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RESEARCH ARTICLE

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Predicting the extent of nodal involvement for node positive breast cancer patients: Development and validation of a novel tool

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Abstract

Background: This study aimed to develop an easy to use prediction model to predict the risk of having a total of 1 to 2, ≥3, or ≥4 positive axillary lymph nodes (LNs), for patients with sentinel lymph node (SLN) positive breast cancer.

Methods: Data of 911 SLN positive breast cancer patients were used for model development. The model was validated externally in an independent population of 180 patients with SLN positive breast cancer.

Results: Final pathology after ALND showed additional positive LN for 259 (28%) of the patients. A total of 726 (81%) out of 911 patients had a total of 1 to 2 positive nodes, whereas 175 (19%) had ≥3 positive LNs. The model included three predictors: the tumor size (in mm), the presence of a negative SLN, and the size of the SLN metastases (in mm). At external validation, the model showed a good discriminative ability (area under the curve = 0.82; 95% confidence interval = 0.74-0.90) and good calibration over the full range of predicted probabilities.

Ingrid van den Hoven and David van Klaveren contributed equally to this study.

Conclusion: This new and validated model predicts the extent of nodal involvement in node-positive breast cancer and will be useful for counseling patients regarding their personalized axillary treatment.

KEYWORDS
area under curve, breast neoplasms, nomograms, sentinel lymph node

1 | INTRODUCTION

The axillary treatment of breast cancer has changed significantly over time. After the implementation of the sentinel lymph node biopsy (SLNB) procedure, only patients with sentinel lymph node (SLN) metastases were selected for treatment by a completion axillary lymph node dissection (ALND). The IBCSG 23-01 study showed that a completion ALND could be omitted for patients with micrometastases.[1] Furthermore, the ACOSOG Z0011 trial showed that for a selected subgroup of patients, a small volume of disease left behind in the axilla does not compromise the oncological safety, in terms of recurrence and disease-free and overall survival.[2] Also, the results of the AMAROS trial, published in 2014, changed our perspective on axillary treatment showing that both radiotherapy, as well as surgery, can provide excellent regional control.[3] These studies have had a significant impact on the management of the axilla.[4]

It is obvious that the trend is heading towards a less invasive surgical treatment of the axilla. ALND has lost its importance for determining the need of adjuvant systemic treatment[4,5] and gradually seems to lose its importance for locoregional control. However, there remain several subgroups of breast cancer patients for whom treatment of the axilla may still be necessary. These include patients who were found to be node positive with ultrasound-guided lymph node biopsy (UGLNB). This appears to be a different group of node-positive patients with less favorable disease characteristics and a worse disease-free and overall survival as compared with those with SLN positive disease.[6,7] Another group may be the patients who are treated with a mastectomy rather than breast-conserving surgery (BCS), as radiotherapy may partially include the axilla when used as adjuvant treatment after BCS.[8]

In the last decade, the focus was set on finding patients with SLN positive breast cancer with a low risk of additional nodal involvement, for whom a completion ALND could be omitted. Several predictive systems have been developed to help identifying such patients.[9-17] Now that also a low risk of limited nodal involvement is increasingly accepted to omit further axillary treatment, it is time to search for the patients at high risk for extensive nodal involvement who may still benefit from additional treatment of the axilla. Presently, three predictive models have been proposed, that predict the risk of having four or more positive axillary lymph nodes (LNs).[18-20] The main purpose of these models is to help decide on the extent of radiation and/or systemic therapy and whether an immediate breast reconstruction can be offered to these patients.[18-20] To our knowledge, there is no model, that predicts the extent of nodal involvement.

The aim of the present study was to develop a tool for predicting the extent of nodal involvement in node-positive breast cancer patients. Such a tool may then be used for counseling in the clinical decision-making process, in the present "treat none—unless" era, regarding the additional axillary treatment strategies.

2 | METHODS

2.1 | Study population

The study population consisted of three consecutively selected patient groups. The original patient series for model development were identified from the Netherlands Cancer Registry (NCR) of the South region of the Netherlands in which 10 hospitals participated. The dataset included breast cancer patients with SLN-metastases who were treated between January 2007 and December 2008. For two of these hospitals, the Máxima Medical Center (MMC) and the Jeroen Bosch Hospital, data from the years 2000 to 2006 were also available as were data of MMC from the additional years of 2009 to 2011. The second group consisted of patients with SLN positive disease from the Gelderse Vallei Hospital and was used for external validation of the developed prediction model. The third group of patients were those found to have the node-positive disease by UGLNB and who were treated at the MMC between January 2006 and December 2011.[6] In accordance with Dutch guidelines[21] all patients had sonographic evaluation of the axilla after mammography and clinical evaluation. UGLNB (with cytological and/or histological sampling) was performed on suspicious axillary LNs as previously described.[6] All patients included in the present study underwent a completion ALND. Patients receiving neoadjuvant treatment, those with stage IV breast cancer and patients with a clinical $N_{2\text{-}3}$ axillary status or without a completion ALND were excluded from the study.

2.2 | Data accrual

Data were collected from an existing database of the NCR and from the patients' medical charts and pathology reports. The following data were collected: age at diagnosis, lateralization of the tumor, type of surgery, tumor morphology, tumor size (mm),

histological grade (conform modified Bloom and Richardson classification), presence of lymphovascular invasion (LVI), multifocality, estrogen and progesterone receptor status, and Her2Neu status. Histopathological data of the LNs included: total number of resected and positive/negatives nodes for both the SLNB-procedure and the ALND, the size of the largest metastases of the SLN as a continuous variable (in mm) and categorized as macrometastases (>2 mm), micrometastases (>0.2 but ≤2 mm) or isolated tumor cells (ITC) (≤0.2 mm) and the presence of extracapsular extension in the SLN.

The total number of axillary LNs was computed by adding the total number of nodes harvested during SLNB to the number of nodes that were found by ALND. The total number of positive axillary LNs was divided into three categories: 1 to 2, ≥3, or ≥4 positive LNs. For tumor grade, LVI, hormonal receptor and Her2Neu status, the size of the SLN metastases, and the presence of extracapsular extension there were some missing values. When values for LVI were missing and were not reported in the pathology report, LVI was assumed to be absent. Other missing values were imputed 20 times with the mice (multiple imputations with chained equations) algorithms in R software allowing all observed values to be analyzed.[22,23] The imputation model included all predictors and the total number of positive axillary LNs. We compared results without and with the imputation of missing values in a sensitivity analysis.

2.3 | Predictors and model development

Candidate predictors for axillary lymph node involvement were included in the analysis based on the literature and previously reported models. These included the models that predict the risk of having four or more involved axillary LNs.[9-20] We developed a model to predict the number of positive non-SLNs, and thus the total number of positive LNs. We used proportional-odds-logistic-regression-analysis to model the association between predictors and the number of positive non-SLNs. We checked the proportional-odds-assumption graphically for all potential predictors. We evaluated the strength of each predictor by its univariable odds ratio, and by its multivariable odds ratio together with its likelihood ratio χ^2 test statistic minus twice the degrees of freedom. The latter is consistent with Akaike's information criterion which balances the goodness-of-fit of a model with its complexity, and was also used to select predictors into a final model.[24] The patients in the UGLNB-group were also analyzed as described before, because we wanted to provide predictions for all node-positive breast cancer patients, regardless of the method of the detection. However, the analysis showed no additional predictors that could discriminate between low and high-risk patients because the method of detection was the strongest predictor for extensive nodal involvement. Consequently, we did not develop a separate model and only the overall probabilities of having a total of 1 to 2, ≥3, or ≥4 positive LNs were derived from the present dataset.

2.4 | Presentation of the prediction model

For easy calculation of the probability of having a particular number of positive LNs, we presented the final model with a score chart based on the regression coefficients of the final proportional odds model.[24,25] Predictor values were translated into a sum score that can be used to read the probability of having a total of 1 to 2, ≥3, or ≥4 positive LNs from a Table, given the number of positive SLNs.

2.5 | Validation of the new prediction model

We validated predictions of having ≥3 positive LNs for patients with <3 positive SLNs within the development data and the external validation data. We used validation plots to visualize the performance of the model.[26] The ability of our model to predict ≥4 positive LNs was compared with the previously developed nomograms by Katz et al, Meretoja et al, and Chagpar et al[18-20] We assessed the calibration of our model by the calibration slope and the calibration-in-the-large.[25] We assessed the discriminative ability by the area under the curve (AUC) of the receiver operating characteristic curve. Since we are assessing predictions of binary outcomes, the AUC is equal to the c-index, which estimates the probability that the risk prediction of a randomly chosen patient with the outcome is higher than the risk prediction of a randomly chosen patient without the outcome.

For proportional-odds-regression-analysis and validation of prediction models, we used R package rms (version 2.13.1; R Foundation for Statistical Computing, Vienna, Austria)

3 | RESULTS

A total of 1230 patients with node-positive breast cancer were included in this study. The model development population consisted of 911 patients, the external validation population of 180 and the UGLNB-group of 139 patients. Of the 911 patients from the model development population, 349 (38%) underwent a mastectomy and 562 (62%) were treated with BCS. For 259 (28%) patients, the final pathology showed additional positive LNs after completion of ALND. Of these, 175 (19%) had a total of three or more involved axillary LNs (Table 1). The observed overall proportions of patients in the UGLNB-group with a total of 1 to 2, ≥3, or ≥4 positive LNs were 37%, 63%, and 51%, respectively.

3.1 | Predictors and model development

The univariable analysis showed the following significant predictors for additional axillary lymph node involvement: tumor size (mm), tumor grade, LVI, presence of a negative SLN, >1 positive SLN, SLN macrometastases, an SLN metastases size >5 mm, and the presence of extracapsular extension. Predictor effects of age >65-year mulitfocality of the tumor, invasive lobular carcinoma morphology, a positive ER status, a positive PR status, and a positive Her2Neu status were nonsignificant but in the expected direction (Table 2).

TABLE 1 Characteristics of the total study population

	Development group		External validation group		UGLNB group	
Variables	**N**	**%**	**N**	**%**	**N**	**%**
Age at diagnosis (y)						
≤50	297	32.6	59	32.8	42	30.2
>50 ≤65	363	39.8	68	37.8	38	27.3
>65	251	27.6	53	29.4	59	42.4
Laterality						
Left	473	51.9	93	51.7	78	56.1
Right	437	48.0	87	48.3	61	43.9
Missing	1	0.1	0	0	0	0
Type of surgery						
BCS	562	61.7	97	53.9	49	35.3
Mastectomy	349	38.3	83	46.1	90	64.7
Tumor size (mm)						
≤5	20	2.2	3	1.7	2	1.4
6-10	72	7.9	12	6.7	3	2.2
11-20	446	49.0	99	55.0	23	16.5
21-30	270	29.6	50	27.8	102	73.4
31-50	90	9.9	14	7.8	9	6.5
>50	13	1.4	2	1.1	0	0
Multifocal						
Yes	112	12.3	24	13.3	24	17.3
No	799	87.7	156	86.7	111	79.9
Missing	0	0	0	0	4	2.9
Morphology						
IDC	722	79.3	130	72.2	108	72.7
ILC	156	17.1	30	6.7	23	16.5
Other	33	3.6	20	11.1	8	5.8
Tumor grade						
1	263	28.8	34	18.9	23	16.5
2	421	46.2	89	49.4	75	54.0
3	155	17.0	52	28.9	38	27.3
Missing	72	7.9	5	2.8	3	2.2
LVI						
Yes	179	19.6	26	14.4	34	24.5
No	421	46.2	121	67.2	80	57.6
Missing	311	34.1	33	18.3	25	18.0
ER status						
Positive	780	85.6	146	81.1	100	71.9
Negative	114	12.5	34	18.9	39	28.1
Missing	17	1.9	0	0	0	0
PR status						
Positive	673	73.9	120	66.7	80	57.6
Negative	183	20.1	60	33.3	59	42.4
Missing	55	6.0	0	0	0	0
Her2Neu status						
Positive	80	8.8	24	13.3	26	18.7
Negative	613	67.3	125	69.4	113	81.3
Missing	218	23.9	31	17.2	0	0
SLNs positive						
1	755	82.9	152	84.4		
2	124	13.6	23	12.8		
3	21	2.3	4	2.2		
>3	11	1.2	1	0.6		
SLN Metastases (mm)						
ITC (<0.2)	37	4.1	9	5.0		
Micro (0.2-2.0)	242	26.6	50	27.8		
Macro (>2.0)	485	53.2	118	65.6		
Missing	147	16.1	3	1.7		

(Continues)

TABLE 1 (Continued)

Variables	Development group		External validation group		UGLNB group	
	N	%	N	%	N	%
Extracapsular extension						
Yes	184	20.2	29	16.1		
No	650	71.3	86	47.8		
Missing	77	8.5	65	36.1		
Total number of positive lymph nodes						
1-2	736	80.8	148	82.2	51	36.7
≥3	175	19.2	32	17.8	88	64.0
≥4	111	12.2	24	13.3	71	51.1
Overall	911		180		139	

Abbreviations: ITC, isolated tumor cells; LVI, lymphovascular invasion; SLN, sentinel lymph node.

The proportional odds assumption was well satisfied upon graphical inspection. The effects of the predictors were reasonably constant across any cut-off level for the extent of lymph node positivity (Figure S1, the constant horizontal distance between any two of the three symbols).

The most important predictors in the multivariable analysis were (odds ratio [OR] and 95% confidence interval [CI]): tumor size in mm (OR = 1.04; 95% CI = 1.02-1.05) the presence of a negative SLN (OR = 0.48; 95% CI = 0.35-0.67), the size of the SLN metastases (in mm) (OR = 1.17; 95% CI = 1.13-1.22) and the presence of extracapsular extension (OR = 1.50; 95% CI = 1.01-2.25) as shown in Table 3.

The regression coefficients in a complete case analysis of the full model (n = 301) were very similar to the analyses based on imputed data. Furthermore, none of the other variables were identified as predictive in the complete case analysis. (Table S1).

3.2 | Presentation of the prediction model

In the final model the following three predictors were selected: the size of the tumor in mm, the presence of a negative SLN, and the size of the SLN metastases in mm (Table 3). The model is presented as a simple score chart (Figure 1). For example, a patient with an SLN metastasis size of 8 mm, a tumor size of 25 mm, and no negative SLN has predicted probabilities of 73%, 27%, and 17% of having a total of 1 to 2, ≥3, or ≥ 4 positive LNs, respectively. The effect of extracapsular extension appeared to be nonsignificant after backward selection ($P = .12$), and the impact of adding ECE to the model was thus negligible.

3.3 | Validation of the prediction model

The model predictions of having ≥3 positive LNs (for patients with <3 positive SLNs) were validated within the development data and the external validation data (Figure 2). In both the apparent and external validation, the model showed a very good discriminative ability with AUCs of 0.80 (95% CI = 0.76-0.84) and 0.82 (95% CI = 0.74-0.90), respectively. Calibration was good over the complete range of predicted probabilities in both the apparent and external validation (Figure 2). When the actual size of the SLN metastases (in mm) is not provided, assigning eight points for macrometastases gives a good approximation. The performance of the model then remained satisfactory with an AUC of 0.79 (95% CI = 0.75-0.83) in apparent validation and 0.80 (95% CI = 0.72-0.88) at external validation (Figure S2).

3.4 | Comparison with previously developed models

When predicting the probability of having ≥4 positive LNs (for patients with less than four positive SLNs), the discriminative ability of our new model was equally good or even better in the external validation data (AUC = 0.82; 95% CI = 0.74-0.90) as compared with the three previously developed predictive systems (18-20) (AUC's of 0.82, 0.80, and 0.66, respectively). Furthermore, calibration was also superior for the newly developed prediction model (Figure S3).

4 | DISCUSSION

Early stage breast cancer patients, with limited nodal involvement, are no longer subjected to a completion ALND, based on the results of the IBCSG 23-01, AMAROS, and Z0011 trials.[1-3] Because the evidence for omitting further axillary treatment in patients with extensive nodal involvement is lacking, it is useful to predict the extent of nodal involvement.

We have developed a novel model that predicts the risk of having a total of 1 to 2, ≥3, or ≥4 positive LNs using only three predictors: tumor size (in mm), the presence of a negative SLN and the size of the SLN metastases (in mm). Although the presence of extracapsular extension also showed to be a significant predictor in both univariable and multivariable analysis we chose to incorporate only the three strongest predictors. This did not affect model performance and was in line with the aim of this study to keep the model as simple and user-friendly as possible. The discriminative ability of the model was good (AUC of 0.80) and it showed adequate calibration over the complete range of predicted probabilities. Furthermore, the model

TABLE 2 Univariable associations between predictors and the number of additional positive lymph nodes

			Additional positive lymph nodes			%			Odds	Lower	Upper
Predictors	**Level**	**N**	**≥1**	**≥2**	**≥3**	**≥1**	**≥2**	**≥3**	**Ratio**	**0.95**	**0.95**
Age at diagnosis	≤50	297	89	51	29	30	17	10	1.00		
(y)	>50 ≤65	363	104	56	40	29	15	11	0.94	0.68	1.31
	>65	251	66	31	18	26	12	7	0.81	0.56	1.17
Laterality (left)	No	437	130	70	42	30	016	10	1.00		
	Yes	473	129	68	45	27	14	10	0.89	0.67	1.18
Mastectomy	No	562	157	82	53	28	15	9	1.00		
	Yes	349	102	56	34	29	16	10	1.07	0.80	1.43
Tumor size (mm)	≤15	327	65	30	19	20	9	6	1.00		
	<15 ≤25	400	114	48	30	29	12	8	1.56	1.10	2.20
	>25	184	80	60	38	43	33	21	3.52	2.38	5.22
Multifocal	No	799	223	117	72	28	15	9	1.00		
	Yes	112	36	21	15	32	19	13	1.26	0.83	1.92
Morphology (ILC)	No	755	210	104	65	28	14	9	1.00		
	Yes	156	49	34	22	31	22	14	1.29	0.89	1.87
Tumor grade	1	263	61	30	21	23	11	8	1.00		
	2	421	134	73	43	32	17	10	1.54	1.09	2.18
	3+	155	54	30	21	35	19	14	1.84	1.21	2.80
LVI	No	732	196	100	60	27	14	8	1.00		
	Yes	179	63	38	27	35	21	15	1.55	1.10	2.18
ER positive	No	114	36	22	14	32	19	12	1.00		
	Yes	780	223	116	73	29	15	9	0.84	0.55	1.27
PR positive	No	183	56	31	21	31	17	11	1.00		
	Yes	673	194	104	64	29	15	10	0.91	0.64	1.29
Her2Neu positive	No	613	158	88	54	26	14	9	1.00		
	Yes	80	30	14	8	38	18	10	1.60	1.00	2.56
SLNs negative	0	518	179	101	65	35	19	13	1.00		
	1	260	54	24	16	21	9	6	0.49	0.34	0.69
	2+	133	26	13	6	20	10	5	0.45	0.29	0.72
SLNs positive	1	755	195	96	58	26	13	8	1.00		
	2+	156	64	42	29	41	27	19	2.15	1.52	3.05
Macrometastases	No	279	36	12	5	13	4	2	1.00		
	Yes	485	177	102	65	36	21	13	4.05	2.73	6.00
Size of SLN	≤2	218	24	7	3	11	3	1	1.00		
metastases (mm)	>2 ≤5	183	36	13	9	20	7	5	1.99	1.14	3.47
	>5	207	97	58	32	47	28	15	7.56	4.58	12.47
ECE	No	651	156	77	47	24	12	7	1.00		
	Yes	184	85	51	35	46	28	19	2.78	2.00	3.86
Overall		911	259	138	87	0.28	0.15	0.10			

Note: Odds ratios are estimated with proportional odds regression analysis.

Abbreviations: ECE, extracapsular extension; ER, estrogen receptor status; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor status; SLN(s), sentinel lymph node(s).

TABLE 3 Multivariable associations between predictors and the number of additional positive lymph nodes, based on a model with all potential predictors (Full model) and a model with the three strongest predictors (Selected model)

Predictors	Odds ratio	Lower 0.95	Upper 0.95	χ^2	df	P
Full model						
Age at diagnosis (10 y)	0.94	0.83	1.07	0.8	1	.3638
Laterality (left)	0.96	0.70	1.31	0.1	1	.8057
Mastectomy	0.77	0.55	1.08	2.2	1	.1362
Tumor size (mm)	1.04	1.02	1.05	20.7	1	<.0001
Multifocality	1.18	0.73	1.91	0.5	1	.4947
Morphology (ILC)	1.16	0.75	1.81	0.4	1	.5068
Tumor grade 2:1	1.42	0.96	2.11	4.2	2	.1216
Tumor grade 3:1	1.65	0.98	2.79			
LVI	1.14	0.78	1.69	0.5	1	.4946
ER positive	0.92	0.52	1.65	0.1	1	.7883
PR positive	1.09	0.68	1.77	0.1	1	.7128
Her2Neu positive	1.35	0.82	2.23	1.4	1	.2437
SLNs negative	0.47	0.34	0.66	19.3	1	<.0001
SLNs positive	1.41	0.95	2.10	2.9	1	.0899
Size of SLN metastases (mm)	1.15	1.10	1.21	41.1	1	<.0001
ECE	1.50	1.01	2.25	4.0	1	.0466
Selected model						
Tumor size (mm)	1.04	1.02	1.05	26.6	1	<.0001
SLNs negative	0.48	0.35	0.67	19.3	1	<.0001
Size of SLN metastases (mm)	1.17	1.13	1.22	63.5	1	<.0001

Note: Odds ratios are estimated with proportional odds regression analysis.

Abbreviations: ECE, extracapsular extension; ER, estrogen receptor status; ILC, invasive lobular carcinoma; LVI, lymphovascular invasion; PR, progesterone receptor status; SLN(s), sentinel lymph node(s).

was validated in an independent external patient population and showed good discrimination (AUC 0.82) and calibration.

Because we wanted to provide risk predictions for all node-positive breast cancer patients, regardless of the method of detection, also an UGLNB-group was analyzed. However, when the lymph node metastases are detected by ultrasound, this staging method by itself seems to be the most important predictor for extensive nodal involvement given the fact that 63% of these patients had ≥3 positive LNs. These findings are in concordance with the results of Schipper et al[27], that showed that the finding of suspicious nodes with ultrasound resulted in pN2-pN3 disease in 41.2% of the patients. For this patient group, we found no additional predictors that could further discriminate between low- and high-risk patients. Consequently, we decided that the development of a separate model for this group was not relevant. Because these patients also need counseling regarding the axillary treatment strategy, the overall risk estimates of having a total of 1 to 2, ≥3, or ≥4 positive LNs are also visualized in our prediction tool.

Previously published models were mostly developed before the publication of the Z0011-trial results and are intended to identify patients at low risk for additional nodal involvement for whom a completion ALND could be omitted.[9-14,16,17] The few models that have been designed to predict the risk of having ≥4 involved LNs were used to guide decisions on the extent of radiation and systemic therapy regimens.[18-20] To our knowledge our model is the first that actually predicts the extent of nodal involvement, therefore easily classifying patients to have limited nodal involvement (1-2 positive LNs, corresponding to the conclusions of Z0011) or extensive lymph node involvement (≥3 positive LNs). Although it was not a primary goal of this study, our model also predicts the risk of having ≥4 positive LNs. This is another cut-off-point for extensive nodal involvement that is used to decide about the need for additional axillary irradiation. The new model was compared with the existing three models that predict ≥4 positive LNs and outperformed the other models in terms of discriminative ability and calibration for our Dutch population.

The variables included in our new prediction tool already proved to be strongly associated with nodal involvement in other models and validation studies. Furthermore, other previously reported models included up to nine variables, resulting in more complex calculations and a less user-friendly model.[15] The present study shows that model performance can still be very good when only a few but strongly prognostic variables are included.

Our study has limitations. A retrospectively collected database was used that contained some missing values. The size of the SLN metastases (in mm) is a strong predictor for extensive nodal involvement, however, the actual size was not always provided. Although our model also works based on the presence or absence of a macrometastasis in the SLN, with acceptable model performance, we recommend that the actual size of the SLN metastases should be reported consistently by pathologists to enable more accurate predictions. The risk predictions for patients that were found node positive by UGLNB are based on relatively small sample size. Therefore, we are currently investigating whether these risks will be similar in a larger population.

Some clinicians have already abandoned the use of ALND for SLN positive patients. However, we must be aware of the generalization of the conclusions of the Z0011-trial, as these are only applicable to about 6% of the total breast cancer population.[28] An advantage of our new model is that the online tool can visualize the predicted risk of the extent of nodal disease for each individual patient. Therefore the model can be a useful tool in counseling patients, to help them understand their risks. Because the model gives no actual treatment recommendations, or a given cut-off point, the risks and benefits of further axillary treatment need to be weighed individually. Following the results of the Z0011 and AMAROS trials, it appears reasonable to give no further axillary treatment to patients that are very likely to have limited nodal involvement (1-2 positive LNs) provided that adjuvant systemic treatment is offered, and consider radiation therapy of the axilla or a completion ALND when they are at risk for extensive nodal involvement (≥3 positive LNs). We strongly advise against the omission of further axillary treatment for patients with a high risk of having ≥4 positive LNs.

In conclusion, we have developed and validated a new model that predicts the extent of nodal involvement in node-positive breast cancer patients. This new tool will particularly be useful for counseling patients regarding their personalized axillary treatment.

Sum score =

Size largest SLN metastasis (mm)

+ 0.25 x tumor size (mm)

+ 5 if no negative SLN was found

	LN+ when 1 SLN+			LN+ when 2 SLN+			LN+ when 3 SLN+		
Sum score	1-2	≥3	≥4	1-2	≥3	≥4	1-2	≥3	≥4
<1	98	1.8	1.0	95	4.6	1.8	0	100	4.6
1	98	2.1	1.2	95	5.4	2.1	0	100	5.4
2	98	2.5	1.4	94	6.2	2.5	0	100	6.2
3	97	2.9	1.6	93	7.2	2.9	0	100	7.2
4	97	3.4	1.8	92	8.3	3.4	0	100	8.3
5	96	3.9	2.1	90	9.6	3.9	0	100	9.6
6	95	4.6	2.5	89	11	4.6	0	100	11
7	95	5.3	2.9	87	13	5.3	0	100	13
8	94	6.1	3.4	86	14	6.1	0	100	14
9	93	7.1	3.9	83	17	7.1	0	100	17
10	92	8.2	4.6	81	19	8.2	0	100	19
11	91	9.5	5.3	79	21	9.5	0	100	21
12	89	11	6.2	76	24	11	0	100	24
13	88	12	7.1	73	27	12	0	100	27
14	86	14	8.2	70	30	14	0	100	30
15	84	16	9.5	66	34	16	0	100	34
16	81	19	11	63	37	19	0	100	37
17	79	21	13	59	41	21	0	100	41
18	76	24	14	55	45	24	0	100	45
19	73	27	16	51	49	27	0	100	49
20	70	30	19	47	53	30	0	100	53
21	67	33	21	44	56	33	0	100	56
22+	63	37	24	40	60	37	0	100	60

FIGURE 1 Score chart for the probability of finding a total of 1 to 2, ≥3, or ≥4 positive lymph nodes. For example, in a patient with one positive sentinel lymph node (SLN) with a largest size of the metastasis of 8 mm, a tumor size of 25 mm, and no negative SLN found, the score is calculated as follows: [8] (8 mm largest metastasis size) + [0.25 × 25] (25 mm tumor size) + [5] (if no negative SLN was found), which makes a (rounded) sum score of 19 points. The probabilities can then be read from the chart on the horizontal line following the 19 (sum score). The probability of having only 1 to 2 nodes positive is 73%, the risk of having ≥3 positive lymph nodes is 27% and the risk of having ≥4 is 17%. For a similar patients with a negative SLN the sum score would be 14: [8] + [0.25 × 25] + 0. And the corresponding probabilities of having 1 to 2, ≥ 3, or ≥ 4 positive lymph nodes would be 86%, 14%, and 8.2%, respectively

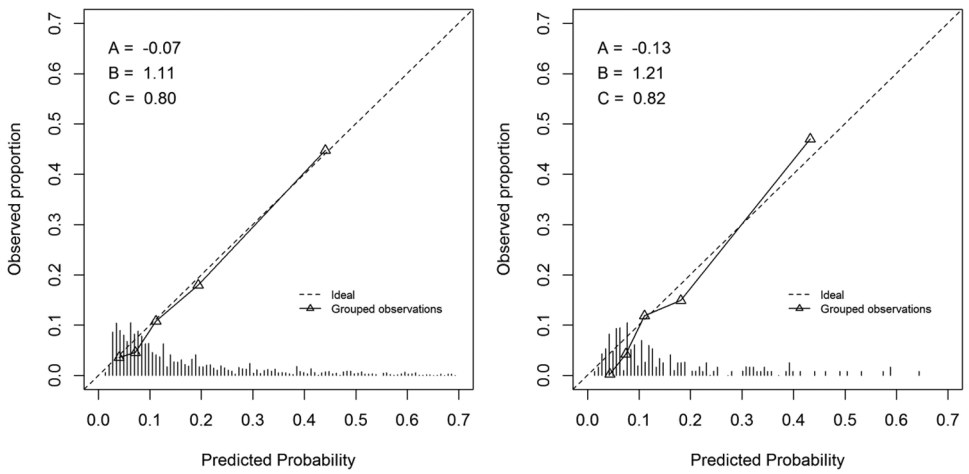

FIGURE 2 Internal (left) and external (right) validation of the predicted probability of ≥3 positive lymph nodes (when the number of positive SLNs is <3). The distribution of predicted risks for ≥3 or more positive axillary lymph nodes is shown at the bottom of the graphs. The triangles indicate the observed proportions by quartiles of predicted risks. SLN, sentinel lymph node

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DATA ACCESSIBILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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