical N0 disease, the ypN0 distribution of biologic subtypes was 96 (100.0%) for HR-positive/HER2-negative disease, 60 (96.8%) for HR-positive/HER2-positive disease, 13 (100.0%) for HR-negative/HER2-positive disease, and 17 (94.4%) for TNBC (**Supplementary Table 1**).

Table 3. Pathologic ApCR according to BpCR stratified by clinical tumor and lymph node status

Variables	BpCR			Non-BpCR		
	ApCR	Non-ApCR	*p*-value	ApCR	Non-ApCR	*p*-value
cN0 status			0.007			0.396
cT1	26 (92.9)	2 (7.1)		60 (81.1)	14 (18.9)	
cT2	231 (100.0)	0 (0.0)		745 (79.8)	188 (20.2)	
cT3	44 (97.8)	1 (2.2)		165 (77.5)	53 (22.5)	
cT1-3	301 (99.0)	3 (1.0)		970 (79.2)	255 (20.8)	
cN1 status			0.001			0.034
cT1	79 (79.8)	22 (20.2)		64 (28.3)	162 (71.7)	
cT2	413 (87.9)	49 (12.1)		544 (37.0)	925 (63.0)	
cT3	109 (87.9)	15 (12.1)		181 (33.7)	356 (66.3)	
cT1-3	601 (87.5)	86 (12.5)		789 (34.9)	1,473 (65.1)	
cN2 status			0.050			0.211
cT1	23 (74.2)	8 (25.8)		13 (30.2)	30 (69.8)	
cT2	153 (84.5)	28 (15.5)		160 (34.6)	303 (65.4)	
cT3	44 (89.8)	5 (10.2)		69 (27.0)	187 (73.0)	
cT1-3	220 (84.3)	41 (15.7)		242 (31.8)	520 (68.2)	
cN0-2 status			< 0.001			0.144
cT1	128 (80.0)	32 (20.0)		137 (39.9)	206 (60.1)	
cT2	797 (91.1)	77 (8.9)		1,449 (50.6)	1,416 (49.4)	
cT3	197 (90.4)	21 (9.6)		415 (41.0)	596 (59.0)	
cT1-3	1,122 (89.6)	130 (10.4)		2,001 (47.4)	2,218 (52.6)	

Values are presented as number of patients (%).
ApCR = axillary pathologic complete response; BpCR = breast pathologic complete response.

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Table 4. Pathologic nodal stages after neoadjuvant chemotherapy according to BpCR and clinical lymph nodal stage

Clinical lymph node status	Total		ypN0		ypN1		ypN2	
	Number	%	Number	%	Number	%	Number	%
BpCR	1,427							
cN0	307	24.2	304	99.0	4	1.0	0	0.0
cN1	695	54.8	606	87.2	79	11.4	10	1.4
cN2	266	21.0	223	83.1	36	13.0	7	3.9
cN0-2	1,268*		1,133	88.7	118	9.6	17	1.6
Non-BpCR	5,147							
cN0	1,229	28.8	972	79.1	223	18.2	34	2.7
cN1	2,267	52.2	791	34.9	1,148	50.6	328	14.5
cN2	765	19.0	242	31.6	293	38.3	230	30.1
cN0-2	4,261†		2,055	48.2	1,664	39.0	592	13.8
Total								
cN0	1,536	27.8	1,276	83.1	227	14.7	34	2.2
cN1	2,962	53.6	1,397	47.2	1,227	41.4	338	11.4
cN2	1,031	18.6	465	45.1	329	31.9	237	23.0
cN0-2	5,529‡		3,138	56.8	1,782	32.2	609	11.0

BpCR = breast pathologic complete response.
*Missing data, n = 159; †Missing data, n = 886; ‡Missing data, n = 1,045.

DISCUSSION

The results of this study demonstrated an extremely high rate of ApCR in patients with cN0 disease and BpCR after NACT. Only 1.0% of cN0 and BpCR patients showed ypN1 disease. Predicting ApCR after NACT in patients with BC is important for identifying patients who require less aggressive axillary surgery as a treatment option. In addition, forecasts will be useful for designing future trials to validate the usefulness of patient selection criteria to accurately predict ApCR and to consider axillary surgery omission after NACT.

This study observed higher rates of ypCR in HER2-positive disease. Compared to HR-positive/HER2-negative disease, NACT is currently recommended in HER2-positive or TNBC cases, even in early BC [16,17]. Patients with initial cN0 or N1 and TNBC or HER2-positive breast cancer who achieve BpCR at surgery have a low risk of nodal metastasis (**Table 5**) [12,13,18-22]. These findings are concordant with the results of the present study. Among patients with BC who undergo NACT followed by surgery and radiotherapy, an ypCR in patients with TNBC and HER2 subtypes after NACT is associated with better disease-free survival and overall survival rates [23,24]. Furthermore, patients with radiologic complete response (CR), not ypCR, after NACT were more likely to experience better recurrence-free or overall survival [25].

Table 5. Summary of previous studies of ypN+ rate after NACT with BpCR

Studies	Number	Clinical stage before NACT	ER+/HER2−	HER2+	TNBC	Overall
Barron et al. [12]	6,023	cT1-2, cN0	4.0%	1.6%	1.6%	1.8%
	2,941	cT1-2, cN1	30.5%	12.4%	14.1%	15.8%
Samiei et al. [22]	442	cT1-3, cN0	6.7%	0.9%	1.5%	2.3%
	396	cT1-3, cN1	68.1%	51.9%	51.5%	55.3%
Tadros et al. [13]	114	cT1-2, cN0	NA	0%	0%	0%
	77	cT1-2, cN1	NA	11.9%	8.6%	10.4%
Choi et al. [14]	56	cT1-3, cN0	0%	5.0%	3.6%	3.6%
	36	cT1-3, cN1	20.0%	4.5%	33.3%	13.9%

NACT = neoadjuvant chemotherapy; BpCR = breast pathologic complete response; ER = estrogen receptor; HER2 = human epidermal growth factor-2; TNBC = triple-negative breast cancer.

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Many surgeons are eager to perform surgical de-escalation with oncological safety, especially in patients with radiologic CR after NACT in TNBC or HER2-positive BC cases. Surgical de-escalation is a common option in BC treatment because of modern advances in early detection, systemic treatment, and imaging for accurate diagnosis. According to the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32, the American College of Surgeons Oncology Group (ASCOG) Z0011, and After Mapping Of the Axilla: Radiotherapy Or Surgery (AMAROS) trials, approximately 80% of cN0 patients were among patients with one or two SLN metastases who were eligible to receive radiotherapy after breast surgery to avoid ALND, which resulted in approximately 94% of patients avoiding ALND [26-28]. Although SLNB is a minimally invasive surgery, the complications include lymphedema and upper limb dysfunction. Thus, recent trials such as the Sentinel mode versus Observation after axillary UltrasouND (SOUND) and Intergroup-Sentinel-Mamma (INSEMA) studies examined whether patients with early breast cancer patients with cT1N0 could omit SLNB [29-31]. In the BOOG 2013-08 and No Axillary sUrgical Treatment In clinically Lymph node-negative patients after UltraSonography (NAUTILUS) trials, patients with cT1 or cT2 and cN0 breast cancer treated with breast-conserving surgery and radiotherapy were randomized into SLNB or no axillary surgery groups [32,33]. In these trials, patients diagnosed with cN0 disease by physical and radiologic methods were randomly divided into SLNB and no axillary surgery groups.

Several clinical trials are just beginning of in neoadjuvant settings. The Avoiding Sentinel Lymph Node Biopsy in Breast Cancer Patients After Neoadjuvant Chemotherapy (ASICS) study, which includes a prospective, non-inferiority cohort, single-arm registration trial, is designed to evaluate SLNB omission in patients with cN0 who are HER2-positive or TNBC and who achieved radiologic CR of the breast on magnetic resonance imaging. The primary outcome is the 5-year axillary recurrence [34]. Similarly, the European Breast Cancer Research Association of Surgical Trialists (EUBREAST-01), a multicenter, prospective, single-arm study, is designed to evaluate axillary surgery omission in patients with cN0 who are HER2-positive or TNBC and who achieve radiologic and BpCRs [35]. Furthermore, in Korea, the Avoid axillary Sentinel Lymph node biopsy After Neoadjuvant chemotherapy (ASLAN) trial, which a multicenter, prospective, single-arm study, is conducting to evaluate axillary surgery omission in patients with cN0-1, HER2-positive or TNBC who achieve BpCR [36]. In the present study, 99.0% of patients with axillary cN0 and BpCR disease showed pN0 disease. Axillary surgery omission is currently being investigated in patients with breast CR after NACT. Both clinical trials were designed to fundamentally test the concordance with the results of the present study.

This study was not a prospective randomized clinical trial; thus, the distribution of patients and limited surgical methods might have biased our results regarding regional control. The ypCR rates in HER2-type and TNBC in our study were relatively low because they also contained a past NACT regimen. In the case of clinical staging, it is difficult to make an accurate definition because there is no choice but to rely on data. As almost half of the patients underwent SLNB alone, some patients may have residual axillary disease because of the false-negative rate of SLNB after NACT, which may lead to an underestimation of the metastatic burden of the axilla. In addition, no radiological findings or physical examination data were examined after NACT in this study. These limitations are offset by the large sample size, which enhanced the ability to provide precise estimates of pathologic node metastasis state. These data may also serve as a basis for future controlled trial studies.

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In conclusion, BpCR was highly correlated with ApCR after NACT. In patients with cN0 and BpCR, the risk of missing axillary nodal metastasis was low after NACT. Further research on axillary surgery omission in patients with cN0 disease is needed.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Extent of lymph node status according to BpCR and clinical lymph node status stratified by molecular subtype

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Appendix 1. Member of Korean Breast Cancer Society

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