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ORIGINAL ARTICLE – BREAST ONCOLOGY

# A Simple Nomogram to Evaluate the Risk of Nonsentinel Node Metastases in Breast Cancer Patients with Minimal Sentinel Node Involvement

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## ABSTRACT

**Background.** Tumor-positive sentinel node biopsy (SNB) suggests a risk of nonsentinel node metastases in breast cancer. This risk is lower after micrometastasis or isolated tumor cells (ITC) in the sentinel node (SN), and recent studies suggest that completion axillary lymph node dissection (ALND) might not improve outcome in these patients. We aim to validate existing predictive models and to develop a new model for micrometastatic and ITC patients.

**Methods.** A series of 484 patients with micrometastases or ITC in SN followed by ALND was used to evaluate factors affecting nonsentinel node involvement. Logistic regression analysis was performed to construct a predictive model, which was validated by a separate series of 51 patients.

**Results.** Only 7.2% of patients had additional metastases on completion ALND. Tumor diameter and multifocality associated with nonsentinel status on multivariate analysis. A predictive model was constructed showing good [area under the curve (AUC) 0.791] discrimination in the validation series. Previously published models performed poorly in our patient population.

**Conclusions.** Nonsentinel node metastases are rare with micrometastasis or ITC in SN. Most published predictive models for nonsentinel node involvement perform poorly in the present patient population. We developed a new predictive model which seems to perform well in discriminating patients with more than 10% risk of additional metastases. However, the presented nomogram needs to be validated with an independent patient series to evaluate its accuracy, especially for high-risk patients.

Diagnostic axillary lymph node dissection (ALND) has been fundamentally replaced by sentinel node biopsy (SNB) in nodal staging of breast cancer during the recent decade. SNB is associated with less morbidity of the upper limb when compared with ALND.[1] However, only patients who avoid ALND benefit from the advantages of SNB.

Tumor-positive SNB implicates an approximately 50% risk of additional nonsentinel node metastases in the axilla, and completion ALND has been considered the golden standard whenever a metastasis is found in the sentinel node (SN).[2] When considering tumor-positive SNB findings with only micrometastasis or isolated tumor cells (ITC) in the SN, the risk for additional nonsentinel metastases decreases to 10–15%.[3] Completion ALND has been routinely performed in these patients as well, due to a considerable risk of additional lymph node metastases.[3–6] This paradigm has, however, been changing recently owing to the development of mathematical models for predicting patient-specific risk of nonsentinel node metastases. These models use various patient-, tumor-, and SN-related variables to predict the nonsentinel node metastasis risk and aim to identify patients with low risk of additional metastases in whom completion ALND could be avoided.[7–20]

Almost all such predictive models are based on all sizes of SN metastases and tend to best predict nonsentinel node status in a setting of larger SN metastases.[21] The low prevalence of nonsentinel node involvement after micrometastasis or ITC finding in SN makes this patient population especially intriguing when considering omission of

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completion ALND. Only recently has a single study been published presenting a nomogram to predict nonsentinel node involvement specifically in a micrometastatic SN setting.[15]

On the other hand, recent significant studies suggest that completion ALND after tumor-positive SNB might not improve survival at all.[22–24] The randomized American College of Surgeons Oncology Group (ACOSOG) Z0011 trial demonstrated similar outcome in the ALND and SNB-only arms, despite a nonsentinel node involvement rate of 27% in the ALND arm.[24] However, all patients in this trial underwent breast-conserving treatment with whole-breast radiation, and it is therefore unclear whether the results can be generalized also to mastectomy patients without radiotherapy or to breast-conserving treatment with partial breast radiotherapy. In fact, mastectomy without radiotherapy has been reported to increase the incidence of axillary recurrences after tumor-negative SNB.[25,26]

For these reasons, patients with SN micrometastases or ITC and with substantial risk of nonsentinel node metastases might benefit from completion ALND. The aim of the present study is to examine risk of and risk factors for nonsentinel node metastases in breast cancer patients with micrometastasis or ITC in SN. We further aim to test the performance and to validate existing predictive models, and if found inadequate to develop a novel predictive model specifically for such patient population.

## PATIENTS AND METHODS

### *Patients and Surgery*

Patient, SNB procedure, tumor, and follow-up data are prospectively gathered into Helsinki sentinel node database. Altogether, 3,418 patients with invasive breast cancer underwent SNB between September 2003 and January 2011 at the Breast Surgery Unit of Helsinki University Central Hospital.

Patients with micrometastasis or ITC in their SN ($n = 537$) operated between September 2003 and May 2010 were selected from the database to form the main patient population of this study. Level I–II completion ALND was usually performed in all patients with tumor-positive SNB, also in patients with micrometastases or ITC.[3–5,27] ALND was, however, omitted in 24 patients with micrometastases and 29 patients with ITC due to surgeon or patient preference, typically due to severe comorbidities or due to intraoperatively negative SNB and patient preference for no further operations at time of final histology. These 53 patients were excluded.

The remaining 484 patients with micrometastases ($n = 278$) or ITC ($n = 206$) and with completion ALND performed form the final study cohort. This cohort was used to evaluate factors affecting nonsentinel status and to construct a predictive model. The predictive model was then validated by a consecutive series of 51 patients with micrometastases or ITC in SN and completion ALND, operated between May 2010 and January 2011 at the same center with similar methods and protocols.

Preoperative axillary ultrasound was performed in all patients, and fine-needle biopsy was performed whenever suspicious nodes were encountered. Patients underwent either wide local excision or mastectomy as the breast operation. Preoperative lymphoscintigraphy and intraoperative identification with gamma probe and blue dye were used to perform SNB, as described in detail in our previous report.[28]

### *Histopathology*

Specialized breast pathologists evaluated the surgical breast specimen for histological tumor size (largest diameter), multifocality, histological type, tumor grade, lymphovascular invasion, hormone receptor status, human epidermal growth factor receptor 2 (Her-2) oncogene amplification status, and proliferation index MIB-1. In multifocal tumors the largest diameter of the largest focus was recorded. Hormone receptor status and MIB-1 were assessed using immunohistochemistry. Her-2 status was initially assessed using immunohistochemistry, and when considered positive the result was validated by chromogenic in situ hybridization. Histological classification and tumor staging and grading were based on the World Health Organization classification of tumors.[29]

Sentinel nodes were sliced into 1–1.5-mm-thick sections perpendicular to their long axis and arranged on prefrozen Tissue-Tek® OCT™ compound. Touch preparations from the surface and frozen sections from two levels were made from these slices; these were then stained with toluidine blue and viewed. In addition, rapid intraoperative immunohistochemistry (Cyto-Nel Ultrapid; Immuno Diagnostics Oy, Hämeenlinna, Finland) was used. Remaining tissue was fixed in formalin, and embedded in paraffin. Two sections were stained with hematoxylin and eosin (H&E), in addition to AE1/AE3 cytokeratin immunohistochemical staining (Dako Cytomation, Clostrup, Denmark).

Lymph nodes in the ALND specimens were wholly embedded in paraffin, and H&E sections were prepared from two levels, 200 µm apart. Tumor deposits were classified as micrometastases when not larger than 2 mm and as ITC when not larger than 0.2 mm.[29]

### *Statistical Methods*

Univariate analysis was performed to determine factors associated with nonsentinel node metastases. Chi-squared test was used for categorical variables and Mann–Whitney *U* test for continuous variables. All variables with $p$ value less than 0.15 were then included into a logistic regression analysis using backward stepwise method. Variables with $p$ value $<0.05$ were considered statistically significant in the multivariate analysis and were included in the final predictive model.

The resulting multivariate predictive model was then validated with the separate validation series. Discrimination of the model was assessed using area under the receiver operating characteristic curve (AUC). Calibration of the model was evaluated using the Hosmer–Lemeshow goodness-of-fit test. Sensitivity, specificity, and clinical utility (low-risk subgroup separation) of the model were determined for cutoff values of 10% and 15% predicted probabilities of additional metastases.

The main patient population was used to validate the existing predictive models by determining their AUC, sensitivity, specificity, and clinical utility values. PASW statistics 18 (SPSS Inc., Chicago, IL) software was used to perform the statistical analyses.

### *Ethical Considerations*

The project plan was approved by the Ethical Committee of Helsinki University Central Hospital. Written informed consent was obtained from all patients.

## RESULTS

Only 35 of the 484 study group patients (7.2%) were found to have additional metastases in their completion ALND specimen. Nonsentinel metastases were found in 23 (9.0%) patients with micrometastasis in SN and in 12 (6.2%) patients with ITC. The median number of lymph nodes examined in the ALND specimens was 17 (range 4–42) in patients with and 16 (range 4–43) in patients without nonsentinel node metastases ($p = 0.194$). The median number of metastatic nonsentinel nodes in patients with nonsentinel node involvement was one (range 1–6 nodes). When classified according to the largest nonsentinel metastasis, 21 patients had macrometastases, 9 had micrometastases, and 5 had ITC.

Patient and tumor characteristics for the main patient population are given in Table 1. Tumor diameter, multifocality, lymphovascular invasion, and tumor location had $p$ values of less than 0.15 and were included in the multivariate analysis. The results of the backward stepwise binary logistic regression analysis are given in Table 2. Tumor diameter ($p = 0.002$) and multifocality ($p = 0.039$) were found to be the only statistically significant variables associating with nonsentinel metastases on ALND.

The multivariate binary logistic regression analysis produced the following mathematical predictive model for presence of nonsentinel metastases in our patient series, with $p$ denoting the probability of nonsentinel metastases:

$$p = \frac{\mathrm{Exp}(-3.422 + 0.832[\text{if multifocal tumor}] + 0.031 \times \text{tumor diameter}[\text{mm}])}{1 + \mathrm{Exp}(-3.422 + 0.832[\text{if multifocal tumor}] + 0.031 \times \text{tumor diameter } [\text{mm}])}.$$

On the basis of this equation, we drew two simple nomograms to graphically evaluate the risk of nonsentinel metastases separately for unifocal and multifocal tumors (Table 3); for example, the predicted probability of nonsentinel node metastases is 26.1% in a patient with a multifocal tumor and the largest focus being 50 mm in histological diameter.

The Hosmer–Lemeshow test produced a $p$ value of 0.452, indicating that the multivariate model fits and calibrates well for the patient population. The AUC for the main patient population was 0.682 (0.592–0.771; 95% confidence interval), suggesting fairly good discrimination. With a 10% cutoff value for predicted probability, our model had sensitivity of 38.2% and specificity of 85.7%. Our model selects 84.1% of patients to have a predicted risk of less than 10% for additional metastases, showing good clinical utility (Table 4). For the higher cutoff value of 15% predicted probability, our model selects 95.6% of patients to the low-risk group with corresponding sensitivity of 14.7% and specificity of 96.4%. This means that our model predicts only 4.4% of patients in our series to have higher than 15% risk of additional metastases. With this 15% risk as a cutoff point, the model selects patients into either low-risk or high-risk groups with rather low sensitivity but high specificity. Only 13 of the 484 patients had higher than 20% predicted probability, and only 4 patients had higher than 30% predicted probability of additional metastases.

We identified 14 previously published predictive models from the literature.[7–20] All of them except for the Marseille nomogram included also SN macrometastases.[15] We were unable to validate the Adelaide decision aid, since it includes a variable, the proportion of SN replaced by

**TABLE 1** Univariate analysis comparing patients with additional metastases on axillary lymph node dissection with those with no additional metastases

| | No additional metastases on ALND ($n = 449$) | Additional metastases on ALND ($n = 35$) | All patients ($n = 484$) | $p$ |
|---|---|---|---|---|
| Patient age (years) | | | | 0.726 |
| Mean (range) | 59 (30–95) | 58 (37–83) | 59 (30–95) | |
| Body mass index (kg/m$^2$) | | | | 0.863 |
| Mean (range) | 25.8 (16.6–43.7) | 25.3 (17.9–35.6) | 25.8 (16.6–43.7) | |
| Histological diameter of the primary tumor (mm) | | | | 0.075 |
| Mean (range) | 18 (2–140) | 26 (3–120) | 18 (2–140) | |
| Multifocality of the primary tumor | | | | 0.057 |
| No | 377 | 25 | 402 | |
| Yes | 72 | 10 | 82 | |
| Lymphovascular invasion in the primary tumor | | | | 0.118 |
| No | 344 | 22 | 366 | |
| Yes | 105 | 12 | 117 | |
| Estrogen receptor status | | | | 0.397 |
| Negative | 44 | 5 | 49 | |
| Positive | 405 | 30 | 435 | |
| Progesterone receptor status | | | | 0.874 |
| Negative | 134 | 10 | 144 | |
| Positive | 315 | 25 | 340 | |
| MIB-1 proliferation index | | | | 0.415 |
| Negative | 60 | 3 | 63 | |
| Positive | 388 | 32 | 420 | |
| Her-2 status | | | | 0.252 |
| Negative | 370 | 32 | 402 | |
| Positive | 53 | 2 | 55 | |
| Palpability of the primary tumor | | | | 0.896 |
| Palpable | 316 | 25 | 341 | |
| Impalpable | 133 | 10 | 143 | |
| Histological grade of the primary tumor | | | | 0.742 |
| Grade I–II | 308 | 25 | 333 | |
| Grade III | 140 | 10 | 150 | |
| Histology of the primary tumor | | | | 0.418 |
| Ductal carcinoma | 290 | 19 | 309 | |
| Lobular carcinoma | 80 | 9 | 89 | |
| Any other histology | 79 | 7 | 86 | |
| Primary tumor location | | | | 0.064 |
| Medial or central | 159 | 7 | 166 | |
| Lateral | 290 | 28 | 318 | |
| Number of sentinel nodes harvested on SNB | | | | 0.916 |
| One | 122 | 11 | 133 | |
| Two | 136 | 9 | 145 | |
| Three | 95 | 8 | 103 | |
| Four or more | 96 | 7 | 103 | |

**TABLE 1** continued

| | No additional metastases on ALND (*n* = 449) | Additional metastases on ALND (*n* = 35) | All patients (*n* = 484) | *p* |
|---|---|---|---|---|
| Number of nonsentinel nodes harvested in SNB | | | | 0.915 |
| None | 346 | 28 | 374 | |
| One | 71 | 5 | 76 | |
| Two or more | 32 | 2 | 34 | |
| Number of negative sentinel nodes on SNB | | | | 0.921 |
| None | 147 | 13 | 160 | |
| One | 122 | 8 | 130 | |
| Two | 96 | 8 | 104 | |
| Three or more | 84 | 6 | 90 | |
| Number of positive sentinel nodes on SNB | | | | 0.663 |
| One | 396 | 30 | 426 | |
| Two or more | 53 | 5 | 58 | |
| Sentinel node ratio (positive/all sentinel nodes) | | | | 0.306 |
| 0–0.5 | 295 | 20 | 315 | |
| >0.5 | 154 | 15 | 169 | |
| Detection method of the sentinel node metastasis | | | | 0.457 |
| Frozen-section analysis | 316 | 27 | 343 | |
| Paraffin hematoxylin and eosin staining | 43 | 4 | 47 | |
| Paraffin immunohistochemistry | 90 | 4 | 94 | |
| Size of the sentinel node metastasis | | | | 0.304 |
| Isolated tumor cells | 194 | 12 | 206 | |
| Micrometastasis | 255 | 23 | 278 | |
| Size of nonsentinel node metastasis | | | | |
| Isolated tumor cells | | 5 | | |
| Micrometastasis | | 9 | | |
| Macrometastasis | | 21 | | |

**TABLE 2** Binary logistic multiple regression analysis of variables with *p* value <0.15 on univariate analysis using the backward stepwise method

| | Coefficient | Standard error | Wald | *p* | Odds ratio | 95% CI for odds ratio | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Tumor diameter (mm) | 0.031 | 0.010 | 9.703 | 0.002 | 1.032 | 1.012 | 1.052 |
| Tumor multifocality | 0.832 | 0.403 | 4.269 | 0.039 | 2.299 | 1.044 | 5.064 |
| Tumor localization | 0.712 | 0.442 | 2.598 | 0.107 | 2.037 | 0.857 | 4.841 |
| Lymphovascular invasion | 0.450 | 0.390 | 1.331 | 0.249 | 1.568 | 0.730 | 3.369 |
| Constant | −3.422 | 0.321 | 113.538 | 0.000 | 0.033 | | |

*CI* confidence interval

metastasis, which is not recorded in our database.[9] All of the other predictive models were validated by applying the predictive models to our main patient population of 484 patients and calculating either the predicted probability for additional metastases or a score given by the model. AUC was determined for all of the models, as well as sensitivity,

**TABLE 3** Nomograms to predict nonsentinel node metastases in unifocal and multifocal tumors. Tumor size indicates largest tumor diameter and in multifocal tumors the diameter of the largest focus

| Unifocal tumor | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Tumor size (mm) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 |
| Risk of additional metastases (%) | 3.2 | 3.4 | 3.6 | 3.8 | 4.0 | 4.3 | 4.5 | 4.8 | 5.1 | 5.4 | 5.7 | 6.6 | 7.6 | 8.8 | 10.1 | 11.6 | 13.3 | 15.2 | 17.3 |
| Multifocal tumor | | | | | | | | | | | | | | | | | | | |
| Tumor size (mm) | 0 | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 25 | 30 | 35 | 40 | 45 | 50 | 55 | 60 |
| Risk of additional metastases (%) | 7.0 | 7.4 | 7.8 | 8.3 | 8.8 | 9.3 | 9.8 | 10.4 | 11.0 | 11.6 | 12.2 | 14.0 | 16.0 | 18.2 | 20.6 | 23.2 | 26.1 | 29.2 | 32.5 |

"Helsinki" indicates calibration plot for the main patient population of 484 patients

**TABLE 4** Different models for predicting nonsentinel node status after tumor-positive SNB

| Study | Year | No. of patients | Cut threshold | AUC (95% CI) | Sensitivity (%) | Specificity (%) | Clinical utility (%) |
|---|---|---|---|---|---|---|---|
| MSKCC | 2003 | 702 | ≤10% | 0.611 (0.510–0.712) | 91.4 | 18.3 | 17.6 |
| MDA | 2003 | 131 | ≤0 points | 0.547 (0.435–0.658) | 42.9 | 75.5 | 74.2 |
| Saidi | 2004 | 116 | ≤2 points | 0.571 (0.473–0.670) | 74.1 | 31.6 | 31.2 |
| Adelaide | 2004 | 82 | Unable to validate | | | | |
| Tenon | 2005 | 71 | ≤3.5 points | 0.590 (0.492–0.688) | 25.7 | 72.2 | 81.6 |
| Mayo | 2005 | 574 | ≤10% | 0.602 (0.502–0.703) | 91.4 | 16.5 | 15.9 |
| Louisville | 2006 | 1,253 | ≤1 point | 0.576 (0.470–0.683) | 97.1 | 15.6 | 1.6 |
| Cambridge | 2007 | 118 | ≤10% | 0.515 (0.410–0.621) | 68.6 | 27.8 | 28.1 |
| Marseille | 2008 | 909 | ≤10% | 0.617 (0.531–0.704) | 91.4 | 25.8 | 24.6 |
| Stanford | 2008 | 285 | ≤10% | 0.629 (0.531–0.727) | 68.6 | 49.0 | 47.7 |
| Seoul | 2008 | 184 | ≤1 point | 0.599 (0.487–0.710) | 54.3 | 61.2 | 60.1 |
| Turkish | 2009 | 607 | ≤10% | 0.566 (0.455–0.676) | 37.1 | 76.4 | 75.4 |
| Czech | 2009 | 330 | ≤10% | 0.633 (0.533–0.733) | 80.0 | 39.9 | 38.4 |
| Ljubljana | 2010 | 534 | ≤10% | 0.586 (0.480–0.691) | 94.3 | 10.0 | 9.7 |
| Helsinki[a] | | 484 | ≤10% | 0.682 (0.592–0.771) | 38.2 | 85.7 | 84.1 |
| Helsinki[b] | | 51 | ≤10% | 0.791 (0.637–0.945) | 80.0 | 76.1 | 70.6 |

[a] Main population of 484 patients

[b] Validation series of 51 patients used to validate the model from the main patient population

specificity, and clinical utility for either a cutoff value of 10% predicted probability or a cutoff threshold value given by the scoring system (Table 4). Four of the best preforming models were divided into quintiles, for which the actual probability of nonsentinel metastases was calculated. The actual versus predicted probabilities were plotted to determine the calibration of these different models in our main patient series (Fig. 1). The reference line in Fig. 1 indicates an ideal calibration with perfect concordance between predicted and actual probabilities.

The validation series of 51 patients is described in Table 5. We applied our previously established predictive model to this validation series and found good correspondence between the predicted probabilities and actual observations with AUC of 0.791 (0.637–0.945; 95% confidence interval). With the cutoff value of 10% predicted probability the model showed sensitivity of 80.0%, specificity of 76.1%, and clinical utility of 70.6% when applied to the validation series (Table 4). All of the patients in the validation series had predicted probability of additional metastases less than 15%, and therefore this higher cutoff value could not be validated.

## DISCUSSION

### *Factors Affecting Nonsentinel Status*

Factors affecting nonsentinel node involvement after tumor-positive SNB have been studied since the advent of SNB procedures. The goal has been to identify individual patients at such low risk of additional metastases that completion ALND can be safely omitted. Several patient, tumor, and SNB procedure-specific risk factors have been identified, some of which have been reproducible by following studies and some not. Among our patients with micrometastases or ITC, we identified only two risk factors

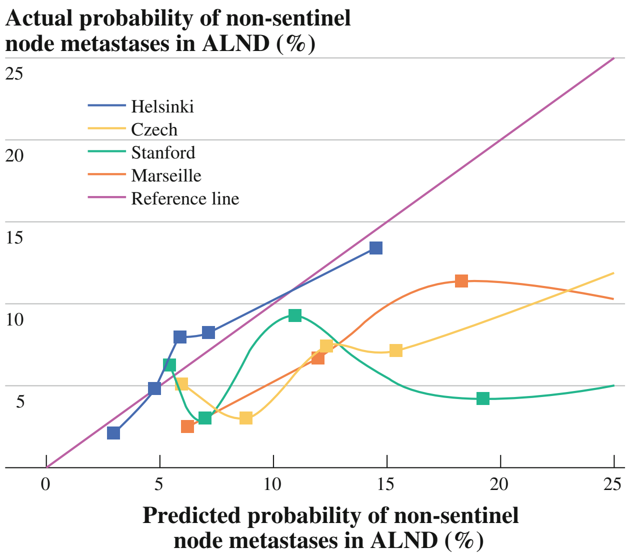

**FIG. 1** Calibration plot for four predictive models with the patient population of 484 patients split into quintiles to calculate the predicted and actual probability of nonsentinel node metastases in axillary lymph node dissection (ALND)

for nonsentinel node involvement, both being tumor related, namely increasing tumor diameter and multifocality. Tumor diameter is a variable in the majority of the existing models.[8,10–13,15–17,19,20] However, multifocality is included in only two of them.[7,20]

Increasing tumor diameter and multifocality have both been shown to increase the overall risk of metastatic axillary lymph nodes and therefore also the likelihood of tumor-positive SNB.[30,31] It seems reasonable that risk factors for axillary lymph node metastases in general turn out to be risk factors for nonsentinel metastases after tumor-positive SNB.

### *Predictive Models in Micrometastasis and ITC*

All but one of the existing predictive models are based on patient populations including SN macrometastases. Consequently they do not perform so well in a patient population with only micrometastasis or ITC in SN, possibly due to the much lower prevalence of additional axillary involvement in such setting.[3,21] The low prevalence of residual axillary disease after micrometastasis or ITC in SN makes it difficult to predict nonsentinel involvement and requires large patient series for statistical associations to arise.

The nonsentinel node involvement rate of 7.2% in our present series is remarkably low and considerably lower than in previously published studies. A meta-analysis published in 2004 and based on 25 previous studies reported a nonsentinel node involvement rate of approximately 15% in micrometastatic SN patients.[3] Preoperative axillary ultrasound has been performed in all our patients and fine-needle biopsy taken whenever suspicious nodes are found. If fine-needle biopsy reveals a metastasis, the patient undergoes direct ALND without SNB. This may, in part, lower the rate of axillary involvement in SN in general and also nonsentinel node involvement rate, as at least some macrometastases are found preoperatively.[32]

### *Validation of Other Models*

The validation of previously published predictive models showed them all to perform relatively poorly in our patient population. The AUC values for all of the models, including our own, were less than 0.7, which is somewhat low in comparison with other validation models published.[18,21,33–37] The majority of these models are designed for all sizes of SN metastasis, and they tend to work best with macrometastases. Coutant et al. validated seven of the published predictive models with a patient population of 561 patients, of whom 246 had micrometastasis or ITC in SN.[21] They showed consistently lower AUC values for the predictive models for the subgroup of micrometastasis or ITC in SN.[21]

The Czech, Stanford, and Marseille models performed best in terms of AUC values. However, all of these models showed poor clinical utility by selecting only 38.4, 47.7, and 24.6% of patients, respectively, to the low-risk group. These models also showed poor calibration, as they all tended to predict excessively high probabilities for nonsentinel node involvement (Fig. 1).

### *Analysis of Our New Model*

Predictive models are known to work best in the center where they were developed and therefore require validation in other independent patient populations before being adapted to clinical use. Therefore, we developed a new predictive model from a logistic regression analysis and included only the two statistically significant variables: tumor diameter and multifocality. This new model is astonishingly simple and yet performs rather well, at least in our unit. The model shows AUC of 0.682 on the main patient population and 0.791 on the validation series. A recent validation study of seven of the published predictive models showed AUC ranging from 0.60 to 0.81 for a patient series of 246 patients with micrometastasis or ITC in SN, corresponding well to our present results.[21]

With a cutoff value of 10% predicted probability, our new model shows very good clinical utility by selecting 84.1% of the main population and 70.6% of the validation series patients to the low-risk group. With a cutoff value of

**TABLE 5** Patient and tumor characteristics of the validation series

| | No additional metastases on ALND ($n = 46$) | Additional metastases on ALND ($n = 5$) | All patients ($n = 51$) |
|---|---|---|---|
| Patient age (years) | | | |
| Mean (range) | 60 (40–81) | 54 (41–64) | 60 (40–81) |
| Histological diameter of the primary tumor (mm) | | | |
| Mean (range) | 20 (2–50) | 18 (15–20) | 19 (2–50) |
| Multifocality of the primary tumor | | | |
| No | 39 | 1 | 40 |
| Yes | 7 | 4 | 11 |
| Lymphovascular invasion in the primary tumor | | | |
| No | 37 | 3 | 40 |
| Yes | 9 | 2 | 11 |
| Estrogen receptor status | | | |
| Negative | 4 | 0 | 4 |
| Positive | 42 | 5 | 47 |
| Progesterone receptor status | | | |
| Negative | 15 | 2 | 17 |
| Positive | 31 | 3 | 34 |
| MIB-1 proliferation index | | | |
| Negative | 5 | 0 | 5 |
| Positive | 41 | 5 | 46 |
| Her-2 status | | | |
| Negative | 42 | 4 | 46 |
| Positive | 4 | 1 | 5 |
| Palpability of the primary tumor | | | |
| Impalpable | 17 | 0 | 17 |
| Palpable | 29 | 5 | 34 |
| Histological grade of the primary tumor | | | |
| Grade I–II | 34 | 3 | 37 |
| Grade III | 12 | 2 | 14 |
| Histology of the primary tumor | | | |
| Ductal carcinoma | 28 | 4 | 32 |
| Lobular carcinoma | 10 | 1 | 11 |
| Any other histology | 8 | 0 | 8 |
| Primary tumor location | | | |
| Medial or central | 12 | 2 | 14 |
| Lateral | 34 | 3 | 37 |
| Number of sentinel nodes harvested in SNB | | | |
| One | 14 | 1 | 15 |
| Two | 14 | 1 | 15 |
| Three | 17 | 2 | 19 |
| Four or more | 1 | 1 | 2 |
| Number of nonsentinel nodes harvested on SNB | | | |
| None | 39 | 2 | 41 |
| One | 6 | 2 | 8 |
| Two or more | 1 | 1 | 2 |
| Detection method of the sentinel node metastasis | | | |
| Frozen-section analysis | 33 | 4 | 37 |
| Paraffin hematoxylin and eosin staining | 3 | 0 | 3 |
| Paraffin immunohistochemistry | 10 | 1 | 11 |
| Size of the sentinel node metastasis | | | |
| Isolated tumor cells | 24 | 2 | 26 |
| Micrometastasis | 22 | 3 | 25 |
| Size of nonsentinel node metastasis | | | |
| Isolated tumor cells | | 1 | |
| Micrometastasis | | | |
| Macrometastasis | | 4 | |

15% predicted probability, the model selects 95.6% of patients to the low-risk group, but regrettably this could not be validated since none of the patients in the validation series had predicted probability higher than 15%.

Our model is also well calibrated and shows good fit in terms of Hosmer–Lemeshow test. Furthermore, the simplicity of our model makes it very easy to use in clinical practice, either by the included graphical nomogram or by the predictive equation.

### *Is ALND Needed in Any Patients with Micrometastases or ITC?*

The 7.2% prevalence of nonsentinel node metastases in our patient series leads to the question of whether ALND is warranted in any of the patients. In a meta-analysis including 8,059 patients with SNB and backup ALND, the false-negative rate of SNB was roughly 8% and the average prevalence of axillary metastases was 42%.[2] These figures indicate that approximately 6% of patients will have residual disease in the axilla after tumor-negative SNB, which is only slightly less than the 7.2% prevalence of nonsentinel node metastases observed in the present study. Furthermore, in the ACOSOG Z0011 trial the prevalence of nonsentinel node metastases was 27% in the ALND arm, suggesting a 27% risk of residual axillary disease in the SNB-only arm.[23,24] However, omitting ALND did not lead to more regional recurrences or survival disadvantage in general.[23,24]

Predictive models for nonsentinel node involvement have been developed to identify patients at such low risk of additional metastases that ALND can be omitted. This paradigm may well be changing into whether the predictive models are able to identify patients at such high risk of residual disease that ALND would be warranted.

### *Limitations of the Present Study*

The validation series of this study is rather small and is from the same center as the main patient population. Furthermore, only a very small proportion of patients in our main patient population had predicted risk of additional metastases higher than 20% (13 patients) or 30% (4 patients), and none of the patients in the validation series had predicted risk higher than 15%. For these reasons, our nomogram needs to be externally validated using an independent patient series to evaluate its accuracy, especially when predicting high risk of additional metastases.

## CONCLUSIONS

A very small percentage of patients with micrometastasis or ITC in SN have additional metastases on ALND. Most published predictive models for nonsentinel node involvement perform poorly in the present patient population. We developed a new predictive model which seems to perform well in discriminating patients with more than 10% risk of additional metastases. However, the presented nomogram needs to be validated using an independent patient series to evaluate its accuracy, especially for high-risk patients.

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