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%) patients 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% (1,211/1,352) 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.
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 cT1-3/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 ypNO 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 χ² 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-project.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-
Primary invasive BC patients underwent NACT followed by surgery 2010.01–2020.03 (n = 10,361)

Enrolled patients (n = 6,597)

cT4  
cN3  
Distant metastasis at presentation and after NACT  
PABC  
No axillary surgery  
ypT4 after NACT  
ypN3 after NACT

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  |

(continued to the next page)
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 ($p < 0.001$).
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 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.

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

| Variables                  | ApCR  | Non-ApCR | p-value | ApCR  | Non-ApCR | p-value |
|----------------------------|-------|----------|---------|-------|----------|---------|
| cN0 status                 |       |          |         |       |          |         |
| cT1                        | 26 (92.9) | 2 (7.1) | 0.007   | 60 (81.1) | 14 (18.9) | 0.396 |
| 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                 |       |          |         |       |          |         |
| cT1                        | 79 (79.8) | 22 (20.2) | 0.001   | 64 (28.3) | 162 (71.7) | 0.034 |
| 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                 |       |          |         |       |          |         |
| cT1                        | 23 (74.2) | 8 (25.8) | 0.050   | 13 (30.2) | 30 (69.8) | 0.211 |
| 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               |       |          |         |       |          |         |
| cT1                        | 128 (80.0) | 32 (20.0) | < 0.001 | 137 (39.9) | 206 (60.1) | 0.144 |
| 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.
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 4. Pathologic nodal stages after neoadjuvant chemotherapy according to BpCR and clinical lymph nodal stage

| Clinical lymph node status | Total | %  | ypN0 | %  | ypN1 | %  | ypN2 | %  |
|----------------------------|-------|----|------|----|------|----|------|----|
| BpCR                       | 1,427 |    | 307  | 24.2 | 304  | 99.0 | 4    | 1.0 |
| cN0                        | 307   |    | 304  | 99.0 | 4    | 1.0  | 0    | 0.0 |
| cN1                        | 695   |    | 606  | 87.2 | 79   | 11.4 | 10   | 1.4 |
| cN2                        | 266   |    | 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 |    | 1,229| 28.8 | 972  | 79.1 | 223  | 18.2 |
| cN0                        | 1,229 |    | 972  | 79.1 | 223  | 18.2 | 34   | 2.7 |
| cN1                        | 2,267 |    | 791  | 34.9 | 1,148| 50.6 | 328  | 14.5 |
| cN2                        | 765   |    | 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                      | 6,574 |    | 1,536| 27.8 | 1,276| 83.1 | 227  | 14.7 |
| cN0                        | 1,536 |    | 1,276| 83.1 | 227  | 14.7 | 34   | 2.2 |
| cN1                        | 2,962 |    | 1,397| 47.2 | 1,227| 41.4 | 338  | 11.4 |
| cN2                        | 765   |    | 242  | 31.6 | 293  | 38.3 | 230  | 30.1 |
| cN0-2                      | 4,261 |    | 2,055| 48.2 | 1,664| 39.0 | 592  | 13.8 |

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

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              | cT2-2, cN0                  | 30.5%     | 12.4%  | 14.1% | 15.8% |
| Samiei et al. [22] | 442   | cT1-3, cN0                  | 6.7%      | 0.3%  | 1.5% | 2.3%    |
| 396                | cT3-3, cN0                  | 68.3%     | 51.9%  | 51.5% | 55.3% |
| Tadros et al. [13] | 114   | cT1-2, cN0                  | NA        | 11.9% | 8.6% | 10.4%   |
| Choi et al. [14]   | 56    | cT1-3, cN0                  | 0%        | 5.0%  | 3.6% | 3.6%    |
| 36                 | cT3-3, 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.
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 Ultrasoundography (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 is 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.
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

Click here to view

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Appendix 1. Member of Korean Breast Cancer Society

Sei Hyun Ahn1, Dong-Young Noh1, Seok Jin Nam1, Eun Sook Lee4, Byeong-Woo Park3, Woo Chul Noh6, Jung Han Yoon2, Soo Jung Lee4, Eun Kyu Lee3, Joon Jeong3, Sehwan Han3, Ho Yong Park2, Nam-Sun Paik3, Young Tae Bae34, Hyouk Jin Lee4, Heung kyu Park4, Seung Sang Ko7, Woo-Chan Park18, Young Jin Suh19, Sung Hoo Jung20, Se Heon Cho31, Sei Joong Kim42, Se Jeong Oh23, Byung Kyun Ko34, Ku Sang Kim35, Chanheun Park26, Byung Joo Song27, Ki-Tae Wang8, Je Ryong Kim, Jeoung Won Bae10, Jeong-Soo Kim31, Sun Hee Kang22, Geumhee Gwak33, Jee Hyun Lee34, Tae Hyun Kim35, Myungchul Chang36, Sung Yong Kim7, Jung Sun Lee38, Jeong-Yoon Song39, Hai Lin Park40, Sun Young Min41, Young-Hyun Yang42, Sung Hwan Park43, Jong-Min Baek44, Lee Su Kim45, Dong Won Ryu46, Kweon Cheon Kim47, Min Sung Chung48, Hee Boong Park49, Cheol Wan Lim50, Un Jong Choi51, Beom Seok Kwak52, Young Sam Park53, Hyuk Jai Shin54, Young Jin Choi55, Doyil Kim56, Airi Han57, Jong Hyun Koh58, Sangyong Choi59, Daesung Yoon60, Soo Youn Choi61, Shin Hee Chul62, Jae Il Kim63, Jae Hyuck Choi64, Jin Woo Ryu65, Chang Dae Ko66, Il Kyun Lee67, Dong Seok Lee68, Seunghye Choi69, Youn Ki Min70, Young San Jeon71, Eun-Hwa Park72

1Asan Medical Center; 2Seoul National University Hospital; 3Samsung Medical Center; 4National Cancer Center; 5Yonsei University Severance Hospital; 6Korea Cancer Center Hospital; 7Chonnam National University Hwasun Hospital; 8Yeungnam University Medical Center; 9Seoul National University Bundang Hospital; 10Yonsei University Gangnam Severance Hospital; 11Ajou University School of Medicine; 12Kyungpook National University Medical Center; 13Ewha Womans University Mokdong Hospital; 14Pusan National University Hospital; 15Saegyo Hospital; 16Gachon University Gil Hospital; 17Dankook University Cheil General Hospital and Women’s Healthcare Center; 18The Catholic University of Korea Seoul St. Mary’s Hospital; 19The Catholic University of Korea St. Vincent’s Hospital; 20Chonbuk National University Hospital; 21Dong-A University Hospital; 22Inha University Hospital; 23The Catholic University of Korea Incheon St. Mary’s Hospital; 24Ulsan University Hospital; 25Ulsan City Hospital; 26Sungkyunkwan University Kangbuk Samsung Hospital; 27The Catholic University of Korea Bucheon St. Mary’s Hospital; 28Seoul Metropolitan Government-Seoul National University Boramae Medical Center; 29Chungnam National University Hospital; 30Korea University Anam Hospital; 31The Catholic University of Korea Uijeongbu St. Mary’s Hospital; 32Keimyung University Dongсан Medical Center; 33Inje University Sanggye Paik Hospital; 34Soongchunhyang University Seoul Hospital; 35Inje University Busan Paik Hospital; 36Dankook University Cheonan Hospital; 37Inje University Haeundae Paik Hospital; 38Kyung Hee University Hospital at Gangdong; 39Gangnam CHA University Hospital; 40Kyung Hee University Medical Center; 41Konkuk University Medical Center; 42Catholic University of Daegu Hospital; 43The Catholic University of Korea Yoeuido St. Mary’s Hospital; 44Hallym University Hallym Sacred Heart Hospital; 45Kosin University Gospel Hospital; 46Chosun University Hospital; 47Hanyang University Seoul Hospital; 48Park Hee Boong Surgical Clinic; 49Soochunhyang University Bucheon Hospital; 50Wonkwang University Hospital; 51Dongguk University Ilsan Hospital; 52Presbyterian Medical Center; 53Myongji Hospital; 54Chungbuk National University Hospital; 55MizMedi Hospital; 56Yonsei University Wonju Severance Christian Hospital; 57Cheongju St. Mary’s Hospital; 58Gwangmyung Sun Ae Hospital; 59Konyang University Hospital; 60Hallym University Kangdong Sacred Heart Hospital; 61Chung-Ang University Hospital; 62Inje University Ilsan Paik Hospital; 63Jeju National University Hospital; 64Chungmu General Hospital; 65Dr. Ko’s breast Clinic; 66The Catholic Kwandong University International St. Mary’s Hospital; 67Bun Hong Hospital; 68The Catholic University of Korea St. Paul’s Hospital; 69Cheju Halla General Hospital; 70Goo University; 71Ulsan University Gangneung Asan Hospital

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