Non-Sentinel Node Metastasis Prediction During Surgery in Patients with Breast Cancer with One to Three Positive Sentinel Node(s) Upon Frozen Biopsy Result Following Neoadjuvant Chemotherapy

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Abstract

We aimed to develop a tool that could accurately predict the possibility of non-sentinel lymph node metastasis (NSLNM) during surgery, permitting surgeons to intraoperatively decide the extent of further axillary lymph node dissection (ALND) for patients with one to three positive sentinel lymph node(s) (SLN) following neoadjuvant chemotherapy (NAC). In this retrospective analysis, we included records of 558 patients who were treated between 2005 and 2019. Using chi-square and logistic regression with a bootstrapped, backward elimination method, 13 factors were assessed for their utility in predicting NSLNM. Based on the results of the univariate analysis, the number of positive SLN(s), number of frozen nodes, progesterone receptor (PR) positivity, and clinical N stage were selected for the multivariate analysis and used to generate a nomogram for residual nodal disease prediction. The resulting nomogram was validated using a more recent, different time window patient group at the AMC. The area under the receiver operating characteristic curve of this formula was 0.709 (95% confidence interval [CI], 0.658–0.761) and 0.715 (95% CI, 0.634–0.796) for the development and validation sets, respectively. This newly developed AMC nomogram could be useful for surgeons for intraoperative guidance in determining the extent of further axillary surgery.

Introduction

Although previous trials on the survival benefit for patients who underwent neoadjuvant chemotherapy (NAC) failed to demonstrate a relative superiority over those treated with adjuvant chemotherapy, the addition of NAC for treatment of eligible patients with breast cancer has been widely accepted. NAC can help reduce the need for total mastectomy, complete axillary lymph node dissection (ALND), and associated morbidity without increasing locoregional recurrence [1]. Sentinel lymph node biopsy (SLNB), following NAC in patients with clinically positive axilla, resulted in acceptable accuracy, thereby establishing it as a viable axillary management strategy [1–3]. Our institutional practice pattern has also included SLNB as the initial approach for the axilla following NAC unless the patient has a significant disease burden or progressive disease.

According to the recent National Comprehensive Cancer Network (NCCN) guidelines, complete ALND is the standard surgical management for patients presenting with node-positive breast cancer following NAC [4]. In a study including 104 patients who received NAC, Jeruss et al. demonstrated that the patients had a positive SLN and underwent ALND between 1997 and 2005 [5]. Of their research cohort, 44% did not have positive non-SLNs. They evaluated factors, such as lymphovascular invasion (LVI), method of SLN metastasis detection, multicentricity, ALN status at presentation, and pathological tumor size to predict additional NSLNM. Based on this finding, they derived the MD Anderson nomogram, which has a significant area under the receiver operating characteristic (ROC) curve (AUC) value. In addition, in a study by Gimbergues et al., 132 patients were followed prospectively between 2001 and 2007; all the patients were administered NAC and underwent SLN biopsy with ALND levels I and II [6]. Gimbergues et al. reported that 47.1% of their patient population did not have NSLNM, and they tested the accuracy of

previous nomograms from the Memorial Sloan-Kettering Cancer Center, MD Anderson Cancer Center, and Tenon Hospital with AUC values ranging from 0.7 to 0.8.

However, these nomograms are mostly based on factors from a final pathology report following surgery, such as LVI, pathologic tumor size, and the size of SLN metastasis, among others. Thus, when indicated, patients are expected to undergo further axillary dissection on a separate schedule. In this study, we retrospectively analyzed patient data from the Asan Medical Center (AMC) to develop a nomogram that could help predict the possibility of NSLNM based on the available clinical information before and during a planned surgery.

Methods

Patients

We reviewed the data from patients who had breast surgery with ALND following NAC between 2005 and 2019. Patients with one to three metastasis-positive sentinel node(s) treated using standard axillary procedure were included in the study. All eligible patients underwent clinical assessment at an outpatient clinic by physical examination and ultrasonography to determine the clinical stage. Ultrasonography-guided FNA or core needle biopsy were needed to confirm the N0 or N1 nodal status. According to the oncologists at AMC, all the included patients received a full course of standard neoadjuvant therapy. Owing to ALND, we could identify the patients with or without residual nodal disease based on the final pathology reports. We excluded patients who had bilateral breast cancer, inflammatory breast cancer, or had distant metastasis at the time of presentation, as well as those who had more than four sentinel nodes positive for metastasis intraoperatively and required further ALND. The reason for excluding patients with more than 4 sentinel nodes was based on the clinical practice protocol that ALND was considered more appropriate axillary management for patients with advanced nodal metastasis for oncologic safety. However, we included clinical patients with T4 (2.2% of the total patients), based on the clinical response to NAC, who were also treated with adjuvant radiotherapy postoperatively. We also excluded patients who received incomplete NAC owing to intolerance or refusal. Finally, 558 patients were chosen for further analysis, and the patients underwent sentinel node biopsy and proceeded towards ALND. The records of 384 patients treated between 2005 and 2016 were utilized for the development of the prediction model, and the data of 174 patients treated from 2017 to 2019 were used to validate the generated prediction model.

The data of the patients were reviewed for the total number of metastatic nodes on the final pathology report, intraoperative frozen section biopsy result of sentinel node(s), presence or absence of additional metastatic non-sentinel nodes and number, tumor invasion depth, tumor biology, initial clinical stage before chemotherapy, and radiology report of ultrasonogram or magnetic resonance imaging (MRI) of the breast before and after chemotherapy.

Since the study was based on retrospective clinical data, informed consent was waived and approved by the Asan Medical Center Institutional Review Board, Seoul, South Korea (20171341).

Preoperative Chemotherapy And Slnb Mapping Method

NAC was administered to a patient every 3 weeks, and a regimen was selected from among standard proposed regimens based on the clinical stage or tumor biology of the patient. Although standard regimens are constantly evolving, the oncologists at our institution generally followed the most recent NCCN guideline of the time. Anti-HER2 therapy was performed in 118 patients among 121 patients. The surgery was performed 3–4 weeks following the completion of preoperative chemotherapy. We assessed the patient's response to NAC using either an ultrasonogram or an MRI of the breast before and after treatment. According to the Revised Response Evaluation Criteria in Solid Tumors (version 1.1), we defined partial remission as a decrease of more than 30% in the sum of the longest diameters of the target lesions compared to the baseline. In addition, the term *complete remission* was considered upon the disappearance of all the target lesions. All the tumors that did not meet the above criteria were classified as stable disease.

We used ^{99m} Tc-sulfur colloid diluted in normal saline as a radiopharmaceutical agent with gamma probe detection (NeoProbe2000, US surgical, Norwalk, CT) for SLN identification. We injected the mapping agent periareolarly and massaged the breast for 5 minutes. Along with the most radioactive nodes, clinically enlarged and firm or palpable axillary lymph nodes without an active gamma signal were excised and counted as part of the total number of SLNs. Although we did not use blue dye for the dual mapping method owing to the surgeons' preference, more than 3 sentinel nodes were usually examined for frozen biopsy. The mean number of examined frozen nodes was 4.08 (Standard Deviation (SD) 1.5) in all the patients.

Statistical analysis

In order to identify significant factors that predict the possibility of residual disease in non-sentinel nodes, we first included the following parameters in the univariate analysis: age at diagnosis, tumor grade, hormone receptor score, HER2 status, classification into four subtypes (HR+/HER2−, HR+/HER2+, HR-HER2+, HR−/HER2−), Ki-67, clinical T stage and N stage before NAC and its degree of response to therapy, number of metastatic sentinel nodes, total number of submitted sentinel nodes for frozen section biopsy, and the greatest tumor invasion depth of the sentinel nodes.

We used the data from 384 patients treated between 2005 and 2016 for the development of the prediction model and the data from 174 patients treated from 2017 to 2019 for validation. In the development set, a univariate assessment of these factors was performed using a logistic regression model. A multivariable logistic regression model was used to further analyze and generate a prediction model for the possibility of residual nodal disease following NAC when one to three sentinel nodes were positive intraoperatively. The predictors for the multivariable model were selected using backward

elimination in more than half of the 1000 bootstrap resamples. The final model was estimated using penalized maximum likelihood and was presented as a nomogram. The discrimination ability of the nomogram was assessed by using the AUC. The calibration ability was assessed using the calibration plot and the Hosmer–Lemeshow test. We performed an internal validation with bootstrapping with 1000 iterations, calculating optimism-corrected AUC (C statistics). In the validation set, the discrimination and calibration abilities were also evaluated. All the tests were two-sided, and a *p*-value of less than 0.05 was considered statistically significant. Statistical analysis was conducted using SPSS statistics version 23.0 (IBM Corp., Armonk, USA) and R (version 3.6.1; R Foundation for Statistical Computing, https://www.R-project.org).

Results

Baseline characteristics

Table 1 shows the demographics of the 558 patients whose clinical data were used to develop the nomogram. In total, the majority of the patients were under the age of 50 (63.6%), had a single SLN metastasis at the time of surgery (50.9%), had three to five frozen biopsies sent for pathologic confirmation of the SLN status (66.1%), and were in clinical T stage 2 (63.4%). A substantial portion (74.4%) of our patients had clinical N1 stage. The N1 status was determined clinically, pathologically, and radiologically. The majority of tumors were low grade (81%), estrogen receptor (ER) positive (80.6%), progesterone receptor (PR) positive (66.5%), human epidermal growth factor receptor 2 (HER2) negative (78.3%), biological subtype of hormone receptor positive, and HER2 negative (78.3%).

Table 1
Baseline patient characteristics and association between residual disease and clinicopathologic variables

	Total	Residual disease		*P*-value
		No	Yes	
Number of patients	558	313	245	
Age				0.035
< 50 years	355 (63.6)	211 (67.4)	144 (58.8)	
≥ 50 years	203 (36.4)	102 (32.6)	101 (41.2)	
Tumor grade				0.002
G1/G2	452 (81.0)	242 (77.3)	210 (85.7)	
G3	102 (18.3)	71 (22.7)	31 (12.7)	
Unknown	4 (0.7)	0 (0.0)	4 (1.6)	
Estrogen receptor				0.007
Negative	108 (19.4)	73 (23.3)	35 (14.3)	
Positive	450 (80.6)	240 (76.7)	210 (85.7)	
Progesterone receptor				0.011
Negative	187 (33.5)	119 (38.0)	68 (27.8)	
Positive	371 (66.5)	194 (62.0)	177 (72.2)	
HER2 status				0.393
Negative	437 (78.3)	241 (77.0)	196 (80.0)	
Positive	121 (21.7)	72 (23.0)	49 (20.0)	
Biological subtype				0.039
HR+/HER2-	379 (67.9)	199 (63.6)	180 (73.5)	
HR+/HER2+	72 (12.9)	41 (13.1)	31 (12.7)	
HR-/HER2+	44 (7.9)	30 (9.6)	14 (5.7)	
HR-/HER2-	63 (11.3)	43 (13.7)	20 (8.2)	
Initial T stage				0.165
1	54 (9.7)	32 (10.2)	22 (9.0)	
2	354 (63.4)	208 (66.5)	146 (59.6)	

	Total	Residual disease		*P*-value
3	138 (24.7)	66 (21.1)	72 (29.4)	
4	12 (2.2)	7 (2.2)	5 (2.0)	
Initial N stage				< 0.001
0	92 (16.5)	65 (20.7)	27 (11.0)	
1	415 (74.4)	229 (73.2)	186 (75.9)	
2	51 (9.1)	19 (6.1)	32 (13.1)	
Response to NAC				0.891
Complete remission	22 (3.9)	14 (4.5)	8 (3.3)	
Partial remission	406 (72.8)	228 (72.8)	178 (72.7)	
Stable disease	119 (21.3)	65 (20.8)	54 (22.0)	
Progressive disease	11 (2.0)	6 (1.9)	5 (2.0)	
Surgery type				0.079
Breast-conserving surgery	258 (46.2)	155 (49.5)	103 (42.0)	
Mastectomy	300 (53.8)	158 (50.5)	142 (58.0)	
Number of positive SLNs				< 0.001
1	284 (50.9)	185 (59.1)	99 (40.4))	
2	203 (36.4)	106 (33.9)	97 (39.6)	
3	71 (12.7)	22 (7.0)	49 (20.0)	
Pathologic T stage				0.001
0	29 (5.2)	18 (5.8)	11 (4.5)	
1	235 (42.1)	150 (47.9)	85 (34.7)	
2	238 (42.7)	124 (39.6)	114 (46.5)	
3	56 (10.0)	21 (6.7)	35 (14.3)	
Pathologic N stage				< 0.001
1	419 (75.1)	309 (98.7)	110 (44.9)	
2	139 (24.9)	4 (1.3)	135 (55.1)	
SLN: sentinel lymph node				
NAC: neoadjuvant chemotherapy				

	Total	Residual disease	*P*-value
Response to NAC: followed the Revised Response Evaluation Criteria in Solid Tumors guideline, version 1.1			
HER2: Human epidermal growth factor receptor 2			

As shown in Table 1, the baseline characteristics of patients with or without residual nodal disease varied significantly. Residual nodal disease refers to the positive non-sentinel node(s), which was confirmed by a permanent pathology report. The residual nodal disease group had more ER-positive patients (85.7%, $p = 0.007$) and more PR-positive patients (72.2%, $p = 0.011$) than the no nodal residual disease group. In addition, patients with nodal residual disease had a higher initial N stage ($p < 0.001$), higher number of positive SLN ($p < 0.001$), higher pathologic T stage ($p = 0.001$), and higher N stage ($p < 0.001$) than those without nodal residual disease.

Table 2 shows the clinicopathologic information of patients based on their baseline and validation groups. The median age was 46.4 years (range 24–74) and 48.3 years (range 26–78) for the test population and the validation group, respectively. The hormone receptor status and HER2 positivity did not significantly differ between the two groups. The mean clinical tumor size before NAC was 44.2 mm (SD: 20.3 mm) and 38.2 mm (SD: 18.7 mm) in the test population and validation group, respectively. The mean pathologic tumor size following NAC was 21.4 mm (SD: 15.9 mm) for the test population (50.1% mean reduction) and 18.7 mm (SD: 14.2 mm) (50.2% mean reduction) for the validation group. Clinical parameters of both the groups of the patients exhibited no significant difference except for the clinical N stage, where the proportion of patients with N2 was 7.3% in the test group and 16.2% in the validation group. The number of positive SLN(s) at the time of surgery and the proportion of patients with the residual nodal disease were critical parameters in developing the nomogram, and its *p*-values failed to demonstrate statistical significance. The number of frozen nodes was 4.09 (SD: 1.6) in the baseline group and 4.05 (SD: 1.5) in the validation group (p = 0.77). The mean number of total nodes, which include both frozen and permanent biopsy, was 14.6 and 14.0 in the baseline group and validation group, respectively ($p = 0.16$). Supplementary Table S1 shows the comparison of the detailed clinicopathologic factors between the baseline and validation groups based on residual nodal disease.

Table 2
Comparison of the baseline group and validation group

	Baseline group	Validation group	*P*-value
Number of patients	384	174	
Age at diagnosis			0.203
< 50 years	251 (65.4)	104 (59.8)	
≥ 50 years	133 (34.6)	70 (40.2)	
Tumor grade			0.849
G1/G2	313 (81.5)	143 (82.2)	
G3	71 (18.5)	31 (17.8)	
Estrogen receptor			0.698
Negative	76 (19.7)	32 (18.4)	
Positive	308 (80.3)	142 (81.6)	
Progesterone receptor			0.475
Negative	125 (32.6)	62 (35.6)	
Positive	259 (67.4)	112 (64.4)	
HER2 status			0.545
Negative	298 (77.6)	139 (79.9)	
Positive	86 (22.4)	35 (20.1)	
Biological subtype			0.359
HR+/HER2-	260 (67.7)	119 (68.4)	
HR+/HER2+	49 (12.8)	23 (13.2)	
HR−/HER2+	35 (9.1)	9 (5.2)	
HR−/HER2-	40 (10.4)	23 (13.2)	
Clinical T stage			0.051
T1	32 (8.4)	22 (12.6)	
T2	245 (63.8)	109 (62.6)	
T3	95 (24.7)	43 (24.8)	

HER2: Human epidermal growth factor receptor 2

	Baseline group	Validation group	*P*-value
T4	12 (3.1)	0	
Clinical N stage			0.032
N0	70 (18.2)	22 (12.6)	
N1	286 (74.5)	129 (74.2)	
N2	28 (7.3)	23 (16.2)	
Surgery type			0.309
Breast-conserving surgery	172 (44.8)	86 (49.4)	
Total mastectomy	212 (55.2)	88 (50.6)	
Number of positive SLN(s)			0.608
1	190 (49.5)	94 (54.0)	
2	144 (37.5)	59 (33.9)	
3	50 (13.0)	21 (12.1)	
Residual nodal disease			0.942
Absent	215 (56.0)	98 (56.3)	
Present	169 (44.0)	76 (43.7)	
Mean invasion depth in SLN (mm)	5.3 (0.3–30)	5.7 (0.3–23)	0.294
Response to NAC			0.128
Complete remission	18 (4.7)	4 (2.3)	
Partial remission (≥ 30% reduction)	269 (70.1)	137 (78.7)	
Stable disease	90 (23.4)	29 (16.7)	
Progressive Disease	7 (1.8)	4 (2.3)	
SLN: sentinel lymph node			
NAC: neoadjuvant chemotherapy			
Response to NAC: followed the Revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline, version 1.1			
HER2: Human epidermal growth factor receptor 2			

Factors for predicting NSLNM and the development of a nomogram

We aimed to develop a tool that could link routinely measured clinical factors to the actual probability of NSLNM during surgery. Table 3 displays the detailed analysis results. In the univariate analysis, the number of positive SLN(s), number of frozen nodes, tumor grade, ER and PR positivity, clinical N stage, and biological subtype were found to be significantly associated with the possibility of residual nodal disease. The odds ratio increased consistently with the number of positive SLN(s) and the initial N stage. In a multivariate stepwise logistic regression analysis, the number of metastatic SLN(s), number of frozen SLN(s), PR positivity, and preoperative clinical N stage were found to be independent predictors of NSLNM. These four variables were included to develop the nomogram (Fig. 1) The AUC value of this formula was 0.709 (95% confidence interval [CI], 0.658–0.761, Hosmer–Lemeshow test *p*-value 0.176) for the development set (Table 4.)

Table 3
Result of logistic regression for residual nodal disease

		Univariable				Multivariable			
Parameter		**Odds ratio**	**95% CI**		P **value**	**Odds ratio**	**95% CI**		*P*-**value**
Number of positive SLN(s)	1	1			< 0.001	1			0.001
	2	1.836	1.180	2.856	0.007	2.040	1.279	3.256	0.003
	3	2.754	1.453	5.219	0.002	3.027	1.571	5.831	0.001
Number of frozen SLN(s)		0.848	0.747	0.963	0.011	0.770	0.670	0.885	0.000
Invasion depth of SLN(s)		1.047	0.995	1.103	0.079				
Age at diagnosis		1.005	0.983	1.028	0.645				
Tumor grade	1	1			0.040				
	2	1.491	0.350	6.348	0.589				
	3	0.748	0.164	3.412	0.708				
HER2 status	1	0.742	0.454	1.212	0.233				
Estrogen receptor	0–2	1							
	> 2	2.241	1.301	3.860	0.004				
Progesterone receptor	0–2	1				1			
	> 2	1.901	1.220	2.964	0.005	2.142	1.343	3.416	0.001
Biological subtype	1: LumA	1.892	0.935	3.831	0.076				
	2: LumB	1.997	0.845	4.718	0.115				

SLN: sentinel lymph node

NAC: neoadjuvant chemotherapy

HER2: Human epidermal growth factor receptor 2

CI: confidence interval

		Univariable				Multivariable			
	3: HER2	0.615	0.220	1.723	0.355				
	4: Triple negative	1			0.012				
Ki-67 status		0.995	0.987	1.003	0.238				
	> 20	1.136	0.712	1.813	0.593				
Initial T stage	1	1			0.112				
	2	1.149	0.538	2.457	0.719				
	3	2.016	0.886	4.585	0.095				
	4	1.190	0.308	4.604	0.801				
Initial N stage	0	1			< 0.001	1			< 0.001
	1	2.269	1.275	4.035	0.005	2.584	1.438	4.642	0.002
	2	5.667	2.187	14.683	0.000	5.743	2.240	14.722	0.000
Response to NAC	1 = 100%	1			0.958				
	2 = 30–99%	0.836	0.444	1.573	0.579				
	3 = 0–29%	0.851	0.417	1.738	0.658				
	4 = < 0%	0.818	0.164	4.072	0.806				
SLN: sentinel lymph node									
NAC: neoadjuvant chemotherapy									
HER2: Human epidermal growth factor receptor 2									
CI: confidence interval									

Table 4
Discrimination and calibration ability of the developed nomogram

							Hosmer–Lemeshow test		
		N	Residual	AUC	95% CI		X-squared	DF	P-value
Development	2005–2016	384	169	0.709	0.658	0.761	8.957	6	0.176
Validation	2017–2019	174	76	0.715	0.634	0.796	10.535	6	0.104

AUC (area under the receiver operating characteristic curve) = C statistics

CI: confidence interval

*Optimism corrected C statistic by 1000 bootstrap resamples

In order to test the discrimination ability of the nomogram, we conducted an independent validation study using the data from a different cohort of 174 patients who underwent surgery at the AMC from 2017 to 2019. The AUC value of this formula was 0.715 (95% CI, 0.634–0.796, Hosmer–Lemeshow test *p*-value, 0.104) for the validation set (Table 4, Fig. 2) Since the null hypothesis (H_0) for this Hosmer–Lemeshow's test was that this model was a good fit for the data, a *p*-value greater than 0.05 was considered a suitable prediction model.

Table 5 describes the sensitivity, specificity, positive predictive value, and negative predictive value according to each threshold value for the assessment of the nomogram. A positive predictive value of this table indicates the ability to predict the actual probability of remnant malignant nodal disease when a surgeon proceeded to a full ALND after a positive SLNB result was reported.

Table 5
Specific parameter values of the nomogram according to the various cutoffs.

Threshold for probability (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
15	99	4	45	80
22	95	18	48	78
28	90	31	51	76
43	73	64	61	70
63	25	89	64	54
67	14	95	69	52
84	1	100	100	50
PPV: positive predictive value				
NPV: negative predictive value				

Discussion

Although traditional axillary surgery remains one of the standard management options, optimal treatment of the axilla has been an evolving area aimed at reducing its related morbidity. According to the most recent NCCN guidelines for invasive breast cancer, standard ALND or SLNB is recommended in selected cases when the nodes are clinically negative following NAC and fine-needle aspiration (FNA), or core biopsy is positive before preoperative chemotherapy [4]. ALND, as a means for achieving local disease control, carries an indisputable and often unacceptable risk of complications, such as seroma, infection, and lymphedema [7]. However, previous studies that analyzed patients with primary breast cancer or who underwent NAC found that 40–60% of those who underwent ALND had no residual axillary disease [5, 6, 8]. In our study population, 56% of the patients had no residual nodal metastasis following axillary dissection, which was performed owing to a positive sentinel nodal biopsy result at the time of surgery. Thus, a substantial portion of patients may have been subjected to the significant morbidity of extensive axillary surgery without receiving any clinical benefit. Therefore, our study aimed to determine a tool that allows a surgeon to be more discerning in choosing a subgroup of patients who may be spared from the possible morbidity of ALND based on available clinical information before and during a scheduled surgery. Our nomogram was composed of the following four variables: number of metastatic SLN(s), number of frozen nodes, PR positivity, and preoperative clinical N stage. These parameters were available before proceeding towards a complete ALND. The prognostic role of PR positivity has been well known, and it was also reflected as one of the statistically significant factors for the nomogram [9, 10].

Relatively few models have been proposed for predicting NSLNM for patients who underwent NAC. Thus, we reviewed several nomograms for patients who were treated with or without NAC and compared them with this study's results [5, 11–15]. One of the most widely used nomograms was developed by Van Zee et al., which included eight statistically significant variables of pathological size, LVI, method of detection, number of positive SLNs, multifocality, and number of negative SLNs [15]. ER status and nuclear grade were included in the model but failed to demonstrate a significant association with the likelihood of NSLNM. The overall discriminative ability of this nomogram, as measured by the ROC curve, was 0.76 for the retrospective population. The AUC value for the corresponding prospective population was 0.77. However, this model is only applicable to patients without NAC. Patients who were treated with NAC may require another version of the nomogram to accurately predict NSLNM. Moreover, the variables, such as pathological tumor size and LVI, may not always be available in a routine frozen section pathology during surgery.

Jeruss et al. proposed a model for predicting the likelihood of NSLNM(s) in patients with a positive SLN following preoperative chemotherapy [5]. They included the following five clinicopathologic factors: method of detection of SLN metastasis, multicentricity, initial lymph node status, pathologic tumor size, and LVI. The AUC of this model was 0.85, and the bootstrap-corrected AUC was 0.76. Since their study population included only patients with one metastatic sentinel node who underwent NAC, the applicability of this nomogram to patients with more than one nodal disease burden may be limited. The variables of this nomogram also included pathologic tumor size and LVI, which overlapped with the previous prediction model proposed by Van Zee et al. In many institutions, both parameters may be available only in a permanent pathology report.

Ryu et al. proposed another prediction model of NSLNM for patients who received preoperative chemotherapy [14]. They created a nomogram composed of the following four variables: pathologic T stage, LVI, SLN metastasis size, and number of positive SLN metastases. Their nomogram exhibited an AUC value of 0.791 and 0.705 for the internal and external validation cohorts, respectively. The number of patients included in the developing cohort was 197, while the number of patients included in the external validation cohort was 30. To develop the nomogram, we analyzed 384 patients' data and tested the formula with the data of 174 patients from different time windows. Besides the difference in the number of patients included the data involved 57 patients who were SLN negative but underwent ALND, whereas our study included only patients with one to three positive SLN(s) for analysis.

Despite the similarities and differences, the aforementioned studies and our study share the goal of accurately predicting NSLNM in patients who have undergone either upfront surgery or NAC followed by surgery. The results may help a surgeon be more discerning in determining the candidates for ALND. Each surgeon indeed has his/her own threshold to decide whether to proceed towards complete ALND or de-escalate axillary management, which could be influenced by setting an individual cut-off value using this nomogram. Parameters presented in Table 5 could be utilized as a reference. However, various clinicopathologic factors, including initial nodal status and response to chemotherapy, need to be comprehensively considered for optimal decision-making.

However, de-escalation of axillary surgery in eligible patients might raise concerns about possible residual metastatic nodal disease and the associated risk of tumor recurrence in the future. Nguyen et al. discovered a significant shift in the axillary surgery trend for patients with clinical N1 treated with NAC, with SLN surgery becoming more common while ALND becoming less common [16]. Although de-escalation of axillary surgery following NAC has been an increasing trend, significant prospective data regarding disease recurrence and related survival are lacking [17].

A retrospective study compared the survival result between SLNB alone and complete extent ALND in patients with one to three positive sentinel nodes on intraoperative frozen biopsy following preoperative chemotherapy [18]. After a median follow-up of 59.4 months for 483 patients (SLNB alone, 188; ALND, 295), no significant difference was observed in the survival between the two groups of patients. The analysis suggested that limited axillary surgery may be one of the possible surgical options for selected eligible patients.

On the other hand, Almahariq et al. reported that SLNB alone was associated with significantly lower survival than the ALND group (Hazards ratio [HR] 1.7, 95% CI 1.3–2.2, $p < 0.001$), with an estimated 5-year overall survival of 71% in the SLNB-only group compared with 77% of the ALND group ($p = 0.01$), upon comparing the survival of a total of 1617 eligible patients with ypN1 in the National Cancer Database [19]. However, they found that SLNB may have comparable results with ALND in the selected patients with luminal A or B tumors with a single metastatic lymph node disease (HR 1.03, 95% CI 0.59–1.8, $p = 0.91$). They were cautious about reducing the extent of axillary surgery; however, they also demonstrated that limiting axillary surgery may be feasible in some selected patients with favorable tumor biology. Until further conclusive clinical data is published, we believe that a more cautious approach to patients with ypN1 breast cancer is still appropriate; however, being more discerning in choosing eligible patients is worthwhile for reducing the range of axillary management.

There are several limitations to this study. Considering the single institutional, retrospective nature of this study, we acknowledge the potential existence of selection bias among eligible patients. Heterogeneity was observed in baseline patient characteristics between the test and validation groups. The baseline group had a higher proportion of patients with clinical N0, whereas the validation cohort had a higher proportion of patients with clinical N2. Despite its different period of the treatment time window, the resulting nomogram was validated only in a patient cohort from a single institution. External validation with a sufficient number of patients and patients with different background demographic data should be conducted to further validate the correlation of this proposed nomogram.

Conclusion

The ultimate goal is to tailor appropriate axillary surgery based on each patients' disease status so that only patients who are expected to benefit from ALND are subjected to the possible morbidity. Moreover, we hope to spare patients who may not gain significant benefit from the extensive procedure. For patients with one to three positive SLN(s) following preoperative chemotherapy, this nomogram could provide

clinically useful information to a surgeon about whether to proceed with further axillary dissection. Thus, this nomogram could be considered as an additional guiding tool to decide ALND intraoperatively, allowing a patient to avoid a separate surgical session of ALND. However, optimal management of axilla for breast cancer is a constantly evolving area; thus, multidisciplinary discussions regarding further axillary nodal clearance, adjuvant chemotherapy or endocrine therapy, and radiotherapy are critical.

Declarations

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Competing Interests

The authors declare that they have no conflict of interest.

Author Contributions

Jung Whan Chun wrote the main manuscript text. Sae Byul Lee designed and conducted the research. Jong Won Lee, Hee Jeong Kim, Il Yong Chung, Jisun Kim, Beom Seok Ko, Byung Ho Son, and Sei-Hyun Ahn supervised the process of the research. All authors reviewed the manuscript.

Data availability

The datasets analyzed during the current study are not publicly available due to individual privacy (which included patient verification number of the institution) but are available from the corresponding author on reasonable request.

Ethical approval

All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the tenets of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards

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Figures

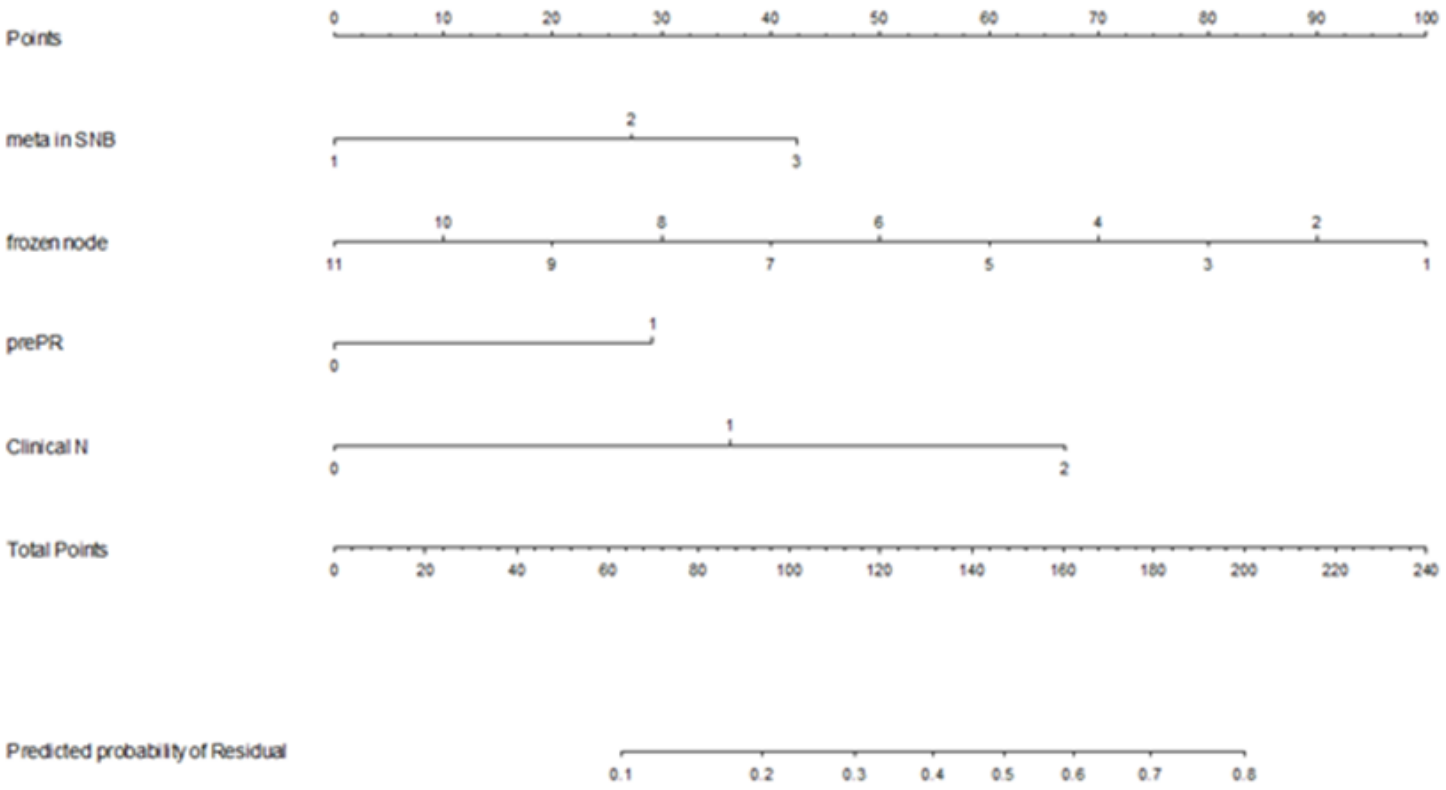

Figure 1

The nomogram to predict non-sentinel lymph node metastasis in patients with breast cancer with one to three positive sentinel lymph node(s) on a frozen biopsy result

*meta in SNB: number of positive sentinel node(s) by frozen biopsy during surgery

*frozen node: total number of examined axillary nodes by frozen biopsy during surgery

*prePR: Progesterone receptor positivity (0: negative, 1: positive)

*clinical N: clinical N stage determined by physical exam and pathologic and radiologic assessment.

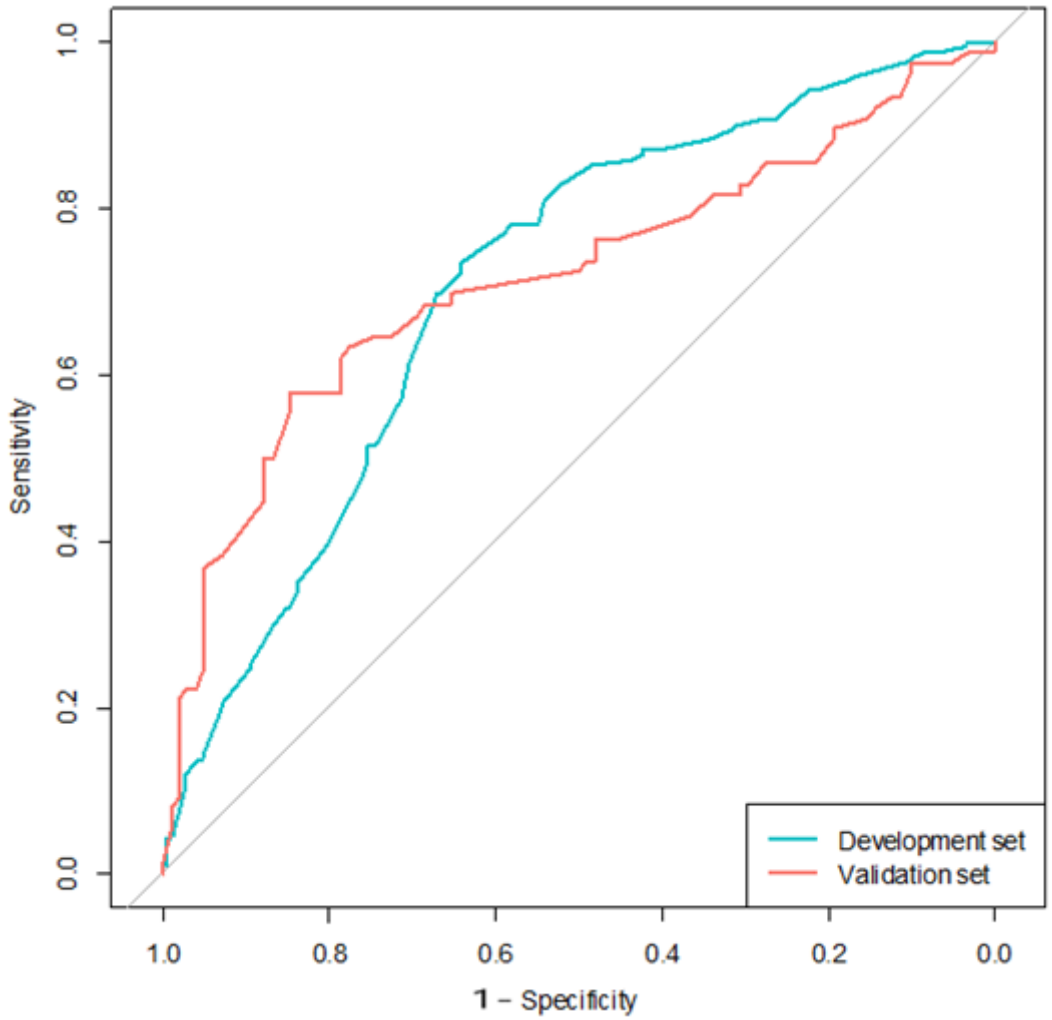

Figure 2

Receiver operating characteristic curve (ROC) of the nomogram. The area under the ROC curve was 0.709 in the development set and 0.715 in the validation set.

Supplementary Files

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- Supplementarytable.docx