Improved Model for Predicting Axillary Response to Neoadjuvant Chemotherapy in Patients with Clinically Node-Positive Breast Cancer

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INTRODUCTION

Neoadjuvant chemotherapy (NAC) is currently regarded as the standard and primary treatment for patients with locally advanced breast cancer [1,2]. Axillary lymph node (LN) status is an important prognostic factor in breast cancer patients, being associated with the risk of locoregional recurrence and metastasis and guiding locoregional and systemic treatment decisions. NAC reduces breast tumor burden, increasing the ability to perform breast conservation and axillary conservation surgery [3-6]. Another advantage of NAC is that long-term prognosis, including locoregional and survival outcomes, is improved in patients who achieve pathologic complete response (pCR) in the breast and axilla [7,8], with nodal pCR being a more important prognostic factor than breast pCR [7,9]. NAC can convert 40% to 75% of patients presenting with clinical axillary LN-positive disease to node-negative status [8,10]. In addition, axillary LN dissection (ALND) can be omitted for patients who achieve axillary pCR, avoiding postoperative complications such as lymphedema, arm pain, and reduced arm movement [11,12]. Identifying patients who do not require ALND requires a noninvasive method, approximating the accuracy of ALND, to evaluate axillary LN response to NAC. To date, clinically node-positive patients have undergone ALND, regardless of nodal response, after NAC.

Other clinical trials have tested the suitability of sentinel LN biopsy (SLNB) after NAC for patients with clinically node-positive breast cancer. SLNB, however, has a relatively low true positive rate, ranging from 80% to 90%, while also having a relatively high false negative rate, up to 30% when only one...
sentinel LN was removed [10,13]. Few previous studies have evaluated methods to improve the ability of axillary LN status to predict axillary pCR, and to improve the accuracy of SLNB in patients with clinically node-positive breast cancer after NAC. Therefore, additional tools may prove helpful in estimating axillary nodal response to NAC in patients with clinical node-positive breast cancer, and in identifying which patients who do not require ALND. Models have been designed to predict the probabilities or risks of clinical outcomes, thereby assisting clinicians and patients in determining how to manage breast cancer [14,15]. These models have limitations, however, because they did not evaluate tumor response after NAC, but because they were not validated using data from an institution not involved in model development. This study evaluated factors predictive of axillary pCR and compared the model based on our data, which approximates the accuracy of axillary LN status, to identify patients with clinically node-positive breast cancer who achieved axillary pCR after NAC.

**METHODS**

**Patient population**

A total of 2,619 patients underwent surgery for malignant breast cancer at the Seoul St. Mary’s Hospital, The Catholic University of Korea from January 2010 to December 2015. Data were prospectively collected from all patients and reviewed retrospectively. Of the 2,619 patients, 260 had clinical stage II or III primary breast cancer and underwent NAC followed by radical surgery (Figure 1). Core needle biopsy specimens of all primary tumors and axillary LNs were obtained before NAC. All patients had undergone breast magnetic resonance imaging (MRI) before and during NAC, with the last MRI performed prior to undergoing surgery. Of these 260 patients, 59 were excluded, including 43 without cytologically proven axillary LN metastasis, six who received another chemotherapy regimen, and 10 who discontinued NAC before completion. The remaining 201 patients were confirmed as having axillary LN metastasis and underwent radical operation of the primary tumor with concurrent ALND. All the patients received sequential chemotherapy or combination chemotherapy, consisting of anthracycline and taxane.

This study protocol was approved by the Institutional Review Board of Seoul St. Mary’s Hospital (KC 16RISI0859), which waived the requirement for informed consent because of the retrospective design of the study.

**Definition of tumor response rate and clinical response**

Tumor and axillary LN response rates were evaluated on breast MRI by two experienced radiologists based on visual assessments and calculations. The tumor response rate was calculated as the percentage of tumors and axillary LNs showing reductions in size according to the Response Evaluation Criteria in Solid Tumors 1.1 criteria [16,17]. The longest tumor diameter and a short axis axillary LN diameter greater than 1.5 cm were defined as the target lesion. Breast MRI results before NAC (baseline) and after NAC (before surgery) were compared. Individual lesion diameters are calculated as the sum of the diameters of all lesions. Clinical response was classified as complete response (CR), partial response, stable disease, or progressive disease (PD). CR was defined as the disappearance of all target lesions and partial response as a ≥ 30% reduction in the sum of the longest diameters of target lesions, relative to the sum of the diameters at baseline. PD was defined as a ≥ 20% increase in the sum of the longest diameters of target lesions, relative to the smallest sum in the study as reference; and stable disease was not defined as intermediary between partial response and PD [16,17].

**Pathological diagnosis**

Axillary LN status was evaluated by core needle biopsy before NAC. Biopsy samples were assayed for expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, and their histologic grade was evaluated. Positive ER and PR status was defined as an Allred score ≥ 3 or nuclear staining ≥ 1%. HER2 status was determined by immunohistochemistry (IHC) or
fluorescence in situ hybridization (FISH), with positive HER2 status defined as an IHC score of 3+ or 2+ with HER2 gene amplification confirmed by FISH. The amplification ratio was defined as the HER2 gene locus copy number relative to chromosome 17 centromere copy number, with an amplification ratio ≥ 2.0 considered positive. Ki-67 was dichotomized by the percentage of cells expressing Ki-67 (<14% and ≥14%). Breast cancers into the four different subtypes: luminal A (ER+ or PR+, HER2−, and Ki-67 <14%); luminal B ([ER+ or PR+, HER2−, and Ki-67 ≥14%] or [ER+ or PR+ and HER2+]); HER2 (ER− and PR− and HER2+); and triple-negative breast cancer (ER− and PR− and HER2−). All IHC results were interpreted by a single pathologist. Responses of the primary breast tumor and axillary LNs to NAC were recorded. Axillary pCR was defined as the complete absence of previously visible micrometastases and macrometastases (>0.2 mm) in axillary LNs following NAC.

Model construction and evaluation of performance
The predictive accuracy of models estimating residual nodal metastasis in patients with clinically node positive breast cancer after NAC was determined by receiver operating characteristic (ROC) curve analysis. To develop a new model, the dataset was analyzed by univariate and multivariate logistic regression analysis. This new model was subsequently used to predict the likelihood of patients achieving axillary pCR to NAC. Construction of this new model included factors such as independent predictors (p < 0.05) in the multivariate logistic regression model, as well as clinically significant predictors from other studies, as well as statistically relevant factors. The discriminatory performance of each model, defined as its ability to distinguish among patients with different responses or events, was assessed by measuring the area under ROC curves (AUC). The statistical differences among different AUCs were also investigated.

Statistical analysis
Differences in continuous variables between groups of patients who did and did not achieve axillary pCR were assessed by the t-test or Wilcoxon rank sum test, and differences in categorical variables were analyzed by the chi-square test or Fisher exact test. Categorical variables are presented as number (%) or mean ± standard deviation (SD), and continuous variables as median (interquartile range). Simple and multivariate logistic regression models were calculated and used to analyze the relationship between covariates, as determined by odds ratio (OR) and 95% confidence interval (CI). The predictive performance of each model was presented as sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), with differences between models calculated by comparing AUCs. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, USA), with a p-value less than 0.05 considered statistically significant.

RESULTS

Patient characteristics
To investigate whether each factor was predictive of axillary LN pCR in response to NAC, the patients were assigned to groups that did and did not achieve LN pCR (Table 1). Of the 201 women investigated, 68 (33.8%) achieved axillary LN pCR, whereas 133 (66.2%) had residual axillary disease after NAC. Patients who achieved axillary pCR tended to be younger (<50 years). Tumors with higher histologic grade and higher Ki-67 expression were significantly more common in patients who did than did not achieve axillary pCR. In contrast, negative ER and PR status, positive HER2 status, and tumors with early clinical and nodal stage did not differ significantly in the two groups.

Clinical response to neoadjuvant chemotherapy
Mean tumor diameters before and after NAC were 4.58 ± 2.24 cm and 1.92 ± 1.89 cm, respectively, whereas mean axillary LN diameters before and after NAC were 1.85 ± 0.85 cm and 0.77 ± 0.50 cm, respectively (Tables 1 and 2). Tumor and axillary LN sizes throughout treatment were significantly smaller in patients who did than did not achieve axillary pCR. The clinical CR rate was significantly higher in patients who did than did not achieve axillary pCR (16.2% vs. 3.8%, p = 0.004).

The mean overall tumor response rate was significantly higher in patients who did than did not achieve axillary pCR (57.9% ± 26.5% vs. 42.3% ± 22.2%, p < 0.001). The median tumor response rate for all 201 patients was 47.1% (−10.1%–100%). Using the median as the cutoff value, we found that tumor response rate was significantly higher in patients who did than did not achieve axillary pCR (70.6% [48/68] vs. 38.4% [51/133], p < 0.001) (Table 2).

Predictors of axillary lymph node pathologic complete response
Table 3 shows univariate and multivariate analyses of factors possible predictive of achieving axillary LN pCR. Univariate logistic regression analysis showed that patients with a high tumor response rate (≥47.1%) were more likely to achieve axillary pCR than patients with a lower tumor response rate (OR, 3.859; 95% CI, 2.059–7.230). Higher histo-
Table 1. Comparison of patient clinicopathologic characteristics between the axillary LN pCR and non-axillary LN pCR before NAC

| Baseline characteristic | Axillary LN-pCR | p-value |
|-------------------------|----------------|---------|
|                         | No (n=133) | Yes (n=68) |         |
| Age (yr)* | 49.11± 9.49 | 47.57± 9.64 | 0.283 |
| <50 | 64 (48.1) | 42 (61.8) | 0.067 |
| ≥50 | 69 (51.9) | 26 (38.2) |       |
| Menopausal | 0.666 |       |         |
| Premenopausal | 74 (55.6) | 40 (58.8) |       |
| Postmenopausal | 59 (44.4) | 28 (41.2) |       |
| Breast operation | 0.071 |       |         |
| Wide excision | 47 (35.3) | 33 (48.5) |       |
| Mastectomy | 86 (64.7) | 35 (51.5) |       |
| Clinical tumor stage | 0.922 |       |         |
| T1 | 10 (7.5) | 6 (8.8) |       |
| T2 | 66 (49.6) | 31 (45.6) |       |
| T3 | 52 (39.1) | 28 (41.2) |       |
| T4 | 5 (3.8) | 3 (4.4) |       |
| Clinical nodal stage | 0.571 |       |         |
| N1 | 85 (63.9) | 45 (66.2) |       |
| N2 | 35 (26.3) | 14 (20.6) |       |
| N3 | 13 (9.8) | 9 (13.2) |       |
| Primary tumor size (cm)* | 4.43± 2.33 | 4.58± 2.24 | 0.463 |
| Axillary LN size (cm)* | 1.82± 0.95 | 1.85± 0.85 | 0.651 |
| Histologic type | 0.629 |       |         |
| IDC | 125 (94.0) | 68 (97.1) |       |
| ILC | 6 (4.5) | 2 (2.9) |       |
| Other | 2 (1.5) | 0 |       |
| Histologic grade | 0.002 |       |         |
| Grade 1 or 2 | 99 (74.4) | 36 (52.9) |       |
| Grade 3 | 34 (25.6) | 32 (47.1) |       |
| ER | 0.086 |       |         |
| Negative | 46 (34.6) | 32 (47.1) |       |
| Positive | 87 (65.4) | 36 (52.9) |       |
| PR | 0.151 |       |         |
| Negative | 72 (54.1) | 44 (64.7) |       |
| Positive | 61 (45.9) | 24 (35.3) |       |
| HER2 | 0.917 |       |         |
| Negative | 89 (66.9) | 46 (67.7) |       |
| Positive | 44 (33.1) | 22 (32.3) |       |
| Ki-67 | 0.031 |       |         |
| Low | 60 (45.1) | 20 (29.4) |       |
| High | 73 (54.9) | 48 (70.6) |       |
| Subtype | 0.374 |       |         |
| Luminal A | 48 (36.1) | 15 (22.1) |       |
| Luminal B | 28 (20.8) | 23 (33.8) |       |
| HER2 | 24 (18.0) | 14 (20.6) |       |
| TNBC | 23 (17.3) | 16 (23.5) |       |

*p-value of significant difference between Recurrence, by chi-square, Fisher exact. Student t-test or Wilcoxon rank sum test.

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Table 2. Comparison of patient clinicopathologic response between the axillary LN pCR and non-axillary LN pCR after NAC

| Variable | Axillary LN-pCR | p-value |
|----------|----------------|---------|
|          | No (n=133) | Yes (n=68) |         |
| Pathologic tumor stage |         |         | <0.001 |
| T0 or Tis | 10 (7.5) | 26 (38.2) |       |
| T1 | 46 (34.6) | 27 (39.7) |       |
| T2 | 58 (43.6) | 13 (19.1) |       |
| T3 or T4 | 19 (14.3) | 2 (2.9) |       |
| Pathologic nodal stage |         |         | <0.001 |
| N0 | 0 | 68 (100) |       |
| N1 | 72 (54.1) | 0 |       |
| N2 | 38 (28.6) | 0 |       |
| N3 | 23 (17.3) | 0 |       |
| Primary tumor size after NAC (cm)* | 2.64± 2.02 | 1.92± 1.89 | 0.004 |
| Axillary LN size after NAC (cm)* | 0.96± 0.53 | 0.77± 0.50 | 0.031 |
| Clinical response | 0.004 |       |         |
| Stable or partial | 128 (96.3) | 57 (83.8) |       |
| Complete | 5 (3.8) | 11 (16.2) |       |
| Tumor response rate (%)* | 42.3± 22.2 | 57.9± 26.5 | <0.001 |
| ≥ 47.1 | 51 (38.4) | 48 (70.6) | <0.001 |
| < 47.1 | 82 (61.7) | 20 (29.4) |       |

*p-value of significant difference between Recurrence, by chi-square, Fisher exact and Wilcoxon rank sum test.

LN=lymph node; pCR=pathologic complete response; NAC=neoadjuvant chemotherapy.

*Mean± SD.

logic grade, higher Ki-67 score, clinical response, and axillary LN size after NAC were found to be significantly predictive of pCR. Multivariate analyses using axillary LN pCR after NAC as a dependent variable showed that higher histologic grade (p = 0.031; OR, 2.537; 95% CI, 1.087–5.925) and higher (≥ 47.1%) tumor response rate (p = 0.001; OR, 3.212; 95% CI, 1.584–6.515) were significantly associated with an increased probability of achieving axillary pCR. In contrast, older patients were less likely than younger patients to achieve axillary pCR (p = 0.018; OR, 0.433; 95% CI, 0.217–0.865). ER status, HER2 status, histologic grade, and Ki-67 expression were significantly associated with axillary LN pCR.

Assessment of the prediction model

Previous studies have shown that axillary pCR was associated with younger age, high histologic grade, higher Ki-67 expression, ER-negativity, and HER2-positivity [14,15]. We constructed a basic model based on these results and statistically significant variables in our study, including age, ER-status, HER2-status, histologic grade, and Ki-67 expression, to determine whether this model could predict the probability of our patients achieving axillary pCR. We eliminated the negative effect of our small-size population, which was shown to result in a wide CI. We then attempted to develop a new mod-
el, based on the independent predictors of axillary pCR shown in our multivariate logistic regression analysis. To determine whether a model that included tumor response rate would affect the axillary nodal response to NAC, we developed a model dichotomizing tumor response rate as ≥ 47.1% or < 47.1%. We found that the model that included tumor response rate had a sensitivity of 42.7%, a specificity of 82.7%, a PPV of 55.8%, and an NPV of 73.8% in predicting axillary pCR (Table 4). The ROC plots in Figure 2 showed that the model that included tumor response rate had an AUC of 0.732 (95% CI, 0.661–0.804), with better discriminatory ability than other models ($p = 0.022$; 95% CI, 0.012–0.154) (Table 5, Figure 2). We found that, compared with other predictive factors including clinical response and axillary LN size after NAC, the tumor response rate was the most important predictor and enhanced the performance of our model.

**Table 3.** Univariate and multivariate logistic regression analysis of variable factors for predicting axillary LN pCR

| Variable                        | OR (95% CI) | $p$-value | Adjusted OR (95% CI) | $p$-value |
|---------------------------------|-------------|-----------|----------------------|-----------|
| Age (yr)                        |             |           |                      |           |
| < 50                            | Reference   | 0.068     | Reference            | 0.018     |
| ≥ 50                            | 0.574 (0.316–1.042) | 0.433 (0.217–0.865) | 0.817     |
| ER                              |             |           |                      |           |
| Negative                        | Reference   | 0.087     | Reference            | 0.809     |
| Positive                        | 0.595 (0.328–1.079) | 0.899 (0.366–2.212) |           |
| HER2                            |             |           |                      |           |
| Negative                        | Reference   | 0.663     | Reference            |           |
| Positive                        | 0.849 (0.407–1.772) | 1.136 (0.404–3.190) |           |
| Ki-67                           |             |           |                      |           |
| Low                             | Reference   | 0.033     | Reference            | 0.641     |
| High                            | 1.972 (1.057–3.679) | 1.207 (0.548–2.654) |           |
| Histologic grade                |             |           |                      |           |
| Grade 1 or 2                    | Reference   | 0.003     | Reference            | 0.031     |
| Grade 3                         | 2.588 (1.399–4.788) | 2.537 (1.087–5.925) |           |
| Clinical response               |             |           |                      |           |
| Stable or partial               | Reference   | 0.005     | Reference            | 0.088     |
| Complete                        | 4.940 (1.641–14.875) | 3.030 (0.849–10.813) |           |
| Axillary LN size after NAC (cm) |             |           |                      |           |
| Negative                        | 0.467 (0.250–0.873) | 0.017 | 0.719 (0.350–1.474) | 0.368     |
| Positive                        | 12           | 19        |                      |           |
| Positive                        | 116          | 40        |                      |           |
| Positive                        | 17           | 28        |                      |           |
| Positive                        | 120          | 45        |                      |           |
| Positive                        | 13           | 23        |                      |           |
| Positive                        | 110          | 39        |                      |           |
| Positive                        | 23           | 29        |                      |           |
| Tumor response rate (%)         | < 0.001      | 0.001     |                      |           |

Statistics were carried out using logistic regression analysis. LN= lymph node; pCR= pathologic complete response; OR= odds ratio; CI= confidence interval; ER= estrogen receptor; HER2= human epidermal growth factor receptor 2; NAC= neoadjuvant chemotherapy.

**Table 4.** Summary of the difference of prediction performance between the models

| Model | Predicted result | Axillary LN-pCR No. | Sensitivity (95% CI) | Specificity (95% CI) | PPV (95% CI) | NPV (95% CI) |
|-------|------------------|---------------------|----------------------|----------------------|--------------|--------------|
|       |                  | Observed result     |                      |                      |              |              |
|       |                  | Negative            | 0.279 (0.173–0.386)  | 0.910 (0.861–0.959)  | 0.613 (0.441–0.784) | 0.712 (0.644–0.780) |
|       |                  | Positive            | 0.412 (0.295–0.529)  | 0.872 (0.815–0.929)  | 0.622 (0.481–0.764) | 0.744 (0.675–0.812) |
|       |                  | Positive            | 0.338 (0.226–0.451)  | 0.902 (0.852–0.953)  | 0.639 (0.482–0.796) | 0.727 (0.659–0.795) |
|       |                  | Positive            | 0.427 (0.309–0.544)  | 0.827 (0.763–0.891)  | 0.558 (0.423–0.693) | 0.738 (0.668–0.809) |

Model 1: age, estrogen receptor status, human epidermal growth factor receptor 2 status, histologic grade, Ki-67; Model 2: Model 1+clinical response; Model 3: Model 1=axillary lymph node size after neoadjuvant chemotherapy (cm); Model 4: Model 1+tumor response rate. LN= lymph node; pCR= pathologic complete response; CI= confidence interval; PPV= positive predictive value; NPV= negative predictive value.
DISCUSSION

Multivariate analysis of our patients showed that lower age (< 50 years), higher histologic grade, and higher tumor response rate (≥ 47.1%) were significant independent predictors of an increased likelihood of achieving axillary pCR. Of these factors, tumor response rate was one of the most reliable and should be included in models predicting axillary response. Other models for predicting axillary LN pCR have included factors unrelated to nodal status and did not include tumor response rate after NAC [14,15]. Our model, which included tumor response rate, was a better predictor of the probability of achieving axillary LN pCR. A comparison of models that did and did not include tumor response rate found that the model that included response rate, as evaluated by breast MRI, had a significantly improved predicted accuracy, with an AUC of 0.732 (95% CI, 0.661–0.804) and significantly better predictive power than other models (p = 0.022; 95% CI, 0.012–0.154).

NAC has become a standard treatment in patients with clinically node positive breast cancer, resulting in an axillary response [18,19] and the conversion of 40% to 75% of patients from node-positive to node-negative status [8,10]. Patients who achieved axillary pCR had better 5-year overall (93% vs. 72%) and relapse-free (87% vs. 60%) survival rates than patients with residual nodal disease [8]. However, current guidelines for the standard management of patients who achieve CR have not been adjusted accordingly, despite high nodal pCR rates [20]. Most patients with axillary LN metastases before NAC undergo ALND, which has been associated with complication such as lymphedema, arm pain, and reduced arm movement due to shoulder dysfunction [11,12,21,22].

To better understand patient outcomes and to identify patients who can omit ALND, it is necessary to improve the accuracy of axillary nodal status based on SLNB. SLNB has been used to predict pCR of axillary LNs after NAC in patients with breast cancer and cytologically confirmed nodal metastasis. Accurate identification of the SLNB in patients likely to achieve nodal pCR, who may benefit from axilla-conserving surgery, is difficult. Cytologic node-positive breast cancer patients who underwent SLNB after NAC and achieved nodal conversion were found to have a false negative rate as high as 20% if one SLN was removed, with the number of harvested SLNs determined by the false negative rate of SLNB after NAC [13]. The accurate determination of axillary nodal status may be improved by the detection of two or more SLNs, by using a dual-tracer for mapping, by using IHC for pathologic evaluation, and by ensuring the removal of the axillary LN initially identified as being a nodal metastasis by marking with a clip [23]. Therefore, in developing a model with improved performance, we added noninvasive predicting factors such as tumor response rate. Although clinical responses may be predictive of axillary pCR in response to NAC, many patients do not achieve clinical CR, with most patients who receive NAC achieving partial response. Therefore, clinical response is predictive of axillary pCR in few patients. Because partial response is defined as a ≥ 30% reduction in tumor size, clinical

\[ \text{Figure 2. Receiver operating characteristics curve (ROC) of the each models to predict axillary pathologic complete response. The area under the ROC curve is 0.732, 95% confidence interval (0.661–0.804) in model 4.} \]

### Table 5. Comparison difference of AUC each models

| Model       | AUC   | Standard error | 95% CI       | p-value |
|-------------|-------|----------------|--------------|---------|
| Model 1     | 0.649 | 0.042          | 0.568–0.731  |         |
| Model 2     | 0.692 | 0.041          | 0.612–0.771  |         |
| Model 3     | 0.682 | 0.041          | 0.602–0.761  |         |
| Model 4     | 0.732 | 0.037          | 0.661–0.804  |         |

The difference of prediction performance between the models were presented the ROC curve (AUC) between the models. Model 1: age, estrogen receptor status, human epidermal growth factor receptor 2 status, histologic grade, Ki-67; Model 2: Model 1+clinical response; Model 3: Model 1+axillary lymph node size after neoadjuvant chemotherapy (cm); Model 4: Model 1+tumor response rate. AUC=area under receiver operating characteristic (ROC) curves; CI=confidence interval.
partial response results in various tumor response rates. Because we found that tumor response rate was associated with axillary pCR and may be predictive in additional patients, we incorporated tumor response rate into our model. We also showed that tumor response could be easily determined by measuring tumor diameter and axillary LN diameter on breast MRI. Radiologic results have shown diagnostic value in evaluating axillary LN metastases after NAC, with combinations that included MRI showing greater sensitivity in detecting positive axillary LN metastases [24]. Breast MRI is included in the standard workup of patients undergoing NAC in our institution, with tumor response rate determined by measuring tumor and axillary LN diameter on breast MRI before and after NAC. Tumor response rate is an easily measured clinicopathologic variable, allowing simple and rapid prediction of axillary pCR. This parameter can be used in making treatment decisions and in clinical trials [25]. Patients with a higher tumor response rate are more likely to achieve axillary LN pCR. SLNBs negative for metastases indicate that ALND can be safely omitted, thereby avoiding the postoperative complications of this procedure.

Our study had several advantages compared with previous studies predicting axillary pCR after NAC in patients with cytologically proven nodal metastasis [14,15,26]. Most importantly, these previous studies did not include tumor and nodal response rates to NAC. Tumor response rate offers several advantages compared with alternative methods for assessing axillary pCR after NAC. First, in contrast to SLNB, the prediction of axillary pCR based on tumor response rate is non-invasive, reducing associated morbidity. Second, because breast MRI is included in standard initial workup of patients with breast cancer before, tumor response rate can be readily calculated by comparing MRI results before and after NAC. Moreover, this procedure is covered by the national health insurance in Korea, eliminating the need for additional procedures, such as diagnostic tests and surgical procedures. Third, core needle biopsy was used to confirm all patients with axillary LN metastases before NAC, making our results more accurate than those of previous studies.

Our study also had several limitations. First, it was retrospective in design, involving a limited number of patients at a single institution. The study results were not validated externally, and median tumor response rate may have limited the generalizability of our findings. Second, our study included only patients who underwent NAC, followed by radical surgery including ALND. The false negative rate of SLNB is an important indicator of cytologically confirmed nodal metastasis. We did not compare the pathological status of the SLN to the remainder of LNs in the axilla following ALND. Third, the patients with HER2-positive tumors did not include those who received NAC that included trastuzumab. Assessments of tumor response rates to NAC using combinations of radiologic measurements are required, as are well-controlled, prospective studies in large numbers of patients.

In conclusion, this study evaluated the ability of various factors to predict axillary LN pCR in breast cancer patients treated with NAC and compared models based on these predictors. Tumor response rate was the most important predictor of axillary LN pCR in response to NAC. Use of models that include tumor response rates may avoid the need for unnecessary axillary LN dissection.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

REFERENCES

1. Bear HD, Anderson S, Smith RE, Geyer CE Jr, Mamounas EP, Fisher B, et al. Sequential preoperative or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer. National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2006;24:2019-27.
2. Cunningham JD, Weiss SE, Ahmed S, Bratton JM, Blewesi II, Tartter PI, et al. The efficacy of neoadjuvant chemotherapy compared to postoperative therapy in the treatment of locally advanced breast cancer. Cancer Invest 1998;16:80-6.
3. Mauri D, Pavlidi N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97:188-94.
4. Navarro-Cecilia J, Dueñas-Rodriguez B, Luque-López C, Ramírez-Expósito MJ, Martínez-Ferrol J, Ruiz-Mateas A, et al. Intraoperative sentinel node biopsy by one-step nucleic acid amplification (OSNA) avoids axillary lymphadenectomy in women with breast cancer treated with neoadjuvant chemotherapy. Eur J Surg Oncol 2013;39:873-9.
5. Rouzier R, Mathieu MC, Saderis I, Younis E, Rajan R, Garbay JR, et al. Breast-conversing surgery after neoadjuvant anthracycline-based chemotherapy for large breast tumors. Cancer 2004;101:918-25.
6. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowl Project B-18. J Natl Cancer Inst Monogr 2001;30:96-102.
7. Gonzalez-Angulo AM, McGuire SE, Buchholz TA, Tucker SL, Kuerer HM, Rouzier R, et al. Factors predictive of distant metastases in patients with breast cancer who have a pathologic complete response after neoadjuvant chemotherapy. J Clin Oncol 2005;23:7098-104.
8. Hennesy BT, Hortobagyi GN, Rouzier R, Kuerer H, Sneige N, Buzdar AU, et al. Outcome after pathologic complete eradication of cytologically proven breast cancer axillary node metastases following primary chemotherapy. J Clin Oncol 2005;23:9304-11.
9. Rouzier R, Extra JM, Klijajienko J, Falcoù MC, Asselain B, Vincent-Salomon A, et al. Incidence and prognostic significance of complete
axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. J Clin Oncol 2002;20:1304-10.
10. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310:1455-61.
11. Lucci A, McCall LM, Beitsch PD, Whitworth PW, Reintgen DS, Blumencranz PW, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. J Clin Oncol 2007;25:3657-63.
12. Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst 2006;98:599-609.
13. Kuehn T, Bauerfeind I, Fehm T, Hege B, Hausschild M, Helms G, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14:609-18.
14. Jin X, Jiang YZ, Chen S, Shao ZM, Di GH. A nomogram for predicting the pathological response of axillary lymph node metastasis in breast cancer patients. Sci Rep 2016;6:32585.
15. Vila J, Mittendorf EA, Farante G, Bassett RL, Veronesi P, Galimberti V, et al. Nomograms for predicting axillary response to neoadjuvant chemotherapy in clinically node-negative patients with breast cancer. Ann Surg Oncol 2016;23:3501-9.
16. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
17. Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000;92:205-16.
18. Alvarado R, Yi M, Le-Petross H, Gilcrease M, Mittendorf EA, Bedrosian I, et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. Ann Surg Oncol 2012;19:3177-84.
19. Straver ME, Rutgers EJ, Russell NS, Oldenburg HS, Rodenhuis S, Wesseling J, et al. Towards rational axillary treatment in relation to neoadjuvant therapy in breast cancer. Eur J Cancer 2009;45:2284-92.
20. Vugts G, Maaskant-Braat AL, de Roos WK, Voogd AC, Nieuwenhuijen GA. Management of the axilla after neoadjuvant chemotherapy for clinically node positive breast cancer: a nationwide survey study in the Netherlands. Eur J Surg Oncol 2016;42:956-64.
21. Fleissig A, Fallowfield LJ, Langridge CI, Johnson L, Newcombe RG, Dixon JM, et al. Post-operative arm morbidity and quality of life: results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat 2006;95:279-93.
22. Kakuda JT, Stuntz M, Trivedi V, Klein SR, Vargas HIL. Objective assessment of axillary morbidity in breast cancer treatment. Am Surg 1999;65:995-8.
23. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol 2016;34:1072-8.
24. You S, Kang DK, Jung YS, An YS, Jeon GS, Kim TH. Evaluation of lymph node status after neoadjuvant chemotherapy in breast cancer patients: comparison of diagnostic performance of ultrasound, MRI and [18F]-FDG PET/CT. Br J Radiol 2015;88:20150143.
25. Partridge SC, Gibbs JE, Lu Y, Esserman LJ, Tripathy D, Wolverton DS, et al. MRI measurements of breast tumor volume predict response to neoadjuvant chemotherapy and recurrence-free survival. AJR Am J Roentgenol 2005;184:1774-81.
26. Schipper RJ, Moosdorff M, Nelemans PJ, Nieuwenhuijzen GA, de Vries B, Strobbe LJ, et al. A model to predict pathologic complete response of axillary lymph nodes to neoadjuvant chemotherapy (immuno)therapy in patients with clinically node-positive breast cancer. Clin Breast Cancer 2014;14:315-22.