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.
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. 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. 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 locoregional control. These studies have had a significant impact on the management of the axilla.

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 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. 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.

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. 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). 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. 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. In accordance with Dutch guidelines 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. All patients included in the present study underwent a completion ALND. Patients receiving neo-adjuvant treatment, those with stage IV breast cancer and patients with a clinical N2,3 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. 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.

### 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. 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 \( \chi^2 \) 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. 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.

### 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. 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.

### 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. 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. We assessed the calibration of our model by the calibration slope and the calibration-in-the-large. 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)

### 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.

### 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 multifocality 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).
| Variables                      | Development group | External validation group | UGLNB group |
|-------------------------------|-------------------|---------------------------|-------------|
|                               | 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   | 0     | 0   |
| **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)
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 ≥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 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   | 100.0 | 180   | 100.0 | 139   |       |

Abbreviations: ITC, isolated tumor cells; LVI, lymphovascular invasion; SLN, sentinel lymph node.
### TABLE 2 Univariable associations between predictors and the number of additional positive lymph nodes

| Predictors                        | Level | N  | Additional positive lymph nodes | %   | Odds Ratio | Lower 0.95 | Upper 0.95 |
|-----------------------------------|-------|----|---------------------------------|-----|------------|------------|------------|
|                                   |       |    |                                 |     |            |            |            |
|                                   |       |    |                                 |     |            |            |            |
| Age at diagnosis                  | ≤50   | 297| ≥1                               | 89  | 0.95       | 0.95       | 1.00       |
|                                   | >50 ≤65| 363| ≥2                               | 104 | 0.95       | 0.95       | 1.00       |
|                                   | >65    | 251| ≥3                               | 130 | 0.95       | 0.95       | 1.00       |
| Laterality (left)                 | No    | 437| ≥1                               | 129 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 473| ≥2                               | 130 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 130 | 0.95       | 0.95       | 1.00       |
| Mastectomy                        | No    | 562| ≥1                               | 157 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 349| ≥2                               | 102 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 102 | 0.95       | 0.95       | 1.00       |
| Tumor size (mm)                   | ≤15   | 327| ≥1                               | 65  | 0.95       | 0.95       | 1.00       |
|                                   | <15 ≤25| 400| ≥2                               | 114 | 0.95       | 0.95       | 1.00       |
|                                   | >25    | 184| ≥3                               | 80  | 0.95       | 0.95       | 1.00       |
| Multifocal                        | No    | 799| ≥1                               | 223 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 112| ≥2                               | 36  | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 36  | 0.95       | 0.95       | 1.00       |
| Morphology (ILC)                  | No    | 755| ≥1                               | 210 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 156| ≥2                               | 49  | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 49  | 0.95       | 0.95       | 1.00       |
| Tumor grade                       | 1     | 263| ≥1                               | 61  | 0.95       | 0.95       | 1.00       |
|                                   | 2     | 421| ≥2                               | 134 | 0.95       | 0.95       | 1.00       |
|                                   | 3+    | 155| ≥3                               | 54  | 0.95       | 0.95       | 1.00       |
| LVI                               | No    | 732| ≥1                               | 196 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 179| ≥2                               | 63  | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 63  | 0.95       | 0.95       | 1.00       |
| ER positive                       | No    | 114| ≥1                               | 36  | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 780| ≥2                               | 223 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 223 | 0.95       | 0.95       | 1.00       |
| PR positive                       | No    | 183| ≥1                               | 56  | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 673| ≥2                               | 194 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 194 | 0.95       | 0.95       | 1.00       |
| Her2Neu positive                  | No    | 613| ≥1                               | 158 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 613| ≥2                               | 158 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 158 | 0.95       | 0.95       | 1.00       |
| SLNs negative                     | 0     | 518| ≥1                               | 179 | 0.95       | 0.95       | 1.00       |
|                                   | 1     | 260| ≥2                               | 54  | 0.95       | 0.95       | 1.00       |
|                                   | 2+    | 133| ≥3                               | 26  | 0.95       | 0.95       | 1.00       |
| SLNs positive                     | 1     | 755| ≥1                               | 195 | 0.95       | 0.95       | 1.00       |
|                                   | 2+    | 156| ≥2                               | 64  | 0.95       | 0.95       | 1.00       |
| Macrometastases                   | No    | 279| ≥1                               | 36  | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 485| ≥2                               | 177 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 177 | 0.95       | 0.95       | 1.00       |
| Size of SLN metastases (mm)       | ≤2    | 218| ≥1                               | 24  | 0.95       | 0.95       | 1.00       |
|                                   | >2 ≤5| 183| ≥2                               | 36  | 0.95       | 0.95       | 1.00       |
|                                   | >5    | 207| ≥3                               | 97  | 0.95       | 0.95       | 1.00       |
| ECE                               | No    | 651| ≥1                               | 156 | 0.95       | 0.95       | 1.00       |
|                                   | Yes   | 184| ≥2                               | 85  | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 85  | 0.95       | 0.95       | 1.00       |
| Overall                           |       | 911| ≥1                               | 259 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥2                               | 259 | 0.95       | 0.95       | 1.00       |
|                                   |       |    | ≥3                               | 259 | 0.95       | 0.95       | 1.00       |

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 designed to predict the risk of having ≥4 involved LNs were used to guide decisions on the extent of radiation and systemic therapy regimens.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.

**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 95% | Upper 95% | \( \chi^2 \) | 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 | 1 |    |         |
| 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 | .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. 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).
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) + \[0.25 \times 25\] (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: \[8\] + \[0.25 \times 25\] + 0. And the corresponding probabilities of having 1 to 2, ≥3, or ≥4 positive lymph nodes would be 86%, 14%, and 8.2%, respectively.

| Sum score | LN+ when 1 SLN+ | LN+ when 2 SLN+ | LN+ when 3 SLN+ |
|-----------|-----------------|-----------------|-----------------|
| <1        | 1-2             | ≥3              | ≥4              |
| 1         | 95              | 1.8             | 1.0             |
| 2         | 95              | 1.2             | 1.0             |
| 3         | 94              | 2.5             | 1.2             |
| 4         | 93              | 2.9             | 1.6             |
| 5         | 92              | 3.4             | 1.8             |
| 6         | 91              | 3.9             | 2.1             |
| 7         | 90              | 4.6             | 2.5             |
| 8         | 89              | 5.3             | 2.9             |
| 9         | 88              | 6.1             | 3.4             |
| 10        | 87              | 7.1             | 3.9             |
| 11        | 86              | 8.2             | 4.6             |
| 12        | 85              | 9.5             | 5.3             |
| 13        | 84              | 10.6            | 6.2             |
| 14        | 83              | 11.9            | 7.1             |
| 15        | 82              | 13.2            | 8.2             |
| 16        | 81              | 14.5            | 9.5             |
| 17        | 80              | 15.8            | 10.6            |
| 18        | 79              | 17.1            | 11.9            |
| 19        | 78              | 18.4            | 13.2            |
| 20        | 77              | 19.7            | 14.5            |
| 21        | 76              | 21.0            | 15.8            |
| ≥22       | 75              | 22.3            | 17.1            |

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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